

Risk Prediction With Procalcitonin and Clinical Rules in Community-Acquired Pneumonia

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Study objective: The Pneumonia Severity Index and CURB-65 predict outcomes in community-acquired pneumonia but have limitations. Procalcitonin, a biomarker of bacterial infection, may provide prognostic information in community-acquired pneumonia. Our objective is to describe the pattern of procalcitonin in community-acquired pneumonia and determine whether procalcitonin provides prognostic information beyond the Pneumonia Severity Index and CURB-65.

Methods: We conducted a multicenter prospective cohort study in 28 community and teaching emergency departments. Patients presenting with a clinical and radiographic diagnosis of community-acquired pneumonia were enrolled. We stratified procalcitonin levels a priori into 4 tiers: I: less than 0.1; II: greater than 0.1 to less than 0.25; III: greater than 0.25 to less than 0.5; and IV: greater than 0.5 ng/mL. Primary outcome was 30-day mortality.

Results: One thousand six hundred fifty-one patients formed the study cohort. Procalcitonin levels were broadly spread across tiers: 32.8% (I), 21.6% (II), 10.2% (III), and 35.4% (IV). Used alone, procalcitonin had modest test characteristics: specificity (35%), sensitivity (92%), positive likelihood ratio (1.41), and negative likelihood ratio (0.22). Adding procalcitonin to the Pneumonia Severity Index in all subjects minimally improved performance. Adding procalcitonin to low-risk Pneumonia Severity Index subjects (classes I to III) provided no additional information. However, subjects in procalcitonin tier I had low 30-day mortality, regardless of clinical risk, including those in higher risk classes (1.5% versus 1.6% for those in Pneumonia Severity Index classes I to III versus classes IV/V). Among high-risk Pneumonia Severity Index subjects (classes IV/V), one quarter (126/546) were in procalcitonin tier I, and the negative likelihood ratio of procalcitonin tier I was 0.09. Procalcitonin tier I was also associated with lower burden of other adverse outcomes. Similar results were observed with CURB-65 stratification.

Conclusion: Selective use of procalcitonin as an adjunct to existing rules may offer additional prognostic information in high-risk patients. [Ann Emerg Med. 2008;52:48-58.]

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INTRODUCTION

Background

Community-acquired pneumonia accounts for 1.3 million hospitalizations in the United States each year¹ at a cost of \$8.4 billion.² It is the most common cause of severe sepsis³

and infection-related death.⁴ Key to the safe and efficient management of community-acquired pneumonia is the ability to reliably predict who will fare well or poorly. The Pneumonia Severity Index⁵ and CURB-65 (Confusion, Uremia, Respiratory rate, low blood pressure, age 65 years or older)⁶ are clinical rules that identify a subset of individuals at low risk of death who are candidates for outpatient care.^{7,8}

Editor's Capsule Summary

What is already known on this topic

Procalcitonin is a biomarker that appears to correlate with bacterial infection.

What question this study addressed

Does a procalcitonin level add prognostic information for pneumonia patients in conjunction with scoring systems such as the Pneumonia Severity Index or CURB-65?

What this study adds to our knowledge

Among 1,651 patients with community-acquired pneumonia in 28 US emergency departments, procalcitonin levels did not add prognostic information for most pneumonia patients. Among higher-risk groups by Pneumonia Severity Index score, low procalcitonin level predicted lower mortality.

How this might change clinical practice

Clinicians should continue using validated prognostic scoring systems for pneumonia. Low procalcitonin level could be considered as a factor for selected patients who would otherwise be considered high risk to be treated in a lower acuity setting.

However, all remaining patients are classified as high risk, usually prompting hospital admission and parenteral antibiotics, even though a large proportion may do well.⁹ Thus, there has been considerable interest in the development of rapidly available biomarkers that might confer additional prognostic information.¹⁰

Importance

Procalcitonin is a calcitonin precursor that is generally increased in bacterial infections but low in viral infections.¹¹ Procalcitonin has good discrimination for bacterial infections and sepsis,¹²⁻¹⁵ and 3 trials used low procalcitonin levels to withhold antibiotics in emergency department (ED) patients presenting with respiratory illnesses.¹⁶⁻¹⁸ However, 2 recent meta-analyses concluded that procalcitonin could not reliably differentiate sepsis from noninfectious inflammation in critically ill patients¹⁹ and had only moderate diagnostic performance for identifying bacteremia in ED patients.²⁰ Furthermore, the prognostic value of procalcitonin measurement beyond existing prediction rules is unclear. Masia et al²¹ observed that patients with high Pneumonia Severity Index scores had higher procalcitonin levels and that higher concentrations were associated with mortality and complications,²¹ but Beovic et al²³ found no association between procalcitonin and Pneumonia Severity Index score.²² These single center studies were limited by small sample sizes and used older procalcitonin assays with low sensitivity.²³

Goals of This Investigation

Our goal was to determine the prognostic utility of a newer, high-sensitivity procalcitonin assay for 30-day mortality and assess its value beyond established clinical prediction rules. We tested this assay within a multicenter, prospective cohort of patients presenting to the ED with a clinical and radiographic diagnosis of community-acquired pneumonia. We hypothesized that an early singular procalcitonin measurement would aid risk assessment beyond that available from the Pneumonia Severity Index and CURB-65.

