

# Morphological Spectrum of Bone Marrow Changes in Patients of Chronic Kidney Disease: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Bone marrow investigations are crucial for Chronic Kidney Disease (CKD) patients with anaemia because they monitor iron stores and reveal morphological abnormalities. In the context of CKD, the examination of bone marrow plays a crucial role in assessing iron levels in individuals with anaemia, as well as providing valuable insights into the specific morphological alterations that occur in CKD patients.

**Aim:** To determine the bone marrow changes and bone marrow iron storage in the patients with CKD; and to study the association between haematological parameters and different CKD stages.

**Materials and Methods:** This cross-sectional study design enrolled 50 CKD patients in the Department of Pathology at MLB Medical College, Jhansi, Uttar Pradesh, India from December 2021 to November 2022. Each patient underwent bone marrow biopsy examination. The Medonic-M Series, an automated haematological analyser, performed the Complete Blood Count (CBC) with red cell indices. Perl's staining and the Gale Grading Systems were used for assessing iron storage. Descriptive analysis employed frequency and proportions for categorical variables, while mean and

Standard Deviation (SD) were used for continuous variables. One-way ANOVA was used to compare differences between variables. Data was collected, compiled, tabulated, entered into a Microsoft Excel sheet, and analysed using Statistical Package for the Social Sciences (SPSS) version 23.0.

**Results:** The study included 50 cases, with the majority of patients being in their fifth and sixth decades of life. Of the total cases, 28 (56%) were males and 22 (44%) were females. Most patients were in Stage-V CKD (N=28, 56%), followed by Stage-III (N=16, 32%), and Stage-IV (N=6, 12%). Among the haematological variables, the difference in Haemoglobin (Hb) was statistically significant (p-value=0.001) in all CKD stages. Iron absorption was found to be normal in 58% (n=29) of patients and increased in 32.00% (n=16) of cases. A total of 26 (52%) out of 50 CKD patients had normocellular bone marrow biopsy and bone marrow smears.

**Conclusion:** Bone marrow examination is undervalued but may be beneficial for CKD patients with anaemia, erythropoietin resistance, thrombocytopenia, or pancytopenia. This method should be considered in centres, whenever possible.

**Keywords:** Haemoglobin, Pancytopenia, Thrombocytopenia

## INTRODUCTION

The CKD is a broad term encompassing various primary disease processes that lead to the persistence of structural or functional abnormalities in the kidneys for a minimum of three months. Premature mortality and reduced quality of life are closely associated. Untreated instances may culminate in End Stage Renal Disease (ESRD), ultimately requiring dialysis [1,2].

In the context of India's population exceeding one billion, the escalating prevalence of CKD is anticipated to present significant challenges for both the healthcare sector and the economy in the forthcoming years. According to recent estimates, the age-adjusted incidence rate of ESRD in India is approximately 229 per million population (pmp). Moreover, each year, over 100,000 new patients are enrolled in renal replacement programmes in India [3,4].

The bone marrow biopsy is a valuable diagnostic tool for the identification and classification of diverse haematologic disorders. In the context of CKD, investigations of the bone marrow hold particular significance as they allow for the assessment of iron reserves in patients presenting with anaemia, as well as, providing valuable insights into the morphological alterations that manifest in CKD patients [5]. The definition of CKD used in this study was based on the persistence of kidney damage or an estimated Glomerular Filtration Rate (eGFR) below 60 mL/min per 1.73 m<sup>2</sup> for a duration exceeding three months [6].

Thus, the aim of the present study was to examine morphological changes in the bone marrow among individuals diagnosed with CKD. The study also aimed to determine bone marrow iron storage

in the studied CKD patients and the association between different haematological parameters and CKD stages.

## MATERIALS AND METHODS

This hospital-based cross-sectional study design enrolled 50 cases that reported to the Department of Pathology of MLB Medical College, Jhansi, Uttar Pradesh, India from December 2021 to November 2022 (12 months duration). The study was undertaken after obtaining prior approval from the ethical committee of the institution (Certificate No. 3126/IEC/I/2022-23), and it adhered to the principles enumerated in the Declaration of Helsinki.

