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Original Research Article

Prevalence and Pattern of Peripheral Neuropathy in Rheumatoid Arthritis - A Hospital Based Observational Study

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease primarily affecting joints, but peripheral neuropathy (PN) is an under recognized extra-articular manifestation. Overlapping musculoskeletal symptoms often obscure its diagnosis. This study aimed to assess the prevalence, types, and predictors of PN in RA patients.

Methods and Materials: This prospective observational study included 60 patients fulfilling the 1987 ACR criteria for RA. Clinical, laboratory, and electrophysiological assessments were conducted. Nerve conduction studies of the median, ulnar, peroneal, tibial, and sural nerves were performed. Demographic, hematological, and serological parameters were compared between PN-positive and PN-negative groups. Statistical analysis employed Fisher's exact test, unpaired t-test, and logistic regression.

Results: Peripheral neuropathy was detected in 26 patients (43.3%). Mixed sensorimotor neuropathy (42.3%) was the most frequent pattern, followed by sensory (23.1%), motor (19.2%), carpal tunnel syndrome (7.7%), and mononeuritis multiplex (7.7%). PN-positive patients were older (45.9 vs. 36.7 years, $p < 0.0001$), had longer disease duration (8.2 vs. 5.1 years, $p = 0.004$), higher ESR (39.8 vs. 29.0 mm/hr, $p = 0.0007$), and increased RF and anti-CCP positivity. Logistic regression identified age >40 years (OR 2.43, $p = 0.011$), ESR >40 mm/hr (OR 2.65, $p = 0.046$), anti-CCP positivity (OR 3.49, $p = 0.032$), and RA duration >10 years (OR 2.07, $p = 0.015$) as independent predictors of PN.

Conclusion: Peripheral neuropathy is prevalent in RA, with nearly half of patients affected, most commonly by sensorimotor neuropathy. Older age, prolonged disease duration, elevated ESR, and anti-CCP positivity are significant risk factors. Routine electrophysiological testing should be considered in high-risk RA patients for early detection and management.

Keywords: Rheumatoid Arthritis, Peripheral Neuropathy, Sensorimotor Neuropathy, Anti-CCP Antibody, Electrophysiology.

Introduction

Rheumatoid arthritis is a chronic immune-inflammatory systemic disease which affects synovial joints with possibility of extra-articular manifestations[1]. Rheumatoid arthritis prevalence is approximately 0.8% (0.3 to 2.1%) of population worldwide[2]. Our Indian data suggest prevalence to be around 0.65 to 0.75%[3].

Rheumatoid arthritis is primarily a joint disease, but extra-articular manifestation can be detected in any organ system and may occasionally precede the onset of arthritis. Most common neurological manifestation in rheumatoid arthritis is entrapment neuropathy which is secondary to proliferative synovitis[4].

About 33.2% of the patients develop neurological problems during their lifetime[5].Peripheral nerve involvement in rheumatoid arthritis includes compressive neuropathy, which is by far the commonest, distal sensory and combined sensorimotor neuropathy[6].

Although the underlying pathology resulting in rheumatoid neuropathy is not clear, ischemia secondary to vasculitis with characteristic axonal loss and humoral mechanisms such as the deposition of immune complexes and fixation of complement are thought to be important factors[7]. The arteritis of small vessels commonly fibrinoid type and immune globin's are demonstrated in walls of the vessels[8].

The presence of peripheral neuropathy in patients with rheumatoid arthritis is difficult to recognize as patients often related neurological symptoms to

joint disease. It is also difficult to assess neurological system in the presence of severe joint disease[7]. Hence our current study is undertaken to evaluate the prevalence and pattern of neuropathy in rheumatoid arthritis and to correlate it with disease parameter and other extra-articular involvement.

Methodology:

Study Design: This prospective study was conducted among patients attending OPD or admitted to the hospital with diagnosis of rheumatoid arthritis, with or without clinical evidence of neuropathy, satisfying the inclusion and exclusion criteria will be taken for the study. Patients were recruited who provided informed consent, and the study received ethical approval from the Institutional ethics committee (**SNMC/IEC/2024/2409-10**.)

