

Role of Nerve Conduction Velocity and Pre Albumin to Fibrinogen Ratio in Diagnosing Diabetic Polyneuropathy: A Comparative Analytical Study

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Abstract

Background:

In the current millennial era, diabetes mellitus has emerged as a global pandemic accounting for multiple morbid complications. Diabetic polyneuropathy (DPN) is one such disabling complication.

Aim and objectives:

To analyse and compare the association between pre albumin to fibrinogen ratio (PFR) and electro diagnostic test among diabetes mellitus patients.

Material and methods

This present study was taken up in a Mahatma Gandhi Medical College Hospital and Research Institute. Over hundred (100) diabetes mellitus patients were enrolled along with an equal number of control group individuals. Different parameter which including, electrophysiological analysis in the form of nerve conduction studies, perception threshold for vibration (VPT), biochemical as well as hematological parameters, including fibrinogen levels were assessed. Depending on the values of pre albumin to fibrinogen ratio, patients were categorized in various groups. Clinical parameters were assessed in both groups.

Results: Age ($P < 0.002$), duration of disease ($P < 0.002$), Creatinine levels ($P = 0.008$) and NLR levels ($P < 0.001$) among diabetic group was significantly higher. DPN group was significantly higher, while FPG ($P = 0.041$), TC ($P = 0.027$), AFR ($P < 0.001$) and PFR ($P < 0.001$) was reduced significantly. The percentage of DPN and VPT in the lowest PFR tertile was significantly higher than that in the middle PFR tertile and the highest PFR tertile ($P < 0.001$). NCV in the lowest PFR tertile was significantly lower than that in the middle PFR tertile and the highest PFR tertile between ($P < 0.01-0.003$). Correlation analysis showed that PFR were negatively associated with the VPT ($P < 0.001$), while nerve conduction velocity for median motor and sensory nerve, for peroneal motor and sensory nerve ($P < 0.001$) was positively correlated with PFR, Once these values were adjusted to potentially related factors, PFR is independently correlated to diabetic polyneuropathy ($P = 0.008$). The area under the ROC curve was 0.627.

Conclusion: This study will be first of its kind which proves that PFR can be a key component associated with DPN in T2DM,

Keywords: Diabetes mellitus, Nerve conduction study, Diabetic peripheral neuropathy; vibrating perception threshold;

Introduction

Diabetes mellitus is associated with disabling complications such as neuropathies. Among these neuropathies the most common form is a distal sensorimotor polyneuropathy usually symmetrical and chronic type which is also known as diabetic polyneuropathy, with a prevalence of about 50%. (1, 2) Diabetes mellitus (T2DM) is a type of metabolic disease usually chronic in nature, and is associated with hyperglycaemia and increased resistance for insulin in the body (2, 3) and is accompanied by peripheral nerve dysfunction in individual, which involves various mechanisms along with pathological changes of diabetic polyneuropathy (4) T2DM is also considered to be induced due to lifestyle modifications such as high consumption of carbohydrates, weight gain and lack of exercise. This disease has an increasing prevalence worldwide and is a major global public health burden (1, 2, 3). According to the International Diabetes Federation, there are currently around 366 million diabetes mellitus patients worldwide with an expecting increase in number to 522 million by 2030 (4). Peripheral neuropathy associated with diabetes is the most complicated pathological change with an incidence of approximately 50%. Diabetic polyneuropathy is always associated with morbid conditions which results in a huge economic burden for the patients suffering from T2DM for treatment (5, 6). Furthermore, DPN is associated with severe complications which include foot ulcer, infection, gangrene, and non-traumatic lower limb amputation. These conditions can cause a serious impact on patient's quality of life (7, 8). This type of neuropathy is considered as an inflammatory disease but its pathogenesis which is related with diabetes mellitus is not fully elucidated (9, 10, 11, 12). There are reports showing an association of occurrence of inflammation, the occurrence of oxidative stress, and mitochondrial dysfunction. (3-7) The Oxidative stress which is induced due to hyperglycaemia is arbitrated by different identified and known pathways like glycolysis. (7,8) In addition to this the mitochondrial dysfunction there is also production of free radicals and a reactive oxygen species. The production of these free radicals production can cause peroxidation of lipids, modification of the proteins, and can also damage the ne, leading to degeneration of axons and demyelination of segments. (7-10) According to the Academy of Neurology of America, there must be at presence of at least one of the few criteria's for the diagnosis of diabetic neuropathy which includes signs, symptoms, nerve conduction assessment, and autonomic function test. [5, 11] Although nerve conduction studies are not frequently used for diagnosis or to assess the prognosis of neuropathy, these tests can be used for evaluating the ability of the electrical conduction among sensory and motor nerves during the disease course (12-15, 18). Poor glycaemic state of control is most of the time responsible for vascular complications. [6, 16] (HbA1c) glycated haemoglobin is known for its established biomarker for assessment of glucose control and is also known as an indicator for assessment of the possibility of micro vascular problems. [7,17] Fibrinogen (FIB) is a biomarker used to assess coagulation and chronic inflammatory status and a high FIB level is correlated with systemic inflammation and its impairment is also associated with micro vascular complications in

