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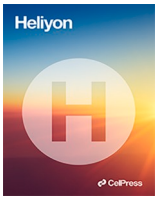

Research article

Decreased Serum CTRP3 level was associated with connective tissue diseases

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ABSTRACT

Objective: Complement C1q tumor necrosis factor-related protein 3 (CTRP3) and 9 (CTRP9) are two of the most extensively studied adipokines, known for their diverse biological functions. However, it remains unclear whether serum levels of CTRP3 or CTRP9 are associated with connective tissue diseases (CTD).

Methods: Serum CTRP3 and CTRP9 levels were measured by enzyme-linked immune sorbent assay (ELISA) and analyzed in patients with rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), ankylosing spondylitis (AS), undifferentiated connective tissue disease (UCTD), as well as in healthy controls (HCs).

Results: Serum CTRP3 levels were all significantly lower in patients with RA, SLE, pSS and AS compared with HCs. However, there were no significant differences in serum CTRP9 levels between patients with RA, SLE, pSS, or AS and HCs. In pSS patients, CTRP3 showed a weak correlation with blood glucose, creatinine, and urine acid in pSS patients, while no correlations were observed between serum CTRP3 levels and clinical or laboratory indices in RA, SLE or AS patients. Stable associations between CTRP3 and RA, SLE, pSS and AS were evaluated using multivariate logistics regression analysis. Receiver operating characteristic (ROC) curves were plotted to evaluated CTRP3 as a marker for RA, SLE, pSS and AS, yielding area under curve (AUC) values of 0.691, 0.727, 0.658 and 0.694, respectively.

Conclusion: Decreased serum CTRP3 levels were associated with RA, SLE, pSS and AS.

1. Introduction

The term Complement C1q tumor necrosis factor-related proteins (CTRPs) are a newly identified family of secreted proteins that share sequence homology with adiponectin. This family is continually expanding, now comprising 15 members in addition to adiponectin. Recently, increasing evidence suggested that CTRP family played a crucial role in physiological and pathological process

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across a wide range of diseases, with CTRP3 and CTRP9 being the most extensively studied [1,2]. The CTRP3 and CTRP9 had been found to involve in endocrine secretion [3,4], lipid metabolism [5], immunoregulation [6], inflammatory responses [7], vascular calcification [8], ventricular remodeling [9], etc.

Connective tissue diseases (CTD) is a large heterogeneous group of diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (pSS), ankylosing spondylitis (AS), polymyositis/dermatomyositis, undifferentiated connective tissue diseases (UCTD), etc. The occurrence and progression of CTD are closely related to factors such as inflammation, immunoregulation [10], gut microflora [11], circadian rhythm [12], etc. Despite some advances, the precise and complex pathophysiological processes underlying CTD remain unclear, and patients continue to suffer from poorly controlled autoimmune responses. In a mouse model of rheumatoid arthritis, CTRP3 has been found to involved in disease progression. The expression levels of CTRP3 were significantly lower in neuropsychiatric systemic lupus erythematosus patients compared with either healthy controls (HCs) or non-neuropsychiatric systemic lupus erythematosus patients. Currently, our understanding of the roles of CTRP3 and CTRP9 in patients with CTD is limited.

In this study, we presently sought to investigate the relationship between serum levels of CTRP3 and CTRP9 and various subgroups of CTD. Our findings revealed a decrease in serum CTRP3 levels in patients with RA, SLE, pSS, and AS. Notebly, the relationship between CTRP3 and RA, SLE, pSS and AS was stable, suggesting its potential utility as a biomarker.

2. Materials and methods

2.1. Study subjects and data collection

This study involving human participants was approved by the ethics committee of the First People's Hospital of Wenling (Zhejiang, China), the authorization number is KY-2019-1013-01. Written informed consent was not required in this study according to the institution policy, since data was from routine medical records and this study did not influence subsequent management of patients. From June 2021 to December 2021, a total of 289 patients, including outpatients and inpatients, were consecutively recruited from Department of Rheumatology at the First People's Hospital of Wenling (Zhejiang, China). RA was diagnosed based on American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) 2010 classification criteria [13]. SLE was diagnosed based on EULAR/ACR 2019 classification criteria sets for systemic lupus erythematosus [14]. The definition of pSS was based on revised vision of European diagnostic Criteria proposed by the American-European Consensus Group [15]. AS was defined based on the modified New York criteria for AS [16]. UCTD is characterized by serological and clinical manifestations suggestive of a CTD, but does not meet the criteria for any defined CTD.

Patients with metabolic disorders, cardiovascular diseases, neurological diseases, severe hepatic or renal dysfunction, hematological disorders, chronic inflammatory diseases, infectious diseases, those undergoing treatment with medications that might affect metabolism, or those with a history of tumors, recent surgery, or blood transfusion were excluded from the study. In addition, 74 healthy individuals were recruited as the HCs. These individuals visited the First People's Hospital of Wenling (Zhejiang, China) for routine physical examinations and had no known diseases. Clinical and laboratory data including gender, age, body mass index (BMI), triglycerides and total cholesterol were extracted from electronic medical records.

