

# Impact and Association of Anaemia Severity and Its Treatment With Quality of Life of Breast Cancer Patients in Malaysia

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## Research Article

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# Abstract

**Purpose** This study aimed to assess the level of anaemia severity, evaluate the current treatment practice of anaemia, and to determine the association between anaemia level and its management on quality of life of breast cancer patients in Malaysia.

**Methods** A prospective study design was conducted among breast cancer patients in multicancer centers in Malaysia including three follow ups. Clinical data were collected from their medical records and at each follow up, they were required to fill in a functional assessment chronic therapy (FACT-An) questionnaire. Descriptive and inferential statistical analysis were done using SPSS.

**Results** Out of 120 participants, 32% received anaemia treatment. Out of 32% who received anti-anaemic medication, the majority of patients (87%) were prescribed with iron supplementation and only 13% received combination of blood transfusion and iron therapy and no one received erythropoietin stimulating agents (ESAs). Findings reported that the curve of the mean of QOL score and Hb level significantly declined across the three follow-ups ( $p < 0.005$ ). Statistical tests also indicated a significant association between anti-anaemic treatments with haemoglobin level and QOL scores. However, this association was insufficient to significantly improve QOL or palliate anaemia severity among participants.

**Conclusion** There is still a lot of gaps to improve in the management of anaemia among breast cancer patients to show a significant improvement in haemoglobin level. Therefore, respective organisations and oncologists are required to raise awareness about the optimal treatment of anaemia among breast cancer patients, as a result, improve general wellbeing of them.

## Introduction

Breast cancer is the most prevalent form of cancer among females globally (1). It is the second most common cancer among Malaysian women, accounting for approximately 31% of total cancer case (2). It has been found that breast cancer patients suffering from various medical issues either due to cancer itself, anti-neoplastic chemotherapy, or both. One of the major side effects is anaemia. Anaemia is common in cancer, its incidence ranging from 63% (3) to 83% (4) amongst solid cancer patients. Incidence of anaemia in cancer patients was reported to be 41% before receiving chemotherapy but increased to 43.1% upon anti-neoplastic therapy (5). Increased incidence of anaemia among cancer patients will negatively impact both patients QOL (6), worsening the progression of disease and affect anti-cancer treatments (7). This can significantly reduce their survival rate, specifically among those treated with chemotherapy (8-12). HRQOL is defined as a multi-dimensional aspect that could be used as a prognostic indicator for treatment of breast cancer patients and for survival (13 ;14). Montazeri A (15) suggested in his review article that information and data provided by cancer patients via QOL assessments, is very helpful for clinical decision-making and better patient treatment. Therefore, evaluating anemia treatment and its impact on cancer patients QOL found to be an essential matter.

Bohlius et al., (16) & Hassan BA et al., (17) revealed in their studies the importance of evaluation of management of anemia in cancer patients. This is due to the fact that evaluation and treatment of anemia will significantly increase the response to antineoplastic *therapy*, improve QOL, increase survival and improve clinical outcomes (18). A large number of studies demonstrated and recommended the use of erythropoiesis-stimulating agents (ESAs) in treatment of anemia among cancer patients (19). ESAs will significantly increase hemoglobin levels, reduce the need of blood transfusion requirements, and improve quality of life, (19 ;18). However, there is still limited number of studies that have focused mainly on evaluating the management of anameia among breast cancer patients, and its relation to patients' quality of life. Hence, the current study aimed to detect and evaluate treatment given to breast cancer patient suffering from anaemia and to determine its impact on cancer patients QOL.

## **Patients And Methods**

### **Study design and setting**

This is a prospective, observational, and longitudinal design among breast cancer patients in multi-cancer centres in Malaysia which are Hospital Kuala Lumpur (HKL), University Malaya Medical Centre (UMMC), and Institute Kanser Negara (IKN), Putrajaya, Malaysia. The present study conducted for 8 months starting from July 2019 to February 2020. The study enrolled 120 anaemic breast cancer patients who fulfilled stipulated inclusion criteria.

