Research Article

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Neuropathic Foot and Ankle in Rheumatoid Arthritis; Ultrasound and Nerve Conduction Study

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Abstract

Rheumatoid arthritis (RA) is a common chronic systemic autoimmune disease that primarily affects the lining of the synovial joints which symmetrically involves the small joints, can cause cartilage and bone damage and associated with progressive disability, premature deaths, and socioeconomic burdens. Despite the recent advancement in RA treatment, neuropathic pain remains a cause of persistent pain even in controlled disease activity.

Keywords: Neuropathic foot • Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a common chronic systemic autoimmune disease that primarily affects the lining of the synovial joints which symmetrically involves the small joints, can cause cartilage and bone damage and associated with progressive disability, premature deaths, and socioeconomic burdens [1,2]. Despite the recent advancement in RA treatment, neuropathic pain remains a cause of persistent pain even in controlled disease activity [3]. In RA, the etiology of neuropathic pain (NP) could be suggested by: nerve compression, associated comorbidities and vascuilitis [4]. The prevalence of clinical neuropathy is variable in different studies, and it can cause functional disability [2]. Foot and ankle pain is highly prevalent in RA and peripheral neuropathy is a common contributor to it [5,6]. In previous studies, it was found that the most foot neuropathies are of posterior tibial nerve, peroneal entrapment and pure sensory axonal neuropathy [6]. For evaluation of neuropathic foot and ankle in RA, electrophysiological and imaging techniques can be very useful, but these modalities need time and physician expertise, so the use of pain questionnaires like Pain-DETECT questionnaire (PD-Q) can provide an easy and rapid way of evaluating presence of NP and the different types of it [7]. Nerve conduction study (NCS) is the electrodiagnostic evaluation of the function of peripheral nerves, it can provide information regarding the presence, severity and location of a lesion, symmetricity of neuropathy, polyneuropathy and mononeuropathies. Also, the functional modality most involved (sensory or motor) and the predominant pattern of pathology (e.g., axonal, demyelinating, or both) [8]. Neuromascular ultrasound (NMUS) can assess anatomical abnormalities that can't be evaluated by NCS [9]. NMUS being noninvasive and inexpensive diagnostic modality, it has been introduced as a complement to NCS for diagnosis of nerve conditions [10].

Objectives

We aim to measure the prevalence of neuropathic pain in RA patients with ankle and foot pain using the PD-Q, assess the effectiveness of the pain-DETECT score as a

diagnostic tool to distinguish between different types of NP and evaluate the role of neuromuscular ultra sound (NMUS) and nerve conduction study (NCS) in assessment of neuropathic foot and ankle in RA patients.

Patients and Methods

Cross-sectional study, we enrolled 250 patients, who were diagnosed as rheumatoid arthritis according to 2010 ACR/EULAR Rheumatoid arthritis classification criteria [11]. All Patients enrolled in this study were from those attended to the Physical Medicine, Rheumatology and Rehabilitation inpatient department and outpatient clinic, at Assiut University Hospitals.

Inclusion criteria

Adult RA patients > 18 years old, complaining of foot or ankle pain. Exclusion criteria: presence of other autoimmune diseases and any comorbidities causing peripheral neuropathy such as: Diabetes mellitus, lumbar disc prolapse, end-stage renal disease, local trauma or surgery.

All the patients were assessed clinically, full medical history, laboratory examination included (Erythrocyte sedimentation rate (ESR), complete blood count (CBC), liver and kidney function tests, rheumatoid factor (RF), random blood glucose).

Disease activity assessment: using the Disease activity index 28 ESR (DAS28-ESR) [12].

Neuropathic pain assessment: Using the arabic version of PainDETECT questionnaire (PD-Q) [13].

Then according to the score of the PD-Q, the patients were re-classified to two groups:

- Patients Unlikely to have NP (PD-Q<12)
- Patients likely or maybe having NP (PD-Q>12), these patients were subjected to Nerve conduction studies (NCS) using Nihon Kohden MB9300 device, techniques and reference numbers were according to Preston and Shapiro "Electromyography and Neuromuscular Disorders" book, Fourth edition [14], to common peroneal, posterior tibial, and sural nerves (motor, sensory, F wave) and musculoskeletal and neuromuscular ultrasound using MyLabSeven by Esaote, with linear transducer of 10-19 MHz device, 14 joints were examined, including: Tibio talar joints, Subtalar joints, Talonavicular joints, 1st and 2nd MTP joints, 1st IP and 2nd PIP joint, each joint was evaluated according to musculoskeletal ultrasound 10 score in a standardized manner based on the guidelines of the European League Against Rheumatism (EULAR) [15]. All joints were evaluated using joint inflammation parameters and joint damage parameters, as follows:

Inflammation parameters

Synovial proliferation-qualitative and semi-quantitative (SPQ and SPSQ)

Semi-quantitative evaluation (SPSQ)

- Grade 0 (absence)
- Grade 1 (small hypoechoic/anechoic line beneath joint capsule)
- Grade 2 (joint capsule elevated parallel to joint area) and
- Grade 3 (strong distension of joint capsule)

Qualitative evaluation (SPQ): binary evaluation-0 (absent) or 1 (present, if Grade 2 or 3 semi-quantitative scores).

Synovial blood flow-by power doppler (PD)

Semi-quantitative (PDSQ)

- Grade 0 (no flow in synovium)
- Grade 1 (single vessel signals)
- Grade 2 (confluent vessel signals in less than half the area of the synovium)
- Grade 3 (vessel signals in more than half the area of the synovium)

Qualitative (PDQ): binary evaluation-0 (absent) or 1 (present, if Grade 1 semi-quantitative score).

Tenosynovitis: defined as a hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath (tenosynovitis is evaluated and graded on a greyscale-US (GSUS) and power doppler-US (PDUS) qualitative score:

Qualitative (TNGSQ): binary evaluation-0 (absent) or 1 (present).

Qualitative (TNPDQ): binary evaluation-0 (absent) or 1 (present).

