Lefeng Zhang, Xuefeng Wang, Xiaozhen Ji and Suhua Zou*

Changes of serum neopterin and its significance as biomarker in prediction the prognosis of patients with acute pancreatitis

https://doi.org/10.1515/labmed-2020-0013
Received February 8, 2020; accepted May 27, 2020; published online July 21, 2020

Abstract

Objectives: To investigate the dynamic changes of serum neopterin and its significance as biomarker in prediction the prognosis of patients with acute pancreatitis.

Methods: 54 cases with confirmed diagnosis of acute pancreatitis were included in the present work. Of the included 54 cases, 21 were mild acute pancreatitis and other 33 were severe diseases. For the 33 severe cases, nine were finally dead and 24 were survived. The serological neopterin level of the 54 acute pancreatitis was continuously examined at the time point of days 0 (diagnosis), 1 (24 h after diagnosis), 2, 4, 8 and 14 by the enzyme linked immunosorbent assay (ELISA). The severity or death risk of the acute pancreatitis patients was predicted by the serological neopterin.

Results: The serological neopterin was gradually increasing from days 0 to 8, but descending at day 14 in mild and survival groups. For days 8 and 14, the serological levels of neopterin in severe group were higher than those of mild group with statistical difference (p<0.05). The serum neopterin was statistical different in the time point of day 8 and day 14 between death and survival groups (p<0.05). For day 8, the serological neopterin as biomarker for death prediction sensitivity and specificity were 77.78% (33.99–97.19%) and 95.83% (78.88–99.89%) respectively with the AUC of 0.94 (95% CI:0.87–1.00). For day 14, the death prediction sensitivity and specificity were 77.78% (33.99–97.19%) and 95.83% (78.88–99.89%) respectively with the AUC of 0.94 (95% CI:0.87–1.00).

Conclusions: Serological neopterin level was elevated with the development of the pancreatitis. Continuously monitoring the serum neopterin may helpful for prediction death risk of acute pancreatitis. In the later phase of disease beginning on day 8, neopterin levels may be used for risk assessment and possibly change of therapy regiment.

Keywords: acute pancreatitis; death prediction; diagnosis; neopterin; serological marker.

Introduction

Acute pancreatitis (AP) is a common and frequently diagnosed disease clinically. The clinical manifestations are quite different between mild and severe AP cases [1]. The treatment and prognosis of mild and severe cases are also quite different. Severe acute pancreatitis (SAP) had the characteristics of onset urgently, rapid progression, complex condition, multiple complications and high mortality, which require timely and urgent effective treatment [2]. Although receiving proper treatment, the mortality rate of SAP is remain about 20–30% [3–5]. Therefore, it is important to predict and evaluate the severity of AP in early stage.

In recent years, with the continuous progress of diagnosis and treatment of SAP, a variety of clinical scores and laboratory indicators that can predict the prognosis of the disease in early stage, such as Rason score, acute physiology and chronic health evaluation II (APACHE II) score, computed tomography severity index (CTSI) score, and sequential organ failure assessment (SOFA) score. The above scores for AP severity evaluation have their own advantages in clinical application, but also had their own limitations such as low sensitivity or specificity. Therefore, it is important to identify clinical markers, which are accurate, efficient, and operable with high sensitivity and specificity for AP severity or death risk prediction.

*Corresponding author: Suhua Zou
Department of Nephrology, Lishui People’s Hospital, No.15 Dazhong Road, Lishui City Zhejiang Province 32300, P.R. China, E-mail: zvd783@163.com
Leifeng Zhang: Department of Emergency, The Second People’s Hospital of Lishui, Lishui, Zhejiang, P.R. China
Xuefeng Wang: Department of Emergency, Zhuji Affiliated Hospital of Shaoxing University, Shaoxing, Zhejiang, P.R. China
Xiaozhen Ji: Department of ICU, Longquan People’s Hospital, Longquan, Zhejiang, P.R. China

Open Access. © 2020 Lefeng Zhang et al., published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.
Neopterin is a catabolic product of guanosine triphosphate (GTP) which belongs to the chemical group known as pteridines. Neopterin is one of the important markers reflecting the cellular immune state mediated by lymphocyte macrophage axis in vivo [6], and its clinical significance has been paid more and more attention. It has been confirmed that neopterin concentration was obviously elevated in serum or urine in patients with inflammatory disease [7, 8], autoimmune disease. However, the dynamic changes of serum neopterin and its significance as biomarker in prediction the prognosis of patients with AP is unclear yet.

