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Original Research Article

Study of Anemia in Non-Hematological Malignancies: Incidence, Pattern, Severity and Hematological Parameters — A Prospective Study

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Conflict of interest: Nil

Abstract

Background: Anemia is the most frequently encountered hematological complication in non-hematological malignancies, adversely affecting quality of life, treatment tolerance, and prognosis. The European Cancer Anemia Survey (ECAS) documented a prevalence of 39.3% at enrollment, rising to 67% during the survey period.

Objectives: To study the incidence, pattern, and severity of anemia in adult patients with solid malignancies, and to evaluate comprehensive hematological and iron study parameters.

Methods: A prospective observational study was conducted (October 2023–June 2025) at the Department of Pathology, MGMCH. Sixty newly diagnosed, treatment-naïve patients (34 males, 26 females; aged 19–69 years; Hb <12 g/dL) with confirmed non-hematological malignancies underwent complete hemogram (Sysmex XP-100), peripheral blood film (Leishman stain), and iron studies (serum iron, TIBC, serum ferritin by CLIA).

Results: Mean age was 54.82 ± 11.70 years with male predominance (56.7%). Mild anemia predominated (51.7%), followed by moderate (33.3%) and severe (15%). Normocytic normochromic pattern was most common on peripheral blood film (56.7%). Serum ferritin was elevated in 50%, normal serum iron in 68.3%, and normal TIBC in 73.3% of patients.

Conclusion: Anemia is universal in non-hematological malignancies and increases in severity with age. Integrated early hematological assessment is essential for optimal oncological management.

Keywords: Cancer-related anemia; Non-hematological malignancy; Hematological parameters; Serum ferritin; TIBC; Peripheral blood film; Solid tumors.

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Introduction

Malignancies represent one of the leading causes of global mortality, accounting for an estimated 10 million deaths annually. Anemia is the most frequent hematological complication in patients with solid tumors, occurring in 30–90% of patients depending on tumor type, stage, and treatment status. The ECAS, enrolling 15,367 patients across 24 European countries, established an anemia prevalence of 39.3% at enrollment rising to 67% during treatment, with sub-optimal management in the majority. [1,2]

Cancer-related anemia (CRA) is multifactorial in origin. The dominant mechanisms include chronic inflammatory cytokine-mediated erythropoiesis suppression (anemia of chronic disease), iron deficiency from blood loss or functional sequestration, blunted erythropoietin (EPO) response, bone marrow infiltration, and myelosuppression from anticancer therapy. Pro-inflammatory cytokines — interleukin-1, interleukin-6, interferon-gamma, and tumor necrosis factor-alpha — produced by tumor and host immune cells suppress erythroid differentiation, reduce EPO production, and upregulate hepcidin, which in turn sequesters iron within reticuloendothelial cells. [3,4,5]

Clinically, anemia impairs quality of life, exacerbates fatigue, reduces treatment tolerance, and independently predicts poorer survival. Caro et al. demonstrated that anemia increased the risk of mortality by approximately 65% across multiple malignancy types. Tumor hypoxia resultant from anemia drives genomic instability, promotes angiogenesis, and confers resistance to

radiotherapy and chemotherapy. [6,7] Despite global data, limited Indian prospective studies have characterized the full spectrum of hematological findings — including iron studies — in treatment-naïve rural patients with solid malignancies. The present study was undertaken to systematically document the incidence, pattern, severity, and hematological correlates of anemia in such a cohort. [8]

Review of Literature

Major Epidemiological Surveys: The ECAS, the largest prospective epidemiological study of CRA, identified five independent predictors of anemia: low baseline Hb, gynaecological or lung malignancy, female sex, treatment with platinum chemotherapy, and non-colorectal cancer type. Hemoglobin levels were significantly correlated with performance status and quality of life, yet 61% of anemic patients received no treatment. [1]

The Australian Cancer Anemia Survey (ACAS) documented anemia in 35% of patients at enrollment and 57% at any time during the 6-month study, with blood transfusion as the most common intervention (36%). The Polish Cancer Anemia Survey (POLCAS) reported 71% cumulative prevalence, with lung and head-and-neck cancers carrying the worst prognosis; only 32% of eligible patients received treatment. [9,10]

Pathophysiology: Iron metabolism involves three sequential steps: dietary absorption, systemic regulation, and cellular uptake and release. Dietary non-haem iron is reduced from ferric to ferrous by ferrireductase and transported across the brush-border membrane via divalent metal transporter-1 (DMT-1). Transmembrane export via ferroportin-1 is followed by oxidation by hephaestin before binding to plasma transferrin for systemic delivery to erythroid precursors in the bone marrow. [11]

Hepcidin, a 25-amino-acid hepatic peptide upregulated by IL-6 during chronic inflammation, is the master regulator of iron homeostasis. By binding and inducing degradation of ferroportin on enterocytes and macrophages, hepcidin sequesters iron in storage compartments, reducing erythropoietic iron availability.