2.2. Sample collection and measurement of CTRP3 and CTRP9

Blood routine and blood biochemistry examinations were promptly performed at the clinical laboratory in the hospital. The remaining samples were immediately processed by centrifugation at 3000*g* for 10 min at 4 °C. To avoid repeated freezing and thawing, each remaining sample was divided into 200 μL aliquots and frozen immediately at −80 °C for subsequent analysis.

Serum CTRP3/CTRP9 concentrations were determined by a commercially available enzyme-linked immune sorbent assay (ELISA) kit (Enzyme-linked Biotechnology, Shanghai, China). The assay kit utilized purified human CTRP3/CTRP9 antibodies to coat microtiter plate wells, creating a solid-phase antibody. Samples were then added to the wells, forming an antibody-antigen-enzyme-antibody complex. Following substrate reaction, measurements were taken at a wavelength of 450 nm. The resulting color intensity was positively correlated with the concentration of CTRP3/CTRP9 in the samples. Both the inter-assay and intra-assay coefficients of variation (CVs) were less than 10 %, respectively. The mean minimum detectable dose for human CTRP3 and CTRP9 were less than 0.1 ng/ml and 1.0 ng/ml, respectively.

2.3. Statistical analysis

Continuous variables were present as median (interquartile range, IQR). Data normality was determined by the Shapiro-Wilk test. Student *t*-test was used to compare normally distributed data, while the Mann-Whitney *U* test or Kruskal-Wallis H nonparametric test were used to compare the non-normally distributed data between two groups. The comparison between unmatched data was adjusted by gender and/or age with binary logistic regression. Multivariate analysis was performed using logistic regression, adjusting for clinically relevant factors. ROC curve analysis was used to determine diagnostic ability, and the cut-off point was calculated according to the Youden index. A significance level of $P < 0.05$ was considered statistically significant. Data analyses were conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA) or GraphPad Prism 8 software.

3. Results

3.1. Baseline characteristics of the study participants

A total of 74 HCs, 128 RA patients, 82 SLE patients, 28 pSS patients, 21 AS patients, and 30 UCTD patients were included in this study. The baseline characteristics of these subgroups are presented in Table 1.

3.2. Comparison of serum CTRP3 and CTRP9 levels between the subgroups and HCs

Serum CTRP3 levels were significantly decreased in RA, SLE, pSS and AS patients compared with HCs. SLE patients showed the lowest CTRP3 level (18.50 ng/ml [IQR, 13.96–23.04], $P < 0.001$), followed by RA (20.08 ng/ml [IQR, 17.35–23.44], $P < 0.001$), AS

Table 1
Clinical and laboratory characteristics in various CTD patients and HCs.

