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Utility of specific laboratory biomarkers to predict severe sepsis in pediatric patients with SIRS

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ABSTRACT

Objective: To identify the association between readily available laboratory biomarkers and the development of severe sepsis in children presenting to the emergency department (ED) with systemic inflammatory response syndrome (SIRS).

Methods: In this retrospective cohort study, ED patient encounters from June 2018 to June 2019 that triggered an automated sepsis alert based on SIRS criteria were analyzed. Encounters were included if the patient had any of the following laboratory tests sent within 6 h of ED arrival: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactic acid, and procalcitonin. For each of the biomarkers, a receiver operating characteristic (ROC) curve was created for our primary outcome, severe sepsis within 24 h of ED disposition, and our secondary outcome, severe sepsis with a positive bacterial culture. For each ROC curve, we calculated the area under the curve (AUC) with 95% confidence intervals (95% CI) and created cutoff points to achieve 90% sensitivity and 90% sensitivity for the primary and secondary outcomes.

Results: During the study period, 4349/61,195 (7.1%) encounters triggered an automated sepsis alert. Of those, 1207/4349 (27.8%) had one of the candidate biomarkers sent within 6 h of ED arrival and were included in the study. A total of 100/1207 (8.3%) met criteria for severe sepsis within 24 h of arrival, and 41/100 severe sepsis cases (41%) were deemed culture-positive. Procalcitonin had the highest AUC for identifying severe sepsis [0.62 (95% CI 0.52–0.73)] while ESR and CRP had the highest AUC for culture-positive sepsis [0.68 (95% CI 0.47–0.89) and 0.67 (95% CI 0.53–0.81), respectively]. At 90% sensitivity for detecting severe sepsis, all of the biomarker threshold values fell within that laboratory test's normal range. At 90% specificity for severe sepsis, threshold values were as follows: procalcitonin 2.72 ng/mL, CRP 16.79 mg/dL, ESR 79.5 mm/h and lactic acid 3.6 mmol/L.

Conclusion: Our data indicate that CRP, ESR, lactic acid, and procalcitonin elevations were all specific, but not sensitive, in identifying children in the ED with SIRS who go on to develop severe sepsis.

1. Introduction

Sepsis is a leading cause of morbidity, mortality, and health care utilization in infants and children in the United States [1-6]. Sepsis contributes to 19% of all deaths globally, with the highest age-specific incidence in children younger than 5 years [7-9]. Pediatric sepsis resulted in 0.7% of all hospital encounters, with an incidence of 2.8% in inpatients in the United States [1,9]. Recent studies have found an incidence of pediatric sepsis in up to 8% of all pediatric intensive care unit (PICU) admissions [10], contributing to 1 in 4 deaths in the PICU [11]. In 2016, severe sepsis hospitalizations accounted for $7.3 billion of $40.3 billion (18.1%) in nationwide estimated pediatric hospitalization costs [12]. Rapid recognition of sepsis and prompt resuscitation with intravenous (IV) fluids and antibiotics have been shown to decrease mortality [13-16]. However, to avoid inappropriate use of these resources, it is necessary to differentiate children with severe sepsis from those with infections that may be self-limited or amenable to less intensive treatment.

The 2005 International Pediatric Sepsis Definition Consensus Conference classified sepsis as known or suspected infection in the presence of

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systemic inflammatory response syndrome (SIRS) and severe sepsis as sepsis plus one of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome (ARDS), or two or more organ dysfunctions (respiratory, renal, neurologic, hematologic, or hepatic) [16-18]. Many studies have shown that SIRS and sepsis are extremely common in pediatric emergency department (ED) patients, and the presence of SIRS alone is a poor predictor of progression to the organ dysfunction that defines severe sepsis [19-21]. A variety of serum biomarkers have been utilized to help clinicians make this important distinction. Some biomarkers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), are non-specific markers of inflammation [22]. Others, such as procalcitonin may be more specific for the presence of bacterial infection [23]. Still others, such as lactic acid, are markers of impaired end organ perfusion [24]. Despite decades of their clinical use in sepsis detection, there is a relative paucity of data on their performance in distinguishing children with uncomplicated infection from those who have or will develop organ dysfunction [20,25]. More recently, novel biomarkers such as presepsin, sTREM-1, and cytokine assays, have been reported to be more specific and sensitive for detection of sepsis than traditional laboratory tests, but they are not yet readily available at the bedside [26-30].

