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EVALUATION OF THE DISCRIMINATORY POWER OF RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE ANALYSIS IN IDENTIFYING CARDIO METABOLIC RISK IN TYPE II MALE DIABETICS

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ABSTRACT
The study explores the rational of ROC analysis for cardio metabolic risk (CMR) in type 2 male diabetics with a mean age of 49.98±10.74. Obesity indices were assessed and Receiver Operating Characteristic (ROC) Analysis was performed independently on 200 male diabetic subjects. Statistical significance was obtained corresponding to AUC of each parameter. Cut off values as determined by Youden's index were 23.30 kg/m^2(BMI), 90.50 cm (WC), 1.01(WHR) and 0.54 (WHtR). The optimum cut off for WHtR remained close to the standard cut off value of 0.5 indicating WHtR as the best predictive value for evaluating metabolic risk. The AUC for WHR is observed to be the lowest and insignificant (AUC 0.590, p=0.067) amongst all the four indices. AUC for WC is significantly high (AUC 0.753, p <0.0001) while WHtR showed AUC of 0.737(p<0.001) thereby confirming its ability to be a better predictor of cardio metabolic risk factors followed by BMI (AUC 0.687, p<0.0001). The study validates the usefulness of ROC as an evaluation tool for identifying diabetics at cardio metabolic risk.

KEYWORDS: Cardio Metabolic Risk, Youden's Index, Area Under Curve (AUC).

1. INTRODUCTION

Obesity is associated with diabetes mellitus, poor glycemic control and cardio vascular morbidity and mortality. Because of the rapid change in lifestyle in India, there is a grave concern that diabetes may become epidemic. India is now regarded the second capital of diabetes first being China. Diabetes increases the risk of micro vascular and macro vascular complications and premature death in the general population and results in a huge economic burden for society. The global obesity epidemic indicates no signs of abating, and is fueling an explosion in number of diabetics worldwide. Obesity and type 2 diabetes are of serious health concern. The term 'diabesity' has been coined to define obesity dependent diabetes.

Cardio Metabolic Risk (CMR) in type 2 diabetics could be additive or synergistic for CVD. In type 2 diabetes an increased cardiovascular risk often exists for several years before the onset of biochemical hyperglycemia. During this phase obesity and insulin resistance are often present, associated with hypertension and dyslipidemia, usually referred as metabolic syndrome. These risk factors may lead to the early development of CHD **(Haffner S., et al.,)**.

The ROC curve is a fundamental tool for diagnostic test evaluation. The diagnostic performance of a test or the accuracy of a test to discriminate diseased cases from normal cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis. In a Receiver Operating Characteristic (ROC) curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. A test with perfect discrimination (no overlap in the two distributions) has a ROC curve that passes through the upper left corner (100% sensitivity, 100% specificity) as shown in **Figure 1.** Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test **(Zweig M., & Campbell G., 1993).**

The validity assessment of each obesity index was carried out in terms of area under curve (AUC), sensitivity and specificity. The statistical significance

was obtained corresponding to AUC of each parameter. The screening potential of BMI, WC, WHR and WHtR for adult cardio metabolic risk in type 2 male diabetics was analyzed by applying Receiving Operating Characteristic (ROC) Curves.

2. MATERIALS AND METHODS

2.1 Participants

The study was conducted at Diabetes Care and Research Centre, Nagpur, Maharashtra. 200 type 2 diabetic males above the age of 25 years with diabetic history of at least 1 year were included in the study. Type 1 diabetics, smokers, alcoholics and subjects with hepatic, renal, endocrine disorders and those on lipid lowering agents were excluded from the study. Informed written consent was obtained from every participant.

2.2 Measures

2.2.1 Anthropometry

A predesigned format was used to record the anthropometric measurements (height, weight, waist circumference and hip circumference) of the subjects. Body Mass Index (BMI), Waist Hip Ratio (WHR) and Waist Height Ratio (WHtR) were determined and recorded. The threshold cut off values adopted for anthropometric parameters for all the male subjects were BMI =>22.9 kg/m², WC =>90 cm, WHR =>0.90 and WHtR =>0.50.

