

Electrophysiology in Early Diagnosis of Distal Symmetric Polyneuropathy in Patients Undergoing Chemotherapy

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Outline

Background

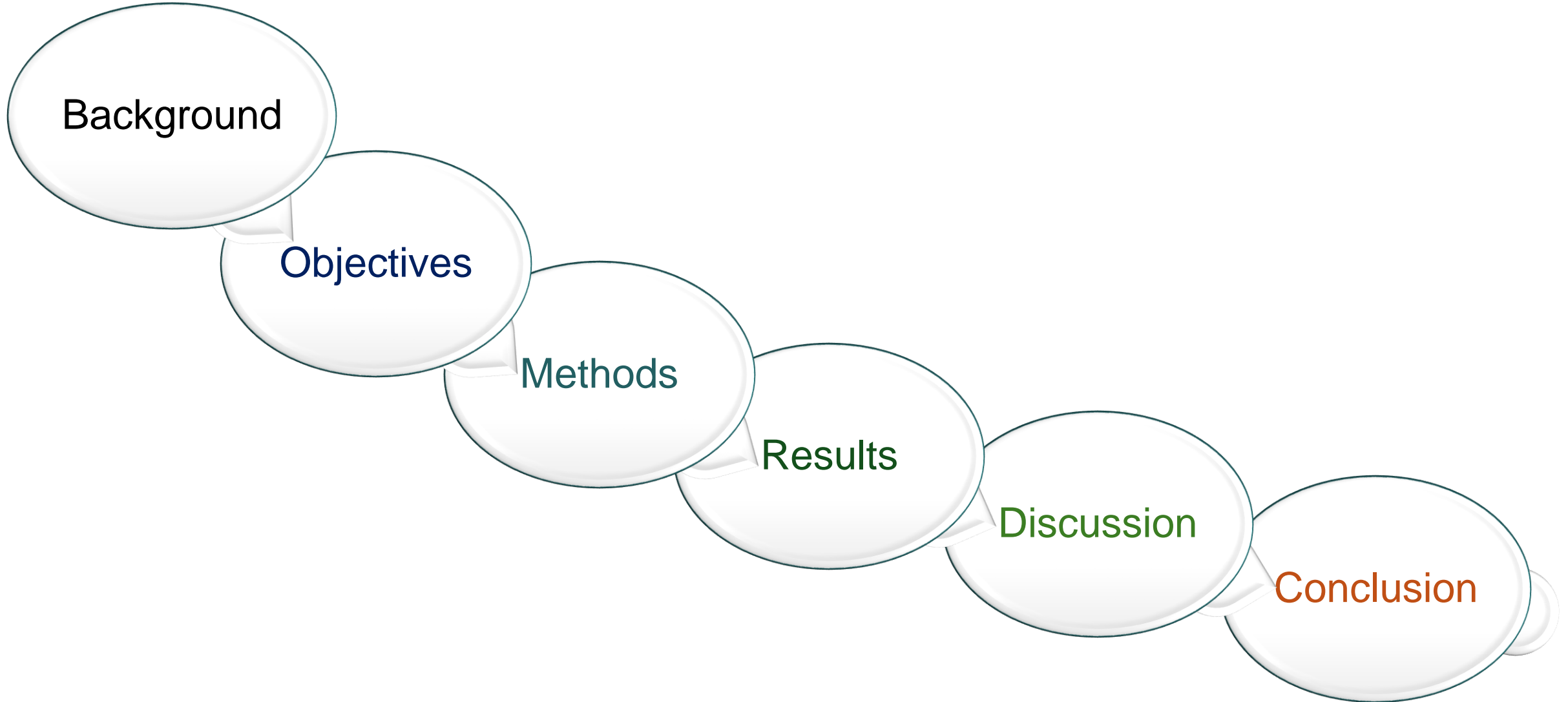
Objectives

Methods

Results

Discussion

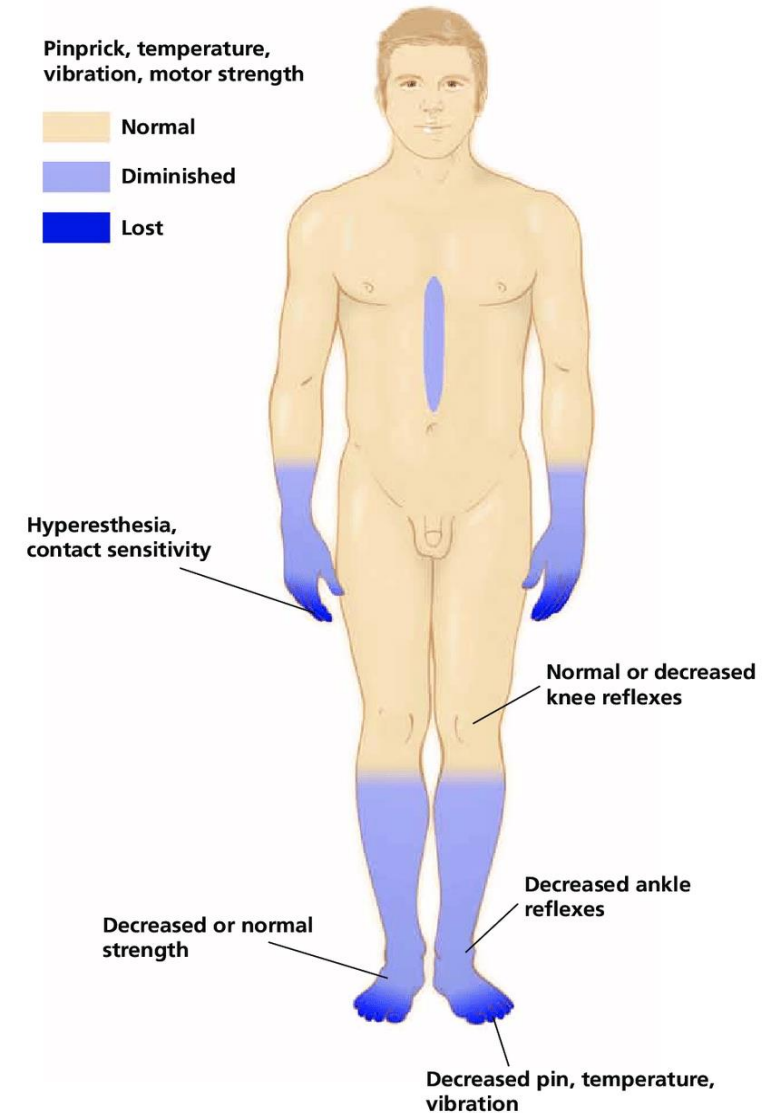
Conclusion

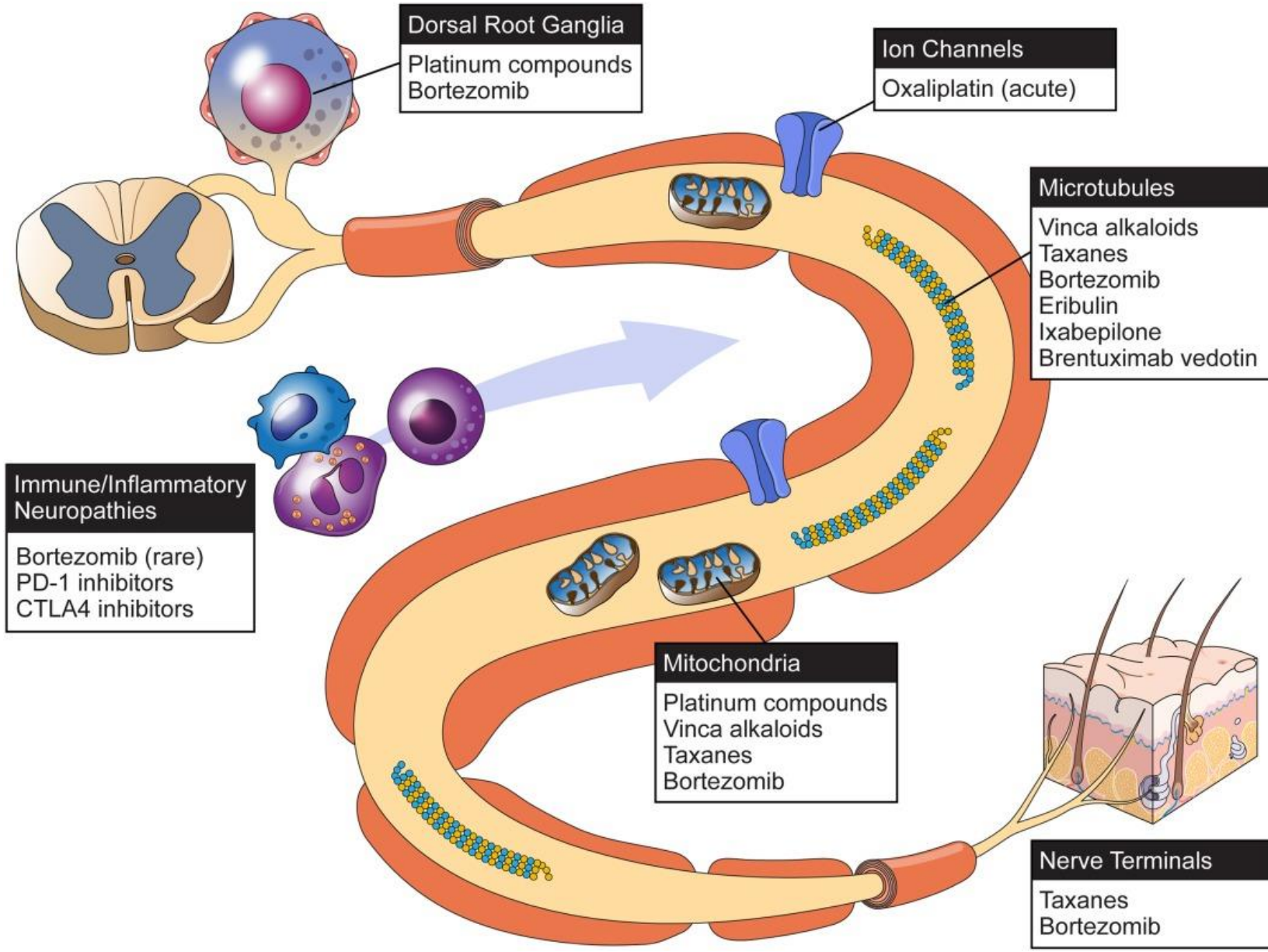


Background

Distal Symmetric Polyneuropathy (DSP)

- tingling, numbness, weakness and burning pain
- “stocking and glove” pattern
- sensory, motor or autonomic nerves may be affected





Objectives

Early diagnosis is crucial for guiding treatment.

In this study, we aimed;

- To determine a new electrophysiological parameter for detection of early axonal loss

using nerve conduction studies.

Methods

Ethical Approval and Statistical Power Analyses

- Bezmialem Vakıf University Ethics Committee in **May 2023**
- Bezmialem Vakıf University Academic Board in February 2023
- Scientific and Technological Research Council of Turkey (TÜBİTAK A2209)
- Based on previous studies, with a confidence level of 95% and a power of 80%, assuming a mean difference of 0.15 units and a standard deviation of 0.15, it has been calculated that a minimum of 21 participants is required for each group, totaling 42 participants (Pinar Kahraman Koytak, et al, 2016)

Recruitment of participants into the study

- **Patients:**
 - 22 patients, undergoing chemotherapy
 - experiencing symptoms such as numbness/tingling, burning/chilling, pain, and imbalance in the feet, suggestive of polyneuropathy,
- **Control group:**
 - 30 healthy volunteers
 - with similar age and sex distribution as the patients,
 - including researchers conducting the study, their relatives, and auxiliary healthcare personnel.

All participants:

- Age, sex, height, weight, BMI
- Neurological examination

Patients:

- Cancer type
- Chemotherapeutic agents
- Symptoms
- The temporal relationship between the onset of symptoms and chemotherapy



Clinical Evaluation of Polyneuropathy

• Michigan Neuropathy Screening Instrument (MNSI)

Appendix A. Michigan Neuropathy Screening Instrument

A. History *(To be completed by the person with diabetes)*

Please take a few minutes to answer the following questions about the feeling in your legs and feet. Check Yes or No based on how you usually feel. Thank you.