	HCs (n = 74)	RA (n = 128)	SLE (n = 82)	pSS (n = 28)	AS (n = 21)	UCTD (n = 30)
Sex(F/M)	65/9	106/22	78/4	27/1	10/11	25/5
P		0.340	0.176	0.353	***<0.001	0.542
Age	57(48.75–63.5)	55.5(47–63)	40.5(30–51)	51(45–56.5)	47(33.5–54.5)	43.5(34.25–56)
P		0.606	***<0.001	*0.038	***<0.001	***<0.001
BMI	23(21.2–24.85)	21.88(20.28–24.61)	21.41(20.14–23.89)	22.28(20.44–23.4)	23.15(21.4–25.66)	21.84(19.73–23.83)
P		0.099	0.694	0.543	0.391	0.328
WBC (10^9/L)	5.205(4.735–6.025)	6.005(4.613–7.248)	5.020(3.973–6.228)	4.935(3.668–6.515)	5.990(4.690–6.855)	5.435(4.153–6.598)
P		0.1424	0.193	0.133	0.503	0.825
RBC (10^{12}/L)	4.495(4.2–4.758)	4.23(4.013–4.49)	4.12(3.908–4.34)	4.415(4.113–4.64)	4.83(4.445–5.14)	4.32(3.948–4.66)
P		***<0.001	***<0.001	0.167	*0.032	*0.045
PLT (10^9/L)	220.5(188–260)	239(188–286)	207.5(170.8–267)	205(176–232.5)	230(204.5–291)	188(159.3–231.8)
P		0.094	0.280	0.091	0.739	*0.044
Neu (10^9/L)	2.865(2.475–3.535)	3.59(2.53–4.925)	3.07(2.275–3.868)	2.73(1.78–3.685)	3.55(2.495–4.435)	3.71(2.408–4.325)
P		*0.0129	0.656	0.306	0.289	0.379
Lym (10^9/L)	1.925(1.433–2.275)	1.52(1.29–1.778)	1.37(1.103–1.77)	1.5(1.193–1.845)	1.63(1.435–2.195)	1.465(1.165–1.798)
P		***<0.001	***<0.001	**0.007	0.323	**0.008
Mon (10^9/L)	0.34(0.29–0.3975)	0.45(0.37–0.5975)	0.5(0.408–0.673)	0.435(0.348–0.563)	0.45(0.36–0.525)	0.435(0.365–0.5)
P		***<0.001	***<0.001	**0.001	*0.023	***<0.001
Hb (g/L)	136(130–142)	128(122–136)	126(119–135)	132(120.3–142.8)	142(124–154.5)	133(125.5–140.3)
P		***<0.001	***<0.001	0.074	*0.017	0.537
ESR (mm/h)		20(11.75–33.25)	23.5(16.25–32)	17(9.5–34.5)	16(6.75–21.25)	28(15.25–45)
Glu (mmol/L)	5.39(5.033–5.683)	5.04(4.695–5.275)	4.62(4.25–4.85)	4.825(4.548–5.123)	4.9(4.765–5.18)	5.02(4.613–5.208)
P		***<0.001	***<0.001	***<0.001	0.057	**0.003
ALB (g/L)	44.15(42.4–45.43)	41.5(37.9–43.6)	41.4(39.2–43.3)	43.5(42.48–45.1)	44(42.25–45.4)	43.25(40.75–45.65)
P		***<0.001	***<0.001	0.283	0.917	*0.047
ALT (U/L)	17.1(13.95–23.13)	17.7(14.05–22.43)	15.2(11.7–20.45)	16.5(12.85–20.35)	19.5(14.1–25.8)	13.05(10.68–18.68)
P		0.966	0.942	0.273	0.298	0.075
TC (mmol/L)	5.665(5.015–6.515)	5.455(4.645–6.45)	4.66(4.105–5.538)	4.54(3.85–5.27)	5.035(4.618–5.41)	4.67(4–5.87)
P		0.222	**0.005	***<0.001	0.154	*0.021
TG (mmol/L)	1.225(0.948–1.845)	1.13(0.87–1.61)	1.305(0.993–1.655)	1.09(0.78–1.4)	1.39(0.888–1.898)	1.3(1.01–1.79)
P		0.342	0.259	0.248	0.291	0.787
HDL (mmol/L)	1.395(1.188–1.545)	1.55(1.37–1.92)	1.36(1.203–1.638)	1.3(1.08–1.39)	1.33(1.115–1.555)	1.32(1.07–1.62)
P		***<0.001	0.116	0.354	0.438	0.802
LDL (mmol/L)	3.74(3.108–4.313)	3.45(2.88–4.03)	2.955(2.503–3.47)	2.83(2.39–3.67)	3.25(2.868–3.495)	3.22(2.6–3.72)
P		*0.035	**0.003	***<0.001	0.274	0.059
TBil (μmmol/L)	11.95(9.55–14.93)	11.3(9.2–14.3)	9.7(8–13.35)	11.05(9.6–14.93)	11.9(10.45–14.05)	11.95(9.725–14.55)
P		0.280	*0.045	0.654	0.745	0.336
Cr (μmmol/L)	57.6(53.3–66.18)	56.5(50–63)	58.15(51.43–64.85)	57.75(51.3–65.85)	62.8(54.25–69.45)	57(49.68–67.93)
P		0.130	0.674	0.849	0.209	0.685
UA (μmmol/L)	304(274–339.3)	238(193.8–288.3)	281(241.5–336.5)	286(243.8–324.5)	302(262–354)	286(239.3–363.3)
P		***<0.001	0.519	0.149	0.550	0.761
CRP (ug/ml)		3.13(0.855–9.765)	1.06(0.42–2.76)	1.325(0.493–2.723)	5.1(1.26–13.93)	0.865(0.428–2.133)
RF (U/ml)		53.81(23.63–161.4)				
NLR	1.82(1.24–2.09)	2.63(1.64–3.26)	2.51(1.54–2.83)	1.96(1.22–2.29)	2.13(1.34–2.75)	2.70(1.59–3.53)
		***<0.001	***<0.001	0.435	0.176	***0.002
PLR	127.6(93.89–162.2)	168.9(120.6–209.8)	160.5(119.0–199.5)	143.3(101.5–180.9)	143.8(106.0–171.2)	153.1(100.3–182.5)
		***<0.001	***<0.001	0.077	0.167	0.141

HCs indicates healthy controls; RA, rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; pSS, primary Sjogren's syndrome patients; AS, Ankylosing Spondylitis; UCTD, undifferentiated connective tissue diseases patients. BMI, body mass indexes; WBC, white blood cell; RBC, Red blood cell; PLT, platelet; Neu, neutrophil; Mon, monocyte; Hb, Hemoglobin; ESR, erythrocyte sedimentation rate; Glu, Glucose; ALB, Albumin; ALT, alanine aminotransferase; TC, total cholesterol; TG, Triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TBil, total bilirubin; Cr, Creatinine; UA, uric acid; CRP, C-reactive protein; RF, rheumatoid factor; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

(19.91 ng/ml [IQR, 16.75–23.10] $P = 0.002$) and pSS (20.99 ng/ml [IQR, 17.78–23.75] $P = 0.009$). However, the serum CTRP3 levels between UCTD (22.64 ng/ml [IQR, 20.30–35.62] $P = 0.058$) and HCs (24.84 ng/ml [IQR, 17.23–31.29]) were not significant (shown in Fig. 1A). No significant difference was found in CTRP9 levels between the RA (222.9 ng/ml [IQR, 197.3–261.7] $P = 0.152$), SLE (232 ng/ml [IQR, 193.6–273.9] $P = 0.377$), pSS (238.9 ng/ml [IQR, 206.3–279.3] $P = 0.647$, AS (223.6 ng/ml [IQR, 175.5–276.8] $P = 0.094$) or UCTD (261.4 ng/ml [IQR, 238.0–281.9] $P = 0.445$) patients and HCs (236.8 ng/ml [IQR, 162.8–313.0]) (shown in Fig. 1B).

