ORIGINAL ARTICLE

Evaluation of Reticulin Fibrosis in Benign Hematologic Disorders in Lahore, Pakistan: A Cross-Sectional Study

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ABSTRACT

Objective: To assess reticulin fibrosis in benign hematologic disorders and to understand the impact of benign hematologic disorders on the immune system.

Study Design: Cross-sectional study.

Place and Duration of Study: The study was conducted at the Department of Hematology, Sheikh Zayed Hospital, Lahore, Pakistan from January 2023 to June 2023.

Methods: Patients who had benign hematologic disorders, such as iron deficiency anemia, Megaloblastic Anemia, Aplastic Anemia, and Immune Thrombocytopenic Purpura, were included in the research. Patients with Malignant hematologic disorders and Individuals undergoing chemotherapy for any malignant disease were excluded. There were 96 cases total in the sample, 24 for each illness. Following processing in the histology department, the data for reticulin fibers were analyzed using bone marrow samples from the anterior iliac spine. An institutional ethics panel approved the research, and informed consent was acquired.

Results: The study found that the gender distribution of cases was significantly different among the four groups. The average age of cases was not different among the four groups. Still, the Immune Thrombocytopenic Purpura group had the lowest average age of 40.5 years, and the Aplastic anemia group had the highest average age of 46.7 years. Among the hematological parameters, the hemoglobin level was the highest among the Immune Thrombocytopenic Purpura group, with an average of 10.8±1.9 g/dl. The median total leukocyte count for Iron Deficiency Anemia was 6.3, while the median total leukocyte count for megaloblastic anemia was 3.2, Aplastic Anemia was 1.8, and Immune Thrombocytopenic Purpura was 8.0. The median RDW count for Iron Deficiency Anemia was 42.0, Megaloblastic Anemia was 50.0, Aplastic Anemia was 48.5, and ITP was 48.0.

Conclusion: The study concluded that female gender, higher Hemoglobin level, higher MCH, Red blood cell count, and lower platelet count may also help support the diagnosis of Immune Thrombocytopenic Purpura. Identifying these parameters as diagnostic markers requires further research to confirm their status.

Keywords: *Aplastic Anemia, Hematologic, Iron Deficiency Anemia, Immune Thrombocytopenic Purpura, Megaloblastic Anemia, Reticulin Fibrosis.*

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Introduction

Hematologic disorders involve issues with blood cell lines like red and white blood cells, platelets, spleen, bone marrow, and lymph nodes. There are benign and malignant types, with malignant disorders being cancerous and challenging to manage, arising from abnormal cell lines or bone marrow, and consisting of myeloma, leukemia, and lymphoma.[1] Unlike malignant, benign hematologic disorders are non-cancerous conditions that affect bleeding, clotting, red blood cells, white blood cells, and platelets. Management of these disorders is possible with

medicines and lifestyle modifications.[2] Reticulin fibrosis appears in several benign conditions, which include different types of nutritional anemia, such as iron deficiency anemia, megaloblastic anemia, and folic acid deficiency anemia.[3] Bleeding disorders are haemophilia, coagulation defects, von Willebrand's disease, and immune thrombocytopenia.[4]

Bone marrow comprises cells, extracellular matrix, and ground substances. It contains collagen fibers and reticular fibers. These fibers are visible on trichrome and reticulin stains, respectively.[5] Reticulosis means increased reticular fiber numbers, density, thickness, and proportion to the normal hemopoietic tissue. Reticular fibers are increased in various malignant and benign hematological disorders. After mounting the bone marrow tissue in reticulin stain, these fibers are visible under a microscope. Bone marrow examination is a valuable diagnostic tool for predicting the prognosis and diagnosis of various diseases.[6] Understanding chemotherapeutic responses in malignant hematological disorders is aided by bone marrow examination in conditions such as iron deficiency anemia (IDA), a global problem mainly affecting females due to lower intake and menorrhagia, leading to reduced hemopoiesis and hypoxia.[7]

Megaloblastic anemia (MA) is caused by folate deficiency, vitamin B12 deficiency, and intrinsic factor deficiency. In MA, bone marrow presents with reactive, hyper-segmented neutrophils and megaloblasts. Aplastic anemia (AA) presents with decreased all three cellular lines due to acquired or idiopathic underlying causes. Immune-mediated thrombocytopenic purpura (ITP) is an autoimmune disorder in which autoantibodies cause peripheral destruction of platelets.[8]

A recent study in Pakistan reported megaloblastic erythropoietic hyperplasia as the utmost outcome of bone marrow evaluation, which was further segregated to vitamin B12 deficiency, which was highest at 52.08%, followed by 33.34% folate deficiency. In comparison, 14.58% had both types of deficiencies.[9] The exact prevalence of AA is not properly reported, but it is rare in North American and Western populations compared to the Asian population.

