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Original Research Article

BLOOD ON THE LINE: HAEMATOLOGICAL FOOTPRINTS ACROSS THE SPECTRUM OF CHRONIC KIDNEY DISEASE

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ABSTRACT

Background: Chronic kidney disease (CKD) is a progressive disorder associated with a wide range of systemic complications, among which haematological abnormalities are common and clinically important. This study evaluated the pattern and severity of clinico-haematological manifestations across different stages of CKD in a tertiary care setting. **Materials and Methods:** This hospital-based cross-sectional study was conducted at hospitals attached to Bangalore Medical College and Research Institute between August 2022 and January 2024. One hundred patients with CKD, staged according to KDIGO criteria, were enrolled after informed consent. Complete haemogram, peripheral smear, serum iron profile, vitamin B12, folic acid, and serum calcium and phosphorus were analysed and correlated with CKD stage using the Kruskal-Wallis test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered significant). **Result:** The cohort had a mean age of 49.9 ± 14.0 years with a male predominance (61%); 77% of patients were in CKD stage 5. Mean haemoglobin was 7.97 ± 1.76 g/dL, and 89% of patients were anaemic, most commonly of moderate severity (44%). Peripheral smear showed a normocytic normochromic pattern in the majority (62%), followed by microcytic hypochromic (23%) and dimorphic (14%) patterns. Iron-profile analysis showed anaemia of CKD alone in 62%, isolated iron deficiency in 17%, and a mixed pattern in 21%. Folic acid deficiency (47%) was considerably more common than vitamin B12 deficiency (8%). Thrombocytopenia was present in 31% of patients and was significantly associated with bleeding manifestations ($p = 0.001$), though not with CKD stage. Leucocytosis (29%) was more frequent than leucopenia (3%). On comparing stage 4 with stage 5 disease, haemoglobin ($p = 0.003$) and phosphorus ($p = 0.011$) differed significantly, as did the type of anaemia, pallor, and hyperphosphataemia on categorical analysis. **Conclusion:** Anaemia is the most consistent and clinically significant haematological abnormality in CKD, worsening with disease progression and driven by a multifactorial process that extends beyond erythropoietin deficiency to iron, folate, and vitamin B12 status. Thrombocytopenia and leucocyte abnormalities, though less strongly tied to CKD stage, carry clinical relevance through their association with bleeding risk. Routine haematological surveillance across all CKD stages is warranted for early detection and targeted management.

INTRODUCTION

Chronic kidney disease (CKD) is a progressive condition marked by the gradual loss of kidney function, with an estimated global prevalence of 11–13% and substantial associated morbidity, mortality, and healthcare cost.[1] Its pathophysiology involves glomerular hyperfiltration, chronic systemic inflammation, oxidative stress, and the accumulation of uraemic toxins, all of which contribute to disease progression and to a wide range of systemic complications.[2]

Haematological abnormalities are among the most consistent systemic manifestations of CKD. Anaemia is the most prevalent of these, affecting approximately half of patients with stage 3–5 disease.

Its pathogenesis is multifactorial, involving erythropoietin deficiency, shortened red-cell survival, iron-metabolism disturbances driven by hepcidin dysregulation, chronic inflammation, and accumulation of uraemic toxins that suppress erythropoiesis.[3] Beyond anaemia, leucopenia, thrombocytopenia, and qualitative platelet dysfunction have also been reported, the latter contributing to an increased bleeding tendency, particularly in patients undergoing invasive procedures or dialysis.[4,5]

The severity of these abnormalities tends to track with disease stage, as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) classification, which stratifies CKD into five stages using estimated glomerular filtration rate (eGFR) and markers of kidney damage — from stage 1 (eGFR ≥90 mL/min/1.73m² with evidence of kidney damage) to stage 5 or end-stage renal disease (eGFR <15 mL/min/1.73m²).[6] Despite this recognised association, the relative contribution of individual haematological derangements — red cell, white cell, and platelet lines together with micronutrient status — at each stage of CKD remains incompletely characterised, particularly in Indian tertiary-care populations.

This study was undertaken to systematically evaluate red blood cell parameters, total leucocyte and platelet counts, iron profile, vitamin B12 and folic acid status, and their correlation with CKD stage in patients presenting to a tertiary care hospital.

Objectives

- To estimate the changes in red blood cell (RBC) parameters, total leucocyte counts, and platelet counts in patients with CKD.
- To correlate these haematological changes with the different stages of CKD.

