Critical Review Form
Diagnostic Test

PGY-2

A latent class approach for sepsis diagnosis supports use of procalcitonin in the emergency room for diagnosis of severe sepsis. BMC Anesthesiol. 2013 Sep 19;13(1):23.

Objectives: **"to estimate the diagnostic accuracy of these three biomarkers [c-reactive protein, procalcitonin, d-dimer] as diagnostic tests for sepsis, with the application of the latent class analysis, in patients at the ER admittance with a presumptive infection as main diagnosis." (p. 2)**

Methods: **This single center, prospective observational study was performed at a university-based hospital in Medellin, Columbia from August 2007 to February 2009. Patients 18 years of age or older admitted from the emergency department (ED) within the previous 24 hours with any of the following were eligible for enrollment: 1) Any confirmed or suspected infectious disease; 2) fever of unknown origin; 3) delirium or encephalopathy of unknown origin; or 4) hypotension not explained by hemorrhage, myocardial infarction, stroke, or heart failure. Exclusion criteria included: 1) refusal to be enrolled by the patient, family, or attending physician; 2) antimicrobial therapy administered at another hospital prior to enrollment; 3) discharge home or transfer to another facility within 24 hours of admission; 4) homelessness or inability of the patient to follow-up; or 5) previous enrollment in the study.**

Patients were recruited by 3 physicians and 2 trained nurses from Monday to Saturday. Baseline clinical data was collected, SOFA and APACHE II scores were calculated, and blood samples were obtained within 24 hours of ED presentation. Relevant data from the medical record was recorded daily, using a standardized case report form, for the first 7 days of hospitalization. C-reactive protein, procalcitonin, and d-dimer were measured at the time of study enrollment and the following morning. Patients were classified as having no infection, having an infection without sepsis, or having sepsis based on expert consensus. Three clinicians (an internist, a critical care physician, and an infectious disease physician), blinded to biomarker results, individually reviewed clinical, microbiologic, laboratory, and radiologic data for the first 7 days of hospitalization. Each clinician established a diagnosis individually, then established the final diagnosis by consensus in cases where there was disagreement. There was complete agreement in 65% of cases.

There were 1795 eligible patients, of whom 765 were included. The mean age was 51.4 years and 49% were male. The median duration of symptoms prior to presentation was 72 hours (interquartile range [IQR] 24 to 192 hours). Diabetes mellitus was present in 19% of subjects, COPD in 12%, chronic renal failure in 11%,

corticosteroid or chemotherapy use in the previous 3 months in 9%, and trauma or surgery in the previous month in 7%. The suspected source of infection was respiratory in 23%, skin and soft tissue in 23%, urinary in 17%, and intra-abdominal infection in 12%; the source was cited as "others" in 13% and was undetermined in 12%. The median SOFA score was 2 (IQR 1-4) and the median APACHE II score was 9 (IQR 5-14). There were 505 patients (66%) classified with sepsis, 112 (15%) with infection but no sepsis, and 148 (19%) without infection. The inter-rater reliability was measured for the determination of sepsis vs. no sepsis (κ = 0.65) and infectious with vs. without sepsis (κ = 0.73).

<table>
<tr><th colspan="2">Guide</th><th>Comments</th></tr>
<tr><td>I.</td><td>Are the results valid?</td><td></td></tr>
<tr><td>A.</td><td>Did clinicians face diagnostic uncertainty?</td><td>Yes. The patients enrolled had signs or symptoms consistent with possible sepsis, but without absolute confirmation. While the degree of uncertainty would likely differ from patient to patient, the diagnosis of sepsis remains difficult in many patients presenting to the ED.</td></tr>
<tr><td>B.</td><td>Was there a blind comparison with an independent gold standard applied similarly to the treatment group and to the control group?
(Confirmation Bias)</td><td>Yes and no. There is no true "gold standard" for the diagnosis of sepsis. Cultures, for example, are frequently negative in patients with sepsis (Bates 1997).

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<tr><td>C.</td><td>Did the results of the test being evaluated influence the decision to perform the gold standard?
(Ascertainment Bias)</td><td>No. CRP, d-dimer, and PCT were checked on all patients included in the study.</td></tr>
<tr><td>II.</td><td>What are the results?</td><td></td></tr>
<tr><td>A.</td><td>What likelihood ratios were associated with the range of possible test results?</td><td>ROC curve analysis yielded a cut-off of 7.8 mg/dl for CRP, 1616 ng/ml for d-dimer, and 0.3 ng/ml for PCT.

