# Clinical Preview
## Serum procalcitonin and the admission decision in CAP


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For the **study by Self and colleagues** see *Chest* 2016; **150:** 819–28

The site of care decision is one of the most important in the management of community acquired pneumonia (CAP). Mortality is typically 10–12% for those admitted to the hospital, but can exceed 30% in those admitted to the intensive care unit (ICU). However, patients who are admitted first to the medical ward, and then deteriorate and need ICU care, have a mortality rate that is twice as high as for those admitted directly to the ICU. Thus, we could improve patient outcomes if we could better identify which patients are likely to deteriorate after admission. The criteria for ICU admission vary from hospital to hospital, and while this decision might not be fully objective, one approach has been to develop prediction tools for those who will need intensive respiratory and vasopressor support (IRVS) during their hospital stay.

In the October issue of *Chest*, Self and colleagues used the multicentre EPIC database to examine the best way to identify, on admission, those CAP patients who will require IRVS (intubation for respiratory failure or vasopressors for septic shock) in the first 72 h. Of 1770 CAP patients, 115 (6·5%) required IRVS, and the admission serum level of the inflammatory biomarker procalcitonin (PCT), correlated well with the need for IRVS. Those patients with low PCT levels (<0·05 ng/ml) had a 4% risk of IRVS, while those with the highest levels (>10 ng/ml) had a 22·4% risk. When biomarker levels were added to clinical data, the predictive value increased further. If the patient had three minor criteria for severe CAP, using the 2007 ATS/IDSA guidelines, and a high PCT level, the risk for IRVS was 36·2%, whereas those patients with the same three minor criteria and a low PCT level had only a 13·2% risk. The investigators also developed a logistic regression model associating the risk of IRVS with any PCT value. They identified 370 patients as high risk (using a PCT cutoff value of ≥0·83 ng/ml), who were not identified by clinical criteria, and 33 of these patients needed IRVS. These findings suggest that an elevated PCT level might make it necessary to carefully consider the site of care decision, and to consider ICU monitoring, even when the clinical need for ICU admission is uncertain. This observation is extremely important, because underestimation of severity of illness in a patient who will need IRVS would be a serious error. In this study, unlike other studies in which a low score was almost always a sign of good prognosis, it was unclear whether a patient with a high clinical severity of illness could be safely observed out of the ICU, if the PCT value is low.

The findings in this study support observations from other investigations. PCT was initially recognised as an inflammatory biomarker, mostly produced by the liver as an acute phase reactant, with levels rising in the presence of bacterial, but not viral infection. Early studies showed its value in defining which patients with respiratory tract infection (particularly CAP and bronchitis) could benefit from antibiotic therapy. Then research showed that serial measurements of PCT could be used to guide the duration of antibiotic therapy for patients with CAP, as well as for those with sepsis from multiple sources. A number of investigators have also correlated PCT measurements with prognosis in CAP.Some studies found that using either the Pneumonia Severity Index or the CURB-65 score, that the risk of death was low if the PCT values were low, regardless of the severity score. Additionally, some data suggest that patients who are admitted to the ICU after hospital admission have a higher initial PCT value than those who are safely managed on the ward. Not only is PCT elevated in those with more severe illness, but serial measurements also have prognostic value, and rising levels correlate with a greater likelihood of mortality or pneumonia complications.

Should PCT levels become a routine part of the site of care decision in CAP? The current study in *Chest* shows the potential value of this information, but more discriminating values might have come from repeat measurements during the first 72 h, because not every patient with a single elevated level needed IRVS. Additionally, some patients need hospital admission but are clinically well enough that they are unlikely to need ICU care, and in this population, it might not be valuable to measure PCT to guide the site of care decision. The greatest value could come for those with a borderline need for ICU care, where high initial PCT values, or rising serial values might help guide management and indicate a need for ICU observation, while low initial values might reassure the clinician about the safety of continued care outside of the ICU.

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CHEST

# Procalcitonin in Severe Community-Acquired Pneumonia

## Some Precision Medicine Ready for Prime Time

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Community-acquired pneumonia (CAP) is the third most common cause of death globally.[1] The estimated costs for treating CAP exceeded $9 billion per year in the mid-1990s in the United States, more than half being attributed to inpatient care.[2] Approximately 20% to 40% of patients with CAP are treated in the hospital, and 10% require admission to the ICU owing to the need for ventilator support or to septic shock. The mortality rate among patients treated in the ICU for severe CAP ranges from 19% to 50%.[3] Survival depends on a combination of host factors (genetic, age, comorbidities, defenses), pathogens (virulence, serotypes), and therapy. A genome-wide association study of survivors of sepsis due to pneumonia demonstrated that common variants in the *FER* gene are strongly associated with survival, explaining why certain patients with low bacterial burden are still susceptible to fatal outcomes.[4] It is widely accepted that clinical judgment is inadequate to assess disease severity.

FOR RELATED ARTICLE SEE PAGE 819

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Accordingly, several severity scores have been developed and validated widely, with the aim of guiding the initial site of treatment and appropriate level of intervention. However, while clinical scores are recommended for clinical decision-making in the evaluation of patients with CAP, they are not exempt from weaknesses, in particular regarding positive predictive values.[5] Accordingly, the PSI (pneumonia severity index) score and CURB-65 are clinical rules that identify a subset of individuals at low risk of death who could be treated on an ambulatory basis. All remaining patients are classified as "high risk," for whom hospital admission is recommended despite the fact that a significant percentage of these patients can be safely treated at home.[5] Most sensitive tests with a low false negative rate such as the PSI require that physicians gather data on 20 parameters including a detailed medical history, physical examination, and further investigations such as arterial blood gas measurements and chest radiograph, thus precluding their applicability in a busy ED setting.[6] The CURB-65 score is easier to calculate. However, because it does not directly address comorbidities, it underestimates mortality risk in elderly patients with other underlying diseases. In contrast, SMART-COP (systolic blood pressure, multilobar chest radiography involvement, albumin level, respiratory rate, tachycardia, confusion, oxygenation, and arterial pH) performed better than both the CURB-65 and PSI but failed to identify younger patients (< 50 years of age) requiring mechanical ventilation and/or inotropic support due to CAP.[7] In addition, the PSI and CURB-65 might have good discriminatory power for mortality, but their ability as predictors of ICU admission is no more than fair. Delayed ICU admission was identified as an important risk factor for short-term mortality, leading the Infectious Diseases Society of America and American Thoracic Society (ATS) to develop criteria to identify patients requiring direct ICU referral. It is clear that patients fulfilling major criteria (endotracheal intubation and mechanical ventilation; shock requiring vasopressors) should be considered for ICU admission; however, there is still controversy about the value of the minor criteria. ICU care is costly and a limited resource world-wide.

