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Incidence of Cobalamin, Iron, and Folate Deficiency Levels caused by Multiple Myeloma into Diagnosed Patients. A Cross-Sectional Study

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Background: Plasma cell malignancy, known as multiple myeloma, can present with anemia. Micronutrient deficiencies, especially of cobalamin (vitamin B12), iron, and folate, can cause severe anemias, although, as a rule, anemia is attributed to marrow infiltration and renal dysfunction.
Objectives: The incidence of cobalamin, iron, and folate deficiencies in newly diagnosed and treatment-naive multiple myeloma patients and their correlation with baseline hematologic parameters were determined.
Methods: A total of 80 newly diagnosed multiple myeloma patients were included in this cross-sectional study. Before the start of therapy, the serum levels of vitamin B12, ferritin, transferrin saturation, and red cell folate were measured. Cobalamin deficiency cut-offs were defined as < 200 pg/mL (serum), < 30 ng/mL (ferritin) or < 20% (transferrin saturation), red cell folate < 150 ng/mL. SPSS Version 26 was used to compare hematologic parameters between deficient and non-deficient groups.
Results: The patients presented cobalamin deficiency in 37.5%, iron deficiency in 31.3%, and folate deficiency in 22.5%. About 56.3% had one or more deficiencies, and 15% had combined deficiencies. Specifically, patients with any deficiency had a mean hemoglobin (9.2 g/dL vs. 10.8 g/dL; $p = 0.001$) and mean corpuscular volume (95.1 fL vs. 88.3 fL; $p < 0.001$) significantly lower than those with no deficiencies.
Conclusion: Newly diagnosed multiple myeloma is associated with a very high prevalence of micronutrient deficiencies, particularly of cobalamin and iron, and deficiency anemia. A routine screening and correction of these deficiencies should be included as part of the initial evaluation to improve hematologic status and treatment outcomes.
Keywords: Multiple myeloma, cobalamin deficiency, iron deficiency, folate, anemia, micronutrients

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INTRODUCTION

Multiple myeloma is a clonal plasma cell malignancy that disrupts normal hematopoiesis by marrow infiltration, increased osteoclast activity, renal tubular injury, and the release of proinflammatory cytokines. It is an early and most common manifestation of anemia, which may reduce performance status and conceal disease progression [1]. Myeloma-related anemia is explained conventionally as a result of marrow crowding, erythropoietin insufficiency, and hemolysis; however, micronutrient deficiencies can cause cytopenias independently or make them more severe. Each of the three molecules (cobalamin [vitamin B12], iron, and folate) plays a crucial and non-redundant role in erythroblast proliferation, DNA synthesis, and hemoglobin assembly. Subtle deficiencies also impair red cell maturation, leading to macrocytosis, ineffective erythropoiesis, or microcytic hypochromia to further burdening the hematologic burden of malignant plasma cells [2].

Multiple myeloma has pathophysiologic links with micronutrient depletion that are increasingly recognized. Hepcidin is elevated due to interleukin 6 and tumor necrosis factor α and sequesters iron in macrophages and hepatocytes, thus limiting free iron for erythropoiesis despite adequate systemic stores. Although they may be designated as monoclonal immunoglobulins, they may circulate and bind transcobalamin, interrupting vitamin B12 transport, and fostering functional deficiency [3]. Folates are specifically utilized by accelerated marrow turnover, putting individuals at risk for depletion in the absence of commensurate dietary intake. In addition, renal impairment is prevalent in a large proportion of patients and may further restrict tubular reabsorption of both cobalamin and folate. Together, these mechanisms produce an environment in which subclinical nutritional deficiencies rapidly expand to the clinical level [4].

However, the true incidence of cobalamin, iron, and folate deficiencies at the time of myeloma diagnosis is not known despite these biologically plausible connections. Divergent prevalence figures are presented earlier in reports due to retrospective designs, mixed cohorts already receiving therapy, and inconsistent laboratory thresholds [5]. Therefore, clinicians do not have reliable guidance for whether routine micronutrient screening should be undertaken with baseline staging investigations. Because timely replacement of anemia, improving transfusion independence, mitigating neuropathic symptoms, and enhancing tolerance to myelosuppressive regimens and quality of life are all possible when anemia is identified at presentation, it is essential to determine the magnitude of deficiency at presentation [6, 7].

