Assessment of Risk Factors Associated with Anaemia Severity among Breast Cancer Patients Undergoing Chemotherapy in Malaysia

Fares M.S Muthanna¹, Mahnathi Karuppannan¹*, Bassam Abdul Rasool Hassan², Ali Haider Mohammed³

¹Department of Pharmacy Practice, Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia.
²Department of Pharmacy, Al Rafidain University College, 10001, Baghdad, Iraq
³School of Pharmacy, Monash University Malaysia, Jalan Lagoon Selatan, 47500 Bandar Sunway, Selangor, Malaysia

ABSTRACT

Objectives: The purpose of this study was to determine the association between anaemia severity and risk factors among breast cancer patients.

Methods: A prospective study design was conducted in three different oncology centres in Malaysia where 120 anaemic breast cancer patients (haemoglobin < 12 g/dL) were identified through medical chart review. Patients were followed-up for three cycles of chemotherapy and data such as haemoglobin (Hb) levels and demographic or clinical data were also recorded on each follow-up. Data were analysed using SPSS.

Results: The average mean of Hb level of all follow-ups was 10.34 ± 0.73 g/dL. A chi-square and multiple logistic regression analysis revealed a significant strong association between anaemia severity and associated risk factors, i.e., demographic data (age, body mass index [BMI], and marital status), chemotherapy data (dose delay, number of regimens, and type of chemotherapy), and cancer stage.

Conclusion: Factors that have a great impact on anaemia severity were identified in which oncologist and healthcare professionals can take them into consideration to reduce the negative effect of anaemia on patients’ health care. Besides, results of such studies could significantly help in developing effective treatment guidelines for this crucial medical issue.

Keywords: Anaemia, Breast Cancer, Chemotherapy, Malaysia

Correspondence:
Mahnathi Karuppannan
Department of Pharmacy Practice, Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor, Malaysia.
Email: k.mahnathi@yahoo.com

INTRODUCTION

Breast cancer is the most popular cancer in females globally. It is the second most common cancer among Malaysian women in which it accounts about 32% of the total cancer. (1). Anaemia (haemoglobin < 12 g/dL) is common in cancer and has a very high incidence ranging from 30-90% (2) in cancer patients. The incidence of anaemia in patients diagnosed with cancer was found to be 29% at earlier stage, raised to 49% at late stage, and spiked to 89% after receiving chemotherapy (3). Increased incidence of anaemia in cancer patients led to increased morbidity and decreased sensitivity to chemotherapy, and even shorter survival (4). In addition, anaemia in breast cancer patients has been found to delay response to chemotherapy and causing patients to wish to die (5). Based on published studies, the evaluation of anaemia in breast cancer patients becomes important in helping oncologists, health providers, and patients to make decisions and choose appropriate interventions (6). Documenting data on anaemia in medical files is not a popular practice among oncologists and healthcare professionals and is neglected in breast cancer patients (7). As a result, screening, assessment, and treatment of cancer-related anaemia is not prioritised by physicians and healthcare providers (9).

Several factors are correlated with the incidence of anaemia severity in cancer patients. The predominant factors include socio-demographic characteristics (10), biological factors (11), types of cancer (10), and chemotherapy (12). Demographic factors such as increasing age (13,10), race e.g., Hispanics (10, 15) and gender e.g., women, played an important role in the occurrence of cancer related anaemia. In addition, variables such as chemotherapy regimen (17,18, 19, 20, 21, 22) and chemotherapy type (23; 10), dose delay or dose reduction (24,25), all induced anaemia among cancer patients. Furthermore, cancer itself (19,18) and cancer type (26,18) contributed to initiation of anaemia among cancer patients. Moreover, the effect of neoplasm (by direct invasion of bone marrow), anti-neoplastic treatment (surgery, hormonal therapy, radiotherapy, targeted therapy), and the effect of cytokines released by cancer cells, all induced anaemia in cancer patients (27). This study aimed to determine the risk factors associated with severity of anaemia among breast cancer patients receiving chemotherapy.