Inclusion and exclusion criteria: Patients diagnosed with Rheumatoid Arthritis according to the 1987 Revised ACR Classification Criteria were included in the study, with a correlation to relevant laboratory data. Exclusion criteria encompassed individuals with diabetes mellitus, renal failure, chronic alcoholism, retroviral disease, liver disease, thyroid disease, pregnancy, or those undergoing specific drug treatments.

Data Collection: All patients included in the study were thoroughly evaluated using clinical and laboratory methods. Each patient underwent a nerve conduction study (NCS) of the median, ulnar, common peroneal, and sural nerves. The study measured compound muscle action potential (CMAP), sensory nerve action potential (SNAP), distal and proximal latencies, and nerve conduction velocities. Key laboratory investigations included haemoglobin percentage (Hb%), total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), platelet count, C-reactive protein (CRP), and rheumatoid factor (RF)/Anti-CCP antibody. Electrophysiological studies were conducted using the Medelec-Synergy EMG instrument, with skin temperature maintained between 31 and 32 degrees Celsius, as nerve conduction velocity increases by 2.4 m/s per degree from 29 to 38°C. Motor nerve conduction studies, including F-waves, were performed bilaterally on the median, ulnar, peroneal, and posterior tibial nerves, while sensory nerve conduction studies were performed on the median, ulnar, superficial peroneal, and sural nerves. Latency of the H-wave was measured bilaterally, with motor nerve conduction assessed using the belly-tendon method and sensory nerve conduction studied antidromically. Amplitudes were determined from base-to-peak values, and conduction velocities were compared to reference values from our centre.

Polyneuropathy was diagnosed when at least three abnormal parameters were identified. For diagnosing carpal tunnel syndrome (CTS), the "mid-palm" technique was employed when median CMAP latency exceeded 4.2 ms or median SNAP latency exceeded 3.6 ms. The median nerve was stimulated at the palm with a 14-cm distance to the wrist, and CTS was confirmed when the palm-to-wrist latency ratio was lower than 50%.

Statistical Analysis: Data cleaning and analysis were done using M.S. Excel and SPSS-Statistical Software (version:23). Statistical analysis done by Fishers exact test, Unpaired-t test. Multivariate analysis of factors determined by logistic regression. P value <0.05 is taken as significant correlation with confidence interval of 95%.

Results

In the present study, 60 participants were recruited, of whom 26 (43.33%) tested positive for peripheral neuropathy, while 36 (56.67%) tested negative. Among the types of neuropathies identified through nerve conduction studies, the most prevalent was mixed neuropathy, affecting 11 participants (42.31%). Sensory neuropathy was observed in 6 participants (23.08%), and motor neuropathy was present in 9 participants (15%). Carpal tunnel syndrome and mononeuritis multiplex were less common, each affecting 2 participants (3%)(Table 01).

Table 1: Peripheral Neuropathy and types of Neuropathies

Variables	Frequency (%)
Peripheral Neuropathy,	
Positive	26 (43.33)
Negative	34 (56.667)
Types of Neuropathies,	
Sensory Motor Neuropathy	11 (42.31)
Mononeuritis Multiplex	2 (7.69)
Sensory Neuropathy	6 (23.08)
Motor Neuropathy	5 (19.23)
Carpel Tunnel Syndrome	2 (7.69)

Demographics and clinical characteristics: The evaluation and comparison of demographic and clinical variables between the two groups revealed several findings. The PN positive group had a higher mean age (45.85 ± 8.99 years) compared to the PN negative group (36.65 ± 6.87 years) with a statistically significant difference ($p < 0.0001$). (Table 02). The age distribution analysis shows that most subjects in the PN positive group were in the 41-50 years age range (46.15%), with a mean age of 45.85 years.

Conversely, in the PN negative group, the majority were in the 31-40 years age range (58.82%), with a mean age of 36.65 years. The unpaired t-test indicates a statistically significant association between age distribution and the intervention groups ($p < 0.0001$). (Figure 01)Gender analysis showed that females predominated in both groups, with 73.08% in the PN positive group and 88.24% in the PN negative group ($p = 0.1329$). Haemoglobin levels were similar across groups, with no significant difference ($p = 0.8231$)(Table 02).ESR values showed a significant difference, with higher ESR in the PN positive group (mean 39.77 mm/hr) compared to the PN negative group ($p = 0.0007$)(Table 01).The ESR distribution analysis indicates that most subjects in both the PN positive and PN negative groups were in the 21-40 mm/hr range, with 65.38% in the PN positive group and 67.65% in the PN negative group, both having a mean ESR of 39.77 mm/hr. The unpaired t-test shows a statistically significant association between ESR distribution and the intervention groups ($p = 0.0007$), suggesting that ESR levels are significantly different between these groups. (Figure 02) However, complete blood count variables showed no significant differences between the groups ($p > 0.05$).CRP status was not significantly different between the groups, with both having most CRP-negative subjects ($p = 0.8891$).