MATERIALS AND METHODS

Study Design and Setting

We conducted a multicenter, prospective, cohort study of patients presenting to the EDs of 28 teaching and nonteaching hospitals in southwestern Pennsylvania, Connecticut, southern Michigan, and western Tennessee between November 2001 and November 2003 (Genetic and Inflammatory Markers of Sepsis study). A specific aim of the Genetic and Inflammatory Markers of Sepsis study was to develop and validate risk prediction tools according to information available early in the course of disease. As part of this aim, we sought to determine the prognostic utility of procalcitonin for 30-day mortality.

Selection of Participants

Eligible subjects were older than 18 years and had a clinical and radiologic diagnosis of pneumonia according to Fine et al.⁵ We excluded those transferred from another hospital, discharged from a hospital within the previous 10 days, with an episode of pneumonia within the past 30 days, receiving chronic mechanical ventilation, with cystic fibrosis, with active pulmonary tuberculosis, with a known positive HIV antibody titer, having alcoholism with evidence of end-organ damage, admitted for palliative care, enrolled previously in the Genetic and Inflammatory Markers of Sepsis Study, incarcerated, and who were pregnant. We obtained informed consent from the subject or proxy. The institutional review boards of the University of Pittsburgh and all participating sites approved the study.

Data Collection and Processing

We gathered baseline and sequential clinical information by structured patient or proxy interviews, bedside assessment by study nurses, and structured medical record reviews. Median time from ED admission to day 1 blood sample collection was 1.3 hours. We did not obtain day 1 samples from patients presenting after 11 PM or on weekends and holidays for logistic reasons. Study personnel collected blood sample into pyrogen-free vials containing heparin and separated plasma by centrifugation within 1 hour. Plasma was frozen and shipped on dry ice to our central laboratory in Pittsburgh. We tracked clinical data and blood samples with unique anonymized identification numbers, merging data only after assay completion. We observed strict data confidentiality and audited

clinical data and assays for accuracy, including random chart audits, repeated blood assays, and computer flags for inconsistencies.

Methods of Measurement

We measured procalcitonin with a time-resolved, amplified cryptate emission assay (Kryptor PCT; Brahms, Hennigsdorf, Germany). The assay has a functional assay sensitivity of 0.06 ng/mL, and at 0.1 ng/mL the coefficient of variation is 10% to 15%.²⁴ Study nurses ascertained deaths in hospital. Postdischarge deaths were ascertained by telephone and National Death Index search. We enrolled subjects between November 2001 and November 2003, locked clinical data in 2004, completed assays in 2005, and petitioned complete National Death Index data when they became available in 2006.

We prospectively assessed severity of illness with the Pneumonia Severity Index.⁵ We calculated CURB-65 retrospectively with altered mental status or a new change in Glasgow Coma Scale score as proxy measures for confusion.²⁵ According to previous studies, we stratified procalcitonin into 4 tiers: tier I: less than 0.1; tier II: greater than 0.1 to less than 0.25; tier III: greater than 0.25 to less than 0.5; and tier IV: greater than 0.5 ng/mL.¹⁶⁻¹⁸ We defined a clinically significant positive culture result according to published guidelines and previous literature.²⁶⁻³³ For example, single blood cultures that yielded coagulase-negative staphylococci and sputum cultures that yielded normal oral flora were not counted as clinically significant. We defined severe sepsis as infection plus acute organ dysfunction, following international consensus criteria.³⁴ Acute organ dysfunction was defined as a new Sequential Organ Failure Assessment score of greater than 2 in any of 6 organ systems.³⁵

Outcome Measures

Our primary outcome was 30-day mortality, the traditional endpoint used for clinical prediction rules in community-acquired pneumonia, including the Pneumonia Severity Index and CURB-65. Secondary outcomes included 90-day mortality, length of stay, and ICU admission.

Primary Data Analysis

We generated descriptive data, comparing initial presentation and outcome measures across procalcitonin tiers. To test for trends across procalcitonin tiers for ordinal variables, we used the Jonckheere-Terpstra trend test. To test for differences across procalcitonin tiers for continuous variables, we used the Kruskal-Wallis test.

To understand the prognostic utility of procalcitonin and the 2 clinical prediction rules as standalone tests, we first generated Kaplan-Meier plots of 30-day mortality by category (tier, class, or group). We then generated test characteristics (sensitivity, specificity, negative and positive likelihood ratios) for each test, dichotomized into low and high risk. A positive likelihood ratio greater than 10 and a negative likelihood ratio less than 0.1 may

be considered to provide strong evidence to rule in or rule out the condition of interest.³⁶ We defined low risk as classes I to III for Pneumonia Severity Index, group 1 for CURB-65, and tier I (<0.1 ng/mL) for procalcitonin, according to previous criteria.^{5,18,37}

To understand the value of adding procalcitonin to the Pneumonia Severity Index, we first generated 30-day mortality Kaplan-Meier plots, stratified by procalcitonin tier within each Pneumonia Severity Index class. Second, we assessed the change in test characteristics for a logistic regression model in which procalcitonin was added to a model with Pneumonia Severity Index alone. This approach assumes both “tests” (Pneumonia Severity Index and procalcitonin) are performed in all patients. We derived and validated models with a 3:1 random split of the overall cohort, fitting with all possible combinations of Pneumonia Severity Index, procalcitonin, and the corresponding interaction term. These models were also fit with the Pneumonia Severity Index and procalcitonin treated as categorical variables. Third, because one could selectively order procalcitonin measurement, depending on the clinical risk assessment, we assessed the test characteristics of procalcitonin within the clinical low- and high-risk strata. We used the same approach to determine the prognostic value of adding procalcitonin to CURB-65. Analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC).

