"RENAL DYSFUNCTION IN CHILDREN WITH TRANSFUSION DEPENDENT BETA-THALASSEMIA MAJOR-A ONE YEAR HOSPITAL BASED CROSS SECTIONAL OBSERVATIONAL STUDY"

By

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Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"RENAL DYSFUNCTION IN CHILDREN WITH TRANSFUSION DEPENDENT β THALASSEMIA MAJOR – A CROSS SECTIONAL OBSERVATIONAL STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

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LIST OF ABBREVIATIONS USED

β	-	Beta
/cumm	-	Per cubic millimetre
ACE	-	Angiotensin-converting enzyme
AEs	-	Adverse events
ANOVA	-	Analysis of variance
ARMS	-	Amplification refractory mutation system
BT	-	Blood transfusion
BMT	-	Bone marrow transplant
BTM	-	B thalassemia major
CBC	-	Complete blood count
CI	-	Confidence interval
CNS	-	Central nervous system
CVS	-	Cardiovascular system
DC	-	Differential count
DFX	-	Deferasirox
DNA	-	Deoxyribonucleic acid
EPO	-	Erythropoietin
FDA	-	Food and drugs administration
fl	-	Femto litre
g/dl	-	Grams per decilitre
gm%	-	gram percent
Hb	-	Haemoglobin
HbA	-	Haemoglobin A
HbA2	-	Haemoglobin A2
HbC/ β	-	Haemoglobin C/beta
HЬD	-	Haemoglobin D

HЬE	-	Haemoglobin E
HbE/ β	-	Haemoglobin E /beta
HЬF	-	Fetal hemoglobin
HbS/ β	-	Haemoglobin S/beta
HBsAg	-	Surface antigen for hepatitis B virus
HCV	-	Hepatitis C virus
HIV	-	Human immunodeficiency virus
HLA	-	Human leukocyte antigen
HPLC	-	High performance liquid chromatography
hr	-	Hour
HSCT	-	Hematopoietic stem-cell transplantation
HU	-	Hydroxyurea
i.e.,	-	That is,
Jak2	-	Janus kinase 2
Kg/m^2	-	Kilograms per square meter
LCR	-	Locus control region
LDH	-	Lactate dehydrogenase
MCH	-	Mean Corpuscular Hemoglobin
MCHC	-	Mean corpuscular haemoglobin concentration
MCV	-	Mean corpuscular volume
mg/kg	-	Milligrams per kilogram
min	-	Minute
ml/kg	-	Milli litre per Kilogram
ml/kg/day	-	Milli litre per kilogram per day
mm	-	Milli meters
mo	-	Month
mRNA	-	Messenger ribonucleic acid

n	-	Total number
ng/ml	-	Nanograms per milli litre
NIH	-	National institute of health
NTDT	-	Non transfusion dependent thalassemia
p	-	Probability value
PC	-	Platelet count
PCR	-	Polymerase chain reaction
pg.	-	Pico gram
PRC	-	Packed red blood cell
RBC	-	Red blood cells
RCT	-	Randomized clinical trial
RCTs	-	Randomized controlled trials
RDW	-	Red cell distribution width
RS	-	Respiratory system
SD	-	Standard deviation
SEM	-	Standard error mean
TM	-	Thalassemia major
TI	-	Thalassemia intermedia
vs.	-	Versus
WBC	-	White blood cell
α2	-	Alpha 2

ABSTRACT

Renal Dysfunction in children with Transfusion Dependent Beta-Thalassemia Major- A One Year Hospital Based Cross Sectional Observational Study.

Dr Nithya Reddy Nelvoy1, Dr Sujata M Jali2

Objectives

To evaluate for the renal dysfunction in children with transfusion dependent beta-thalassemia major and co-relation between ferritin levels and renal dysfucntion

Methods

This is a hospital based Cross Sectional Observational Study done between January 2019 to December 2019 which enrolled 40 children up to age of 18 years who were diagnosed with Beta Thalassemia Major and are on oral iron chelators for more than and equal to 6 years, registered in our Thalassemia Day Care. Sociodemographic and clinical data was collected. Outcome was assessed using lab parameters like ferritin, urea, creatinine, Beta 2 Microglobulin and also eGFR was calculated using Modified Schwartz Formula.

Results

Mean age was 13.20±2.95 years, male to female ratio 1.8:1. Majority of the patients had 8 years duration of thalassemia. All the 40 patients were on deferasirox and 15 were on combination therapy. Among this 19 patients had renal dysfunction (any of them with abnormal urea or creatinine or beta 2 microglobulin or eGFR). More the ferritin levels higher were the chances of renal dysfunction

Mean Z-scores of 42 patients was -1.15 + 1.49 S.D. The prevalence of low BMD was seen in 61.9% children. Mean Z-score significantly improved after 6 months of treatment (-2.18 + 0.83 S.D to -1.72 + 0.6, p value <0.0001). Low BMD

was statistically significant with longer duration of disease(r = -0.5843, p value < 0.0001), short stature, low BMI and high ferritin levels.

Conclusion

Renal dysfunction was seen in 47.5 % of the patients who were diagnosed with Beta Thalassemia Major and were on iron chelation therapy. More the duration of the disease and duration iron chelators more was the renal dysfunction. Regular monitoring of the biochemical parameters to be done and based on the values, the dose of iron chelators to be adjusted.

Keywords: Beta Thalassemia Major, Renal dysfunction, Iron chelators, Beta 2 Microglobulin, eGFR.

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INTRODUCTION

"Thalassemia is a group of blood disorders, the most common inherited hemoglobinopathies characterized by partly or entirely decreased synthesis of regular globin chains and ineffective erythropoiesis (1). They have an autosomal recessive inheritance and are most typical single gene disorders globally, more prevalent in the Mediterranean, Indian Sub-continent, Southeast Asia and Africa (1). Based on the involvement of globin chains, Thalassemia is classified as alpha and beta-thalassemia.

Thalassemia is a heterogenous disorder with varied phenotypes, ethnicities accounts for the global public health problem(2). It is estimated that around 3,00,000-4,00,000 children are born in the world with some hemoglobin disorder every year, out of which around 1,00,000 children with thalassemia are contributed by India(3). Thalassemia is more commonly seen in low and middle income countries. Worldwide 56,000 conceptions are having thalassemia disorder, out of which 30,000 have Thalassemia major(4). Northern India is having high carrier rate of about 3-15% when compared to Southern India which is 1-3%(3).

Thalassemia is more commonly seen in low and middle income countries. It is estimated that the cost for the repeated travel for the hospital admission, supportive care and the medications for the management in thalassemia major cost around 1,00,000 to 2,50,000 lakhs/ year in India (5)

β-thalassemia's are characterized by partly or completely beta globin chains suppression and excessive production of alpha globin chain. β-thalassemia's are more common than α-thalassemia's. Based on the extent of production of globin chains, manifestations range from mild anemia to transfusion dependance.

The age of presentation in β-thalassemia major will be usually between 6-24 months with Hepato-splenomegaly, mild jaundice and severe microcytic anemia. Regular bloodtransfusions and chelating agents are the mainstay treatment in thalassemia major, which will increase the life expectancy of the patient.

The age of presentation in beta thalssemia major will be usually between 6-24 months with repeated episodes of fever, Hepato-splenomegaly, mild jaundice and severe microcytic anemia. Regular blood transfusions and the chelating agents was the main stay of treatment in thalassemia major, which will increase the expectancy of the patient.

In recent years, since the blood transfusions facility has increased especially in patients with transfusion-dependent thalassemia major, the life expectancy of the patients has increased. However the associated iron overload leads to significant complications. The major one being the iron overload in multiple organs. The source of iron is from the GI Tract absorption, iron from the ineffective erythropoiesis, iron form the repeated blood transfusions. Out of all the organs the iron deposition in kidney and the further effects are least known. The iron chelators which are used to prevent the iron overload also are nephrotoxic.

As per Kidney Disease Improving Global Outcomes (KDIGO), “CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.” Even in the patients who are well treated the prevalence of renal dysfunction is 40-50%. Etiology of renal dysfunction is multifactorial i.e both disease per se and adverse effects of the drugs.

Renal dysfunction can be diagnosed by the Renal function tests, excretion levels of the electrolytes. The measurement is easy and also cost effective. The

upcoming investigations like β 2 microglobulin, cystatin C, N-acetyl-beta-d-Glucosaminidase (NAG). They have higher advantage because of high sensitivity and specificity of the test. Because of its high cost, limited availability, and lack of expert interpretation, it is inconvenient for mass screening, especially in underdeveloped countries like India(6). Increased levels of ferritin are also known to cause renal dysfunction, thus levels of ferritin are also important.

Main stay of management of renal dysfunction is prevention which can be achieved by the treatment of iron overload with chelating agents, avoid using of the drugs known to cause renal dysfunction. Desferoxamine, Deferiprone, and Deferasirox are the three iron chelators that are currently in use. To prevent iron overload complications, it is used as a monotherapy or in combination. Parenteral desferoxamine has previously been used successfully in combination with the oral iron chelators deferiprone or deferasirox, but at the expense of repeated painful injections and poor compliance.

Combined chelation results in a constant presence of chelating agent in the patient's circulation, preventing free Labile Plasma Iron (LPI) entry into cells and thus protecting from reactive oxygen species that are mostly responsible for organ damage, resulting in better & enhanced chelation and a decrease in total body iron as measured by Serum Ferritin (SF) levels at regular intervals(9).

There are very few studies regarding the prevalence of renal dysfunction in transfusion depenedent thalassemia children in India. Thus this study aimed to investigate the presence of renal dysfunction in children and young adults with beta thalassemia major, using both common and advanced indexes and to correlate possible findings to iron chelation therapy and is likely the first of its kind.

OBJECTIVES

The objectives of this study were:

PRIMARY:

To evaluate for the renal dysfunction in children with transfusion dependent beta-thalassemia major

SECONDARY:

1) To look for the incidence of renal dysfunction in children with transfusion dependent beta-thalassemia major

2) Relation between the levels of serum ferritin and renal dysfunction

REVIEW OF LITERATURE

Thalassemia is a type of hemolytic anaemia which is inherited disorders of globin chains. Thalassemia is a heterogeneous group of single-gene disorders more common in parts of the world, like Mediterranean, Indian Sub-continent, Southeast Asia and Africa(1). This disorder is also known as Mediterranean anemia because thalassemia is even more prevalent in Mediterranean region.

β-Thalassemia :

β thalassemia is a global health problem inherited in the mendelian fashion autosomal recessive inheritance. According to the World Health Organization it is the most common inherited genetic disorder. 95 % of the thalassemia births worldwide were from Middle Eastern, Asian and Indian regions(2). Thalassemia is commonly seen in people of African descent. The highest incidences are reported in Cyprus (14%), Sardinia (12%) and South-East Asia(3). In India the disease is higher in Sindhis, Punjabis, Khatris, Gujaratis, Mahars, Lohanas. It is higher among muslims and Christian communities.

HISTORICAL

In the 20th century beginning, European physicians noticed an anaemia syndrome in Italian children with severe anaemia. They also noticed enlargement of spleen in infancy along with poor growth and early death. The first clinical description of thalassemia is given by Detroit paediatricians Thomas B.Cooley and Pearl Lee. Cooley and Lee had described four Italian children with anaemia, discolouration of the skin, sclera enlargement of spleen and liver. Red blood cells of these children have increased resistance to hypotonic solutions and the peripheral blood smear showed moderate leukocytosis with nucleated erythrocytes. They used to have hemolytic facies with prominent cranial and facial bones.

Previously chronic childhood anaemias were named under a group called as Von Jaksch's anaemia, later it was separated by Cooley and Lee and named it as "Erythroblastic anaemia or Cooley's anaemia.

The term 'thalassemia' was coined by Whipple and Bradford in 1932, which was taken from the Greek word 'Thalassa' meaning 'black sea', and 'mia' meaning 'blood'. Based on the severity, Valentine and Neel classified the milder forms of Cooley's anaemia as 'Thalassemia minor' and the more severe entity as 'Thalassemia major'. In 1925, it was described that the disease was running in the families by Rietti and told to be familial condition. In 1936, Lehndorff first proposed that the condition is also inherited.

Mukerjee reported the first case of beta-thalassemia from India in 1938 from Calcutta. In 1935, Sheldon described the severe pathologic sequelae associated with iron overload.

Wolman in 1964 was the first to suggest that chronic blood transfusion may be able to prevent many of the problems of the disease. Lesky, et al and Model, et al. in 1974 were able to initiate clinical trials with desferrioxamine, an iron chelator, in an attempt to promote the excretion of large percentage of transfusional iron overload. Deferiprone an oral iron chelator was discovered in 1981. In 1982 Dr E Donald Thomas performed the first bone marrow transplantation on a thalassemic patient. The first bone marrow transplantation in India was successfully done by Dr M. Chandy at Christian Medical College, Vellore.

Historical landmarks in the field of hemoglobin and thalassemia.

Year	Landmark	Author
1628	Circulation of the blood	Harvey
1862	Oxygen binding pigment is named 'hemoglobin'	Hoppe – Seyler
1866	Fetal blood is alkali-resistant	Korber
1913	Structure of haem	Kuster
1925-1927	Molecular weight of hemoglobin	Adair, Svedberg
1925	Description of 'thalassemia'	Cooley, Lee
1932	Term 'thalassemia' first used	Whipple & Bradford
1937-1944	Inheritance of thalassemia	Caminopetros,Neel, Valentine, Silvestroni
1938	First case of thalassemia	Dr.Mukherjee
1944-1946	Sickle-cell thalassemia	Silvestroni, Bianco
1948	Alkali-resistant hemoglobin in thalassemia	Vecchio
1949	Malaria hypothesis	Haldane
1955	HbA2 raised in some thalassemia	Kunkel & Wallenuis
1957	Ineffective erythropoiesis in thalassemia	Sturgeon & Finch
1958	Adult hemoglobin controlled by two gene Loci	Smith & Torbert
1959	Three – dimensional structure of hemoglobin	Perutz
1959	α andβ thalassemia hypothesis	Ingram and Stretton
1960-1963	Structure of α, β, γ and δ chains	Konigsberg et al, Schroeder et al., Jones et al, Braunitzer et al., Hill et al
1962	Chelation therapy – Desferrioxamine	Sephton – Smith
1964	High level transfusion for thalassemia	Waldman
1965	Imbalanced globin synthesis in α andβ Thalassemia	Weatherall, Clegg
1966	Consequences of globin imbalance	Nathan, Gunn
1970	Genetics of α thalassemia	Na-Nakron and Wasi
1973	Dominantly inherited β thalassemia	Weatherall et al

1974	Liver iron level controlled by Desferrioxamine	Barry et al
1979	Restriction – fragment length polymorphism for prenatal diagnosis	Kan and Dozy
1979	Stop – codon mutation in β globin mRNA	Chang and Kan
1979	β Thalassemia due to gene deletion	Orkin et al
1980-1981	Globin genes sequenced	Lawn et al., Spritz et al., Barralle et al
1981	Mutations in β thalassemia cloned in DNA	Spritz et al., Westaway and Williamson.

DEFINITION:

"β thalassemia is a group of hereditary blood disorders characterized by reduced or absent β globin chain synthesis, resulting in reduced haemoglobin in red blood cells, decreased RBC production and anaemia." They are inherited in the autosomal recessive pattern.

Annual births with major haemoglobin disorders

b-thalassemia major	22,989
HbE b thalassemia	19,128
HbH disease	9568
Hb Bart's hydrops (a0/a0)	5183
SS disease	217,331
SC disease	54,736
S b thalassemia	11,074

β thalassemia can be classified into:

B THALASSEMIA
Thalassemia major
Thalassemia intermedia
Thalassemia minor
β thalassemia with associated Hemoglobin anomalies HbC/ β thalassemia HbE/ β thalassemia HbS/ β thalassemia
• Hereditary persistence of fetal hemoglobin and β thalassemia
• Autosomal dominant β thalassemia
• β thalassemia associated with other manifestations
o β thalassemia-trichothiodystrophy
o X-linked thrombocytopenia with thalassemia.

The phenotypes of homozygous or genetic heterozygous compound β-thalassemia's include Thalassemia major and Thalassemia intermedia. Patients with thalassemia major manifest by 2 years of life and needs blood transfusions regularly for their survival. Thalassemia intermedia manifests in late ages and does not require regular blood transfusions. Heterozygous β-thalassemia manifests in clinically silent carrier state, except in the rare dominant forms. HbC/ β-thalassemia and HbE/β thalassemia manifests in a wide range of spectrum and phenotypes of severity.

Epidemiology

β-thalassemia is a global health problem and the commonest hemoglobinopathies. Mutations, base substitutions or insertion of nucleotides in β-globin genes will cause β-thalassemia. β-thalassemia is more common in certain geographical areas/populations because mutations are relatively population specific.

WORLD WIDE DISTRIBUTION OF THALASSEMIA

The incidence of symptomatic β thalassemia major individuals throughout the world is estimated as 1 in 100,000. As per Thalassemia International Federation (TIF,) throughout the world, only 2,00,000 β-thalassemia patients are present and taking treatment on registration regularly. HbE/β thalassemia is the most common combination of β thalassemia with abnormal haemoglobin or structural haemoglobin variant and has a high prevalence in Southeast Asia, with a carrier frequency of 50%.

Due to the migration of people, Thalassemia is now present in almost all the nations of the world and intermarriage between varied ethnic groups. 1.5% of the global population has a carrier state for β-thalassemia. Secondary to migration of population between different regions, marriage between different ethnic groups, races, thalassemia is prevalent in almost every country. In India, the overall beta-thalassemia carrier rate is estimated to be 4.05% and incidence of β-thalassemia homozygotes births to be 11,316 per year.

Table 1. Common types of β thalassaemia, their severity and ethnic distribution

Population	B-geneMutation	HGVS nomenclature	Severity
Indian	-619del	NG_000007.3:g.71609_72227del619	β^0
Mediterranean	-101	HBB:c.-151C>T	β^{++}
Black	-88	HBB:c.-138C>T	β^{++}
Mediterranean, African	-87	HBB:c.-137C>T HBB:c.-137C>G HBB:c.-137C>A	β^{++}
Japanese	-31	HBB:c.-81A>G	β^{++}
African	-29	HBB:c.-79A>G	β^{++}
Southeast Asian	-28	HBB:c.-78A>G	β^{++}
Black	-26	HBB:c.-76A>C	β^{++}
Mediterranean	codon 5	HBB:c.17_18delCT	β^0
Mediterranean, African-American	codon 6	HBB:c.20delA	β^0
Southeast Asian	Codon 17	HBB:c.52A>T	β^0
Mediterranean, Asian, Indian	IVS1-nt1	HBB:c.92+1G>A	β^0
Mediterranean, Asian, Indian	IVS1-nt5	HBB:c.92+5G>A	β^0
Mediterranean	IVS1-nt6	HBB:c.92+6T>C	$\beta^{0/+}$
Mediterranean	IVS1-nt110	HBB:c.93-21G>A	β^+
Southeast Asian	HbE	HBB:c.79G>T	β^{++}
Mediterranean	HbKnossos	HBB:c.82G>T	β^{++}
Mediterranean	codon 39	HBB:c.118C>T	β^0
Southeast Asian	codon 41/42	HBB:c.126_129delCTTT	β^0
Chinese	IVS2-nt654	HBB:c.316-197C>T	β^+
Mediterranean	IVS2-nt745	HBB:c.316-106C>G	β^+
African-American	AATAAA to AACAAA	HBB:c.*+110T>C	β^{++}
Mediterranean	AATAAA to AACGAA	HBB:c.*+111A>G	β^{++}

INDIA

β-thalassemia is the commonest single-gene haemoglobinopathy in Indian population. India comprises ten per cent of the total world thalassemia births every year. Grow K et al. The β – thalassemia carrier frequency varies from 3.0 to 17.0% In India(4).

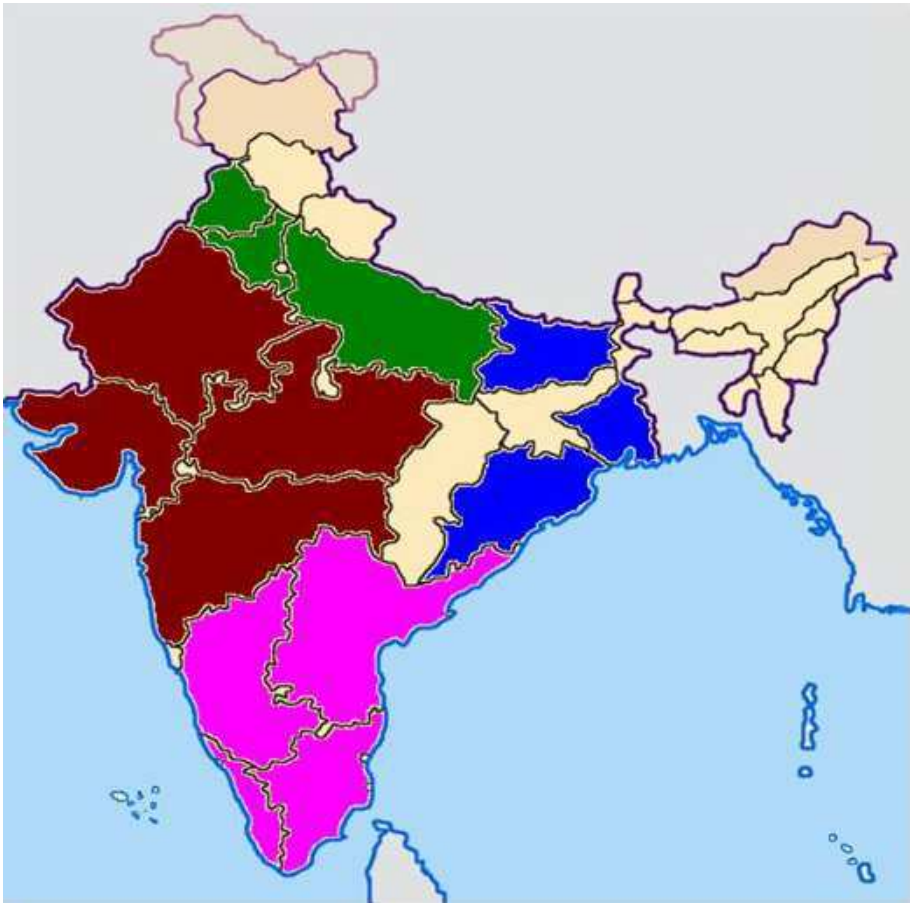


Figure 1. Map showing distribution of beta thalassemia in India

In India, as per WHO update on β-thalassemia, an overall carrier frequency of 3–4% was seen, which would render the carrier rate between 35.6 and 47.5 million nationwide. Prenatal diagnosis and detection of carrier status are required to decrease the mutant load in the gene pool.

In a non-Mediterranean region, the first case of Thalassemia was reported from India. Chouhan DM [1983] reported that beta-thalassaemia has been observed in different castes and communities like Gujaratis, Sindhis, Marathas, Khojas, Bori Muslims, Jains, Baniyas and Punjabis.

India is a multilingual country with different religions, which are further subdivided into different castes. Consanguineous marriage is commonly seen and accounts for an estimated 10.4% of world population, as they follow their specific

caste. Due to more consanguineous marriages and the lack of premarital checkup in India, it leads to many disorders. Thalassemia is one of them. In almost every community, thalassemia will be seen.

Hereditary Transmission

Beta thalassemia show autosomal recessive inheritance pattern. Affected child parents will be heterozygotes and contain a single copy of pathogenic gene mutation in the beta-globin chain. 25 % chances of children getting affected if parents are heterozygotes, 50% chances of asymptomatic carrier, & 25% chances of not getting affected & carrier.

Thalassemia syndromes are classified based on the blood transfusion requirement, clinical severity into

A) Transfusion Dependent Thalassemia's (TDTs)

B) Non-Transfusion Dependent Thalassemia's (NTDTs)

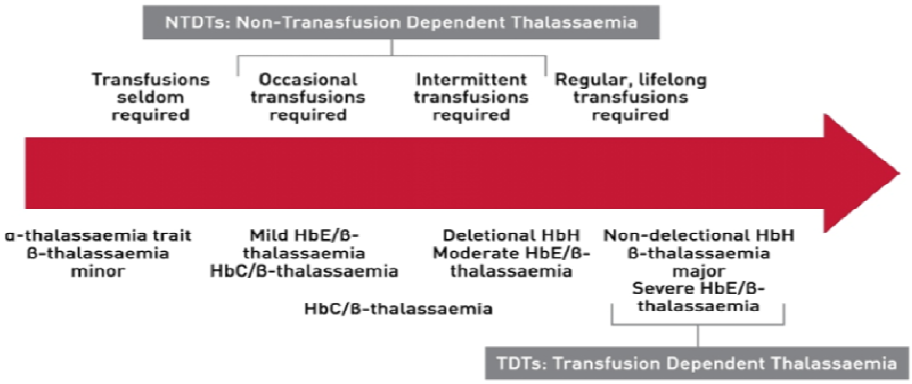


Figure 2. Phenotypic classification of thalassaemia syndromes based on clinical severity and transfusion requirement.

TDT's would be requiring regular blood transfusions, iron chelating agents to avoid iron overload. They will be presenting at an early age with increasing pallor, abdominal distension and respiratory distress.

Phenotypic heterogeneity

β-thalassemia is having three forms

1. Thalassaemia Major also called "Cooley's Anaemia" or "Mediterranean Anaemia"
2. "β-thalassaemia carrier - Thalassaemia Intermedia & Thalassaemia Minor"
3. β-thalassaemia trait / heterozygous β-thalassaemia

PATHOPHYSIOLOGY:

Basic defect present in β-thalassemia is decreased or lacking of β-globin chains production with relative excessive synthesis of α-chains.

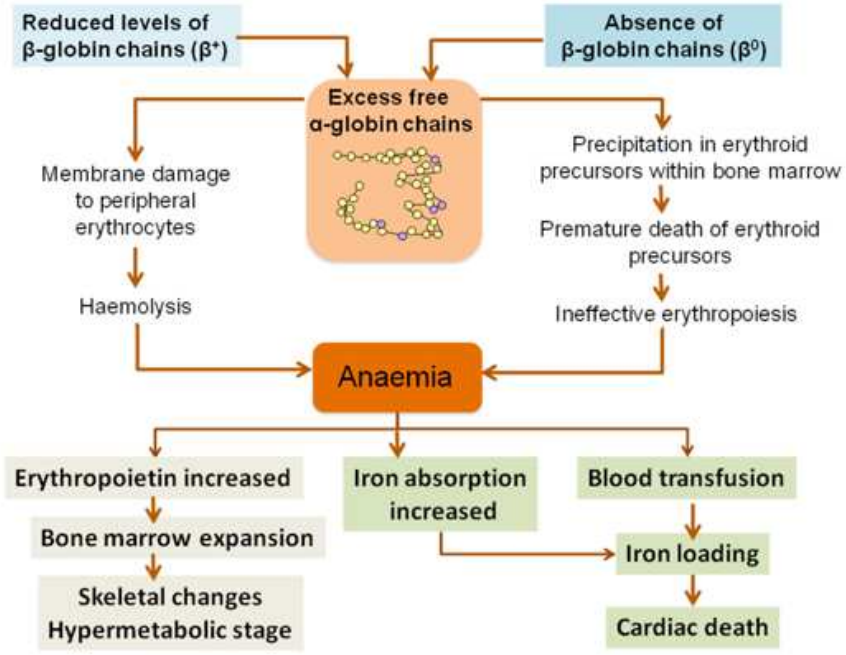


Figure 3. Figure showing pathogenesis of Thalassemia

Direct significant changes are

- Decrease in haemoglobin synthesis.
- globin chain synthesis imbalance.

Ø Decreased haemoglobin production causing reduction of mean cell haemoglobin and mean cell volume has a minor clinical significance.

Ø Increased levels of erythropoietin is the first response to anaemia and ineffective erythropoiesis, causing severe erythroid hyperplasia, skeletal deformities, osteoporosis and contributes to splenomegaly.

EVALUATION

Usual age of presentation of β-thalassemia major will be between 6-24 months characterized by

Family history

Beta thalassemia show autosomal recessive inheritance pattern. Affected child parents will be heterozygotes and contain a single copy of pathogenic gene mutation in the beta-globin chain. 25 % chances of children getting affected if parents are heterozygotes, 50% chances of asymptomatic carrier, & 25% chances of not getting affected & carrier.

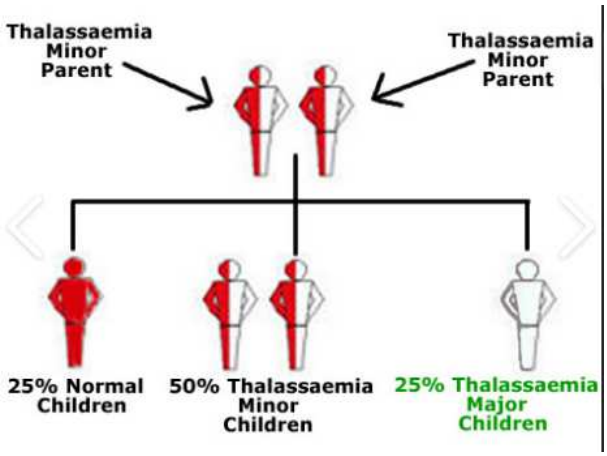


Figure 4. Showing pattern of inheritance if Thalassemia

Thus a detailed family history must be taken which includes

History of consanguinity

Any history of repeated blood transfusions in the family

Any history of deaths in the family due to thalassemia

Any history of splenectomy in the family

Clinical history

General features

Pallor

Fatigue

Dyspnoea on exertion

Poor appetite

Poor growth

Palpitations

Figure 5. showing Pallor

Features of hemolysis

Jaundice

Excessive erythropoiesis (in cases of improper treatment or unavailability of transfusion facilities)

Maxillary overgrowth (chipmunk facies)

Prominence of malar eminences

Depression of nasal bridge

Exposure of upper central teeth

Frontal bossing

Cortical thinning causing increased porosity

Delayed pneumatisation of sinuses

Hepatosplenomegaly

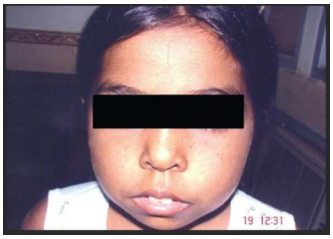


Figure 6. showing Malar prominence with dental malocclusion

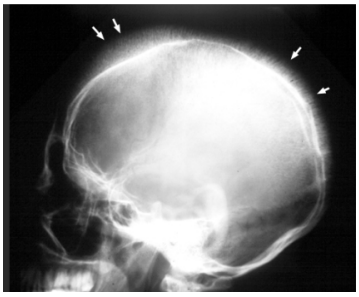


Figure 7. showing hair on end appearance of the skull

INVESTIGATIONS

Complete hemogram

β-Thalassemia major is considered by decreased Hemoglobin parameters (<7 g/dl). RBC indices have microcytic hypochromic anemia, MCV between > 50 < 70 Femto litre and MCH between > 12< 20 pg. WBC may be falsely raised due to the misinterpretation of nucleated RBC as WBC. Reticulocytois is present.

Peripheral blood smear

RBC will show moderate to severe anisocytosis, teardrop cells, microcytic hypochromic and nucleated RBC's. Degree of low haemoglobin levels will be correlated with the number of erythroblasts and will be more in number post-splenectomy. Few morphologic changes will be seen in RBC's for carriers than affected individuals. Erythroblasts are generally not seen.

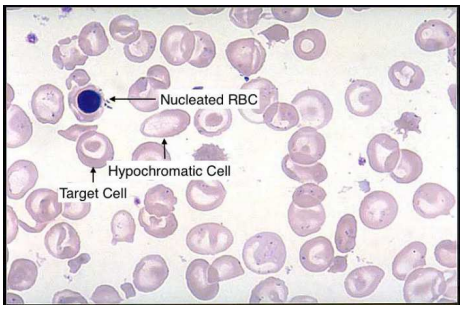


Figure 8. Peripheral Smear of patient with Thalassemia

HPLC/electrophoresis

HPLC electrophoresis is diagnostic, investigation of choice and advised both for the child and parents to look for transmission of the genes. β-thalassemia type will vary depending on the Hb pattern. HbA will be absent in ß0 thalassemia homozygotes and HbF institutes 92-95% of total Hb. HbA levels will be in between 10 - 30% and HbF in range of 70 - 90% In homozygotes of β-thalassemia and ß+/ ß0 genetic compounds. HmA2 varies in beta-thalassemia homozygotes and it is higher in beta-thalassemia minor.

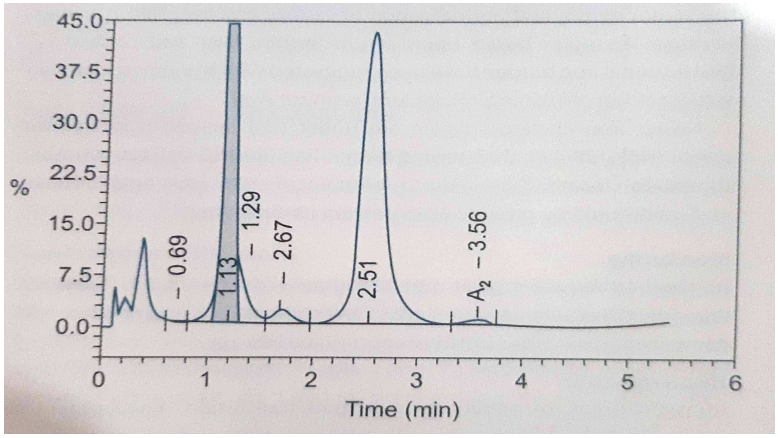


Figure 9. showing Hb Electrophoresis

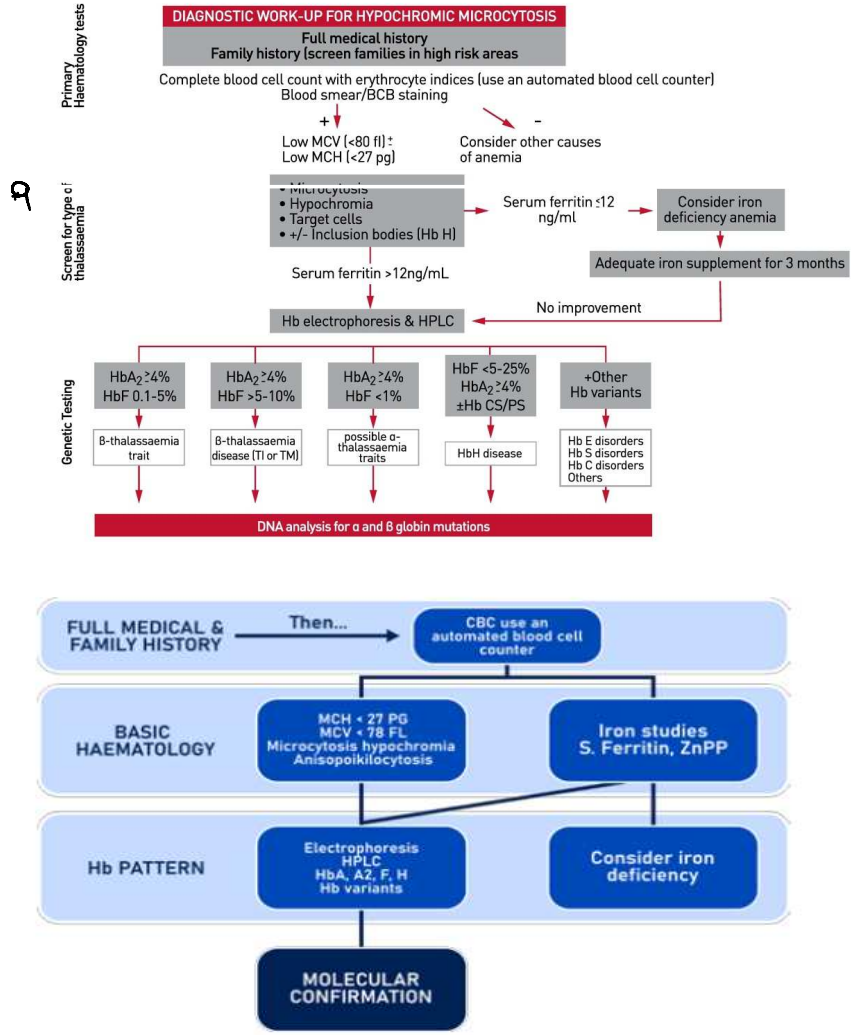


Figure 11. showing the approach for patient suspecting Thalassemia

Diagnosis of thalassemia in parents and antenatal screening

In the parents Hb electrophoresis is done and based on the levels of HbA1, HbA2, and HbF they can be diagnosed if they are carriers of thalassemia.