MATERIALS AND METHODS

Study design and setting: This was a hospital-based, cross-sectional, observational study conducted in hospitals attached to Bangalore Medical College and Research Institute (BMCRI), Bengaluru, between August 2022 and January 2024, following approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants.

Participants: One hundred consecutive patients diagnosed with CKD of any aetiology, meeting KDIGO criteria irrespective of underlying cause, were enrolled. eGFR was calculated using the MDRD study equation: eGFR = 175 × (standardised serum creatinine)$^{-1.154}$ × (age)$^{-0.203}$ (× 0.742 for women). Sample size was calculated at 92 (rounded to 100) based on an expected proportion of 0.6, 10% precision, and 95% confidence, using estimates from a prior published series.

Investigations: All enrolled patients underwent a complete haemogram, peripheral blood smear examination (for anaemia morphology and haemolysis features), serum iron profile (serum iron, total iron-binding capacity, ferritin), blood urea and serum creatinine, and serum vitamin B12 and folic acid assays. Bone marrow biopsy was performed where clinically indicated. All parameters were correlated against KDIGO CKD stage.

Statistical analysis: Data were analysed using Jamovi (version 2.4), built on R (version 4.1). Continuous variables are reported as mean ± standard deviation and were compared across CKD stages using the Kruskal-Wallis test (one-way non-parametric ANOVA); pairwise comparisons between stage 4 and stage 5 used the Mann-Whitney U test. Categorical variables are reported as frequencies and percentages and were compared using the chi-square test of association. A p-value <0.05 was considered statistically significant (*p<0.05, **p<0.01, ***p<0.001).

RESULTS

The study included 100 participants (mean age 49.9 ± 14.0 years, range 20–75 years; 61% male, 39% female). The distribution across CKD stages was heavily weighted toward advanced disease: stage 2 (1%), stage 3A (2%), stage 3B (5%), stage 4 (15%), and stage 5 (77%). Mean eGFR was 11.72 ± 8.98 mL/min/1.73m² and fell progressively with advancing stage — from 46.0 mL/min/1.73m² in stage 3A to 19.6 in stage 4 and 8.03 in stage 5 (Kruskal-Wallis, $p < 0.001$). Neither age ($p = 0.077$) nor sex distribution ($p = 0.292$) differed significantly across CKD stages.

Red cell parameters and anaemia: Mean haemoglobin (Hb) in the cohort was 7.97 ± 1.76 g/dL, with a trend toward a significant decline across CKD stages (Kruskal-Wallis, $p = 0.055$) that reached significance between stage 4 (9.3 ± 2.18 g/dL) and stage 5 (7.73 ± 1.49 g/dL) (Mann-Whitney U, $p = 0.003$). Overall, 89% of patients were anaemic (Hb <10 g/dL): 44% moderate (Hb 7–9 g/dL), 29% severe (Hb <7 g/dL), and 16% mild (Hb 9–10 g/dL); 11% had normal Hb.

Mean corpuscular volume (MCV) averaged 85.04 ± 7.39 fL and showed no significant trend by stage ($p = 0.377$), consistent with a predominantly normocytic pattern. Peripheral smear findings confirmed this: normocytic normochromic morphology in 62%, microcytic hypochromic in 23%, and dimorphic in 14% of patients, with a significant association between smear pattern and CKD stage (χ^2, $p < 0.001$). Pallor was present in 80% of patients and was significantly associated with more advanced CKD stage (χ^2, $p = 0.020$).

Iron profile and other nutritional deficiencies: Based on the iron profile, 62% of patients had a pattern consistent with anaemia of CKD alone, 17% had isolated iron-deficiency anaemia, and 21% showed a mixed picture of anaemia of CKD with iron deficiency. There was no overall significant association between anaemia type and CKD stage (χ^2, $p = 0.214$), though restricting analysis to stages 4 and

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5 revealed a significant association (p = 0.033), with stage 4 more often showing anaemia of CKD and stage 5 more often showing iron deficiency or a mixed pattern.

Vitamin B12 deficiency was present in 8% of patients, and its frequency differed significantly by CKD stage (χ^2, p = 0.001), being less common in later stages. Folic acid deficiency was considerably more prevalent (47%) but was not significantly associated with CKD stage (p = 0.394). Among the 14 patients with dimorphic anaemia, 5 had vitamin B12 deficiency and 11 had folic acid deficiency.

