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

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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

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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 were 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 (± SD11.27), 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 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%)
BMI (kg/m2)	Underweight	12 (10%)
	Normal	60 (50%)
	Overweight	34 (28.3%)
	obese	14 (11.7%)
Employment status	working	86 (71.1%)
	housewife	34 (28.3%)
Menstrual status	Pre menopause	33 (27.5%)
	Post menopause	87 (72.5)
Stage of Breast Cancer	Stage I	5 (4.2%)
	Stage II	29 (24.2 %)
	Stage III	62 (51.7 %)
	Stage IV	24 (20 %)

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 7.8.00 g/dl to 11.9 g/dl with a mean of 10.34 ± 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 2: Chemotherapy data among breast cancer cases (N=120)

Variable		Frequency, n (%)
Number of Chemotherapy medications*	1	35 (29.2%)
	2	25 (20.8%)
	3	35 (29.2%)
	4	24 (20%)
	5	1 (0.8%)

Dose Reduction **	Reduced	23 (19.2%)
	Not reduced	97 (80.8%)
Dose Delay ***	Delayed	62 (51.7%)
	Not delayed	58 (48.3%)
Number of chemotherapy Regimen*	1	93 (77.5%)
	>1	27 (22.5%)

*__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 snaemia) in breast cancer patients (N= 120)

Variable		1st Follow up N (%)	2nd Follow up N (%)	3rd Follow up N (%)
Hb [a] level	Mild (10-12) g/dL	92 (76.7)	79 (65.8)	67 (55.8)
	Moderate (8-10) g/dL	28 (23.3)	41 (34.2)	53 (43.3)
	Severe (6-8) g/dL	0 (0)	0 (0)	1(0. 8)

[a]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.

Variable	Anaemia severity		P - Value
	Mild Frequency, n (%)	Moderate Frequency, n (%)	
Age (years)	< 60	53 (59.6%)	36 (40.4%)	0.034
	≥ 60	25 (80.6%)	6 (19.4%)	
Race	Malay	47 (61%)	30 (39%)	0.54*
	Indians	10 (71.4%)	4 (28.6%)	
	Chinese	20 (74.1%)	7 (25.9%)	
	Others	1 (50%)	1 (50%)	
(BMI) kg/m^2	Not Obese	71 (71%)	29 (29%)	0.002
	Obese	7 (35%)	13 (65%)	
Menopausal Status	Pre	21 (63.6%)	12 (36.4%)	0.834*
	Post	57 (65.5%)	30 (34.5%)	
Employment Status	Working	53 (61.6%)	33 (38.4%)	0.154*
	Housewives	25 (73.5%)	9 (26.5%)	
Marital status	Married	67 (62%)	41 (38%)	0.041*
	Un married	11 (91.7%)	1 (8.3%)	
Cancer Stage	Stage I	5 (100%)	0 (0%)	0.017
	Stage II	24 (82.8%)	5 (17.2%)	
	Stage III	37 (59.7%)	25 (40.3%)	
	Stage IV	12 (50%)	12 (50%)	
Dose delay	Delayed	46 (74.2%)	16 (25.8%)	0.036
	Not delayed	32 (55.2 %)	26 (44.8%)	
Number of regimens	1	65 (69.9%)	28 (30.1%)	0.042
	> 1	13 (48.1%)	14 (51.9%)	
Dose reduction	Reduced	17 (73.9 %)	6 (26.1 %)	0.57
	Not reduced	43 (64.2%)	24 (35.8%)	
	Not detected	18 (60%)	12 (40%)	
Number of medications	1	23 (65.7%)	12 (34.3%)	0.81
	2	17 (68%)	8 (32%)	
	3	22 (62.9%)	13 (37.1%)	
	4	16 (66.7%)	8 (33.3%)	
	5	0 (0%)	1 (100%)	
FEC	Yes	37 (68.5 %)	17 (31.5%)	0.57
	No	41 (62.1%)	25 (37.9%)	
Docetaxel	Yes	31 (68.9%)	14 (31.1%)	0.56
	No	47 (62.7%)	28 (37.3%)	
TC	Yes	9 (100%)	0 (0%)	0.02
	No	69 (62.2%)	42 (37.8%)	
AC	Yes	2 (28.6%)	5 (71.4%)	0.04
	No	76 (67.3%)	37 (32.7%)	

Gemcitabine/Carboplatin	Yes	2 (28.6%)	5 (71.4%)	0.05
	No	76 (65%)	37 (35%)	

*Fisher Exact Test, BMI: body mass index, FEC:5-fluorouracil+epirubicin +cyclophosphamide, TC: Taxotere+ cyclophosphamide, AC: doxorubicin+ cyclophosphamide
$p < 0.05$ level of significance

