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EFFECTS OF COLCHICINE ADJUVANT THERAPY ON DISEASE CONTROL, SERUM NALP3, SICAM-1, MMP-9 AND MMP-13 IN PATIENTS WITH CORONARY HEART DISEASE AND ACUTE GOUT ATTACK

EFEKTI ADJUVANTNE TERAPIJE KOLHICINOM NA KONTROLU BOLESTI, SERUM NALP3, SICAM-1, MMP-9 I MMP-13 KOD PACIJENATA SA KORONARNOM BOLEŠĆU SRCA I AKUTNIM NAPADOM GIHTA

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Summary

Background: To investigate the impact of colchicine adjuvant therapy on disease control and serum levels of nucleotide-binding oligomerization domain-like receptor (NALP) 3, soluble intercellular adhesion molecule (sICAM)-1, matrix metalloproteinase (MMP)-9, and MMP-13 in patients with coronary heart disease (CHD) complicated by acute gout attacks.

Methods: Ninety-two patients with CHD and acute gout attacks admitted to our hospital from October 2021 to January 2023 were randomly divided into an observation group and a control group, with 46 patients in each group. The control group received conventional treatment, while the observation group received colchicine adjuvant therapy on top of the control group's treatment for 7 days. Clinical efficacy in both groups was assessed. Before and after treatment, cardiac function indicators (left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular posterior wall thickness (LVPWT)), vascular endothelial function indicators (sICAM-1, endothelin-1 (ET-1), and vascular endothelial growth factor (VEGF)), inflammatory factors (NALP3, MMP-9, MMP-13) levels, changes in immune cell populations (CD3+ lymphocytes, CD3+CD4+ lymphocytes, CD3+CD8+ lymphocytes ratio, and CD3+CD4+/CD3+CD8+ ratio) were compared, and the incidence of adverse reactions was recorded. Three months after treatment, the occurrence of major adverse cardiovascular events was also recorded.

Kratak sadržaj

Uvod: Cilj je bio da se istraži uticaj adjuvantne terapije kolhicinom na kontrolu bolesti i nivoe u serumu receptora sličnog domenu oligomerizacije koji se vezuje za nukleotide (NALP) 3, rastvorljivog intercelularnog adhezionog molekula (sICAM)-1, matriks metaloproteinaze (MMP)-9 i MMP-13 kod pacijenata sa koronarnom bolešću srca (CHD) komplikovanom akutnim napadima gihta.

Metode: Devedeset i dva pacijenta sa KBS i akutnim napadima gihta primljena u našu bolnicu od oktobra 2021. do januara 2023. nasumično su podeljena u posmatračku i kontrolnu grupu, sa po 46 pacijenata u svakoj grupi. Kontrolna grupa je primila konvencionalni tretman, dok je posmatračka grupa primala pomoćnu terapiju kolhicinom pored tretmana kontrolne grupe tokom 7 dana. Procenjena je klinička efikasnost u obe grupe. Pre i posle tretmana, indikatori srčane funkcije (ejekciona frakcija leve komore (LVEF), end-dijastolni prečnik leve komore (LVEDD), debljina zadnjeg zida leve komore (LVPVT)), indikatori funkcije vaskularnog endotela (sICAM-1, endotelin-1 (ET-1) i faktor rasta vaskularnog endotela (VEGF)), nivoi inflamatornih faktora (NALP3, MMP-9, MMP-13), promene u populaciji imunih ćelija (CD3+ limfociti, CD3+ CD4+ limfociti, odnos CD3+CD8+ limfocita, i CD3+ CD4+/CD3+CD8+ odnos) i zabeležena je učestalost neželjenih reakcija. Tri meseca nakon tretmana zabeležena je i pojava velikih neželjenih kardiovaskularnih događaja.

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Results: The total effective rate in the observation group was significantly higher than that in the control group (93.48% vs 79.07%) (P<0.05). After treatment, the levels of NALP3, MMP-9, and MMP-13 in both groups decreased, with the observation group being lower than the control group (P<0.05). After treatment, LVPWT and LVEDD levels in the observation group were lower than those in the control group, and LVEF was higher (P<0.05). After treatment, the levels of ET-1 and sICAM-1 in the observation group were lower than those in the control group, and VEGF levels were higher (P<0.05). After treatment, the proportions of CD3+ lymphocytes, CD3+CD4+ lymphocytes, and CD3+CD4+/CD3+CD8+ ratio were significantly higher in the observation group than in the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). The occurrence of major adverse cardiovascular events in the observation group was lower than that in the control group (2.17% vs 13.04%).
Conclusions: Colchicine adjuvant therapy improves the efficacy of CHD patients with acute gout attacks, helps improve cardiac function and vascular endothelial function, reduces serum levels of NALP3, sICAM-1, MMP-9, and MMP-13, enhances patient immunity, and controls disease progression.

Keywords: colchicine, coronary heart disease, acute gout attack, nucleotide binding oligomerization domain-like receptor protein 3, soluble intercellular adhesion molecule-1, matrix metalloproteinase-9, matrix metalloproteinase-13, cardiac function

Rezultati: Ukupna efektivna stopa u posmatranoj grupi bila je značajno viša od one u kontrolnoj grupi (93,48% naspram 79,07%) (P<0,05). Nakon tretmana, nivoi NALP3, MMP-9 i MMP-13 u obe grupe su se smanjili, pri čemu je posmatrana grupa bila niža od kontrolne grupe (P<0,05). Nakon tretmana, nivoi LVPVT i LVEDD u posmatranoj grupi bili su niži od onih u kontrolnoj grupi, a LVEF viši (P<0,05). Nakon tretmana, nivoi ET-1 i sICAM-1 u posmatranoj grupi bili su niži od onih u kontrolnoj grupi, a nivoi VEGF-a viši (P<0,05). Nakon tretmana, proporcije CD3+ limfocita, CD3+CD4+ limfocita i odnos CD3+ CD4+/CD3+CD8+ bili su značajno veći u posmatranoj grupi nego u kontrolnoj grupi (P<0,05). Nije bilo značajne razlike u incidenci neželjenih reakcija između dve grupe (P>0,05). Pojava velikih neželjenih kardiovaskularnih događaja u posmatranoj grupi bila je manja nego u kontrolnoj grupi (2,17% prema 13,04%).
Zaključak: Adjuvantna terapija kolhicinom poboljšava efikasnost pacijenata sa KBS sa akutnim napadima gihta, pomaže u poboljšanju funkcije srca i vaskularnog endotela, smanjuje nivoe NALP3, sICAM-1, MMP-9 i MMP-13 u serumu, poboljšava imunitet pacijenata i kontroliše progresiju bolesti.

