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A COMPARATIVE RESEARCH TO CORRELATE LEVEL OF THALASSEMIA MARKERS AMONG THALASSEMIA CONTROLS, MAJOR AND INTERMEDIA PATIENTS

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Abstract:

Background: *Thalassemia remains to be the procured hemoglobinopathy due to the quantitative defect in globin chain mix. Clinically, thalassemia is divided into thalassemia genuine (TM), thalassemia intermedia (TI) and thalassemia minor. Various studies have proven the augmentation event of thromboembolic events, especially in TI. Therefore, the plasma levels of the thrombin-antithrombin complex (TAT) and the prothrombin fragment1+2 (F1+2) should be extended in these individuals.*

Objective: *The objective of the current study was to associate levels of those markers in thalassemia main, thalassemia intermedia in addition standard fit measured patients.*

Methodology: *One relative cross-sectional study was performed at Thalassemia Prevention Center of Mayo Hospital and Lahore General Hospital. The hard and fast 24 common strong masses, 24 Thalassemia Major (TM) and 24 Thalassemia Intermedia patients shared in the assessment. Plasma levels of TAT complex and F1+2 were measured in all blood tests. The data were recorded and researched.*

Results: *The average duration of control remained 13.6 ± 8.1 years, and in cases with heavy and thalassemic intermedia it was 13.94 ± 8.69 years and 13.64 ± 8.5 years exclusively. The mean age was demonstrably the same at all three social events, p-regard > 0.05. 11 (45.83%) individuals and 13 (54.17%) women were fused under controls also TI bundles, including real thalassemia, 14 (58.33%) individuals and 10 (41.67%) women. The mean thrombin-antithrombin complex among controls was 3.4±0.8, among cases with thalassemia major 5.0±1.9 and thalassemia intermedia 6.4±2.7 with a quantifiably enormous mean differentiation between study meetings (p-value=0.001). The mean prothrombin F1+2among control was 0.94±.19, among cases with thalassemia major 1.10±1.7 and thalassemia intermedia 1.36±0.27 with a really significant mean difference between social occasions of the examination (p-value=0.001), with the main estimates of those markers in TI.*

Conclusion: *The hypercoagulable condition stayed established in thalassemia major and Intermedia when it looked different in terms of control of social affairs, as evidenced by increasingly increased measurements of TAT and F1+2 in both thalassemia meetings. While the mean thrombin-antithrombin complex (ng/ml) and the mean prothrombin F1+2 (nmol/L) value in the TI were most important with p-value < 0.05.*

Keywords: *Thalassemia main, thalassemia Intermedia, plasma levels, thrombin-antithrombin composite, Prothrombin fragment1+2 (F1+2)*

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INTRODUCTION:

In Europe, at the start of the 20th century clinicians had become well informed about an infancy syndrome that was associated with anemia and enlargement of the spleen. Two Detroit pediatricians Thomas B. Cooley and Pearl Lee were the first who gave clinical explanation of this disease as Cooley's anemia (Cooley et al., 1927). George Whipple used the term thalassemia for the first time for this syndrome (Whipple and Bradford, 1936). Thalassemia was named as the disease was first reported in people of Mediterranean origin. Later condition was described as thalassemia major after understanding the genetics. Concurrently, an Italian researcher Riette observed a disease with similar presentations as Cooley's anemia but severity of disease was mild to moderate, later this condition was known as thalassemia intermedia. Later in 1943 in Italy, two recognized hematologists Ezio Silverstone and Ida Bianco, reported a condition "microcitoma" in healthy subjects, due to some hereditary anomaly.

In 1945-1946 Silvestroni and Bianco performed further researches and proved that a sick child with Cooley's anemia was actually a homozygous condition that happened only if both his parents transfer their 'microcitemia' mutation to the child. This was first step toward the understanding of genetics of thalassaemia (Canali S., 2005). In 1960 it was suggested that thalassaemias was a genetic disease related in to unbalanced globin chain synthesis in RBCs (Ingram and Stretton, 1959). After that Simple laboratory techniques developed to analyze levels of hemoglobin A2 to diagnose β thalassaemia (Marengo-Rowe, 1965).

David Weatherall and others performed research by labeling radioactive amino acids to the reticulocyte of thalassaemic patients and showed that in thalassaemic patients, alpha- or beta-globin chain production was reduced and unbalanced synthesis of globin chains resulted in disease (Weatherall et al., 1965). Further researches were performed to determine the level at which genetic defect could occur in thalassaemia. A continuation of studies confirmed a quantitative or qualitative defect of specific messenger RNA coupled with various translation defects of the mRNA to protein results in different thalassaemia subtypes (Housman et al., 1973). It became clear that several structural gene loci on chromosome 11 and 16 i.e., alpha, delta, beta and gamma chain genetic loci, were responsible for the synthesis of their specific globin chains (Forget and Cohen, 2000).

