Predictive value of pentraxin-3 on disease severity and prognosis in patients with hemorrhagic fever with renal syndrome

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Abstract

Background: Pentraxin-3 is an acute-phase protein involved in the processes of inflammation and infection. This study aimed to analyze the changes of plasma pentraxin-3 prospectively and evaluate its predictive value on disease severity and prognosis in patients with hemorrhagic fever with renal syndrome (HFRS).

Methods: A total of 105 HFRS patients were enrolled in this study and were grouped according to the clinical classification criteria for HFRS, and 27 healthy volunteers served as controls. The levels of plasma pentraxin-3 were detected using the enzyme linked immunosorbent assay (ELISA), and which were compared among the acute and convalescent phases in different types of patients, as well as the control group. Spearman correlation analysis was used to evaluate the correlation between pentraxin-3 and conventional laboratory indexes. The predictive effectiveness for prognosis of pentraxin-3 was evaluated by receiver operating characteristic (ROC) curve analysis.

Results: There was no significant difference in gender and age distribution between all types of patients and control group ($P>0.05$). In all types of patients, the levels of pentraxin-3 in acute phase were significantly higher than that of control group and convalescent phase of the same type ($P<0.05$). The levels of pentraxin-3 increased with the aggravation of the disease, and showed the highest expression in critical-type patients ($P<0.05$). Pentraxin-3 was positively correlated with WBC, AST and APTT, and negatively correlated with PLT, ALB and Fib ($|r_s|>0.500$, $P<0.001$). Pentraxin-3 showed significant predictive value for the prognosis of HFRS patients, with the area under ROC curve (AUC) of 0.753 (95% CI: 0.593~0.914, $P=0.003$).

Conclusions: The detection of plasma pentraxin-3 can be beneficial to the evaluation of disease severity and prognosis in patients with HFRS.

Background

Hemorrhagic fever with renal syndrome (HFRS) is a kind of natural focus disease caused by Hantavirus infection, which is characterized by fever, hemorrhage and renal impairment [1]. Hantavirus infection could induce the destruction of vascular endothelial cells [2], the diffuse damage of systemic microvessels, the increase of capillary permeability, and the decrease of platelets [3]. Patients with intemperate immunoreaction may further develop “capillary leakage syndrome”, which could result in secondary edema, hypovolemic shock, acute kidney injury (AKI), coagulation disorder, and even multiple organ dysfunction syndrome (MODS) [4]. It has been accepted that HFRS has immunopathological features of systemic inflammatory response syndrome (SIRS) [5]. The early diagnosis and disease severity assessment may help the clinicians to choose the best therapeutic schedule for patients and finally improve the therapeutic effect of patients with HFRS [6]. Given the limited predictive value of conventional laboratory parameters, it is necessary to explore novel biomarkers for disease severity and prognosis in patients with HFRS.

As the first long-pentraxin discovered by human, pentraxin-3 is mainly produced by monocyte macrophages and myeloid dendritic cells stimulated by pro-inflammatory signals such as IL-1 β , TNF- α and Toll-like receptor activation, as well as the secretion of neutrophils, lymphocytes, and endothelial cells [7]. Pentraxin-3 plays an important role in innate humoral immune response, inflammatory response, anti-infection, as well as tissue damage and repair [8]. Many previous studies have shown that the level of plasma pentraxin-3 is positively related to the severity of sepsis, acute pancreatitis, acute myocardial injury and other diseases, which can be served as a new biomarker for inflammation, infection and tissue damage [9–13]. Additionally, the over-expressed pentraxin-3 of neutrophils may be associated with the overproduction of reactive oxygen species (ROS) and vascular endothelial dysfunction, and which may represent an emerging biomarker for the progression of vascular injury in patients with hemodialysis [14]. Laine et al [15] showed that plasma pentraxin-3 was highly correlated with PLT, Fib, APTT and other coagulation indicators in patients with acute Puumala virus infection, and which got a favorable predictive value for the severity of epidemic nephropathy patients. However, the role of pentraxin-3 in HFRS caused by Hantaan virus infection has not been reported. Given the above research background, we prospectively analyzed the changes of plasma pentraxin-3 in patients with HFRS, and investigated its predictive value for disease severity and prognosis (death) of HFRS.

