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Original Research Article

Beta Thalassemia and its variant: A Clinicopathological correlation of 100 cases in Bihar, India

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Abstract

Background: Thalassemia is a heterogeneous group of genetical disorders of hemoglobin (Hb) characterized by reduced or absent production of globin chains. It is the major health problem in the Indian subcontinent as the prevalence rate of beta thalassemia mutations is as high as 17% in some populations. The overall prevalence of β-thalassemia trait is 2.78 % and varies from 1.48 to 3.64 % in different states, while the prevalence of β-thalassemia trait in 59 ethnic groups varies from 0 to 9.3 %

Materials and Methods: This study was conducted in the department of pathology of a tertiary care teaching medical colleges and hematology centre in Bihar, India from August 2017 to December 2018. Patients who came with weakness, history of multiple blood transfusions and abnormal hemograms suggestive of anemia with microcytic hypochromic blood pictures, and also those patients who had a positive family history of thalassemia were included in the study.

Result: During the study period of 1 year and 3 months, a total of 100 cases were studied. The age of the patients ranged between 4 months (Female), beta thalassemia major and 55(Male) years, beta thalassemia intermedia. Male female ration was 3.76. The most common thalassemia in this study was Beta thalassemia major (52%) and second was Beta E thalassemia major (31%)

Conclusion: study of incidence and prevalence of common Beta Thalassemias in a particular region helps to formulate appropriate preventive and therapeutic strategies.

Keywords: Beta Thalassemia, HPLC, Autosomal E thalassemia transfusion Ferritin Splenomegaly.

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1. Introduction

Thalassemia is a heterogeneous group of genetical disorders of hemoglobin (Hb) characterized by reduced or absent production of globin chains. It is the commonest single gene disorder in the world first noted in the Mediterranean population and causing a significant morbidity and mortality in India and abroad. [1,2] The prevalence of thalassemia varies with geographic locations. It has been estimated that in India, 0.37 per 1,000 foetuses have Hb disorder. [3]

It is the major health problem in the Indian subcontinent as the prevalence rate of beta thalassemia mutations is as high as 17% in some populations. IVS-I-5 (G-->C) is the most common beta-thalassemia allele in the Indian population .The overall prevalence of β-thalassemia trait is 2.78 % and varies from 1.48 to 3.64 % in different states, while the prevalence of β-thalassemia trait in 59 ethnic groups varies from 0 to 9.3 % [4] Hb E-β thalassemia and sickle beta thalassemia are also common Hb disorders, which are reported to be quite prevalent in many parts of India.[5,6] The other significant hemoglobinopathies prevalent in India are HbE, sickle-cell anemia, and HbD. [6-9]

High-performance liquid chromatography (HPLC) is one of the best methods for the screening and detection of various hemoglobinopathies and provides rapid, reproducible, and precise results. The HPLC-CE is a rapid, reproducible and precise technique. The reliability of HbA2 measurement by HPLC for the detection of beta thalassaemia trait and B-E thalassemia without any false positive or false negative results is of great advantage. HPLC may be an appropriate method for rapid screening in population surveys for beta thalassemia and hemoglobin variants carriers. Due to the high incidence of cases, in our country this is very important for their clinical management and the genetic and anthropological impact of an early and precise diagnosis. [10,11] Detail clinical history including family history and hematologic parameters such as complete blood count, reticulocyte count, and red cell morphology are often required to confirm the diagnosis. Serum ferritin, iron, transferring and saturation are also done in few cases to rule out concurrent iron deficiency anemia and thalassemia.

The present study attempted to find out the occurrence of different Hb variants in the population of Bihar in India so that a definite plan of action regarding the diagnostic, preventive, and therapeutic strategies can be formulated to minimize more serious disorders in future generations.

2. Materials and Methods

This study was conducted in the department of pathology of a tertiary care teaching medical colleges and hematology centre in Bihar, India from August 2017 to December 2018. [Table 1] Patients who came with weakness, history of multiple blood transfusions and abnormal hemograms suggestive of anemia with microcytic hypochromic blood pictures, and also those patients who had a positive family history of thalassemia were included in the study. Patients having microcytic hypochromic blood picture with serum iron profile suggestive of iron deficiency anemia were excluded from study. Transfusion-dependent children and adults were also included. Patients with HPLC reports suggestive or diagnostic of Beta-thallasemia were included in this study. [Table 1] Those came without reports of HB Electrophoresis or HB HPLC was advised same investigations. If HPLC reports did not prove diagnosis of Beta Thalassemia were excluded from study. However, patients with history of blood transfusion within the last 1 month were excluded. Complete blood count (CBC) [Table 2], peripheral blood smear (PBS) and HPLC studies were done of both parents of affected children, whenever possible. Detailed clinical history and family history were obtained of each patient. Past history of blood transfusion, if present, was noted. In few cases, bone marrow aspiration was also done.