MATERIALS AND METHODS

The study was a prospective observational longitudinal, multi-centre study design that was conducted for eight months starting from July 2019 to March 2020 and included 120 anaemic breast cancer patients who fulfilled the inclusion criteria. The study was conducted in the oncology and day care department of Hospital Kuala Lumpur (HKL), Institut Kanser Negara (IKN), Putrajaya, and University Malaya Medical Centre (UMMC), Malaysia. Patients were followed up for three chemotherapy cycles. The clinical and demographic data were recorded at all three follow-ups sessions. Medication and lab reports for each patient were traced through the registration number using the online medical record of the respective hospitals.

Study population

Participants were anaemic with Hb less than 12 g/dL, aged 18 years old and above, diagnosed breast cancer patients, and received chemotherapy with a planned three consecutive cycles starting from cycle 2. However, cancer patients with inherited anaemia, suffering from
bleeding or haematological, and psychological disorders or those who were in first cycle of chemotherapy or received hormonal therapy, radiotherapy, or endocrine therapy, were excluded.

**Data collection**
A researcher went through the patients’ medical files in the ward to identify those who were experiencing anaemia (Hb ≤ 12 g/dL). Hb levels was measured before each cycle. The demographic data collected were age, race, occupation, body mass index (BMI), social history, and marital status. Meanwhile, the clinical data recorded were cancer stage, type of chemotherapy regimen, chemotherapy dose (including if there was any delay or dose reduction), and Hb levels. Chemotherapy dose delay was defined as the dose delay of ≥3 days (28) from the first follow-up, and dose reduction was defined as the dose reduced ≥10% from the first follow-up on the same regimen (29, 30). Chemotherapy regimen combination is defined as a combination of more than one chemotherapy drugs (e.g., 5-fluorouracil, epirubicin, cyclophosphamide (FEC) is one regimen but a combination of three medications) (31).

**Data analysis**
Data was analysed using SPSS Version 23.0 (IBM Corp), and the results were expressed as mean and standard deviation (SD) or median (IQR). Comparisons with p < 0.05 were statistically significant. Chi-square analysis and multiple logistic regression were performed to determine the relationship between anaemia severity and the associated risk factors. P-value < 0.05 was considered significant for all analyses performed. For the prospective analysis, time points of patient assessments were set for every 21 days. Haemoglobin level was assessed on the same day of chemotherapy cycles. Because of the small numbers of observations for patients with severe anaemia (Hb 6–8 g/dL), we combined both severe and moderate anaemia grade to the moderate category (Hb 7–10 g/dL).

For the retrospective analysis, data were collected from files, medical records, and digital data. Estimated mean scores and 95% confidence intervals were calculated for Hb levels. Statistical differences in the mean scores were evaluated between the three follow-up periods.

**RESULTS**
Out of 120 respondents, the majority were elderly (n = 89; 74.2%), with a mean age of 52.63 (± SD 11.27). Malay ethnic (n = 77; 64.2%), married (n = 108; 90%), and post-menopausal women (n = 87; 72.5%). Most of the patients (n = 96; 80%) were at the early stages of breast cancer (I, II, and III) and a small number of them were at stage IV (n = 24; 20%). Other demographic and clinical data are summarised in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>52.63 (± SD 11.27)</td>
</tr>
<tr>
<td>Age</td>
<td>≥ 60: 89 (74.2%); &lt; 60: 31 (25.8%)</td>
</tr>
<tr>
<td>Race</td>
<td>Malay: 77 (64.2%); Chinese: 27 (22.5%); Indian: 14 (11.7%); Others: 2 (1.7%)</td>
</tr>
<tr>
<td>Marital status</td>
<td>Married: 108 (90%); Single: 8 (6.7%); Divorced: 4 (3.3%)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>Underweight: 12 (10%); Normal: 60 (50%); Overweight: 34 (28.3%); Obese: 14 (11.7%)</td>
</tr>
<tr>
<td>Employment status</td>
<td>Working: 86 (71.1%); Housewife: 34 (28.3%)</td>
</tr>
<tr>
<td>Menstrual status</td>
<td>Pre-menopause: 33 (27.5%); Post-menopause: 87 (72.5%)</td>
</tr>
</tbody>
</table>

**Chemotherapy data**
Most of the patients were treated with a single chemotherapy regimen (n = 93; 77.5%), while the rest were treated with a combination regimen (n = 27; 22.5%). Only a minority of the patients (n = 23; 19.2%) had a reduction in their chemotherapy dose. Whereas 51.7% (n = 62) of the patients had a delay in their chemotherapy treatment. Other details are shown in Table 2.