Sensitivity Analyses

To complete sensitivity analyses, we explored the effects of reclassifying Pneumonia Severity Index classes I to III subjects as high risk if they were hypoxic⁵ and excluding patients who were subsequently ruled out for community-acquired pneumonia during their hospitalization. Because of the large number of variables for the analysis stratifying and comparing the baseline presentation of high-risk patients by procalcitonin tier I versus tiers II to IV, we chose a significance level of $P < .01$. For all other analyses, we assumed significance at $P < .05$.

RESULTS

Characteristics of Study Subjects

Of the 2,320 subjects enrolled in the Genetic and Inflammatory Markers of Sepsis study, 1,651 (71.2%) had a day 1 procalcitonin test and formed the study cohort. Pneumonia Severity Index was measured in the ED in 1,384 (83.8%) of the 1,651 study cohort subjects (Figure 1). The study cohort was predominantly white, underlying disease was common, approximately half were identified as high risk by the Pneumonia Severity Index and CURB-65 clinical risk rules, and most were admitted to the hospital. Few subjects identified in the ED as having community-acquired pneumonia were subsequently “ruled out for community-acquired pneumonia” by the inpatient clinical team (Table 1). Severe sepsis developed in one quarter, and 30-day mortality was 6.4% overall (Table 2) and 15.0% and 11.3% in those labeled as high risk by Pneumonia Severity Index and CURB-65, respectively (Tables E1 and E2; available online at <http://www.annemergmed.com>).

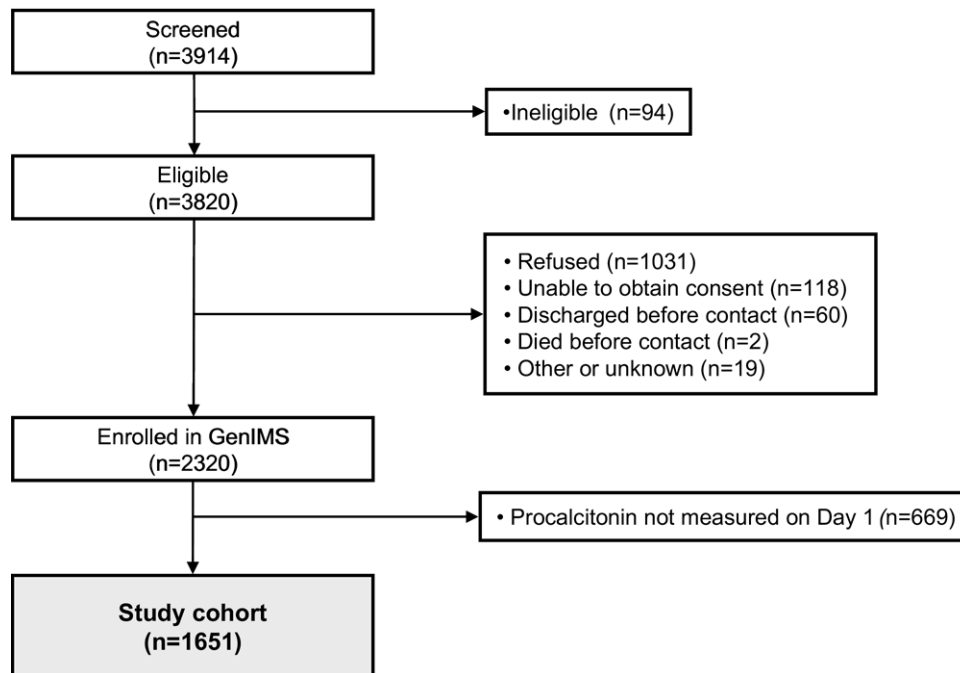


Figure 1. Flow diagram of study. *Gen IMS*, Genetic and Inflammatory Markers of Sepsis study.

Table 1. Study cohort demographic and clinical characteristics (n=1,651).

Variable	Value
Age, y, mean (SD)	65.0 (18.5)
Sex, male, No. (%)	860 (52)
Race, No. (%)	
White	1,336 (81)
Black	227 (14)
Other	88 (5)
Previous antibiotics, No. (%)	271 (16)
Pre-enrollment duration of symptoms, mean (SD), median	4.8 (14.5), 3.0
Charlson comorbidity index	
Mean (SD), median	1.69 (2.12), 1.0
Index >0, No. (%)	1,094 (66%)
PSI*	
Mean (SD), median	82.0 (34.3), 80.5
Class, No. (%)	
I, II	541 (39)
III	297 (21)
IV	419 (30)
V	127 (9)
CURB-65	
Mean (SD), median	1.57 (1.19), 1.0
Group, No. (%)	
1	826 (50)
2	421 (25)
3	404 (24)
ED discharges, No. (%)	265 (16)
Ruled out for CAP, No. (%)	94 (6)

PSI, Pneumonia Severity Index; *CURB-65*, Confusion, Uremia, Respiratory rate, low blood pressure, age 65 years or older; *CAP*, community-acquired pneumonia.
*PSI was measured in the ED in 1,384 (83.8%) subjects. There were no significant differences between subjects who did and did not have a PSI measured.

The mean procalcitonin level at presentation was 3.4 ng/mL, but levels were broadly spread (SD 16.5), such that 542 (32.8%) were in tier I, 356 (21.6%) in tier II, 169 (10.2%) in tier III, and 584 (35.4%) in tier IV. Higher procalcitonin tiers were associated with more clinical signs of infection and a worse course and outcome (Table 2). For example, subjects in the lowest tier had the lowest severity scores, lowest likelihood of developing clinically significant cultures, and lowest rates of severe sepsis, mechanical ventilation, ICU admission, and death. Lowest procalcitonin tier patients were also the most likely to be discharged from the ED and, if admitted, to be subsequently ruled out for community-acquired pneumonia (Table 2). Among subjects who developed severe sepsis, those in the lowest procalcitonin tier were less likely to develop central nervous system (5.3% versus 24.2%; $P=.0001$), cardiovascular system (4.0% versus 11.0%; $P=.08$), and greater than 3 organ (1.3% versus 16.5%; $P=.0001$) system dysfunctions and had more organ failure-free days in the first 30 days (25.5 versus 18.5; $P<.0001$) compared with those in procalcitonin tiers II to IV.