Table 5: Strength of Relationship between anaemia severity and risk factors

Variable	Total Anaemia Severity				
	b	OR	CI (95%)		P value
Cancer Stage VI	Reference				
Cancer stage I	-21.115	0.01	.001	0.242	0.91
Cancer stage II	-2.755	15.6	.012	.334	0.001
Cancer stage III	-.879	2.4	.126	1.370	0.149
No dose delay	Reference				
Dose Delay	1.266	3.362	3.545	9.399	0.011
One chemotherapy regimen	Reference				
> 1 regimen	1.058	3.289	2.880	8.949	0.068
Elderly Age > 60 years	Reference				
Young Age ≤ 60 years	-1.700	3.561	.183	.642	0.008
Not obese (BMI kg/m^2 ≤25)	Reference				
Obese (BMI kg/m^2>25)	1.636	4.515	5.133	19.305	0.016
Not married	Reference				
Married	-2.159	10	.115	1.237	0.074

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. Kifle 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

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REFERENCES

1. Azizah Ab M, Nor Saleha IT, Noor Hashimah A, Asmah ZA, Mastulu W. (2015). Malaysian National Cancer Registry report 2007-2011 (Putrajaya, National Cancer Institute, Ministry of Health Malaysia). https://www.crc.gov.my/wp-186 content/uploads/documents/report/MNCRRrepor2 007-2011.pdf
2. Pourali L, Taghizadeh A, Akhoundi MR, Varshoei F, Zarifian A, Andalibi MS. Frequency of Chemotherapy Induced Anaemia in Breast Cancer Patients. Iranian Journal of Cancer Prevention. 2017 Jan;10(1).
3. Xu H, Xu L, Page JH, Cannavale K, Sattayapiwat O, Rodriguez R, Chao C. Incidence of anaemia in patients diagnosed with solid tumors receiving chemotherapy, 2010–2013. Clinical epidemiology. 2016; 8:61.
4. Calabrich, A., & Katz, A. Management of anaemia in cancer patients. Future Oncology. (London, England), 2011 .7(4), 507–517.
5. Harper P, Littlewood T. Anaemia of cancer: impact on patient fatigue and long-term outcome. Oncology. 2005;69(Suppl. 2):2-7.
6. Bottomley A. The cancer patient and quality of life. The oncologist. 2002 Apr;7(2):120-5.
7. Goldrick A, Olivotto IA, Alexander CS, et al. Anaemia is a common but neglected complication of adjuvant chemotherapy for early breast cancer. *Curr Oncol*. 2007;14(6):227–233. doi:10.3747/co.2007
8. Joly F, Lange M, Dos Santos M, Vaz-Luis I, Di Meglio A. Long-Term Fatigue and Cognitive Disorders in Breast Cancer Survivors. Cancers. 2019 Dec;11(12):1896.
9. Piper BF, Borneman T, Sun VC, Koczywas M, Uman G, Ferrell B, James RL. Cancer-related fatigue: role of oncology nurses in translating National Comprehensive Cancer Network assessment guidelines into practice. Clinical Journal of Oncology Nursing. 2008 Oct 2;12.
10. Cardenas-Turanzas M, Cesta MA, Wakefield C, Wallace SK, Puana R, Price KJ, Nates JL. Factors associated with anaemia in patients with cancer admitted to an intensive care unit. Journal of critical care. 2010 Mar 1;25(1):112-9.
11. Madeddu C, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V, Macciò A. Pathogenesis and treatment options of cancer related anaemia: perspective for a targeted mechanism-based approach. Frontiers in physiology. 2018 Sep 20; 9:1294.
12. Yang S, Chu S, Gao Y, Ai Q, Liu Y, Li X, Chen N. A narrative review of Cancer-Related Fatigue (CRF) and its possible pathogenesis. Cells. 2019 Jul;8(7):738.
13. Cheng K, Zhao F, Gao F, Dong H, Men H-T, Chen Y, et al (2012). Factors Potentially Associated with Chemotherapy-induced Anemia in Patients with Solid Cancers. Asian Pacific Journal of Cancer Prevention; 13 (10):5057-5061.

