Iron overload in children with leukaemia: Experience of The Only Department of Pediatric Hematology Oncology in Kuwait

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Abstract:

Children with leukaemia are prone to severe anaemia due to the disease itself and the medication; they usually receive multiple blood transfusions throughout their treatment when they develop severe anaemia as a side effect of the disease and chemotherapy received. This is an observational cross-sectional study of 50 children who were diagnosed with leukaemia and treated at NBK paediatric haematology and oncology department, Sabah hospital. The aim of this study was to see whether intense chemotherapy affects the amount of blood transfusions received, hence leading to iron overload. Serum ferritin level was tested in each patient who were at different stages of treatment (after parents' consent). Forty-four children were receiving their chemotherapy at the time of sampling and were at different stages of their treatment, whereas six children have already completed their chemotherapy in accordance to their chemotherapy treatment protocol. Serum ferritin level was observed to be increasing as the patient progress in treatment. The risk of the disease and multiple blood transfusions might lead to increased level of serum ferritin level (multiple correlation coefficient 0.664, coefficient of determination =38%) however they were not only the only determinant of the iron overload. Most children have received multiple blood transfusions by the end of chemotherapy treatment protocol (p=0.001). Iron overload has an accumulative effect that can still be clearly seen towards the end of chemotherapy protocol.

Key words: ALL, iron overload, blood transfusion

1. INTRODUCTION

1.1. Chemotherapy protocols for children with leukaemia over the last four decades have been developing, and as a consequence the survival rates have increased as well as the transfusion demands [Nottage et al., 2013]. Iron overload as a result of repeated packed red cells (PRC) transfusions is a common finding in patients with acute leukaemia, and affect the overall management and survival.

1.2 Children usually develop pancytopenia because of leukaemia itself and secondary to chemotherapy, hence they may require multiple blood transfusions [Barton & Bertoli 2011].

1.3 Chemotherapy agents may sustain injuries to vital organs such as the heart or the kidneys, which can adversely affect the quality of life for these patients years after cessation of the therapy. Multiple blood transfusions may expose patients with leukaemia to bacterial, viral infections and immune injury, as well iron overload [Unal et al., 2014]; moreover iron overload have been shown to cause medical complications to other vital organs such as the heart, liver and endocrine glands [Arman, Kim, Rhodes, Sainvilmm & Cutter, 2011]. These complications need further medical attention and can harmfully affect the overall survival. Iron overload is a bad prognostic indicator and is associated with inferior post HSCT survival for those patients who may eventually require hematopoietic stem cell transplantation (HSCT) [Arman, Kim, Rhodes, Sainvilmm & Cutter, 2011, Sirvent et al., 2017]. Serum ferritin might be an indicator for iron overload, however there are other more sensitive tools to diagnose clearly iron overload specifically in the vital organs such as MR2T* [Unal et al., 2014, Bebeshko et al.,2013]. Management of iron overload in adults have drastically improved their haemopoiesis as well as survival as was shown in many studies [Matsuki , 2012, Fukushima et al., 2011]. The aim of this study was to study the presence of iron overload in children with leukaemia at our centre, whether the risk of the disease has an effect on the need for blood transfusion and hence lead to iron overload.

2. AIM AND METHODS OF THE STUDY

2.1. This is an observational cross-sectional study approved by the ethics committee of the Ministry of Health of Kuwait, of 50 children who were diagnosed with leukaemia, and treated at NBK paediatric haematology and oncology department, Sabah hospital in state of Kuwait. The aim of this study was to see whether intensive chemotherapy affects the amount of blood transfusions received, hence leading to iron overload. We studied patient charts as well as serum ferritin levels in 50 children who were at different phases of chemotherapy from March to August in 2014. Parents were interviewed before enrolment into this study, and consents were taken for participating in the study and for blood sampling. The identity of the patients was protected. Serum ferritin level was tested in each patient while they were at different stages of treatment. During this study some

children were receiving their treatment at inpatients wards; others were seen at either Monday ongoing chemotherapy clinic, or on Thursday off-chemotherapy clinic. The samples for serum ferritin were analyzed by the hospital biochemistry lab.

