EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Coden USA: EJBPBO
Volume: 13
Issue: 7
Year: 2026

ANAEMIA AMONG ELDERLY INPATIENTS: CLINICOPATHOLOGICAL SPECTRUM AND CHARACTERISTICS OF UNEXPLAINED ANAEMIA

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DOI: https://doi.org/10.5281/zenodo.21054507

How to cite this Article: Hardik Jain[1]*, Purvi A. Trambadiya[2], Sudha Jain[3], Gunjan Gandhi[4]. (2026). Anaemia Among Elderly Inpatients: Clinicopathological Spectrum And Characteristics Of Unexplained Anaemia. European Journal of Biomedical and Pharmaceutical Sciences, 13(7), 212-218.

Article Received on 04/06/2026 **Article Revised on 24/06/2026** **Article Published on 01/07/2026**

ABSTRACT

Background: Anaemia in older adults is common, clinically important, and often multifactorial. A proportion of patients remain without an identifiable cause despite evaluation and are classified as having unexplained anaemia. **Objective:** To describe the clinico-haematological profile, morphological patterns, aetiological spectrum, and diagnostic implications of anaemia in elderly hospitalised patients, with special emphasis on unexplained anaemia. **Methods:** This hospital-based observational study included 367 elderly inpatients (≥60 years) with anaemia at a tertiary care teaching hospital in South Gujarat. Clinical findings, complete blood count, peripheral smear, reticulocyte count, iron studies, vitamin B12 and folate levels, renal and liver function tests, and other relevant investigations were reviewed. Unexplained anaemia was diagnosed after exclusion of identifiable causes. **Results:** The mean age was 68.48 ± 7.46 years and 59.9% were male. Moderate anaemia was most common (54.2%). Normocytic normochromic morphology predominated (40.33%). Iron deficiency anaemia was the leading identifiable cause (17.98%), followed by anaemia of chronic disease (13.35%), unexplained anaemia (12.81%), and vitamin B12 deficiency (12.53%). Among unexplained cases, 40.43% were aged ≥80 years, 82.98% showed normocytic morphology, and 76.60% had reticulocyte counts of 1–2%. **Conclusion:** Anaemia in elderly inpatients is heterogeneous and frequently multifactorial. Unexplained anaemia accounted for 12.81% of cases and was characterised by advanced age, normocytic morphology, and limited reticulocyte response, highlighting the need for structured evaluation and follow-up.

KEYWORDS: geriatric anaemia, unexplained anaemia, normocytic anaemia, reticulocyte count, elderly.

INTRODUCTION

Anaemia is a common and clinically important syndrome in older adults. It may be detected during evaluation of acute illness, chronic disease, infection, renal dysfunction, nutritional deficiency, malignancy, occult blood loss, or unexplained functional decline. The World Health Organization (WHO) defines anaemia using haemoglobin thresholds below 13 g/dL in men and below 12 g/dL in non-pregnant women, while recognising that haemoglobin cutoffs are population-based tools requiring clinical interpretation.[1]

Geriatric anaemia differs from anaemia in younger adults because it is often chronic, mild to moderate, multifactorial, and under-recognised. Oyedeji et al. emphasised that older age predisposes to nutritional deficiency, inflammatory disorders, chronic kidney disease, and haematological malignancy, and that systematic evaluation helps avoid both undertreatment and overtreatment.[2] Guralnik et al. similarly noted that even mild anaemia in older adults is associated with poorer physical function, quality of life, hospitalisation, and mortality, and should not be regarded as a normal consequence of ageing.[3]

The diagnostic spectrum includes nutritional deficiency, anaemia of inflammation or chronic disease, chronic kidney disease, liver disease, blood loss, haemolysis, haemoglobinopathy, malignancy, marrow failure, medication-associated anaemia, and unexplained anaemia. Stauder et al. described anaemia in older age as a heterogeneous condition ranging from reactive and nutritional causes to clonal marrow disorders.[4] Unexplained anaemia of ageing is assigned when careful clinical and laboratory assessment fails to identify a reversible or classifiable cause; proposed mechanisms include inadequate erythropoietin production or response, inflammatory iron restriction, renal-endocrine changes, androgen deficiency, reduced haematopoietic stem cell reserve, clonal haematopoiesis, and early myelodysplastic evolution.[2-5]