2.2.2 Biochemical Parameters

All the biochemical tests were performed at the laboratory of the study center. Individual blood markers included glycemic profile (FBG, PMBG, and HbA1c) and lipid profile (TC, LDL and HDL). Blood pressure was measured using an electronic blood pressure device while the subjects were seated following a five-minute relaxation period.

Metabolic syndrome (MS) was diagnosed according to the National Cholesterol Education Program **(NCEP ATP-III)** criteria. MS was recognized as having at least two of the following risk factors along with diabetes FBG (>110 mg/dl): WC (>80cm), high triglycerides (TG) (>150 mg/dl), low high-density lipoprotein cholesterol (HDL-C) (<40), blood pressure (>120/80 mmHg).

2.3 Statistical Analysis

SPSS version 18.0 was used for all the statistical analysis. Data on anthropometric measurements and cardio metabolic risk factors was compiled; means and standard deviation were calculated. Pearson's correlation coefficient was applied to the data and interpreted.

All variables were converted to direct variables i.e., 1= no risk and 2= risk based on standard reference values for male diabetic subjects. A new variable 'risk' was created based on the five indicators of cardio metabolic risk factors wherein, if three or more risk factors were observed, it was recorded as 'risk'. The association of BMI, WC, WHR and WHtR with this new variable was estimated using Receiver Operating Characteristic (ROC) curve analysis. The cut off values for each index was determined by applying Youden's index.

3. RESULTS AND DISCUSSION

3.1 Anthropometric Measurements

Base line data of diabetic subjects is presented in **Table 1.** The study subjects showed a mean height of 167.87± 6.49, mean weight of 72.84± 13.86and mean BMI was 25.76 ±4.20. **Gupta K., et al.,** reported on the prevalence of obesity in diabetics with a higher percentage of subjects in the obese grade I category.

The mean WC measurement of the subjects was 97.07 ±10.51. WHR measures the ratio of WC to HC unlike BMI which calculates the ratio of weight to height. The mean WHR was also observed to be higher (1.00 ±0.05) than the cutoff value. In this study, in addition to conventional indices of central obesity, WHtR was included as a screening tool. A mean value of 0.57 ±0.05as compared to the standard cut off value of 0.5 was observed. **Ashwell M., and Gibson S.,** stated that compared to BMI, WHtR was more closely associated with CVD risk factors among both men and women.

3.2 Biochemical Parameters

The mean levels of glycemic parameters of the subjects are presented in **Table 1.**

The mean FBG value was 169.41± 58.45. Observation from **Figure 2** reveals a high FBG in 91.5% of subjects. PMBG of the subjects reflect a similar trend as observed in case of FBG. The mean PMBG of the subjects is 260.80± 86.48 with 94.5% showing values above 180mg/dl. The data on HbA1C presented in **Table 1** shows a significantly higher (p=0.000) level in males (8.84 ±2.13) indicating uncontrolled diabetes. A prominently high FBG level is observed in 91.5% of males. A high percentage of subjects (86.5%) showed HbA1C values much higher than the normal value of <6.5% suggested for diabetics indicating uncontrolled diabetes. **Gupta K., et al.,** have also reported a similar trend in the mean fasting and post meal blood glucose levels falling above the recommendations for diabetics.

3.3 Obesity Indices vs. Glycemic Profile

Table 2 shows the distribution of diabetic subjects based on obesity indices vs. glycemic profile.

Observations of the study reveal that irrespective of normal or elevated BMI, WC, WHR and WHtR of all the diabetic subjects showed elevated values of FBG, PMBG and HbA1c.

