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ORIGINAL ARTICLE

Clinical characteristics of rheumatoid arthritis patients with peripheral neuropathy and potential related risk factors

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Abstract

Objectives To investigate potential risk factors of peripheral neuropathy (PN) in rheumatoid arthritis patients (RA).

Methods Eighty-eight patients with RA were enrolled in this study, including patients with PN ($n = 44$; 28 patients with multiple nerves (MN) involvement and 16 patients with single nerve (SN) involvement) and without ($n = 44$) peripheral neuropathy were enrolled. Their clinical features were comprehensively collected including symptoms/signs, lab results, electromyogram data. *T* test or chi-squared test and further binary regression analysis were used to explore risk factors based on analyzing these clinical features.

Results There was no difference as regards patients' age (59.50 ± 8.11 vs 58.68 ± 11.44 years), gender ratio (female/male, 29:15 vs 29:15), and disease duration (6.34 ± 7.87 vs 8.13 ± 9.52 months) between patients with and without PN. RA patients with PN had lower total protein (61.13 ± 7.06 vs 66.06 ± 6.44 g/L), anti-CCP levels (239.13 ± 203.77 vs 361.41 ± 168.09 U/ml) compared with control patients, while patients with MN had higher inflammatory parameters (white blood cells, platelet, C-reactive protein (CRP), erythrocyte sedimentation rate, rheumatoid factor) than patients with SN ($p < 0.05$). Low total protein (< 63 g/L, 30/44 vs. 12/44) and anti-CCP (< 285.7 U/ml, 27/44 vs. 11/44) were risk factors for patients with PN, while CRP (> 6 mg/L, 26/28 vs. 6/16) and PLT (> 243×10^9/L, 25/28 vs.5/16) were related to the development of MN.

Conclusions RA patients with PN, especially MN can present various clinical symptoms, which will aggravate patients' anxiety and depression status. The increase of blood platelet, and CRP levels and decrease of blood albumin are probable risk factors for PN in RA patients.

Keywords Peripheral neuropathy · Rheumatoid arthritis · Risk factors

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder that mainly involves patients' joints. The prevalence of RA patients is about from 0.2–0.3% in Eastern Asians to 0.5–1% in many populations of European ancestry and to 5–7% in American Indians [1, 2]. It can occur in any age of the population and any gender but mostly in the female aged 40–60 years.

Although RA predominantly involves joint, it is a systemic disorder, which can affect patients' skin, respiratory, cardiovascular, and nervous system. The main agony of patients with RA is arthralgia and function loss of involved joints [3]. However, neural involvement might also contribute to body dysfunction and compromised life quality. According to the previous report, peripheral neuropathy (PN) in patients with RA can reduce sensation over the distribution of the affected nerve, which may be also associated with muscle wasting and functional impairment [4]. Another report showed that the neural involvement in patients with RA was associated with significant morbidity and even reduced lifespan in some cases [5, 6]. Therefore, patients' neural involvement was worthy to be taken into account in clinical practices.

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According to previous reports, patients with PN can present subclinical and clinical symptoms [5, 7]. About two-thirds patients manifested as subclinical neuropathy without obvious symptoms [6–8], while patients with obvious neuropathic symptoms account variably from 0.5% to 85% [7, 9, 11]. In those patients with clinical neuropathy, peripheral nerve involvement can manifest as pure motor neuropathy, pure sensory neuropathy, mononeuritis multiplex, and carpal tunnel syndrome. The suggestive causes include nerve entrapment, drug toxicity, vasculitis, pression from surrounding swollen arthral tissue, and rarely amyloidosis [10–14]. As a whole, this neural involvement would hugely affect the patients' living quality and compromise treatment effect.

Currently, the most applicable examination to diagnose neural disorder in RA patients is to perform electromyography when patients complain of peripheral neural symptoms [11, 12, 14]. However, the neurologic syndromes in the early period can be various and nonspecific, and the peripheral neuropathy can progress quickly or develop slowly [5–8]. Nonspecific neurologic manifestations in RA patients may be easily overlooked until they develop serious neural injury. Thus, it is crucial to discover some clinical risk factors to predict patients' neural involvement. Some clinical risk factors will help the attending physician to enhance the awareness of these complications to improve the early diagnostic rate of PN. Early treatment is often helpful in averting the development of serious neurologic complications in RA patients [7]. In previous studies, although neuropathy in RA patients has been analyzed, they mainly focused on the incidence, types of various PN rather than the risk or predictive factors, which are more important to alert physicians about potential neural impairment.

Therefore, in the present study, we aim to explore the potential risk factors of PN in those RA patients by analyzing and comparing multiple clinical characteristics between patients with and without PN in RA.