In India, the burden of anaemia among older adults is substantial. Daniel et al. reported a pooled prevalence of 68.3% among people aged 60 years and above in a systematic review and meta-analysis of Indian studies, although estimates varied by region, setting, sampling strategy, and haemoglobin estimation method.[6] Hospital-based cohorts may show a greater burden of moderate and severe anaemia because admitted elderly patients frequently have acute infection superimposed on chronic nutritional, inflammatory, renal, or malignant disease. The present study was therefore undertaken to describe the clinicopathological profile of anaemia among elderly inpatients in South Gujarat and to characterise the unexplained anaemia subgroup.

OBJECTIVES

1. To describe the age and sex distribution, anaemia severity, peripheral smear morphology, comorbidity profile, reticulocyte response, and aetiological distribution among elderly hospitalised patients with anaemia.
2. To analyse the unexplained anaemia subgroup after exclusion of identifiable nutritional, inflammatory, infectious, renal, hepatic, haemolytic, malignant, blood-loss, haemoglobinopathy, and clinically evident secondary causes.
3. To interpret the diagnostic implications of unexplained anaemia in relation to ageing, chronic low-grade inflammation, renal-endocrine alterations, marrow senescence, and possible clonal haematopoietic pathology.

MATERIALS AND METHODS

Study design and setting

This was a hospital-based observational study conducted among elderly anaemic patients admitted to the Medicine ward of a tertiary care teaching hospital in South Gujarat. Laboratory evaluation and morphological review were performed in the Department of Pathology.

Study duration and sample size

The total study duration was 18 months, comprising 12 months of data collection, 3 months of data entry, and 3 months of analysis and write-up. Sample size was calculated using OpenEpi version 3.01 with a 95% confidence interval and 5% absolute precision, using an expected prevalence of 60.7% from published Indian literature. The minimum required sample size was 367 participants, who were enrolled consecutively.

Eligibility criteria

The inclusion criteria were age 60 years or older, inpatient admission to the Medicine ward, and anaemia on automated haematology analysis, defined as haemoglobin less than 13 g/dL in males and less than 12 g/dL in females. The exclusion criteria were outpatient status, admission to departments other than Medicine, haemoglobin within normal limits, blood transfusion within the preceding 12 weeks, and inability or unwillingness to provide informed consent.

Clinical and laboratory evaluation

A structured case record proforma was used to record demographic data, presenting complaints, comorbidities, and clinical findings. Comorbidities assessed included hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, COPD/asthma, cardiac disease, neurological illness, malignancy, chronic alcohol intake, and smoking. Haematological investigations included five-part automated complete blood count with haemoglobin, haematocrit, red cell indices, red cell distribution width, total leukocyte count, and platelet count. Peripheral blood smears were stained with Giemsa stain and examined microscopically. Morphological classification was based on smear findings and red cell indices.

Ancillary investigations

Biochemical workup included serum iron, total iron-binding capacity, ferritin, vitamin B12, folate, renal function tests, liver function tests, electrolytes, and lactate dehydrogenase. Additional investigations, including malaria/dengue testing, thyroid function tests, sickling test, direct Coombs test, multiple myeloma workup, stool and urine examination for blood loss, and radiological studies, were performed when clinically indicated.

Definition of unexplained anaemia

Unexplained anaemia was defined as anaemia in an elderly patient in whom no definite cause could be established after clinical evaluation and relevant laboratory investigations. Cases were labelled unexplained only after exclusion of nutritional deficiency, chronic kidney disease, hepatic disease, overt or occult blood loss, haemolysis, infection-related anaemia, malignancy-associated anaemia, multiple myeloma, haemoglobinopathy, and other clinically evident secondary causes. The term therefore denotes unexplained anaemia after the available routine hospital workup, not after exhaustive molecular or marrow evaluation.