Reticulin and collagen bone marrow fibrosis can be quantified using various grading systems. Multiple studies have shown that 76% of healthy subjects present 1 grade, 19% present 0 grade, and 5% present two grades. However, the occurrence of reticulin fibrosis among benign bleeding disorders is scarcely studied, and a recent study on IDA female patients has also endorsed its significance in the diagnosis and demonstration of the disease.[10] The study aimed to understand the impact of benign hematologic disorders on the immune system.

Methods

The cross-sectional study was conducted at the Department of Hematology, Sheikh Zayed Hospital Lahore, Pakistan from January 2023 to June 2023 after obtaining approval from the Institutional Review Board of Sheikh Zayed Federal Postgraduate Medical Institute, Lahore, Pakistan, held on date: 22nd June 2022 vide letter no: SZMC/IRB/Internal/87-A/2022. Patients from IDA, MA, ITP, and AA were included in the study. The sample size was 96 cases (24 cases for each type of disorder), with a 95% confidence level and a 10% margin of error, with the expected frequency of fibrosis Grade-1 52% in ITP.[11] The sample size calculation was based on the formula for estimating a proportion in a population: $n=Z^2 \cdot p \cdot (1-p)/E^2$. Inclusion Criteria included adults, males, and females, as well as patients with iron deficiency anemia, megaloblastic anemia, and aplastic anemia. Patients with Malignant hematologic disorders and Individuals undergoing chemotherapy for any malignant disease were excluded.

The study collected data on cases of benign hematologic disorders using bone marrow biopsies from the anterior iliac spine. Bone marrow biopsy was chosen from the anterior iliac spine because it is easily accessible, safe, and adequate for sampling. It has a broad, flat surface, minimal complications, a lower risk of injury to vital structures, a favorable site for benign hematologic disorders, and lower patient discomfort. The biopsies were fixed in 10% neutral-buffered formalin and processed in the histopathology department. The tissues were embedded in paraffin wax and sectioned on a microtome. Reticulin staining was performed on each slide in the histopathology department, followed by deparaffinization, washing, oxidation,

bleaching, treatment with ferric chloride, washing, and drying. Microscopy was performed to observe the stained slides at low, medium, and high power. Different findings related to reticulin fibers were recorded. The study aimed to understand the impact of benign hematologic disorders on the immune system.

Data was entered and analyzed using the Statistical Package for Social Sciences software version 21. Descriptive variables were presented as frequencies and percentages, while numerical variables were presented as means and standard deviations. Patients were divided into four groups, including IDA, MA, AA, and ITP.

Results

The study found that there are four different hematological disorders: Iron Deficiency Anemia (IDA), Megaloblastic Anemia (MA), Aplastic Anemia (AA), and ITP. The study also found that the gender distribution of the cases was significantly different among the four groups. The IDA and ITP groups were markedly higher among females, while the MA group was more common among males. The gender was equally distributed among Aplastic anemia cases, as presented in the figure.1.

