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Research Paper

Assessment of the Relationship between Plasma Ferritin Levels and Quality Of Life among Patients with Haematological Cancers in Abuja Nigeria.

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ABSTRACT: *The treatment of haematological cancers involves both definitive and supportive therapies. Blood transfusion is unarguably the most important component of the supportive therapy. However, unregulated blood transfusions can lead to iron overload and its attendant end organ destruction. Elevated ferritin levels have been linked to worsening clinical conditions in cancer patients by several mechanisms including but not limited to increased proliferation, angiogenesis, therapy resistance and immunosuppression.*
*Blood transfusion may therefore have a deleterious effect in patients with haematological cancers and as such, the relationship between plasma ferritin levels and quality of life among these patientsin Abuja Nigeria was assessed.**Method:** Eighty-eight (88) adult patients with haematological cancers were enrolled and the number of units of blood transfused in the course of their treatment recorded. The plasma ferritin and highly sensitive C reactive protein (HSCRP) of the patients werealso determined using an electrochemilunescence based assay. The quality of life (QOL) was calculated using the Functional Assessment in Cancer Therapy General 7 version 4 (FACT G7 ver 4) health related quality of life assessment scale. The relationship between the number of units of blood transfused and plasma ferritin levels was determined using the Spearman Rho correlation coefficient while the relationship between plasma ferritin levels of the patients and their QOL was determined using Pearson's correlation coefficient.**Result**: 68.2% of patients with haematological cancers received blood transfusion in the course of their treatment, while 15.9% of the transfused patients had more than 10 units of blood transfused. The mean plasma ferritin level of the transfused patients' population was 1062.82 ng/ml while the mean QOL score was 18.32. The patients with chronic myeloid leukaemia (CML) have the highest QOL score of 22.1 and those with acute lymphoid leukaemia (ALL) have the lowest QOL score of 12.3 on a 28-point scale. There is a positive correlation between the number of units of blood transfused and plasma ferritin levels ($r = 0.773$, $p<0.001$) and a negative correlation between plasma ferritin levels and quality of life (QOL) ($r = -0.435$; $p < 0.001$).*
***CONCLUSION**: This study found an inverse relationship between plasma ferritin levels and QOL in multiply transfused patients with haematological cancers. Thus, increase in the units of blood transfused and plasma ferritin level inadvertently leads to decreased quality of life (QOL) in haematological cancer patients.The rational use of blood transfusion in the management of haematological malignancies and periodic assessment of their QOL to ensure better QOL are recommended.*
KEYWORDS: *Blood transfusion, ferritin, HSCRP, quality of life, haematological cancers*

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I. INTRODUCTION

Anaemia is the commonest complication of haematological cancers and blood transfusion is the major supportive therapy in the management of haematological cancers despite all the advances aimed at reducing blood use[1]. Even in solid tumours, about 15% of the patients would require blood transfusion despite the use of erythropoietin[2]. One of the major complications of blood transfusions is iron overload with its associated organ deposition and eventual destruction. Ferritin despite being an acute phase reactant is also used as a marker of iron overload and studies have shown a linear relationship between ferritin levels and blood transfusion[3,4]. Ferritin levels are increased in cancer patients either as a result of increased blood transfusion or in response to background inflammation in cancer.

Ferritin has also been implicated in aiding cancer progression. The interpretation of serum ferritin levels is with caution as some factors such as inflammation increases the level of ferritin in the serum due to the fact that ferritin itself is an acute phase reactant[5,6] Some researchers recommend that serum ferritin greater than 1000µg/L requires further evaluation by haematologist even in the presence of elevated C-reactive proteins[7].

The possible role of ferritin in tumourigenesis has been demonstrated in earlier studies using cell cultures. Buss *et al* has clearly stated in a 2003 review article that deferoxamine has anti-tumour activity on cell cultures thereby establishing that ferritin has a role in cancer initiation and progression and well as the synergistic effect of iron chelators in cancer therapy[8].