Anaemic breast cancer patients identified based on blood analysis results i.e., haemoglobin level in their medical files. Inclusion criteria stipulated were patients aged 18 and above, Hb  $\leq$  12 g/dL, diagnosed with breast cancer regardless of stage, currently receiving chemotherapy and able to understand as well as sign the informed consent. While the exclusion criteria stipulated were patients with haematological, inherited disease, pancreatitis or dementia. Besides that, those receiving different management procedure such as radiotherapy, biological therapy or endocrine therapy and those at their first cycle of chemotherapy, were also excluded from the study.

### **Research instrument and data collection procedure**

Upon identification, the specific patient was approached to participate in the study. The patient was then briefed regarding the purpose of the study. Upon agreeing, a consent form was provided to be signed. Subsequently, patients were provided with the Functional Assessment of Cancer Therapy- Anaemia (FACT-An) questionnaire according to patient's language preference (i.e. Bahasa Melayu or English version) to measure QOL. Permission to use the research instruments (both English and Bahasa Melayu version) was obtained from the developers and validated accordingly. The questionnaire took 10-15 minutes to complete, and patients were followed-up for the next two cycles of chemotherapy (total three cycles). Besides that, Hb levels were measured prior to each cycle. In addition, demographic, clinical, and anaemia treatments data, were collected from patients' medical records.

### **Data Analysis**

Data was analysed via SPSS Version 25. Estimated mean scores and 95% confidence intervals were calculated for QOL score and Hb levels, evaluated based on all three follow ups. Difference in mean scores for all three follow ups was observed and findings were expressed as mean and standard deviation (SD). Computation of results were done in accordance with FACT-G group guidelines. Chi-Square and multiple logistic regression analysis were performed to determine relationship between anaemia severity and anti-anaemic treatment. In addition, one-way repeated measured MANOVA was performed to identify relationship between anti-anaemic medications and both dependent variables (QOL and Hb levels) along the three subsequent follow ups. To overcome problems related to data mining, post hoc analysis was conducted using Bonferroni adjustments to identify differences between each cycle. Significance level was set at  $p < 0.05$  for all analyses.

## Results

From the 120 respondents, majority were elderly ( $n=89$ ; 74.2%) with mean age of 52.63 ( $\pm$  SD 11.26), Malay ( $n = 77$ ; 64.2%), married ( $n=108$ ; 90%), and postmenopausal ( $n=87$ ; 72.5%). Only 39 (32.5%) patients received anti-anaemic management. Out of the 39 patients who received anaemia treatment, about 87% of the patients were treated with only iron supplements while 13% received iron products and underwent blood transfusion. None of the patients received Erythropoiesis-stimulating agents (ESAs), the main form of management for cancer-related anaemia. Furthermore, more than two third of the anaemic patients ( $n = 81$ , 67.5%) were not treated for anaemia. Additional clinical and demographic data are shown in Table 1.

**Table 1 Demographic data in Breast Cancer Patients undergoing Chemotherapy (N= 120)**

Variable		N (%)
Mean age		52.63 (SD 11.27)
Age	≥ 60	89 (74.2%)
	< 60	31 (25.8%)
Race	Malay	77 (64.2%)
	Indian	14 (11.7%)
	Chinese	27 (22.5)
	Others	2 (1.7%)
Marital status	Married	108 (90%)
	Single	8 (6.7%)
	Divorced	4 (3.3%)
Stage of Breast Cancer	Stage I	5 (4.2%)
	Stage II	29 (24.2 %)
	Stage III	62 (51.7 %)
	Stage IV	24 (20 %)
Anti-anaemic medications	Treated	33 (27.5%)
	Un treated	81 (67.5%)
	Un detected	6 (5%)
Type of anti-anaemic treatment	Iron Supplementation	34 (87.2%)
	Blood transfusion	2 (5.1%)
	Mixed	3 (7.7%)
	ESAs	0 (0%)

**Treated = All patients received anti-anaemic treatment , Un-treated = Patients who did receive any type of anti-anaemic medication ,Un detected = Patients who received anti-anaemic medication either at 1<sup>st</sup> or 2<sup>nd</sup> or 3<sup>rd</sup> interviews . ESAs = Erythropoietin Stimulating Agents . Mixed = iron therapy + blood transfusion**

