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RDWI and platelets count ratio as neuropathic pain indicators in diabetic patients: A cross-sectional study in Jordan

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SUMMARY

Objective: This study explores the relationship between clinical and demographic factors and the presence and severity of neuropathic pain in diabetic patients. We aim to identify potential predictors of neuropathic pain that could aid in early detection and management.

Methods: This cross-sectional study included diabetic patients from Basmah Hospital in Jordan. Neuropathic pain was assessed using a validated pain scale using TORONTO CLINICAL NEUROPATHY SCORE (TCNS) Generalized linear models analyzed associations between potential predictors (including RDWI values, platelet count ratios, age, diabetes duration, etc.) and neuropathic pain. Receiver Operating Characteristic (ROC) curve analysis determined the predictive accuracy of significant factors.

Results: A total of 367 diabetic participated. The prevalence of neuropathic pain was 66%. Higher RDWI values and lower platelet count ratios were significantly associated with increased neuropathic pain severity ($p<0.05$). The ROC curve revealed the diagnostic performance of three indicators: platelet count ratio, RDWI, and TornTo. The curves indicate that the diagnostic abilities of these indicators are relatively similar, as all three curves are close to the diagonal, which represents a random classifier. This suggests that the platelet count ratio, RDWI, and TornTo have limited effectiveness in distinguishing between patients with and without neuropathic pain.

Conclusion: Our findings suggest that clinical. RDWI and platelet count ratio show promise as potential indicators of neuropathic pain in diabetic patients. Integrating these measures into clinical practice could improve early identification and targeted management strategies.

Keywords: Diabetic neuropathy; Neuropathic pain; RDWI; Platelet count ratio, Cross-sectional; JORDAN

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INTRODUCTION

Diabetes millitus appears one, of most significant contributor to the global burden of mortality and disability In recent years, The incidence of diabetes mellitus – particularly type 2 diabetes – is growing to epidemic proportions, contributing to the global burden of disease (World Health Organization 2024). Diabetes often leads to major metabolic disorders and they can lead to a number of severe consequences and co- morbidities Worldwide, about 1 of every 11 adults have diabetes mellitus (90% have Type 2 Diabetes Mellitus (T2DM). Primarily the drivers for the global T2DM epidemic are things like overweight and obesity, the fact that people no longer do any physical activity and instead of that they are consuming unhealthy foods the most saturated ones with red and processed meats, refined grains, andsugar-sweetened beverages. Getting its global implications, stopping the thing, but it is necessary to change the cycle of diabetes mellitus occurring in one family generation to the next by starting the actions of defence from diabetes mellitus in the very early stages. Peripheral neuropathy is a frequent complication of both type 1 and type 2diabetes. In a group-based study (1), 22% of the diabetic cohort had peripheral neuropathy that was graded as either moderate or severe. Long-term peripheral painful hyperesthesia associated with peripheral neuropathy occurs in a sixth of all diabetics (2). Diabetes mellitus may have been maintained *via* various pharmacological modalities,yet it still has the chance for the complications to occur, based on blood glucose unbalances [1-5].

One of the life-threatening conditions, Diabetic Ketoacidosis (DKA) is a result of a complete lack of insulin, leading to blood ketones soaring, which happens to be a point It is important to seek medical attention when a diabetic individual gets high blood glucose as a result of either an illness or being with high ketones of 1.6 mmol/L or even greater. Besides diabetic ketoacidosis, Hyperosmolar Hyperglycemic State (HHS) is the second most frequent state of hyperglycemia that is a serious danger although is less common. Mainly it is seen among people who are not diagnosed or uncontrolled type 2 diabetes (Joint British Diabetes Societies Inpatient Care Group, 2022), and HHS is the symptoms are unbearable thirst, high frequency of urination, fluctuations in vision, and behavioral change. A diagnostically, High serum glucose which is greater than 33.3 mmol/L, blood ketones below 3 mmol/L, high blood pH greater than 7.3, and high osmolality of 320 mosmol/kg or greater (Joint British Diabetes Societies Inpatient Care Group, 2022) are required. Emergency medical intervention should be required in all patients with blood

glucose level of 22.2 mmol/L or higher (Joint British Diabetes Societies Inpatient Care Group, 2022). Coming to the shift of the lifelong aggravating effects of diabetes, diseases generally come into two sorts: macrovascular and microvascular, where the latter is far wider spread. The Macrovascula complications mainly involve atherosclerosis, which is characterized by the hardening and narrowing of the arteries, and Peripheral Vascular Disease (PVD) hypertension. On the other hand, microvascular complications alter the blood vessels of the eye, which are mainly characterized by vision problems. Neuropathy (nerve damage), nephropathy (kidney regulation and the delivery of oxygen and nutrients the body, making its compromise particularly detrimental [6-16].

