Am J Transl Res 2021;13(7):7914-7920
www.ajtr.org /ISSN:1943-8141/AJTR0128443

Original Article

The correlation of serum Vaspin, S100A12 and PCT levels with the severity of ulcerative colitis and its clinical significance

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Received December 17, 2020; Accepted March 29, 2021; Epub July 15, 2021; Published July 30, 2021

Abstract: Objective: This study aimed to investigate the correlation between Vaspin, S100A12 and PCT levels and ulcerative colitis (UC). Methods: This study included 104 patients with UC from November 2018 to June 2020 as the experimental group, including 37 cases in remission and 67 cases in an active phase; patients in an active phase were classified into 17 cases of mild, 37 cases of moderate and 13 cases of severe according to Modified Mayo Endoscopic Score (MMES). There were 104 patients as healthy controls during the same period who were enrolled as the control group. Serum levels of Vaspin, S100A12, PCT, inflammatory factors and immunoglobulins were compared between two groups and the correlation between serum levels of each index and the severity of UC was analyzed. Results: Compared with the control group, serum Vaspin, S100A12, and PCT levels were higher in the experimental group, and serum Vaspin, S100A12, and PCT levels were higher in the active phase than in the remission phase ($P < 0.05$). Serum Vaspin, S100A12, PCT, IL-6, IL-17, TNF-α levels: Severe patients > moderate patients > mild patients; Serum IgA, IgG levels: Severe < moderate < mild ($P < 0.05$). As shown by Spearman analysis, serum Vaspin, S100A12, PCT, IL-6, IL-17, and TNF-α levels were positively correlated with ($r=0.317$, $P=0.021$) while serum IgA and IgM were negatively correlated with the severity of UC disease ($r=-0.418$, $P=0.007$). Conclusion: Serum Vaspin, S100A12, PCT and inflammatory factor levels were positively correlated with the severity of UC disease, and they showed significance in the assessment of the severity and prognosis of UC.

Keywords: Ulcerative colitis, disease severity, Vaspin, S100A12, PCT

Introduction

Ulcerative colitis is an inflammatory bowel disease (IBD) that causes inflammation and ulcers (sores) in the digestive tract by unknown pathogenesis; mostly occurring in the intestinal mucosal layer, and is characterized by ulcerative lesions with diffuse mucosal inflammation [1, 2]. UC pathogenesis has not been completely clarified, and it is mostly thought to be related to abnormal innate immune response within the intestinal mucosa, infection by intestinal mucosal pathogens and genetic inheritance [3, 4]. During the onset of UC, there are a large number of activated immune cells that have infiltrated in the inflamed intestinal mucosa, such as macrophages, neutrophils, B cells, dendritic cells, T cells, etc., which promote the production of inflammatory mediators, resulting in a severe inflammatory response [5]. S100A12 is a calcium-binding protein that is associated with the development and progression of inflammatory lesions such as inflammatory bowel disease [6]. Calcitoninogen (PCT) is an acute phase protein whose levels are significantly increased when inflammation is present in the body.

Adipokines control energy balance in the body and mediate many inflammatory and immune responses, and multiple factors can show antagonistic and synergistic effects [7]. Visceral adipose-specific serine protease inhibitor (Vaspin) expressed in adipose tissue reduces the expression of pro-inflammatory adipocytokines such as tumor necrosis factor-α (TNF-α), resistin and leptin, and enhances glucose tolerance and insulin sensitivity [8]. In addition, Vaspin can exert anti-inflammatory effects by inhibiting the release of inflammatory mediators,

which are closely associated with the pathogenesis and progression of UC [9]. A study by Jiao et al. [10] showed that serum Vaspin level of patients with UC was significantly increased, and the level in patients with UC in an active phase was higher than that in patients with remission. The level of serum Vaspin in patients with UC in an active phase increased gradually with the aggravation of the disease, suggesting that the level of serum Vaspin has a certain reference value for the early judgment of the severity of UC. This study focused on monitoring the changes of serum Vaspin, S100A12 and PCT levels in patients with varying degrees of UC, aiming to analyze the clinical significance of the changes of serum Vaspin, S100A12 and PCT levels in patients with ulcerative colitis.