14. Gao, F., Cheng, K., Zhao, F., Chen, Y., Li, L., Dong, H., … Liu, J. (2011). Prevalence and Characteristics of Anemia in Patients with Solid Cancers at Diagnosis in Southwest China, 12, 2825–2828.
15. Patel, K. V., Harris, T. B., Faulhaber, M., Angleman, S. B., Connelly, S., Bauer, D. C., Kuller, L. H., Newman, A. B., & Guralnik, J. M. (2007). Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood*, *109*(11), 4663–4670.
16. John, G. K., Sanamandra, S., & Shet, A. S. (2011). Cancer Related Anemia in the Developing World: Risk Factors and Treatment Patterns. Health Services and Outcomes Research. 18 (21).
17. Hassan, B. A., & Yusoff, Z. B. (2011). Treatment patterns and outcomes in 199 management of solid cancer patients suffering from anemia in Penang hospital. Asian Pacific journal of cancer prevention: APJCP, 12(6), 1573–1576.
18. Xu, H., Xu, L., Page, J. H., Cannavale, K., Sattayapiwat, O., Rodriguez, R., et al. (2016). Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clinical epidemiology, 8, 61–71.
19. Macciò, A., Madeddu, C., Gramignano, G., Mulas, C., Tanca, L., Cherchi, M. C., et al. (2015). The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. Haematologica, 100(1), 124–132.
20. Ludwig, H., Van Belle, S., Barrett-Lee, P., Birgegård, G., Bokemeyer, C., Gascón, P., et al. (2004). The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. European journal of cancer (Oxford, England: 1990), 40(15), 2293–2306.
21. Birgegård, G., Aapro, M. S., Bokemeyer, C., Dicato, M., Drings, P., Hornedo, J., et al. (2005). Cancer-related anemia: pathogenesis, prevalence and treatment. Oncology, 68 Suppl 1, 3–11.
22. Cannavale, K., Xu, H., Xu, L., Sattayapiwat, O., Rodriguez, R., Bohac, C., Page, J., & Chao, C. (2019). Epidemiology of Chemotherapy-Induced Anemia in Patients with Non-Hodgkin Lymphoma. *The Permanente journal*, *23*, 18-252.
23. Adeel, M., Asif, M., Faisal, M. N., Chaudary, M. H., Malik, M. S., & Khalid, M. (2019). Comparative study of adjuvant chemotherapeutic efficacy of docetaxel plus cyclophosphamide and doxorubicin plus cyclophosphamide in female breast cancer. Cancer management and research, 11, 727–739.
24. Family L, Xu L, Xu H, Cannavale K, Sattayapiwat O, Page JH, Bohac C, Chao C. The effect of chemotherapy-induced anaemia on dose reduction and dose delay. Supportive Care in Cancer. 2016 Oct 1;24(10):4263-71.
25. Lyman G. H. (2006). Chemotherapy dose intensity and quality cancer care. Oncology (Williston Park, N.Y.), 20(14 Suppl 9), 16–25.
26. Mercadante, S., Gebbia, V., Marrazzo, A., & Filosto, S. (2000). Anaemia in cancer: pathophysiology and treatment. *Cancer treatment reviews*, *26*(4), 303–311.
27. (27Aapro, M., Österborg, A., Gascón, P., Ludwig, H., & Beguin, Y. (2012). Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. Annals of oncology: official journal of the European Society for Medical Oncology, 23(8), 1954–1962.
28. Xu H, Chao C, Xu L, Cannavale K, Sattiyapiwat O, Page J, Rodriguez R, Family L. Pattern of dose delay and dose reduction among cancer patients treated with chemotherapy.2015. e20705- e20705.
29. Denduluri N, Lyman GH, Wang Y, Morrow PK, Barron R, Patt D, Bhowmik D, Li X, Bhor M, Fox P, Dhanda R. Chemotherapy dose intensity and overall survival among patients with advanced breast or ovarian cancer. Clinical breast cancer. 2018 Oct 1;18(5):380-6.
30. Liutkauskiene S, Grizas S, Jureniene K, Suipyte J, Statnickaite A, Juozaityte E. Retrospective analysis of the impact of anthracycline dose reduction and chemotherapy delays on the outcomes of early breast cancer molecular subtypes. BMC cancer. 2018 Dec;18(1):1-9.
31. Yap TA, Omlin A, De Bono JS. Development of therapeutic combinations targeting major cancer signaling pathways. Journal of Clinical Oncology. 2013 Apr 20;31(12):1592-605.
32. Kifle E, Hussein M, Alemu J, Tigeneh W. Prevalence of anaemia and associated factors among newly diagnosed patients with solid malignancy at Tikur Anbessa specialized hospital, radiotherapy center, Addis Ababa, Ethiopia. Advances in hematology. 2019 Oct 20;2019.
33. Kanuri G, Sawhney R, Varghese J, Britto M, Shet A. Iron deficiency anaemia coexists with cancer related anaemia and adversely impacts quality of life. PloS one. 2016 Sep 28;11(9):e0163817
34. Hassan BA, Yusoff ZB, Hassali MA, Othman SB. Association and correlation of different chemotherapeutic regimens and doses with onset and severity of anaemia among solid cancer patients. Asian Pac J Cancer Prev. 2011 Jan 1;12(10):2753-8.
35. Bach V, Schruckmayer G, Sam I, Kemmler G, Stauder R. Prevalence and possible causes of anaemia in the elderly: a cross-sectional analysis of a large European university hospital cohort. Clinical interventions in aging. 2014; 9:1187.
36. Weinert D. Age-dependent changes of the circadian system. Chronobiology international. 2000 Jan 1;17(3):261-83.
37. Dawson D, Noy YI, Härmä M, Åkerstedt T, Belenky G. Modelling fatigue and the use of fatigue models in work settings. Accident Analysis & Prevention. 2011 Mar 1;43(2):549-64.
38. Joosten E, Pelemans W, Hiele M, Noyen J, Verhaeghe R, Boogaerts MA. Prevalence and causes of anaemia in a geriatric hospitalized population. Gerontology. 1992;38(1-2):111-7.
39. Kim YJ, Do Han K, Cho KH, Kim YH, Park YG. Anaemia and health-related quality of life in South Korea: data from the Korean national health and nutrition examination survey 2008–2016. BMC public health. 2019 Dec 1;19(1):735.
40. Abdel-Razeq H, Hashem H. Recent update in the pathogenesis and treatment of chemotherapy and cancer induced anaemia. Critical Reviews in Oncology/Hematology. 2020 Jan 1; 145:102837.
41. Gautam S, Min H, Kim H, Jeong HS. Determining factors for the prevalence of anaemia in women of reproductive age in Nepal: Evidence from recent national survey data. PloS one. 2019 Jun 12;14(6): e0218288.