2.2 The majority of children were diagnosed with ALL pre B leukaemia, and they received an average total of 37 months of chemotherapy. Results were analysed using SPSS software (version 20.0 for Windows). SPSS was used for all statistical analyses for categorical variables.

3. RESULTS

3.1 Chemotherapy regimen for children with acute lymphoblastic leukaemia usually starts with induction phase, where the child receives 4-6 weeks of intensive induction chemotherapy, followed by 3 months on average with intensive chemotherapy, and then by maintenance chemotherapy for an average of 32 months. The chemotherapy for children diagnosed with acute myeloid leukaemia is given in courses, and usually completed in 5 months on average. Children with chronic myeloid leukemic usually start and continue their biological target therapy indefinitely.

3.2. In this study the serum ferritin levels were studied in 50 children (Figure 7.1) who were at different phases of therapy (figure 7.2), and most of the patients were diagnosed with pre B ALL (figure 7.3). The age group of the patients ranged between less than one year to 16 years old, and most patients (80%) were below 12 years of age (Figure 7.1). Forty-four children were receiving their chemotherapy at the time of sampling and were at different stages of their scheduled chemotherapy protocol, whereas six children have already completed their chemotherapy in accordance to their chemotherapy treatment protocol (Figure 7.4). Twelve children had low risk disease, and 38 children had intermediate or high risk disease. There were 29 males and 21 females, and There were 38 children with a serum ferritin level above 400 µg/l (76%), and 22 children had a serum ferritin level more than 1000 µg/l (44%) (Figure 7.5). The mean serum ferritin level of all patients was 991.66 µg/l, the median was 811.8 µg/l, and the mode 525 µg/l. The maximum value recorded was 5044 µg/l, and the minimum was 19.5 µg/l. Higher serum ferritin levels were specifically observed at the beginning of the therapy during induction and intensive treatment; however the level was seen at a lower rate during maintenance and after completion of therapy. It was expected that the level would return to normal upon the completion of treatment; however, it was still observed to be higher than normal level in 57% of patients, and at level needed chelating treatment in 28% of patients (figure 7.6). When we looked at specific relationships between these factors, we found that there is a poor correlation between the number of blood transfusion and serum ferritin level (P =0.014, Pearson correlation coefficient R = 0.363, R square = 0.132), applying simple linear regression, this might be due to small sample size, the coefficient of determination indicates that only 13% of the variation in serum ferritin level can be explained by the number of blood transfusion (figure 7.7). There was no significant difference in the serum ferritin level among different risk protocols (Kruscal–Wallis P=0.046). The multiple correlation coefficient was = 0.664, the coefficient of determination was 38.4% , which means independent variable (

number of blood transfusion and high risk protocol) can explain 38% of the variation in serum ferritin level.

4. DISCUSSION

4.1. Children with leukaemia need multiple transfusions during chemotherapy, which might lead to transfusion-related complications [Halonen et al., 2003, Webb & Anderson, 1997]; one of which is iron overload. Iron overload in children with leukaemia has been observed and described in the literature as well as in this study [Halonen et al., 2003].

4.2. Serum ferritin level has been shown to be a good indicator for iron overload in patients with leukaemia, who had to receive many blood transfusions during their chemotherapy treatment [Bebeshko et al.,2013]. The mean serum ferritin level for all patients was 991.66 µg/l, which was significantly higher than average (normal range from 30 to 400 microgram/L). A worthwhile note observed was that a high percentage of patients have a serum ferritin level of more than 1000 microgram/L during induction and intensive phase of chemotherapy (67%), and as chemotherapy progressed to maintenance. The serum ferritin was still significantly high in 28% of children who completed their treatment. As expected those children who were receiving more intensive treatment had higher level of serum ferritin. It was observed in this study that the risk of the disease and the frequency of blood transfusions may increase the level of serum ferritin levels, however they might not be the sole cause of the increase of the level of the serum ferritin, other factors might have a role in the overall iron overload in these children, as was seen in other studies [Eng & Fish, 2011]; however, towards the end of treatment most children have already received multiple blood transfusions. Therefore we conclude from this study that iron overload has an accumulative effect that can still be clearly seen towards the end of the chemotherapy protocol, and after completion of chemotherapy.