Rheumatoid factor status was significantly higher in the PN positive group (96.15%) compared to the PN negative group (67.65%) ($p< 0.05$). Anti-CCP antibody status was also significantly different, with higher positivity in the PN positive group (69.23%) versus the PN negative group (91.18%) ($p = 0.0288$).

The study found a meaningful association between rheumatoid factor and anti-CCP antibody status with the presence of PN (Table 02). The RA duration distribution table shows that most subjects in the PN-positive group were in the 6-10 years category (53.85%), with a mean RA duration of 8.23 years. In contrast, most subjects in the PN-negative group were in the ≤ 5 years category (67.65%), with a mean RA duration of 5.06 years ($p = 0.0004$)(Table 02) (Figure 03).

Table 2: Demographics and clinical characteristics

Variables	Cohort	PN +	PN -	P-value
Age	40.63±9.04	45.85 ±8.99	36.65±6.87	<0.0001*
Gender,				
Male	11 (18.33)	7(26.92)	4(11.76)	0.1329
Female	49 (81.67)	19 (73.08)	30 (88.24)	
Haemoglobin	11.63± 1.47	11.68 ±1.53	11.59 ±1.44	0.8231
ESR Distribution	33.65± 12.63	39.77±14.48	28.97±8.63	0.0007*
CBC,				
Total Count		9073.08± 1708.59	9132.35±2249.00	0.9113
Polymorphs		67.96±5.64	69.26±7.97	0.4814
Lymphocytes		29.35±5.95	27.15±7.34	0.2178
Monocytes		2.96±1.84	3.00±2.89	0.9530
Platelets		2.73±0.77	2.42±0.82	0.1421
CRP Status (mg/dl),				
Negative	26(43.33)	11(42.31)	15(44.12)	0.8891
Positive	34(56.67)	15(57.69)	19(55.88)	
RF Status,				
Negative	12(20.00)	1(3.85)	11(32.35)	
Positive	48(80.00)	25(96.15)	23 (67.65)	0.0064*
Anti-CCP Antibody Status,				
Negative	49(81.67)	31(91.18)	18 (69.23)	0.0288*
Positive	11(18.33)	3(8.82)	8 (30.77)	
Neuropathic Symptoms Status,				
Yes	7 (11.67)	5 (19.23)	2(5.88)	0. 1198
No	53 (88.33)	21(80.77)	32(94.12)	
Duration of RA Distribution	6.43±3.60	8.23± 3.73	5.06±2.84	0.004*

Abbreviation: CBC: Complete Blood Count; CRP:C - reactive protein; ESR: Erythrocyte Sedimentation Rate; RA: Rheumatoid Arthritis; RF: Rheumatoid Factor;*: Significance

