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Serum levels of procalcitonin and high sensitivity C-reactive protein are associated with long-term mortality in acute ischemic stroke

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ABSTRACT

Objective: The aim of this study is to assess the prognostic value of systemic inflammation, as measured by the inflammatory biomarkers PCT and Hs-CRP, to predict the long-term mortality in ischemic stroke patients.
Methods: We prospectively studied 374 patients with ischemic stroke who were admitted within 24 h after the onset of symptoms. Serum levels of PCT, Hs-CRP and NIH stroke scale (NIHSS) were measured at the time of admission. Clinical follow-up was performed at 1 year. The prognostic value of PCT to predict the mortality within one year was compared with Hs-CRP, NIHSS and with other known outcome predictors.
Results: In the 64 non-survival patients, serum PCT levels were significantly ($P < 0.0001$) higher compared with those in survival patients. Multivariate COX regression analysis showed that log-transformed PCT and Hs-CRP were independent mortality predictors with adjusted hazard ratio of 4.24 (95% confidence interval [CI], 2.42–6.30) and 15.37 (95% confidence interval [CI], 3.25–41.08). The area under the receiver operating characteristic curve of PCT and Hs-CRP were 0.89 (95% CI, 0.85–0.93) and 0.68 (95% CI, 0.59–0.77) for mortality, respectively.
Conclusion: Serum levels of PCT and HS-CRP at admission were independent predictor of long-term mortality after ischemic stroke in a Chinese sample.

1. Introduction

Ischemic stroke is the third leading cause of mortality in most countries in the world and China has 2.5 million new stroke cases each year and 7.5 million stroke survivors [1]. Mortality after 1 year ranges between 21% and 27%; 15% to 30% of survivors are permanently disabled [2]. An early risk assessment with estimate of the severity of disease and prognosis is pivotal for optimized care and allocation of healthcare resources to improve outcome [3].

Inflammatory processes have fundamental roles in stroke in both the etiology of ischemic cerebrovascular disease and the pathophysiology of cerebral ischemia [4]. Inflammatory markers (fibrinogen and CRP) predicted the stroke severity and outcome [5]. It has been reported that it is possible to use the increase in the concentration of acute phase reactants and especially the high sensitivity C-reactive protein (Hs-CRP) to help predict future cerebrovascular mortality [6]. Procalcitonin (PCT) was a protein of 116 amino-acids with a molecular weight of 13 kDa. The probable site of PCT production during inflammation is the neuroendocrine cells in the lungs or intestine [7]. Mimoz et al. [8] found that an early and transient release of PCT into the circulation was observed after severe trauma and the amount of circulating PCT seemed proportional to the severity of tissue injury and hypovolemia, yet unrelated to infection, indicating an inflammation-related induction of PCT.

Data from large-sample studies in China about the relationship between inflammatory biomarkers and mortality in stroke patients are rare, and evidences in statistically strong power are needed. Thus, the primary aim of our prospective cohort study was to assess the prognostic value of systemic inflammation, as measured by the inflammatory biomarkers PCT and Hs-CRP, to predict the long-term mortality in ischemic stroke patients.

2. Method

2.1. Patients and study design

We conducted a prospective cohort study at the Shanghai Tenth People's Hospital. From September 2010 to October 2013, all patients with an acute ischemic stroke event were included. Patients were eligible for inclusion if they were admitted to the emergency department with an acute ischemic stroke defined according to the World Health Organization criteria [9] and with symptom onset within 24 h. we excluded patients with intracranial hemorrhage, a history of recent surgery or trauma during the preceding 2 months, renal insufficiency (creatinine >1.5 mg/dl), malignancy, febrile disorders, acute or chronic inflammatory

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disease at study enrollment (which were defined by physical examination, past medical history and white blood count test), autoimmune diseases, severe edema or a prior myocardial infarction onset < 3 months, as well as those with a history of valvular heart disease, or intracardiac thrombus on echocardiograph. In addition, patients with no evidence of infarction on CT or MRI within 24 h after symptom onset were excluded from the study.

The control cases ($N = 200$) were of similar age and gender distribution to the AIS patients. They had no known diseases and were not using any medication. The median age of controls included in this study was 69 (IQR, 62–79) years and 45.0% were women. A detailed medical history was taken and clinical and laboratory examinations were performed on all participants in both groups. The study was approved by the local ethics committee of Shanghai Tenth People's Hospital of Tongji University. The patients or their relatives gave written informed consent prior to entering the study.

2.2. Clinical variables

The following clinical and demographical data were taken: age, gender, stroke etiology, blood pressure, leukocyte count, and presence of risk factors (ie, age; sex; smoking history; hypercholesterolemia; history of hypertension, diabetes mellitus, previous ischemic stroke, or transient ischemic attack, respectively; positive family history for myocardial infarction, stroke, or transient ischemic attack). Stroke cause was determined according to the criteria of the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification [10], which distinguishes large-artery arteriosclerosis cardio embolism, small-artery occlusion, other causative factor, and undetermined causative factor. The clinical stroke syndrome was determined by applying the criteria of the Oxfordshire Community Stroke Project: total anterior circulation syndrome (TACS); partial anterior circulation syndrome (PACS); lacunar syndrome (LACS); and posterior circulation syndrome (POCS) [11]. The National Institutes of Health Stroke Scale (NIHSS) score was assessed on admission (with greater scores indicating increasing severity) [12].

