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ORIGINAL ARTICLE

Extent of iron induced organ damage in patients with hematological disorders.

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ABSTRACT… Objective: To determine the extent of iron induced organ damage in patients of Haematological disorders who are transfusion dependent, presenting in the emergency department of SZH, Lahore. **Study Design:** Cross Sectional study. **Setting:** Department of Emergency, Shaikh Zayed Hospital, Lahore. **Period:** December 25, 2020 to June 24, 2021. **Methods:** A total of 100 patients aged 10-60 years, of both genders, diagnosed with haematological disorders, and receiving multiple blood transfusions were included in this study. Demographic details were noted including name, age, sex, diagnosis, duration of receiving transfusions and number of transfusions received per month. Patients were evaluated clinically for organ damage including pulmonary, hepatic, renal, and cardiac organs using Denver MOF score. **Results:** Mean age of patients was 35.33±14.27 years. Mean duration of receiving transfusion was 6.69±2.71 months. There were 67 (67%) males and 33 (33%) female patients. Primary diagnosis was Autoimmune Haemolytic Anemia (AIHA) in 18 (18.00%) patients, Aplastic anemia in 34 (34%) patients, Thalassemia in 37 (37%) patients and Myelodysplastic syndrome (MDS) in 11 (11%) patients. Multiple organ damage was found in 23 (23%) patients. Pulmonary damage was diagnosed in 21 (21%) patients, hepatic damage in 21 (21 %) patients, renal damage in 20 (20%) patients and cardiac damage in 15 (15%) patients. **Conclusion:** There is a high frequency of multi-organ damage in patients of Haematological disorders requiring chronic blood transfusions. In this study, multi-organ damage was diagnosed in 23% patients requiring chronic blood transfusion.

Key words: Hematological Disorders, Iron Toxicity, MOF Score, Transfusion Dependent Anemia.

INTRODUCTION

The devastating effect of the accrued iron from chronic blood transfusions necessitates a more finely tuned approach to limit its complications, as well as its treatment.[1] Conventional treatment for transfusion dependent patients with haematological disorders involves lifelong supportive care with regular blood transfusions that lead to unavoidable iron build up that can result in significant organ damage.[2-4] Regular red blood cell transfusion is a rapid and effective treatment for refractory chronic anemia, including Thalassemia, sickle cell anemia, myelodysplastic syndrome(MDS), and aplastic anemia.[5] Multi-organ damage was found in 24% cases who received multiple transfusions for some disease.[6] Transfusional hemosiderosis, particularly in the liver or heart, can cause considerable morbidity and eventually can be fatal. Myocardial iron overload develops in 17% to 27% of transfusion-dependent MDS patients.[7] Around 70% to 80% of regularly transfused MDS patients develop hepatic iron overload.[8] Although iron is necessary for life, iron overload is potentially harmful because iron can also catalyze the formation of injurious reactive oxygen species.[9]

Patients receiving regular RBC transfusions, are at risk for iron toxicity[10] One unit of RBCs contains approximately 200 mg of heme iron, more than 100 times the quantity absorbed from the diet daily. A patient with a transfusion-dependent anemia requiring 2 units of RBCs per month would receive 24 units per year, or approximately 100 units over 4 years, the latter resulting in an accumulation of 20 g of iron, which is seven times greater than the normal total mass of body iron. RBC transfusion is generally believed, in both adults and children, to be unnecessary when the Hb is 10 g/dL. It is within the gray zone between

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Hb levels of 6-10 g/dL that questions frequently arise whether to transfuse a patient or not. With the increasing awareness of the hazards inherent to blood transfusion, potential benefits from a transfusion should always be weighed against the potential risks.[11]