Haemoglobin gene occur in two clusters, one on chromosome 11 as ε, γ, δ and β and other is on chromosome 16 as ζ and α . The α chain gene occur in duplicate and both α genes are in active state. There are four alleles for α globin chain production in each individual (Hoffbrand and Moss; 2016).

Epidemiology of thalassaemia:

WHO, March of Dime, 2006 data suggested that carrier state percentage of different haemoglobinopathies in World's population is about 7% and incidence of severe homozygous states of haemoglobinopathies is about 3, 00,000 -- 5, 00,000 new cases per year (Kumar R., 2013).

Beta thalassaemia is reported all over the world, but more frequently in Mediterranean, Southeast Asian and African populations due to high consanguineous marriage and malarial prevalence in these areas. β-thalassaemia carriers are approximately 1.5% of the world's population. β-thalassaemia is highly prevalent; up to 90 million cases have been reported to be carriers across the world and about 50% of these carriers are of South East Asian origin (Colah et al., 2010a). There is very limited Data on the epidemiology of non-transfusion dependent thalassaemia (NTDT) (Weatherall, 2012). Up to 68,000 new cases of different thalassaemia syndromes are reported each year (Weatherall and clegg, 2008; Modell and Darlison, 2008). Each year new cases of carrier state are highest in percentage. About 23,000 children are born with β-thalassaemia major each year but β-thalassaemia intermedia is reported in few ill-defined number of children (Weatherall and Clegg, 2001; Weatherall, 2012). β-thalassemia intermedia has a varying and low prevalence in different populations than TM and carriers. Eastern Mediterranean and Africa have highest frequency of β-thalassaemia carriers (Weatherall and Clegg, 2001). Mediterranean origin patients usually present with sever anaemia and other symptoms of disease than African patients. This is due to different genetic mutations in both areas as African population have beta-zero (β^0) thalassaemia gene on the other hand beta-plus (β^+) thalassaemia gene is common in Africa (Pooja, 2016).

Thalassaemia is the most frequently occurring single gene disease, with highest prevalence in malaria endemic areas (Africa, Mediterranean area and Australasia). High percentage of thalassaemia population are found in Cyprus (14%), Southeast Asia and Sardinia (10.3%) (Pooja, 2016). Immigrants from endemic areas resulted in spread of disease throughout the world. In the Asia and

Middle East countries the frequency varies between 2 to 5% while in North African countries, the prevalence of β-thalassaemia lies between 2 to 9%. On the other hand in the America and UK the prevalence of thalassaemia is still very low and mainly the immigrant population is affected by the disease. Asian countries like Pakistan, India, Indonesia, China, Thailand and The Maldives have high frequency of β-thalassaemia (Weatherall and Clegg, 2001b).

Modell and Darlison estimated annual incidence rate of children affected with the β-thalassaemia in different regions. They found that minimum estimates can be made on basis of limited published research data. In different countries micro-mapping showed regional variations in diseased population (Modell and Darlison, 2008).

Pakistan is endemic area of thalassaemia and documentary register is available here. It has been estimated that around 5000-9000 children with different β-thalassaemia syndrome born per year. About 9.8 million carriers prevalence is estimated in general population with a frequency of carrier state between 5–7% (Ansari et al., 2011,). In a study conducted at Mayo HospitalHospital, screening of 674 first degree relatives of registered Thalassaemia major patients, showed frequency of 61% for different types of thalassaemia disorders, including 51.9% for β-Thalassemia trait within families of children with TM (Majeed et al., 2013).

In 1986 Khan and Hayee revealed a prevalence of the alpha thalassaemia to be 0.94% in population in and around Lahore and another study in Northern areas of Pakistan in 1991 prevalence of α - thalassaemia gene has been found to be 2.4%. Similarly in Bahawalpur prevalence of alpha thalassaemia is around 0.97% (Malik et al., 2016)

Pathophysiology of thalassaemia:

Adult haemoglobin (Hb A-$\alpha_2\beta_2$) constitutes 95-98% of total haemoglobin. The thalassaemias are classified on the name of globin chain whose synthesis is absent or decreased. As alpha chain-related conditions are called alpha thalassaemia and beta chains mutation can result in beta thalassaemia (Hoffbrand and Moss, 2011).

