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Clinical Profile of Anemia in SLE

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Abstract
SLE is a multisystem autoimmune disease with significant morbidity and mortality in women of young and child bearing age. The prognosis is still poor in certain ethnic groups like Indians and Hispanics as compared to the western population. Haematological abnormalities are one of the integral criteria for disease classification as specified by the American Rheumatic Association, yet there is a paucity of information regarding their temporal progression and impact on the course of the disease. This prospective study was carried out on forty five patients with SLE in the Department of General Medicine, Govt TD Medical College, Alappuzha with specific emphasis on anaemia and its correlation with the myriad presentations of SLE. The most common haematological abnormality detected in our study was Anaemia, with Iron deficiency Anaemia, Anaemia of Chronic Disease and Auto Immune Hemolytic Anaemia (IHA) being the most common subtypes. Further, Anaemia was significantly associated with Lupus Nephritis but not any other major organ involvement. No significant association was found between anaemia and serum creatinine, but a negative correlation was observed between the two, with higher creatinine values associated with lower haemoglobin levels. Appropriate treatment showed a significant improvement in Haemoglobin levels across all subtypes of anaemia.

Materials and Methods

This prospective study was carried out on all consecutive patients diagnosed to have SLE in the Department Of General Medicine at Government T D Medical College, Alappuzha during the year 2011-2012 with the following objectives:

1) Determination of the spectrum of clinical presentations, prevalence and etiological profile of Anaemia in patients detected to have SLE during the study period.
2) Assessment of the aetiology and interventions to correct the Anaemia.
3) Determination of the impact of interventions over a period of three months of follow-up.

This study was carried out on the 45 in-patients and out-patients more than 18 years old who attended Medicine department and included both established and newly diagnosed cases with SLE. The revised American Rheumatic Association Criteria updated 1997 was used to diagnose SLE. Patients unwilling to be a part of the study and those admitted with terminal illnesses attributable to other causes were excluded from the study.

All the patients meeting the inclusion criteria were evaluated with detailed history, clinical examination and laboratory investigations with special emphasis on haematological abnormalities. Special attention was given to elicit history of past treatments, abortions, arterial or venous thrombosis and other haematological presentations. All patients were made to undergo a detailed physical examination and subsequently, a structured Proforma with emphasis on different features of SLE, involvement of other organ systems (i.e. Skin, Genito-urinary, Gastro-intestinal, Cardiovascular and Respiratory System) was filled.

The panel of Haematological investigations included Haemoglobin, Peripheral Smear, Total WBC counts, Differential WBC counts, Platelet counts, Coomb's test, Reticulocyte count ant other blood indices. In relevant cases, ANA, Anti-ds DNA and APLA were also done.

Treatment was initiated dependent on the aetiology found behind the anaemia and response was assessed at the end of 3 months by rechecking the Haemoglobin levels.

Definitions Used:

1) Anaemia: WHO Haemoglobin<12 g% in Females and <14g% in Males. Severe Anaemia- Haemoglobin < 8g%
2) Iron Deficiency Anaemia: Hypochromicity on smear with low Ferritin and MCV< 75fL.
3) Anaemia of Chronic Disease: DCT negative normocytic normochromic anaemia
4) Hemolytic Anaemia: DCT positive anaemia with reticulocytosis.

Computer software, Statistical Package for Social Sciences (SPSS) version 17 was used for data analysis. To elucidate the associations and comparisons between different parameters and their proportions, Chi square (χ^2) test was used as nonparametric test. Logistic regression analysis was performed and for all statistical evaluations, a two-tailed probability of value, < 0.05 was considered significant.

Observation

Of the 45 patients studied, majority were of the age group 20-30 years.

The age in our study group varied from a minimum of 20 yrs to a maximum of >40 yrs.

Table & Chart No 1: Age Distribution

Age	Frequency	Percent
<20	8	17.8
20-30	21	46.7
30-40	13	28.9
>40	3	6.7
Total	45	100

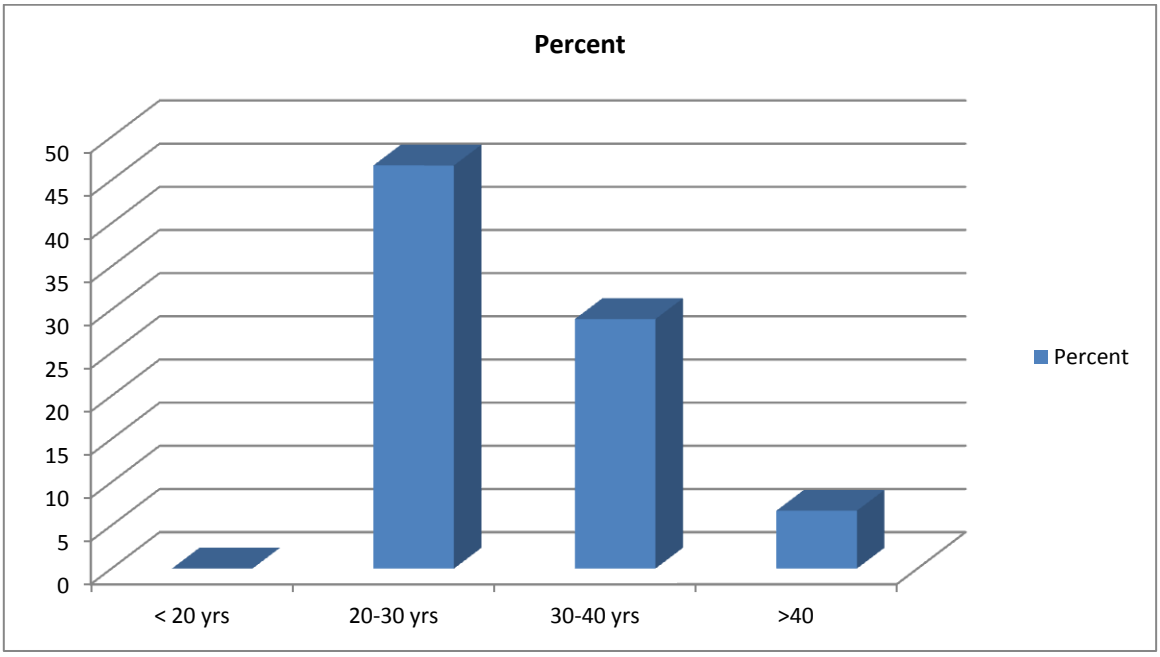
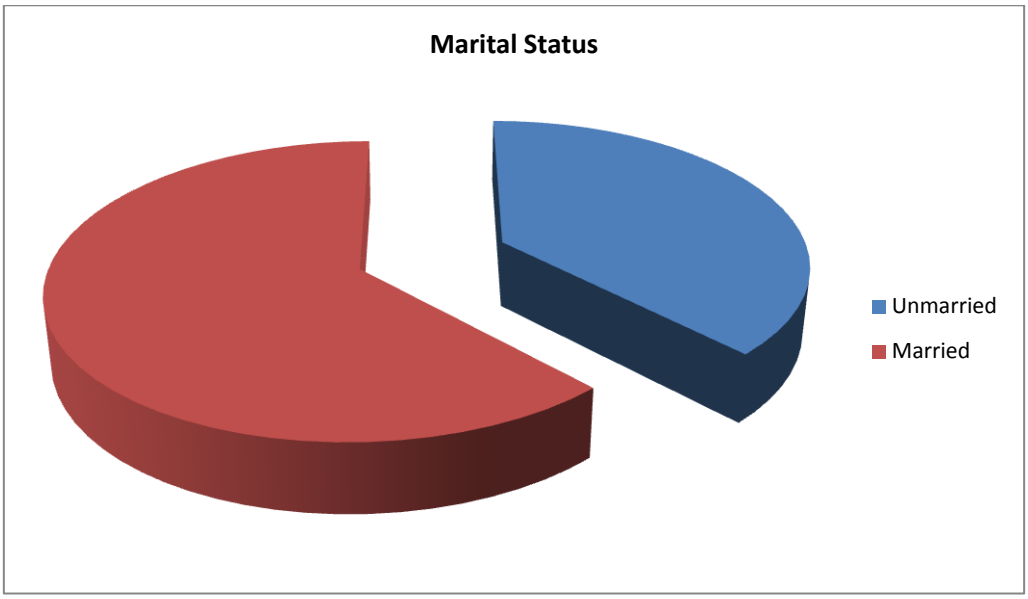


Table & Chart No2: Marital Status

Marital Status	Frequency	Percentage
Unmarried	17	37.8
Married	28	62.2
Total	45	100



In our study group, 54% of the married women had history of at least one abortion.