Blood samples were collected in ethylene diamine tetrachloride acetate (EDTA) vials and analyzed with automated cell counter for complete blood counts. Serum was also collected for liver function tests and serum iron, transferring saturation, ferritin. Cobalamin, and folate levels, Direct Coomb's and Indirect Coomb's tests were done in special patients. For each patient, a peripheral blood smear (PBS) was prepared and stained with Leishman stain and observed microscopically for red cells morphology. Bone marrow slides were stained with Leishman stain and examined microscopically. Hb variant analysis was studied for various hemoglobinopathies and variants. In few cases, capillary HB electrophoresis was also done. The tests were performed on Biorad D -10 variant using beta thalassemia short program (Bio-Rad Laboratories, California, USA). The graph with values for each case was obtained and analyzed as per guideline. Those patients already having HPLC studies with diagnosis of thalassemia were not done again and only noted values and photographs were taken.

3. Result

During the study period of 1 year and 3 months, a total of 100 cases were studied. The age of the patients ranged between 4 months (Female), beta thalassemia major and 55(Male) years, beta thalassemia intermedia [Table 1]. Male female ration was 3.76. [Table 1] The most common thalassemia in this study was Beta thalassemia major (52%) and second was Beta E thalassemia major (31%).[Table 2] The Beta thalassemia intermedia constituted 12%. The Beta trait and others constituted 5%. HPLC variant analysis was available in 82 % & and Capillary HB electrophoresis was available in 18%. The very high value of A2 in HPLC? was considered as BE thalassemia and capillary electrophoresis provided separate values of A2 and E hemoglobin.[Table 3] One patient had allogeneic bone marrow transplantation with relapsed thalassemia and other one had direct Coombs' test positive in this study. HPLC parameters revealed raised HBA2 in Beta Thalassemia trait and intermedia. In Beta Thalassemia major HBE was markedly raised and HBA2 in normal range. Naturally, HBA was markedly decreased. Clinical severity was well correlated with level of haemoglobin F (HBF).

On hematological parameters side, minimum hemoglobin was 2.16gm/dl in Beta Thalassemia major and minimum MCV was 55.3fl/L. (Table 4) Two cases were Direct Cooms' positive with features of autoimmune hemolytic anemia and difficulty in cross matching. However they became Cooms' negative after a course of steroid.

Bone marrow findings were available in few cases, having finding of normoblastic erythroid hyperplasia. PBS revealed microcytic hypochromic picture in 100% cases and target cells in most cases. [Figure 1) Nucleated RBC was present in severe cases.

Serum iron profile (TIBC, Ferritin, Iron) was normal in newly diagnosed patients and serum ferritin was raised in multiple transfused patients.

Most common clinical presentation was severe pallor with weakness with difficulty in walking and playing in children and short of breath in adolescents. Malar prominence (full cheek bone), frontal bossing, abdominal distension and hypertrophy of maxillae were common facial bone features [2-4]. Splenomegaly was most common organomegaly. Few cases have also hepatomegaly either due to extramedullary hematopoiesis or hemochromatosis due to iron deposition.

Important radiological findings were osteoporosis and osteopenia. The most common Hb abnormality detected was β (beta) thalassemia major. They are referred to tertiary hematology centre for further management, disability certificate and registration in Thalassemia society.