This mechanism underpins the anemia of chronic disease observed in malignancy. EPO production is blunted in cancer: Miller et al. demonstrated inappropriately low serum EPO in cancer patients versus iron-deficiency anemia controls matched for hemoglobin ($p=0.0001$). [3,4,12]

Bone marrow infiltration occurs in approximately 20% of non-hematological malignancies, most commonly from breast, prostate, lung, thyroid, and renal primaries. Myelophthisis displaces normal hematopoietic elements, producing a leukoerythroblastic blood picture and progressive cytopenias. [13]

Iron Studies in Malignancy: Serum ferritin — an acute-phase reactant synthesized in excess under TNF-alpha and IL-1 stimulation — is commonly elevated in malignancy, reflecting both increased iron stores and the inflammatory state.

Khanna et al. (2017) reported mean serum ferritin of 162.47 ng/mL in oral squamous cell carcinoma, falling after successful treatment.

Reduced TIBC in cancer reflects decreased transferrin synthesis driven by inflammation, as documented by Rajamaki et al. and Rodgers et al., who attributed this to hepcidin-mediated suppression of iron export. [14,15]

Aims and Objectives: The present study was undertaken with the following objectives:

- To determine the incidence and pattern of anemia in adult patients with non-hematological malignancies attending a rural tertiary care hospital.
- To assess the severity of anemia based on hemoglobin concentration, stratified by sex and age group.
- To evaluate hematological parameters — including RBC indices, serum iron, TIBC, and serum ferritin — in the context of various solid malignancies.

Materials and Methods

Study Design and Setting: A prospective observational cross-sectional study was conducted at the Department of Pathology, tertiary Care centre, Jaipur, Rajasthan from October 2023 to June 2025.

Participants: Sixty consecutive, newly diagnosed, treatment-naïve patients with histologically, cytologically, or radiologically confirmed non-hematological malignancies and hemoglobin <12 g/dL were enrolled (aged 19–69 years).

Exclusion criteria were: relapsed disease, ongoing chemotherapy/radiotherapy, prior surgery for the same malignancy, and significant systemic comorbidities (cardiac, renal, or hepatic disease) independently capable of impairing hematopoiesis.

Laboratory Methods: Two mL venous blood (K2-EDTA) were processed within 30 minutes of collection. Complete blood count was performed on Sysmex XP-100 (DC detection; oxyhemoglobin method for Hb). Peripheral blood films were stained with Leishman stain and classified morphologically.

Serum iron and TIBC were measured by the ferrozine spectrophotometric method (570 nm); serum ferritin was quantified by

Chemiluminescence Immunoassay (CLIA). Reference ranges: serum iron 50–150 µg/dL; TIBC 250–370 µg/dL; serum ferritin 12–50 ng/mL.

Anemia Classification

Table 1: WHO Criteria for Anemia Severity Classification

Severity	Hemoglobin (g/dL)	WHO Grade
Mild	10.0 – 11.9	Grade 1
Moderate	8.0 – 9.9	Grade 2
Severe	< 8.0	Grade 3

Table 1. WHO anemia severity criteria applied in the present study.

Statistical Analysis: Data are expressed as mean ± SD (quantitative) or frequency/percentage (categorical). Chi-square (χ^2) test, independent t-test, and one-way ANOVA were used. Significance was set at $p < 0.05$. Analysis was performed in IBM SPSS Statistics v21.

Results

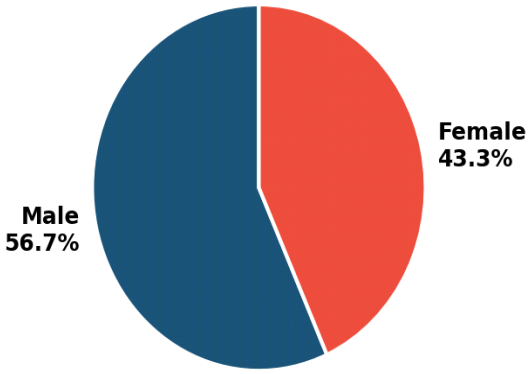
Demographic Profile: Of 60 patients, 34 (56.7%) were male and 26 (43.3%) female. Mean age was 54.82 ± 11.70 years. The 61–69-year age group had the highest representation (40%), confirming increasing cancer incidence with advancing age (Table 2; Figures 1–2).