H/o Abortion	Frequency	Percentage
Present	15	53.57
Absent	13	46.42
Total	28	100

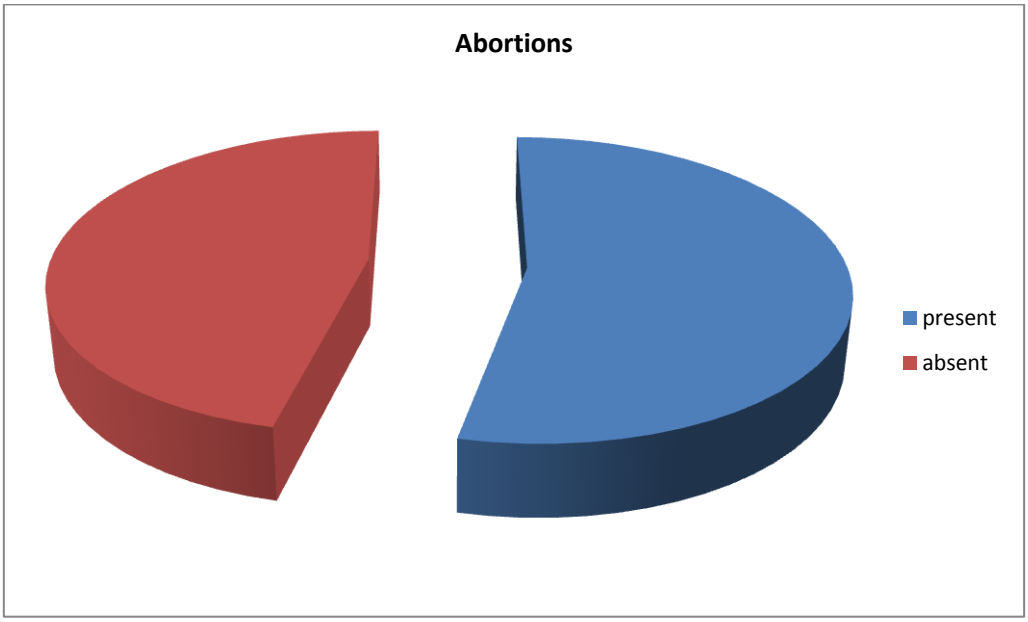


Table & Chart No 3: Abortion Rates

Eleven patients of the study group had APLA positivity and 7 of these had h/o abortions.

APLA Status	Abortions
Positive	7
Negative	4

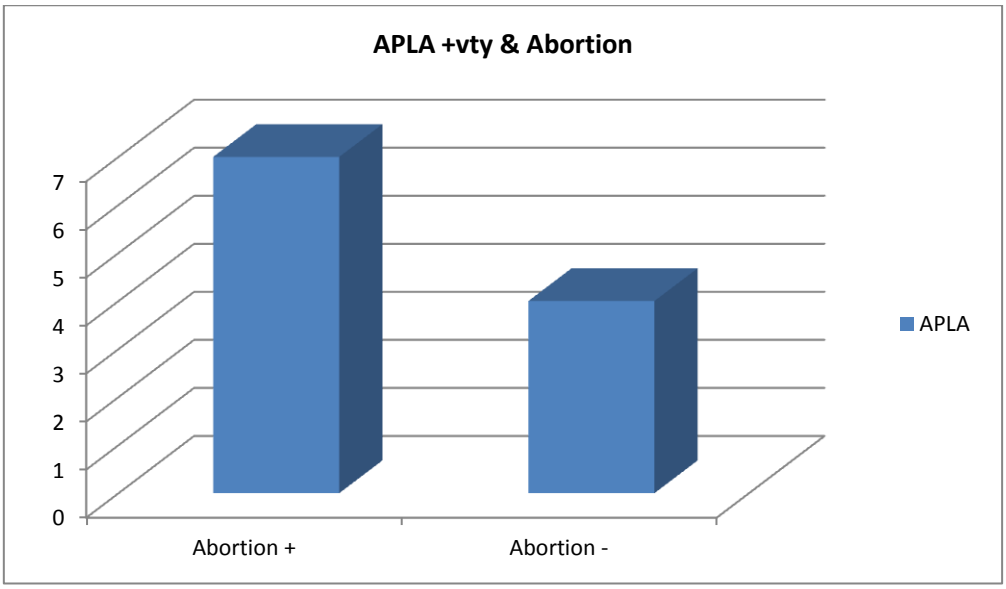


Table & Chart No 4: Abortions and APLA positivity

80% patients in our study group had normal Blood pressure and only 20% had elevated blood pressures.

BP	Frequency	Percentage
Normal	36	80
High	9	20
Total	45	100

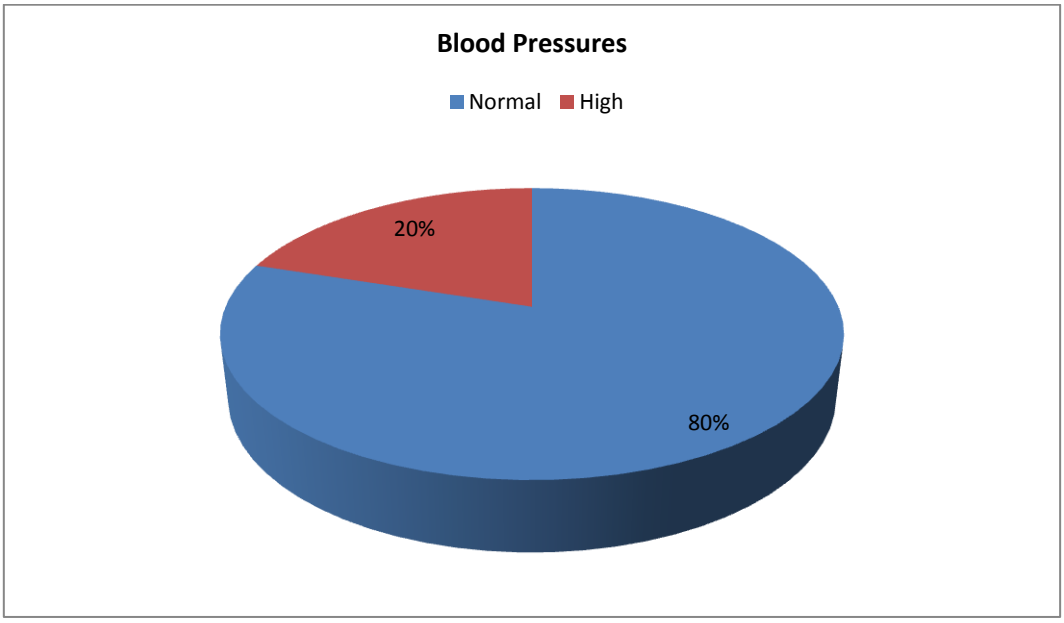


Table & Chart No 5: Distribution of Blood Pressure

64.4% patients in our study group had tested positive for Anti- ds DNA and only 35.6% were negative for Anti-dsDNA.

Anti- dsDNA	Frequency	Percentage
Absent	16	35.6
Present	29	64.4
Total	45	100

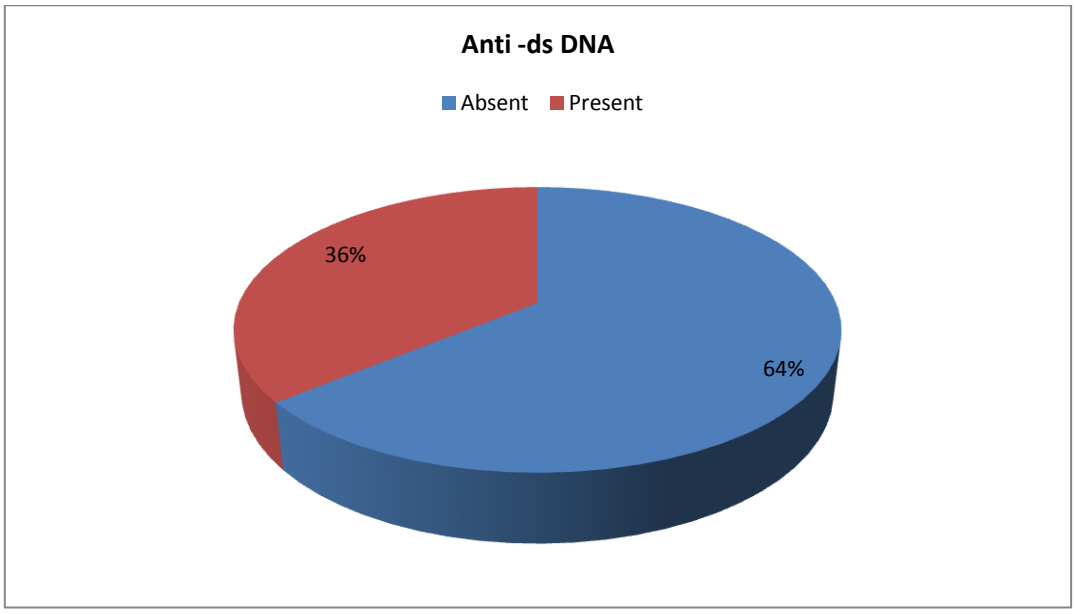


Table & Chart No 6: Distribution Of Anti- ds DNA

86.7% patients in our study group had normal creatinine values as against 13.3% with elevated creatinine.