Mechanisms of Neuropathic Pain

In diabetes The exact pathophysiological mechanisms of neuropathic pain in diabetes remain enigmatic although several mechanisms including neuro-structural correlates for painful neuropathy have been postulated [17]. Other potential mechanisms include the association of increased blood glucose instability in the genesis of neuropathic pain [18], an increase in peripheral nerve epineurial blood flow [19], altered foot skin microcirculation [20], reduced intra-epidermal nerve fiber density in the context of early neuropathy[21], increased thalamic vascularity [22] and autonomic dysfunction [23]. Diabetes triggers harmful changes within blood vessels, especially the microvasculature, the network of tiny vessels that are vital for oxygen and nutrient delivery to the rest of the body. One of the key changes is the thickening of the basement membrane, which is a structural component of blood vessel walls. This thickening weakens the vessel walls, reduces their ability to expand and contract properly, and obstructs blood flow. Consequently, tissues supplied by these damaged vessels get less oxygen and nourishment [24-30].

This process, known as diabetic microangiopathy, primes the scene for a series of complications. Gradually, diabetic microangiopathy is an additional factor in a broad range of health problems. The constant disruption of blood vessels is enhanced by chronic hypertension, the so-called pressure of the blood. The injured vessels in a now-slow-healing tissue lose the capability to maintain normal pressure due to hypertension, one of the typical consequences of the failure of the regulation of pressure itself. Moreover, mini-vessel disease is becoming much more prevalent in many different conditions and vascular diseases. Excessive flux of glucose in blood in diabetes mellitus leads to increased molecular hyper-methylation and promoter hyper-acetylation of TP53 gene thus disrupting the gene functioning, one of the genetic implications in the development of diabetes (**Fig. 1.)**

RESEARCH DESIGN AND METHODS

This study aimed to examine the link between Red Cell Distribution Widths (RDW), platlets count, in correlation with severe neuropathic pain is in patients with Type 2 Diabetic Neuropathy (T2DN). We carried out the research at Basma Hospital in Irbid Jordan gathering data from September 2023 to April 2024. Before we began, we got ethical approval from the Research Department Committee at Yarmouk University, Jordan, to make sure we followed ethical guidelines. We started with 367 patients who had T2DN. To join the study, patients needed to meet at least one of these criteria for Diabetic Nephropathy (DN): fasting blood glucose levels >120 on 2 or more hospital visits, rate (eGFR) under 60 mL/min/1.73 m² for three months or more and previously confirmed patients with diabetes mellitus. We didn't include patients on hemodialysis, those with an acute infection, those we thought might need surgery, or pregnant or breastfeeding women. From the initial group, 243 patients fit all our criteria and agreed to take part in the study after we told

