Original Article

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Association of Anaemia with Metastasis in Non Haematological Malignancies: A Cross-sectional Study

Internal Medicine Section

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ABSTRACT

Introduction: Anaemia and cancer are two non communicable diseases with high global prevalence. The presence of anaemia in cancer patients is common, and its aetiology is multifactorial.

Aim: To analyse the clinical profile, type and severity of anaemia in non haematological malignancies and to determine how the presence of metastasis affects it.

Materials and Methods: A cross-sectional study was conducted in the Department of General Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India, between January 2022 and December 2023. Out of 1,294 patients diagnosed with malignancy, 190 subjects were analysed. The study included patients over 18 years of age diagnosed with non haematological malignancies who had anaemia according to the World Health Organisation (WHO) definition {females with Haemoglobin (Hb) <12 g/dL; males with Hb <13 g/dL}. The subjects were divided into two groups: patients with and without metastatic disease. All patients underwent complete haemogram, iron studies, serum vitamin B12 levels and serum folate levels. Anaemia was classified into types: normocytic anaemia, microcytic anaemia and macrocytic anaemia. The student's t-test, Chi-square test and Fisher's exact test were used to analyse and interpret the collected data.

Results: Of the 190 selected subjects, 80 (42.1%) (group A) had metastatic disease, while 110 (57.9%) (group B) had no evidence of metastasis. The mean±Standard Deviation (SD) age of patients in group A was 55.43±11.12 years and in group B was 54.38±9.8 years. There were 90 males and 100 females in the study. The most common cause of anaemia was found to be chemotherapy-induced anaemia. The most common type of anaemia among all study subjects was normocytic anaemia (52.1%). The prevalence of severe anaemia was significantly higher in patients with metastatic cancers compared to those without metastatic cancers (p-value=0.0003).

Conclusion: Chemotherapy-induced and normocytic anaemia were the most common types of anaemia in non haematological malignancies. Severe anaemia was more prevalent in patients with metastatic cancers. Anaemia in cancer patients should be monitored and managed optimally to improve outcomes.

Keywords: Breast neoplasms, Carcinoma, Head and neck neoplasms, Neoplasm metastasis

INTRODUCTION

Nearly 1.62 billion people worldwide are affected by anaemia, making it a serious public health problem, particularly among the extreme age groups. Cancer is one of the significant causes of anaemia. The pathogenesis of anaemia in cancer is multifactorial. Globally, the prevalence of cancer is constantly on the rise; in 2022, there were an estimated 19 million new cancer cases worldwide [1]. Several complications can occur, involving multiple organ systems in patients with malignancies. According to a recent study, anaemia is the most common haematological abnormality in patients with cancer, with a prevalence of nearly 50% [2].

Anaemia in cancer can be divided into two main categories: anaemia due to chronic inflammation associated with malignancy, where anaemia precedes the diagnosis of cancer, and anaemia that occurs as a side-effect of cancer therapy, where Haemoglobin (Hb) concentrations are normal before the medical management of cancer [3]. Studies have shown that anaemia-induced tissue hypoxia enhances tumour growth and cell proliferation [4,5]. Cancer patients with anaemia often have a poor response to cancer treatments, as anaemia can lead to the development of resistance to chemotherapy. This resistance manifests in several ways: by stimulating angiogenesis and gene mutations, increasing resistance to apoptosis, and decreasing the formation of chemotherapy/radiotherapy-generated free radicals, thereby reducing the tumour-killing effects of drugs [6]. Additionally, anaemia in cancer patients further compromises their quality of life [7].

Although several studies have assessed the impact of anaemia in cancer, the authors could not find any studies that specifically evaluate the effect of anaemia on patients with metastasis compared to those without metastasis [8,9]. Hence, the current study was conducted to investigate the clinical profile, prevalence and severity of anaemia in non haematological malignancies, as well as, to understand how the presence of metastasis affects these factors.