Serum Creatinine	Frequency	Percentage
Normal	39	86.7
Elevated	6	13.3
Total	45	100

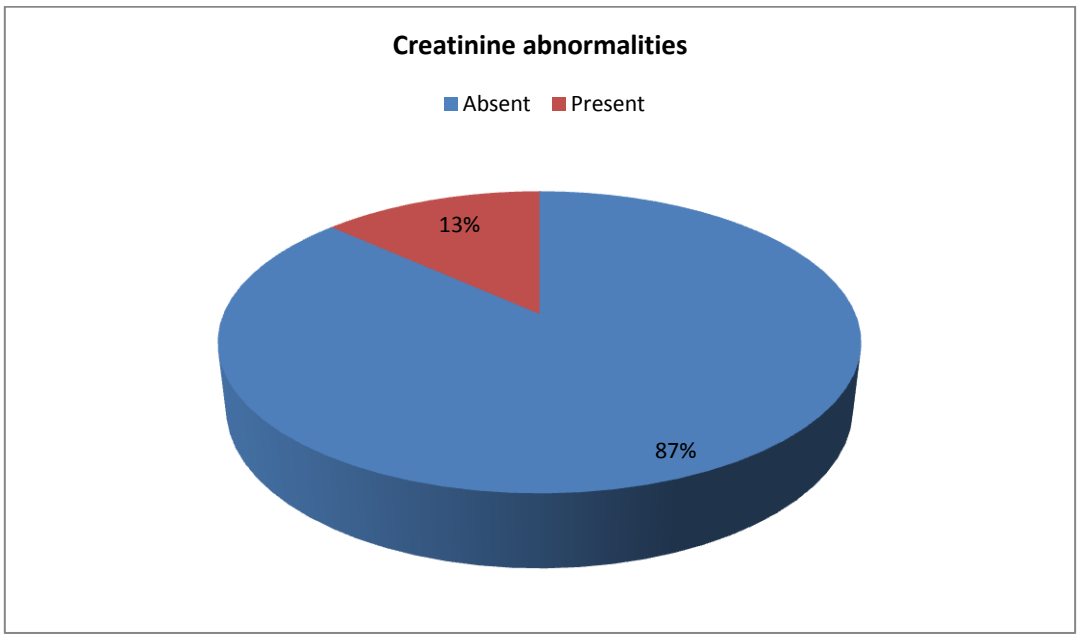
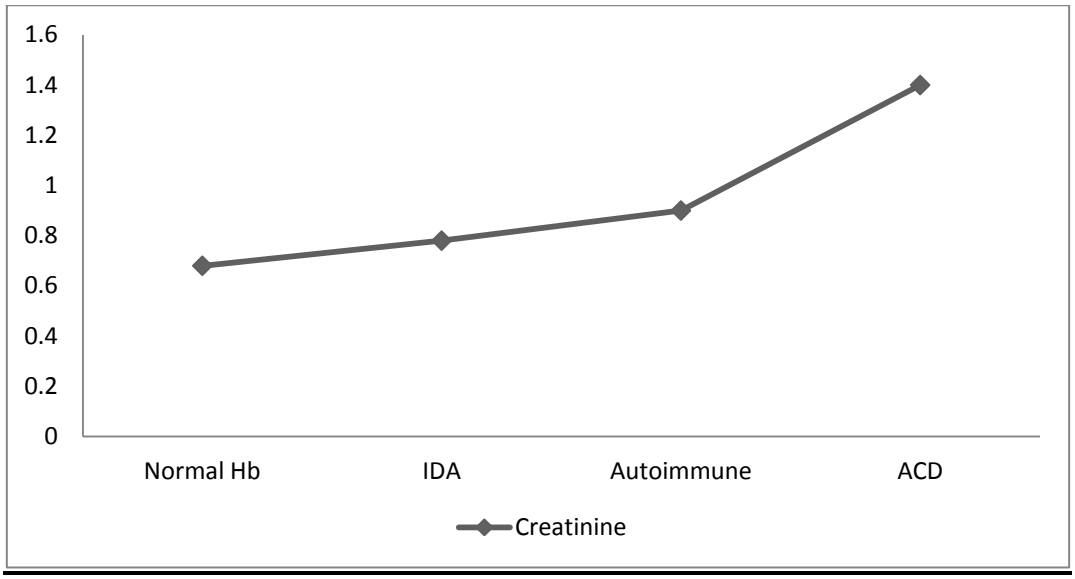


Table & Chart No 7: Abnormal Creatinine

Analysis of the creatinine values in patients in our study group revealed that even though anaemia of chronic diseases was associated with higher creatinine values, this was not statistically significant. This could be possibly attributed to the lower prevalence of renal derangement in RFTs in our study group.



Further, analysis of the spectrum of symptoms revealed arthritis as the most frequent, followed by serositis and neurological manifestations.

Arthritis was the predominant symptom in our group, and RA Factor positivity was seen in all the seven, and 3 of them had been treated as Rheumatoid Arthritis before diagnosing as SLE.

Symptoms	Frequency	Percent
Arthritis	35	77.8
Serositis	9	20.0
Neuro-SLE	2	4.4
APLA	15	33.3
RA Factor	7	15.6

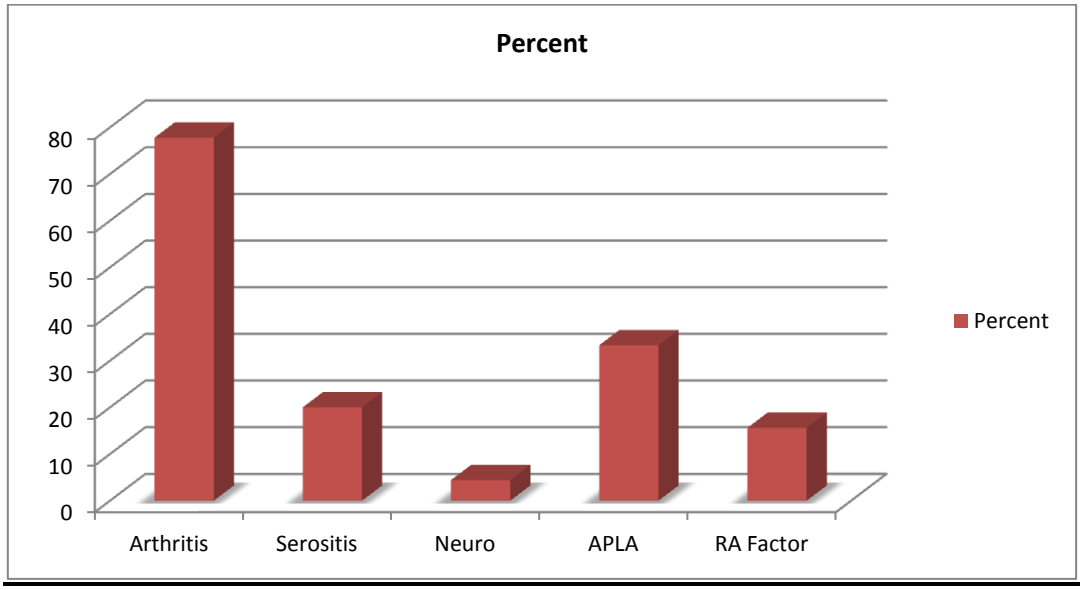


Table & Chart No 9: Immunology & Symptoms

Peripheral smear in our study group revealed Microcytic hypochromic anemia in 40% and normocytic normochromic anemia in 60% of the patients.

