Procalcitonin and C-reactive protein levels as biomarkers to determine gastrointestinal involvement in adult Henoch-Schönlein purpura patients

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ABSTRACT

Objective: To investigate the association of procalcitonin (PCT) and C-reactive protein (CRP) levels with gastrointestinal (GI) involvement in adult Henoch-Schönlein purpura (HSP) patients.
Method. A retrospective study using clinical data and serum PCT and CRP levels from 121 adult HSP patients was performed.
Results: The proportion of male HSP patients with GI involvement was significantly higher compared to patients without GI involvement. PCT and CRP levels in adult HSP patients with GI involvement were higher compared to patients without GI involvement ($P<0.05$); Among the patients with GI involvement, those with GI hemorrhage had significant higher PCT and CRP levels ($P<0.05$); the median PCT value was lower compared to the threshold value for systemic infection. There was a positive correlation between PCT and CRP levels in HSP patients with GI involvement and GI bleeding ($P<0.05$). ROC curve analysis demonstrated that the PCT and CRP cutoff levels of 0.07 ng/ml and 29.35 mg/L respectively had optimal diagnostic efficacy for GI bleeding in adult HSP patients.
Conclusion: Elevated serum PCT and CRP levels were significantly associated with GI involvement in adult HSP patients, especially for GI bleeding. PCT levels correlated well with CRP levels.

Keywords: Purpura Henoch-Schönlein; Gastrointestinal tract; Hemorrhage; Procalcitonin; C-Reactive Protein.

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INTRODUCTION

Henoch-Schönlein purpura (HSP) is an extensive systemic vasculitis that mainly occurs in children, however its manifestation is not uncommon in adults. It is characterized by vascular deposits of IgA-dominant immune complexes and leukocytoclasia. The exact pathogenesis is still unclear but is considered to be an immune-related inflammatory disease. The typical clinical manifestation is non-platelet-reducing palpable purpura. It can affect the joints, kidneys and gastrointestinal tract. The majority of the cases are benign, but severe organ involvement can occur. Gastrointestinal (GI) involvement is generally an acute onset, which generaly manifests with as abdominal cramps, but in severe cases, GI bleeding could occur. A small number of patients may manifest intussusception, infarction or perforation.

Procalcitonin (PCT), a precursor of calcitonin, is a sensitive biomarker for diagnosing systemic bacterial infections and assessing its severity. Its levels are extremely low in healthy individuals. C-reactive protein (CRP) is an acute phase protein that is significantly elevated during acute infections and stress. However, several recent studies have demonstrated that PCT levels are elevated in some non-infectious inflammatory diseases[1-9]. A previous study demonstrated that PCT levels were higher in children with HSP who had renal damage compared to those without renal damage[10]. Several studies have also demonstrated that HSP patients with GI symptoms or GI bleeding had elevated CRP levels[7-9]. However, there are only a few studies regarding PCT levels in HSP patients with GI involvement, especially among adult patients. If PCT and CRP can be used as biomarkers for predicting GI involvement or GI bleeding in adult HSP patients, testing them can help doctors detect and monitor patients at risk as early as possible.

In this study we retrospectively analyzed the changes

in PCT and CRP levels in hospitalized adult HSP patients with GI involvement.

PATIENTS AND METHODS

PATIENTS

Adult HSP patients who were hospitalized in the dermatology department in Sichuan Provincial people's hospital between January 2013 and April 2017 were included in this study. Diagnosis of the disease was based on the European League against Rheumatism/Pediatric Rheumatology European Society (EULAR/PReS) diagnostic criteria for HSP[11]. Patient exclusion criteria were as follows: 1 - with other serious systemic diseases, acute or chronic systemic infections, other immune system diseases, malignant tumors; 2 - use of glucocorticoids and/or immunosuppressive agents in the last 4 weeks; 3 - bacterial infections of the gastrointestinal tract; 4 - severe trauma and surgery in the last 4 weeks; 5 - patients lacking PCT and CRP data. If the patient developed GI symptoms such as nausea, vomiting, abdominal pain, diarrhea, melena and excluded gastrointestinal organic changes, the patients were considered to have GI involvement; GI hemorrhage was present if the fecal occult blood test was positive for three consecutive tests and/or appeared as black and/or red watery stools (was evaluated based on food consumed and drug factors confounding the readings). The study was approved by the hospital's research ethics committee.