The imbalanced synthesis of α- and β- globin chains in thalassemia (an inherited form of anemia) leads to ineffective erythropoiesis and chronic hemolytic anemia. The targets of transfusion have been outlined in several practice guidelines, and the recommendations from the United States (Children's Hospital, Oakland, CA) and the Thalassemia International Federation (TIF) are summarized in Table-I.[12] Patients with severe aplastic anemia require repeat red blood cell transfusions as conservative therapy. Therefore, these patients are at an increased risk of iron overload and its related complications.[13,14] Blood transfusion in aplastic anemia is necessary when hemoglobin levels <7 g / dl.[15] Blood transfusion in autoimmune hemolytic anemia (AIHA) may only be needed in situations when a patient has neurological symptoms, or experiences chest pain, or has rapidly progressing anemia, or develop early signs of heart failure. The dose of transfusion should be one unit at a time in adults and 10 mL/kg in children followed by assessing whether the symptoms have improved.[16] Most patients with MDS will develop symptomatic anemia and require RBC transfusions at some point in their clinical course. Depending on the risk categories defined by the International Prognostic Scoring System (IPSS), from low to high risk, 39%-79% of patients were reported to be RBC transfusion-dependent. Only the smallest effective dose is recommended to relieve symptoms of anemia or to return the patient to a safe Hb level (7-8 g/dL in stable, noncardiac in-patients).[17]

Screening is necessary for the diagnosis of iron overload and monitoring after the diagnosis. Serum Ferritin is a reasonable marker of the direction and magnitude of change in iron burden.[18] Serum Transferrin saturation measures the proportion of Transferrin bound to iron and is derived by dividing serum iron by total iron-binding capacity.[19] Tissue iron can be visualized and quantified by a number of imaging techniques (CT, NRS, MRI And SQUID)[20] Liver biopsy is the most accurate test for LIC, but it is an invasive procedure. The Denver MOF score grades (from 0-3) four organ dysfunctions (lung, kidney, liver, and heart) and defines MOF as a total score more than 3. (Table-II)[21] Organ dysfunction was defined using the Denver MOF score. The MOF score is calculated as the sum of the simultaneously obtained individual organ scores. Single organ dysfunction is defined as an organ failure grade exceeding 0; MOF is defined as a total score of 4 or higher occurring 48 hours after injury.[22] The rationale of this study is to determine the extent of organ damage in blood transfusion dependent patients, which have been diagnosed with a haematological disorder, presenting in emergency department. Due to the lack of sufficient local evidence this study will provide useful information about our local population and also recommend the screening of Multi-transfused patients to prevent organ damage.

METHODS

This cross-sectional study took place at emergency department of Sheikh Zayed Hospital, Lahore, Pakistan spanning from December 25, 2020 to June 24, 2021. Approval for the study protocol was obtained from the Technical and ethical review committee/Institutional Review and research advisory Board (SZMC/IRB/INT/216/2020) (22-10-2020), ensuring adherence to ethical standards in human subjects research.

The research study comprised 100 individuals with transfusion dependent anemias considering expected percentage of multiple organ damage i.e., 24% in blood transfusion dependent patients in emergency department ranging in age from 10-60 years of both genders. Participants were sourced from emergency department of sheikh Zayed hospital, Lahore.

Inclusion Criteria

Patients aged 10-60 years, both genders, receiving multiple blood transfusions (as per operational definition). Serum Ferritin Level for all the patients was measured to be more than1000ng/ml.

Exclusion Criteria
Exclusion criteria comprised of patients with history of organ damage or chronic disease of any organ before diagnosis of transfusion dependent disease. Malignancy, Isolated head injuries or spinal cord injuries (external or extremity injury score ≤2) (on medical record) was also considered as exclusion criteria.

A total of 100 patients aged 10-60 years, of both genders, diagnosed with haematological disorders, and receiving multiple blood transfusions were included in this study. Prior to data collection, all participants provided informed consent. Properly structured questionnaire included Demographic details like name, age, sex, diagnosis, duration of receiving transfusions and number of transfusions receive per month. Then patients were evaluated clinically for organ damage including pulmonary, hepatic, renal, and cardiac organs using Denver MOF score (as per operational definition). Patients with organ damage were managed as per standard protocol.

The Denver MOF score grades (from 0-3) four organ dysfunctions (lung, kidney, liver, and heart) and defines MOF as a total score more than 3. Organ dysfunction was defined using the Denver MOF score.

Data analysis was performed by using SPSS v. 23. Mean and Standard Deviation were calculated for continuous variables like age, duration of receiving transfusion. Frequency and percentage were calculated for qualitative variables like gender, diagnosis, number of transfusions receive per month and multi-organ damage. Data was stratified for age, sex, diagnosis, duration of receiving transfusions and number of transfusions receive per month. Post-stratification, chi-square test was applied to compare multi-organ damage in stratified group. P-value≤0.05 was taken as significant.