Peripheral Smear	Frequency	Percent
Microcytic Hypochromic Anaemia	18	40
Normocytic Normochromic Anaemia	27	60

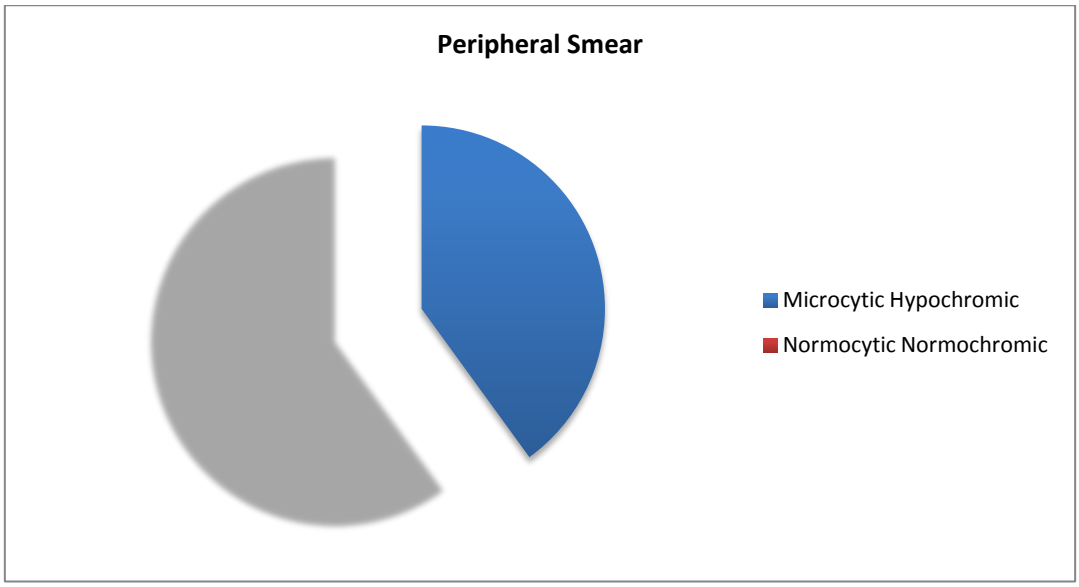
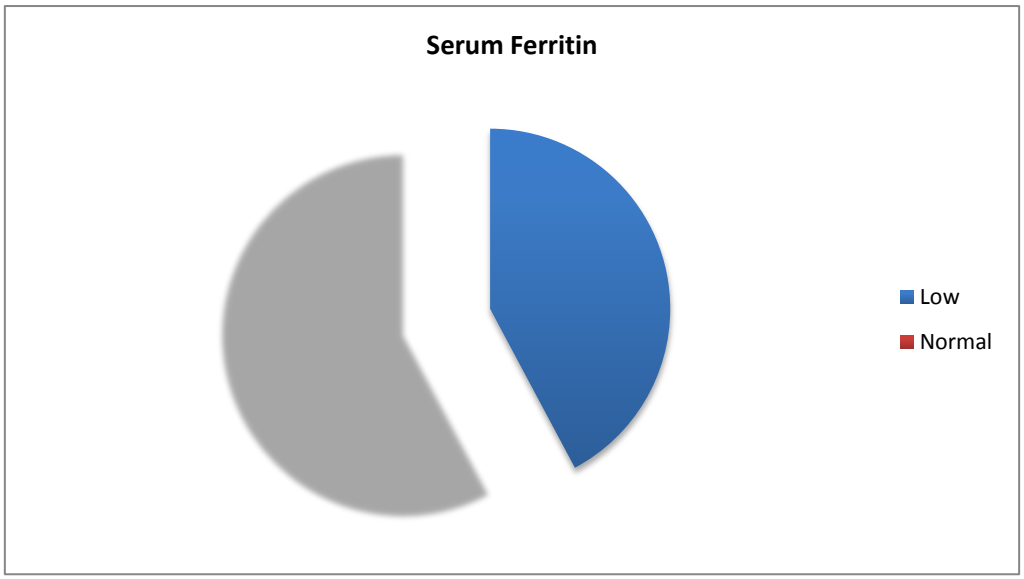


Table & Chart No 9: Immunology & Symptoms

Assessment of serum Ferritin levels in our study group revealed low levels in 42.20% and normal levels 57.8% of the patients.

Ferrritin	Frequency	Percent
Low	19	42.2
Normal	26	57.8



Assessment of Platelet counts in our study group revealed low levels in 17.8% and normal levels in 82.2% of the patients. Serum SGPT was normal in 73.3% and elevated only in 26.7% of the study group. Stool Occult blood was positive and GI loss was the cause and/or the contributory factor in more than 50% of Iron deficiency cases our study group.

Factor	Normal (%)	Low (%)	Elevated (%)
Platelet count	82.2	17.8	0
SGPT	73.3	0	26.7
Leucocyte	68.9	31.1	0

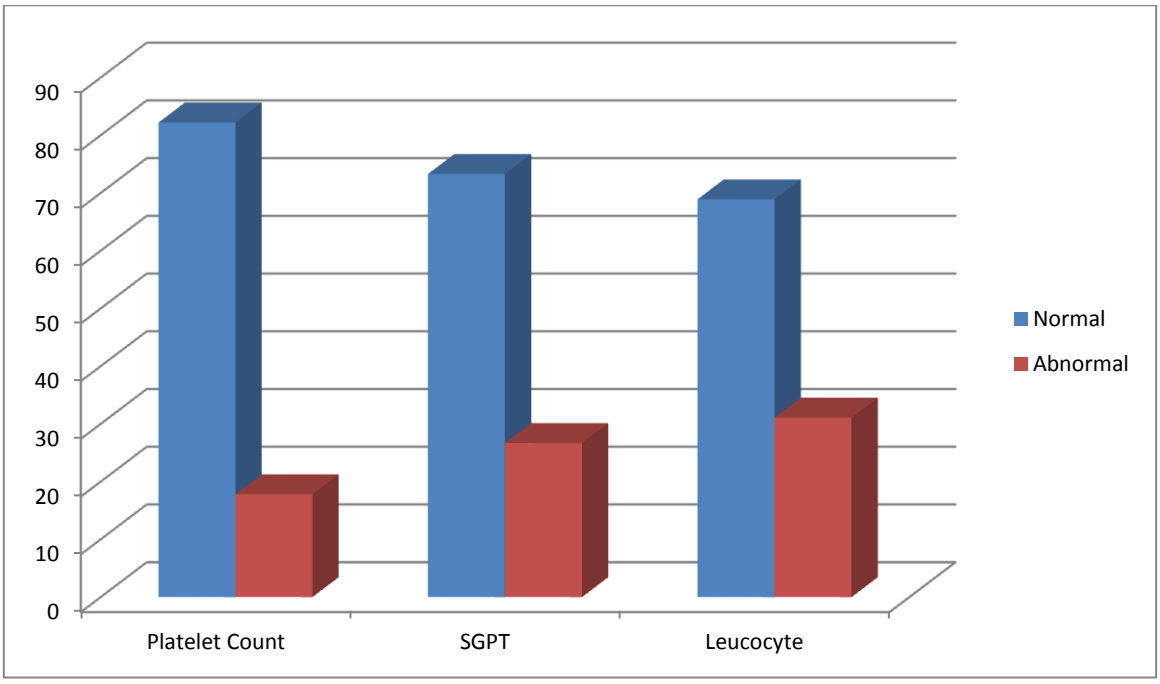


Table & Chart No 10: Serum SGPT, Leucocyte and Platelet counts

Urine Analysis revealed normal study only in 33.3% of our study group, while microscopic albuminuria was found in 35.6% of our patients. 22 patients had Albuminuria, 2 had Haematuria and 6 had both albuminuria and heamaturia.

Urine Analysis	Frequency	Percent
Normal	15	33.3
Microscopic Albuminuria	16	35.6
Nephritic Proteinuria	2	4.4
Nephrotic Proteinuria	4	8.9
Proteinuria and hematuria	5	11.1
Hematuria	3	6.7
Total	45	100