Methods and materials

Study population

This was a cross-sectional and observational case-control study. In this study, 834 RA patients' admissions were observed and screened from July, 2015 to November, 2016 in our center (Department of Rheumatology, Linyi People's Hospital, Linyi City, China). All patients with RA fulfilled the 1987 ACR criteria for RA [15]. RA patients were excluded if they (a) had systemic diseases or conditions associated with neuropathy (i.e., other autoimmune diseases before RA, diabetes mellitus, cancer, hepatitis, spinal compression diseases, hypothyroidism, and amyloidosis), (b) took other drugs that affect the metabolism of nerve cells, or (c) were diagnosed with an acute or chronic infection. The inclusion criteria included patients with (1) definite RA, (2) peripheral neural symptoms or signs, (3) the electromyogram abnormalities to show the neurogenic damage, and (4) the willingness to participate this study. Among them, 44 patients with PN were enrolled, and 7 RA patients with obvious neurological symptoms refused to perform electromyogram and did not join in this research. After these 44 patients with PN were enrolled, corresponding age, gender, and disease duration-matched RA patients without PN who would like to perform electromyogram were selected. The peripheral condition of all those patients has been verified by electromyogram. Additionally, no difference was observed regarding patients' drug usage between two groups (Supplementary Table 1).

Data collection

General information, full clinical records were collected in the present study, which included age, gender, lifestyle (alcohol intake, smoking habit), disease duration, clinical symptoms, neurological signs, lab results, and electromyogram data. In terms of clinical symptoms and signs, general RA-related, as well as neural symptoms/signs, were collected. In terms of neurological examination, motor system (amyotrophy, fasciculation, myodynamia, muscular tension), sensory nerve (algesthesia, pselaphesia, thermesthesia, topesthesia, seismesthesia, kinesthesia), reflex (superficial reflex, deep reflex, pathologic reflex), and autonomic symptoms (hydrosis, adiapneustia, alacrimia) were examined. The specific neural injury features were obtained from electromyogram results.

Lab tests included blood routine test (hemoglobin, white blood cells, platelet, erythrocyte sedimentation rate, C-reactive protein (CRP), liver function test, protein (total protein, albumin, globulin), rheumatoid factor, and auto-antibody detection (anti-cyclic citrullinated peptides, anti-nuclear antibody and anti-extractable nuclear antigens antibody).

Electromyogram

Electrophysiological studies were performed with our standard laboratory methods in accordance with the recommended protocol of the American Association of Electrodiagnostic Medicine using the Dantec KeyPoint EMG instrument (Denmark). Specifically, electrophysiological study was done for both motor conductions and sensory conductions. In motor conductions, distal latency, conduction velocity, amplitude, F wave, and H-wave were assessed. The summation of all the underlying individual muscle fiber action potentials was represented by the compound muscle action potential (CMAP).

In sensory conductions, distal latency, conduction velocity, and amplitude were assessed. Entrapment neuropathy: Patients have local pain or other clinical manifestations of nerve injury, and the electrophysiological examinations confirmed which nerve (such as median nerve, ulnar nerve or posterior interosseous nerve) was neurogenic injury.

Disease assessment

Regarding RA disease activity, all patients were assessed according disease activity score 28 (DAS28) [16], while with respect to neural involvement, neuropathy total symptom score-6 (NTSS-6) [17], neuropathy disability score (NDS) [18], and Toronto clinical scoring system (TCSS) [19] were applied. Moreover, hospital anxiety and depression score (anxiety component, HAD-A) and hospital anxiety and depression score (depression component, HAD-D) [20] and the health assessment questionnaire (HAQ) [21] were used to assess patients' psychological and physical status. As a whole, all enrolled patients were assessed from four aspects: patients' subjective symptoms, neurological examination, electromyogram results, and functional assessment.

Statistical analysis

All those variables mentioned above were compared between different groups by *T* test or chi-squared test. For ESR, CRP, and platelet data in control group, since their distribution skewed to right, 8% of right-most data was excluded when comparing these data to corresponding data in other groups. Patients' measurable parameters were described as mean ± standard deviation, while the numerical indicators were presented as the ratio. For those measurement parameters with the significant differences, the receiver operating characteristic curve (ROC) was applied to evaluate their performance to differentiate patients with or without PN. In addition, the cut-off value was obtained to transform these measurable parameters into bivariate data that can be enrolled in further logistic regression analysis. Binary regression analysis was performed with the forward selection method to assess risk factors for patients with neuropathy. All statistical analyses were performed using SPSS version 20.0 (Chicago, IL, USA). P values < 0.05 were considered to indicate statistically significant differences.