3.3. Correlation of serum CTRP3 levels with blood routine indexes and biochemical

Since there were statistical differences of serum CTRP3 levels between HCs and patients with RA, SLE, pSS or AS, we further analyzed the relationship between serum CTRP3 levels and laboratory indexes. As the result shown in Table 2, none of the laboratory and clinical indicators was associated with CTRP3 in RA, SLE or AS patients. In pSS patients, CTRP3 was positively correlated with glucose and negatively correlated with creatinine and urine acid, which are weak (shown in Table 2).

3.4. Multivariate logistic regression analysis of RA, SLE, pSS and AS and serum CTRP3 levels

As a group of systemic disease, CTD was influenced by many confounding factors. To evaluate whether serum CTRP3 was an independent predictor, the variables with $P < 0.05$ in Table 1 were included. The result revealed that the relationships between serum CTRP3 levels and RA (shown in Table 3), SLE (shown in Table 4), pSS (shown in Table 5) and AS (shown in Table 6) were all stable.

3.5. ROC curve evaluation of CTRP3 for RA, SLE, pSS and AS diagnosis

ROC curve analysis was used to evaluate the diagnostic ability of CTRP3 to discriminate the presence of various CTD from HCs. The AUC value for CTRP3 in discriminating RA, SLE, pSS and AS patients from HCs were 0.691 (95 % CI, 0.605–0.777, $P < 0.001$), 0.727 (95 % CI, 0.647–0.806, $P < 0.001$), 0.658 (95 % CI, 0.554–0.761, $P = 0.014$) and 0.694 (95 % CI, 0.588–0.799, $P = 0.007$), respectively. The best cut-off values for CTRP3 as diagnostic markers of RA, SLE, pSS and AS were 24.98 ng/ml (sensitivity of 86.72 %, a specificity of 55.41 %), 19.34 ng/ml (sensitivity of 59.76 %, specificity of 72.97 %), 25.91 ng/ml (sensitivity of 85.71 %, a specificity of 52.70 %), 21.89 ng/ml (sensitivity of 66.67 %, specificity of 67.57 %), respectively (shown in Fig. 2A–D).

4. Discussion

In the present study, we comprehensively and systematically evaluated CTRP3 and CTRP9 levels in various CTD patients. Our novel contributions include the following:for the first time, we assessed serum levels of CTRP3 and CTRP9 in various CTD patients and HCs. The results revealed that CTRP3 levels were significantly decreased in RA,SLE, pSS and AS patients compared to HCs, while serum CTRP9 level did not significant differences between any CTD subgroup and HCs. Furthermore, CTRP3 was not found to be associated with clinical and laboratory indices in RA, SLE or AS patients, but exhibited a weak correlation with blood glucose, creatinine and urine acid in pSS patients. Additionally, CTRP3 emerged as an independent predictor for RA, SLE, pSS and AS. Finally, CTRP3 showed a potential biomarker for discriminating RA, SLE, pSS and AS from HCs.

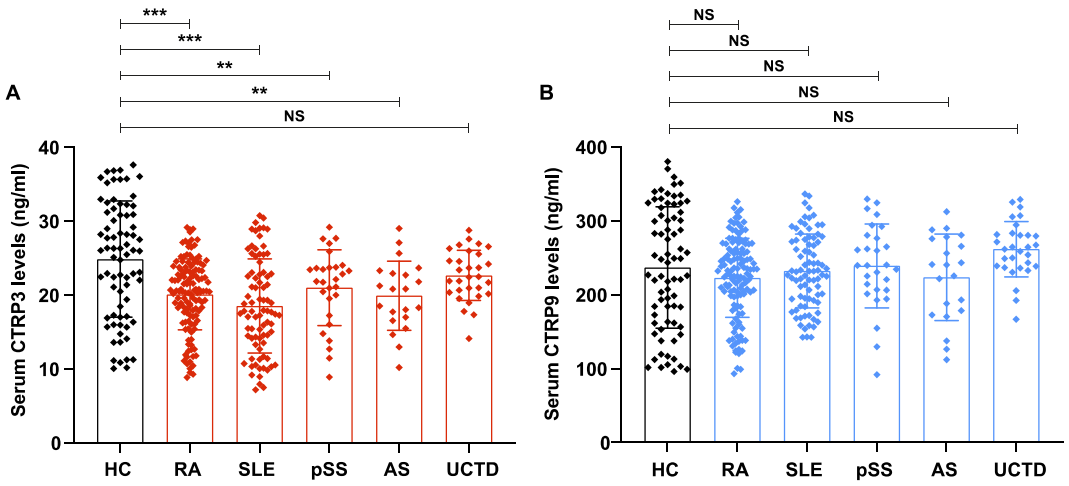

Fig. 1. Comparison of serum CTRP3(A) and CTRP9(B) levels in various CTD patients and healthy controls. A. Serum CTRP3 levels were compared between patients with RA (n = 128), SLE (n = 82), pSS (n = 28), AS (n = 21), UCTD (n = 30) and HC (n = 74). B. Serum CTRP9 levels were compared between patients with RA(n = 128), SLE (n = 82), pSS (n = 28), AS (n = 21), UCTD (n = 30) and HC (n = 74). HC, healthy controls; RA, rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; pSS, primary Sjogren's syndrome patients; AS, Ankylosing Spondylitis; UCTD, undifferentiated connective tissue diseases patients. NS, not significant. $^{**}P < 0.01$, $^{***}P < 0.001$.