4.3. An important observation is that most children have a higher level of serum ferritin from the early stages of chemotherapy even after few blood transfusions, which suggests that multiple blood transfusions might not be the sole cause of iron overload [Olcay et al., 2914, Lipshultz et al., 2013, Reitman AJ, Coates TD, Freyer DR, 2015], and this was clearly demonstrated in another aspect of our study as there was no relation between the frequency of blood transfusions and serum ferritin level.

4.4. Children with leukaemia and iron overload need a more subjective measure of their iron overload such as imaging with MRI2T* and gene deletion studies. Both of which were unfortunately out of the scope of this study. Imaging studies with MRI T2* might reveal iron overload in organs such as the heart and liver [Unal et al., 2014], which will demonstrate further the need for a long term follow up post chemotherapy with serum ferritin and MRI T2* to be worthwhile [Vag, kentouche, krumbein, Reichenbach,2011, Ruccione et al., 2014].

4.5. The use of iron chelating agents should be given a serious thought, if there is evidence of iron overload in organs. Investigation for iron overload should be tested in each stage of any chemotherapy protocol, and consider treatment in case of positive evidence of iron overload, which can persist for a long time after completion of chemotherapy and cessation of transfusions [Rascon et al., 2014], to avoid long term complications due to iron overload in major organs such as the heart or the liver, and can increase the cost of treatment for these patients [Lipshultz et al., 2013, Kim etal., 2009].

4.6. This cross-sectional study might not predict the long term effect of iron overload; however, it gave us an insight to the problem of iron overload in children with leukaemia, which had a positive impact in our practice. We need a cohort study to evaluate other causative factors that might lead to iron overload, the effect of iron overload on major body organs such as the heart and the liver, and whether chelating therapy can increase the quality of life or improves survival [Rascon et al., 2014].

5. CONCLUSION

5.1. Children with leukaemia can develop iron overload due to necessary multiple blood transfusions received during their long term chemotherapy treatment that needs to be investigated further and possibly treated. We still need to study the effect of iron overload on survival, and whether treatment can have a role in the overall survival perhaps in a larger prospective study.

Declaration of interest:

The authors have nothing to disclose

6. REFERENCES

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7. Appendix

Sex	
Male	29
Females	21
Nationality	
Kuwaiti	28
Non Kuwaiti	22
Age groups	
≤ 5 years	21
6-11 years	19
12-16	10
Total	50