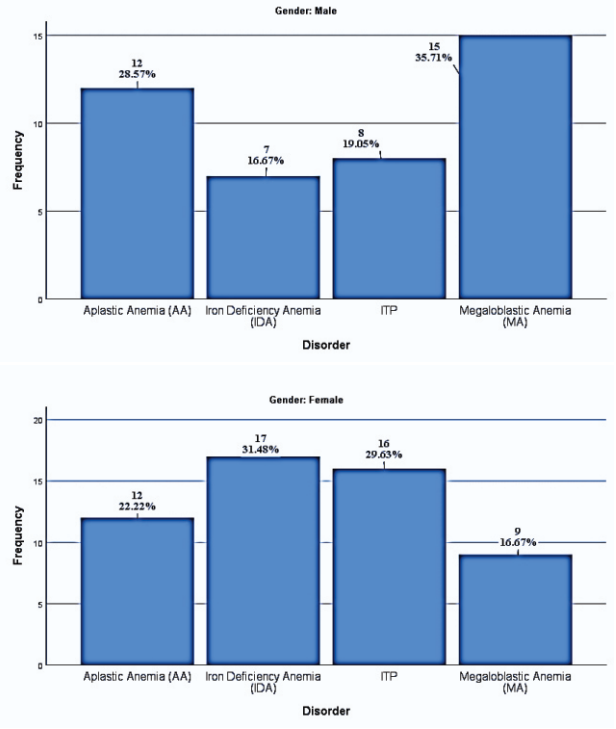

Fig.1: Gender Distribution of Cases for Four Hematological Disorders

The results are distributed by gender in figure.1. Megaloblastic Anemia was most common among males (35.7%), and ITP was most common among females (29.6%). Females were more afflicted by Iron Deficiency Anemia (31.5%), while males were afflicted by Megaloblastic Anemia (35.7%). The distribution between genders was the same for Aplastic Anemia. This indicates that Megaloblastic Anemia is more frequent in men than women, Iron Deficiency Anemia and ITP are more common in women than men.

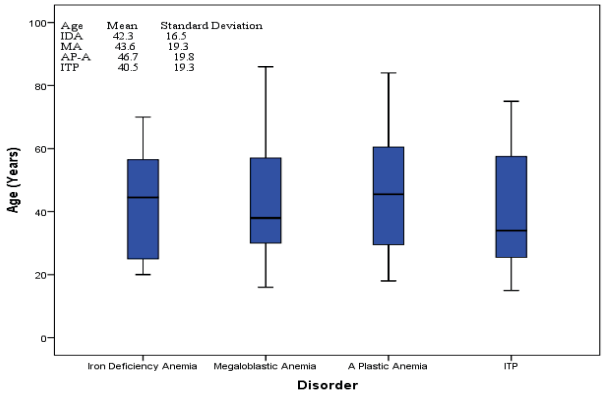

Fig.2: Age Distribution with Four Hematological Disorders

The average age of the cases was not different among the four groups. However, the ITP group had the lowest average age of 40.5 years, and the Aplastic anemia group had the highest average age of 46.7 years. (Figure. 2) Individuals with Iron Deficiency Anemia are an average of 42.3 years, while those with Megaloblastic Anemia are slightly older (43.6 years). On average, Aplastic Anemia affects older men (46.7 years), whereas those with idiopathic thrombocytopenic purpura are the youngest (40.5 years). Each disorder's standard deviation indicates the extent of variation in age within each group.

The table 1 and 2 compares the Mean Cell Volume (MCV) using an ANOVA by disorder type. The F statistic (3.20) indicates significant differences in MCV associated with the groups (*P* value = 0.027). When compared with post hoc tests, there is a substantial difference in MCV only between Iron deficiency anemia and ITP (*P* = 0.035), and other comparisons are not significant (*P* > 0.05).

The difference was insignificant. Among hematological parameters, the hemoglobin level was highest among the ITP group, 10.8±1.9 g/dl.

(Table-1). The other three groups had almost the same averages. The difference among the four groups was significantly different, with a *P*-value <0.001.

Table-1: Distribution of hemoglobin level for cases with four different Disorders

Disorder	Hemoglobin level (g/dL)	
	Mean	Standard Deviation
Iron Deficiency Anemia	8.7	2.1
Megaloblastic Anemia	8.8	1.9
Aplastic Anemia	8.7	1.7
ITP	10.8	1.9

Table-2: ANOVA and Post-hoc Comparison of Mean Cell Volume (MCV) Across Four Disorder Types

	Sum of Squares (SS)	df	Mean Square (MS)	*F-statistic*	*P*-value
Between Groups	817.92	3	272.64	3.20	0.027
Within Groups	7839.53	92	85.29		
Total	8657.45	95			

(I) Disorder	(J) Disorder	Mean Difference (I-J)	Std. Error	*P*-value
Iron Deficiency Anemia	Megaloblastic Anemia	-6.11	2.66	.107
	Aplastic Anemia	-6.52	2.66	.076
	ITP	-7.35*	2.66	.035
Megaloblastic Anemia	Iron Deficiency Anemia	6.11	2.66	.107
	Aplastic Anemia	-.40	2.66	.999
	ITP	-1.24	2.66	.966
Aplastic Anemia	Iron Deficiency Anemia	6.52	2.66	.076
	Megaloblastic Anemia	.40	2.66	.999
	ITP	-.84	2.66	.989
ITP	Iron Deficiency Anemia	7.35*	2.66	.035
	Megaloblastic Anemia	1.24	2.66	.966
	Aplastic Anemia	.84	2.66	.989