1. Are your legs and/or feet numb? Yes No
2. Do you ever have any burning pain in your legs and/or feet? Yes No
3. Are your feet too sensitive to touch? Yes No
4. Do you get muscle cramps in your legs and/or feet? Yes No
5. Do you ever have any prickling feelings in your legs or feet? Yes No
6. Does it hurt when the bed covers touch your skin? Yes No
7. When you get into the tub or shower, are you able to tell the hot water from the cold water? Yes No
8. Have you ever had an open sore on your foot? Yes No
9. Has your doctor ever told you that you have diabetic neuropathy? Yes No
10. Do you feel weak all over most of the time? Yes No
11. Are your symptoms worse at night? Yes No
12. Do your legs hurt when you walk? Yes No
13. Are you able to sense your feet when you walk? Yes No
14. Is the skin on your feet so dry that it cracks open? Yes No
15. Have you ever had an amputation? Yes No

Total _____

(MNSI-A)

Michigan tool for screening of neuropathy			
Physical examination			
1 - Foot appearance - Abnormal (feet deformity): hammer toes, superposed toes, hallux valgus, articular subluxation, prominent metatarsal heads, medium convexity			
2 - Ulceration.			
3 - Achilles reflex.			
4 - Vibratory sensation on the dorsum of the 1st toe.			
5 - 10-gram-monofilaments on the dorsum.			
Total: / 10 points			
Physical examination			
Normal	Yes (0)	No (1)	
Ulceration	Absent (0)	Present (1)	
	D	D	
	E	E	
Achilles reflex	Present (0)	Present/reinforcement (0,5)	Absent (0)
	D	D	D
	E	E	E
Vibratory perception	Present (0)	Diminished (0,5)	Absent (1)
	D	D	D
	E	E	E
10-gram-monofilament	Present (0)	Diminished (0,5)	Absent (1)
	D	D	D
	E	E	E
Total: / 10 points			

(MNSI-B)

- Semmes-Weinstein monofilament (10 g – 5.07 mm) test

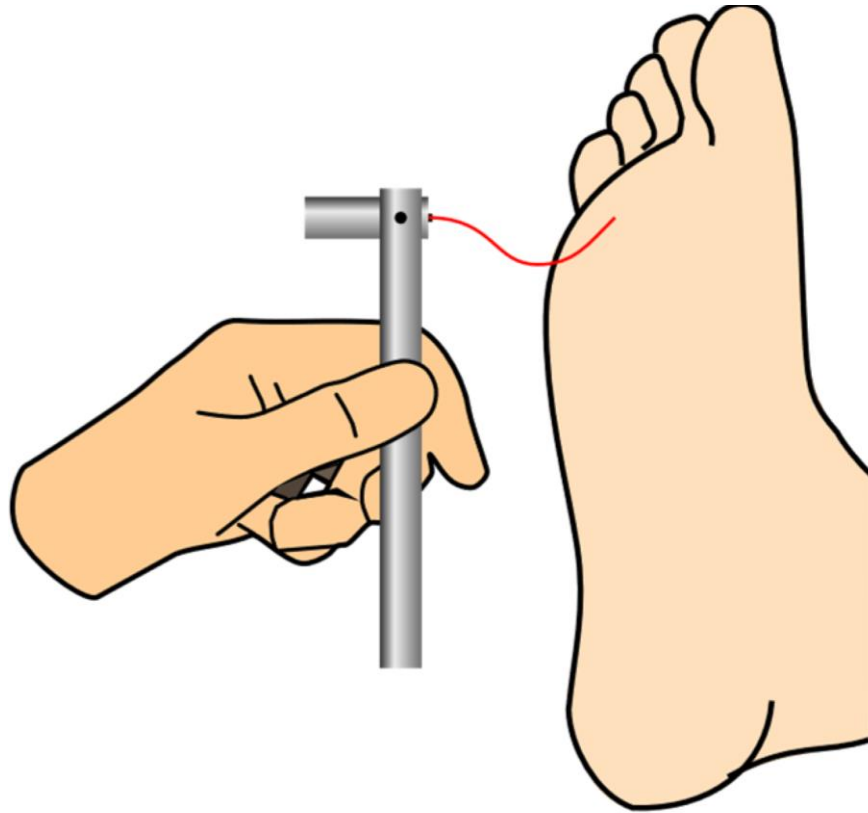


Fig. Points of application of the Semmes-Weinstein monofilament test

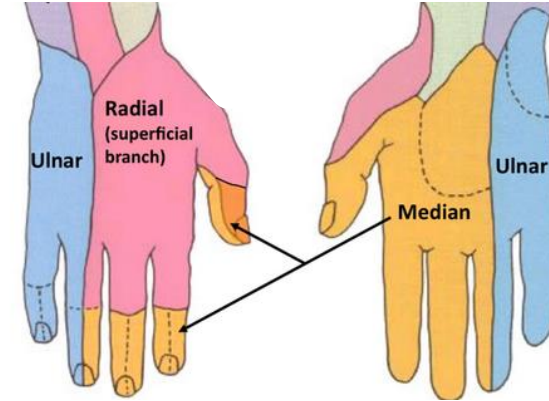
- Patients clinically determined to have neuropathy based on
 - ✓ neurological examination,
 - ✓ Michigan Neuropathy Screening Instrument (MNSI), and
 - ✓ monofilament testingwere included in the electrophysiological study.
- Finally, 20 cancer patients with clinical polyneuropathy were included.