**Materials and methods**

**Patients**

This work was approved by the Ethical Committee of the Second People’s Hospital of Lishui. The signed written informed consent was obtained from all the included subjects. 54 cases with confirmed diagnosis of AP were included in the present work. Of the included 54 cases, 21 were mild AP and other 33 were sever diseases. For the 33 severe cases, nine were finally dead and 24 were survived. The patients inclusion criteria were: (1) The age of the subjects ranged from 18 to 70 without limitation of gender; (2) AP diagnosed according to the AP Guideline [9]; and (3) Patients provide the written informed consent for the research. Exclusion criteria were: (1) Patients with a medical history of chronic pancreatitis; (2) Subjects with malignant carcinoma; (3) Pregnant women; and (4) Patients died within 14 days after diagnosis.

**Serological neopterin detection**

The serological neopterin of the 54 AP was continuously examined at the time point of days 0 (diagnosis), 1 (24 h after diagnosis), 2, 4, 8 and 14 by the enzyme linked immunosorbent assay (ELISA) (Tecan Group Ltd., Männedorf, Switzerland). Two millilitre of peripheral venous blood was taken from cases at each time points and the upper serum was separated and stored in a refrigerator at −20 °C for testing after centrifugation.

**Statistical analysis**

The data were calculated by SPSS17.0 software (SPSS, Inc., Chicago, IL, USA). The plot was drawn by Graphpad Prism 7.0 software (http://www.graphpad.com/scientific-software/prism/). The measurement data was analyzed by student-t test. Diagnostic performance was calculated according to the equation of sensitivity=true positive/(true positive + false negative), specificity=true negative/(true negative + false positive). The receiver operating characteristics (ROC) curve was used to evaluate the feasibility of serum neopterin as biomarker for AP severity or death prediction.

**Results**

**Serum neopterin levels of different time points between mild and severe groups**

The serum neopterin were tested continuously at the time points of 0 (diagnosis), day 1 (24 h after diagnosis), day 2, day 4, day 8 and day 14. The serological neopterin levels were not statistical different from days 0 to 4 between mild

![Figure 1: Scatter plot of serological neopterin level at days 8, 14 in different groups.](http://www.example.com/figure1.png)

(A) Scatter plot of serological neopterin level at day 8; (B) Scatter plot of serological neopterin level at day 14.
Death and severity prediction for neopterin as serological marker in acute pancreatitis

Due to the difference of serological neopterin between groups at the time point of days 8 and 14, the diagnostic performance of serological neopterin as biomarker for AP severity or death risk was evaluated, Table 1. For day 8, the serological neopterin as biomarker for death prediction sensitivity and specificity were 88.89% (95% CI: 51.75–99.72%) and 83.33% (95% CI: 62.62–95.26%) respectively with an area under the curve (AUC) of 0.95 (95% CI: 0.88–1.00). For day 14, the death prediction sensitivity and specificity were 77.78% (95% CI: 33.99–97.19%) and 95.83% (95% CI: 78.88–99.89%) respectively with the AUC of 0.94 (95% CI: 0.87–1.00) (Figure 3).

Discussion

In the present work, we found that the serological neopterin was gradually increased from days 0 to 8, but descending at day 14 in mild and survival groups. However, at day 14, the serum neopterin level was not obviously decreased for death group. This indicated that the serum neopterin level may maintain longer period of time for the increase trend for seriously groups. At days 8 and 14, the serological levels of neopterin in sever and death group were significant high than those of mild and survival groups with statistical difference (p<0.05). Due to the significant difference in days 8 and 14, the neopterin can be used as biomarker for death prediction. We also found that serological neopterin level was elevated with the development of the pancreatitis in the first 4 days. Continuously monitoring the serum neopterin may be helpful for prediction the disease severity and death risk for AP.

It is important to evaluate the risk factors of early death in SAP [10]. The Japanese severity score (JSS) [11], which covers 18 risk factors, is generally used to assess the severity of AP and predict the progress of AP to SAP. However, the JSS was complex for clinical application. In addition, Ranson score [12, 13], BISAP score [14], APACHE II score [15] and SOFA score

Table 1: Diagnosis performance of serum neopterin as biomarker for acute pancreatitis severity and death prediction.

| Diagnosis | Sensitivity (95% CI) | Specificity (95% CI) | AUC (95% CI) | Cut off |
|-----------|----------------------|----------------------|--------------|--------|
| Severity  |                      |                      |              |        |
| Day 8     | 63.64% (45.12–79.63%)| 66.67% (43.03–85.41%)| 0.68 (0.54–0.82%) | 7.69   |
| Day 14    | 69.70% (51.29–84.41%)| 61.90% (38.44–81.89%)| 0.72 (0.59–0.86%) | 5.56   |
| Death     |                      |                      |              |        |
| Day 8     | 88.89% (51.75–99.72%)| 83.33% (62.62–95.26%)| 0.95 (0.88–1.00%) | 10.34  |
| Day 14    | 77.78% (33.99–97.19%)| 95.83% (78.88–99.89%)| 0.94 (0.87–1.00%) | 11.91  |
system were also applied for severity evaluation in patients with AP, but with their own limitations such as low sensitivity or low specificity. In addition, for clinical practice, it was found that the above scoring systems are complex and cumbersome with limited clinical application.

