

## **HAEMATOLOGICAL PROFILE IN DIABETICS IN INDIA , ADDING TO DISEASE MORBIDITY:**

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## **ABSTRACT**

**Background:** *Diabetics are burdened with glycemia and an decreased haemoglobin value also contributes, to increase the risk of development and also progression of micro vascular and macro vascular complications of diabetes.*

**Objectives:**

*To study incidence of anaemia in diabetics with normal renal function, in comparison to non- diabetics who have normal renal function.*

**Design:** *An analytical cross sectional study comparing diabetics with normal renal function and non-diabetics with normal renal function.*

**Settings :** *It was conducted in hospitals attached to KMC Mangalore between September 2016 to July 2018. Group 1 - Diabetics as per ADA criteria. Group 2 - Non diabetics (RBS < 200).*

**Materials and Methods:**

*The estimated glomerular filtration rate (eGFR) was calculated using Cockcroft-Gault Equation. Only those with eGFR>60 ml/min were included. Using the WHO criteria, the prevalence of anaemia was checked for. Duration of diabetes and prevalence of anaemia was correlated.*

**Sample Size:** *The sample size was 100. Both groups had 50 cases.*

**Results:** *In our study it was seen that 56 % of the diabetics were anaemic as compared to only 30 % of the non-diabetics. The p value was 0.0001. The odds ratio calculated showed that diabetics were 2.97 times more likely to have anaemia as compared to non-diabetics. Anaemic patients had an average of 9.68 years of diabetes. The non anaemic patients had an average of 6.32 years of diabetes. The p value was 0.038. The mean glycosylated haemoglobin amongst the anaemic patients was 7.2 and 6.9 amongst non anaemic patients. The p value was 0.450. The most common type of anaemia amongst diabetics was found to be normocytic normochromic anaemia. Amongst the non-diabetics microcytic hypochromic anaemia was the most common.*

**Conclusion:** *In our study it was seen that even in the absence of renal failure, the prevalence of anaemia was higher amongst diabetics as compared to non-diabetics. Longer duration and poorer control diabetes was also associated with a higher prevalence of anaemia.*

**Limitations:**

*Iron studies, Red cell indices were not done. Diabetic complications were not studied. Kidney size was not assessed by Ultrasound.*

**Conflicts of Interest:**

*It was a self-sponsored study.*

**Key Words:** *Normocytic Anemia in Diabetics*

*Chronic anemia in Diabetes*

*Anemia in Diabetes with out CKD*

**Introduction:**

Diabetes mellitus includes a group of metabolic disorders which share a common biochemical derangement - hyperglycemia. Prevalence of diabetes is ever increasing with estimated 415 million affected worldwide.<sup>1</sup>

Generalized fatigability is a common symptom of diabetes. The presence of undiagnosed anaemia can further worsen the fatigability. Anaemia has been noted to be more prevalent amongst diabetics especially those with nephropathy. Multiple studies done world-wide have concluded that the micro vascular and macro vascular complications of diabetes result in a large reduction in the quality and duration of life of the patient.

Anaemia has been found to be more austere amongst diabetics and the onset of anaemia is also earlier. A decreased haemoglobin value also contributes, to increase the risk of development and also progression of micro vascular and macro vascular complications of diabetes. Using the WHO criteria for diagnosing anaemia, it is found that nearly 25% of diabetics have anaemia that warrant further investigation.<sup>2</sup>

However not many studies have been done, to check for anaemia in diabetics who have no renal disease. Since it is known that patients with anaemia are at an advanced risk of developing macro and micro vascular complications of diabetes mellitus, it seems only logical that the anaemia should be evaluated and treated with greater vigour.

This study was undertaken to determine whether diabetics who have normal renal function are anaemic. Since anaemia can significantly impact the overall well-being of an individual, earlier diagnosis and treatment can improve the quality of life and possibly reduce the progression of the complications associated with diabetes

### **METHODS:**

It was an analytical cross sectional study, with comparison of two groups involved. One group included diabetics (Group 1) with normal renal function. Another group consisted of non- diabetics (Group 2) with normal renal function. It was conducted over a 2 year period in Kasturba Medical College Mangalore and attached hospitals. Samples were chosen by simple random sampling.