In beta thalassaemia reduction in beta chain causes excess alpha chains to precipitate in erythroblasts and mature red cells. So these precipitates lead to ineffective erythropoiesis and extra vascular haemolysis of red cells in the spleen. This disproportion of alpha to beta globin chains result in increase in the percentage of minor hemoglobin, such as Hb-F or Hb-A2 or other unusual types of hemoglobin synthesis. Production of excess gamma chains helps to decrease excess alpha chain by forming haemoglobin F. The severity of disease depends on the number of globin genes mutated. Rare forms of thalassaemia are due to mutations of δ and γ chains. The imbalance between α and β globin chains resulted in defective red cells production. Pathogenesis is the same for thalassaemia major and intermedia, only difference is clinical severity that is moderate in TI and severe in TM. In β-thalassaemia free unbound α globin chains are present in red cells precursors due to either reduced or absence β globin chains. These free α chains also precipitate in precursor erythroid cells in the bone marrow and interfere with further maturation of these cells to mature red cells and can cause premature destruction of these cells in the bone marrow (ineffective erythropoiesis). In mature red cells these free α chain precipitates can cause membrane damage and either extravascular or intravascular early destruction of these red cells leading to shortened life span and target cells formation. Peripheral haemolysis and resulting anaemia stimulate the increase erythropoietin production from kidneys that further stimulates the process of erythropoiesis in bone marrow. Erythroid hyperplasia results in bone marrow expansion and further increase in ineffective erythropoiesis. In thalassaemia intermedia anaemia is compensated by erythroid hyperplasia in bone marrow and extramedullary erythropoiesis and transfusions are rarely required but in thalassaemia major this anemia causes failure to thrive and regular transfusions are required The hypertrophy of erythroid marrow can lead to expansion of flat bone of face, osteoporosis, and fracture of long bones (Zaino., 1980).

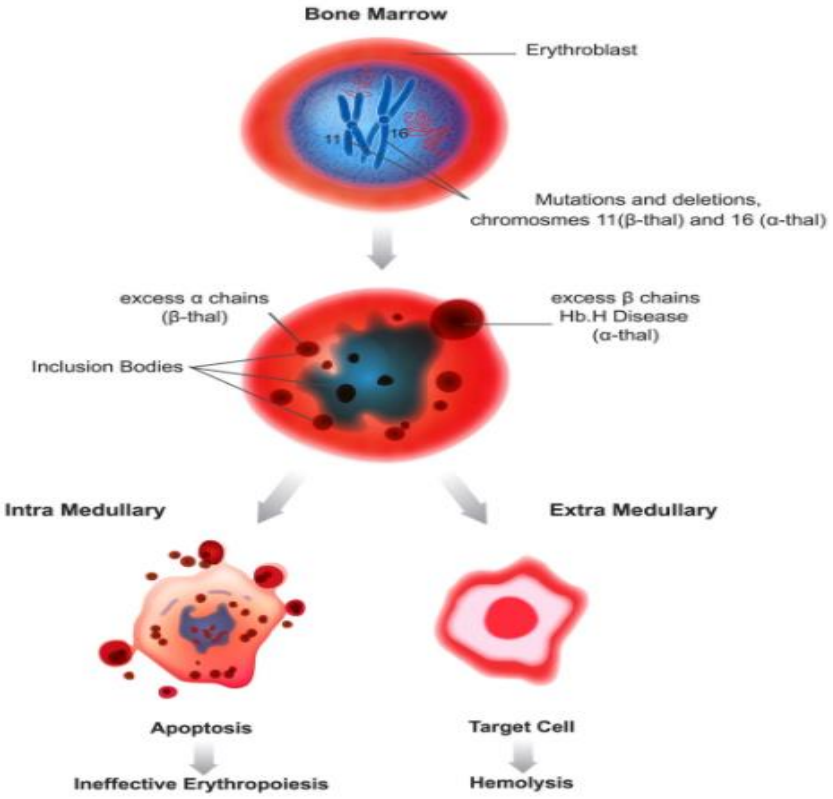

Figure – I: Mechanism of Haemolysis in Thalassaemia (Rachmilewitz and Giardina, 2011)

Classification of thalassaemia disorders:
Different types of thalassaemia and related disorders can be due to several different types of genetic combinations. Mutations in one or more chains of globin chains lead to reduction or total absence of respective globin chains. Different combinations of these mutations lead to different clinical presentations of thalassaemia (Thein and Raees, 2011).