Statistical analysis

Data were entered in Microsoft Excel 2021 and analysed using Microsoft Excel 2021 and IBM SPSS Statistics version 26. Continuous variables were expressed as mean, standard deviation, minimum, and maximum values. Categorical variables were summarised as frequencies and percentages. Subgroup patterns were described using cross-tabulations. As the study was descriptive, inferential statistical testing was not performed.

Ethical considerations

Institutional Ethics Committee approval was obtained before enrolment, with reference number IEC/ SMIMER: 127-10/01/2025. Written informed consent was obtained from all participants. Patient confidentiality was maintained throughout data collection, analysis, and reporting.

RESULTS AND DISCUSSION

Demographic profile

A total of 367 elderly patients with anaemia were enrolled. Mean age was 68.48 +/- 7.46 years (range, 60-95 years). The largest proportion of participants belonged to the 60-64-year age group (124, 33.8%), followed by 65-69 years (90, 24.5%), 70-74 years (62, 16.9%), 75-79 years (56, 15.3%), and 80 years or older (35, 9.5%). Males constituted 220 participants (59.9%) and females 147 (40.1%).

Table 1: Age and sex distribution of study participants (n=367).

Age group (years)	Male n (%)	Female n (%)	Total n (%)
60-64	116 (52.7)	28 (19.0)	124 (33.8)
65-69	55 (25.0)	35 (23.8)	90 (24.5)
70-74	24 (10.9)	38 (25.9)	62 (16.9)
75-79	15 (6.8)	41 (27.9)	56 (15.3)
>=80	10 (4.5)	25 (17.0)	35 (9.5)
Total	220 (59.9)	147 (40.1)	367 (100)

Clinical presentation and comorbidities

Fever was the most common presenting symptom (294, 80.1%), followed by generalised weakness/fatigue (276, 75.2%), pallor (245, 66.8%), breathlessness (122, 33.2%), dizziness or giddiness (91, 24.8%), and pedal oedema (52, 14.2%). More than half of the participants had no documented chronic illness (207, 56.4%). Among recorded comorbidities and exposures, hypertension was most frequent (91, 24.8%), followed by chronic alcohol intake or smoking (73, 19.9%), diabetes mellitus (61, 16.6%), COPD/asthma (40, 10.9%), and chronic kidney disease (36, 9.8%).

Table 2: Clinical presentations and comorbidities among elderly patients with anaemia (n=367).

Clinical feature/comorbidity	Frequency	Percentage (%)
Fever	294	80.1
Generalised weakness/fatigue	276	75.2
Pallor	245	66.8
Breathlessness	122	33.2
Dizziness/giddiness	91	24.8
Pedal oedema	52	14.2
No chronic illness	207	56.4
Hypertension	91	24.8
Chronic alcohol intake/smoking	73	19.9
Diabetes mellitus	61	16.6
COPD/asthma	40	10.9
Chronic kidney disease	36	9.8

Haemoglobin levels and severity of anaemia

Mean haemoglobin was 9.11 +/- 2.01 g/dL in males and 8.33 +/- 2.00 g/dL in females. Moderate anaemia was the dominant severity category overall (199, 54.2%), followed by severe anaemia (104, 28.3%) and mild anaemia (64, 17.4%).

Table 3: Sex-wise severity distribution of anaemia (n=367).

Severity	Male n (%)	Female n (%)	Total n (%)
Mild (Hb 10-12.9/10-11.9 g/dL)	40 (18.2)	24 (16.3)	64 (17.4)
Moderate (Hb 8-9.9 g/dL)	115 (52.3)	84 (57.1)	199 (54.2)
Severe (Hb <8 g/dL)	65 (29.5)	39 (26.5)	104 (28.3)
Total	220 (100)	147 (100)	367 (100)

Morphological patterns

Peripheral smear examination revealed normocytic normochromic anaemia to be the most common morphological pattern (148, 40.33%), followed by microcytic hypochromic anaemia (120, 32.70%), macrocytic anaemia (90, 24.52%), and dimorphic anaemia (9, 2.45%).