#### **Inclusion Criteria (Group 1)**

1. Patients who had been diagnosed as having diabetes mellitus
2. Type 1 and Type 2 diabetics were included.

#### **Inclusion Criteria (Group 2)**

1. Non diabetics patients (RBS<200)

#### **Exclusion Criteria (Group 1)**

1. Patients with decreased renal function eGFR< 60ml/min regardless of aetiology.
2. Patients with GI abnormalities like malabsorption syndromes, haemorrhoids, chronic liver disease etc.
3. Patients with acute kidney injury
4. Patients in sepsis
5. Patients having been diagnosed with any malignancy
6. Patients already on treatment for anaemia regardless of glycemic status.

7. Pregnant women
8. Patients on bone marrow suppressive drugs or any drugs likely to result in anaemia.
9. Patients on nephrotoxic drugs
10. Patients having drug induced diabetes

#### Exclusion Criteria (Group 2)

1. Patients having been diagnosed as having diabetes mellitus
2. Patients with decreased renal function ( eGFR< 60ml/min) regardless of the aetiology.
3. Patients with acute kidney injury
4. Patients in sepsis
5. Patients having been diagnosed with any malignancy
6. Patients already on treatment for anaemia regardless
7. Pregnant women
8. Patients on bone marrow suppressive drugs or any drugs likely to result in anaemia.
9. Patients on nephrotoxic drugs.
10. Patients with history of recent haemorrhage.

The study was initiated only after approval from the Institutional Ethics Committee was obtained. History taking and clinical examination of the patient was done after obtaining the informed consent. A random blood sugar test was done to see whether the patient was diabetic or not.

#### For Diabetics:

The age of the patient in years was noted. Weight of the patient in kilograms was noted. A venous blood sample, of 5ml was drawn under aseptic precaution and transferred to 2 different EDTA vacutainers and one plain vacutainer.

One EDTA vacutainer blood was used to determine the haemoglobin. The WHO criteria, was used to define anaemia in patients:<sup>3</sup>

- 1) Males: Haemoglobin < 13g/dl

2) Females: Haemoglobin < 12g/dl

Another other EDTA vacutainer was used to do the peripheral smear (p. smear), if the patient was found to be anaemic. The type of anaemia was then classified into microcytic, normocytic, or macrocytic anaemia.

The plain vacutainer blood was used to determine the creatinine value. The estimated glomerular filtration rate (eGFR) was then calculated using the Cockcroft-Gault Equation.<sup>4</sup>

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Patients having eGFR>60 ml/min/1.72m<sup>2</sup> were considered to have normal renal function.<sup>5</sup> Urine was sent for urine routine examination and patients having >5 pus cells/ hpf were excluded from the study.

The glycated haemoglobin(glycol hb) was also determined by a sample drawn in an EDTA vacutainer.

#### Comparison Group

Comparison group population was selected by simple random sampling. The above mentioned procedure was followed for them as well. Statistical analysis was done after data collection.

#### STATSTICAL ANALYSIS

It was done using descriptive statistics. Correlation of diabetes with anaemia was done using Chi Square Test and Fishers exact test. Correlation of duration of diabetes and glyco hb with anaemia was done with t- test and chi square test. ROC analysis was performed to obtain an optimum cut off value for duration of diabetes with anaemia and glyco Hb with anaemia; with appropriate sensitivity and specificity. Statistical package SPSS vrs.17.0 was used to do the analysis and p<0.5 was considered significant.

#### RESULTS:

A total of 50 diabetics and 50 non diabetics were studied over duration of 2 years.

The average age in the diabetic group was 56.34 years and in the non-diabetic group was 54.18 years. The age ranged from 25 years to 82 years amongst the diabetics. It ranged from 29 years to 83 years amongst the non-diabetics. **(Table 1)**

Among the diabetics 34 % (n=17) were females and 66% (n=33) were males and among the non-diabetics 46% (n=23) were female and 54% (n=27) were males. **(Table 2)**

Out of the 50 diabetics, 38% (n=19) had an Hb>14g/dl, 34% (n=17) had Hb between 12-14g/dl, 14% (n=7) had Hb between 10-12g/dl, and 14% (n=7) had Hb<10g/dl. **(Figure 1)**

Amongst the non-diabetics, 50% (n=25) had Hb>14g/dl, 24% (n=12) had Hb between 12-14g/dl, 20% (n=10) had Hb between 10-12g/dl, and 6% (n=3) had Hb<10g/dl. **(Figure 1)**

Amongst the diabetics 21.2%(n=7) of the males and none of the females had Hb>14g/dl, 42.2% (n=14) of males and 29.4% (n=5) of females had Hb between 12-14g/dl, 30.3% (n=10) of males, and 41.2% (n=7) of females had Hb between 10-12g/dl, and 6.1% (n=2) of males and 29.4% (n=5) of females had Hb<10g/dl. **(Figure 2)**

Amongst the non-diabetics 37% (n=10) of the males and none of the females had Hb>14g/dl, 55.6% (n=15) of males and 43.5% (n=10) of females had Hb between 12-14g/dl, 7.4% (n=2) of males and 43.5% (n=10) of females had Hb between 10-12g/dl, and 0% of the males and 13% (n=3) had Hb<10g/dl **(Figure 3)**.