The mortality rate of SAP is high. According to the AP guideline, the mortality rate of AP patients was less than 10% [17]. However, the mortality rate of SAP patients was as high as 36–50% [18].

In the present work, 33 patients with SAP died in nine cases, the mortality rate was 27.3%, which was consistent with the previous publications. The prognosis of patients with SAP is complicated. The high mortality rate is mainly caused by uncontrollable systemic or local inflammation leading to systemic inflammatory response syndrome (SIRS), which leads to multiple organ failure and death. This situation mostly occurs in the early stage (within 2 weeks), so most of the clinical deaths occur about 2 weeks after diagnosis.

At present, sepsis, septic shock and multiple organ dysfunction syndromes are considered to be the dynamic process of pathophysiological changes and clinical severity changes of severe pancreatitis [19, 20]. The essence is that the body’s systemic inflammatory response continues to intensify and worsen, and the balance between the metabolic anti-inflammatory responses is destroyed, which is one of the main causes of the occurrence and death of the severe acute pancreas [21, 22]. Neopterin can promote the synthesis and participates in the pathological process of inflammatory reaction [23]. Ci et al. found that the serum neopterin level of trauma patients and critical ill patients was higher than that of the healthy controls and serum neopterin level was positively correlated with the severity of the disease [24]. Studies have demonstrated that serum neopterin levels in patients with sepsis were elevated and can be used as a promising biomarker for multiple organ dysfunction syndrome (MODS) diagnosis in patients with sepsis [25–27]. In our work, the findings demonstrated that serum neopterin may reflect the severity of AP at a late stage and may be a potential serological maker for death prediction, which was in accordance with the previous studies. However, patients died within 14 days were not included and analyzed. The serum neopterin may be elevated more early in early death patients. Another limitation was that disease severity prediction sensitivity and specificity were not high, which indicated that measuring of neopterin in the beginning may not change any clinical decision. Therefore, combination of several makers included scores such as Ranson score, APACHE II score, Glasgow score and serum neopterin may improve the death prediction value. Therefore further, studies of comprehensive analysis of inflammatory biomarkers and clinical scores are need.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The work was approved by the Ethical Committee of the Second People’s Hospital of Lishui.

