ORIGINAL ARTICLE

A Prospective 1-Year Study of Renal Recovery in Pigment Nephropathy: Insights Beyond the Acute Phase

Prem Shankar Patel[1*], Archana[2], Pinki Kumari[3], Prit Pal Singh[4], Om Kumar[5]

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Abstract

Background: Pigment nephropathy is an underrecognized cause of acute kidney injury. Data from northern India is scarce. The present study aims to assess the clinical characteristics and outcomes of pigment nephropathy in this region.

Materials and methods: We analyzed the demographics, etiology, and outcomes of 20 patients with biopsy-proven pigment nephropathy.

Results: The mean age was 27.75 years (range: 13–52), with a male-to-female ratio of 18:2. The average peak serum creatinine was 12.09 mg/dL (range: 0.84–22.3). Rhabdomyolysis was identified in 14 (70%) and hemolysis in 6 patients (30%). The rhabdomyolysis was attributed to hypokalemia, infection, strenuous exercise, physical trauma, inflammatory myositis, neuroleptic malignant syndrome, and heat stroke. The hemolysis was caused by paroxysmal nocturnal hemoglobinuria, thrombotic microangiopathy, transfusion reaction, rifampicin, and physical stress. The majority of patients (85%) required hemodialysis, with a mean of 6 sessions (range: 3–17). The mean duration of hospitalization was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6). All 20 patients survived and achieved complete renal recovery. Of the 20 patients, 13 completed at least 1 year of follow-up, 4 were lost to follow-up, and 3 remain under observation. At 1 year, all 13 patients had normal serum creatinine. None progressed to chronic kidney disease.

Conclusion: Of 20 patients (4.1%) with pigment-induced acute kidney injury (AKI), 70% had myoglobin- and 30% hemoglobin-induced nephropathy. Common causes included hypokalemia, infection, strenuous activity, and paroxysmal nocturnal hemoglobinuria. Hemodialysis was required in 85%, with an average hospital stay of 15.3 days. Among 13 patients with a 1-year follow-up, none developed chronic kidney disease. Overall prognosis appears favorable; however, larger studies with extended follow-up are needed to better characterize long-term outcomes in pigment nephropathy.

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Introduction

Pigment nephropathy is an important yet underrecognized entity within the broad spectrum of acute kidney injury (AKI), contributes up-to 10% of AKI.[1] Heme pigments are primarily generated through two processes: rhabdomyolysis and hemolysis. Rhabdomyolysis can be traumatic, exertional, or nonexertional in origin.[2] Hemoglobinopathies, paroxysmal nocturnal hemoglobinuria, malaria, transfusion reactions, prosthetic heart valves, and certain drugs are the important causes of intravascular hemolysis and hemoglobin cast nephropathy.[3–5] Free heme pigments cause direct tubular injury and lead to tubular obstruction via pigment cast formation. Rhabdomyolysis is biochemically characterized by high serum creatine phosphokinase, myoglobin levels, lactate dehydrogenase, and hemolysis by unconjugated hyperbilirubinemia, high serum LDH, and an elevated reticulocyte count. Pathophysiologically, pigment nephropathy is characterized by vasoconstriction, proximal tubular epithelial cell injury, and distal tubule blockage due to pigment cast formation.[2,6] Rhabdomyolysis can present with an asymptomatic rise in creatine phosphokinase to deadly acute kidney injury, though weakness and myalgia are the most common presenting symptoms. As there is no established treatment for pigment nephropathy, the focus remains on prevention. The prognosis of pigment nephropathy is favorable; in the majority, renal function recovers completely.[7,8] However, the studies have shown an increased risk of chronic kidney disease (CKD).[8,9] The etiology and outcomes of pigment nephropathy have been variably reported across studies worldwide, including different regions of India.[7–9] Only a few case reports and retrospective studies have been published from southern India.[4,9] Data from northern India is scarce. The present study aims to analyze the clinical characteristics and outcomes of pigment nephropathy in this region.