It was seen that anaemia was more prevalent in the diabetic group as compared to the non-diabetic group. 56 % (n=28) of the diabetics were anaemic as compared to only 30 % (n=15) of the non-diabetics who were found to be anaemic. **(Table 3 and Figure 4)**.

The p value as calculated by the Chi-square test was found to be 0.0001.

The odds ratio calculated showed that diabetics were 2.97 (CI: 1.304-6.764) times more likely to have anaemia as compared to non-diabetics.

Amongst the diabetics 57.1% had normocytic normochromic anaemia (n= 16) and 42.9%(n=12) had microcytic hypochromic anaemia. In the non-diabetic population 93.3% (n=14) had microcytic hypochromic anaemia and 6.7% (n=1) had normocytic normochromic anaemia.

The duration of diabetes varied from 1 year to 15 years. It was observed that amongst the anaemic patients 53.6 % (n=15) had diabetes for > 10 years, 21.4 % (n=6) had diabetes for a duration between 6- 10 years and 25% (n=7) had diabetes between 1-5 years. Amongst the non anaemic patients only 18.2% (n=4) had diabetes for more than 10 years. 36.4% (n=8) had

diabetes for 6-10 years and 45.4% (n=10) had diabetes for 1-5 years (**Table 4**). It was seen that the anaemic patients had an average of 9.68 years of diabetes. This was significantly more than the non anaemic patients who had diabetes for 6.32 years on an average.

The p value calculated by the Chi square test/ Fisher's exact p test was found to be 0.038, which is significant. The ROC curve shows that patients with an average duration of diabetes for 7.5 years and 9 years had the highest sensitivity and specificity for prevalence of anaemia (**Figure 5**).

Amongst the anaemics it was seen that the glyco hb was >6.5 in 89.3% cases as compared to only 10.7% who had a glyco Hb < 6.5. The mean glyco hb amongst the anaemic patients was 7.2. Amongst the non anaemic patients the mean glyco hb was 6.9. The p value as calculated by the Chi square test/ Fishers exact test was 0.450 which is significant. The ROC curve showed that patients with a glyco hb of 7.05 had the highest sensitivity and specificity with respect to prevalence of anaemia and could hence be used as a cut-off (**Figure 6**).

## **DISCUSSION**

It is a well-known fact that anaemia is common in diabetes once nephropathy sets in.

Our study aimed at showing that even in the absence of renal failure diabetics were more likely to have anaemia as compared to non- diabetics. None of the patients that we studied had renal failure.

Out of the 100 patients studied, 50 were diabetic and 50 non diabetic. Our study results and analysis showed that anaemia was indeed more common in diabetics as compared to the non-diabetics. In our study, 56 % of the diabetics were found to be anaemic as compared to only 37 % of the non-diabetics who were anaemic. The p value was found to be 0.0001, which is very significant. The odds ratio for a patient who is diabetic having anaemia as compared to a non-diabetic having anaemia was found to be 2.97. In other words a diabetic was 2.97 times more likely to have anaemia as compare to a non-diabetic even in the absence of renal failure. The studies done by Antwi- Bafour et al, Craig et al, Thomas et al, Feteh et al had patients with diabetes having a lower average haemoglobin value as compared to non- diabetics.<sup>6, 7, 8, 9</sup> However anaemia was more prevalent among diabetics applying the WHO criteria for anaemia.<sup>3</sup> In a study done by Makadiya et al.<sup>10</sup> It was seen that anaemia was present in 37%

of the diabetic patients as compared to only 12% in the non-diabetics. A study done by Adejumo et al and Kojima et al also had similar findings.<sup>11, 12</sup>

An Indian study, showed that 66% of the total subjects in the study who were found to be anaemic were also seen to have diabetes. Thomas *et al* found 83 of 204 patients (41%) with diabetes had anaemia. In another study by Thomas *et al*, it was seen that out of 722 diabetic patients 23.3% of had anaemia. A study done by Grossman et al showed that in patients with normal renal function anaemia was more common amongst diabetics as compared to non-diabetics. A total of 890 patients were studied and anaemia was observed in 48 (10.8%) subjects in the diabetic group and in only 12 (2.7%) subjects in the non-diabetic group with  $p < 0.001$  showing that the findings were highly significant.