T2DM patients (13,14, 15). Albumin (ALB) is a nutritional marker and an inflammation marker and studies have reported that serum ALB is unconventionally associated with peripheral nerve function among diabetic patients with albuminuria (16-17). Studies have also shown that pre albumin (PALB) is another key type of marker to assess the dietetics. It is more subtle in assessment of under nutrition than albumin (18, 19). In addition, previous studies have also confirmed that PALB values are also inversely related to CRP values in inflammation (20, 21, 22). Studies have also reported that PALB to FIB ratio, (PFR) is a new inflammatory marker, which is closely related to acute pancreatitis and cancer (23, 24). Therefore, we speculate that PFR may also be associated with DPN in T2DM. The use of PALB and the FIB serum biomarkers is one of the useful tools in various research aspects as it is simple and cheap to use. However, no study has been undertaken so far to assess the prognostic role of PFR in diabetic polyneuropathy. This study will help to assess the role of PFR for diagnosis and predicting the prognosis with its optimal range variations among diabetic polyneuropathy patients.

Materials and methods

Study design and patients

This prospective comparative study was conducted from January 2018 to December 2019, on 100 type 2 diabetes patients. After getting the ethics committee approval the patients were recruited from the in-patient department of neurology MGMCRI, Puducherry. Prior informed consent was obtained from each patient after explaining the purpose, nature, and procedure of the study. The diagnosis is based on standard WHO guidelines (25).

Exclusion criteria: Patients with alcohol abuse, vitamin D deficiency, liver dysfunctions, renal dysfunctions[GFR]<60mL/min/1.73m²), acute cerebral infarction, amyotrophic lateral sclerosis, Alzheimer disease, Parkinson disease, and other disorders of CNS were excluded from this study.

Methodology

Data collection and laboratory assessments

The patient's age and their medical history, physiological variables like BMI and blood pressure were recorded. After an overnight fast of 12 hours, the patient's hemoglobin A1c (HbA1c, Variant II, Bio-Rad, USA), blood cells count (Automatic Blood cell analyzer, Sysmex XN9000, Japan), biochemical parameters test (Automatic biochemical analyzer, Roche Cobas 8000, Switzerland), and fibrinogen (FIB, CS5100, Sysmex Corporation, Japanese) were analyzed respectively. Neutrophil to lymphocyte ratio (NLR) is the ratio of neutrophil (10⁹/L) to lymphocyte (10⁹/L). Analysis of Albumin to Fibrinogen Ratio (AFR), PFR (mg/g) ratio was done in recruited patients. The perception for vibration threshold (VPT) was measured by a trained technician using a digital vibration threshold detector (Sensitometer A200, Beijing blue time's Technology Co.) The results between 0 and 15 volts were considered as a Non-DPN group, while results

of more than 25 volts were defined as the DPN group. NCS was performed for median motor nerve (MMN), peroneal motor nerve (PMN), median sensory nerve (MSN), and peroneal sensory nerve (PSN) in both limbs, using electromyography (EMG) machine (Keypoint 9033A07, Dantec Co., Denmark). The local skin temperature was maintained at 32°C to 33.