Results

Clinical characteristics

General information, lab results, and disease assessment data are shown in Table 1, while clinical characteristics or neural examination results are demonstrated in Table 2. As shown in Table 1, the mean ages of RA patients with and without PN were 59.50 (SD = 8.11) and 58.68 years (SD = 11.44) respectively, and the gender ratio was same in both groups (female/male, 29:15). In addition, based on the patients' neural involvement [22], patients can be divided into patients with multiple nerves (MN) involvement (including 11 polyneuropathy and 17 mononeuritis multiplex) and patients with single nerve (SN) involvement (including 4 mononeuropathy and 12 entrapment neuropathy (10 carpal tunnel syndrome, 0 tarsal tunnel syndrome, 0 entrapment of posterior interosseous and 2 ulnar nerves)) whose information is also shown in Tables 1 and 2. With respect to patients' peripheral neural symptoms, 43 (97.73%) patients were accompanied with numbness, which was the commonest symptom in patients with PN, while the aching feeling was the second frequently occurred symptom, presenting in 24 (54.55%) patients. In addition, 20 (45.45%) patients had acanthesthesia; 16 (36.36%) patients felt weakness and 11 (25%) patients suffered from electrical sensation and burning sensation respectively.

In terms of neurological examination, common abnormal sensory nervous presentations included decreased algesthesia (29, 65.91%), decreased pselaphesia (27, 61.36%), abnormal seismesthesia (20, 45.45%), and abnormal thermesthesia (18, 40.91%). As for the motor system, 23 (52.27%) patients presented abnormal myodynamia. In addition, abnormal deep reflex occurred in 37 (84.09%) patients. Among them, the common abnormal deep reflex was decreased knee jerk reflex (19, 43.18%) followed with decreased ankle reflex (17, 38.64%) and disappeared ankle reflex (16, 36.36%). Other characteristics of neural symptoms or signs can be seen in Table 2.

On the other hand, according to the results of electromyogram, 30 (68.18%) patients were accompanied with sensory motor damage involvement; 6 (13.64%) patients were accompanied with pure motor damage involvement; 8 (18.18%) patients were accompanied with pure sensory damage involvement. The carpal tunnel syndrome had a high incidence of 10 (22.73%, Table 2).

Comparison between patients with and without PN and potential risk factors

No significant differences were observed between patients with PN and control patients in terms of basic characteristics such as age, gender ratio, and disease activity status (DAS > 2.6) etc. (Table 1). With respect to lab results, patients with PN had statistically lower total protein (61.13 ± 7.06 vs. 66.06 ± 6.44 g/L), globulin (31.85 ± 5.63 vs. 34.64 ± 5.08 g/L), and anti-CCP antibody (239.13 ± 203.77 vs. 361.41 ± 168.09 U/ml) levels