Figure 7.1: Patients' demographic data

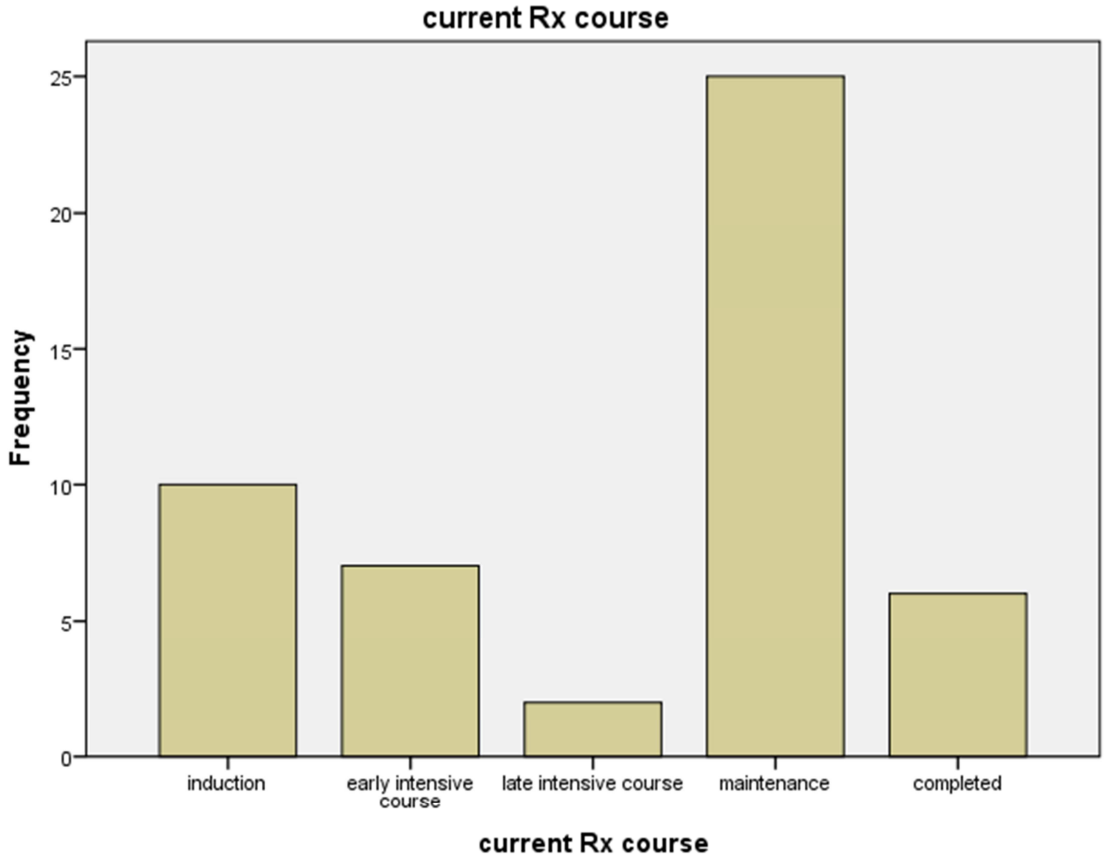

Figure 7.2: The stage of treatment of patients during sampling for serum ferritin in this study

