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Is N-terminal pro-B-type natriuretic peptide ready for 'prime time' in severe pneumonia?

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Severe pneumonia is a complex systemic process that requires a careful clinical assessment, the consideration of comorbidities and potential complications, and an understanding of the pathophysiology of inflammation. Severity assessment in pneumonia is important for risk stratification, prognosis and to determine the need for intensive care unit (ICU) admission. This information is imperative, given that delayed transfer to the ICU is associated with adverse outcomes in patients with community-acquired pneumonia[1] (CAP). Several clinical scores have been validated to identify patients with CAP and healthcare-associated pneumonia requiring ICU admission, and among them, the 2007 Infectious Diseases Society of America/American Thoracic Society minor criteria appear to be a suitable predictor of ICU admission and 30-day mortality.[2,3] However, none of these clinical scores have been substantially successful in assessing the severity and predicting the need for ICU admission in severe pneumonia.

In recent years, the limitations in clinical scores have increased the focus on biomarkers, which alone, or as a complement of clinical scores, have become an important tool in predicting severity of pneumonia.[2] Elevated serum levels of biomarkers can be found in the presence of inflammation, infection and comorbid conditions.[2] These assays have attractive characteristics, including rapid results, simplicity and reproducibility, and in most cases, they are cost-effective. Furthermore, biomarkers may be useful in predicting short- and long-term prognosis of patients with pneumonia. Among available biomarkers, procalcitonin

CONFLICT OF INTEREST STATEMENT

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and C-reactive protein are commonly used in CAP, as indicators of severity of disease and predictors of mortality.[4] In addition, procalcitonin assists clinicians in the decision for the need for antibiotic therapy. Midregional pro-adrenomedullin, a cardiac biomarker, increases the accuracy of the clinical assessment scores (pneumonia severity index and CURB-65) and is a better predictor of short- and long-term mortality in CAP.[5]

Pro-B-type natriuretic peptide (BNP) is a prohormone secreted in response to myocardial stretch, volume overload and elevated end-diastolic pressure from cardiac myocytes. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a 76 amino acid peptide produced by the cleavage of proBNP into an active BNP and an inactive NT-proBNP.[6] NT-proBNP appears to have a longer half-life and fewer preanalytic issues than those seen with BNP.[6] Both peptides have been used in the assessment and prognosis of congestive heart failure, myocardial infarction, pulmonary embolism and sepsis. In pneumonia, NT-proBNP, BNP and midregional proatrial natriuretic peptide have shown to have good correlation with clinical scores and to be important predictors of short- and long-term mortality in the emergency department and in hospitalized patients with CAP.[7]

In this issue of *Respirology*, Lin and colleagues present important information about the potential value of NT-proBNP as a prognostic marker for pneumonia in the ICU setting. The authors report, prospectively, the plasma levels of this biomarker measured upon ICU admission in a cohort of 216 patients with pneumonia (40% healthcare-associated pneumonia, 35% CAP and 25% hospital-acquired pneumonia).[8] The mean NT-proBNP levels in 30-day survivors (5658 ± 9240 pg/mL) was significantly lower than the levels in 30-day non-survivors (11 938 ± 13 121 pg/mL, $P = 0.001$). The area under the curve of the NT-proBNP was comparable to that of APACHE II score and Infectious Diseases Society Of America/American Thoracic Society 2007 minor criteria (0.715, 0.75, 0.65, respectively) in predicting 30-day mortality. After adding NT-proBNP to the APACHE II score, the area under the curve increased from 0.754 to 0.794 ($P = 0.048$); however, no increase was seen when added to the Infectious Diseases Society Of America/American Thoracic Society 2007 minor criteria. Patients with acute cardiac events were excluded, and the proportion of patients with underlying congestive heart failure or coronary artery disease was not different between survivors and non-survivors.

These findings are in line with two recent studies evaluating cardiac biomarkers in pneumonia, but unique for being the first study in patients admitted to the ICU and excluding acute cardiac events. In a study by Nowak and collaborators in patients with CAP presenting to the emergency department, NT-proBNP, BNP and midregional proatrial natriuretic peptide levels were higher among short- and long-term non-survivors, when compared with survivors.[7] The area under the curve for the three biomarkers was comparable to that of pneumonia severity index score for prediction of short- and long-term mortality.[7] Similarly, in a retrospective study of hospitalized patients with CAP, non-survivors had higher NT-proBNP levels as compared with survivors.[9] NT-proBNP was an independent predictor of mortality with the area under the curve comparable to pneumonia severity index and CURB-65, but inferior to that of APACHE II score which did not significantly increase when the biomarker was added to the score.[9] This latter finding differs from those reported by Lin and collaborators.[8] Therefore, NT-proBNP, midregional proatrial

natriuretic peptide and midregional pro-adrenomedullin are cardiac biomarkers that can significantly predict mortality, highlighting the high frequency and importance of cardiovascular complications in CAP.[10] Because there is an important association of pneumonia and secondary heart disease, cardiac biomarkers may provide more discriminating information about prognosis in CAP than inflammatory biomarkers. In addition, the fact that the use of cardiovascular biomarkers as presented by Lin *et al*. in the current study raise a concern that severity of disease and subsequent mortality in patients with pneumonia maybe associated with cardiovascular events that occur during hospitalization or after discharge, and not necessarily present on admission.

Severe pneumonia, like other severe infections, has systemic repercussions. This paradigm has been tested by a large number of clinical prediction methods with some limitations. Clinical scores take into account measurement of variables at one specific time although many of these variables are dynamic. Biomarkers do not allow individual prediction of aetiology, but may provide additional information regarding clinical evolution, as biomarkers are dynamic and can be measured daily. In fact, biomarkers may improve the prognostic information provided by clinical scoring systems and aid the clinician in the decision-making process when considering ICU admission.

Until new data are available, both clinical scores and biomarkers should be incorporated in the physician's clinical decision-making process, when considering prognosis and ICU admission in patients with severe pneumonia. Future research studies should couple diagnostic and subsequent intervention strategies in order to improve outcomes in critically ill patients with pneumonia.

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