# PREVALENCE OF ANEMIA IN PATIENTS WITH SOLID TUMORS: A SINGLE CENTER CROSS-SECTIONAL STUDY AT A TERTIARY CARE CENTER IN WEST INDIA

**Oncology**

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## ABSTRACT

**Background:** Anemia is one of the most frequently reported problems in patients with cancer. It is a frequent finding in cancer patients, occurring in >40% of cases.

**Methods:** To evaluate the distribution, the main causes, and the possible correlations of anemia with type and stage of cancer in a population of patients with solid tumors, we carried out a cross sectional observational study on a cohort of 127 subjects.

**Results:** Anemia was observed in 58.4% of patients, with an increase in the prevalence with increasing age regardless of gender difference. In more than one-half (59.1% )of anemic patients, anemia was mild. Moderate to severe anemia was seen in 27.6% and 13.4% cases respectively. Iron deficiency was the commonest etiology for anemia in cases with solid tumors (54.33%) followed by anemia due to chronic disease (41.73%). Mild anemia was relatively more common in cases with CNS tumors and Breast carcinoma while severe anemia was associated with lymphomas and colorectal carcinoma.

**Conclusion**: Our data confirm the high prevalence of anemia in patients hospitalized in an Oncology unit, with a remarkable burden of mild forms, and of chronic inflammation's pathogenic mechanism. Correlations with comorbidities and duration of hospital stay highlight the crucial part played by anemia in determining the clinical complexity of such patients.

## KEYWORDS

Anemia, Iron deficiency anemia, Anemia of Chronic Disease, Solid Tumors

## 1. INTRODUCTION

Anemia is a global public health problem which affects both the developing and the developed nations and it is an indicator of poor nutrition and poor human health. [1]. Anemia is one of the most common health problems in India which is much more prevalent in the rural than in the urban areas [2,3]. The National Family Health Survey-4 data showed that 53% of the women and 22.7% of the men are anaemic [4].

Anemia is one of the most frequently reported problems in patients with cancer. It is a frequent finding in cancer patients, occurring in >40% of cases [5]. Anemia is often considered a side effect of cancer therapy; however, many patients are already anemic before the start of any treatment. Anemic cancer patients can be divided into two major groups: those with hemoglobin (Hb) concentration in the normal range prior to medical treatment (often receiving adjuvant cancer therapy after surgery, with at most microscopic tumor burden); here, the occurrence of anemia during cancer therapy should be considered a specific side effect of treatment; and those with preceding cancer-related anemia (often undergoing cancer therapy for clinically detectable tumors): here, cancer-related anemia may be a consequence of the chronic inflammation present in patients with advanced cancer. In patients treated with chemotherapy, the incidence of anemia may rise to 90% . Anemia has also been identified as an adverse prognostic factor and exerts a negative influence on the quality of life of cancer patients as it may contribute to cancer-induced fatigue.

For any cancer patient with Hb of less than 11 g/dl or below the lower limit of normal by $\geq 2$ g/dl, the 2011 National Comprehensive Cancer Network (NCCN) guidelines recommend complete evaluation of its cause [6]. Once CBC with indices, reticulocyte count and examination of peripheral blood smear are done for morphology, additional tests may be required to identify the cause (hemolysis, heredity, nutritional, renal, hemorrhage and therapy induced myelosuppression). If no cause is identified, the patient is presumed to have anemia of chronic illness/cancer [5].

Anemia and associated symptoms commonly manifest in cancer patients and may have a considerable impact on outcomes. Preliminary studies suggest that overall survival and loco-regional control following radiation therapy may be compromised by anemia, and recent preliminary data also suggest that anemia may be related to poorer outcomes following chemotherapy. Health-related quality of life of cancer patients is also significantly reduced by anemia.

In the present study, we aimed to assess the prevalence of anemia in patients with different types of solid malignancies and evaluated the pattern of anemia based on various clinical features and hematological parameters.

## 2. PATIENTS AND METHODS

### 2.1 Study design
We carried out cross-sectional observational study on a cohort of consecutive adult patients with solid tumors admitted to an Oncology unit of a tertiary care center in western India during the 2018-2019 period.

### 2.2 Population
We enrolled all patients whose demographic, clinical and anamnestic data were available. Laboratory results were extracted from the laboratory database. All consenting adult patients more than 18 years of age with a fresh histo-pathological diagnosis of solid tumors detected with anemia were included in the study. All patients below 18 years of age, patients with hematological malignancies except lymphomas and those already on chemotherapy or radiotherapy were excluded. Patients who were already on treatment for long standing anemias unrelated to malignancy were also excluded.