Joint damage parameters

Bone erosions: Defined as an interruption of the bone surface on two perpendicular planes, graded on a qualitative and semi-quantitative score:

Semi-quantitative (BESQ):

- Grade 0 (regular bone surface)
- Grade 1 (irregular bone surface without formation of defect seen on two planes)

- Grade 2 (formation of defect on bone surface seen on two planes) and
- Grade 3 (bone defect causing extensive bone destruction)

Qualitative (BEQ): binary evaluation-0 (absent) or 1 (present, if Grade 2 or 3 semi-quantitative scores).

Cartilage damage: is evaluated using the following semi-quantitative and qualitative scoring system: Semi-quantitative (CDSQ):

- Grade 0 (normal hyaline cartilage)
- Grade 1 (loss of sharpness of superficial margin of hyaline cartilage)
- Grade 2 (partial thickness defect of cartilage layer)
- Grade 3 (full thickness defect of cartilage layer with normal subchondral bone profile)
- Grade 4 (complete loss of cartilage layer and subchondral bone involvement)

Qualitative (CDQ): binary evaluation-0 (absent) or 1 (present, if Grade 2 or 3semi-quantitative scores).

NMUS: The following nerves were examined bilaterally

- Tibial nerve at the tarsal tunnel
- Deep peroneal nerve at anterior ankle
- Sural nerve in posterolateral aspect of lower leg were assessed for the cross-sectional area (CSA), with reference range values were according to a study done by Cartwright et al in 2008. (Cartwright et al., 2008) [16].

Statistical analyses: were performed using IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as frequencies and percentages, while Chi-square test and Fisher's exact test were used for comparisons between groups. Continuous data were reported as mean ± SD or median (MinMax) and tested for normality using the Shapiro-Wilkes test. Where continuous data were normally distributed, the one-way ANOVA was used for comparisons between groups; where data were non-normally distributed, the Kruskal Wallis test was used. Pearsons'correlation coefficients were used to assess the correlation between two quantitative parameters. Diagnostic performance of pain-Detect score in the study to predict neuropathic pain etiology in patients with RA was determined by ROC curve. P value <0.05 was considered statistically significant.

Results

A total of 250 patients diagnosed with rheumatoid arthritis (RA) according to 2010 ACR/EULAR Rheumatoid arthritis classification criteria [11] were screened for neuropathic pain in the foot and ankle using the pain-DETECT questionnaire. Of these patients, 99 (39.6%) were identified as having neuropathic pain, with 53 (53.5%) classified as likely to have and 46 (46.5%) as possibly having neuropathic pain according to Pain-DETECT questionnaire. Ultrasound and electrophysiological studies were conducted on these patients to determine the etiology of the pain, resulting in three distinct groups: Patients with isolated nerve pathology (31 patients, 31.3%), Patients with isolated joint pathology (35 patients, 35.4%), and Patients with combined pathology (33 patients, 33.3%). Table 1 provides demographic and clinical characteristics of the studied patients. The mean age of the participants was 45.36 ± 11.54 years, with a majority of female patients (88%), 13% were passive smokers and 8.1% were smokers and 20% of the patients had hypertension, there was no significant difference in the age between the three groups (p=0.149). Patients with joint pathology had a longer disease duration compared to patients with nerve pathology or combined pathology (median duration of 12, 10, and 8 years, respectively) which was statistically significant (p=0.012). Regarding drug therapy, patients with joint pathology had a higher percentage of steroid use compared to patients with nerve pathology or combined pathology (77.1%, 41.9%, and 63.6%, respectively) which was statistically significant (p=0.013). On the other hand, patients with nerve pathology were significantly higher in use of hydroxychloroquine as 100% of them use it compared to 94.3% in joint pathology and 84.8% in combined pathology (p=0.046). There was no statistically significant difference in type of treatment between groups as regard use of single, double DMARDs or biologic treatment. Patients with joint pathology had a higher prevalence of any deformity compared to patients with nerve pathology or combined pathology (74.3%, 22.6%, and 42.4%, respectively) which was statistically significant (P= <0.001). Ankle deformity was the most common type of deformity observed in all three groups, with the highest prevalence seen in patients with joint pathology (74.3%), which was statistically significant (P=0.001). Patients with joint pathology also had a higher prevalence of MTP and forefoot deformities compared to the other two groups which also was significant (P=0.001). Regarding disease activity and pain-DETECT score in the studied groups of patients. Patients with joint pathology had a higher DAS-28 ESR score compared to patients with nerve pathology or combined pathology (mean score of 5.64, 4.48, and 4.77, respectively) which was statistically significant (P=0.016). Patients with joint pathology also

Table 1: Demographic data, Disease activity and pain-DETECT score according to etiologic groups.

Characteristic	Nerve pathology (n = 31)	Joint pathology (n = 35)	Combined pathology (n = 33)		p-value^
Age (years)	48.71 ± 11.95	43.66 ± 10.54	44.03 ± 11.84		0.149
Sex					
Female	28 (90.3%)	32 (91.4%)	27 (82%)		0.505
Male	3 (9.7%)	3 (8.6%)	6 (18%)		
Occupation					
Housewife	26 (84%)	30 (86%)	25 (76%)		0.972
Employer	2 (6.5%)	1 (2.9%)	2 (6.1%)		
Worker	2 (6.5%)	2 (5.7%)	3 (9.1%)		
Farmer	1 (3.2%)	2 (5.7%)	2 (6.1%)		
Student	0 (0%)	0 (0%)	1 (3.0%)		
Special Habit					
No	23 (74.2%)	27 (77.1%)	28 (85.0%)		0.142
Passive smoker	5 (16.1%)	7 (20.0%)	1 (3.0%)		
Smoker	3 (9.7%)	1 (2.9%)	4 (12.0%)		
Hypertension					
No	24 (77.0%)	27 (77.0%)	28 (85.0%)		0.676
Yes	7 (23.0%)	8 (23.0%)	5 (15.0%)		
DAS-28 ESR	4.48 ± 1.87	5.64 ± 1.65	4.77 ± 1.56	0.016*	
Disease activity index					
High	11 (35.5%)	22 (62.9%)	18 (54.5%)	0.227	
Moderate	12 (38.7%)	11 (31.4%)	10 (30.3%)		
Low	2 (6.5%)	1 (2.9%)	2 (6.1%)		
Remission	6 (19.4%)	1 (2.9%)	3 (9.1%)		
ESR	36 (4-130)	48 (22-130)	37 (11-120)	0.011*	
Positive RF	25 (80.6%)	33 (94.3%)	24 (72.7%)	0.058	
Pain-DETECT score	21.55 ± 3.60	17.51 ± 2.87	19.27 ± 3.14	<0.001*	
Neuropathic pain					
Likely	24 (77%)	13 (37%)	16 (48%)	0.004*	
Possible	7 (23%)	22 (63%)	17 (52%)		