Table 2: Sex-wise and Age-wise Distribution of Study Participants

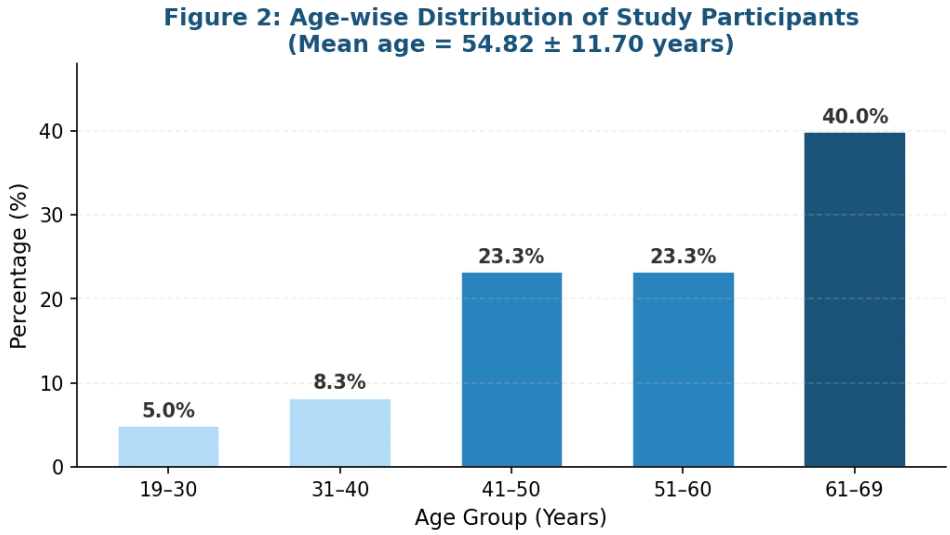
Variable	Subcategory — n (%)	Total
Sex	Male — 34 (56.7%)	60 (100%)
	Female — 26 (43.3%)	60 (100%)
Age 19–30 yrs	3 (5.0%)	
Age 31–40 yrs	5 (8.3%)	
Age 41–50 yrs	14 (23.3%)	
Age 51–60 yrs	14 (23.3%)	
Age 61–69 yrs	24 (40.0%)	Mean: 54.82 ± 11.70 yrs

Table 2. Demographic distribution (n=60).

Figure 1: Sex-wise Distribution of Study Participants (n=60)



[Figure 1: Sex-wise distribution of study participants (n=60). Males predominated at 56.7%.]



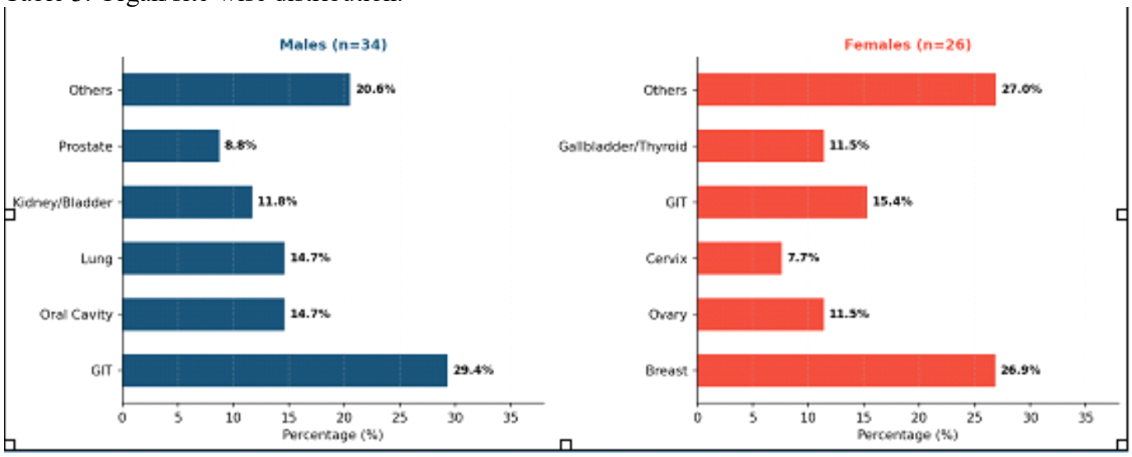
[Figure 2: Age-wise distribution of study participants. The 61–69-year age group had the highest frequency (40%).]

