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From the authors:

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With regard to the Pneumonia Severity Index (PSI), most subsequent risk scores and prognostic markers in community-acquired pneumonia (CAP) research focused on 30-day mortality despite the well-known limitations of this end-point. Mortality may not be a directly related to infection, but rather due to comorbidities, advanced age or secondary complications within the follow-up period. In fact, within the Procalcitonin-Guided Antibiotic Therapy and Hospitalisation in Patients with Lower Respiratory Tract Infections (ProHOSP) study, deaths were evenly distributed within the 30-day follow-up, as demonstrated in the Kaplan–Meier plot. When restricting our analysis to short-term mortality within the first 3 days after admission, procalcitonin (PCT) showed a superior prognostic performance (area under the curve (AUC) 0.68). Also, considering not only initial but also follow-up PCT levels within our study significantly improved the prognostic performance of PCT. This was also true in a previous *Legionella* sp. CAP study [1] and intensive care unit (ICU) studies [2, 3]. Therefore, we advocate the use of PCT for prognostication in an in-patient CAP setting primarily in combination with a clinical risk score that also incorporates static risk factors, such as age and comorbidities, and consideration of the kinetic of the marker over time, as nondecreasing levels point to adverse outcome.

There are several possible explanations of the difference in discrimination of PCT in our study (AUC 0.60) [4] and the previous CAPNETZ study (AUC 0.80) [5]. First, antibiotic pre-treatment may affect the prognostic performance of PCT, as patients who are admitted to the hospital with secondary treatment failure show some decrease in PCT levels from its peak value, but these patients are still at high risk for an adverse outcome. However, restricting our analysis to patients without antibiotic pre-treatment did not significantly improve the prognostic performance of PCT (AUC 0.61). Secondly, due to differences in study design compared with CAPNETZ, patients in ProHOSP had, on average, greater disease severity, reflected by higher rates of in-patient treatment (94.6 *versus* 66.6%), higher median PCT values of in-patients (0.51 *versus* 0.24 $\mu g \cdot L^{-1}$) and higher mortality rates (5.4 *versus* 4.5%) [5, 6]. Previously, it has been shown that an initial PCT level $<0.25\ \mu g \cdot L^{-1}$ rules out bacteraemic CAP with a 90% negative predictive value [7] and safely discriminates patients with pneumonic respiratory infection requiring antibiotics from those with bronchitis not requiring antibiotics [6, 8]. Thus, in a lower risk population, PCT may, in fact, help to differentiate patients with CAP (and thus expected to be at higher risk) from those with non-CAP respiratory infection (and at lower mortality risk). This is also supported when looking at the prognostic performance of PCT in the earlier Procalcitonin-Guided Treatment on Antibiotic Use and Outcome in Lower Respiratory Tract Infections (ProRESP) study. In the overall cohort of 243 patients, 87 with CAP, the prognostic performance for mortality prediction of PCT was 0.78. Yet, the AUC of PCT decreased to 0.55 when only considering CAP patients within this study. Again, when considering all patients with respiratory infections in ProHOSP, the AUC of PCT was 0.65 and decreased to 0.60 when restricted to CAP patients [4]. Finally, in the Procalcitonin Guidance of Antibiotic Therapy in Community-Acquired Pneumonia (ProCAP) study, including only CAP patients, the AUC of PCT was 0.61 [9]. These findings suggest that in lower risk settings and/or a population with mixed respiratory infection, initial PCT level may be helpful to identify CAP patients and, thereby, provide more prognostic information concerning expected mortality. In contrast, in higher risk populations, initial PCT may have limited prognostic accuracy and repeated PCT measurements are clearly preferable.

Restricting the analysis to only high risk patients (PSI class >4 or CURB-65 score>2 (confusion, urea $>7\ mmol \cdot L^{-1}$, respiratory frequency $\geqslant 30\ breaths \cdot min^{-1}$, systolic blood pressure <90 mmHg or diastolic blood pressure $\leqslant 60$ mmHg and age $\geqslant 65$ yrs)) and only one PCT cut-off of $0.25\ \mu g \cdot L^{-1}$, as suggested by S. Krüger and co-workers, shows a better separation of survivors and nonsurvivors, particularly in the early study period, which does not, however, reach statistical significance in the overall 30-day period (fig. 1). This is also in accordance with a CAP study from Pittsburgh, PA, USA demonstrating a significant effect of low PCT to rule out mortality in high-risk CAP patients [10].