RESULTS

AGE
Mean age of patients included in this study was 35.33±14.27 years. Minimum age was 13 years and maximum age was 60 years (Table-III).

GENDER
There were more males as compared to the females. There were 67 (67%) males and 33 (33%) female patients (Figure-1).

Transfusion Duration
Mean duration of receiving transfusion was 6.69±2.71 months. Minimum duration was 03 months and maximum duration was 15 months (Table-IV).

MOF Score
Mean multi-organ failure score was 3.43±0.51. Minimum score was 03 and maximum score was 04 (Table-V).

Hematological Disorders
On analysis of primary diagnosis, AIHA was found in 18 (18%) patients, Aplastic anemia in 34 (34%) patients, Thalassemia in 37 (37%) patients and MDS in 11 (11%) patients (Figure-2).

Frequency
Frequency of number of transfusions per month was 1/month in 27 patients (27%), 2/month in 40 patients (40%), 3/month in 24 patients (24%), 4/month in 8 patients (8%) and 5/month in 1 patient (1%) patients (Figure-3).

Organ Damage
On analysis of clinical findings, pulmonary damage was diagnosed in 21 (21%) patients, hepatic damage in 21 (21%) patients, renal damage in 20 (20%) patients and cardiac damage in 15 (15%) patients (Table-VI).

Multi-Organ Damage
Multi-organ damage was found in 23 (23.00%) and it was not found in 77 (77.00%) patients (Figure-4).

Correlation
Stratification of age was performed, and no association of age was found with multi- organ damage. In patients having age 10-39 years, multi-organ damage was found in 19 (82.6%) patients. In patients having age 40-60 years, multi-organ

damage was found in 04 (17.4%) patients. This result was statistically significant with p-value of 0.001 (Table-VII). Stratification of gender was also performed, and no association of gender was found with multi-organ damage. 16 of 23 with multi organ failure were males (69.6%). 7 of 23 patients with multiple organ failure were females (30.40%). This result was statistically insignificant with p-value of 0.766 (Table-VIII). Stratification was also performed based on primary diagnosis, duration of receiving transfusion and number of receiving transfusion per month. There was no association was found of these variables with multi-organ damage.

	Children's HospitalOakland	Thalassemia InternationalFederation
Laboratory criteria for initiating regular transfusion	Hb 7 g/dL at steady state, on2 occasions, 2 weeks apart	Hb 7 g/dL on 2 occasions, 2 weeksapart
Clinical criteria for initiating regular transfusion	Poor growth; dysmorphic bone changes; inability to maintaindaily routines and activities; evidence of organdysfunction, cardiac disease,or pulmonary hypertension	Facial changes; poor growth;fractures; clinically significant extramedullary hematopoiesis

Table-I. Recommendations for transfusion therapy for transfusion- dependent thalassemia[23]

Dysfunction	GRADE 0	Grade 1	Grade 2	Grade 3
A.Pulmonary PaO_2/F_{IO2} ratio †	>250	200-250	100-200	≤100
B.Renal creatinine level, mg/dl	≤1.8	1.8-2.5	2.5-5.0	>5.0
C.Hepatic totalBilirubin Level,mg/dl	≤2.0	2.0-4.0	4.0-8.0	>8.0
D.Cardiacscore ‡	No inotropesand CI>3.0L/min.M_2	Minimal inotropes or CI <3.0 L/min.M_2	Moderate inotropes	High inotropes

Table-II. Denver Multiple Organ Failure (MOF) Score[22]

Abbreviations: CI, cardiac index; FIO2, fraction of inspired oxygen. SI conversion: To convert renal creatinine to micromoles per liter, multiply by 88.4; total bilirubin to micromoles per liter, multiply by 17.1.

*Multiple organ failure score equals A + B +C +D not due to chronic disease. An MOF score greater than 3 indicates MOF.

†Values adjusted for altitude.