Table 2
Association between serum CTRP3 levels and clinical and laboratory characteristics in patients with RA, SLE, pSS and AS.

	RA		SLE		pSS		AS	
	r	*P*	r	*P*	r	*P*	r	*P*
Age	0.126	0.158	0.326	0.003	−0.312	0.106	−0.345	0.126
BMI	0.043	0.691	−0.046	0.725	−0.048	0.842	−0.118	0.746
WBC (10^9/L)	−0.087	0.328	−0.039	0.731	0.026	0.894	−0.329	0.145
RBC (10^{12}/L)	−0.098	0.274	0.133	0.234	0.020	0.919	−0.193	0.403
PLT (10^9/L)	−0.155	0.081	0.090	0.424	−0.250	0.199	0.390	0.390
Neu (10^9/L)	−0.084	0.344	−0.122	0.275	0.007	0.973	−0.253	0.269
Lym (10^9/L)	−0.037	0.683	0.238	0.031	0.152	0.441	−0.265	0.246
Mon (10^9/L)	−0.002	0.982	−0.035	0.753	−0.010	0.959	−0.295	0.195
Hb (g/L)	0.086	0.335	0.207	0.063	−0.085	0.667	−0.047	0.839
ESR (mm/h)	−0.037	0.679	−0.099	0.379	−0.149	0.448	0.171	0.460
Glu (mmol/L)	0.049	0.590	0.142	0.206	0.407	*0.039	0.295	0.194
ALB (g/L)	0.069	0.440	0.116	0.305	0.023	0.911	0.084	0.716
ALT (U/L)	−0.059	0.509	−0.067	0.554	−0.013	0.950	−0.398	0.074
TC (mmol/L)	0.178	0.129	0.103	0.363	0.114	0.604	−0.185	0.609
TG (mmol/L)	0.066	0.573	0.004	0.975	0.084	0.704	−0.016	0.964
HDL (mmol/L)	0.046	0.697	−0.008	0.941	−0.020	0.927	0.147	0.685
LDL (mmol/L)	0.186	0.111	0.089	0.431	0.150	0.496	−0.096	0.793
TBil (μmmol/L)	0.054	0.546	−0.020	0.878	−0.046	0.824	0.284	0.212
Cr (μmmol/L)	0.151	0.092	0.044	0.702	−0.479	*0.013	−0.003	0.989
UA (μmmol/L)	−0.051	0.568	−0.046	0.684	−0.389	*0.049	−0.005	0.982
CRP (ug/ml)	−0.148	0.111	−0.020	0.873	−0.085	0.721	−0.326	0.201
RF (U/ml)	−0.025	0.794						
NLR	−0.029	0.743	−0.189	0.090	−0.124	0.531	−0.029	0.901
PLR	−0.085	0.340	−0.126	0.260	−0.2339	0.231	0.444	*0.044

RA indicates rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; pSS, primary Sjogren's syndrome; AS, ankylosing Spondylitis; BMI, Body Mass Index; WBC, white blood cell; RBC, Red blood cell; PLT, Platelet; Neu, Neutrophil; Lym, Lymphocyte; Mon, Monocyte; Hb, Hemoglobin; ESR, erythrocyte sedimentation rate; Glu, Glucose; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low density lipoprotein; TBil, total bilirubin; Cr, creatinine; UA, uric acid; CRP, C-reactive protein; RF, rheumatoid factor; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. *$P < 0.05$.

Table 3
Multivariate logistic regression analysis of RA risks.

	B	S.E.	OR	95%CI	*P*
CTRP3	−0.148	0.050	0.862	0.782–0.95	**0.003
Sex	−0.687	1.030	0.503	0.067–3.789	0.505
Age	0.030	0.031	1.030	0.969–1.095	0.343
RBC	−0.463	1.087	0.629	0.075–5.295	0.670
Neu	0.090	0.619	1.094	0.325–3.681	0.884
Lym	−2.523	0.992	0.080	0.011–0.56	*0.011
Mon	0.013	0.004	1.013	1.006–1.021	***<0.001
Hb	−0.074	0.039	0.929	0.861–1.003	0.059
Glu	−1.957	0.751	0.141	0.032–0.616	**0.009
ALB	−0.094	0.109	0.910	0.735–1.128	0.389
HDL	3.125	1.223	22.751	2.071–249.874	*0.011
UA	−0.020	0.007	0.980	0.968–0.994	**0.004
NLR	0.327	0.749	1.387	0.32–6.019	0.662
PLR	−0.008	0.009	0.992	0.975–1.008	0.332