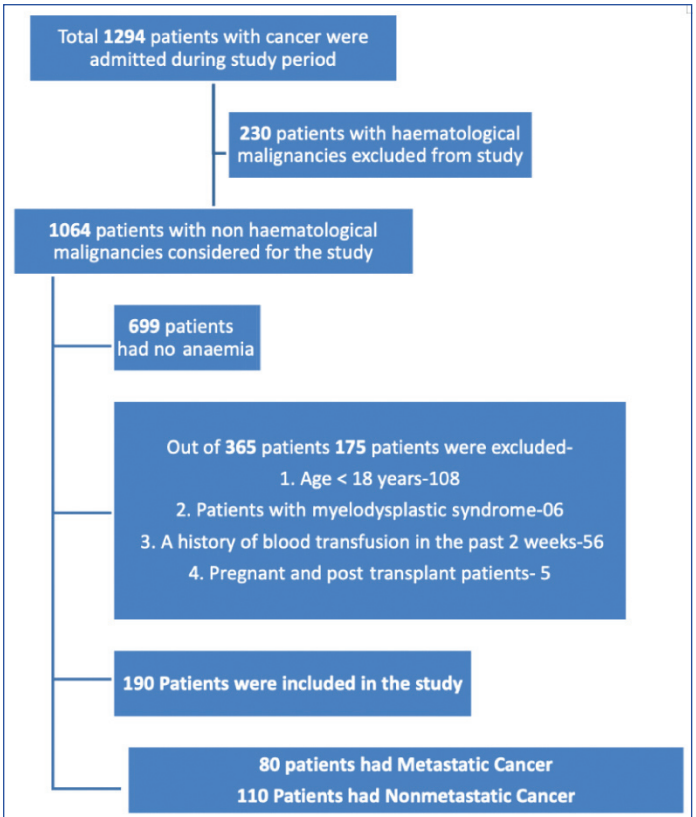
MATERIALS AND METHODS

The present cross-sectional study was conducted in the Department of General Medicine, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, India, between January 2022 and December 2023 on 190 patients. The study commenced after receiving approval from the Institutional Ethics and Scientific Committee (IEC no- IESC/PGS/2020/17) and obtaining fully informed written consent from the study participants.

Inclusion criteria: Patients with age greater than 18 years, diagnosed with non haematological malignancies (solid organ tumours) and patients who met the following WHO criteria for the diagnosis of anaemia: females with Hb levels less than 12 g/dL and males with Hb levels less than 13 g/dL were included in the study [10].

Exclusion criteria: Patients under 18 years of age, with an unknown primary tumour site, myelodysplastic syndrome, a history of blood transfusion in the past two weeks, and those who are HIV positive, pregnant, or post-transplant (including both bone marrow and solid organ transplants) were excluded from the study. The patient selection algorithm is presented in [Table/Fig-1].

Sample size calculation: The prevalence of anaemia in patients with cancer is reported to be 49.7%, with a 95% confidence interval and



[Table/Fig-1]: Patient selection algorithm.

an acceptable error of 7.5%. The minimum sample size calculated was 171 [2]; however, 190 participants were included in the study. The software used for the calculations was WinPepi version 11.38.

Study Procedure

Eligible patients for the study were enrolled after providing written informed consent and confirming the diagnosis of non haematological malignancy through biopsy or Fluorodeoxyglucose Positron Emission Tomography (FDG-PET). The patients were divided into two groups: those with metastasis (n=80) and those without metastasis (n=100). All patients underwent the following investigations: Hb levels, Red Blood Cell (RBC) count, and blood indices, including Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Red cell Distribution Width (RDW) and Corrected Reticulocyte Count (CRC). Additionally, iron studies were performed, which included serum iron, serum ferritin, transferrin saturation percentage, Total Iron-binding Capacity (TIBC), serum vitamin B12 levels and serum folate levels. Urine routine and microscopy were conducted to examine for gross and microscopic haematuria, while stool routine microscopy and occult blood tests were also performed. Based on Hb levels, anaemia was classified as mild, moderate, or severe according to WHO criteria [11].

STATISTICAL ANALYSIS

The data were compiled using Microsoft Excel 2010. The analysis was conducted using OpenEpi software version 2.3 and Statistical Package for the Social Sciences (SPSS) software version 15.0 (Armonk, NY: IBM Corp.). The association between categorical variables was calculated using the Chi-square test or Fisher's exact test. The association between continuous variables was assessed using the Student's t-test. All tests were two-tailed, with a p-value of less than 0.05 considered statistically significant.

RESULTS

Out of 190 study subjects, 80 (42.1%) had metastatic disease (Group A), while 110 (57.9%) had no evidence of metastasis (Group B). There were 90 males and 100 females in the study. [Table/Fig-2] presents the demographic parameters and clinical symptoms of the study subjects. Groups A and B had comparable demographic parameters (p-value >0.05). However, the symptoms of weight loss, fatigue and loss of appetite were more pronounced in patients with metastatic disease (p-value <0.05). A total of 69 out of 190 (36.31%) patients reported experiencing bleeding from various sites at least once before their cancer was diagnosed.