Results of Pearson's correlation coefficient **(Table 2)** shows negative but highly significant relationship of BMI to FBG (r-0.200, p=0.000) PMBG (r-0.207, p=0.000) and significant to HbA1c (r-0.116, p=0.020). Very low negative correlation is observed between WC

and glycemic parameters. The association is observed to be non-significant with respect to HbA1c. However, FBG and PMBG show a negative and highly significant relationship to WC (r -0.133, p=0.008 and r -0.150, p=0.003 respectively). Insignificant relationship of WHR to FBG, PPBG and HbA1c is observed. Observations from the table reveal a very low negative relationship of WHtR to all the three glycemic parameters viz., FBG (r -0.187) PMBG (r -0.186) and HbA1c (-0.113). However, the relationship is observed to be highly significant between FBG, PMBG (p=0.000) and significant in HbA1c (p=0.024) to WHtR.

3.4 Cardio Metabolic Risk

Figure 3 shows the distribution of subjects based on the cardio metabolic risk as assessed by high values of WC, BP, TG, HDL and FBG. Central obesity was noted in 96% and high FBG values were observed in 98% of subjects. Hypertension and high TG was seen in 67% and 65% subjects respectively. 68% of subjects had low HDL levels. Each of the conditions have an associated effect, but clustering together they become synergistic, leading to CVD risk. Based on this risk assessment, 75.5% of the diabetic subjects were at risk of CVD **(Figure 4)**

3.5 Receiver Operating Characteristic (ROC) Curve Analysis

ROC was performed for all the indices independently to determine the validity in discriminating risk and non-risk group for CVD. The point on the ROC, which represented the largest sum of sensitivity and specificity, was chosen to obtain the optimal cut-off point for each of these four measurements in predicting cardio metabolic risk. The validity assessment of each parameter was carried out in terms of area under curve (AUC), sensitivity and specificity. The statistical significance was obtained corresponding to AUC of each parameter.

3.5.1 Body Mass Index (BMI)

Figure5 provides the ROC plot for BMI of males. The standardized data on BMI for males was subjected to ROC analysis, which resulted into an AUC of 0.687 [95% CI: 0.591 – 0.783] with a corresponding p-value < 0.0001, indicating significantly higher area as compared to 0.5. The optimum sensitivity and specificity were 0.78 and 0.56 respectively for a cut-off BMI value of 23.30 kg/m^2.

3.5.2 Waist Circumference (WC)

Figure6 provides the ROC plot for waist circumference of males. The standardized waist circumference data for males was used for ROC analysis which resulted into an AUC of 0.753 [95% CI: 0.663 – 0.844] with a corresponding p-value < 0.0001, indicating significantly higher AUC as compared to null value of 0.5. The optimum sensitivity and specificity obtained were 0.806 and 0.711 respectively for a cut-off level of 90.50 cm.

3.5.3 Waist Hip Ratio (WHR)

ROC plot was obtained for standardized waist hip ratio for males as shown in **Figure 7**. The AUC was 0.590 [95% CI: 0.494 – 0.685] with a p-value of 0.067, indicating insignificantly different AUC as compared to null value of 0.5. The optimum sensitivity and specificity obtained were 0.516 and 0.667 respectively for a cut-off point 1.01.

3.5.4 Waist Height Ratio (WHtR)

ROC plot was obtained for standardized waist height ratio for males as shown in **Figure 8** The AUC was 0.737 [95% CI: 0.649 – 0.825] with a p-value < 0.0001, indicating significantly higher AUC as compared to null value of 0.5. The optimum sensitivity and specificity obtained were 0.806 and 0.600 respectively for a cut-off point 0.54.

Table 4 presents the AUC for obesity indices. WHR shows the lowest AUC (0.590). WC (0.753) followed by WHtR (0.737) shows the highest AUC thereby confirming its ability to be a better predictor of cardio metabolic risk factors than BMI and WHR.