METHODOLOGY:

A cross sectional comparative study was conducted. Study population was selected from registered thalassaemic patients of Government Thalassaemia Prevention Centre, Mayo HospitalHospital and Sundus foundation. Research tests were performed in Lahore general hospital, Lahore.24 for thalassaemia major, 24 for thalassaemia intermedia and 24 for healthy individuals were included in the study. Total study population of 72 was divided into 3 groups. A detailed clinical history of all individuals taking part in study was taken. Previous laboratory investigation were noted. Blood samples of all individuals were collected in blue topped vacutainer containing 3.2% disodium citrate as an anticoagulant. 1.8ml blood in 0.2ml sodium citrate solution i.e. 9:1 ratio was taken and within half hour, centrifuged at 3000rpm for 10 minutes to separate plasma. Plasma samples were separated in aliquot and these aliquots were stored at -20º. Tests were performed within one month of sample collection.

RESULTS:

AGE DISTRIBUTION AMONG STUDY GROUPS:
The mean age of controls was 13.6 ± 8.1 years, and of cases with thalassaemia major and Intermedia was 13.94±8.69 years and 13.64 ± 8.52 years respectively. The mean age was statistically same in all three groups with p-value 0.97. There is no significant difference in the age of the three groups

AGE GROUPS DISTRIBUTION IN ALL GROUPS
As shown in bar chart above, 14(19.44%) adults and 10(13.84%) children of total population are present there in each study group. In each study group population14 (58.33%) subjects were less than 15years old children and 10 (41.67%) were between15-29 years old adults i.e. statistically insignificant.

Gender distribution in all groups:

In the pie chart above it is shown that among controls group 11 (45.83%) males and 13 (54.17%) females were included, among cases with thalassaemia major 14 (58.33%) males and 10 (41.67%) females and among cases with thalassaemia intermedia 11 (45.83) males and 13 (54.17%) females were included. Gender distribution was equal in all groups

Comparison of tat complex in study groups:

Mean and SD thrombin-antithrombin complex among controls was 3.4±0.8ng/ml (2-5ng/ml), among cases with thalassaemia major mean and SD value was 5.0 ±1.9ng/ml (1-9ng/ml) and thalassaemia intermedia was 6.5±2.7ng/ml (2-11.3ng/ml). There was statistically significant difference among mean TAT between all three study groups (p-value=0.001). TI patients have highest mean TAT complex levels. More than 50% of patients of TI and TM had TAT levels more than 5ng/ml i.e. above the upper limit of normal healthy control value.

Error bar chart showing mean tat of different study groups:

Error bar chart representation of mean ±1SD of all three groups is given above. The mean of all the groups were represented by the black marker i.e. 3.5, 5.0 and 6.5ng/ml in control, TM and TI respectively. The length of the bar above and below the mean was the spread of data around the mean i.e. ±1SD. There was some overlapping among the SD of three groups but statistical test one way ANOVA showed that data is statistically significant among all the three groups.

Pair-wise comparison of tat complex between groups:

Comparison between mean of TAT of different study groups showed that mean Thrombin-antithrombin complex (ng/ml) was significantly higher in TM and TI as compared to controls. p value between means of TM and Control was equal to 0.015 and between TI and control was 0.001. While within thalassaemic patients mean Thrombin-antithrombin complex (ng/ml) was statistically higher in thalassaemia Intermedia than in major with p-value 0.037. This means a significantly high TAT in the patients of TI as compared to TM. About 54.2% patients of TI had high TAT than normal control group.

Comparison of prothrombin f1+2 in all study groups:

Mean prothrombin F1+2 among controls was 0.94±0.19 nmol/L (0.60-1.3 nmol/L), among cases with Thalassaemia major was 1.11±1.7 nmol/L (0.80-1.4 nmol/L) and thalassaemia intermedia was 1.26±0.17 nmol/L (0.90-1.63 nmol/L). There was statistically significant difference among mean F1+2 of all three study groups (p-value=0.001). TI patients have highest mean F1+2 levels. About 16.7% patients of TI and 4.2% of TM had F1+2 value above 1.3 nmol/L.

Error bar chart showing mean f1+2 of different study groups:

Error bar chart representation of mean ±1SD of all three groups is given above. The mean of all the groups was represented by the black marker i.e. 0.95, 1.11 and 1.26nmol/L in control, TM and TI. The length of the bar above and below the mean was the spread of data around the mean i.e. ±1SD. There was some overlapping among the SD of three groups but statistical test one way ANOVA showed that data is statistically significant among all the three groups

Pair-wise comparison of f1+2 between groups:

Comparison between mean of F1+2 of different study groups showed that mean F1+2 (nmol/L) was significantly higher in thalassaemic patients as compared to controls. p value between means of TM and Control was equal to 0.003 and between TI and control was 0.001. While within thalassaemic patients mean F1+2 (nmol/L) was statistically higher in thalassaemia Intermedia than in major with p-value 0.016. This shows a significantly high F1+2 (nmol/L) in the patients of TI as compared to TM. About 16% patients of TI had high F1+2 (nmol/L) than normal control group.