The objective of this study is to identify the association between laboratory biomarkers generally available for clinical use and the development of severe sepsis in children presenting to the ED with SIRS.

2. Methods

2.1. Study design and setting

This is a retrospective cohort study of patient encounters from the emergency department (ED) of a quaternary care, free-standing children's hospital.

2.2. Selection of participants

A data warehouse was queried for all ED encounters from June 5, 2018 to June 5, 2019 where a patient triggered an automated sepsis alert embedded in the hospital electronic health record based on SIRS criteria [17] with respiratory rate thresholds modified to improve alert sensitivity [20]. SIRS criteria was defined as meeting ≥2 of the following criteria, 1 of which must be temperature or WBC count: pyrexia (>38.5 °C) or hypothermia (<36 °C), age-dependent tachycardia or bradycardia, tachypnea or need for mechanical ventilation, abnormal WBC count or >10% bands [17]. Encounters were included if the patient had any of the following biomarkers obtained within 6 h of ED arrival: CRP, ESR, lactic acid, or procalcitonin.

2.3. Outcome

To identify possible cases of severe sepsis, encounters that met any of the following criteria were manually reviewed by one of the study authors: (1) an International Classification of Diseases, 10th Revision (ICD-10) code for severe sepsis or septic shock (R65.20 and R65.21) entered at any time during the ED or inpatient encounter, (2) clinician use of the ED septic shock order set, (3) any patient admitted from the ED to an ICU or intermediate care unit within 72 h of ED disposition, or (4) patient died within 72 h of ED disposition. Encounters were considered to be positive for severe sepsis if the patient met the International Pediatric Sepsis Consensus Conference [17] definition of severe sepsis or septic shock between the time of ED arrival and 24 h after ED disposition or had an ICD-10 code for severe sepsis or septic shock entered for the ED encounter or within 24 h of ED disposition. Patients who had a cardiac arrest before meeting criteria for severe sepsis were not considered severe sepsis cases.

Our secondary outcome, culture-positive sepsis, was defined by a positive culture with a known or presumed pathogen obtained from one of the following sites in the first 24 h of the hospital stay: blood, urine, wound, cerebrospinal fluid, pleural fluid, synovial fluid, or peritoneal fluid. A patient with a positive respiratory culture was considered to have culture-positive sepsis only if they also had either (1) pneumonia diagnosed on chest imaging or by the clinical team or (2) presence of increased ventilatory settings for chronically ventilated patients with negative viral respiratory testing. We excluded positive results from genital swabs, stool samples, and pre-operative or surveillance testing. For patients with a positive culture of a possible or suspected contaminant such as known skin flora, additional chart review was performed and the patient was considered to have a true positive culture if they were treated as such by the clinical team.

2.4. Data collection

We collected the following data on each eligible encounter: results of all laboratory testing, patient age, sex, race, ethnicity, antibiotics and fluids administered in the ED, need for vasoactive medications, need for intubation, and disposition from the ED. We identified patients with complex chronic conditions according to the classification system outlined by Feudtner et al. [31].

For patients who had more than one result for a given lab test within 6 h of ED arrival, only the first value was used for analysis.

Study data were collected and managed using the REDCap (Research Electronic Data Capture, Nashville, TN) electronic data capture tools hosted at Boston Children's Hospital.

This study was approved by the hospital Institutional Review Board with a waiver of consent.

2.5. Statistical analysis

In order to assess for differences in relevant demographic, historical, and clinical data between children with severe sepsis and septic shock and those without, means for normally distributed, continuous variables were calculated and compared using the Student's *t*-test; medians were calculated for non-normally distributed continuous variables and compared using the Wilcoxon rank sum test; and proportions were compared using the chi-squared test.