Ključne reči: kolhicin, koronarna bolest srca, akutni napad gihta, receptorski protein 3 nalik domeni oligomerizacije vezivanja nukleotida, rastvorljivi međućelijski adhezioni molekul-1, matriks metaloproteinaza-9, matriks metaloproteinaza-13, srčana funkcija

Introduction

Coronary heart disease (CHD), as a cardiovascular disease, is the most common type of organ damage caused by atherosclerosis, predominantly affecting the middle-aged and elderly population. It has a high incidence, disability rate, and mortality rate (1). Given the close association between the occurrence of cardiovascular diseases and high uric acid levels, and because high uric acid is a direct cause of acute gout attacks (2), CHD patients often experience acute gout attacks, significantly worsening their condition. Therefore, early control and active treatment have a positive impact on improving the patient's condition and promoting recovery.

Currently, the clinical treatment of CHD patients with acute gout attacks mainly focuses on antiplatelet therapy, lipid regulation, control of risk factors, and uric acid reduction. However, in recent years, increasing evidence suggests that inflammation plays a significant role in the formation and progression of atherosclerosis (3). It is thus speculated that anti-inflammatory treatment will become a new direction in the treatment of CHD. Previous research by Ridker PM and others has also shown that anti-inflammatory treatment can improve the prognosis of CHD patients (4).

Colchicine is a lipophilic alkaloid extracted from autumn crocus and has been approved for use in the treatment of acute gout and familial Mediterranean fever, showing significant efficacy (5). As an anti-inflammatory drug, it has been found to have broad prospects in the secondary prevention of CHD, promoting plaque stability, reducing acute plaque events, and major adverse cardiovascular events (6, 7).

Given these considerations, this study will use colchicine as adjuvant therapy for CHD patients with acute gout attacks to investigate its effects on disease control, serum levels of nucleotide-binding oligomerization domain-like receptor protein (NALP) 3, soluble intercellular adhesion molecules (sICAM)-1, matrix metalloproteinase (MMP)-9, MMP-13, and immune function cells.

Materials and Methods

This study was approved by the ethics committee of Cangzhou Central Hospital (approval number: 2022-051-02(z)). Signed written informed consents were obtained from the patients and/or guardians.

Basic Characteristics

A total of 92 patients with CHD complicated by acute gout attacks, who were admitted to our hospital from October 2021 to January 2023, were selected for this study. They were divided into an observation group and a control group, with 46 patients in each group. Control group: Male/Female = 39/7, age

(average age) 53 to 79 (66.28 ± 4.43) years, New York Heart Association (NYHA) classification: I/II/III/IV = 6/15/18/7 cases, body mass index (BMI, average BMI) 21 to 26 (23.24 ± 1.12) kg/m^2; Observation group: Male/Female = 40/6, age (average age) 53 to 79 (66.59 ± 4.27) years, NYHA classification: I/II/III/IV = 4/13/17/12 cases, BMI (average BMI) 21 to 26 (23.51 ± 1.05) kg/m^2. There were no significant differences in baseline data between the two groups ($P > 0.05$). This study was approved by the hospital ethics committee. Inclusion criteria: All patients met the diagnostic criteria for CHD (8) and acute gout attack (9). Patients and their families were informed about this study. Exclusion criteria: Patients with allergies to the medications used in this study; patients with psychiatric disorders; patients with other types of cardiovascular diseases; patients with significant liver or kidney dysfunction; patients with autoimmune diseases.

Drug Treatment

The control group received standard treatment, which included: Aspirin (Italy Bayer HealthCare Manufacturing S.r.l., National Drug Approval HJ20160685, 100 mg×30 tablets): 1 tablet per dose, once daily, taken orally after meals. Clopidogrel bisulfate tablets (Lepu Pharmaceutical Co., Ltd., National Drug Approval H20123116, 75 mg×10 tablets): 1 tablet per dose, once daily. Atorvastatin calcium tablets (Fujian Dongrui Pharmaceutical Co., Ltd., National Drug Approval H20193043, 10 mg×28 tablets): 1 tablet per dose, once daily. Telmisartan tablets (Beijing Fuyuan Pharmaceutical Co., Ltd., National Drug Approval H20050996, 40 mg×14 tablets): 1 tablet per dose, once daily. Bisoprolol fumarate tablets (Beijing Huasu Pharmaceutical Co., Ltd., National Drug Approval H10970082, 5 mg×10 tablets): 1 tablet per dose, once daily. Isosorbide dinitrate tablets (Lunan Better Pharmaceutical Co., Ltd., National Drug Approval H10940039, 20 mg×48 tablets): 2–3 times daily, 10–20 mg per dose. The observation group, in addition to the medications administered to the control group, received adjunctive therapy with colchicine (Guangdong Bidi Pharmaceutical Co., Ltd., National Drug Approval H20113208, 0.5 mg×20 tablets). The dosage was 0.5mg per dose, three times daily initially, and was adjusted to 0.5 mg per dose, twice daily once the condition improved. Both groups continued their medication regimen for 7 days.

Observation Parameters

Clinical Efficacy: At the end of the treatment, the clinical efficacy was evaluated based on reference to previous literature (10) and categorized into three groups: significant efficacy, efficacy, and inefficacy. Significant efficacy: Patients exhibited a significant improvement in clinical symptoms, good recovery of joint function, nearly normal electrocardiogram (ECG) results, and a return to nearly normal laboratory indicator levels. Efficacy: Patients experienced improvements in clinical symptoms and joint function, with ECG and laboratory indicators showing improvement. Inefficacy: Patients did not show improvements in clinical symptoms, joint function, ECG results, or laboratory indicator levels, and may have even worsened. The total effective rate was calculated as the sum of the significant efficacy rate and the efficacy rate.

Inflammatory Factors: Prior to treatment and at the end of treatment, fasting venous blood samples (3 mL) were collected from the patients. After centrifugation (3000 r/min, 10 min, 10 cm radius), the upper clear liquid was collected and stored at -40 °C for further analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of NALP3, MMP-9, and MMP-13. The reagents and kits were purchased from Shanghai XunYa Biotechnology Co., Ltd., and the measurements were performed strictly following the manufacturer's instructions.