Informed consent was obtained from each patient fulfilling the inclusion criteria, prior to their enrolment in the study.

**Inclusion criteria:** Male and female patients of all age groups diagnosed with advanced CKD, who had kidney damage with a reduction in GFR below 59 mL/min/1.73 m<sup>2</sup> for more than three months, were included in the study.

**Exclusion criteria:** Any patient with contraindication for bone marrow biopsy, such as haemorrhagic disorders like haemophilia and concomitant use of anticoagulants, those with skin infection or recent radiation therapy at the sampling site, and those with bone marrow disorders such as osteoporosis, osteomyelitis, or osteogenesis imperfecta. All patients who refused to give informed consent and patients with marked thrombocytopenia (platelet count <0.40 lac/cumm) were excluded.

The individuals who met the predetermined criteria for inclusion were subjected to routine investigations, including a Complete

Blood Count (CBC), HbA1c assessment, and bone marrow biopsy examination. The selection of patients was conducted through non-probability convenient sampling. The study gathered demographic information such as age, sex, and comorbidities including diabetes mellitus, hypertension, malignancy, hypothyroidism, and ischemic heart disease. Additionally, the indication and outcomes of the bone marrow were documented. The relevant patient information for the study was documented on a pre-designed and structured proforma, customised for the research.

**Procedure for Perl's staining:** The procedure followed for Perl's staining was similar to a study conducted by Dharwadkar A et al., and the grading of bone marrow smears was conducted using the conventional Gale's method [7,8].

**Grading of bone marrow storage iron [8]:** The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation. Following this, the categorisation of CKD was established into different stages dependent on the eGFR measurement [9].

The CBC with red cell indices was conducted utilising the Medonic-M Series, a fully automated haematological analyser that is currently installed in the central pathology laboratory. The preparation of peripheral blood smears was conducted on all patients, followed by staining with Leishman stain. Subsequently, a comprehensive examination of the general picture was performed. According to the established criteria, patients were classified as anaemic if their Hb levels were below 13 g/dL for males and 12 g/dL for females [10].

**Definition of bone marrow cellularity used in the current study:** Specifically, hypercellular marrow is characterised by the presence of more than 70% cellular elements, normocellular marrow contains between 30% and 70% cellular elements, and hypocellular marrow is defined as containing less than 30% cellular elements [11,12]. For the present study, we investigated haematological parameters and morphological changes observed in the bone marrow of patients with CKD.

## STATISTICAL ANALYSIS

The statistical software used for this study was IBM SPSS, version 23.0. The present study employed a descriptive analysis approach to report the findings. Continuous variables were presented as mean values accompanied by their corresponding Standard Deviation (SD). Conversely, categorical variables were represented as percentages. The statistical significance of differences in continuous variables was assessed using the one-way ANOVA test. Meanwhile, the chi-square test was employed to investigate potential associations between categorical variables. A p-value <0.05 was considered statistically significant at a 95% confidence interval.

## RESULTS

A total of 50 patients with Chronic Kidney Disease (CKD) were included in the study. Among them, 28 (56%) were males and 22 (44%) were females. The mean age of the CKD patients was 44.51 years. The age range of the patients varied from 10 to 80 years, with the majority falling in the 5<sup>th</sup> and 6<sup>th</sup> decades of life [Table/Fig-1].

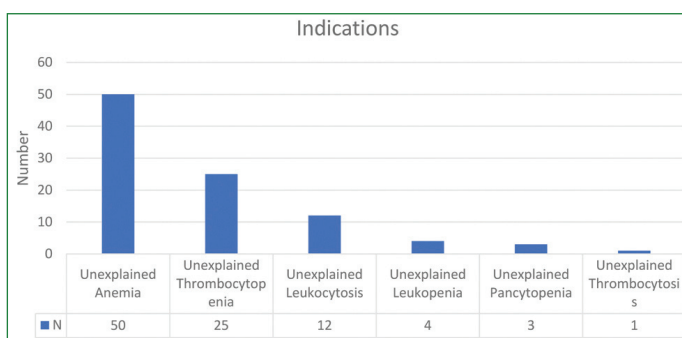
The study revealed that the most prevalent stage of CKD was Stage-V, accounting for 28 cases (56%). This was followed by Stage-III, observed in 16 patients (32%), and Stage-IV, observed in 6 CKD cases (12%) [Table/Fig-1].