Malignancy Distribution: GIT malignancy was the most common site in males (29.4%), followed by oral cavity and lung (14.7% each). In females, breast carcinoma predominated (26.9%), followed by ovary and cervix (Table 3; Figure 3).

Table 3. Organ/Site-wise Distribution of Malignancy by Sex

Primary Site	Males n (%)	Females n (%)	Total n (%)
GIT (Colorectal/Gastric)	10 (29.4)	4 (15.4)	14 (23.3)
Breast	0 (0)	7 (26.9)	7 (11.7)
Oral Cavity	5 (14.7)	2 (7.7)	7 (11.7)
Lung	5 (14.7)	1 (3.8)	6 (10.0)
Cervix	0 (0)	2 (7.7)	2 (3.3)
Ovary	0 (0)	3 (11.5)	3 (5.0)
Kidney/Bladder	4 (11.8)	0 (0)	4 (6.7)
Gallbladder/Thyroid	2 (5.9)	4 (15.4)	6 (10.0)
Others	8 (23.5)	3 (11.5)	11 (18.3)

Table 3. Organ/site-wise distribution.



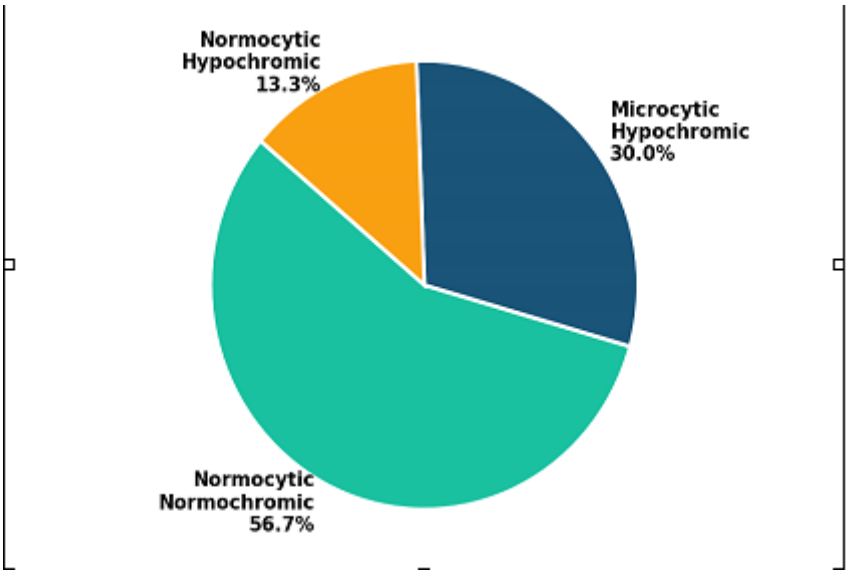
[Figure 3: Organ/site-wise distribution of malignancy by sex. GIT malignancy predominates in males; breast carcinoma in females.]

Peripheral Blood Film: Normocytic normochromic morphology was most common (56.7%), reflecting anemia of chronic disease as the dominant mechanism. Microcytic hypochromic pattern (30.0%) indicated concurrent iron deficiency in nearly one-third of patients (Table 4; Figure 4).

Table 4. Peripheral Blood Film Morphology

Morphological Pattern	n	% (of 60)
Normocytic Normochromic	34	56.7
Microcytic Hypochromic	18	30.0
Normocytic Hypochromic	8	13.3
Total	**60**	**100.0**

Table 4. Peripheral blood film distribution (n=60).