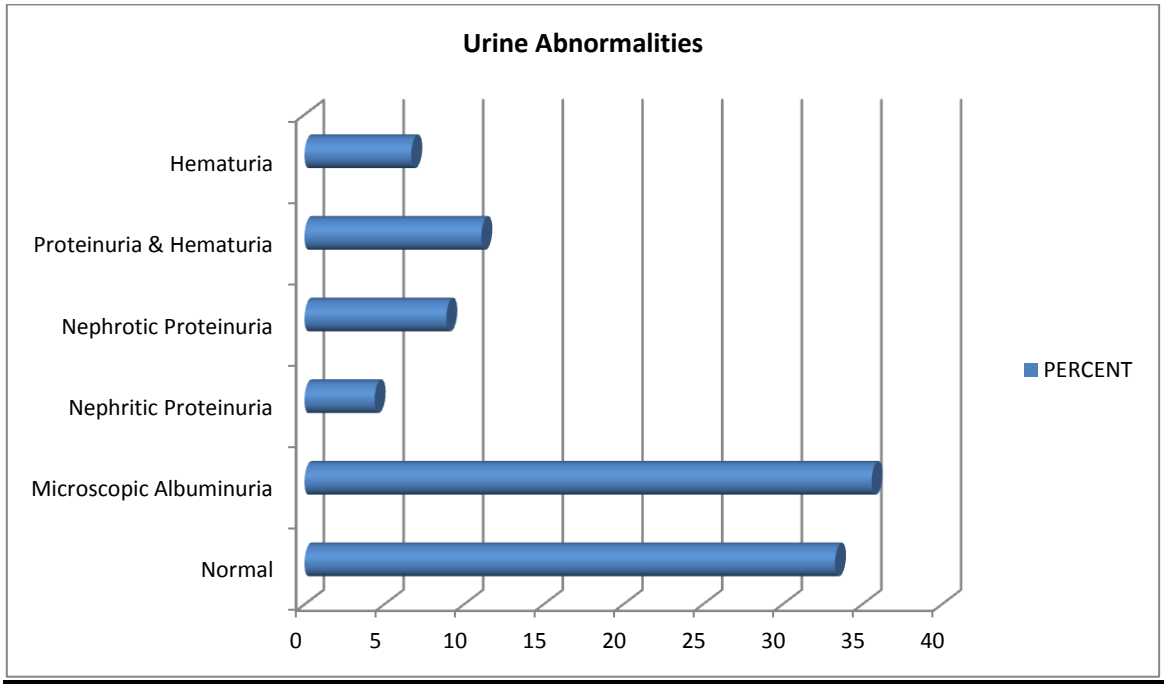
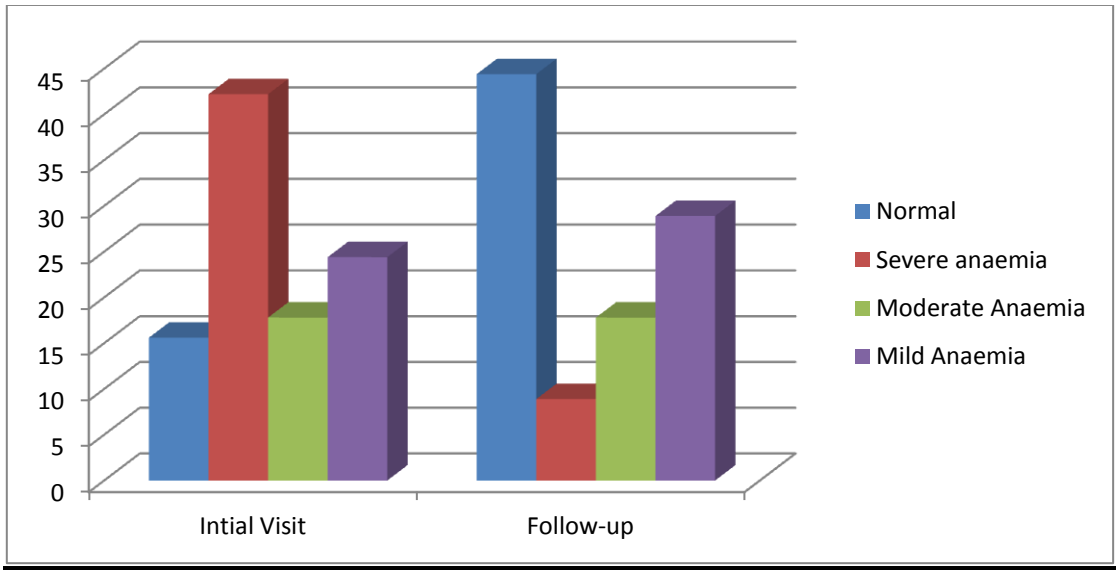


Table & Chart No 11: Urine Analysis

At the time of enrolment in the study, 84.4% had anaemia. Of these, 8.9% had severe anaemia (< 8 Gm%). Most of the patients were severely anaemic at the time of presentation and enrolment into the study and during the course of interventions, irrespective of the severity, there was significant improvement.

Hemoglobin	Initial Value (%)	Follow-Up Value (%)
Severe Anaemia	42.2	8.9
Moderate Anaemia	17.8	17.8
Mild Anaemia	24.4	28.9
Normal	15.6	44.4
Total	100	100



Initial Hemoglobin	Follow-Up				Total
	Severe Anaemia	Moderate Anaemia	Mild Anaemia	Normal	
Severe anaemia	4	6	3	6	19
Moderate Anaemia	0	2	4	2	8
Mild Anaemia	0	0	6	5	11
Normal	0	0	0	7	7
Total	4	8	13	20	45

There was a mean increase in Haemoglobin by 2.717 during the follow-up period.

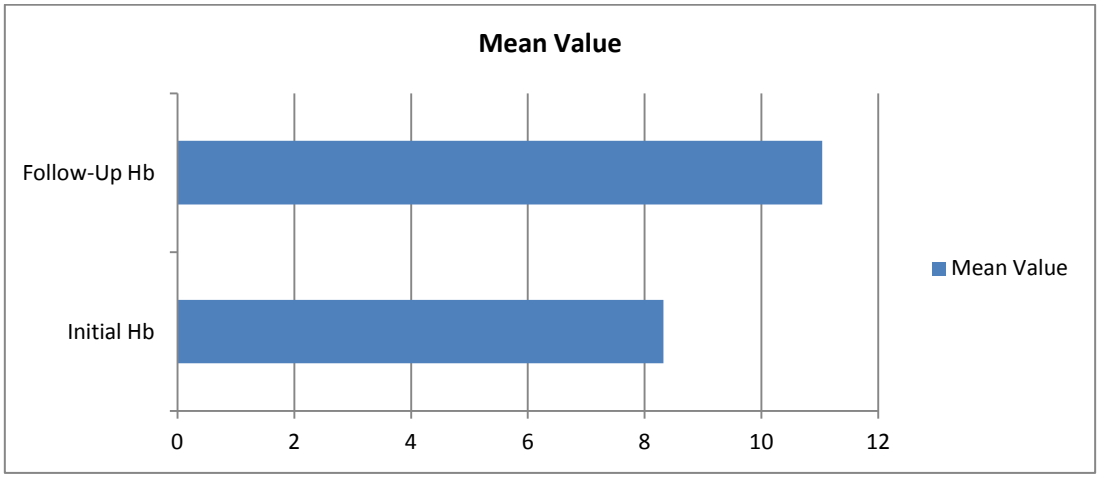
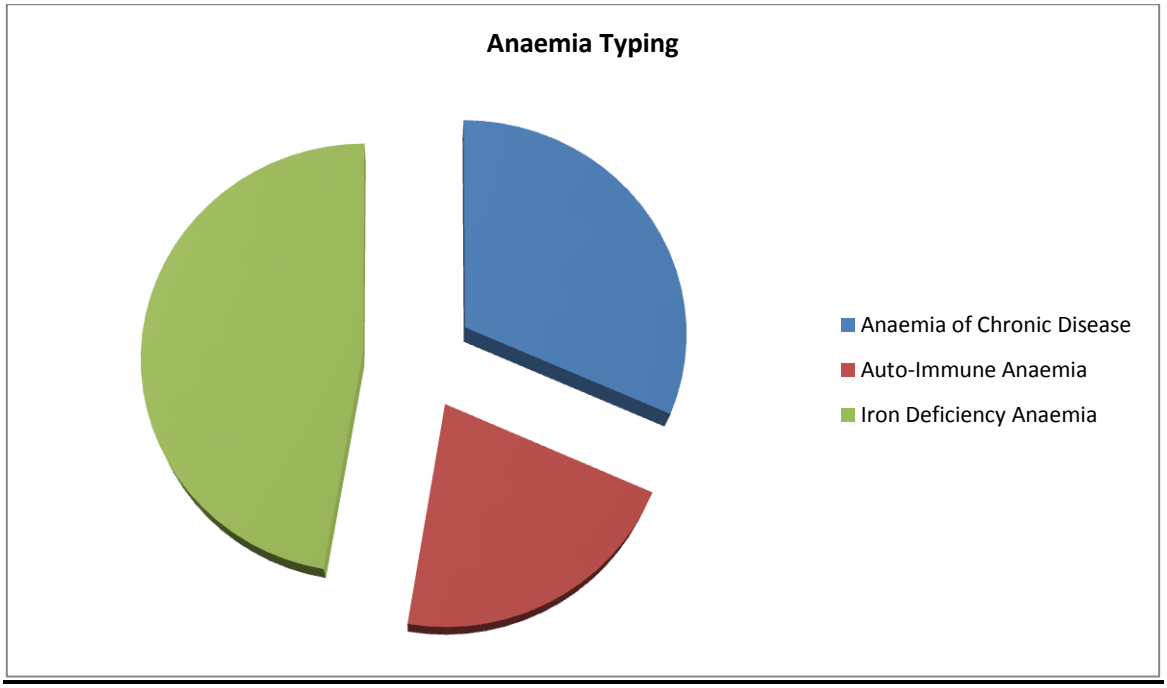