Biomarkers are laboratory tests reflecting a disease process. Ideally, they are easily measured, objective, and

dynamic. Biomarkers and clinical scoring systems are expected to capture and reflect different aspects of the host factors and response to therapy. Thus, there is increasing interest in biomarkers both as stand-alone tests and layered on top of clinical risk scores for enhanced risk assessment.

Procalcitonin is a classic "hormokine," which is secreted alongside the hormonal pathway in a cytokine-like manner. There is evidence suggesting that the development of severe sepsis and septic shock as a complication of pneumonia is associated with activation of the immune system. Procalcitonin is not accurate enough to enable the diagnosis of pneumonia as a stand-alone test. However, procalcitonin values vary according to the severity of pneumonia, and this association is stronger than that between disease severity and other clinical and laboratory variables. Besides being well known for its ability to decrease antibiotic prescription in CAP, ventilator-associated pneumonia, and COPD exacerbations without compromising clinical outcomes,[8-10] procalcitonin also provides prognostic information in respiratory infections.[11,12] There is a robust association between higher procalcitonin levels and adverse outcomes in patients with CAP. In this issue of *CHEST*, Self et al[13] demonstrate that in a large cohort of adults hospitalized with CAP included in the EPIC (Etiology of Pneumonia in the Community) multicenter study conducted by the Centers for Disease Control and Prevention, procalcitonin is strongly associated with the risk of invasive respiratory or vasopressor support (IRVS) within 72 hours of admission. Undetectable procalcitonin ($\leq$ 0.05 ng/mL) was associated with a 4% risk of IRVS, whereas concentrations of 10 ng/mL denoted a risk for IRVS of 22%. Procalcitonin was associated with pneumonia severity as assessed by the ATS minor criteria, PSI, and SMART-COP score. Most importantly, procalcitonin significantly improved risk stratification, applying the routinely used binary system (low-high risk) of each of the evaluated scores. For illustration, more than two-thirds of the patients requiring IRVS did not fulfill all three ATS minor criteria, considered to indicate the need for ICU admission. Interestingly, 50% of the included patients had procalcitonin levels below 0.15 ng/mL at admission despite "clinical and radiological evidence of CAP." The number of patients with very low levels of procalcitonin in this study is surprisingly high and merits emphasis. Procalcitonin concentrations $<$ 0.25 ng/mL are usually thought to indicate no need for antibiotic therapy. Accordingly, procalcitonin concentrations $<$ 0.25 ng/mL have been used to withhold or discontinue antibiotics in most of the randomized studies evaluating procalcitonin guidance, which have included more than 4,000 patients in various clinical settings.[8] The fact that CAP is a clinical diagnosis with inherent subjectivity raises the possibility that some of these patients with low procalcitonin levels might not actually have had pneumonia. In accordance with previous data, although the risk of IVRS increased linearly up to 10 ng/mL, a "dose response" was not observed for very high procalcitonin levels ($>$ 10 ng/mL). This study further supports the notion that procalcitonin has limited prognostic accuracy as a stand-alone test. It also does not seem to outperform the risk estimation of a combination of clinical and laboratorial parameters. However, it also emphasizes its potential to capture nuances elusive to the clinical assessment, which do not seem to be consistently reflected even in elaborated severity scores recommended for clinical routine use.

Not all community-acquired pneumonia episodes are similar. Successful CAP management requires treatment strategies to take individual variability into account. To apply this concept we need methods to characterize patients, including fast, point-of-care approaches. Clinicians are looking forward to being able to identify specific immune profiles indicating protective rather than pathologic immune responses. Analyses of thousands of molecular signs by transcriptome will likely provide more diagnostic accuracy than the measurement of a single or a few biomarkers. Genomics and other new sciences might offer the opportunity to further improve diagnosis and prediction in the near future, but we should not allow too much information (or hope) to paralyze decision-making. While it is clear that no single biomarker can consistently predict prognosis, for now, procalcitonin may help to transfer the probability of risk derived from a population to an individual patient. A randomized study evaluating the outcome and cost-effectiveness of a procalcitonin-refined clinical score in severe CAP is needed. Then this new stratification paradigm has the potential to save money and lives.

## References


1. Klein Klouwenberg PM, Ong DS, Bos LD, et al. Interobserver agreement of Centers for Disease Control and Prevention criteria for classifying infections in critically ill patients. *Crit Care Med*. 2013;41(10):2373-2378.
2. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax*. 2012;67(1):71-79.

3. Woodhead M, Welch CA, Harrison DA, Bellingan G, Ayres JG. Community-acquired pneumonia on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database. *Crit Care*. 2006;10(suppl 2):S1.

4. Rautanen A, Mills TC, Gordon AC, et al. Genome-wide association study of survival from sepsis due to pneumonia: an observational cohort study. *Lancet Respir Med*. 2015;3(1):53-60.

5. Marrie TJ, Huang JQ. Admission is not always necessary for patients with community-acquired pneumonia in risk classes IV and V diagnosed in the emergency room. *Can Respir J*. 2007;14(4):212-216.

6. Loke YK, Kwok CS, Niruban A, Myint PK. Value of severity scales in predicting mortality from community-acquired pneumonia: systematic review and meta-analysis. *Thorax*. 2010;65(10):884-890.

7. Chalmers JD, Singanayagam A, Hill AT. Predicting the need for mechanical ventilation and/or inotropic support for young adults admitted to the hospital with community-acquired pneumonia. *Clin Infect Dis*. 2008;47(12):1571-1574.

8. Schuetz P, Muller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev*. 2012;9:CD007498.

9. Stolz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J*. 2009;34(6):1364-1375.

10. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest*. 2007;131(1):9-19.

11. Masia M, Gutierrez F, Shum C, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. *Chest*. 2005;128(4):2223-2229.

12. Boeck L, Eggimann P, Smyrnios N, et al. Midregional pro-atrial natriuretic peptide and procalcitonin improve survival prediction in VAP. *Eur Respir J*. 2011;37(3):595-603.

13. Self WH, Grijalva CG, Williams DJ, et al. Procalcitonin as an early marker of the need for invasive respiratory or vasopressor support in adults with community-acquired pneumonia. *Chest*. 2016;150(4):819-828.

CHEST

# Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia

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**BACKGROUND:** Predicting the need for intensive care among adults with community-acquired pneumonia (CAP) remains challenging.