Main Results

As standalone tests, the Pneumonia Severity Index, CURB-65, and procalcitonin had similar characteristics. For each, 30-day mortality generally increased with increasing category (Figures 2 and 3; Table 2). In addition, after dichotomizing of subjects as “high” or “low” risk, each test alone had moderate specificity (35% to 64%), high sensitivity (87% to 92%), low positive likelihood ratios (1.41 to 2.43), and modest negative likelihood ratios (0.20 to 0.23) (Table 3). Simply adding the procalcitonin test result to the Pneumonia Severity Index score in all subjects led to only minimal improvement in test

Table 2. Initial presentation and outcomes, by procalcitonin tier.

No. (%)	P Value*	All	Procalcitonin Tier (ng/mL)			
			I (<0.1)	II (≥0.1, <0.25)	III (≥0.25, <0.5)	IV (≥0.5)
Initial presentation		1,651 (100)	542 (32.8)	356 (21.6)	169 (10.2)	584 (35.4)
SIRS criteria, No. (%)						
SIRS by WBC	.0018	1,475 (96)	449 (93)	317 (96)	157 (97)	552 (97)
SIRS by temperature	<.0001	766 (47)	155 (29)	169 (48)	87 (52)	355 (61)
SIRS by respiratory	.1292	1,605 (97)	532 (99)	341 (96)	166 (99)	566 (97)
SIRS by pulse rate	<.0001	1,138 (76)	312 (67)	239 (73)	116 (74)	471 (85)
Total number of SIRS criteria met, mean (SD)	<.0001	3.02 (0.87)	2.67 (0.85)	2.99 (0.87)	3.11 (0.82)	3.33 (0.78)
Pneumonia Severity Index						
Mean (SD)	<.0001	82.0 (34.3)	71.2 (30.9)	83.9 (33.7)	86.8 (32.9)	89.7 (35.5)
Class, No. (%)						
I, II	<.0001	541 (39)	224 (48)	109 (37)	52 (35)	156 (33)
III		297 (21)	112 (24)	66 (22)	28 (19)	91 (19)
IV		419 (30)	110 (24)	91 (31)	55 (37)	163 (34)
V		127 (9)	16 (3)	29 (10)	13 (9)	69 (14)
CURB-65						
Mean (SD), median	<.0001	1.57 (1.19), 1.0	1.16 (1.06), 1.0	1.56 (1.15), 2.0	1.73 (1.19), 2.0	1.91 (1.22), 2.0
Group, No. (%)						
1	<.0001	826 (50)	361 (67)	172 (48)	70 (41)	223 (38)
2		421 (25)	111 (20)	99 (28)	48 (28)	163 (28)
3		404 (24)	70 (13)	85 (24)	51 (30)	198 (34)
Previous antibiotics, No. (%)	.0707	271 (16)	103 (19)	64 (18)	23 (14)	81 (14)
Outcomes, No. (%)						
30-Day mortality	<.0001	106 (6.4)	8 (1.5)	30 (8.4)	16 (9.5)	52 (8.9)
90-Day mortality	<.0001	161 (9.8)	24 (4.4)	41 (11.5)	26 (15.4)	70 (12.0)
Hospital LOS (admitted patients), mean (SD), median	<.0001	6.2 (5.3), 5.0	5.1 (4.4), 4.0	6.3 (5.4), 5.0	6.9 (5.2), 5.0	7.0 (5.9), 5.5
ICU admission	<.0001	215 (13)	42 (8)	48 (13)	20 (12)	105 (18)
ED discharges	<.0001	265 (16)	137 (25)	62 (17)	16 (9)	50 (9)
Ruled out for CAP	.040	94 (6)	38 (7)	24 (7)	6 (4)	26 (4)
Clinically significant culture	<.0001	215 (13)	34 (6)	29 (8)	22 (13)	130 (22)
Severe sepsis	<.0001	423 (26)	91 (17)	99 (28)	51 (30)	182 (31)
Severe sepsis on day 1	<.0001	202 (12)	33 (6)	43 (12)	26 (15)	100 (17)
Mechanical ventilation	.0002	89 (5)	14 (3)	23 (6)	6 (4)	46 (8)

SIRS, Systemic inflammatory response syndrome; LOS, length of stay.

*Test for trend across procalcitonin tiers, with the Jonckheere-Terpstra test for trend for ordinal variables, and test for differences across procalcitonin tiers with the Kruskal-Wallis test for continuous variables.

performance. In the derivation cohort, sensitivity increased from 71.8% to 76.1%, specificity from 77.3% to 79.8%, and area under the receiver operating curve from 0.83 to 0.85. Similarly, in the validation cohort, sensitivity and specificity changed from 78.0% to 78.3% and from 75.2% to 78.9%. Results were similar when procalcitonin level was added to CURB-65 score.