In our study a larger proportion of the females were seen to have anaemia as compared to the males. Amongst the diabetics it was seen that 70.6% of the females had anaemia as compared to 42.4% of the males. Even amongst the non-diabetics a similar trend was observed.

The study done by Makadiya et al concurred this finding. Their study observed that anaemia was present in 13% of the men and 31% of the women suggesting that risk of anaemia is affected by gender ( $p < 0.05$ ). The study done by Adejumo et al also showed that females were more likely to have anaemia as compared to males. Bonakdaran *et al* also found that females had more anaemia than male patients but the difference was not significant.<sup>13</sup>

Craig *et al* showed that 17.8% of male diabetic patients and 11.8% of females could be classified as anaemic. In the study by Cawood *et al* it was reported that 11% of males and 16% of females from 270 type 2 diabetic patients were anaemic.<sup>14</sup> The study done by Emma English et al also had similar findings wherein they found that a larger proportion of female diabetics had deranged red cell indices.<sup>15</sup>

The most common type of anaemia in our study was normocytic normochromic type in diabetics accounting for 57.1%. Microcytic hypochromic anaemia was more common amongst the non-diabetics in our study accounting for 93.3%.

In a study done by Kaushik et al it was seen that amongst diabetics 57.14% had microcytic hypochromic anaemia and 42.86% had normocytic normochromic anaemia.<sup>16</sup> The study done by Adejumo et al showed that amongst the diabetics, most of the patients they studied had microcytic hypochromic anaemia. This might be explained by the fact that their study was based in an area where there was a higher incidence of iron deficiency.

It was also seen in our study that the longer the patient had diabetes more was the likelihood he/she would have anaemia. In our study the anaemic patients had an average duration of 9.68 years of the disease. This was significantly more than the non anaemic patients who had diabetes for 6.32 years on an average. The p value was found to be 0.038, which is significant.

In the study done by Adejumo et al they found that patients with more severe anaemia had a longer duration of diabetes as compared to those who had a lesser degree of anaemia. Catherine et al also found that there was positive relation between duration of diabetes and development of anaemia. Abate et al also observed that longer duration of diabetes was associated with higher degree of renal failure and anaemia.<sup>17</sup> Antwar et al noted that amongst the population they studied the patients with more severe anaemia had an average duration of diabetes that was more than those who had only a mild derangement in haemoglobin.

The glycol hb, which reflects an average control of blood sugars over a 3 month period, amongst the anaemic patients was found to be 7.2 on an average. Amongst the non anaemic patients the glyco hb average was 6.9. This was a significant finding as indicated by a p value of 0.041.

The study done by Adejumo et al, showed that patients with glyco Hb>8 had more severe anaemia as compared to those with lower values of glyco Hb. The study done by Craig et al showed that even in the absence of renal impairment, the diabetics with glyco Hb>7.5 had a higher prevalence of anaemia. The studies done by, Steven et al, Abate et al, English et al, Antwi- bafour et al, Barbieri et al and Thomas et al all noted that poorer glycaemic control was associated with a higher risk of anaemia.<sup>18</sup>

The findings of our study were in correlation with our aims and objectives. The findings of our study are also consistent with the available literature on the subject.

There were a few limitations in our study. Iron studies were not done for the patients

Red cell indices were not done. Ultrasound abdomen was not done to look for kidney size. Microvascular and macrovascular complications of diabetes were not looked for like neuropathy, retinopathy, peripheral vascular disease, ischaemic heart disease.

## **CONCLUSION**

In our study it was seen that even in the absence of renal failure, the prevalence of anaemia was higher amongst patients with diabetes as compared to those without diabetes. Anaemia was more prevalent amongst those patients who had a longer duration of diabetes. The most common type of anaemia that was present amongst the diabetics was seen to be normocytic normochromic anaemia. Furthermore patients with poorer glycaemic control, as indicated by a higher glyco hb value, were seen to have a higher prevalence of anaemia.