In the antenatal clinic the women with early pregnancy and the couples desiring for pre pregnancy testing undergo nestroff and red cell indices, if positive then the husband is also tested if he is negative, the attenders to be coucelled that there is no risk of thalassemia major in the children. But if he is positive then HbA2 to be tested, if it is greater than 3.5% and if the parents are known carriers and history of affected children should undergo DNA studies for mutations, if not identified then cordocentesis is done more than 18 weeks for globin chain synthesis in the blood, if 10-12 weeks CVS is done. If the foetus is normal or carrier then pregnancy is continued. If the child is affected then the pregnancy is terminated.

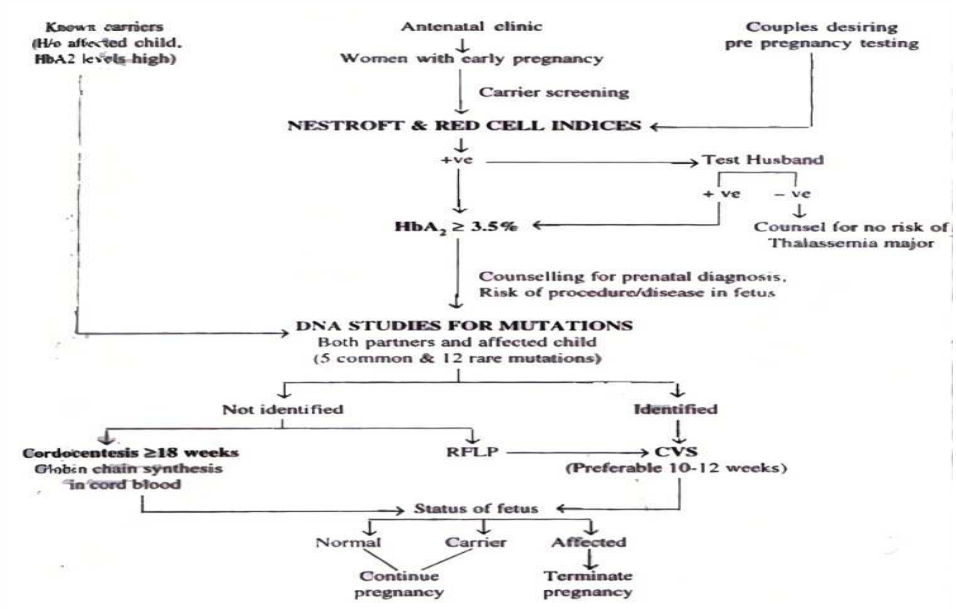
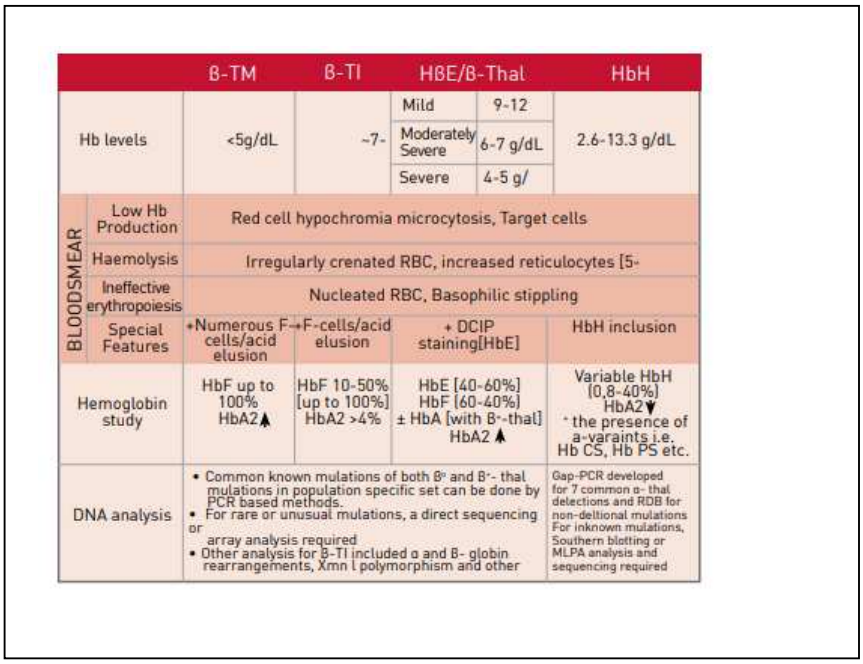


Figure 12. Approach to Suspected Thalassemia in Antenatal checkup



		β-TM	β-TI	HβE/β-Thal		HbH
Hb levels		<5g/dL	~7-	Mild	9-12	2.6-13.3 g/dL
				Moderately Severe	6-7 g/dL	
				Severe	4-5 g/	
BLOODSMEAR	Low Hb Production	Red cell hypochromia microcytosis, Target cells				
	Haemolysis	Irregularly crenated RBC, increased reticulocytes [5-				
	Ineffective erythropoiesis	Nucleated RBC, Basophilic stippling				
	Special Features	+Numerous F→F-cells/acid elusion		+ DCIP staining[HbE]		HbH inclusion
Hemoglobin study		HbF up to 100% HbA2↑	HbF 10-50% [up to 100%] HbA2 >4%	HbE [40-60%] HbF [60-40%] ± HbA [with β⁺-thal] HbA2 ↑		Variable HbH [0,8-40%] HbA2↓ * the presence of a-varaints i.e. Hb CS, Hb PS etc.
DNA analysis		• Common known mulations of both β⁰ and β⁺- thal mulations in population specific set can be done by PCR based methods. • For rare or unusual mulations, a direct sequencing or array analysis required • Other analysis for β-TI included α and β- globin rearrangements, Xmn I polymorphism and other				Gap-PCR developed for 7 common α- thal delections and RDB for non-deltional mulations For inknown mulations, Southern blotting or MLPA analysis and sequencing required

Figure 13: Summary showing diagnostic measures of thalassemia and hemoglobinopathies

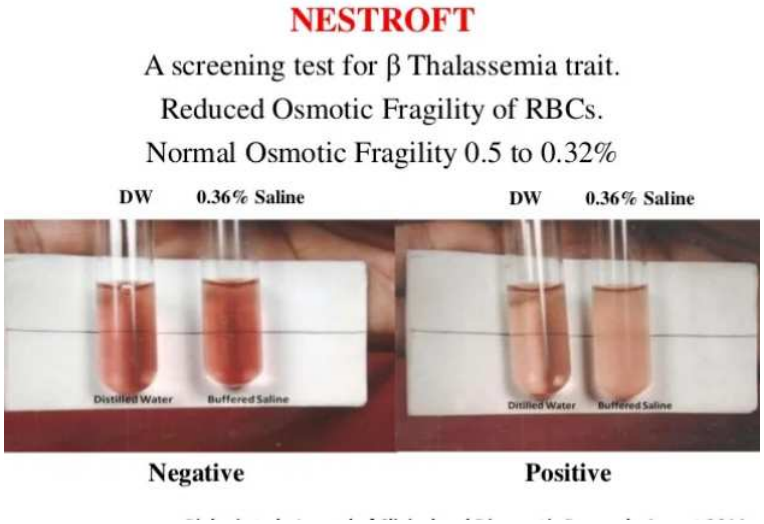


Figure 14 Nestroft test

TREATMENT:

Treatment of beta Thalassemia is lifelong. Main stay of therapy includes regular blood transfusion. If no regular transfusions and chelation therapy available, the majority of children could not survive until the age of 20- 23 years.

Pillars of Clinical Management of β-thalassemia:

1. Blood Transfusion
2. Iron Chelation
3. Multidisciplinary Care - mainly are
    a. Heart
    b. Liver
    c.Osteoporosis
    d. Endocrine
    e. Infection.
4. Supplements
    a. Vitamin B Complex
    b. Folic acid
    c. Calcium

Haemoglobin levels should be maintained at least 9 to 10 g per deciliter with regular transfusion therapy, which allows improved growth and development and also reduces hepatosplenomegaly, skeletal deformities.

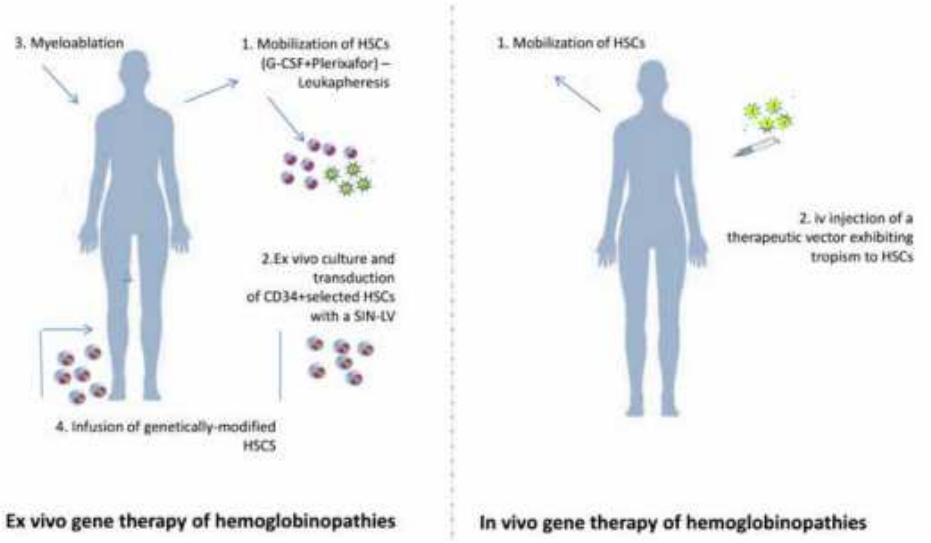


Figure 14. s

Therapy	Advantages	Disadvantages
Blood transfusion	• Suppresses ineffective erythropoiesis, thus limiting downstream pathophysiological complications • Regular transfusion plus iron chelation therapy is associated with improved long-term survival in TDT • Role in ameliorating certain morbidities in observational studies with NTDT	• Lifelong transfusions required every 2-5 weeks in TDT • Risks of blood-borne infection, alloimmunization, and iron overload
Iron chelation	• Long-term use improves liver and myocardial iron levels and function, and improves endocrine function in TDT • Can reduce systemic and hepatic iron burden in NTDT • Oral formulations now available	• Not effective for all patients • Frequent side effects that require regular monitoring • Demanding regimen of parenteral formulation • Poor adherence among some patients • High cost
Hydroxyurea	• May improve haematological outcomes in specific NTDT populations • Low cost	• Lack of robust evidence of benefit
Splenectomy	• May improve growth, QoL, and haemoglobin concentration, thus avoiding transfusions for some patients	• Risk of sepsis • Increasing awareness of other risks from NTDT studies, including venous thrombosis and other vascular manifestations • May reduce ability to scavenge toxic free iron species, as evident from NTDT studies
HSCT	• Potentially curative for patients with TDT • 90% survival rate in patients; disease-free survival rates > 80% in TDT • Improves HRQoL of children with severe disease • Long-term cost-effectiveness	• Appropriate only for a subset of patients ○ Young age ○ Compatible sibling donor • 5-10% risk of mortality ○ Intensive myeloablative conditioning required, graft-versus-host disease, and graft failure • Potential impairment of fertility • Requires access to technology at major treatment centre • Substantial one-off cost of procedure

HRQoL, health-related quality of life; HSCT, haematopoietic stem cell transplantation; NTDT, non-transfusion-dependent thalassaemia; TDT, transfusion-dependent thalassaemia; QoL, quality of life.

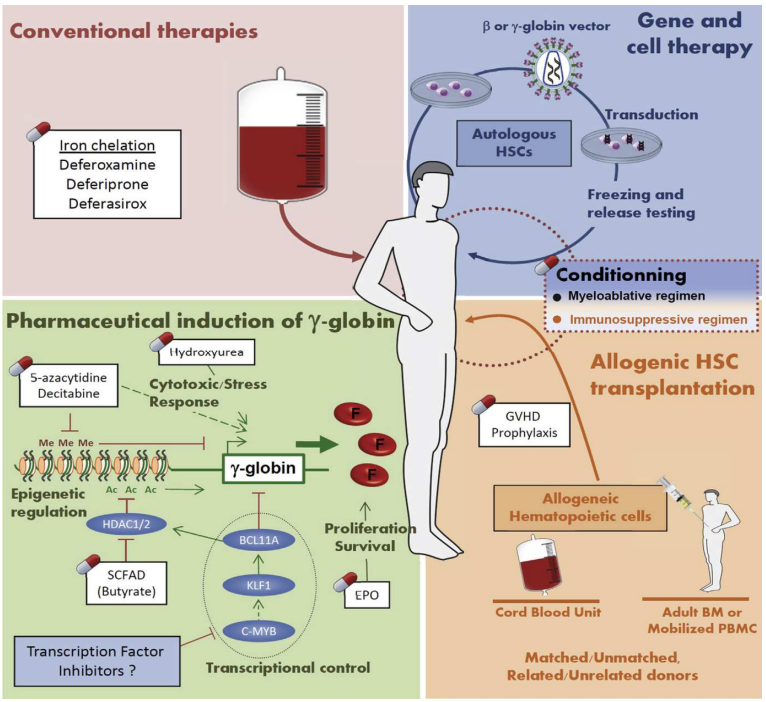


Figure 15. Current treatment options for thalassemia

COMPLICATIONS

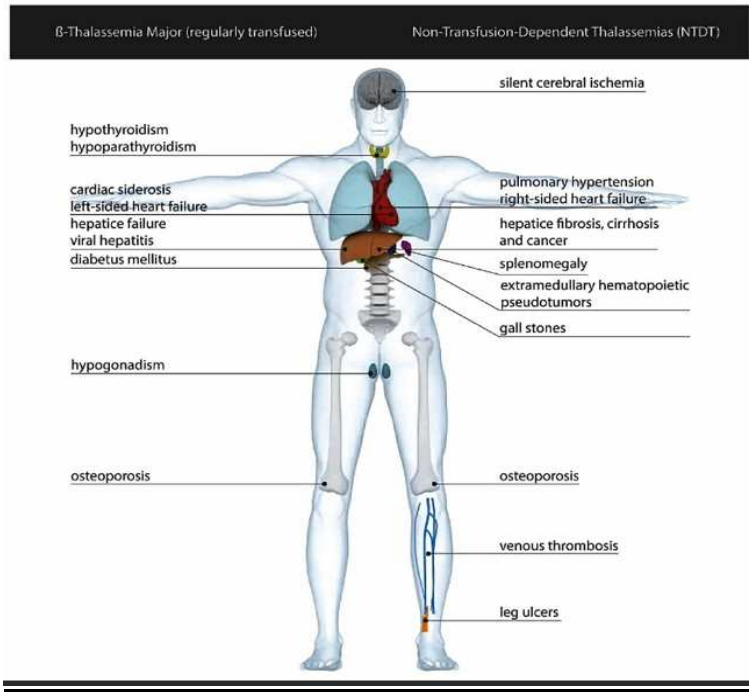


FIGURE SHOWING COMPLICATIONS OF THALASSEMIA

RENAL DYSFUNCTION IN THALASSEMIA

INTRODUCTION:

Renal dysfunction is a common morbidity associated with β thalassemia major patients. As the age of thalassemia patients increases, due to repeated blood transfusions, iron overload which is leading to renal dysfunction which is a major problem.

DEFINITION:

As per Kidney Disease Improving Global Outcomes (KDIGO), "CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health." Bhaduri M, Gama RM, Copeland T, Balagamage A, Patel P, Warmington E, Sarris I, Nicholaides K, Bramham K. Systematic review of pregnancy and renal outcomes for women with chronic kidney disease receiving assisted reproductive therapy. Journal of Nephrology. 2022 Nov 18:1-0.

INCIDENCE:

Incidence of renal dysfunction is increasing nowadays because of improvement in treatment modalities, availability of blood transfusion facilities along with chelating agents and management of complications at different levels of care. Based on different studies, the prevalence of renal dysfunction in well-treated Thalassemia major patients varies with a frequency of 40–50% in the studied population.

PREVALENCE OF RENAL COMPLICATIONS IN DIFFERENT STUDIES:

In a study done by Christos Demosthenous, et al, Renal dysfunction is the fourth most common complication in Transfusion dependent Thalassemia after endocrine (44.7%), Cardiovascular (41.3%), and Hepatic (40.5%) diseases in the same group of people. It also stated that Around 60 % of patients with β Thalassemia have reported to develop tubular dysfunction. Out of them the common presentations are tubulopathy, such as proteinuria (8.6%), hypercalciuria (12.9%), hypercalciuria (12.9%) and β2-microglobin (13.5%)

In a study done by Tunc et al mentioned that due to deferasirox related adverse effects around 87.5% of patients had proteinuria, in 37.5 % of patients there was increase in serum creatinine.

In a study done by Rheault et al there was elevated protein to creatinine ratio, urine calcium to creatinine ratio and urine β 2 microglobulin.

In a study done by Cappellini MD et al. mentioned that due to deferasirox and defiprone serum creatinine has increased in 14% of the patients.

In a study done by Katopodis et al. mentioned that renal abnormality in patients with β thalassemia due to chronic anemia there is increase in prostaglandin which leads to glomerular hyperfiltration and glomerulosclerosis

ETIOPATHOGENESIS:

Renal dysfunction is multifactorial and complex. It can be divided into damage caused secondary to thalassemia and treatment related

RENAL DYSFUNCTION SECONDARY TO THALASSEMIA

Thalassemia syndromes is group of hemolytic disorders due defective synthesis of hemoglobin leading to ineffective erythropoiesis. Transfusions of packed red blood cells is the main mode of treating thalassemia. Depending on level of hemoglobin in thalassemia, the frequency of transfusions may vary to maintain health.

A.Iron overload

Iron is reactive when compared to the other substances and can alternate between two ionic states that is Fe^{+3} and Fe^{+2} during this reaction there is production and loss of electrons along with production of toxic compounds like free radicals. Free radicals are known to cause damage to the various cell organelles, lipid membranes and also the nucleic acids like DNA. Physiologically the iron doesn't cause damage as it is bound along with transferrin. On the other hand, in iron overload the capacity to bind with transferrin is exceeded both in cells and in the plasma compartment. This results in the formation of free iron both in the cells and plasma thus leading damage of many tissues. Amount of free iron is directly proportional to the risk of infections and neoplasia. It could be fatal if not treated with chelation therapy.

The reactive oxygen species which have been produced cause caspase activation, DNA damage, organelle damage, lipid peroxidation there by causing cell death. They lead to fibrosis of the tissue by collagen synthesis.

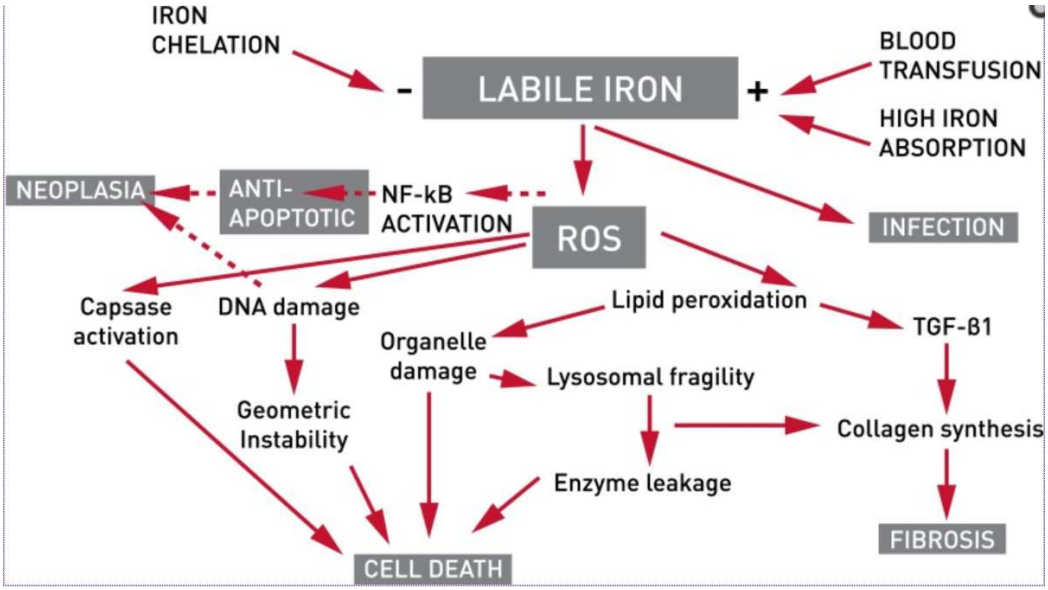


Figure 17. Pathogenesis of iron overload

The following are the methods by which iron is deposited

1.Packed Red Blood Cells Transfusion

420 mL of PRBC contains around 200 mg of iron, approximately 0.47mg in each ml of transfused preparation. Irrespective of whether the blood used is packed, semi-packed, if the whole unit is given. The other method of calculating amount of iron in the transfused preparations id by multiplying 1.16 to the amount of hematocrit in transfused cell preparations. This can be done where organizational systems to measure the hematocrit of transfused blood product is available. Otherwise, rough estimation is better option. The amount of transfusion to be done in thalassemia in a recommended scheme is equivalent of 100–200 ml of PRBC per kg body weight in a year to be transfused this is equivalent to 116-232 mg iron/kg body weight/year, or 0.32-0.64 mg/kg/day. In absence of chelation the amount of iron accumulated is mentioned below.

Table 3. Table showing rate of iron overload related with blood transfusion

PATIENTS WEIGHT	20 kg	35 kg	50 kg	65 kg
Pure red cells vol. ml/year	2,000-4,000	3,500-7,000	5,000-10,000	6,500-13,000
Yearly iron loading (g)	2.3-4.6	4.1-8.2	5.8-11.6	7.5-15.1
Daily Iron loading (mg)	6.3-12.6	11.2-22.5	15.9-31.8	20.5-41.4

2.GI Tract Absorption

This is minor mode leading to iron overload when compared to iron overload due to blood transfusion. But it contributes to overload in non-transfusion dependent anemia. Physiologically around 1-2mg/day is absorbed from the gut. In children with thalassemia not on regular transfusion the iron absorption will be increasing several fold. According to a study it is observed that iron absorption exceeds the amount iron lost when the multiplication of the red cell precursor in bone marrow is 5 times the normal individual. For the same reason transfusion regimens are planned in such a way that the hemoglobin is above 9gm/dl to prevent the precursor expansion. The patients who are not regularly transfused the absorption of iron increases to approximately to 3-5 mg/day or even higher, which increases an iron overload by one to two grams in a year.

Thalassemia, iron overload and the chelating drugs are known to affect many organ systems, such as the heart, lungs, liver, and endocrine glands.

B.Chronic anemia/hypoxia

The duration of the disease, the frequency of blood transfusion is directly proportional to the renal dysfunction and complications. Anaemia along with chronic hypoxia causes oxidative stress and lipid peroxidation which may lead to tubular dysfucntion Hypoxia itself causes differentiation of tubular cells to myofibroblasts,

along with activation of fibroblasts that causes alteration of extracellular matrix metabolism of tubular and glomerular cells and finally leading to the obliteration of peritubular capillaries [5-7].

RENAL DYSFUNCTION DUE TO TREATMENT

A.Iron chelators

An increase in serum creatinine ≥30% on at least two consecutive readings was observed in 38% of patients receiving DFX, most frequently at doses of 20 mg/ kg and 30 mg/kg (Cappellini et al., 2006). These increases were sometimes transient. Causes of increasing creatinine should also be considered in patients on DFX therapy.

Elevation of urine calcium and cystatin C are also seen in patients on DFX or DFP and DFO, whereas elevation of β2 microglobulin was seen in patients on DFX only (Economou et al., 2010). Case reports of renal tubular acidosis (Fanconi syndrome) with electrolyte imbalance, and metabolic acidosis due to tubular dysfunction have been rarely reported in adults and children taking DFX (Rheault et al., 2011; Grangé et al., 2010)

Tubular dysfunction children with beta thalassemia has been related to iron overload, anaemia, hypoxia and also iron chelator toxicity [8-11]. Iron chelation itself is nephrotoxic. It is also known to cause relative iron depletion causing abnormal mitochondrial function and abnormal arachidonic acid cascade. Tubuloglomerular feedback and vasoconstriction of afferent arteriole along with decrease in GFR

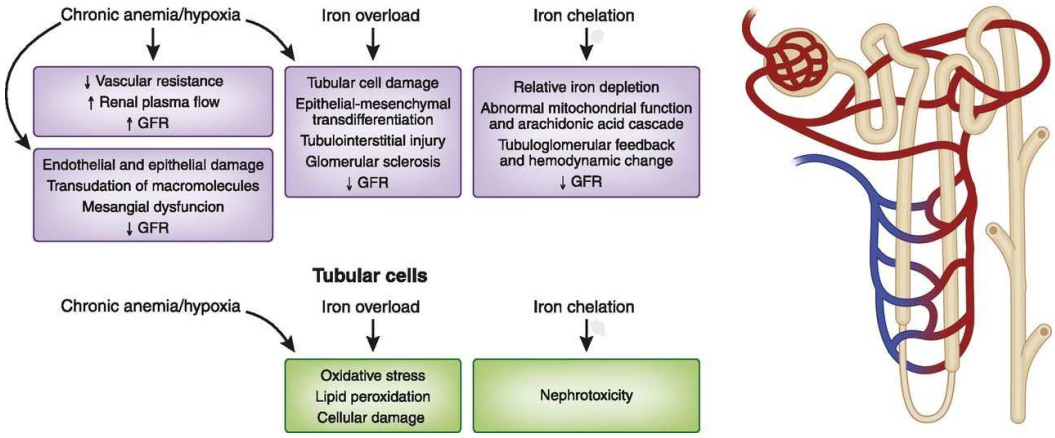


Figure 18: Etiopathogenesis of Renal Dysfunction in Thalassemia

B.NSAID's, COX-2 Inhibitors which are used for pain relief and antipyretic treatment causes vasoconstriction of afferent arterioles

C.Vitamin D, Calcium supplementation leads to Hypercalciuria, Calcium stones

D.In addition to the above, splenectomy itself is independent risk factor for tubular abnormalities. Marked elevation of serum ferritin was seen in splenectomised when compared to other non splenectomised patients[12].

CLINICAL FEATURES OF RENAL DYSFUNCTION

- **Anorexia**
- **Failure to thrive**
- **Fatigue**
- **Growth impairment**

Growth impairment is the most common visible complication in children with renal dysfunction [13–15]. As the GFR decreases the amount of growth impairment increases [13, 14]. North American Pediatric Transplant Cooperative Study conducted a study in 2006 in 5000 children which showed that 35% of children with CKD are stunted and their height is less than 3rd percentile. There was a correlation between GFR and height for standard deviation score (HtSDS) respectively, −3.2, −1.9, −1.5 and −0.9 for GFR 50 mL/min/1.73 m2 [15, 16]. Also other factors like malnutrition, metabolic acidosis, mineral and bone disorders, anemia, fluid and electrolyte abnormalities cause even more retardation [17–19]. In addition to alteration in growth hormone metabolism and also mediator of growth harmone, insulin-like growth factor-I (IGF-I) also cause growth retardation [20, 21]. Nutrition also effects the GH-IGF-I axis. Thus improper nutrition because of anorexia or vomiting is another important factor contributing to growth impairment at that age.

Mineral and bone disorder

Mineral and bone disorder is a disorder of metabolism of mineral and bone because of underlying renal dysfunction that can be identified by the presence of one or more findings like: abnormalities in calcium (Ca), phosphorus(P), parathyroid hormone (PTH) or metabolism of vitamin D; abnormalities in bone histology and

pathology along with growth and strength, [22]. Renal osteodystrophy is bone pathology seen in renal dysfunction. Chronic metabolic acidosis which in renal dysfunction also causes increased bone resorption.

- **Hypertension**

Hypertension is one of the earliest presentation, and the rate of hypertension increases as the GFR decreases[23, 24]. A recent study revealed that 54% of the patients showed renal dysfunction and 48% were still hypertensive even when on antihypertensive medication. Hypertension is an important precursor for cardiovascular abnormality [25]. 38% of patient with masked hypertension in renal the CKiD cohort study had masked hypertension that is normal office blood pressure but elevated ambulatory blood pressure, which is another known risk factor for LVH [24, 25].

- **Cardiovascular complications**

Many studies have shown that cardiovascular anomalies begin at early stages of renal failure [26, 27]. Most common cause of cardiovascular death in children is due to arrhythmias followed by valve diseases, cardiomyopathy and cardiac arrest [28, 29].

- **Electrolyte disorders**

Metabolic acidosis and hyperkalemia are important electrolye imbalances. The earliest one being the metabolic acidosis (it is due to low acid excretion and reduced reabsorption of bicarbonate). Hyperkalemia is due to resistance of the distal tubule to aldosterone.

INVESTIGATIONS FOR RENAL DYSFUCNTION

CBC: Kidney is involved in the production of erythropoietin, which inturn causes the production of haemoglobin. Thus in renal dysfunction the haemoglobin levels are invariably low

Renal function test: it includes both urea and creatinine. Creatinine is elevated in cases of glomerular dysfunction. Serum creatinine has a specificity of 99.9% and sensitivity of 12.6 %.

Electrolytes: In renal dysfunction due to the abnormal excretion of the electrolytes there is variation in sodium and potassium.

As kidney is involved in the absorption and metabolism of calcium in renal dysfunction calcium levels are low

Urinary protein

Proteinuria may be present in about a quarter of thalassaemia major patients, irrespective of the underlying chelation therapy, with average values about three times that of healthy controls (Economou et al., 2010). Monthly urine testing for protein, which is helpful in establishing trends in proteinuria.

Monitoring Of Iron Overload

Serum levels of ferritin is an indirect measure of iron stores in the body. It is esay to measure and can also be done repeatedly as it is inexpensive. Serum ferritin measurement has both advantages and disadvantages mentioned below.

ADVANTAGES	DISADVANTAGES
Easy to assess repeatedly	Indirect estimate of iron burden
Inexpensive	Increased by inflammation
Trend identification possible with repeat samples	Cannot determine iron balance directly
Long term control linked to outcome	Non-linear response to iron load at high levels
Useful for dose adjustment as iron levels fall	Absence of decrease doesn't exclude response

Decreasing trend of serum ferritin indirectly indicates that the iron overload is decreasing. But on the other hand the ferritin levels might also increase in cases of inflammation thus increasing trend doesn't definitely indicate increase in iron overload. So clinical assessment also plays an important role. Various studies have shown a direct link between serum ferritin levels and prognosis of the patient.

Urinary beta 2 microglobulin: β-2 microglobulin is a low molecular-weight protein that is freely filtered by glomeruli, reabsorbed by proximal convulted renal tubule and destroyed. So serum β-2 microglobulin is very low in the healthy individuals, but its level increases in case of inflammatory, immunologic and neoplastic events, tubular dysfunction. This test is 49% sensitive and 52% specificity.

Urinary cystatin : Cystatin-C is low-molecular-weight non-glycosylated protein that can inhibit cysteine protease, synthesized and secreted by all human nucleated cells. Cystatin-C is a sensitive biomarker for glomerular filtration rate (GFR) and not secreted by the renal tubules or reabsorbed back into the serum. It is better than creatinine clearance in the diagnosis of renal function impairment, as it is not affected by height, sex, diet, and muscle mass. It has sensitivity of 84.6% and specificity of 86.7%.

Abdominal USG and pelvis: to look for the corticomedullary differentiation

TREATMENT OF RENAL DYSFUNCTION

1)Iron overload

Need for iron chelators

Iron overload is due to increase in iron uptake over a sustained period of time, either due to repeated PRBC transfusion or high-rate absorption of iron through the gut. Both these mechanisms are seen in thalassaemia, out of these repeated PRBC transfusion is the leading cause in transfusion dependent anaemia, on the other hand

increased absorption from gut is in non-transfusion dependent anaemia. The main mode of treatment in thalassemia major is PRBC transfusion. Thus the iron overload here is inevitable.

Not all the iron in the body is available for chelation, only a small amount of body iron is available for chelation at a particular time. Iron chelators react with iron of low molecular weight (labile iron) in a better way when compared to iron stored in form of ferritin or hemosiderin. This low molecular weight iron is available at all the times, thus chelation would be better if it is present at all times that is it should be there 24 hours a day. Labile iron is mainly derived by two ways 1. From the breakdown of red cells in macrophages, physiologically it is around 20mg/day 2. From the catabolism of ferritin stored in cells. Mostly the iron is stored in the hepatocytes, the iron chelated in hepatocytes is excreted into the biliary system from there into the plasma and finally excreted in the urine. The amount of chelated iron which is eliminated in faeces or urine varies with each chelator. Chelated iron with Deferoxamine around half through faeces and remaining through urine, with deferasirox mostly excreted through urine and with deferiprone excreted through faeces. The iron which is chelated by deferoxamine is mainly derived from the catabolism of red cells by macrophages, the iron chelated by deferiprone is derived from hepatocytes and macrophages. The endocrine and the cardiovascular system lack the mechanism of iron storage and and release which the liver has (liver always has cellular iron available for chelation at any point of time). Therefore it takes more time to remove iron from endocrine and heart when compared to liver.

The main aim of using iron chelators is to decrease the amount of iron accumulation due to blood transfusion by increasing the excretion in both urine and faeces. Iron is also required for the physiological needs. So, the use of iron chelation

should balance both the benefits and unwanted effects of the excessive chelation, by careful monitoring of its dose. The next major challenge in chelation therapy is to achieve compliance of patients to the regimens over a long period that is life long, discontinuation for a small period of time can cause damaging effects.

Dosing of iron chelators

Deferoxamine is to be started after two-three years after starting transfusion, is given regularly in adequate doses 5 times in a week. In β thalassemia it is started before tissue damage is caused by the deposited iron due to repeated transfusions. No study has been done regarding the time to start deferoxamine but clinically it is started after 10-20 transfusions or if the serum level of ferritin is above 1000 µg/l. If it is started before 3 years of age then careful monitoring of growth and development and also dose should be reduced. It is administered mostly subcutaneously by infusion pump method slowly over 8-12 hrs solution over 5 days per week. In places where pre-filled balloon infusers are present it will be easy to maintain the drug compliance. Till the age of growth has reached the maximum dose should not reach 40mg/kg. The recommended dose is 20-40mg/kg in children and 50-60mg/kg in adults.

Regarding deferiprone multiple studies showed that at a dose of 75mg/kg/day in three doses. In a study which mentioned that it is effective in reducing serum ferritin if it is 2500 µg/dl and not with values below 2500 µg/dl.

However, the first line of management for iron chelation remains deferasirox. it is taken orally mixed with water once daily before meals. A minimum dose of 20 mg/kg is given to thalassemia major patients who has taken 10-20 blood transfusion.