Statistical analysis

Data analysis was done using (SPSS) Version 22.0. Data was expressed as mean and \pm SD. Non-normally distributed data were expressed as median and interquartile range (IQR) and was analyzed using a non-parametric test (Wilcoxon test). The Categorical variables were presented as frequencies and proportions and were analysed using chi square test. Spearman's correlation analysis was used for evaluating the association of various variables of diabetic polyneuropathy. Binary logistics regression analysis was performed to evaluate the association between pre albumin to fibrinogen ratio (PFR) and diabetic polyneuropathy (DPN) P value of < 0.05 was considered as statistically significant

Results

Demographics of the study population

The clinical characteristics of the study population are shown in Table 1. Compared with Non-DPN group, age ($P < 0.002$), duration ($P < 0.002$), creatinine ($P = 0.008$) and NLR ($P < 0.001$) were significantly increased in DPN group, while fasting plasma glucose (FPG, $P = 0.041$), total cholesterol (TC, $P = 0.027$), AFR ($P < 0.001$) and PFR ($P < 0.001$) were significantly decreased in DPN group. There was no significant difference in body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HbA1c, alanine aminotransferase (ALT), urea nitrogen (UN), uric acid (UA), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and highly sensitive C-reactive protein (hs-CRP) between the two groups. Interestingly, pre albumin to fibrinogen ratio was significantly low among the diabetic polyneuropathy patients (Table 1, $P < 0.001$).

On the basis of PFR levels patients were divided into (the lowest set at < 80.85 , the middle $80.85-114.85$, the highest tertile at ≥ 114.85). The percentage of DPN in different tertiles of PFR was 58.2%, 39.5%, and 33.3% in the lowest, middle and highest tertile group (Fig.1A). Diabetic polyneuropathy was significantly common and higher in the lowest group or tertile than the middle and the highest tertile (Fig.1A, $P < 0.001$). We also analyzed the differences between VPT and NCV among the tertile groups. VPT in the lowest tertile group was significantly higher than that in the middle tertile and the highest tertile (Fig.1B, $P < 0.001$). NCV in the lowest tertile was significantly lower than that in the middle tertile and the highest tertile (Fig.1C, Fig1D, Fig.1E, Fig1F, $P < 0.01-0.001$).

Association between PFR and DPN

Spearman's correlation analysis showed the PFR was negatively correlated with VPT (Table 2), while the PFR was positively correlated with median motor NCV ($P < 0.001$), peroneal motor NCV ($P < 0.001$), median sensory NCV ($P < 0.001$), and peroneal sensory NCV

($P < 0.001$, Table 2). Binary logistic regression analysis was performed to assess the correlation ship between pre albumin to fibrinogen ratio and diabetic polyneuropathy. Analysis was derived based on categories of different groups. Group A included only PFR; Group B included the age and the duration to the diviner of group A ($P = 0.005$); Group C had FPG and TC as a diviner for group B ($P = 0.007$); Group D included creatinine levels as a diviner of group 3 ($P = 0.004$); Group E included NLR and AFR to the predictors for Group D ($P = 0.008$). This analysis showed that PFR is independently correlated with DPN (Table 3). The diagnostic role of PFR in diabetic polyneuropathy was assessed by ROC curve (Fig. 4) The area under the curve was 0.627 ($P = 0.001$).