In hematologic cancers, serum ferritin levels have shown a positive correlation in detection of disease progression and remission. Fukushima *et al* showed that by reducing the serum ferritin levels by iron chelation, refractory acute leukaemia patientsachieved complete remission thereafter[9]. Serum ferritin levels can also predict prognosis even in pre chemotherapy and chemotherapeutic phases[10–12]. In bone marrow transplantation, serum ferritin levels have become a major prognostic factor in transplanted patients irrespective of individual disease risk.[13]The pathway of ferritin associated cancer progression is not completely clear but several theories have been proposed such as the anti-apoptotic effect of ferritin in cancer cells[14]. It was also proposed that ferritin supplies its iron to the tumour cells and tumour microenvironment for growth of the cancer cells via a non-transferring pathway. The lipocalin-2 and siderophores have been shown to be involved in this non transferring associated transport of iron to tumour cells via a programming effect from the tumour cells to the macrophages[15].

The assessment of health-related quality of life (HRQOL) in cancer patients has been an object of intense research in recent years. It has become a more accurate predictor of survival and clinical outcomes than other parameters such as the performance status[16]. The WHO quality of life group defined it as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns[17]. HRQOL covers the subjective perceptions of the positive and negative aspects of cancer patients' symptoms, including physical, emotional, social, and cognitive functions and, importantly, disease symptoms and side effects of treatment. The FACT-G is a HRQOL assessment questionnaire developed by Cella *et al* in USA and has been used in several cancer studies[18–20]. The FACT-G7 is a rapid version of FACT-G in assessing HRQOL in cancer patients and can be used even in outpatient

consultations. It is a 7-item questionnaire derived from FACT-G version 4 consisting of 3-item from physical wellbeing of (fatigue, pain and nausea), 3-item from the functional well-being (enjoyment of life, contentment with QOL, and sleep) and 1-item from emotional well-being (worry about condition worsening).[21] The FACT-G7 has been validated in several studies in cancer patients[21–23].

II. MATERIALS AND METHOD

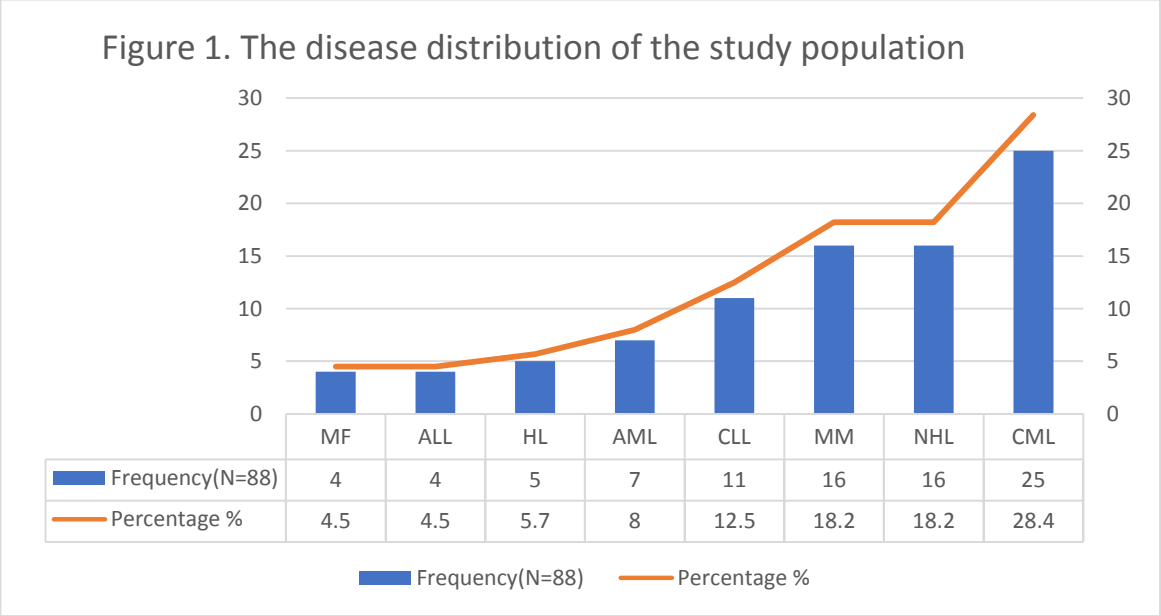
This is a hospital based cross-sectional study conducted at the University of Abuja Teaching Hospital and National Hospital Abuja, Nigeria. These are the two major tertiary health facilities offering cancer care in the Abuja metropolis. They are the major referral centres for the federal capital territory and the adjoining Nasarawa, Minna, Kogi, Benue, and Kaduna states