CATEGORY	DFO (DEFEROXAMINE)	DFP (DEFERIPRONE)	DFX (DEFERASIROX)
Children age 2-6 years	First line for TM	Insufficient information for licensing	First line in USA Second line when DFO contra- indicated or inadequate in Europe
Children age >6 years and adults	First line TM	If other chelation (FDA 2011) or DFO not tolerated or ineffective	First line TM First line NTDT
Route	s.c./i.m. or i.v injection	Oral, tablet or liquid	Oral, dispersed tablet
Dosage and frequency	20-60 mg/kg 5-7 x / week, 50 mg/kg in EU Children's dose up to 40 mg/kg	75 -100 mg/kg/day in 3 divided doses daily	14-28 mg/kg/day once daily for film coated tablet. Lower doses in NTDT
Contra-indications	- Pregnancy (but has been used in 3rd trimester) - Hypersensitivity	- Pregnancy - History of neutropenia or condition with under-lying risk of cytopenia - Hypersensitivity including Henoch Schönlein purpura: urticaria and periorbital oedema with skin rash	- Pregnancy - Hypersensitivity - Estimated creatinine clearance <60 ml/min - Hepatic impairment or renal failure
Precautions	– Monitor ferritin; if it falls to <1000 µg/l, reduce dose (so mean daily dose/fer-ritin remains <0.025) - Monitor audiometry regularly, particularly as ferritin falls - Monitor eyes regu-larly including electroretinography if on high doses - Fever suggestive of septicaemia with organisms that used ferrioxamine (Yers-inia, Klebsiella)	- Measure neutrophil count (ANC) before starting and monitor ANC weekly - For neutropenia : ANC < 1.5 x 10^9 /l interrupt treatment - For agranulocytosis (ANC < 1.5 x 10^9 /l), consider hospitalisation - Advise patients to report immediately symptoms of infection; interrupt if fever develops - Monitor for symptoms of arthropathy	- Monitor creatinine trends for 1st 4 weeks after starting or after dose escala-tion, then monthly - If rapid fall in serum ferritin to <1000 µg/l, dose reduce. If ferritin 500 µg/l consider very low doses. - Proteinuria may occur, occasionally with renal tubular acidosis. Monitor urine protein regularly

CATEGORY	DFO (DEFEROXAMINE)	DFP (DEFERIPRONE)	DFX (DEFERASIROX)
	-Renal failure or diminishing renal function with other comorbidities	- Monitor liver function regularly - No guidance on dose adjustment at low ferritin	- Prescribing to the elderly, non-fatal gastrointestinal bleeding, ulceration, and irritation may occur; caution with drugs of known ulcerogenic or haemorrhagic potential, (e.g. NSAIDs, corticosteroids, oral bisphosphonates, and anticoagulants) - Hypersensitivity reactions - Monitor liver function regularly
Potential drug interactions	- Co-administration with prochlorperazine may lead to temporary impairment of consciousness. - Gallium-67: Imaging results may be distorted by rapid urinary excretion of deferoxamine-bound gallium-67. Discontinuation 48 hours prior to scintigraphy is advisable	- Theoretical interactions with UGT1A6 inhibitors (e.g. diclofenac, probenecid or silymarin (milk thistle)) - Avoid concomitant use with drugs associated with neutropenia - Gallium-67 as with DFO - Oral preparations containing polyvalent cations (e.g., aluminium containing antacids, and zinc) allow at least a 4-hour interval	- Theoretical interactions with drugs metabolized by CYP3A4 e.g. midazolam -Theoretical interactions with drugs metabolized by CYP1A2 e.g. theophylline - Gallium-67 as with DFO - Oral preparations containing polyvalent cations as with DFP

ADVERSE EFFECTS OF IRON CHELATORS

Hearing problems like sensory neural hearing loss, deafness mainly with high doses of deferoxamine. If the sensory neural loss is minor then it is reversible but if sensory neural deficit is major it is irreversible. Tinnitus is also not uncommon. Yearly audiometry is to be advised to patients on deferoxamine.

Visual disturbances like cataracts, retinal effects, night blindness, impaired colour vision can be seen but with deferoxamine but very rare. They are seen in cases where high doses are used that is >100mg/kg/day. Treatment is temporarily withheld during such cases and restarted at lower after complication resolve

Growth retardation can occur if deferoxamine is administered at a high dose and specially if it is started at a age less than 3 years. It doesn't respond even to growth harmone supplementation

Skeletal changes like bone changes similar to rickets, genu valgum, these changes are permanent and thus should be monitored closely.

Skin reactions like itching, erythema can be seen if deferoxamine is not diluted properly, extravasation of deferoxamine can cause ulceration.

Hypersensitivity is very rare, but in such case alternate chelator to be used.

Neutropenia, agranulocytosis and thrombocytopenia: Deferiprone can cause these complications which can in-turn cause infections, sepsis and even death of the patient. Deferiprone can cause bone marrow hypoplasia and neutropenia

Gastrointestinal symptoms Nausea, vomiting, either increase or decreased appetite

Hepatic effects: Altered levels of AST and ALT is seen with the use of Deferiprone and deferoxamine. Variation of the enzymes twice the upper limit should be investigated.

2)Growth impairment

Increasing caloric intake by at minimum 80% of requirements has effectively improved growth in children who developed CKD [30, 31]. For children above 2 years treatment with recombinant human growth hormone has been effective without any major adverse effects [32–35].

3)Mineral and bone disorder

Management of mineral and bone disorder is very important in renal dysfunction as altered levels of calcium and phosphorus metabolism causes disturbance in the bone remodeling. Dietary restriction is advisable for dietary restriction. Phosphate binders may be necessary in some patients [36]. Supplementation of calcium (calcium based phosphate binders like calcium carbonate) and vitamin D

4)Hypertension:

Various studies done showed that effective control of hypertension reduces cardiovascular morbidity and mortality [37–39]. To improve the diagnosis of hypertension in paediatric renal dysfunction patients, a 24-h ambulatory blood pressure monitoring should be performed whenever possible. The use of RAAS-I should be part of an effective antihypertensive medication management. It is used when the blood pressure is consistently above the 90th percentile for the age, sex and height. The goal of the therapy is to maintain the blood pressure in 50th – 75th percentile. Others are Angiotensin converting enzyme inhibitor or angiotensin receptor blocker. These two are both renoprotective and antiproteinuric effect.

5)Electrolyte imbalance

Metabolic acidosis is managed by bicarbonate infusion and the level is maintained at 22 mEq/L. Management of hyperkalemia is by dietary restriction and use of sodium polystyrene sulfonate (orally, rectally or mixed with meals)

6)Cardiovascular:

An effective control of hyperphosphataemia, hyperparathyroidism, anaemia and hypertension could improve the survival and the future global health of these patients.

COMPLICATIONS

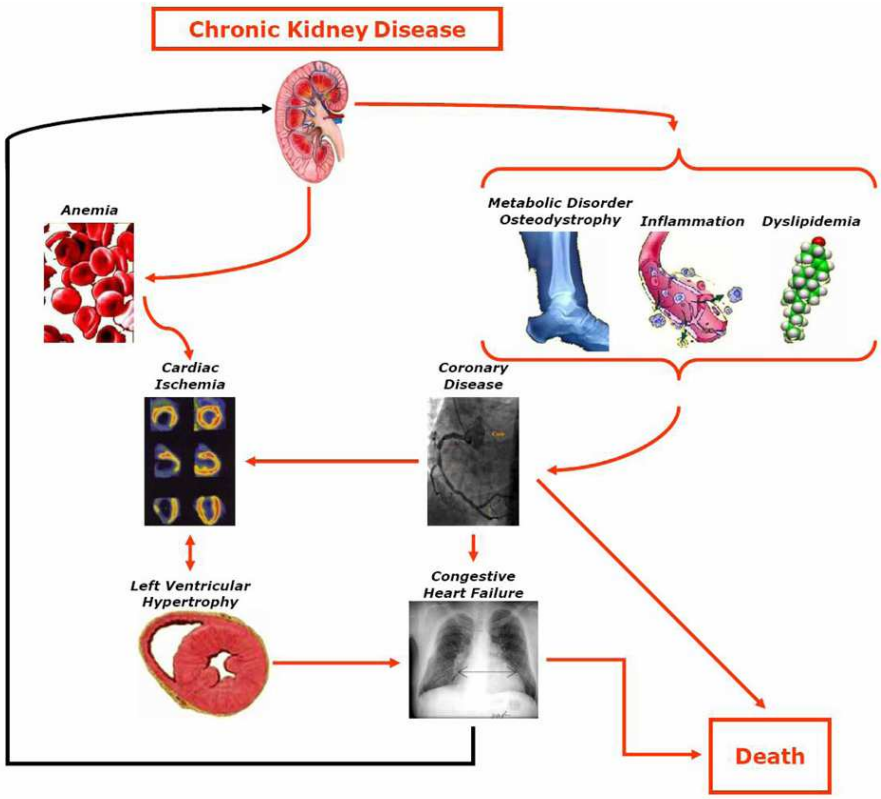


Figure showing complications of renal dysfunction

- Anemia
- Metabolic osteodystrophy
- Dyslipidemia
- Coronary artery disease
- Cardiac ischemia
- Left ventricular hypertrophy
- Congestive cardiac failure

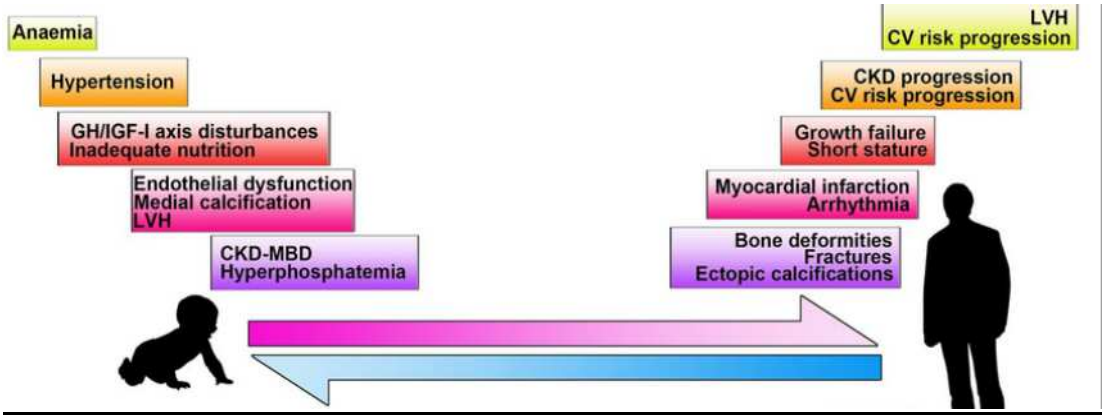


Figure showing long term effects of renal dysfunction

MATERIAL AND METHODS

This study was done from January 2021 to December 2021 under the Paediatrics Department, KLES Dr.Prabhakhar Kore Hospital & Medical Research Center, Belagavi.

Study Design:

Cross Sectional Observational Study

Study duration:

One year i.e. from January 2021 to December 2021

Place of study:

KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi

Source of Data:

Registered patients of Transfusion-dependent beta thalassemia on iron chelators for more than and equal to 6 years at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Selection criteria

Inclusion Criteria:

1. Transfusion dependent β-Thalassemia Major Patients receiving on oral iron chelator for more than or equal to 6 years

Exclusion Criteria:

1. Non transfusion dependent anemia

2. Other haemoglobinopathies like sickle cell disease

3. History of renal disorders in the past

4. History of Hypertension and Diabetes

Sample size:

1. Formula used for sample size calculation is

$$n - \frac{(100-p)Z^2}{E^2}$$

n- is the sample size required,

p- is the percentage occurrence of a state or condition (proportion or prevalence),

E- is the percentage maximum error required,

Z- is the value corresponding to level of confidence required.

2. Incidence of renal failure is 11% [1]

With percentage of maximum error as 10% at 95% confidence level sample size is given by

$$n = \frac{11 \times 09 \times (1.96)^2}{10^2}$$

$$n = 37.60 \approx 38$$

Minimum sample size required is 38.

Informed Consent:

The parents of children who fulfil the eligibility criteria will be briefed about the nature of the study and written informed consent will be taken for enrolment in the study. (Annexure I).

Methodology:

Children receiving oral iron chelator for more than or equal to 6 years who are registered in thalassemia day-care centre of KLE Dr Prabhakar Kore Charitable Hospital & Medical Research Centre affiliated to KLE Academy of Higher Education and Research's JN Medical College, BELAGAVI and who fulfil inclusion criteria will be chosen. After detailed history, informed consent will be obtained from the parents after explaining the purpose of the study. The participant's data will be recorded in a structured pro forma (AnnexureII). All the children receiving oral iron chelation therapy for a period of more than or equal to 6 years are taken. Out of those using random sampling methods 40 thalassemia children are taken. Biochemical and metabolic tests including CBC, Serum ferritin, Serum urea, serum creatinine, serum sodium, serum potassium. A 24-hour urine specimen was collected for the determination of creatinine, sodium, potassium, calcium, and albumin. From these levels of Fractional excretion of sodium, Fractional excretion of potassium are calculated. Creatinine clearance was evaluated in all the children using the following formula creatinine clearance (in milli litres per minute per 1.73m2) = [(urine volume * urine creatinine) / [(serum creatinine*1440)] *(1.73m2body surface) In addition to the conventional renal biochemistries urinary β2-microglobulin in a fresh, first morning urine sample were measured. It is measured by chemiluminescence method.

Investigations:

1. Complete blood count

2. Serum ferritin levels

3. Renal function tests

4. Serum electrolytes

5. 24hr urine specimen creatinine

6.24hr urine specimen sodium

7.24hr urine specimen potassium

8.24hr urine specimen calcium

9.24hr urine specimen albumin

10. β2microglobulin

Complete blood count estimation was done at the time of admission to assess pre-transfusion Hemoglobin as a part of the guidelines.

Renal function tests were done at the time of enrolment to look for any renal dysfunction.

Serum ferritin levels to correlate between iron over load and renal dysfunction.

A 24-hour urine specimen was collected for the determination of creatinine, sodium, potassium, calcium, and albumin. From these levels of Fractional excretion of sodium, Fractional excretion of potassium are calculated to know the glomerular dysfunction.

Urinary β2-microglobulin in a fresh, first morning urine sample were measured to know the tubular dysfunction

SAMPLE COLLECTION: Blood will be collected from the venous route while securing an IV line. One EDTA bulb containing 1 millilitre will be sent for CBC. Another plain bulb containing 4ml will be sent for testing urea, creatinine, sodium, potassium and serum ferritin. In a sterile container 10ml of 24-hour urine specimen was collected for the determination of creatinine, sodium, potassium, calcium for the levels of Fractional excretion of sodium, Fractional excretion of potassium are calculated. In a sterile container 10ml of 24-hour urine specimen was collected for the determination of urine albumin. In another sterile container 10 ml of early morning urine sample is collected for urinary β2-microglobulin is measured.

- Estimation of Hemoglobin was done by Cyanomethaemoglobin method on Mindray CAL 80 analyser, before the commencement of the study.
- Estimation of ferritin levels was done by electrochemiluminescence immunoassay (ECLIA) on Cobas analyser (COBAS E 601) before the commencement of the study.
-Estimation of urinary beta 2 microgobulin is measured by chemiluminescence on atellica analyser (ATELLICA CH 930)

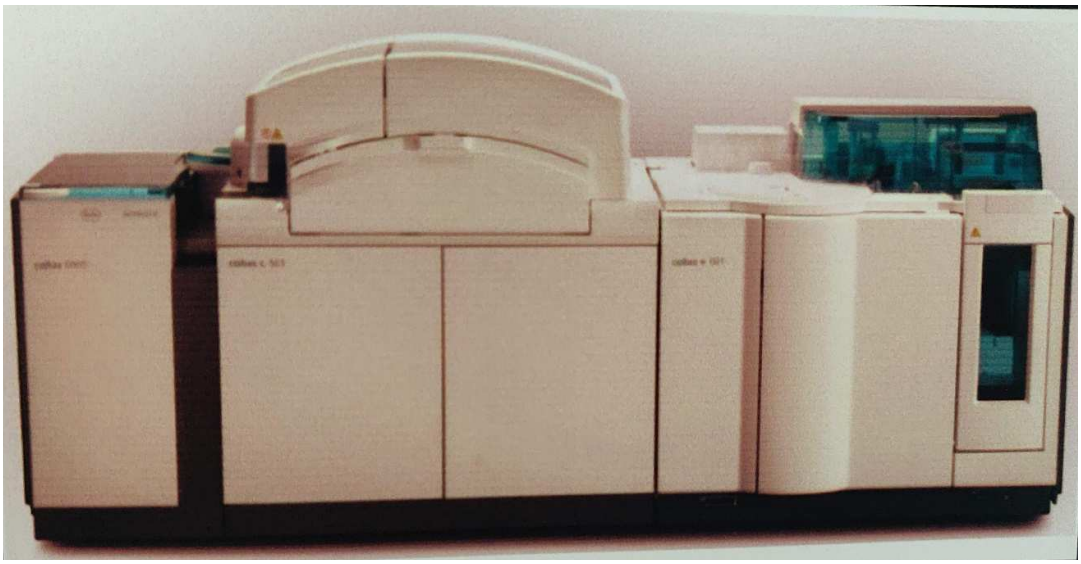
• Urea – urease UV method
• Creatinine – enzymatic method(IFCC-IDMS)

Beckmann coulter used for analysis of complete blood picture

BECKMAN Machine to measure creatinine

Msldz400 clinical centrifuge for serum urea

MSLEA 02 machine to calculate electrolytes



COBAS analyser used for estimation of serum ferritin

ATELLICA analyser for measurement of urinary beta 2 microglobulin

FOLLOW UP : The children were treated and followed up to 6months of treatment to evaluate the efficacy and compliance of deferiprone in intervention group.

Data analysis was done using SPSS version 20.00. For the continuous quantitative variables mean and standard deviation will be calculated. The inter group continuous variables will be compared using suitable tools of statistics like unpaired student's t test. Two quantitative variables, within a group, will be compared using student's paired t test.

The categorical data will be expressed in terms of rates, ratios and percentages. The association between the outcome, clinical and demographic characteristics will be tested using Chi-square test or Fisher's exact test.

Discrete variables will be represented by median.

Nonparametric tests will be used for comparing discrete variables.

Suitable graphs will be used to depict the comparison.

For all the tests the value of p less than 5% (0.05) will be considered significant

Reference values for renal dysfunction

S. Creatinine	0.5-0.95mg/dl
S. Urea	17-49mg/dl
U. Creatinine	980-2200mgs/day
U. Sodium	40-220mEq/day
U. Potassium	40-80mEq/day
U. Albumin	<0.5g/L
U. Beta 2 Microglobulin	<300mcg/L

RESULTS

METHOD:

Data is analyzed using statistical software **R version 4.1.2**. Categorical variables were represented using counts and percentage, whereas continuous variables were summarized using mean, SD, minimum and maximum. Both categorical and continuous variables represent with suitable graphics.

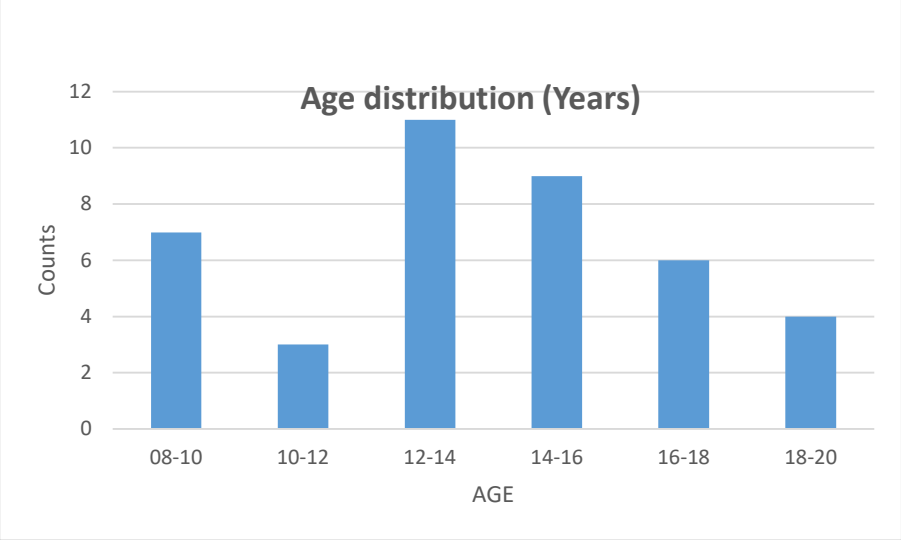
SUMMARY:

The summary and graphs of particular variables are represented below

Age Group (Years)	Counts	Percentage
8-10	7	17.50%
10-12	3	7.50%
12-14	11	27.50%
14-16	10	25.00%
16-18	10	25.00%
Total	40	100.00%

Table1 : Distribution of age

Mean age is 13.20±2.95 years, with minimum age of 8 years and maximum age of 18 years.

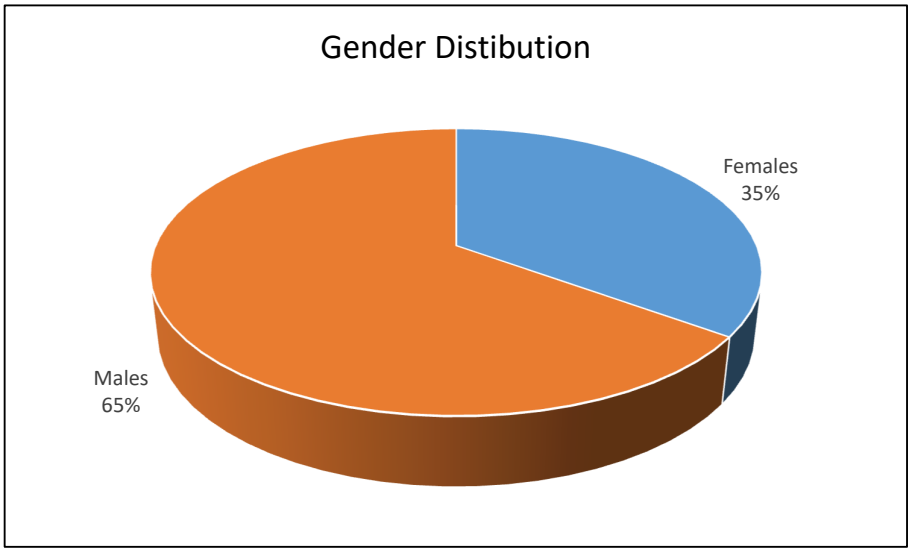


Graph 1 : Distribution of age

Table 2: Distribution of Gender

Gender	Counts	Percentage
Females	14	35.00%
Males	26	65.00%
Total	40	100%

Graph 2 : Distribution of gender

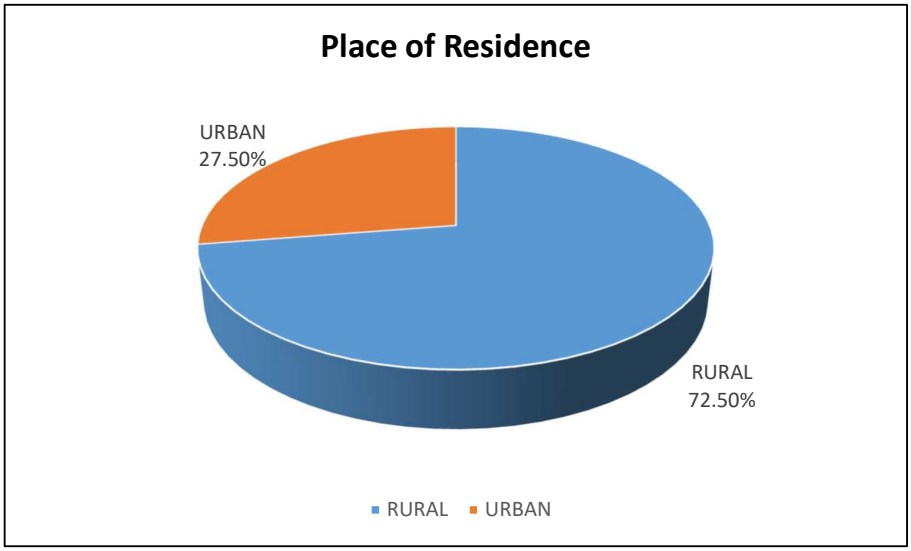


In the present study most of the patients were male (65%) and 35% of the patients were female.

Table 3: Distribution of Area

Area	Counts	Percentage
RURAL	29	72.50%
URBAN	11	27.50%
Total	40	100.00%

Graph 3 : Distribution of Area

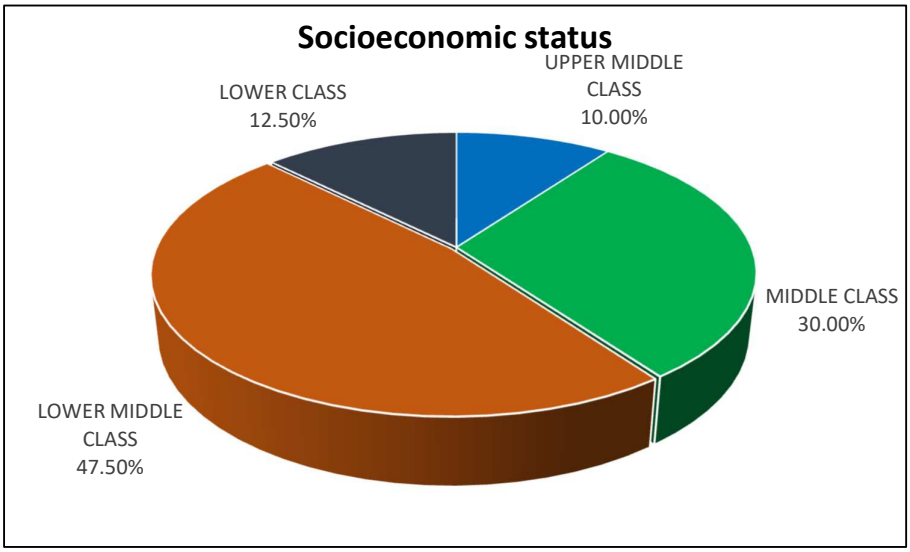


Most of the patients in the present study were from Rural area(72.50%) remaining were from Urban area (27.50%).

Table 4: Distribution of socioeconomic status

Socioeconomic status	Counts	Percentage
UPPER MIDDLE CLASS	4	10.00%
MIDDLE CLASS	12	30.00%
LOWER MIDDLE CLASS	19	47.50%
LOWER CLASS	5	12.50%
Total	40	100.00%

Graph 4: Distribution of socioeconomic status

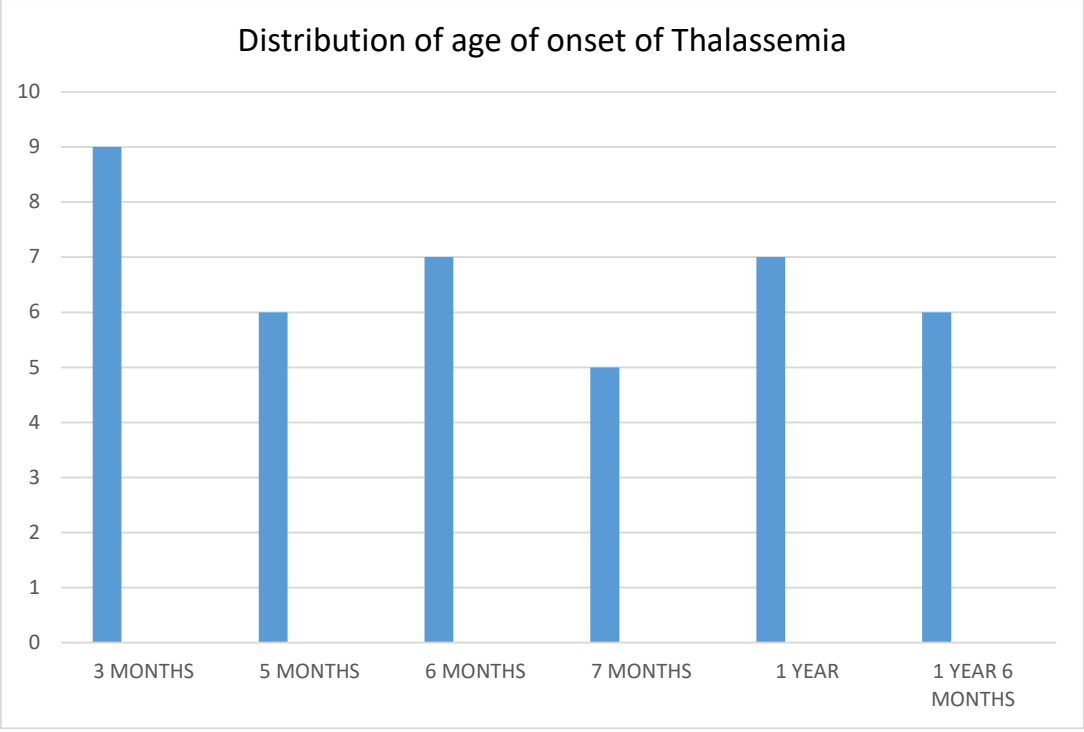


Most of the patients were from Lower Middle class (47.50%), middle class patients were about 30% , Lower class patients were 12.50% and Upper middle class patients were 10%.

Table 5a: Distribution of age of onset of Thalassemia

Age of onset	Counts	Percentage
3 MONTHS	9	22.50%
5 MONTHS	6	15.00%
6 MONTHS	7	17.50%
7 MONTHS	5	12.50%
1 YEAR	7	17.50%
1 YEAR 6 MONTHS	6	15.00%
Total	40	100.00%

Graph 5a : Bar graph showing Age of onset of Thalassemia

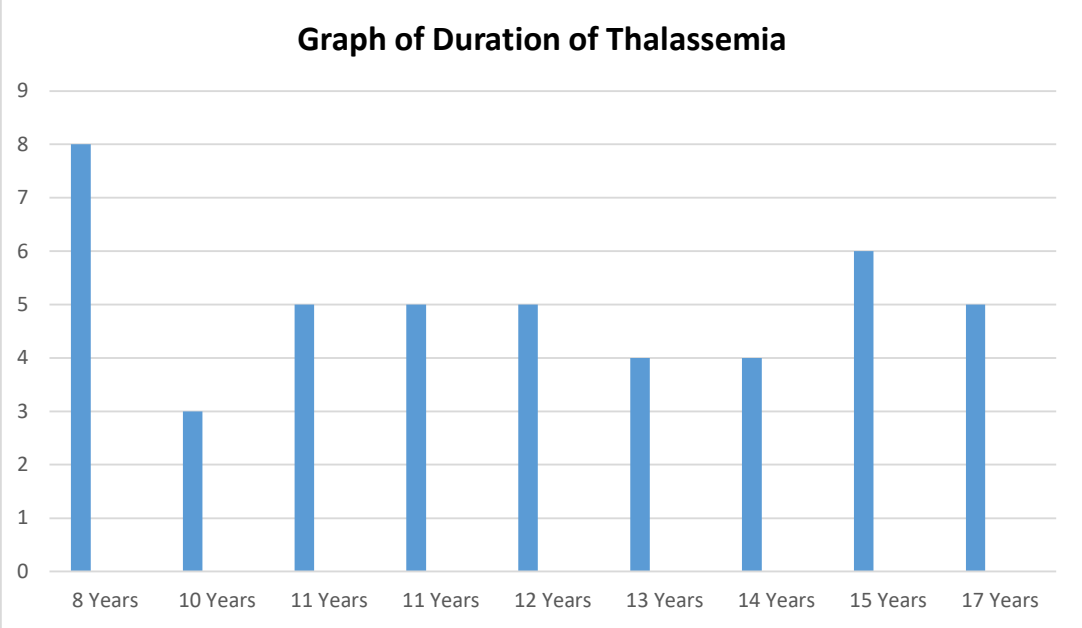


Among the 40 patients 9 patients have age of onset as 3 months, 7 patients have age of onset as 6 months, 7 patients have age of onset as 1 year. These three age of onset are the highest recorded among the 40 patients.

Table 5b: Table of Duration of Thalassemia

Duration of the disease	Count	Percentage
8 years	8	20%
10 years	3	7.5%
11 years	5	12.5%
12 years	5	12.5%
13 years	4	10%
14 years	4	10%
15 years	6	15%
17 years	5	12.5%
Total	40	100%

Graph 5b : Bar graph showing duration of thalassemia

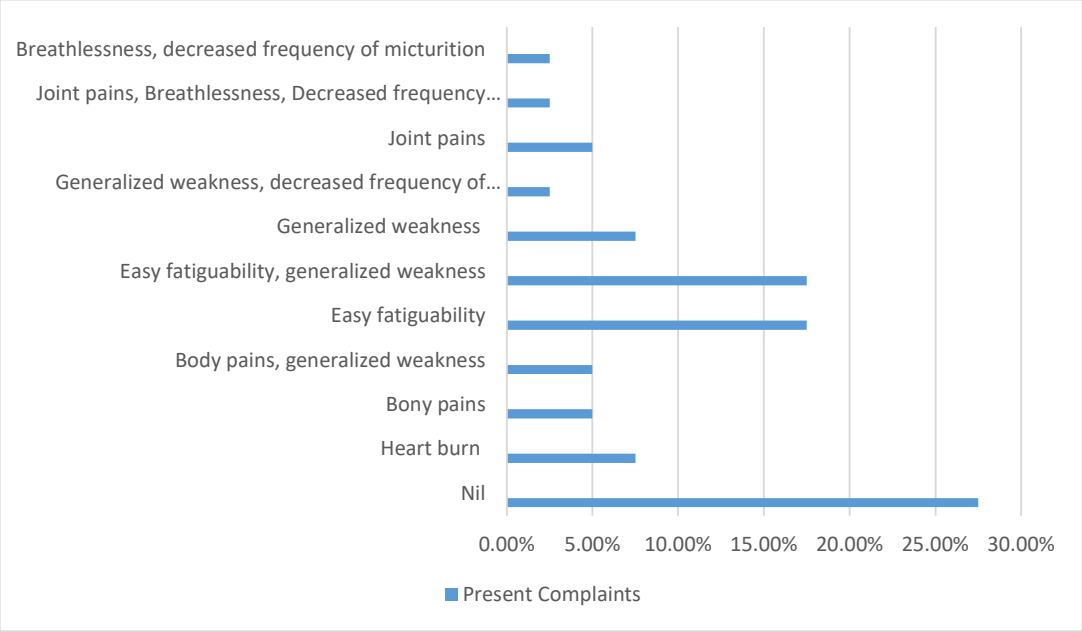


Among the 40 patients 8 patients have duration of disease for 8 years, 6 patients have duration of disease for 15 years.

