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Original article

Correlation of inflammatory and cardiovascular biomarkers with pneumonia severity scores

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ABSTRACT

Purpose: To assess the correlation of procalcitonin (PCT), C-reactive protein (CRP), neopterin, mid-regional pro-atrial natriuretic peptide (MR-proANP), and mid-regional pro-adrenomedullin (MR-proADM) with severity risk scores: severe CAP (SCAP) and SMART-COP in patients with community-acquired pneumonia (CAP), as well as short term prognosis and to determine the correlation with mortality risk scores.
Methods: Eighty-five patients with a final diagnosis of pneumonia were consecutively included during a two month period. Epidemiological, clinical, microbiological, and radiological data were recorded. Patients were stratified according to the PSI, CURB-65, SCAP and SMART-COP. Complications were defined as respiratory failure/shock, need of ICU, and death. Plasma samples were collected at admission.
Results: MR-proANP and MR-proADM showed significantly higher levels in high risk SCAP group in comparison to low risk. When considering SMART-COP none of the biomarkers showed statistical differences. MR-proADM levels were high in patients with high risk of needing intensive respiratory or vasopressor support according to SMRT-CO. Neopterin and MR-proADM were significantly higher in patients that developed complications. PCT and MR-proADM showed significantly higher levels in cases of a definite bacterial diagnosis in comparison to probable bacterial, and unknown origin. MR-proANP and MR-proADM levels increased statistically according to PSI and CURB-65.
Conclusions: Biomarker levels are higher in pneumonia patients with a poorer prognosis according to SCAP and SMART-COP indexes, and to the development of complications.
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Correlación entre los niveles de biomarcadores inflamatorios y cardiovasculares con los índices de severidad de neumonía

Palabras clave:
Biomarcadores
Neumonía
Pronóstico
Índices de severidad

RESUMEN

Objetivo: Establecer la correlación entre los niveles de procalcitonina (PCT), proteína C reactiva, neopterina, pro-péptido natriurético auricular (MR-proANP) y pro-adrenomedulina (MR-proADM) y los índices de severidad: severe CAP (SCAP) y SMART-COP en pacientes con neumonía adquirida en la comunidad (NAC), así como el pronóstico a corto plazo, y confirmar su correlación con los índices de severidad PSI y CURB-65.
Métodos: Ochenta y cinco pacientes con diagnóstico final de NAC fueron incluidos de forma consecutiva durante 2 meses. Se recogieron los datos epidemiológicos, clínicos, microbiológicos y radiológicos. Los pacientes se clasificaron en función del PSI, CURB-65, SCAP y SMART-COP. Las complicaciones se definieron como insuficiencia respiratoria/shock, ingreso en la UCI o muerte. Las muestras de plasma se recogieron en el momento del ingreso hospitalario.

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Resultados: Los niveles de MR-proANP y MR-proADM fueron significativamente superiores en aquellos pacientes clasificados como alto riesgo según SCAP en comparación con los de bajo riesgo. Al considerar SMART-COP ninguno de los biomarcadores mostró significación estadística. Los niveles de MR-proADM fueron superiores en los pacientes con alto riesgo de necesitar soporte intensivo/vasopresor según SMRT-CO. Los valores de neopterina y MR-proADM fueron significativamente superiores en pacientes que desarrollaron alguna complicación. En los casos con diagnóstico bacteriano de seguridad, se observaron niveles significativamente más elevados de PCT y MR-proADM, respecto de los casos de probable origen bacteriano o origen desconocido. Los niveles de MR-proANP y MR-proADM se incrementaron en función del PSI y de CURB-65.

Conclusiones: Los niveles de biomarcadores son superiores en pacientes con peor pronóstico, según los índices de severidad evaluados, así como con el desarrollo de complicaciones.

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Introduction

The optimal management of community-acquired pneumonia (CAP) requires clinical decisions regarding the initial site of care and therapy. Appropriate decisions in this setting are important for an adequate patient care and correct allocation of resources.