had a higher percentage of high disease activity index (62.9%) compared to patients with nerve pathology or combined pathology. Additionally, patients with nerve pathology had a higher pain-DETECT score compared to patients with joint pathology or combined pathology which was statistically significant (P= <0.001). Table 2 presents the musculoskeletal ultrasound 10 scores for the three different groups of patients. The data indicates that patients with joint pathology had a significantly higher synovial proliferation score, with a median value of 12 compared to nerve pathology (median value of 2) and combined pathology (median value of 4) (p<0.001). Patients with joint pathology also had a higher tenosynovitis gray scale score, with a median value of 2 compared to nerve pathology (median value of 0) and combined pathology (median value of 0) (p<0.001). On the other hand, patients with nerve pathology had a significantly lower power doppler score, with a median value of 0 compared to joint pathology (median value of 1) and combined pathology (median value of 1) (p=0.029). Moreover, the data shows that patients with joint pathology had the highest scores for synovial proliferation-SQ (median=27), bone erosion-SQ (median=15), and cartilage damage-SQ (median=12) compared to nerve pathology and combined pathology. Meanwhile, patients with nerve pathology had the lowest scores for all parameters. Table 2 also shows the cross-sectional area (CSA) of the tibial, peroneal, and sural nerves in the three studied groups of RA patients. The mean CSA values for the studied nerves were higher in patients with nerve pathology compared to those with joint pathology, and this difference was statistically significant difference in peroneal and sural nerves (p-value = 0.028 and 0.008 respectively). Table 3 shows the results of NCS of the studied nerves, regarding the tibial nerve motor studies in the examined feet of the studied RA groups, the mean values for amplitude and nerve conduction velocity (NCV) were not significantly different between the three studied groups. However, the mean of latency and F wave latency was significantly higher in patients with nerve pathology compared to those with joint pathology or a combined pathology

Table 2: Musculoskeletal ultrasound 10 scores.

	Nerve pathology(n = 31)	Joint pathology(n = 35)	Combined pathology(n = 33)	p-value^
Synovial proliferation-Q	2 (1-8)	12 (1-16)	4 (2-16)	<0.001*
Synovial proliferation-SQ	4 (2-16)	27 (1-48)	10 (2-36)	<0.001*
Power doppler-Q	0 (0-2)	1 (0-16)	1 (0-6)	0.029*
Power doppler-SQ	0 (0-4)	2 (0-20)	1 (0-12)	0.025*
Tenosynovitis gray scale-Q	0 (0-3)	2 (0-10)	0 (0-9)	<0.001*
Tenosynovitis gray scale-SQ	0 (0-2)	0 (0-6)	0 (0-2)	0.015*
Bone erosion-Q	0 (0-2)	12 (0-12)	2 (0-12)	<0.001*
Bone erosion-SQ	0 (0-6)	15 (0-36)	3 (0-36)	<0.001*
Cartilage damage-Q	0 (0-4)	4 (0-4)	2 (0-4)	<0.001*
Cartilage damage-SQ	0 (0-12)	12 (0-16)	2 (0-16)	<0.001*
CSA	**Nerve pathology (n = 62)**	**Joint pathology (n = 65)**	**Combined pathology (n = 65)**	**p-value^**
Tibial	15.43 ± 5.86	14.00 ± 5.09	13.86 ± 5.65	0.214
Peroneal	13.96 ± 5.08	12.04 ± 4.32	13.81 ± 4.02	0.028*
Sural	9.30 ± 1.82	8.24 ± 2.41	8.97 ± 1.46	0.008*

Table 3: Nerve conduction of Tibial, Peroneal nerve motor studies, Sural and superficial peroneal sensory studies.

Tibial nerve	**Nerve pathology (n = 62)**	**Joint pathology (n = 65)**	**Combined pathology (n = 65)**	**p-value^**
Latency	4.45 ± 1.49	3.70 ± 0.82	3.91 ± 0.79	<0.001*
Prolonged latency	21 (34%)	9 (14%)	13 (20%)	0.022*
Amplitude	5.63 ± 2.91	5.55 ± 2.99	5.72 ± 2.80	0.948
Decreased amplitude	22 (35%)	20 (31%)	20 (31%)	0.808
NCV	66.07 ± 9.88	69.83 ± 12.21	68.14 ± 9.58	0.141
Decreased NCV	2 (3.2%)	5 (7.7%)	2 (3.1%)	0.515
F wave latency	29.43 ± 3.17	27.33 ± 2.87	29.03 ± 3.40	<0.001*
Prolonged F wave	13 (21%)	5 (7.7%)	14 (22%)	0.058
. . Peroneal nerve				
Latency	3.30 ± 0.82	3.33 ± 1.74	3.06 ± 1.00	0.407
Prolonged latency	17 (27%)	13 (20%)	8 (12%)	0.102
Amplitude	4.68 ± 1.55	5.08 ± 2.90	5.50 ± 2.32	0.146
Decreased amplitude	8 (13%)	14 (22%)	4 (6.2%)	0.037*
NCV	70.68 ± 14.57	76.08 ± 12.44	71.35 ± 12.85	0.045*
Decreased NCV	5 (8.1%)	0 (0%)	1 (1.5%)	0.017*
Sural nerve				
Latency	4.13 ± 1.03	3.66 ± 0.92	3.92 ± 0.99	0.029*
Prolonged latency	44 (71%)	28 (43%)	35 (54%)	0.006*
Amplitude	18.93 ± 11.51	27.09 ± 14.39	19.61 ± 11.97	<0.001*
Decreased amplitude	38 (61%)	24 (37%)	39 (60%)	0.008*
NCV	35.66 ± 10.56	41.86 ± 8.91	38.51 ± 8.30	0.001*
Decreased NCV	55 (89%)	43 (66%)	50 (77%)	0.010*
Superficial peroneal				
Latency	3.92 ± 1.66	3.00 ± 0.51	3.22 ± 0.70	<0.001*
Prolonged latency	32 (52%)	15 (23%)	24 (37%)	0.004*
Amplitude	20.10 ± 16.64	22.85 ± 14.61	16.72 ± 10.89	0.028*
Decreased amplitude	8 (13%)	3 (4.6%)	10 (15%)	0.12
NCV	39.87 ± 12.31	47.94 ± 9.59	45.42 ± 10.40	<0.001*
Decreased NCV	31 (50%)	12 (18%)	21 (32%)	<0.001*