Table 6: Distribution of present complaints

PRESENT COMPLAINTS	Counts	Percentage
BREATHLESSNESS,DECREASED FREQUENCY OF MICTURITION	1	2.50%
JOINT PAINS,BREATHLESSNESS,DECREASED FREQUENCY OF MICTURITION	1	2.50%
JOINT PAINS	2	5.00%
GENERALISED WEAKNESS,DECREASED FREQUENCY MICTURITION	1	2.50%
GENERALISED WEAKNESS	3	7.50%
EASY FATIGUABILITY,GENERALISED WEAKNESS	7	17.50%
EASY FATIGUABILITY	7	17.50%
BONY PAINS,GENERALISED WEAKNESS	2	5.00%
BONY PAINS	2	5.00%
HEART BURN	3	7.50%
NIL	11	27.50%
Total	40	100.00%

Graph 6 : Bar graph showing present complaints

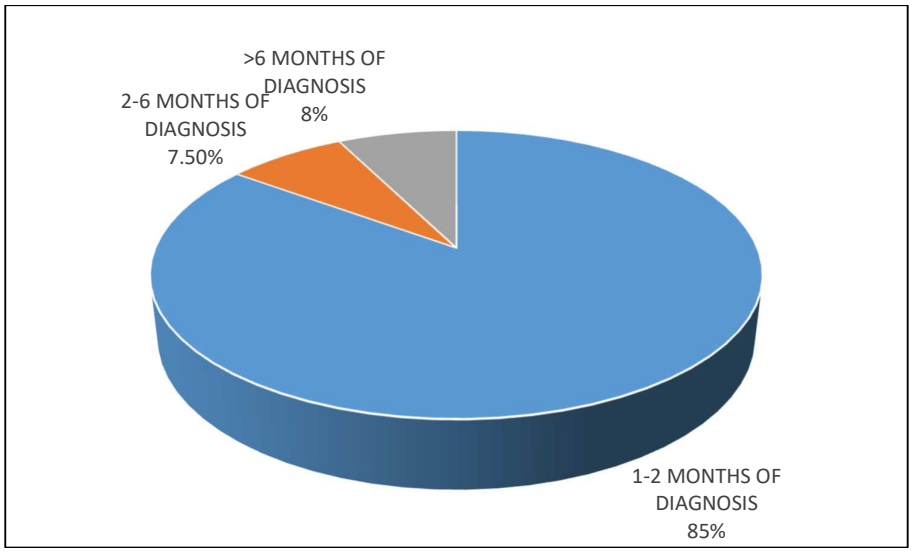


Among the 40 patients, 11 patients do not have any present complaints (27.50%). Easy fatiguability was observed in 7 patients (17.50%). Easy fatiguability,generalised weaknesswere observed in 7 patients (17.50%). Easy fatiguability,generalised weakness were the highest observed present complaints in the present study.

Table 7: Distribution of blood transfusion history after diagnosis

Blood transfusion history	Counts	Percentage
1-2 MONTHS OF DIAGNOSIS	34	85.00%
2-6 MONTHS OF DIAGNOSIS	3	7.50%
>6 MONTHS OF DIAGNOSIS	3	7.50%
Total	40	100.00%

Graph 7 Pie-chart showing Distribution of Blood transfusion history after diagnosis

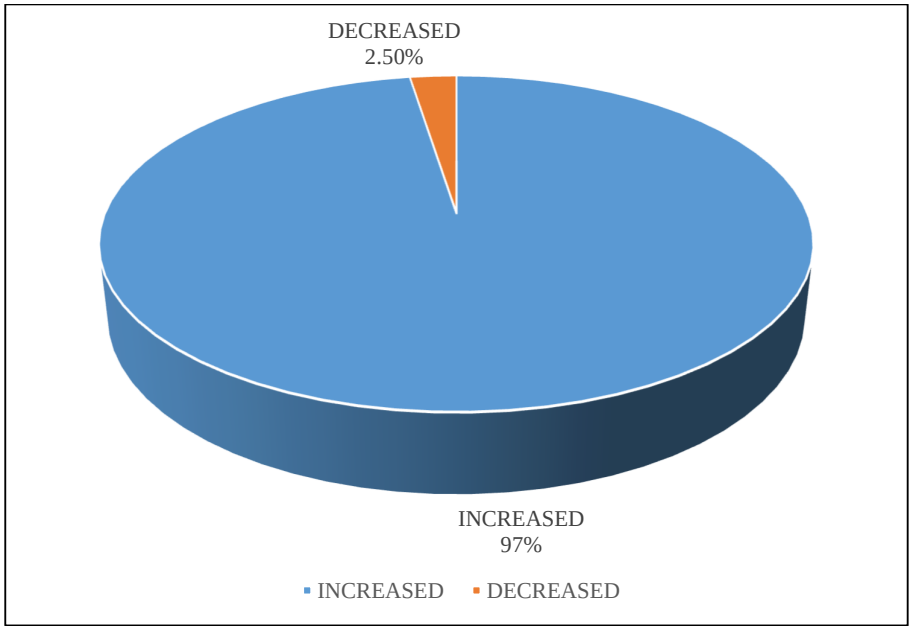


Most of the patients in the present study have blood transfusion history of 1-2 MONTH OF DIAGNOSIS (85%). Blood transfusion history of >6 MONTHS OF DIAGNOSIS was 8% and 2-6 MONTHS OF DIAGNOSIS was 7.50%.

Table 8: Distribution of frequency of blood transfusion

Frequency of blood transfusion	Counts	Percentage
INCREASED	39	97.50%
DECREASED	1	2.50%
Total	40	100.00%

Graph 8: Pie-chart showing Frequency of blood transfusion

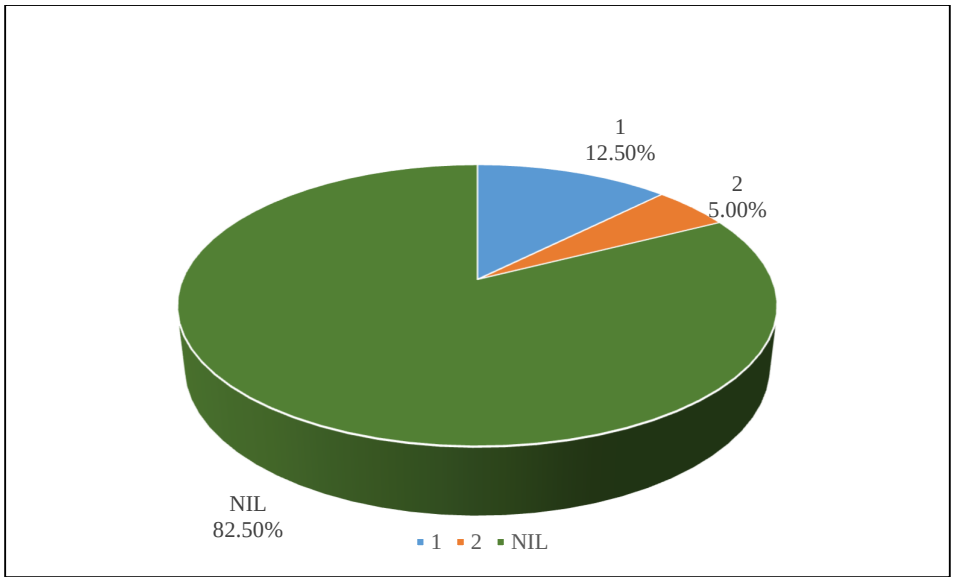


In the present study, its found that 39 people have found Increased blood transfusion (97.50%), and only 1 patients have decreased blood transfusion (2.50%).

Table 9a: Number of patients with transfusion related reactions

NO: OF REACTIONS	Counts	Percentage
1	5	12.50%
2	2	5.00%
NIL	33	82.50%
Total	40	100.00%

Graph 9a: Pie-chart showing number of patients with transfusion related reactions

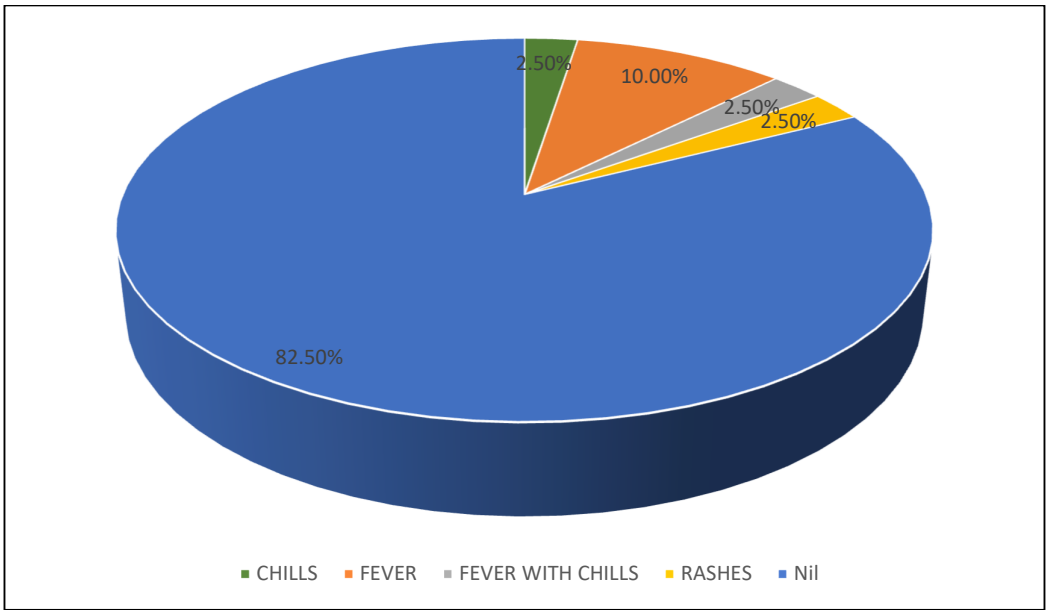


In the present study, its found that 33 people have no reaction to blood transfusion (82.50%), five(12.50%) people have only one reaction to blood transfusion, two (5%) people have two reaction to blood transfusion.

Table 9b: Distribution of type of reaction related to blood transfusion

Reaction in blood transfusion	Counts	Percentage
CHILLS	1	2.50%
FEVER	4	10.00%
FEVER WITH CHILLS	1	2.50%
RASHES	1	2.50%
Nil	33	82.50%
Total	40	100.00%

Graph 9b: Pie-chart showing type of reaction related to blood transfusion

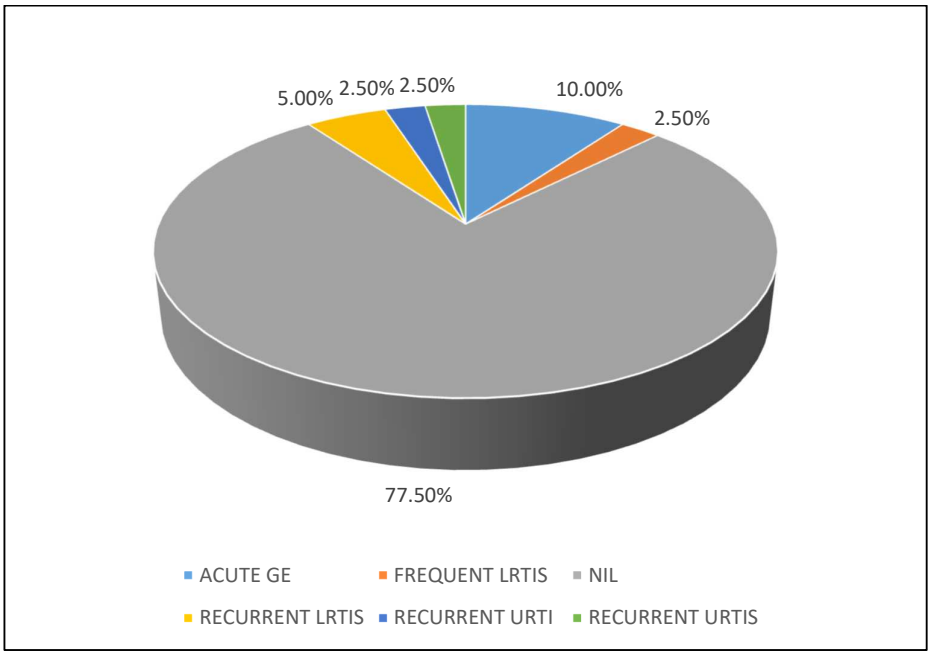


Fever is the most got reaction due to blood transfusion (10%), 33 people have no reaction to blood transfusion (82.50%).

Table 10: Non Blood Transfusion related reactions in Thalassemia patients

Other infection	Counts	Percentage
ACUTE GE	4	10.00
FREQUENT LRTIS	1	2.50
NIL	31	77.50
RECURRENT LRTIS	2	5.00
RECURRENT URTI	1	2.50
RECURRENT URTIS	1	2.50
Total	40	100.00

Graph 10: Non Blood Transfusion related reactions in Thalassemia patients

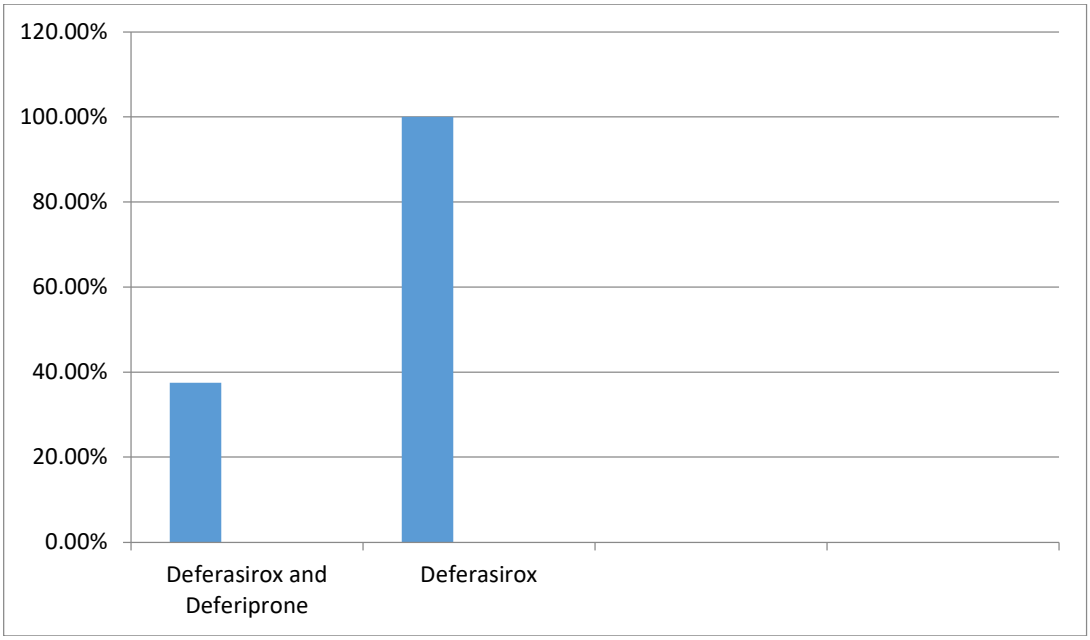


In the present study, four people have ACUTE GE infection (10%), two people have RECURRENT LRTIS (2%), other reactions occurred in once in one person each.

Table 11: Thalassemia patients who are on iron chelators

IRON CHELATORS	Counts	Percentage
Deferasirox and Deferiprone	**15**	**37.5%**
Deferasirox	**40**	**100%**

Graph 11: Thalassemia patients who are on iron chelators



In the present study 15 patients (37.50%) are on both deferiprone and deferasirox, all the patients are on deferasirox

Table 12a: Deferasirox doses in Thalassemia patients

DEFERASIROX: DOSE	Counts	Percentage
1000MG/DAY	13	32.50
1250MG/DAY	5	12.50
1500MG/DAY	7	17.50
1750MG/DAY	2	5.00
2250MG/DAY	1	2.50
500MG/DAY	5	12.50
750MG/DAY	7	17.50
Total	40	100.00

Above table and graph gives the summary of deferasirox dose and we can observe that 13 (32.50%) patients were provided with 1000MG/Day dose. Below graphs represent the Distribution of patients on deferasirox dose

Graph 12a: Deferasirox doses in Thalassemia patients

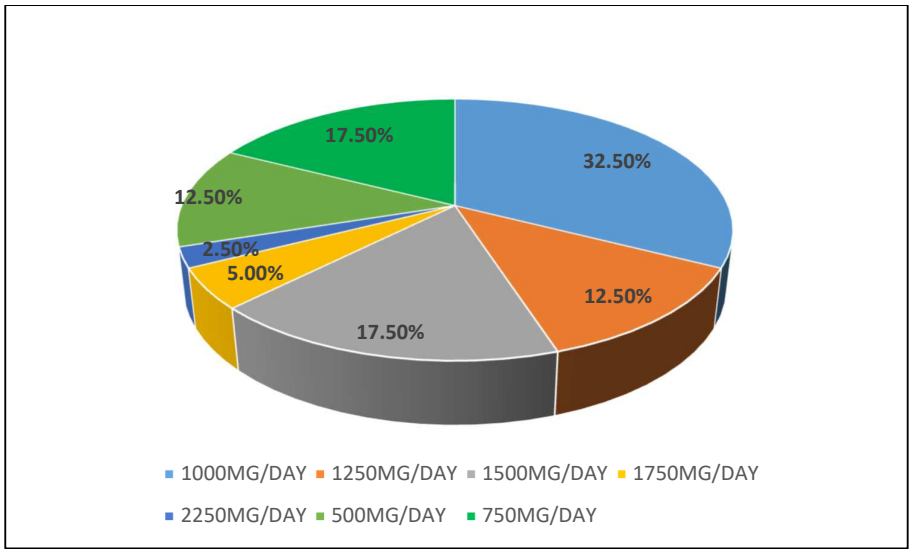
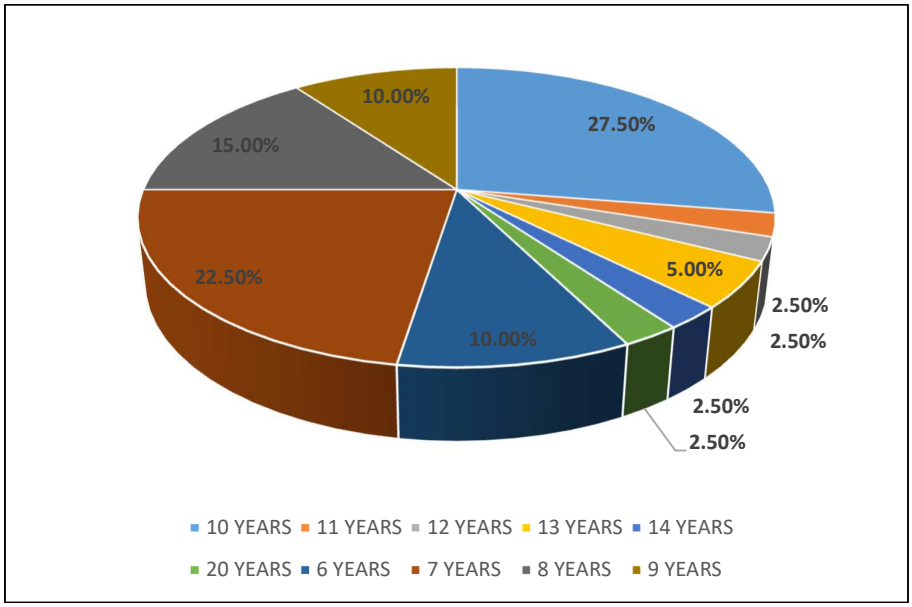


Table 12b: Deferasirox duration in Thalassemia patients

DEFERASIROX: DURATION	Counts	Percentage
10 YEARS	11	27.50
11 YEARS	1	2.50
12 YEARS	1	2.50
13 YEARS	2	5.00
14 YEARS	1	2.50
20 YEARS	1	2.50
6 YEARS	4	10.00
7 YEARS	9	22.50
8 YEARS	6	15.00
9 YEARS	4	10.00
Total	40	100.00

Graph 12b: Deferasirox duration in Thalassemia patients

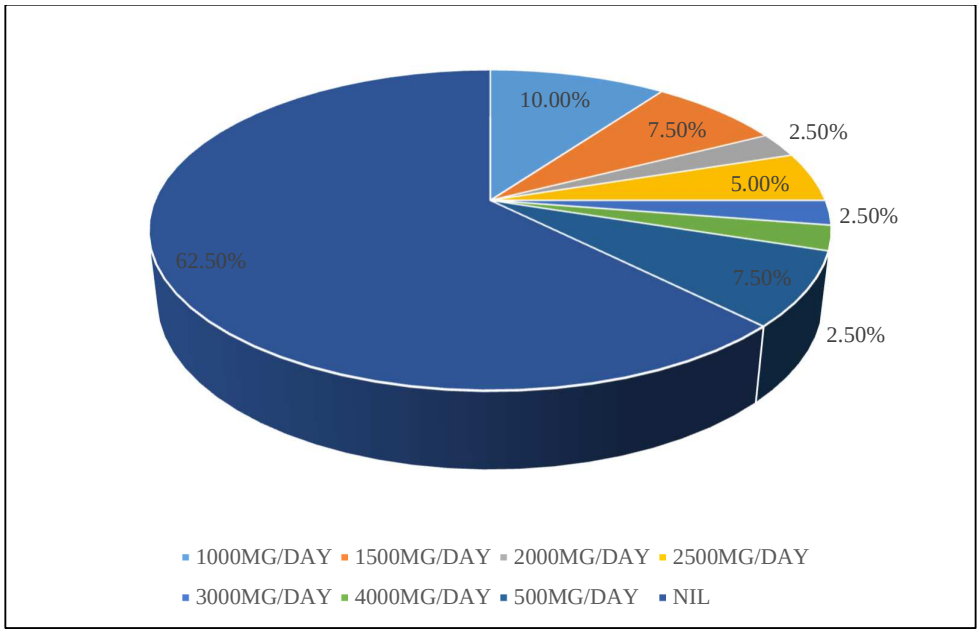


Above table gives the summary of deferasirox duration and we can observe that 11 (27.50%) patients were reported a duration of 10 Years. Below graphs represent the Distribution of patients on deferasirox duration.

Table 13a: Deferiprone doses in Thalassemia patients

DEFERIPRONE: DOSE	Counts	Percentage
1000MG/DAY	4	10
1500MG/DAY	3	7.5
2000MG/DAY	1	2.5
2500MG/DAY	2	5
3000MG/DAY	1	2.5
4000MG/DAY	1	2.5
500MG/DAY	3	7.5
NIL	25	62.5
Total	40	100

Graph 13a: Deferiprone doses in Thalassemia patients



Deferiprone dose of 1000MG/Day was taken by 4 patients, 1500MG/Day was taken by 3 patients, 500MG/Day was taken by 3 patients, 2500MG/Day was taken by 2 patients, remaining doses were taken by one person each.

Table 13b: Duration of deferiprone taken in patients

DEFERIPRONE: DURATION	Counts	Percentage
1 YEAR	2	5.00
3 MONTHS	1	2.50
3 YEARS	3	7.50
5 MONTHS	1	2.50
5 YEARS	1	2.50
6 MONTHS	2	5.00
6 YEARS	2	5.00
7 MONTHS	3	7.50
NA	25	62.50
Total	40	100.00

Deferiprone duration of 7 MONTHS were found in three patients, also 3 YEARS were found in three patients. 6 MONTHS were found in two patients and 6 YEARS were found in two patients, 3 MONTHS, 5 MONTHS, 5 YEARS were found in 1 patient each.

Graph 13b: Duration of deferiprone taken in patients

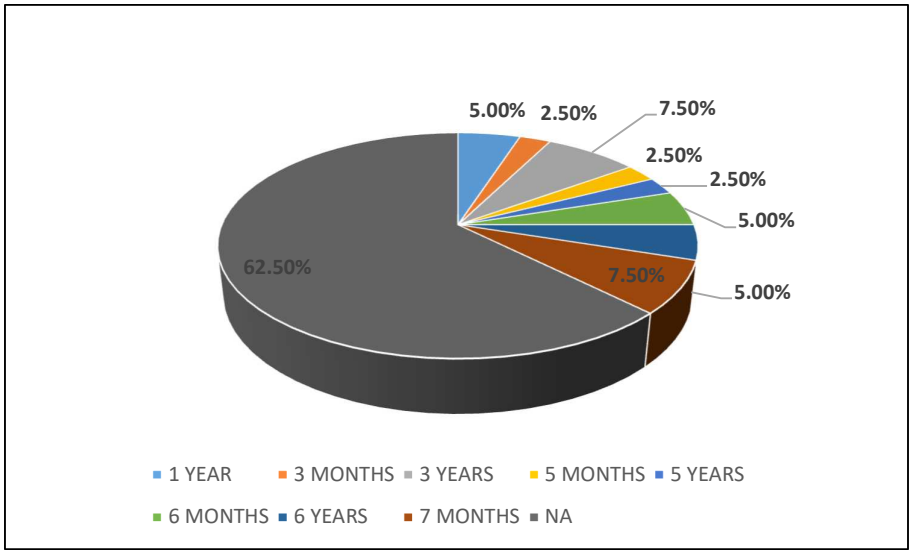


Table 14: Ditribution of treatment history in past

TREATMENT HISTORY IN PAST	Counts	Percent
NIL	34	85.00
SPLENECTOMY DONE	5	12.50
TRIVIAL MR,TR,AR	1	2.50
Total	40	100.00

Above table gives the summary of treatment history in past of the patients and we can observe that 05 (12.50%) patients were reported SPLENECTOMY as a past treatment history. Below graphs represent the Distribution of patients on treatment history in past.

Graph 14: Distribution of treatment history in past

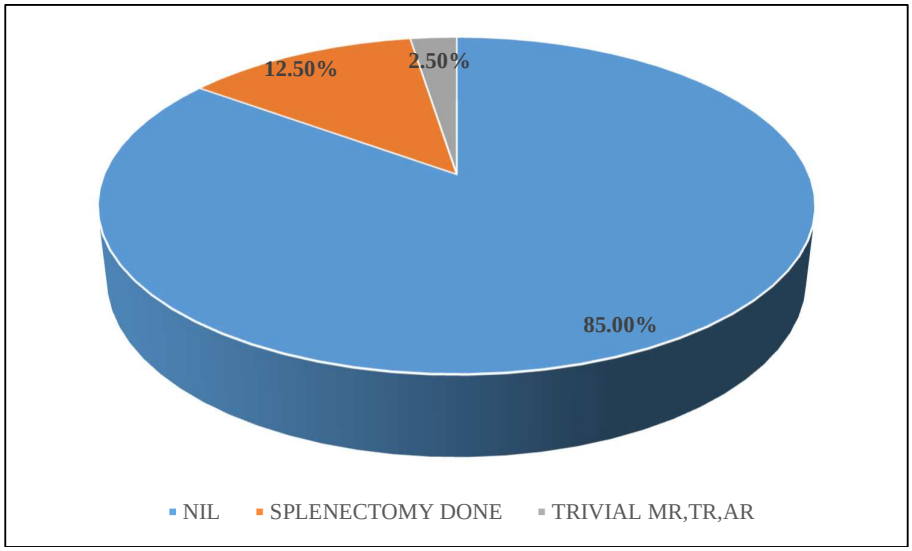


Table 15: Distribution of consanguineous / nonconsanguineos

Consanguineous/non consanguineous	Counts	Percentage
CM	15	37.50
NCM	25	62.50
Total	40	100.00

Above table gives the summary of consanguineous/non consanguineous among the patients and we can observe that 25 (62.50%) patients were reported NCM. Below graphs represent the Distribution of consanguineous/non consanguineous.

Graph 15: Distribution of CONSANGUIEOUS/NON CONSANGUINEOS

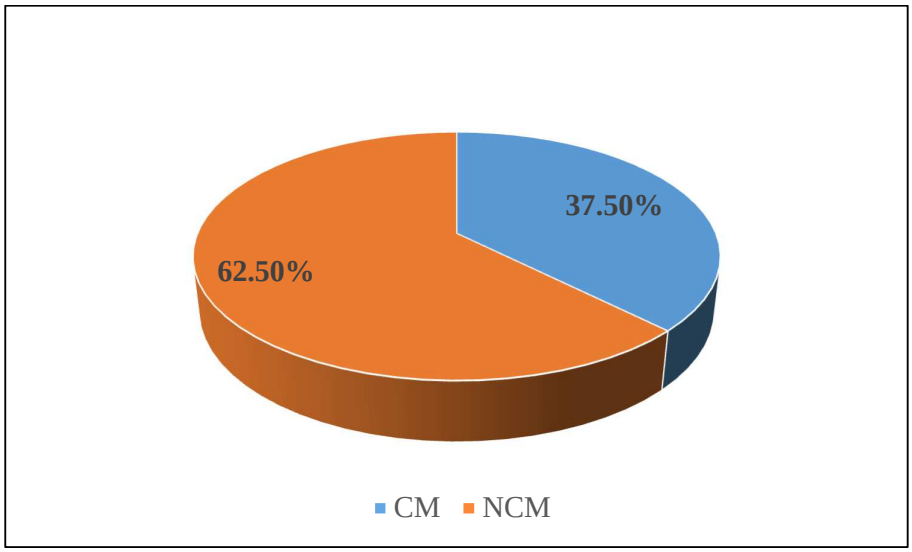


Table 16: Distribution of Sibling status

SIBLING STATUS	Counts	Percentage
NO	35	87.50
YES	5	12.50
Total	40	100.00

Above table gives the summary of number of patients siblings affected and we can observe that 35 (87.50%) patients were reported No i.e. patients siblings were not affected. Below graphs represent the Distribution of Sibling status.

Graph 16: Distribution of sibling status

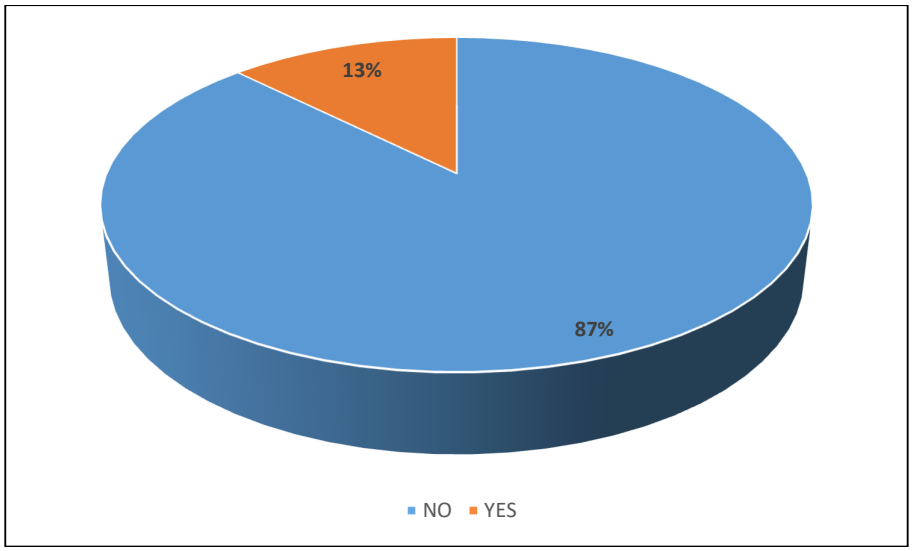


Table 17: Number of Sibling deaths

Siblings death	Counts	Percentage
Yes	3	7.50
No	37	92.50
Total	40	100.00

Above table gives the summary of number of patients siblings deaths and we can observe that 37 (92.50%) patients were reported No i.e. patients siblings were not died. Below graphs represent the Distribution of Sibling death.

Graph 17: Number of Sibling deaths

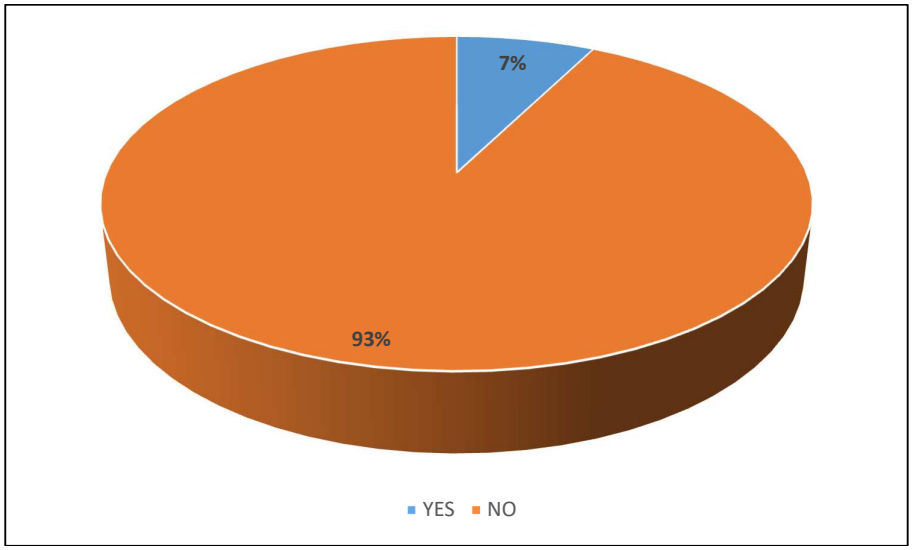


Table 18: Distribution of signs in faces

Signs in faces	Counts	Percentage
NORMAL	7	17.50%
FRONTAL BOSSING	2	5.00%
HYPERTELORISM,PROTRUDED JAW	1	2.50%
THALASSEMIC FACIES	9	22.50%
DEPRESSED NASAL BRIDGE,WIDE EYES	1	2.50%
DEPRESSED NASAL BRIDGE,HYPERTELORISM	1	2.50%
DEPRESSED NASAL BRIDGE,THALASSEMIC FACIES,FRONTAL BOSSING	2	5.00%
DEPRESSED NASAL BRIDGE,THALASSEMIC FACIES	1	2.50%
DEPRESSED NASAL BRIDGE	16	40.00%
Total	40	100.00%

Above table gives the summary sings in faces and it was observed that 16 (40%) patients were having reported DEPRESSED NASAL BRIDGE faces sign. Below graphs represent the Distribution of signs in faces

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Graph 18: Distribution of signs in faces

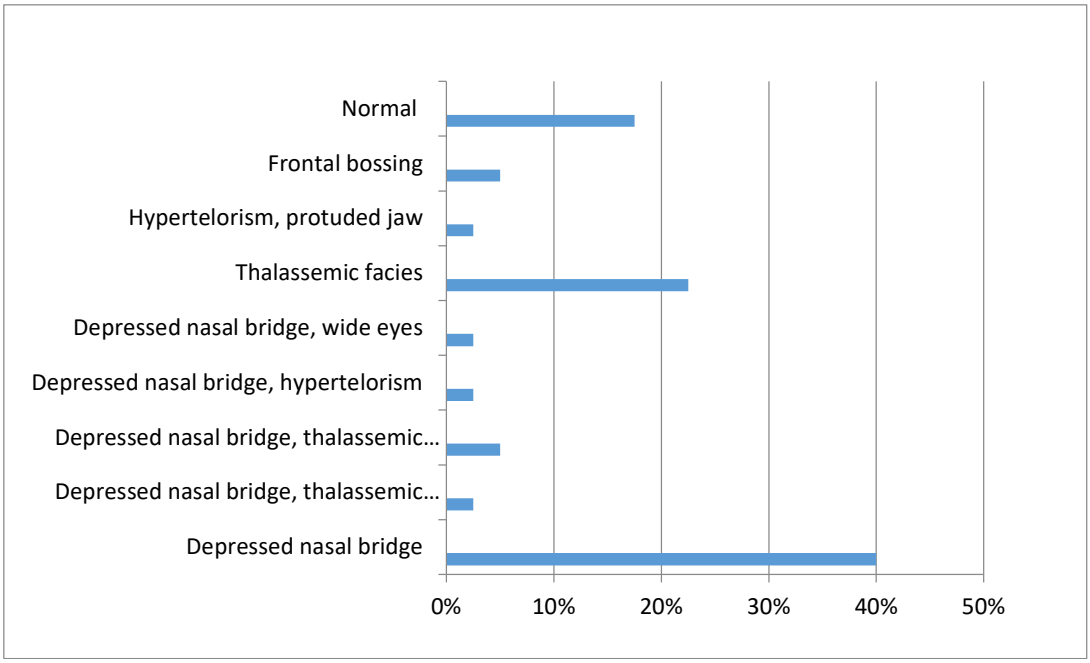

Table 19: Distribution of signs in eyes

EYES	Counts	Percentage
NORMAL	9	22.50%
ICTERUS, HYPERTELORISM	1	2.50%
ICTERUS	1	2.50%
PALLOR, HYPERTELORISM	1	2.50%
PALLOR	28	70.00%
Total	40	100.00%

Above table gives the summary sings in eyes and it was observed that 28 (70%) patients were having reported PALLOR signs in eyes. Below graphs represent the Distribution of signs in eyes.