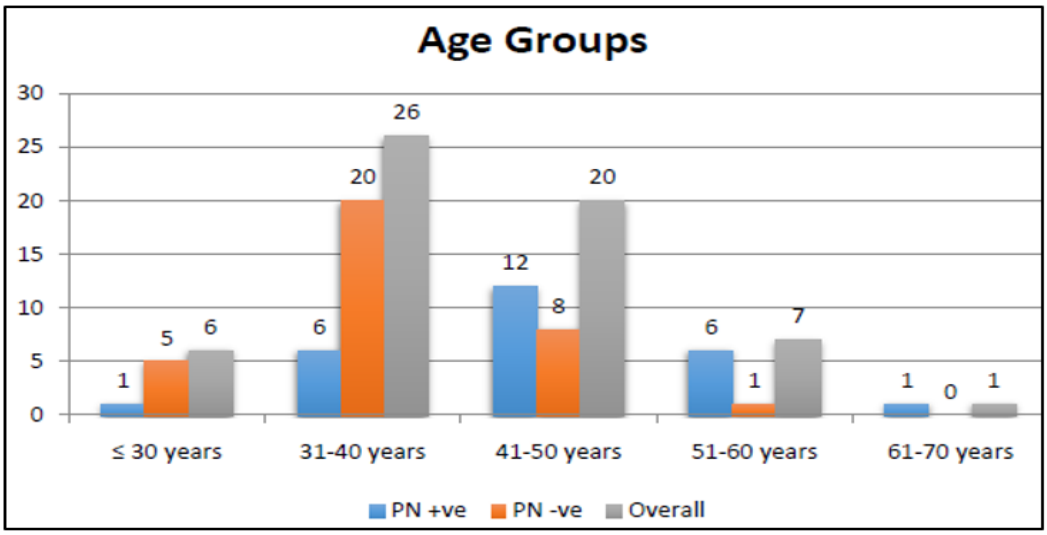

Figure 1: Age distribution across PN positive and negative groups

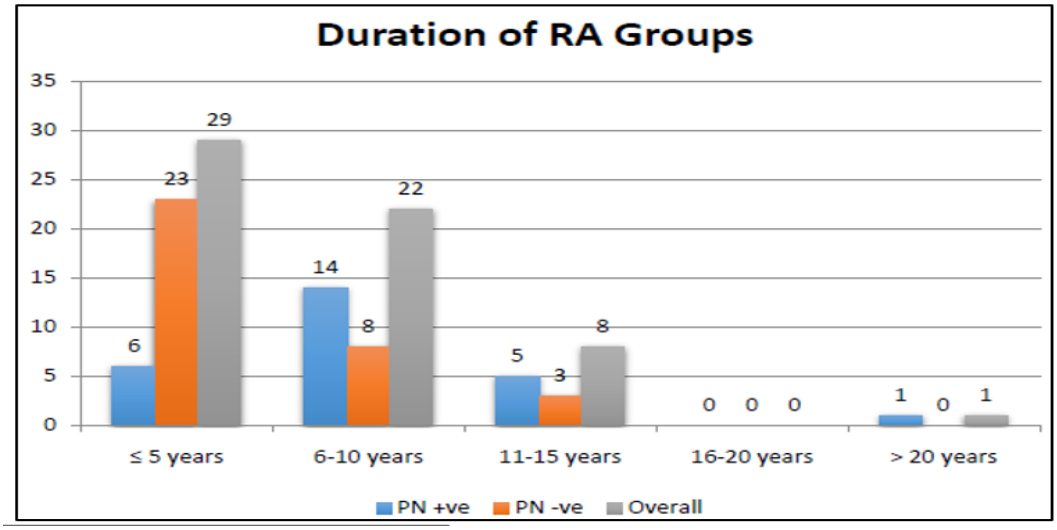

Figure 2: ESR distribution across PN positive and negative groups

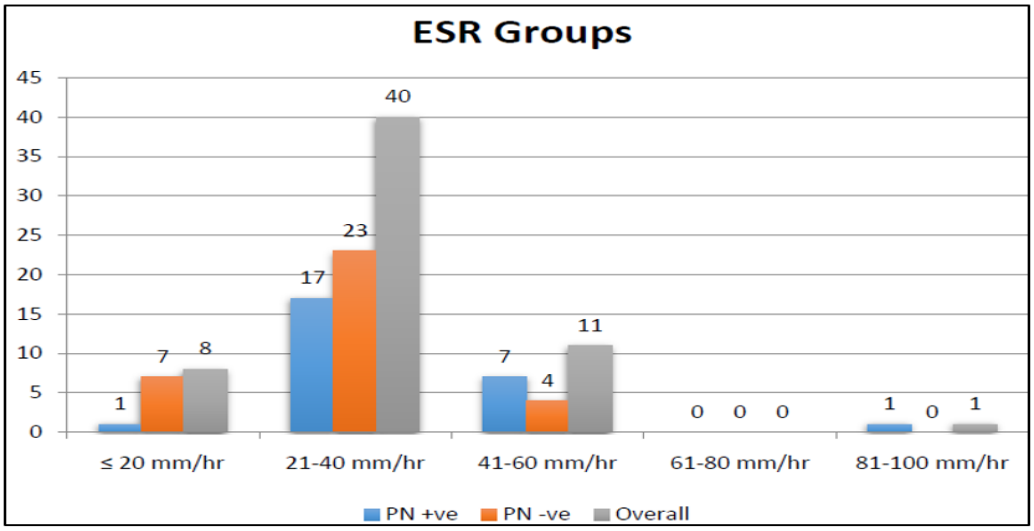

Figure 3: Duration of RA distribution across PN positive and negative groups

Regarding the management status, most subjects in both the PN-positive group (83.08%) and the PN-negative group (61.76%) did not take steroids ($p = 0.3573$). In contrast, all subjects in the PN-positive group (100%) and the majority in the PN-negative group (70.59%) were on DMARDs medication ($p = 0.0288$).

Table 3: Management status

Variables	Cohort	PN +	PN -	P-value
Steroid Medication Status				
Yes	20 (33.33)	7 (26.92)	13 (38.24)	0.3573
No	40 (66.67)	19 (73.08)	21 (61.76)	
DMARDs Medication Status,				
Yes				
No	50(83.33)	26 (100.00)	24 (70.59)	0.0022*
	10(16.67)	0 (0.00)	10 (29.41)	

Abbreviation: DMARD: Disease-Modifying Antirheumatic Drugs; *: Significance
Multivariate analysis demonstrated that after adjusting of basic variables and rheumatoid arthritis.

The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.43 times significantly more when age is greater than 40 years than in patients less than 40 years. (P-value = 0.0112)

The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.65 times significantly more when ESR is greater than 40 mm/hr than in patients less than 40 mm/hr. (p-value =0.0457)The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 1.49 times significantly more when anti CCP antibody positivity exists than in patients less than in patients with anti CCP antibody negativity. (P-value =0.0322)

The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.07 times significantly more when the duration of RA is more than 10 years than in patients with less than 10 years duration. (P-value =0.0145)

Table 4: Multivariate analysis of factors associated with peripheral neuropathy in RA as determined by logistic regression

Variable	Odds ratio	95% CI	P-value
Age (> 40 years)	2.43	1.47-4.01	0.0112 *
Gender (Male)	1.75	1.04-2.93	0.1141