Table 1. Diagnostic accuracy of initial tests for the diagnosis of sepsis (95% CI)
<table>
<tr><td></td><td>CRP</td><td>D-dimer</td><td>PCT</td></tr>
<tr><td>AUC (ROC)</td><td>0.71 (0.67-0.74)</td><td>0.55 (0.51-0.58)</td><td>0.69 (0.65-0.72)</td></tr>
<tr><td>Sensitivity</td><td>66.6% (62-71%)</td><td>51.4% (47-56%)</td><td>63.8% (59-68%)</td></tr>
<tr><td>Specificity</td><td>66.1% (60-72%)</td><td>51.6% (45%-58%)</td><td>63.9% (58-70%)</td></tr>
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		LR+ | 1.97 (1.64-2.36) | 1.06 (0.91-1.24) | 1.77 (1.48-2.11) LR- | 0.50 (0.44-0.58) | 0.94 (0.82-1.08) | 0.57 (0.49-0.65) Table 2. Diagnostic accuracy of repeat tests (95% CI) | | CRP | D-dimer | PCT | AUC (ROC) | 0.72 (0.68-0.75) | 0.55 (0.51-0.58) | 0.70 (0.67-0.73) Sensitivity | 68.9% (64-73%) | 52.7% (48-57%) | 67.2% (63-71%) Specificity | 68.7% (62-74%) | 52.7% (46%-59%) | 66.4% (60-74%) LR+ | 2.20 (1.81-2.68) | 1.12 (0.95-1.31) | 2.00 (1.65-2.41) LR- | 0.45 (0.39-0.53) | 0.90 (0.78-1.03) | 0.49 (0.43-0.57)
III.	**How can I apply the results to patient care?**	
A.	**Will the reproducibility of the test result and its interpretation be satisfactory in my clinical setting?**	Yes. These are laboratory tests that are easily reproduced. It is important to note that different assays will result in different values for the same lab test, and this will need to be taken into account.
B.	**Are the results applicable to the patients in my practice?**	No. We are often faced with the dilemma of differentiating septic from non-septic, clinically unstable, patients. This is often difficult, and a lab test to help make this differentiation would be invaluable in helping to direct treatment and work-up. The current study, however, presents diagnostic accuracy for differentiation of sepsis from no sepsis, which includes both those without infection AND those with infection but no sepsis. As the study did not require the presence of 2 or more SIRS criteria, the diagnostic accuracies of the biomarkers are less useful.
C.	**Will the results change my management strategy?**	No. The diagnostic test characteristics for these 3 lab values were poor, with positive LRs between 1 and 2, and negative LRs between 0.5 and 1. Such values mean that the results of the tests will do little to influence disease probability. These tests, in isolation, cannot be used to differentiate sepsis from non-infectious SIRS. Clinical decision rules utilizing these tests have not yet been developed or validated, making their use as part of a broader clinical picture difficult to envision
D.	**Will patients be better off as a result of the test?**	No. As these tests do not help differentiate sepsis from non-infectious SIRS, they cannot be used to make decisions regarding treatment or further work-up.

Limitations:

1. **Single center study conducted at a smaller hospital with low volume (<22K per year) in Columbia. The incidence, and hence pre-test probability, of sepsis is likely much lower in this setting (external vailidity).**

2. **It is interesting that patients with infectious symptoms, but without criteria for sepsis were included in the study. This limits the study's ability to evaluate the test characteristics ability to diagnose sepsis.**

3. **Over half of patients eligible for inclusion (1030 of 1795) were excluded. Over half were excluded due to being hospitalized for > 24 hours or for refusing to participate.**

4. **There was complete agreement on the final diagnosis (no infection, infection without sepsis, sepsis) in only 65% of cases (kappa = 0.65 for sepsis-no sepsis and 0.73 for infection with and without sepsis). Without a clear gold standard, the diagnostic test characteristics may not be entirely accurate.**

Bottom Line

The current study reports poor LRs for CRP, D-dimer, and PCT in the differentiation of septic from non-septic patients (all between 0.5 and 2.0). Unfortunately, the study included all patients with suspected infection, rather than only those with 2 or more SIRS criteria, making the conclusions less clinically applicable. Those patients with either suspected infection or no infection without SIRS criteria would be easily distinguished from septic patients based on clinical grounds alone, and thus would not need biomarker assessment to make this determination.