In conclusion, there is evidence that: 1) increased PCT levels of $>0.25\ \mu g \cdot L^{-1}$ dose-dependently identify patients at higher risk for (bacteraemia) CAP in a low-risk population with mixed respiratory infections; 2) not decreasing PCT levels during follow-up despite antibiotic therapy identifies patients not responding to therapy, possibly resulting in adverse outcomes; and 3) low PCT levels of $<0.25\ \mu g \cdot L^{-1}$ help to rule out mortality

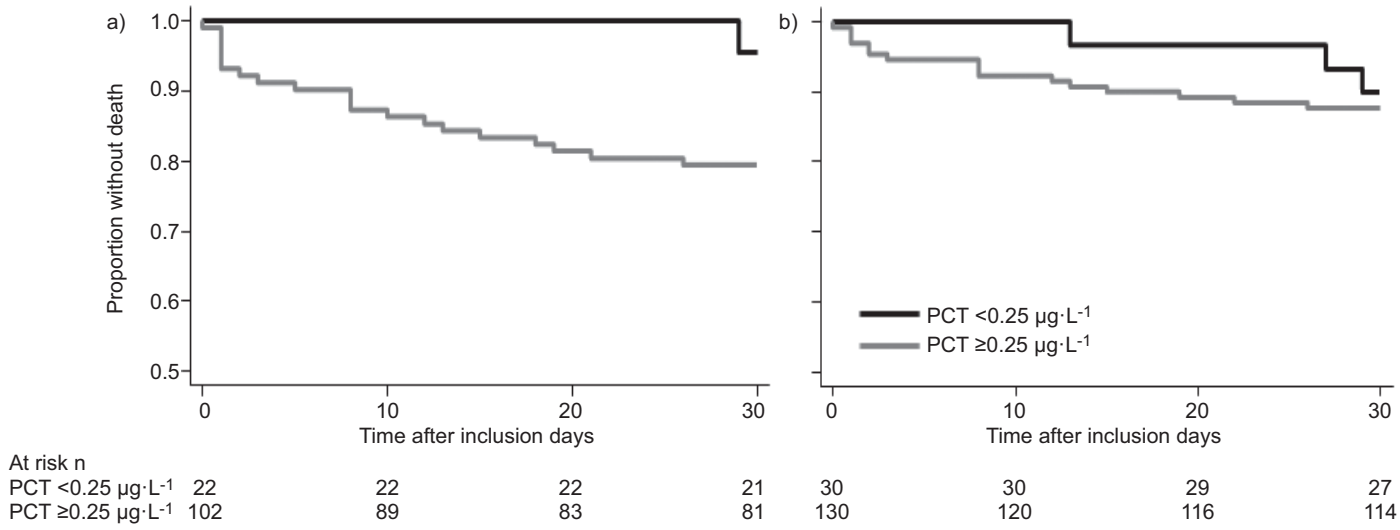

FIGURE 1. Risk for mortality within the 30-day follow-up in high-risk patients with a) Pneumonia Severity Index >4 (log-rank p=0.07) or b) CURB-65 score >2 (confusion, urea >7 mmol·L^{-1}, respiratory frequency ⩾30 breaths·min^{-1}, systolic blood pressure <90 mmHg or diastolic blood pressure ⩽60 mmHg, and age ⩾65 yrs) stratified according to an initial procalcitonin (PCT) cut-off level of 0.25 μg·L^{-1}. a) p=0.07, b) p=0.25.

and other adverse outcomes in CAP patients with high clinical risk scores. The recently completed randomised controlled Procalcitonin and Survival Study (PASS) study investigated whether using PCT as a prognostic marker improves patient management in the ICU setting [11]; similar efforts should be made for patients with respiratory infections outside the ICU setting, to investigate whether PCT adds useful prognostic information and, thereby, improves the daily clinical management and outcomes of patients with CAP.

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