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Systemic inflammation response index (SIRI) as a predictor for predicting inflammatory bowel disease (IBD) severity.

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Abstract

Peripheral venous blood markers may reflect the systematic inflammatory response condition. Various indices have been used to evaluate Inflammatory Bowel Disease (IBD), however, there is no ideal maker to assess the IBD activity and severity. We aim to investigate the potential value of Systemic Inflammation Response Index (SIRI) in IBD patients, and use it to predict the disease activity and severity. We designed a retrospective study to evaluate the SIRI in estimating disease severity in patients with IBD. We enrolled 210 patients with IBD, included 110 cases of Ulcerative Colitis (UC) and 100 cases of Crohn's Disease (CD) in our hospital, between May 2011 and October 2014. The blood samples were collected from the IBD patients before any treatment of antibiotics, steroids and surgery. The categorical variables were provided with frequencies and percentages (%), and using the Chi-square test. The univariate and multivariate logistic regression model analysis were used to determine the demographic and clinicopathological features with active IBD. The optimal cut-off value of SIRI by Receiver Operating Characteristic curve (ROC) was 0.86×10^9/L, and patients were stratified into 2 groups: a low SIRI group (SIRI$<0.86 \times 10^9$/L) and a high SIRI group (SIRI $\geq 0.86 \times 10^9$/L). A high SIRI was significantly correlated with active IBD (P=0.019), CRP (P=0.002), ESR (P<0.001), NLR (P<0.001) and MLR (P<0.001). The active IBD was statistically significant between the two groups (P=0.019). Compared with the inactive IBD, the mild active and moderate active IBD were not statistically significant (P=0.907, 0.137), however, the severe active IBD was statistically significant (P<0.001). There was statistically significant of the different severity of active IBD between low SIRI group and high SIRI group (P=0.003). Multivariate analysis indicated that the CRP, ESR and SIRI were independently associated with active IBD. SIRI is cost-effective and convenient indicator in IBD patients and may be a new promising marker of the disease severity in IBD. High SIRI may help the doctors to make decisions for patients with active IBD.

Keywords: Systemic inflammation response index, Inflammatory bowel disease, Ulcerative colitis, Crohn's disease, C-reactive protein, Erythrocyte sedimentation rate.

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Introduction

Inflammatory Bowel Disease (IBD) is one of the common disease with dysregulation inflammation in the gastrointestinal tract, and severely influencing the physical and mental health of people [1]. IBD is a complex disorder with immune system, microbiota, genetic and environmental influences, and includes Ulcerative Colitis (UC) and Crohn's Disease (CD), which are associated with aberrant immune [2,3]. Intestinal neoplasms and inflammation are determinate relationships with each other, and acknowledged as a long term complication of IBD [4]. UC is a chronic and relapsing inflammatory disease, and causes continuous inflammation of the colorectal mucosa [5]. CD is a chronic and remitting inflammatory disease with an unknown etiology, and involves many factors, such as immune mediated response, genetic susceptibility factor and environmental factor [6].

One study of Western population-based has indicated that the risk of Colorectal Cancer (CRC) with IBD was higher than without IBD, and the disease still has a poor prognosis and leads hundreds of thousands of deaths annually [7]. However, with the better IBD management, the CRC with IBD was decreasing by effectively and efficiently suppressing intestinal inflammation [8]. The IBD incidence rate in Western countries is higher than the rates in Asian countries, but the incidence of IBD in Asian countries has been rapidly rising and the burden of this disease has been increasing, too [9]. Although some techniques have been used for diagnose, they are invasive techniques, such as histopathologic, endoscopic and so forth, and often time-consuming and expensive. Peripheral blood tests at the time of diagnosis and treatment can reflect

inflammatory conditions within the IBD, and is also an ideal non-invasive test [10]. Evaluation of peripheral blood parameters including white blood cell (W), Neutrophil (N), Lymphocyte (L), Monocyte (M), Platelet (P) counts, as well as SIRI (N × M/L), which are indicators of systematic inflammatory response condition, and have been widely proposed as a useful biomarker of systemic inflammation responses [11-14].

As far as I'm concerned, an integrated indicator based on peripheral neutrophil, monocyte, and lymphocyte counts has not yet been reported in IBD, and might be better able to reflect the balance of host inflammatory and immune status. The aim of present study is to predict the severity in peripheral blood samples from patients with IBD.