All participants underwent bone marrow examination due to unexplained anaemia. The indications for performing bone marrow examinations included thrombocytopenia, unexplained leucocytosis, unexplained leukopenia, pancytopenia, and thrombocytosis. These conditions were observed in 25 (50%), 12 (24%), 4 (8%), 3 (6%), and 1 (2%) of cases, respectively (refer to [Table/Fig-2]).

Anaemia was observed in all patients diagnosed with CKD. Investigation of haematological parameters in CKD patients revealed a progressive decrease in Haemoglobin (Hb) levels as the disease

Age group (in years)	CKD-III (n=16)	CKD-IV (n=6)	CKD-V (n=28)
10-20	2	0	1
21-30	3	0	2
31-40	3	1	4
41-50	0	2	6
51-60	4	2	9
61-70	3	1	5
71-80	1	0	1
Gender			
Male	10	2	16
Female	6	4	12

[Table/Fig-1]: Demographic distribution of CKD patients (n=50).



[Table/Fig-2]: Indications for Bone Marrow Examination (n=50).

progressed from Stage-III (10.39±2.53 g/dL) to Stage-IV (7.20±1.63 g/dL). Statistical analysis showed a significant difference in mean Hb levels (p=0.001), while the remaining haematological parameters did not show statistical significance (p>0.05) [Table/Fig-3].

Stage of CKD	Haemoglobin (g/dL)	WBC (x10 <sup>9</sup> /L)	Platelet count (x10 <sup>9</sup> /L)	MCV (fL)
	Range (Mean±SD)	Range (Mean±SD)	Range (Mean±SD)	Range (Mean±SD)
CKD-III	6.20-16.80 (10.39±2.53)	1500-20500 (11597.69±6305.45)	0.24-8.60 (2.01±2.16)	60-99.7 (82.13±10.60)
CKD-IV	3.00-11.80 (7.34±3.09)	1500-11400 (5680±3690.46)	0.13-2.09 (1.26±0.62)	52-130.9 (85.77±20.50)
CKD-V	4.70-10.40 (7.20±1.63)	2300-36600 (10625.93±7356.45)	0.18-3.23 (1.5693±0.75)	51.20-98.80 (81.77±8.76)
ANOVA	7.652	2.691	1.074	0.403
p-value	<b>0.001</b>	0.078	0.350	0.671

[Table/Fig-3]: Haematological parameters in patients of CKD (N=50). Data presented as mean±SD or number; \*p<0.05 was considered significant

Peripheral blood examination results indicated that a significant proportion of patients, specifically 68% (n=34), exhibited a normocytic normochromic anaemic presentation. Furthermore, 10 patients (20%) exhibited dimorphic anaemia, while the study reported that 5 cases had microcytic hypochromic anaemia and 1 subject had megaloblastic anaemia [Table/Fig-4].

Type of anaemia	(N=50)	%
Normocytic normochromic anaemia	34	68
Dimorphic anaemia	10	20
Microcytic hypochromic anaemia (iron deficiency anaemia)	5	10
Megaloblastic anaemia	1	2
Total	50	100

[Table/Fig-4]: Distribution of CKD as per type of Anaemia (N=50).

In patients with CKD, a significant proportion of subjects exhibited unremarkable iron absorption, as evidenced by Perl's Prussian Blue Stain reaction. The study results indicated that 16 patients exhibited an increase in iron uptake on the stain reaction, while 5 patients (10%) showed no iron uptake [Table/Fig-5].