Mortality at 30 days was low among subjects identified as low risk by the clinical prediction rules (1.4% for Pneumonia Severity Index classes I to III and 1.6% for CURB-65 group 1), and there was no additional prognostic advantage when results were stratified by procalcitonin tier (Figures 2 and 3; Table 3). However, among those identified as high risk by Pneumonia Severity Index score, 23.1% (126/546) had a procalcitonin level in tier I. In this subgroup, only 2 subjects died by day 30, yielding a mortality rate of 1.6%, similar to that of the low-risk subjects. In contrast, mortality was higher in the Pneumonia Severity Index class IV/V subjects who had a procalcitonin tier

greater than I (19.0% [80/420]; $P<.0001$) (Figure 2). The negative likelihood ratio for a low procalcitonin level within clinically high-risk subjects was 0.09 (Table 3). Results were similar with CURB-65: 21.9% (181/825) of CURB-65 group 2/3 subjects had a procalcitonin level in tier I, and mortality was 2.2% (4/181) versus 13.8% (89/644) for subjects with procalcitonin levels in tier I versus tiers II to IV ($P<.0001$), yielding a negative likelihood ratio for a low procalcitonin of 0.18 (Figure 3 and Table 3).

Sensitivity Analyses

We explored possible reasons for the large mortality difference by procalcitonin tier among subjects identified clinically as high risk. Some clinical signs were worse for those with higher procalcitonin tiers in comparison with those in tier I, but differences were generally modest, and many other aspects of clinical presentation were similar. For example, those in

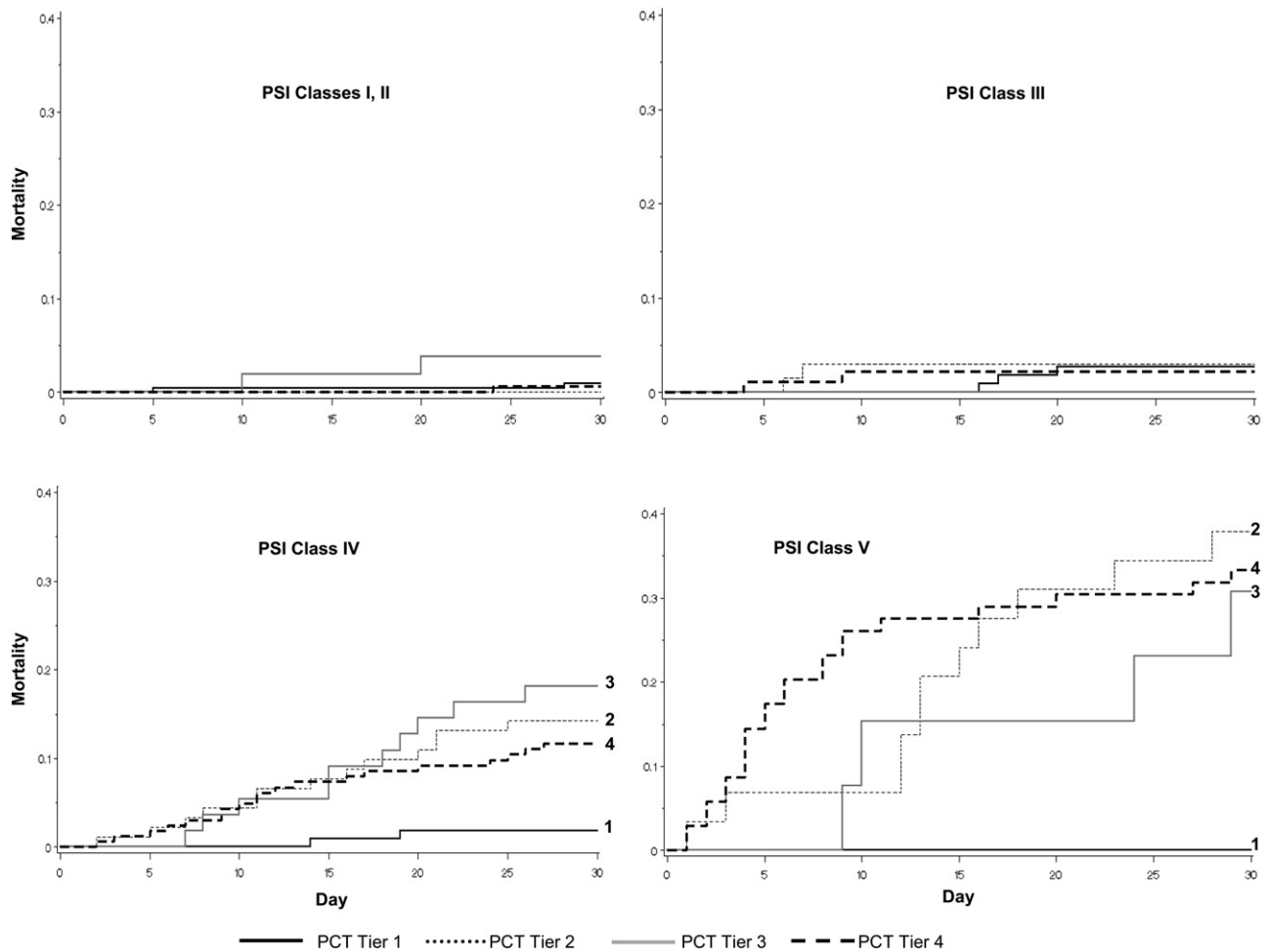


Figure 2. Kaplan-Meier survival curves, by Pneumonia Severity Index class and procalcitonin tier. In Pneumonia Severity Index classes I to III, mortality was low, and stratification by procalcitonin tier did not provide additional information. In Pneumonia Severity Index classes IV/V, patients with a procalcitonin level less than 0.1 ng/mL had the lowest 30-day mortality. *PCT*, Procalcitonin.