Table 1: HPLC Parameters OF B- Thalassemia and variants

Case no	Age in Years	Sex	HBF	HBA	HBA2	HBE	HBA2+E	Diagnosis	Remark
1	4	M	24.00	37.50			38.50	HBE Major	
2	6	F	18.10	26.90			45.00	HBE Major	
3	1	M	10.20	85.10	3.80			Beta INTER	
4	1	M	29.50	66.10	4..40			Beta Major	
5	5	F	90.00	8.0	2.00			Beta Major	
6	2.5	M	88.00	9.70	2.30			Beta Major	
7	1.5	M	80.00	17.90	2.10			Beta Major	
8	35	F	0.50	91.00	4.5			Beta TRAIT	Carrier
9	55	M	1.50	90.00	8.50			Beta Inter	
10	33	M	6.5	22.3	8.00	63.2		HBE	HB CAP ZONE ELECTRO
11	14	M	12.5	74.50	13.0			Beta Inter	
12	14	M	94.40	3.50	2.10			Beta Major	
13	7m	M	80.30	22.20	2.50			Beta Major	
14	9m	M	75.10	22.60	2.30			Beta Major	
15	22	M	35.00	56.30	8.70			Beta Inter	
16	7	M	10.50	81.70	7.80			Beta Inter	
17	5	M	89.50	8.10	2.40			Beta Major	
18	8	M	93.80	4.20	2.00			Beta Major	
19	2	M	90.50	7.40	2.10			Beta Major	
20	11	M	85.35	12.20	2.45			Beta Major	
21	5	M	30.50	40.50	29.00			HBE Major	
22	11m	M	91.50	6.40	2.10			Beta Major	
23	7 m	M	35.2	61.8	2.5			Beta Major	
24	1	M	79.5	15.3	2.2			Beta Major	
25	2.5	M	88.50	9.10	2.40			Beta Major	
26	2	M	10.50	37.00			52.50	HBE Major	
27	3	F	32.9	7.4			55	HBE	
28	4m	F	36.9	60.7	2.4			Beta Major	
29	2	M	28.70	21.80			49.50	HBE Major	
30	2	M	15.60	24.40			60.00	HBE Major	
31	5	M	87.50	10.10	2.40			Beta Major	
32	3	M	0.5	91.2	8.3			Trait	
33	11m	F	90.5	10.00				Beta Major	
34	4	M	2 3 .0	20.2			56.8	HBE Major	
35	10	M	85.50	12.1	2.40			Beta Major	
36	14	M	12.70	6.60	2.90		71.10	HBE Major	
37	12	M	10.80	7.20	2.50		79.50	HBE Major	
38	15	M	38.10	4.6	6.0	51.3		HBE Major	CAP ZONE
39	11	M	3.9	78.5	5.1			HE TRAIT	
40	10	F	48.1	4.4	6.0	41.5		HBE M	
41	11	M	30.1	12.6	6.0	51.3		HBE Major	
42	1	M	12.56	71.30	3.60			Beta Major	
43	4	F	91.00	4.60	3.30			Beta Major	
44	5	M	21.4	12.5	65.5			HBE Major	
45	28	F	0.8	83.2	5.2			Beta TRAIT	
46	4	M	16.6	80.2	4.9			Beta Inter	
47	2	M	92.6	4.0	3.4			Beta Major	
48	1	M	95.2	2.3	2.5			Beta Major	
49	14	M	92.2	5.O	2.8			Beta Major	
50	7m	M	95.2	2.8	2.0			Beta Major	
51	1	M	94.5	2.5	3.0			Beta Major	
52	1	M	95.2	2.O	2.8			Beta Major	BROTHER
53	4	M	15.60	6.30		74.2		HBE Major	
54	35	F	1.0	93.5	5.5			Beta Inter	
55	7m	M	90.50	7.00	2.50			Beta Major	

Table 1 Continue……..