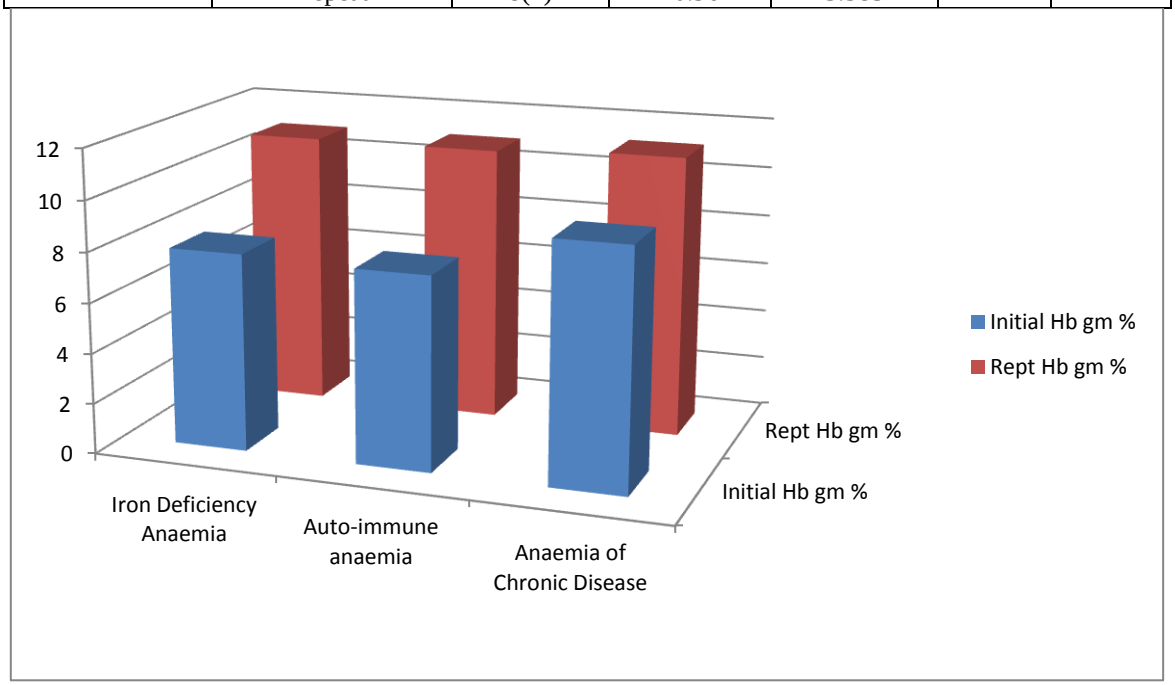
Table & Chart No 12: Anaemia Analysis

At the time of enrolment in the study, majority (40%) of our patients had Iron Deficiency anaemia, 17.8% had auto-immune Anaemia and 26.7% had Anaemia of chronic diseases.

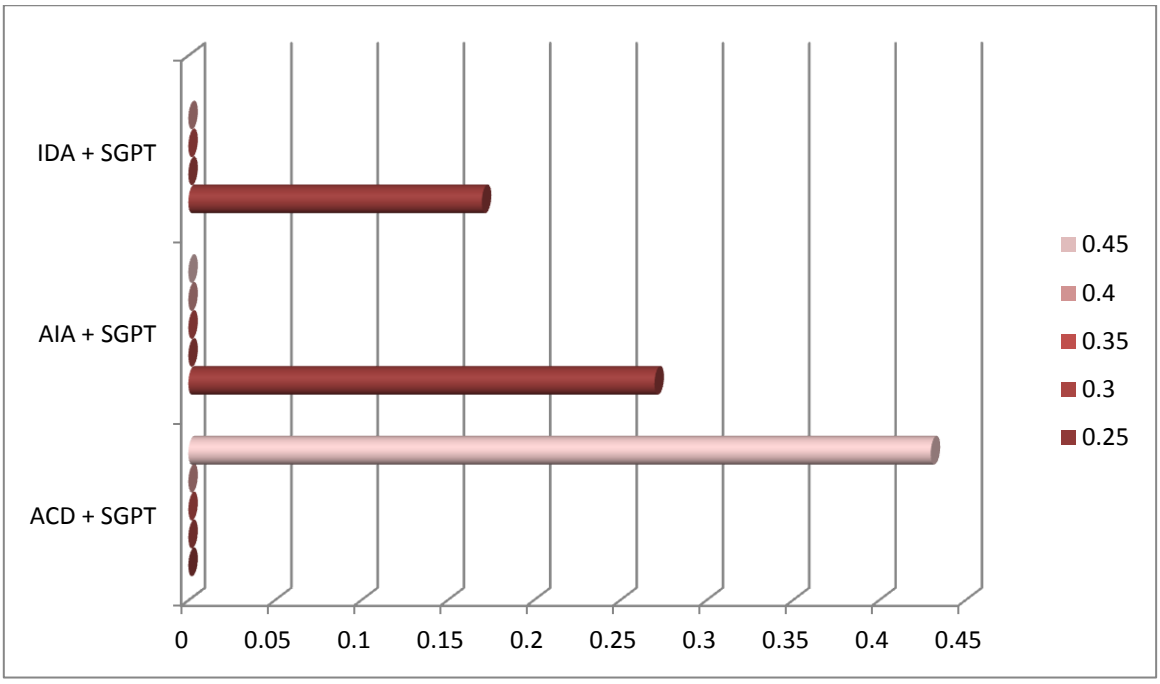


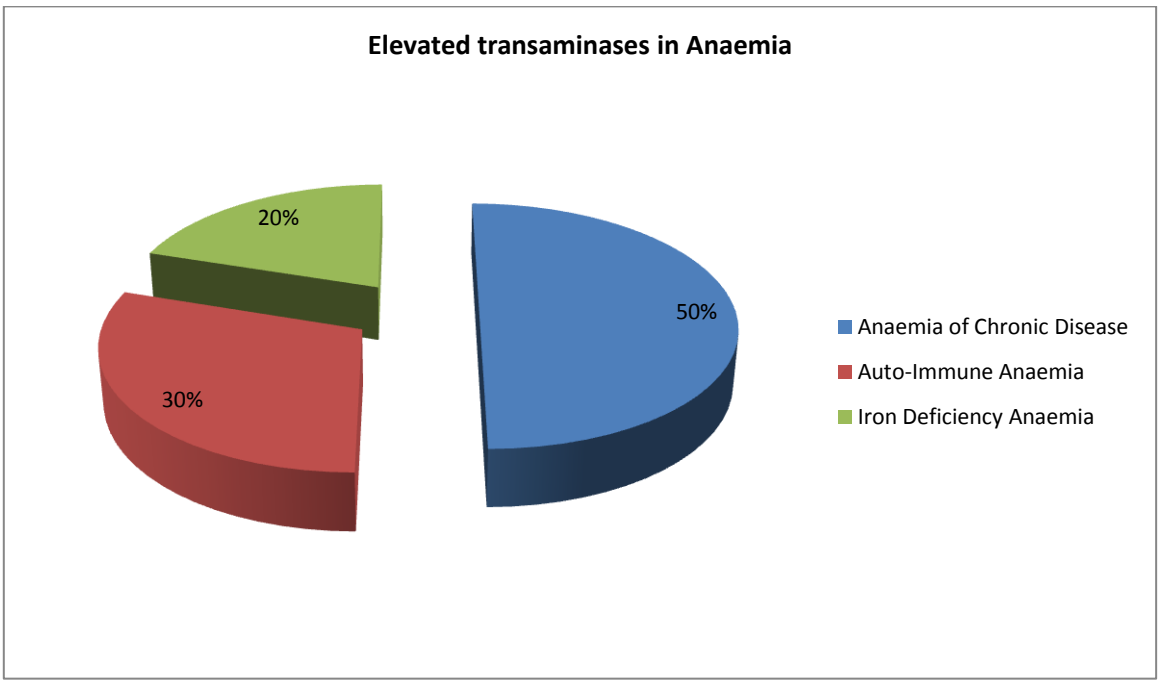
Sequential analysis of the improvement in Haemoglobin levels revealed a statistically significant improvement in all the three types of Anaemia.

Type	Haemoglobin					
Anaemia of Chronic Disease	Initial	12(n)	9.45 gm%	2.248 gm%	3.234	0.008
	Repeat	12(n)	11.19	1.609		
Iron Deficiency Disease	Initial	18(n)	7.86	1.866	5.37	0
	Repeat	18(n)	10.98	2.155		
Auto-Immune Anaemia	Initial	8(n)	7.69	2.142	3.1	0.017
	Repeat	8(n)	10.96	3.385		



Further analysis revealed an association between SGPT levels and anaemia of chronic disease but not with the other types of anaemia and none of these were found to be statistically significant.