(p-value < 0.001). Regarding the peroneal nerve motor studies in the examined feet, the mean value for NCV was significantly higher in patients with joint pathology compared to those with nerve pathology (p-value = 0.045). Percentage of the patients with decreased amplitude was significantly higher in patients with joint pathology compared to those with nerve pathology or combined pathology (p-value = 0.037) while percentage of decreased NCV was higher in nerve pathology group (p-value = 0.017). Regarding the sural nerve sensory studies in the examined feet of the three studied groups, the mean values for latency was significantly higher in patients with nerve pathology compared to those with joint pathology or combined pathology (p-value = 0.029). The mean value for amplitude and NCV were significantly lower in patients with nerve pathology compared to those with joint pathology or combined pathology.(p-value < 0.001). Furthermore, the percentage of patients with prolonged latency, decreased amplitude and decreased NCV was also significantly higher in patients with nerve pathology compared to those with joint pathology or combined pathology (p-value = 0.006, 0.008 and 0.010 respectively). Finally, regarding the superficial peroneal nerve sensory studies in the examined feet of the three studied groups, the mean values for latency, amplitude and NCV were significantly different between different patient groups (p-value < 0.05). The percentage of patients with prolonged latency and decreased NCV was significantly higher in patients with nerve pathology compared to those with joint pathology or combined pathology (p-value = 0.004 and <0.001, respectively). Regarding correlation between the pain-DETECT score and CSA of the studied nerves, The correlation coefficients (r-values) and p-values are reported for each nerve Figure 1. All three nerves have a significant positive correlation (p-value< 0.001). The tibial nerve has a correlation coefficient of 0.373, the peroneal nerve has a coefficient of 0.537, and the sural nerve has a coefficient of 0.563. In the correlation between the pain-DETECT score and nerve conduction studies, the results reveal that for the tibial nerve; both latency and f-wave latency show a significant positive correlation with the score, while amplitude and NCV have a significant negative correlation Figure 2. As for the peroneal nerve, only NCV demonstrated a significant negative correlation Figure 3. Regarding the sural nerve; latency has a significant positive correlation, while amplitude and NCV have a significant negative correlation with the score (Figure 4). Finally, for the SP nerve, the latency is positively correlated with the score, while NCV is negatively correlated Figure 5.

Performance of the pain-DETECT score for predicting the etiology of neuropathic pain: Table 4 compared the nerve pathology to joint pathology and a cut-off point of >21 for the pain-DETECT score has an Area under the curve (AUC) of 0.784, sensitivity of 54.84%, and specificity of 93.85%, with a diagnostic accuracy of 74.8%. While in comparison of nerve pathology to combined pathology, a cut-off point of >18 for the pain-DETECT has an AUC of 0.680, sensitivity of 77.42%, and specificity of 50.77%, with a diagnostic accuracy of 63.8%. Meanwhile performance of the pain-DETECT for predicting isolated nerve pathology, with a cut-off point of >21 showed an AUC of 0.732, sensitivity of 54.84%, and specificity of 83.08%, with a diagnostic accuracy of 74.0%.

Discussion

Rheumatoid arthritis (RA) is a chronic systemic

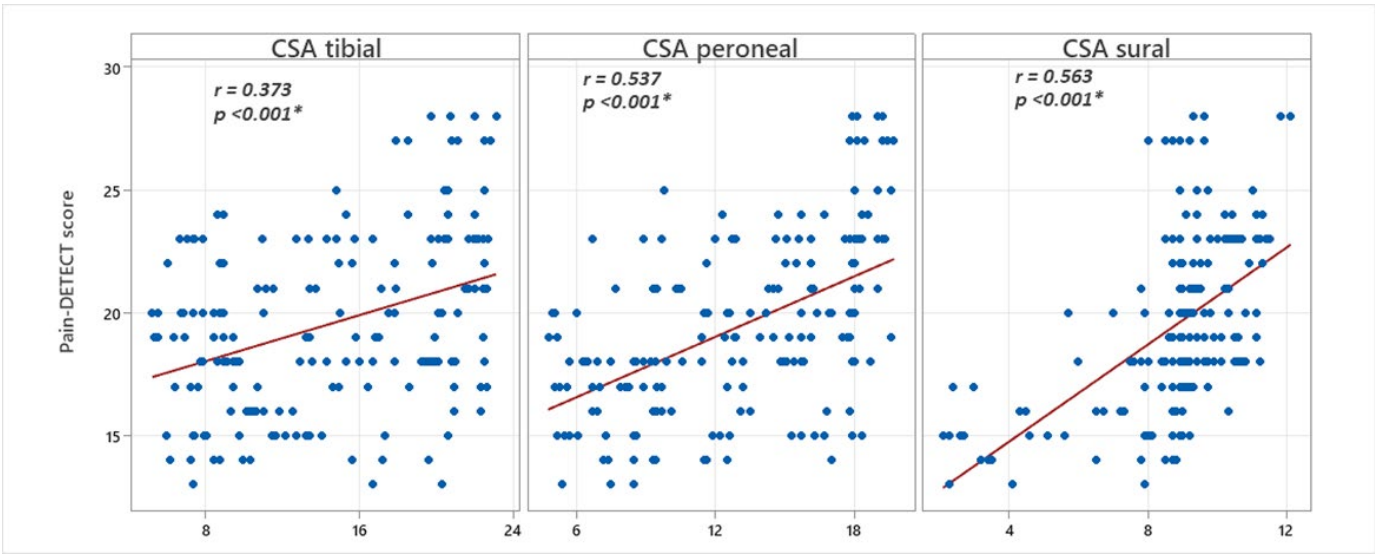

Figure 1: Correlation between pain-DETECT score and CSA of the three studied nerves.