**Haemoglobin Levels & QOL across Three Consecutive Follow ups**

Average mean and standard deviation for Hb levels was  $10.34 \pm 0.73$  (mean  $\pm$  SD). The mean of Hb for patients for the first follow-up was  $10.64 \pm 0.85$ ,  $10.26 \pm 0.85$  for the second follow-up, and  $10.13 \pm 0.83$  g/dL for the third follow-up. Results reveal a decline in Hb levels across the three follow ups (i.e., increased anaemia severity across the three follow ups). Average mean and SD for overall quality of life (QOL) was  $96.38 \pm 16.15$ . Mean for QOL at first follow-up ( $108.96 \pm 20.94$ ) was higher than mean for QOL at second follow-up ( $95.11 \pm 17.58$ ). Mean for third follow-up was the lowest ( $85.06 \pm 25.88$ ) signifying a drop in QOL among anaemic cancer patients along the three follow ups as shown in Table 2.

**Table 2: Mean of Hb level (severity of anaemia) and QOL in Breast Cancer Patients (N= 120)**

Hb g/dL		(Mean $\pm$ SD)
Total Average Hb		$10.34 \pm 0.73$
Hb g / dL	Mild (10-12) g/dL	78 (65%)
	Moderate (8-10) g/dL	41 (3.7%)
	Severe (6-8) g/dL	1 (0.83%)
<b>QOL Total (0-188)</b>		$96.38 \pm 16.15$
QOL FACT-An	1 <sup>st</sup> Follow up (0-188)	$108.96 \pm 20.94$
	2 <sup>nd</sup> Follow up (0-188)	$95.11 \pm 17.58$
	3 <sup>rd</sup> Follow up (0-188)	$85.06 \pm 25.88$

<sup>a</sup>Hb – Hemoglobin

### Relationship between anaemia severity with anti-anaemic treatments

A logistic regression test indicated the strength of association between patients treated with iron supplementation and anaemia severity among breast cancer patients. Though the odd ratio value was high (4.2), the relationship remained negative ( $b = -1.435$ ). Hence signifying that the use of iron supplements will not improve or palliate severity of anaemia among cancer patients (Table 3).

Table 3 Relationship between anaemia Severity and Types of anti-anaemic Treatment

Variable	Total Anaemia Severity				
	b	OR	CI (95%)	P value	
<b>No Medication Recorded</b>	Reference				
Iron supplements	-1.435	4.2	1.77	9.9	0.001
Blood transfusion	22.45	15.2	.001	0.005	0.99
Mixed <sup>x</sup>	22.45	15.2	.001	0.005	0.99

<sup>x</sup> compared to no medication detected

Mixed <sup>x</sup> = Iron therapy + Blood Transfusion

OR = Odd Ratio

### Evaluation of the mean of Hb Levels and QOL along three follow-ups

One-way repeated-measured ANOVA determined that the mean of QOL scores and Hb levels differed significantly across three follow-ups ( $F[1.30, 154.79] = 54.49, p < .001$ ) for QOL score and ( $F[1.7, 207.3] = 30.83$ ) for Hb levels. A post-hoc pairwise comparison using the Bonferroni correction showed a statistically significant decrease in the mean QOL score and Hb level between the first follow-up and second follow-up (108.96 vs 95.11,  $p < 0.001$ ) for QOL and (10.64 vs 10.23,  $p < 0.001$ ) for Hb level, and statistically significant decline in QOL in the third follow-up when compared to the second follow-up (95.11 vs 85.06,  $p = 0.000$  for QOL and 10.26 vs 10.13,  $p = 0.000$  for Hb level). In addition, results showed that the curve of the mean of QOL score and Hb level significantly declined across the three follow-ups (108.96, 95.108, and 85.058), with  $p = < 0.001$  for QOL scores and (10.64, 10.26, and 10.13)  $p = < 0.001$  for the Hb level (Figure 1 and 2).