Materials and Methods

Patient selection

We enrolled 210 patients with IBD, included 110 cases of UC and 100 cases of CD in our hospital, between May 2011 and October 2014. All patients with IBD were confirmed in accordance with pathological evidence, standard clinical, radiological, endoscopic and laboratory. The present study was conducted under the understanding and written consent of each patient and kin. This study was approved by the ethics committee of our hospital and in accordance with the ethical standards of the Declaration of Helsinki and its later ethical standards. Informed consent was obtained from all individual participants. The clinical and demographic data of patients were extracted from the patients' medical records. Inclusion criteria included: (1) patients with IBD were confirmed in accordance with endoscopic evaluation with tissue histology; (2) aged ≥ 18 y; (3) no previous treatment, such as antibiotics, steroids and immunosuppressive agents. Exclusion criteria included: (1) patients with any chronic systemic disease, such as diabetes mellitus, hypertension, atherosclerotic heart diseases, hyperthyroidism, and adrenal insufficiency; (2) with any other malignancy or autoimmune disease; (3) patients with serious complications, such as infections, intestinal tuberculosis and ischemia.

Disease activity or severity

UC activity was evaluated by using Simple Clinical Colitis Activity Index (SCCAI), where SCCAI scores under 3 were considered inactive, SCCAI scores above 3 was considered active. And SCCAI scores of 3-5 were considered mild, SCCAI scores of 6-11 were considered moderate, SCCAI scores of above 12 were considered severe [15]. Crohn's disease severity was defined by CD Activity Index (CDAI), where CDAI scores under 150 were considered inactive, CDAI scores above 150 were considered active [16]. Moreover, the activity of CD was evaluated by defined as mild (CDAI scores of 150-220), moderate (CDAI scores of 221-450) and severe (CDAI scores of above 450).

Blood sample

The peripheral venous blood samples were collected from the IBD patients before any treatment of antibiotics, steroids and surgery. These blood samples were collected into a sterile Ethylenediaminetetraacetic Acid (EDTA) tube. SIRI was defined as N × M/L, where N, M, and L are the pretreatment peripheral neutrophil, monocyte, and lymphocyte counts, respectively.

Statistical analysis

All statistical analyses were performing using Statistical Package for Social Sciences (SPSS) 19.0 (SPSS Inc., Chicago, IL, USA) and GraphPad prism software (version 5.0; GraphPad Inc., La Jolla, CA, USA). Receiver Operating Characteristic (ROC) curve analysis was used to decide the optimal cut-off values of SIRI and other inflammatory markers. The categorical variables were provided with frequencies and percentages (%), and the Chi-square test was used to compare these categorical variables. The univariate and multivariate logistic regression model analysis were used to determine the demographic and clinicopathological features with active IBD. Results were reported as Hazard Ratios (HR) and 95% Confidence Intervals (CI), and to assess the relative risk. A two-tailed $P<0.05$ was considered statistically significant.

Results

The demographic and clinicopathological features of IBD

We enrolled 210 patients in this study. The Receiver Operating Characteristic curve (ROC) analysis revealed that the optimal cut-off value of SIRI for active IBD was 0.86×10^9/L. The SIRI of 0.86×10^9/L had the highest sensitivity and specificity for active IBD. Hence, patients were stratified into 2 groups: a low SIRI group (SIRI<0.86×10^9/L) and a high SIRI group (SIRI ≥ 0.86×10^9/L). Table 1 shows the difference in demographic and clinicopathological features of the two SIRI groups. There are 107 IBD patients (51.0%) in the low SIRI group and 103 IBD patients (49.0%) in the high SIRI group. There were 119 males and 91 females, respectively. The median age was 31 y, range 27-51 y; a median BMI (Body Mass Index) was 20.1 Kg/m^2, range 17.8-22.7 Kg/m^2. A high SIRI was significantly correlated with active IBD (P=0.019), CRP (P=0.002), ESR (P<0.001), NLR (P<0.001) and MLR (P<0.001).

Table 1. *Demographic and clinicopathological features of two SIRI groups* .