Table 4: Morphological patterns on peripheral blood smear (n=367).

Morphological pattern	Frequency	Percentage (%)
Normocytic normochromic	148	40.33
Microcytic hypochromic	120	32.70
Macrocytic	90	24.52
Dimorphic	9	2.45
Total	367	100

Aetiological distribution

Iron deficiency anaemia was the most common single identifiable aetiology (66, 17.98%), followed by anaemia of chronic disease (49, 13.35%), unexplained anaemia (47, 12.81%), vitamin B12 deficiency (46, 12.53%), infection-related anaemia of chronic disease (43, 11.72%), infection with vitamin B12 deficiency (35, 9.54%), and infection with iron deficiency anaemia (29, 7.90%).

Table 5: Aetiological distribution of anaemia (n=367).

Aetiology	Frequency	Percentage (%)
Iron deficiency anaemia	66	17.98
Anaemia of chronic disease	49	13.35
Unexplained anaemia	47	12.81
Vitamin B12 deficiency	46	12.53
Infection + ACD (mixed)	43	11.72
Infection + Vitamin B12 deficiency	35	9.54
Infection + IDA (mixed)	29	7.90
Sickle cell anaemia	10	2.72
Combined nutritional deficiency	9	2.45
Malignancy-associated	7	1.91
Others	26	7.09
Total	367	100

Unexplained anaemia subgroup

Unexplained anaemia was diagnosed in 47 patients (12.81%) after systematic exclusion of identifiable causes using the available diagnostic workup. This subgroup was enriched for very elderly patients: 19 (40.43%) were aged 80 years or older, 16 (34.04%) were aged 70-79 years, and 12 (25.53%) were aged 60-69 years. Males constituted 29 cases (61.70%) and females 18 cases (38.30%). Mild anaemia predominated (32, 68.09%), followed by moderate (13, 27.66%) and severe anaemia (2, 4.25%).

Table 6: Clinicopathological characteristics of unexplained anaemia cases (n=47).

Parameter	Frequency	Percentage (%)
Age 60-69 years	12	25.53
Age 70-79 years	16	34.04
Age >=80 years	19	40.43
Male	29	61.70
Female	18	38.30
Mild anaemia	32	68.09
Moderate anaemia	13	27.66
Severe anaemia	2	4.25
No chronic illness	19	40.42
Diabetes mellitus	6	12.77
Hypertension	5	10.64
Cardiac disease	5	10.64
Neurological illness	5	10.64
COPD/asthma	3	6.38
Drug history	3	6.38
Hypertension + diabetes mellitus	1	2.13

Normocytic normochromic morphology was the dominant pattern among unexplained cases and was present in 39 of 47 patients (82.98%). It was observed in 27 of 32 mild cases (84.38%), 11 of 13 moderate cases (84.62%), and 1 of 2 severe cases (50.0%). Reticulocyte count was 1-2% in 36 patients (76.60%), below 1% in 8 patients (17.02%), and above 2% in 3 patients (6.38%), suggesting limited compensatory erythropoiesis in most cases.

Table 7: Severity, morphology, and reticulocyte response in unexplained anaemia cases (n=47).

Parameter	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Normocytic normochromic	27 (84.38)	11 (84.62)	1 (50.0)	39 (82.98)
Microcytic hypochromic	4 (12.50)	2 (15.38)	1 (50.0)	7 (14.89)
Dimorphic	1 (3.12)	0 (0)	0 (0)	1 (2.13)
Total morphology	32 (100)	13 (100)	2 (100)	47 (100)
Reticulocyte count <1%	-	-	-	8 (17.02)
Reticulocyte count 1-2%	-	-	-	36 (76.60)
Reticulocyte count >2%	-	-	-	3 (6.38)