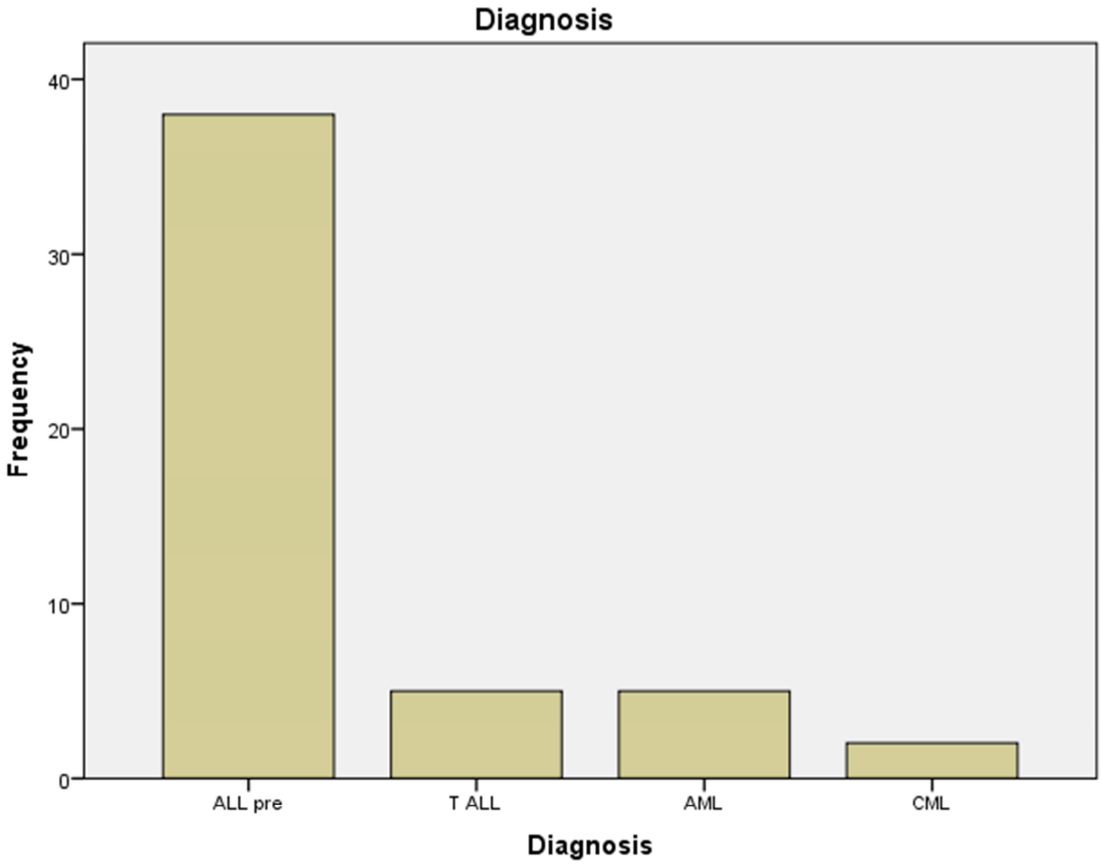

Figure 7.3: The frequencies of different types of childhood leukemia in this study

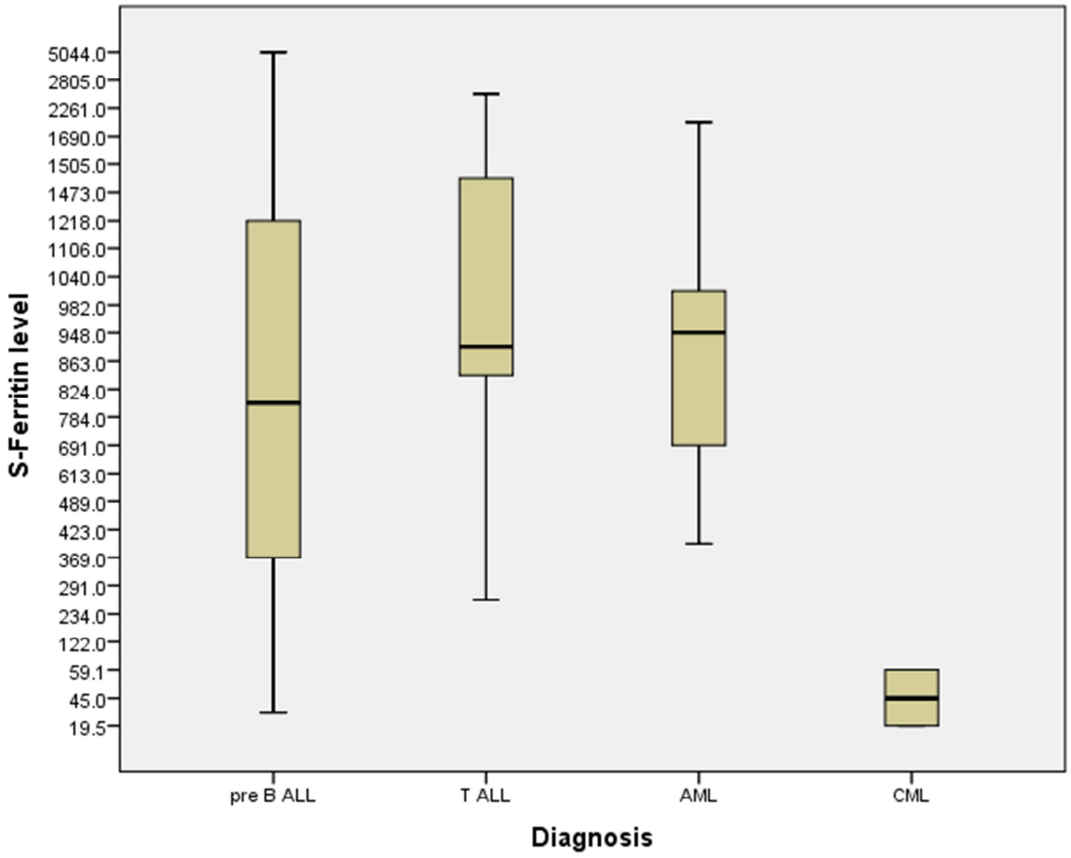

Figure 7.4: Illustrates the diagnosis of leukemia and serum ferritin level for all patients in this study