Demographic parameters	Group A, n=80 n (%)	Group B, n=110 n (%)	p-value
Mean±SD age (years)	55.43±11.12	54.38±9.8	0.7764$
Age groups (years)			
<20	1 (1.25)	1 (0.90)	0.7987#
21-30	2 (2.5)	3 (2.72)	
31-40	8 (10)	10 (9.09)	
41-50	16 (20)	24 (21.81)	
51-60	24 (30)	33 (30)	
>60	29 (36.25)	39 (35.45)	
Gender			
Female (n=100)	43 (53.75)	57 (51.81)	0.8110#
Male (n=90)	37 (46.25)	53 (48.18)	
Body Mass Index (BMI)			
<18.5 kg/m^2- Underweight (n=57)	24 (30)	33 (30)	0.9222#
18.5-24.9 kg/m^2- Normal (n=106)	45 (56.25)	61 (55.45)	
>25 kg/m^2- Normal (n=27)	11 (13.75)	16 (14.54)	
Clinical features of anaemia			
Weight loss and fatigue (n=90)	55 (68.75)	35 (31.81)	0.0441 (S)#
Bleeding manifestations (n=69)	30 (37.5)	39 (35.45)	0.6544#
Breathlessness (n=31)	18 (22.5)	13 (11.81)	0.0876#
Loss of appetite (n=27)	18 (22.5)	9 (8.18)	0.0332 (S)#
Pallor (n=170)	72 (90)	98 (89.09)	0.7865#
Bleeding sites (n=69)			
Bleeding per rectum (n=21)	9 (11.25)	12 (10.90)	-
Malena (n=16)	7 (8.75)	9 (8.18)	-
Gum bleed/epistaxis (n=9)	4 (5)	5 (4.54)	-
Per vaginal bleed (n=13)	5 (6.25)	8 (7.27)	-
Haemoptysis (n=4)	2 (2.5)	2 (1.81)	-
Haematemesis (n=4)	2 (2.5)	2 (1.81)	-
Haematuria (n=2)	1 (1.25)	1 (0.90)	-

[Table/Fig-2]: Demographic parameters and clinical symptoms of study subjects.
$Student's t-test applied; #Chi-square test

Based on the anatomical location of the malignant lesions, breast cancers were the most common, with 43 (22.6%) patients, followed by Gastrointestinal (GI) cancers, which comprised 47 (24.7%) patients among those with anaemia [Table/Fig-3]. According to

Organ systems involved	Group A, n=80 n (%)	Group B, n=110 n (%)
Head and neck	16 (20)	22 (20)
Lung	8 (10)	10 (9.09)
Breast	18 (22.5)	25 (22.72)
Gastrointestinal (GI)	19 (23.75)	28 (25.45)
Hepatobiliary	4 (5)	6 (5.45)
Genitourinary/gynaecological	11 (13.75)	13 (11.81)
Others*	4 (5)	6 (5.45)

[Table/Fig-3]: Distribution of study subjects based on the anatomical location of the malignant lesions.
*Other organ systems included musculoskeletal cancers, dermatological cancers and adrenal cancers

the histopathological diagnosis, 22 patients with Head and Neck Cancers (HNC) and 12 patients with gynaecological cancers had Squamous cell carcinoma. On the other hand, 22 patients with breast cancers had Invasive ductal carcinoma.

Out of a total of 190 patients, 110 (57.8%) had chemotherapy-induced anaemia (the patients were not anaemic prior to starting cancer treatment). Additionally, 75 (39.4%) patients were diagnosed with Cancer-related Anaemia (CRA), based on normal ferritin levels and no other apparent causes of anaemia, such as bleeding or marrow involvement, which could be attributed to cancer-associated chronic inflammation. Furthermore, 5 (2.6%) patients had anaemia due to chronic kidney disease. The types of anaemia observed on peripheral blood smears in the study subjects are presented in [Table/Fig-4]. There was a significant association between the different types of anaemia and metastatic cancers (p-value=0.02), with normocytic anaemia being the most common type among these patients.