Graph 19: Distribution of signs in eyes

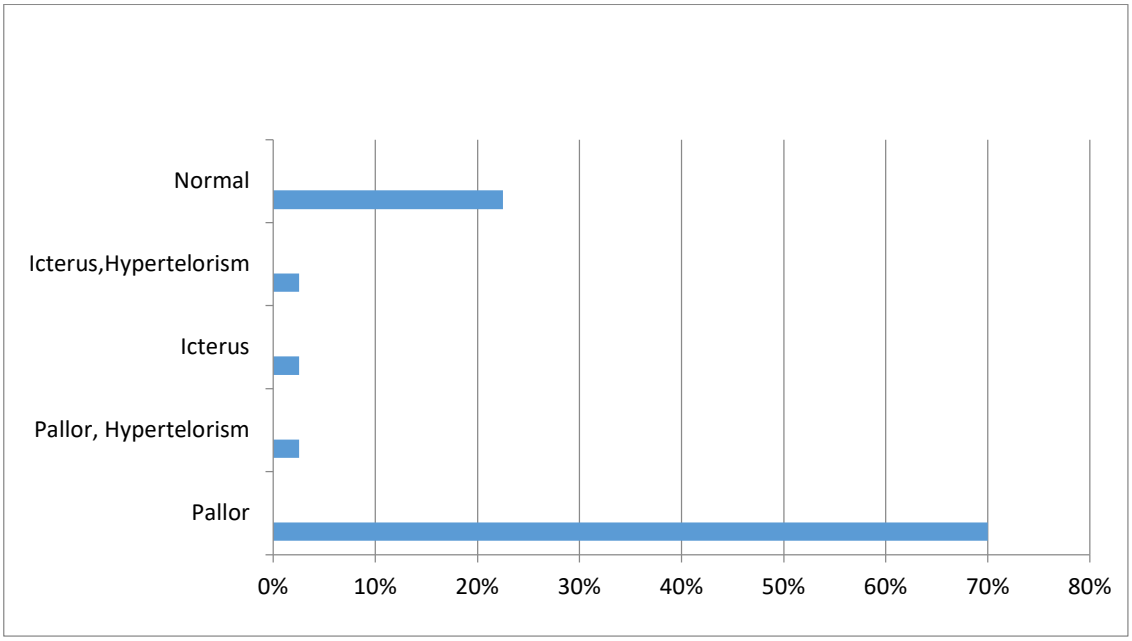

Table 20: Distribution of signs in oral cavity

ORAL CAVITY	Counts	Percentage
HYPERPLASIA OF MAXILLARY BONE	18	45.00%
HYPERPLASIA OF MAXILLARY BONE, DENTAL MALOOCLUSION	1	2.50%
PROTRUDED TEETH	1	2.50%
DENTAL MALALIGNMENT	6	15.00%
DENTAL MALOOCLUSION	7	17.50%
NORMAL	7	17.50%
Total	40	100.00%

Above table gives the summary sings in oral cavity and it was observed that 18 (45%) patients were having reported HYPERPLASIA OF MAXILLARY BONE signs in oral cavity. Below graphs represent the Distribution of signs in oral cavity.

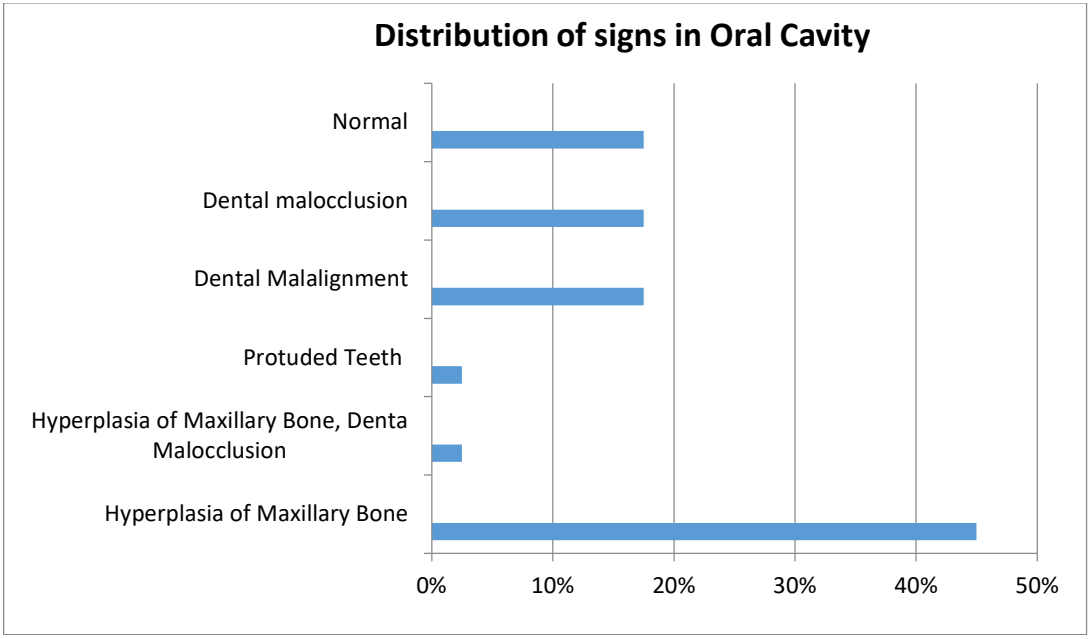

Table 21: Distribution of presence of ODEMA

ODEMA	Counts	Percentage
NO	37	92.50
YES	3	7.50
Total	40	100.00

Above table gives the summary of presence of ODEMA and only 3 (7.50%) patients reported the presence of ODEMA. Below graphs represent the Distribution of presence of ODEMA.

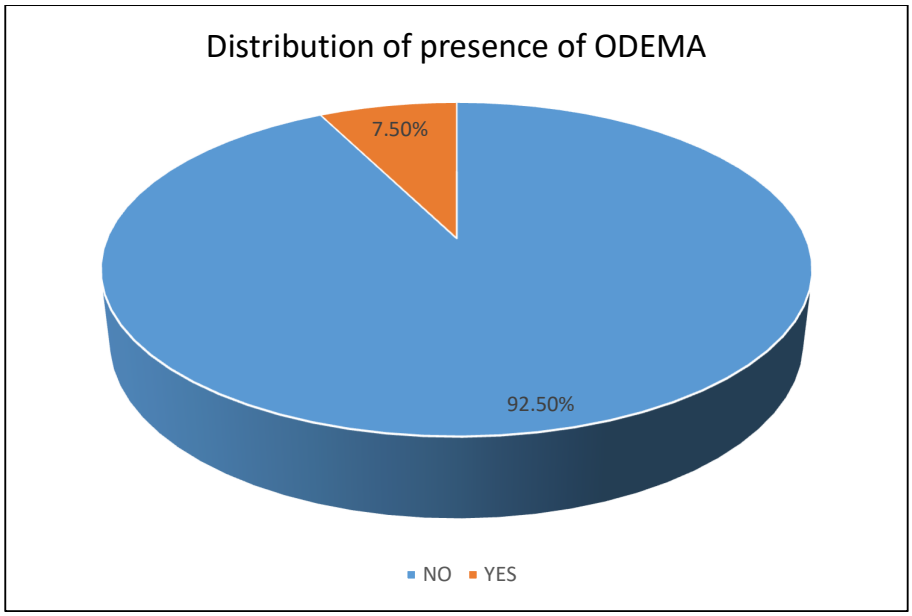

Table 22: Distribution of hepatomegaly patients

LIVER SPAN:1ST	Counts	Percentage
10CM	6	15.00
11CM	1	2.50
12CM	6	15.00
13CM	12	30.00
14CM	9	22.50
7CM	2	5.00
8CM	3	7.50
9CM	1	2.50
Total	40	100.00

Above table gives the summary of hepatomegaly patients and 12 (30%) patients observed the LIVER SPAN of 13CM. Below graphs represent the Distribution of hepatomegaly patients.

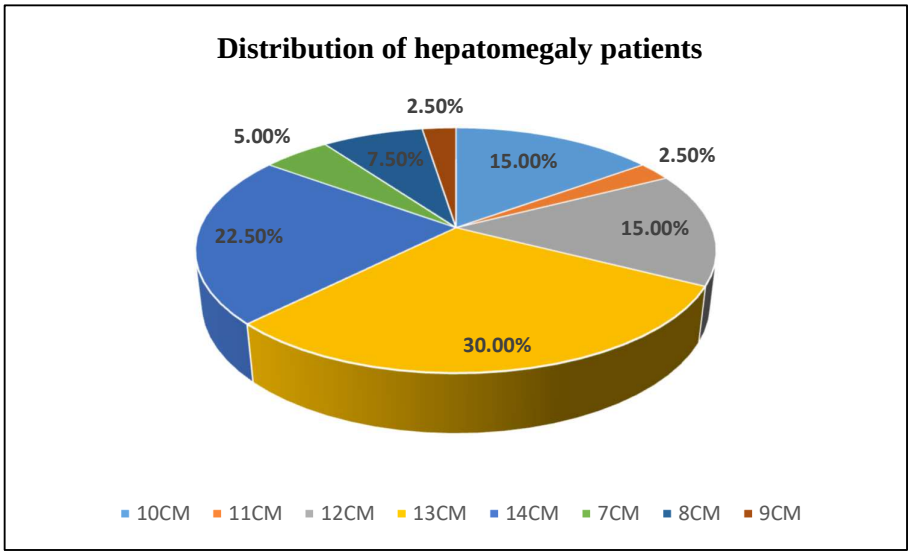

Table 23: Distribution of splenomegaly patients

SPLEEN SPAN:1ST	Counts	Percentage
1CM BELOWLCM	3	7.50
2CM BELOW LCM	7	17.50
3CM BELOW LCM	5	12.50
4CM BELOW LCM	3	7.50
5CM BELOW LCM	2	5.00
6CM BELOW LCM	1	2.50
NIL	17	42.50
NOT PALPABLE	2	5.00
Total	40	100.00

Above table gives the summary of splenomegaly patients and 07 (17.50%) patients observed the SPLEEN SPAN of 2CM BELOW LCM. Below graphs represent the Distribution of splenomegaly patients.

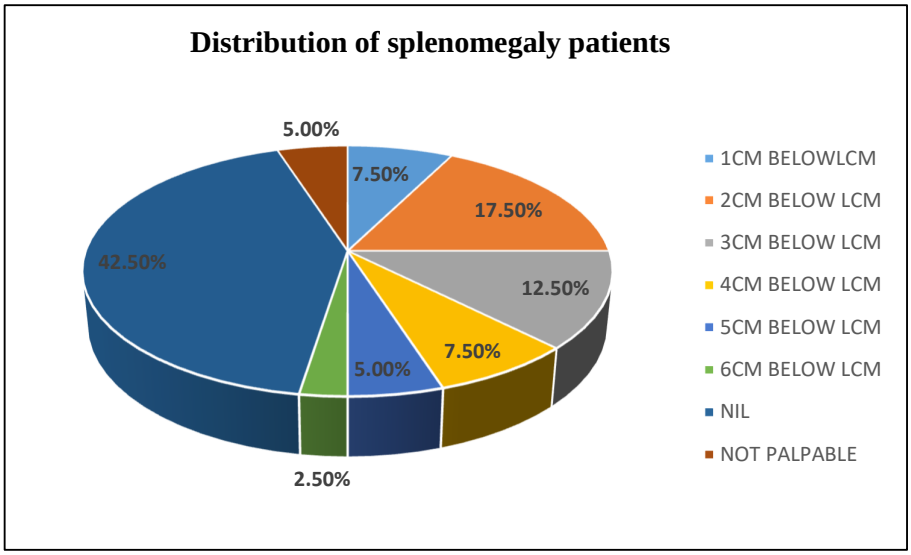

Table 24: Distribution of Albumin

24HR:ALBUMIN	Counts	Percentage
<0.1	8	20.00
<0.3	1	2.50
<0.5	31	77.50
Total	40	100.00

Above table gives the summary of Albumin and 31 (17.50%) patients observed the Albumin of <0.5. Below graphs represent the Distribution of Albumin of patients.

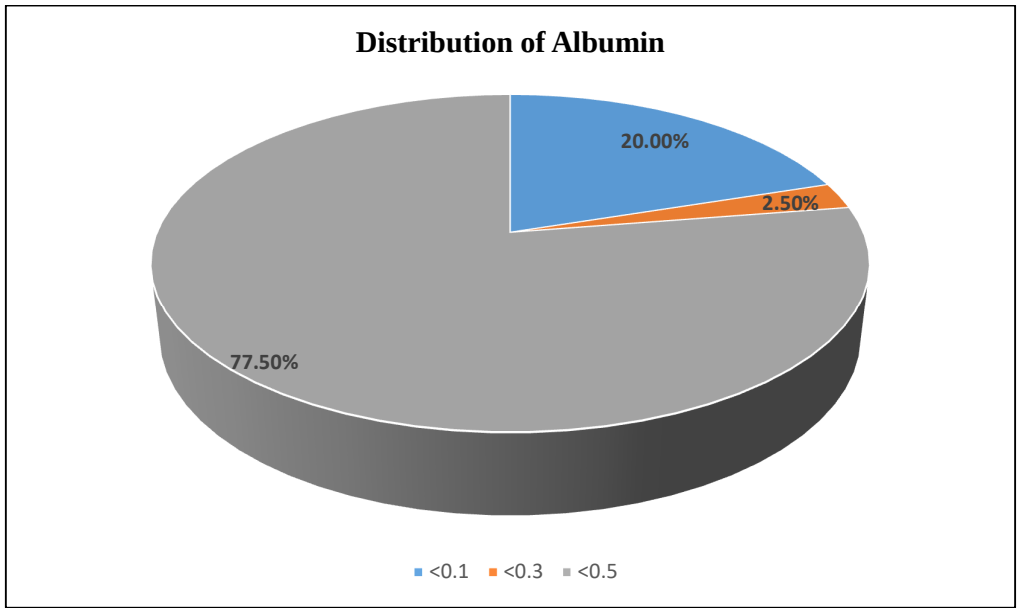

Table 25: Summary of continuous variables

Variable	N	Mean	SD	Minimum	Maximum
AGE	40	13.20	2.95	8.00	18.00
Hb(mg/dl)	40	8.66	1.07	5.90	10.90
UREA	40	30.13	20.53	12.00	98.00
CREATININE	40	0.68	0.19	0.3	1.2
FERRITIN	40	3540.63	2261.16	670.00	10173.00
24HR:CREATININE	40	601.17	564.30	48.20	2805.00
24HR:SODIUM	40	527.20	838.57	41.80	3705.00
24HR:POTASSIUM	40	91.43	135.82	5.05	631.50
24HR:CALCIUM	40	121.61	113.58	11.20	497.60
U.BETA 2 MG	40	667.32	951.28	10.80	7713.00
FE Na	40	0.75	1.41	0.02	7.00
FE K	40	2.19	3.15	0.16	16.00
CREATININE CL	40	119.79	55.11	36.70	304.50
eGFR	40	112.21	52.59	38.8	278.8

The above table summarizes the continuous variables by Mean, SD, Minimum, Maximum. For each continuous variable is represented using a box plot below. The red circle indicates the mean of each variable. The white circle represent the observation which are not in the normal range.

Table 26: Comparison of age and levels of Beta 2 Microglobulin (N=40)

Age	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
8-13 Years	1 (6.25%)	16 (66.67%)	14.339	<0.001
13-18 Years	15 (93.75%)	8 (33.33%)		

The levels of Beta 2 Microglobulin and the Age is found to be significant with a P-value of <0.001, with majority of 15 (93.75%) participants within 13-18 Years Of Age.

Figure 25: Cluster bar chart of comparison of age and levels of Beta 2 Microglobulin (N=40)

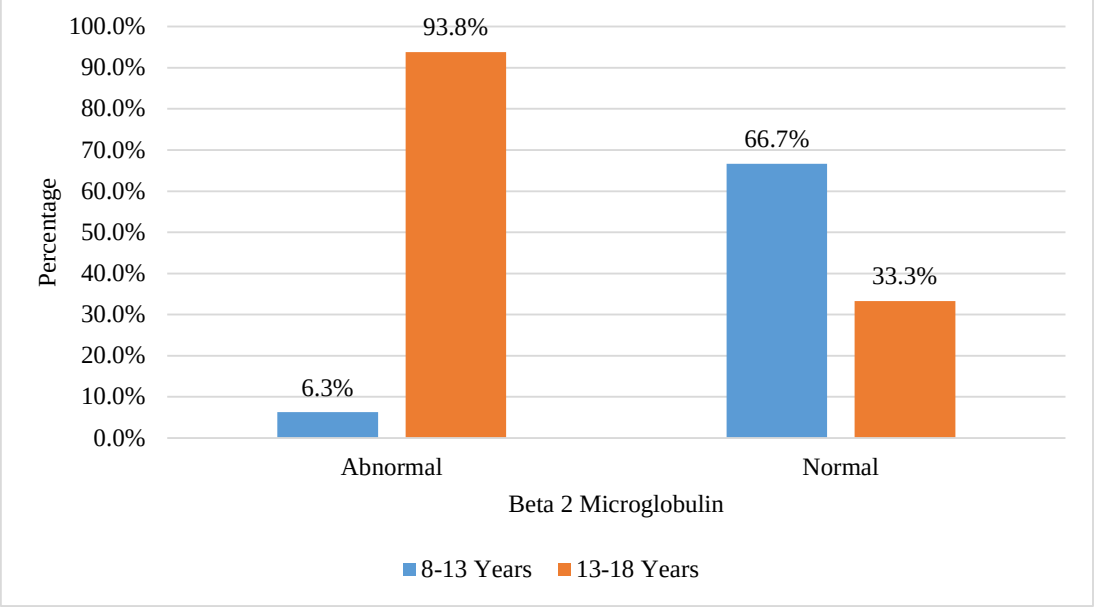

Table 27: Comparison of age and levels of urea (N=40)

Age	Urea		Chi square	P value
	Abnormal (N=4)	Normal (N=36)		
8-13 Years	0 (0%)	17 (47.22%)	3.67	0.040
13-18 Years	4 (100%)	19 (52.78%)		

The levels of Urea and the Age is found to be significant with a P- value of 0.040, with majority of 4 (100%) participants within 13-18 Years of Age.

Figure 26: Cluster bar chart of comparison of age and levels urea (N=40)

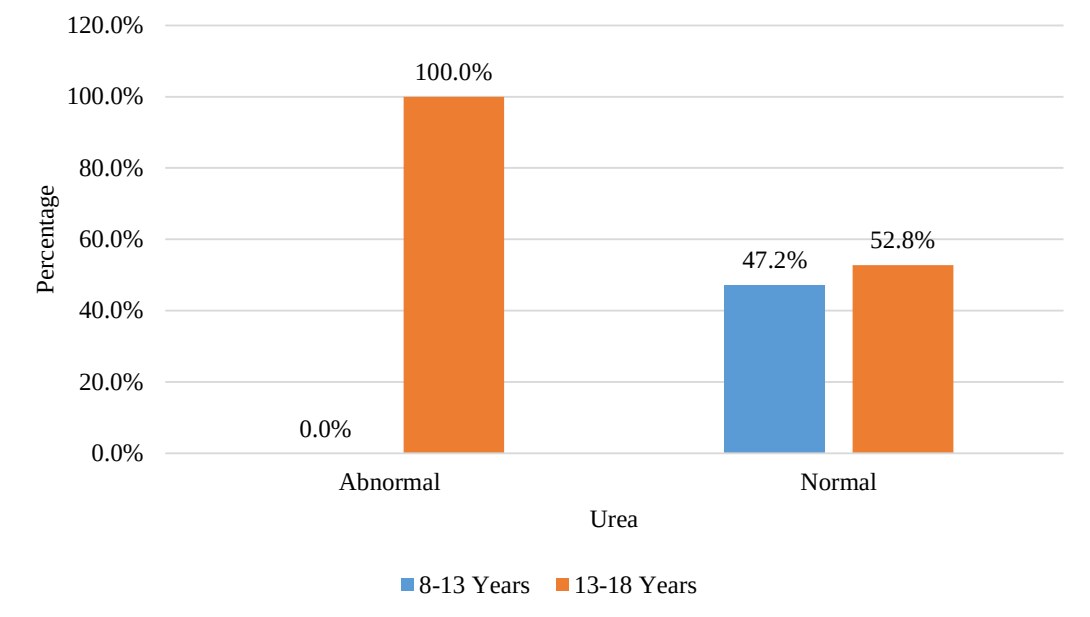

Table 28: Comparison of age and levels of Creatinine (N=40)

Age	Creatinine		Chi square	P value
	Abnormal (N=7)	Normal (N=33)		
8-13 Years	0 (0%)	17 (51.52%)	6.27	0.012
13-18 Years	7 (100%)	16 (48.48%)		

The difference in levels of Creatinine and the Age is found to be significant with a P-value of 0.012, with majority of 7 (100%) participants within 13-18 Years of Age.

Figure 27: Cluster bar chart of comparison of age and Creatinine levels (N=40)

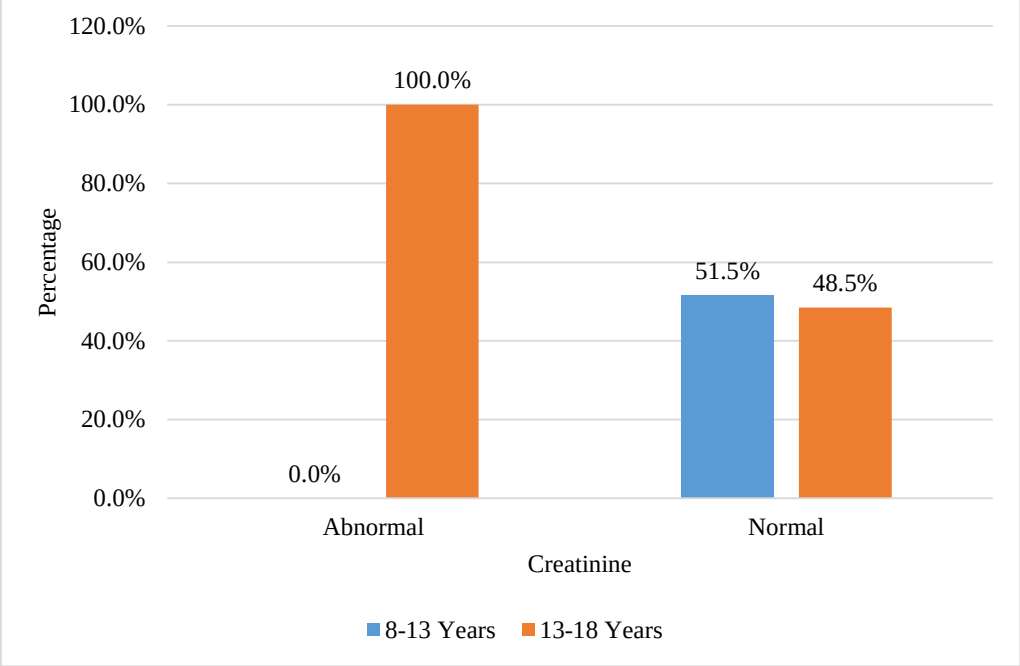

Table 29: Comparison of age and EGFR value (N=40)

Age	EGFR		Chi square	P value
	Normal (N=25)	Abnormal (N=15)		
8-13 Years	13 (52%)	4 (26.67%)	2.462	0.117
13-18 Years	12 (48%)	11 (73.33%)		

The difference in EGFR value and the Age is found to be insignificant with a P- value of 0.117, with majority of 11 (73.33%) participants within 13-18 Years Of Age.

Figure 28: Cluster bar chart of comparison of age and EGFR value (N=40)

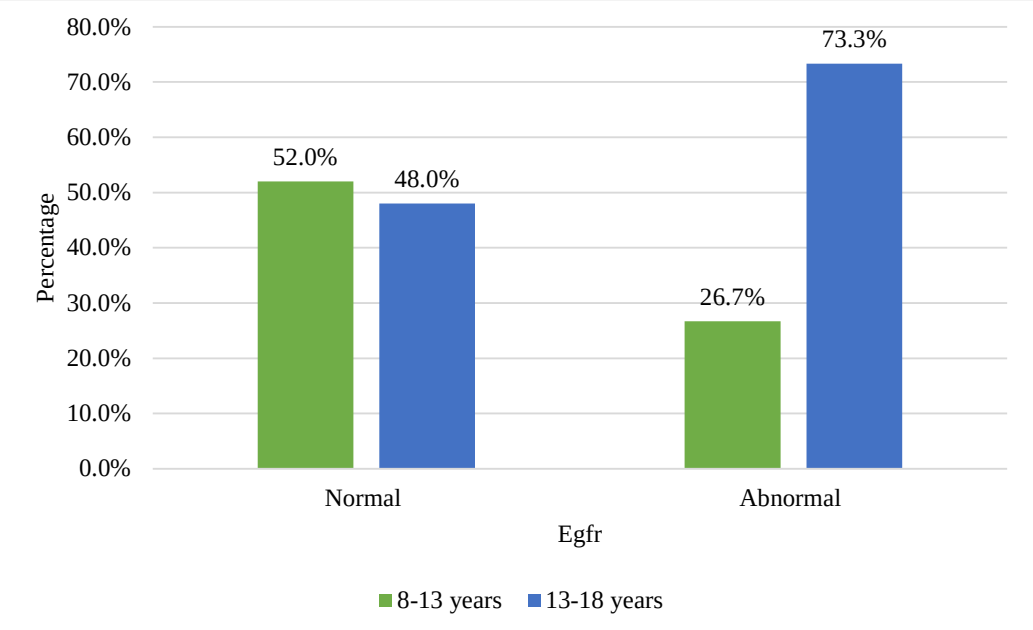

Table 30: Comparison of duration of thalassemia and beta-2 microglobulin levels (N=40)

Duration Of Thalassemia (Years)	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
8-12 Years	1 (6.25%)	20 (83.33%)	22.874	<0.001
12-17 Years	15 (93.75%)	4 (16.67%)		

The difference in Beta 2 Microglobulin levels and the Duration of Thalassemia (Years) is found to be significant with a P- value of <0.001, with majority of 15 (93.75%) participants within 12-17 Years of Duration of Thalassemia (Years).

Figure 29: Cluster bar chart of comparison of duration of thalassemia and beta-2 microglobulin levels (N=40)

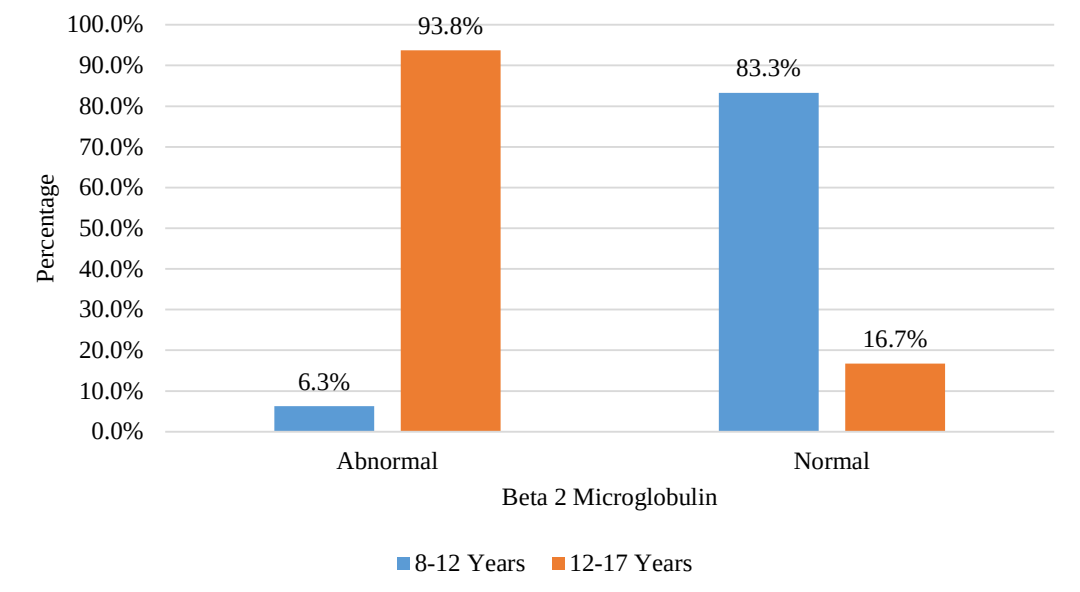

Table 31: Comparison of duration of thalassemia and urea levels (N=40)

Duration Of Thalassemia (Years)	Urea		Chi square	P value
	Abnormal (N=4)	Normal (N=36)		
8-12 Years	0 (0%)	21 (58.33%)	4.91	0.027
12-17 Years	4 (100%)	15 (41.67%)		

The difference in Urea levels and the Duration of Thalassemia (Years) is found to be significant with a P- value of 0.027, with majority of 4 (100%) participants within 12-17 Years of Duration of Thalassemia (Years).

Figure 30 Cluster bar chart of comparison of duration of thalassemia and Urea levels (N=40)

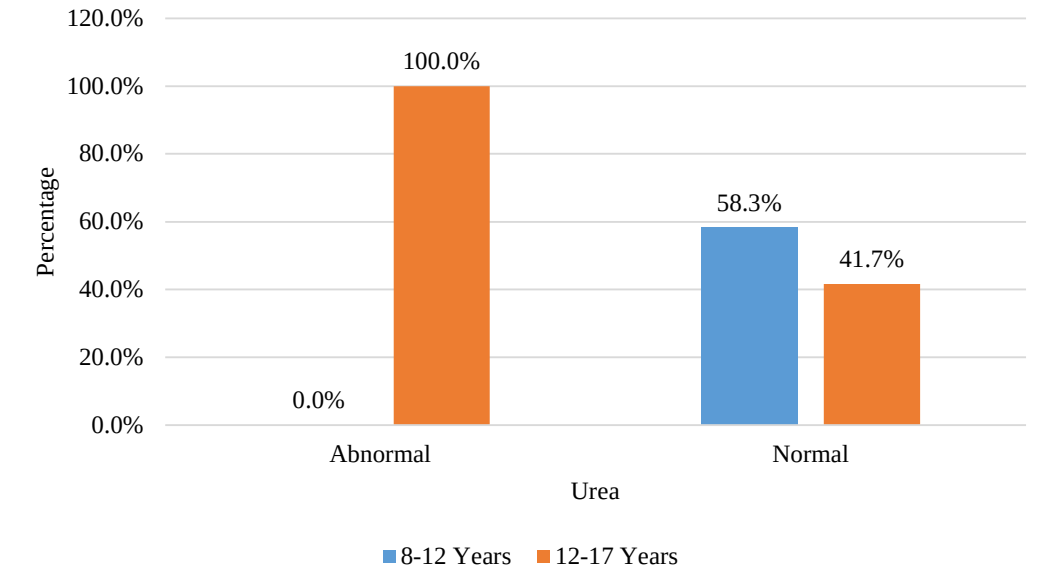

Table 32: Comparison of duration of thalassemia and creatinine levels (N=40)

Duration Of Thalassemia (Years)	Creatinine		Chi square	P value
	Abnormal (N=7)	Normal (N=33)		
8-12 Years	0 (0%)	21 (63.64%)	9.09	0.002
12-17 Years	7 (100%)	12 (36.36%)		

The difference in Creatinine levels and the Duration of Thalassemia (Years) is found to be significant with a P- value of 0.002, with majority of 7 (100%) participants within 12-17 Years of Duration of Thalassemia (Years).

Figure 31: Cluster bar chart of comparison of duration of thalassemia and Creatinine levels (N=40)

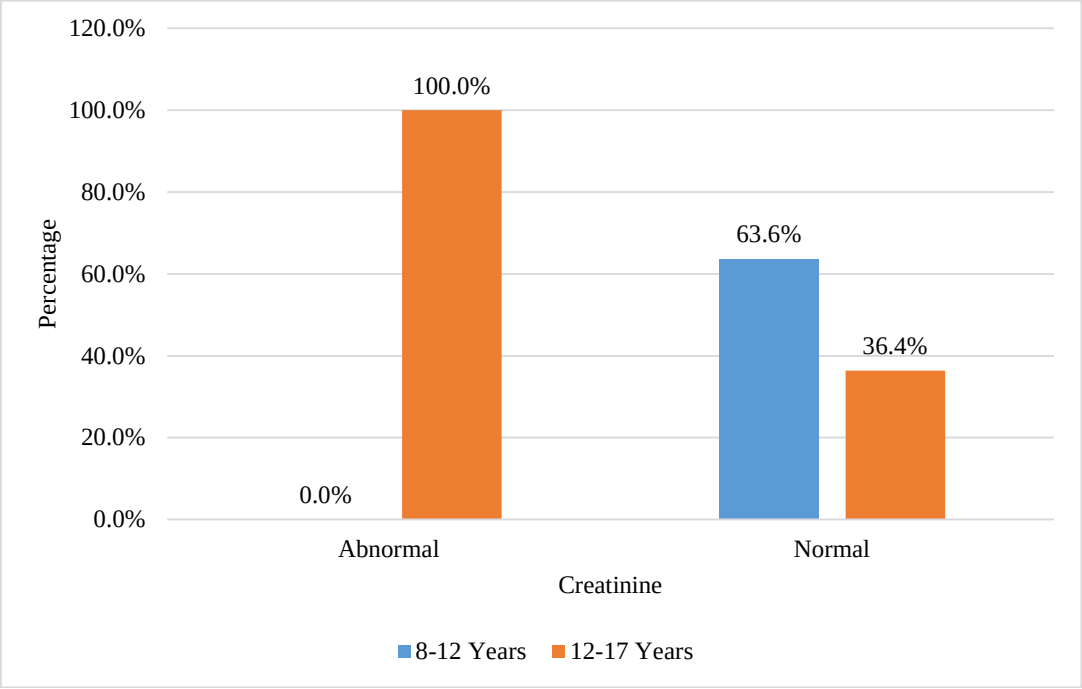

Table 33: Comparison of duration of thalassemia and EGFR value (N=40)

Duration Of Thalassemia (Years)	EGFR		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
8-12 Years	1 (6.25%)	20 (83.33%)	22.874	<0.001
12-17 Years	15 (93.75%)	4 (16.67%)		

The difference in EGFR value and the Duration of Thalassemia (Years) is found to be significant with a P- value of <0.001, with majority of 15 (93.75%) participants within 12-17 Years of Duration of Thalassemia (Years).

Figure 32: Cluster bar chart of comparison of duration of thalassemia and EGFR value (N=40)

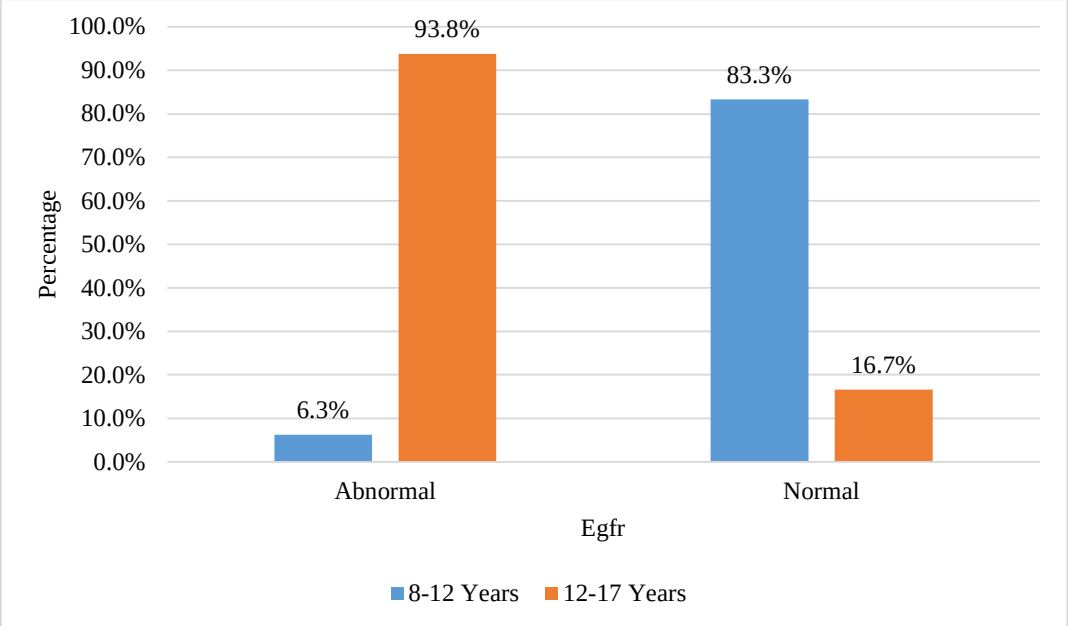

Table 34: Comparison of Duration of Deferasirox and beta-2 microglobulin levels (N=40)

Duration Of Deferasirox (Years)	Beta 2 Microglobulin		Chi square	Fisher exact P value
	Abnormal (N=16)	Normal (N=24)		
6-10 Years	13 (81.25%)	21 (87.5%)	3.50	0.034
11-14 Years	3 (18.75%)	3 (12.5%)		

The difference in Beta 2 Microglobulin levels and the Duration of Deferasirox (Years) is found to be significant with a P- value of 0.034, with majority of 13 (81.25%) participants within 6-10 Years of Duration of Deferasirox (Years).

