Peptides 51 (2014) 4–8

Contents lists available at ScienceDirect

Peptides

journal homepage: www.elsevier.com/locate/peptides

Plasma copeptin levels are associated with prognosis of severe acute pancreatitis

Gao Sang[a,1], Jian-Min Du[b,1], Yong-Yi Chen[c,*], Yang-Bo Chen[d], Jun-Xian Chen[e], Yong-Can Chen[e]

[a] Department of Paediatrics, Tongde Hospital Zhejiang Chinese Medical University, 234 Gucui Road, Hangzhou 310012, China
[b] Department of Paediatrics, The First People's Hospital of Hangzhou, Nanjing Medical University, 261 Huansha Road, Hangzhou 310006, China
[c] Department of Traditional Chinese Internal Medicine, Tongde Hospital Zhejiang Chinese Medical University, 234 Gucui Road, Hangzhou 310012, China
[d] Intensive Care Unit, Tongde Hospital Zhejiang Chinese Medical University, 234 Gucui Road, Hangzhou 310012, China
[e] Department of Gastroenterology, Tongde Hospital Zhejiang Chinese Medical University, 234 Gucui Road, Hangzhou 310012, China

ARTICLE INFO

Article history:
Received 28 August 2013
Received in revised form 15 October 2013
Accepted 15 October 2013
Available online 30 October 2013

Keywords:
Copeptin
Severe acute pancreatitis
Prognosis
Biomarker

ABSTRACT

Copeptin reflects the individual stress level, and is correlated with outcomes of critical illness. This study was designed to evaluate its relationship with disease severity, local complications, organ failure and mortality of severe acute pancreatitis (SAP). Seventy-eight SAP patients and 78 sex- and age-matched healthy individuals were recruited. Plasma samples were obtained on admission from SAP patients and at study entry from healthy individuals. Copeptin concentration was determined using enzyme-linked immunosorbent assay. Plasma copeptin level was obviously higher in patients than in healthy individuals, was identified as an independent predictor of local complications, organ failure and in-hospital mortality, was highly associated with traditional predictors of disease severity and mortality including the Acute Physiology and Chronic Health Care Evaluation II score, Ranson score, multiple organ dysfunction score, sequential organ failure assessment score, and predicted local complications, organ failure, and in-hospital mortality of SAP patients with high areas under receiver operating characteristic curve. Furthermore, its predictive value was similar to the traditional predictors'. However, it could not improve these traditional predictors' predictive values. Therefore, increased plasma copeptin level is associated with disease severity and identified as a novel prognostic marker of local complications, organ failure and mortality after SAP.

1. Introduction

Acute pancreatitis is defined as an acute inflammatory process of the pancreas that may involve peripancreatic tissues or remote organ systems [7]. According to the recent revision of the Atlanta classification and definitions for acute pancreatitis (2012), severe acute pancreatitis (SAP) and moderately SAP are characterized by organ failure and/or local pancreatic complications, and is associated with high mortality rate [2]. The Acute Physiology and Chronic Health Care Evaluation II (APCHCE II) score, Ranson score, multiple organ dysfunction score (MODS) and sequential organ failure assessment (SOFA) score have been developed for the early prediction of disease severity and mortality of SAP, and further enable an earlier risk stratification of SAP patients and assist physicians to start appropriate therapy [1,14,18,19,21].

Copeptin, a surrogate marker for arginine vasopressin (AVP), is a 39-amino-acid glycopeptide of currently unknown physiological function, and has a longer half-life than AVP, which makes it easier to detect and also reflects the individual stress level [10]. As a prognostic marker, copeptin levels were highly associated with disease severity and mortality of critically ill patients experiencing traumatic brain injury, hemorrhagic or ischemic stroke, myocardial infarction and community-acquired pneumonia [4–6,11,12,22]. Plasma copeptin levels have also been found to be elevated in SAP [8]. The present study aimed further to investigate changes of plasma copeptin levels in SAP patients and also determine whether copeptin was associated with disease severity, local complications, organ failure and mortality in a group of SAP patients.

2. Materials and methods

2.1. Study population

This prospective study enrolled seventy-eight consecutive patients with SAP admitted to Tongde Hospital Zhejiang Chinese

* Corresponding author. Tel.: +86 0571 89972114; fax: +86 0571 88853199.
E-mail address: gstongde@63.com (Y.-Y. Chen).
[1] These authors contributed equally to this work.

0196-9781/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.peptides.2013.10.019

Medical University, Hangzhou, China between August 2009 and December 2012. The diagnosis of SAP was made based on the criteria proposed by the International Atlanta Symposium on Acute Pancreatitis in 2012 [2]. Exclusion criteria were pregnant women, less than 18 years of age, cardiac or neurological disorders, malignant disease, chronic inflammatory disease, preexisting organ failure, chronic obstructive airways disease and immunosuppressive disorders. A control group consisted of 78 healthy age- and sex-matched subjects. Written and informed consent to participate in the study was obtained from them or their relatives. This protocol was approved by the local institutional Ethics Committee before implementation.

2.2. Clinical assessment

Age, gender, body mass index, the period between onset of pain and hospital-admission, etiology of SAP, and types of treatments were recorded. The 48-h Ranson score, the APACHE II score, MODS, and SOFA score were also collected for evaluation of severity of the disease [1,14,18,19,21]. Local complications included acute peripancreatic fluid collections, pancreatic pseudocycts, acute necrotic collections and/or walled-off necrosis [2]. Organ failure is defined as a modified Marshall score of 2 or more for 1 (or more) of the 3 organ systems most commonly affected by SAP: respiratory, cardiovascular, and renal [2]. Outcome was assessed as in-hospital mortality.