Correlation between tat and f1+2 in all groups:

TAT and F1+2 both were observed to be higher in TI than TM as compared to control. A correlation was present between these two markers of thrombin generation in the study groups. Pearson coefficient of correlation between TAT and F1+2 is equal to 0.721 with p value < 0.01 that means a strong positive correlation between both these markers of in vivo coagulation activation, is present. Both of these markers had linear relationship and both were increased in patients with hypercoagulable state. A positive correlation between F1+2 and TAT. Value of r= 0.72 (p <0.01). A positive correlation indicates that increase in on variable is associated with increase in the level of other variable.

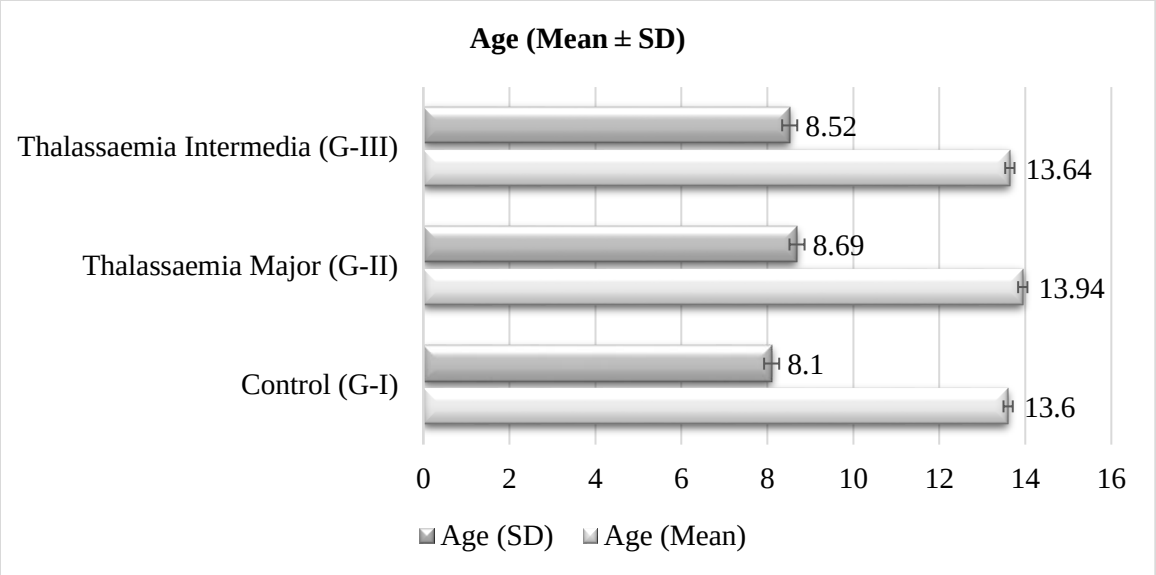

Figure – II: Age (Mean and Standard Deviation)