Material and methods

Clinical data

One hundred and four patients with UC in our hospital from November 2018 to June 2020 were selected as the experimental group, including 37 cases in remission and 67 cases in the active phase; the patients in the active phase were classified into 17 cases of mild, 37 cases of moderate and 13 cases of severe according to MMES. Another 104 healthy patients were selected as the control group. Inclusion criteria: all patients in the experimental group met the clinical diagnostic criteria for UC [11] and were diagnosed by histopathological examination; aged 32-62 years; none of them received any biological agents or immunosuppressive therapy at 4 weeks prior to participation in the study; clinical data were complete and detailed. This study was reviewed and approved by the ethics committee of our hospital. All the patients provided written informed consent before participating in the study. Exclusion criteria: those with intestinal diseases such as amebic enteritis and bacillary dysentery; those who were comorbid with hypertension, coronary heart disease or diabetes mellitus; those with serious liver, lung, kidney and other organ insufficiency; those with urinary system diseases or hematological system diseases; those with malignant tumors; those with autoimmune system diseases; pregnant and lactating women; and those with incomplete clinical data.

Methods

In both groups, 5 mL of fasting cubital venous blood was drawn in the early morning. After treatment by anticoagulation with heparin sodium, the blood was centrifuged for 10 min (3000 r/min). The serum and plasma were separated, and the serum was stored at -80°C for testing. Enzyme-linked immunosorbent assay was used to determine serum Vaspin, S100A12, IL-6, IL-17, TNF-α, IgA, IgG, IgM levels using MB-80 rapid microbial detector (Beijing Jinshanchuan Technology Development Co., Ltd.), and kits (Beijing Equation Biotechnology Co., Ltd.); Serum PCT level was determined by immunohistochemiluminescence method using CX-V automatic biochemical analyzer (Beckman, US) and kits (BRAHMS, Berlin, Germany). The kit and instrument operating instructions were strictly followed.

Outcome measurement

(1) Levels of serum Vaspin, S100A12, PCT, inflammatory factors and immunoglobulins between the two groups were compared, and the correlation between serum indicators and the severity of UC was analyzed.

(2) Assessment of gut microbiota dysbiosis. The Atlas of Human Intestinal Protozoa [12] was used to classify the gut microbiota dysbiosis as four types: normal, I, II, and III.

Statistical analysis

With SPSS 19.0 as the analysis tool, measurement data was expressed as ($\overline{x}$ ± s), and examined by *t* test, and LSD-t test was used for two-way comparison. Count data expressed as percentages was tested using χ^2 test, and Spearman's test was used for correlation analysis. $P < 0.05$ indicated significant differences.

Results

Baseline data

There was no significant difference in age, sex, and body mass index between two groups ($P > 0.05$), which were comparable (**Table 1**).

Table 1. Comparison of baseline data (n/χ ± S)

Group	Number of cases	Male/female	Age (years)	Body mass index (kg/m^2)	Clinical staging	Modified Mayo scores
					Remission/ active phase	Mild/moderate/ severe
Experimental group	104	60/44	45.8±11.5	22.61±2.15	37/67	17/37/13
Control group	104	61/43	46.1±11.2	21.98±2.37	-	-
χ^2/t		0.020	0.191	2.008		-
P		0.888	0.849	0.051		-

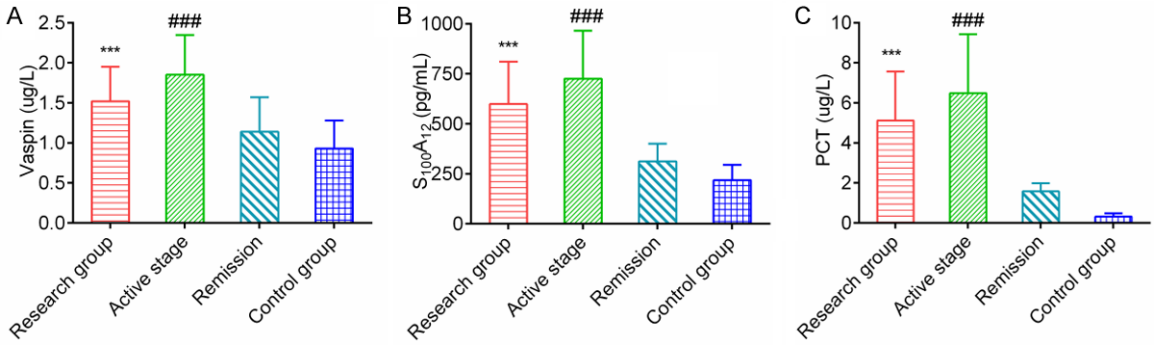

Figure 1. Comparison of serum Vaspin, S100A12, and PCT levels. Note: A: Vaspin (μg/L); B: S100A12 (pg/mL); C: PCT (μg/L). Compared with controls, $^{***}P < 0.001$; compared with remission phase, $^{###}P < 0.001$.