### 2.3 Laboratory techniques
All laboratory tests were performed on blood sample collected by venipuncture by the Central Laboratory of the tertiary care center. Complete blood count (CBC) was determined by impedentiometric methodology using UniCel DxH 800 analysis system (Beckman Coulter, Brea, CA). Serum iron was measured colorimetrically using Abbott Architect c16000 analyzer (Diamond Diagnostics, Holliston, MA). Transferrin and ferritin were determined via nephelometric and chemoluminescence method, respectively, using Dimension VISTA 1500 Intelligent Lab System (Siemens, München, Germany). Folate and vitamin B12 were measured through chemo-luminescence technique using IMMULITE 2000 XPi system (Siemens, München, Germany).

### 2.4 Diagnosis of anemia
We considered the first hemoglobin value, measured at the admission, for all analyses. The diagnosis of anemia was based on the WHO criteria [16], and severity levels were defined on grounds of the following values: mild anemia, Hb 10.0–11.9 g/dL in females and Hb 10.0–12.9 g/dL in males; moderate anemia, Hb 8.0–9.9 g/dL; severe

anemia, Hb < 8.0 g/dL. To classify the types of anemia according to etiology, laboratory parameters and, in some cases, the anamnestic data were used. Anemia of chronic inflammation was diagnosed for low serum iron level (< 60 μg/dL), without evidence of iron deficiency, and serum value of CRP at least 3 times higher than the upper limit of reference interval. Iron deficiency was defined as serum level of ferritin < 50 μg/dL, vitamin B12 deficiency as serum level of vitamin B12 < 200 pg/mL, and folate deficiency as serum folate concentration < 2 ng/mL. Anemia was considered multifactorial in the presence of two or more inclusion criteria. If anemic patients could not be classified into any of the above categories, they were considered as having unexplained anemia.

Histopathological reports of the solid malignancies were taken as basis for classifying type of tumor and stage of tumor. Severity and type of anemia was correlated with site and type of malignancy.

### 2.5 Statistical Analysis
The quantitative data was represented as their mean ± SD. Categorical and nominal data was expressed in frequency and percentage and analyzed by using chi-square test. The significance threshold of p value will be set at <0.05. All analysis were carried out by using SPSS software version 21.

## 3. RESULTS
Of the 127 patients, about half of the cases were above 60 years of age with mean age being 64.32 years. The study population included 55.9% males to 44.1% females. Common malignancies observed were breast carcinoma (22.8%) followed by head and neck carcinoma (including oral carcinoma – 18.1%), cervical carcinoma (16.5%), Lung carcinoma (14.2%) and colorectal carcinoma (12.6%) (Table 1). Easy fatigability (79.53%) was the most common presenting symptoms in majority of the cases followed by generalized weakness (58.27%) and dyspnea on exertion (52.76%). Pallor was present in all cases while raised JVP and koilonychia was observed in 3.94% and 7.09% cases respectively.

**Table 1. Distribution of cases as per type of Malignancies**

| Type of Malignancies | N | % |
|---|---|---|
| Breast Ca | 29 | 22.8% |
| Head & Neck Ca | 23 | 18.1% |
| Cervical Ca | 21 | 16.5% |
| Lung Ca | 18 | 14.2% |
| Colorectal Ca | 16 | 12.6% |
| Oesophageal & GI Ca | 7 | 5.5% |
| CNS Tumors | 6 | 4.7% |
| Hematological Malignancies(Lymphomas] | 5 | 3.9% |
| Others | 2 | 1.6% |
| Total | 127 | 100.0% |

Mild anemia was observed in 59.1% cases while moderate to severe anemia was seen in 27.6% and 13.4% cases respectively (Figure 1). Iron deficiency was the commonest etiology for anemia in cases with solid tumors (54.33%) followed by anemia due to chronic disease (41.73%). Megaloblastic anemia was seen in 3.94% cases.

Mild anemia was relatively more common in cases with CNS tumors and Breast carcinoma while severe anemia was associated with lymphomas and colorectal carcinoma (Table 2).

**Table 2. Association of type of Malignancy with severity of Anemia**

| Type of Malignancy | N | Mild Anemia | | Mod/ Severe Anemia | |
|---|---|---|---|---|---|
| Breast Ca | 29 | 21 | 72.4% | 8 | 27.6% |
| Head & Neck Ca | 23 | 14 | 60.9% | 9 | 39.1% |
| Cervical Ca | 21 | 13 | 61.9% | 8 | 38.1% |
| Lung Ca | 18 | 10 | 55.6% | 8 | 44.4% |
| Colorectal Ca | 16 | 6 | 37.5% | 10 | 62.5% |
| Oesophageal & GI Ca | 7 | 3 | 42.9% | 4 | 57.1% |
| CNS Tumors | 6 | 5 | 83.3% | 1 | 16.7% |
| Lymphoma | 5 | 1 | 20.0% | 4 | 80.0% |
| Others | 2 | 2 | 100.0% | 0 | 0.0% |
| Total | 127 | 75 | 59.1% | 52 | 40.9% |

A significant association was observed between severity of anemia and stage of tumor with 31.3% cases of stage I carcinoma had severe anemia as compared to 100% cases of stage IV (Table 3).