Table 3. Test characteristics of alternative risk-assessment strategies for 30-day mortality.

Risk-Assessment Strategy	No.	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Specificity	Sensitivity
Using each test alone in all patients					
PSI*	1,384	2.43 (2.18–2.70)	0.20 (0.12–0.34)	0.64	0.87
CURB-65 [†]	1,651	1.85 (1.70–2.02)	0.23 (0.14–0.39)	0.53	0.88
Procalcitonin [‡]	1,651	1.41 (1.32–1.51)	0.22 (0.11–0.43)	0.35	0.92
Using procalcitonin in low-risk patients[‡]					
PSI classes I–III	838	0.97 (0.60–1.58)	1.04 (0.53–2.04)	0.40	0.58
CURB-65 group 1	826	1.23 (0.85–1.78)	0.70 (0.31–1.59)	0.44	0.69
Using procalcitonin in high-risk patients[‡]					
PSI classes IV/V	546	1.33 (1.25–1.42)	0.09 (0.02–0.36)	0.27	0.98
CURB-65 group 2/3	825	1.26 (1.19–1.34)	0.18 (0.07–0.47)	0.24	0.96

CI, Confidence interval.

*PSI classes IV/V vs classes I–III.

[†]CURB-65 group 2/3 vs group 1.

[‡]Procalcitonin level >0.1 ng/mL vs procalcitonin level <0.1 ng/mL.

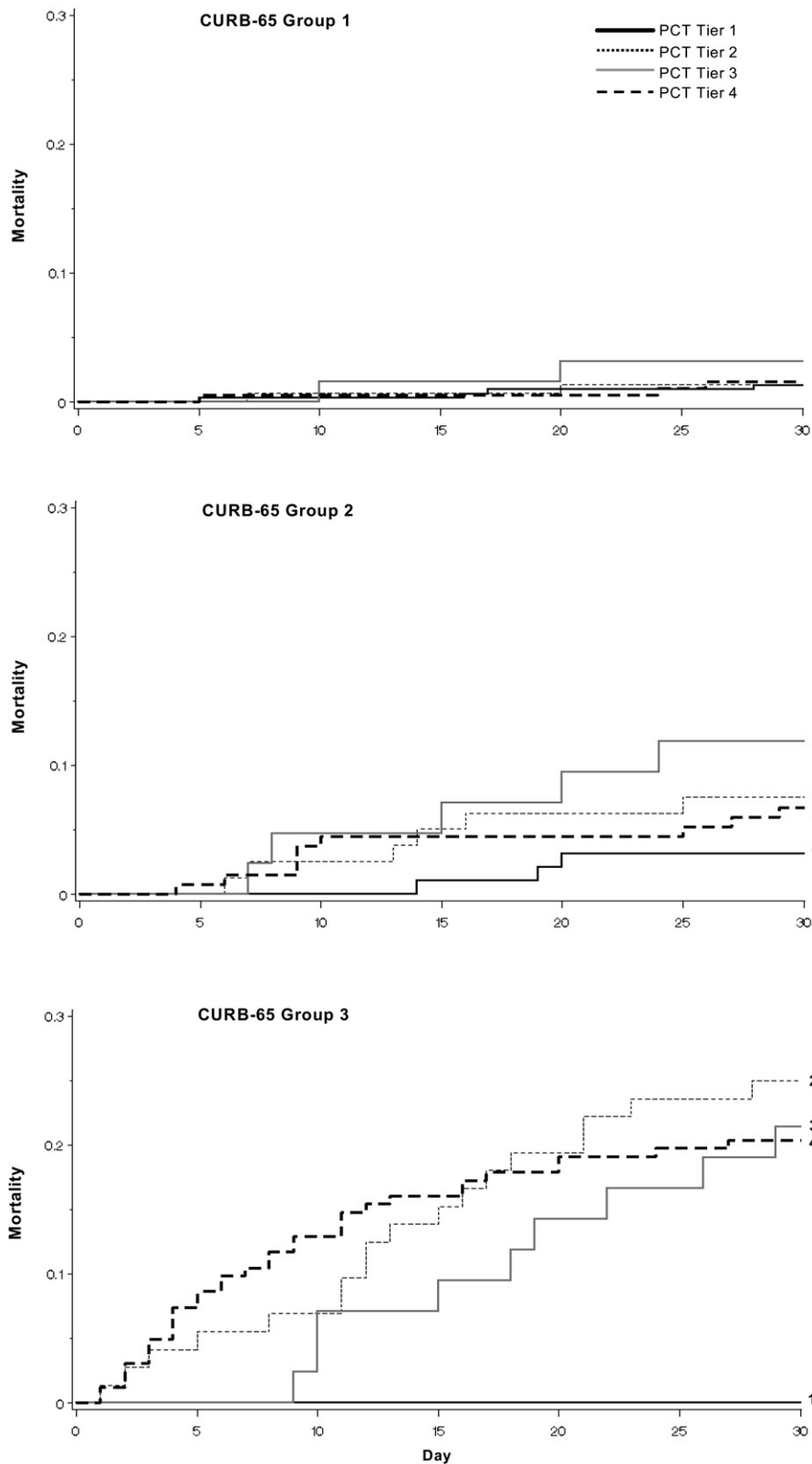


Figure 3. Kaplan-Meier survival curves, by CURB-65 group and procalcitonin tier. In CURB-65 group 1 patients, mortality was low, and stratification by procalcitonin tier did not provide additional information. In CURB-65 groups 2/3, patients with a procalcitonin level less than 0.1 ng/mL had the lowest 30-day mortality.

procalcitonin tiers II to IV were more likely to have renal impairment, altered mental status, fever, and leukocytosis but no more likely to be hypoxic, tachypneic, tachycardic, hypotensive, or thrombocytopenic or have abnormal blood glucose or sodium levels. There were also no differences in age, race, sex, Charlson comorbidity level, functional status, duration of symptoms, or domicile (nursing home versus home).