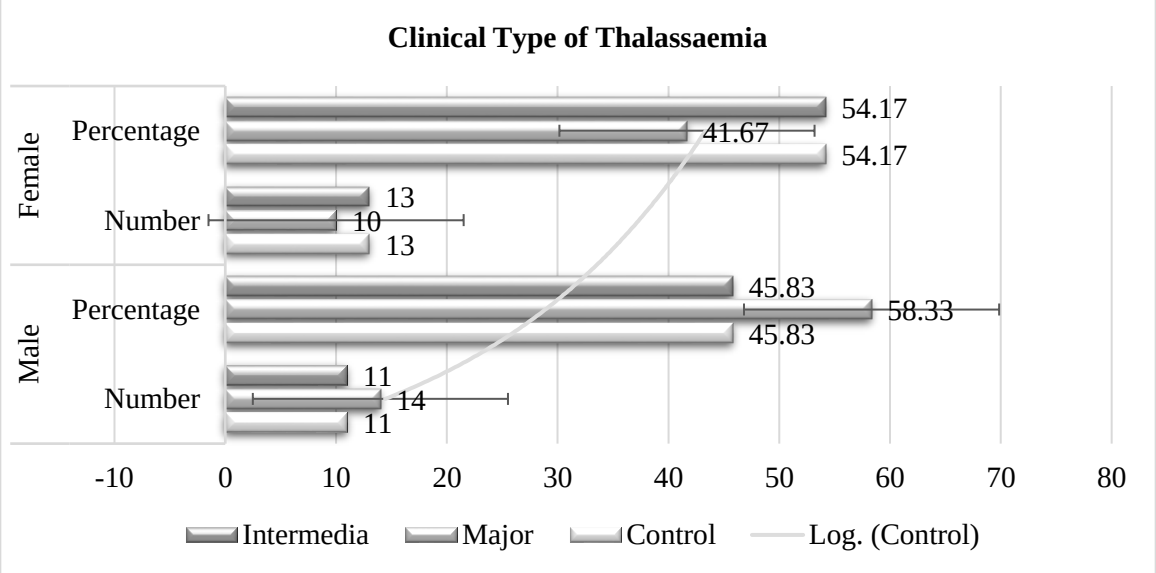

Figure – III: Clinical Types of Thalassemia

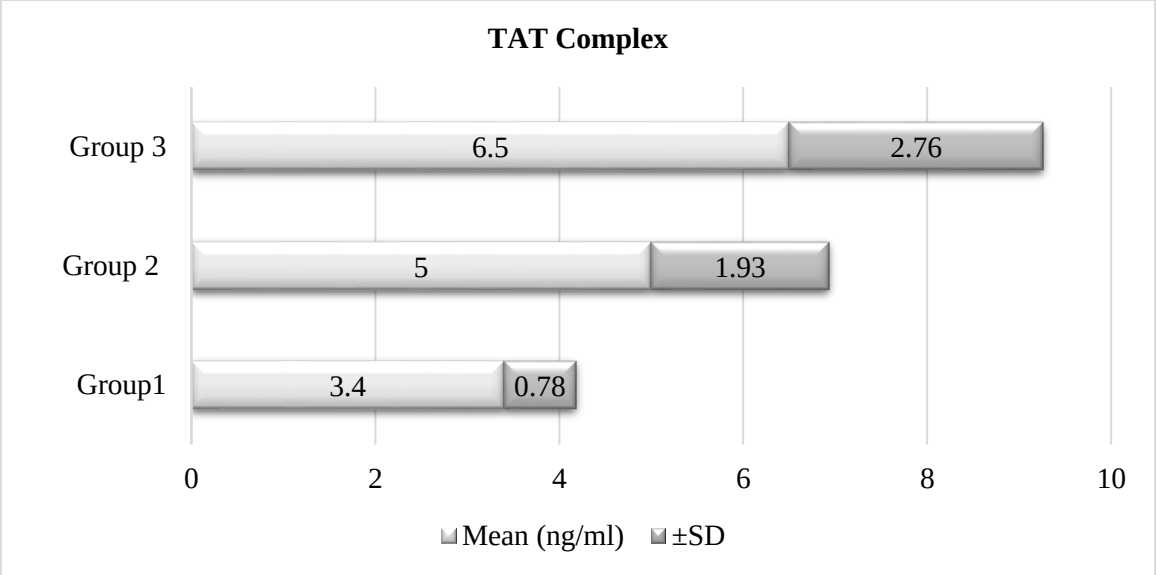

Figure – IV: TAT Complex (Mean and Standard Deviation)