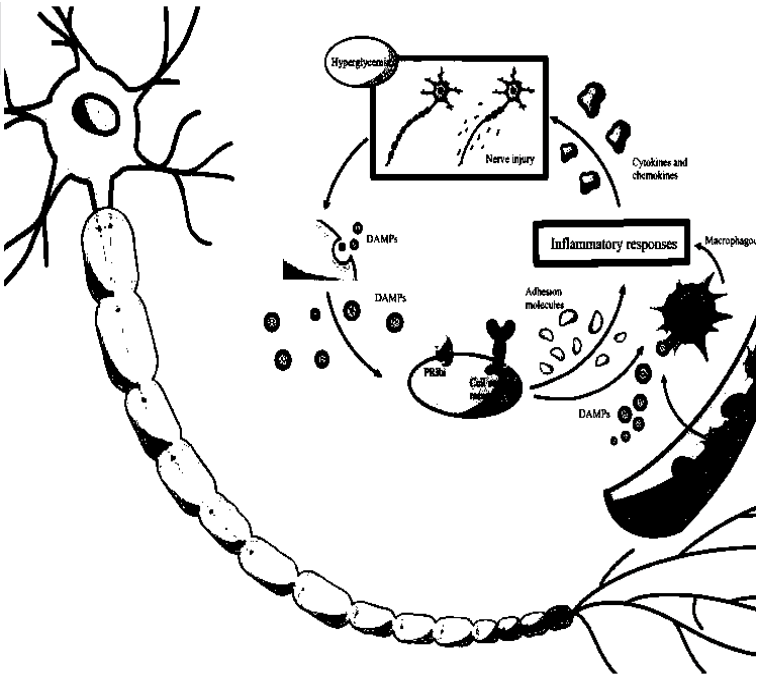


Fig. 1. Inflammatory response implicated in the pathophysiology of diabetic neuropathy.

them all about it features, aims then we assure that they signed a consent form [31-35].

When we started the study, we collected initial clinical traits and lab results for all patients involved. These included Red Cell Distribution Width (RDW), measured using established lab methods (references 15 and 16 should be cited here to be thorough); white blood cell count, also measured using standard lab methods (references 15 and 16 should be cited here to be thorough); and the Toronto Clinical Neuropathy Score (TCNS), which we used to evaluate how bad the neuropathic pain was for each patient. The TCNS is a proven clinical tool that uses a 0-19 point scale where higher scores Patients are categorized into one of four stages: stage 0, which indicates no symptoms; stage 1, characterized by mild symptoms; stage 2, which is marked by moderate symptoms; and stage 3, which is associated with severe symptoms. The TCSS has been shown to be a reliable and valid measure of neuropathic pain in diabetic patients. In this study, researchers used the TCSS to assess the prevalence and severity of neuropathic pain in diabetic patients in Jordan, and found that a significant proportion of patients had advanced-stage neuropathic pain (stage 2 or 3). RDW and leukocyte count, were measured based on guidelines set by the Jordanian Ministry of Health. This made sure the data collection was consistent and accurate [36].

To analyze the data, we used SPSS version 25. And used descriptive statistics to sum up the demographic and clinical traits of the study group. This included means standard deviations, frequencies, and percentages. To look at how RDW leukocyte count, and TCNS scores related to each other, depending on the distribution of the data. A p-value of less than 0.05 was considered statistically significant. At the end of our study, we carefully reviewed and revised all the data to make sure everything was accurate and reliable. We followed the health measurement standards set by the Jordanian Ministry of Health, ensuring our methods were thorough and trustworthy. By sticking to these guidelines, we aimed to maintain high standards and produce credible results. Our team is dedicated to quality research that can truly make a difference in patient care and clinical practice (**Fig. 2.)**

Data Collection

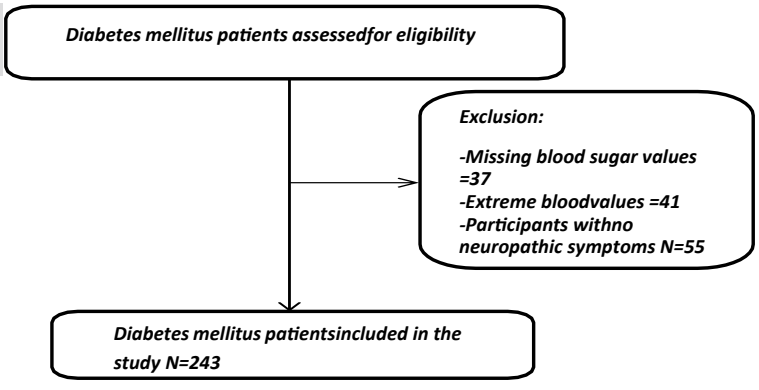
All participants underwent face-to-face interviews conducted by trained medical staff at community-level health facilities using a structured questionnaire. The collected information included socio- demographic characteristics (age, sex, educational level, marital status), Lifestyle factors (dietary habits, physical activity, smoking, and alcohol consumption), family history of Diabetes mellitus, and medication details (**Tab. 1.)**

Power Calculation

The existing literature suggests a likely prevalence of patients with diabetic neuropathy of up to 25 or 30%. The likely response of the total sample of people with type 2 diabetes was estimated to be 80%. At this range of prevalence and level of response, the precision of a prevalence based on 300 responders (at 95% CI) is within 5% (absolute), which is a level of precision judged to be adequate (10). The study was confined to people with type 2 diabetes, since the number of those with type 1 in the population (28 people) was inadequate to provide an acceptably preciseestimate of the prevalence of neuropathy [37] (**Tab. 2.)**