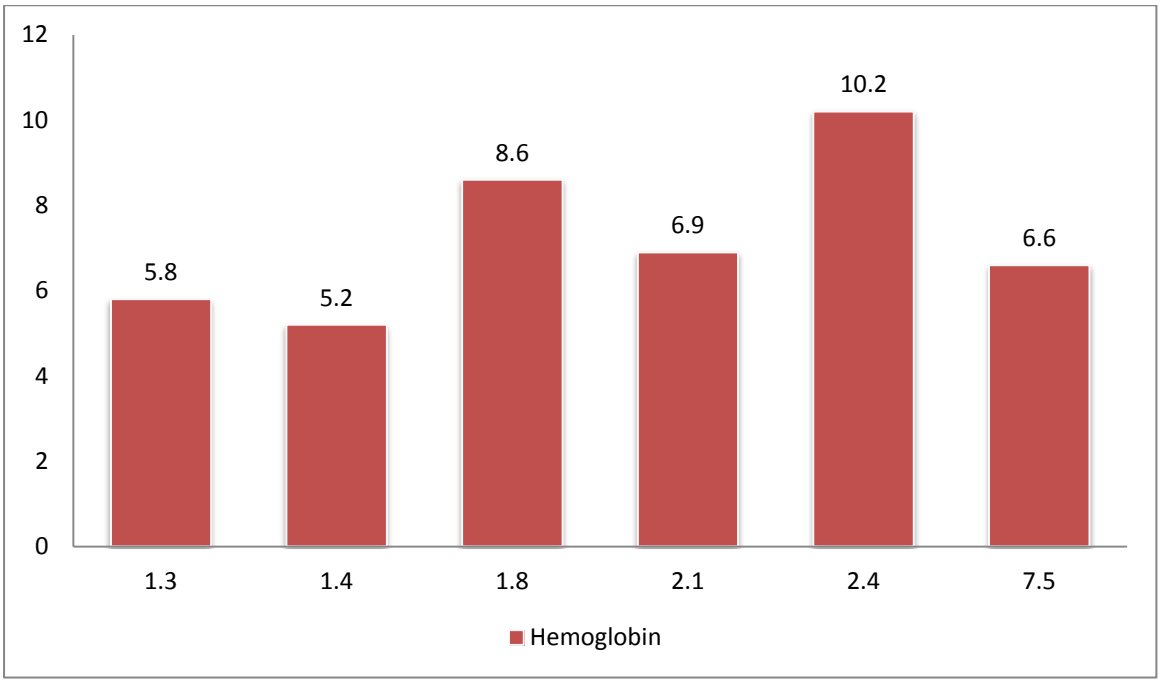




In our study group, 31.1% patients had leucopenia at first visit as compared to 17.8% at the follow-up visit. Similarly 8 of our patients had thrombocytopenia at first visit as compared to 2 at follow-up visit.

Parameter	**Frequency** (1^{st} visit)	**Frequency** (follow-up visit)
Leucopenia	14	8
Thrombocytopenia	8	2

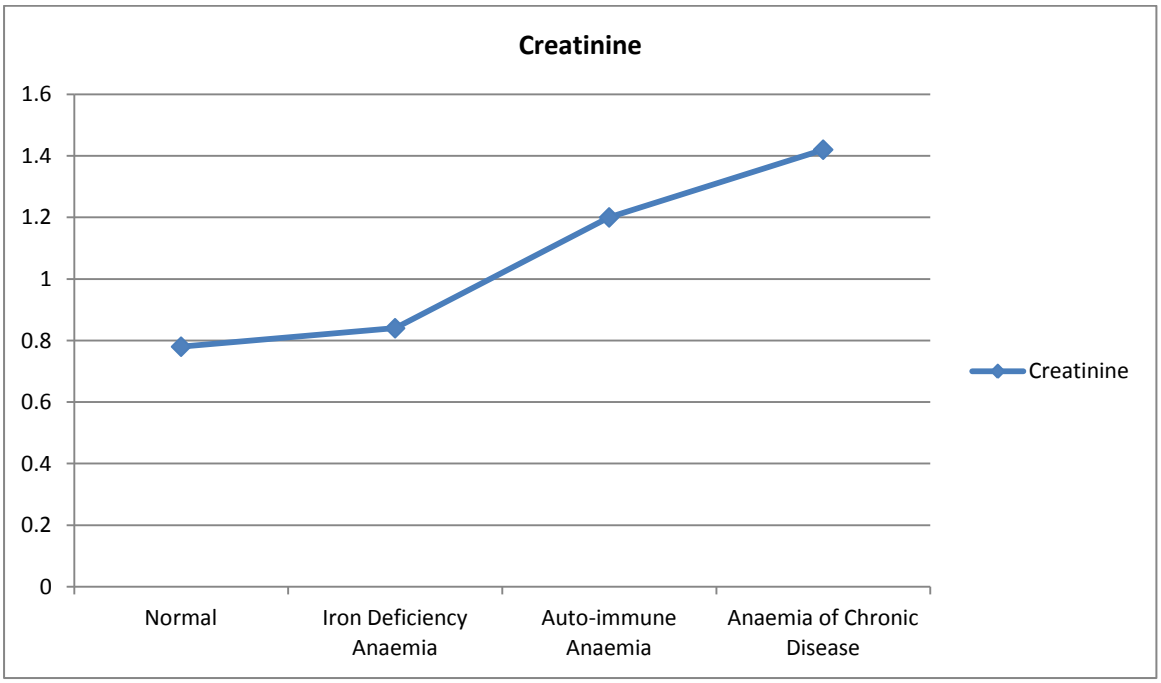
In our study, no significant correlation could be made out between absolute value of Haemoglobin and serum Creatinine.



Similarly, there was no significant correlation between type of anaemia and serum Creatinine.

Anaemia	N	Mean	SD	F	P value
Normal HB	7	0.743	0.2149	0.670	0.576
Anaemia of Chronic Disease	12	1.392	1.9528		
Iron Deficiency Anaemia	18	0.939	0.4161		
Auto-immune Anaemia	8	1.013	0.4794		
Total	45	1.042	1.0560		

Figure showing trend of creatinine with different types of Anaemia



Attempts were made to analyse associations between different subtypes of Anaemia and presence of Anti-ds DNA, RA Factor, APLA and arthritis and none of these associations were statistically significant.

Figure showing Anti-dsDNA presence with different types of Anaemia

Anaemia	Anti-ds DNA				Total	
	Absent		Present			
	N	%	N	%	N	%
Normal	4	25	3	10.3	7	15.6
Anaemia of Chronic Disease	4	25	8	27.6	12	26.7
Iron Deficiency Anaemia	5	31.3	13	44.8	18	40
Auto-immune Anaemia	3	18.8	5	17.2	8	17.8
Total	16	100	29	100	45	100

Figure showing RA Factor in different types of Anaemia

Anaemia	RA Factor				Total	
	Absent		Present			
	N	%	N	%	N	%
Normal	7	18.4	0	0	7	15.6
Anaemia of Chronic Disease	9	23.7	3	42.9	12	26.7
Iron Deficiency Anaemia	15	39.5	3	42.9	18	40
Auto-immune Anaemia	7	18.4	1	14.3	8	17.8
Total	38	100	7	100	45	100

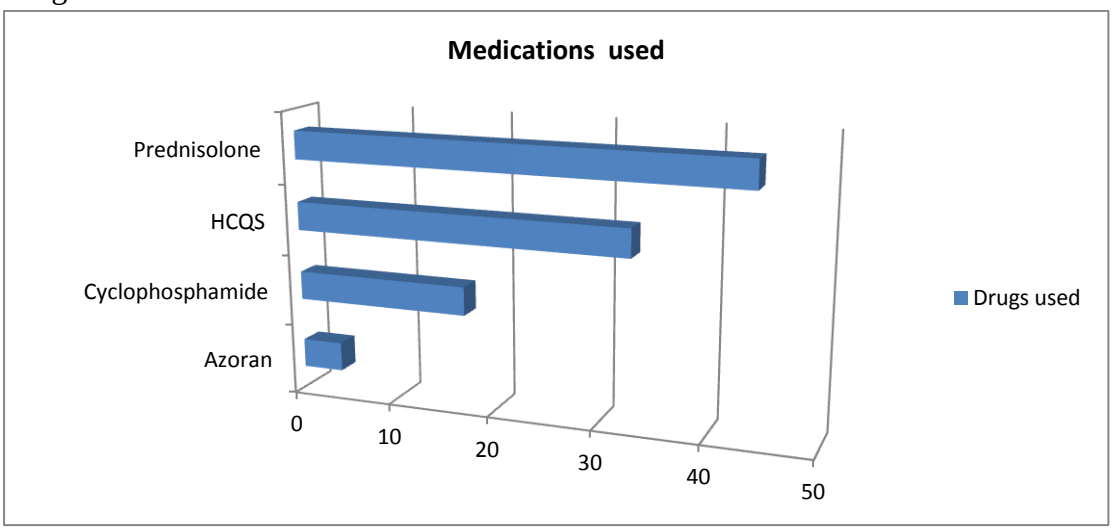
Figure showing APLA in different types of Anaemia

Anaemia	APLA				Total	
	Absent		Present			
	N	%	N	%	N	%
Normal	4	13.3	3	20	7	15.6
Anaemia of Chronic Disease	10	33.3	2	13.3	12	26.7
Iron Deficiency Anaemia	10	33.3	8	53.3	18	40
Auto-immune Anaemia	6	20	2	13.3	8	17.8
Total	30	100	15	100	45	100