Eighty-eight (88) consenting haematological cancer patients that meet the inclusion criteria and assessing care in any of the facilities mentioned above were recruited. Blood sample was obtained from each patient for determination of their plasma ferritin and highly sensitive C-reactive protein levels using a chemiluminescence based assay. A well-structured questionnaire was administered to the patients to obtain biodata and blood transfusion history.The quality of life (QOL) of the study group was assessed using the functional assessment in cancer therapy-general 7 version 4 (FACT-G7 Ver 4) assessment questionnaires.

Data was analysed using computer software, statistical package for social sciences (SPSS) version 18. Descriptive statistics such as mean, frequency, standard deviation and percentages were expressed in tables and graphs. Pearson's and Spearman rho correlation coefficients were used to test for relationships among the various variables. The value for statistical significance was set at p value <0.05. Ethical approval for the study was obtained from the Research Ethical Committees of the University of Abuja Teaching Hospital and National Hospital Abuja prior to commencement of study.

III. RESULTS

Eighty-eight (88) patients diagnosed with haematological cancers were enrolled in the study, 38 (43%) were females and 50 (57%) were males. The mean ± SD age of the study population is 46.8 ± 15.2 years with a median age of 47 years. The youngest and oldest being 17and 76 years respectively. Among the haematological cancers studied, CML was the highest 25 (28.4%) in occurrence while ALL and MF were the lowest 4 (4.5%). The distribution of the haematological cancers in the study population is summarised in *figure 1*.



The distribution of the Plasma ferritin and inflammation status among the study population are summarised in *table 1*. The mean plasma ferritin level of the study group is 1062.98 ± 988.57 ng/ml. The inflammation status as measured by serum levels of HSCRP are shown in *table 1*.with a mean value of 29.54 ± 28.46 mg/L.

Table 1. The distribution of plasma ferritin and HSCRP of the study population

FERRITIN (ng/ml)	HSCRP (mg/L)	
Mean	1062.98	29.54
Median	613.50	20.42
Mode	3112.00	1.46
Std. deviation	988.57	28.46

The transfusion status of the study population showed that 60 (68.2%) of the patients were transfused in the course of their treatment while 28 (31.8%) never had transfusion. Also, among the transfused patients, 28.4%, 23.9% and 15.9% of the patients had 1-4units, 5-9units and >10 units of blood transfusion respectively. This transfusion status is summarised in *table 2*

Table 2. The transfusion status of the study population.

Transfusion status	Frequency(N=88)	Percent (%)
Yes	60	68.2
No	28	31.8

Transfusion units	Frequency(N=60)	Percent (%)
1-4	25	28.4
5-9	21	23.9
≥10	14	15.9

The relationships between blood transfusion units, plasma ferritin and HSCRP are summarised in *table 3*. There is a positive correlation between HSCRP and plasma ferritin levels (r = 0.480, p<0.001) using Pearson's correlation coefficient. There is also a positive