### Association between Anaemia Treatment and Hb Level & QOL

One way repeated measured MANOVA was used to determine if there was any significant effect between (anti-anaemia treatments) as independent variable and Hb and QOL as dependent variables at three follow ups. There was a statistically significant difference in Hb levels and QOL scores based on anti-anaemic medications,  $F(12.224) = 2.138, p = 0.016$ ; Wilks Lambda = 0.805,  $\eta^2 = 0.103$  (table 4).

### Table 4 : Mean of Anaemia Treatment Across Three Follow Ups

Multivariate Tests					
Variables	Wilks' Lambda	F	df	Sig	$\eta^2$
Anaemia management	0.805	2.138	12,22	0.016	0.103

$\eta^2$ = partial Eta square

Univariate analysis between anti-anaemic treatment and both Hb levels and QOL scores across the three follow ups indicated a significant association between anti-anaemic treatment with Hb levels across three follow ups and QOL scores at 1<sup>st</sup> and 2<sup>nd</sup> follow ups .While no association at 3<sup>rd</sup> follow ups as shown in table 5.

Table 5: Association between anti-anaemic medications and Hb level + QOL at 3 follow ups

Variables	F(df)	F	Sig	$\eta^2$	
Anti-anemic treatment	Hb 1 <sup>st</sup> Follow up	2.117	6.8	0.002	0.10
	Hb 2 <sup>nd</sup> Follow up	12.4	<0.001	0.17	
	Hb 3 <sup>rd</sup> Follow up	3.9	0.023	0.06	
	QOL 1 <sup>st</sup> Follow up	3.4	0.036	0.05	
	QOL 2 <sup>nd</sup> Follow up	6.9	<0.001	0.10	
	QOL 3 <sup>rd</sup> Follow up	1.6	0.020	0.02	

$\eta^2$ = partial Eta square

## Discussion

This study is considered the first of its kind to evaluate the association between anaemia severity and its treatment with quality of life among breast cancer patients in Malaysia. It is proved that cancer-related anaemia (CRA) adversely affects quality of life (6, 20) and is associated with reduced overall survival (21). Correction of anaemia in cancer patients has the potential to improve treatment efficacy and increase survival (22). To the best of our knowledge, this is the first multi-center, prospective work in Malaysia evaluating anaemia treatment among breast cancer patients. Pourali L. (5) and colleagues

mentioned that prevalence and severity of anaemia among breast cancer patients in their advanced stages have been well documented, but the same cannot be said those amongst those in the earlier stages. Hence signifying the value of this study as it focuses on detection and evaluation of anti-anaemic treatment among breast patients across various stages (5). Imran M et al., (23) whom conducted a study amongst female breast cancer patients in Saudi Arabia to assess their QOL mentioned that there was a direct relationship between choice of treatments used for breast cancer patients, side effects, medical issues, and QOL.

Our data indicated that, the mean for haemoglobin level declined across the three follow ups. Meaning the number of patients who were suffering from moderate anaemia was increasing. This indicates that treatments used for treating and/or palliating anaemia within this study may not be enough to improve Hb levels. In line with these findings, Busti et al. (18) denotes that CRA treatment is only considered effective haemoglobin level improves significantly, specifically among those with mild and moderate anaemia. Moreover, Aapro et al. (24) in his study highlights that the main objectives for CRA treatment is to palliate and/or treat anaemia besides improving QOL among cancer patients with anaemia (24). However, results from this study shows otherwise.