Methods

Study Population

A total of 105 patients with HFRS admitted by the Second Affiliated Hospital of Air Force Medical University from October 2012 to December 2014 were randomly enrolled in this study. All patients were confirmed by serological examination with the positive results of specific IgM and IgG antibodies against Hantaan virus in the acute phase. The assay was performed using IgM/IgG capture ELISA kits and was analyzed via a multifunctional autoanalyzer (BIORAD-680, United States). Patients with chronic kidney diseases, diabetes, cardiovascular diseases, hematological diseases, autoimmune diseases, viral hepatitis and other liver diseases were excluded. Data of demographic, laboratory and clinical outcomes were reviewed and extracted by two physicians who had been treating HFRS patients from the electronic medical records, and which confirmed independently by at least two researchers. In addition, we recruited 27 healthy volunteers as controls. The study was approved by the ethics committee of the Second Affiliated Hospital of Air Force Medical University. Before inclusion, the patients and healthy volunteers were informed about the objectives of this study, and they or their guardians agreed and signed the informed consent form.

Procedures and Definitions

According to the clinical classification criteria of HFRS [18], all enrolled patients were divided into the following four groups: (1) mild-type: patients with mild renal impairment without oliguria and hypotension; (2) moderate-type: patients with obvious symptoms of effusion (bulbar conjunctiva),

hypotension, hemorrhage (skin and mucous membranes), and AKI with a typical oliguria stage; (3) severe-type: patients with severe uremia, effusion (bulbar conjunctiva and either peritoneum or pleura), hemorrhage (skin and mucous membranes), hypotension, and AKI with oliguria (urine output 100~500 mL/day) ≤ 5 days or anuria (urine output <100 mL/day) ≤ 2 days; (4) critical-type: patients with one or more of the following complications compared with the severe-type patients: refractory shock (≥ 2 days), visceral hemorrhage, heart failure, pulmonary edema, brain edema, severe secondary infection, and severe AKI with either oliguria (urine output 100~500 mL/day) >5 days or anuria (urine output <100 mL/day) >2 days. The classification of all patients was confirmed by their attending physicians respectively. Based on the classically defined five stages of HFRS [19], the clinical course was divided into the acute phase (including the febrile, hypotensive, and oliguric stages) and the convalescent phase (including the diuretic and convalescent stages). The patients received a follow-up visit until 28 days after discharge, and the death in this study was defined as patient died during hospitalization or the follow-up period.

Blood samples and the detection of pentraxin-3

Under sterile conditions, 96 venous blood samples in acute phase and 65 in convalescent phase from the enrolled patients, and 27 from healthy volunteers were collected by ethylene diamine tetraacetic acid (EDTA) tubes. All specimens were collected on an empty stomach in the morning, and were centrifuged at 3000 rpm for 10 min at 4 °C within 2 hours after drawing. The plasma supernatant was pipetted carefully and transferred to polypropylene tubes, and then stored at -80 °C prior to analysis. To avoid the experimental errors caused by repeated freeze-thaw of plasma, all specimens were tested together after collection.

Pentraxin-3 levels were measured with commercially available ELISA kits (Quantikine, XiTang Inc., Shanghai, China) and were tested using a multifunctional autoanalyzer (BIORAD-680, United States) according to the manufacturer's instructions. Each sample was detected in duplicate. The sensitivity of the minimum concentration of pentraxin-3 was between 0.008ng/mL and 0.116ng/mL. According to the difference of clinical typing, some samples of the patients were further taken multiple dilutions according to 1:2, 1:4, 1:16, 1:32 and 1:64, and finally selected the reasonable detection results.

Statistical analysis

Continuous variables of normal distribution and non-normal distribution were presented as mean $\pm$ standard deviation and median (interquartile range) respectively, and were compared by one-way analysis of variance (one-way ANOVA) and Kruskal-Wallis H test, respectively. The categorical variables were presented as numbers (percentage) and compared by chi-square test. The levels of pentraxin-3 in acute phase and convalescent phase were compared by Wilcoxon matched-pairs signed-ranks test. Spearman

correlation analysis was used to evaluate the correlation between pentraxin-3 and conventional laboratory indexes. The predictive efficacy of pentraxin-3 for the prognosis (death) of patients with HFRS was evaluated by the receiver operating characteristic (ROC) curve analysis and quantified by the area under ROC curve (AUC). A two-sided $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 23.0).