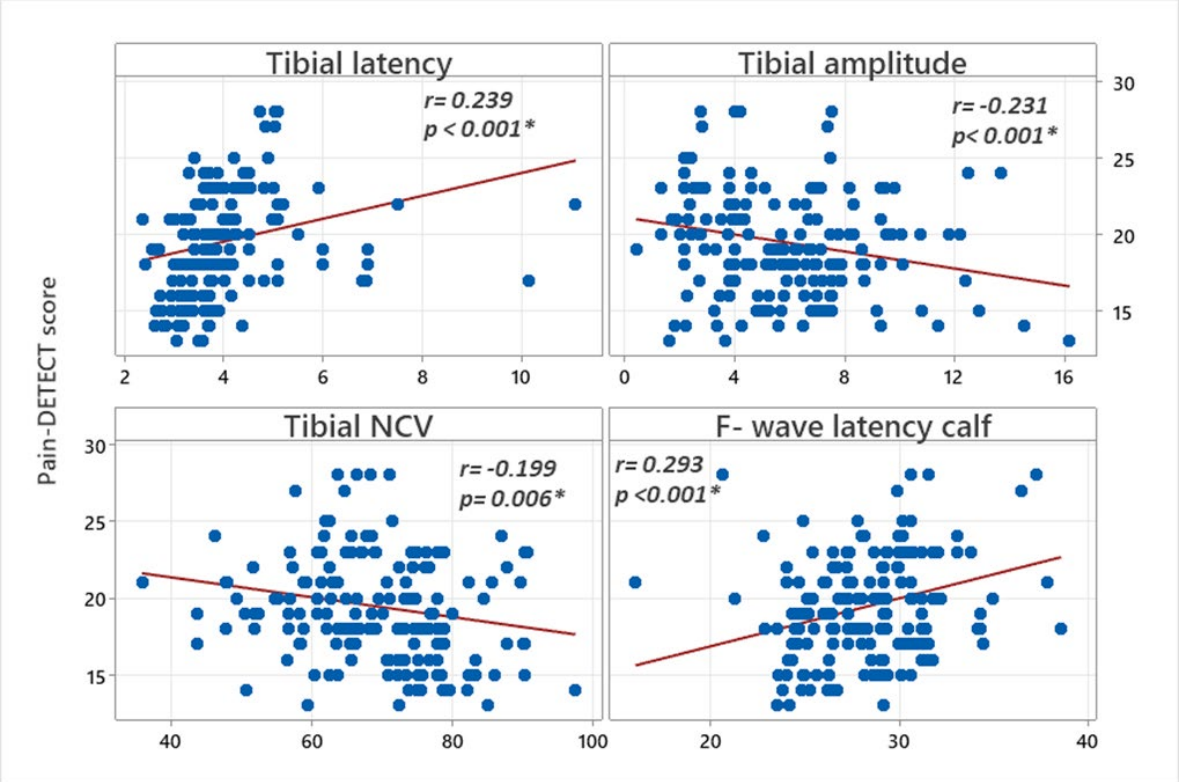

Figure 2: Correlation between pain-DETECT score and tibial nerve studies.

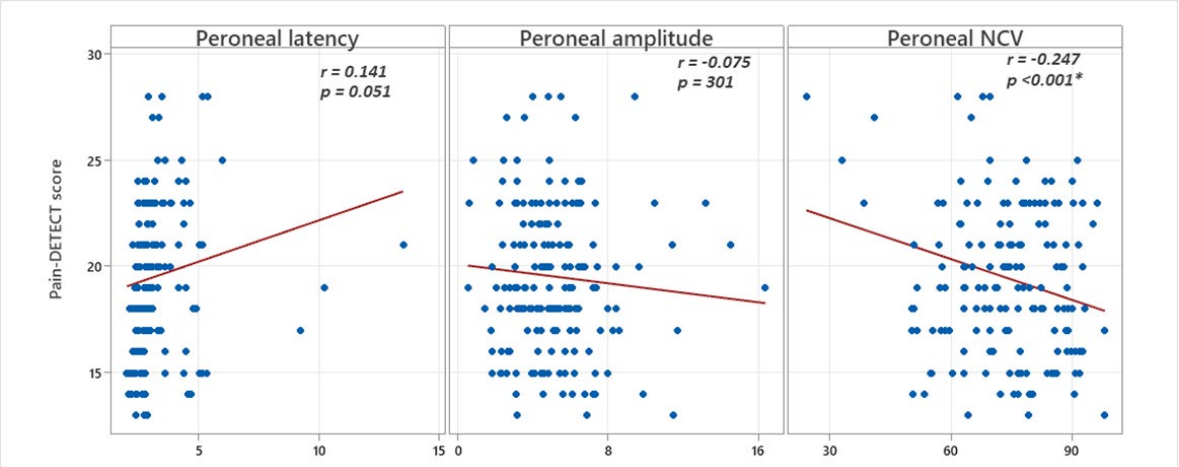

Figure 3: Correlation between pain-DETECT score and peroneal nerve studies.

inflammatory disorder predominantly affecting synovial joints. The inflammatory response within the joint synovium leads to joint erosion, ligament laxity, and subsequent deformity [17]. Clinical involvement of the peripheral nervous system may be asymptomatic in the early stages of the disease or may present with a wide variety of symptoms such as pain, paresthesias, and muscle weakness. These symptoms may mimic and overlap with those of arthritis. In presence of severe joint disease, restriction of movement, pain, and deformities, symptoms of neuropathy may be overlooked or overestimated [18]. We aim to estimate the prevalence of neuropathic pain (NP) in RA patients with ankle and foot pain using the pain-DETECT questionnaire and to assess the effectiveness of the painDETECT score as a diagnostic tool to distinguish between different types of NP. Furthermore, the study aimed to evaluate the role of neuromuscular ultrasound (NMUS) and nerve conduction study (NCS) in assessment of neuropathic foot and ankle in RA patients. This is a cross sectional