Electrophysiological Evaluation of Polyneuropathy

Sensory nerve conduction studies

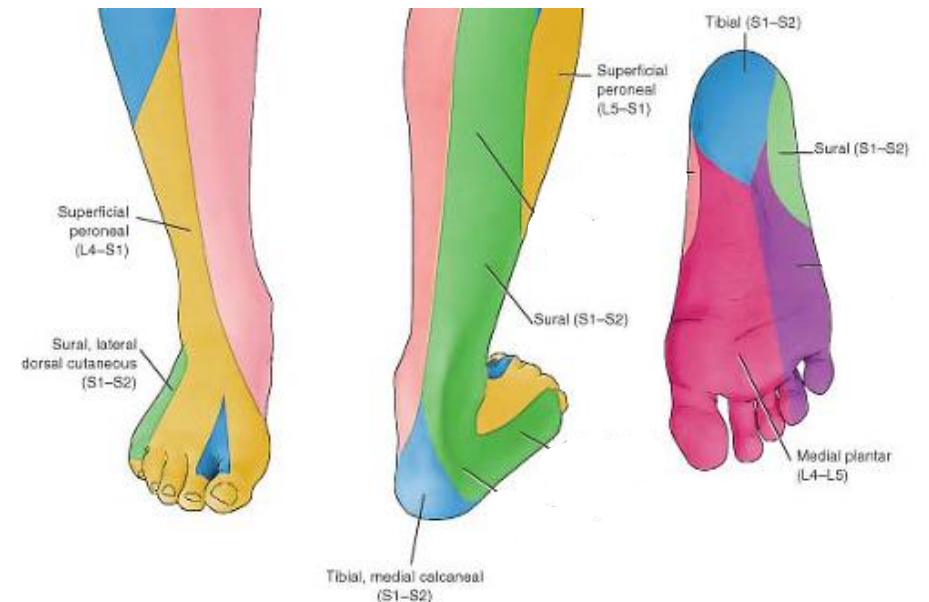
- **Upper extremities:**

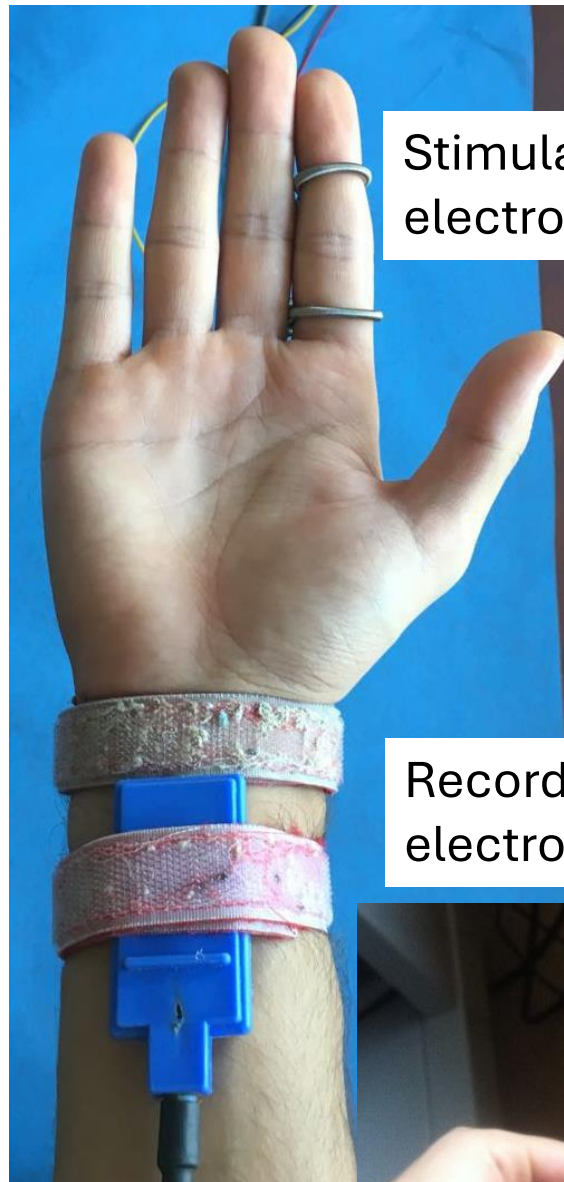
- Radial
- Median
- Ulnar



- **Lower extremities:**

- Medial femoral cutaneous
- Sural,
- Superficial peroneal
- Medial plantar





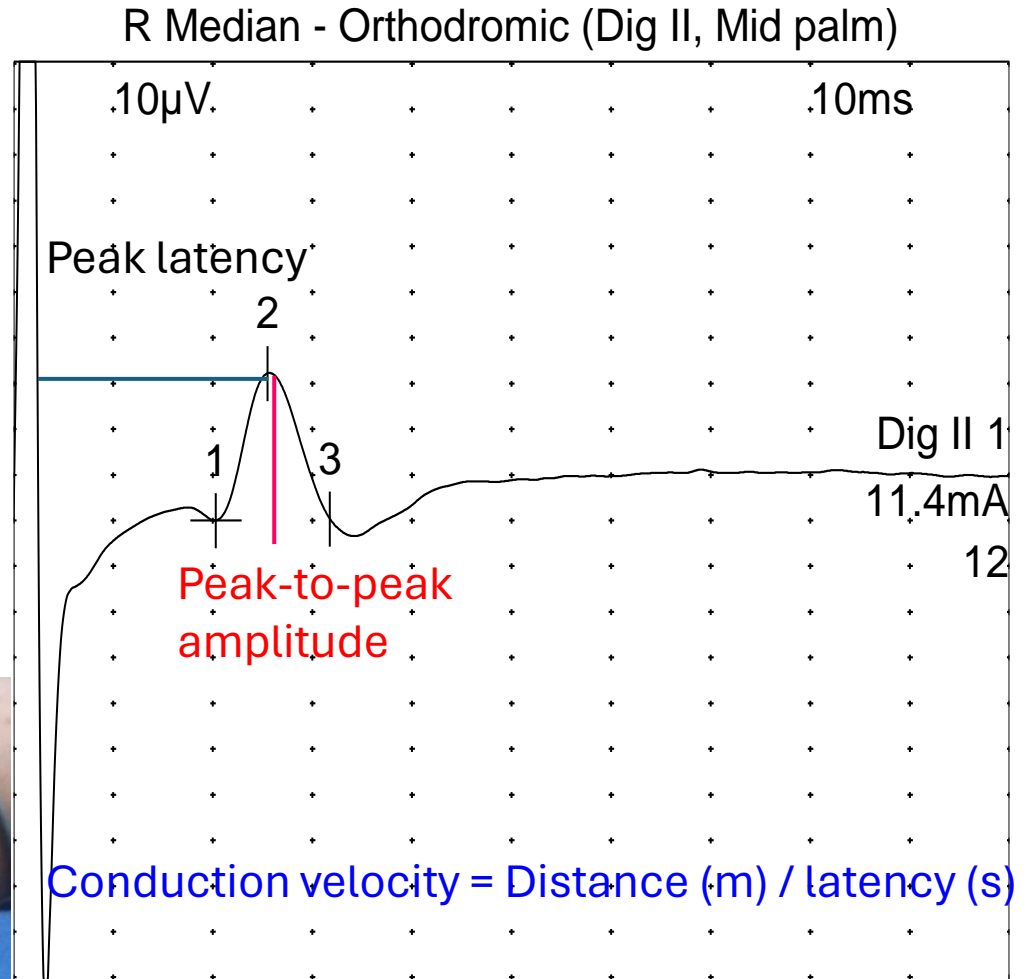