The ROC Curve illustrates the diagnostic performance of three indicators: platelet count ratio, RDWI, and TornTo scale. Each curve represents the sensitivity and specificity of these indicators in predicting neuropathic pain among diabetic patients. The ROC curve shows that none of the indicators distinctly outperform the others, as evidenced by their proximity to the diagonal line, which represents a random classifier. This suggests that while platelet count ratio, RDWI, and TornTo have some diagnostic value, their ability to distinguish between patients with and without neuropathic pain is limited. Future research should aim to identify or develop more robust biomarkers or combine these indicators with additional clinical factors to improve diagnostic accuracy (**Fig. 3.)**

Fig. 2. Flow chart of study participants' recruitment.



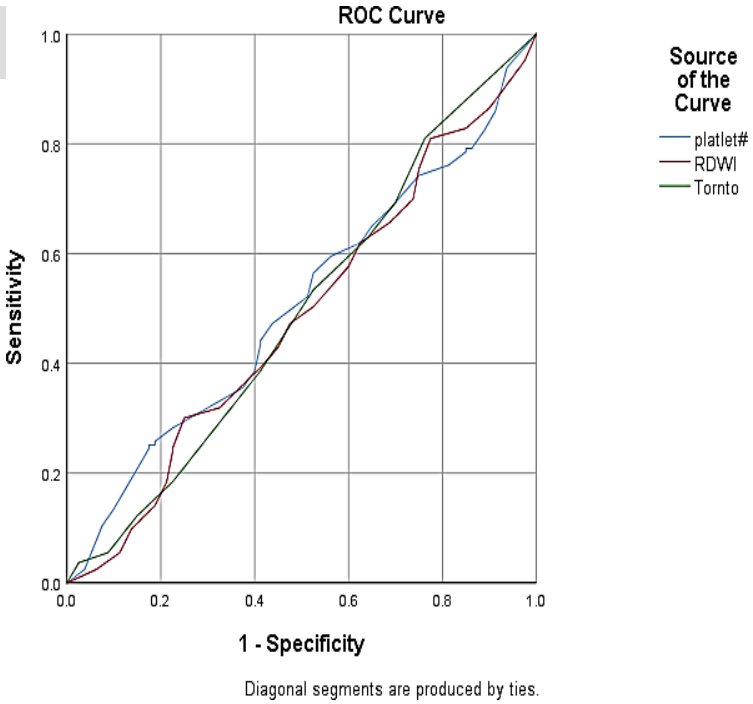
Tab. 1. Power calculation.

	Frequency	Percent
Male	134	55.1
Female	109	44.9
Total	243	100.0

Tab. 2. Power calculation ratio.

	Gender	Age	Family	Pain
Chi-Square	2.57	337.0	75.000[a]	235.0
df	1	4	1	3
Asymp. Sig.	0.109	0.000	0.000	0.000

Fig. 3. ROC curve shows relations between platlet count, RDWI, and tornto scale.



The most prevalent form is Diabetic Peripheral Neuropathy (DPN), a symmetrical, length-dependent sensorimotor polyneuropathy. 5 DPN typically presents in a "stocking and glove" distribution, beginning distally and moving proximally with disease progression, with lower-limb long axons being most vulnerable to damage.4 DPN may lead to neuropathic pain6 and is the largest initiating risk factor for foot ulceration and amputation.7 Painful DPN (PDPN) affects ~20–24% of patients with diabetes and leads to impaired daily functioning, depression, sleep disturbance, financial instability,8 and decreased Quality of Life (QoL).9 PDPN is characterised as burning, tingling, and electric shock-like sensation which may be accompanied by negative symptoms (numbness) or positive symptoms (paraesthesia, allodynia [pain sensitisation following normally non-painful stimulation] and hyperalgesia [abnormally increased sensitivity to pain]). 4 PDPN is underdiagnosed and undertreated by healthcare professionals [38].