Park Y. S., and Kim J. S., also reported that WHtR has the best predictive value for evaluating the metabolic risk factors compared to BMI or WC. **Jayawardana R., et al.,** reported that in all adults, males and females the AUC of WHtR was significantly higher than that of BMI, WC and WHR in diabetes mellitus, pre diabetes, hypertension, metabolic syndrome and hypercholesterolemia. **Hong X., et al.,** also reported from their data on ROC curve analysis that AUC of WHtR was the highest in both males and females. They concluded that WHtR might serve as a simple but most effective index of hyperglycemia. **Schneider H.J., et al.,** reported that short subjects were at a higher risk and had a 30% higher prevalence of metabolic syndrome than tall subjects when grouped by WC and not by WHtR, and recommended that WHtR rather than WC should be included in the definition of metabolic syndrome.

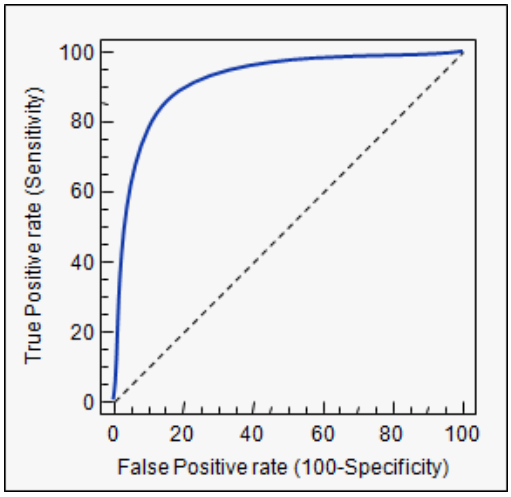

Figure 1: ROC Curve Showing the Test Accuracy.

Table 1: Baseline Characteristics of Subjects.

Variables	Mean (n=200)	Std. Deviation	Std. Error Mean
Height (cm)	167.87	6.49	0.45
Weight (kg)	72.84	13.86	0.98
BMI (kg/m²)	25.76	4.20	0.29
WC (cm)	97.07	10.51	0.74
HC (cm)	97.03	9.86	0.69
WHR	1.00	0.05	0.00
WHtR	0.57	0.05	0.00
FBG (mg/dl)	169.41	58.45	4.13
PMBG (mg/dl)	260.80	86.48	6.11
HbA1c (%)	8.84	2.13	0.15

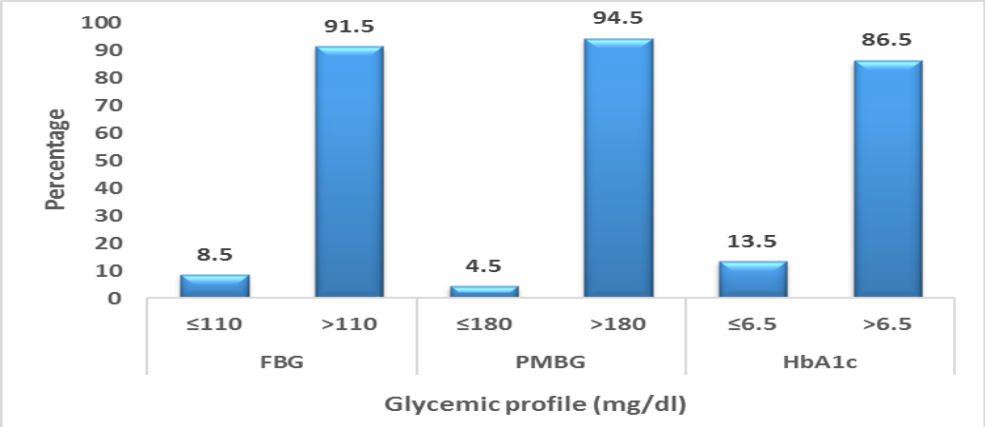

Figure 2: Distribution of Subjects (%) Based on Glycemic Profile.

Table 2: Association of Glycemic Profile with Obesity Indices.