Within clinically high-risk subjects, those in procalcitonin tier I also had lower 90-day mortality (Pneumonia Severity Index 9% versus 26%, $P < .001$; CURB-65 9% versus 19%, $P = .0004$) and, in those identified as high risk by CURB-65, shorter length of stay (6.7 days versus 7.9 days; $P = .002$) and reduced likelihood of ICU admission (13% versus 21%; $P = .01$) compared with those in procalcitonin tiers II to IV. Neither excluding subjects who ruled out for community-acquired pneumonia nor reclassifying hypoxic Pneumonia Severity Index class I to III subjects as “high risk” significantly changed our results.

LIMITATIONS

We chose 30-day mortality as the primary outcome, following the methodology of the original Pneumonia Severity Index and CURB-65 studies. Other outcomes are important and not necessarily correlated with mortality. Nevertheless, subjects with a low procalcitonin level appeared to have lower rates of many other outcomes, including mortality measured at different points (Tables E1 and E2; available online at <http://www.annemergmed.com>). Second, although procalcitonin tier I was consistently associated with a low mortality, a “dose response” was not observed across procalcitonin tiers II to IV, with similar 30-day mortality rates across these tiers (range 8.4% to 9.5%) (Table 2). Thus, only the lowest range of procalcitonin levels is associated with low mortality. Third, community-acquired pneumonia is a clinical diagnosis with inherent subjectivity. A recent acute bronchitis review noted that a procalcitonin level less than 0.1 ng/mL may be able to safely discriminate between acute bronchitis and community-acquired pneumonia but that more data were needed,³⁸ raising the possibility that some of our cohort with a low procalcitonin level, although diagnosed clinically and radiographically with community-acquired pneumonia by their treating physicians, may not actually have had pneumonia. However, all Genetic and Inflammatory Markers of Sepsis patients met the community-acquired pneumonia criteria of Fine et al,⁵ an expected low percentage of patients were later deemed not to have community-acquired pneumonia, this percentage did not markedly vary by procalcitonin tier (range 4% to 7%), and eliminating these patients from our analyses had minimal effect. Last, as with the Pneumonia Severity Index, CURB-65, or any other clinical decision adjunct, procalcitonin level must be interpreted in the context of the individual patient, and clinical judgment is always necessary.

DISCUSSION

More than a century ago, it was observed that “. . . the result of a laboratory test should have, in a given case, the same value as a cardinal symptom or an approved clinical sign . . . many . . . forget this, and fail to correlate the laboratory findings with the clinical findings.”³⁹ We also observed that used alone, procalcitonin performed similarly to existing clinical prediction rules but that indiscriminately adding procalcitonin to all patients, regardless of clinical risk category, provided little additional information. However, clinical prediction rules have 2 important limitations: physicians may misapply or not remember them, and within a given risk category there can be a significant range in outcome. We therefore sought to determine whether procalcitonin could address these concerns, first as a standalone test and then as a layer on top of clinical risk assessment.

Our main finding was that in a large, contemporaneous cohort of patients diagnosed in the ED with community-acquired pneumonia, patients with a procalcitonin level less than 0.1 ng/mL had a low 30-day mortality rate, even in patients defined as high risk by established clinical risk-prediction rules. Thus, adding procalcitonin to the assessment of high clinical risk patients significantly improved the ability to rule out the likelihood of death. There are, however, important caveats to these observations.

First, although a procalcitonin level less than 0.1 ng/mL in high-risk subjects had a low likelihood ratio for death, the relatively wide 95% confidence interval merits caution. Second, a good outcome for a high-risk subject could either be because the risk prediction tool was inadequately discriminant or because the ensuing care averted an adverse outcome. Thus, a retrospective identification of a rule or test with potentially valuable test characteristics should be followed up by prospective assessment of its effect on clinical decisionmaking and outcomes. The potential of the Pneumonia Severity Index was not fully understood until Marrie et al⁴⁰ and Yealy et al³⁷ demonstrated that it could help physicians safely withhold hospital admission and intravenous antibiotics. We similarly recommend that procalcitonin as an adjunct to clinical tools be tested prospectively before wider use.

Our primary goal was to determine how procalcitonin might enhance existing community-acquired pneumonia prediction rules and decisionmaking. We recognize that physicians often do not explicitly calculate the Pneumonia Severity Index in daily clinical practice. However, the same factors that comprise Pneumonia Severity Index and other prediction rules also go into the bedside clinical judgment many physicians use to guide their decisions. Our results therefore suggest that procalcitonin may aid decisionmaking in high-risk patients, defined explicitly or implicitly with the Pneumonia Severity Index or a similar tool. Most important, we again emphasize that procalcitonin level should never be used in isolation to make clinical decisions and does not replace physician assessment.

Current community-acquired pneumonia guidelines recommend that clinically high-risk patients be hospitalized and that ICU admission be considered for patients in the highest risk categories.^{7,41,42} Of interest, Marrie and Huang⁴³ also observed that many clinically high-risk patients might be safely treated at home. Our data suggest that procalcitonin may aid in identifying Pneumonia Severity Index/CURB 65 high-risk patients who will rarely experience mortality and other complications. Thus, there could be considerable benefits, both in terms of conserved resources and antibiotic management, if one could better stratify high-risk patients. Prospective studies are needed to determine whether procalcitonin can improve physician management decisions and outcomes in high-risk patients.