42. Menzie CM, Yanoff LB, Denkinger BI, 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.
43. Väyrynen JP, Tuomisto A, Väyrynen SA, Klintrup K, Karhu T, Mäkelä J, Herzig KH, Karttunen TJ, Mäkinen MJ. Preoperative anaemia in colorectal cancer: relationships with tumor characteristics, systemic inflammation, and survival. Scientific reports. 2018 Jan 18;8(1):1-1.
44. Liu X, Qiu H, Huang Y, Xu D, Li W, Li Y, Chen Y, Zhou Z, Sun X. Impact of preoperative anaemia on outcomes in patients undergoing curative resection for gastric cancer: a single-institution retrospective analysis of 2163 Chinese patients. Cancer medicine. 2018 Feb;7(2):360-9.
45. Caro JJ, Salas M, Ward A, Goss G. Anaemia as an independent prognostic factor for survival in patients with cancer: a systematic, quantitative review. Cancer. 2001 Jun 15;91(12):2214-21.
46. Gilreath, J. A., Stenehjem, D. D., & Rodgers, G. M. (2014). Diagnosis and treatment of cancer-related anemia. American journal of hematology, 89(2), 203–212.
47. Birgegård G, Aapro MS, Bokemeyer C, Dicato M, Drings P, Hornedo J, Krzakowski M, Ludwig H, Pecorelli S, Schmoll HJ, Schneider M. Cancer-related anaemia: pathogenesis, prevalence and treatment. Oncology. 2005;68(Suppl. 1):3-11.
48. Rodgers GM, Becker PS, Blinder M, Cella D, Chanan-Khan A, Cleeland C, Coccia PF, Djulbegovic B, Gilreath JA, Kraut EH, Matulonis UA. Cancer-and chemotherapy-induced anaemia. Journal of the National Comprehensive Cancer Network. 2012 May 1;10(5):628-53.
49. Zhang B, Dong JN, Sun P, Feng C, Liu YC. Effect of therapeutic care for treating fatigue in patients with breast cancer receiving chemotherapy. Medicine. 2017 Aug;96(33).
50. Henry D. Haematological toxicities associated with dose-intensive chemotherapy, the role for and use of recombinant growth factors. Annals of oncology. 1997 Jan 1;8: S7-10.
51. Kaner Z, Ochayon DE, Shahaf G, Baranovski BM, Bahar N, Mizrahi M, Lewis EC. Acute phase protein α1-antitrypsin reduces the bacterial burden in mice by selective modulation of innate cell responses. The Journal of infectious diseases. 2015 May 1;211(9):1489-98.
52. Mohammed, A. H., Blebil, A., Dujaili, J., & Rasool-Hassan, B. A. (2020). The Risk and Impact of COVID-19 Pandemic on Immunosuppressed Patients: Cancer, HIV, and Solid Organ Transplant Recipients. AIDS reviews, 22(3), 151-157.