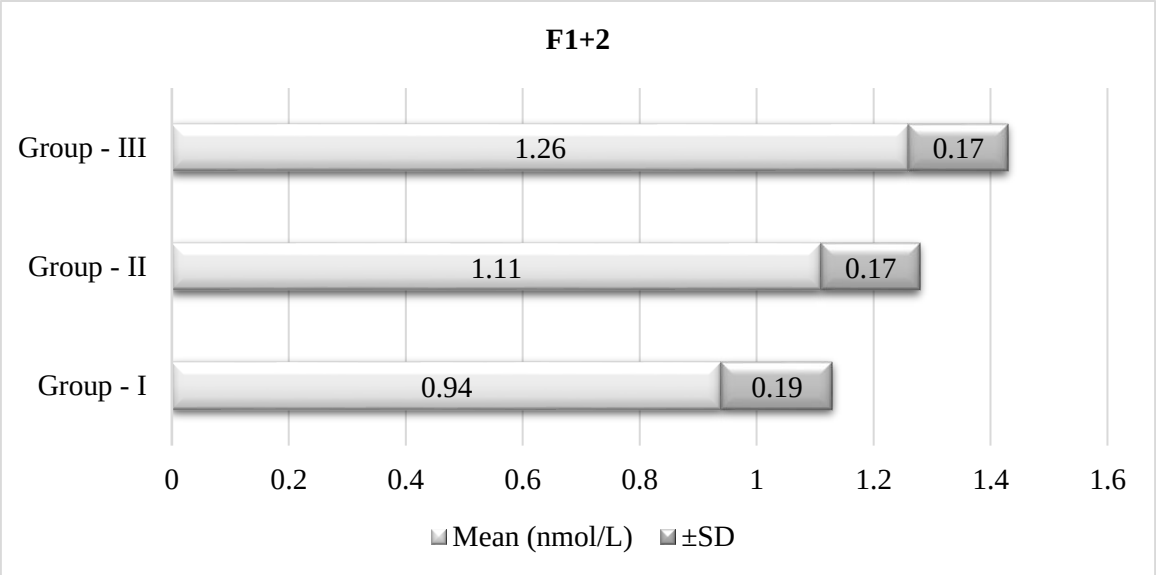

Figure – V: F1+2 (Mean and Standard Deviation)

DISCUSSION:

While comparing mean F1+2 between TI and TM, a significantly high mean F1+2 with p value 0.016. The result indicates a more hypercoagulable state among the patients of TI than TM. This result was in concordance to the study conducted by Cappellini et al., 2000, in which plasma F1+2 levels were found to be significantly increased in TI than TM and in control population a p value of less than 0.05. Cappellini et al., 2000 compared the markers of coagulation activation like plasma antithrombin, F1+2 and D-dimer levels in TM and TI. A significantly increased plasma coagulation activation markers like F1+2 ($p<0.05$) and d-dimers ($p<0.001$) in splenectomized TI than TM and control groups were found. Antithrombin levels were also decreased in both TI and TM. AT levels were supposed to be reduced as it has to make 1:1 molecular complex with increased thrombin leading to the formation of increased TAT in thalassaemia.

In 2012 Sirachainan conducted a study on thalassaemia patients. Hypercoagulable state was confirmed in patients with severe β-thalassaemia

major disease with high levels of plasma coagulation activation markers i.e. TAT and F1+2 than control healthy group. Then after bone marrow transplantation these levels again measured at the median follow-up time of 70.3 months. Decrease in levels of TAT, F1+2 and D-dimer confirmed that hypercoagulable state in thalassaemia was due to inherited defect of red cells. In present study two coagulation activation markers i.e. TAT and F1+2 were in linear positive correlation with each other, r=0.72 and p value 0.01 indicated a strong positive correlation. This result is inconsistent with the study on TI by Atichartakan et al., 2002, in which both F1+2 and TAT were correlated r=76.9 and p value 0.001.

The results of our study have important clinical implications. In the light of results by international studies and in our study it is evident that patients with thalassaemia intermedia are at higher risk of thrombosis. Therefore careful and consistent observation of these patients should be considered. More researches are also suggested in this area to unearth further related aspects. Each patient should be assessed individually and high risk patients should be identified early. All the intrinsic risk factors like type of thalassaemia, circulating RBCs count etc as well as extrinsic factors like splenectomy, transfusion naivety, etc should be considered in each patient individually. Regular monitoring and proper management of these high risk patients can reduce the incidence of thrombotic complications and can improve the quality of life of these patients.

Short-term antiplatelet or antithrombotic prophylaxis with heparin can be given during and after any surgical procedure, even in young thalassaemia patients. Splenectomized thalassaemia intermedia patients should be assessed and prophylaxis may be required during prolonged immobilization, surgery and pregnancy etc, when they are at increased risk of developing thrombotic manifestations. Oral contraceptive drugs should not be given to these patients. Long term use of anticoagulant drugs if required should be closely monitored as risk of bleeding are there. All these considerations can reduce the burden of this complication. Preventive and prophylactic measures if required will be very cost effective and will improve the quality of life of these patients.

Thalassaemia is an inherited hemolytic disorder caused by a partial or complete deficiency of α- or β-globin chain synthesis. Thalassaemia is genetic disorder and Pakistan is an endemic area of different genetic mutations causing thalassaemia. With the improved management, many complications of this persistent disease are becoming apparent. Thrombosis in thalassaemic patients is one of the important complications that is becoming evident and causing increase rate of mortality and morbidity in these patients. The goal of current study was to identify the hypercoagulable state in thalassaemia patients by measuring the markers of coagulation activation and also comparing the levels of these markers in two subtypes of thalassaemia i.e. TI and TM.

As already explained in literature review thalassaemic red cells, platelets and several other factors may be involved in the in vivo coagulation activation and cause a procoagulant state in thalassaemia. This hypercoagulable state in thalassaemia in the presence of several others factors can lead to development of clinical thrombosis. Incidence of these thromboembolic events is even higher in patients of TI than TM. Thalassaemia intermedia subtype, transfusion naivety and splenectomy have been observed to be associated with more pronounced hypercoagulable state in thalassaemia.