RBC indicates Red blood cell; Neu, Neutrophil; Lym, Lymphocyte; Mon, Monocyte; Hb, Hemoglobin; Glu, Glucose; ALB, albumin; HDL, high-density lipoprotein; UA, uric acid; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

CTRPs, a highly conserved family of adiponectin paralogs, play crucial roles in various physiological and pathological processes, including blood lipid regulation [3], insulin sensitization [17] and anti-inflammatory effects. Among all CTRPs, CTRP3 has been investigated extensively and shows great potential for clinical applications. CTRP3 had been found to play important regulatory roles in post-ischemic cardiac remodeling and cardiac disfunction, diabetes mellitus, diabetic cardiomyopathy, high-fat diet-induced male reproductive dysfunction, tendinopathy, etc [18–20]. Recently, CTRP3 has been reported to exert a protective role in the development of collagen-induced arthritis in mice [21]. However, the expression of CTRP3 has shown contradictory results in RA patients and RA mouse models, with decreased expression in RA patients and increased expression in RA mouse models [21]. This discrepancy might be due to species differences. In SLE patients, especially those with neuropsychiatric SLE, the expression level of CTRP3 was significantly decreased [22]. Consistent with these findings, our study demonstrated decreased serum CTRP3 levels in SLE patients. Furthermore, we performed the correlation analysis between CTRP3 and clinical laboratory indexes in RA and SLE patients. CTRP3 did not show correlation with blood routine and biochemical indices. In addition, we investigated the relationship between CTRP3 and

Table 4
Multivariate logistic regression analysis of SLE risks.

	B	S.E.	OR	95%CI	*P*
CTRP3	−0.119	0.057	0.888	0.793–0.993	*0.038
Sex	−0.585	1.227	0.557	0.05–6.171	0.633
Age	−0.073	0.033	0.929	0.871–0.992	*0.028
RBC	−3.731	1.499	0.024	0.001–0.452	*0.013
Lym	−2.830	1.415	0.059	0.004–0.946	*0.046
Mon	0.017	0.005	1.018	1.008–1.027	***<0.001
Hb	0.005	0.060	1.005	0.894–1.13	0.927
Glu	−3.292	1.018	0.037	0.005–0.273	**0.001
TC	0.407	1.004	1.502	0.21–10.74	0.685
LDL	0.122	1.269	1.129	0.094–13.579	0.924
TBil	−0.031	0.091	0.969	0.812–1.158	0.731
NLR	−0.397	0.449	0.672	0.279–1.62	0.376
PLR	0.007	0.011	1.007	0.987–1.029	0.488

RBC indicates Red blood cell; Lym, Lymphocyte; Mon, Monocyte; Hb, Hemoglobin; Glu, Glucose; TC, total cholesterol; LDL, low density lipoprotein; TBil, total bilirubin; $*P < 0.05$, $***P < 0.001$.

Table 5
Multivariate logistic regression analysis of pSS risks.

	B	S.E.	OR	95%CI	*P*
CTRP3	−0.136	0.066	0.873	0.767–0.993	*0.039
Sex	3.461	3.453	31.838	0.037–27682.408	0.316
Age	−0.037	0.042	0.964	0.888–1.046	0.373
Lym	−3.534	1.128	0.029	0.003–0.266	**0.002
Mon	0.016	0.005	1.016	1.007–1.025	***<0.001
Glu	−2.324	1.134	0.098	0.011–0.903	*0.040
TC	−3.078	1.714	0.046	0.002–1.326	0.073
LDL	3.125	2.370	22.757	0.219–2367.571	0.187

Lym indicates Lymphocyte; Mon, Monocyte; Glu, Glucose; TC, total cholesterol; LDL, low density lipoprotein; $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

Table 6
Multivariate logistic regression analysis of AS risks.

	B	S.E.	OR	95%CI	*P*
CTRP3	−0.258	0.116	0.773	0.616–0.97	*0.026
Sex	−2.454	1.402	0.086	0.005–1.342	0.080
Age	0.003	0.052	1.003	0.905–1.112	0.949
RBC	1.728	1.722	5.628	0.193–164.436	0.316
PLT	0.015	0.010	1.015	0.996–1.035	0.124
Lym	−2.939	1.429	0.053	0.003–0.871	*0.040
Mon	0.009	0.005	1.009	1–1.018	0.046
Glu	0.107	0.714	1.113	0.274–4.51	0.881
ALB	0.298	0.273	1.347	0.788–2.3	0.276
TC	−1.648	0.915	0.192	0.032–1.155	0.072

RBC indicates Red blood cell; PLT, Platelet; Lym, Lymphocyte; Mon, Monocyte; Glu, Glucose; ALB, albumin; TC, total cholesterol; $*P < 0.05$.

inflammatory biomarkers, such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which were elevated in both RA and SLE patients and can distinguish them from HCs [23,24]. However, neither NLR nor PLR showed correlation with CTRP3.

