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Letter to the Editors

Apoptosis inhibitor of macrophage differentiates bacteria from influenza or COVID-19 in hospitalized adults with community-acquired pneumonia

Dear Editor,

We read with interest the report by Li and colleagues in this journal who showed that serum smyloid A (SAA) was a biomarker of severe Coronavirus Disease and poor prognosis.[1] Rapidly and accurately differentiating between viral and bacterial infections in community-acquired pneumonia (CAP) is critical for prescribing appropriate therapy, especially in epidemic contexts such as influenza or coronavirus disease 19 (COVID-19).[2, 3]

We have reported that apoptosis inhibitor of macrophage (AIM, also called CD5L) production was elevated after bacterial infection,[4, 5] and it may predict mortality in the patients with sepsis.[6] Herein, we present evidence that AIM might be a biomarker in distinguishing between bacterial and viral infection in hospitalized adults with CAP.

In the first cohort study, 765 adult patients with CAP were enrolled at the Department of Respiratory and Critical Care Medicine of the First Affiliated Hospital of Chongqing Medical University from September 2017 to January 2020. All enrolled patients had clinical signs and radiographic evidence of CAP.[7] Influenza patients were defined as those with a positive virus result detected on viral nucleic acid testing. Bacterial infections were confirmed by microbiological evidence of bacterial infection. We classified patients into two groups based on laboratory test results: I, pure bacterial infection (detection of any bacteria other than virus); II, pure influenza (detection of influenza viruses A and B without co-detection of bacteria). CAP caused by mixed influenza and bacterial infection were excluded from analysis. Finally, 683 CAP patients did not meet the criteria, and 51 CAP patients had pure bacterial infection and 31 had pure influenza (Table 1). 62 sex- and age-matched healthy volunteers were recruited as healthy controls.

In the second cohort study from February 2020 to January 2021, 39 hospitalized patients with pure COVID-19 from the Department of Laboratory Medicine of Chongqing Public Health Medical Center, 47 hospitalized patients with pure bacterial infection from Department of Respiratory and Critical Care Medicine of the First Affiliated Hospital of Chongqing Medical University, and 51 healthy volunteers were enrolled (Table 1).

The following base-line variables were also recorded at enrollment: Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, body temperature, white blood cells (WBC) count, serum levels of C-reactive protein (CRP) and procalcitonin (PCT), presence of shock, and the use of mechanical ventilation. The in-hospital mortality was also recorded. Serum levels of AIM were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kit (Catalog# MBS064988; MyBioSource). This study was approved by the Research Ethics Committee of the First Affiliated Hospital of the Chongqing Medical University ((numbers 2021-187 and 2015–156).

Differences in continuous variables were estimated using the Mann–Whitney *U* test. Differences in categorical variables were calculated using the Fisher's exact or the Chi square test as appropriate. The ability of biomarker levels to discriminate between bacterial and viral infections was investigated by means of receiver operating characteristic (ROC) curve analysis. Area under the curve (AUC) was calculated. Sensitivity, specificity, and likelihood ratio (LR) values were calculated using AIM cut-points of 368 ng/ml, 430 ng/ml, and 567 ng/ml.

During the first study period, 51 CAP patients with pure bacterial infection and 31 with pure influenza were collected (Table 1). CAP patients with proven bacterial infection and those with influenza virus infection were not different in terms of demographics and chronic comorbidities. The severity of CAP on hospital admission was comparable between groups, as indicated by similar SOFA and APACHE-II scores, as well as similar percentages of shock and mechanical ventilation requirement. As expected, the levels of WBC, neutrophils, lymphocytes, CRP, and PCT were significantly higher in CAP with pure bacterial infection than those in CAP with pure influenza.

As shown in Fig. 1A, AIM concentrations were significantly elevated in the sera from CAP patients with influenza and those with bacterial infection than from healthy volunteers. Interestingly, serum AIM concentrations were significantly higher in bacterial group on the day of hospital admission when compared with influenza group. Next, we compared the AUC of AIM, PCT and CRP to differentiate bacterial infection from influenza by performing a ROC curve analysis (Fig. 1B), and the best AUC was observed for circulating AIM concentration at the day of hospital admission (0.90, 95% confidence interval [CI], 0.83–0.96). The AUC for PCT and CRP were, respectively 0.81 (95% CI, 0.71–90) and 0.73 (95% CI, 0.62–0.85). An AIM threshold of ≥430 ng/mL discriminated bacterial infection from influenza with a sensitivity of 80.6% (95% CI, 62.5%–92.5%) and specificity of 84.3% (95% CI, 71.4%–93.0%).

The second cohort study included 39 CAP patients with pure COVID-19 infection and 47 CAP patients with pure bacterial infection (Table 1). There were no significance differences in demographics, chronic comorbidities, severity of illness, and in-hospital morbidity and mortality between bacterial group and COVID-19 group. With regard to circulating AIM as shown in Fig. 1C, AIM concentrations were significantly higher in bacterial infection compared to COVID-19. Analysis of AUC [95% CI] showed that serum AIM concentration (0.97 [95% CI, 0.95–1.00]) robustly discriminated bacterial infection from COVID-19 in the patients with CAP on day of hospital admission (Fig. 1D).

PCT-guided therapy has successfully reduced antibiotics in selected populations of patients with respiratory infections.[7,8] How-

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