Stimulating electrode

Recording electrode

Median nerve

-Ortodromic sensory nerve conduction study

Measurement of distance



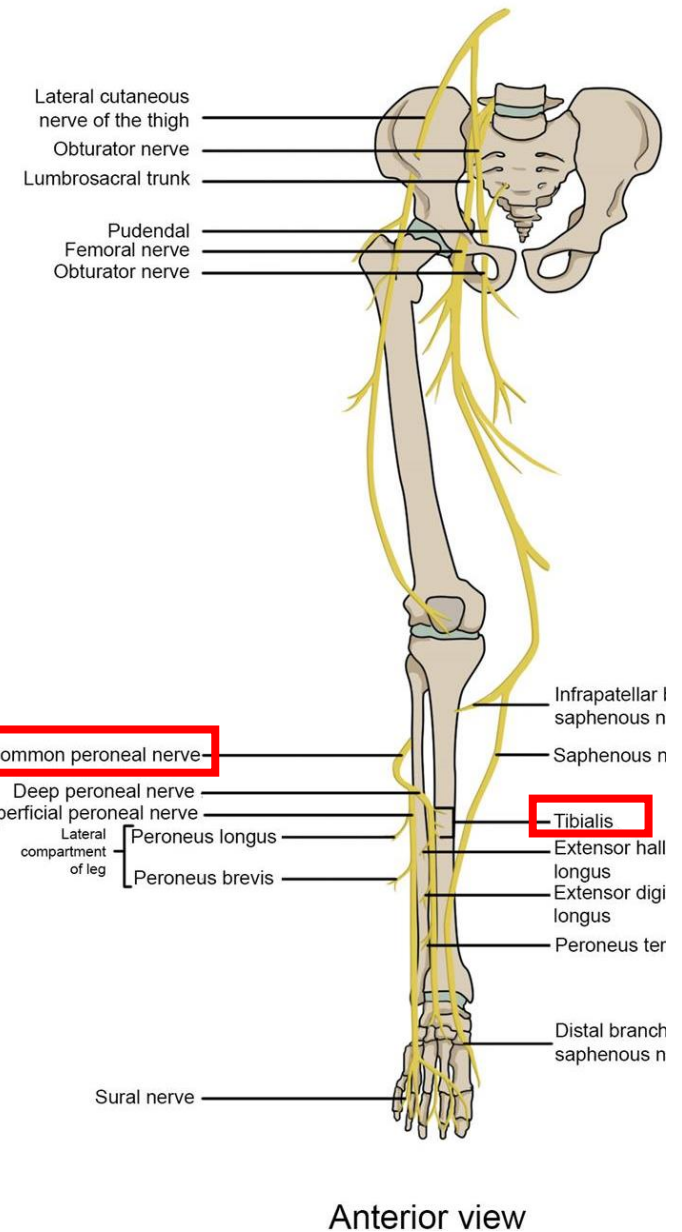
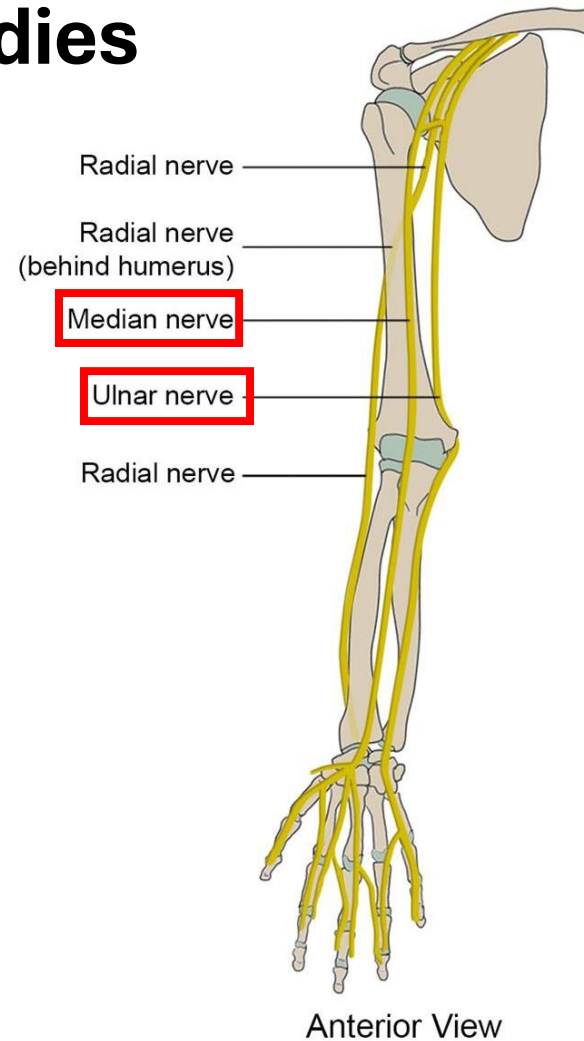
Motor nerve conduction studies

Upper extremities:

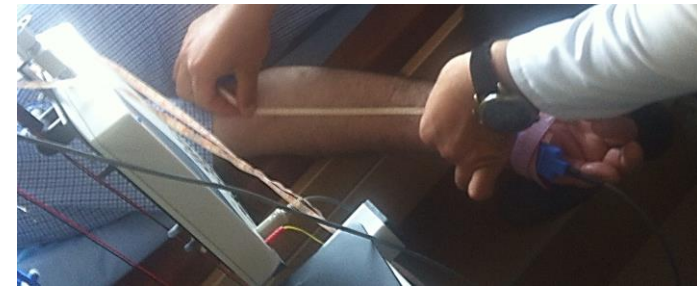
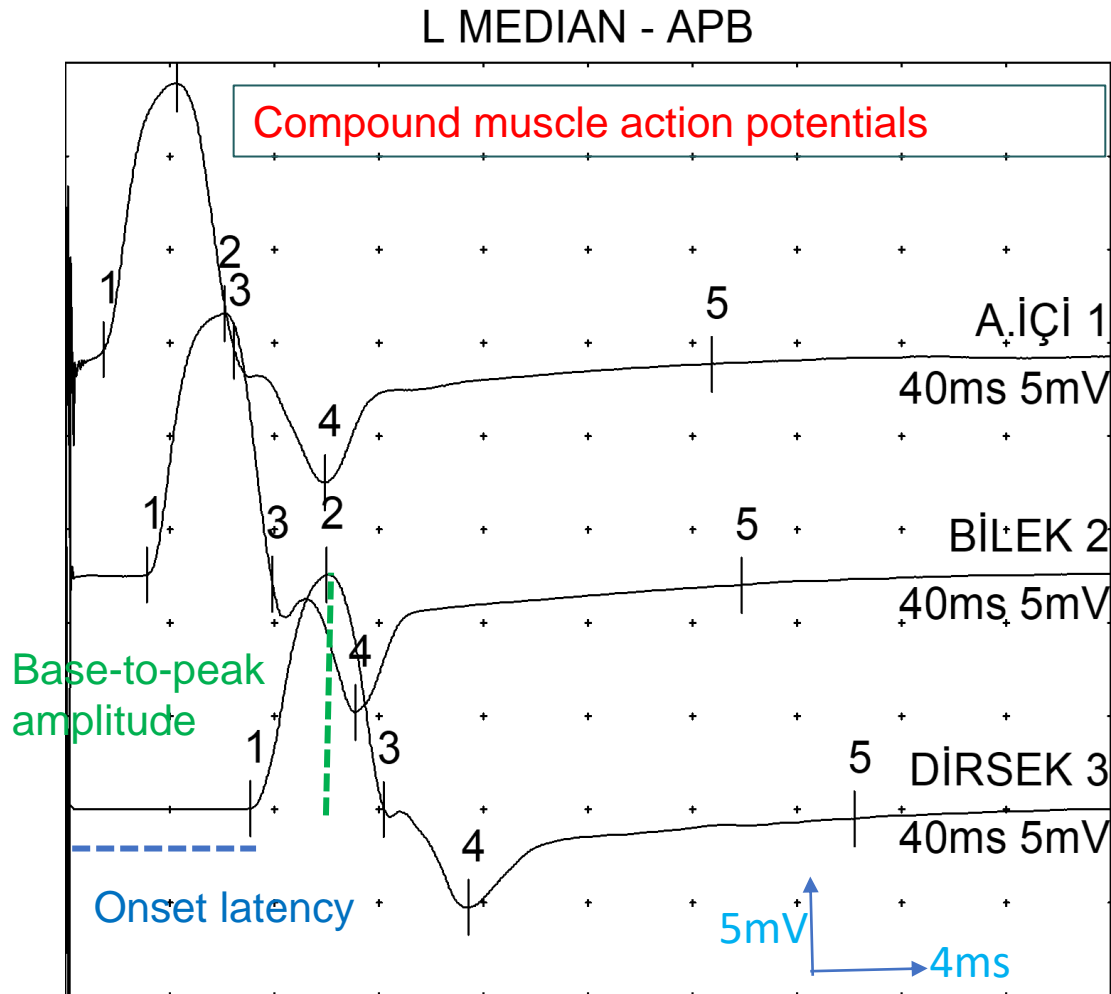
- median
- ulnar