Groups	Normocytic anaemia, n=99 (52.1%)	Microcytic anaemia, n=81 (42.63%)	Macrocytic anaemia, n=10 (5.26%)	p-value
Group A, n=80 n (%)	50 (62.5)	25 (31.25)	5 (6.25)	0.02*
Group B, n=110 n (%)	49 (44.54)	56 (50.9)	5 (4.54)	

[Table/Fig-4]: Prevalence of type of anaemia based on the peripheral blood smear findings in the study subjects.
Chi-square test; *The p-value <0.05 was considered statistically significant

The distribution of study subjects according to the severity of anaemia and its association with metastasis is shown in [Table/Fig-5]. A total of 22/190 (11.57%) patients with cancer had severe anaemia. Severe anaemia was present in a significantly higher number of patients with metastases, 17 (21.25%) compared to those without metastases, 5 (4.54%) (p-value=0.0003).

Severity of anaemia	Group A, n=80 n (%)	Group B, n=110 n (%)	p-value
Mild anaemia	21 (26.25)	39 (35.45)	0.177
Moderate anaemia	42 (52.5)	66 (60)	0.3027
Severe anaemia	17 (21.25)	5 (4.54)	0.0003*

[Table/Fig-5]: Distribution of patients as per the type and severity of anaemia (as per WHO criteria) and its association with metastasis.
Chi-square test

The mean values of Hb and other blood parameters in the study subjects [Table/Fig-6] [12]. The average Hb, CRC, MCV, MCHC, and RBC counts were significantly lower in patients with metastasis compared to those without metastasis (p-value <0.05).

Blood parameters (Normal values)	Group A, n=80 Mean±SD	Group B, n=110 Mean±SD	p-value
Haemoglobin (Hb) (Male- 14.0-17.5 g/dL and Female- 12.3-15.3 g/dL)*	8.65±1.55	9.11±1.55	<0.00001*
CRC	1.76±0.27	1.85±0.27	0.04*
MCH (27.5-33.2 pg)*	26.72±4.37	27.51±3.73	0.272
MCHC (33.4-35.5 g/dL)*	32.07±1.40	32.66±1.21	0.0074*
MCV (80-96 fL)*	80.87±17.72	75.65±17.77	0.0446*
RBC count (Male- 4.52-5.90×10^6/µL Female- 4.1-5.1×10^6/µL)*	3.57±0.63	3.83±0.60	0.008*
RDW (11.6-14.6%)*	18.34±4.56	17.38±3.41	0.095
Serum ferritin (12-300 ng/mL)*	83.24±26.17	90.24±27.98	0.0842
Serum iron (50-160 µg/dL)*	35.15±5.89	34.40±8.06	0.1221
Folate levels (5-21 µg/L)*	10.50±0.215	10.50±1.73	0.8921
Vitamin B12 levels (150-670 pmol /L)*	400.89±316.85	322.98±237.83	0.2006
TIBC (250-400 µg/dL)*	367.43±68.98	370.53±71.82	0.3455
Transferrin saturation (20-55%)*	11.89±3.69	11.32±3.53	0.6772

[Table/Fig-6]: Haemogram parameters in patients with and without metastases [12]*.
Student t-test; CRC: Corrected reticulocyte count; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; MCV: Mean corpuscular volume; RBC: Red blood cell; RDW: Red cell distribution width; TIBC: Total iron binding capacity

DISCUSSION

The current study involved a total of 190 subjects, most of them were in their 4th to 5th decade of life, with a slight female preponderance. Eighty out of 190 patients had metastatic cancers at the time of enrollment in the study. More than 36% of the study subjects had experienced at least one episode of bleeding before admission, with per rectal bleeding being the most common site. Chemotherapy-induced, normocytic and microcytic anaemia were the most common types encountered. Patients with metastatic disease had significantly higher chances of having severe anaemia (Hb <8 gm%) and worse haemogram parameters compared to patients without metastasis.

Globally, the incidence of cancer is on the rise. In India, the cancer incidence for the year 2022 was approximately 100.4 per lakh population, meaning that one in nine people is likely to develop cancer [13]. With the increasing trend of cancer burden in society, it is crucial to identify the patterns and epidemiology of the disease to establish reliable strategies for both primary and secondary cancer prevention. Cancer is associated with a myriad of complications that affect various systems, including haematological, cardiovascular, metabolic, endocrine and immunological systems, from its symptomatology to diagnosis and treatment.

