KANSAS JOURNAL of MEDICINE

# Causes of Anemia in Patients Seen in a Rural Community Hematology Clinic

Sarah M. Featherstone, B.S.[1], William F. Cathcart-Rake, M.D.[1], Rosey Zackula, M.A.[2], Larry K. Beck, M.D.[1,3]
[1]University of Kansas School of Medicine-Salina, Salina, KS
[2]University of Kansas School of Medicine-Wichita, Wichita, KS
Office of Research
[3]Tammy Walker Cancer Center, Salina, KS

*Received Jan. 9, 2022; Accepted for publication March 11, 2022; Published online May 17, 2022*
*https://doi.org/10.17161/kjm.vol15.16363*

## ABSTRACT

**Introduction.** Anemia is a common medical disorder seen in consultation by hematologists. This study was performed to determine the incidence of the etiologies causing anemia in patients referred to the hematologists at Tammy Walker Cancer Center (TWCC) in the rural Kansas community of Salina. An additional goal of the study was to compare the frequencies of different etiologies for anemia in this cohort of patients with those previously reported by four academic medical centers.

**Methods.** A retrospective review of the medical records of 152 patients seen at TWCC between August 2015 and May 2019 was performed. The patient's history and physical exam, complete blood count, and various additional hematologic studies ordered at the discretion of the TWCC hematologist were used to determine the etiology of each patient's anemia.

**Results.** The most common causes of anemia found in the chart review were iron deficiency (48.7%), hematologic malignancy (14.5%), chronic inflammation (13.8%), renal insufficiency (11.2%), and unexplained anemia (9.9%). While the incidences of anemia due to hematologic malignancy, chronic inflammation, and renal insufficiency were like that reported previously by four academic medical centers, significantly more iron deficiency and less unexplained anemia were found in the patients referred to TWCC.

**Conclusions.** The causes of anemia in patients seen at TWCC were similar to those reported by academic medical centers; however, the incidences were different. The differences in findings may reflect dissimilarities in the demographics of referral populations, the duration, and extent of the evaluation at TWCC, or referral patterns.

***Kans J Med 2022;15:170-174***

## INTRODUCTION

In 2012, the prevalence of anemia in the United States was estimated to be 7.1%, representing an increase of 3.1% since 2003.[1] The rising prevalence of anemia is concerning due to the adverse events associated with the impairment of oxygen delivery to tissues leading to organ dysfunction and the compensatory cardiovascular mechanisms such as increased stroke volume and heart rate.[2] Anemia is particularly problematic for the older population. A systematic review of studies of the effects of anemia in older patients found that anemia was associated with a greater risk for cardiovascular disease and cognitive impairment, as well as more frequent hospitalizations, longer hospitalizations, and increased mortality.[3] In older patients, anemia increased the risk for death, first all-cause hospitalization, and first cardiovascular hospitalization.[4] Recognition and correction of the underlying cause for the anemia, resulting in an increase in the hemoglobin level, was associated with improved quality of life in patients with cancer, chronic kidney disease, HIV/AIDS, rheumatoid arthritis, inflammatory bowel disease, heart failure, and diabetes, and in surgical patients.[2]

Multiple studies have described the etiology, effects, and treatment of anemia and found a significant proportion of patients without a readily identifiable cause for anemia.[5-8] The NHANES III study of the approximately three million anemic patients older than 66 reported that 33.6% of the cases had no readily identifiable cause.[5] A prospective study of outpatients older than 65 with anemia referred to the hematology clinics at either Stanford Hospital and Clinics or Veteran Affairs Palo Alto Health Care System also found that 35% of the anemia cases remained unexplained after a complete workup.[6] A similar study of outpatients aged 65 years and older referred to the University of Chicago Hematology Clinic without a known hematologic malignancy, cancer chemotherapy, or radiation therapy completed within the previous six months, reported 44% of patients had unexplained anemia after a hematologic workup.[7] Finally, in a study by Ania et al.[8], the cause of 16% of the anemia in men and women of Olmsted County, Minnesota was uncertain.