Lower extremities:

- tibial
- peroneal from m. extensor digitorum communis



Median motor nerve conduction study



Conduction velocity = distance (m) / difference of latencies (s)

- **Sensory nerve action potential amplitude ratios**

$$\text{SRAR} = \frac{\text{Sural SNAP amplitude}}{\text{Radial SNAP amplitude}}$$

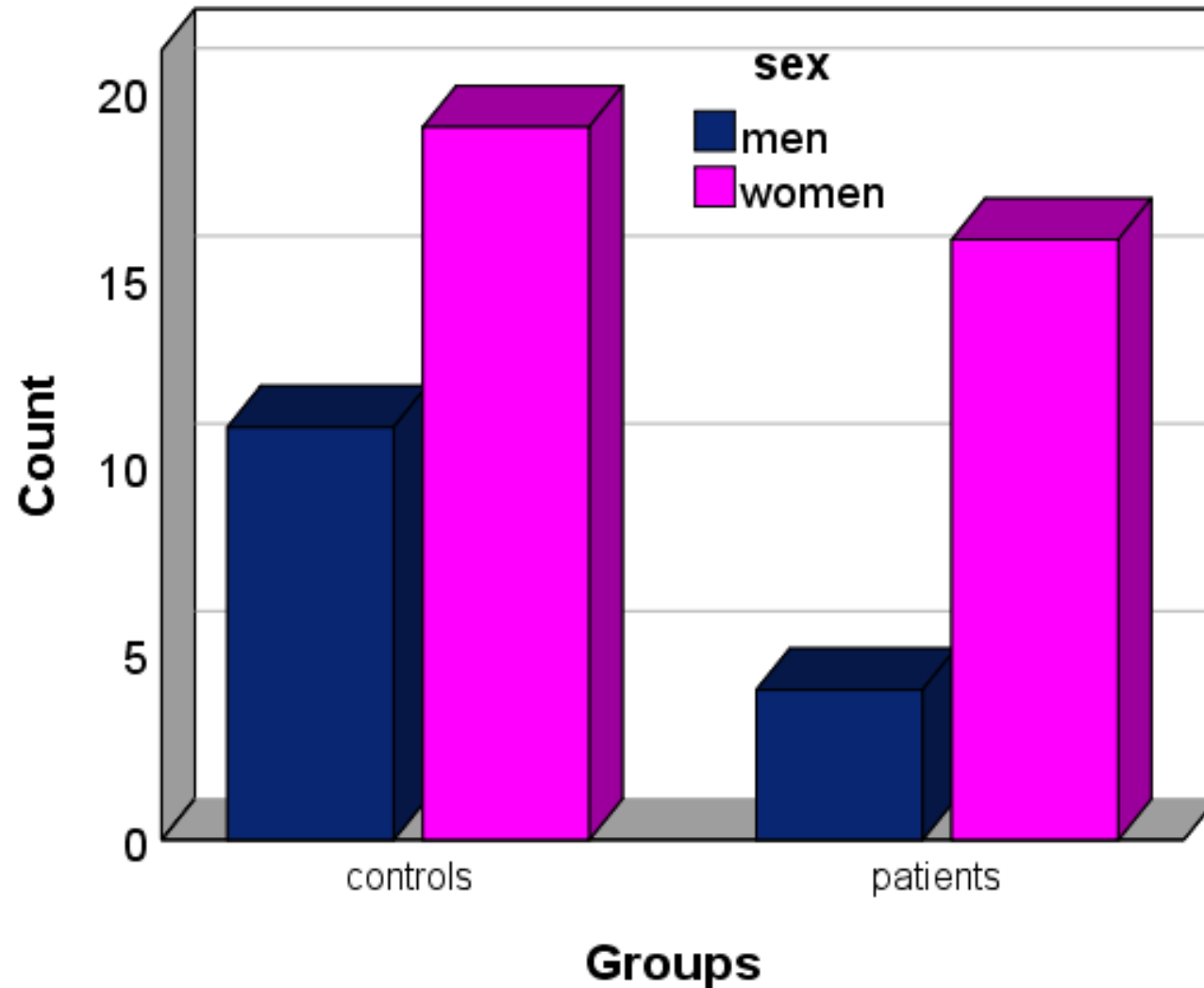
$$\text{SMFCAR} = \frac{\text{Sural SNAP amplitude}}{\text{Medial femoral cutaneous SNAP amplitude}}$$

$$\text{MPRAR} = \frac{\text{Medial plantar SNAP amplitude}}{\text{Radial SNAP amplitude}}$$

Statistical Analysis

- Statistical analyses were performed using **SPSS Software** (version 25.0; IBM, Armonk, NY, USA).
- **Descriptive statistics** for continuous variables were presented as **mean \pm standard deviation (sd)** and **categorical variables** were given as **count (%)**.
- The **Shapiro-Wilk test** was used to check if a variable was normally distributed.
- **Student's T-test** was used for comparing normally distributed continuous variables and the Mann-Whitney U test was used if the data were not normally distributed. **Chi-Square Test** was used for comparing categorical variables.
- **A receiver operating characteristic (ROC) analysis** was conducted to determine the SPAR, SMFCAR, and MPRAR threshold values that will discriminate between the patient and control groups. Sensitivity and (1-specificity) values were calculated when the patient and control groups were considered together.