Figure 33: Cluster bar chart of comparison of duration of Deferasirox and beta-2 microglobulin levels (N=40)

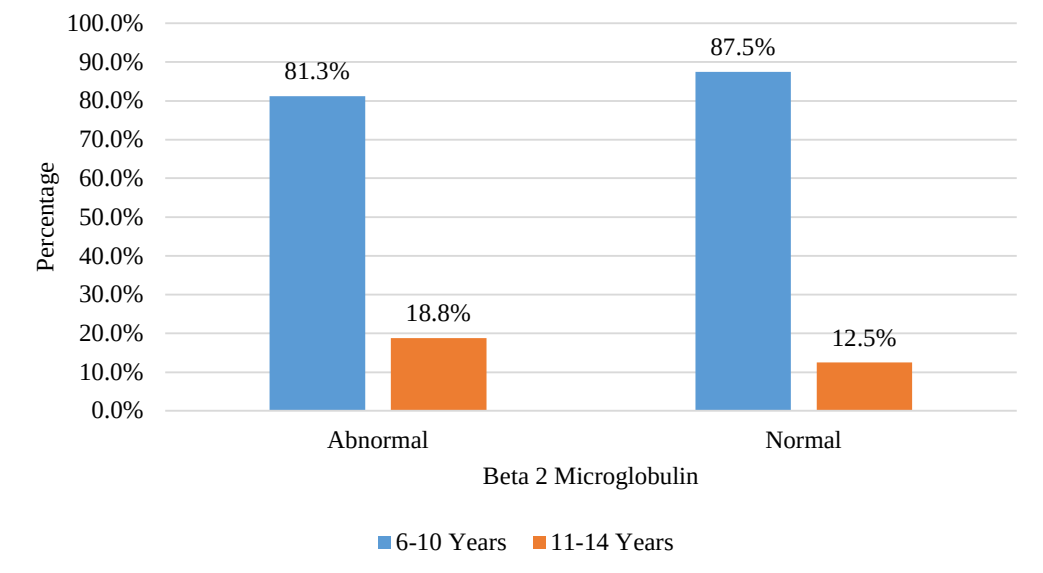

Table 35: Comparison of duration of deferasirox and Urea levels (N=40)

Duration Of Deferasirox (Years)	Urea		Chi square	P value
	Abnormal (N=4)	Normal (N=36)		
6-10 Years	4 (100%)	30 (83.33%)	0.784	0.376
11-14 Years	0 (0%)	6 (16.67%)		

The difference in Urea levels and Duration Of Deferasirox (Years) is found to be insignificant with a P- value of 0.376, with majority of 4 (100%) participants within 6-10 Years of Duration Of Deferasirox (Years).

Figure 34: Cluster bar chart of comparison of duration of deferasirox and urea levels (N=40)

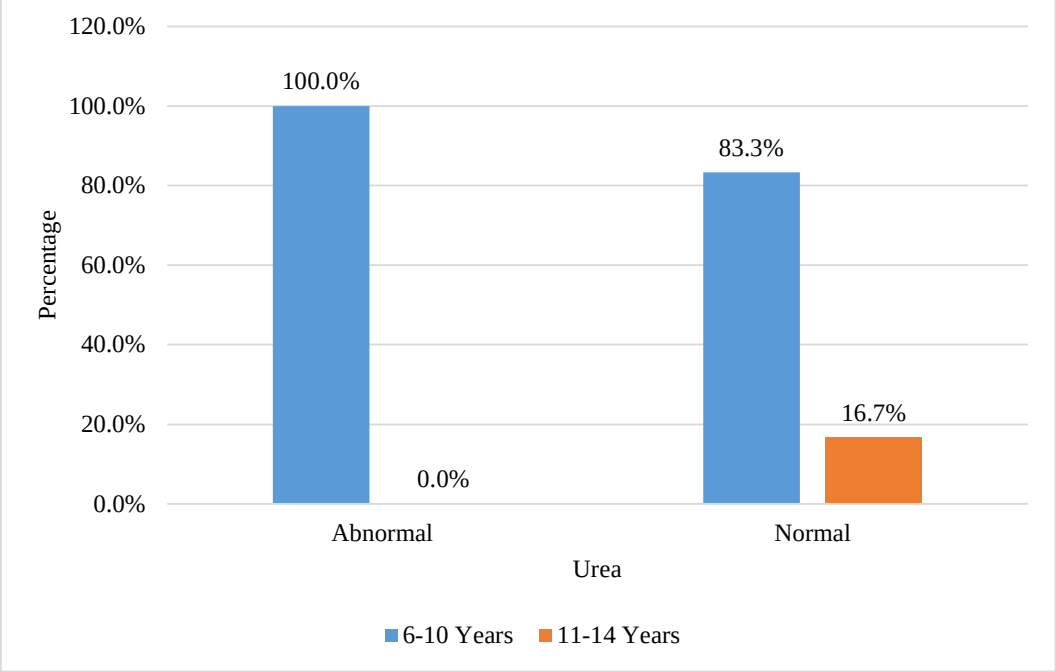

Table 36: Comparison of duration of deferasirox and creatinine levels (N=40)

Duration Of Deferasirox (Years)	Creatinine		Chi square	Fisher exact P value
	Abnormal (N=7)	Normal (N=33)		
6-10 Years	6 (85.71%)	28 (84.85%)	4.50	0.003
11-14 Years	1 (14.29%)	5 (15.15%)		

The difference in Creatinine levels and the Duration of Deferasirox (Years) is found to be significant with a P- value of 0.003, with majority of 13 6 (85.71%) participants within 6-10 Years of Duration of Deferasirox (Years).

Figure 35: Cluster bar chart of comparison of duration of deferasirox and creatinine levels (N=40)

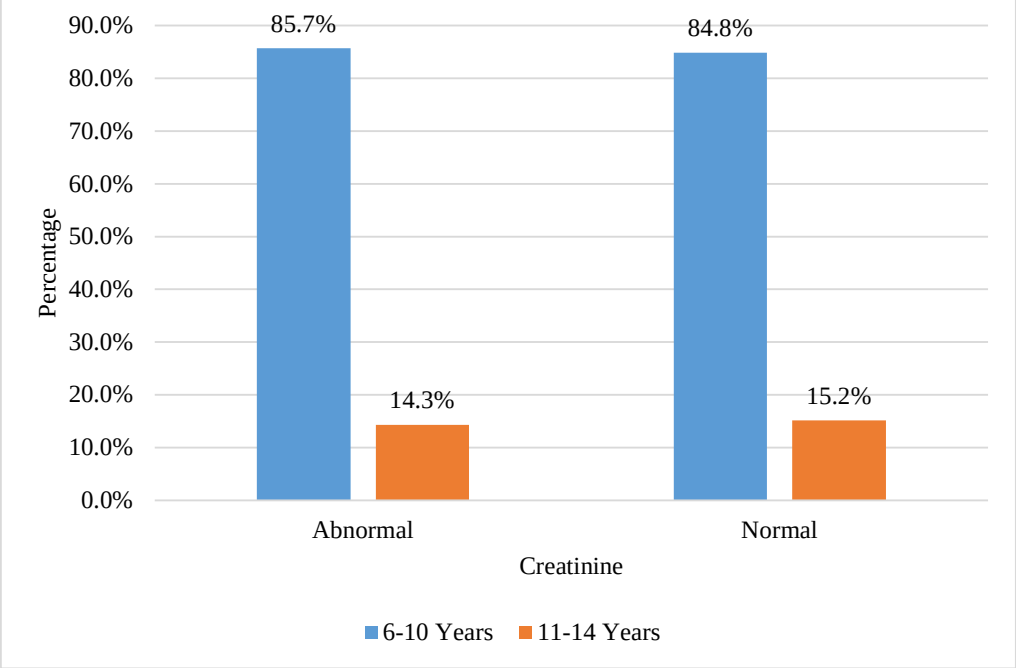

Table 37: Comparison of duration of deferasirox and EGFR (N=40)

Duration Of Deferasirox (Years)	EGFR		Chi square	Fisher exact P value
	Abnormal (N=16)	Normal (N=24)		
6-10 Years	12 (75%)	22 (91.67%)	2.99	0.043
11-14 Years	4 (25%)	2 (8.33%)		

The difference in EGFR values and Duration Of Deferasirox (Years) is found to be significant with a Fisher exact P- value of 0.043, with majority of 22 (91.67%) participants within 6-10 Years of Duration Of Deferasirox (Years).

Figure 36: Cluster bar chart of comparison of duration of defariox between EGFR (N=40)

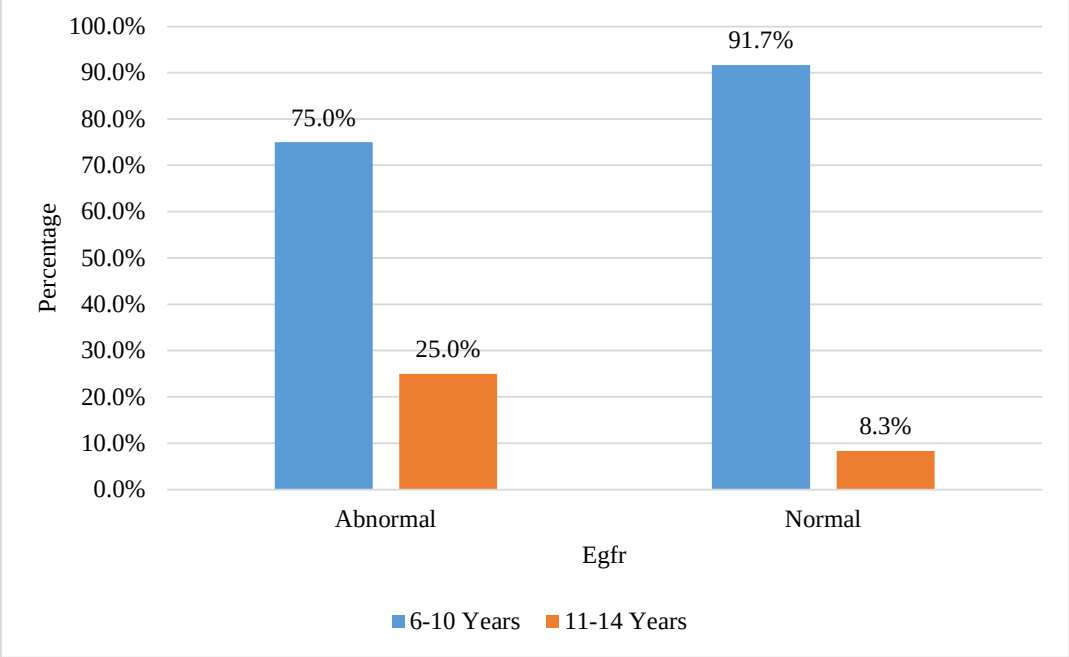

Table 38: Correlation of ferritin levels with beta-2 microglobulin levels (N=40)

Level Of Ferritin	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
<=2500	3 (18.75%)	14 (58.33%)	6.155	0.013
>2500	13 (81.25%)	10 (41.67%)		

The correlation of Levels of Ferritin with Beta 2 Microglobulin is found to be significant with a P- value of 0.013, with majority of 13 (81.25%) participants within >2500 of Level of Ferritin.

Figure 37: Cluster bar chart Correlation of Ferritin levels with beta-2 microglobulin (N=40)

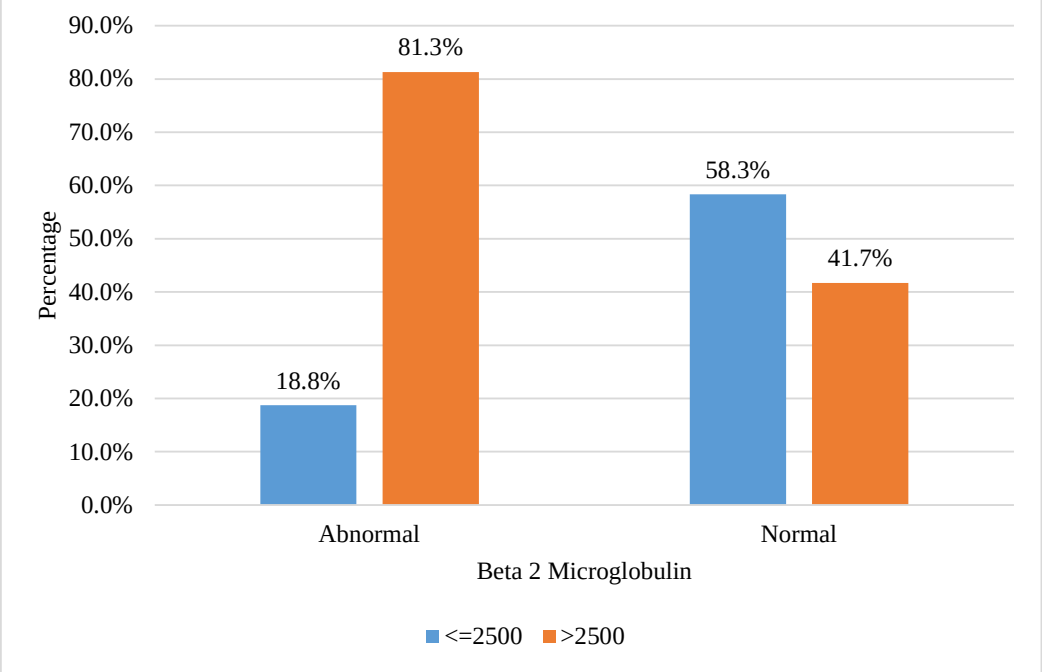

Table 39: Correlation of ferritin levels with Urea levels (N=40)

Level Of Ferritin	Urea		Chi square	P value
	Abnormal (N=4)	Normal (N=36)		
<=2500	0 (0%)	17 (47.22%)	3.34	0.046
>2500	4 (100%)	19 (52.78%)		

The correlation of Levels of Ferritin with Urea levels is found to be significant with a P- value of 0.046, with majority of 4 (100%) participants within >2500 of Level Of Ferritin.

Figure 38: Cluster bar chart of Correlation of ferritin levels with Urea levels (N=40)

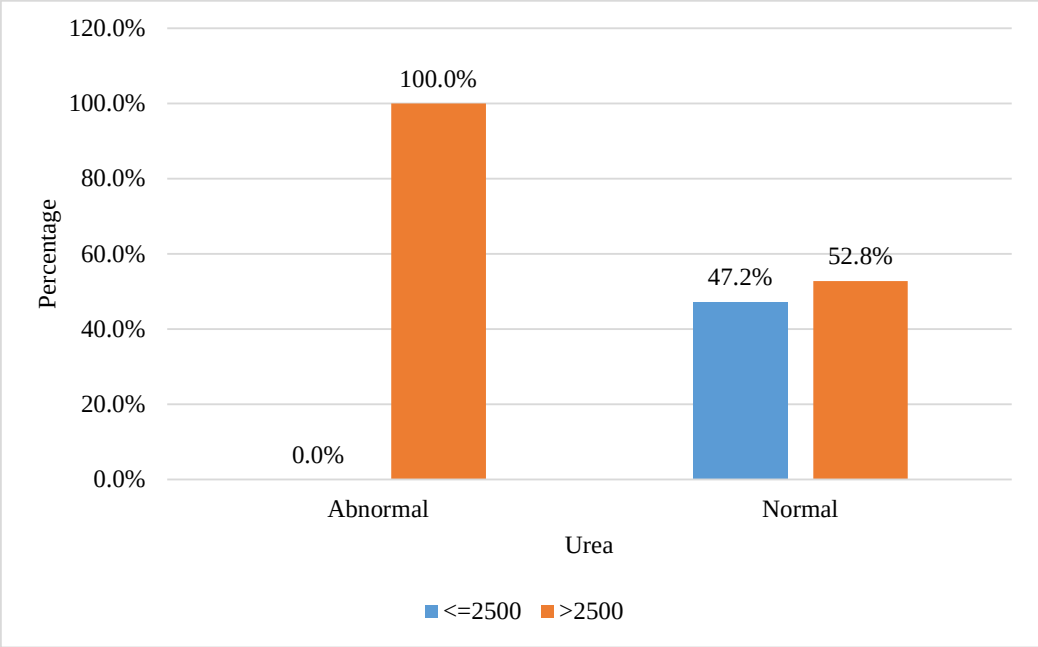

Table 40: Comparison of levels of ferritin between Creatinine (N=40)

Level Of Ferritin	Creatinine		Chi square	P value
	Abnormal (N=7)	Normal (N=33)		
<=2500	0 (0%)	17 (51.52%)	6.27	0.012
>2500	7 (100%)	16 (48.48%)		

The difference in Creatinine between the Level Of Ferritin is found to be significant with a P- value of 0.012 , with majority of 4 7 (100%) participants within >2500 of Level Of Ferritin

Figure 39: Cluster bar chart of comparison of levels of ferritin between Creatinine (N=40)

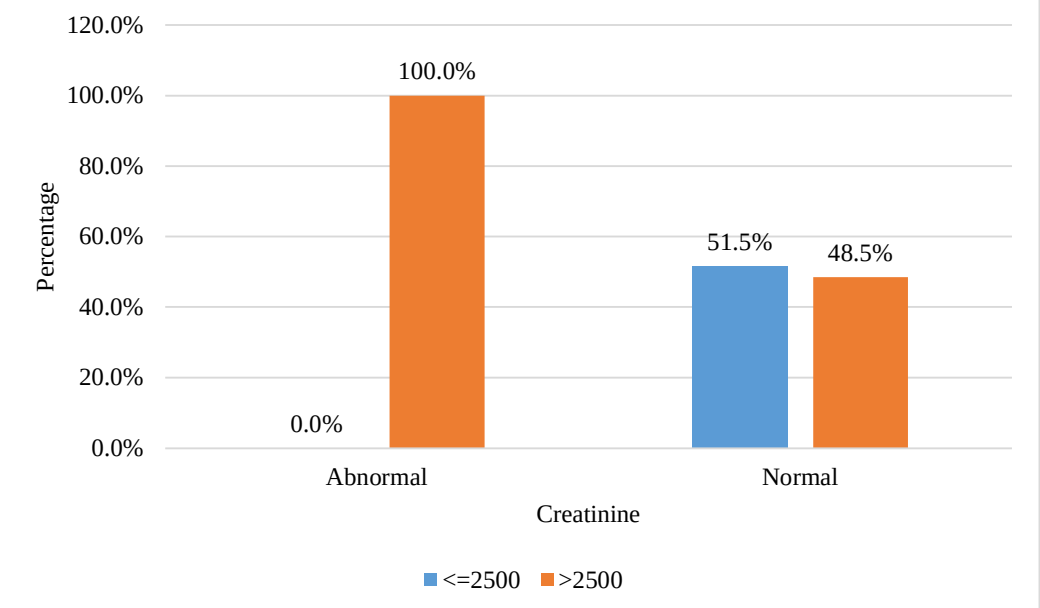

Table 41: Comparison of levels of ferritin between EGFR (N=40)

Level Of Ferritin	EGFR		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
<=2500	1 (6.25%)	16 (66.67%)	14.339	<0.001
>2500	15 (93.75%)	8 (33.33%)		

The difference in EGFR between the Level Of Ferritin is found to be significant with a P- value of <0.001, with majority of 15 (93.75%) participants within >2500 of Level Of Ferritin.

Figure 40: Cluster bar chart of comparison of levels of ferritin EGFR (N=40)

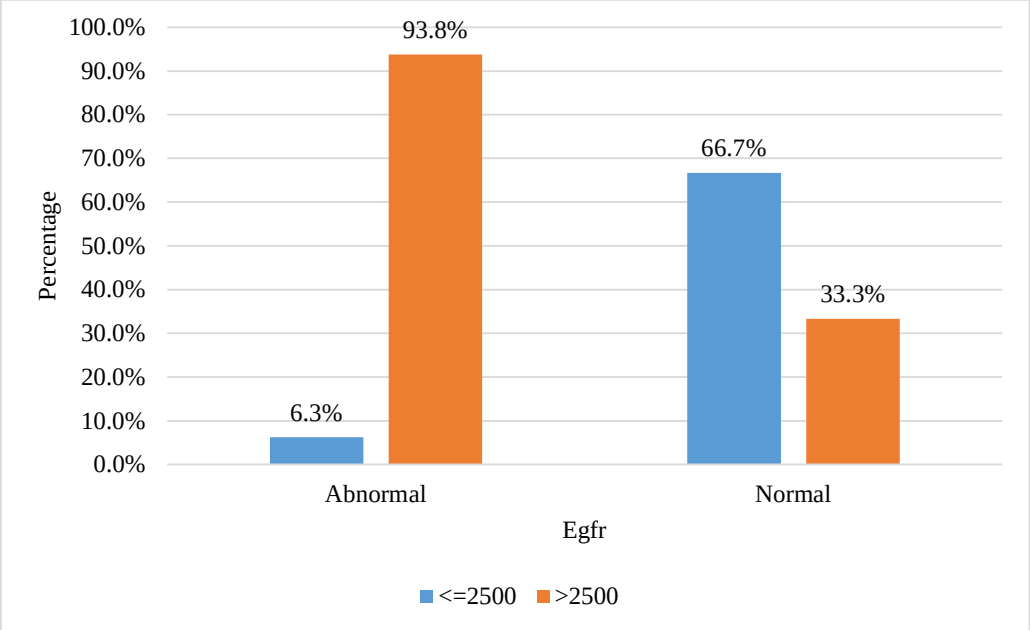

Table 42: Comparison of urea between beta-2 microglobulin (N=40)

Urea	Beta 2 Microglobulin		Chi square	Fisher exact P value
	Abnormal (N=16)	Normal (N=24)		
Abnormal	3 (18.75%)	1 (4.17%)	3.269	0.039
Normal	13 (81.25%)	23 (95.83%)		

The difference in Beta 2 Microglobulin between the Urea is found to be significant with a P- value of 0.039, with majority of 23 (95.83%) participants within Normal Of Urea.

Figure 41: Cluster bar chart of comparison of urea between beta-2 microglobulin (N=40)

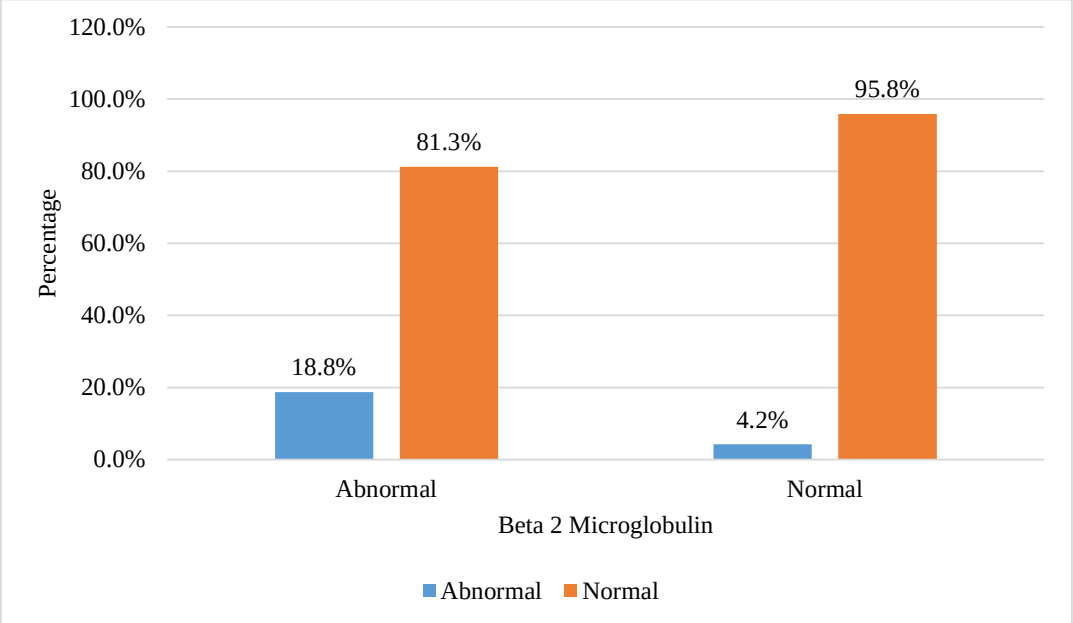

Table 43: Predictive validity of Urea in predicting Beta-2 Microglobulin (N=40)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	18.75%	4.05%	45.65%
Specificity	95.83%	78.88%	99.89%
False positive rate	4.17%	0.11%	21.12%
False negative rate	81.25%	54.35%	95.95%
Positive predictive value	75.00%	19.41%	99.37%
Negative predictive value	63.89%	46.22%	79.18%
Diagnostic accuracy	65.00%	48.32%	79.37%

The Urea had sensitivity of 18.75% (95% CI 4.05% to 45.65%) in predicting 'Beta-2 Microglobulin Specificity was 95.83% (95% CI 78.88% to 99.89%), false positive rate was 4.17% (95% CI 0.11% to 21.12%), false negative rate was 81.25% (95% CI 54.35% to 95.95%), positive predictive value was 75.00% (95% CI 19.41% to 99.37%), negative predictive value was 63.89% (95% CI 46.22% to 79.18%), and the total diagnostic accuracy was 65.00% (95% CI 48.32% to 79.37%).

Table 44: Comparison of creatinine between beta-2 microglobulin (N=40)

Creatinine	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
Abnormal	7 (43.75%)	0 (0%)	12.73	<0.001
Normal	9 (56.25%)	24 (100%)		

The difference in Beta 2 Microglobulin between the Creatinine is found to be significant with a P- value of <0.001 , with majority of 24 (100%) participants within Normal of Creatinine.

Figure 42: Cluster bar chart of comparison of creatinine between beta-2 microglobulin (N=40)

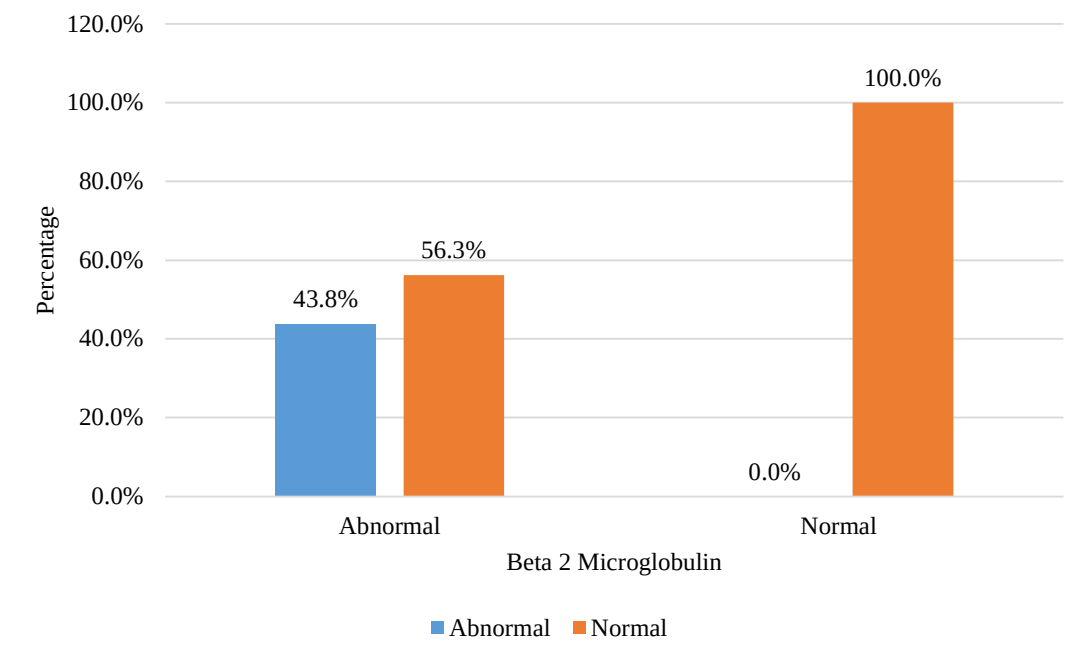

Table 45: Predictive validity of CREATININE in predicting Beta-2 Microglobulin (N=40)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	43.75%	19.75%	70.12%
Specificity	100.00%	85.75%	100.00%
False positive rate	0.00%	0.00%	14.25%
False negative rate	56.25%	29.88%	80.25%
Positive predictive value	100.00%	59.04%	100.00%
Negative predictive value	72.73%	54.48%	86.70%
Diagnostic accuracy	77.50%	61.55%	89.16%

The Creatinine had sensitivity of 43.75% (95% CI 19.75% to 70.12%) in predicting ‘Beta-2 Microglobulin Specificity was 100.00% (95% CI 85.75% to 100.00%), false positive rate was 0.00% (95% CI 0.00% to 14.25%), false negative rate was 56.25% (95% CI 29.88% to 80.25%), positive predictive value was 100.00% (95% CI 59.04% to 100.00%), negative predictive value was 72.73% (95% CI 54.48% to 86.70%), and the total diagnostic accuracy was 77.50% (95% CI 61.55% to 89.16%).

Table 46: Comparison of urea along with creatinine between beta-2 microglobulin (N=40)

Urea Along with Creatinine	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
Abnormal	2 (12.5%)	0 (0%)	3.16	0.076
Normal	14 (87.5%)	24 (100%)		

The difference in Beta 2 Microglobulin between the Urea Along with Creatinine is found to be significant with a P- value of 0.076, with majority of 24 (100%) participants within Urea Along with Creatinine.

Figure 43: Cluster bar chart of comparison of urea along with creatinine between beta-2 microglobulin (N=40)

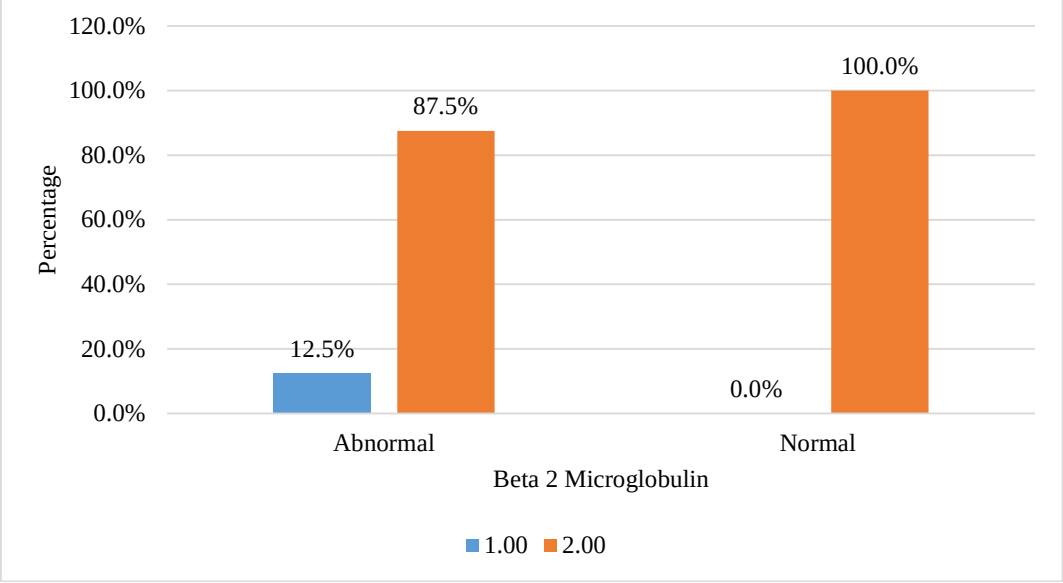

Table 47: Predictive validity of Urea along with creatinine in predicting Beta-2 Microglobulin (N=40)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	12.50%	1.55%	38.35%
Specificity	100.00%	85.75%	100.00%
False positive rate	0.00%	0.00%	14.25%
False negative rate	87.50%	61.65%	98.45%
Positive predictive value	100.00%	15.81%	100.00%
Negative predictive value	63.16%	45.99%	78.19%
Diagnostic accuracy	65.00%	48.32%	79.37%

The Urea along with creatinine had sensitivity of 12.50% (95% CI 1.55% to 38.35%) in predicting ‘Beta-2 Microglobulin Specificity was 100.00% (95% CI 85.75% to 100.00%), false positive rate was 0.00% (95% CI 0.00% to 14.25%), false negative rate was 87.50% (95% CI 61.65% to 98.45%), positive predictive value was 100.00% (95% CI 15.81% to 100.00%), negative predictive value was 63.16% (95% CI 45.99% to 78.19%), and the total diagnostic accuracy was 65.00% (95% CI 48.32% to 79.37%).

Table 48: Comparison of beta-2 microglobulin between EGFR (N=40)

EGFR	Beta 2 Microglobulin		Chi square	P value
	Abnormal (N=16)	Normal (N=24)		
Abnormal	13 (81.25%)	3 (12.5%)	18.906	<0.001
Normal	3 (18.75%)	21 (87.5%)		

The difference in Beta 2 Microglobulin between the EGFR is found to be significant with a P- value of <0.001, with majority of 21 (87.5%) participants within Normal Of EGFR.