Cardiac Function: Before treatment and at the end of treatment, a color Doppler ultrasound machine (Instrument: GE, LOC-ZQ9, USA) was used to measure the left ventricular posterior wall thickness (LVPWT), left ventricular end-diastolic diameter (LVEDD), and left ventricular ejection fraction (LVEF) of the patients.

Endothelial Function: Before treatment and at the end of treatment, fasting venous blood samples (3 mL) were collected from the patients. After centrifugation (3000 r/min, 10 min, 10 cm radius), the upper clear liquid was collected and stored at -40 °C for further analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of endothelin-1 (ET-1), soluble intercellular adhesion molecule-1 (sICAM-1), and vascular endothelial growth factor (VEGF). The reagents and kits were purchased from Shanghai Enzyme Research Biotechnology Co., Ltd., and the measurements were performed strictly following the manufacturer's instructions.

Detection of Immune Function Cells: Before and after treatment, 3 mL of peripheral blood was collected from patients and placed in EDTA anticoagulant tubes. From each blood sample, 100 μL was taken and 5 μL of CD45-Percp, CD3-FITC, CD8-PE, and CD4-APC monoclonal antibodies were added separately. After incubation in the dark for 30 minutes, 1 mL of lysing reagent was added to lyse red blood cells. After thorough mixing and centrifugation, the supernatant was removed. The cells were washed twice with PBS and then analyzed using the BD FACS Canto flow cytometer to detect changes in the proportions of immune function cells, including CD3+ lymphocytes, CD3+CD4+ lymphocytes, and CD3+

CD8+ lymphocytes, in peripheral blood before and after treatment. The immune function index (CD3+ CD4+/CD3+CD8+ ratio) was also calculated.

Adverse Reactions: Adverse reactions occurring during the treatment period in both groups were recorded. These primarily included nausea, vomiting, headache, gastrointestinal bleeding, digestive tract bleeding, diarrhea, etc. If a patient experienced multiple adverse reactions, only the most severe one was recorded.

Major Cardiovascular Events: Three months after the end of treatment, both groups were followed up to record the occurrence of major cardiovascular events, including cardiovascular death, myocardial infarction, and stroke.

Statistical Analysis

Data processing was performed using Statistic Package for Social Science (SPSS) 22.0 software (IBM, Armonk, NY, USA). For cardiac function, vascular endothelial function, and inflammatory factor levels, which all followed a normal distribution and are represented as (mean ± standard deviation), differences between groups were analyzed using the two-sample independent t-test. For comparisons within each group before and after treatment, paired t-tests were used. Categorical data such as adverse reactions, gender, and efficacy were presented as (n (%)), and chi-square tests were employed. A significance level of $P < 0.05$ was considered statistically significant.

Results

Comparison of Total Effective Rates between the Two Groups

The total effective rate in the observation group was significantly higher than that in the control group (93.48% vs. 79.07%) ($P < 0.05$). Detail information was shown in *Table I*.

Comparison of Inflammatory Factor Levels between the Two Groups

Before treatment, there were no significant differences in NALP3, MMP-9, and MMP-13 levels between the two groups ($P > 0.05$). After treatment, the levels of NALP3, MMP-9, and MMP-13 decreased in both groups, with the observation group showing lower levels compared to the control group ($P < 0.05$). Detail information was shown in *Table II*.

Comparison of Cardiac Function between the Two Groups

Before treatment, there were no significant differences in LVPWT, LVEDD, and LVEF levels between the two groups ($P > 0.05$). After treatment, the LVPWT and LVEDD levels in the observation group were lower than those in the control group, while the LVEF was higher in the observation group compared to the control group ($P < 0.05$). Detail information was shown in *Table III*.

Comparison of Endothelial Function between the Two Groups

After treatment, the levels of ET-1 and sICAM-1 decreased, while the level of VEGF increased in both groups. Additionally, the observation group had lower

Table I Comparison of Total Effective Rates between the Two Groups (n (%), n=46).

Group	Significant efficacy	Efficacy	Inefficacy	total effective rate
Observation group	29	14	3	93.48
Control group	21	16	9	79.07
χ^2				3.955
P-value				0.047

Table II Comparison of Inflammatory Factor Levels between the Two Groups ($\bar{x}\pm s$, n=46).

Group	NALP3 (ng/L)		MMP-9 (ng/mL)		MMP-13 (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	9.64±2.13	7.15±1.06*#	187.58±26.35	143.51±14.70*#	105.64±9.78	82.51±5.13*#
Control group	9.57±2.08	8.49±1.23*	188.62±27.81	159.08±16.77*	105.24±9.11	90.75±6.38*
T	0.159	5.597	0.184	4.732	0.203	6.827
P-value	0.874	<0.001	0.854	<0.001	0.840	<0.001

*Compared to before treatment, P<0.05; #compared to the control group, P<0.05.

Table III Comparison of Cardiac Function between the Two Groups ($\bar{x}\pm s$, n=46).

Group	LVPWT (mm)		LVEDD (mm)		LVEF (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	15.14±2.28	8.37±1.14*#	53.54±3.61	44.30±2.15*#	40.65±2.33	53.80±2.34*#
Control group	15.29±2.07	10.92±1.23*	53.93±3.26	48.71±2.12*	40.71±2.48	47.22±1.09*
T	0.330	10.313	0.544	9.906	0.120	17.288
P value	0.742	<0.001	0.588	<0.001	0.905	<0.001

*Compared to before treatment, P<0.05; #compared to the control group, P<0.05.

Table IV Comparison of Endothelial Function between the Two Groups ($\bar{x}\pm s$, n=46).

Group	ET-1 (pg/mL)		sICAM-1 (ng/mL)		VEGF (ng/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	75.26±4.12	51.84±3.08*#	304.86±26.91	127.55±21.03*#	123.51±23.81	203.66±31.87*#
Control group	75.38±4.20	59.75±3.54*#	305.11±25.72	156.97±23.44*	124.17±22.53	184.54±25.16*
t	0.138	11.433	0.046	6.336	0.137	3.194
P-value	0.890	<0.001	0.964	<0.001	0.892	0.002

*Compared to before treatment, P<0.05; #compared to the control group, P<0.05.

Table V Comparison of Immune Function Cells between the Two Groups ($\bar{x}\pm s$, n=46).