Variables	low SIRI (n=107)	high SIRI (n=103)	χ^2	P
Age (y)			1.913	0.167
<31	49 (45.8%)	57 (55.3%)		
≥ 31	58 (54.2%)	46 (44.7%)		

gender			0.207	0.649
Male	59 (55.1%)	60 (58.3%)		
Female	48 (44.9%)	43 (41.7%)		
BMI (Kg/m^2)			1.605	0.205
<20.1	53 (49.5%)	60 (58.3%)		
≥ 20.1	54 (50.5%)	43 (41.7%)		
IBD			5.533	0.019
Active	46 (43.0%)	61 (59.2%)		
Inactive	61 (57.0%)	42 (40.8%)		
UC (n=110)			4.180	0.041
Active	24 (22.4%)	28 (27.2%)		
Inactive	38 (35.5%)	20 (19.4%)		
CD (n=100)			1.235	0.267
Active	22 (20.6%)	33 (32.0%)		
Inactive	23 (21.5%)	22 (21.4%)		
Smoking				
Yes	62 (57.9%)	57 (55.3%)	0.145	0.703
No	45 (42.1%)	46 (44.7%)		
Alcohol habit			1.863	0.172
Yes	45 (42.1%)	53 (51.5%)		
No	62 (57.9%)	50 (48.5%)		
CRP (mg/dl)			9.239	0.002
<33.5	64 (59.8%)	40 (38.8%)		
≥ 33.5	43 (40.2%)	63 (61.2%)		
ESR (mm/H)			13.891	< 0.001
<23.5	67 (62.6%)	38 (36.9%)		
≥ 23.5	40 (37.4%)	65 (63.1%)		
NLR			14.866	< 0.001
<2.20	72 (67.3%)	42 (40.8%)		
≥ 2.20	35 (32.7%)	61 (59.2%)		
MLR			11.950	< 0.001
<0.25	65 (60.7%)	38 (36.9%)		
≥ 0.25	42 (39.3%)	65 (63.1%)		

IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease; BMI: Body Mass Index; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate.

Disease severity of two SIRI groups

The Simple Clinical Colitis Activity Index (SCCAI) and CD Activity Index (CDAI) were used to evaluated the UC and CD activity, respectively. And the severity of UC and CD was evaluated by different scores of SCCAI or CDAI. In low SIRI group, 61 patients were inactive, 46 patients were active, respectively. In high SIRI group, 42 patients were inactive, 61 patients were active, respectively. Moreover, in low SIRI group, 23 patients were mild active, 15 patients were moderate active, 8 patients were severe active, respectively; in high SIRI group, 14 patients were mild active, 20 patients were moderate active, 27 patients were severe active, respectively. The active IBD was statistically significant between the two groups (P=0.019). Compared with the inactive IBD, the mild active and moderate active IBD were not statistically significant (P=0.907, 0.137), however, the severe active IBD was statistically significant (P<0.001) (Table 2 and Figure 1). Table 3 shows that the different severity of active IBD patients, and there was statistically significant of the different severity of active IBD between low SIRI group and high SIRI group (P=0.003) (Figure 2).

Table 2. *Disease severity for IBD of two SIRI groups.*

Variables	Low SIRI (n=107)	High SIRI (n=103)	χ^2	P
Inactive	61 (57.0%)	42 (40.8%)	5.533	0.019
Mild	23 (21.5%)	14 (13.6%)	0.014	0.907#
Moderate	15 (14.0%)	20 (19.4%)	2.205	0.137#
Severe	8 (7.5%)	27 (26.2%)	12.403	<0.001#

#Compared with the inactive IBD patients

Table 3. *Disease severity for active IBD of two SIRI groups.*

Variables	Low SIRI (n=46)	High SIRI (n=61)	χ^2	P
Mild	23 (50.0%)	14 (23.0%)	11.338	0.003
Moderate	15 (32.6%)	20 (32.8%)		
Severe	8 (17.4%)	27 (44.2%)		

Univariate and multivariate analyses for IBD patients of SIRI

The univariate and multivariate logistic regression model analysis were used to explore the associations of the demographic and clinicopathological features with active IBD. Univariate analysis indicated that the CRP, ESR, SIRI, NLR and MLR had a statistically significant association with active IBD (Table 4). Multivariate analysis indicated that the CRP, ESR and SIRI were independently associated with active IBD (CRP: Hazard Ratios (HR), 1.874, 95% Confidence Intervals (CI), 1.545-2.438; ESR: HR, 1.612, 95% CI, 1.028-2.231; SIRI: HR, 1.865, 95% CI, 1.268-2.389; respectively) (Table 4). Therefore, the CRP, ESR and SIRI were the parameter capable of discriminating active from active IBD.