**Anaemia data**
Severity of anaemia was categorized as mild, moderate, and severe. Hemoglobin level for the whole patients ranged from 7.80 ± 0.73 (mean ± SD). The mean of hemoglobin for patients in 1st Follow up was 10.64 ± 0.85, in 2nd Follow up was 10.26 ± 0.85, and in 3rd Follow up was 10.13 ± 0.83 g/dL. Generally, result of current study showed that there is a drop down in the level of hemoglobin along the three follow ups i.e., anaemia severity is increasing along the three follow ups as shown in table 3.

**Table 1: Demographic data in breast cancer patients undergoing chemotherapy (N=120)**

**Table 2: Chemotherapy data among breast cancer cases (N=120)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Chemotherapy medications*</td>
<td>1: 35 (29.2%); 2: 25 (20.8%); 3: 35 (29.2%); 4: 24 (20%); 5: 1 (0.8%)</td>
</tr>
</tbody>
</table>
Assessment of Risk Factors Associated with Anaemia Severity among Breast Cancer Patients Undergoing Chemotherapy in Malaysia

<table>
<thead>
<tr>
<th>Dose Reduction **</th>
<th>Reduced 23 (19.2%)</th>
<th>Not reduced 97 (80.8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Delay ***</td>
<td>Delayed 62 (51.7%)</td>
<td>Not delayed 58 (48.3%)</td>
</tr>
<tr>
<td>Number of chemotherapy Regimen*</td>
<td>1 93 (77.5%)</td>
<td>&gt;1 27 (22.5%)</td>
</tr>
</tbody>
</table>

*Number of chemotherapies: Example FEC is one regimen and consist of 3 medications
**Dose Reduction: When dose reduced ≥10% of 1st chemotherapy follow-up of the same regimen
***Dose delay: When dose delay >3 days of the 1st follow-up

Table 3: Hemoglobin level (severity of anaemia) in breast cancer patients (N= 120)

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st Follow up</th>
<th>2nd Follow up</th>
<th>3rd Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb * level</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Mild (10-12) g/dL</td>
<td>92 (76.7)</td>
<td>79 (65.8)</td>
<td>67 (55.8)</td>
</tr>
<tr>
<td>Moderate (8-10) g/dL</td>
<td>20 (23.3)</td>
<td>41 (34.2)</td>
<td>53 (43.3)</td>
</tr>
<tr>
<td>Severe (6-8) g/dL</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>10 (8.3)</td>
</tr>
</tbody>
</table>

*Hb – Hemoglobin

Association between risk factors and anaemia severity
As shown in table 4, chi-square indicated a significant association between anaemia severity and sociodemographic profiles (increased age, BMI [obese], and married patients), advanced stage, and chemotherapy dose delay (p <0.05). A logistic binary regression test (Table 5) was used to determine the strength of association between anaemia severity and risk factors. The severity of anaemia increased as the cancer stage increased. Patients at stage II were 15.6 times less likely to develop severe anaemia compared to patients at an advanced stage. In addition, our data also showed that the severity of anaemia increased among elderly patients, i.e., about 3.6 times more than young adult patients. Similarly, patients who had delayed dose were about 3.36 times more likely to develop severe anaemia compared to patients without a dose delay. Furthermore, obese breast cancer patients were 4.5 times more likely to experience severe anaemia compared with non-obese patients.