Group	CD3+ (%)		CD3+ CD4+ (%)		CD3+ CD8+ (%)		CD3+CD4+/ CD3+CD8+ (%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	56.76±3.55	72.35±5.07*#	26.42±3.67	41.14±3.33*#	25.56±2.98	27.98±3.07	0.95±0.11	1.42±0.18*#
Control group	56.34±3.87	65.23±5.26*	25.93±3.11	32.45±3.48*	26.67±2.58	28.86±3.14	0.93±0.12	1.15±0.19*
t	0.324	15.636	0.242	12.747	0.119	0.535	0.106	10.116
P-value	0.425	<0.001	0.364	<0.001	0.385	0.414	0.289	<0.001

*Compared to before treatment, P<0.05; #compared to the control group, P<0.05.

levels of ET-1 and sICAM-1 compared to the control group, and higher levels of VEGF ($P < 0.05$). Detail information was shown in *Table IV*.

Comparison of Immune Function Cells between the Two Groups

Using flow cytometry, changes in immune cell function were detected in both groups before and after treatment. Before treatment, there were no sig-

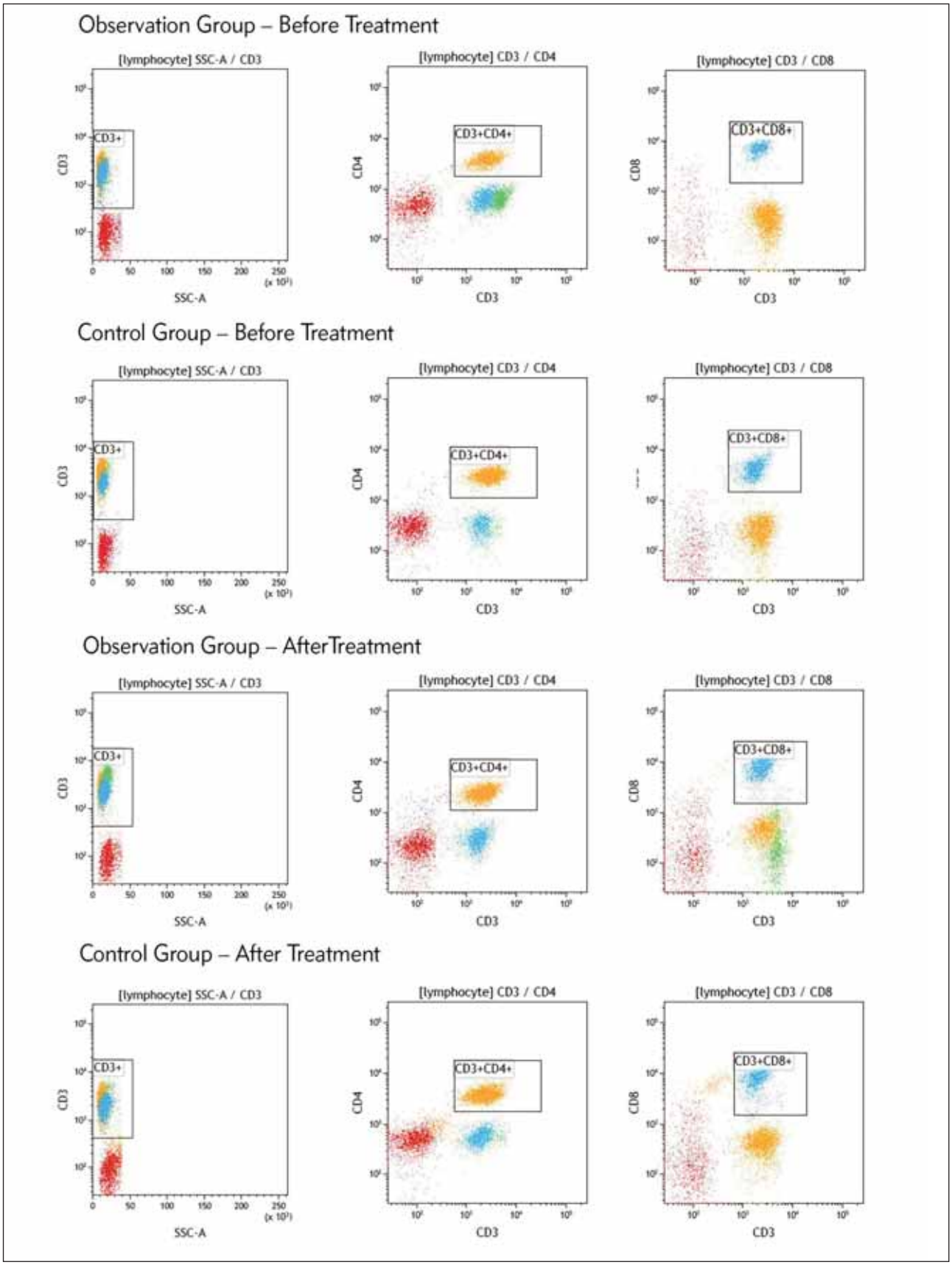

Figure 1 Flow Cytometry Analysis of Changes in Immune Cell Subsets in Peripheral Blood of Patients in Two Groups Before and After Treatment: Left: CD3+ Lymphocyte Subpopulation; Middle: CD3+CD4+ Lymphocyte Subpopulation; Right: CD3+CD8+ Lymphocyte Subpopulation.

Table VI Comparison of Adverse Reactions between the Two Groups (n (%), n=46).

Group	Nausea	Vomiting	Headache	Gastrointestinal bleeding	Digestive tract bleeding	Diarrhea	Total incidence of adverse reactions
Observation group	2	3	1	2	1	3	12 (26.09)
Control group	1	2	2	1	2	1	9 (19.56)
χ^2							0.555
P value							0.456

nificant differences in the proportions of CD3+ lymphocytes, CD3+CD4+ lymphocytes, CD3+CD8+ lymphocytes, and the immune function index (CD3+CD4+/CD3+CD8+ ratio) in peripheral blood between the two groups ($P > 0.05$). However, after treatment, the proportions of CD3+ lymphocytes, CD3+CD4+ lymphocytes, and the CD3+CD4+/CD3+CD8+ ratio increased significantly in both groups ($P < 0.05$). Moreover, the observation group showed significantly higher proportions of CD3+ lymphocytes, CD3+CD4+ lymphocytes, and a higher CD3+CD4+/CD3+CD8+ ratio compared to the control group ($P < 0.05$). The detailed information was presented in *Figure 1* and *Table V*.

Comparison of Adverse Reactions between the Two Groups

There were no significant differences in the occurrence rates of adverse reactions between the two groups ($P > 0.05$). The detailed information was shown in *Table VI*.