The primary purpose of this report was to examine the causes of anemia and prevalence of unexplained anemia in patients referred to a rural community hematology clinic for an initial evaluation of a primary diagnosis of anemia. A secondary aim was to compare the etiologies for anemia found at TWCC with the published findings of four major academic medical centers.

## METHODS

A retrospective medical record review was conducted of all patients referred to Tammy Walker Cancer Center (TWCC) in Salina, Kansas from August 2015 through May 2019, specifically for the evaluation and treatment of anemia. Salina is a community of approximately 48,000 in rural north central Kansas.

Anemia was defined using the World Health Organization criteria: a hemoglobin (Hb) of less than 12.0 g/dL for women and less than 13.0 g/dL for men.[9] Records were excluded if anemia was not the initial cause for the referral or if the patient was referred for evaluation of anemia discovered after a prior diagnosis or treatment of a non-hematologic malignancy within the preceding five years.

Each patient's Hb, hematocrit, white blood cell count (WBC) and platelet count, mean corpuscular volume (MCV), red blood cell distribution width (RDW), and reticulocyte count determined by the referring physician, if available, were reviewed. The additional diagnostic laboratory studies deemed appropriate by the TWCC hematologist also were reviewed. A complete blood count (CBC) and a complete metabolic panel invariably were repeated by the TWCC hematologist. Depending on the initial presentation of the patient, additional studies included iron studies, B-12 and folate levels, serum protein electrophoresis, coagulation studies, and bone marrow aspiration/biopsy with flow cytometry and cytogenetic studies. Final diagnoses were

determined by the TWCC physician after completion of the hematologic workup. Some patients were diagnosed as having multiple contributory causes to their anemia.

The number and percentage of the total cases represented by each etiology were calculated and compared to the results of four previously published reports on the etiologies of anemia.[5-8] For each diagnosis, the percentage of males and females, median age, and age range were reported, as well as the median values and ranges of select hematologic values including WBC, Hb, platelet count, MCV, and RDW.

The study was approved by the Salina Regional Health Center Institutional Review Board.

## RESULTS

The study population totaled 152 patients (56 males and 96 females), ranging in age from 16 to 95 years old. The median age of patients at their initial visit was 71.5 years old and 67.1% of the total study population was greater than 60 years old. The basic hematologic data of the study population are summarized in Table 1. The median hemoglobin seen in the patients reviewed in this study was 10.2 g/dL. Nineteen (12.5%) of the TWCC patients had severe anemia (Hb levels less than 8.0 g/dL). Anemia in the absence of leukopenia or thrombocytopenia was seen in 59.2% of patients.

**Table 1. Demographic and basic hematologic values of TWCC population.**

| Parameter | Median | Range |
|---|---|---|
| Age (years) | 71.5 | 16 - 95 |
| Hemoglobin (g/dL) | 10.2 | 5.7 - 13 |
| WBC (109/dL) | 6.7 | 1.4 - 60.3 |
| Platelet count (109/dL) | 252.5 | 8.4 - 677 |

The final etiologies for the cause of anemia are summarized in Table 2. Demographic information and basic hematologic values associated with each diagnosis are summarized in Tables 3 and 4, respectively. Iron deficiency was the most common etiology of anemia seen in the TWCC population (48.7% of patients). Nearly one-third of patients with iron deficiency anemia (15.8% of all patients in the study) were determined to have a gastrointestinal bleed by clinical history or after referral to gastroenterologist for further workup. Malabsorption due to a previously diagnosed condition, such as gastric bypass, and a history of heavy menstruation contributed to the iron deficiency in other cases. Unfortunately, the cause for iron deficiency anemia could not be determined in 25.7% of the patients in this group.