Based on the presence or absence of GI involvement, 121 patients were divided into the GI involvement group and the non-GI involvement group. Patients with GI involvement were further divided into the GI bleeding group and the non-bleeding group.

CLINICAL DATA AND PCT/CRP MEASUREMENTS

This study was a single-center retrospective analysis. The general characteristics, clinical manifestations and laboratory data of all patients were retrieved from the hospital's inpatient medical records database. PCT levels were measured using the enzyme-linked immunofluorescence assay, which had a detection limit of 0.05 ng/ml. Nephelometry immunoassay was used to measure CRP levels, with levels<0.5 mg/L defined as the reference range for healthy individuals.

STATISTICAL ANALYSIS

Data were analyzed using the SPSS version 20.0 (SPSS, Inc., Chicago, Illinois, USA). All quantitative variables conforming to normal distribution were expressed as mean±standard deviation and skewed distribution data were expressed as median (range). Independent sample *t*-tests were used to compare differences in quantitative data conforming to normal distribution between two groups; while Mann Whitney *U* test was used to compare differences between two independent samples that did not conform to normal distribution. Chi-square test was performed to determine count data. Correlation was evaluated using Spearman correlation analysis. Two receiver operating characteristic (ROC) curves were plotted to evaluate the diagnostic performance of PCT and CRP with respect to GI bleeding in adult HSP patients. $P<0.05$ was considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

One hundred and twenty-one patients were enrolled in this study and included 76 males and 45 females with the male to female ratio 1.69:1. Patient age ranged from 16 to 79 (32.50±17.47) years. All the patients had palpable purpura. Sixty-one patients (50.41%) had GI tract symptoms, 32 patients (26.45%) had arthritis/ /arthralgia and 21 patients (17.36%) had kidney damage. Based on the grouping criteria described previously, there were 61patients in the GI involvement group and 60 patients in the non-GI involvement group. For the 61 patients with GI involvement, 34 were in the GI bleeding group and 27 were in the non-bleeding group. The number of males in the GI involvement group was higher compared to the non-GI involvement group ($P<0.05$). There were no significant differences in age between the two groups. There were no significant differences in age and gender between the GI bleeding group and the non-bleeding group.

COMPARISON OF PCT AND CRP LEVELS BETWEEN THE GI INVOLVEMENT GROUP AND NON-GI INVOLVEMENT GROUP

PCT levels in the GI involvement group and non-GI involvement group were 0.08 (0.05~1.76) ng/ml and 0.05(0.05~0.11) ng/ml, respectively. CRP levels in the two groups were 18.90 (0.50~157.40) mg/L and 3.20(0.20~92.97) mg/L, respectively. PCT and CRP levels were both significantly higher in the GI involvement group compared to the non-GI involvement group ($P<0.05$) (Table I).

TABLE I. COMPARISON OF PCT AND CRP LEVELS BETWEEN THE GI INVOLVEMENT GROUP AND NON-GI INVOLVEMENT GROUP

Parameters	GI involvement group (n=61)	non-GI involvement group (n=60)	χ^2/t/Z	P-value
Age (years)	30.10±16.19	34.93±18.52	t=1.530	0.129
Gender (male/female)	47/14	29/31	χ^2=10.678	0.001
CRP (mg/L)	18.90 (0.50~157.40)	3.20 (0.20~92.97)	Z=-4.763	0.000
PCT (ng/ml)	0.08 (0.05~136)	0.05 (0.05~0.11)	Z=-5.515	0.000

GI: gastrointestinal; CRP: C-reactive protein; PCT: procalcitonin

TABLE II. COMPARISON OF PCT AND CRP LEVELS BETWEEN THE GI BLEEDING GROUP AND NON-GI BLEEDING GROUP

Parameters	GI involvement group (n=34)	non-GI involvement group (n=27)	χ^2/t/Z	P-value
Age (years)	29.71±16.23	30.63±16.39	t=0.220	0.827
Gender (male/female)	28/6	19/8	χ^2=1.222	0.269
CRP (mglL)	34.77 (0.50~74.20)	9.21 (0.50~157.40)	Z=-3.602	0.000
PCT (ng/ml)	0.13 (0.05~1.76)	0.05 (0.05~0.59)	Z=-3.259	0.001

GI: gastrointestinal; CRP: C-reactive protein; PCT: procalcitonin.