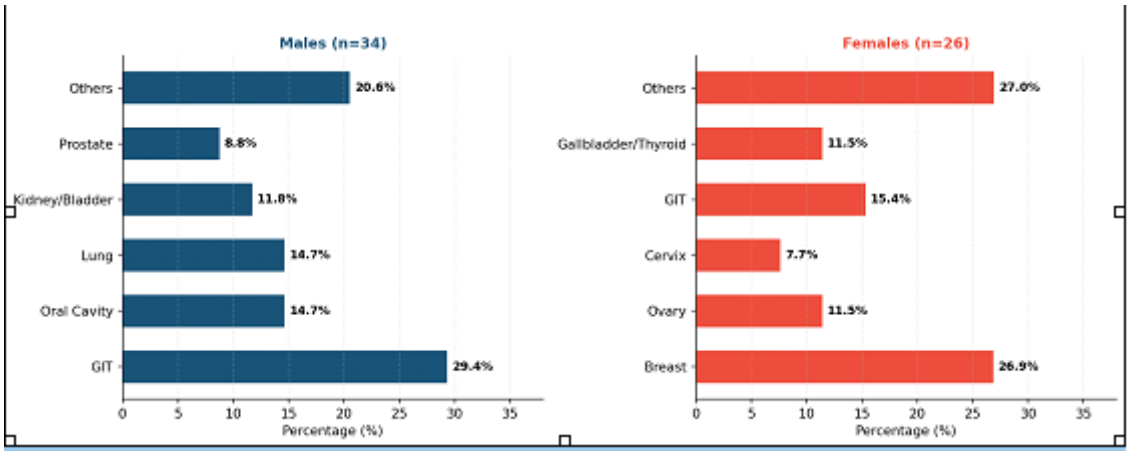
[Figure 4: Distribution of peripheral blood film morphology. Normocytic normochromic pattern (56.7%) was most frequent, consistent with anemia of chronic disease.]

Severity of Anemia: Mild anemia predominated (51.7%), followed by moderate (33.3%) and severe (15%). Males showed higher rates of moderate (44.1%) and severe anemia (17.6%) compared to females (mild predominance: 69.2%). Chi-square analysis (χ^2=5.844, p>0.05) showed no statistically significant sex difference (Table 5; Figure 5).

Table 5. Sex-wise Distribution According to Severity of Anemia

Sex	Severe (<8)	Moderate (8–9.9)	Mild (10–11.9)	Total
Male	6 (17.6%)	15 (44.1%)	13 (38.2%)	34 (100%)
Female	3 (11.5%)	5 (19.2%)	18 (69.2%)	26 (100%)
Total	9 (15.0%)	20 (33.3%)	31 (51.7%)	60 (100%)

Table 5. Severity of anemia by sex (χ^2=5.844, p>0.05).



[Figure 5: Sex-wise distribution according to severity of anemia. Mild anemia predominates in females; moderate anemia is more prevalent in males.]

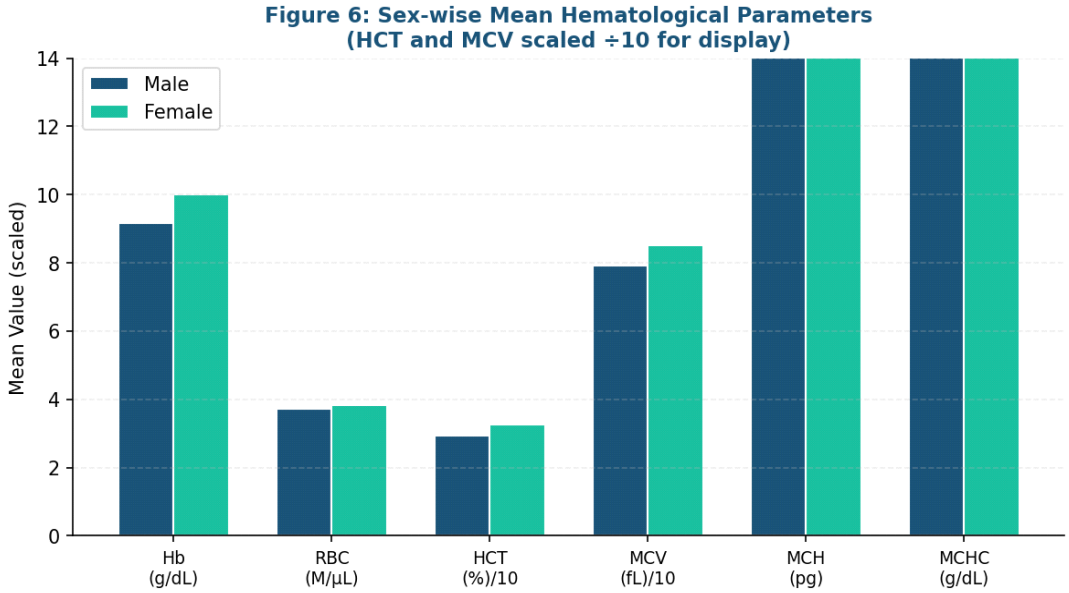
Hematological Parameters: Mean values are summarized in Table 6. Males had lower mean Hb (9.16 vs 10.0 g/dL), RBC (3.71 vs 3.84 M/µL), HCT (29.41 vs 32.56%), MCV (79.3 vs 85.08 fL), and MCH (25.2 vs 26.15 pg) compared to females. MCHC was marginally higher in males (31.17 vs 30.58 g/dL).