**METHODS:** Using a multicenter prospective cohort study of adults hospitalized with CAP, we evaluated the association of serum procalcitonin (PCT) concentration at hospital presentation with the need for invasive respiratory or vasopressor support (IRVS), or both, within 72 h. Logistic regression was used to model this association, with results reported as the estimated risk of IRVS for a given PCT concentration. We also assessed whether the addition of PCT changed the performance of established pneumonia severity scores, including the pneumonia severity index and the American Thoracic Society minor criteria, for prediction of IRVS.

**RESULTS:** Of 1,770 enrolled patients, 115 required IRVS (6.5%). Using the logistic regression model, PCT concentration had a strong association with IRVS risk. Undetectable PCT ($<$ 0.05 ng/mL) was associated with a 4% (95% CI, 3.1%-5.1%) risk of IRVS. For concentrations $<$ 10 ng/mL, PCT had an approximate linear association with IRVS risk: for each 1 ng/mL increase in PCT, there was a 1% to 2% absolute increase in the risk of IRVS. With a PCT concentration of 10 ng/mL, the risk of IRVS was 22.4% (95% CI, 16.3%-30.1%) and remained relatively constant for all concentrations $>$ 10 ng/mL. When added to each pneumonia severity score, PCT contributed significant additional risk information for the prediction of IRVS.

**CONCLUSIONS:** Serum PCT concentration was strongly associated with the risk of requiring IRVS among adults hospitalized with CAP and is potentially useful for guiding decisions about ICU admission.

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**KEY WORDS:** biomarkers; pneumonia; prognosis; respiratory failure; septic shock

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**ABBREVIATIONS:** ATS = American Thoracic Society; AUC = area under the curve; CAP = community-acquired pneumonia; IQR = interquartile range; IRVS = invasive respiratory or vasopressor support; PCT = procalcitonin; PSI = pneumonia severity index; ROC = receiver operating characteristic

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Pneumonia accounts for approximately 63,000 deaths, 1.2 million hospitalizations, 2.3 million ED visits, and $10 billion in hospital costs in the United States annually.[1-3] Assessment of illness severity and the risk for clinical deterioration at the time of initial diagnosis are essential for optimal pneumonia management, including selection of the best site of care (outpatient, inpatient general floor, or ICU).[4-6] However, early severity assessment and risk stratification for community-acquired pneumonia (CAP) are challenging because overt clinical signs at presentation are not highly predictive of which patients will experience deterioration of their condition.[7,8]

Although several guidelines and clinical scoring systems exist to assist clinicians with early severity assessment,[4,9-13] some of these resources are difficult to use in routine practice, and both overestimation and underestimation of CAP severity continue to result in suboptimal admission decisions.[14-16] ICU admission improves outcomes for patients who require invasive respiratory or vasopressor support (IRVS) (ie, intubation for respiratory failure or vasopressors for septic shock) at any time during their hospitalization.[14] However, ICU care is a costly and limited resource.[17,18] Therefore, objective easy to use measures that aid clinicians in determining a patient's risk for subsequently requiring IRVS would be useful for guiding ICU admission decisions.[11,19,20]

Procalcitonin (PCT) is a prohormone of calcitonin that is emerging as a clinical biomarker.[21-25] PCT concentrations tend to be higher in patients with pneumonia who have more severe infections.[25-30] However, PCT has not previously been evaluated as a marker for patients who require IRVS, a highly relevant outcome for ICU admission decision-making.[11,19,20] Therefore, we evaluated the association of a single serum PCT measurement at hospital presentation with the need for IRVS during the subsequent 72 h among adults hospitalized with CAP. We also evaluated the additive value of PCT when used in conjunction with several existing pneumonia severity scores.

## Methods

We conducted a prospective cohort study of adults hospitalized with CAP nested in the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study.[31] Institutional review boards at the enrolling centers and the CDC approved the protocol (IRB No. 091422 at Vanderbilt University). Informed consent was obtained from all participants.

### Patient Recruitment

The EPIC study included adults (≥ 18 years) hospitalized with CAP at three hospitals in Chicago, Illinois and two hospitals in Nashville, Tennessee between January 2010 and June 2012.[31] All enrolled patients had clinical and radiographic evidence of CAP; detailed eligibility criteria have been described previously.[31] Sera were obtained and banked from enrolled patients at the time of hospital presentation. For the current study, we included adult patients in the EPIC cohort who had adequate serum volume for PCT measurement (200 μL).

### Procalcitonin Measurement

The primary exposure variable was serum PCT concentration. Two research laboratories—one in Chicago and one in Nashville—performed PCT measurements using the miniVIDAS instrument and VIDAS B.R.A.H.M.S. PCT immunoassay kits (BioMerieux) according to the package insert.[32] The lower limit of PCT detection was 0.05 ng/mL. Laboratory personnel performing PCT measurements were blinded to all clinical information. Clinicians caring for enrolled patients were blinded to PCT results.

### Outcome

The primary study outcome was IRVS, defined as intubation for respiratory failure or vasopressor administration for septic shock within 72 h of hospital presentation. IRVS was selected as the primary outcome because it provides a more objective assessment of critical illness than does ICU admission, which may be driven by factors other than illness severity.[11,19,20] A window of 72 h was chosen to limit the outcome to manifestations most likely related to CAP and not delayed nosocomial complications.[4,33]

### Pneumonia Severity Scores

We calculated pneumonia severity scores indicative of the patient's condition at the time of hospital presentation, including the American Thoracic Society minor criteria for severe CAP (ATS minor criteria),[4,34] pneumonia severity index (PSI),[9] and SMART-COP.[11]

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### Statistical Analysis

PCT distributions were compared between patients who required IRVS and those who did not using the Wilcoxon rank-sum test. We also constructed a nonparametric receiver operating characteristic (ROC) curve for PCT to discriminate between patients who did and those who did not require IRVS; the area under the curve (AUC) was calculated. For comparison with PCT, an ROC curve for WBC count, a biomarker currently in widespread clinical use for CAP, was also constructed. We also performed these analyses after stratifying the population by the initial location of hospital admission: general medical floor vs ICU.

### Logistic Regression Models

We used logistic regression models to assess the association of PCT concentration and the risk of IRVS. Since PCT values were skewed, we modeled PCT values using a restricted cubic spline function with four knots located at the fifth, 35th, 65th, and 95th percentile of PCT distribution.[35] We then estimated the risk of IRVS according to PCT values, using the predictive probabilities from the logistic regression models.

We also evaluated whether PCT added predictive risk information to existing severity scores (ATS minor criteria, PSI, and SMART-COP). We constructed logistic regression models using each of the severity scores as the sole predictor and IRVS as the outcome. We then added PCT as a predictor to each of the severity score models and conducted likelihood ratio tests comparing the models with and those without PCT. These tests examined whether PCT had a statistically significant additive contribution to each of the severity scores for predicting IRVS.