Recent studies have increasingly confirmed that inflammation regulates the occurrence and progression of CTD. Acting as an anti-inflammatory mediator, CTRP3 was negatively associated with several inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, C-reactive protein and erythrocyte sedimentation rate [25]. Several studies found that CTRP3 exerts anti-inflammatory effects through various signaling pathways in multiple inflammation-related diseases. In psoriasis, adipocyte-derived CTRP3 exerts anti-inflammatory effects via the LAMP1-STAT3 axis [26]. CTRP3 also alleviates Ox-LDL-induced inflammatory responses and endothelial dysfunction in mouse aortic endothelial cells by activating the PI3K/Akt/eNOS pathway (30887395). Additionally, CTRP3 serves as a novel regulator of inflammation and apoptosis linked to depressive-like behavior by modulating the p38 and JNK signaling pathways [27]. However, in RA or SLE patients, CTRP3 showed no association with CRP or ESR, suggesting that CTRP3 may regulate RA or SLE independently of anti-inflammatory mechanisms. Besides its anti-inflammatory role, CTRP3 also involved in metabolism and immune regulation. At present, the majority of studies consistently show that CTRP3 levels are decreased in the blood of obese patients, and it effectively reduces the production of inflammatory factors, suppresses the activation of inflammatory signals, and diminishes lipid formation [28]. CTRP3 was considered as a promising therapeutic target for managing metabolic syndrome or obesity.

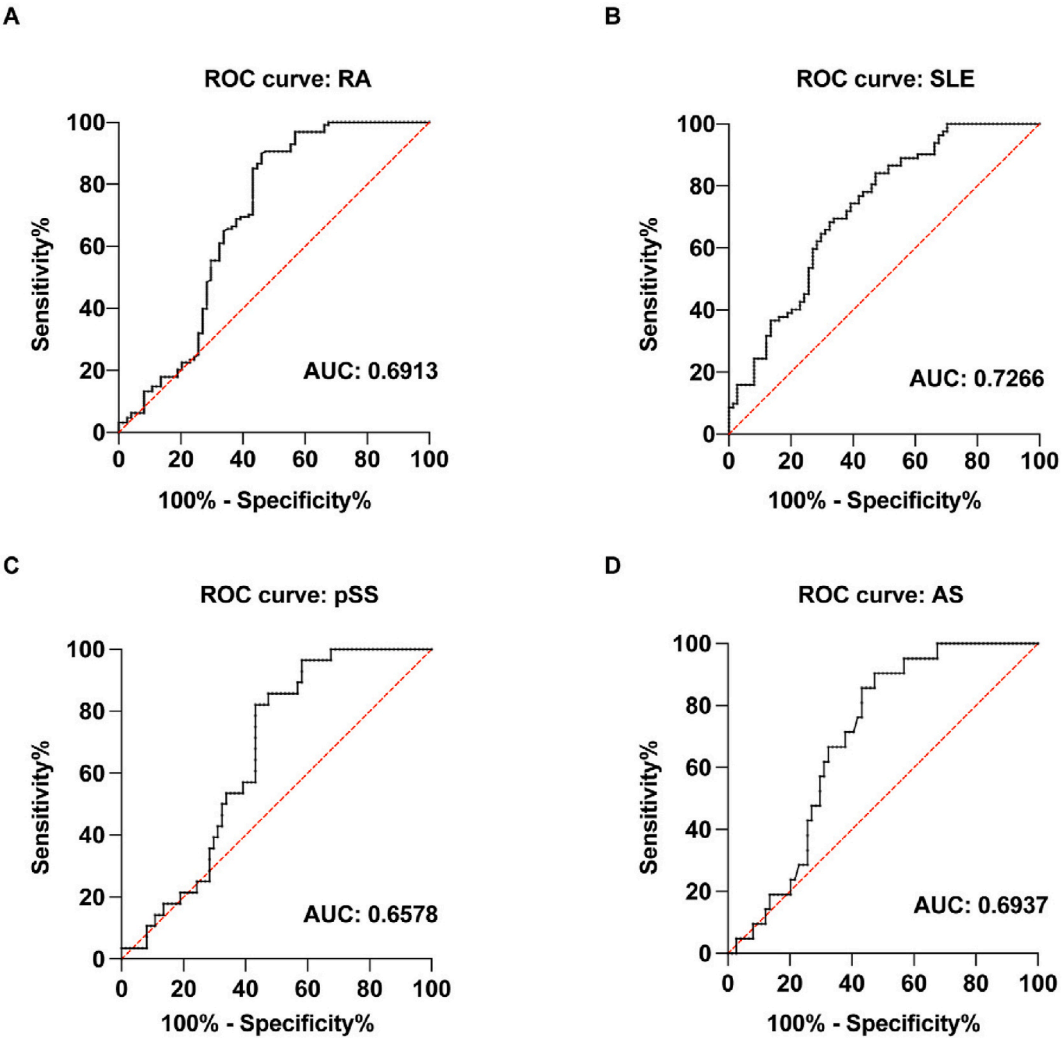

Fig. 2. ROC curves of serum CTRP3 for predicting RA,SLE,pSS and AS. AUC indicates area under curve. A. ROC was performed for analysis of CTRP3 of RA patients (n = 128) and healthy controls (n = 74). B. ROC was performed for analysis of CTRP3 of SLE patients (n = 82) and HC (n = 74). C. ROC was performed for analysis of CTRP3 of pSS patients (n = 28) and HC (n = 74). D. ROC was performed for analysis of CTRP3 of AS patients (n = 21) and HC (n = 74). ROC, receiver operating characteristic; HC, healthy controls; RA, rheumatoid arthritis; SLE, Systemic Lupus Erythematosus; pSS, primary Sjogren's syndrome patients; AS, Ankylosing Spondyliti; AUC, area under the ROC curve.