Results



Patients: 20

16 women, 4 men

Controls: 30

19 women, 11 men

Chi-Square test. $p=0.208$

Variable	Controls N=30		Patients N=20		Test Stas.	p
	Mean (sd)	Median (min-max)	Mean (sd)	Median (min-max)		
Age (years)	58.4 (13)	58 (35 - 80)	59 (12.6)	62.5 (34 - 78)	-0.155	0.878
Height (cm)	163 (10)	163.5 (145 - 187)	163 (7.3)	162 (152 - 182)	0.000	1
Weight (kg)	69.1 (12.8)	70 (44 - 94)	72.7 (11.9)	74.5 (48 - 89)	-0.983	0.331
BMI (kg/m ²)	26 (4.7)	26.1 (19 - 38)	27.4 (4.5)	27.4 (20.5 - 34.4)	-1.002	0.321

Type of Cancer

Breast	5
Lung	3
Stomach	3
Ovary	2
Colon	2
Cervix	1
Rectum	1
Kidney	1
Prostate	1
Nasopharynx	1

Chemotherapeutics

Paclitaxel	9
Oxaliplatin	6
Carboplatin	4
Cisplatin	2
Docetaxel	1
Nivolumab	1
Bevacizumab	3
Capecitabine	1
Trastuzumab	3
Gefitinib	1
Gemcitabine	1
Emtansine	1
Fluorouracil	1
Etoposide	1

Patients

Variable	Patients N=20	
	Mean (sd)	Median (min-max)
Time elapsed between the chemotherapy and the onset of symptoms (months)	2.89 (2.85)	2 (1 - 12)
Duration of symptoms (months)	4.16 (4.74)	2 (1 - 18)
MNSI-A	5.47 (1.93)	5 (3 - 8)
MNSI-B	4.26 (1.85)	4.5 (1 - 8)

Nerve Conduction Studies

Sensory nerve conduction studies	controls					patients					Test Stas*.	p
	N	Mean	Std. Dev.	Min	Max	N	Mean	Std. Dev.	Min	Max		
Radial lat.	48	2.2	0.28	1.56	2.71	39	2.4	0.35	1.83	3.23	-2.819	0.006
Radial amp.	48	28.0	8.74	13.70	53.00	39	19.4	5.80	7.50	32.00	5.274	<0.001
Radial CV	48	60.0	7.41	50.00	75.00	39	55.8	10.95	44.70	78.30	2.123	0.037
Medial femoral cutaneous lat.	60	2.9	0.33	2.23	3.67	32	3.3	0.35	2.66	4.08	-6.127	<0.001
Medial femoral cutaneous amp.	60	5.7	2.05	1.60	10.50	37	4.4	2.81	0.00	12.20	2.696	0.008
Medial femoral cutaneous CV	60	61.4	8.97	43.00	83.30	32	54.1	7.50	42.20	68.00	3.964	<0.001

CV: conduction velocity, lat.: latency, amp.:amplitude, *student T test

Sensory nerve conduction studies	controls					patients					Test Stas.*	p
	N	Mean	Std. Dev.	Min.	Max.	N	Mean	Std. Dev.	Min.	Max.		
Sural lat.	55	3.0	0.29	2.35	3.75	37	3.2	0.57	2.18	4.60	-2.707	0.008
Sural amp.	55	18.9	7.49	9.80	45.70	39	8.6	4.28	0.00	20.60	7.765	<0.001
Sural CV	55	53.7	5.78	46.00	67.70	37	49.6	7.76	35.50	65.10	2.964	0.004
Sup. Peroneal lat.	55	2.7	0.38	2.00	3.54	36	3.0	0.51	1.83	4.28	-3.499	0.001
Sup. Peroneal amp.	55	11.2	4.62	3.00	25.90	38	6.6	4.94	0.00	25.60	4.544	<0.001
Sup. Peroneal CV	55	52.5	7.50	40.20	76.90	36	46.1	5.82	28.50	59.90	4.340	<0.001
Medial plantar lat.	48	2.9	0.58	2.15	5.71	19	3.3	0.62	2.40	4.67	-2.087	0.041
Medial plantar amp.	48	10.6	6.55	2.50	33.40	38	2.2	2.49	0.00	7.80	7.484	<0.001
Medial plantar CV	45	52.6	7.40	40.00	69.10	19	46.4	6.43	36.90	60.90	3.176	0.002