Table 1 Patients' clinical characteristics

Parameters	Patients with PN			Control patients	*P* value[#]	*P* value[*]	*P* value[&]	*P* value
	MN (*N* = 28)	SN (*N* = 16)	Total (*N* = 44)	(*N* = 44)				
Age (M ± SD)	58.03 ± 7.96	61.87 ± 8.04	59.50 ± 8.11	58.68 ± 11.44	> 0.05	> 0.05	> 0.05	> 0.05
Gender (F:M)	13:9	16:6	29:15	29:15	> 0.05	> 0.05	> 0.05	> 0.05
Disease duration (M ± SD)	6.12 ± 4.95	6.74 ± 11.54	6.34 ± 7.87	8.13 ± 9.52	> 0.05	> 0.05	> 0.05	> 0.05
Treatment duration (M ± SD)	3.82 ± 4.16	3.75 ± 8.54	3.79 ± 6.02	4.82 ± 6.12	> 0.05	> 0.05	> 0.05	> 0.05
PN duration (M ± SD)	1.78 ± 3.81	1.28 ± 2.74	1.53 ± 3.29	/	>0.05	/	/	/
PN treatment duration (M ± SD)	0.92 ± 2.32	0.65 ± 0.74	0.82 ± 1.90	/	> 0.05	/	/	/
Smoking (*n*, %)	5 (17.86)	1 (6.25)	6 (13.64)	6 (13.64)	> 0.05	> 0.05	> 0.05	> 0.05
Drinking (*n*, %)	4 (14.29)	0 (0)	4 (9.09)	7 (15.91)	> 0.05	> 0.05	> 0.05	> 0.05
Rash (*n*, %)	9 (32.14)	0 (0)	9 (20.45)	5 (11.36)	0.01	> 0.05	> 0.05	> 0.05
Lab results								
Hb (g/L, M ± SD)	119.32 ± 17.89	121.09 ± 11.22	119.96 ± 15.67	121.08 ± 20.36	> 0.05	> 0.05	> 0.05	> 0.05
WBC ($\times 10^9$/L, M ± SD)	*9.21 ± 3.29*	*6.24 ± 2.19*	8.13 ± 3.25	6.86 ± 2.65	*0.04*	*0.00*	> 0.05	> 0.05
PLT ($\times 10^9$/L, M ± SD)	*348.71 ± 123.32*	*249.31 ± 88.22*	299.05 ± 121.81	269.60 ± 93.30[a]	*0.00*	> 0.05	> 0.05	> 0.05
ESR (mm/h, M ± SD)	*60.96 ± 30.45*	*30.25 ± 25.87*	49.8 ± 32.23	45.06 ± 26.20[a]	*0.00*	*0.02*	> 0.05	> 0.05
CRP (mg/L, M ± SD)	*63.16 ± 44.76*	*20.17 ± 31.51*	47.53 ± 45.19	34.74 ± 26.82[a]	*0.00*	*0.03*	> 0.05	> 0.05
TP (g/L, M ± SD)	60.05 ± 7.29	63.00 ± 6.45	61.13 ± 7.06	66.06 ± 6.44	> 0.05	*0.00*	> 0.05	*0.00*
A (g/L, M ± SD)	*27.89 ± 5.47*	*32.81 ± 5.35*	29.67 ± 5.86	31.42 ± 4.83	*0.00*	*0.01*	> 0.05	>0.05
G (g/L, M ± SD)	32.79 ± 5.55	30.20 ± 5.56	31.85 ± 5.63	34.64 ± 5.08	> 0.05	> 0.05	*0.01*	*0.02*
AST (IU/L, M ± SD)	16.46 ± 5.21	20.18 ± 8.76	17.81 ± 6.86	18.42 ± 6.44	> 0.05	> 0.05	> 0.05	> 0.05
ALT (IU/L, M ± SD)	21.09 ± 10.64	27.07 ± 19.95	23.26 ± 14.77	20.11 ± 10.14	> 0.05	> 0.05	> 0.05	> 0.05
IgG (g/L, M ± SD)	10.79 ± 2.68	14.07 ± 4.67	12.10 ± 3.86	10.50 ± 2.40	> 0.05	> 0.05	> 0.05	> 0.05
IgA (g/L, M ± SD)	2.73 ± 1.18	2.54 ± 0.95	2.56 ± 1.07	1.90 ± 0.73	> 0.05	0.02	> 0.05	> 0.05
IgM (g/L, M ± SD)	1.45 ± 0.47	1.75 ± 0.71	1.57 ± 0.58	1.21 ± 0.48	> 0.05	> 0.05	> 0.05	> 0.05
RF (IU/mL, M ± SD)	*430.61 ± 388.54*	*135.93 ± 179.72*	323.4 ± 355.84	314.49 ± 483.41	*0.00*	> 0.05	> 0.05	> 0.05
Anti-CCP (U/ml, M ± SD)	250.15 ± 190.08	223.29 ± 227.47	239.13 ± 203.77	361.41 ± 168.09	> 0.05	*0.02*	*0.01*	*0.00*
Positive ENA (*n*, %)	4(14.29)	4 (31.82)	8 (18.18)	9 (20.45)	> 0.05	> 0.05	> 0.05	0.60
Positive ANA (*n*, %)	15 (53.57)	9 (56.25)	24 (54.55)	18 (40.91)	> 0.05	> 0.05	> 0.05	1.00
Disease assessment								
DAS28 (M ± SD)	3.48 ± 1.05	3.35 ± 1.00	3.43 ± 1.02	3.51 ± 0.94	> 0.05	> 0.05	> 0.05	> 0.05
HAQ (M ± SD)	*29.68 ± 15.24*	*15.25 ± 12.88*	24.05 ± 15.88	22.08 ± 14.85	*0.04*	> 0.05	> 0.05	> 0.05
HAD-A (M ±S D)	10.95 ± 5.40	9.11 ± 4.94	10.36 ± 5.23	7.87 ± 3.92	> 0.05	*0.00*	> 0.05	*0.03*
HAD-D (M ± SD)	13.11 ± 4.73	10.78 ± 4.82	12.36 ± 4.79	9.56 ± 4.74	> 0.05	*0.01*	> 0.05	*0.02*
NTSS6 (M ± SD)	9.69 ± 6.34	5.38 ± 2.29	7.96 ± 5.44	0.49 ± 0.94	> 0.05	*0.00*	*0.00*	*0.00*
NDS (M ± SD)	*5.29 ± 3.35*	*1.94 ± 3.19*	4.07 ± 3.64	0.28 ± 0.94	*0.00*	*0.00*	*0.01*	*0.00*
TCSS (M ± SD)	*10.86 ± 4.40*	*5.50 ± 4.05*	8.91 ± 4.96	1.85 ± 2.41	*0.00*	*0.00*	*0.00*	*0.00*
DAS28 > 2.6 (*n*)	21 (75.00)	13 (81.25)	34 (77.27)	33 (75)	> 0.05	> 0.05	> 0.05	> 0.05