**Table 3. Association of stage of Malignancy with severity of anemia**

| Stage of Malignancy | N | Mild Anemia | | Mod/ Severe Anemia | |
|---|---|---|---|---|---|
| Stage I | 96 | 66 | 68.8% | 30 | 31.3% |
| Stage II | 18 | 7 | 38.9% | 11 | 61.1% |
| Stage III | 9 | 2 | 22.2% | 7 | 77.8% |
| Stage IV | 4 | 0 | 0.0% | 4 | 100.0% |
| Total | 127 | 75 | 59.1% | 52 | 40.9% |

**Table 4. Association of type of malignancy with etiology of Anemia**

| Type of Malignancy | N | IDA | | Anemia of Chronic Disease | | Megaloblastic Anemia | |
|---|---|---|---|---|---|---|---|
| Breast Ca | 29 | 11 | 37.9% | 18 | 62.1% | 0 | 0.0% |
| Head & Neck Ca | 23 | 13 | 56.5% | 10 | 43.5% | 0 | 0.0% |
| Cervical Ca | 21 | 10 | 47.6% | 11 | 52.4% | 0 | 0.0% |
| Lung Ca | 18 | 9 | 50.0% | 8 | 44.4% | 1 | 5.6% |
| Colorectal Ca | 16 | 12 | 75.0% | 3 | 18.8% | 1 | 6.3% |
| Oesophageal & GI Ca | 7 | 5 | 71.4% | 1 | 14.3% | 1 | 14.3% |
| CNS Tumors | 6 | 3 | 50.0% | 2 | 33.3% | 1 | 16.7% |
| Hematological Malignancies | 5 | 5 | 100.0% | 0 | 0.0% | 0 | 0.0% |
| Others | 2 | 1 | 50.0% | 0 | 0.0% | 1 | 50.0% |
| Total | 127 | 69 | 54.3% | 53 | 41.7% | 5 | 3.9% |

Iron deficiency anemia was relatively more common in cases with haematological and GI malignancies while anemia of chronic disease was associated with breast and cervical carcinoma (Table 4).

## DISCUSSION
The present study included 127 patients of solid tumors with anemia, with mean age of 64.32 +/- 14.16 years, maximum of the study subjects were males (56%). Similar age at presentation has been observed by other authors, Toledano A et al. [13] in their study observed median age of patients was 64 years (21-90 years) and 44% were male. Ludwig H et al. [14] also observed mean age of patients as 65.0 (22.5–96.8), with male preponderance, 59% of their subjects were males. Risk of developing cancer increases with age, more than a third (36%) of all cancers are diagnosed in people aged 75 yrs or over. Over half (53%) of all cancers occur in people aged 50-74 yrs [15].

Anemia was classified as per WHO classification and maximum number of patients in present study had mild anemia (59.1%) while 27.6% and 13.4% were moderate and severely anemic. Prevalence and grading of anemia as per tumor type was evaluated and it was observed that maximum patients of Lymphomas (80%) and colorectal cancer (62%) were severely anemic at the time of diagnosis, followed by esophageal, GI (57%) and lung cancer (44%). Patients of all other tumours presented with mild anemia.

Hemoglobin levels were seen to further deteriorate with advancing stages of disease i.e patients of stage III and stage IV malignancies were observed to have moderate to severe anemia. In the advanced stages of hematologic malignancies, bone marrow involvement often leads to progressive anemia. In addition, interaction between tumor cell populations and the immune system can lead to the release of cytokines, especially interferon-γ, interleukin-1 and tumor-necrosis factor-α. This release disrupts endogenous erythropoietin synthesis in the kidney and suppresses differentiation of erythroid precursor cells in the bone marrow. As a result, patients with tumor anemia can have relatively low levels of erythropoietin for the grade of anemia observed. They also stated that in the advanced stages of lymphomas, bone marrow involvement often leads to progressive anaemia, as seen in present study [10].