Iron uptake	CKD (N=50)	%
Normal	29	58
Increased	16	32
No iron	5	10
Total	50	100

**[Table/Fig-5]:** Perl's blue stain reaction for iron uptake (N=50).

Bone marrow biopsies were performed on all 50 patients diagnosed with CKD. Among them, 26 cases (52%) exhibited normocellular bone marrow. Additionally, 10 cases (20%) showed mixed deficiency or dimorphic anaemia on bone marrow biopsy findings, and 5 CKD cases (10%) were associated with microcytic hypochromic anaemia. Furthermore, 6% of patients had hypocellular bone marrow [Table/Fig-6].

BM biopsy findings	CKD (N=50)	%
Normocellular bone marrow	26	52
Mixed deficiency (dimorphicaemia)	10	20
Microcytic hypochromic anaemia	5	10
Hypocellular bone marrow	3	6
Cellular marrow with mildly suppressed myelopoiesis	2	4
Myelofibrosis	1	2
Megaloblastic anaemia	1	2
Myeloproliferative disorder (essential thrombocythemia)	1	2
Myeloproliferative neoplasm	1	2

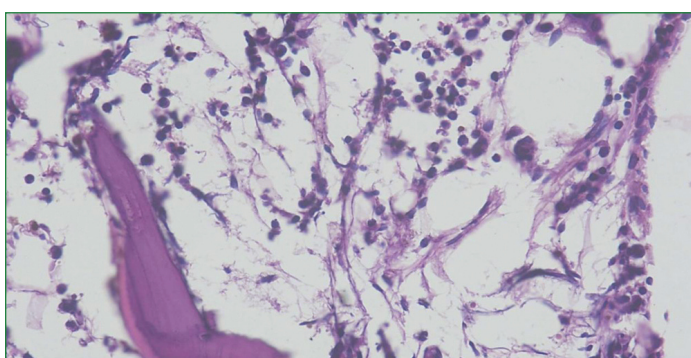
**[Table/Fig-6]:** Bone marrow biopsy findings in CKD patients (N=50).

The bone marrow analysis revealed several noteworthy findings, including the presence of cellular marrow with mildly suppressed myelopoiesis, myeloproliferative disorder (specifically essential thrombocythemia), myelofibrosis, myeloproliferative neoplasm, and megaloblastic anaemia [Table/Fig-6].

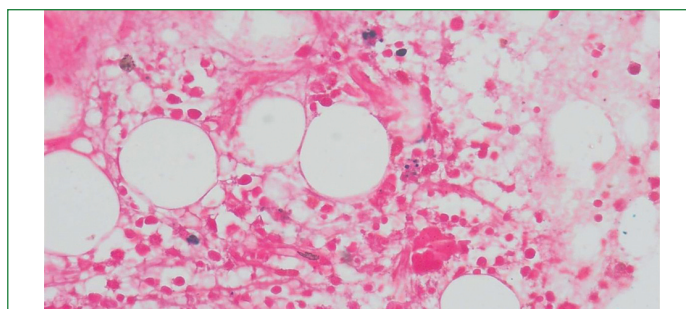
In this study, 26 cases (52%) showed normocellular bone marrow. Among the CKD stages, Stage-V accounted for 18 patients (36%), followed by CKD-III with 5 patients (10%) and CKD-IV with 3 patients (6%). Hypocellular bone marrow was found in only 6% of CKD Stage-V patients [Table/Fig-7]. The bone marrow examination of a 56-year-old male patient with CKD Stage-V showed normocellular marrow with predominantly normoblastic maturation [Table/Fig-8], along with normal iron stores [Table/Fig-9]. Similarly, cases of different CKD stages exhibited varying staining of bone marrow cells, resulting in different levels of cellularity [Table/Fig-10-13].