These sex-based differences were statistically significant for HCT, MCV, and MCHC (Table 6; Figure 6).

Table 6: Sex-wise Mean Hematological Parameters

Parameter (Reference Range)	Male (Mean)	Female (Mean)
Hb — g/dL (12–16 M, 11.5–15.5 F)	9.16	10.00
RBC — M/µL (4.5–5.9 M, 4.0–5.2 F)	3.71	3.84
HCT — % (41–53 M, 36–46 F)	29.41	32.56
MCV — fL (80–100)	79.30	85.08
MCH — pg (26–34)	25.20	26.15
MCHC — g/dL (31–37)	31.17	30.58
RDW — fL (39–46)	52.62	48.86

Table 6. Mean hematological parameters by sex (M = males, F = females).



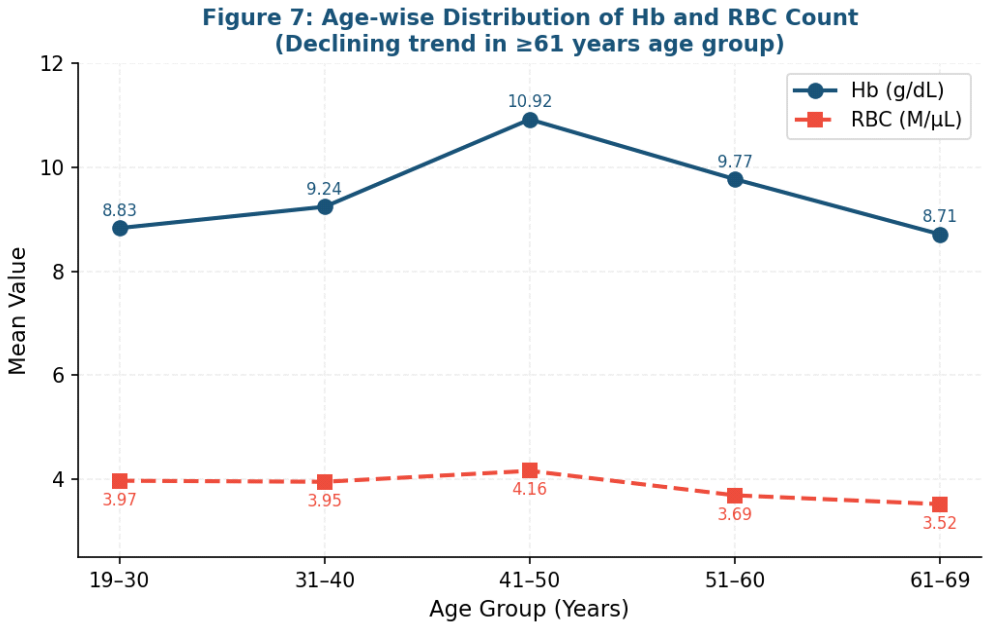
[Figure 6: Sex-wise mean hematological parameters. Values scaled for display (HCT and MCV divided by 10). Males show lower Hb, RBC, and MCV; higher MCHC and RDW.]

Age-wise Hematological Trends: Patients aged >60 years had the lowest mean Hb (8.71 g/dL), RBC count (3.52 M/µL), and HCT (28.72%), while exhibiting the highest mean RDW (54.74 fL), reflecting progressive anemia with aging. Patients aged <40 years had the lowest MCV and MCH, suggesting a higher contribution of iron deficiency in younger patients (Table 7; Figure 7).

Table 7: Age-wise Distribution of Key Hematological Parameters

Age (yrs)	Hb (g/dL)	RBC (M/µL)	HCT (%)	MCV (fL)	RDW (fL)
19–30	8.83	3.97	30.43	75.30	44.06
31–40	9.24	3.95	29.44	74.90	52.30
41–50	10.92	4.16	34.42	83.74	47.59
51–60	9.77	3.69	31.20	84.47	49.01
61–69	8.71	3.52	28.72	81.37	54.74

Table 7. Age-wise mean hematological parameters.