Comparison of the Incidence of Major Cardiovascular Events between the Two Groups

In the observation group, there was only 1 case of myocardial infarction, resulting in a major cardiovascular event incidence rate of 2.17%. In the control group, there were 3 cases of stroke, 2 cases of myocardial infarction, and 1 case of cardiovascular death, resulting in a major cardiovascular event incidence rate of 13.04%. Upon comparison, the major cardiovascular event incidence rate in the observation group was lower than that in the control group ($\chi^2=3.866$, $P=0.049$).

Discussion

Research has shown that high uric acid levels are the end product of purine metabolism and the underlying cause of acute gout attacks, which is related to CHD (11). In recent years, the rapid aging of the population and improved living standards in China have led to an increasing incidence of CHD. This has resulted in a substantial rise in the number of patients with acute gout attacks complicating CHD. This not only poses a significant threat to the lives of patients but also increases the economic and societal burdens. Therefore, adopting safe and effective treatment measures is of great importance for controlling disease progression and improving prognosis. There is a growing interest in anti-inflammatory treatment for CHD patients with acute gout attacks, as recent studies have highlighted the role of inflammation in the development of atherosclerosis (12). Colchicine, as a cost-effective anti-inflammatory drug, has a wide range of anti-inflammatory effects. Hence, this study applied colchicine as an adjunctive therapy for CHD patients with acute gout attacks, aiming to explore its effects on disease control and its impact on relevant inflammatory factors and vascular endothelial function factors.

In the current study, the observation group showed a higher overall clinical effective rate compared to the control group, indicating that colchicine adjuvant therapy is beneficial for improving the clinical efficacy in patients with CHD and acute gout attacks. It plays a positive role in controlling the further development of the disease. This effect may be related to the anti-inflammatory, immunosuppressive, anti-fibrotic, and cardiovascular protective properties of colchicine. Additionally, a study conducted by Wang Pengfei et al. (13) also demonstrated that colchicine had good efficacy in treating patients with angina pectoris and acute gout, leading to improvements in gout and serum markers. This finding aligns with the results of the current study.

CHD is a chronic vascular inflammatory condition characterized by the accumulation of subendothelial lipoproteins, triggering abnormal immune responses and resulting in the formation of inflammatory plaques (14). Furthermore, research has indicated a close association between inflammatory responses and both CHD and acute gout attacks (15–16). Serum NALP3 plays a critical role in the inflammatory response, as it activates caspase-1, which in turn regulates the maturation of interleukins (IL)-1β and IL-18 in white blood cells. This activation

leads to the release of other pro-inflammatory cytokines, exacerbating inflammation and contributing to the development of CHD and acute gout attacks. In atherosclerosis, infiltrating inflammatory cells release substantial amounts of MMP-9, enhancing the activity of other inflammatory mediators and further amplifying the inflammatory response, ultimately resulting in abnormally elevated levels of MMP-9 in patients (17). Additionally, MMP-9 can specifically bind to extracellular matrix components, promoting the formation of unstable plaques (18). MMP-13, another collagenase, is involved in various inflammatory reactions and can severely impair heart function by degrading native fibrillar collagen, leading to cardiac atrophy (19). In this study, after treatment, the observation group exhibited reduced levels of NALP3, MMP-9, and MMP-13 compared to the control group, suggesting that adjunctive treatment with colchicine is beneficial for alleviating inflammation and lowering serum NALP3, MMP-9, and MMP-13 levels in patients with CHD and concurrent acute gout attacks. It is likely that colchicine aggregates within neutrophils, interfering with their adhesion, recruitment, and deformation by affecting relevant chemotactic factors, thereby reducing urate crystal-induced inflammatory responses. Furthermore, colchicine can inhibit pore formation induced by urate receptor activation, reducing inflammasome activation (20). Moreover, colchicine can stimulate M2 macrophages to increase the expression of transforming growth factor-beta (TGF-β), which limits the proliferation and activity of smooth muscle cells and fibroblasts, thereby promoting the resolution and healing of plaque inflammation (21). This leads to a reduction in inflammatory responses and a decrease in serum NALP3, MMP-9, and MMP-13 levels.

Vascular endothelial dysfunction plays a role in the development of CHD combined with acute gout attacks. ET-1, as a vasoconstrictive peptide, can induce vascular constriction. Elevated levels of ET-1 can led to insufficient myocardial blood supply. sICAM-1 can increase plaque vulnerability and is often used as an important biochemical indicator to assess the severity of CHD (22). VEGF promotes endothelial cell regeneration and angiogenesis. When endothelial function is impaired, it can lead to coronary artery narrowing and myocardial ischemia and hypoxia, resulting in reduced VEGF levels. This study demonstrates that after treatment, the observation group had lower levels of ET-1 and sICAM-1 compared to the control group, while VEGF levels were higher than in the control group. This suggests that adjunctive treatment with colchicine is beneficial for improving endothelial dysfunction in patients with CHD and concurrent acute gout attacks. This may be due to colchicine's effective uric acid-lowering properties, which reduce urate crystal deposition, thereby minimizing damage to the vascular endothelium and preventing thrombus formation. Furthermore, colchicine can inhibit the interaction between white blood cells and platelets, reduce endothelial cell selectin expression, and exert anti-platelet aggregation effects, thus protecting endothelial function (23). In this study, after treatment, the observation group had lower levels of LVPWT and LVEDD while LVEF was higher compared to the control group, indicating that adjunctive colchicine treatment in patients with CHD and concurrent acute gout attacks is associated with improved heart function. This improvement may be attributed to colchicine's anti-inflammatory properties and its role in improving endothelial function. The study also found that the observation group had a lower rate of major cardiovascular events compared to the control group, which is consistent with previous research (20). This suggests that adjunctive colchicine therapy has a positive impact on reducing the occurrence of major cardiovascular events. Additionally, research by Fiolet et al. (24) also demonstrated that colchicine treatment can reduce the risk of cardiovascular events in stable CHD patients.

Furthermore, the study showed that the immune cell subsets (CD3+ lymphocytes, CD3+CD4+ lymphocytes ratio) and immune index (CD3+CD4+/CD3+CD8+ ratio) in the observation group were significantly higher than in the control group, indicating that colchicine adjunctive therapy can enhance the immune response recovery in patients with CHD and concurrent acute gout attacks. Finally, the study found no significant difference in the incidence of adverse reactions between the two groups, reaffirming the safety of adjunctive colchicine therapy. However this paper still has some shortcomings. Firstly, the adequacy of the sample size was not calculated for this study, however we collected a more than adequate number of patients. Secondly this is a single centre study, which may limit the application of the results of this study. In the future we will conduct a multi-centre study.