This hospital-based observational study describes the clinico-haematological spectrum of anaemia among 367 elderly inpatients at a tertiary care centre in South Gujarat, with focused analysis of unexplained anaemia. The overall cohort showed the expected diversity of geriatric anaemia, including iron deficiency, anaemia of chronic disease, vitamin B12 deficiency, infection-related anaemia, haemoglobinopathy, malignancy-associated anaemia, mixed aetiologies, and unexplained anaemia. This distribution is consistent with the systematic diagnostic approach recommended by Oyedeji et al. and supports evaluation of treatable causes before attributing anaemia to ageing alone.[2]

Mean age was 68.48 +/- 7.46 years and the cohort was weighted toward the 60-64-year age group. Indian hospital-based studies by Sharma et al., Bhasin and Rao, Agravat et al., and Krishnamurthy et al. also reported substantial anaemia burden in the early elderly decades, with normocytic morphology and treatable causes frequently represented.[7-10] By contrast, Soraci et al. reported a mean age of 82.7 years among hospitalised older Italian patients, highlighting how referral patterns, population age structure, and healthcare access may influence the age distribution of inpatient anaemia cohorts.[11]

Fever was recorded in 80.1% of participants, highlighting the acute-on-chronic nature of anaemia in this inpatient tropical setting. Infection and inflammation can alter iron indices and obscure the distinction between absolute iron deficiency and anaemia of inflammation. This likely contributed to the prominence of mixed diagnostic categories such as infection with iron deficiency and infection with vitamin B12 deficiency. The finding reinforces that anaemia evaluation in hospitalised elderly patients should account for acute infection while avoiding premature closure on infection alone.

Moderate anaemia was the most frequent severity category (54.2%), while severe anaemia was present in 28.3%. Normocytic normochromic morphology was the most common smear pattern (40.33%). This pattern is consistent with reports by Sharma et al., Agravat et al., and Krishnamurthy et al., and with the broader geriatric anaemia literature in which chronic inflammation, renal-endocrine impairment, marrow ageing, and multifactorial disease often present with normocytic indices.[4,7,9,10] The sizeable macrocytic fraction (24.52%) and vitamin B12 deficiency burden (12.53%) indicate that nutritional deficiency remains a key correctable contributor in this population.

Iron deficiency anaemia was the most common identifiable single cause (17.98%). Burton et al. emphasised that iron deficiency anaemia in older adults requires evaluation for the underlying cause rather than haemoglobin correction alone, because gastrointestinal blood loss, impaired absorption, inflammatory bowel disease, malignancy, medication exposure, and chronic inflammatory states may contribute.[12] The lower proportion of pure iron deficiency in this cohort compared with Sharma et al. may reflect assignment of clinically mixed patients to infection-associated categories.[7]

Unexplained anaemia accounted for 12.81% of cases. This proportion is clinically meaningful even though it is below the approximately one-third distribution described by Guralnik et al. and Oyedeji et al. in some population-based frameworks of geriatric anaemia.[2,3] The lower proportion may reflect the hospital setting, where acute infection, chronic disease, renal dysfunction, nutritional deficiency, and mixed causes are frequently demonstrable. Conversely, the persistent unexplained fraction underscores that routine hospital investigations do not reliably detect early marrow senescence, clonal haematopoiesis, subtle inflammatory derangements, endocrine contributors, or early myelodysplastic evolution.

The age distribution of unexplained anaemia was notable. Although the overall cohort was concentrated in the 60-64-year group, 40.43% of unexplained cases occurred in patients aged 80 years or older. Guralnik et al., Stauder et al., and van Zeventer et al. described increasing importance of unexplained anaemia, marrow

ageing, and clonal haematopoiesis with advancing age.[3-5] In very elderly patients without demonstrable nutritional, inflammatory, infectious, renal, malignant, haemolytic, haemoglobinopathy, or blood-loss causes, plausible mechanisms include marrow ageing, reduced erythropoietin responsiveness, low-grade inflammation, androgen deficiency, clonal haematopoiesis, and early myelodysplastic change.