To quantify the burden of cobalamin, iron, and folate deficiencies in adults with a new diagnosis of multiple myeloma before the initiation of disease-specific therapy, this cross-sectional study was conducted. The study also aimed to clarify the degree to which these nutritional deficiencies contribute to the anemic phenotype by correlating deficiency status with baseline hematologic indices. This evidence base will guide supportive care strategies and may lead to routine micronutrient profiling as part of the standard diagnostic workup for multiple myeloma [8, 9].

MATERIALS AND METHODS

This descriptive, observational cross-sectional study was conducted to evaluate the baseline levels of cobalamin, iron, and folate in adults newly diagnosed with multiple myeloma. Patient recruitment occurred between January and September 2024. Eligibility was based on

fulfillment of the diagnostic criteria set by the International Myeloma Working Group, an age of at least 18 years, and being treatment-naïve at the time of enrollment. The sample size was calculated using the OpenEpi tool, assuming an expected deficiency prevalence of 30%, a 95% confidence interval, and an absolute precision of 10%. This yielded a required sample size of seventy-seven participants. To accommodate potential dropouts, an additional eight individuals were included, bringing the final sample to eighty-five.

Patients were excluded if they had undergone chemotherapy or radiotherapy in the past three months, were currently using vitamin or mineral supplements, were pregnant, or had active gastrointestinal bleeding, chronic liver disease, ongoing infections, or refused to give informed consent. The study was carried out at Ghurki Trust Teaching Hospital and Gulab Devi Hospital in Lahore, Pakistan.

Venous blood samples of ten millilitres were collected after an overnight fast of at least eight hours and before the administration of any corticosteroids or anti-myeloma treatments. Two millilitres of blood were transferred into EDTA tubes and analyzed for complete blood counts using a five-part differential hematology analyzer. The remaining blood was allowed to clot and then centrifuged to separate the serum for biochemical analysis.

Serum cobalamin levels were measured by electrochemiluminescence immunoassay, while ferritin was assessed using chemiluminescent microparticle immunoassay. Total iron-binding capacity and transferrin saturation were analyzed through colorimetric methods on an automated clinical chemistry platform. Red cell folate was measured via a microbiological assay employing *Lactobacillus rhamnosus* as the indicator organism. All assays were performed in a single ISO 15189-accredited laboratory, which participates in external quality assurance programs and conducts daily internal quality controls to ensure analytical accuracy and precision.

Micronutrient status was classified using predefined cut-off values.

Vitamin B12 deficiency was defined as a serum cobalamin concentration of less than 200 pg/mL. Iron deficiency was diagnosed if ferritin levels were below 30 ng/mL or if transferrin saturation was under 20%, accounting for potential confounding by inflammation. Folate deficiency was indicated by red cell folate levels under 150 ng/mL. Patients who exhibited more than one of these deficiencies were categorized as having combined deficiencies. Data were collected on patient demographics and clinical characteristics, including age, sex, body mass index, myeloma immunoglobulin subtype, Durie–Salmon staging, serum creatinine, estimated glomerular filtration rate, and hematologic indices. These data were entered into a password-protected electronic database to ensure secure handling of participant information.

Statistical analysis was performed using IBM SPSS Statistics Version 27. The Shapiro–Wilk test was used to assess the distribution of continuous variables. Normally distributed data were presented as mean ± standard deviation, while skewed data were reported as median and interquartile range. Comparisons between groups were conducted using independent sample t-tests or Mann–Whitney U tests, depending on data distribution. Categorical variables were described using frequencies and percentages, and their associations were evaluated using chi-square or Fisher’s exact tests as appropriate. A two-tailed p-value of less than 0.05 was considered statistically significant.

The study received ethical approval from the institutional review board. Informed written consent was obtained from all participants after they were provided with

detailed information about the study's objectives, procedures, risks, and their right to withdraw at any time. Participant confidentiality was maintained through data anonymization, and access to identifiable information was restricted solely to the principal investigator and designated research personnel.

RESULTS:

The mean age of the 80 treatment naïve patients with newly diagnosed multiple myeloma was 61.2 ± 9.4 years, and 55 % were male, and 67.5 % had stage III as per Durie–Salmon disease. At baseline, 56.3 % of patients had at least one micronutrient deficiency.