In conclusion, adjunctive treatment with colchicine in patients with CHD and concurrent acute gout attacks has shown superior therapeutic efficacy. It helps reduce inflammation, improve endothelial function and cardiac function, promotes immune recovery, and reduces the occurrence of major cardiovascular events.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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PREDICTIVE VALUE OF SYSTEMIC IMMUNE INFLAMMATION INDEX COMBINED WITH COAGULATION INDEX IN TRAUMATIC COAGULOPATHY IN PATIENTS WITH SEVERE TRAUMA

PREDIKTIVNA VREDNOST INDEKSA SISTEMSKE INFLAMACIJE IMUNOG SISTEMA U KOMBINACIJI SA INDEKSOM KOAGULACIJE KOD TRAUMATSKE KOAGULOPATIJE KOD PACIJENATA SA TEŠKOM TRAUMOM

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Summary

Background: Traumatic coagulopathy (TIC) poses a significant challenge in the management of severe trauma cases. Early identification of TIC and its risk factors is vital for initiating timely interventions. The systemic immune inflammation index (SII), a composite marker of inflammation and immune response, alongside conventional coagulation indices, may hold promise in predicting TIC. Here, this study aimed to evaluate the predictive value of combining SII with coagulation indices for TIC in severe trauma patients, with the goal of enhancing early detection and guiding prompt therapeutic strategies.
Methods: The clinical data of patients with severe trauma treated in our hospital from January 2022 to December 2022 were retrospectively selected. According to the outcome of TIC, the patients were divided into TIC group (n = 50) and non-TIC group (n = 50). The general data, SII and individual indexes of the two groups were compared, and the influencing factors of TIC were analyzed by multivariate Logistics regression. ROC analysis of SII combined with blood coagulation index to predict traumatic coagulation in patients with severe trauma.
Results: There was no significant difference in general data between the two groups. SII in TIC group was significantly higher than that in non-TIC group. neutrophil count (NEU), platelet count (PLT), lymphocyte count (LYM), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB) level, and D-Dimer (D-D) level in TIC group were higher than those in non-TIC group, while

Kratak sadržaj

Uvod: Traumatska koagulopatija (TIC) predstavlja značajan izazov u lečenju teških traumatskih slučajeva. Rana identifikacija TIC-a i njegovih faktora rizika je od vitalnog značaja za započinjanje pravovremenih intervencija. Indeks sistemske imune inflamacije (SII), kompozitni marker upale i imunološkog odgovora, zajedno sa konvencionalnim indeksima koagulacije, može koristiti u predviđanju TIC-a. Ovde je ova studija imala za cilj da proceni prediktivnu vrednost kombinovanja SII sa indeksima koagulacije za TIC kod pacijenata sa teškim traumama, sa ciljem poboljšanja ranog otkrivanja i vođenja brzih terapijskih strategija.
Metode: Retrospektivno su odabrani klinički podaci pacijenata sa teškom traumom lečenih u našoj bolnici od januara 2022. do decembra 2022. godine. Prema ishodu TIC-a, pacijenti su podeljeni u TIC grupu (n = 50) i ne-TIC grupu (n = 50). Upoređeni su opšti podaci, SII i pojedinačni indeksi dve grupe, a faktori uticaja na TIC analizirani su multivarijantnom logističkom regresijom. ROC analiza SII u kombinaciji sa indeksom koagulacije krvi za predviđanje traumatske koagulacije kod pacijenata sa teškom traumom.
Rezultati: Nije bilo značajne razlike u opštim podacima između dve grupe. SII u TIC grupi je bio značajno veći nego u grupi bez TIC. Broj neutrofila (NEU), broj trombocita (PLT), broj limfocita (LIM), aktivirano parcijalno tromboplastinsko vreme (APTT), protrombinsko vreme (PT), nivo fibrinogena (FIB) i nivo D-dimera (D-D) u TIC grupi su bili veći od onih u ne-TIC grupi, dok je LIM, FIB bio niži od onih u ne-TIC grupi. Logistička regresiona analiza je pokazala da su

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LYM, FIB was lower than that in non-TIC group. The logistic regression analysis showed that APTT, D-Dimer, FIB, PT, and SII were independent factors that significantly influenced TIC. The area under the curve of TIC in patients with severe trauma with SII combined with coagulation index was 0.883, and the standard error was 0.032 (95%CI:0.8195~0.9461). The best cut-off value was 0.65. The sensitivity and specificity were 80.3, 84.2 respectively. **Conclusions:** SII combined with coagulation index has high predictive value for TIC in patients with severe trauma. By monitoring these indexes, we can more accurately predict the occurrence of TIC and take effective treatment measures in time.

Keywords: Systemic immune inflammatory index, coagulation index, severe trauma, traumatic coagulopathy

APTT, D-dimer, FIB, PT i SII nezavisni faktori koji su značajno uticali na TIC. Površina ispod krive TIC kod pacijenata sa teškom traumom sa SII u kombinaciji sa indeksom koagulacije bila je 0,883, a standardna greška 0,032 (95%CI: 0,8195~0,9461). Najbolja granična vrednost bila je 0,65. Osetljivost i specifičnost su 80,3, odnosno 84,2.
Zaključak: SII u kombinaciji sa indeksom koagulacije ima visoku prediktivnu vrednost za TIC kod pacijenata sa teškom traumom. Praćenjem ovih indeksa možemo preciznije predvideti pojavu TIC-a i na vreme preduzeti efikasne mere lečenja.

Ključne reči: sistemski imunološki inflamatorni indeks, indeks koagulacije, teške traume, traumatska koagulopatija

Introduction

Traumatic coagulopathy (TIC) is a disorder affecting the coagulation process that occurs following severe trauma (1). Research has revealed that among patients suffering from severe trauma, the incidence of TIC stands at roughly 25%–35%, with affected individuals exhibiting a heightened propensity for blood loss, increased necessity for blood transfusions, and a greater risk of encountering multiple organ failure when contrasted with trauma patients who do not present TIC (2). Early recognition and understanding of the risk factors associated with TIC can lead to timely interventions that positively impact patient treatment and prognosis (3). Therefore, investigating and analyzing predictive indicators related to TIC holds significant clinical value. Currently, the prediction of traumatic coagulation in patients with severe trauma primarily relies on the patients' medical history, physiological parameters, and laboratory test results, but these methods lack accuracy and are prone to bias (4). The systemic immune inflammatory index (SII), which is based on peripheral blood neutrophils, platelets, and lymphocytes, serves as a useful reference for clinical assessments of disease progression, prognosis, and treatment effectiveness (5). SII has been demonstrated to possess clinical prognostic value in malignant tumors. Coagulation indexes, including activation of neutrophil count (NEU), platelet count (PLT), lymphocyte count (LYM), activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen (FIB) level, and D-Dimer (D-D) level, have specific normal ranges and clinical implications, providing direct insights into the functional state of the coagulation system (6). Abnormal changes in these coagulation indexes can indicate the presence of underlying diseases. However, limited studies have examined the application of SII and coagulation indexes in TIC among patients with severe trauma. This study aims to investigate the predictive value of combining SII with coagulation parameters in patients with severe trauma for TIC.