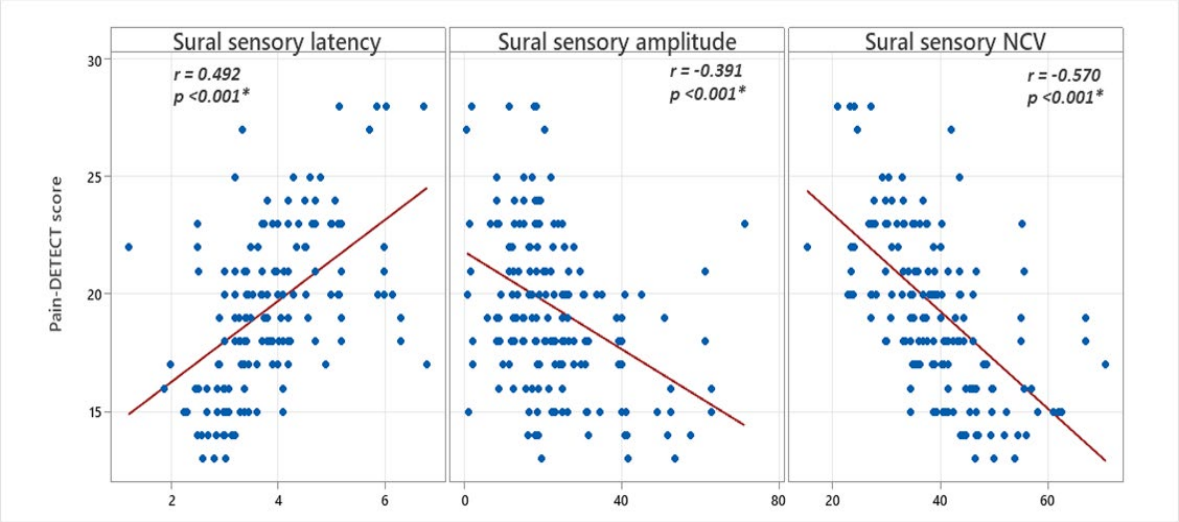

Figure 4: Correlation between pain-DETECT score and sural nerve studies.

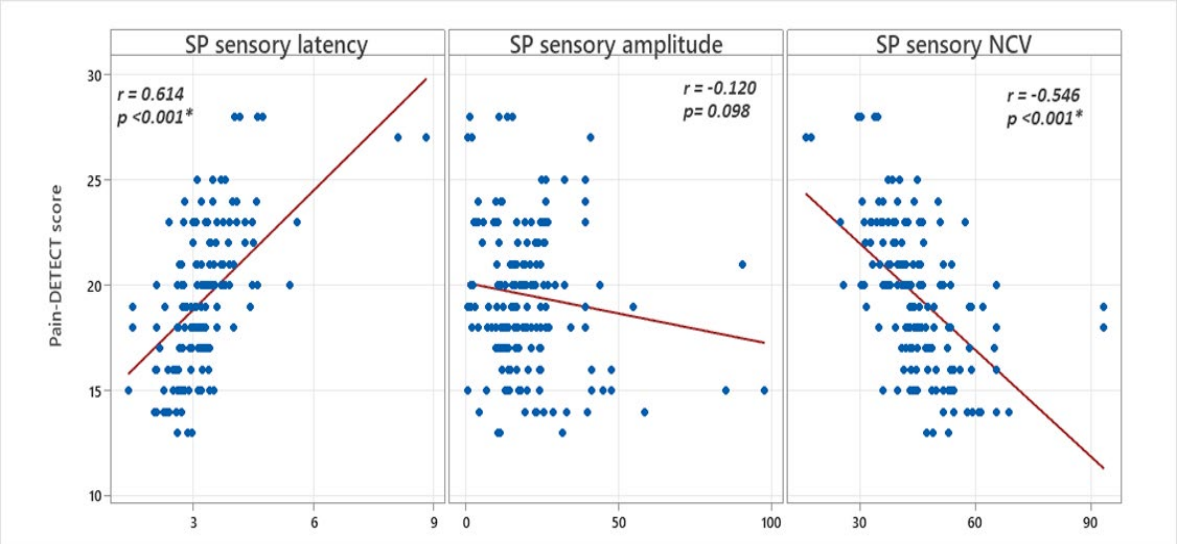

Figure 5: Correlation between pain-DETECT score and SP nerve studies.

Table 4: Performance of pain-DTECT score for prediction of neuropathic pain etiology (Nerve pathology vs. Joint pathology, combined pathology and Isolated nerve pathology).

Cut off point	AUC	Sensitivity	95% CI of sensitivity	Specificity	95% CI of specificity	Diagnostic Accuracy
Joint pathology						
>21	0.784	54.84	41.7-67.5	93.85	85.0-98.3	74.80%
Combined pathology						
>18	0.68	77.42	65.0-87.1	50.77	38.1-63.4	63.80%
Isolated nerve pathology						
>21	0.732	54.84	41.7-67.5	83.08	75.5-89.1	74.00%

study conducted on 250 RA patients, diagnosed according to 2010 ACR/EULAR Rheumatoid arthritis classification criteria [11] with foot and ankle pain, attending outpatient clinic and inpatient department of Rheumatology, Rehabilitation and Physical Medicine, Assiut University Hospitals. Of these patients, 99 (39.6%) were identified as having NP, with 53 (53.5%) classified as likely to have and 46 (46.5%) as possibly having NP according to pain-DETECT score. In RA patients, the prevalence of foot pain has been reported in varying numbers within the published literature. Although patients with RA complain of foot pain and