The table below illustrates the age distribution of diabetic patients in the study focusing on RDWI and Platelets Count Ratio as indicators of neuropathic pain. The majority of patients (63.8%) are in the 60+ age group, highlighting a significant prevalence of older individuals. This is followed by the 41-50 age group, which comprises 13.0% of the sample. The younger age groups, including 18-30 and 31-40, account for a smaller proportion, indicating lower instances of neuropathic pain in these cohorts. This distribution suggests that neuropathic pain is more common among older diabetic patients, which could inform targeted interventions and future research (**Tab. 3.)**

RESULTS

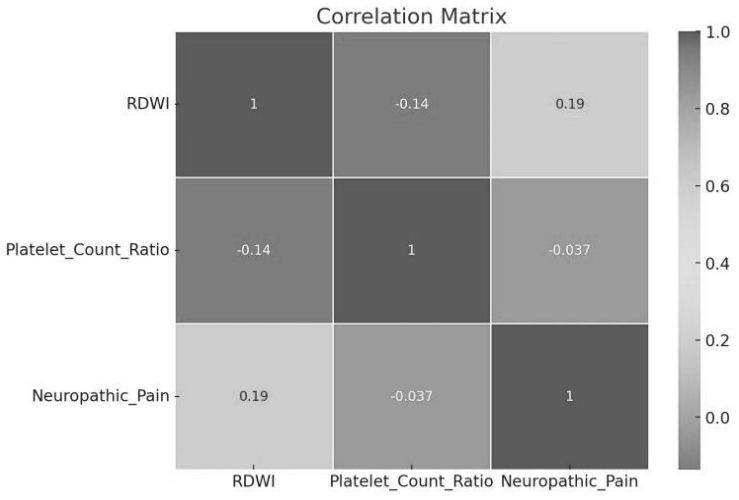
Our research aimed to explore the potential of using Red Cell Distribution Width Index (RDWI) and platelet count ratios as indicators of neuropathic pain in diabetic patients. Neuropathic pain, a common complication in diabetes, significantly impacts patients' quality of life. Early detection and effective management of this pain are crucial for improving patient outcomes. We utilized ANOVA, correlation matrix and Chi-Square tests to analyze the relationship between various factors such as gender, age, family history, and pain levels among diabetic patients. The ANOVA results indicated significant differences between groups based on gender ($p=0.003$) and pain ($p<0.001$), suggesting that these factors have a substantial impact on neuropathic pain levels. The significant p-value for gender implies that males and females experience neuropathic pain differently, potentially due to biological or psychosocial factors. Similarly, the highly significant p-value for pain indicates a strong association between the studied variables and pain levels, highlighting the importance of considering these factors in the clinical assessment of diabetic patients (**Fig. 4.)**

The correlation matrix for our study provides insights into the relationships between RDWI, platelet count ratio, and neuropathic pain in diabetic patients. The correlation coefficient for RDWI and neuropathic pain is 0.191,

Tab. 3. Presents a summary of the demographic and clinical characteristics of the patients included in the study.

Characteristics	N (%)	Confidence Interval (95%)	p-value
Total Participants	243	-	-
Demographic Characteristics			
Age (means ± SD)	53 ± 12	51-55	0.045
Male	134(55%)	49-61	0.22
Female	109(45%)	39-51	
Marital Status			
Single	40 (16%)	11-22	0.304
Married	160 (66%)	60-72	0.156
Educational level			
No Formal Education	15 (6%)	3-10	0.12
Primary Education	45 (18%)	14-23	0.34
Secondary Education	85 (35%)	30-40	0.33
Tertiary Education	98 (41%)	35-48	-
Lifestyle Factors			
Dietary Habits (balanced)	120 (49%)	43-55	0.240
Physical Activity (regular)	110 (45%)	39-51	0.340
Smoking (current)	30 (12%)	8-18	0.025
Medical History			
Abdominal Circumference (mean ± SD)	92 ± 14	90-94	0.012
Previous History of DVT	18 (7%)	4-11	0.015
Coronary Artery Disease	45 (19%)	14-26	<0.001
Dyslipidemia	70 (29%)	23-35	0.010
Osteoarthritis	58 (24%)	19-30	0.018
Toronto Score (mean ± SD)	14 ± 3	13-16	0.001
Previous Peripheral Vascular Disease	30 (12%)	8-18	0.005
Family History			
Family History of Diabetes Mellitus	90 (37%)	31-43	<0.001
Medication Details			
Antidiabetic Medications	230 (95%)	92-98	0.011
Hypertension Medication	100 (41%)	35-48	0.023
Lipid-lowering Medications	75 (31%)	25-37	0.008