However, 2 clinically important questions merit emphasis. First, is a low procalcitonin level in a high-risk patient clinically obvious and only a “costly surrogate measure of health status”?⁴⁴ We believe not, because these patients did not appear different from other high-risk patients across a wide range of baseline variables, suggesting that a low procalcitonin level is not particularly obvious at the bedside. Second, why did those patients with high clinical risk scores, yet low procalcitonin levels, do so well? We found that a low procalcitonin level was associated with shorter length of stay, lower proportions of mechanical ventilation and ICU admission, and a more benign severe sepsis phenotype. This observation suggests that although community-acquired pneumonia patients with high clinical risk scores often already have severe sepsis at ED presentation or develop it later, a low procalcitonin level portends a less severe course, potentially explaining the associated low mortality.

Our observational study design does not allow us to address whether procalcitonin can be useful in guiding antibiotic treatment, according to ability to determine bacterial infection. Instead, our work focused on procalcitonin level and links to adverse outcomes in those already diagnosed with community-acquired pneumonia. We recognize, however, that these 2 domains, although theoretically distinct, are practically intermingled. For example, patients with community-acquired pneumonia who have positive blood culture results tend to fare worse, and low procalcitonin level is associated with both low positive culture rates and low mortality.

We conclude that in a large, multicenter, community-acquired pneumonia cohort, patients in the lowest procalcitonin tier (<0.1 ng/mL) were at a low risk of death, regardless of clinical risk. Used indiscriminately, procalcitonin level provided little additional information over Pneumonia Severity Index score and CURB-65 risk assessment. However, a selective 2-tiered approach of first performing a clinical risk assessment and then obtaining procalcitonin level only in those judged to be high risk offers potentially important value.

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APPENDIX.

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Table E1. Procalcitonin, Pneumonia Severity Index, mortality, and severe sepsis.

Procalcitonin Tier (ng/mL)	No.	30-Day Mortality (%)	90-Day Mortality (%)	Severe Sepsis (%)	Severe Sepsis on Day 1 (%)
PSI classes I, II					
<0.1	224	2 (1)	3 (1)	15 (7)	4 (2)
≥0.1, <0.25	109	0	0	11 (10)	5 (5)
≥0.25, <0.5	52	2 (4)	2 (4)	9 (17)	4 (8)
≥0.5	156	1 (1)	1 (1)	19 (12)	10 (6)
Total	541	5 (1)	6 (1)	54 (10)	23 (4)
PSI class III					
<0.1	112	3 (3)	8 (7)	11 (10)	3 (3)
≥0.1, <0.25	66	2 (3)	3 (5)	20 (30)	6 (9)
≥0.25, <0.5	28	0	1 (4)	4 (14)	0
≥0.5	91	2 (2)	3 (3)	22 (24)	9 (10)
Total	297	7 (2)	15 (5)	57 (19)	18 (6)
PSI class IV					
<0.1	110	2 (2)	11 (10)	42 (38)	13 (12)
≥0.1, <0.25	91	13 (14)	15 (16)	33 (36)	14 (15)
≥0.25, <0.5	55	10 (18)	16 (29)	25 (45)	15 (27)
≥0.5	163	19 (12)	31 (19)	62 (38)	34 (21)
Total	419	44 (11)	73 (17)	162 (39)	76 (18)
PSI class V					
<0.1	16	0	0	8 (50)	8 (50)
≥0.1, <0.25	29	11 (38)	16 (55)	19 (66)	9 (31)
≥0.25, <0.5	13	4 (31)	5 (38)	5 (38)	3 (23)
≥0.5	69	23 (33)	27 (39)	44 (64)	29 (42)
Total	127	38 (30)	48 (38)	76 (60)	49 (39)

Table E2. Procalcitonin, CURB-65, mortality and severe sepsis.

Procalcitonin Tier (ng/mL)	No.	30-Day Mortality (%)	90-Day Mortality (%)	Severe Sepsis (%)	Severe Sepsis on Day 1 (%)
CURB-65 group 1					
<0.1	361	4 (1)	8 (2)	35 (10)	12 (3)
≥0.1, <0.25	172	3 (2)	4 (2)	28 (16)	11 (6)
≥0.25, <0.5	70	2 (3)	2 (3)	16 (23)	5 (7)
≥0.5	223	4 (2)	6 (3)	39 (17)	16 (7)
Total	826	13 (2)	20 (2)	118 (14)	44 (5)
CURB-65 group 2					
<0.1	111	4 (4)	9 (8)	33 (30)	11 (10)
≥0.1, <0.25	99	8 (8)	13 (13)	26 (26)	11 (11)
≥0.25, <0.5	48	5 (10)	11 (23)	16 (33)	9 (19)
≥0.5	163	10 (6)	17 (10)	46 (28)	17 (10)
Total	421	27 (6)	50 (12)	121 (29)	48 (11)
CURB-65 group 3					
<0.1	70	0	7 (10)	23 (33)	10 (14)
≥0.1, <0.25	85	19 (22)	24 (28)	45 (53)	21 (25)
≥0.25, <0.5	51	9 (18)	13 (25)	19 (37)	12 (24)
≥0.5	198	38 (19)	47 (24)	97 (49)	67 (34)
Total	404	66 (16)	91 (23)	184 (46)	110 (27)
CURB-65,.					