Tukey HSD

Table-3: Distribution of RBC for cases with four different Disorders

Disorder	Red Blood Cell ($10^{\wedge 6}$ /uL)		
	Median	Q1	Q3
Iron Deficiency Anemia	4.2	4.0	4.5
Megaloblastic Anemia	4.6	4.5	4.9
Aplastic Anemia	4.7	4.5	5.0
ITP	4.9	4.7	5.1

The mean cell volume (MCV) significantly differed among the four groups, with a *P*-value of 0.027. The ITP group had a substantially higher average than IDA, with a *P*-value of 0.035. The Aplastic anemia group also had a higher average MCV than IDA, but the difference was insignificant, with a *P*-value of 0.076. (Table-2). All other differences were not statistically significant.

The table-2 compares the Mean Cell Volume (MCV) using an ANOVA by disorder type. The F statistic

(3.20) indicates significant differences in MCV associated with the groups (*P*-value = 0.027). When compared with post hoc tests, there is a considerable difference in MCV only between Iron deficiency anemia and ITP (*P* = 0.035), and other comparisons are not substantial (*P* > 0.05).

The average for MCHC was highest for the ITP group, with a median (IQR) level of 34 (34-36), and lowest for IDA, with a median (IQR) level of 31.9 (30-32). This difference was found to be highly significant overall, with a *P*-value <0.001. The median MCH was also lowest in IDA and highest in ITP. The overall difference was highly significant, with a *P*-value <0.001. The IDA group had a median RBC of 4.2 (4.0-4.5), which was the lowest, and the ITP had the highest, which was 4.9 (4.7-5.1). (Table-3).

Compared to all other groups, platelet counts had a median of 183.0 (151.0- 333.0). The median levels for MA, AA, and ITP were 87.5 (53.5-167.0), 30.0 (12.5-53.0), and 29.0 (11.0-50), respectively. The overall difference was noticeable; IDA had highly significant differences from all other groups. The correlation analysis shows a strong correlation among various hematological parameters. RBC count (0.69), mean cell volume (0.49), and hematocrit (0.60) positively correlate with hemoglobin levels, while monocytes (-0.94) have a strong negative correlation with them. While MCV has a very high positive correlation with RBC count (0.96) and with hematocrit (0.98), the correlation with platelet count is very strong and negative (-0.96). RBC is strongly associated with MCHC (0.95), while MCV (0.93) and platelet count show a strong inverse correlation (MCHC -0.99, RBC -0.96). TLC has a moderate positive correlation with hemoglobin (0.74) and a negative correlation with monocytes (0.52). There is a strong inverse correlation (-0.94) between distributions of neutrophils and eosinophils. These findings of strong interdependencies between red cell indices and platelet count and between platelet count and WBC components (monocytes, lymphocytes, neutrophils) showed mixed correlation.

Discussion

The study identified four hematological disorders: Iron Deficiency Anemia (IDA), Megaloblastic Anemia (MA), Aplastic Anemia (AA), and ITP. The gender distribution significantly differed among the four groups, with IDA and ITP groups being more common among females. The average age of the cases was not different. Still, the ITP group had the lowest average age of 40.5 years, while the Aplastic anemia group had the highest average age of 46.7 years. The hemoglobin level was highest among the ITP group, with the other three groups having similar averages. The mean cell volume (MCV) significantly differed among the four groups, with the ITP group having the highest average. The IDA group had the lowest median red blood cell count, while the ITP group had the highest. The median levels for MA, AA, and ITP were 87.5, 30.0, and 29.0, respectively.