**Table 2. Etiology of anemia in TWCC study population.**

| Etiology of Anemia | Males Number (%) | Females Number (%) | Total Number (%) |
|---|---|---|---|
| Iron deficiency | 22 (39.3%) | 52 (54.29%) | 74 (48.7%) |
| Hematologic malignancy | 11 (19.6%) | 11 (11.5%) | 22 (14.4%) |
| Anemia of chronic inflammation | 5 (8.9%) | 16 (16.7% | 21 (13.8%) |
| Renal insufficiency | 9 (16.1%) | 8 (8.3%) | 17 (11.2%) |
| B-12/folate deficiency | 7 (12.5%) | 4 (4.2%) | 11 (7.2%) |
| Other | 7 (12.5%) | 7 (7.3%) | 14 (9.2%) |
| Unknown | 4 (7.1%) | 11 (11.5%) | 15 (9.9%) |

**Table 3. Demographics of patients with a given diagnosis.**

| Etiology of Anemia | Male (%) | Female (%) | Median Age (years) | Age Range (years) |
|---|---|---|---|---|
| Iron deficiency | 29.7 | 70.3 | 63 | 16 - 91 |
| Hematologic malignancy | 50.0 | 50.0 | 75 | 58 - 95 |
| Anemia of chronic inflammation | 23.8 | 76.2 | 70 | 39 - 93 |
| Renal insufficiency | 52.9 | 47.1 | 75 | 51 - 90 |
| B-12/folate deficiency | 63.6 | 36.4 | 75 | 50 - 85 |
| Other | 50.0 | 50.0 | 59.5 | 27 - 91 |
| Unknown | 26.7 | 73.3 | 78 | 35 - 95 |

The median age of the iron deficiency group of patients was 63 years, considerably younger than the median age of the patients with other causes of anemia in this study, except for those in the "other" category. Furthermore, iron deficiency contributed to the anemia in 83.3% of patients that were 40 years old or younger. Iron deficiency was more common in women; 70.3% of those affected by iron deficiency were women. While iron deficiency was the most common cause of anemia in both males and females, it accounted for only 39.3% of the total cases of anemia in males compared to 54.2% of the total cases of anemia in females. This difference was most pronounced in iron-deficiency patients under the age of 50, which accounted for 20 women and only 4 men. Patients with iron deficiency tended to have a lower hemoglobin value (9.9 g/dL) than those patients determined to have other causes for their anemia, other than renal insufficiency.

Hematologic malignancy was the second leading cause for anemia, accounting for 14.5% of all cases. Myelodysplastic syndrome (MDS) was the most common neoplastic process seen (12 patients or 54.5% of hematologic malignancies). Less common types of hematologic malignancy included multiple myeloma (three patients), monoclonal gammopathy of unknown significance (two patients), chronic lymphocytic leukemia (two patients), acute myeloid leukemia (two patients; one of these patients had a prior history of MDS as well), B cell lymphoblastic leukemia (one patient), and T cell large granular lymphocyte leukemia (one patient). Hematologic malignancies contributing to anemia were more common in older individuals, with the median age of those affected being 75 years old. Hematologic malignancies showed a higher prevalence in males (16.1%) than females (8.3%). Most patients with a hematologic malignancy had abnormalities in their white blood cell count or platelet count, in addition to their anemia. The median WBC count and platelet counts were below normal in the TWCC patients, although the range was wide. Over 70% had an abnormality in either WBC or platelet count and 55% had abnormalities in both. The median RDW also was elevated in this group at 16.9. Sixteen of the 22 patients (73%) with a hematologic malignancy had an elevated RDW.

Anemia of chronic inflammation was diagnosed in 13.8% of all TWCC patients. Anemia of chronic inflammation showed the greatest female predominance of any etiology of anemia in this study,