Figure 44: Cluster bar chart of comparison of beta-2 microglobulin between EGFR (N=40)

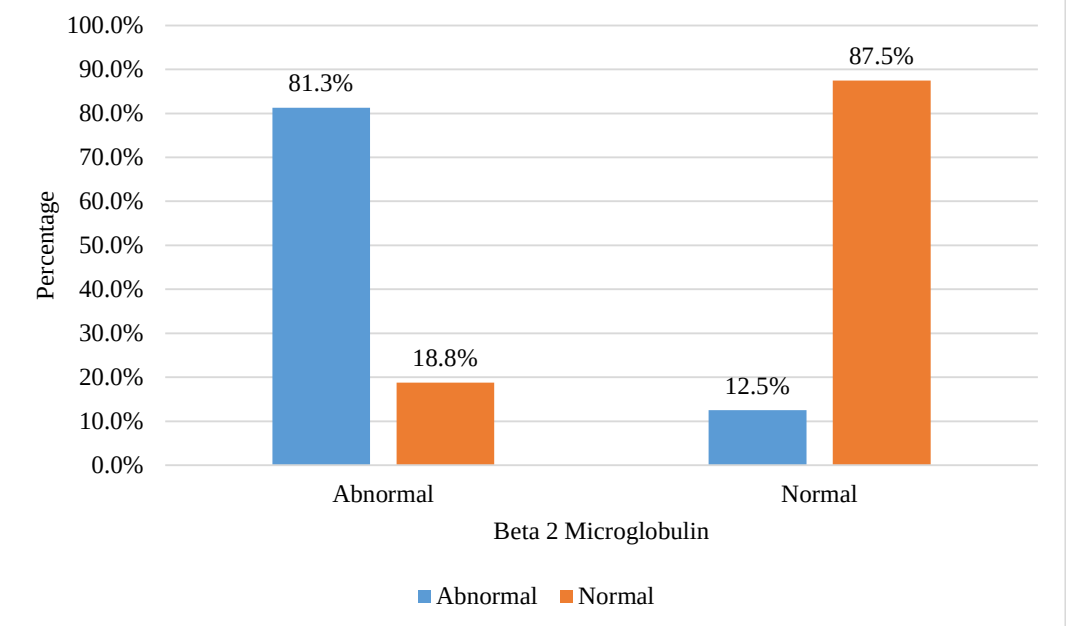

Table 49: Predictive validity of EGFR in predicting Beta-2 Microglobulin (N=40)

Parameter	Value	95% CI	
		Lower	Upper
Sensitivity	81.25%	54.35%	95.95%
Specificity	87.50%	67.64%	97.34%
False positive rate	12.50%	2.66%	32.36%
False negative rate	18.75%	4.05%	45.65%
Positive predictive value	81.25%	54.35%	95.95%
Negative predictive value	87.50%	67.64%	97.34%
Diagnostic accuracy	85.00%	70.16%	94.29%

The EGFR had sensitivity of 81.25% (95% CI 54.35% to 95.95%) in predicting 'Beta-2 Microglobulin Specificity was 87.50% (95% CI 67.64% to 97.34%), false positive rate was 12.50% (95% CI 2.66% to 32.36%), false negative rate was 18.75% (95% CI 4.05% to 45.65%), positive predictive value was 81.25% (95% CI 54.35% to 95.95%), negative predictive value was 87.50% (95% CI 67.64% to 97.34%), and the total diagnostic accuracy was 85.00% (85% CI 70.16% to 94.29%).

DISCUSSION

Beta thalassemia is a common genetic disorder inherited by autosomal recessive pattern of inheritance. It is a common important health condition requiring repeated blood transfusions. Due to the chronic blood transfusions, there is iron deposition in multiple organs such as pituitary glands leading to various endocrine abnormalities, endocrine organs, heart, kidney and skeletal.

Overload of iron in kidney due to the multiple blood transfusions received in these children is known to be a leading cause of renal dysfunction among children with transfusion-dependent β-thalassemia major. It is one of the common morbidities seen in transfusion-dependent thalassemia patients. Its incidence is increasing because of the increased survival rates with the advanced mode of thalassemia treatment.

Renal Dysfunction in beta-thalassemia is due to multiple factors like repeated transfusions leading to iron overload, as an adverse effect of the iron chelators, due to hypoxia secondary to anaemia. It is very important to identify the renal dysfunction as early as possible to avoid chronic complications like metabolic osteodystrophy, dyslipidemia, coronary artery disease, left ventricular hypertrophy. As a conventional method renal function tests have been used for the diagnosis of renal dysfunction. The newer methods like measurement of urinary beta 2 microglobulin for the same can be used.

Prevention of Renal dysfunction in beta thalassemia is by regular monitoring of ferritin levels, regular transfusions and also adjusting doses of iron chelators accordingly. The present study was an attempt to evaluate for the renal dysfunction by

using the conventional methods along with newer investigations like urinary beta 2 microglobulin

This hospital-based longitudinal study was done from January 2021 to December 2021.

The minimum effective sample size to estimate the renal dysfunction was 40. There are 237 registered cases of thalassemia in thalassemia day care unit, under the Department of Paediatrics, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi. Out of 237 cases, 58 cases are transfusion-dependent thalassemia major aged between 8 to 18 years who fulfilled the inclusion criteria. However, based on computerized randomization, 40 children were enrolled. All these 40 children were admitted in the thalassemia day care ward and tested for regular investigations like complete blood picture, serum creatinine, serum urea. From the creatinine and the height of the patients eGFR is calculated by using Schwartz equation. Along with this serum ferritin is monitored to look for the amount of iron overload. With these routine investigations urinary Beta 2 Microglobulin is checked from the early morning urine sample. The patients are provided with a 500ml bottle to collect 24 hour urine sample from which 24 hour urinary sodium, 24 hour urinary potassium, 24 hour urinary calcium, 24 hour urinary creatinine were calculated.

In the present study, most of the children were boys 26 (65%) and 14(35 %) of the children were girls and the boy to girl ratio was 1.8:1 suggesting male preponderance. The male predominance observed in the present study was in study done by for Frequency of Glomerular Dysfunction in Children with Beta Thalassaemia Major Basma A Ali and et al where out of total 100 children with beta thalassemia major 28 girls (28%) and 72 boys (72%)[40]. Study done by Ali Ahmadzadeh et.al did

study on renal dysfunction in paediatric population with beta thalassemia out of the 140 patients 72 (51.4%) were males and 68 (48.6%) were females also shown male predominance agreement to our present study[41]..Ideally, β-thalassemia major which is having an autosomal recessive inheritance, so males and females should be in equal proportion but the higher proportion was seen in males in the present study. The disparity in the present study could be explained due to the gender inequality in our population, where male children are cared better in health-seeking and brought to hospital regularly as it is a chronic illness.

In this study, age ranged from 8 to 18 years. The mean age was 13.20 $\pm$ 2.95 years and the median age was 12 years. In the present study, more number of patients are of the age 12-14 i.e 27.50%, followed by 10 patients (25%) each between 14-16 years and 16-18 years. The age group is in agreement to a similar study done by Asmaa A Mahmoud et al assessment of subclinical renal glomerular and tubular dysfunction in children with beta thalassemia major [42].

Concerning demographic characteristics, in the present study, the majority of the children 29 (72.5%) belong to the rural area. Most of the patients were from lower middle class 19 (47.50%).

Concerning history, in this study 7 (17.5%) children had a history of easy fatiguability or generalized weakness, followed by heart burn in 3 (7.5%) children. Gastrointestinal disturbances, including nausea, vomiting, and abdominal pain, are common[43].

The most common age of onset of Thalassemia is at 3 months of age that is 9 (22.50%). All the subjects included in the present study were having duration of

Thalassemia more than and equal to 8 years, with majority of the patients with disease since 8 years that is around 8 patients (20%), followed by 11, 12 and 17 years with 5 patients (12.50%) in each group. Most of the patients in the present study have blood transfusion history of 1-2 month of diagnosis (85%). Blood transfusion history of >6 months of diagnosis was 8% and 2-6 months of diagnosis was 7.50%. In the present study, it is found that 39 people have found increased blood transfusion (97.50%), and only 1 patients have decreased blood transfusion (2.50%). In the present study, it is found that 33 people have no reaction to blood transfusion (82.50%), five (12.50%) people have only one reaction to blood transfusion, two (5%) people have two reaction to blood transfusion. Fever is the most common reaction due to blood transfusion (10%), 33 people have no reaction to blood transfusion (82.50%).

In the present study 15 patients (37.50%) are on both deferiprone and deferasirox. All the children (100%) were under chelation therapy (deferasirox), multivitamins and folic acid. History of splenectomy was noted in 12.50% of the children.

In the present study we can observe that majority of the patient 13 (32.50%) patients were provided with 1000MG/Day of deferasirox dose and 11 (27.50%) patients were reported a duration of 10 Years of deferasirox.

Furthermore, the history of consanguineous marriage was reported by 15 (37.50 %) of the children parents. Thalassemia status of the siblings in the family was positive in 5 children (12.50%) and the death of the sibling was seen in 3 families (7.50%). Study done by Padma et.al in thalassemia has shown that out of a total 180 children, 39 (21.6%) children were born to consanguineous parents and remaining 141 (78.3%) to non-consanguineous parents.

PREVALENCE OF RENAL DYSFUNCTION :

Out of 40 children, 19 (47.5%) are having abnormal renal parameters and 11 (52.5%) have normal renal parameters. Study conducted by Economou and et al. showed abnormal renal parameters in 36% of the patients. This study was done in 42 patients aged between 4-23 years.Economou M, Printza N, Teli A, Tzimouli V, Tsatra I, Papachristou F, Athanassiou-Metaxa M. Renal dysfunction in patients with beta-thalassemia major receiving iron chelation therapy either with deferoxamine and deferiprone or with deferasirox. Acta haematologica. 2010;123(3):148-52..

Relation between gender and renal dysfunction:

In the present study, most of the children were boys 26 (65%) and 14(35 %) out of which 15 males had renal dysfunction and 4 females had renal dysfunction with a p-value of 0.079 showing that there is no association between gender and renal dysfucntion

Relation between the duration of thalassemia and renal dysfunction:

In the present study, a significant correlation was found between years of onset of thalassemia and renal dysfunction. The duration of thalassemia in children was divided into 2 groups that is between 8-12 years and 13-17 years. The levels of beta 2 microglobulin, urea, creatinine and eGFR are higher in the patients with thalassemia for the higher duration with a p-value of <0.001, 0.027, 0.002 and <0.001 respectively.

Correlation between iron chelators and renal dysfunction:

Out of 40 children, all the 40 patients are on deferasirox and 15 patients were on both deferasirox and deferiprone. In the present study the duration of deferasirox were divided into two groups that is 6-10 years and 11-14 years with majority of patients between 6-10 years. The levels of beta 2 microglobulin, creatinine and eGFR are higher in the patients using deferasirox for the higher duration with a p-value of 0.034, 0.003 and 0.043 respectively. There was no significant relation between the levels of urea and duration of disease, with p-value of 0.376. In a study done by Cathleen Michelle A Dee and et al Eighteen patients were on iron chelators included. Nine (50%) patients were on deferasirox, three (16.7%) on deferoxamine, two (11.1%) on deferiprone and four (22.2%) were on combination deferiprone and deferoxamine. Twelve (66.7%) patients had renal tubular dysfunction, including all nine patients (50%) on deferasirox [44].

Correlation between ferritin levels and renal dysfunction

In the present study, out of 40 children, 17 children had ferritin levels below 2500 and 23 had ferritin levels above 2500. There was positive correlation with the renal dysfunction with levels of ferritin. The levels of beta 2 microglobulin, urea, creatinine, eGFR are higher in the patients with levels of ferritin more than 2500 with a p-value of 0.013, 0.046, 0.012, <0.001 respectively.

Comparison between Urea and Beta 2 Microglobulin

The Urea had sensitivity of 18.75% (95% CI 4.05% to 45.65%) in predicting renal dysfunction 'Beta-2 Microglobulin Specificity was 95.83% (95% CI 78.88% to 99.89%), false positive rate was 4.17% (95% CI 0.11% to 21.12%), false negative rate was 81.25% (95% CI 54.35% to 95.95%), positive predictive value was 75.00% (95% CI 19.41% to 99.37%), negative predictive value was 63.89% (95% CI 46.22% to 79.18%), and the total diagnostic accuracy was 65.00% (95% CI 48.32% to 79.37%)

Comparison between Creatinine and Beta 2 Microglobulin

The Creatinine had sensitivity of 43.75% (95% CI 19.75% to 70.12%) in predicting renal dysfunction 'Beta-2 Microglobulin Specificity was 100.00% (95% CI 85.75% to 100.00%), false positive rate was 0.00% (95% CI 0.00% to 14.25%), false negative rate was 56.25% (95% CI 29.88% to 80.25%), positive predictive value was 100.00% (95% CI 59.04% to 100.00%), negative predictive value was 72.73% (95% CI 54.48% to 86.70%), and the total diagnostic accuracy was 77.50% (95% CI 61.55% to 89.16%).

Comparison between Urea and Creatinine and Beta 2 Microglobulin

The Urea along with creatinine had sensitivity of 12.50% (95% CI 1.55% to 38.35%) in predicting renal dysfunction 'Beta-2 Microglobulin Specificity was 100.00% (95% CI 85.75% to 100.00%), false positive rate was 0.00% (95% CI 0.00% to 14.25%), false negative rate was 87.50% (95% CI 61.65% to 98.45%), positive predictive value was 100.00% (95% CI 15.81% to 100.00%), negative predictive value was 63.16% (95% CI 45.99% to 78.19%), and the total diagnostic accuracy was 65.00% (95% CI 48.32% to 79.37%).

Comparison between eGFR and Beta 2 Microglobulin

The EGFR had sensitivity of 81.25% (95% CI 54.35% to 95.95%) in predicting renal dysfunction 'Beta-2 Microglobulin Specificity was 87.50% (95% CI 67.64% to 97.34%), false positive rate was 12.50% (95% CI 2.66% to 32.36%), false negative rate was 18.75% (95% CI 4.05% to 45.65%), positive predictive value was 81.25% (95% CI 54.35% to 95.95%), negative predictive value was 87.50% (95% CI 67.64% to 97.34%), and the total diagnostic accuracy was 85.00% (85% CI 70.16% to 94.29%).

CONCLUSION

Overall the finding of the present study was that transfusion dependent Beta Thalassemia patients who were on iron chelators had renal dysfunction. Prevalence of renal dysfunction in the present study is 47.5%. Renal dysfunction is more with the increasing age and there is no gender predisposition. Apart from this the incidence of renal dysfunction is increasing with the increase in the duration of iron chelators, with no relation to the number of iron chelators. So annual check-up of renal parameters assessment will be helpful. While the findings of the present study need further validation as it was viz. single centre study, relatively smaller sample size. Hence further multi-centric studies involving large sample size with long term follow up covering more patients may focus on the precise role of renal parameters in the prevention of renal dysfucntion in patients with transfusion-dependent thalassemia.

SUMMARY

Renal Dysfunction is one of commonest complication in children suffering from transfusion dependent Beta Thalassemia. However, there are very few studies about the evaluation of renal dysfunction in transfusion-dependent thalassemia children in India. This study was aimed to know the prevalence of Renal Dysfunction in transfusion dependent Beta Thalassemia Major and to correlate it with levels of ferritin.

This hospital-based longitudinal study was done from January 2021 to December 2021. The minimum effective sample size to estimate the renal dysfunction was 38. There are 237 registered cases of thalassemia in thalassemia day care unit, under the Department of Pediatrics, KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi. Out of 237 cases, 58 cases are transfusion-dependent thalassemia major aged between 8 to 18 years which fulfilled the inclusion criteria. However, based on computerized randomization, 40 children were enrolled.

These patients were all on regular treatment with blood transfusions, chelating agents, multivitamins & folic acid. These children were tested for renal dysfunction by doing the routine investigations, along with other urine investigations like beta 2 microglobulin, eGFR was calculated. 47% showed renal dysfunction, follow up with routine investigations and also the advanced methods are recommended for the prevention and early identification of renal dysfunction.

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ANNEXURE I – CONSENT FORM

Principal Investigator: REG NO. BM0120012

Guide: Dr. _____

You are hereby requested to involve yourself and your child in the above said research to beconducted at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from July 2020 to May 2021 by me.

Introduction

Participation of your child will help us to know the early identification of any renal dysfunction in transfusion dependent thalassemia major who are on oral iron chelators for a long period. You are free to discontinue the participation in the study any time for any reasonand u will not be paid any reimbursement for participation in research. Hence involving yourchild in study is your voluntary decision.

Voluntary participation

You and your child's participation in this study is your voluntary decision. Whether to participate or not to participate will not affect your current or future relationship with the KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. You are free to discontinue the participation in the study at any time for any reasons and you will not be paidany reimbursement for participation in the research.

Risk: There are no risks involved

Benefit: Identification of renal dysfunction at an early age if any present.

Use of photography/Identifying details: Any photography or identification details will bedisclosed only with your permission.

Storage of sample: The samples collected will be sent to the laboratory for further processing.

Privacy and Confidentiality

The only people who will know that you are a research participant are member of the research team. No information about you or provided by you, during research will be disclosed to others without your written consent. When the results of the research are published or discussed in the conferences, no information will be disclosed that would revealyour identity. Any information obtained in connections with this study and that can be identified with you remain confidential and will be disclosed only with your permission.

Financial incentive for participation

You or your child will not receive any financial assistance for participating in this study.

Queries

If you have any queries you may contact

REG NO. BM0120012, Post Graduate StudentDepartment of Pediatrics

JNMC, Belagavi-590010

Dr. _____

MBBS, MD (Pediatrics)

Professor, Department of PediatricsJNMC, Belagavi-590010

If you have any questions about your rights or research participation you may contact

DR HAESHA HEGDECHAIRPERSON
KLE ACADEMY OF HIGHER EDUCATION & RESEARCH, JAWAHARLAL NEHRU MEDICAL COLLEGE,
IEC AND SCIENTIST D, ICMRBELAGAVI- 590010,
9480422500

ou will be given a copy of this form for your information and to keep for your records.

STATEMENT OF CONSENT

I hereby voluntarily agree for me and my child's participation in this study. I understand thateven if I choose to allow my child to take part in this study I have the liberty to withdraw at any time. My signature below indicates that I have read or have been told about this entire consent form including the risks and benefits and have had all my questions answered. I willbe given a copy of this consent form.

Signature of the patient (If the child is above 12 years): _____

Date: _____

Name: _____

Signature of the authorized representative/ parent: _____

Date: _____

Name:_____

Relation to the Subject: _____

Signature of the witness: _____ Date: _____

Name: _____

Signature of investigator: _____ Date: _____

Name: _____

ANNEXURES II – PROFORMA

ANNEXURE-II (PROFORMA) **(GROUP I/II)**

INFORMATION OF CHILD:

Name/ID No.:

Age

Sex:

Address:

Socioeconomic status: class I II III IV

SES CLASS	REVISED INCOME CATEGORIES FOR ALL INDIA 2014	
1. Upper class	≥ 5357	
2. Upper middle class	2652-5356	
3. Middle class	1570-2651	
4. Lower middle class	812-1569	
5. Lower class	≤ 811	

Parent's educational status:

Mother - High school / PUC / degree / University

Father - High school / PUC / degree / University

Phone no –

Std:

DETAILS OF THALASSEMIA HISTORY:

- Age of onset of thalassemia:
- Management history:
- Drugs: chelating agents:

Deferiprone-

Dose:

Duration

Deferasirox-

Dose:

Duration:

Any other: Pantoprazole/ Ca / FA / Zinc / BC

(YES/NO)

BLOOD TRANSFUSION HISTORY:

Onsetof transfusion	1-2months of diagnosis	2-6months of diagnosis	>6months of diagnosis

Frequency of blood transfusions- _____ months/year

If frequency of blood transfusions has increased/decreased

No of reactions: 1/2/3/4

Type - fever / chills / others

- H/o infections in the past – HIV/ HBsAg
- Others

History of Present Illness:

- Heart burn
- Vomiting
- Abdominal pain
- Joint pains
- Fever

Treatment History in past:

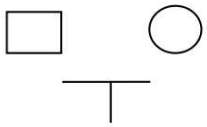
IMMUNISATION HISTORY:

VACCINES	PRIMARY	BOOSTER
BCG		
DPT		
OPV		
HEPATITIS		
MEASLES		
MMR		
TYPHOID		

FAMILY HISTORY:

INFORMATION OF PARENTS-

Consanguineous / non consanguineous:



Siblings of the child & their thalassemia status:

Deaths of the siblings: Yes / No

EXAMINATION:

General Physical Examination-

Vitals:

HR-

RR-

CFT-

Temperature-

BP-

ANTHROPOMETRY:

	Measured	Expected	Percentile
Weight			
Height			
BMI			

Inference -

Head to Toe-

Face-

Eyes-

Ears-

Oral cavity-

Neck-

Chest-

Abdomen-

Extremities-

Congenital markers-

Skin-

Other Systems:

CVS:

RS:

PA:

Liver span	
Spleen span	

Other-

CNS:

Investigations:

BLOOD INVESTIGATIONS

Hb	
PCV	

PLT	
RBC	
WBC	
DLC	
S.Ferritin	
S.Urea	
S.Creatinine	
S.Sodium	
S.Potassium	
Bicarbonate	

URINARY TESTS (24hr sample)

U.Creatinine	
U.Sodium	
U.Potassium	
U.Calcium	
U.Albumin	
U.β_2-Microglobulin (early morning sample)	

Fractional excretion of Sodium	
Fractional Excretion of potassium	
Creatinine Clearance	

ANNEXURE -III - KEY TO MASTERCHART

RURAL-1

URBAN-2

SOCIOECONOMIC STATUS

UPPER CLASS-1

UPPER MIDDLE CLASS-2

MIDDLE CLASS-3

LOWER MIDDLE CLASS-4

LOWER CLASS-5

PARENT'S EDUCATIONAL STATUS

NIL-1

HIGH SCHOOL-2

PUC-3

DEGREE-4

UNIVERSITY-5

ANY PRESENT COMPLAINTS

NIL-1

BONY PAINS -2

EASY FATIGUABILITY-3

GENERALISED WEAKNESS-4

JOINT PAINS-5

FEVER-6

BREATHLESSNESS-7

FREQUENT GE INFECTIONS -8

ABDOMINAL PAIN-9

HEART BURN-10

DECREASED FREQUENCY OF MICTURITION-11

ODEMA-12

H/O UTI-13

BURNING MICTURITION-14

HEMATURIA-15

BLOOD TRANSFUSION HISTORY

1-2 MONTHS OF DIAGNOSIS -1

2-6 MONTHS OF DIAGNOSIS -2

>6 MONTHS OF DIAGNOSIS -3

FREQUENCY OF BLOOD TRANSFUSION

INCREASED -1

DECREASED-2

H/O TRANMISSION RELATED INFECTIONS IN PAST

NIL-1

HIV-2

HBSAG-2

STD-3

MALARIA-4

ANY OTHER DRUGS

PANTOPRAZOLE-1

CA-2

FA-3

ZINC-4

B COMPLEX-5

CONSANGUINOUS/NON CONSANGUINOUS MARRIAGE

CM-1

NCM-2

DEATH OF SIBLING

YES-1

NO-2

ANTENATAL TESTING

YES-1

NO-2

IMMUNISATION HISTORY

FULLY IMMUNISED-1

NOT FULLY IMMUNISED-2

HEPATITIS B VACCINE TAKEN -3

HEPATITIS B VACCINE NOT TAKEN -4

O/E

FACE-

DEPRESSED NASAL BRIDGE-1

THALASSEMIC FACIES-2

HYPERTELORISM-3

FRONTAL BOSSING-4

WIDE EYES-5

NORMAL -6

PROTRUDED JAW-7

EYES

PALLOR-1

ICTERUS-2

HYPERTELORISM-3

LEFT EYE MILD PTOSIS-4

NORMAL-5

ORAL CAVITY

HYPERPLASIA OF MAXILLARY BONE-1

PROTRUDED TEETH-2

DENTAL MALALIGNMENT-3

DENTAL MALOOCLUSION-4

NORMAL-5

NECK

NORMAL-1

EXCORIATION MARKS-2

LYMPH NODES PALPABLE -3

ABDOMEN

EVERTED UMBILICUS-1

MILD DISTENSION-2

NORMAL-3

SPLENECTOMY SCAR-4

EXTREMITIES

NORMAL-1

DRY SKIN-2

EXCORIATION MARKS -3

CLUBBING-4

PALLOR - 5

SKIN

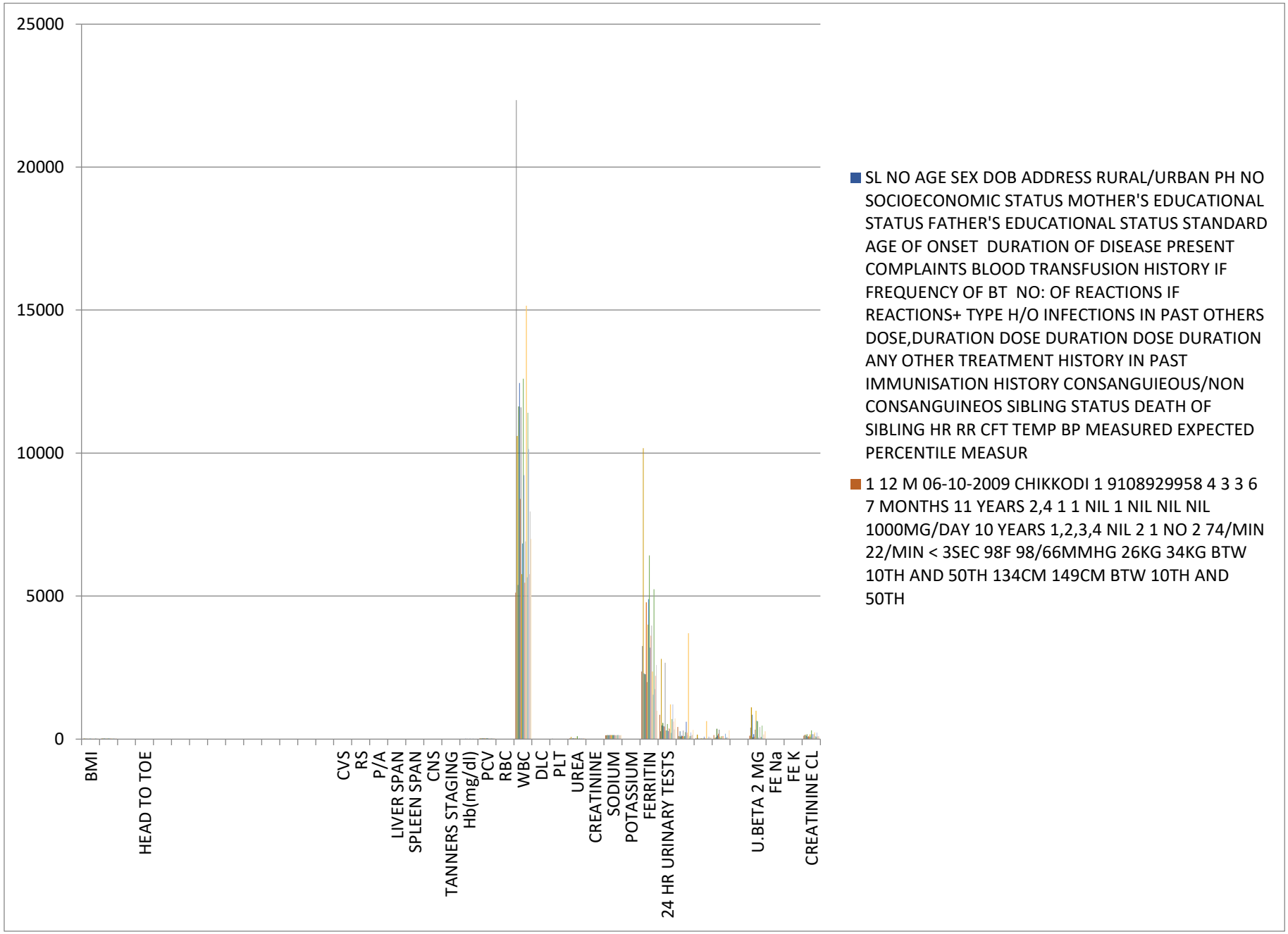
NORMAL-1

HYPERPIGMENTATION-2

ICTERUS-3

PALLOR-4

EXCORIATION MARKS -5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SPLEEN SPAN
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Hb(mg/dl)
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RBC
WBC
DLC
PLT
UREA
CREATININE
SODIUM
POTASSIUM
FERRITIN
24 HR URINARY TESTS
U.BETA 2 MG
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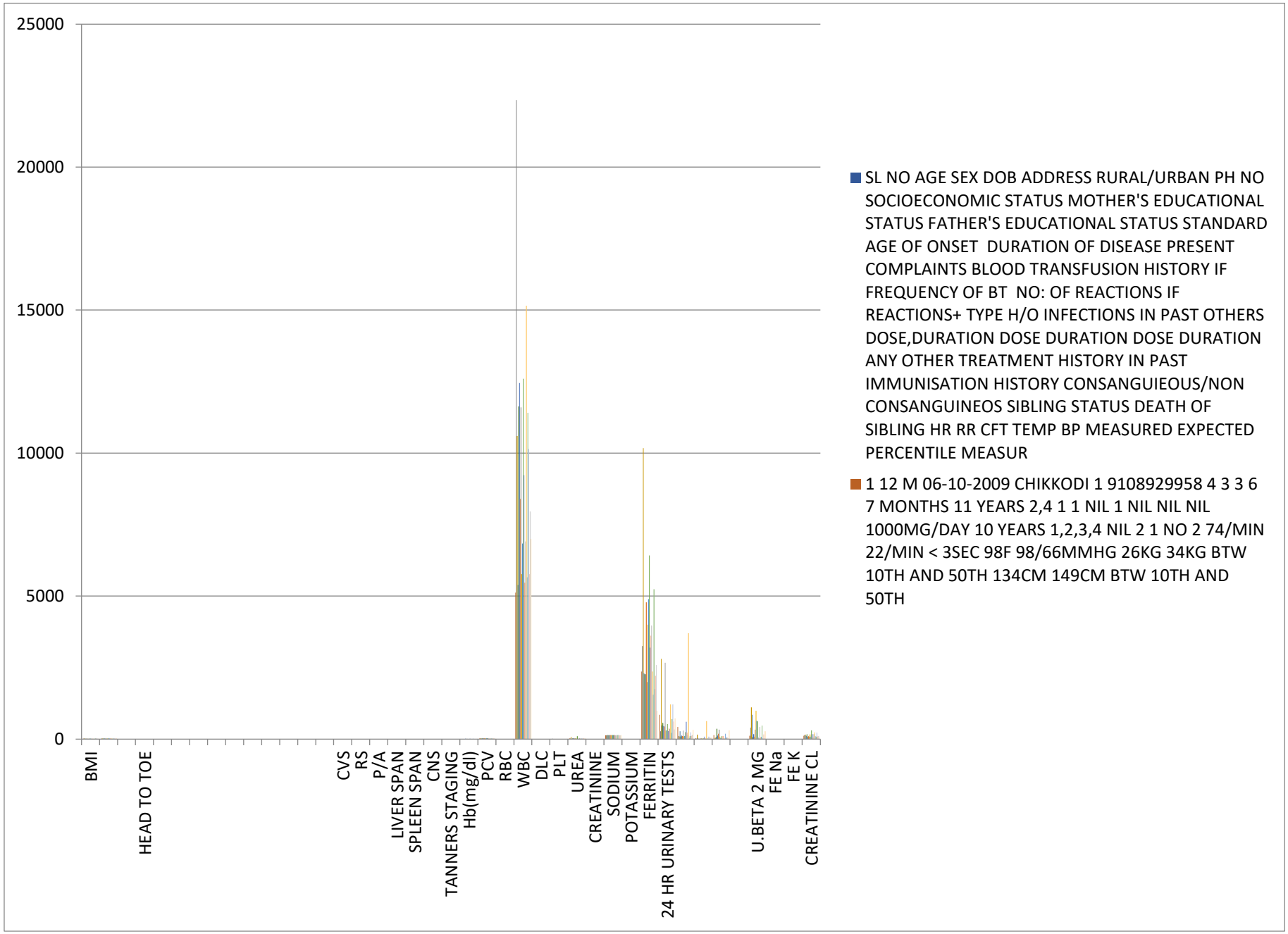
1 12 M 06-10-2009 CHIKKODI 1 9108929958 4 3 3 6 7 MONTHS 11 YEARS 2,4 1 1 NIL 1 NIL NIL NIL 1000MG/DAY 10 YEARS 1,2,3,4 NIL 2 1 NO 2 74/MIN 22/MIN < 3SEC 98F 98/66MMHG 26KG 34KG BTW 10TH AND 50TH 134CM 149CM BTW 10TH AND 50TH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Hb(mg/dl)
PCV
RBC
WBC
DLC
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CREATININE
SODIUM
POTASSIUM
FERRITIN
24 HR URINARY TESTS
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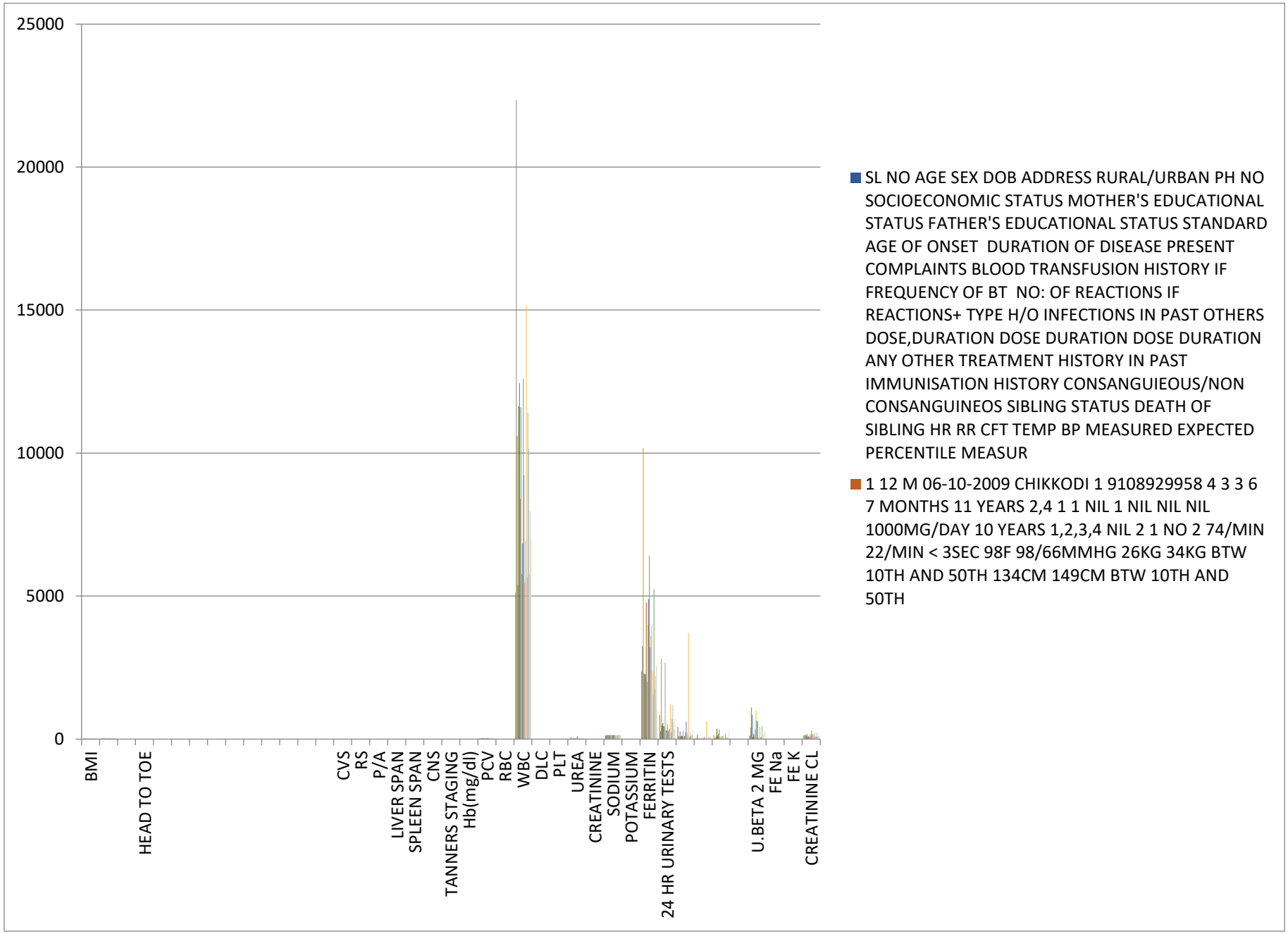
1 12 M 06-10-2009 CHIKKODI 1 9108929958 4 3 3 6 7 MONTHS 11 YEARS 2,4 1 1 NIL 1 NIL NIL NIL 1000MG/DAY 10 YEARS 1,2,3,4 NIL 2 1 NO 2 74/MIN 22/MIN < 3SEC 98F 98/66MMHG 26KG 34KG BTW 10TH AND 50TH 134CM 149CM BTW 10TH AND 50TH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SPLEEN SPAN
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Hb(mg/dl)
PCV
RBC
WBC
DLC
PLT
UREA
CREATININE
SODIUM
POTASSIUM
FERRITIN
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U.BETA 2 MG
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1 12 M 06-10-2009 CHIKKODI 1 9108929958 4 3 3 6 7 MONTHS 11 YEARS 2,4 1 1 NIL 1 NIL NIL NIL 1000MG/DAY 10 YEARS 1,2,3,4 NIL 2 1 NO 2 74/MIN 22/MIN < 3SEC 98F 98/66MMHG 26KG 34KG BTW 10TH AND 50TH 134CM 149CM BTW 10TH AND 50TH