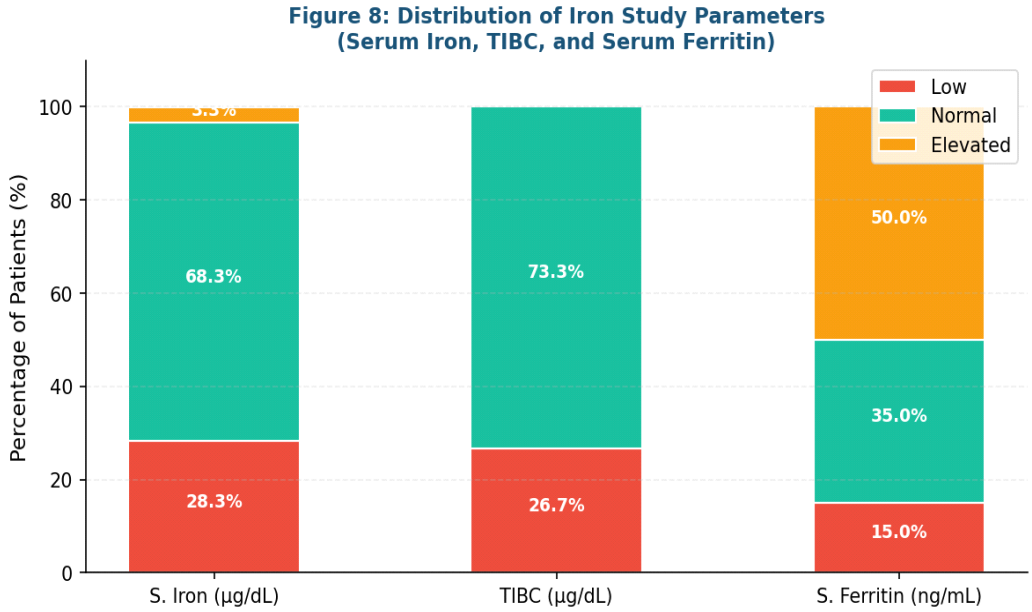
[Figure 7: Age-wise distribution of mean Hb and RBC count across age groups. Both parameters decline in the ≥61-year cohort.]

Iron Studies: Normal serum iron was present in 68.3% of patients; 28.3% had low serum iron. TIBC was normal in 73.3% and reduced in 26.7%. Serum ferritin was elevated (>50 ng/mL) in 50%, normal in 35%, and low in 15% of patients (Table 8; Figure 8). Mean iron study values differed by sex, with males showing lower serum iron (49.05 vs 67.02 µg/dL) and lower serum ferritin (79.60 vs 111.95 ng/mL) compared to females.

Table 8: Iron Study Parameters — Distribution and Sex-wise Mean Values

Parameter	Low n (%)	Normal n (%)	Elevated n (%)	Mean: Male / Female
Serum Iron (µg/dL) ref: 50–150	17 (28.3)	41 (68.3)	2 (3.3)	49.05 / 67.02
TIBC (µg/dL) ref: 250–370	16 (26.7)	44 (73.3)	0 (0)	291.22 / 270.32
Serum Ferritin (ng/mL) ref: 12–50	9 (15.0)	21 (35.0)	30 (50.0)	79.60 / 111.95

Table 8. Distribution and sex-wise mean values of iron study parameters (n=60).



[Figure 8: Distribution of iron study parameters — Serum Iron, TIBC, and Serum Ferritin — classified as low, normal, and elevated. Elevated serum ferritin in 50% reflects acute-phase inflammatory response.]

Malignancy Type and Anemia Severity: Mild anemia predominated in breast, lung, and cervical carcinoma. Moderate anemia was the dominant grade in GIT malignancies, attributable to chronic occult blood loss. This pattern was consistent with findings by Chowdhary et al. (2020) (Table 9).

Table 9: Association of Malignancy Type with Severity of Anemia

Malignancy Type	Predominant Grade	Proposed Mechanism
Breast Carcinoma	Mild	Anemia of chronic disease (ACD)
Lung Carcinoma	Mild	Chronic inflammation; blunted EPO
Cervical Carcinoma	Mild–Moderate	Chronic blood loss + ACD
GIT Malignancy	Moderate	Chronic occult blood loss + ACD
Oral Cavity	Mild–Moderate	Nutritional deficiency + ACD
Kidney/Bladder	Mild–Moderate	EPO deficiency + blood loss

Table 9. Association of malignancy type with anemia severity (ACD = Anemia of Chronic Disease).