Case no	Age in Years	Sex	HBF	HBA	HBA2	HBE	HBA2+E	Diagnosis	Remark
56	7	M	94.5	3.5	2.0			Beta Major	
57	28	F	90.5	6.5	3.0			Beta Major	
58	3	M	12.8	21.4		64.8		HBE Major	
59	4	M	91.5	6.5	2.0			Beta Major	
60	14	M	92.00	6.5	1.5			Beta Major	
61	4	M	91.00	6.5	2.5			Beta Major	
62	12	M	34.8	5.0		53.1		HBE M	
63	14	M	90.50	7.5	2.0			Beta Major	
64	8m	F	93.10	4.90	2.0			Beta Major	
65	4	M	21.8	17.4		60.8		HBE Major	
66	22	F	68.2	25.8	6.0			B THAL INTER	DAT+
67	4	M	21.0	17.2		61.8		HBE Major	FE,MB
68	7	M	20.5	14.4		65.1		HBE Major	
69	5m	M	85.10	11.60	3.30			Beta Major	
70	5	M	41.4	2.8	6.1	49.7		HBE Major	
71	9	M	0.8	80.2	8.2			Beta Inter	
72	5	M	20.5	19.5		60.0		HBE	
73	5MO	M	87.10	9.60	3.30			Beta Major	
73	10m	M	85.10	11.40	3.50			Beta Major	
74	16	M	84.10	12.00	3.90			Beta Major	
75	25	F	0.2	94.8	4.6			B TRAIT	
76	5	F	5.6	71.2		21.9		HBE Major	
77	3	M	91.40	6.60	2.00			Beta Major	
78	4	F	21.36	0.00		78.64		HBE Major	MUSLIM
79	6	M	22.4	24.2		53.4		HBE Major	MUSLIM
80	8	M	20.8	29.00		50.2		HBE Major	MUSLIM
81	1.5	M	94.2	2.1	2.3			Beta Major	
82	3	F	90.2	6.3	2.5			Beta Major	
83	5	F	88.5	8.3	2.2			Beta M	
84	7	M	29.8	5.1		65.3		HBE Major	4B 4S,
85	9	M	90.10	4.60	2.30			Beta Major	
86	1	M	24.5	3.5	2.6	30.6		HBE Major	
87	4	M	92.10	2.60	2.30			Beta Major	
88	10	M	90.20	9.70	2.10			Beta Major	
89	1	M	93.30	4.70	2.00			Beta Major	
90	5	M	93.70	4.00	2.30			Beta Major	
91	18	M	92.10	5.60	2.30			HBE Major	
92	1	M	93.40	4.60	2.00			Beta Major	
93	5	M	88.10	8.60	3.30			Beta Major	
94	20	M	2.0	91.5	6.5			B INTER	
95	4	M	2.5	92.0	5.5			B INTER	
96	28	F	0.8	83.2	5.2			B TRAIT	
97	33	M	3.90	78.5	5.1			E TRAIT	
98	4	F	89.10	8.60	2.30			Beta Major	
99	2	F	27.30	5.10			55.1	HBE Major	
100	8	M	80.00	11.50	6.40			Beta Major	

HBF: Haemoglobin F; HBA: hemoglobin; HBE; Hemoglobin E

Table 2: Hematological parameters of B- thalassemia patients

Case No	HB	RBC	MCV	MCH	RDW CV
1	3.90	2.19	66.60	17.80	30.60
2	5.30	2.85	66.80	18.50	34.70
3	4.7	2.5	65.90	17.50	33.50
4	8.90	4.23	60.70	21.0	17.60
5	5.0	2.3	60.50	16.40	32.90
6	3.5	2.10	61.00	16.15	33.12
7	4.00	2.20	60.00	17.25	32.25
8	10.15	5.50	65.10	22.25	19.20
9	6.8	2.5	63.1	24.4	20.8
10	7.5	2.9	61.7	19.8	32.0
11	4.26	2.84	55.30	14.80	37.40
12	3.3	1.87	64.7	17.60	35.00
13	4.9	2.40	59.4	20.6	29.0
14	4.58	8.2	61.0	17.80	31.00
15	5.94	9.1	65.00	18.70	33.00