Concerning anaemia treatment, our data showed that only 32.5% of our respondents received general anti-anaemic treatment (i.e., non-specific anti-anaemic treatment). A large majority did not receive any kind of anti-anaemic medications. Among those who received treatment, almost all received iron supplements (e.g., vit b-complex and multivitamins) while only two respondents were treated with blood transfusion. None were treated with Erythropoiesis-Stimulating Agents (ESAs). As per our data, the use of iron supplements did not improve haemoglobin level across the three follow ups. This finding is consistent with another study conducted in Ethiopia, where only 32% out of its total respondent were treated with supportive treatments - which include blood transfusion and iron supplements (25). Based on the suggestion and recommendation by Hassan BA et al., (17), the future studies should evaluate and improve the guideline used for treating anaemia among cancer patients. This suggestion stemmed from results of their prospective study, which was conducted in a cancer center in Penang, Malaysia. Their results found that treatment of anaemia among solid cancer patients was neither effective nor specific. Their efforts in evaluating treatment was one that is novel and crucial. In addition, Palasamudram and Kaiser, (26) in their study concluded that clinicians and oncologists need to evaluate the negative effects of anaemia towards cancer patients QOL and treat it accordingly. Moreover, Busti et al. (18) mentioned that it is important to determine incidence of anaemia among cancer patients and its impact on cancer patients QOL as it helps identify correct method of treatment (i.e. The right treatment method will significantly enhance QOL among cancer patients). Besides, evaluating and detecting proper treatment methods and guidelines for treating mild and/or moderate anaemia among cancer patients should be the foremost objective (18). This was precisely the focus of the current study. Bohlius et al. (16) also mentioned in their review article that the treatment guideline used for CRA, especially among cancer-patients suffering from non-curative and advanced cancers like breast cancer, need to be evaluated and updated. Besides, there is a need for evaluating the use of erythropoiesis-stimulating agents (ESAs)

among said form of cancer patients to highlight benefits and risks of using ESAs. (16). All of which supports the intent and crucially of the current study.

Statistically, our results showed a significant negative association between anaemia severity with type and pattern of anaemia treatment. This indicates that neither the type nor the pattern of anaemia treatment used was appropriate enough to palliate or solve the main problem i.e., anaemia. Moreover, results across the three follow ups further confirmed that anaemia treatment type and pattern did not improve both anaemia severity and QOL. Therefore, emphasising a need for rectification. Busti et al. (18) explains that iron therapy is only useful in enhancing efficacy of ESAs and reducing the need of blood transfusion. Iron therapy is not to be used as main protocol for treatment of anaemia, as it is in this setting. Busti et al. (18) also recommends that iron therapy should be replaced with ESAs for treatment of anaemia in cancer patients. Therefore, current study also recommends the use of ESAs to treat anaemia among Malaysian cancer patients. Effectiveness of ESAs in treating anaemia in comparison with oral iron has been substantiated by Busti et al. (18) in their study, which showed that the use of ESAs is far more superior than the use of oral and intravenous iron in treating anaemia among cancer patients (18; 27). A reliable indicator of effectiveness of anaemia treatment is the improvement haemoglobin (Hb) level. Specifically, 2g/dL within 4-8 weeks from treatment initiation. Otherwise, it is considered ineffective and must be modified accordingly. Hence strongly endorses findings from the current study.

In addition, we deem the current study to be highly worthy and bears great potential globally. It happens to be the first in Malaysia that has tried to determine the relationship between anaemia treatment and its impact on breast cancer patients QOL, evaluating (i.e. the effectiveness of anaemia treatment among breast cancer patients in palliating and/or reducing the negative impact of anaemia on their QOL). Moreover, Hassen et al. (28) highlights in his study the major and essential need to determine the proper treatment, so that it can significantly improve QOL among breast cancer patients receiving chemotherapy (28). Besides, evaluating the impact of anaemia among breast cancer patients on their QOL will significantly help the clinicians to determine several positive outcomes (28). Direct interviews assessing QOL were found to be highly advantageous in guiding healthcare professionals to attain a clear idea about the patient's QOL, to evaluate patient's medical situation and to tailor treatment accordingly so as to avoid medical problem that may negatively affect patient's QOL (29; 30). Barnadas et al. (31) denotes the necessity to understand impact of cancer disease-associated complications such as anaemia among others, as well as palliative care treatments towards breast cancer patients QOL. Moreover, Chen et al. (32) mentions that studies focused on detecting QOL among women suffering from breast cancer is the cornerstone for evaluating clinical situation, clinical decision making as well as health policy or reimbursement decisions. Though these may be currently obscure, it strongly advocates the importance and novelty of this study.

Overall, there are two key takeaways based on our findings from the MANOVA analysis. The first being anaemia treatments did not significantly improve Hb levels and QOL scores. Even if there were some significant association between anaemia treatments with anaemia severity and/or QOL, there were no improvements of the dependent variables (Hb and QOL) across the three follow ups.