India being a developing country addressing anemia in diabetics which is more likely prior to the onset of chronic kidney disease.

### **Acknowledgement:**

We thank Dr Shishirkumar, Associate Professor, Department of Anatomy, JNUIMSRC, Jaipur (former Associate Professor, Department of Anatomy, Kanachur Institute of Medical Sciences, Mangalore for his help in Research Design and Statistical analysis).

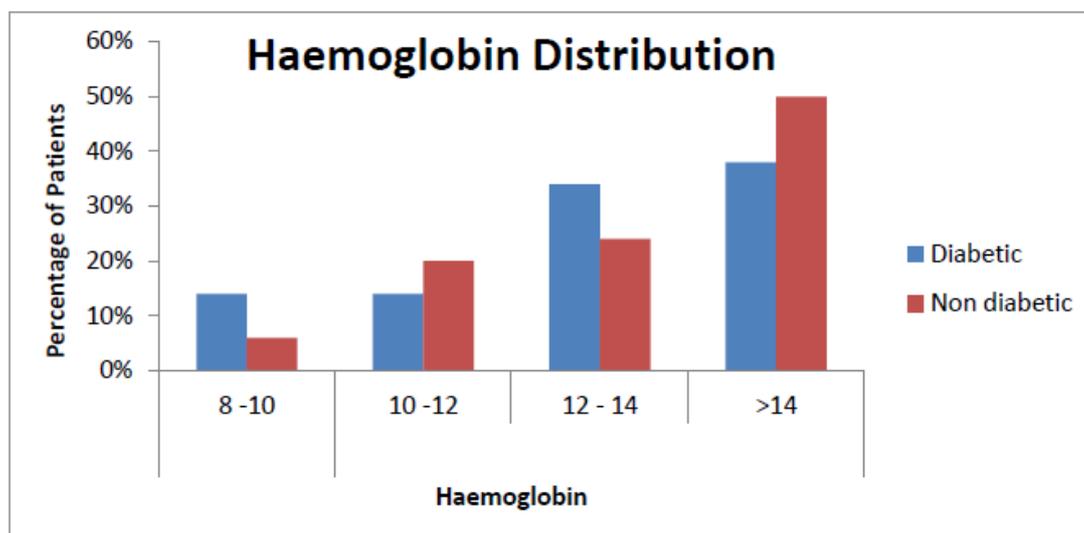
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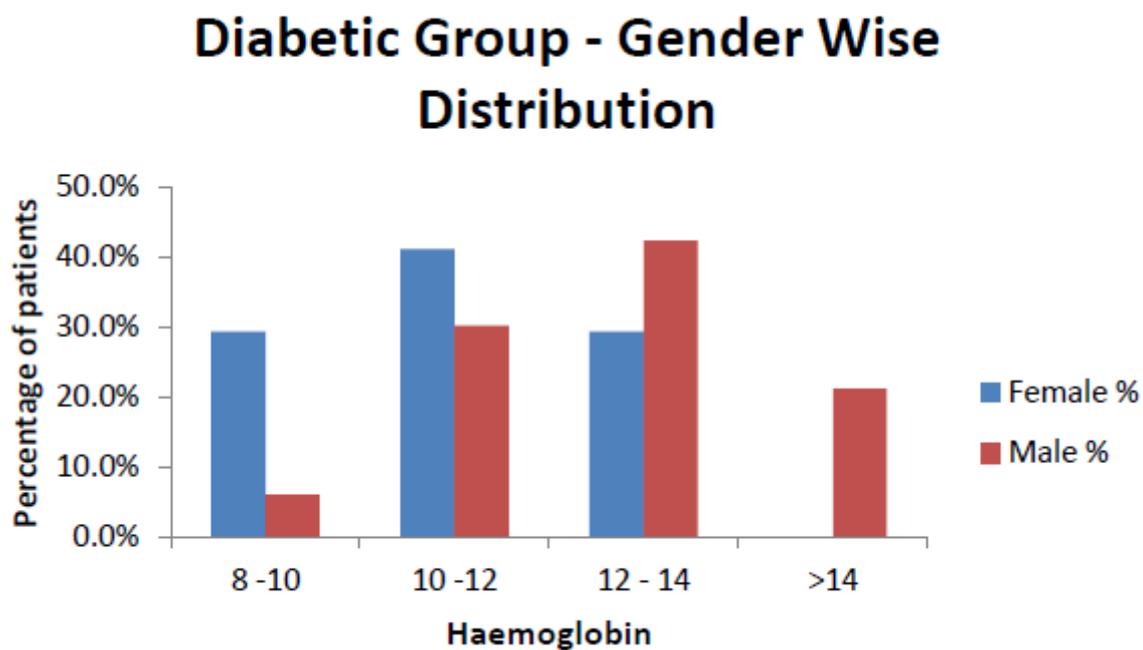
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Annexure:

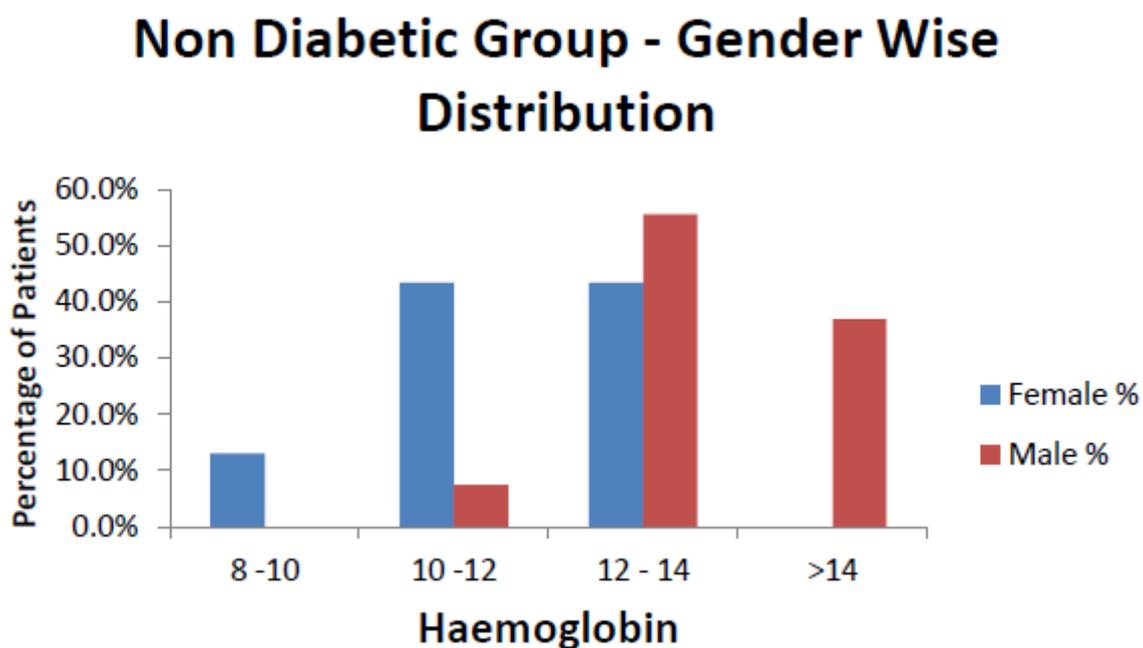
**Figure 1 Haemoglobin Distribution**



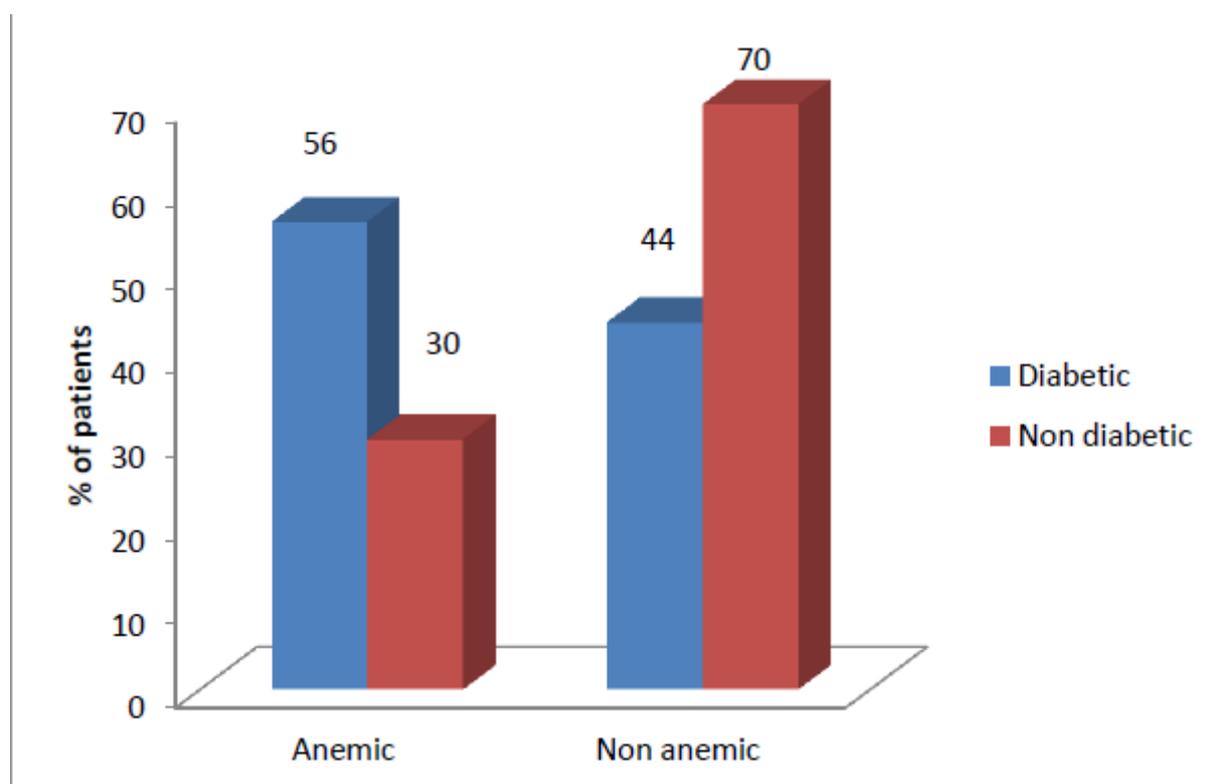
**Figure 2 Diabetic Group –Gender