RA treatment duration was the time of application of glucocorticoids, disease modifying anti-rheumatic drugs and or biological agents. *P* value[#]: comparison between patients with MN and patients with SN; *P* value[*]: comparison between patients with MN and control patients; *P* value[&]: comparison between patients with SN and control patients; *P* value: comparison between total patients with PN and control patients

PN peripheral neuropathy, *MN* polyneuropathy and mononeuritis multiplex, *SN* mononeuropathy and entrapment neuropathy, *Hb* hemoglobin, *WBC*, white blood cell, *PLT*, platelet, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TP* total protein, *A* albumin, *G* globulin, *RF* rheumatoid factor, *HAD-A* Hospital Anxiety and Depression Score (anxiety component), *HAD-D* Hospital Anxiety and Depression Score (depression component), *NTSS-6* Neuropathy Total Symptom Score-6, *NDS* neuropathy disability score, *TCSS* Toronto Clinical Scoring System, *HAQ* Health Assessment Questionnaire

[a] Trimmed mean and SD

in contrast with that of control patients ($p < 0.05$, Table 1). In addition, various assessment scores such as HAD-A, HAD-D, NTSS6, NDS, and TCSS were significantly higher in patients with PN in comparison with

Table 2 The peripheral involvement features of patients in this study

Parameters	RA patients with PN			Control patients	*P* value#	*P* value*	*P* value&	*P* value
	MN (*N* = 28)	SN (*N* = 16)	Total (*N* = 44)	(*N* = 44)				
Present of peripheral neural symptoms	28	16	44	4	> 0.05	*0.00*	*0.00*	*0.00*
Decreased algesthesia	22	7	29	1	*0.02*	*0.00*	*0.00*	*0.00*
Increased algesthesia	3	1	4	1	> 0.05	> 0.05	> 0.05	> 0.05
Decreased pselaphesia	22	5	27	3	*0.00*	*0.00*	*0.01*	*0.00*
Abnormal thermesthesia	15	3	18	0	*0.03*	*0.00*	*0.01*	*0.00*
Abnormal topesthesia	5	1	6	0	> 0.05	*0.00*	> 0.05	*0.03*
Abnormal seismesthesia	17	3	20	1	*0.01*	*0.00*	> 0.05	*0.00*
Abnormal kinesthesia	3	0	3	0	> 0.05	> 0.05	> 0.05	> 0.05
Amyothrophy	6	2	8	2	> 0.05	> 0.05	> 0.05	> 0.05
Fasciculation	1	0	1	0	> 0.05	> 0.05	> 0.05	> 0.05
Abnormal myodynamia	18	5	23	14	> 0.05	*0.02*	> 0.05	> 0.05
Abnormal muscular tension	3	0	3	0	> 0.05	> 0.05	> 0.05	> 0.05
Decreased abdominal skin reflection	0	1	1	0	> 0.05	> 0.05	> 0.05	> 0.05
Deep reflex	24	13	37	16	*0.00*	*0.00*	*0.00*	*0.00*
Decreased biceps reflex	6	4	10	0	> 0.05	*0.00*	*0.04*	*0.00*
Increased biceps reflex	2	0	2	0	> 0.05	> 0.05	> 0.05	> 0.05
Disappeared biceps reflex	2	2	4	0	> 0.05	> 0.05	> 0.05	> 0.05
Decreased triceps reflex	5	4	9	0	> 0.05	*0.01*	*0.04*	*0.00*
Disappeared triceps reflex	2	2	4	0	> 0.05	> 0.05	> 0.05	> 0.05
Increased brachioradialis reflexes	2	0	8	0	> 0.05	> 0.05	> 0.05	*0.00*
Decreased brachioradialis reflexes	4	4	2	0	> 0.05	*0.03*	*0.04*	> 0.05
Disappeared brachioradialis reflexes	1	2	3	0	> 0.05	> 0.05	> 0.05	> 0.05
Decreased knee jerk reflex	9	10	19	7	> 0.05	> 0.05	*0.02*	*0.02*
Increased knee jerk reflex	1	0	1	0	> 0.05	> 0.05	> 0.05	> 0.05
Disappeared knee jerk reflex	5	3	8	3	> 0.05	> 0.05	> 0.05	> 0.05
Pathological reflex	2	0	2	0	> 0.05	> 0.05	> 0.05	> 0.05
Decreased ankle reflex	9	8	17	13	> 0.05	> 0.05	> 0.05	> 0.05
Disappeared ankle reflex	13	3	16	3	> 0.05	*0.00*	> 0.05	*0.00*
Sensory motor	18	12	30	0	0.52	*0.00*	0.00	*0.00*
Pure motor	2	4	6	0	0.17	*0.15*	0.00	*0.02*
Pure sensory	8	0	8	0	0.04	*0.00*	/	*0.01*
Mononeuropathy	1	6	7	0	0.00	*0.39*	0.00	*0.01*
Carpal tunnel syndrome	0	10	10	0	0.00	/	0.00	*0.00*