Furthermore, numerous studies have identified a correlation between the individual components of metabolic syndrome and rheumatoid arthritis. In this regard, a prospective population-based cohort study involving 55,037 participants from the Danish Diet, Cancer, and Health cohort found that women with a high waist circumference were more likely to develop RA compared to those with a low waist circumference [29]. Additionally, CTRP-3 serves as a potent antagonist of peptidoglycan-induced, NOD1-mediated inflammation and LPS-induced NOD1 expression [30]. CTRP3, functioning as an endogenous regulator, can suppress myelin oligodendrocyte glycoprotein-induced IL-17 production from T cells by modulating both T cells and dendritic cells [6]. Abnormal regulation of innate and adaptive immunity is an important factor in the development and progression of rheumatic diseases. Therefore, We speculate that CTRP3 may regulate RA or SLE via potential metabolic and/or immune regulatory pathway.

We also observed CTRP3 was weakly correlated with blood glucose, creatinine and urine acid which was cognized as metabolically relevant indicators in pSS patients. Augusto et al. identified high metabolic syndrome frequency and abnormal adipocytokine profile in pSS. The association of MetS with elevated IL-1beta level suggests that inflammation plays an important role in its pathogenesis [31]. Furthermore, pSS is known as a type of autoimmune disease with multiple organs involved apart from exocrine glands. Renal involvement is one of the most common manifestations of pSS. Our study suggests that CTRP3 might regulate pSS via metabolic pathway and involved in pSS-related renal impairment.

Regarding pSS and AS, CTRP3 expressions had never been reported in patients or animal models before. In this study, our finding demonstrated that the serum CTRP3 levels were significantly decreased in pSS and AS patients, which aligns with its expressions in many other diseases [32–34]. We also found no significant difference in serum CTRP3 levels between UCTD patients and HCs,

supporting the hypothesis that CTRP3 is involved in CTD differentiation. However, few studies have been reported on the biological function of CTRP3 in CTD. Moreover, multivariate analysis revealed that the association between CTRP3 and RA, SLE, pSS AND SLE were all independent of other risk factors. These results suggest that CTRP3 is a novel biomarker.

CTRP9 has been extensively investigated compared to other CTRPs, including CTRP3, suggesting a potential role for CTRP9 in CTD. Of all the CTRP paralogs, CTRP9 shows the highest degree of amino acid identity to adiponectin in its globular C1q domain [2], indicating CTRP9 may have similar functions as adiponectin. Adiponectin is a component of the inflammatory cascade in rheumatoid diseases. However, our study found no difference in CTRP9 expression difference between CTD patients and HCs, suggesting that CTRP9 might not be involved in pathological processes of CTD. As far as we know, this is the first report on CTRP9 expression in patients with various CTDs.

However, this study had several limitations. Firstly, its retrospective cross-sectional design makes it difficult to confirm a causal relation between decreased serum CTRP3 levels and RA, SLE, pSS and AS patients, and the potential mechanism was not investigated. Secondly, the age and gender between every subgroup was not all matched, logistic regression with adjustment age and/or were carried out to eliminate these confounder factors. Thirdly, the numbers of patients for some subgroups of CTD were not ideally balanced with the number of HCs, especially for pSS, AS and UCTD patients, due to the characteristics of theses diseases. In addition, as a single-center study, the overall sample size was relatively small. Therefore, further prospective and randomized clinical trials with larger sample sizes are needed to confirm the role of CTRP3 in RA, SLE, pSS, and AS. Moreover, further studies are needed to elucidate the mechanisms underlying the association between CTRP3 and CTD.

In conclusion, our findings demonstrated that serum CTRP3 levels significantly decreased in patients with RA, SLE and AS compared to HCs, which may broaden our understanding of the multiple biological functions of CTRP3. Of clinical relevance, CTRP3 may serve as a novel therapeutic target for managing CTD. We can speculate that the supplementation of CTRP3 recombinant protein may be an effective treatment strategy to protect CTD patients. Prospective clinical trials are required to confirm the role of CTRP3 in the occurrence and development of CTD.

Ethics statement

This study was approved by the ethics committee of the First People's Hospital of Wenling (Zhejiang, China), the authorization number is KY-2019-1013-01.

Data availability statement

The data are available from the first author on reasonable request.

CRediT authorship contribution statement

Lisha Ma: Writing – review & editing, Writing – original draft, Investigation. **Jiangbo Lin:** Writing – original draft, Formal analysis, Data curation. **Miaoli Shao:** Formal analysis, Data curation. **Binxuan Chen:** Software, Formal analysis, Data curation. **Renfang Zhou:** Writing – review & editing. **Jianfeng Shi:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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