Table 2 Continue……

Case No	HB	RBC	MCV	MCH	RDW CV
16	5.20	2.50	66.10	24.19	34.60
17	5.30	2.40	57.50	18.90	32.00
18	5.50	2.50	70.10	22.19	30.60
19	3.50	2.10	65.60	18.80	25.60
20	5.5	2.9	60.50	15.40	30.90
21	4.50	2.5	55.50	15.40	30.90
22	4.80	2.60	58.00	16.25	31.25
23	9.15	5.50	64.10	22.25	19.20
24	3.3	1.77	63.7	16.60	34.00
25	7.4	2.8	60.7	20.8	31.0
26	4.8	2.20	58.4	21.4	28.0
27	6.2	3.3	70.6	17.80	28.80
28	8.00	4.0	61.0	17.80	31.00
29	7.50	4.1	58.0	14.80	32.00
30	8.90	4.5	58.0	16.80	31.00
31	7.2	3.2	61.0	13.80	30.00
32	8.08	4.0	58.0	16.80	31.00
33	8.50	4.2	59.0	14.80	32.00
34	8.00	4.0	61.0	17.80	33.00
35	8.60	4.5	62.0	18.80	34.50
36	7.58	3.5	61.0	17.80	34.00
37	7.80	4.35	60.0	15.80	33.00
38	8.50	4.30	61.0	16.80	31.00
39	4.4	3.2	52.0	13.50	17.00
40	7.58	3.18	59.0	14.80	34.00
41	8.58	4.20	65.0	19.80	34.00
42	3.80	2.19	64.60	16.80	30.60
43	3.70	2.18	62.60	15.80	30.60
44	4.90	2.19	66.60	17.80	30.60
45	3.70	2.19	63.60	15.80	30.60
46	4.26	2.74	55.30	14.80	32.10
47	4.36	2.84	55.30	13.80	30.40
48	5.26	2.99	56.30	14.80	31.40
49	4.16	2.74	54.30	13.80	33.40
50	4.17	2.83	53.30	12.80	32.50
51	4.26	2.84	55.30	15.80	31.40
52	4.36	2.94	56.30	14.80	32.20
53	4.26	2.84	55.30	14.80	31.10
54	4.26	2.84	55.30	14.80	32.20
55	4.26	2.84	55.30	14.80	30.40
56	4.26	2.84	55.30	14.80	32.40
57	4.26	2.84	55.30	14.80	31.40
58	4.26	2.84	55.30	14.80	31.40
59	4.26	2.84	55.30	14.80	32.40
60	5.26	3.84	57.30	15.80	31.40
61	4.10	2.60	54.20	13.50	32.40
62	4.30	2.94	56.30	16.80	30.40
63	4.16	2.84	55.30	13.80	32.40
64	6.20	3.24	57.30	15.80	33.40
65	5.26	3.20	54.30	14.80	31.10
66	4.26	2.84	55.30	12.80	33.40
67	3.26	2.14	55.30	14.80	34.30
66	4.2	2.81	53.30	13.80	32.40
68	4.16	2.64	54.30	14.80	32.40
69	4.20	3.04	55.30	14.80	31.50
70	4.25	2.85	55.10	14.50	31.30
71	4.26	2.74	55.30	14.80	32.70
72	5.00	2.50	53.30	12.80	30.30
73	3.1	1.52	67.8	20.4	22.20
74	6.2	4.16	58.0	14.90	25.50
75	2.1	1.26	64.7	20.2	22.30
76	2.6	1.27	65.4	20.4	21.20
77	3.8	1.80	64.2	21.4	24.30
78	2.5	1.37	63.0	19.4	21.10

Table 2 Continue……

Case No	HB	RBC	MCV	MCH	RDW CV
79	2.8	1.47	62.4	20.4	24.30
80	3.0	1.25	62.1	20.4	24.10
81	4.6	2.27	65.4	22.1	25.30
82	5.0	2.50	65.2	20.4	24.20
83	6.6	3.27	64.4	21.3	25.30
84	3.7	2.27	65.3	20.4	24.30
85	5.6	2.27	62.9	21.6	24.10
86	5.2	2.15	65.4	22.4	24.30
87	2.6	1.27	65.0	23.4	24.70
88	2.8	1.29	65.4	20.1	22.40
89	3.5	1.37	63.5	21.4	24.10
90	2.3	1.24	61.4	20.0	24.30
91	3.0	1.46	60.2	20.2	25.20
92	3.5	1.56	59.2	19.2	24.20
93	2.8	1.16	58.2	18.5	24.00
94	3.3	3.48	75.0	21.2	27.2
95	7.5	1.36	60.2	21.2	25.2
96	4.0	2.00	64.2	24.2	23.0
97	3.0	1.76	59.2	21.2	26.2
98	4.3	2.46	65.2	25.2	19.2
99	3.1	1.16	58.2	22.5	20.4
100	5.0	2.46	59.2	23.2	24.2

HB: Hemoglobin; RBC: Red Blood Cell; MCV: Mean corpuscular volume; MCH: mean corpuscular hemoglobin; RDW: Red Blood Cell Distribution Width

Table 3: Sex and age distribution

Age		Sex		
Male	Female	Male	Female	Male/Female
1 year	4 months	79	21	3.76

Table 4: Beta Thalassemia and variants

Beta Thalassemia Major	Beta E Thalassemia	Thalassemia Intermedia	Beta/E Thalassemia trait
52	31	12	5