Haemoglobin> 11 gm%	1.02	0.85-2.87	0.1026
ESR >40 mm/hr	2.65	1.67-4.79	0.0457 *
CRP +ve Status	1.75	1.04-2.93	0.4421
RF +ve Status	2	1.21-3.32	0.0966
Anti-CCF Antibody +ve status	3.49	0.88-5.87	0.0322*
Duration of RA > 10 years	2.07	0.74-4.47	0.0145 *
Steroid Intake	2.15	0.87-3.39	0.6832
DMARDs Intake	2.94	0.91-5.05	0.0751

Abbreviation: CRP:C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; RF: Rheumatoid Factor; RA: Rheumatoid Arthritis; DMARD: Disease-Modifying Antirheumatic Drugs;*: Significance

Discussion

In this study we studied 60 patients who were admitted in Mahatma Gandhi Hospital and Mathura Das Hospital, Dr. S.N. Medical College, Jodhpur, Rajasthan. The prevalence of peripheral neuropathy and their relationship with demography, clinical findings, and laboratory values have not been clearly demonstrated in the literature. The prevalence of peripheral neuropathy varies among previous studies, as shown in Table 05 below.

In our present study, we reported a frequency of peripheral neuropathy, including entrapment neuropathy of 43.3% in RA patients, which appears to be lower than that in previous studies with a large series of patients. The frequency of peripheral neuropathy in our study was higher than the frequency of idiopathic polyneuropathy of 8%, reported previously in a population-based epidemiological study[9]. We included RA patients with neurological symptoms in our current study, the prevalence of neuropathy in the electrophysiological study was more than that in other studies. There was no relationship between the neuropathic symptoms and the presence of peripheral neuropathy, which may be because the neuropathic symptoms consist of questions that focus on positive symptoms, such as burning and tingling, which are subjectively reported by the patients and also neuropathic symptoms mimic the symptoms of arthritis. Because of all these reasons, neuropathic symptoms of patients might show a poor correlation with results of electrophysiological studies Comparison between electrophysiological studies of peripheral neuropathy and associated factors in the present and previous studies.