Since current CAP management guidelines from the Infectious Disease Society of America and American Thoracic Society emphasize the ATS minor criteria (e-Table 1) as a tool to assist with ICU admission decisions,[4] we used it as the primary score for detailed comparison with PCT. To determine the contribution of PCT and ATS minor criteria for the prediction of IRVS, we first compared the relative strength of the association between PCT and each of the nine individual ATS minor criteria with IRVS. We constructed a multivariable logistic regression model with IRVS as the outcome and PCT and each of the ATS minor criteria as predictors. Individual predictors were removed from the full model one at a time, and variation in the model deviance was quantified using the difference in the likelihood ratio $\chi^2$ between the full model and the model after removal of the single predictor. Percentage of the full model likelihood ratio $\chi^2$ statistic contributed by each predictor was calculated to demonstrate the relative strength of IRVS prediction for PCT and each of the ATS minor criteria.

### Performance of PCT Added to Pneumonia Severity Scores

We further explored whether PCT contributed risk information to assessments based on established severity scores. In the clinical setting, CAP severity scores are often used to dichotomize patients into high- and low-risk categories.[4] To resemble this real-life binary implementation of severity scores (high risk vs low risk), we evaluated PCT in three separate stratified analyses based on the following criteria: (1) ATS minor criteria, with $\geq$ 3 criteria denoting high risk; [4,34] (2) PSI, with classes IV and V classified as high risk;[9] and (3) SMART-COP, with $\geq$ 3 points denoting high risk.[11] The association of PCT with IRVS was evaluated in each of these subgroups using the rank-sum test, ROC curves, and logistic regression as detailed earlier. We also calculated the number of patients with $<$ 3 ATS minor criteria who would be reclassified as high risk if PCT at various cut points was used as an additional indicator to identify high-risk patients. Statistical analyses were performed with Stata 12 (StataCorp LP).

## Results

Among 2,320 adults with CAP in the EPIC study, 1,770 (76.3%) had adequate serum for PCT measurement and were included in this analysis (Table 1). Characteristics of patients excluded because of not having a PCT measurement were similar to the included patients (e-Table 2). Overall, 115 patients (6.5%) required IRVS within 72 h of hospital presentation, including 47 patients (2.7%) with both invasive respiratory and vasopressor support, 37 patients (2.1%) with respiratory support only, and 31 patients (1.8%) with vasopressor support only. Serum PCT concentrations were higher in patients who required IRVS (median, 1.43 ng/mL; interquartile range [IQR], 0.14-8.22 ng/mL) compared with those who did not (median, 0.14 ng/mL; IQR, $<$ 0.05-0.72 ng/mL) ($P < .01$) (Table 2, e-Fig 1).

Area under the ROC curve for PCT to discriminate between patients with and those without IRVS was 0.69 (95% CI, 0.67-0.71) and was significantly higher than the area for WBC count (0.54; 95% CI, 0.51-0.56) (Fig 1). To illustrate sensitivity, specificity, and the proportion of patients who experienced IRVS at varying PCT cut points, four points representing the 50th, 75th, 90th, and 95th percentile of PCT concentration in the study population were highlighted on the ROC curve (Fig 1). For example, using the 75th percentile of PCT concentration (0.83 ng/mL) as a cut point, sensitivity and specificity for IRVS were 0.55 (95% CI, 0.45-0.64) and 0.77 (95% CI, 0.75-0.79), respectively; 3.9% of patients with a PCT concentration $<$ 0.83 ng/mL experienced IRVS, whereas 14.2% with a concentration greater than this cut point experienced IRVS (e-Table 3).

### Association Between PCT and Risk of IRVS

In logistic regression models, PCT concentration had a strong association with the risk of IRVS (Fig 2). Undetectable PCT using this assay ($<$ 0.05 ng/mL) corresponded to a 4% (95% CI, 3.1%-5.1%) IRVS risk. Between 0.05 ng/mL and 10 ng/mL, PCT concentration had an approximate linear association with IRVS risk, with each incremental increase in PCT concentration of 1 ng/mL corresponding to a 1% to 2% absolute increase in IRVS risk (Fig 2). PCT concentrations of 5 ng/mL and 10 ng/mL were associated with IRVS risks of 14.2% (95% CI, 11.0%-18.1%) and 22.4% (95% CI, 16.3%-30.1%), respectively. IRVS risk plateaued at PCT concentrations $>$ 10 ng/mL.

**TABLE 1** ] Patient Characteristics

| Characteristic | Adults Hospitalized With CAP and PCT Results (N = 1,770) |
|---|---|
| Age, median (IQR), y | 57 (47-70) |
| Female sex, No. (%) | 905 (51.1) |
| Race and ethnicity, No. (%) | |
| Non-Hispanic white | 783 (44.2) |
| Non-Hispanic black | 693 (39.2) |
| Hispanic | 215 (12.2) |
| Other | 79 (4.5) |
| Age groups, No. (%) | |
| 18-44 y | 396 (22.4) |
| 45-64 y | 766 (43.3) |
| 65-79 y | 373 (21.1) |
| ≥ 80 y | 235 (13.3) |
| Chronic medical conditions, No. (%) | |
| Asthma | 459 (25.9) |
| Chronic obstructive lung disease | 367 (20.7) |
| Cancer | 320 (18.1) |
| Chronic heart failure | 318 (18.0) |
| Diabetes mellitus | 438 (24.8) |
| Chronic kidney disease | 271 (15.3) |
| Chronic liver disease | 93 (5.3) |
| Immunosuppression | 294 (16.6) |
| HIV infection | 47 (2.7) |
| Current smoker | 463 (26.2) |
| PSI risk class | |
| I | 339 (19.2) |
| II | 474 (26.8) |
| III | 345 (19.5) |
| IV | 462 (26.1) |
| V | 150 (8.5) |
| Cause of pneumonia, No. (%) | |
| Bacterial | 192 (10.9) |
| Viral | 412 (23.3) |
| Bacterial-viral mixed | 51 (2.9) |
| Fungal/mycobacterial | 15 (0.9) |
| Unknown | 1,100 (62.2) |
| Antibiotic administration before hospital presentation | 325 (18.4) |
| IRVS within 72 h, No. (%) | 115 (6.5) |
| ICU admission as initial disposition, No. (%) | 280 (15.8) |
| Delayed ICU transfer from medical floor,[a] No. (%) | 117 (6.6) |
| Hospital length of stay, median (IQR), d | 3 (2-6) |
| In-hospital death, No. (%) | 37 (2.1) |

CAP = community-acquired pneumonia; IQR = interquartile range; IRVS = invasive respiratory or vasopressor support; PCT = procalcitonin; PSI = pneumonia severity index.