Discussion

Diabetic neuropathy is one of the most common complications associated with diabetes mellitus which leads to severe morbidity, and also affects the quality of life. Appropriate therapeutic approach and proper management of diabetes at the subclinical level can help in decreasing the risk of neuropathy. (8) It is a need of time to analyze the proper methods which will help in identifying the risk of neuropathy among diabetic patients. Analysis of nerve conduction is considered to be the important methods for assessment of peripheral nerve functioning in diabetic neuropathy. (9, 18) Diabetes-related microvascular complications usually include morbid conditions, such as chronic pain, foot ulceration and amputations, and other mortal inflammatory conditions. Coagulation and nutrition are always associated with DPN and also affect the inflammatory process (9-12, 15, 17). The authors too in their previous study concluded that HbA1c and the nerve conduction velocity have inverse correlation as well as there is significant positive correlation with the duration of latency. Poor glycemic control accelerates process of neuronal damage. Therefore, nerve conduction studies can be employed for testing and for the early indication of neuropathy in diabetic patients (18). The present study will be the first evidence suggesting that PFR is closely related to DPN in T2DM. We tried to analyze the relationship between PFR and DPN. The major finding which was observed during the study was that PFR was negatively associated with DPN hence it can be used as a predictor for DPN diagnosis. In this study, we used a novel approach to demonstrate the relationship between PFR and DPN. Fibrinogen is a protein which is involved in platelet aggregation and blood coagulation which is one of the risk factor for vascular events (27). Kobi et al proved that the plasma fibrinogen concentration in the Moroccan population was significantly correlated with coronary heart disease and its severity (28). Besides, the elevated serum levels of fibrinogen were also associated with diabetic end-stage renal disease in patients with T2DM (29). In addition, fibrinogen as a biomarker of chronic inflammation as its high level of fibrinogen is observed in systemic inflammation (13,14). Secondly, albumin is an important nutritional biomarker as well as an inflammatory marker (16). Li et al suggested that serum albumin is an independent biomarker utilized with the peripheral nerve functions in type 2 diabetes mellitus, especially in those patients with albuminuria (17). In addition, recent studies have reported the pre albumin (PALB) is served as another important biomarker for nutritional status and it is more sensitive for assessment of malnutrition than albumin (17,19). Our study confirmed our hypothesis that PFR was

correlated with VPT and NCV. Therefore, PFR can be a predictor for the diagnosis of diabetic polyneuropathy. Although NLR, CRP, and AFR are the classic inflammatory indicators, few studies have also reported that the altered levels of NLR and C reactive proteins has significant role to play in pathogenesis of diabetic polyneuropathy (28, 9). In our study, the differences between NLR, CRP, AFR, and DPN were separately monitored. The NLR in the DPN group was significantly elevated, while AFR and PFR were significantly reduced.

Limitations:

The cross-sectional method has limited us to explore the causal relationship between PFR and DPN. In the future, longitudinal studies may provide better information on these relationships.

Conclusion

This study will be the first evidence to suggest pre albumin to fibrinogen ratio and maybe a key component associated with diabetic polyneuropathy among the patients suffering from Diabetes mellitus.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Acknowledgments

The authors appreciate the time and effort given by all participants. The author would like to thank the management of Mahatma Gandhi Medical College Hospital and Research Institute, Sri Balaji Vidyapeeth for their permission and extended cooperation for the effective conduct of this study.

Abbreviations: Fibrinogen (FIB), Albumin (ALB), pre albumin (PALB), type 2 diabetes mellitus (T2DM), Pre albumin to fibrinogen ratio (PFR), diabetic polyneuropathy (DPN), Vibration perception threshold (VPT), Nerve conduction studies (NCS)

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Table1: Characteristics of the study population.