SL NO	AGE	SEX	DOB	ADDRESS	RURAL/URBAN	PH NO	SOCIOECONOMIC STATUS	MOTHER'S EDUCATIONAL STATUS	FATHER'S EDUCATIONAL STATUS	STANDARD
1	12	M	06-10-2009	CHIKKODI	1	9108929958	4	3	3	6
2	16	M	25-01-2005	ATHANI	1	6363230031	4	2	3	9
3	14	F	20-07-2006	CHIKKODI	1	6366601046	4	2	2	7
4	16	M	24-08-2004	RAMDURG	1	7349627457	4	2	3	10
5	12	F	11-08-2009	ATHANI	1	9686157296	4	2	3	7
6	13	F	30-11-2007	HUKKERI	1	8970705580	4	2	2	8
7	12	M	05-12-2007	YAMAKANMANDI	1	9980013997	4	1	4	7
8	14	M	30-06-2006	BAGALKOT	2	9008328629	4	3	4	8
9	17	M	22-08-2004	HULLKANI	1	7649356676	5	2	2	10
10	16	F	08-03-2005	KADOLLI	1	8050451576	4	2	2	10
11	14	M	27-01-2007	RAMDURG	1	9686518695	4	2	1	8
12	15	M	27-06-2006	KHANAPUR	1	9770887432	3	3	4	9
13	14	M	19-01-2005	HUKKERI	1	9113262983	5	1	2	8
14	14	M	15-05-2007	BELGAUM	2	9877669008	2	2	2	8
15	12	M	01-02-2009	HUKKERI	1	6362630422	4	2	2	5
16	11	M	22-11-2009	BELGAUM	2	9341101414	4	2	2	5
17	18	F	27-02-2004	CHIKKODI	1	9483213957	4	2	2	PUC 2
18	13	F	16-04-2006	RAIBAG	1	9902485069	4	1	2	6
19	13	F	16-12-2007	HOSSUR	1	8884009882	5	2	2	7
20	9	F	02-06-2012	HALIYAL	1	9986921259	3	2	2	2
21	12	F	18-03-2010	CHIKKODI	1	9844331515	3	3	4	6
22	16	M	22-07-2005	GOKAK	1	9611375431	5	2	2	PUC 2
23	12	M	21-11-2007	DHARWAD	2	9449062741	3	2	2	9
24	9	M	01-04-2012	BELGAUM	2	8088152807	3	1	3	4
25	17	M	01-01-2004	RAMDURG	1	9663108731	4	2	2	DEGREE
26	8	F	11-11-2013	ANAGOL	1	7411645844	4	2	2	3
27	18	M	25-01-2003	BELGAUM	2	8296290050	4	3	3	DEGREE
28	9	M	18-05-2012	HUKKERI	1	9837426841	3	2	3	4
29	13	M	16-04-2008	GOKAK	1	9111444391	4	2	2	7
30	11	F	15-03-2011	RAMDURG	1	9481230482	2	1	2	5
31	9	F	23-07-2012	HUBALLI	2	9036525795	2	3	3	4
32	10	M	15-09-2011	ANBUL	1	9595626175	3	2	1	5
33	8	M	26-06-2014	HALIYAL	1	8722524720	5	2	2	2
34	15	M	05-09-2005	KOLHAPUR	2	7038731210	2	2	3	9
35	9	M	17-04-2014	KHANAPUR	2	9880718391	3	1	1	2
36	15	M	15-12-2005	CHIKKODI	1	9494943468	4	2	2	10
37	18	M	25-02-2005	BAGALKOT	2	9414143119	3	2	2	DEGREE
38	12	F	01-01-2009	HUKKERI	1	9003033554	3	2	2	6
39	14	F	06-07-2007	HALIYAL	1	9894661256	3	2	2	8
40	18	M	18-07-2003	BELGAUM	2	9877660090	3	2	2	DEGREE

AGE OF ONSET	DURATION OF DISEASE	PRESENT COMPLAINTS	BLOOD TRANSFUSION HISTORY	IF FREQUENCY OF BT	NO: OF REACTIONS	IF REACTIONS+ TYPE	H/O INFECTIONS IN PAST	OTHERS
7 MONTHS	11 YEARS	2,4	1	1	NIL		1	NIL
1 YEAR 6 MONTHS	15 YEARS	3,4	2	1	NIL		1	ACUTE GE
1 YEAR	15 YEARS	2	2	1	NIL		1	RECURRENT LRTIS
1 YEAR 6 MONTHS	15 YEARS	3,4	3	2	NIL		1	RECURRENT URTI
6 MONTHS	11 YEARS	3	1	1	NIL		1	NIL
1 YEAR 6 MONTHS	11 YEARS	7,11	1	1	NIL		1	RECURRENT LRTIS
3 MONTH	12 YEARS	3,4	1	1	NIL		1	NIL
1 YEAR	13 YEARS	1	3	1	NIL		1	ACUTE GE
1 YEARS 6 MONTHS	15 YEARS	4	3	1	NIL		1	ACUTE GE
1 YEAR 6 MONTHS	15 YEARS	2,4	1	1	NIL		1	RECURRENT URTIS
5 MONTHS	13 YEARS	2	2	1	NIL		1	ACUTE GE
7 MONTHS	14 YEARS	4	1	1	NIL		1	FREQUENT LRTIS
6 MONTHS	13 YEARS	3	1	1	NIL		1	NIL
3MONTHS	14 YEARS	3,4	1	1	NIL		1	NIL
1 YEAR	11 YEARS	1	1	1	NIL		1	NIL
6 MONTHS	10 YEARS	5	1	1	NIL		1	NIL
1 YEAR	17 YEARS	3	1	1	NIL		1	NIL
5 MONTHS	12 YEARS	3	1	1	NIL		1	NIL
5 MONTHS	12 YEARS	3	1	1	NIL		1	NIL
1 YEAR	12 YEARS	1	1	1	NIL		1	NIL
7 MONTHS	8 YEARS	3,4	1	1	NIL		1	NIL
3 MONTHS	12 YEARS	1	1	1	2	FEVER	1	NIL
5 MONTHS	15 YEARS	1	1	1	1	FEVER	1	NIL
1 YEAR 6 MONTHS	10 YEARS	10	1	1	NIL		3	NIL
3 MONTHS	8 YEARS	1	1	1	NIL		1	NIL
3 MONTHS	17 YEARS	10	1	1	1	CHILLS	1	NIL
3 MONTHS	8 YEARS	3,4	1	1	1	EVER WITH CHILL	1	NIL
6 MONTHS	17 YEARS	3	1	1	1	RASHES	1	NIL
4 MONTHS	8 YEARS	4,11	1	1	NIL		1	NIL
3 MONTHS	12 YEARS	1	1	1	NIL		1	NIL
1 YEAR	10 YEARS	3	1	1	1	FEVER	1	NIL
1 YEAR	8 YEARS	3	1	1	NIL		1	NIL
6 MONTHS	8 YEARS	1	1	1	2	FEVER	1	NIL
7 MONTHS	8 YEARS	10	1	1	NIL		1	NIL
6 MONTHS	14 YEARS	1	1	1	NIL		1	NIL
3 MONTHS	8 YEARS	1	1	1	NIL		1	NIL
5 MONTHS	14 YEARS	3,4	1	1	NIL		1	NIL
7 MONTHS	17 YEARS	4	1	1	NIL		1	NIL
6 MONTHS	11 YEARS	5	1	1	NIL		1	NIL
5 MONTHS	13 YEARS	5,7,11	1	1	NIL		1	NIL
3 MONTHS	17 YEARS	1	1	1	NIL		1	NIL

DESFEROXAMINE	DEFERIPRONE		DEFERASIROX		ANY OTHER	TREATMENT HISTORY IN PAST	IMMUNISATION HISTORY	CONSANGUIEOUS/NON CONSANGUINEOS	SIBLING STATUS
DOSE,DURATION	DOSE	DURATION	DOSE	DURATION					
NIL	NIL		1000MG/DAY	10 YEARS	1,2,3,4	NIL	2	1	NO
NIL	NIL		1750MG/DAY	14 YEARS	1,2,3,4,5	SPLENECTOMY DONE	1	1	NO
NIL	1500MG/DAY	3 MONTHS	1750MG/DAY	9 YEARS	1,2,3,5	NIL	1	1	NO
NIL	1500MG/DAY	7 MONTHS	1250MG/DAY	6 YEARS	1,2,3,5	TRIVIAL MR,TR,AR	1	1	NO
NIL	NIL		1000MG/DAY	10 YEARS	1,2,3,5	NIL	2	1	NO
NIL	NIL		1500MG/DAY	12 YEARS	2,3,4,5	NIL	2	2	YES
NIL	NIL		1000MG/DAY	10 YEARS	2,3,4,5	NIL	1	2	YES
NIL	NIL		1250MG/DAY	8 YEARS	1,2,3,5	NIL	2	1	NO
NIL	NIL		500MG/DAY	6 YEARS	2,3,5	NIL	1	2	NO
NIL	4000MG/DAY	7 MONTHS	1000MG/DAY	13 YEARS	2,3,4,5	NIL	1	2	NO
NIL	500MG/DAY	5 MONTHS	1250MG/DAY	9 YEARS	1,2,3,5	SPLENECTOMY DONE	2	2	NO
NIL	NIL		1500MG/DAY	11 YEARS	1,2,3,5	NIL	2	2	NO
NIL	NIL		1500MG/DAY	10 YEARS	2,3,4,5	NIL	1	2	NO
NIL	2000MG/DAY	1 YEAR	1000MG/DAY	10 YEARS	2,3,5	NIL	1	2	NO
NIL	NIL		1000MG/DAY	8 YEARS	2,3,5	SPLENECTOMY DONE	1	2	NO
NIL	NIL		750MG/DAY	10 YEARS	2,3,4,5,6	NIL	1	1	NO
NIL	3000MG/DAY	6 MONTHS	1000MG/DAY	10 YEARS	2,3,5	SPLENECTOMY DONE	1	1	NO
NIL	1500MG/DAY	7 MONTHS	1000MG/DAY	7 YEARS	2,3,4,5	NIL	1	1	NO
NIL	2500MG/DAY	1 YEAR	1250MG/DAY	7 YEARS	2,3,5	NIL	1	2	YES
NIL	NIL		750MG/DAY	7 YEARS	2,3,4,5	NIL	1	2	YES
NIL	NIL		1000MG/DAY	10 YEARS	2,3,5	NIL	1	2	NO
NIL	1000MG/DAY	3 YEARS	1500MG/DAY	15 YEARS	2,3,4,5,6	NIL	1	2	NO
NIL	1000MG/DAY	6 MONTHS	1000MG/DAY	6 YEARS	1,2,3,4,5	NIL	1	2	NO
NIL	NIL		500MG/DAY	7 YEARS	2,3,5	NIL	1	2	NO
NIL	2500MG/DAY	3 YEARS	1500MG/DAY	10 YEARS	2,3,5	NIL	1	1	NO
NIL	NIL		750MG/DAY	8 YEARS	2,3,4,5	NIL	1	2	NO
NIL	NIL		1500MG/DAY	7 YEARS	2,3,4,5	SPLENECTOMY DONE	1	2	NO
NIL	NIL		1000MG/DAY	8 YEARS	2,3,4,5	NIL	1	2	NO
NIL	NIL		750MG/DAY	7 YEARS	2,3,4,5	NIL	1	1	NO
NIL	500MG/DAY	6 YEARS	500MG/DAY	7 YEARS	2,3,4,5	NIL	1	2	YES
NIL	NIL		750MG/DAY	7 YEARS	2,3,4,5	NIL	1	2	NO
NIL	NIL		750MG/DAY	9 YEARS	2,3,5	NIL	1	2	NO
NIL	NIL		500MG/DAY	6 YEARS	2,3,5	NIL	2	2	NO
NIL	500MG/DAY	5 YEARS	1500MG/DAY	8 YEARS	2,3,5	NIL	1	1	NO
NIL	NIL		500MG/DAY	7 YEARS	2,3,4,5	NIL	1	2	NO
NIL	NIL		1250MG/DAY	13 YEARS	2,4,5	NIL	1	1	NO
NIL	1000MG/DAY	6 YEARS	2250MG/DAY	10 YEARS	1,2,3,4	NIL	2	1	NO
NIL	NIL		750MG/DAY	9 YEARS	2,3,5	NIL	1	1	NO
NIL	NIL		1000MG/DAY	8 YEARS	2,3,4,5	NIL	1	2	NO
NIL	1000MG/DAY	3 YEARS	1000MG/DAY	10 YEARS	2,3,4,5	NIL	1	2	NO

DEATH OF SIBLING	VITALS					WEIGHT			HEIGHT			
	HR	RR	CFT	TEMP	BP	MEASURED	EXPECTED	PERCENTILE	MEASURED	EXPECTED	PERCENTILE	MEASURED
2	74/MIN	22/MIN	< 3SEC	98F	98/66MMHG	26KG	34KG	BTW 10TH AND 50TH	134CM	149CM	BTW 10TH AND 50TH	15.29
2	68/MIN	24/MIN	< 3SEC	96.8F	120/70MMHG	40KG	56.8KG	BTW 3RD AND 10TH	150CM	166.5CM	3RD	17.7
2	88/MIN	24/MIN	< 3SEC	98.6F	94/68MMHG	42KG	46.5KG	BTW 10TH AND 50TH	142 CM	155CM	BTW 3RD AND 10TH	17.7
1	72/MIN	24/MIN	< 3SEC	98F	96/74MMHG	31.7KG	59.5KGS	< 3RD	143CM	180CM	<3RD	15.5
2	68/MIN	22/MIN	< 3SEC	98F	102/68MMHG	32.7KG	35.4KG	BTW 10TH AND 50TH	139CM	143.3CM	BTW 10TH AND 50TH	16.36
2	90/MIN	20/MIN	< 3SEC	99F	96/68MMHG	37KG	43KG	BTW 10TH AND 50TH	149CM	153CM	BTW 10TH AND 50TH	16.6
2	96/MIN	20/MIN	< 3SEC	98F	100/60MMHG	22KG	39KG	<3RD	127CM	149CM	<3RD	13.7
2	76/MIN	24/MIN	< 3SEC	98F	94/66MMHG	39KG	46KG	BTW 10TH AND 50TH	157CM	163CM	BTW 10TH AND 50TH	14.4
2	68/MIN	24/MIN	< 3SEC	98F	98/64 MMHG	39KGS	59.5KGS	3RD	139CM	173CM	<3RD	14
2	80/MIN	20/MIN	< 3SEC	98F	100/70MMHG	35KG	49.7KG	BTW 3RD AND 10TH	144CM	156.9CM	BTW 3RD AND 10TH	17.8
2	78/MIN	24/MIN	< 3SEC	98.8F	100/66MMHG	33KG	48.2KGS	BTW 3RD AND 10TH	143CM	159.9CM	3RD	16.3
2	82/MIN	22/MIN	< 3 SEC	99F	102/76MMHG	40KG	48.2KGS	BTW 10TH AND 50TH	156CM	159.9CM	BTW 10TH AND 50TH	16.6
2	88/MIN	22/MIN	<3 SEC	98F	100/60MMHG	27KG	48KG	< 3RD	134CM	159CM	< 3RD	15.29
2	97/MIN	20/MIN	<3 SEC	98.7F	120/70MMHG	30KG	48KG	3RD PERCENTILE	133CM	160CM	<3RD PERCENTILE	16.95
2	78/MIN	22/MIN	<3 SEC	98.4F	110/70MMHG	26KG	39KG	BTW 10 AND 50	135CM	148CM	BTW 3RD AND 10TH	14.26
2	89/MIN	26/MIN	< 3 SEC	98.7F	90/60MMHG	23KG	35KG	BTW 3RD AND 10TH	127CM	142CM	<3RD	14.26
2	94/MIN	22/MIN	< 3 SEC	97.2F	110/70MMHG	48KGS	52KG	BTW 10TH AND 50TH	153CM	157CM	BTW 10TH AND 50TH	21
2	96/MIN	22/MIN	< 3 SEC	98.2F	100/70MMHG	29.9KG	43.6KG	BTW 3RD AND 10TH	130CM	152CM	< 3RD	17.69
1	94/MIN	25/MIN	< 3 SEC	98.6F	110/60MMHG	36KGS	43.6KGS	BTW 10TH AND 50TH	134CM	152.2CM	< 3 RD	20.05
2	78/MIN	24/MIN	< 3 SEC	98.7F	100/60MMHG	21KGS	27.2KGS	BTW 10TH AND 50TH	120CM	131.4CM	BTW 3RD AND 10TH	14.45
2	94/MIN	22/MIN	< 3 SEC	98F	100/60MMHG	30KGS	39.8KGS	10TH	136CM	148.4CM	BTW 3RD AND 10TH	16.22
2	97/MIN	16/MIN	<3 SEC	98F	100/60MMHG	42KGS	62KGS	BTW 3RD AND 10TH	122CM	173CM	< 3RD	18
2	94/MIN	24/MIN	< 3 SEC	98.6F	110/70MMHG	40KGS	48.2KGS	BTW 10TH AND 50TH	140CM	159.9CM	< 3 RD	17.86
2	84/MIN	16/MIN	< 3 SEC	97.8F	120/70MMHG	25KGS	27.9KGS	BTW 10TH AND 50TH	129CM	131.8CM	BTW 10TH AND 50TH	15.02
2	94/MIN	19/MIN	< 3 SEC	98F	110/70MMHG	40.8KGS	61KGS	<3RD	160CM	173CM	<3RD	15.62
2	89/MIN	18/MIN	< 3 SEC	98.2F	110/70MMHG	23KGS	24KGS	50TH	122CM	125CM	50TH	15.45
2	94/MIN	26/MIN	< 3 SEC	98F	120/80MMHG	38KGS	61.6KG	< 3 RD	144CM	158CM	< 3 RD	18.32
2	68/MIN	22/MIN	< 3 SEC	98.5F	110/70MMHG	22KGS	27.9KGS	BTW 10TH AND 50TH	122CM	131.8CM	BTW 10TH AND 50TH	14.78
2	76/MIN	24/MIN	< 3 SEC	98.8F	100/64MMHG	28KGS	43KG	3RD	140CM	152.2CM	BTW 3RD AND 10TH	14.28
1	94/MIN	16/MIN	< 3 SEC	98.5F	110/70MMHG	21KGS	34.7KGS	< 3RD	117CM	142.7CM	< 3RD	15.34
2	98/MIN	16/MIN	< 3 SEC	97.8F	110/70MMHG	20KGS	27.2KGS	BTW 10TH AND 50TH	119CM	131.4CM	BTW 3RD AND 10TH	14.12
2	84/MIN	26/MIN	< 3 SEC	98.6F	100/60MMHG	24KGS	31.1KGS	BTW 10TH AND 50TH	124CM	137.2CM	BTW 3RD AND 10TH	15.93
2	88/MIN	16/MIN	< 3 SEC	97.9F	100/70MMHG	14.5KGS	24.4KGS	< 3 RD	98CM	126.4CM	<3RD	14.9
2	94/MIN	16/MIN	< 3 SEC	98F	110/70MMHG	40KGS	61KGS	< 3RD	148CM	173CM	<3RD	18.26
2	94/MIN	26/MIN	< 3 SEC	98.8F	110/60MMHG	20KGS	27.2KGS	BTW 10TH AND 50TH	130CM	131CM	50TH	11.83
2	74/MIN	22/MIN	< 3 SEC	98.7F	120/70MMHG	44KGS	53.1KGS	BTW 10TH AND 50TH	149CM	164.5CM	BTW 3RD AND 10TH	19.8
2	78/MIN	26/MIN	< 3 SEC	98.6F	112/80MMHG	45KGS	61.6KGS	BTW 3RD AND 10TH	164CM	173.6CM	BTW 10TH AND 50TH	17.57
2	88/MIN	18/MIN	< 3 SEC	98.4F	110/70MMHG	34KGS	39.8KGS	BTW 10TH AND 50TH	133CM	148.4CM	BTW 3RD AND 10TH	19.22
2	98/MIN	26/MIN	< 3 SEC	97.9F	100/60MMHG	27KGS	43.6KGS	3RD	135	150.5CM	<3RD	15.15
2	67/MIN	19/MIN	< 3 SEC	98F	110/60MMHG	46KGS	61.6KGS	BTW 3RD AND 10TH	170CM	173.6CM	BTW 3RD AND 10TH	15.91

BMI		HEAD TO TOE										
EXPECTED	PERCENTILE	FACE	EYES	EARS	ORAL CAVITY	NECK	CHEST	ABDOMEN	EXTREMITIES	ODEMA	CONGENITAL MARKERS	SKIN
17.5	BTW 10TH AND 50TH	1	1	NORMAL	1	1	NORMAL	1	1	NO	NIL	2,4
18.7	BTW 10TH AND 50TH	1	1,3	NORMAL	2	1	NORMAL	4	2	NO	NIL	2
19.4	BTW 10TH AND 50TH	1	1	NORMAL	5	1	NORMAL	3	1	NO	NIL	1
20.5	BTW 3RD AND 10TH	1	1	NORMAL	3	1	NORMAL	3	1	NO	NIL	2,4
18	BTW 10TH AND 50TH	1,5	5	NORMAL	1	2	NORMAL	3	1	NO	NIL	5
18.8	BTW 10TH AND 50TH	6	5	NORMAL	3	1	NORMAL	3	1	NO	NIL	1
17.5	BTW 3RD AND 10TH	3,7	1	NORMAL	5	1	NORMAL	3	1	NO	NIL	2,4
19	BTW 3RS AND 10TH	1	1	NORMAL	3	1	NORMAL	3	1	NO	NIL	2
20.5	<3RD	1	2	NORMAL	3	1	NORMAL	3	1	YES	NIL	2
20.3	BTW 10TH AND 50TH	1	1	NORMAL	3	1	NORMAL	3	1	NO	NIL	2,4
18.7	BTW 10TH AND 50TH	1,2	2,3	NORMAL	1	1	NORMAL	4	1	NO	NIL	2
19.3	BTW 10TH AND 50TH	1,3	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	2
18.7	BTW 10TH AND 50TH	2	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	2
18.7	BTW 10TH AND 50TH	2	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	2
17.7	BTW 5TH AND 10TH	2	1	NORMAL	4	1	NORMAL	4	1	NO	NIL	2
17	BTW 10TH AND 50TH	1	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	2
21	50TH	6	1	NORMAL	1	1	NORMAL	4	1	NO	NIL	1
18.8	BTW 10TH AND 50TH	1	5	NORMAL	5	1	NORMAL	4	1	NO	NIL	2
18.8	BTW 50TH AND 90TH	1	1	NORMAL	1	1	NORMAL	3	5	NO	NIL	2
15.8	BTW 10TH AND 50TH	2	1	NORMAL	4	1	NORMAL	3	1	NO	NIL	2,4
18	BTW 10TH AND 50TH	2	1	NORMAL	1	1	NORMAL	3	5	NO	NIL	2,4
18	50TH	6	1	NORMAL	3	1	NORMAL	3	1	NO	NIL	1
18.7	BTW 10TH AND 50TH	6	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	1
15.9	50TH	6	1	NORMAL	4	1	NORMAL	3	1	NO	NIL	1
21.1	3RD	2	1	NORMAL	5	1	NORMAL	3	5	NO	NIL	2
15.3	50TH	1	5	NORMAL	1	1	NORMAL	3	1	NO	NIL	1
21.1	BTW 10TH AND 50TH	2	5	NORMAL	4	1	NORMAL	4	1	NO	NIL	2
15.9	BTW 10TH AND 50TH	1	5	NORMAL	1	1	NORMAL	3	1	YES	NIL	2
18.8	BTW 3RD AND 10TH	6	1	NORMAL	4	1	NORMAL	3	1	NO	NIL	2
17	BTW 10TH AND 50TH	4	1	NORMAL	4	1	NORMAL	2	1	NO	NIL	1
15.8	BTW 10TH AND 50TH	1,2,4	1	NORMAL	4	1	NORMAL	3	5	NO	NIL	1
16.4	BTW 10TH AND 50TH	4	1	NORMAL	5	3	NORMAL	3	1	NO	NIL	4
15.5	BTW 10TH AND 50TH	1	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	4
21.1	BTW 10TH AND 50TH	2	1	NORMAL	1,4	1	NORMAL	3	1	NO	NIL	1
15.9	< 3RD	2	5	NORMAL	1	1	NORMAL	2	1	YES	NIL	4
19.8	50TH	6	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	4
21.1	BTW 10TH AND 50TH	1	1	NORMAL	5	1	NORMAL	3	1	NO	NIL	1
19	50TH	1,2,4	1	NORMAL	1	1	NORMAL	3	1	NO	NIL	1
18.4	BTW 10TH AND 50TH	1	5	NORMAL	1	3	NORMAL	3	1	NO	NIL	1
21.1	BTW 3RD AND 10TH	1	5	NORMAL	5	1	NORMAL	3	5	NO	NIL	2

CVS	RS	P/A	LIVER SPAN	SPLEEN SPAN	CNS	TANNERS STAGING	Hb(mg/dl)	PCV
			1ST	1ST				
S1,S2+,SHORT SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,MILD DISTENSION	13CM	NOT PALPABLE	NAD	1	8.4	24.1
S1,S2+,SOFT SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NONTENDER,SPLENECTOMY SCAR	12CM	NIL	NAD	3	7.1	22
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NONTENDER	12 CM	1CM BELOWLCM	NAD	1	9.6	27.9
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	10CM	NOT PALPABLE	NAD	2	6	18.6
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	12CM	2CM BELOW LCM	NAD	1	8.7	25.8
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	2CM BELOW LCM	NAD	3	9.9	30.5
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT ,NON TENDER	14CM	2CM BELOW LCM	NAD	1	9.2	25.4
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NONTENDER	13CM	3CM BELOW LCM	NAD	3	10.1	28.3
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	1CM BELOWLCM	NAD	3	9	27
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT ,NON TENDER	14CM	2CM BELOW LCM	NAD	3	9.4	28.6
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER ,SPELNECTOMY SCAR+	14CM	NIL	NAD	2	9.6	28
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER ,BS+	12CM	2CM BELOW LCM	NAD	3	10.2	30.8
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT ,NON TENDER	13CM	3CM BELOW LCM	NAD	3	7.7	22.3
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,MILD DISTENSION	10CM	1CM BELOWLCM	NAD	3	8.1	23
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	10CM	NIL	NAD	3	8.7	25.2
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	10CM	NIL	NAD	2	9.9	28.3
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT, NON TENDER	13CM	NIL	NAD	4	8.2	23.2
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	12CM	3 CM BELOW LCM	NAD	3	8.1	24.8
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT, NON TENDER	13CM	4CM BELOW LCM	NAD	3	8.9	26.4
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	5 CM BELOW LCM	NAD	2	8.4	24.7
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	NIL	NAD	1	8.3	23.4
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	6CM BELOW LCM	NAD	4	8.8	25.2
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT ,NON TENDER	13CM	NIL	NAD	3	8.9	26.1
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT, NON TENDER	8CM	NIL	NAD	1	10.9	32.9
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	4CM BELOW LCM	NAD	4	9.3	28.8
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	12CM	NIL	NAD	2	8.6	24.7
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	NIL	NAD	3	7.6	20.4
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	NIL	NAD	2	9	26.6
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	3CM BELOW LCM	NAD	2	9	25.3
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	8CM	NIL	NAD	1	8.4	24.1
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	8CM	5CM BELOW LCM	NAD	1	8.2	22.9
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	11CM	2CM BELOW LCM	NAD	2	8.2	23.9
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	7CM	NIL	NAD	1	8.4	23.8
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	NIL	NAD	3	9.9	29.1
S1,S2+,NO MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	7CM	NIL	NAD	2	8.2	24.6
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	13CM	3CM BELOW LCM	NAD	2	6.9	21.2
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	9CM	4CM BELOW LCM	NAD	3	5.9	16.1
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	10CM	NIL	NAD	1	10.2	29.6
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	14CM	2CM BELOW LCM	NAD	2	7.9	21.4
S1,S2+,SYSTOLIC MURMUR	AIR ENTRY B/L+	SOFT,NON TENDER	10CM	NIL	NAD	2	8.7	24.9

RBC	WBC	DLC	PLT	UREA	CREATININE	SODIUM	POTASSIUM	FERRITIN	24 HR URINARY TESTS					U.BETA 2 MG	FE Na	FE K	CREATININE CL	eGFR
									CREATININE	SODIUM	POTASSIUM	CALCIUM	ALBUMIN					
3.06	5120	60/35/1/4	3.22	22	0.4	134	3.8	2366	846	423	31.1	141.1	<0.5	116	0.14	0.38	116.5	138.3
2.71	22340	20/53/4/3	11.32	22	0.9	135	4.1	3250	273	107	15.3	11.2	<0.1	399.1	0.14	0.65	137.8	77.43
3.18	10,600	59/37/1/3	2.53	78	1.2	139	4.3	10,173	2805	91.8	152.9	47.6	<0.1	1110	0.94	0.5	154.9	48.87
2.46	5390	51/38/9/2	2.41	13	0.5	140	4.2	2300	481	274	33.75	67.5	<0.5	848.7	0.2	0.8	112.8	118.11
2.78	11,630	60/35/2/3	5.56	26	0.3	135	4.8	2268	565	94.4	8.72	358	<0.1	60.8	3.7	0.9	167.5	191.35
3.77	12,450	57/33/3/5	5.01	32	0.5	139	4.6	2268	454	123	12.58	123	<0.5	173.3	0.1	0.4	79	123.07
2.89	8400	51/44/1/4	2.38	23	0.7	140	4.2	4778	441	111	15.82	186	<0.5	86.7	0.07	0.9	103	131.12
3.23	11,600	38/50/5/7	4.31	27	0.7	137	4.2	1988	2673	295.5	30.32	332.5	<0.5	328	0.048	0.16	81.7	108.06
3.54	5,768	63/32/2/2	4.98	29	0.9	136	4.6	3998	298	88.9	32.4	76.9	<0.1	989	0.08	0.94	166.6	63.78
3.8	6,840	36/60/0/4	2.07	16	0.7	138	4.3	4895	308	111	12.24	32.3	<0.5	643.6	0.15	0.55	85.4	84.96
2.47	12600	62/32/2/4	6.2	98	0.7	136	5.1	6424	527	242.5	22.6	102.5	<0.5	624.3	0.06	0.16	304.5	42.18
3.6	9,230	50/46/1/3	4.67	14	0.7	136	4.6	3199	281	608	86	12.8	<0.5	49.4	0.6	2.66	173	161.07
2.84	5470	60/35/3/2	2.28	17	0.7	137	4	3618	377	228	27.95	106.5	<0.5	24.8	0.35	1.48	60	69.177
2.61	6910	53/39/5/3	2.18	26	1	130	3.5	3969	350	136.5	12.57	24	<0.5	427	0.09	0.3	175	64.428
2.62	15150	49/25/2/4	9.06	12	0.7	134	4.2	2366	1213	3705	631.5	18	<0.3	57.7	1.1.	2.4	231.1	278.77
3.24	5660	41/53/2/4	2.08	19	0.7	142	4.7	1553	219	41.8	5.05	190	<0.5	74	0.05	0.23	103	131.12
2.54	11410	50/46/1/3	6.67	14	0.9	137	4.2	5237	701	111.6	30.85	33.6	<0.1	471	0.09	0.8	85	70.21
3.33	10140	51/42/2/5	6.32	18	0.7	138	4.1	1750	1208	231	84.17	69	<0.5	23.1	0.02	0.33	224.1	268.4
2.87	5770	60/35/2/3	3.01	27	0.4	134	4.4	2216	611.3	115	50.1	44.4	<0.1	166	0.08	1.11	90	138.355
2.83	7960	45/48/2/5	3.72	15	0.7	135	4.2	2588	335	146	46.6	20.4	<0.5	40.3	0.09	3.11	110.8	165.2
3.36	7000	52/40/3/5	3.36	20	0.7	137	4.3	993	720.29	324.7	51.58	307.7	<0.5	272	0.1	0.8	90.7	112.3
3.29	5750	70/26/1/3	1.51	13	0.7	135	3.9	5288	348	640	92.32	49.6	<0.5	10.8	0.5	2.7	169	71.98
2.91	6310	46/50/1/3	2.74	25	0.7	135	3.6	670	48.2	192	23	13.4	<0.5	214	7	5	175	144.55
4.75	9110	44/46/5/5	4.75	18	0.7	130	4.8	2794	993	387	39.56	211.5	<0.5	63.5	0.1	0.69	91	106.55
3.83	6070	59/40/0/1	2.04	87	0.7	138	4	8652	323	120	14.66	132	<0.5	55.2	0.2	1.1	68	66.08
3.07	12030	38/59/1/2	3.31	25	0.7	139	4.2	3845	667	256	28.82	184	<0.5	72.4	0.11	0.41	89.6	125.96
2.25	31290	36/60/2/2	7.24	38	0.7	132	4.6	2538	67.56	156	23	21.9	<0.5	816.2	0.88	3	126.7	118.944
2.95	10530	51/44/2/3	5.81	45	0.7	139	4.3	2278	702.4	2176	284	81.6	<0.5	3969	0.66	2.82	173	38.75
2.69	12020	50/46/1/3	2.68	34	0.7	138	5	1898	289	67.5	76	28.5	<0.5	132	0.06	2.1	105	144.55
3.26	7480	55/37/4/4	3.26	12	0.7	136	4.8	1067	443.52	163.2	10.51	497.6	<0.5	111	0.13	0.23	64	96.64
2.64	5970	40/55/1/4	2.11	18	0.4	136	4.3	3532	425.3	2368	240	150.4	<0.5	119	2.4	7.87	51.6	122.86
2.83	6520	45/47/3/5	3.54	28	0.5	147	4.2	2888	419.9	2376	403.9	54	<0.5	37.9	2.7	16	61.9	102.424
2.75	12030	65/30/2/3	1.93	39	0.3	142	4.2	1213	638.4	1547	330	238	<0.5	279	1.1	8.6	36.7	134.91
3.52	4890	54/38/2/0	2.09	17	0.7	140	4.3	3621	803	177	31.38	243.2	<0.5	3156	0.1	0.63	95.2	87.32
2.83	5520	37/44/6/12	3.81	25	0.4	141	3.7	1315	272.9	52.8	18.3	20.8	<0.5	213	0.09	1.24	52	134.22
2.54	6092	64/32/1/3	3.97	34	0.7	135	4.2	3340	298	2097	209	211.9	<0.5	784.9	4.17	1.3	95.5	76.92
1.96	5908	52/40/3/5	2.98	76	1	139	3	8309	120	290	32.9	209	<0.1	928.6	1.04	5.4	126	67.732
3.2	6502	44/46/5/5	3.98	45	0.7	135	5.4	2404	291	197	20	23.5	<0.5	70.9	0.4	0.5	128.4	137.32
1.98	6730	40/55/1/4	2.86	34	0.7	139	4.9	8789	593	87.8	29.6	32.6	<0.1	3849.8	0.03	0.3	133.9	46.46
2.48	4560	51/44/2/3	7.86	24	0.9	136	4.2	4987	617	128	356	156	<0.5	824.8	0.12	8.24	96.6	78.11