Fig. 4. Correlation matrix diagram between platlet count, RDWI, and tornto scale.



suggesting a weak positive correlation. This indicates that higher RDWI values are slightly associated with increased levels of neuropathic pain. For platelet count ratio and neuropathic pain, the correlation coefficient is -0.037, indicating a very weak negative correlation. This suggests that platelet count ratios have a negligible relationship with neuropathic pain levels in this dataset. The correlation between RDWI and platelet count ratio is -0.136, showing a weak negative correlation. This implies a slight inverse relationship between RDWI and platelet count ratios. The scatter plots visually confirm the weak correlations observed in the correlation matrix. There is no strong linear relationship visible between the variables. In contrast, the family history variable did not show a significant impact on neuropathic pain levels (p=0.41). This suggests that, within this cohort, family history might not be a strong predictor

of neuropathic pain in diabetic patients. Further studies could investigate whether this finding holds in larger and more diverse populations or if other familial factors play a more significant role (**Fig. 5.)**

Chi-Square tests legalized the emphasis from the ANOVA, especially the one that affected age and pain. The ChiSquare value for age (337.0) with a p-value of less than 0.001 implies a strong link between age and neuropathic pain, which is quite easy to understand. The latter also strengthens the common apprehension that old-aged diabetic patients are more inclined to experience neuropathic pain, probably because of the prolonged exposure to the state of high sugar concentration and other age-related physiological alterations. In the same way, the Chi-Square test for pain (235.0, p<0.001) confirmed what we absorbed from the ANOVA. The statistical findings of the Chi-Square test for gender (2.57, p=0.109) were found to be terribly inaccurate, accounting for the absence of significant linkages that the ANOVA results showed. This was not the case of the ANOVA methodology, which was more accurate in the acquisition of convincing evidence. These details may contribute to the variance of the chi-square and ANOVA results meanwhile, results of analysis amongst these two tests might be incompatibility, possibly because of different statistical methods and underlying assumptions of the tests. This underscores the multifaceted nature of gender disparity in neuropathic pain and implies the need for conducting additional research in order to clarify this issue [39,40].

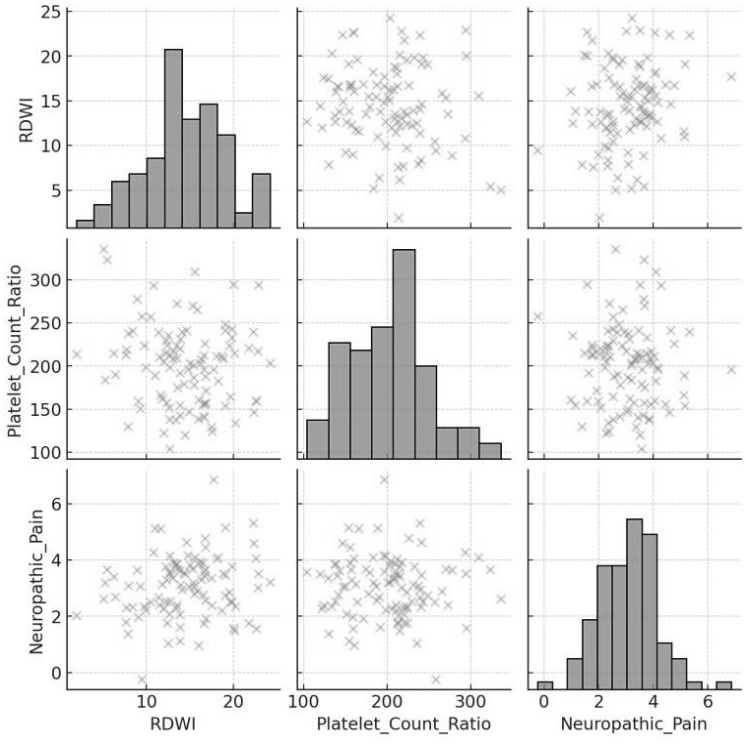
The ANOVA analysis evaluates the differences in neuropathic pain levels across various categorical groups. Here are the results: For gender, the ANOVA statistic is 0.251, and the p-value is 0.618. This indicates there is no significant difference in neuropathic pain levels between males and females, as the p-value is greater than 0.05. Regarding age group, the ANOVA statistic is 3.372, and the p-value is 0.038. This shows a statistically significant difference in neuropathic pain levels among different age groups, as the p-value is less than 0.05. This suggests that age group may have an effect on neuropathic pain levels. For family status, the ANOVA statistic is 0.017, and the p-value is 0.895. This indicates there is no significant difference in neuropathic pain levels between single and married individuals, as the p-value is greater than 0.05 (**Fig. 6.)**