| Variables | Total | Non-DPN | DPN | P Value |
|--------------------------|---------------|---------------|---------------|---------------------|
| N(male/female) | 560 (263:305) | 320 (144:176) | 248 (119:129) | 0.498 |
| Age (years) | 60.3 ± 11.5 | 56.4 ± 11.9 | 65.3 ± 8.6 | <0.002*** |
| Duration (years) | 9.0 ± 7.2 | 7.2 ± 6.6 | 11.2 ± 7.3 | <0.002*** |
| BMI (kg/m ²) | 24.8 ± 3.7 | 25.1 ± 4.0 | 24.5 ± 3.2 | 0.054 |
| SBP (mmHg) | 131.3 ± 17.6 | 131.0 ± 17.6 | 131.6 ± 17.6 | 0.666 |
| DBP (mmHg) | 78.3 ± 9.8 | 78.9 ± 10.0 | 77.4 ± 9.5 | 0.074 |
| HbA1c (%) | 9.3 ± 2.1 | 9.3 ± 2.2 | 9.3 ± 2.0 | 0.891 |
| FPG (mmol/L) | 8.7 ± 3.4 | 8.9 ± 3.4 | 8.3 ± 3.3 | 0.041* |
| ALT (U/L) | 25.7 ± 25.7 | 26.0 ± 19.8 | 25.2 ± 31.7 | 0.727 |
| Crea (µmol/L) | 63.3 ± 15.6 | 61.8 ± 14.9 | 65.3 ± 16.2 | 0.008** |
| UN (mmol/L) | 5.2 ± 1.5 | 5.2 ± 1.4 | 5.4 ± 1.6 | 0.142 |
| UA (mmol/L) | 291.5 ± 88.9 | 294.3 ± 92.0 | 287.9 ± 84.8 | 0.399 |
| TC (mmol/L) | 4.7 ± 1.3 | 4.8 ± 1.3 | 4.5 ± 1.2 | 0.027* |
| TG (mmol/L) | 1.9 ± 2.3 | 2.0 ± 2.3 | 1.8 ± 2.4 | 0.535 |
| HDL(mmol/L) | 1.2 ± 0.4 | 1.1 ± 0.3 | 1.2 ± 0.4 | 0.596 |
| hs-CRP (mg/L) | 3.6 ± 5.4 | 3.5 ± 5.0 | 3.7 ± 5.9 | 0735 |
| NLR | 2.37 ± 1.68 | 2.15 ± 1.11 | 2.64 ± 2.17 | 0.001** |
| AFR | 16.34 ± 4.71 | 17.13 ± 4.53 | 15.33 ± 4.76 | <0.001*** |

PFR (mg/g) 99.10 ± 37.63 106.53 ±38.36 89.51 ±34.44 <0.001***

Data are presented as means ± standard deviations. Data of normal distribution were expressed as means ± standard deviations, data of non-normal distribution was expressed as median and interquartile range (IQR). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; FPG, fasting plasma glucose; ALT, alanine aminotransferase; Crea, creatinine; UN, urea nitrogen; UA, uric acid; TC, total cholesterol; TG, triacylglycerol; HDL, High-density lipoprotein cholesterol; hs-CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; AFR, albumin to fibrinogen ratio; PFR, pre albumin to fibrinogen ratio. P values between <0.05, <0.01, <0.001 were considered statistically significant Table 2 -Association of PFR with parameters of NCV and VPT.

| | PFR | |
|----------|-----------|-----------------|
| | <i>rs</i> | <i>P</i> -value |
| VPT | -0.245 | <0.001*** |
| MMN- NCV | 0.239 | <0.001*** |
| PMN-NCV | 0.313 | <0.001*** |
| MSN-NCV | 0.274 | <0.001*** |
| PSN-NCV | 0.291 | <0.001*** |

P values between 0.05, 0.01, <0.001 were considered statistically significant

Table 3 – Analysis of PFR and its association with the presence of DPN in logistic regression

| | PFR | | |
|---------|----------------|---------------------|---------------------|
| | B (SE) | OR (95%CI) | P Value |
| Group A | -0.517 (0.107) | 0.596 (0.483-0.736) | <0.001*** |
| Group B | -0.333 (0.117) | 0.717 (0.570-0.902) | 0.005** |
| Group C | -0.324 (0.120) | 0.723 (0.572-0.914) | 0.007** |
| Group D | -0.354 (0.121) | 0.702 (0.554-0.891) | 0.004** |
| Group E | -0.474 (0.178) | 0.622 (0.439-0.882) | 0.008** |