[a]Delayed ICU transfer from medical floor was defined as initial hospital admission on the medical floor and then later transfer to an ICU at any time during the index hospitalization for pneumonia.

### *Performance of PCT Added to Pneumonia Severity Scores*

Higher PCT concentration correlated with increasing pneumonia severity at presentation as measured by the number of ATS minor criteria present, PSI score, and SMART-COP score (e-Fig 2). The addition of PCT to each of these pneumonia severity score models increased the area under the ROC curve. For example, area under the ROC curve for the ATS minor criteria alone was 0.75 and improved to 0.78 when PCT was added. Accordingly, the addition of PCT represented a significant improvement in model fit for IRVS for each severity score (likelihood ratio test $P < .01$ for each model). We also found that PCT concentration had a larger contribution to predicting IRVS than any of the individual ATS minor criteria (Fig 3).

After stratification of the study population by each of the scoring systems into low- and high-risk subgroups, higher PCT was associated with greater risk of IRVS in all subgroups (Fig 4, e-Fig 3). For example, without considering PCT, patients classified as low risk by the ATS minor criteria (< 3 criteria present) had a 4.7% (95% CI, 3.7%-5.7%) risk of IRVS. After considering PCT in the low-risk ATS minor criteria subgroup, PCT < 0.05 ng/mL corresponded to a 2.4% (95% CI, 1.7%-3.4%) IRVS risk, whereas a PCT concentration of 10 ng/mL corresponded to a 12.0% (95% CI, 6.4%-21.3%) risk (Fig 4A). Without considering PCT, patients classified as high risk by the ATS minor criteria (≥ 3 criteria present) had a 29.7% (95% CI, 21.7%-37.6%) risk of IRVS. Within this high-risk subgroup by ATS minor criteria, PCT < 0.05 ng/mL was associated with a 13.2% (95% CI, 9.3%-18.5%) IRVS risk, whereas a PCT concentration of 10 ng/mL corresponded to a 36.2% (95% CI, 25.0%-49.1%) risk. Similar results were found with PSI and SMART-COP (Figs 4B, 4C). PCT values in patients with CAP caused by viruses and bacteria are reported separately in e-Appendix 1 and e-Table 4.

**TABLE 2** ] Serum PCT Concentrations for Patients Who Did and Those Who Did Not Require IRVS Within 72 h[a]

| Population | No. | IRVS, No. (%) | Serum PCT, Median (IQR) [ng/mL] | | AUC (95% CI) |
|---|---|---|---|---|---|
| | | | IRVS Present, Range | IRVS Absent, Range | |
| Full study population | 1,170 | 115 (6.5) | 1.43 (0.14-8.22) | 0.14 (< 0.05-0.72) | 0.69 (0.67-0.71) |
| Location of initial admission | | | | | |
| General floor | 1,490 | 39 (2.6) | 1.29 (0.14-6.92) | 0.13 (0.04-0.6) | 0.70 (0.68-0.73) |
| ICU | 280 | 76 (27.1) | 1.47 (0.13-8.88) | 0.47 (0.05-2.75) | 0.60 (0.54-0.65) |
| ATS minor criteria | | | | | |
| < 3 criteria | 1,642 | 77 (4.7) | 0.47 (0.05-4.07) | 0.13 (< 0.05-0.63) | 0.63 (0.61-0.65) |
| ≥ 3 criteria | 128 | 38 (29.7) | 4.82 (1.10-25.9) | 0.75 (0.09-5.68) | 0.68 (0.59-0.76) |
| PSI risk class | | | | | |
| I-III | 1,158 | 42 (3.6) | 0.35 (0.05-5.62) | 0.10 (< 0.05-0.48) | 0.64 (0.62-0.67) |
| IV-V | 612 | 73 (11.9) | 2.30 (0.19-9.54) | 0.28 (0.06-1.39) | 0.67 (0.63-0.71) |
| SMART-COP score | | | | | |
| < 3 points | 1,440 | 50 (3.5) | 0.46 (0.06-5.42) | 0.12 (< 0.05-0.57) | 0.65 (0.62-0.67) |
| ≥ 3 points | 330 | 65 (19.7) | 2.38 (0.19-11.76) | 0.32 (0.07-2.72) | 0.65 (0.59-0.70) |
| Specific subgroups | | | | | |
| Viral cause | 412 | 21 (5.1) | 0.46 (0.05-2.59) | 0.09 (< 0.05-0.52) | 0.65 (0.60-0.70) |
| Bacterial cause | 192 | 33 (17.2) | 5.62 (1.10-27.26) | 0.73 (0.14-6.22) | 0.68 (0.61-0.75) |
| COPD | 367 | 32 (8.7) | 2.69 (0.19-16.09) | 0.10 (< 0.05-0.51) | 0.76 (0.67-0.85) |
| Immunosuppression | 294 | 21 (7.1) | 1.51 (0.41-11.01) | 0.16 (< 0.05-1.08) | 0.76 (0.66-0.86) |
| Antibiotic administration before hospital presentation | 325 | 23 (7.1) | 0.47 (0.05-5.42) | 0.10 (< 0.05-0.38) | 0.70 (0.57-0.82) |

ATS = American Thoracic Society; AUC = area under the curve; ROC = receiver operating characteristic. See Table 1 legend for expansion of other abbreviations.

[a]AUC for ROC curves demonstrate performance of PCT for discriminating patients who required IRVS from those who did not.

To illustrate how using PCT with a specific binary cut point could augment risk stratification by the ATS minor criteria, we developed a classification tree using either ≥ 3 ATS minor criteria or PCT ≥ 0.83 ng/mL to indicate high risk (Fig 5). Using ≥ 3 ATS minor criteria alone to indicate high risk, 77 of the 1,770 total patients (4.4%) were misclassified as low risk and experienced IRVS. Including PCT ≥ 0.83 ng/mL in addition to ≥ 3

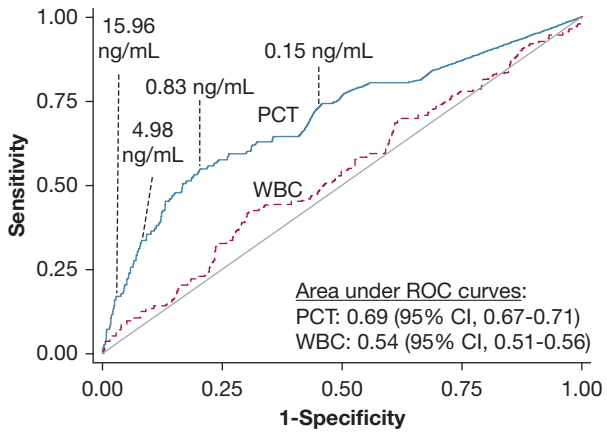


Figure 1 – *Nonparametric ROC curves for PCT and WBC count to identify patients who needed IRVS within 72 h. Selected PCT cut points at the 50th, 75th, 90th, and 95th percentiles of PCT concentration in the population are noted on the PCT curve. IRVS = invasive respiratory or vasopressor support; PCT = procalcitonin; ROC = receiver operating characteristic.*