**Table 4. Median and ranges of basic hematologic values by diagnosis.**

| Etiology of Anemia | | WBCs (109/L) | Hemoglobin (g/dL) | Platelets (109/L) | MCV (fL) | RDW (%) |
|---|---|---|---|---|---|---|
| Iron deficiency | Median | 6.7 | 9.9 | 282 | 82.9 | 17 |
| | Range | 2.6-14.7 | 5.9-13.5 | 8.4-677 | 61.0-100.4 | 12.7-59.6 |
| Neoplasm | Median | 4.3 | 10.0 | 141 | 96.5 | 16.9 |
| | Range | 1.4-60.3 | 5.7-13.1 | 33-578 | 70.0-110.5 | 11.5-36.9 |
| Anemia of chronic inflammation | Median | 7.6 | 10.2 | 237 | 95.6 | 14.1 |
| | Range | 4.1-14.3 | 7.1-12.2 | 106-426 | 81.0-103.5 | 11.9-19.3 |
| Renal insufficiency | Median | 7.3 | 9.8 | 196 | 93.8 | 14.3 |
| | Range | 4.1-13.9 | 7.3-12.7 | 131-432 | 84.6-104.9 | 12.1-16.5 |
| B-12/folate deficiency | Median | 6.2 | 10.1 | 222 | 91.9 | 14.9 |
| | Range | 2.6-9.4 | 6.7-13.3 | 119-305 | 67.1-100.8 | 12.9-21.1 |
| Other | Median | 6.6 | 10.7 | 250 | 87.2 | 15.0 |
| | Range | 4.3-46.1 | 7.1-13.1 | 131-472 | 56.1-114.1 | 13.2-18.2 |
| Unknown | Median | 6.6 | 10.8 | 257 | 96.7 | 14.4 |
| | Range | 2.8-14.7 | 7.4-12.8 | 46-589 | 88.4-106.5 | 12.5-21.1 |

with females accounting for 76.2% of patients in this group. Most patients in this study with anemia of chronic inflammation had a normocytic anemia, as the median MCV was 95.6 $\mu m^3$ and the range was from 81.0 to 103.5 $\mu m^3$.

Renal insufficiency was a contributing cause of anemia for 11.2% of all TWCC patients. Nearly half (8 of 17 or 47.1%) of those with renal insufficiency also had additional contributing factors to their anemia such as iron deficiency and chronic inflammation. Males had a higher prevalence of renal insufficiency associated anemia in this study, with 16.1% of all male cases of anemia caused by renal insufficiency, compared to 11.5% of all female cases of anemia. Renal insufficiency resulted in the lowest median hemoglobin of any etiology in this study with a value of 9.8 g/dL (ranging from 7.3 to 12.7 g/dL). This group also tended to show a normocytic anemia with a median MCV of 93.8 fL (range from 84.6 to 104.9 fL).

Four patients were found to have isolated B-12 deficiency; three were subsequently diagnosed with pernicious anemia. Seven additional patients were shown to have B-12/folate deficiency in addition to iron deficiency. Males showed a higher prevalence of B-12 or folate deficiency in this study with 12.5% of all males affected and only 4.2% of all females. Although, B-12 and folate deficiency are causes of macrocytic anemia, defined as having MCV greater than 100 fL, surprisingly, in this study the median MCV was 91.9 fL (range of 67.1 to 100.8 fL).

Additional etiologies for anemia were found in a very small number of patients in this population, accounting for 14 (9.2%) of the patients with anemia. Three patients were diagnosed with hemoglobinopathies (one each with Hemoglobin C, Hemoglobin E, and Hemoglobin constant spring), two patients were diagnosed with beta thalassemia minor, and one patient was diagnosed with alpha thalassemia (same patient that also had Hemoglobin constant spring). Five patients had hemolytic anemia (one due to pyruvate kinase deficiency, three due to autoimmune hemolytic anemia, and one suspected to be caused by mechanical hemolysis across the patient's prosthetic aortic valve). Finally, the anemia in two patients was attributed to the acute blood loss.

The exact etiology of the anemia in 15 patients (9.9% of the study population) was not determined. The factors that precluded diagnosis varied. Three patients declined further workup after discussion of their mild level of anemia, lack of symptoms, and possibility for anemia resolution without intervention. Two patients declined further evaluation due to severe comorbidities and advanced age. In six patients, no diagnosis was reached despite extensive evaluation; four of these patients experienced only transient anemia (anemia eventually resolved), while two other patients were unable to be diagnosed despite evaluation. A loss to follow-up contributed to the inability to determine a final diagnosis in four patients.