Chemotherapy stage	Total number of patients	S-ferritin level in µg/l	Number of patient	% of patients
Induction	9	>400	8/9	89%
		>1000	6/9	67%
Intensive chemotherapy	9	>400	8/9	89%
		>1000	6/9	67%
Maintenance	25	>400	18/25	72%
		>1000	8/25	32%
Completion	7	>400	4/7	57%
		>1000	2/7	28%

Figure 7.5: This table summarize the stage of chemotherapy treatment of the patients and their of serum ferritin levels.

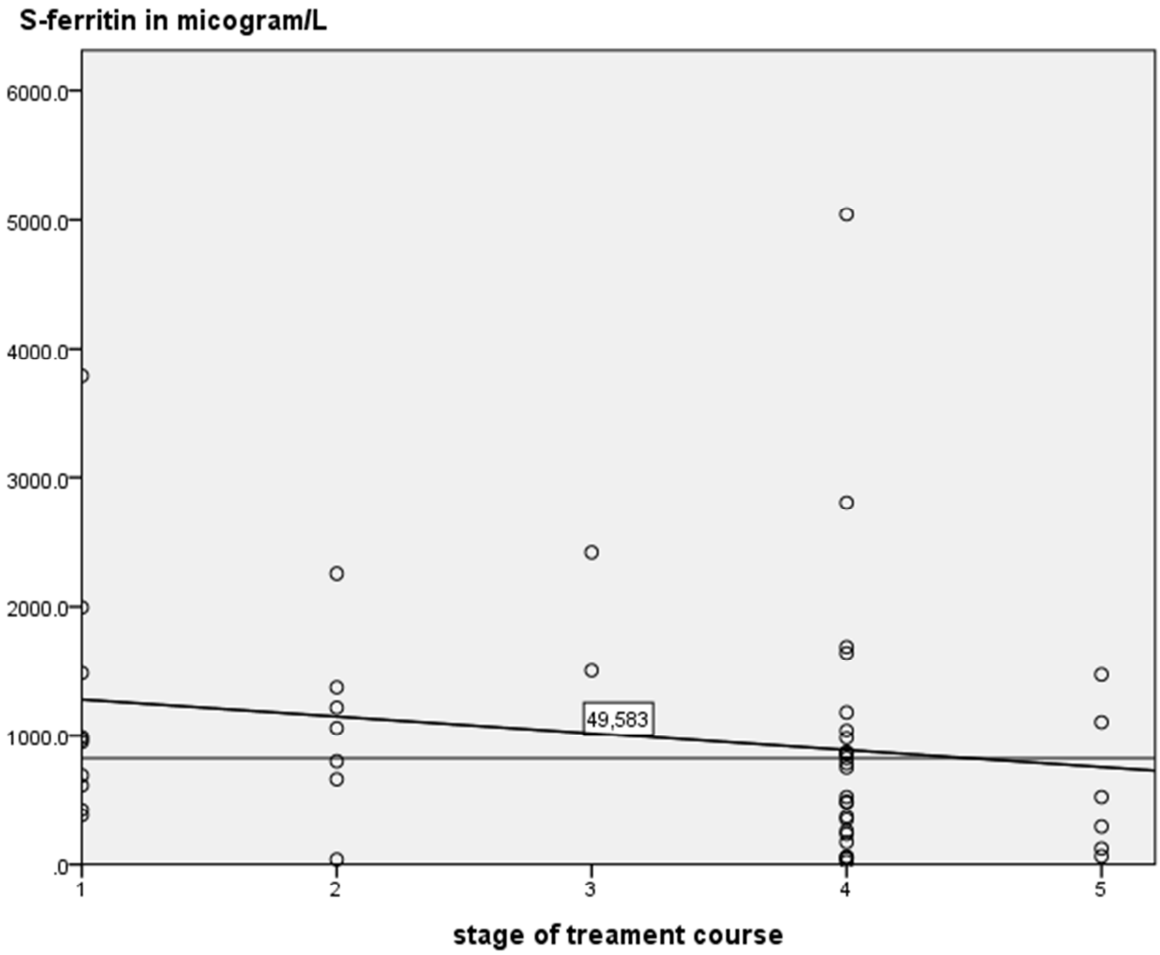

Figure 7.6 : Serum iron level and the stage of disease. The stage of disease as follows: 1=Induction, 2=Early intensification, 3= Late intensification 4=Maintenance 5= Completed chemotherapy

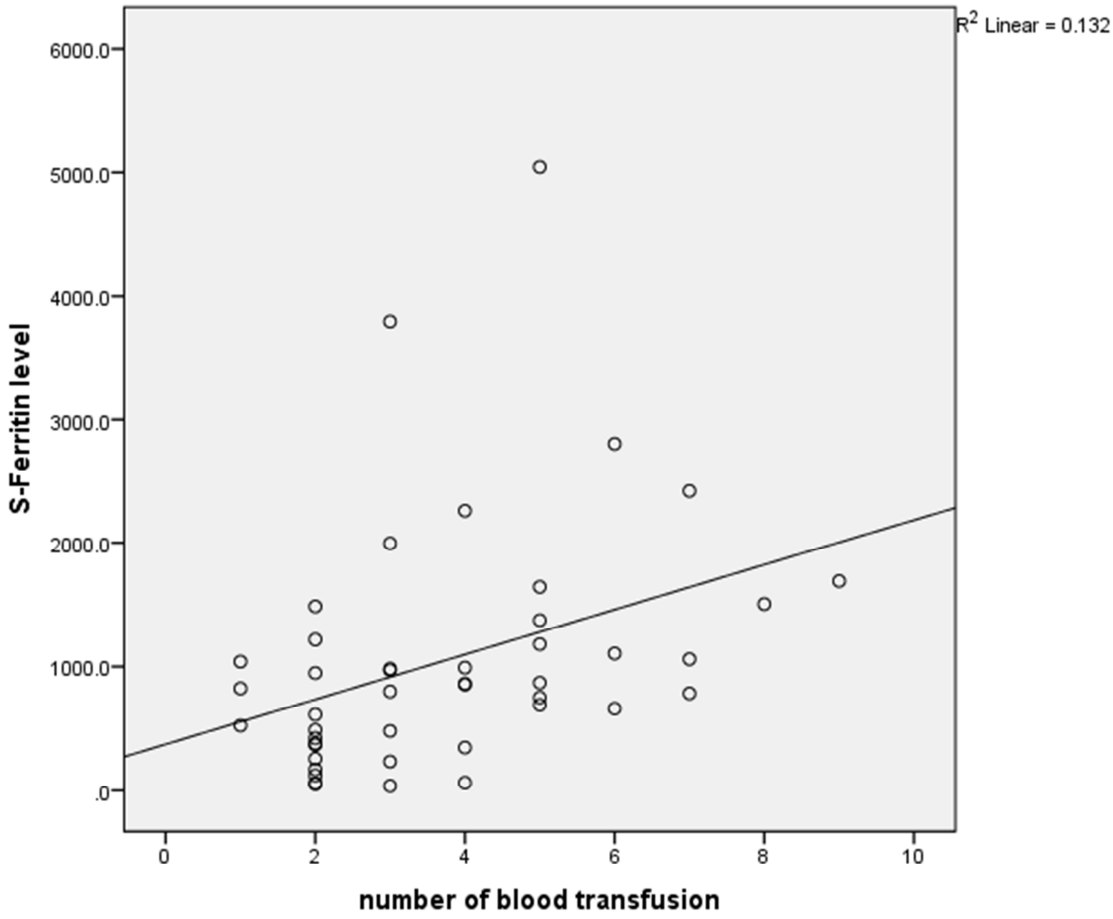

Figure 7.7: The number of blood transfusions and serum Ferritin level