2.3. Determination of copeptin in plasma

The informed consents were obtained from study population or family members in all cases before the blood were collected. Venous blood was drawn at study entry for healthy control and on admission for patients. The blood samples were immediately placed into sterile EDTA test tubes and centrifuged at $1500 \times g$ for 20 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. Plasma copeptin concentrations were measured in duplicate with the method based on the principle of competitive enzyme immunoassay (Phoenix Pharmaceuticals, Belmont, CA) according to the manufacturer's instructions.

2.4. Statistical analysis

Statistical analysis was performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The normality of data distribution was assessed by the Kolmogorovor–Smirnov test or Shapiro–Wilk test. All values are expressed as median (interquartile range), mean ± standard deviation or counts (percentage) unless otherwise specified. Comparisons were made by using (1) chi-square test or Fisher exact test for categorical data, (2) unpaired or paired Student *t* test for continuous normally distributed variables, and (3) the Mann–Whitney *U*-test for continuous non-normally distributed variables. Correlations of copeptin with traditional predictors of disease severity and mortality were assessed by Spearman's correlation coefficient. Multivariable logistic regression analyzes were performed to determine factors that could be considered as independent predictors of the local complications, organ failure, and in-hospital mortality, adjusted by confounding variables according to the results of the univariate analysis. Variables showing $P < 0.1$ in univariate analysis were included in the multivariate model. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curves was configured to establish cutoff point of plasma copeptin level that optimally predicted the local complications, organ failure, and in-hospital mortality with calculated area under curve (AUC) and 95% CI. In a combined logistic-regression model, we estimated the additive benefit of copeptin to traditional predictors of disease severity and mortality for predicting the local complications, organ failure, and in-hospital mortality. A P value <0.05 was considered significant.

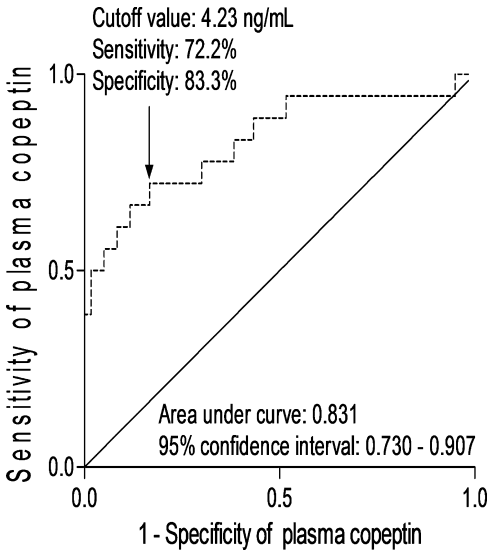

Fig. 1. Graph showing the predictive significance of plasma copeptin level for in-hospital mortality of patients. Receiver operating characteristic curve was constructed based on the sensitivity and specificity of the plasma copeptin concentration for identifying in-hospital mortality. The area under curve was calculated based on the receiver operating characteristic curve and expressed as 95% confidence interval. Area under curve ranges from 0.5 to 1.0. An area under curve closer to 1 indicates a higher predictive power.

3. Results

3.1. Patient characteristics

The main baseline characteristics of the SAP patients are summarized in Table 1. Plasma copeptin level was 3.48 ± 1.32 ng/mL (95% CI 3.18–3.77) in SAP patients, and was obviously higher than that in healthy control (0.23 ± 0.06 ng/mL; 95% CI 0.22–0.25; $P < 0.001$). Plasma copeptin level was highly associated with the APACHE II score ($r = 0.632$, $P < 0.001$), Ranson score ($r = 0.581$, $P < 0.001$), MODS ($r = 0.619$, $P < 0.001$), and SOFA score ($r = 0.513$, $P < 0.001$) using Spearman's correlation coefficient.

3.2. Mortality prediction

The overall in-hospital mortality rate was 23.1% (18 deaths). As tabulated in Table 1, higher plasma copeptin level was associated with in-hospital mortality. A multivariate analysis selected APACHE II score (OR 1.320, 95% CI 1.051–1.697; $P = 0.008$), Ranson score (OR 3.871, 95% CI 1.387–10.601; $P = 0.006$), MODS (OR 2.254, 95% CI 1.169–4.231; $P = 0.009$), SOFA score (OR 2.410, 95% CI 1.254–4.574; $P = 0.004$), and plasma copeptin level (OR 8.102, 95% CI 1.796–31.352; $P = 0.005$) as the independent predictors for in-hospital mortality.

A ROC curve identified that a plasma copeptin level >4.23 ng/mL predicted in-hospital mortality of patients with 72.2% sensitivity and 83.3% specificity (AUC, 0.831; 95% CI 0.730–0.907) (Fig. 1). The predictive value of the copeptin concentration was thus similar to those of APACHE II score (AUC, 0.885; 95% CI 0.793–0.946; $P = 0.327$), Ranson score (AUC, 0.838; 95% CI 0.737–0.912; $P = 0.921$), MODS (AUC, 0.845; 95% CI 0.745–0.917; $P = 0.823$), and SOFA score (AUC, 0.871; 95% CI 0.776–0.936; $P = 0.595$). Copeptin improved the AUCs of APACHE II score, Ranson score, MODS, and SOFA score to 0.887 (95% CI 0.795–0.947), 0.856 (95% CI 0.758–0.925), 0.858