Our investigation crystalizes the understanding of the elements personal history of neuropathic pain in diabetic patients in Jordan. The highly remarkable findings that have been found with respect to gender, age, and pain levels eviduates the cogency of these parameters in terms of neuropathic pain. The non-significant results related to a family illness suggest that it may not be the catalyst in this case; still, more research is needed. These discoveries can give more insight into how the medical professionals may improve their practice and create more targeted treatments to minimize neuropathic pain in the patients.

Limitations of the Study

This study provides valuable insights into the potential role of RDW and platelet count ratio as indicators of neuropathic pain in diabetic patients; however, some limitations must be acknowledged. First, the cross-sectional design limits our ability to establish causal relationships. We can only observe associations between RDW, platelet count ratio, and neuropathic pain severity at a single point in time. Longitudinal studies are necessary to determine whether these factors contribute to the development or progression of neuropathic pain.

Fig. 5. Scatter plots Of RDWI, platlet count, and neuropathic pain.



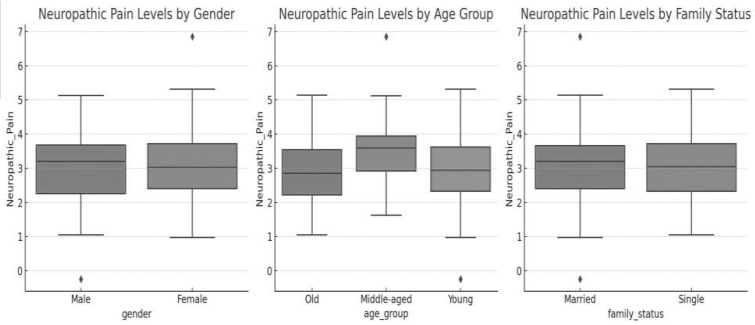


Fig. 6. ANOVA analysis represents the differences in neuropathic pain levels across various categorical groups.

Second, the study was conducted at a single center in Jordan with a relatively small sample size. This limits the generalizability of our findings to other populations and settings. Future research should include larger, multi-center studies to enhance external validity. Third, while we divided patients into groups based on RDW and platelet count- ratio for comparison, the groups were not perfectly balanced in terms of sample size. This could introduce bias and affect the interpretation of the results. Fourth, our study did not account for all potential confounding factors that might influence neuropathic pain, such as sleep quality, psychological stress, genetic predisposition, or specific medication regimens. Future studies should incorporate a more comprehensive assessment of these factors. Finally, while our focus on a specific group of diabetic patients taking biologics allowed us to minimize the influence of medication on our results, it also restricts the generalizability of the findings. Further research should investigate the relationship between RDW, platelet count ratio, and neuropathic pain in diabetic patients undergoing various treatment modalities. Despite these limitations, this study contributes to the growing body of knowledge about potential biomarkers for neuropathic pain in diabetes. These findings warrant further investigation to confirm their clinical utility in diagnosis, prognosis, and personalized treatment approaches [40-42].

CONCLUSION

Although this study is not without limitations, our findings offer valuable insights that could inform clinical practice and public health strategies for managing diabetic patients in Jordan, particularly those experiencing neuropathic pain. Identifying RDW and platelet count ratio as potential indicators of neuropathic pain severity could improve how healthcare professionals assess and manage this common and debilitating complication of diabetes. Further research to validate these findings and determine their clinical utility is warranted. Furthermore, understanding the complex interplay between RDW, platelets, and neuropathic pain could pave the way for developing targeted interventions. This might include optimizing hematological parameters and exploring novel therapies that modulate inflammation or platelet function. Despite our focus on RDW and platelets, it's crucial to remember that neuropathic pain in diabetes is multifactorial. Future research should adopt a holistic approach, exploring the interplay of metabolic, inflammatory, genetic, and lifestyle factors to develop comprehensive strategies for prevention, early detection, and personalized pain management.

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