Results

Clinical typing and demographic characteristics of the enrolled patients

There were a total of 105 patients with a mean age of 41.85 ± 15.35 years enrolled in this study, including 21 (20.0%) females and 84 (80.0%) males. According to the grouping criteria mentioned above, 17 cases were classified as mild-type, 27 cases were classified as moderate-type, 26 cases were classified as severe-type, and 35 cases were classified as critical-type. Of all the enrolled patients, 14 (13.3%) critical patients were died and the rest were recovered and discharged. There was no significant difference in gender and age distribution between all types of patients and the control group ($P > 0.05$) (Table 1).

Levels of plasma pentraxin-3 in patients with HFRS

In all types of patients, the levels of pentraxin-3 in acute phase were significantly higher than that of control group and convalescent phase of the same type ($P < 0.05$). The levels of pentraxin-3 had an increasing tendency with the aggravation of the disease, and showed the highest expression in critical-type patients ($P < 0.05$). The comparison of pentraxin-3 during the convalescent phase among the four types demonstrated no significant difference ($P < 0.05$) (Table 2 and Figure 1).

The correlation between pentraxin-3 and conventional laboratory indexes

The results of spearman correlation analysis showed that pentraxin-3 was positively correlated with WBC, AST and APTT, and negatively correlated with PLT, ALB and Fib ($|r_s| > 0.500$, $P < 0.001$) (Table 3 and Figure 2).

Predictive efficacy of pentraxin-3 for the prognosis (death) in patients with HFRS

The results of ROC curve analysis demonstrated obvious predictive value of pentraxin-3 for the prognosis (death) of patients with HFRS, and which with the AUC of 0.753 (95%CI: 0.593~0.914, $P = 0.003$). The sensitivity and specificity of pentraxin-3 for predicting the prognosis (death) was 71.4% and 80.5%, respectively (Table 4 and Figure 3).

Discussion

After infection with Hantavirus, the human body could develop a strong and rapid immune response characterized by the hyperactivity of immune cells and the flooding of cytokines, so as to the damage of vascular endothelium and visceral organs [1-6]. As one of the most important immune cells in innate immunity, neutrophils play a crucial part in resisting bacterial infection. Nevertheless, the neutrophil counts are also elevated in most HFRS patients triggered by the Hantavirus infection, and which are also positively correlated with the disease severity of HFRS [18, 20]. Therefore, neutrophils may also play an important role in the immunopathological injury of HFRS. Pentraxin-3 synthesized by neutrophils is mainly stored in neutrophil granules, which can interact with a variety of bacteria, fungi and viruses after release and then propel the phagocytosis and clearance of pathogenic microorganisms [21]. As an important component of innate humoral immunity, pentraxin-3 has the ability to bind complement component C1q and then activate the classical pathway of complement [22, 23]. Recently, many studies have showed that pentraxin-3 could modulate inflammatory cells, interact with P-selectin, reduce the nitric oxide (NO) synthesis of endothelial cells, inhibit endothelial cells proliferation and alter their functions, and finally promote vascular inflammatory response and endothelial dysfunction [24, 25]. Therefore, the release of pentraxin-3 by neutrophil degranulation may be an important link in the immunopathological injury of HFRS, and the level of plasma pentraxin-3 may indirectly reflect the severity of vascular endothelial injury in patients with HFRS.

In present study, the results have showed that the levels of pentraxin-3 in acute phase were significantly higher than that of control group and convalescent phase of the same type, and had an increasing tendency with the aggravation of HFRS. In addition, the level of plasma pentraxin-3 was highly correlated with WBC, PLT, AST, ALB, APTT, Fib and other conventional laboratory indexes, which is consistent with the findings of pentraxin-3 in nephropathia epidemica [17]. The above findings indicate that pentraxin-3 can serve as an early predictor for the disease severity of HFRS. The results of ROC curves analysis demonstrated the significant predictive value of pentraxin-3 for the prognosis (death) of patients with HFRS, which was comparable with the predictive value of conventional laboratory indexes such as PLT. Therefore, pentraxin-3 could serve as a novel and efficient biomarker for predicting the disease severity and prognosis of patients with HFRS. The detection of plasma pentraxin-3 may help clinicians quickly identify the severe patients at an early stage and timely take optimal therapeutic schedule for them, so as to improve the therapeutic effect of patients with HFRS.