BM biopsy findings	CKD-III (N=16)	CKD-IV (N=6)	CKD-V (N=28)
Normocellular bone marrow	5	3	18
Hypercellular bone marrow	7	3	5
Hypocellular bone marrow	0	0	3
Mixed cellularity (i.e., both hypocellular and hypercellular)	4	0	2

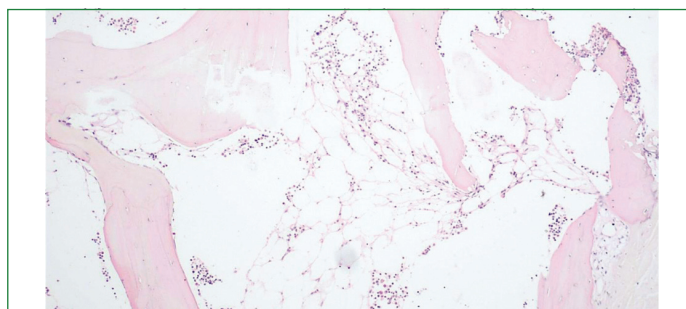
**[Table/Fig-7]:** Bone marrow biopsy cellularity findings in CKD patients (N=50).



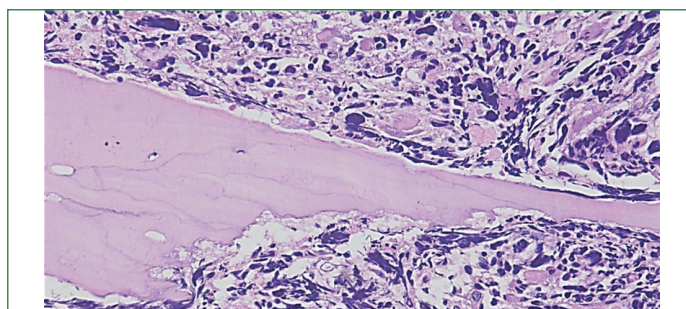
**[Table/Fig-8]:** Bone Marrow Biopsy (40x) 56 years/male, with CKD Stage-V, showing normocellular marrow with predominantly normoblastic maturation.



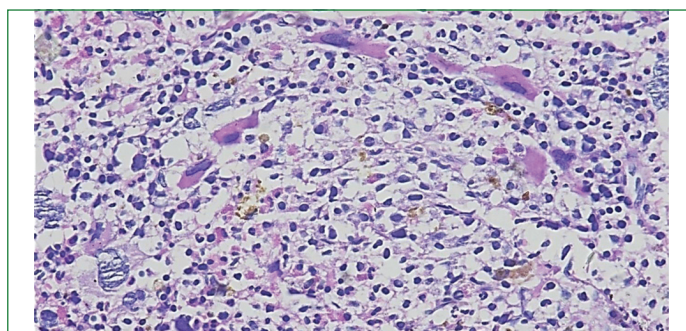
**[Table/Fig-9]:** Bone Marrow Biopsy with Perl's stain (40x), 56 years/male, with CKD Stage-V, showing normocellular marrow with Normal iron store.



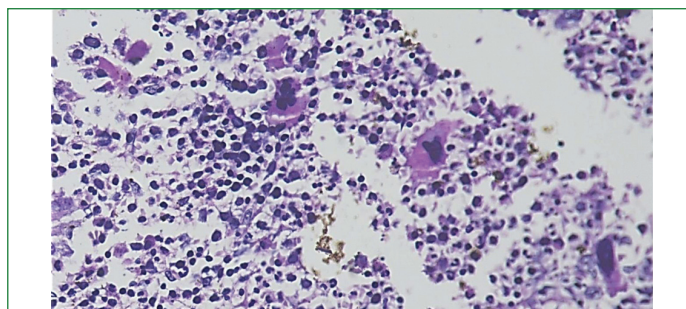
**[Table/Fig-10]:** Bone Marrow Biopsy (10x), 38 years/male, CKD-Stage-V, showing hypocellular marrow.



**[Table/Fig-11]:** Bone Marrow Biopsy (40x), 66 years/female, CKD-Stage-III with myelofibrosis, showing hypocellular marrow with reduced both erythroid and myeloid precursors.



**[Table/Fig-12]:** Bone Marrow Biopsy (40x), 56 years/male, CKD-Stage-III with (Essential Thrombocythemia), showing hypercellular marrow with myeloid and megakaryocytic hyperplasia.



**[Table/Fig-13]:** Bone Marrow Biopsy (40x), 56 years/male, CKD-Stage-III with myeloproliferative neoplasm, showing hypercellular marrow and myeloid hyperplasia comprising of mainly neutrophils and eosinophilic precursors along with megakaryocytic hyperplasia.