P value# : comparison between patients with MN and patients with SN; *P* value* : comparison between patients with MN and control patients; *P* value& : comparison between patients with SN and control patients; *P* value: comparison between total patients with PN and control patients

PN peripheral neuropathy, *MN* polyneuropathy and mononeuritis multiplex, *SN* mononeuropathy and entrapment neuropathy

control patients ($p < 0.05$, Table 1). Using ROC, different cut-off values were obtained for these differential laboratory data (Table 3) which were further transformed into binary data and included into the binary logistic regression model with other significant categorical variables. It was observed that two parameters (anti-CCP (< 285.7 U/ml, 27/44 vs. 11/44, OR = 4.38), total protein (< 63 g/L, 30/44 vs. 12/44, OR = 5.18) were risk factors associated with patients with PN ($p < 0.05$, Table 4).

Comparison between patients with MN and patients without PN and potential risk factors

In contrast with control patients, patients with MN had significantly lower total protein (60.05 ± 7.29 vs. 66.06 ± 6.44 g/L), albumin (27.89 ± 5.47 vs 31.42 ± 4.83 g/L), and anti-CCP (250.15 ± 190.08 vs. 361.41 ± 168.09 U/ml) levels and higher WBC (9.21 ± 3.29 vs. 6.86 ± 2.65 × 10^9/L) levels (Table 1). In addition, higher HAD-A, HAD-D, NTSS6, NDS, and TCSS

Table 3 Univariate analysis for measurement parameters

Variables	AUC	$Value_{cut\ off}$	Sensitivity (%)	Specificity (%)	*P* value
Risk factors for patients with peripheral neuropathy compared with patients without peripheral neuropathy					
Anti-CCP (U/ml)	0.67	< 285.70	59	75.7	0.00
Total protein(g/L)	0.71	< 63.00	70.45	69.23	0.02
Globulin (g/L)	0.66	< 34.40	72.7	61.5	0.00
Risk factors for patients with multiple peripheral neural involvements compared with patients without peripheral neuropathy					
WBC (×109/L)	0.74	> 7.29	75.00	66.67	0.00
Total protein (g/L)	0.77	< 62.20	67.86	74.36	0.00
Albumin (g/L)	0.68	< 27.50	60.71	79.49	0.02
Anti-CCP(U/ml)	0.66	< 262.3	60.87	75.68	0.03
Risk factors for patients with single peripheral neural involvement compared with patients without peripheral neuropathy					
PLT (×109/L)	0.71	< 243	68.75	69.23	0.01
ESR (mm/h)	0.69	< 30	68.75	71.79	0.01
CRP (mg/L)	0.76	< 6	68.75	87.18	0.00
Globulin (g/L)	0.75	< 34.40	87.50	61.54	0.00
Risk factors for patients with multiple peripheral neural involvements compared with patients with single neural involvement					
WBC (×109/L)	0.76	> 5.98	89.29	62.5	0.00
PLT (×109/L)	0.79	> 243	89.29	68.75	0.00
CRP (mg/L)	0.83	> 6	92.86	68.75	0.00
ESR (mm/h)	0.79	> 41	71.43	81.25	0.00
Albumin (g/L)	0.75	≤ 27.5	60.71	87.5	0.00
RF(IU/mL)	0.78	> 96	82.14	62.5	0.00

WBC white cell counts, *CRP* C-reactive protein, *anti-CCP* anti-cyclic citrullinated peptide antibodies, *ESR* erythrocyte sedimentation, *PLT* platelet, *RF* rheumatoid factor, *AUC* area under the curve