Materials and Methods

Subjects

A retrospective selection was conducted on the clinical data of severe trauma patients admitted to our hospital between January 2022 and December 2022. Inclusion criteria consisted of the following: (1) Patients meeting the diagnostic criteria for severe trauma patients (7) with an ISS score of 16 points. (2) Patients with complete clinical data. (3) Patients without a medication history of drugs interfering with coagulation. Exclusion criteria included: (1) Patients with other serious organ diseases. (2) Patients with mental disorders. (3) Patients with hematological disorders. (4) Patients with a history of immunosuppressant use.

Grouping method

Based on the Chinese Expert Consensus on the Diagnosis and Treatment of Traumatic Hypercoagulability (8), it was observed that the APTT or PT showed a 1/2 increase compared to the normal range. Additionally, FIB levels were less than 1 g/L, indicating the presence of TIC. A total of 100 patients were categorized into two groups based on the presence or absence of TIC: 50 patients in the TIC group and 50 patients in the non-TIC group.

Data collection channel

A cohort of 100 individuals was gathered using the electronic medical record system, and their basic information was documented upon admission. Venous blood samples were obtained to examine the following parameters upon admission: NEU, PLT, LYM, APTT, PT, FIB level, and D-D level. The selection of specific coagulation parameters—APTT, PT, FIB, and D-Dimer—is grounded in their established roles in assessing different aspects of the coagulation cascade and their clinical significance in TIC, as previously reported (6). The SII was calculated using the formula SII = neutrophil count × platelet count / lymphocyte count.

Outcome measures

(1) The goal is to assess and contrast the overall data and SII of patients in two separate groups. (2) The objective is to evaluate and compare the specific indicators of patients in two distinct groups. (3) Using multi-factor logistic regression, this study aims to examine the influential factors of TIC. (4) By utilizing ROC analysis on the systemic immune inflammatory index in conjunction with the coagulation index, the intention is to predict the occurrence of traumatic coagulation disease in patients with severe trauma. Additionally, this analysis seeks to determine the area under the curve, sensitivity, and specificity.

Statistical analysis

The collected data underwent analysis using Statistic Package for Social Science (SPSS) 27.0 (IBM, Armonk, NY, USA). The normally distributed data were represented as $\bar{x}\pm S$. To compare the data, an independent sample t-test was employed. On the other hand, count data were presented as either the number of cases or rates. For comparison, the χ^2 test or Fisher's exact method was conducted. Single factor and binary Logistics regression analyses were conducted to examine the influencing factors of TIC in severe trauma patients. To assess the predictive value of the combined SII and coagulation index for TIC in severe trauma patients, an ROC curve was utilized. A significance level of $P<0.05$ was employed.

Results

General information and SII status of patients in both groups

There was no statistically significant difference in overall data among TIC and non-TIC groups ($P>0.05$). The SII in the TIC group exhibited a substantially greater value compared to the non-TIC group ($P<0.001$), as indicated in *Table I*.

Comparison of individual indicators between the two groups

In the TIC group, the NEU, PLT count, APTT, Dmurd, and PT levels were significantly higher in the TIC group compared to the non-TIC group ($P<0.05$). Conversely, the LYM count and FIB levels were significantly lower in the TIC group compared to the non-TIC group ($P<0.05$), as indicated in *Table II*.

Multivariate Logistics regression analysis of influencing factors of TIC

In the analysis of patients with severe trauma, the independent variables, namely APTT, D-Dimer,

Table I Analysis of general data and SII between the two groups.

Index	cases	Gender male (female)	Years (age)	SII
TIC group	50	35 (15)	45.41±5.12	1325.45±341.26
Non-TIC group	50	37 (13)	46.26±5.36	1081.11±311.37
t/X^2		0.198	0.811	3.740
P		0.906	0.419	0.000

Table II Comparison of individual indexes between the two groups.

Index	TIC group (n=50)	Non-TIC group (n=50)	t	P
NEU ($\times 10^9$/L)	7.79±3.61	6.58±1.62	2.162	0.033
PLT ($\times 10^9$/L)	20.16±5.22	12.34±5.26	7.462	0.000
LYM ($\times 10^9$/L)	1.66±0.08	1.74±0.09	4.698	0.000
APTT (s)	63.76±19.46	54.43±18.26	2.472	0.015
D-D (ng/mL)	50.28±17.45	36.11±15.44	4.300	0.000
FIB (g/L)	1.76±0.04	2.05±0.11	17.520	0.000
PT (s)	24.14±10.13	19.16±10.41	2.424	0.017

Table III Multivariate Logistics regression analysis of influencing factors of TIC.

Risk factors	β	SE	Ward	OR	95%CI	P
APTT	0.745	0.264	7.959	2.106	1.255~3.533	<0.001
D-Dimer	0.050	0.021	5.611	1.051	1.009~1.095	<0.001
FIB	0.713	0.277	6.634	2.041	1.186~3.513	0.011
PT	0.004	0.012	0.111	1.004	0.981~1.028	0.010
SII	0.021	0.011	3.570	1.021	0.999~1.043	<0.001

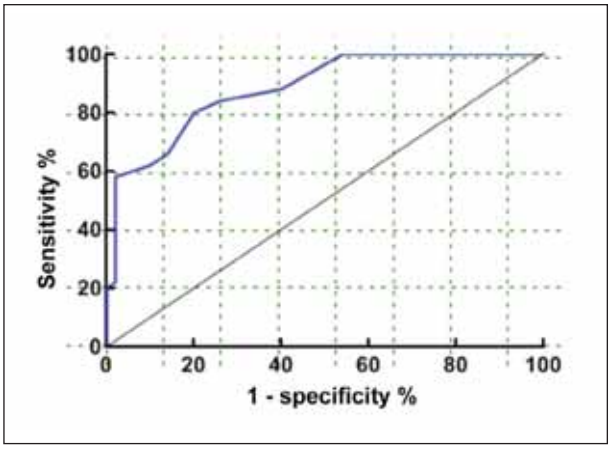

Figure 1 Predictive value of ROC Analysis of SII combined with Coagulation Indexes in predicting TIC in patients with severe Trauma.