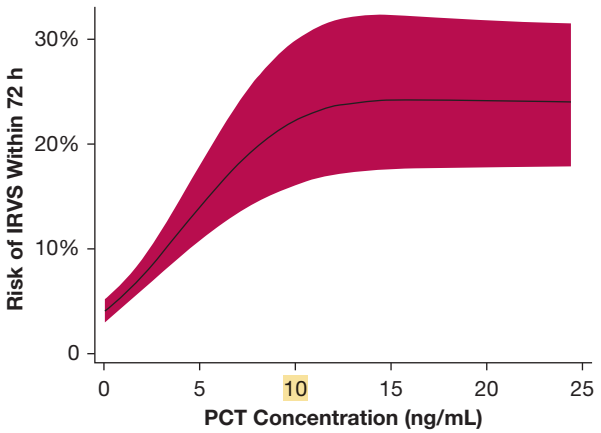


Figure 2 – *Risk of IRVS within 72 h of hospital presentation according to initial serum PCT concentration. The plot was truncated at a PCT concentration of 25 ng/mL because of the small number of patients with PCT concentrations > 25 ng/mL. The 95% CI band is denoted with red shading. See Figure 1 legend for expansion of abbreviations.*

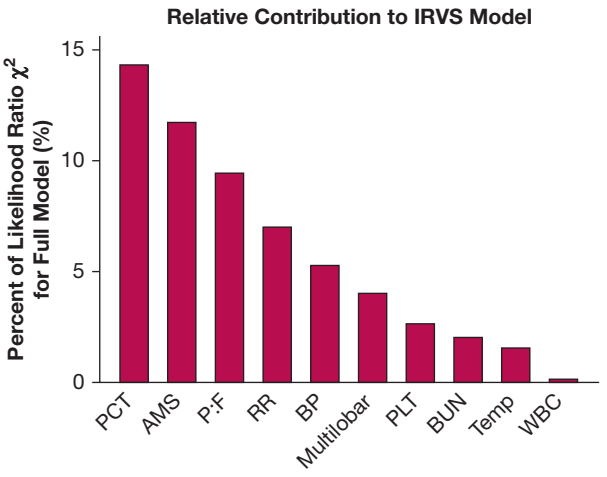


Figure 3 – *Relative contribution of PCT concentration and each of the American Thoracic Society (ATS) minor criteria to the prediction model for IRVS. The ATS minor criteria include AMS, partial pressure of oxygen to fraction of inspired oxygen ratio ≤ 250 (P:F), RR ≥ 30/min (RR), systolic BP < 90 mm Hg (BP), multilobar pulmonary infiltrates (Multilobar), platelets < 100,000 cells/mm$^3$ (PLT); BUN ≥ 20 mg/dL (BUN); temperature < 36° C (Temp); WBC count < 4,000 cells/mm$^3$ (WBC). AMS = altered mental status; RR = respiratory rate. See Figure 1 legend for expansion of other abbreviations.*

ATS minor criteria as a high-risk indicator reduced the number of patients with IRVS misclassified as low risk to 44 (2.49%). Adding PCT ≥ 0.83 ng/mL as a high-risk indicator resulted in 370 additional patients being classified as high risk, with 33 of them correctly classified as having IRVS.

## Discussion

In this multicenter study of adults hospitalized with CAP, serum PCT concentrations at hospital presentation were strongly associated with the risk of IRVS during the following 72 h. Patients with PCT concentrations of 5 ng/mL and 10 ng/mL were approximately three and five times more likely to require IRVS than patients with PCT < 0.05ng/mL, respectively, suggesting that PCT is potentially a useful test to help guide ICU admission decisions. Incorporation of PCT with clinical gestalt and clinical scoring systems is likely to improve identification of patients needing intensive care; however, the accuracy of PCT for IRVS is not strong enough to base clinical decisions solely on PCT results.

Our results suggest that PCT complements other tools clinicians use to guide ICU admission decisions. As expected, higher scores for several pneumonia severity scoring systems were associated with IRVS. However, adding PCT to each of these scores improved the ability to identify patients who required IRVS. The presence of ≥ 3 ATS minor criteria is a high-risk situation that clinicians often consider as a warning sign for impending respiratory failure or shock.[4] However, in this study, 67% of the 115 patients who required IRVS had < 3 ATS minor criteria. An elevated PCT level may help identify these patients without overt clinical signs of impending respiratory failure or shock but who would benefit from early ICU admission. For example, in this study, a PCT concentration of 10 ng/mL in patients with < 3 ATS minor criteria corresponded to a 12% risk of IRVS, a risk level that may warrant consideration for admission to an ICU or another setting that can ensure close monitoring.

Similar to our findings, prior studies have demonstrated an association between higher PCT levels at the time of acute presentation and adverse outcomes in patients with CAP.[26-30,36,37] Huang et al[27] found that adding PCT to PSI scores improved prognostic accuracy for 30-day mortality among patients with CAP in PSI risk classes IV-V. Ramirez et al[30] found that combining PCT with the ATS minor criteria helped identify patients admitted to an ICU, including those with delayed ICU transfer. In a recent meta-analysis, Kutz et al[36] found that PCT levels in the ED, but not in primary care clinics or in the ICU, correlated with treatment failure and mortality, suggesting that PCT measurement may be most useful for risk stratification of undifferentiated patients in the ED setting.

In most prior studies,[27,28,30] PCT concentrations were analyzed after categorizing them into groups using various cut points (eg, 0.25 ng/mL). An advantage of our study was the use of PCT as a continuous variable to demonstrate a strong association with IRVS across a broad range of PCT concentrations. As demonstrated in Figure 2, increasing PCT concentrations up to 10 ng/mL correlated with increasing IRVS risk. Using PCT concentrations on a continuous scale without introducing binary cut points to define "positive" and "negative" values retained more information and provided the most predictive power.