Discussion

Demographics and Malignancy Distribution: The male predominance (56.7%) is consistent with published Indian and global data, attributed to higher tobacco use, occupational carcinogen exposure, and sex-specific cancer biology.

The mean age of 54.82 years reflects the established peak of solid tumor incidence in India in the fifth to sixth decades. GIT malignancy was the most common site in males, mirroring Mathur et al. (2020) who reported lung and GIT predominance in Indian males. Breast carcinoma was the leading malignancy in females, consistent with Siegel et al. (2020) and national registry data. [8,13]

Severity of Anemia: Mild anemia predominated (51.7%) in the present study, concordant with POLCAS (82.1%), ACAS (78%), and Chowdhary et al. (59.1%). ECAS reported a higher proportion of moderate anemia (49.2%), likely reflecting a more heavily pre-treated cohort. Males had higher rates of moderate and severe anemia compared to females, consistent with the predominance of hemorrhagic GIT malignancies in males. The statistically non-significant sex difference (χ^2=5.844, p>0.05) suggests that, while anemia is universal, sex does not independently determine grade. [1,9,10,15]

Peripheral Blood Film: Normocytic normochromic morphology (56.7%) was the predominant pattern, consistent with Almorish et al. (56.1%), reflecting anemia of chronic disease as the primary mechanism. Microcytic hypochromic pattern (30%) confirms concurrent iron deficiency in a substantial minority, likely reflecting tumor-related blood loss or nutritional deficiency superimposed on the chronic inflammatory state. This is in contrast to Chowdhary et al. (48.2% microcytic) and Kifle et al. (30.9% microcytic), whose cohorts had higher rates of iron deficiency. [12,15]

Hematological Parameters: Median hematological values in the present study (Hb 9.52 g/dL, RBC 3.77 M/mm³, HCT 30.77%, MCV 81.80 fL, MCHC 30.92 g/dL) closely parallel those reported in ECAS (Hb 9.6, RBC 3.3, HCT 29.6%, MCV 89 fL, MCHC 33 g/dL), confirming that CRA in the Indian rural setting mirrors global patterns. The declining Hb and HCT with advancing age (lowest in 61–69 year group) is consistent with the known age-related decline in hematopoietic reserve documented by Groarke and Young (2019). [1,14]

Iron Studies: Normal serum iron (68.3%) and TIBC (73.3%) in the majority of patients support anemia of chronic disease as the dominant mechanism. Reduced TIBC in 26.7% reflects decreased transferrin synthesis driven by inflammatory cytokines. Elevated serum ferritin in 50% — an acute-phase reactant — is consistent with the chronic inflammatory iron-sequestration state of CRA, as described by Adamson (2008). Only 2 patients had the classical triad of reduced serum iron + reduced TIBC + normal ferritin (pure ACD), emphasizing the multifactorial and mixed nature of CRA. [4,5,15]

Conclusion

The present study of 60 treatment-naïve patients with non-hematological malignancies yielded the following conclusions:

Male sex predominated (56.7%); maximum malignancy burden was in the 61–69-year age group (40%), confirming increasing cancer incidence with advancing age.

Mild anemia was the predominant grade (51.7%); moderate anemia was more prevalent in males and in GIT malignancies; mild anemia predominated in breast, lung, and cervical carcinoma.

Normocytic normochromic morphology was the most common peripheral blood film pattern (56.7%), consistent with anemia of chronic disease as the dominant mechanism.

Males had lower mean Hb, RBC, HCT, MCV, and MCH; statistically significant sex-based differences

were found for HCT ($p<0.05$), MCV ($p<0.05$), and MCHC ($p<0.05$).

The pattern of iron studies — normal serum iron (68.3%), normal TIBC (73.3%), and elevated serum ferritin (50%) — is characteristic of cancer-related anemia of chronic disease with inflammatory iron sequestration.

Comprehensive hematological assessment including hemogram, peripheral blood film, serum iron, TIBC, and serum ferritin should be integrated into routine oncological workup for early identification and management of CRA to reduce treatment-related morbidity and improve patient outcomes.

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Patient Consent: Written informed consent was obtained from all participants in English and Hindi.

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