Platelet count and bleeding manifestations: Mean platelet count was 2.05 ± 0.94 lakh cells/mm³, without significant variation by CKD stage (p = 0.494). Thrombocytopenia was present in 31% of patients but was not significantly associated with CKD stage (p = 0.125). Bleeding manifestations occurred in 13% of patients overall, again without significant association with stage (p = 0.860); however, thrombocytopenia was strongly and significantly associated with bleeding manifestations — 9 of 31 patients with thrombocytopenia bled, compared with 4 of 69 without (χ^2, p = 0.001).

Total leucocyte count and mineral parameters: Mean total leucocyte count (TC) was 9,769 ± 5,287 cells/mm³, with no significant trend by stage (p = 0.684). Leucocytosis (TC >11,000) was observed in 29% of patients and leucopenia (TC <4,000) in 3%. Mean serum calcium (8.19 ± 2.62 mg/dL) also did not vary significantly by stage (p = 0.384), though hypocalcaemia was common overall (72%). Mean serum phosphorus was 5.85 ± 2.06 mg/dL and, while the overall trend across stages was non-significant (p = 0.141), phosphorus rose significantly from stage 4 (4.57 ± 1.09 mg/dL) to stage 5 (6.13 ± 2.18 mg/dL) (Mann-Whitney U, p = 0.011); hyperphosphataemia (71% overall) was also significantly more frequent in stage 5 when stages 4 and 5 were compared directly (χ^2, p = 0.026).

Comparison between stage 4 and stage 5 CKD: Because 92 of 100 patients belonged to stages 4 or 5, a focused pairwise comparison was performed between these groups. Significant differences were seen in eGFR, haemoglobin, and phosphorus [Table 1], while type of anaemia, pallor, and hyperphosphataemia showed significant categorical association with stage [Table 2]. Sex, thrombocytopenia, peripheral smear pattern, bleeding manifestations, vitamin B12 and folic acid deficiency, and hypocalcaemia did not differ significantly between the two groups.

Table 1: Comparison of continuous parameters between CKD stage 4 and stage 5

Parameter	Stage 4 (n=15)	Stage 5 (n=77)	p-value
eGFR (mL/min/1.73m²)	19.6 ± 3.78	8.03 ± 3.40	<0.001***
Haemoglobin (g/dL)	9.3 ± 2.18	7.73 ± 1.49	0.003**
MCV (fL)	84.7 ± 6.82	84.9 ± 7.16	0.891
Total count (cells/µL)	11881 ± 10096	9467 ± 3993	0.665
Platelet count (lakh/µL)	2.00 ± 0.79	2.07 ± 1.00	0.945
Vitamin B12 (pg/mL)	783 ± 709	672 ± 634	0.719
Folic acid (ng/mL)	5.35 ± 2.29	5.86 ± 3.73	0.878
Calcium (mg/dL)	8.73 ± 2.67	8.13 ± 2.71	0.236
Phosphorus (mg/dL)	4.57 ± 1.09	6.13 ± 2.18	0.011*

Table 2: Association of categorical parameters with CKD stage 4 vs. stage 5 (chi-square)

Parameter	p-value
Sex	0.751
Anaemia type	0.033*
Pallor	0.002**
Peripheral smear pattern	0.801
Thrombocytopenia	0.711
Bleeding manifestations	0.923
Vitamin B12 deficiency	0.243
Folic acid deficiency	0.697
Hypocalcaemia	0.961
Hyper phosphate aemia	0.026*

Table 3: Summary of haematological and biochemical parameters in the overall cohort (N=100)

Parameter	Value
Mean age (years)	49.9 ± 14.0
Male : Female	61 : 39
Mean eGFR (mL/min/1.73m²)	11.72 ± 8.98
Mean haemoglobin (g/dL)	7.97 ± 1.76
Anaemia (Hb <10 g/dL)	89%
Mean MCV (fL)	85.04 ± 7.39
Normocytic normochromic pattern on smear	62%
Iron deficiency (isolated or mixed)	38%
Folic acid deficiency	47%
Vitamin B12 deficiency	8%
Thrombocytopenia	31%
Bleeding manifestations	13%
Leucocytosis / Leucopenia	29% / 3%

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Hypocalcaemia	72%
Hyperphosphataemia	71%

DISCUSSION

The majority of this study population belonged to the fifth decade of life (mean age 49.9 years), comparable to the mean age of 52 years reported by Belurkar and Shastry,[7] though somewhat younger than the sixth-decade predominance reported in other series,[7677] a difference that may reflect regional variation in risk-factor prevalence. A male predominance (61%) was also consistent with prior studies, in which the male proportion ranged from 60–81%,[8] reinforcing the broader observation that CKD risk factors are more prevalent among men.