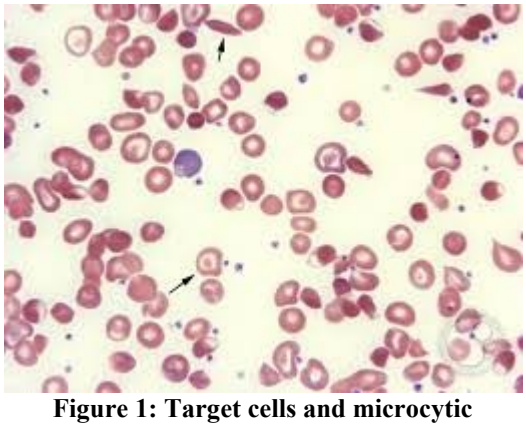

Figure 1: Target cells and microcytic

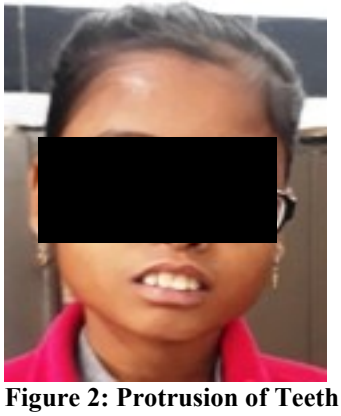

Figure 2: Protrusion of Teeth

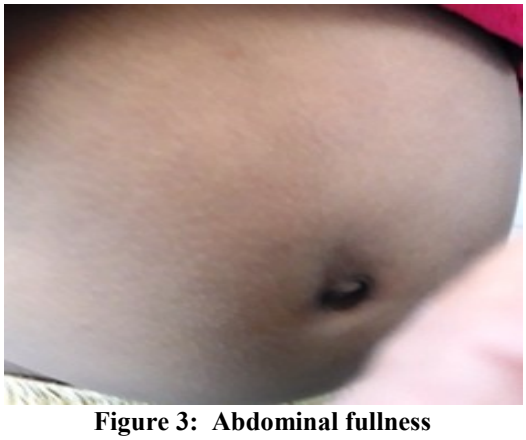

Figure 3: Abdominal fullness

Figure 4: Malar Prominence

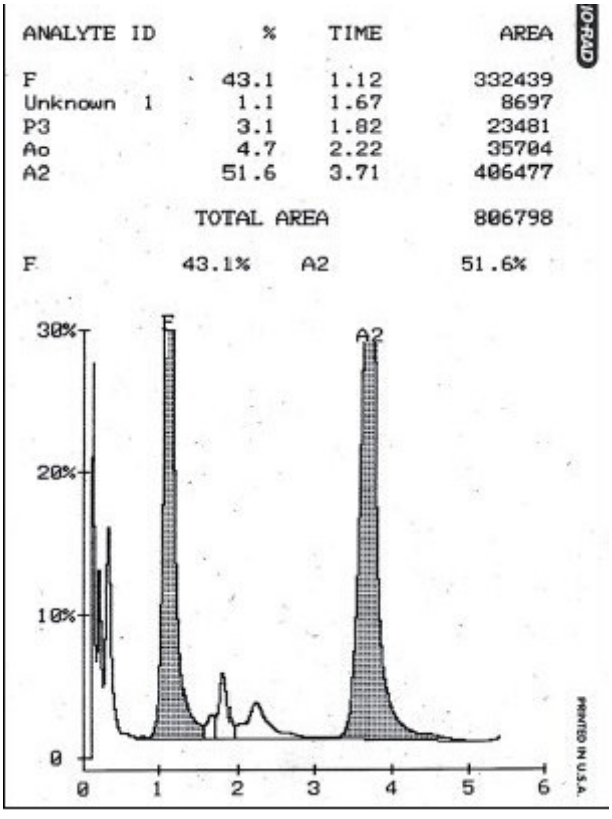

Figure 5: BE Thalassemia

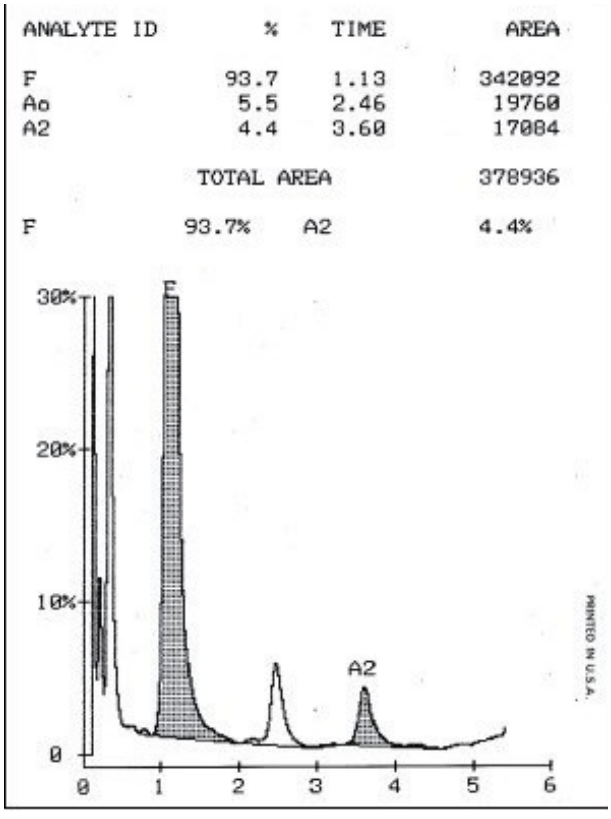

Figure 6: Beta Thalassemia major

4. Discussion

Thalassemia is autosomal recessive inherited disorders, affecting the globin component of the Hb molecule. These disorders, which were mainly confined to certain areas, religions, castes, and tribes, particularly with endogamous norms of marriages, are now widely prevalent all over the world across the castes and religions. This is because of the migration of various races over the ages and hence, being home to an assortment of sociocultural, linguistic, and ethnically diverse people.[12,15,16] Thalassemias are the major health problem in the Indian subcontinent as the prevalence rate of beta thalassemia mutations is as high as 17% in some populations.

This study was conducted primarily with patients of Bihar, India. In our present cross-sectional study, the prevalence of Hb disorders was found to be 11.15%.

An important finding was the high incidence of HbE beta thalassemia major (1.16%). Worldwide approximately 50% of severe beta thalassemia major patients are of HbE beta thalassemia. [19] These patients presented with a variable clinical picture ranging from a condition indistinguishable from beta thalassemia major requiring blood transfusions from infancy to a mild form of thalassemia intermedia showing a mild asymptomatic anemia. The Indian Council of Medical Research (ICMR) study reported a higher incidence of 1.44% in the general population. [20] The prevalence of HbE trait was found in 3.02% cases. A study conducted in the rural areas of West Bengal reported the prevalence of HbE trait to be 3.86% and that of Eβ thalassemia to be 1.25%.