The morphology and reticulocyte findings further support this interpretation. Among unexplained cases, 39 of 47 had normocytic morphology and most had reticulocyte counts in the 1-2% range. This pattern indicates limited compensatory erythropoiesis rather than the brisk response expected in acute blood loss or active haemolysis. Ferrucci et al. reported that unexplained anaemia in older persons may be characterised by relatively low erythropoietin levels and low pro-inflammatory markers, supporting an inadequate erythropoietic response in at least a subset of patients.[13] However, normocytic morphology is not specific; early nutritional deficiency, chronic kidney disease, anaemia of inflammation, occult malignancy, and mixed states can appear normocytic. Therefore, normocytic unexplained anaemia should prompt structured exclusion and follow-up rather than diagnostic closure.

Clonal haematopoiesis deserves careful and balanced interpretation. van Zeventer et al. found clonal haematopoiesis more frequently among older individuals with anaemia than among matched controls, including those with unexplained anaemia.[5] Among individuals aged 80 years or older, van Zeventer et al. also showed that clonal haematopoiesis was common, but its clinical significance depended on mutation pattern and context.[14] Therefore, clonal haematopoiesis is not equivalent to overt haematological malignancy. Mutation results require interpretation alongside complete blood counts, smear morphology, marrow findings, cytogenetics, and the clinical course.

This study has several strengths. It included a relatively large inpatient elderly cohort, used consecutive sampling, and integrated clinical assessment with complete blood counts, peripheral smear morphology, reticulocyte assessment, iron studies, vitamin B12/folate status, renal and liver function assessment, infection workup, and selected targeted investigations. The findings are particularly relevant to tertiary-care practice in tropical and resource-variable settings where infection, nutritional deficiency, chronic disease, and mixed anaemia frequently coexist.

The limitations of this study include its single-centre, Medicine-ward design, which limits generalisability to community, surgical, oncology, and long-term-care populations. Some ancillary tests were performed selectively rather than uniformly. Bone marrow examination, inflammatory markers, erythropoietin levels, testosterone, hepcidin, cytogenetics, and molecular testing for clonal haematopoiesis were not systematically available. Therefore, unexplained anaemia in this manuscript means unexplained after the available routine hospital workup, not after exhaustive haematological evaluation.

Suggested diagnostic approach

- Confirm anaemia using haemoglobin thresholds and grade its severity.
- Classify morphology using red cell indices and peripheral blood smear findings.
- Evaluate common and reversible causes: iron deficiency, vitamin B12/folate deficiency, renal and liver disease, infection, chronic inflammation, blood loss, haemolysis, medication exposure, and haemoglobinopathy where relevant.
- Assess for malignancy or marrow disease when red flags are present, including pancytopenia, abnormal leukocyte or platelet counts, abnormal smear findings, constitutional symptoms, organomegaly, progressive anaemia, or persistent unexplained cytopenia.
- For persistent unexplained anaemia, repeat CBC and reticulocyte count, reassess nutritional, renal, inflammatory, and bleeding parameters, and consider haematology referral for bone marrow evaluation, cytogenetics, or molecular testing when clinically indicated.

CONCLUSION

Anaemia among elderly inpatients in this tertiary-care cohort was heterogeneous and frequently multifactorial. Iron deficiency, anaemia of chronic disease, vitamin B12 deficiency, infection-related anaemia, haemoglobinopathy, malignancy-associated anaemia, and mixed causes were all represented. Unexplained anaemia accounted for 12.81% of cases and was enriched among very elderly patients. It was characterised predominantly by mild to moderate severity, normocytic morphology, and limited reticulocyte response. These findings support treating unexplained anaemia as a diagnosis of exclusion that requires systematic evaluation, planned follow-up, and escalation when red-flag features suggest marrow, clonal, endocrine, renal, inflammatory, or malignant mechanisms.

ACKNOWLEDGEMENTS

Nil.

FUNDING

No funding was received for this study.

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