COMPARISON OF PCT AND CRP LEVELS BETWEEN THE GI BLEEDING AND NON-GI BLEEDING SUBGROUPS FOR PATIENTS WITH GI INVOLVEMENT

In the GI bleeding group, PCT and CRP levels were significantly elevated compared to patients in the non-GI bleeding group [0.13(0.05~1.76) vs. 0.05(0.05~0.59), 34.77(0.50~74.2) vs. 9.21(0.50~157.4), P<0.05] (Table II).

CORRELATION BETWEEN PCT AND CRP LEVELS IN ADULT HSP PATIENTS WITH GI INVOLVEMENT AND GI BLEEDING

There was a significant positive correlation between PCT and CRP levels in HSP patients with GI involvement (r=0.498, P<0.05) (Figure 1a). PCT and CRP levels were also positively correlated in HSP patients with GI bleeding (r=0.403, P<0.05) (Figure 1b).

DIAGNOSTIC EFFICACY OF PCT AND CRP LEVELS FOR GI BLEEDING IN ADULT HSP PATIENTS

Two ROC curves were plotted to evaluate the diagnostic performance of PCT and CRP for GI bleeding in adult HSP patients. With 1-specificity as the x-axis and sensitivity as the y-axis, the areas under the curves for PCT and CRP were 0.819 and 0.816 with 95% CI (0.725-0.913) and (0.727-0.906), respectively (P<0.05). The cutoff value for PCT was 0.07ng/ml, where sensitivity (73.5%) and specificity (86.2%) had the best combination. The optimal cutoff value for CRP was 29.35mg/L, with sensitivity and specificity of 64.7% and 94.3%, respectively.

DISCUSSION

Henoch-Schönlein purpura (HSP) is an immune-mediated systemic leukocytoclastic small-vessel vasculitis. The specific pathogenesis is complex and has not yet been fully elucidated. It is hypothesized that the abnormal immune system and dysregulated immune-inflammatory response maybe the key pathogenic mechanism for HSP[12-13]. Multiple organs and systems may be affected in HSP patients, with GI involvement (especially GI bleeding) being a serious complication. In the majority of previous studies, the incidence of HSP in male patients was higher compared to females[14-15], however there have been no specific epidemiological studies to confirm these results, especially for HSP patients with GI involvement. Our retrospective study found that in adult HSP patients with GI involvement,

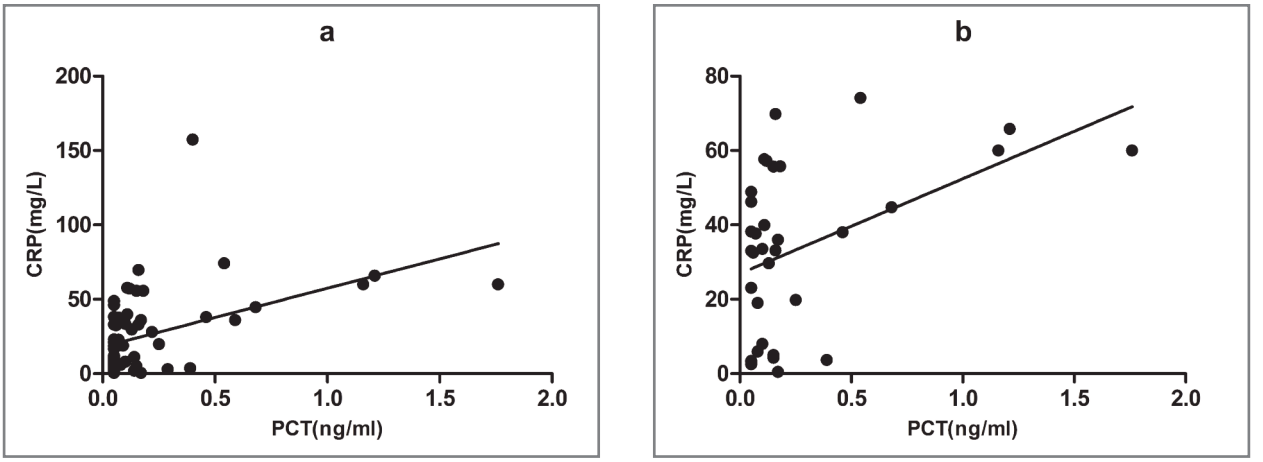

FIGURE 1. Correlation between Procalcitonin (PCT) and C-reactive protein (CRP) levels in adult Henoch-Schönlein purpura (HSP) patients with gastrointestinal (GI) involvement (a) and GI bleeding (b)