‡Cardiac score: minimal inotrope levels, dopamine or dobutamine level less than 5 μg/kg per minute; high inotrope levels, dopamine or dobutamine level greater than 15 μg/kg per minute; moderate inotrope levels, dopamine or dobutamine 5 to 15 μg/kg per minute.

Age (Years)	
Mean	35.33
S.D.	14.27
Minimum	13
Maximum	60

Table-III. Descriptive statistics of age in MOF secondary to iron overload inHaematological disorders (n=100)

Duration of receiving transfusion (Months)	
Mean	6.69
S.D.	2.71
Minimum	03
Maximum	15

Table-IV. Descriptive statistics of duration of receiving transfusion in MOF secondary to iron overload in Haematological disorders (n=100)

Multi-Organ Failure Score	
Mean	3.43
S.D.	0.51
Minimum	03
Maximum	04

Table-V. Descriptive statistics of multi-organ failure score secondary to iron overload in haematological disorders

Organ/s Showing Features of Damage	Frequency	Percentage (%)
Pulmonary damage	21	21.00
Hepatic damage	21	21.00
Renal damage	20	20.00
Cardiac damage	15	15.00
Multiple organs showing damage	23	23%

Table-VI. Frequency of organ/s damage in 100 patients of iron overload in haematological disorders

Age Group	Multi-Organ Damage		P-Value*
	Yes	No	
10-39 Years	19 (82.60%)	33 (42.90%)	0.001
40-60 Years	04 (17.40%)	44 (57.10%)	

Table-VII. Association of Age with Multi-Organ Damage secondary to iron overload in haematological disorders…n=100
p value is ≤0.05

Gender	Multi-Organ Damage		P-Value*
	Yes	No	
Male	16 (69.60%)	51 (66.20%)	0.766
Female	07 (30.40%)	26 (33.80%)	

Table-VIII. Association of Gender with Multi-Organ Damage secondary to ironoverload in haematological disorders…..n=100
p value is ≤0.05

Primary Diagnosis		Multi-Organ Damage		P-Value*
		Yes	No	
AIHA	Yes	03 (13.00%)	15 (19.50%)	0.46
	No	20 (87%)	62 (80.5%)	
Aplastic Anemia	Yes	08 (34.80%)	26 (33.80%)	0.92
	No	15 (65.2%)	51 (66.2%)	
Thalassemia	Yes	11 (47.80%)	26 (33.80%)	0.22
	No	12 (52.2%)	51 (66.2%)	
MDS	Yes	01 (4.30%)	10 (13.00%)	0.24
	No	22 (95.7%)	67 (87.0%)	

Table-IX. Association of Primary Diagnosis with Multi-Organ Damagesecondary to iron overload in haematological disorders…n=100
significant p value is ≤0.05

Duration of Receiving Transfusion	Multi-Organ Damage		P-value
	Yes	No	
03-06 Months	16 (69.60%)	41 (53.20%)	0.165
07-15 Months	07 (30.40%)	36 (46.80%)	

Table-X. Association of duration of receiving transfusion with Multi-OrganDamage secondary to iron overload in haematological disorders…n=100
***Significant p value is ≤ 0.05**

Number of Transfusion Received Per Month		Multi-Organ Damage		P-Value *
		Yes	No	
01	Yes	07 (30.40%)	20 (26.00%)	0.67
	No	16 (69.6%)	57 (74%)	
02	Yes	10 (43.50%)	30 (39.0%)	0.70
	No	13 (56.7%)	47 (61.0%)	
03	Yes	03 (13.0%)	21 (27.30%)	0.16
	No	20 (87%)	56 (72.7%)	
04	Yes	02 (8.70%)	06 (7.80%)	0.88
	No	21 (91.3%)	71 (92.2%)	
05	Yes	01 (4.30%)	0 (0.0%)	0.07
	No	22 (95.7%)	77 (100%)	

Table-XI. Association of number of transfusions received per month with Multi-Organ Damage secondary to iron overload in haematological disorders
significant p value is ≤0.05