## DISCUSSION

In this study, the bone marrow examination findings were normocellular in most cases (n=26). CKD Stage-V included 18 (36%) of patients, followed by CKD-III with 5 patients (10%) and CKD-IV with 3 patients (6%). A similar study conducted by Nasir K et al., revealed that 91 (51.7%) patients had normocellular bone marrow on bone marrow biopsy [13]. Hypercellular bone marrow was found in 7 CKD-III patients (14%), followed by 5 CKD-V patients (10%) and 3 CKD-IV patients (6%). A study by Callen IR and Limarzi LR on CKD patients' bone marrow aspiration findings revealed that 80% of patients had hypercellular bone marrow [14]. Hypocellular bone marrow was found in only 6.00% of CKD Stage-V patients. According to the findings of the study done by Eschbach JW et al., 53.3% of CKD patients had hypocellular bone marrow [15]. Sikole A et al., reported that 60.00% of ESKD patients receiving chronic dialysis had hypocellular bone marrow [16]. Another study by Weng CH et al., showed that 51.3% of ESRD patients receiving continuous dialysis had hypocellular bone marrow [17]. In a study conducted by Hsieh CC et al., bone marrow biopsy findings revealed that the overall incidence of hypocellular marrow was 55.6% [18]. Mixed cellularity, i.e., both hypocellular and hypercellular bone marrow, was found in 4 patients (8%) of CKD-III, followed by 2 patients (4%) of CKD-V, with none of the cases in CKD-IV. None of the studies showed a correlation between CKD stages and bone marrow cellularity. However, CKD Stage-V predominantly showed normocellular marrow, followed by hypercellular marrow.

Within the scope of the present study, it was observed that half of the patients diagnosed with CKD were aged 50 years or older. The elderly population exhibits a significant incidence of CKD. The observed trend can be primarily attributed to the rising incidence of conventional risk factors associated with CKD, including but not limited to diabetes, hypertension, and Cardiovascular Disease (CVD) [19].

According to a study conducted by Anupama YJ et al., among rural Karnataka residents, the mean age of CKD cases was determined to be 52.73±17.08 years [20]. Similarly, Jayasumana C et al., conducted a study among Sri Lankan farmers, revealing that the mean age of CKD cases was 45.5 years in men and 47.4 years in women [21]. The findings of the Million Death Study, a nationally representative mortality survey conducted in India, indicate that the age-standardised burden of renal deaths was most pronounced among individuals aged 45-69 years [22]. Coresh J et al., found a higher prevalence of CKD in older age groups [23]. In their study, age, hypertension, and diabetes were significant indicators of CKD [23]. Notably, 11% of individuals aged 65 years and above, without hypertension or diabetes, were found to have Stage-III or more severe CKD.

The study revealed a higher prevalence of CKD among men compared to women, which was also observed in a multicentre hospital-based registry of CKD patients in India [24].

More than half of the patients in the study were in CKD Stage-V, followed by Stage-III (32%) and Stage-IV (12%).

The primary indication for bone marrow examination among patients with CKD in the study was unexplained anaemia, present in all cases (100%, n=50). This was followed by unexplained thrombocytopenia, observed in 50.00% (n=25) of cases. Additional observations included the presence of unexplained leukocytosis in 24.00% (n=12) of cases, unexplained leukopenia in 8.00% (n=4) of cases, unexplained pancytopenia in 6.00% (n=3) of cases, and unexplained thrombocytosis in 2.00% (n=1) of cases. According to a study conducted by Nasir K et al., the most frequent reason for bone marrow examination in patients with CKD was pancytopenia, accounting for 28.40% of cases [13]. This was followed by unexplained thrombocytopenia observed in 24.40% of cases and unexplained anaemia in 22.20% of cases.