Table 5: Comparison between electrophysiological studies of peripheral neuropathy and associated factors in the present and previous studies

STUDY	No of Patients	Type of peripheral neuropathy					Associated factors
		SM	S	M	MM	CTS	
Fleming et al.	102	0	15	3	0	53	*
Agarwal et al.	108	25	28	0	7	11	Absence of DTR, presence of vasculitis
Lanzillo et al.	40	26	0	0	0	3	*
Nadkar et al.	31	6	0	4	4	1	*
Bayrak et al.	60	8	2	0	0	*	Duration of RA, NSS, NDS, DAS 28
Mikyung Sim et al.	30	2	1	0	0	7	Age, anti CCP antibody
Present study	100	17	11	9	3	4	Age, anti CCP antibody, duration of RA, ESR

Abbreviation: SM: sensorimotor; S: sensory; M: motor; MM: mononeuritis multiplex; CTS: carpal tunnel syndrome; DTR: deep tendon reflex; RA: rheumatoid arthritis; NSS: neuropathy symptom score; NDS: neuropathy disability score; DAS 28:28-joint disease activity score; Anti-CCP: anti-cyclic citrullinated peptide.

In present study we found significant correlation between peripheral neuropathy and the age of the patients, ESR, duration of RA and Anti-CCP antibodies. In present study, we did not find significant association between peripheral neuropathy and Gender, Neuropathic symptoms, CRP and type of medication. We found that RA patients with peripheral neuropathy were older than RA patients without peripheral neuropathy. Age is a known risk factor for polyneuropathy(10), and RA patients with peripheral neuropathy in our study showed similar results. However, the prevalence of peripheral neuropathy in patients with RA in this study was higher than that of peripheral neuropathy in patients without the underlying disease.

The most important finding of our study was that patients who were positive for anti-CCP antibody showed an increased risk of peripheral neuropathy. The anti-CCP antibody has become a focus of attention for diagnosis, and it is a marker of severe RA[11]. New study reported that anti-CCP antibody is associated with human leukocyte antigen (HLA) class II RA-related susceptibility alleles and with severe disease manifestations[12]. Some authors have observed a tendency for positive association between anti-CCP antibody titter with extra-articular manifestations in RA, but there is no data on the effects of anti-CCP antibody on the development of peripheral neuropathy[13,14,15]. Our present study is one of the studies to investigate the relationship between anti-CCP antibody and the development of peripheral neuropathy in RA patients. In our study anti CCP antibody status between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased incidence of anti CCP antibody positivity in PN +ve group compared to PN –ve group (percentage difference of 21.95, 71% higher). Also, the effect of anti-CCP antibody on peripheral neuropathy seems to increase with age. Our study was limited by small sample size and cross-sectional design. We were unable to conduct an electrophysiological study for the same duration from symptom onset. Also, we were unable to determine the definite cause of peripheral neuropathy and CTS in this study, whether it was due to direct nerve injury or due to joint deformity or was an independent disease. Furthermore, longitudinal studies in a large population are needed. It is difficult to distinguish the symptoms of peripheral neuropathy and those of arthritis, also the subjective symptoms of patients do not correlate with electrophysiological results. Hence, electrophysiological studies should be performed in patients with RA, particular in older patients and anti-CCP antibody positive patients.

Conclusion

The study findings indicate that gender, haemoglobin levels, complete blood counts, CRP, steroid medication, and neuropathic symptoms do not significantly influence the presence of peripheral neuropathy in patients with rheumatoid arthritis (RA). However, when comparing patients with and without peripheral neuropathy, several key observations were made:

Peripheral neuropathy in RA patients is more prevalent in older age groups. Additionally, RA patients with peripheral neuropathy tend to have elevated ESR levels, a higher incidence of RA factor positivity, and increased Anti-CCP antibody positivity. Moreover, peripheral neuropathy is associated with a longer duration of RA. There is also a notably higher incidence of DMARDs medication use among RA patients with peripheral neuropathy. These findings suggest that certain clinical features and treatment patterns are more common in RA patients who develop peripheral neuropathy. Future research should focus on identifying more precise biomarkers for early detection of peripheral neuropathy in RA patients and developing personalized treatment strategies to

reduce the incidence and severity of neuropathy. Additionally, exploring novel therapeutic approaches could further enhance the management of neuropathy in RA.

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