disability because of foot problems, physicians generally overlook or neglect the feet in routine clinical examination. This is may be because feet and ankles are not included as a part of the Disease Activity Score (28 joints) (DAS28) scoring system, which is generally used to assess disease activity and helps to define clinical remission of the disease. Hence, patients in remission may suffer from foot disease activity, as shown in the previous studies [19]. In the study by [2] which aimed to explore the prevalence and patterns of peripheral neuropathy in individuals with RA, the reported incidence of peripheral neuropathy was 75.28%. Within their study, a predominant proportion of participants exhibited asymmetrical sensory motor axonal neuropathy, which was concomitant with NP. The higher percentage in their study compared to this study can be attributed to their comprehensive assessment including all cases of peripheral neuropathy, rather than solely focusing on individuals experiencing pain. In alignment with our own findings, studies conducted by [20] and [21] reported nearly the same prevalence of peripheral neuropathy in RA patients (39.2% and 33% respectively). Furthermore, [22] reported that 24.2% of their patient cohort displayed sensory manifestations of peripheral neuropathy, inclusive of pain. In our study, the mean age of the participants was 45.36 ± 11.54 years, with a majority of female patients (88%). This was in agreement with the study done by [23] who studied one hundred and seventy six patients with RA with female predominance. In harmony [24] reported that, the mean age was 45.4 ± 8.3 years old. There was female predominance (90%) and male about (10%). This also emphasizes the higher prevalence of RA in females than in males, whereas the sex ratio is typically around 3: 1 [25] In another study by [16] found that the mean age of the studied patient groups was 45.9 years old. [26] in their study on a retrospective analysis of nerve ultrasound changes in electrophysiologically confirmed cases showed that mean age was 50.5 years old. This association of gender and presence of peripheral neuropathy was not in accordance with the studies conducted by [27]. Interestingly, [28] reported that male gender was significantly associated with the presence of peripheral neuropathy. [2] Described a significant association of increasing age and presence of peripheral neuropathy. Thus, one of the secondary causes of peripheral neuropathy in geriatric population might be RA. Moreover, [29,30] reported that this association with age was significant. To distinguish between causes of NP in RA patients' ultrasound and electrophysiological studies usually used. In accordance with this methodology, our study employed these assessments to classify patients into three discrete categories: Patients with isolated nerve pathology (31 patients, 31.3%), patients with isolated joint pathology (35 patients, 35.4%), and patients with combined pathology (33 patients, 33.3%). Regarding characteristics of participants according to etiology, in our study, the mean age of nerve pathology group was higher than the joint pathology and the combined pathology groups (48.71± 11.95, 43.66 ± 10.54, 44.03 ± 11.84, respectively) which may indicate that the pain of nerve pathology takes more time to develop and so patients complain later of it. However, this difference was not statistically significant (p=0.149). In our study, joint pathology had a longer disease duration compared to patients with nerve pathology or combined pathology (median duration of 12, 10, and 8 years, respectively), which was statistically significant (p=0.012). This was in agreement with studies conducted by [29,31] and [2] as they found a positive association between the presence of neuropathy and disease duration. These findings were explained by [32] who hypothesized that the NP was more common in patients with long-term RA due to more joint destruction, and history of joint surgeries. In our study, patients with joint pathology had a higher percentage of steroid use compared to patients with nerve pathology or combined pathology (77.1%, 41.9%, and 63.6%, respectively) which reached statistical significance (p=0.013). On the other hand, patients with nerve pathology had a significantly higher percentage of use of hydroxychloroquine (HQ) (100%) compared to 94.3% in joint pathology and 84.8% in combined pathology, which was statistically significant (p=0.046). There was no statistically significant difference in type of treatment between groups as regard use of single, double DMARs or biologic treatment. Our results regarding steroid use was in agreement with studies conducted by [33] and [20]. However, [2] reported there was no significant association found between presence of neuropathy and prior use of steroids. The significant association between HQ use and nerve pathology in our study was in agreement with a case report done by [34] which discussed development of peripheral neuropathy and proximal myopathy in patients using HQ, which indicate that the long use of HQ might be a cause of neuropathic pain in RA population. In our study, patients with joint pathology exhibited a higher prevalence of deformities including ankle, metatarsophalangeal (MTP) and forefoot deformities compared to those with nerve pathology or combined pathology (74.3%, 22.6%, and 42.4%, respectively) which was statistically significant in all deformities (p<0.001). Among these deformities, ankle deformity was the most prevalent across all three groups (74.3%, 19.4% and 39.4%). These findings were anticipated, considering that joint pathology often leads to joint destruction and consequent deformity