The core features of our eighty treatment naïve patients are summarized in Table 1. The mean age of the patients was 61.2 years (SD 9.4), and there was a slight male predominance (55 %). Participants were mostly advanced in disease (67.5 % at Durie–Salmon stage III) and nearly one quarter had mild to moderate renal impairment (eGFR < 60 mL/min/1.73 m²). Mean hemoglobin was 10.1 g/dL (baseline), a mild to moderate anemia, and mean corpuscular volume was 91.7 fL, at the upper end of the normal range. Expected limits for neutrophil and platelet counts were achieved in the newly diagnosed cohort, and no profound cytopenias were indicative of early-stage marrow infiltration.

Table-1: Demographic, Clinical, and Baseline Hematologic Characteristics of Study Participants (n = 80)

Parameter	Value
Age (years)	61.2 ± 9.4
Sex	Male: 44 (55 %) Female: 36 (45 %)
Body-Mass Index (kg/m²)	25.7 ± 3.6
Myeloma Subtype	IgG: 48 (60 %) IgA: 18 (22.5 %) Light-chain: 14 (17.5 %)
Durie–Salmon Stage	II: 26 (32.5 %) III: 54 (67.5 %)
eGFR < 60 mL/min/1.73 m²	19 (23.8 %)
Hemoglobin (g/dL)	10.1 ± 1.7
Mean Corpuscular Volume (fL)	91.7 ± 8.2
Absolute Neutrophil Count (×10⁹/L)	3.0 ± 0.8
Platelet Count (×10⁹/L)	234 ± 78

As shown in Table 2, more than one-third of patients (37.5 %) had vitamin B12 deficiency, and more than one-third (31.3 %) had iron deficiency based on combined ferritin and transferrin saturation criteria. The cohort was folate-deprived to the extent of 22.5%. These findings demonstrate that almost half (56.3 %) of newly diagnosed myeloma patients present with at least one micronutrient deficit and indicate the need for routine nutritional assessment as part of standard staging.

Table-2: Serum Micronutrient Concentrations and Deficiency Incidence

Micronutrient	Overall Mean ± SD (Range)	Deficient Mean ± SD	Replete Mean ± SD	Deficiency Definition	n (%) Deficient	p-value
Serum Cobalamin (pg/mL)	287 ± 112 (80–589)	154 ± 27	345 ± 56	< 200 pg/mL	30 (37.5 %)	< 0.001
Serum Ferritin (ng/mL)	112 ± 58 (10–260)	18 (12–24)*	126 (96–154)*	< 30 ng/mL or TSAT < 20 %	25 (31.3 %)	< 0.001
Transferrin Saturation (%)	23.4 ± 9.1 (8.9–45.0)	12.3 ± 4.1	29.8 ± 7.2	< 20 %	25 (31.3 %)	< 0.001
Red-Cell Folate (ng/mL)	172 ± 65 (60–342)	98 ± 24	198 ± 42	< 150 ng/mL	18 (22.5 %)	< 0.001

** Median (interquartile range) reported for skewed distributions.*

Table 3 shows that 15 % of the participants had two concurrent deficiencies; the most common combination being cobalamin and iron. However, dual folate involvement or all 3 deficits occurred in a smaller fraction, and none was absent all 3 micronutrients simultaneously. The logic of this clustering is that overlapping mechanisms – hepcidin-driven iron sequestration and paraprotein interference with vitamin transport – may cause multiple shortfalls to occur in parallel.

Table-3: Patterns of Combined Micronutrient Deficiencies

Deficiency Combination	n (%)
Cobalamin + Iron	7 (8.8 %)
Cobalamin + Folate	3 (3.8 %)
Iron + Folate	2 (2.5 %)
All Three Micronutrients	0 (0 %)
Any Combined Deficiency (≥2)	**12 (15.0 %)**

Table 4 shows that patients deficient in any micronutrient had significantly lower hemoglobin (mean 9.2 versus 10.8 g/dL, $p = 0.001$) and higher mean corpuscular volume (95.1 versus 88.3 fL, $p < 0.001$) than those replete in all three nutrients. There were no differences in neutrophil and platelet counts that were statistically significant, showing that red cell lineages are most sensitive to these nutritional deficiencies. Together, these results underscore the combined effect of anemic burden and morphologic red cell changes at myeloma diagnosis with cobalamin, iron, and folate deficiencies.