For each of the following biomarkers, we compared median values with inter-quartile ranges and created a receiver operating characteristic (ROC) curve for our primary outcome, severe sepsis, and our secondary outcome, culture-positive sepsis: ESR, CRP, procalcitonin, and lactic acid. For each ROC curve, we calculated the area under the curve (AUC) with 95% confidence intervals (95% CI). Finally, we report cutoff points for each biomarker chosen to achieve 90% sensitivity and 90% specificity for the respective outcomes.

All analyses were performed using SPSS (IBM SPSS Statistics for Windows 2020. Armonk, NY: IBM Corp.)

3. Results

A patient triggered an automated sepsis alert in 4349/61,195 (7.1%) encounters during the study period. All 4349 patients had temperature, heart rate and respiratory rate measured at least once during their ED visit and 2553/4349 (58.7%) had a WBC performed within 6 h of ED arrival. 1207/4349 (27.8%) had one of the candidate biomarkers sent within 6 h of ED arrival: 753 CRP, 478 ESR, 365 lactic acid, and 373 procalcitonin. Patients who were excluded were younger (median 4.1 years vs 6.8 years, $p < 0.001$), less likely to have sepsis (0.5% vs 8.3%, $p < 0.001$) and more likely to be discharged home (67% vs 27%, $p < 0.001$) than patients who were included.

Only 100/1207 (8.3%) met criteria for severe sepsis within 24 h of ED arrival and 41/100 (41%) severe sepsis cases were culture-positive. The characteristics of patients with severe sepsis are compared to those without in Table 1. Patients with severe sepsis were younger, more likely to have a complex chronic condition, more likely to have positive

Table 1
Characteristics of study patients with and without severe sepsis.

	Severe sepsis (%) (*N* = 100)	No severe sepsis (%) (*N* = 1107)	p
Median age (years) (IQ range)	6 (0, 19.7)	13 (3.2, 22.9)	<0.001
<30d	3 (3%)	16 (1.4%)	
31d to 11 mo	5 (5%)	169 (15.3%)	
1 yr to 6 yrs	14 (14%)	366 (33.1%)	
7–12 yrs	27 (27%)	167 (15.1%)	
>12 yrs	51 (51%)	388 (35.1%)	
Female sex	54 (54%)	521 (47.1%)	0.184
Race and Ethnicity:			
White race	48 (48%)	544 (49.1%)	0.83
Hispanic ethnicity	23 (23%)	175 (15.8%)	0.06
Complex chronic condition	34 (34%)	248 (22.4%)	0.009
Laboratory data			
Positive blood culture	14 (14%)	33 (3%)	<0.001
Positive urine culture	14 (14%)	70 (6.3%)	0.004
Positive CSF culture	0 (0%)	3 (0.2%)	0.6
Disposition			
Discharged to home	0 (0%)	329 (29.7%)	<0.001
General inpatient unit	24 (24%)	646 (58.4%)	
Intensive care unit	76 (76%)	130 (11.7%)	
Death within 30 days	2 (2%)	5 (0.4%)	0.05

cultures and more likely to be admitted to the hospital than those without severe sepsis.

We compare median values with interquartile ranges for each of the studied biomarkers (CRP, ESR, lactic acid, and procalcitonin) in Table 2. The AUC's for the detection of severe sepsis and culture positive sepsis, and threshold values to achieve 90% sensitivity and 90% specificity for each outcome, are shown in Table 3. ROC curves for CRP, ESR, lactic acid, and procalcitonin are shown in Figs. 1a-d, respectively.

4. Discussion

This study demonstrates that several readily available biomarkers are specific, but not sensitive, in identifying children in the ED with SIRS who will go on to develop severe sepsis. In particular, procalcitonin had the highest area under the receiver operating curve for identifying severe sepsis, though AUC's for all four biomarkers were similar. Each of the studied biomarkers performed slightly better at identifying culture-positive sepsis than all-cause severe sepsis, but still lacked the sensitivity that would be necessary for a clinically useful screening test. These results may help to inform clinical decision making at the bedside regarding which children with SIRS should undergo resuscitation with intravenous fluids and antibiotics and may require admission to the hospital or intensive care.