formation, which contrasts with the scenario of pure nerve pathology. To our knowledge, there was no previous studies that investigated the association between types of deformities and the different pathologic types of NP in RA. In our study, patients with joint pathology had a higher DAS-28 ESR score compared to patients with nerve pathology or combined pathology (mean score of 5.64, 4.48, and 4.77, respectively), which reached statistical significant (p=0.016). This was in agreement with [35] that evaluated the association between tarsal tunnel syndrome in RA and disease activity. Also [2] found significant association between DAS-28 and presence of peripheral neuropathy, and also in agreement with [6], who aimed to evaluate neuropathic foot pain in patients with RA using electrophysiological studies and musculoskeletal ultrasound (MSUS) to address the association between these findings and disease activity. They found a significant correlation between presence of functional incapacity in patients with RA with neuropathy and disease activity. However in contrast to our study, studies by [30,36] stated that rheumatoid neuropathy occurs irrespective of the disease activity level. Moreover, [37] stated that high disease activity was not a predictor of rheumatoid vasculitis which can be a cause of pure nerve affection in RA. In our study, acute phase reactant (ESR) was significantly higher in the joint pathology group, in comparison with nerve pathology and combined pathology groups. (mean score of 48, 36 and 37, respectively), which was statistically significant (p=0.011). This was in agreement with [2] who reported that a significant association was found between inflammatory markers of disease activity (ESR, CRP) and peripheral neuropathy in their study. In our study, while there was a higher positive rheumatoid factor (RF) percentages among patients with joint pathology (94.3%) compared to nerve pathology (80.6%) and combined pathology (72.7%). However, the observed differences did not reach statistical significance (p = 0.058). A similar result was reported by [28] and [20]. However, this was in contrast with [2] who reported that RF positivity was found to be significantly associated with presence of peripheral neuropathy irrespective of its cause. As ultrasound and electrophysiological studies may take time and need trained physician to be used in diagnosis of NP etiology, it is important to find other tools to help in diagnosis. In this study, painDETECT questionnaire was used to evaluate the different causes of NP. In our study, patients with nerve pathology had a higher painDETECT score compared to patients with joint pathology or combined pathology (mean score of 21.55 ± 3.60, 17.51 ± 2.87 and 19.27 ± 3.14, respectively), which was statistically significant (P= <0.001). To our knowledge, no previous studies investigated the role of questionnaires such as pain-DETECT score in distinguishing the causes of NP. However, in a study by [38] in which he used the pain-DETECT questionnaire in RA patients to assess pain characteristics in autoimmune conditions, there was a clear positive correlation between VAS scores and painDETECT scores, suggesting that the high levels of pain reported on the VAS also correlated with high neuropathic pain scores, which is in agreement with our study. In our study, to evaluate the efficacy of pain-DETECT score in distinguishing between causes of NP, the correlation between the painDETECT score and cross sectional area (CSA) of the studied nerves (Tibial, common peroneal and sural nerves) was evaluated. All three nerves have a significant positive correlation with Pain-DETECT score (p-value< 0.001), thus emphasizing our results that nerve pathology resulted in higher questionnaire scores. The tibial nerve has a correlation coefficient of 0.373, the peroneal nerve has a coefficient of 0.537, and the sural nerve has a coefficient of 0.563. Our reports on the performance of the pain-DETECT for predicting isolated nerve pathology, with a cut-off point of >21 having a diagnostic accuracy of 74.0%. So, using of pain-DETECT score may be useful in cases of NP with nerve pathology especially if high score > 21 which help in management of cases until performance of further investigations. Further modalities were done in this study to investigate the different causes of NP in RA patients, these were NCS, MSUS and NMUS. In our study, MSUS scores measured according to the "musculoskeletal ultrasound score 10" [15] were higher in joint pathology group, in comparison to nerve pathology group which had the lowest scores for all parameters and combined pathology groups, this difference was statistically significant in all parameters, with p value of 0.029 in power doppler-Q score, 0.025 in power Doppler-SQ score, 0.015 in tenosynovitis grey scale-SQ score, and p-value< 0.001 in the other studied parameters. In agreement with our study, [6] reported that, a positive power doppler (PD) signal and joint erosions are considered to be associated with disease activity on the basis of their prevalence in the active patients when compared with the inactive ones. Also in keeping-up with our results, a previous study by [39], displayed similar ankle PD findings. Explanation for this finding was discussed by [40] who suggested that disease activity is closely associated to presence of hyper vascularity (PD changes), which may contribute to the development of erosions and other forms of structural damage which leads to NP. In our study, mean CSA values for the studied nerves were higher in patients with nerve pathology compared to those with joint pathology and combined pathology, and this difference was statistically significant in peroneal and sural nerves

(p-value = 0.028 and 0.008 respectively). This is in accordance with [41] who reported that the CSA of tibial nerve significantly larger in tarsal tunnel syndrome (TTS) group compared with the controls (mean 13.8 ± 4.4mm2 in controls vs. 20.6 ± 8.5 mm2 in patients). Moreover, [42] found that US revealed larger CSA in 84 % of cases in his study to determine the role of US in posteriomedial TTS diagnosis. In our study, the mean values for amplitude, and nerve conduction velocity (NCV) of the tibial nerve motor studies in the examined feet were not significantly different between patients with joint pathology, nerve pathology, or combined pathology. However, the mean of latency and F wave latency was significantly higher in patients with nerve pathology compared to those with joint pathology or a combination of both (p-value < 0.001), this findings may be due to the demyelinating nature of RA associated neuropathy which affect motor latency more than amplitude. In agreement with our study, [6] where he used NCS in diagnosis of foot and ankle neuropathy in 50 RA patients, he reported that the electrophysiological diagnosis of tibial nerve affection was encountered in 18 (36%) patients. Also, in a study by [43], where he examined 48 RA patients for the presence of tibial neuropathy and found that 25% of patients had a definite delay in the distal motor latency of the tibial nerve. In our study, regarding the peroneal nerve motor studies in the examined feet, the mean value for NCV was significantly higher in patients with joint pathology compared to those with nerve pathology (p= 0.045). The percentage of patients with decreased amplitude was significantly higher in patients with joint pathology compared to those with nerve pathology or a combination of both (p-value = 0.037), which may be explained by the more prevalence of nerve compression with ankle deformity and arthritis. It was in disagreement with [6], where there was no significant affection of peroneal nerve NCV or amplitude. In our study regarding sural nerve, all parameters of NCS (distal latency, amplitude and NCV) were significantly affected in nerve pathology group in comparison to joint pathology or combined pathology groups, this difference in NCS parameters reached statistical significance (p values of distal latency, amplitude and NCV= 0.006, 0.008 and 0.010, respectively), these findings can be due to the fact that pure neuropathy affect sensory nerves before motor nerves. This was in agreement with [44], where he found decreased sural NCV in relation to RA activity. However, [30] didn't find such findings. In our study regarding superficial peroneal nerve, percentage of patients with prolonged latency and decreased NCV was significantly higher in patients with nerve pathology compared to those with joint pathology or combined pathology which reached statistical significance (p-value = 0.004 and <0.001, respectively). Unfortunately and to our knowledge, no previous studies investigated the electrophysiologic study of superficial peroneal sensory nerve; this could be due to the difficult technique of studying this nerve.

Conclusion

NP in RA patients with ankle and foot pain using the pain-DETECT questionnaire and neuromuscular ultrasound (NMUS) with nerve conduction study (NCS) is considered to be valuable in detection of neuropathic foot and ankle and differentiate it from joints arthritis. Pain-DETECT score is considered an effective diagnostic tool to distinguish between different types of NP and predicting isolated nerve pathology in RA patients.

Study limitations

It was cross sectional, single center study which inherently restricts the ability to follow-up patients, in terms of generalizability of the findings. We recommend to take a multicenter longitudinal study, such an approach would allow for a broader scope of data collection, increased diversity in patients population, thereby enhance the reliability and applicability of the results, also, follow up of those patients help to confirm the results and allow accurate management of RA patients.

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