References

1. Group of Pancreas Surgery, Chinese Society of Surgery, Association CM. The guideline of diagnosis and treatment of severe acute pancreatitis. Zhonghua Wai Ke Za Zhi 2007;45:727–9.
2. Greenberg JA, Hsu J, Bawazeer M, Marshall J, Friedman JO, Nathens A, et al. Clinical practice guideline: management of acute pancreatitis. Can J Surg 2016;59:128–60.
3. Rohan Jeyarajah D, Osman HG, Patel S. Severe acute pancreatitis attacks are associated with significant morbidity and mortality. Curr Probl Surg 2014;51:370–2.
4. Amálio SM, Macedo MA, Carvalho SM, Moreno RP. Mortality assessment in patients with severe acute pancreatitis: a comparative study of specific and general severity indices. Rev Bras Ter Intensiva 2012;24:246–51.
5. Shêiko VS, Panasenko SI, Dolzhkovyi SV. Mortality analysis in acute severe pancreatitis using objective assessment of the patient state severity and polyorgan dysfunction. Klin Khir 2011:25–7.
6. Brown AE, Webster HK, Teja-Isavadharm P, Keeratithakul D. Macrophage activation in falciparum malaria as measured by neopterin and interferon-gamma. Clin Exp Immunol 1990;82:97–101.
7. Kaufmann P, Tilz GP, Demel U, Wachter H, Kreijs GJ, Fuchs D. Neopterin plasma concentrations predict the course of severe acute pancreatitis. Clin Chem Lab Med 1998;36:29–34.
8. Uomo G, Spada OA, Manes G, Feola B, Misso S, Cavallera A, et al. Neopterin in acute pancreatitis. Scand J Gastroenterol 1996;31:1032–6.
9. Crockett S, Falck-Ytter Y, Wani S, Gardner TB. Acute pancreatitis guideline. Gastroenterology 2018;154:1102.
10. Bota S, Sporea I, Sirli R, Popescu A, Strain M, Focsâ M, et al. Predictive factors for severe evolution in acute pancreatitis and a new score for predicting a severe outcome. Ann Gastroenterol 2013;26:356–62.
11. Ikeura T, Horibe M, Sanui M, Sasaki M, Kuwagata Y, Nishi K, et al. Validation of the efficacy of the prognostic factor score in the Japanese severity criteria for severe acute pancreatitis: a large multicenter study. European Journal of Gastroenterol HEPATOL 2017;5:389–97.
12. Valverde-López F, Matas-Cobos AM, Alegria-Motte C, Jiménez-Rosales R, Úbeda-Muñoz M, Redondo-Cerezo E., BISAP, RANSON, lactate and others biomarkers in prediction of severe acute pancreatitis in a European cohort. J Gastroenterol Hepatol 2017;32:1649–56.
13. Echempati SR, Hydo LJ, Barie PS. Severity scoring for prognostication in patients with severe acute pancreatitis: comparative analysis of the Ranson score and the APACHE III score. Arch Surg 2002;137:730–6.
14. Arif A, Jaleel F, Rashid K. Accuracy of BISAP score in prediction of severe acute pancreatitis. Pak J Med Sci 2019;35:1008–12.
15. Escobar-Arellano R, Guraieb-Barragán E, Mansanares-Hernández A, Sánchez-Valdivieso EA. Sensitivity, specificity and reliability of the POP score vs. APACHE II score as predictors of severe acute biliary pancreatitis. Cir Cir 2019;87:402–9.
16. Tee YS, Fang HY, Kuo IM, Lin YS, Huang SF, Yu MC. Serial evaluation of the SOFA score is reliable for predicting mortality in acute severe pancreatitis. Medicine (Baltimore) 2018;97:e9654.
17. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013;108:1400–15. https://doi.org/10.1038/ajg.2013.218.1416.
18. Hirata K, Mayumi T, Ohtsuki M, Matsuno S, Takada T. Clinical guideline of acute pancreatitis based on evidences. Nihon Shokakibyo Gakkai Zasshi 2003;100:965–73.
19. John BJ, Sambandam S, Garg P, Singh G, Kaur M, Baskaran R, et al. Persistent systemic inflammatory response syndrome predicts the need for tertiary care in acute pancreatitis. Acta Gastroenterol Belg 2017;80:377–80.
20. Ni Q, Zhang W, Sun K, Yin C, An J, Shang D. In vitro effects of emodin on peritoneal macrophage intercellular adhesion molecule-3 in a rat model of severe acute pancreatitis/systemic inflammatory response syndrome. Biomed Rep 2014;2:63–8.
21. Nauca PC, Weinstein TA, Dolinger MT, Miller JM, Kohn N, Bitton S, et al. Validation of lipase and systemic inflammatory response syndrome as prognostic indicators in pediatric acute pancreatitis: a retrospective analysis. J Pediatr Gastroenterol Nutr 2019;68:389–93.
22. Jain S, Midha S, Mahapatra SJ, Gupta S, Sharma MK, Nayak B, et al. Interleukin-6 significantly improves predictive value of systemic inflammatory response syndrome for predicting severe acute pancreatitis. Pancreatology 2018;18:500–6. https://doi.org/10.1016/j.pan.2018.05.002. May 14.
23. Yasar M, Uysal B, Kaldırımı U, Oztas Y, Sadır S, Ozler M, et al. Poly(ADP-ribose)-polymerase inhibition modulates experimental acute necrotizing pancreatitis-induced oxidative stress, bacterial translocation and neopterin concentrations in rats. Exp Biol Med (Maywood) 2010;235:1126–33.
24. Xiong W, Ouyang J, Li H, Jiang W, Han W, Fu Y, et al. The predictive value of serum neopterin for multiple organ dysfunction syndrome in severe burn patients. Pteridines 2018;29:196–200.
25. Zhang X, Chen Q, Ni S, Xiang Z, Zhou X, Huang Y. Serum neopterin and its significance as biomarker in differentiation of MODS from sepsis. Pteridines 2018;29:201–5.
26. Strohmaier W, Redl H, Schlag G, Inthorn D. D-erythro-neopterin plasma levels in intensive care patients with and without septic complications. Crit Care Med 1987;15:757–60.
27. Pellegrini K, Neurauteur G, Wirlleton B, Fleming AW, Peterson VM, Fuchs D. Enhanced enzymatic degradation of tryptophan by indoleamine 2,3-dioxygenase contributes to the tryptophan-deficient state seen after major trauma. Shock 2005;23:209–15.