Secondly, anaemia treatment (i.e., the entire treatment plan) must be replaced with a proper treatment guideline designed specifically to treat anaemia among cancer patients in Malaysia. The reason being though significant associations were found among anti-anaemic treatment used with anaemia severity and QOL, the effect of the treatment remains weak. Meaning it neither improved anaemia severity nor patients QOL, as indicated by low value of partial Eta squared in accordance to guideline by Cohen, Miles and Shevlin (33) (i.e.  $\eta^2 = 0.01$  weak,  $\eta^2 = 0.06$  moderate,  $\eta^2 = 0.14$  strong) .

## Conclusion

Findings from this study found that anaemia treatments used among anaemic breast cancer patients were ineffective enough to palliate anaemia severity or improve quality of life. Therefore, there is an urgent need to improve anaemia treatment guideline for effective management of anaemia as well as to improve QOL among breast cancer patients. There is a need to use strategies that will unfetter the QOL of cancer patients so that they will have a better sense of control over their illness and treatment.

## Declarations

**Funding:** The authors declare that there was no funding for this work.

**Conflicts of interest/Competing interests:** The authors have declared no conflicts of interest for this article.

**Availability of data and material:** Data and materials are available upon request.

**Code availability:** N\A

**Authors' contributions:** B.A.R.H. designed the study and F.M.S.M. conducted, analysed data, and drafted the study. M.K. also analysed data and proofread the study. A.H.M. and M.K. reviewed and edited the drafted study. All Authors stated that they had complete access to the study data that support the publication.

**Ethics approval:** All the aspects and protocols of this study were reviewed and approved by Clinical Research Centre (CRC) of UiTM ( REC/392/19), HKL (HCRC.IIR-2019-07-163), IKN (IKN/500-5/1/25 Jld 4 (18), UMMC & Medical Research Ethical Centre (MREC) (NMRR -18-3902-45218). Researcher adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines.

**Consent to participate:** Participants were briefed about the purpose of the study, and their consent was taken prior to be involved in the study.

**Consent for publication:** Participants and respective ethics committee are aware that findings of this study are going to be published.