Table 4. *Univariate and multivariate logistic regression model analyses for IBD of SIRI.*

Variables	Univariate analysis, HR (95% CI)	P	Multivariate analysis, HR (95% CI)	P

Age (y)		0.786		
<31	1 (Reference)			
≥ 31	0.736 (0.542-1.204)			
Gender		0.378		
Male	1 (Reference)			
Female	0.815 (0.671-1.158)			
BMI (Kg/m^2)		0.705		
<20.1	1 (Reference)			
≥ 20.1	0.698 (0.520-1.218)			
Smoking		0.178		
Yes	1 (Reference)			
No	0.925 (0.668-1.281)			
Alcohol habit		0.219		
Yes	1 (Reference)			
No	1.278 (0.925-1.628)			
CRP (mg/dl)		0.004		0.022
<33.5	1 (Reference)		1 (reference)	
≥ 33.5	1.399 (1.005-1.795)		1.874 (1.545-2.438)	
ESR (mm/H)		0.014		0.031
<23.5	1 (Reference)		1 (reference)	
≥ 23.5	1.545 (0.925-1.929)		1.612 (1.028-2.231)	
SIRI (× 10^9/L)		<0.001		<0.001
<0.86	1 (Reference)		1 (reference)	
≥ 0.86	2.571 (1.935-3.124)		1.865 (1.268-2.389)	
NLR		<0.001		0.516
<2.20	1 (Reference)		1 (reference)	
≥ 2.20	2.055 (1.544-2.687)		1.012 (0.798-1.727)	
MLR		<0.001		0.729
<0.25	1 (Reference)		1 (reference)	
≥ 0.25	1.827 (1.109-2.318)		0.866 (0.547-1.426)	

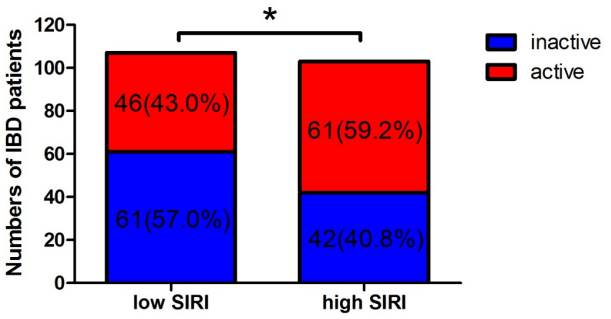

Figure 1. *Disease active for IBD of two SIRI groups (*P<0.05).*

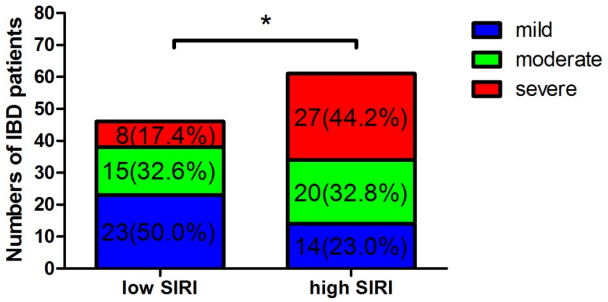

Figure 2. *Disease severity for active IBD of two SIRI groups (*P<0.05).*

Discussion

Ulcerative colitis and Crohn's disease, the main type of inflammatory bowel disease, are associated with dysregulated Inflammation and influence the gastrointestinal tract function [17]. There is a balance between the immune system and microbiota in the gastrointestinal tract, and the host immunity against or tolerate the innocuous antigens to keep the optimally balanced [18]. Histopathological examination plays a critical role in the diagnosis and management of IBD, however, this was expensive and invasive [19]. Thus, the endoscopic test, radiological test and laboratory are also used to further confirm the diagnose of IBD. Previous studies indicated that early detection of disease activity and severity could remarkably reduce the mortality of IBD [20-22]. IBD is also characterized by microbiome and environmental factors which are still poorly understood. Some researchers have suggested that the systemic inflammatory response may modulate the host microbiome of IBD, and has received increased attention [23,24]. Lots of studies have indicated that effective and efficient therapy could significantly control clinical symptoms (extraintestinal manifestations), reduce relapse, maintain remission, and improve the quality of life [25-27]. Therefore, selecting an ideal non-invasive test is increasingly expected and needed. As far as we are concerned, the SIRI value in patient with IBD has been rarely researched.