### Limitations

PCT measurements were obtained only from a subset of adults enrolled in the EPIC study; however, clinical and demographic characteristics

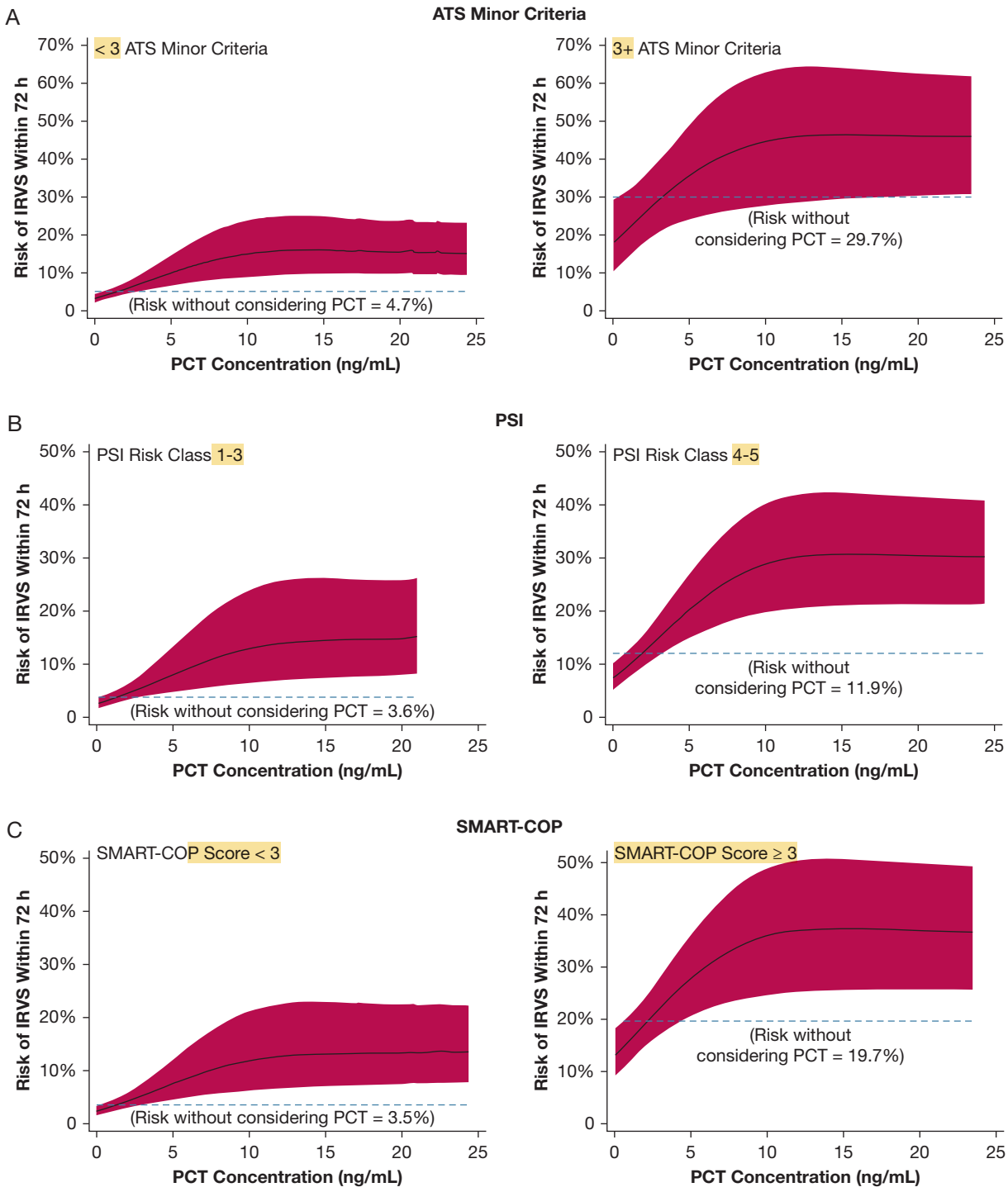


Figure 4 – *Risk of IRVS within 72 h of hospital presentation according to initial serum PCT concentration with the study population stratified into low- and high-risk subgroups by (A) ATS minor criteria, (B) PSI, and (C) SMART-COP. Plots were truncated at a PCT concentration of 25 ng/mL because of the small number of patients with PCT concentrations > 25 ng/mL. The 95% CI band is denoted with red shading. Dashed lines represent IRVS risk in a subgroup alone without considering PCT concentration. ATS = American Thoracic Society; PSI = pneumonia severity index. See Figure 1 legend for expansion of other abbreviations.*

were similar between included (76.3%) and excluded (23.7%) patients (e-Table 2). IRVS was chosen as the primary outcome because it is regarded as an objective measure of CAP-related critical illness,[11,19,20] but we acknowledge that other factors are also important when considering an ICU admission. We did not evaluate mortality as an outcome in this study. Only two patients

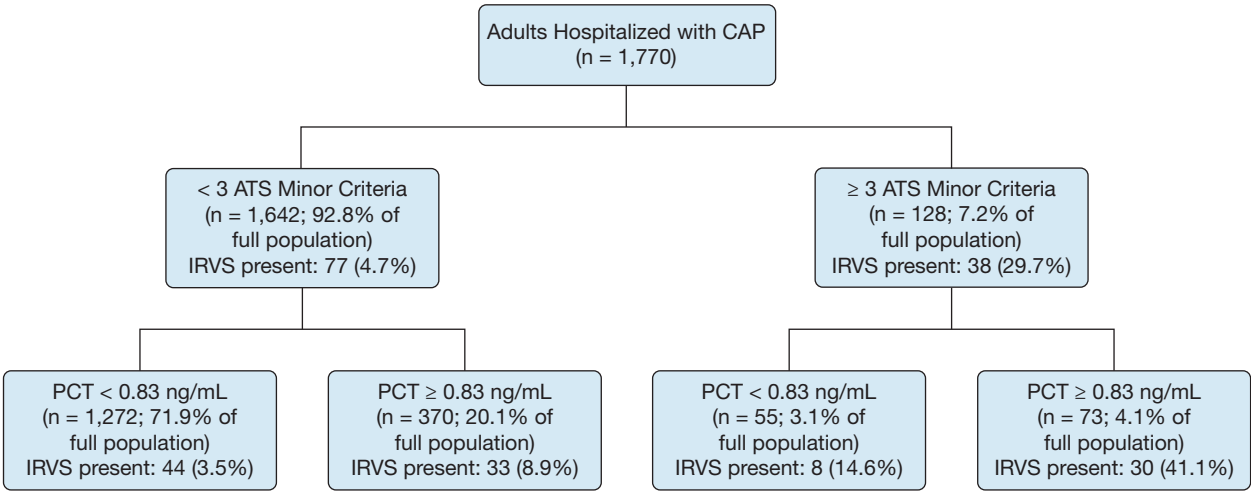


Figure 5 – *Classification tree using a combination of ≥ 3 ATS minor criteria or PCT ≥ 0.83 ng/mL (which was the 75th percentile of PCT concentration in the study population) as high-risk indicators for IRVS among adults hospitalized with CAP. CAP = community-acquired pneumonia. See Figure 1 and 4 legends for expansion of other abbreviations.*

died within 72 h of hospital presentation who did not receive IRVS; excluding these two patients from the analysis had no appreciable effect on the results. Although this study demonstrates an association between PCT and IRVS, effectiveness studies with real-time use of PCT determinations are required to evaluate the impact of PCT on clinical decision-making and patient outcomes.