In India, there exists wide variation in the leading cancer sites based on the age and gender of patients [14]. The median age of diagnosis also varies with different individual cancer types. In the current study, the prevalence of cancer was higher after the age of 40 years (86.8%) compared to those below the age of 40 years, with no significant gender difference. There are conflicting reports regarding the association between Body Mass Index (BMI) and cancer prevalence. In a study conducted by Pati S et al., a high BMI was established as a risk factor for 4-8% of all cancers [15]. On the other hand, a meta-analysis conducted by Dehesh T et al., found no significant correlation between high BMI and the development of breast cancer [16]. In the current study also, BMI varied with different types of cancers, and no statistical significance was established between BMI and metastatic versus non metastatic cancer.

Symptoms such as fatigue, weight loss, loss of appetite, breathlessness, and bleeding manifestations are common at the time of cancer diagnosis, although these symptoms can be attributed to multiple disorders [17,18]. Thus, it is important for physicians to identify the correct cause of these symptoms, as misdiagnosis can worsen the patient's quality of life. In the current study, weight loss and fatigue were prominent symptoms in both metastatic and non-metastatic cancers, often accompanied by anaemia. However, these symptoms were significantly associated with metastatic cancers only (p-value <0.05).

In the present study, the most common sites of malignancy associated with anaemia were GI (n=47), breast (n=43) and HNC

(n=38). Several studies have shown that the prevalence of anaemia is high in solid tumours of breast, gynaecological and GI origin [2,19]. This may be due to the female gender preponderance in breast and gynaecological cancers, as well as, higher chances of bleeding in GI cancers [2]. Lung cancer comprised 9.47% of all cancer patients in the current study, which was slightly higher than the prevalence of lung cancer in the Indian population (5.9%) [20]. The prevalence of HNCs in the current study (20%) was significantly higher than the global prevalence of 7.6% [21]. Most of the HNCs in the current study were of oral and laryngopharyngeal origin (76.13%). This may be attributable to several locoregional factors, such as the prominent consumption of betel nut and chewing tobacco, which are common practices in the Indian subcontinent [22,23].

Anaemia is a common finding in cancer patients. Apart from its usual causes, anaemia in cancer can occur due to blood loss, marrow infiltration, anaemia of chronic disease and treatment-related complications. The prevalence of severe anaemia in the current study was 11.57%. In the general population, severe anaemia (Hb <8 gm%) usually leads to poor performance, making it difficult for patients to perform specific activities of daily living without assistance. The performance status of cancer patients is already compromised due to treatment and disease-related complications, and the presence of severe anaemia can further exacerbate this issue. In the current study, anaemia was significantly more severe in patients suffering from metastatic cancer (n=17) compared to those with non-metastatic cancers (n=5) (p-value=0.0003). In a study by Badheeb AM et al., low Hb levels correlated with poor performance status across all tumour stages [24].

Cancer-related anaemia is a distinct condition caused by chronic inflammation due to malignancy and the release of proinflammatory cytokines by cancer cells, rather than by other mentioned causes [18,25]. CRA is commonly characterised by normocytic anaemia, which was observed in the present study (n=99) [18,23]. Patients in the current study exhibited a low reticulocyte index, low MCV, low serum iron and normal serum ferritin levels. These findings align with those of a study conducted by Schneider C et al., [26].

Worldwide, researchers are striving to understand the evolution of malignant tumours, how they spread, and how to prevent them. However, our understanding of the mechanisms underlying the metastasis of cancers is still in its early stages. Metastasis is a continuous, evolving, heterogeneous and unpredictable complication of cancer [27]. Therefore, it is crucial to diagnose metastasis and its complications in patients with cancer, as early as, possible to improve their outcomes and quality of life.

Limitation(s)

The small sample size makes it difficult to extrapolate the results to the general population. Additionally, the long-term effects of antineoplastic treatment and the impact of iron supplementation were not studied in the patients.

CONCLUSION(S)

The present study indicated that the presence of metastasis was associated with more severe anaemia. Chemotherapy-induced and CRAs were more common in patients with solid organ malignancies. Patients with metastatic cancers frequently exhibited normocytic and microcytic anaemia compared to those without metastasis. Further research, along with proper guidelines for the treatment of chemotherapy-induced and CRA, is urgently needed. The present study is unique as, it examines two distinct groups of cancer patients with anaemia- those with and without metastases and provides insight into which patients should be monitored for the development of anaemia. Anaemia in cancer patients should be suspected, diagnosed early, and managed optimally to improve their quality of life, enhance cancer management, and prevent further complications.

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