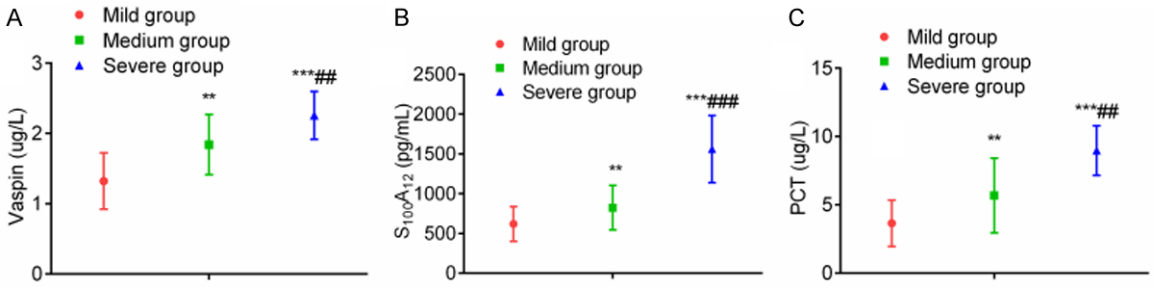

Figure 2. Comparison of serum Vaspin, S100A12, and PCT levels. Note: A: Vaspin (μg/L); B: S100A12 (pg/mL); C: PCT (μg/L). Compared with mild patients, $^{**}P < 0.01$, $^{***}P < 0.001$; compared with moderate patients, $^{###}P < 0.001$.

Comparison of serum Vaspin, S100A12 and PCT levels

Compared with the control group, serum Vaspin, S100A12, and PCT levels were higher in the experimental group and were higher in the active phase than in the remission phase ($P < 0.05$), suggesting that patients with ulcerative colitis exhibited elevated serum levels of the above indicators and they were higher in the active phase (**Figure 1**).

Comparison of serum Vaspin, S100A12, and PCT levels in patients with varying degrees of UC

Patients with severe UC and mild UC showed the highest and lowest serum Vaspin, S100A12, and PCT levels, respectively ($P < 0.05$), suggesting that those serum levels may be closely related to the severity of UC. The more severe the UC, the higher the levels of the above indicators (**Figure 2**).

Comparison of serum inflammatory factor levels in UC patients with varying degrees of UC

Serum IL-6, IL-17, TNF-α levels were highest and lowest in patients with severe UC and mild UC, respectively ($P < 0.05$), indicating that serum inflammatory factor levels are significantly higher in patients with ulcerative colitis, and the more severe the disease, the higher the inflammatory factor levels (**Figure 3**).

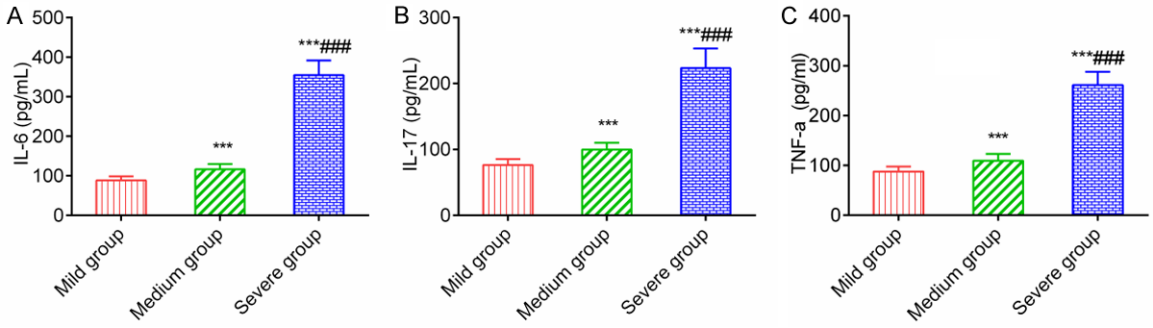

Figure 3. Comparison of serum inflammatory factor levels (pg/mL). Note: A: IL-6 (pg/mL); B: IL-17 (pg/mL); C: TNF-α (pg/mL). Compared with mild patients, $^{***}P < 0.001$; compared with moderate patients, $^{\#\#\#}P < 0.001$.