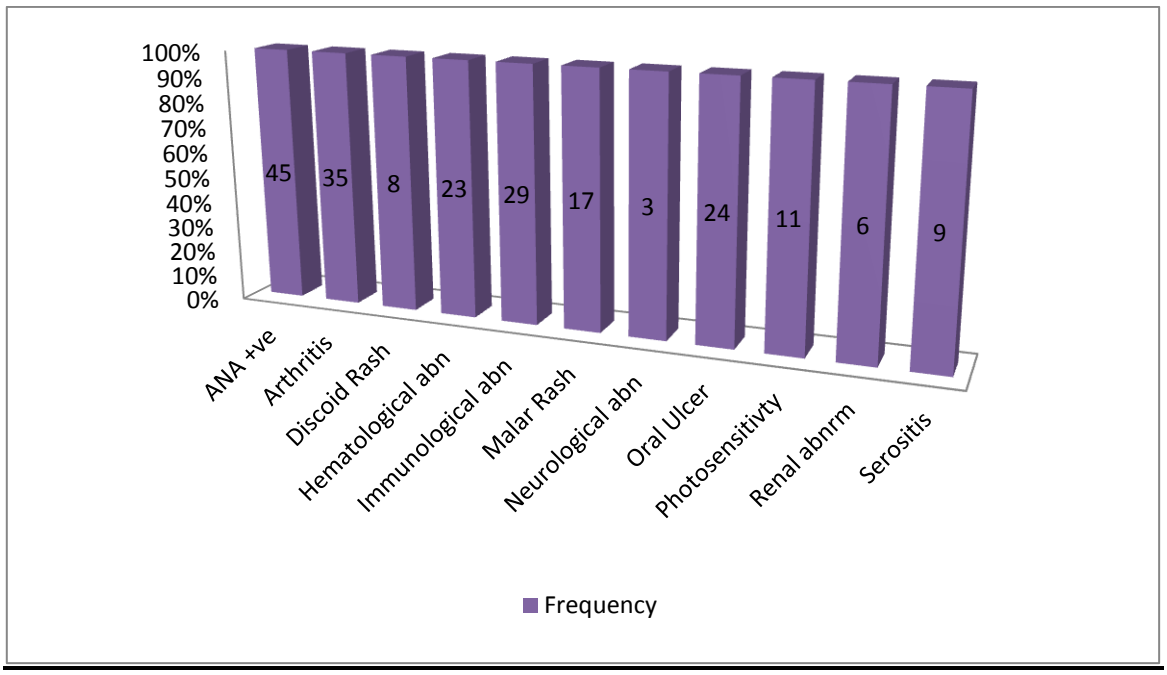
Figure showing Arthritis in different types of Anaemia

Anaemia	Arthritis				Total	
	Absent		Present			
	N	%	N	%	N	%
Normal	3	30	4	11.4	7	15.6
Anaemia of Chronic Disease	2	20	10	28.6	12	26.7
Iron Deficiency Anaemia	4	40	14	40.0	18	40
Auto-immune Anaemia	1	10	7	20.0	8	17.8
Total	10	100	35	100	45	100

Medications including immune-suppressants used were also analysed. 24 patients were on 2 drugs while 15 were on single medication.



The frequency of the various presentations needed for diagnosing SLE were also independently documented in our studies.



Discussion

Our study was a prospective study focussing on haematological problems in 45 patients diagnosed as SLE. Our study subjects were all female patients, similar to findings reported by Malaviyan[1] et al but contrary to the findings of Cameron S et al[2]. These unexpected and discordant findings could probably reflect a geographical variation or biased lack of suspicion in male patients.

Most of our patients were of child bearing age and this finding tallied with reports in studies by others. Malaviyan et al[1] reported a median age of onset of disease as 24.5 years. SLE is a disease with increased incidence in child bearing age[3].

77.8% of our patients had arthritis and athralgia as the pre-dominant clinical feature. Wallace et al[4] reported 92% incidence of arthritis and athralgia in their study group while Kumar A et al[5] reported 75% incidence of the same.

Oral ulcers were seen in 53.3% of our patients, as compared to 50% in studies by Malaviyan[1] et al and 36% by Wallace et al[4]. Our studies thus reported an incidence similar to other Indian studies but higher as compared to western studies, and this could probably be attributed to poor nutritional status.

Malar rash was documented in 37.7% and photosensitivity in 23% of our study group and were comparable to incidence described by Wallace et al in their studies[4].

Thus almost all the clinical features in our study group were similar to findings reported in other studies except for a higher incidence of Oral Ulcers.

ANA positivity was the commonest criterion satisfied in our study group. ANA is the most sensitive indicator of SLE and ANA negative Lupus is a rare clinical entity in our setting. ANA positivity is reported in about 90-95% cases of SLE[6].

Anti-ds DNA antibodies were seen in 64% of our study group and similar to findings reported by Paul BJ et al[7] and Madhavan et al[8]. Anti-ds DNA antibodies are specific for diagnosing SLE[9].

The most common haematological abnormality in our study was Anaemia with incidence of 84.4% and similar to reports by Paul BJ et al but much higher as compared to studies by Budman et al[10]. A co-existent Iron deficiency could probably account for this higher incidence in our study.

Iron deficiency anaemia, Anaemia of chronic diseases and Auto Immune Hemolytic Anaemia were the most common causes of Anaemia in our

study. 40% of our study group had Iron deficiency anaemia which was higher than the findings in study by Voulgardis et al[11]. Stool occult blood was positive in 55% of our patients and probably drug induced erosive gastritis coupled with poor nutritional intake and low dietary iron content lead to GI blood loss.

26.7% of our Anaemic patients had Anaemia of chronic disease and was comparable to the 37.1% incidence reported by Voulgardis et al[11].

Auto Immune Hemolytic Anaemia was seen in 17.8% of our cases and this finding was higher than that reported by Budman et al[10] (10%) but comparable to findings of Miguel C et al[12]. AIHA was diagnosed on the basis of a positive DCT and reticulocytosis. However, further evaluation with Transferrin saturation, Serum Folate and Vitamin B12 levels couldn't be done in our studies due to financial constraints.

A significant co-relation between Anaemia and Lupus Nephritis was found in our study. Varying grades of lupus nephritis was seen in around 66% of our cases. Review of prior literature have also corroborated this association and it is now well recognised that anaemia and coexistent Lupus Nephritis has a dismal prognosis[2,13]. In our study the only mortality was that of a patient with serum creatinine of 7.5 and hence, with a single case of mortality, it was not possible to demonstrate a definite correlation.

42.2% of our patients had lymphopenia as compared to 20% reported by Malaviyan et al[1] and 7.5% by Madhavan et al[8]. This could be probably due to the wide spectrum in disease severity in the different studies. 31% of our patients had leucopenia. No significant association was observed between leucopenia and any other major system involvement.

20% of our patients had thrombocytopenia and 2 of these had severe (< 20,000/mm^2) thrombocytopenia. Budman et al[10] reported 14-26% incidence of thrombocytopenia. Bleeding manifestations attributable to the low platelet counts were not seen in our studies and neither in the other studies.

Studies by Scofield et al[14] and Sultan et al[15] revealed a significant association between thrombocytopenia and major system involvement (Renal, serositis and Neurological) but couldn't be demonstrated in our study and might be due to the very small sample size.

Eleven of our patients had APLA positivity and 7 of these gave history of abortions but this association was not statistically significant. Levin S et al[15] reported lupus anticoagulant in 34% of their cases. It is documented that upto 70% of patients with SLE might develop APLA positivity on prolonged (>20 years) follow-up and the short follow-up interval in our study might account for our discordant findings.

Our study group showed a good response of musculo-skeletal and skin manifestations to low dose steroids and hydroxyl-chloroquine. Patients with major manifestations were offered intensive modalities of treatment (high dose steroids, cyclophosphamide and azathioprine). Blood transfusion was needed in only 3 cases. Despite the high incidence of Anaemia, most of our study group subjects responded to targeted treatment modalities. Cyclophosphamide was given to 2 of the 6 cases with AIHA and co-existent major organ involvement while the rest were given high dose steroids. Iron therapy was given to patients with Iron deficiency Anaemia.

Most of our patients had over-all improvement on follow-up. There was a statistically significant improvement in haemoglobin levels, irrespective of the aetiology. However, this improvement was not seen with lymphopenia, neutropenia or thrombocytopenia. Steroids were the main-stay of treatment and as expected, steroid associated side-effects like infections and GI blood loss were frequent. These were comparable to findings in a similar study by Nossent et al[16].

Conclusions

1) All the 45 patients in our study group were females and most belonged to the 20-30 years age group.

2) Arthritis and athralgia was the most common presenting feature and a high incidence of oral ulcers was noted.
3) Anaemia was the most common haematological abnormality noted, with Iron deficiency anaemia being the most frequent type, followed by Anaemia of chronic diseases and auto immune haemolytic anaemia.
4) 91% of our study group had some type of haematological abnormality and this included anaemia, leukopenia, lymphopenia and thrombocytopenia.
5) GI loss was the most common cause if Iron deficiency Anaemia.
6) Anaemia was associated with some or the other grades of Lupus Nephritis but this was not statistically significant.
7) Aetiology appropriate treatment showed a statistically significant improvement in haemoglobin across all the sub-types of Anaemia.

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