## DISCUSSION

Investigators at the four academic medical centers were chosen to compare the results of this study with limited their study populations to patients 65 years of age and older.[5-8] The TWCC study did not have this age limitation. Table 5 provides a brief comparison of the patient populations in the TWCC study and the four cited studies. Table 6 compares the etiologies for anemia found in the TWCC study with these previous studies. The TWCC study reported a nearly 50% incidence of iron deficiency anemia compared to the 12-25% in the four studies cited. The TWCC study also showed a higher contribution of confirmed GI bleeds (15.8%) to the anemia compared to the 9% reported by Ania et al.[8] Differences in study populations undoubtedly played a significant role in diverse results. For example, the higher incidence of iron deficiency anemia at TWCC may be the result of inclusion of young, menstruating women in the study.

**Table 5. Comparative study populations.**

| Study | Population Studied |
|---|---|
| TWCC | Individuals referred to hematologists at TWCC, Salina, KS for workup of a new diagnosis of anemia between August 2015 and May 2019 (excluded, if prior diagnosis or treatment of non-hematologic malignancy). |
| Guralnik et al.[5] | Participants in Third National Health and Nutrition Examination Survey (NHANES III); older than 65 and anemic. |
| Price et al.[6] | Patients older than 65 and anemic referred between March 2006 and January 2010 to Stanford Hospital and Clinics and Veteran Affairs Palo Alto Health Care Systems outpatient hematology clinics; not institutionalized; ECOG performance ≥ 2; excluded, if had received any red cell transfusion or erythropoiesis-stimulating agent within prior three months, had end-stage liver disease, were dialysis-dependent, had known diagnosis of hematologic malignancy, had predicted survival less than three months due to other comorbidities, or were unlikely to comply with protocol. |
| Artz and Thirman[7] | Patients older than 65 seen in anemia referral clinic from January 2005 - June 2009 at University of Chicago Hematology Clinic; excluded for erythropoietin-stimulating agent hyporesponsiveness, known hematologic malignancy, or cancer chemotherapy or radiation therapy completed within prior six months. |
| Ania et al.[8] | Individuals in Olmstead County, Minnesota older than 65 years old with newly recognized cases of anemia during 1986. |

**Table 6. Comparison of the etiologies of anemia.**

| Parameter | TWCC Study | Guralnik et al.[5] | Price et al.[6] | Artz and Thirman[7] | Ania et al.[8] |
|---|---|---|---|---|---|
| Number of anemic patients evaluated | 152 | 2,096 | 190 | 174 | 618 |
| Male cases (%)/ female cases (%) | 37/63 | Not reported | 85/15 | 69/31 | 39/61 |
| Iron deficiency (% of total) | 48% | 20% | 12% | 25.3% | 14% |
| Hematologic malignancy (% of total) | 14% | Not reported | 22% | 7.5% | 2% |
| Anemia of chronic inflammation (% of total) | 14% | 24% | 6% | 9.8% | 4% |
| Renal insufficiency (% of total) | 11% | 12% | 4% | 3% | 1% |
| B-12/folate deficiency (% of total) | 7% | 14% | 0.5% | 0.6% | 1% |

Although the four academic medical center reports showed some variability in the incidence of anemia due to hematologic malignancies, chronic inflammation, renal insufficiency, and B-12/folate deficiency, when reviewed, they are not too dissimilar from the TWCC results. Interestingly, the incidence of MDS in the TWCC study correlated well with the study performed by Artz and Thirman.[7] Additionally, the anemia of chronic inflammation predominately was seen in females in the TWCC report compared to approximately equal representation in the Ania study[8] or male predominance (61.8%) in the Guralnik study.[5]

The rate of unexplained anemia was much lower (9.9% of total patients studied) in the TWCC study compared with the other studies cited (19-39%). While the reason for the lower incidence of unexplained anemia in the TWCC study was not determined, the duration and extent of evaluation or the referral patterns of physicians may have contributed to differences.

Specifically, the patient population referred to TWCC was not identical to that seen in the other reported studies, and the TWCC hematologists may have taken more time and performed a more exhaustive evaluation to determine the cause of anemia.