Accumulating evidence has demonstrated that the chemokines play a key role not only for homeostasis and optimally balance of immune system but also systemic inflammation [28]. Systemic inflammation is the result of chemokines, immune cells and inflammatory proteins. Chemokines are produced by many of cells including neutrophil, monocyte, lymphocyte and macrophage. These chemokines may present in IBD and play a remarkably role in enhancing the intestinal severity and systemic inflammation [29,30]. In the current study, we developed an SIRI based on the peripheral venous blood Neutrophil (N), Monocyte (M), and Lymphocyte (L) counts, and defined as N × M/L. The SIRI was used to predict the active and severity of IBD, and able to reflect the systemic inflammation. Systemic inflammation was that an increase of neutrophil, and accompanied by a relative decrease of lymphocyte. The neutrophil inhibits the immune system by the cytolytic activity of immune cells, and the lymphocyte

improves the immune system *via* inducing cytotoxic cell death [31].

In the present study, we have demonstrated that the SIRI can predict the active and severity of patients with IBD, and we analysed the relationship between SIRI and demographic and clinicopathological features in patients with IBD. We observed that a high SIRI was significantly correlated with active IBD, CRP, ECR, NLR and MLR. The active IBD was statistically significant between low SIRI group and high SIRI group. Compared with the inactive IBD, the mild active and moderate active IBD were not statistically significant, however, the severe active IBD was statistically significant. Additionally, there was statistically significant of the different severity of active IBD between low SIRI group and high SIRI group. In univariate and multivariate logistic regression model analysis, we found that CRP, ESR and SIRI were independently associated with active IBD.

In this study, we used simple clinical colitis activity index and CD activity index to evaluate the UC and CD activity, respectively. These were widely used in clinical studies. To get accurately intestinal inflammation, we combined the endoscopic evaluation with tissue histology and laboratory markers to evaluate the active of IBD. Previous studies indicated that Neutrophil to Lymphocyte Ratio (NLR) was a useful biomarker of systemic inflammation responses for IBD [32]. The WBC, CRP and ESR were the most commonly inflammation factors to determine the IBD activity. And they could not adequately reflect disease activity since their low sensitivity and specificity for intestinal inflammation. However, there is no ideal marker for predicting the active and severity of IBD [33]. Recently, a new Systemic Inflammation Response Index (SIRI) based on neutrophil, monocyte, and lymphocyte counts was developed and acted as an independent predictor in many neoplastic diseases. And its prediction ability was shown to be better than NLR, MLR, LMR and other factors. Meanwhile, SIRI may provide early decision-making to the doctor to take effective therapy.

Recently, fecal lactoferrin, calprotectin and elastase were also used to evaluate the active IBD as novel inflammatory markers. Although the sensitivity and specificity in detecting the gastrointestinal inflammation, they are also not the ideal markers for IBD, and they are inconvenient to get the sample [34,35]. However, SIRI is a cost-effective and simple biomarker, and be an independent marker in this study, and reflects the active and severity of IBD. The neutrophils function of IBD may result in chronic inflammatory response, and associate with disease activity and epithelial injury of IBD. The lymphocyte function of IBD may influence by the neutrophil to be abnormal in intestinal mucosal [36].

This study has several limitations. Firstly, this study was a retrospective design and single-center design. Therefore, the results may not be representative of the general characteristic. Secondly, this study was enrolled a small number of patients. Hence, we should enrol a larger sample in further study. Thirdly, we have not compared the active IBD and clinical prognosis. Nevertheless, the peripheral blood results may provide a new sight to know the SIRI.

In conclusion, our study has demonstrated that the SIRI is evaluated in patients with IBD, and high SIRI may help the doctors to make decisions for patients with active IBD. SIRI is cost-effective and convenient indicator in IBD patients and may be a new promising marker of the disease severity in IBD. However, large multicenter studies are expected to assess changes in inflammatory markers in larger groups of patients with inflammatory bowel disease.

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