CV: conduction velocity, lat.: latency, amp.:amplitude, *student T test

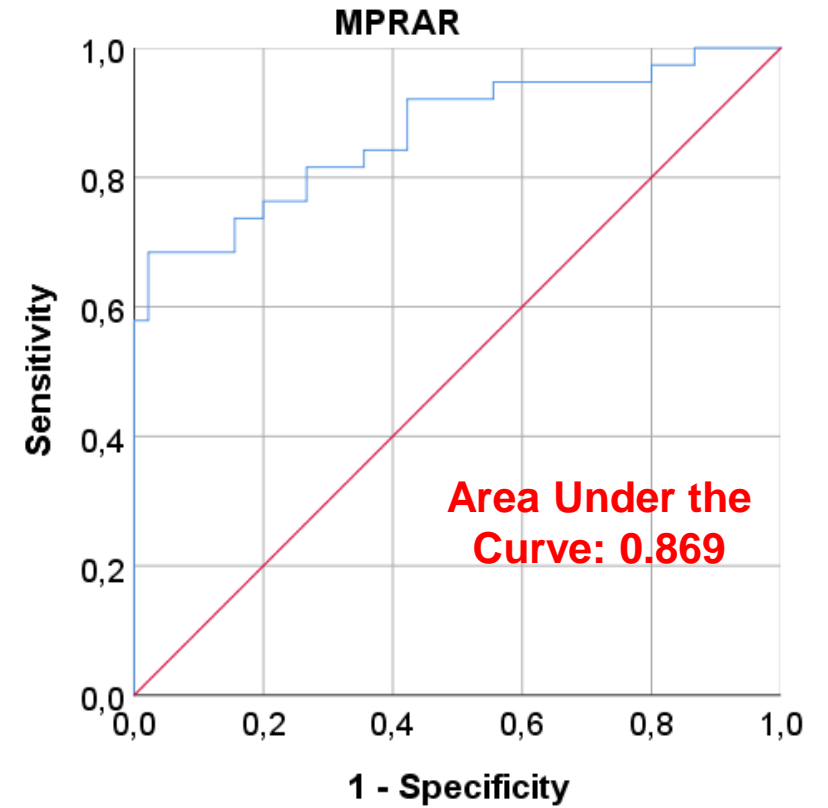
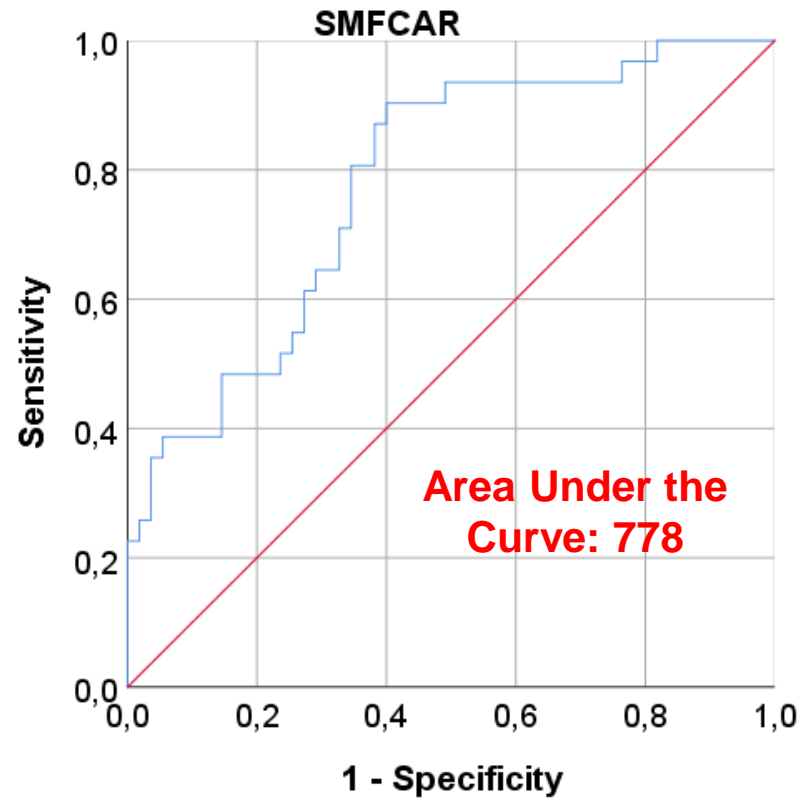
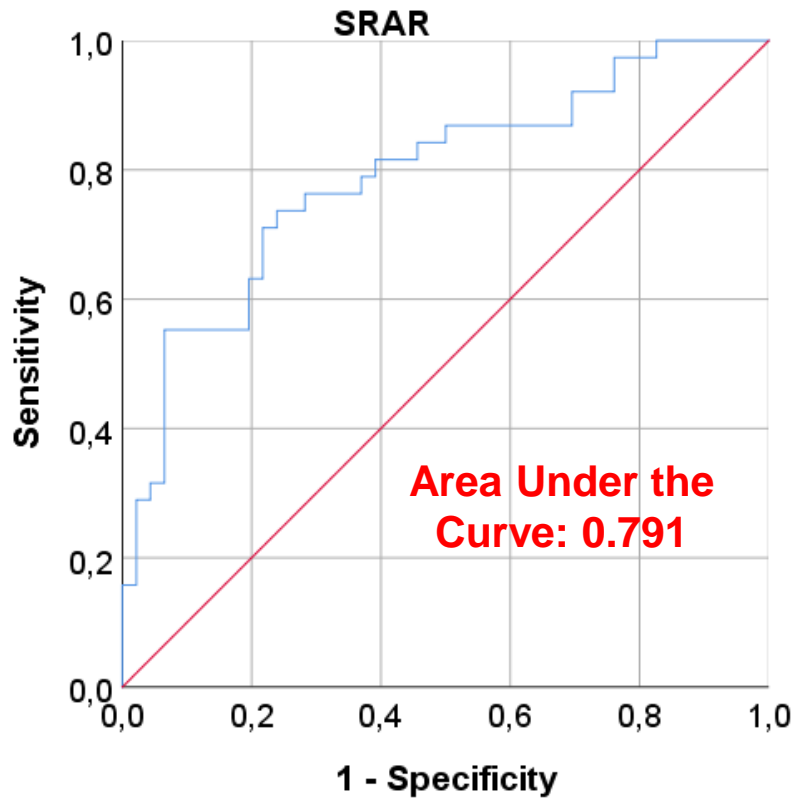
Sensorial Amplitude Ratios

	Controls			Patients			Test Stas.	p
	N	Mean (sd)	min-max	N	Mean (sd)	min-max		
SRAR	46	0.7 (0.28)	0.28 – 1.67	38	0.5 (0.22)	0 – 0.97	4.841	<0.001
SMFCAR	55	3.8 (2.15)	1.12 – 13.69	31	2.1 (1.17)	0 – 4.94	4.054	<0.001
MPRAR	45	0.4 (0.18)	0.12 – 0.90	38	0.1 (0.15)	0 – 0.55	6.527	<0.001

SRAR: Sural-to-Radial Amplitude Ratio

SMFCAR: Sural-to-Medial Femoral Cutaneous Amplitude Ratio

MPRAR: Medial Plantar-to-Radial Amplitude Ratio



	Positive if Less Than	Sensitivity	Specificity
SRAR	0.43	55.3%	93.5%
SMFCAR	1.77	38.7%	94.5%
MPRAR	0.17	68.4%	93.3%

Number of patients diagnosed with polyneuropathy in addition to those diagnosed by routine conduction studies

Amplitude Ratios	Number of patients
Sural-to-Radial Amplitude Ratio (SRAR)	1
Sural-to-Medial Femoral Cutaneous Amplitude Ratio (SMFCAR)	none
Medial Plantar-to-Radial Amplitude Ratio (MPRAR)	3

Discussion

- **Sensory neuropathy** was found to be the most common complication related to chemotherapy, with less involvement of motor nerve fiber.
- Both clinical and EMG findings indicated more pronounced involvement in the **lower extremities**.

- In older patients, age-related changes can be observed in nerve conduction studies. This can make it difficult to evaluate the findings obtained in very mild length-dependent polyneuropathy.
 - In such cases, either **evaluating more distal nerves** such as the dorsal sural or medial plantar nerves **or utilizing amplitude ratios** may be beneficial.

- In this study, **the most significant involvement** was observed in the most distal **medial plantar response** in the lower extremity
- **Sensory amplitude ratios** are other methods used in the identification of mild polyneuropathies
- In mild cases, **MPRAR** was found to be **the most useful ratio** for distinguishing patients from normal controls

Limitations

- Insufficient number of patients
- Differences in patients' diagnosis and treatment

Powerful Sides

- There isn't enough research available on this subject.
- SFMCAR has not been studied before.
- The triple amplitude ratio comparison has not been conducted previously (SRAR, SFMCAR, MPRAR).

Conclusions

- In the electrodiagnosis of length-dependent axonal neuropathies, examination of the most distal nerves is important.
- In this study, it has been shown that mixed medial plantar sensory conduction study and MPRAR contribute additional value to routine nerve conduction studies in detecting very mild cases.
- Patient recruitment for this study will continue.
- The article will be written when reaching 40 patients.

References

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