Anaemia is a prevalent complication observed in patients with CKD. The haematological parameters of the CKD patients under investigation indicate a gradual decline in Hb levels as the disease progresses from Stage III to Stage IV. Statistical analysis revealed a significant difference in the mean Hb level among the three groups, with a p-value of less than 0.05. The observed decline in Hb values suggests a concurrent exacerbation of anaemia severity and CKD progression. According to the findings of the study conducted by Callen IR and Limarzi LR, anaemia worsens as CKD progresses [14].

The investigation findings indicate a gradual decline in Mean Corpuscular Volume (MCV) as CKD advances from Stage III to Stage V. This phenomenon could potentially be attributed to functional iron insufficiency or reduced iron accessibility to the erythroid cells, possibly stemming from chronic inflammation. A separate investigation exhibited a reduction in MCV during the transition from Stage III to Stage IV, while an elevation was observed in Stage V of CKD [20]. Apart from Hb, all other parameters in the haematological investigation were statistically insignificant.

The study revealed that a normocytic normochromic blood picture was the predominant finding, accounting for 68.00% (n=34) of cases. Dimorphic anaemia was the second most common finding, observed in 10 cases (20%). A microcytic hypochromic picture was observed in 5 cases (10%). These findings were similar to those of the studies conducted by Callen IR and Limarzi LR and Singh et al., where the majority of cases exhibited a normocytic normochromic picture [14, 25].

By staining with Perl's Prussian Blue Stain, the majority of cases showed normal uptake in 58.00% (n=29), followed by elevated iron absorption in 32.00% (n=16) of the instances. In their investigation, Talwar VK et al., discovered that 6.5% of individuals had elevated bone marrow iron stores, whereas the remaining 57.7% of cases had negligible bone marrow iron uptake [26]. The study also showed that 62% of the patients had low serum ferritin, and 74% of the patients had serum iron levels below normal. Jairam A et al., demonstrated that the majority of ESRD patients in their research had received parenteral iron treatment prior to admission to their hospital, and iron shortage was observed in those who had not [27]. Iron overload was the result of the widespread use of parenteral iron and frequent transfusions in CKD patients. They also concluded that it is incorrect to define iron overload solely based on serum ferritin levels since CKD patients frequently experience 2-3-fold increases in ferritin (acute phase reactant) levels with inflammatory activation.

The results of the present study on CKD patients who underwent Bone Marrow Biopsy revealed that a majority of the cases, specifically 26 out of 50 cases (52.00%), exhibited Normocellular Bone Marrow following Bone Marrow Biopsy examination. A similar study conducted by Nasir K et al., revealed that 91 (51.70%) patients had normocellular bone marrow on bone marrow biopsy [13]. The present investigation revealed that mixed deficiency (Dimorphic Anemia) accounted for 20.00% (n=10) of the observed cases, while Microcytic Hypochromic Anemia constituted 10.00% of the cases. Additionally, Hypocellular Bone Marrow was detected in 6.00% of the cases. According to the research conducted by Eschbach JW et al., a significant proportion of CKD patients (90) exhibited hypocellular bone marrow, with 53.30% of them showing this characteristic [15]. Cellular marrow with mildly suppressed myelopoiesis (4.00%, n=2), megaloblastic anaemia, and myeloproliferative disorder (essential thrombocythemia) were the remaining cases found to be normocellular on bone marrow aspiration. Myeloproliferative neoplasm and myelofibrosis were other findings that were coincidental in nature.

### Limitation(s)

This was a single-centre research study with a small sample size. This investigation should be conducted in phases, including several college departments and medical institutions, to maximise the likelihood of learning more about the etiopathological elements of CKD.

## CONCLUSION(S)

The CKD poses a significant threat to public health due to its escalating prevalence and associated morbidity and mortality rates. This phenomenon is associated with various haematological conditions that affect the immune system, erythropoiesis, granulopoiesis, platelet function, and coagulation.

Early diagnosis and prompt care have been shown to decrease the mortality and morbidity rates of patients with CKD. The present research findings suggest that bone marrow examination is a significant yet under utilised diagnostic procedure for detecting various underlying diseases that may result in anaemia, erythropoietin resistance, thrombocytopenia, and pancytopenia among individuals with CKD. Therefore, bone marrow examination should be considered for implementation in centres, where feasible.

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