The table shows the regression coefficient and odds ratio regression analysis was performed for evaluating the association between PFR and DPN after adjusting for other clinical and biochemical variables. P values between <0.05, <0.01, <0.001 were considered statistically significant

Figure legend

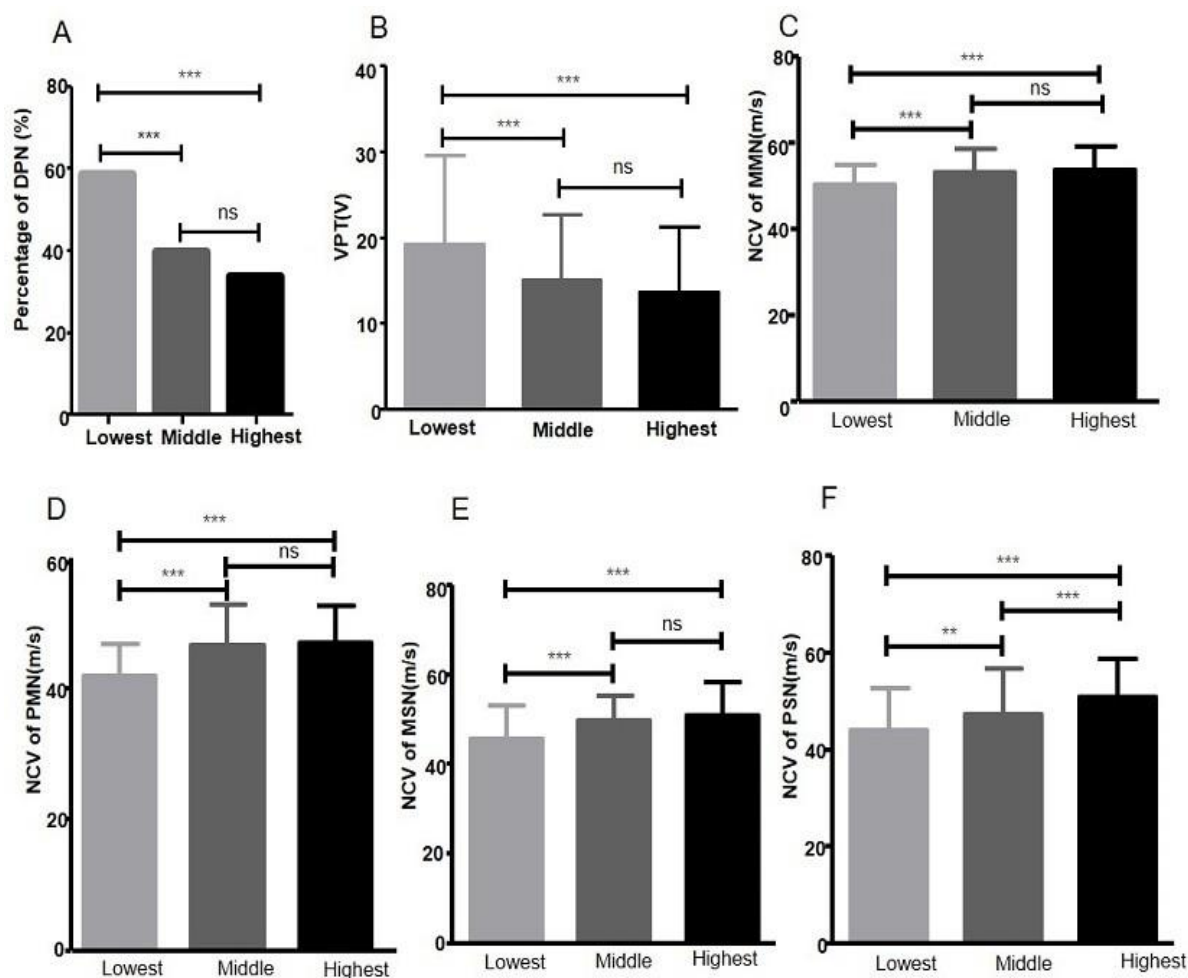
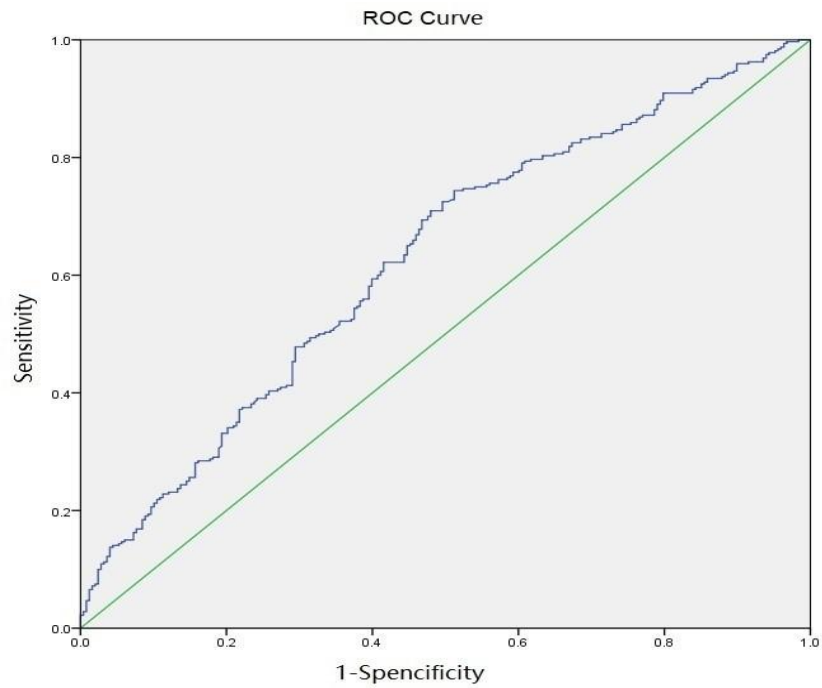