HPLC has been established as a sensitive, specific, and accurate technique for the identification and quantification of different Hb fractions. However, it should be kept in mind that HPLC is limited by its inability to detect α thalassemia and normal HbA2 β thalassemia. Hb variants that elute with the same retention time also cannot be separately identified by HPLC, like HbA2 and HbE elute together, so diagnosis of HbE and HbE Beta thalassemia is problematic. Here Capillary zone Hb electrophoresis may be useful. During interpretation of chromatograms, nutritional anemias must always be taken into account. A low level of HbA2 may be found in severe iron deficiency, thus masking β thalassemia trait. Similarly, cobalamin or folate deficiency may raise HbA2 level, leading to a false diagnosis of thalassemia trait [14] and whenever necessary, HPLC must be followed by molecular studies, such as polymerase chain reaction (PCR), amplification refractory mutation system (ARMS), and other similar tests to determine specific mutations responsible for the Hb disorder HPLC limitation is that it does not give separate result of HBA2 and HBE because both elute at same point, however guideline of interpretation gives accurate diagnosis. In this front, capillary zone electrophoresis is better because it gives separate values of both HBA2 and HBE but has other major limitation in this method.

5. Conclusion

To conclude, Thalassemia is a major health problem in Bihar. Beta Thalassemia major and HbE beta thalassemia are major causes of mortality and morbidity.

Early diagnosis may prevent serious complications. Premarital screening of boys and girls, antenatal diagnosis of father and mother and chorionic biopsy of foetus of both parents affected with thalassemia trait can prevent birth of thalassemia major baby. At therapeutic point, hydroxyurea for BE Thalassemia and beta thalassemia intermedia are effective variably and bone marrow transplantation is good option for thalassemia major. Judicious use of packed red blood cells, not older than 7 days and iron chelating therapy may prevent serious complications. HPLC forms a rapid, accurate, and reproducible tool for the early detection and management of hemoglobinopathies and variants. This is especially important in view of the high incidence of beta thalassemia trait in the Indian subcontinent. Thus, premarital and antenatal screening should be mandatory to prevent the birth of offspring with β thalassemia major. Moreover, knowledge of common Hb patterns in a particular region helps to formulate appropriate preventive and therapeutic strategies

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