In our study, procalcitonin had the highest AUC of any biomarker for distinguishing SIRS from severe sepsis, although the 95% confidence interval overlapped with other biomarkers. These findings are consistent with prior studies that have shown procalcitonin to be one of the most useful biomarkers in predicting severe sepsis in children, although these studies were performed in the pediatric intensive care unit, not in the ED [22,23]. In our study, a procalcitonin level above 2.72 ng/mL had 90% specificity for development of severe sepsis, making it a useful marker of sepsis when elevated to such a level. However, the 90% sensitivity cut-point fell at just 0.08 ng/ml, indicating that even a normal procalcitonin in no way rules out the development of severe sepsis in children with SIRS. Notably, some studies of children in the ICU with sepsis show that higher procalcitonin levels may also predict more severe outcomes such as death [32–35]. While such a finding is beyond the scope of this study, further research may elucidate additional ways that procalcitonin values can help to risk stratify children with infection in the ED.

Lactic acid has been widely studied in adult sepsis, but data in children are more limited. Multiple adult studies have shown the association between mortality and elevated lactate levels [36,37], and lactate-guided resuscitation in critically ill patients with sepsis was associated with reduced mortality [38]. In one pediatric study, higher lactic acid was associated with a greater risk of organ dysfunction and ICU admission [39], while another ED-based study showed that a lactic acid of >4.0 mmol/L was 94% specific and 31% sensitive in identifying organ dysfunction in patients with SIRS [19]. Our study found that a lactic acid above 3.6 mmol/L was 90% specific in identifying severe sepsis, but to achieve 90% sensitivity the cut-off value was just 0.65 mmol/L, well below what is typically considered the normal range (<2 mmol/L) [40]. Interestingly, when comparing median lactate levels between patients with and without sepsis (Table 2), we found that the median lactate levels were higher in the non-sepsis group. This could be explained by alternative causes of elevated lactate, such as seizure activity, exercise, diabetes, malignancy and effects of certain drugs, such as metformin, beta-2 agonists and salicylates [41]. It should be noted that the IQR of the sepsis group was much wider, which supports the idea that a markedly elevated lactate is more indicative of sepsis while more moderate elevations may be seen across a variety of disease states. When compared to other biomarkers, lactic acid may be a later marker of sepsis due to the fact that increases in lactic acid are directly related to tissue hypoperfusion rather than systemic inflammation. It is postulated that normal or modestly elevated lactic acid levels are unlikely to be helpful in differentiating SIRS from severe sepsis early in the clinical course, but may be more useful as a marker later as the disease progresses [42]. Our data support this concept, as significantly elevated lactic acid values were specific for presence or development of severe sepsis.

C-reactive protein and erythrocyte sedimentation rate are widely used laboratory markers of systemic inflammation [43,44]. While these acute phase reactants are frequently elevated during systemic infection [45], their role in sepsis is not as well known [46]. Our study found that CRP above 16.79 mg/dL and ESR above 79.5 mm/h were each 90% specific in identifying severe sepsis among children with SIRS. These findings are consistent with adult literature that shows CRP and ESR can be useful in differentiating sepsis from SIRS [47,48]. We can make a similar conclusion about CRP and ESR as previously described in procalcitonin – marked elevation of these inflammatory markers may help discriminate between SIRS and severe sepsis, while mild-moderate elevations are neither sensitive nor specific.

While most of the biomarkers in our study had improved AUC in detection of culture-positive sepsis compared to all cases of severe sepsis,

Table 2
Comparison of biomarker measurements for patients with and without severe sepsis.