Table 4 Binary logistic regression

Variables	B	SE	Exp(B)	Exp(B) 95% CI	*p* value
Risk factors for patients with peripheral neuropathy compared with patients without peripheral neuropathy					
Anti-CCP (< 285.7 U/ml)	1.47	0.52	4.38	(1.59,12.02)	0.00
TP (< 63 g/L)	1.64	0.51	5.18	(1.90, 14.08)	0.00
Constant	− 1.35	0.44	0.26		0.00
Risk factors for patients with multiple peripheral neural involvements compared with patients without peripheral neuropathy					
WBC (> 7.29 × 109/L)	2.24	0.79	9.4	1.97, 44.38	0.005
TP (<62.2 g/L)	1.90	0.72	6.66	1.62, 27.41	0.009
Anti-CCP(<262.3 U/ml)	2.15	0.80	8.6	1.80, 41.05	0.007
Constant	− 3.48	0.93	0.03		0.00
Risk factors for patients with single peripheral neural involvement compared with patients without peripheral neuropathy					
CRP (< 6 mg/L)	2.43	0.70	11.33	2.85, 45.07	0.001
Constant	− 1.74	0.44	0.18		0.00
Risk factors for patients with multiple peripheral neural involvements compared with patients with single neural involvement					
CRP (> 6 mg/L)	2.63	1.00	13.81	1.92, 99.14	0.007
PLT (> 243 × 109/L)	2.48	0.92	11.97	1.97, 72.72	0.009
Constant	− 2.90	1.08	0.06		0.007

TP total protein, *anti-CCP* anti-cyclic citrullinated peptide antibodies, *CRP* C-reactive protein, *WBC* white blood cell

scores were observed in patients with MN (Table 1). When risk factors were analyzed by using binary logistic regression analysis, low total protein (< 62.2 g/L, 18/28 vs. 9/44, OR = 6.66), WBC (> 7.29 × 109/L, 21/28 vs. 13/44, OR = 9.40), and anti-CCP (< 262.3 U/ml, 13/28 vs. 9/44, OR = 8.60) were proposed to relate patients with MN compared with patients without neuropathy ($p < 0.05$, Table 4).

Comparison between patients with SN and patients without PN and potential risk factors

Compared with control patients, lower levels of globulin (30.20 ± 5.56 vs. 34.64 ± 5.08 g/L) and anti-CCP antibody (223.29 ± 227.47 vs. 361.41 ± 168.09 U/ml) were found in patients with SN ($p < 0.05$, Table 1). Besides, higher NTSS, NDS, and TCSS scores were observed in this subgroup in contrast with control patients. In addition, low levels of CRP (< 6 mg/L, 10/16 vs. 5/39, OR = 11.33) were found to relate with patients' single neural involvement compared with patients without neuropathy ($p < 0.05$, Table 4).

Comparison between patients with MN and patients with SN

Compared with patients with SN, patients with MN had significantly higher WBC (9.21 ± 3.29 vs. 6.24 ± 2.19 × 10^9/L), PLT (348.71 ± 123.32 vs. 299.05 ± 121.81 × 10^9/L), CRP (63.16 ± 44.76 vs. 20.17 ± 31.51 mg/L), ESR (60.96 ± 30.45 vs. 30.25 ± 25.87 mm/h), and anti-CCP levels (250.15 ± 190.08 vs. 223.29 ± 227.47 U/ml), lower albumin level (27.89 ± 5.47 vs. 32.81 ± 5.35 g/L, Table 1, $p < 0.05$). In terms of disease assessment scores, higher scores of HAQ, NDS, and TCSS were observed in patients with MN in contrast with patients with SN (Table 2). When these parameters with differences between these two subgroups were further analyzed by the binary logistic regression analysis as mentioned above, CRP (> 6 mg/L, 26/28 vs. 6/16, OR = 13.81) and PLT (> 243 × 109/L, 25/28 vs.5/16, OR = 14.97) were associated with patients with MN ($p < 0.05$, Table 4). Thus, it was likely that patients with severe inflammation status would accompany MN.

Discussion

In the present study, the differences of clinical features (symptoms, lab results, electromyography data) between patients with and without PN, patients with MN and SN were analyzed. From this study, several points were summarized: (1) low total protein and anti-CCP levels appear to be associated with a higher likelihood for PN in patients with RA; (2) compared with SN, patients with MN had more severe inflammation status and higher CRP and PLT were risk factors for it; (3) although the presence of PN was not related with severe disease status (DAS > 2.6), the other assessment tools such as HAD-A, HAD-D, NTSS6, NDS, TCSS, and HAQ were useful to evaluate neural complications in patients with RA and remind physicians to concern the existence of PN in patients with RA.