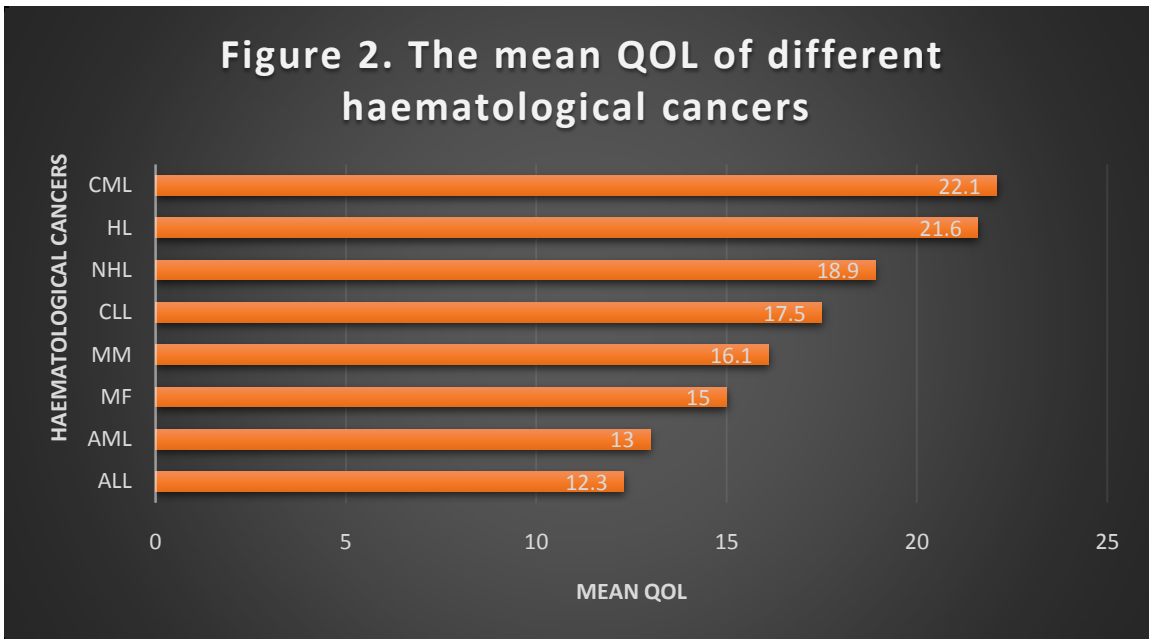
correlation between blood transfusion units and plasma ferritin levels (r = 0.773, p<0.001) using Spearman rho correlation coefficient.

Table 3. The relationships between plasma ferritin levels, blood transfusion units and inflammation.

Relationship	r	P-value
Inflammation - Plasma ferritin levels	0.480	<0.001*
Units of blood transfused - Plasma ferritin levels	0.773	<0.001*

r = Correlation coefficient *significant at 0.05

The distribution of the QOL scores amongst the different haematological malignancies shows that patients with CML and HL has higher QOL scores while the ones with ALL and AML has lower scores, (see *figure 2*).The mean score of QOL is 18.32 ± 6.25 on a 28-point score.



The relationship between plasma ferritin levels and QOL is illustrated in *table 4.* Using Pearson's correlation coefficient, there is a negative correlation between plasma ferritin and QOL (r = -0.435, p < 0.001)

Table 4. The relationship between plasma ferritin levels and QOL

Relationship	r	P-value
Quality of Life - Plasma ferritin levels	-0.435	<0.001

r = Correlation coefficient *significant at 0.05

IV. DISCUSSIONS.

The sociodemographic distribution of the study subjects is in agreement with some African studies on hematologic malignancies[24–26]. The mean age of the study population is 46.8 ± 15.2 years and is similar to the work of Rafeno *et al* in Madagascar, Quedrogo *et al* in

Burkina Faso and Errahhali *et al* in Morocco in whom the mean ages were 49.4 ± 15.5, 42 ± 19.7 and 54 years respectively[24,25,27]. The median age of the study population is 47 years (age range from 17 to 76 years) and is similar to Rafeno *et al* (54 years) but differs from that of Kagu et al in North east Nigeria (22.5 years) due to inclusion of paediatric population (age range from 2 to 80 years) in his study[24,26].