2.3. Neuroimaging

Diagnosis of stroke was based on the results of strict neuroradiological examination (brain computer tomography, magnetic resonance imaging (MRI), or both) according to the *International Classification of Diseases*, ninth revision. MRI with diffusion-weighted imaging (DWI) was available in 221 stroke patients (59.1%). In those patients, DWI lesion volumes were determined by an experienced neurologist (Liu XY) who was unaware of the clinical and laboratory results. The infarct volume was calculated by using the formula $0.5 \times a \times b \times c$ (where a is the maximal longitudinal diameter, b is the maximal transverse diameter perpendicular to a, and c is the number of 10-mm slices containing infarct) [13].

2.4. End points and follow-up

Our study finished 1-year follow-up. The end point of this study was death from any cause within a 1-year follow-up. The death was considered as an outcome variable. 1-year mortality was defined as long-term mortality. Follow-up was performed by two trained medical students with a structured follow-up telephone interview with the patient or, if not possible, with the closest relative or family physician.

2.5. Blood collection and quantification

For the purpose of this study, blood samples of patients who were admitted to hospital were prospectively drawn from the antecubital vein. After centrifugation, serum of the samples were immediately stored at −80 °C before assay. White blood cell (WBC) count, Hs-CRP, PCT and other biochemical measurements were done using standard laboratory methods. PCT levels were measured using Enzyme-Linked Fluorescent Assay by VIDAS B.R.A.H.M.S. (Biomerieux, Durham, USA), and Hs-CRP was analyzed by the Roche Cobas Integra 800 analyzer (Roche Diagnostic, Indianapolis, IN, USA). The lower detection limit was 0 ng/ml and the line range was 0–200 ng/ml. The intra-assay coefficient of variation [CV] and inter-assay CV were 3.54–7.07% and 4.15%–9.86%, respectively.

2.6. Statistical analysis

Discrete variables are summarized as counts (percentage), and continuous variables as medians and interquartile ranges (IQRs). Two-group comparison of not normally distributed data was performed using Mann–Whitney *U* test, and a Kruskal–Wallis one-way analysis of variance was used for multi group comparisons. Correlations among continuous variables were assessed by the Spearman rank-correlation coefficient. In addition, associations between PCT and NIHSS score and infarct volume were also assessed using ordered logistic regression models in multivariable adjustment with possible confounders. Cox regression analysis was assessed by univariate and multivariate analysis to identify independent predictors of mortality and report hazard ratio (HR). Therefore, common logarithmic transformation (ie, log) was performed to obtain normal distribution for skewed variables (ie, PCT and Hs-CRP concentrations). Second, we compared different prognostic risk scores from different predictive models by calculating receiver operating characteristic analysis using ROCR package. Thereby the area under the receiver operating characteristic curve (AUC) is a summary measure over criteria and cut-point choices. Finally, to study the ability of PCT for mortality prediction, we calculated Kaplan–Meier survival curves and stratified patients by PCT quarters. Finally, new reclassification metrics have been shown to provide information about the usefulness of the serum PCT and Hs-CRP. We calculated reclassification model (PCT + Hs-CRP + NHISS) to further investigate the benefit of PCT and Hs-CRP levels as compared with the NIHSS score alone, and results are reported as net reclassification improvement for mortality risk categories. All testing was two tailed, and p values less than 0.05 were considered to indicate statistical significance. All calculations were performed using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA) and the ROCR package (version 1.0-2), which is available from CRAN repository (http://cran.r-project.org/).

3. Results

3.1. Patient characteristics

In our study, from 528 screened patients, the study cohort consisted of 454 patients with AIS at baseline. By the time of follow-up, at 1 year post-stroke, 48 declined the invitation to participate and 32 lost follow-up, leaving 374 individuals. The median age of patients included in this study was 69 (IQR, 63–79) years and 44.9% were women. The median NIHSS score on admission was 10 points (IQR, 6–15). The median time from stroke onset to inclusion in the study was 5.9 (IQR, 2.8–11.2) hours. Sixty-four patients died, thus the mortality rate was 17.1%. In addition, the number of tissue plasminogen activator-treated patients was 112 (29.9%). Basal characteristics of patients with acute ischemic stroke are provided in Table 1.

3.2. Main findings

The results indicated that the serum PCT levels were significantly higher in stroke patients as compared to normal controls [0.78 (IQR, 0.12–1.68) ng/ml vs. 0.01 (IQR, 0.00–0.02)ng/ml; $P < 0.0001$]. PCT levels increased with increasing severity of stroke as defined by the NIHSS score. There was a positive correlation between levels of PCT and NIHSS ($r = 0.225$, $P < 0.0001$; Fig. 1A). There was still a significant positive correction ($P = 0.006$) between PCT serum levels and NIHSS score,