FIB, PT, and SII, were assigned with their respective actual values. The dependent variable in this case was the TIC outcome, which was classified as TIC=1 for diagnosed cases and TIC=0 for non-TIC cases. Through logistics regression analysis, it was determined that APTT, D-Dimer, FIB, PT, and SII were independent factors that significantly influenced TIC in patients with severe trauma (P<0.05) (*Table III*).

Predictive value of ROC Analysis of SII combined with Coagulation Indexes in predicting TIC in patients with severe Trauma

The findings from the ROC analysis demonstrated that the combination of SII and coagulation index yielded an AUC for predicting TIC of 0.883, with a standard error of 0.032. The 95% confidence interval for the AUC ranged from 0.8195 to 0.9461. Moreover, the optimal cut-off value was identified as 0.65. The sensitivity and specificity of this model were 80.3% and 84.2% respectively.

Discussion

Increased bleeding, blood transfusion, multiple organ failure, and death are frequently observed in cases of TIC (9). The mechanism underlying this condition is intricate, involving various factors. Following severe trauma, platelet activation and initiation of the coagulation cascade reaction can occur due to tissue injury and hemorrhagic shock (10). Platelet activation results in the formation of an initial platelet clot, which serves to amplify the coagulation cascade, causing a thrombin burst and subsequent cleavage of fibrinogen into fibrin (11). Fibrin can be degraded into soluble fibrin degradation products through the action of fibrinolytic enzymes. Although it is a common complication in patients with severe trauma, it can be partially prevented and treated (12, 13). This study demonstrates that the combination of SII and blood coagulation indexes can serve as a predictive tool for the occurrence of TIC in patients with severe trauma, offering diagnostic value to some extent.

The findings indicated a significant increase in the SII of the TIC group compared to the non-TIC group. Additionally, the TIC group exhibited higher levels of NEU, PLT, APTT, Dmure D, and PT, while lower levels of LYM count and FIB. In their study, they also observed a strong correlation between APTT, D, PT, PLT, and FIB in predicting the prognosis of TIC patients. The analysis suggests that, in cases of TIC, neutrophils play a crucial role in immune response and inflammation. Neutrophils migrate to the injured area, aiming to eliminate infection and facilitate tissue repair (14). Injured bodies trigger rapid activation and consumption of platelets, potentially leading to immune system suppression. As a result, NEU increases, while PLT and LYM count decrease. The Systemic Immune-Inflammation Index (SII), which reflects the inflammatory response and immune status of the body, is closely associated with NEU, PLT, and LYM count, thus providing a comprehensive assessment (15). Severe trauma often places the body under high stress, triggering a robust activation of inflammatory and immune responses. This excessive activation can induce abnormal activation of the

blood coagulation system and the subsequent development of coagulation disorders. Consequently, the body's inflammatory and immune responses intensify, thereby increasing the risk of TIC and leading to an elevation in SII (16). APTT and PT, commonly used to assess the function of the common coagulation pathway, serve as reliable indicators in evaluating coagulation function. In cases of TIC, the prolongation of APTT and PT occurs as a result of vascular endothelial damage and platelet activation caused by tissue injury and inflammation, which in turn triggers the initiation of the coagulation cascade (17,18). D-dimer, a product formed when plasmin initiates the degradation of fibrin into soluble fibrin, serves as an indicator of the activation of the common coagulation pathway and the breakdown of fibrin under the influence of fibrinolytic enzymes (19). Hence, the elevation of D-dimer levels is observed in TIC. Fibrinogen, a crucial protein in the common coagulation pathway, is often depleted due to inflammatory reactions and liver function impairment. In cases of severe trauma, the concentration of FIB decreases as a result of the stress response, inflammatory reactions, and tissue injury (20).

Logistic regression analysis was employed to investigate the impact of these parameters on TIC in order to delve deeper into their influence. The findings indicated that APTT, D-Dimer, FIB, PT, and SII autonomously influenced TIC in patients with severe trauma. This implies that these markers possess significant predictive value and can serve as independent prognosticators. To further illustrate the predictive value of these markers, ROC analysis was conducted on SII in conjunction with blood coagulation indexes. The results unveiled an AUC of 0.883 and a standard error of 0.032 (95%CI: 0.8195~0.9461) for the combined use of SII and coagulation indexes in severe trauma patients. Additionally, with a best cutoff value of 0.65, the sensitivity and specificity were determined to be 80.3% and 84.2%, respectively, indicating the model's high accuracy in forecasting the occurrence of TIC. The amalgamation of SII and blood coagulation indexes enables a more comprehensive assessment of the coagulation status in severe trauma patients (21). SII signifies the systemic immune inflammatory response, whereas blood coagulation indicators reflect the functionality of the coagulation system. The amalgamation of these two aspects leads to a more accurate prediction of TIC and offers clinicians more valuable reference information (22).

The current study exclusively examined the predictive efficacy of SII in combination with blood coagulation index for TIC in patients with severe trauma. Nonetheless, the small sample size involved in this study may have introduced certain bias. Consequently, the reliability of this conclusion necessitates further verification in future investigations with larger sample sizes. In summary, the combined use of SII and blood coagulation indexes exhibits substantial predictive value for TIC in patients with severe trauma. This predictive value may be attributed to their comprehensive assessment of inflammatory response, immune status, and blood coagulation function. In light of the study's findings, healthcare practitioners in trauma care should integrate the systemic immune inflammation index (SII) with standard coagulation assessments (APTT, PT, FIB, D-Dimer) for early detection of traumatic coagulopathy in severe trauma patients. By closely monitoring these indicators, clinicians can obtain crucial references for accurately predicting the occurrence of TIC. Future research avenues should focus on validating the combined SII and coagulation index model in larger, multicenter cohorts to enhance its generalizability. Longitudinal studies tracking SII and coagulation dynamics may elucidate the temporal relationship between inflammation, immunity, and coagulation post-trauma. Lastly, incorporating emerging biomarkers and advanced analytical techniques, including machine learning algorithms, could refine the predictive accuracy and clinical utility of the model.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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