the number of male patients was significantly higher compared to patients without GI involvement. Whether male patients are more prone to GI symptoms needs confirmation using larger cohorts. Compared to children, adult patients have a relatively higher risk of serious GI bleeding requiring transfusion or surgery, and of death[16]. The aim of the present study was to find biomarkers that closely associate with the risk of GI bleeding in HSP patients. Determining the diagnostic efficacy of these biomarkers will help with early prevention and treatment strategies.

PCT is a precursor of calcitonin with no hormonal activity. The gene is located on chromosome 11 and the protein is composed of 116 amino acids. It is processed into PCT precursors in the rough endoplasmic reticulum of thyroid parafollicular cells after transcription[17]. Proinflammatory cytokines such as TNF-α, IL-6 and IL-8 can stimulate tissues other than thyroid, such as intestines, lungs, and immune cells, to secrete PCT[18]. Under normal physiological conditions, serum PCT levels are lower than 0.05 ng/ml. During systemic bacterial infections, serum PCT level increase, where concentration of 0.5ng/ml is considered the threshold. PCT levels are not influenced by immunosuppression, and elevated levels are positively correlated with the severity of infection[19]. However, recent studies have demonstrated that several non-infectious inflammatory diseases may also be associated with elevated PCT levels, such as systemic lupus erythematosus[1], Kawasaki disease[2-3], adult onset Still's disease[4], severity of illness in non-sepsis critically ill patients[5] and generalized pustular psoriasis[6]. Little is known with regards to the mechanisms regulating PCT levels in these diseases. CRP is an acute phase inflammatory protein and used as a common clinical inflammatory marker. Serum CRP levels in normal healthy individuals are extremely low but can significantly increase during stress conditions. In this study, PCT and CRP levels in adult HSP patients with GI involvement were higher compared to patients without GI involvement. Among the patients with GI involvement, those with GI bleeding had even higher PCT and CRP levels. A positive correlation between PCT and CRP in HSP patients with GI involvement and GI bleeding was observed. It is worth noting that the elevated PCT levels were minor, with a median value below the threshold for systemic bacterial infections (0.5ng/ml). Our findings were partially consistent with the study conducted in children with HSP. The authors in that study found that mild elevated serum PCT levels were significantly associated with GI bleeding but not CRP[20]. The difference between the two studies may be due to differences in immune responses and the physiological status between children and adults. A mild elevation in PCT levels below the systemic infectious threshold (0.5ng/ml) may be the result of a non-specific systemic immune response to GI involvement in HSP. We hypothesize that it may be related to the up-regulation of IL-6, IL-8 and other cytokines to stimulate the release of PCT. This is because previous studies have demonstrated that IL-6 and IL-8 levels were elevated in HSP patients with GI symptoms[21]. In addition, patients with GI involvement, especially GI bleeding, may have substantial GI mucosal barrier injury, and hence may stimulate the synthesis and secre-

tion of PCT directly from intestinal tissue. Furthermore, the risk of infections may increase due to mucosal barrier damage and dysbacteriosis. Hence, these potential systemic infections may lead to elevated PCT levels.

ROC curve analysis showed that the cutoff values for PCT and CRP levels for best diagnostic efficacy of GI bleeding in adult HSP patients were 0.07ng/ml and 29.35mg/L, respectively. Combining these two indicators with patients' clinical symptoms and additional laboratory tests could help in early diagnosis to treat patients with GI bleeding as soon as possible.

However, certain study limitations were apparent. First, no comparison had been made with other hemorrhagic diseases. Second, this study was a single-center retrospective study. Third, hospitalized patients had a relatively more serious condition, the sample cohort was small and patients who were not monitored for CRP and PCT were excluded, hence study bias was unavoidable.

CONCLUSION

In summary, we found that PCT and CRP levels in adult HSP patients with GI involvement were significantly higher compared to patients without GI involvement. In addition, patients with GI bleeding had even higher PCT and CRP levels. PCT and CRP levels had a certain level of diagnostic efficacy for GI bleeding in HSP patients. Multi-center, prospective, larger cohort studies and comparison of multiple GI bleeding diseases are needed to validate our findings.

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