Wise Distribution Haemoglobin Distribution**



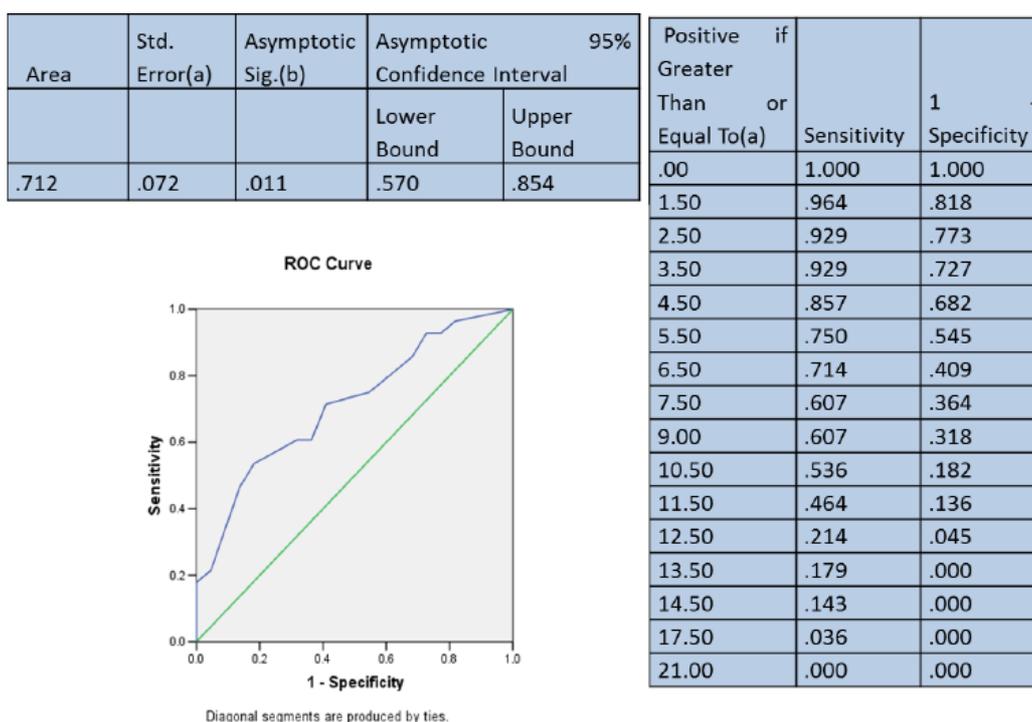
**Figure 3 Non-Diabetic Group –Genderwise Haemoglobin Distribution**