Although various researches were performed globally, but not much focus in this regard has yet been given in Pakistan. We, therefore, aimed to compare hypercoagulable state by measuring the levels of the important plasma coagulation activation markers in thalassaemia major, thalassaemia intermedia and normal healthy controls in order to establish a hypercoagulable state in thalassaemia. In the present study 24 patients of TI, 24 patients of TM and 24 normal healthy controls were included. All three groups were age and sex matched, no significant difference in the age and sex were observed between the groups. The Mean ±SD age of controls was 13.6 ± 8.1 years, and Mean ±SD of cases with Thalassaemia major and intermedia were 13.94 ± 8.69 years and 13.64 ± 8.5 years respectively. The mean age was statistically same in all three groups, p-value > 0.05. Among controls, 11 (45.83%) males and 13 (54.17%) females were included, among cases with thalassaemia major 14 (58.33%) males and 10 (41.67%) females and among cases with thalassaemia intermedia 11 (45.83) males and 13 (54.17%) females were included. There was equal gender distribution among the three study group, p value=0.95 (not significant).

In current study Plasma levels of coagulation activation marker TAT was observed to be significantly increased in thalassaemic population as

compared to normal healthy control with p value <0.001. Among TM cases, 12(50 %) of patients were having high TAT levels than the upper limit of control population, with p value 0.01. Same observations were made by Eldor et al., 1999, he found increased levels of TAT in TM in about 50% of both children and adults study population with p value less than 0.01. Similarly Sirachainan et al., 2012 found that TAT complex levels are significantly higher in transfusion dependent TM patients than normal healthy control population. In another study Sirachainan et al., 2016, comparison was done between the TAT levels in α thalassaemia and β TM and results showed significantly increased TAT in TM patients with p value less than 0.05. In this study mean TAT in healthy was 2.1µg/L as compared to 4.7µg/L in transfusion dependent TM patients.

In present study, 13(54.2 %) TI patients have high TAT than upper limit of control population, with p value 0.001. These results were almost similar as Teli et al, 2012 found increased levels of TAT in 62.5% patients of thalassaemia intermedia. Angchaisuksiri et al., 2007 measured the levels of plasma thrombin-antithrombin in thalassaemia intermedia (β/E thalassaemia) with a p-value for significantly increased TAT was <0.001. In our study comparison of TAT levels between TI and TM patients showed that TI had higher TAT than TM patients with p value < 0.037. These results indicated that in TI the hypercoagulable state is more severe. In present study, F1+2 the other marker of coagulation activation was also significantly increased in thalassaemic population than control population, with p value of significance < 0.001. About 1(4.2%) patient of TM had high F1+2 than upper limit of control population p value 0.003. This observation is in contrast to the study conducted by Eldor et al., 1999. In this study plasma F1+2 levels were found to be insignificant as compared to normal healthy control. In contrast to present study, a study conducted by Sirachainan et al., 2016 also found normal levels of F1+2 in transfusion dependent TM patients. But our study results were inconsistent with results of the study by Sirachainan et al., 2012. In this study significantly increased F1+2 levels were observed in TM patients as compared to normal healthy control.In current study 4(16.7%) patients of TI had high F1+2 with significantly increased mean F1+2 levels as compared to normal healthy population p value 0.001. Similar to our study capellini et al., 2000 also observed higher F1+2 in TI then normal healthy population with p value less than 0.05. In another study Teli et al., 2012 found significantly increased F1+2 in 8.33% cases of TI patients. Angchaisuksiri et al., 2007 concluded that thalassemia intermedia patients had high F1+2 with p value <0.04.

CONCLUSION:

In vivo coagulation indicators remained prolonged in thalassemic cases than in all other fit individuals. The combination of F1+2 in addition TAT in TI and TM presented extended values in TI. This is therefore generally assumed that the relentlessly tested hypercoagulable state is accessible in thalassemia intermedia as thalassemia major, as the TAT and F1+2 coagulation activation markers have been extended especially in TI as TM. Researchers may say that regardless of how TI is the clinically milder clinical type of disease, true complexity can arise in TI. Hypercoagulable conditions present in thalassemia can cause veins and venous thromboembolic events as well as pneumatic hypertension. Therefore, normal control, the random factor to detect verification, and prophylactic treatment may stay important in those patients. Splenectomy, medical system, pregnancy and various conditions that may lead to thrombosis should be carefully evaluated and these patients may require prophylactic medication.

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