Fig.1- Depicts the percentage of diabetic polyneuropathy, perceptions of visual threshold, and nerve conduction study among various tertile groups. Fig.(A) Percentage of DPN in the different PFR tertile groups (58.2%, 39.5%, and 33.3%).fig (B) shows perception of visual threshold among different PFR tertile groups. Fig (C) shows nerve conduction study for MMN among various PFR tertile groups. Fig (D) shows NCV of PMN in the different PFR tertile. Fig (E) shows NCV of MSN in the different PFR tertile. Fig. (F) Shows NCV of PSN in the different PFR tertile. DPN, diabetic peripheral neuropathy;

Abbreviations: VPT, vibration perception threshold; NCV, nerve conduction velocity; MMN, median motor nerve; PMN, peroneal motor nerve; MSN, median sensory nerve; PSN, peroneal sensory nerve. Abbreviations: DPN, diabetic peripheral neuropathy; VPT, vibration perception threshold; NCV, nerve conduction velocity; MMN, median motor nerve; PMN, peroneal motor nerve; MSN, median sensory nerve; PSN, peroneal sensory nerve.

P values between <0.05, <0.01, <0.001 were considered statistically significant

Fig.2- Pre albumin to fibrinogen ratio for the diagnosis of Diabetic polyneuropathy analysis



of ROC curve.

AUC=0.627($P<0.001$).

Abbreviations: PFR, pre albumin to fibrinogen ratio; DPN, diabetic peripheral neuropathy;
AUC, area under ROC curve