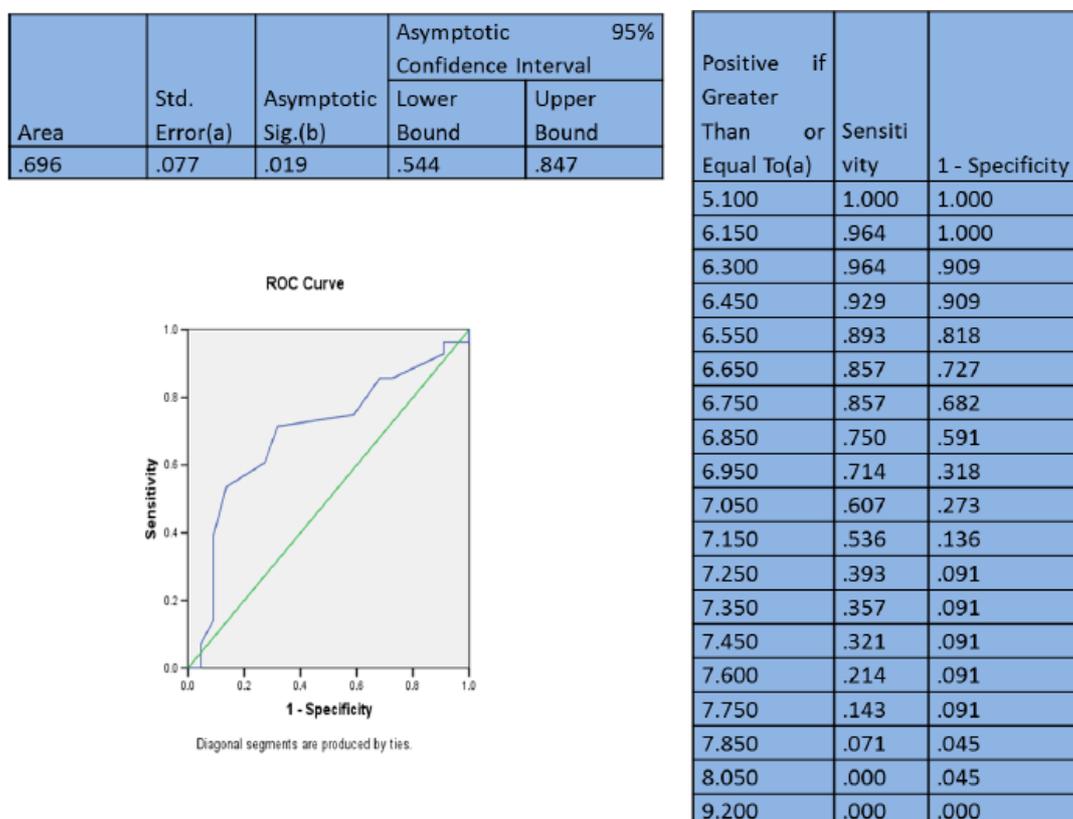
**Figure 4 Anemia Distribution**



**Figure 5: ROC Curve for Duration of Diabetes and Anaemia**



**Figure 6: ROC Glyco-Hb and Anaemia**



**Table 1 Common Causes Of Anaemia**

Age(years)	N	Mean	Std. Deviation
Diabetic	50	56.34	12.75
Non diabetic	50	54.18	14.11
Total	100	55.26	13.43

**Table 2. Gender Wise Distribution Of The Study Sample**

		Diabeti s		Non Diabetics		Total	
		Count	N%	Count	N%	Count	N%
Sex	Females	17	34%	23	46%	40	40%
	Males	33	66%	27	54%	60	60%
	Total	50	100%	50	100%	100	100%

**Table 3. Age Wise Distribution Of The Study Sample**

Groups						
	Diabetic		Non diabetic		Total	
	Count	%	Count	%	Count	%
Anaemi c	28	56.0%	15	30.0%	43	43.0%
Non anaemi c	22	44.0%	35	70.0%	57	57.0%
Total	50	100.0%	50	100.0%	100	100.0%

**Table 4. Duration of Diabetes**

		Anaemic		Non anaemic		Total	
		Count	Column N%	Count	Column N%	Count	Column N%
Duration of diabetes (years)	1 - 5	7	25.0%	10	45.5%	17	34.0%
	6-10	6	21.4%	8	36.4%	14	28.0%
	> 10	15	53.6%	4	18.2%	19	38.0%
	<b>Total</b>	<b>28</b>	<b>100.0%</b>	<b>22</b>	<b>100.0%</b>	<b>50</b>	<b>100.0%</b>