The mean ± SD of plasma ferritin in our study was 1062.98 ± 988.57 ng/ml which is about three times higher than the upper reference limit for ferritin (300ng/ml in women and 400ng/ml in men). The plasma ferritin in our study is higher than that of Xue–Zhong Zhang *et al* among patients with haematological malignancies (782.9 ± 268.8 ng/ml) in the Asian population[28]. Oluboyede *et al* in their study using healthy male and female Nigerian population recorded a comparably low ferritin level (72.4ng/ml in males versus 34.3ng/ml in females)[29]. This increased plasma ferritin level in our study population could be as a result of a combination of background inflammation and increased blood transfusion, but being that plasma ferritin concentration ≥ 1000 ng/ml cannot be wholly explained by inflammation alone, therefore the increased plasma ferritin concentration in this study could be attributed mainly to increased blood transfusions[30].

The HSCRP can detect minimal variations in serum CRP levels even in the range of normal limits and is thus a marker of low grade systemic inflammations[31]. The high mean HSCRP level in the study population (mean ± SD = 29.54 ±28.46mg/L) is comparable to values recorded by Kostiala *et al* (23mg/L) among patients with haematological malignancies[32]. These levels show that there is presence of background systemic inflammation in the patient population.

The relationship between inflammation (HSCRP) and plasma ferritin levels using Pearson's correlation coefficient demonstrated a positive correlation ($r = 0.48$; $p < 0.001$) and is comparable to the work of DePalma *et al* ($r = 0.12$; $p < 0.04$) and Khan *et al* ($r=0.87$' $p < 0.001$)[33,34]. However, the relationship between the units of blood transfused and plasma ferritin using Spearman rho correlation coefficient shows a very strong positive linear relationship that is statistically significant. This is comparable also to the work of Leonard *et al*, ($r = 0.773$; $p < 0.001$ versus $r = 0.740$; $p = 0.001$)[4].

The quality of life (QOL) in the study population using the FACT-G7 assessment scale shows a mean score 18.32, with CML and ALL having the highest and lowest scores (22.1 versus 12.3) respectively. Since higher scores means better quality of life, this therefore means that patients with CML have overall better QOL than patients with ALL[21]. The reason could be that since patients with ALL and AML have more aggressive disease than CML, HL and NHL, then, ALL and AML patients are likely to have more blood transfusions leading to increased ferritin and decreased QOL. Üstündağ *et al* in their study among cancer patients also demonstrated that cancer types significantly affect the quality of life and this is in agreement with the findings in this work[36]

There is also a negative correlation between the plasma ferritin level and QOL ($r = -0.435$; $p < 0.001$). This therefore means that increase in plasma ferritin is associated with reduced QOL, hence an inverse relationship. Since HRQOL is a subjective assessment of the patient's functional, physical and emotional well-being, the moderate association between QOL and plasma ferritin may be attributed to the patient's emotional state of mind of being a cancer patient especially in our environment where treatment for cancer is still rudimentary with high mortality.

V. CONCLUSION

In conclusion, this study has demonstrated an inverse relationship between plasma ferritin and quality of life in haematological cancer patients and therefore effort should be

geared towards appropriate use of blood and blood products in our patients as well as regular iron profiling and iron chelation where necessary. This has become necessary as blood transfusion continues to be at the core of supportive therapies in haematological cancer management.

LIMITATIONS OF STUDY

Responses to specific questions on quality of life was interfered by religious views and faith of the responders especially the question on emotional well-being (GE6). There is no version of the FACT-G7 ver 4 in any local Nigerian language to be able to succinctly convey the meaning of certain questions in the sub-scale.The cancer patients with liver disease were not excluded as liver disease may cause elevation of plasma ferritin.

AUTHORS CONTRIBUTIONS

All the authors participated in the research. **U.G. Ejikeme** conceptualised and designed the study, involved in data collection, analysis and manuscript writing. **T.I. Otu, T.T. Wakama** and O.P. Ogbe involved in study design and manuscript writing. **E.I. David** involved in study design, data analysis and manuscript writing.

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