The pronounced skew toward advanced disease — 77% stage 5 and 15% stage 4, with no stage 1 patients — mirrors the referral pattern seen in other tertiary-care cross-sectional studies,[9] and reflects the fact that early CKD is frequently asymptomatic and under-recognised until advanced stages prompt hospital presentation.

Anaemia emerged as the dominant hematological abnormality, with mean Hb of 7.9 g/dL and a significant decline from stage 4 to stage 5 ($p = 0.003$), somewhat lower than the mean Hb values of 8.4–9.3 g/dL reported elsewhere.[10] The predominance of moderate-to-severe anaemia (73% combined) is broadly consistent with prior work, and pallor — often accentuated by coexisting hypoalbuminaemia — was, as expected, most pronounced in stage 5 disease.

The normocytic normochromic pattern that predominated on peripheral smear (62%), with a normal mean MCV of 85 fL, aligns with the classical description of anaemia of CKD and with comparable studies reporting MCV values of 86–91 fL. The notable minority with microcytic hypochromic (23%) and dimorphic (14%) pictures, however, underscores that iron and combined nutritional deficiencies are far from negligible contributors in this population — a pattern that varied across published series, from a near-exclusive normocytic picture in one cohort to a substantial microcytic burden in another.[11]

Iron-profile analysis found isolated iron deficiency in 17% and a mixed iron-deficiency/anaemia-of-CKD pattern in a further 21%, together implicating iron deficiency in 38% of patients — a considerably higher proportion than the 4% reported by Belurkar and Shastry, a difference plausibly related to that study's retrospective design and partial iron-profile testing. This finding argues for the routine use of iron studies, and where indicated iron supplementation, in CKD patients in this population, given the independently high background prevalence of iron deficiency in India.

Folic acid deficiency (47%) considerably outweighed vitamin B12 deficiency (8%) in this cohort. While no patient had an isolated macrocytic picture, folic acid and vitamin B12 deficiency each contributed to a proportion of the dimorphic anaemia cases observed. Comparable work by Dandge and Variya similarly found substantial vitamin B12 deficiency (47 of 80 cases) that worsened with CKD duration, indicating both micronutrient deficiencies merit systematic screening rather than opportunistic testing.[12]

Total leucocyte count abnormalities were seen in both directions — leucocytosis in 29% and leucopenia in 3% — broadly concordant with prior reports of dual-direction total-count derangement in CKD, albeit with variable statistical significance across studies. Thrombocytopenia was present in 31% of this cohort, a rate comparable to the 29% reported by another series, and was significantly associated with bleeding manifestations ($p = 0.001$), even though thrombocytopenia itself did not track significantly with CKD stage. This dissociation is consistent with the understanding that uraemic bleeding risk in CKD reflects platelet dysfunction and altered platelet-endothelial interaction as much as platelet number.

On focused comparison of stage 4 versus stage 5 disease — the two stages that together comprised 92% of the cohort — haemoglobin, phosphorus, anaemia type, pallor, and hyperphosphataemia all differed significantly, reinforcing that even within "advanced" CKD, meaningful haematological and mineral-metabolism deterioration continues as patients progress toward end-stage disease.

Limitations

- The study was conducted at a single tertiary care centre; some enrolled patients may have received prior treatment elsewhere, which could have influenced baseline haematological values.
- The cross-sectional design permits assessment of association only, and cannot establish causal or temporal relationships between CKD stage and haematological parameters.
- The marked skew toward stage 4–5 disease limited statistical power to characterise haematological changes in earlier CKD stages.

CONCLUSION

This cross-sectional study of 100 patients demonstrates that haematological abnormalities are pervasive across the spectrum of chronic kidney disease and become more pronounced with advancing stage. Anaemia was the most common and clinically significant manifestation, with haemoglobin declining significantly from stage 4 to stage 5; its predominant normocytic normochromic pattern reflects the classical anaemia of CKD, though a clinically relevant minority showed microcytic or dimorphic pictures attributable to iron, folic acid, and vitamin B12 deficiency. Iron deficiency was significantly associated with stage 5 disease, while thrombocytopenia — though not linked to CKD stage

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— was strongly associated with bleeding manifestations, and both leucocytosis and leucopenia were observed without a clear stage-dependent trend. These findings support routine, stage-independent haematological and nutritional surveillance in CKD patients, with particular attention to iron, folate, and vitamin B12 status, to enable earlier detection and targeted management of anaemia, bleeding risk, and infection susceptibility as patients progress toward end-stage renal disease.

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