Table 4: Association between anaemia severity & associated risk factors.
Table 5: Strength of Relationship between anaemia severity and risk factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Anaemia Severity</th>
<th>b</th>
<th>OR</th>
<th>CI (95%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer Stage VI</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer stage I</td>
<td>21.11</td>
<td>0.01</td>
<td>0.24</td>
<td>2</td>
<td>0.91</td>
</tr>
<tr>
<td>Cancer stage II</td>
<td>2.755</td>
<td>0.012</td>
<td>0.334</td>
<td>2</td>
<td>0.001</td>
</tr>
<tr>
<td>Cancer stage III</td>
<td>-8.79</td>
<td>2.4</td>
<td>1.37</td>
<td>0.14</td>
<td>0.9</td>
</tr>
<tr>
<td>No dose delay</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose Delay</td>
<td>1.266</td>
<td>3.54</td>
<td>9.39</td>
<td>9</td>
<td>0.01</td>
</tr>
<tr>
<td>One chemotherapy regimen</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 1 regimen</td>
<td>1.058</td>
<td>3.28</td>
<td>2.88</td>
<td>8.94</td>
<td>0.06</td>
</tr>
<tr>
<td>Elderly Age &gt; 60 years</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young Age ≤ 60 years</td>
<td>-1.70</td>
<td>3.56</td>
<td>1.83</td>
<td>0.642</td>
<td>0.001</td>
</tr>
<tr>
<td>Not obese (BMI kg/m² ≤25)</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (BMI kg/m² &gt;25)</td>
<td>1.636</td>
<td>4.51</td>
<td>5.13</td>
<td>19.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Not married</td>
<td>Refer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>-2.159</td>
<td>10.115</td>
<td>1.23</td>
<td>0.07</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*Fisher Exact Test, BMI: body mass index, FEC5: fluorouracil+epirubicin+cyclophosphamide, TC: Taxotere+ cyclophosphamide, AC: doxorubicin+ cyclophosphamide

DISCUSSION

The results of this study demonstrated a significant correlation between the severity of anaemia and its associated risk factors (demographic, cancer, and chemotherapy).

The main aim of the present study was to determine the relationship between anaemia severity and its associated risk factors in breast cancer patients undergoing chemotherapy. The findings of the current study showed that most of the patients suffered from mild anaemia (65%), while 34.17% suffered from moderate anaemia and 0.8% patient suffered from severe anaemia. Besides, the mean haemoglobin level declined over the three follow-ups. In other words, the number of patients who suffered from moderate anaemia increased, and one patient developed severe anaemia, i.e., declined haemoglobin level at the third follow-up.

To our knowledge, this is the first prospective multi-centre study conducted in Malaysia. Kiffe et al. (32) reported the lack of information on the prevalence of anaemia and risk factors among cancer patients in developing countries, and Malaysia is one of them (32). Similarly, Kanuri et al. (33) mentioned the scarcity of studies that focuses on the prevalence and severity of anaemia among Asian cancer patients. In addition, several factors played a significant role in the incidence of anaemia severity among breast cancer patients, such as management type, age, cancer type, and cancer stage (34, 22, 35). The results of the study indicated a significant association between increased age (≥ 60) and the severity of anaemia. According to WHO, the age group is categorised into two: non-elderly (<60 years) and elderly (≥60). This finding is similar to a study published in Austria that reported a significant correlation between anaemia severity and age (35). In addition, Cheng et al. (22) confirmed that increased age (≥60) correlated significantly with anaemia severity among cancer patients (22). In general, ageing results in the deterioration of the physiological processes. Although there is no known threshold age, the deterioration of biological systems is considered to begin at approximately 45–50 years of age (36). Alteration of the circadian time-keeping system and the physiology of sleep homeostasis often results in anaemia and fatigue (37). Several studies have demonstrated that interleukin-6 (IL-6) levels increase with age and are correlated with the development of anaemia in the elderly (38). As a result, there is a decline in the haematopoietic stem cell reserves and proliferation capacity, which leads to the suppression of erythropoiesis (39).

Body mass index (BMI) indicated a significant association with the severity of anaemia. This finding is consistent with a 2012 meta-analysis study in which obesity in adults was significantly associated with severe anaemia (40). Moreover, our finding is similar to a recent study in Nepal regarding the strong association of obesity with anaemia severity (41). The main cause of the prevalence of anaemia among obese patients is unclear. Obesity may either increase iron deficiency by the inhibition of dietary iron uptake from the duodenum; thus, resulting in anaemia (36) or may cause low iron intake (due to an unbalanced diet), reduced iron absorption in the small intestine, and greater iron requirements caused by a larger blood volume. Besides, obesity is associated with a chronic low-grade inflammation state. For this reason, sequestration of iron through an inflammatory-mediated mechanism can be one of the proposed causes of iron deficiency in obesity (42).