The choice of how to classify patients with multifactorial disease differed from report to report. In the current study, patients deemed to have multifactorial disease were given multiple diagnoses. In Price et al.[6], study investigators determined which of the contributing factors was most clinically relevant. In the studies by Guralnik et al.[5] and Artz and Thirman[7], the cause of anemia was determined in a hierarchical fashion in which diagnoses were excluded in a systematic manner until the diagnosis was reached, though Guralnik additionally included some multifactorial diagnoses such as combined nutrient deficiency.

## CONCLUSIONS

The TWCC study found similar etiologies for anemia as those previously reported by four academic medical centers; however, the incidences of the etiologies were dissimilar. While the incidence of anemia due to hematologic malignancy, chronic inflammation, renal insufficiency, and B-12/folate deficiency were similar to previous reports, significantly more iron deficiency and less unexplained anemia were found in the TWCC study. The differences in findings undoubtedly reflected dissimilarities in the demographics of referral/study populations, duration and extent of evaluation, and referral patterns.

This report provided important information to physicians, especially those caring for anemic patients, regarding the causes and incidence of different anemias in patients seen in a rural hematology clinic. Although consultation with the community hematologist may be an important step in the evaluation of the patient with anemia, it might not need to be the first step. The results of this study provide guidance to the primary care provider regarding the most common causes for anemia seen by community hematologists and a basic evaluation prior to referral. This study found that approximately 80% of patients were affected by one or more of four basic benign types of anemia: iron deficiency, anemia of chronic inflammation, renal insufficiency, and B-12/folate deficiency. Approximately half of patients were affected by iron deficiency anemia, and an additional 30% of patients by anemia of chronic disease, with renal insufficiency and B-12/folate deficiency as less common nonmalignant causes of anemia.

A complete history and physical exam and a CBC and reticulocyte count are important initial diagnostic measures for the primary care physician. The information gleaned enables the classification of the anemia as mild, moderate, or severe, microcytic, normocytic, or macrocytic, and hypoproliferative, normoproliferative, or hyperproliferative and can direct the necessity for further testing. Additional tests, such as

iron studies, inflammatory markers such as C-reactive protein or erythrocyte sedimentation rate, a complete metabolic panel, and vitamin B-12 and folate levels may provide the necessary information to confirm a diagnosis and guide a definitive treatment plan. If a hematologic consultation is desired or warranted, this information will go a long way in helping the consultant care for the patient.

## REFERENCES

[1] Le CHH. The prevalence of anemia and moderate-severe anemia in the US population (NHANES 2003-2012). PLoS ONE 2016; 11(11):e0166635. PMID: 27846276.
[2] Smith RE. The clinical and economic burden of anemia. Am J Manag Care 2010; 16(Suppl Issues):S59-66. PMID: 20297873.
[3] Stauder R, Valent P, Theurl I. Anemia at older age: Etiologies, clinical implications, and management. Blood 2018; 131(5):505-514. PMID: 29141943.
[4] Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. Blood 2006; 107(10):3841-3846. PMID: 16403909.
[5] Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. Blood 2004; 104(8):2263-2268. PMID: 15238427.
[6] Price EA, Mehra R, Holmes TH, Schrier SL. Anemia in older persons: Etiology and evaluation. Blood Cells Mol Dis 2011; 46(2):159-165. PMID: 21208814.
[7] Artz AS, Thirman MJ. Unexplained anemia predominates despite an intensive evaluation in a racially diverse cohort of older adults from a referral anemia clinic. J Gerontol A Biol Med Sci 2011; 66A(8):925-932. PMID: 21659341.
[8] Ania BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton III LJ. Incidence of anemia in older people: An epidemiologic study in a well defined population. J Am Geriatr Soc 1997; 45(7):825-831. PMID: 9215333.
[9] World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. 2011. www.who.iny/vmnis/indicators/haemoglobin.pdf. Accessed 6 January 2022.

*Keywords: anemia, hemoglobins, incidence, iron deficiency, vitamin B-12 deficiency*