Obesity Indices		Percentage distribution	FBG	PMBG	HbA1c
			Mean	**Mean**	**Mean**
BMI	**Normal (n=25)**	12.5	170± 70.96	251.04± 95.71	8.3± 1.84
	Elevated (n= 175)	87.5	144.28± 41.75	221.48± 63.92	8.08± 1.62
WC	**Normal (n=11)**	5.5	160.82± 79.91	230.64± 84.26	8.52± 2.21
	Elevated (n=189)	94.5	146.72± 44.53	224.86± 68.36	8.09± 1.62
WHR	**Normal (n=13)**	6.5	133.92± 34.63	209.69± 66.89	7.62± 1.43
	Elevated (n=187)	93.5	148.44± 47.62	226.25± 69.29	8.14± 1.66
WHtR	**Normal (n=2)**	1	138± 38.18	243.5± 61.51	8.65± 0.49
	Elevated (n=198)	99	147.59± 47.10	224.99± 69.28	8.1± 1.65

Table 3: Correlation of Obesity Predictors with Glycemic Profile of Subjects.

Obesity Indicators		FBG	PMBG	HbA1c
BMI	R	**-0.200**	**-0.207**	**-0.116**
	p value	**0.000**	**0.000**	**0.020**
	p summary	**HS**	**HS**	**S**
WC	R	**-0.133**	**-0.150**	-0.065
	p value	**0.008**	**0.003**	0.196

	p summary	**HS**	**HS**	NS
WHR	R	0.093	0.075	0.082
	p value	0.065	0.132	0.101
	p summary	NS	NS	NS
WHtR	R	**-0.187**	**-0.186**	**-0.113**
	p value	**0.000**	**0.000**	**0.024**
	p summary	**HS**	**HS**	**S**

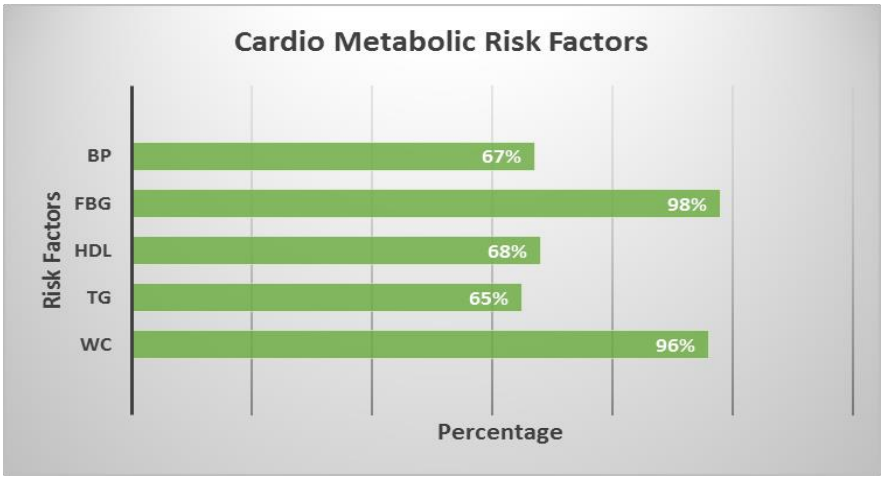

Figure 3: Distribution of Subjects Based on Presence of Cardio Metabolic Risk Factors (%)

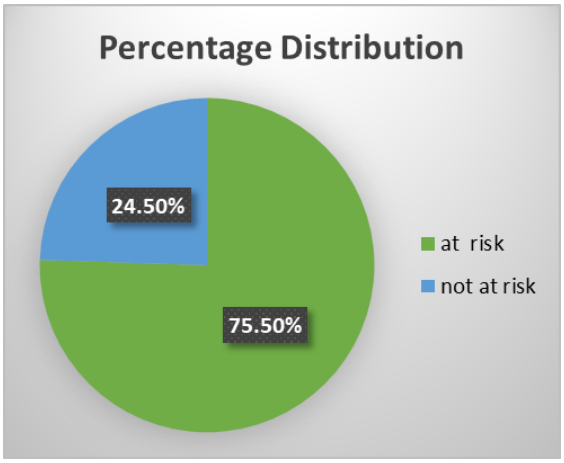

Figure 4: Distribution of Subjects Based on Presence or Absence of Risk.