Regarding severity assessment, several prognostic scores have been developed in order to assess the risk of death, such as the Pneumonia Severity Index (PSI)[1] and CURB-65 (confusion, urea, respiratory rate, blood pressure and age).[2] In general, severity rules consider several clinical, analytical and radiological findings that jointly reflect patient's general condition. Although these rules can be useful for the management of patients with pneumonia, they also present some disadvantages such as age overemphasis and complexity for its calculation. In the last years, two other severity scores have been defined: severe CAP (SCAP) that was developed for identifying patients who are at risk for an adverse outcome and might need ICU admission, being as accurate as current scoring systems[3–5] and SMART-COP, mainly designed for the prediction of patients that are likely to require intensive respiratory or vasopressor support (IRVS).[6] Main drawbacks for these last scores are the lack of consideration for the presence of comorbidities and the need of more testing and validation, although results from a recent meta-analysis indicate their usefulness for the prediction of ICU admission or intensive treatment in patients with CAP.[7] In a study with patients aged <50, SMART-COP was superior to PSI and CURB-65 for the prediction of IRVS, but incorrectly stratified 15% of patients.[8]

In the last years, it has also become more evident that it is also important to consider host inflammatory and cardiovascular response to an infection.[9] Procalcitonin (PCT), C-reactive protein (CRP) and neopterin are examples of biomarkers that can be useful for the management of patients with pneumonia, as a correlation with the etiological origin and the severity has been demonstrated.[10,11] Biomarkers reflecting cardiovascular impairment (including endothelial dysfunction and volume homeostasis) have also emerged as useful tools for pneumonia management.[12,13] Adrenomedullin (ADM) is a member of the CALC-gene family and has potent vasodilating, immune modulating and metabolic properties.[14] Atrial natriuretic peptide (ANP) is synthesized by cardiac atrial myocytes in response to proinflammatory factors, hypoxia and conditions of increased cardiac pressure and volume overload.[15] Biochemical assays aim specifically at the mid-region of the ADM and ANP precursors (MR-proADM and MR-proANP).[16,17] Levels of both biomarkers have been evaluated as severity and prognostic markers in CAP and chronic obstructive pulmonary disease (COPD) exacerbations correlating with PSI, CURB-65, the simpler CRB-65 and prognosis.[18–23] Indeed these biomarkers have shown to improve usefulness of validated scores.[24,25] However, little is known about how these biomarkers correlate with the severity indexes: SCAP and SMART-COP.

Inflammatory and cardiovascular biomarkers have shown to correlate to some extent with etiology, severity of CAP and to mortality risk scores.[13,26] Therefore, we hypothesized that biomarkers should also correlate to severity scores primary aimed to identify patients needing intensive care and even improve its usefulness. Therefore, the main objective of this study was to assess the correlation of PCT, CRP, neopterin, MR-proANP and MR-proADM levels with mortality risk scores, focusing on SCAP and SMART-COP. The secondary objectives were to confirm the correlation of biomarkers with short term mortality and to evaluate its usefulness for identifying bacterial etiology.

Patients and methods

Study design and setting

The study is observational, descriptive and analytical and was approved by the ethical committee of the institution. Population consists of patients attending a tertiary public university hospital with fever and symptoms of lower respiratory tract infection (LRTI) that consulted the medical area of the emergency department (ED) (excluding surgical, gynecological and pediatric areas) and from whom blood cultures were obtained. Patients were consecutively included during two months period. Patients were followed up for 30 days after admission. Pneumonia was defined by clinical (presence of fever, cough and dyspnea) and radiographic signs (pneumonic infiltrate in the chest radiograph), as well as clinical evolution, assessed by expert clinicians and radiologists.[27] Final diagnosis was set according to the clinical judgment mentioned in the emergency and hospital medical files, or in the records of outpatient care. For doubtful cases, a consensus was achieved by three expert clinicians. People conducting the chart abstraction, and reviewing chest X-rays were blinded to the study hypothesis and blinded to biomarkers values.

Data collection and sample processing

Epidemiological, clinical, microbiological, analytical and radiological data were recorded from all cases. Charlson index was also calculated for each patient.[28] Patients were stratified according to the PSI, CURB-65, SCAP and SMART-COP.[1,2,5,6] SMART-COP was calculated if all variables were available. SMRT-CO was applied in cases when either one of the following variables was not recorded: albumin, arterial pH, or Pa O_2. Complications considered were: respiratory failure (Pa O_2 < 60 mmHg), shock (hypotension persisting despite fluid resuscitation and requiring vasopressor therapy),[29] need of ICU admission, and death.

At the time of arrival to the ED, samples were collected for microbiological diagnosis: blood cultures, respiratory specimens for culture and urine for antigen detection. Pneumococcal pneumonia was diagnosed by isolation of *Streptococcus pneumoniae* from blood and/or pleural effusion culture and/or detection of

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