These results are also similar to the findings of Nowaj Sharif et al., which stated that compared to women in advantaged areas, women in the disadvantaged group have more cases of moderate to severe anemia (any anemia), according to the general findings.[12] In one more study by Miriam Lev et al. (2019), their investigation confirmed that obese male and female patients had an increased chance of developing IDA.[13] Incidence of IDA is higher in developing countries due to inadequate consumption of iron-rich foods, decreased bioavailability, and augmented demand related to menstruation among women. The higher distribution of ITP in females, as concluded by this study, also correlates with the findings of Bruna Sobreira Kubrusly et al. (2024), which states that with a female-to-male ratio of 4.7:1, the female sex (82.35%) was much more prevalent for ITP across all age groups.[14] According to a Korean study by Lee et al., ITP is more prevalent in women (female/male ratio: 1.3:1; 95% CI: 1.2–1.4), with patients of all ages included. According to the authors, the frequency among patients aged 20 and 59 was gender-driven.[15] Sage & Powe revealed a 1.9:1 overall female-to-male ratio and a majority of females in middle adulthood. ITP is also more common in women, according to Bennett et al., and it tends to get worse with age. In a study by Dr. Nirali. V. Shah et al. in 2021 describe that ITP affects women more frequently than males, as all autoimmune illnesses do. In their research, two females and two males made up 4 cases (6% of the cases) of ITP. There were 1.6 males for every female in a survey conducted in Nepal. ITP cases were

reported to be 9.33% and 10.5% in two investigations conducted in Nepal. The proportions found in international studies are 6.21%, 14.5%, and 5%.[16] Characteristics of ITP, on the other hand, are also reported to occur among adults at a young age, and females are more prone to disease than males, with a female-to-male ratio of 3.4:1, which is also comparable with the present study. Literature suggests this significant difference may be due to the susceptibility of ITP to the sex hormones of females.[17] A mean hemoglobin level was found to be highest among ITP, which was 10.8±1.9 g/dl in this study. The other three groups had almost the same averages. The difference among the four groups was significant, with a *P*-value <0.001. When compared grou*p*-wise, the ITP had a significantly higher average than all three groups, and there was no difference between the other three groups. The association of hemoglobin is difficult to correlate with ITP due to the great controversy in the literature. An older study has proven the misdiagnosis of IDA as ITP on bone marrow examination. This confirmed the latter due to a high number of megakaryocytes and achieved normal levels of platelets in 48 hours after iron supplementation.[18] Similar findings with as low hemoglobin as 2.7 g/dl in women of 31 years of age were confused with ITP and recovered from the disease on iron supplementation.[19] Another study considered that a hemoglobin level of <12 g/dl among ITP patients may be due to IDA.[20] The mean corpuscular volume (MCV) had a significant difference among the four groups, with a *P*-value of 0.027. The ITP group had a significantly higher average than IDA, with a *P*-value of 0.035. The Aplastic anemia group also had a higher average MCV than IDA, but the difference was insignificant, with a *P*-value of 0.076. All other differences were insignificant among groups. The standard value of MCV is 80-100 fl. 28, while the mean MCV in the present study for IDA remained as low as 74.5±9.9fl. Similarly, mean MCV for MA, AA, and ITP also remained towards lower normal at 80.6±11.0, 81.0±7.8, and 81.9±7.9, respectively, where standard deviation shows that as many as half of the patients in each of the three groups had MCV of <80fl. A relatively new term is being used to differentiate IDA from other anemias. It is said to be anemia of inflammation and essential chronic diseases like autoimmune diseases, infections, and cancer. Further, such conditions may be confused with other types of anemia, and MCV remains normal in such cases of anemia.[21] Whereas in conditions like megaloblastic anemia, MCV remains >100fl, which is not in agreement does not agree with the results of the present study.

Larger sample sizes are needed for future research to determine whether reticulin fibrosis is associated with IDA, MA, AA, and other hematological illnesses.

Conclusion

This study demonstrates that female patients with higher hemoglobin levels and a lower platelet count might show signs of reticulin fibrosis, particularly when experiencing ITP. Identifying these parameters as diagnostic markers requires further research to confirm their status. The diagnosis of reticulin fibrosis depends on histopathological analysis, which is based on fibrosis grades, which function as definitive diagnostic indicators. Additional research must validate whether these markers prove effective for medical diagnosis and screening.

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Author Contributions

YS: Conception and design of the work, writing the original draft, proofreading, and approval for final submission
NF: Manuscript writing for methodology design and investigation
FA: Data acquisition, curation, and statistical analysis
AAV: Validation of data, interpretation, and write-up of results
MF: Revising, editing, and supervising for intellectual content
ME: Writing the original draft, proofreading, and approval for final submission