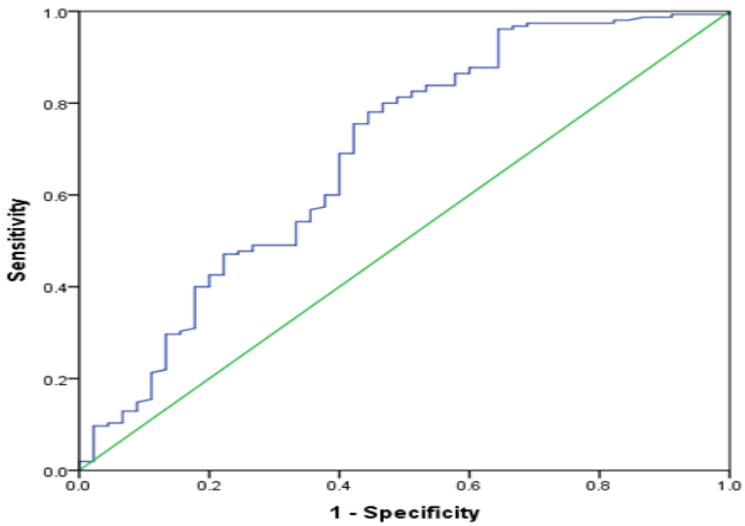

Figure 5: ROC Plot for Body Mass Index.

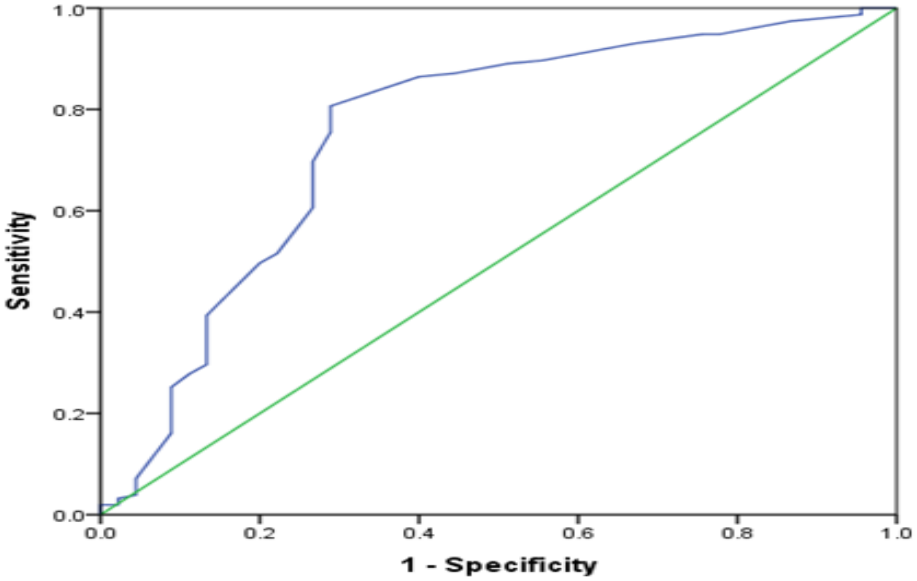

Figure 6: ROC Plot for Waist Circumference.