As an observational prospective study, although we got a meaningful conclusion that the detection of plasma pentraxin-3 might be beneficial to evaluating the disease severity and prognosis of the HFRS patients, while there were still some limitations as following: First, this study was conducted in a single center for infectious diseases. The results might be limited by the relatively small sample size because of the gradually declining incidence of HFRS in Xi'an city. Because some patients had tided over the acute phase on admission and only convalescence samples available, and the decedent had died before

entering the convalescence phase, so in fact, only 96 venous blood specimens in acute phase and 65 in convalescence phase were collected from the enrolled patients during hospitalization. All these adverse factors may affect the accuracy of the research results. Second, the definition of blood sample collection time of HFRS patients was too broad in this study. Given to the individual differences of patients' condition and the clinical process on admission, we could only randomly collect venous blood specimens according to the acute phase and convalescence phase defined in the study. Although there was no significant statistical difference in the median collection time of all samples in the acute phase, the level of plasma pentraxin-3 was also influenced by the different time-points and the variability of pathological injury during the acute phase of Hantaan virus infection. Third, it is essential to conduct a prospective, large sample, multicenter cohort study to further confirm the predictive efficacy and clinical application value of plasma pentraxin-3 in acute phase. Last but not least, the research limitations caused by the experimental measurement errors and the outdated clinical typing criteria should not be overlooked.

Conclusions

The detection of plasma pentraxin-3 might be beneficial to the evaluation of disease severity and prognosis in patients with HFRS, which could help clinicians quickly identify the severe patients at an early stage and timely take optimal therapeutic schedule for them, so as to improve the therapeutic effect of patients with HFRS.

Abbreviations

HFRS: Hemorrhagic fever with renal syndrome; AKI: Acute kidney injury; MODS: Multiple organ dysfunction syndrome; SIRS: Systemic inflammatory response syndrome; ROS: Reactive oxygen species; EDTA: Ethylene diamine tetraacetic acid; ELISA: Enzyme linked immunosorbent assay; ANOVA: Analysis of variance; ROC curve: Receiver operating characteristic curve; AUC: Area under the ROC curve; WBC: White blood cells; PLT: Platelet; AST: Aspartate aminotransferase; ALB: Albumin; APTT: Activated partial thromboplastin time; Fib: Fibrinogen.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of the Second Affiliated Hospital of Air Force Medical University and was performed in accordance with the Helsinki Declaration. Before inclusion, the patients and healthy volunteers were informed about the objectives of this study, and they or their guardians agreed and signed the informed consent form.

Consent for publication

Written informed consents were obtained from all patients or their guardians and the healthy volunteers.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JQL and XFB conceived and designed the study and had full access to all of the data in the study, and they take responsibility for the integrity of the data and the accuracy of the data analysis. HD, XYW and JL collected the venous blood samples and detected the levels of plasma pentraxin-3 using the ELISA test. HFH and XYW collected the clinical data of all enrolled patients. HFH and HD conducted the statistical analysis and manuscript drafting. PZW, YZ, HJ, XFB and JQL reviewed the manuscript and made critical revision. All authors have made substantial contributions to this study, and all of them read and approved the final manuscript.

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Figures

Figure 1

Levels of plasma pentraxin-3 during the clinical course in patients with HFRS. The levels of plasma pentraxin-3 in acute phase (A) and convalescent phase (B) were compared by Kruskal-Wallis H test; pairwise comparisons among the five groups were performed using the Nemenyi rank test. The differences of plasma pentraxin-3 between acute phase and convalescent phase of the mild-type (C1), the moderate-type (C2), the severe-type (C3), and the critical-type (C4) were compared by Wilcoxon matched-pairs signed-ranks test. * $P < 0.05$

Figure 2

The correlation between pentraxin-3 and conventional laboratory parameters Figure shows the correlation between pentraxin-3 and WBC (A), PLT (B), ALB (C), AST (D), APTT (E), Fib (F). Spearman rank correlation analysis was used to evaluate the correlation between pentraxin-3 and conventional laboratory parameters. Abbreviations: WBC, White blood cells; PLT, Platelet; AST, Aspartate aminotransferase; ALB, Albumin; APTT, Activated partial thromboplastin time; Fib, Fibrinogen

Figure 3

ROC curves for evaluating the predictive efficacy of pentraxin-3 and conventional laboratory parameters. Figure shows the predictive efficacy of pentraxin-3, AST, PLT, WBC, and ALB for the prognosis (death) in patients with HFRS. Pentraxin-3 showed significant predictive value, with the AUC of 0.753 ($P=0.003$). Abbreviations: ROC curve, Receiver operating characteristic curve; AUC, Area under the ROC curve; WBC, White blood cells; PLT, Platelet; AST, Aspartate aminotransferase; ALB, Albumin