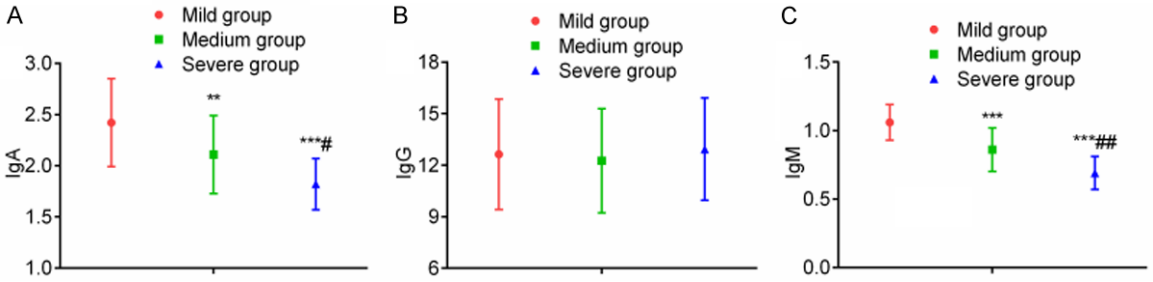

Figure 4. Comparison of serum immunoglobulin levels (g/L). Note: A: IgA (g/L); B: IgG (g/L); C: IgM (g/L). Compared with mild patients, $^{**}P < 0.01$, $^{***}P < 0.001$; compared with moderate patients, $^{\#}P < 0.05$, $^{\#\#}P < 0.01$.

Table 2. Correlation between serum levels of each index and severity of UC

Coefficient	Vaspin	S100A12	PCT	IL-6	IL-17	TNF-α	IgA	IgM
r	0.498	0.523	0.602	0.456	0.613	0.732	-0.516	-0.578
P	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000

Comparison of serum immunoglobulin levels

Serum IgA and IgG levels in patients with severe UC were lower than those in patients with moderate and mild UC, and serum IgA and IgG levels in patients with moderate UC were lower than those in patients with mild UC ($P < 0.05$), showing that patients with ulcerative colitis are accompanied by different degrees of humoral immune deficiency, and the more severe the disease, the more obvious the immune dysfunction (**Figure 4**).

Correlation between the levels of serum indicators and the severity of UC

Spearman analysis found that serum Vaspin, S100A12, PCT, IL-6, IL-17, and TNF-α levels were positively correlated with the severity of UC (r=0.317, P=0.021), and serum IgA and IgM were negatively correlated with the severity of UC (r=-0.418, P=0.007), indicating that serum Vaspin, S100A12, PCT and inflammatory factor levels may reflect the severity of UC and the state of immune dysfunction (**Table 2**).

Comparison of the degree of intestinal dysbiosis in patients with different degrees of UC

The incidence and degree of dysbiosis in severe patients were higher than those in moderate and mild patients, and the incidence and degree of dysbiosis in moderate patients were higher than those in mild patients ($P < 0.05$), suggesting that patients with ulcerative colitis have a high incidence of intestinal dysbiosis. As the severity of UC increases, the incidence of dysbiosis subsequently increases (**Table 3**).

Discussion

UC is one common inflammatory bowel disease, with main symptoms such as diarrhea

Table 3. Comparison of the degree of gut dysbiosis [n (%)]

Group	Number of cases	Normal	I degree of flora dysbiosis	II degree flora dysbiosis	III degree flora dysbiosis	Dysbiosis
Mild patients	17	14 (82.35)	2 (11.76)	1 (5.88)	0 (0.00)	3 (17.65)
Moderate patients	37	18 (48.65)	9 (24.32)	6 (16.22)	4 (10.81)	19 (51.35)$^{\#}$
Severe patients	13	2 (15.38)	1 (7.69)	4 (30.77)	6 (46.15)	11 (84.62)$^{\#\#\#,**}$

Note: Compared with mild patients, $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$; compared with moderate patients, $^{**}P < 0.01$.

and abdominal pain, and it varies in severity. UC has a long course with recurrent episodes. It is hard to cure, and is associated with the development of colon cancer, and is classified as a modern intractable disease by the World Health Organization [13]. According to an epidemiological survey, the prevalence of UC is steadily increasing worldwide [14]. There is still a lack of effective treatment options for UC, coupled with the similarity of its clinical symptoms with tumors in the colon, enteritis, and ischemic enteritis, which can easily lead to under-diagnosis and misdiagnosis and often misses the best treatment window [15, 16]. Therefore, early diagnosis, accurate assessment of the severity of the disease and timely treatment are of great importance to improve the outcomes of UC patients.