## Conclusions

Serum PCT concentration at the time of hospital presentation was significantly associated with the risk of patients with CAP requiring IRVS within 72 h. This association remained strong after adjustment for other tools clinicians use to evaluate pneumonia severity, highlighting that PCT may be a useful marker to assist with ICU admission decisions.

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**Additional information:** The e-Appendix, e-Figures, and e-Tables can be found in the Supplemental Materials section of the online article.

## References

1. Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: Final date for 2005. *Natl Vital Stat Rep*. 2008;56(10):1-20.
2. Pfuntner A, Wier LM, Stocks C. Most frequent conditions in U.S. hospitals, 2010. HCUP Statistical Brief #148. http://www.hcup-us.ahrq.gov/reports/statbriefs/sb148.pdf. Accessed June 15, 2016.
3. Self WH, Grijalva CG, Zhu Y, et al. Rates of emergency department visits due to pneumonia in the United States, July 2006-June 2009. *Acad Emerg Med*. 2013;20(9):957-960.
4. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of American/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S42.
5. Ewig S, Torres A, Woodhead M. Assessment of pneumonia severity: A European perspective. *Eur Respir J*. 2006;27(1):6-8.
6. Niederman MS, Feldman C, Richards GA. Combining information from prognostic scoring tools for CAP: an American view on how to get the best of all worlds. *Eur Respir J*. 2006;27(1):9-11.
7. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patient with community-acquired pneumonia: a meta-analysis. *JAMA*. 1996;275(2):134-141.
8. Dremsizov T, Clermont G, Kellum JA, et al. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? *Chest*. 2006;129(4):968-978.
9. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med*. 1997;336(4):243-250.
10. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax*. 2003;58(5):377-382.
11. Charles PGP, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis*. 2008;47(3):375-384.
12. Renaud B, Labarere J, Coma E, et al. Risk stratification of early admission to the intensive care unit of patients with no major criteria of severe community-acquired pneumonia: development of an international prediction rule. *Crit Care*. 2009;13(2):R54.
13. Espana PP, Capelastegui A, Gorordo I, et al. Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *Am J Respir Crit Care Med*. 2006;174(11):1249-1256.
14. Phua J, Ngerng WJ, Lim TK. The impact of a delay in intensive care unit admission for community-acquired pneumonia. *Eur Respir J*. 2010;36(4):826-833.
15. Dean NC, Jones JP, Aronsky D, et al. Hospital admission decision for patients with community-acquired pneumonia: variability among physicians in an emergency department. *Ann Emerg Med*. 2012;59(1):35-41.
16. Chen LM, Render M, Sales A, et al. Intensive care unit admitting patterns in the Veterans Affairs health care system. *Arch Intern Med*. 2012;172(16):1220-1226.
17. Dasta JF, McLaughlin TP, Mody SH, Piech CT. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. *Crit Care Med*. 2005;33(6):1266-1271.
18. Orsini J, Blaak C, Yeh A, et al. Triage of patients consulted for ICU admission during times of ICU-bed shortage. *J Clin Med Res*. 2014;6(6):463-468.
19. Chalmers JD. ICU admission and severity assessment in community-acquired pneumonia. *Crit Care*. 2009;13(3):156.
20. Renaud B, Santin A. Severe community acquired pneumonia: what should we predict? *Crit Care*. 2009;13(5):421.
21. Assicot M, Gendrel D, Carsin H, et al. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet*. 1993;341(8844):515-518.
22. Schuetz P, Briel M, Mueller B. Clinical outcomes associated with procalcitonin algorithms to guide antibiotic therapy in respiratory tract infections. *JAMA*. 2013;309(7):717-718.
23. Ch Yo, Hsieh PS, Lee Sh, et al. Comparison of the test characteristics of procalcitonin to C-reactive protein and leukocytosis for the detection of serious bacterial infections in children presenting with fever without a source: a systematic review and meta-analysis. *Ann Emerg Med*. 2012;60(5):591-600.
24. Musher DM, Bebko SP, Roig IL. Serum procalcitonin level, viral polymerase chain reaction analysis, and lower respiratory tract infection. *J Infect Dis*. 2014;209(4):631-633.
25. Kruger S, Ewig S, Papassotiriou J, et al. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP: results from the German competence network CAPNETZ. *Respir Res*. 2009;10:65.
26. Masia M, Gutierrez F, Shum C, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patient's outcome research team pneumonia severity index. *Chest*. 2005;128(4):2223-2229.
27. Huang DT, Weissfeld LA, Kellum JA, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med*. 2008;52(1):48-58.

28. Schuetz P, Suter-Widmer I, Chaudri A, et al. Prognostic value of procalcitonin in community-acquired pneumonia. *Eur Respir J*. 2011;37(2):384-392.

29. Kruger S, Ewing S, Marre R, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J*. 2008;31(2):349-355.

30. Ramirez P, Ferrer M, Marti V, et al. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med*. 2011;39(10):2211-2217.

31. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization in US adults. *N Engl J Med*. 2015;373(5):415-427.

32. BioMerieux, Inc. VIDAS B.R.A.H.M.S. PCT. BioMerieux, Inc. website. http://www.biomerieux-diagnostics.com/vidas-brahms-pct. Accessed July 15, 2015.

33. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. 2005;171(4):388-416.

34. Ewig S, Ruiz M, Mensa J, et al. Severe community-acquired pneumonia: assessment of severity criteria. *Am J Respir Crit Care Med*. 1998;158(4):1102-1108.

35. Harrell FE Jr. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression and Survival Analysis*. New York, New York: Springer; 2001.

36. Kutz A, Briel M, Christ-Crain M, et al. Prognostic value of procalcitonin in respiratory tract infections across clinical settings. *Crit Care*. 2015;19:74.

37. Schuetz P, Amin DN, Greenwald JL. Role of procalcitonin in managing adult patients with respiratory tract infections. *Chest*. 2012;141(4):1063-1073.