Biomarker	Sepsis	No Sepsis	*P* value
Median CRP (IQR)	11.42 mg/dL (0 mg/dL – 29.42 mg/dL)	8.78 mg/dL (0 mg/dL – 18.18 mg/dL)	0.08
Median ESR (IQR)	74 mm/h (0 mm/h – 145 mm/h)	43 mm/h (0 mm/h – 113 mm/h)	0.63
Median Lactic Acid (IQR)	1.35 mmol/L (0 mmol/L – 3.15 mmol/L)	1.5 mmol/L (0.8 mmol/L – 2.2 mmol/L)	0.06
Median Procalcitonin (IQR)	3.74 ng/mL (0 ng/mL – 15.35 ng/mL)	0.31 ng/mL (0 ng/mL – 1.27 ng/mL)	0.02

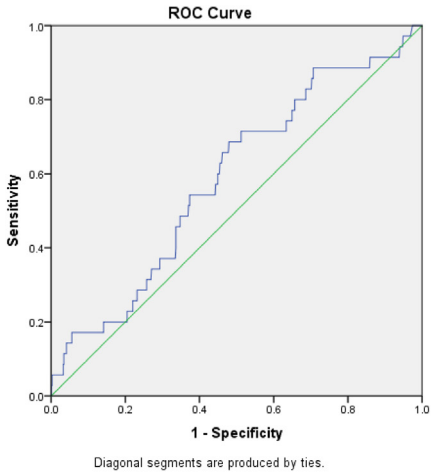
Table 3
Test characteristics of biomarkers for severe sepsis and culture positive sepsis.

Biomarker	AUC severe sepsis (95% CI)	AUC culture + sepsis (95% CI)	Value to reach 90% sensitivity severe sepsis	Value to reach 90% sensitivity culture + sepsis	Value to reach 90% specificity severe sepsis	Value to reach 90% specificity culture + sepsis
C-reactive protein $N = 734$	0.59 (0.49, 0.68)	0.67 (0.53, 0.81)	0.39 mg/dL	0.27 mg/dL	16.79 mg/dL	16.79 mg/dL
Erythrocyte sedimentation rate $N = 471$	0.53 (0.38, 0.69)	0.68 (0.47, 0.89)	3.5 mm/h	7.5 mm/h	79.5 mm/h	80.5 mm/h
Lactic acid $N = 365$	0.57 (0.49, 0.65)	0.61 (0.5, 0.73)	0.65 mmol/L	0.95 mmol/L	3.6 mmol/L	3.85 mmol/L
Procalcitonin $N = 370$	0.62 (0.52, 0.73)	0.63 (0.46, 0.8)	0.08 ng/mL	0.08 ng/mL	2.72 ng/mL	2.92 ng/mL

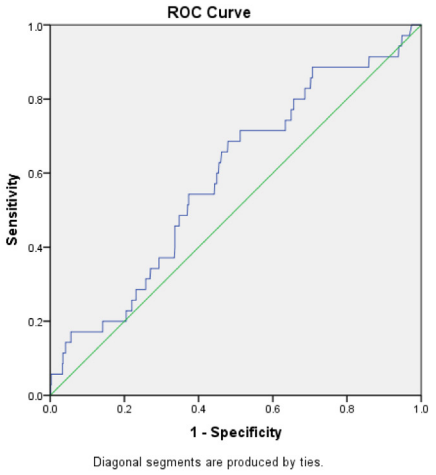
the AUC for ESR and CRP was higher than procalcitonin and lactic acid in predicting severe sepsis with positive cultures. This suggests that these tests may be indicative of the host response to bacterial infection rather than pathways that lead to organ dysfunction. Interestingly, in our data, procalcitonin showed no difference in AUC between all-cause severe sepsis and culture positive severe sepsis. This is in contrast to multiple other studies that show that procalcitonin is sensitive at distinguishing bacterial from viral infections in febrile children [49], as well as one study that showed elevated procalcitonin levels among children with bacterial sepsis compared to children with fungal, viral, or culture-negatives sepsis [34]. The reasons that our study differs from this other body of literature is not clear – it may be due to our small sample size of septic children who had procalcitonin values, the unclear accuracy of culture data in distinguishing bacterial from presumed viral sepsis, or other factors unique to our cohort of patients.