Although the exact etiology and pathogenesis of UC are not explained, there is a basic consensus that commensal bacteria and the inflammatory factors they produce act on genetically immunodeficient individuals to produce a sustained immune response under certain environmental factors, leading to UC [17, 18]. Thus, inflammatory response-related cytokines play a crucial role in the pathogenesis of UC. Vaspin is a novel adipocytokine, mostly expressed in adipose tissue, which enhances glucose tolerance and insulin sensitivity. Evidence has shown that Vaspin is involved in the occurrence of UC and is closely related to the disease progression and prognosis [19]. The serum Vaspin levels of UC patients in this study were significantly higher than those of healthy subjects, fully confirming the correlation between Vaspin and the onset of UC. Another study indicated that Vaspin was effective in reducing inflammatory cytokine TNF-α, pro-inflammatory adipocytokine resistin and leptin expression and increasing anti-inflammatory adipocytokine expression [20]. Serum Vaspin, IL-6, IL-17, TNF-α levels were positively correlated with the severity of UC in this study, i.e., the more severe the UC, the more severe the inflammatory response, and the higher the serum Vaspin and IL-6, IL-17, TNF-α levels. Inflammatory lesions can disrupt the balance of intestinal flora, leading to varying degrees of humoral immune dysfunction in patients with UC, with abnormal expression of immunoglobulins as the main manifestation. In this study, IgA and IgG levels in severe patients were higher than those in moderate patients and mild patients, and serum IgA and IgM were negatively correlated with the severity of UC and the incidence of dysbiosis was higher in severe patients, as evidenced by the increasing degree of humoral immune disorders and dysbiosis with increasing degree of UC.

S100A12, also known as calreticulin, usually exists as a dimer, monomer or complex and is mostly believed to be secreted by the same phagocyte as S100A8/9 (calmodulin), which has significant pro-inflammatory effects and is a protein associated with most inflammatory diseases [21]. S100A12 was mostly used as a promising serum marker in the diagnosis of inflammatory bowel disease, exhibiting good efficiency in infectious diarrhea and irritable bowel syndrome. As the deepening of clinical research, it was found that S100A12 is closely related to UC, and the more severe the condition of UC, the higher the serum S100A12 level [22, 23]. In the present study, the serum S100A12 level was significantly increased after the onset of UC, and it increased with the aggravation of UC, which confirmed the above point. It has been noted that S100A12 levels in UC patients are positively correlated with C-reactive protein level [24]. C-reactive protein is currently used as a diagnostic indicator of the body's inflammatory response. The more severe the condition of UC, the more severe the inflammatory response, and the higher the C-reactive protein level, leading to higher serum S100A12 level.

PCT is a precursor of calcitonin and has no hormone activity. It is mostly produced by thyroid C cells and is degraded into calcitonin and other fragments in the cell. In the normal state, PCT levels are low or even undetectable, and its expression is mainly confined to the lung and thyroid neuroendocrine cells, with the active form stored mainly in cellular secretory granules; whereas in the pathological state, PCT expression is more prevalent and can be released in organ tissues except the thyroid, such as leukocytes, adipocytes, pancreas, kidney and liver. Evidence has shown that elevated serum PCT levels are mainly associated with bacterial toxins and bacterial infection [25]. In this study, serum PCT levels were significantly higher in UC patients than in healthy subjects, suggesting that serum PCT levels are associated with the development of UC. This may be due to the fact that UC is a chronic non-specific inflammatory disease with high levels of inflammatory factors, and PCT is stimulated by inflammatory factors and thus was secreted in large quantities. In addition, the serum PCT level was positively correlated with the severity of UC, indicating that the serum PCT level increased in parallel with the progression of UC.

There are still some shortcomings in this study. The specific pathways of serum Vaspin, S100A12 and PCT in the development of UC have not been studied in detail. The next step is to further study the specific pathways of these factors in the pathogenic process of UC in animal and cell experiments. At the same time, this is a single-center study with a small sample size and it has a short observation time with limited persuasion. Therefore, further clinical multi-channel and multi-center sampling is needed to further explore the relationship between serum Vaspin, S100A12, PCT levels and the conditions of UC patients as well as the correlation between the three.

In conclusion, serum Vaspin, S100A12, PCT and inflammatory factor levels were positively correlated with the severity of UC, and serum Vaspin, S100A12 and PCT levels showed clinical significance in the assessment of the severity of UC.

Disclosure of conflict of interest

None.

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