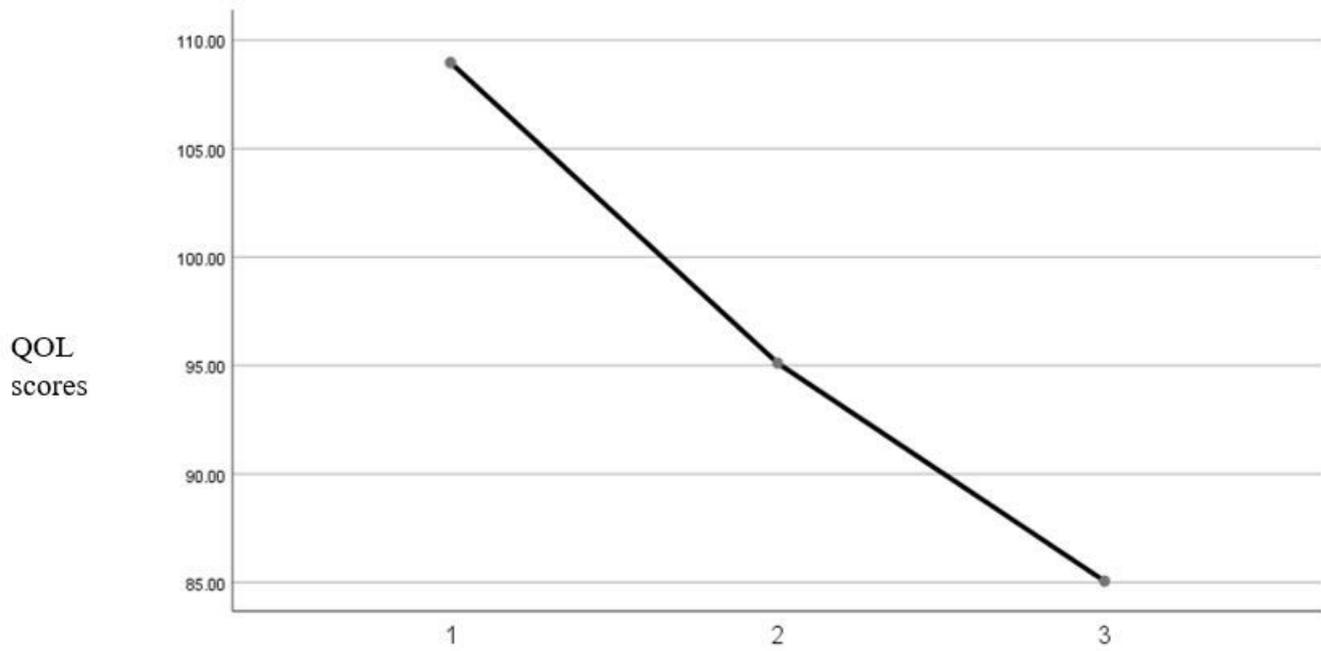
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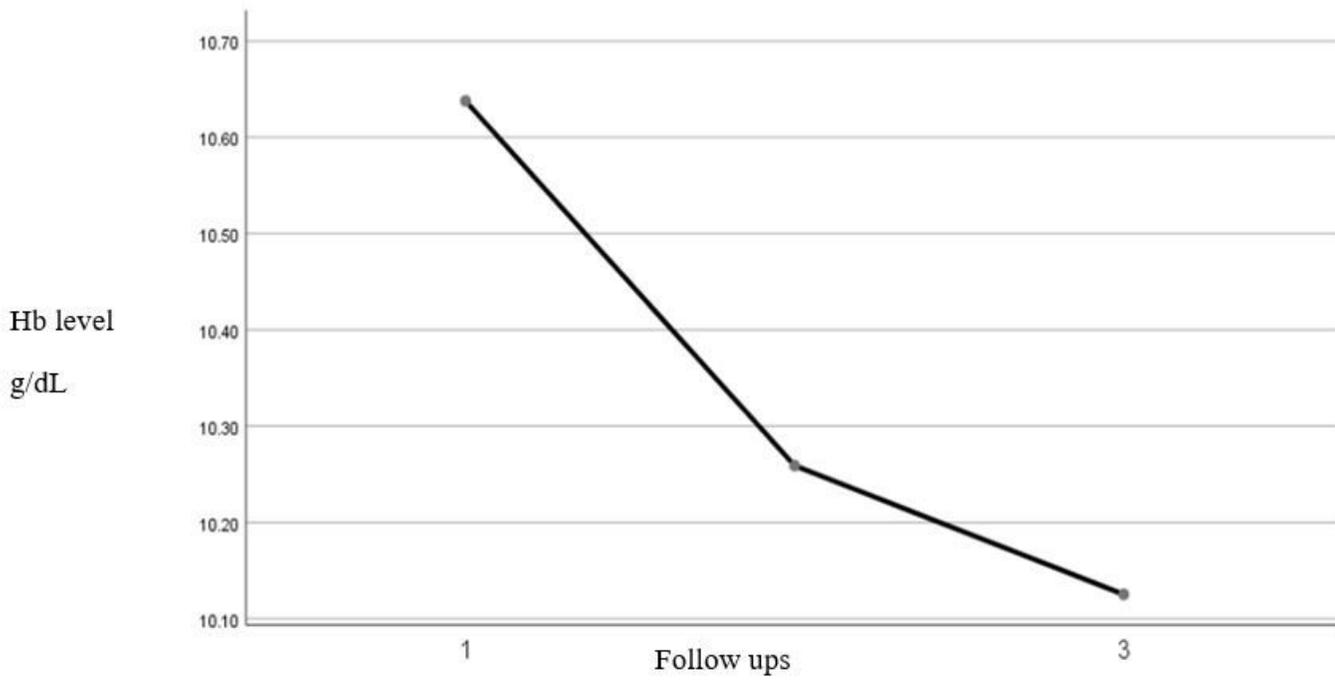
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## Figures



**Figure 1**

QOL scores at three follow ups



**Figure 2**

Hb levels at 3 follow ups