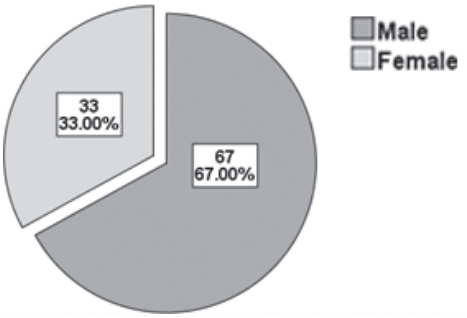

Figure-1. Frequency of Gender in MOF secondary to iron overload in Hematological disorders (n=100)

	Present study	Study by Factor JM et al 33	Study by Vichinskyet al.[34*]	Study by Telfer et al 35*	Study by Bayer et al[36]	Studyby Quinn et al.[38]
Pulmonarysystem	21%	79%	-		-	-
Renal system	20%	-	-		-	28.6%
Cardiacsystem	15%	-	20%	10.3%	86%	-

Table-XIV. Comparison of the six studies showing iron induced organ damage using different clinical criteria

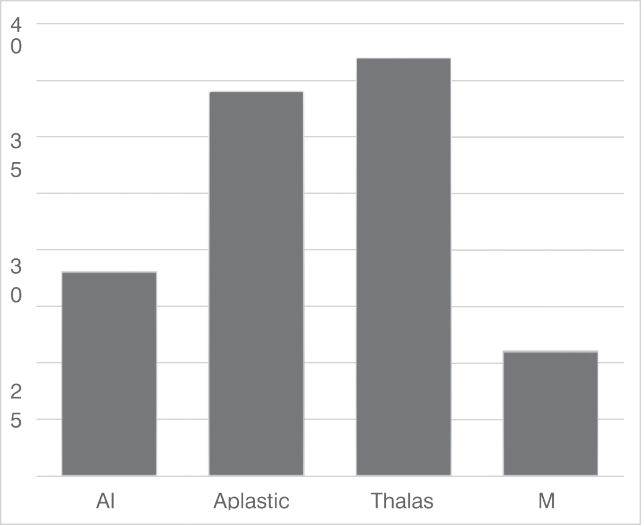

Figure-2. Frequency of Primary Diagnosis in iron overload secondary to iron overload in Haematological disorders (n=100)

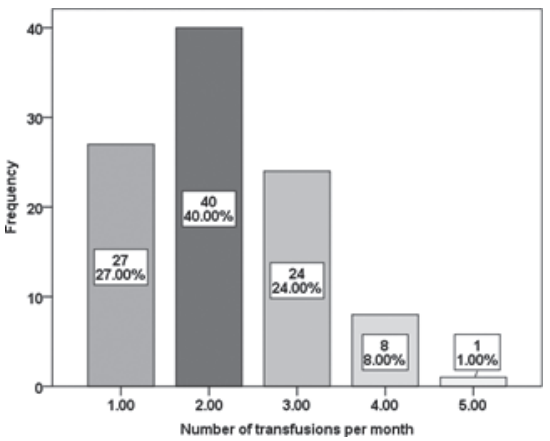

Figure-3. Frequency of Number of Transfusions Per Month in iron overload secondary to iron overload in Haematological disorders (n=100)