In the present study, among patients with neuropathy, the common symptoms were numbness and itching, which indicated the involvement of sensory nerve was relatively common in these patients. From the results of the electromyogram, it also showed the proportion of sensor neuropathy was higher than that of motor neuropathy in this cohort. In previous study, Viskas also reported sensory neuropathy was the most frequent type of PN in a small cohort, while other reports showed that sensorimotor neuropathy was the commonest neuropathy [6, 23]. Thus, the types of PN were various in different populations and some patients may accompany sensory as well as motor neuropathy. Therefore, patients should be carefully examined when they complained of some neuropathy symptoms.

The differences between patients with and without PN were analyzed based on a strict selection of age, sex, and disease duration-matched control patients, which decreased demographic confounding factors and made the data more reliable to focus on the clinical features. In contrast to patients without PN, patients with PN had lower anti-CCP level, which was different from the previous report indicating that the patients with PN were more likely to have positive anti-CCP [24]. But in Sim MK's study [24], 70% of PN was carpal tunnel syndrome. We also found RA patients with carpal tunnel syndrome had higher anti-CCP than patients without PN. So, low levels of anti-CCP may associate with MN rather than carpal tunnel syndrome in RA patients. In fact, there was another report that showed no difference about anti-CCP levels between patients with and without PN [25]. Thus, the relationship between anti-CCP and existence of PN was not confirmative, or perhaps anti-CCP was not a reliable parameter to indicate the risk of PN. We personally assume that the mechanism of peripheral neuropathy was not directly associated with anti-CCP. Therefore, the relationship between PN and anti-CCP remained to be investigated.

However, with regard to DAS28, no difference was found between patients with and without PN in present study, which suggested that the presence of PN was not related to disease activity. This phenomenon was in line with previous study [24]. On the other hand, as for various assessment methods, not only NTSS6, NDS, TCSS but also HAD-A, HAD-D were higher in patients with PN, which implied that neural complications in patients with RA also affected their mental state and living quality. In previous studies, other factors such as long disease duration were also considered as risk factors for the development of PN in patients with RA [24, 26]. In the present study, since the disease duration has been matched between

two groups, no such relationship was found between PN and disease duration.

By comparing patients with single and multiple nerve involvement, the present study found that patients with multiple nerve involvement had higher levels of WBC, PLT, ESR, CRP, and rheumatoid factor but lower level of albumin, which indicated severe inflammation status was a risk factor for patients with multiple neural involvements. According to previous research about PN in patients with RA [27], the most likely mechanism was vasculitis of vasa nervorum. The vasa nervorum would develop into vascular occlusion due to the vasculitis, which was part of the generalized vasculitis in RA. Therefore, if patients had severe inflammation status, it was likely to involve vasa nervorum and reduce the blood supply to the corresponding nerve. Therefore, if patients were diagnosed to have PN, it was imperative to control their inflammation conditions to prevent more neural impairment.

At last, in the present study, it was discovered that patients with PN had lower total protein than patients without neuropathy and patients with MN had lower total protein and albumin than patients with SN. According to one previous study [28], low level of protein (albumin) was also reported in patients with Guillain–Barre syndrome (GBS), which is a typical peripheral neuropathy. And they also demonstrated that administration of this substance to patients who have low albumin appears to be beneficial to the patients with GBS. The potential explanation is that that serum albumin possesses potent antioxidant properties, which inhibit production of free hydroxyl radicals and have the ability to scavenge peroxy radicals [28]. Other parameters that potentially affect levels of total protein in patients included weight, height, IMC, skin folds, etc. But since we did not have this information of these patients, we cannot get any conclusions about this.

Regarding the limitations of this study, several limitations need to be addressed. First, this is a cross-sectional study performed in small samples; thus, the results remain to be verified in a large cohort. Secondly, the type of peripheral neural involvement in patients of this study has not been confirmed pathologically. Furthermore, the effects of medications on the PN have not been completely excluded, since most of patients in this study have already been treated rather than untreated. At last, the causes of entrapment neuropathy were a lot including synovitis, tenosynovitis, joint subluxation, and rheumatoid nodules, but we did not evaluate specifically, which we will pay more attention in our future studies. However, the findings that the low level of total protein levels and high levels of platelet and CRP may associate with PN can alert physicians to pay more attention to patients with these clinical features and take some preventive measures, which will improve early diagnosis rate or decrease patients' risk to develop peripheral neuropathy, and improve their outcomes.

In conclusion, although the development of peripheral neuropathy is not related to disease activity, RA patients with PN, especially MN, can present various clinical symptoms, which will aggravate patients' anxiety and depression status. The increase of blood platelet, and CRP levels, and decrease of blood albumin are probable risk factors for PN in patients with RA.

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Compliance with ethical standards

The study protocol was approved by the Ethics Committees of Linyi People's Hospital and conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent for inclusion in this study.

Disclosures None.

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