Our study has several limitations. First, while heart rate, respiratory rate and temperature were recorded on all patients, most ED patients did not have a WBC obtained because the ordering clinician did not feel it was indicated. It is likely that had this test been done on all ED patients, many more would have triggered SIRS criteria. Second, even

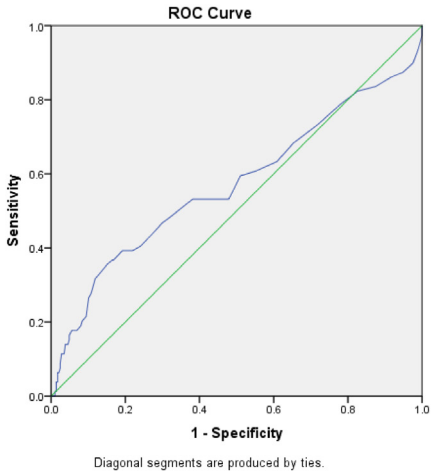
a) CRP: AUC = .588 (95% CI .493, .682)



b) ESR: AUC = .533 (95% CI .375,.691)



c) Lactic Acid: AUC = .570 (95% CI .49, .651)



d) Procalcitonin: AUC = .621 (95% CI .517, .725)

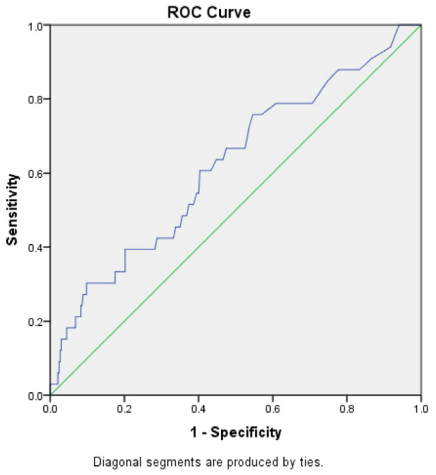


Fig. 1. Area under the curve (AUC) for the receiver operating characteristic (ROC) curve for specific biomarkers to detect severe sepsis.

among those who met SIRS criteria, few of the patients had all of the biomarkers sent, and it is unclear how our data would differ had we been able to measure each laboratory test in all of the patients with SIRS. Another limitation is our inability to comment on the timing of symptom onset, which may affect the degree of biomarker elevation. In this study, we chose to use the International Pediatric sepsis consensus conference criteria for sepsis and severe sepsis, though we recognize that a many different sepsis definitions are used for both clinical and research purposes [50,51]. We also used strict criteria to define our sepsis cohort, including only those who developed cardiovascular or multi-organ dysfunction within 24 h of ED disposition. As a result, we cannot account for patients who were on the pathway to developing severe sepsis but were appropriately treated in the ED and therefore never went on to develop organ dysfunction. We did not account for health conditions such as renal dysfunction, chronic steroid use, autoimmune disease, or immune compromise which are known to affect the reliability of many of these laboratory tests [52,53]. Lastly, our data reflects the experiences of a single institution, which may limit its generalizability.

Early and accurate identification of sepsis is complicated by the lack of pathognomonic symptoms and the highly complex, heterogeneous, and multifaceted host response to infection [54]. Given this complexity, it is highly unlikely that any single biomarker will be able to distinguish between SIRS and severe sepsis. In this study, we did not have sufficient power to create a model looking at whether combinations of biomarkers may perform better than any single biomarker alone. It is likely that a stratification model or decision tree involving combinations of multiple biomarkers could prove to be more accurate in the early identification of sepsis than any one test alone. The Pediatric Sepsis Biomarker Risk Model (PERSEVERE) is an example of a stratification model that uses biomarkers to estimate mortality in children with septic shock [55]. However, the biomarkers used in that model are not widely available for clinical use. In order to improve early sepsis care, we focused on routinely available laboratory tests. Further studies may help elucidate whether the use of these biomarkers as part of a risk stratification model may improve their utility in identifying sepsis.

5. Conclusion

In this ED-based study of pediatric patients, CRP, ESR, lactic acid, and procalcitonin elevations were specific, but not sensitive, in identifying children with SIRS who go on to develop severe sepsis. Elevations in any of these biomarkers above the thresholds described may influence decision-making around administration of fluids, antibiotics, hospital admission and need for intensive care.

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Declarations

The authors report no relationships that could be construed as a conflict of interest.

Declaration of Competing Interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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