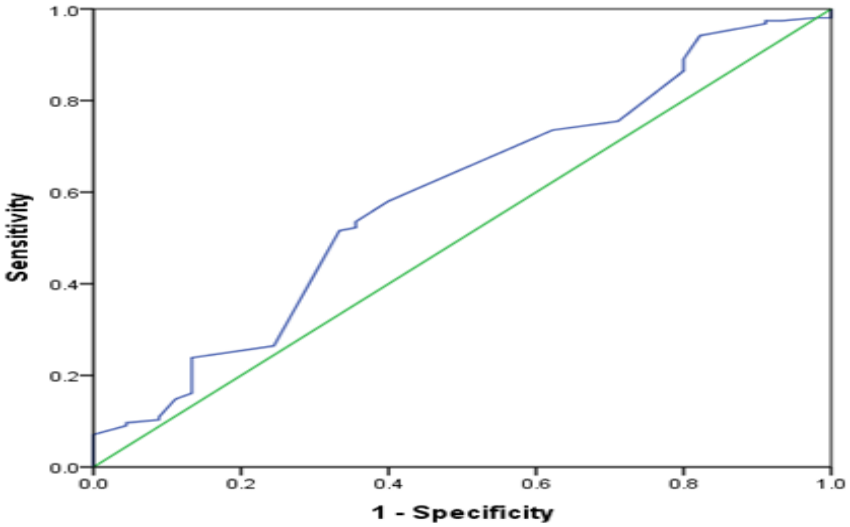

Figure 7: ROC Plot for WHR.

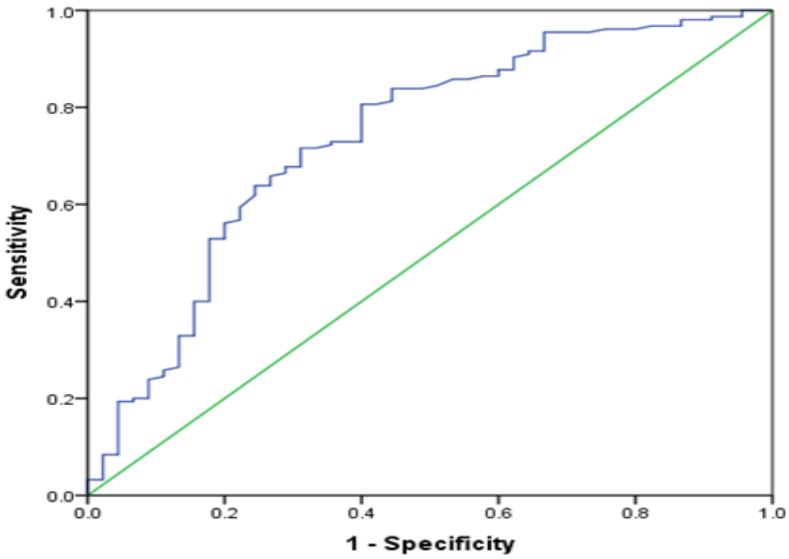

Figure 8: ROC Plot for WHtR.

Table 4: AUC of Obesity Indices.

S.No.	Parameter	AUC	P-value
1	BMI	0.687	<0.0001
2	WC	**0.753**	**<0.0001**
3	WHR	0.590	0.067
4	**WHtR**	**0.737**	**<0.0001**

4. CONCLUSION

The prevalence of metabolic syndrome is increasing worldwide. This increasing trend has been observed in Asian countries. The most effective screening measure must be practical as well as effective. BMI requires measures of weight and height, WC measures central obesity alone and has the complexity of gender differences. Waist hip ratio does not take into account height in defining obesity and hence may under or over evaluate the cardio metabolic risk in tall and short individuals. WHtR requires measures of WC along with height. Uncontrolled diabetes was a significant observation of the study. In spite of being under oral hypoglycemic treatment, the study subjects reflected extremely high FBG, PMBG and HbA1c levels exceeding the standard cut off criteria. Statistical interpretation using Receiver Operating Characteristics (ROC) showed that the Area under Curve (AUC) for WHtR was higher than AUC for BMI and WHR thereby confirming its ability to be a better predictor of cardio metabolic risk factors. A large percentage of diabetic subjects in the present study are under the risk of cardio vascular diseases as assessed by different screening tools for obesity and cardio metabolic risks and therefore reflect a gloomy situation that needs immediate intervention.

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