In addition, findings from the chi-square and logistic regression analyses showed a significant statistical association between anaemia severity and cancer stages. This finding is in agreement with the results of several studies (32, 43, 44, 45, 46, 47), demonstrating a significant correlation between anaemia severity with advanced stages of cancer. Sometimes the cause of anaemia among cancer patients is cancer itself or one of its complications. In general, red blood cells (RBCs) of cancer patients wear out faster than healthy individuals and are not replaced as quickly as needed. Cancer can impede the body’s ability to make new RBCs or interfere with the body’s ability to use stored iron. Cancer cells could also infiltrate the bone marrow and directly suppress haematopoiesis and cause anaemia. Furthermore, the cancer cells release cytokines that can
lead to iron sequestration; hence, reducing the production of RBCs. Tumours may result in chronic blood loss from the tumour site, leading to progressive anaemia from cancer and organ damage (48).

Furthermore, statistically, our data are supported by other results (24, 49), which indicated a strong association between anaemia severity and chemotherapy treatment delay. Zhang and colleagues (49) mentioned that the incidence of anaemia is highly associated with the use of chemotherapy treatment and is highly responsible for chemotherapy treatment delay and dose reduction. Therefore, prevention or treatment of anaemia will significantly help in improving both chemotherapy treatment efficacy and the QOL of cancer patients (49). The incidence of moderate to severe anaemia during the initial cycles of chemotherapy in cancer patients is associated with an increased risk of chemotherapy treatment delay and/or dose reduction in the subsequent chemotherapy cycles, regardless of age, gender, race/ethnicity, cancer stage, platelet counts, liver function, renal function, and history of other comorbidities (50). Results of several studies suggest that the development of moderate to severe anaemia directly impacts the subsequent administration of chemotherapy and may result in a reduced or delayed dose of chemotherapy regimen (24). In addition, many oncologists reduce doses by 20% in hope to limit excess cytotoxic effects on the bone marrow, especially among myelosuppressive cancer. Unfortunately, the 20% dose reduction may lead to a 50% reduction in the cure rate (50). Kaner (51) confirmed in his trial that the administration of pegfilgrastim improved chemotherapy-induced neutropenia that is responsible for dose reduction and dose delay (51,52).

The strengths of the current study are summarised as follows: i) the study findings can be generalised nationwide as it was conducted in multiple venues; ii) the study was based on personal information from individuals that was confirmed through verified medical records as the researcher had full access to the data; iii) the research findings and clinical significance are highly correlated; v) the study findings may serve as the baseline data future studies since no other related study was done within the country.

In Asia, very limited research was conducted to address the correlation between anaemia severity and its associated risk factors of cancer patients undergoing chemotherapy. Furthermore, no study was conducted in Malaysia prior to this research. Therefore, the findings of this study will potentially facilitate healthcare providers, oncologists, and researchers to choose the most appropriate approach for the treatment of breast cancer.

CONCLUSION
This study confirmed a significant relationship between anaemia severity and its associated risk factors. Specific attention should be placed on patients with advanced cancer stage, older, obese or those with dose delay, as these were the subgroups of breast cancer patients that experienced high anaemia severity in the current study. Future intervention studies are highly recommended to determine the effect of anti-anaemic medications on the incidence and severity of anaemia among cancer patients. Besides, results of such studies could significantly help in developing effective treatment guidelines for this crucial medical issue.

The author would like to thank all the staffs at respective hospitals for their assistance and generosity in providing access to the medical records at the clinic.

FUNDING
The authors declare that there was no funding for this work.

REFERENCES


Assessment of Risk Factors Associated with Anaemia Severity among Breast Cancer Patients Undergoing Chemotherapy in Malaysia

42. Menzie CM, Yanoff LB, Denkinger BL, McHugh T, Sebring NG, Calis KA, Yanovski JA. Obesity-related hypoferremia is not explained by differences in reported intake of heme and nonheme iron or intake of dietary factors that can affect iron absorption. Journal of the American Dietetic Association. 2008 Jan 1;108(1):145-8.