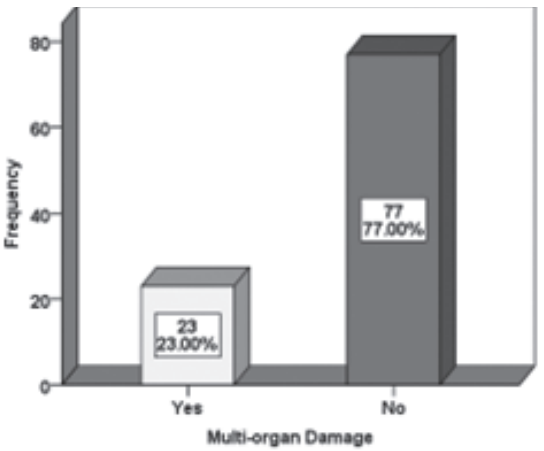

Figure-4. Frequency of Multi-Organ Damage

DISCUSSION

This cross-sectional study was conducted to determine the extent of iron induced organ damage in the patients of haematological disorders presenting in emergency department of Sheikh Zayed hospital, Lahore. A total of 100 patients of both genders aged 10-60 years diagnosed with haematological disorders and receiving multiple transfusions were included in the study. Four disease categories were chosen i-e Autoimmune Haemolytic anemia (AIHA), Thalassemia Major, Myelodysplastic syndrome (MDS) and Aplastic anemia. These patients were evaluated for organ/s damage using Denver MOF score. As per operational definition, multiple transfusions were labeled if at least one transfusions is carried out per month for at least three months. Single organ dysfunctions as per Denver MOF score is defined as organ failure exceeding zero. Multiple organ failure is defined as total score of 4 or higher.[21] Mean age of subjects was 35.33 years (13-60 years) because of inclusion of adult onset diseases in cohort (Table-III). More males (67/100) were included because male predominance is evidenced for major diseases predisposition (idiopathic aplastic anemia and MDS) while females were fewer (33/100) (Figure-1). Thalassemia major has equal incidence in males and females, and AIHA has female predominance (emedicine.medscape.com). Mean duration of receiving transfusions was 6.69 ±2.71 months (Table-IV).

Mean multiple organ failure score was 3.43±0.51 (3.0-4.0) (Table-V). After Analysis of primary diagnosis, prevalence of haematological disorders was: AIHA in 18% patients(most prevalent in females), Aplastic anemia in 34% patients(because of excessive exposure to environmental toxins and infections like hepatitis), Thalassemia major in 37% patients (evidencing the prevalence of consanguineous marriages in Pakistan) and MDS in 11% patients(because of very low incidence in general population i-e 2.5/100,000(www.ncbi.nlm.nih.gov).) (Figure-2). Multiple organ damage was found in 23% patients and was not found in 77% patients (Figure-3). This trend is justified because the patients were evaluated in emergency setting and long term

follow up of the patients was not done otherwise percentages of pulmonary damage would be higher especially cardiac damage that has late manifestation in case of iron overload. p value less than 0.05 is considered significant. The Age group of 40-60 years has a significant association with multiple organ damage (p value=0.001). Whereas, gender of the cohort is not significantly associated with multiple organ damage (p value of 0.76).

On analysis of clinical findings using Denver MOF score, pulmonary damage was diagnosed in 21%, hepatic damage in 21% patients, renal damage in 20% patients and cardiac damage in 15% patients (Table-VI). The study conducted by Vichinsky et al. [24] described the risk of hemosiderosis-induced organ damage in sickle cell anemia and Thalassemia patients and concluded that Thalassemia patients had greater cardiac disease (20% vs. 0%) and endocrine failure (37% vs. 0%) correlating with the present study as cardiac and liver damage were also seen in the latter however exclusion of sickle cell disease in our cohort is there because of its rarity in Pakistan. P.T.Telfer et al[25] demonstrated a group of 32 patients with development of Cirrhosis four of 10 evaluable patients (indicating liver damage). Most complications can be avoided if Ferritin levels can be brought down to <1500μg/l. This conforms to the present study where serum ferritin level above 1000μg/l was associated with evidence of iron overload and organ damage. Increase in pulmonary damage in the study conducted by Factor JM et al.[26] (79%) is detected by more sensitive marker of the lung damage in contrast to less sensitive marker P/F ratio used in our study. Moreover, our study did not evaluate iron overload in TM patients exclusively; rather other disease categories which are less common causes of iron induced pulmonary damage were also part of our cohort, justifying for low percentage of pulmonary damage in our study.

In our study, patients were only evaluated in emergency settings with the help of echocardiography and EF which show cardiac muscle damage i.e, late manifestation of iron overload. While study conducted by Bayer et al.[27] employed ECG and MRI which are more sensitive techniques and recognize defects in conduction pathways and increase in iron content even before cardiac muscle is damaged.

LIMITATIONS

The major limitation of present study is cross-sectional nature. We did not follow the patients for longer periods to determine the outcomes of multi-organ failure patients. Moreover, we did not take into account the confounding factors leading to multi- organ failure. Therefore, larger studies are needed to determine the frequency and factors leading to multi-organ failure.

CONCLUSION

There is a high frequency of multi-organ failure in patients requiring chronic blood transfusions. In this study, multi-organ failure was diagnosed in 23% patients requiring chronic blood transfusions.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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