Ludwig H et al. [8] reported that across most tumor types evaluated, a high prevalence of iron deficiency and moderate to severe anemia was noted in pancreatic (63.2%), colorectal (52.2%) and lung cancer (51.3%) patients. In patients with solid tumors, a significant correlation between tumor stage and anemia was found (P < 0.0001 and P < 0.0001, respectively). The prevalence of anemia increased from 35.4% in stage I – II to 45.2% in stage III and 53.6% in stage IV patients, the corresponding figures for anemia were 18.4%, 29.8% and 41.2%, respectively and these findings are in accordance with the present study. Similar findings have also been reported by Kanuri G et al. they reported that when patients were categorized according to the type of cancer, the mean hemoglobin value was lowest in patients with

a diagnosis of lymphoma followed by lung cancer, GI tumors and cancer of head and neck. There were no demonstrable differences in mean hemoglobin values based on patients cancer stage in their study, this can be attributed to the fact that most of the patients in their study were in stage IV at the time of diagnosis [11]. Wu Y et al. [12] also observed patients with hematologic malignancies were more likely to have anemia at the time of diagnosis, the next highest prevalence for anemia was 53.3% among patients with breast cancer, and 50.9% among patients with non-small cell lung cancer (NSCLC). The clinical manifestation and severity of anemia vary considerably among individual patients. Moderate anemia can typically cause signs and symptoms such as headache, palpitations, tachycardia and shortness of breath. In addition to physical symptoms, the subjective impact of cancer-related anemia on quality of life [13].

We tried to evaluate the most common etiology for anemia in cancer patients. Maximum number of patients had microcytic hypochromic (48.2%) anemia suggesting iron deficiency to be the most important cause of anemia. 38.5% had normocytic normochromic type and rest of them were macrocytic hypochromic and dimorphic. Thus present study observed iron deficiency and anemia of chronic diseases to be the most common etiology. Xu et al. found that approximately 10% of anemic patients were either microcytic or macrocytic; and around 10% of patients were hypochromic [14]. Findings of the present study were supported by Kanuri G et al. [15] they reported that the etiology of cancer related anemia in their setting was mostly iron deficiency anemia. Aapro M et al. [16] also found that the major etiology of anemia in these cancer patients was iron deficiency anemia superimposed on anemia of inflammation. Our findings have also been well supported by Goodenough LT et al. they reported that the major contributor appears to be iron restricted erythropoiesis resulting from anemia of inflammation, absolute iron deficiency or a combination of the two [17]. Iron deficiency was also seen to be highly prevalent in cancer patients in a study by Ludwig H et al. [8]. These data indicate that pre-existing micronutrient deficiencies (e.g. iron deficiency) profoundly influence the development of cancer related anemia, in addition to chemotherapy and tumor cell-released cytokines. A comprehensive evaluation of anemia as well as the underlying conditions, such as the nutritional status and bone marrow function, may help guide anemia management.

Iron deficiency anemia and anemia of chronic diseases were the most common forms of anemia observed and on relating the different types of cancers with the probable etiology of anemia, it was observed that iron deficiency was the most common type of anemia in patients of colorectal (75%), esophageal and GI cancers (71.4%), while anemia of chronic diseases was the most common type seen in patients of Breast cancer (62.1%), cervical cancer (52.4%) and lung cancer (43.5%). Ludwig H et al. [14] also observed that across most tumor types evaluated, a high prevalence of Iron deficiency (ID) anemia was noted. ID rates were highest in pancreatic (63.2%) and colorectal cancer (52.7%). Marks PW et al. [18] reported that anemia of cancer may also be evident at initial diagnosis. Activation of the immune system appears to be the driving force for a global diminution of erythropoiesis, analogous to chronic inflammatory conditions observed in anemia of chronic disease and Breast cancer, prostate cancer, small cell lung cancer, and lymphoma are among the most common tumors associated. They also reported Patients with cancer may develop anemia secondary to poor nutrition in general or due to reduced function in the gastrointestinal (GI) tract to absorb nutrients and Iron deficiency anemia due to blood loss or the inability to absorb iron in the GI tract often occurs in patients with malignancies of the GI tract, including colorectal cancers. Birgegård G et al. also reported similar findings. These findings supported the findings of the present study [19].

## CONCLUSION
The present study has shown that the main etiology of anemia in Indian cancer patients is iron deficiency anemia followed by anemia of chronic diseases. It is a widespread and serious problem especially among colorectal cancer, lung cancer and breast cancer patients. An early evaluation and management of anemia could reduce the incidence of treatment-related anemia in cancer patients.

Newer cancer treatment protocols should be designed keeping in mind the high prevalence of anemia in our cancer patients. Measures directed towards characterization and treatment of anemia should be incorporated as an integral part of our cancer management protocols.

Patients with anemia should be closely monitored, and a vigilant management strategy should be implemented to reduce the risk of morbidity associated with anemia.

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