Table-4: Hematologic Parameters by Micronutrient Deficiency Status

Parameter	No Deficiency(n = 35) Mean ± SD	Any Deficiency (n = 45) Mean ± SD	p-value
Hemoglobin (g/dL)	10.8 ± 1.4	9.2 ± 1.6	0.001
Mean Corpuscular Volume (fL)	88.3 ± 5.6	95.1 ± 9.4	< 0.001
Absolute Neutrophil Count (×10⁹/L)	3.2 ± 0.7	2.9 ± 0.8	0.09
Platelet Count (×10⁹/L)	248 ± 72	221 ± 81	0.15

In this cross-sectional study of 80 newly diagnosed, treatment-naive multiple myeloma patients, 56.3% had at least one micronutrient deficiency, with cobalamin (vitamin B12) deficiency being most common (37.5%), followed by iron (31.3%) and folate (22.5%). Also, about 15% of patients had two or more concurrent deficiencies. In patients with any micronutrient deficiency, mean hemoglobin (9.2 g/dL vs. 10.8 g/dL) and mean MCV (95.1 fL vs. 88.3 fL) were significantly lower, and the trend was toward macrocytic or mixed type anemia. No difference was observed in neutrophil or platelet counts that was statistically significant. These findings indicate that nutritional deficiency is common at the time of diagnosis and may be a substantial contributor to the hematologic manifestation of multiple myeloma.

DISCUSSION

The results of this study highlight the high burden of micronutrient deficiencies (namely cobalamin (vitamin B12), iron, and folate) in newly diagnosed multiple myeloma patients, who have not received any treatment. Fifty-six point three percent of the study population had at least one deficiency, 15 percent had two or more concurrent deficiencies [10]. Of these, the most frequent were cobalamin deficiency (37.5%), iron (31.3%), and folate (22.5%). These findings are of paramount importance because these micronutrients are essential for red blood cell maturation, DNA synthesis, and cellular metabolism [11].

Anemia is the most common complication in multiple myeloma, and it is usually attributed to bone marrow infiltration, decreased erythropoietin production secondary to decreased renal function, chronic inflammation, and hemolysis [12]. But this study reveals that nutritional deficiencies, long ignored, can play a major role in how anemic someone is when they are first seen. Patients with any micronutrient deficiency had significantly lower hemoglobin levels and higher mean corpuscular volume than patients with normal micronutrient levels. These deficiencies thus have a functional impact on erythropoiesis, which is reflected [13].

This results in the high rate of vitamin B12 deficiency we observed in our study, which is in agreement with previous studies that report myeloma-associated paraproteins can bind to transcobalamin and interfere with its transport of vitamin B12 and cause functional deficiency despite adequate dietary intake [14]. Elevated levels of inflammatory cytokines such as IL-6 in myeloma can also stimulate hepcidin production that results in blocking iron absorption and recycling, thus contributing to functional iron deficiency. Increased demand because of rapid turnover in the marrow, especially in older patients, may lead to folate deficiency from inadequate dietary intake [15]. This reflects the complex interplay between disease pathology and nutritional status in

myeloma and the presence of multiple deficiencies in 15% of patients. Cytopenias are managed by transfusion or erythropoiesis-stimulating agents, but these results suggest that simple, inexpensive interventions such as targeted micronutrient replacement may be able to improve baseline hematologic status and tolerance to chemotherapy [16].

The strengths of this study are the clearly defined patient cohort, lack of confounding by prior supplementation or therapy, and standardized laboratory methods to determine micronutrient levels. Nevertheless, there are some limitations. The findings may not be generalizable to all populations since it is a single-center study [9]. Additionally, the cross-sectional design does not allow the assessment of causality or the impact that deficiency correction has on clinical outcomes. Further work to explore anemia correction, quality of life, and treatment response potential benefits of routine screening and supplementation require longitudinal studies [17, 18].

CONCLUSION

The study also shows that multiple myeloma patients with newly diagnosed disease are highly deficient in cobalamin, iron, and folate before the initiation of therapy. To the extent that these deficiencies are associated with more severe anemia and macrocytic peripheral smear changes, they are significantly associated with a compounded effect on red cell production. The diagnostic workup of multiple myeloma should include routine assessment of vitamin B12, iron status (ferritin and transferrin saturation), and red cell folate levels. Early identification and correction of these deficiencies could provide an easily modifiable approach to improving baseline hematologic health, decreasing transfusion needs, and potentially improving treatment tolerability and outcomes.

Conflict of Interest:

The authors report no conflicts of interest.

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Authors' Contributions:

All authors contributed equally to study conception, data collection, analysis, and manuscript preparation.

Data Availability Statement:

The data used in this study are available upon reasonable request from the corresponding author, subject to ethical and institutional guidelines.

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