Materials and Methods

Study Design

The present study is a prospective, 1-year observational study to evaluate the demographics, etiology, and outcomes of biopsy-proven pigment nephropathy diagnosed between June 2022 and May 2025. This study was approved by the institutional ethics committee on October 16, 2024, via letter number: 233/IEC/IGIMS/2024.

Inclusion and Exclusion Criteria

Patients with AKI and evidence of rhabdomyolysis, defined by raised serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and myoglobin levels or hemolysis indicated by elevated LDH, unconjugated bilirubin, and reticulocyte count, individuals undergoing kidney biopsy were assessed for pigment-induced kidney damage. A total of 20 cases of either myoglobin- or hemoglobin-associated pigment nephropathy were included in the analysis: 14 diagnosed as myoglobin cast nephropathy and 6 as hemoglobin cast nephropathy.

Data Collection

A detailed history for all patients, including information on preceding trauma, strenuous exercise, seizures, alcohol or medication intake, as well as demographic characteristics, was obtained. Comprehensive laboratory investigations, including complete blood count, reticulocyte count, blood urea, serum creatinine, serum electrolytes (sodium, potassium, calcium, phosphate), uric acid, serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), serum myoglobin, liver function tests, urine dipstick and microscopy, and urine protein-to-creatinine ratio were recorded. Treatment details during

[1]Associate Professor, Department of Nephrology, Indira Gandhi Institute of Medical Sciences; [2]Assistant Professor, Department of Microbiology, Netaji Subhas Medical College; [3]Senior Resident; [4]Additional Professor; [5]Professor and Head, Department of Nephrology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India; *Corresponding Author

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Table 1: Demographic and biochemical characteristics of a patient with pigment nephropathy ($n = 20$)

Parameters	*Value*
Mean age and range (years)	27.75 years (13–52)
Male: female ratio	18:2
Mean serum creatinine at presentation with range (mg/dL)	9.31 (0.84–22.3)
Mean peak serum creatinine (mg/dL)	12.09
Median LDH with interquartile range (IQR) (IU/L)	702.5 (IQR: 381–1154)
Median CPK with interquartile range (IQR) (IU/L)	2198 (IQR: 41–10655)
Median serum myoglobin with interquartile range (IQR) (ng/dL)	396.45 (IQR: 35–1262.5)
Mean serum calcium (mg/dL)	8.10
Mean serum phosphate (mg/dL)	6.96
Mean serum uric acid (mg/dL)	10.07
Mean serum potassium (mEq/L)	4.70
Mean number of hemodialysis	6
Mean duration of hospital stays with range (days)	15.3 (4–30)
Mean recovery time with range (weeks)	3.1 (2–6)

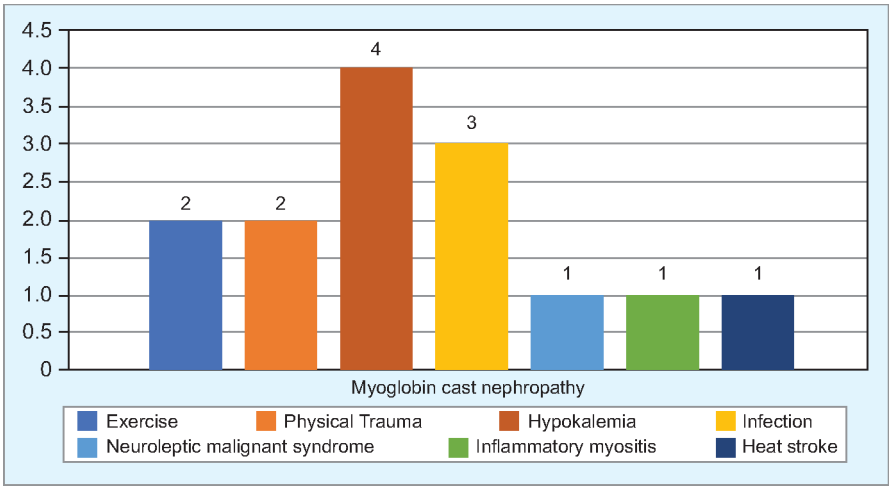

Fig. 2: Etiology of myoglobin cast nephropathy in study population ($n = 14$)

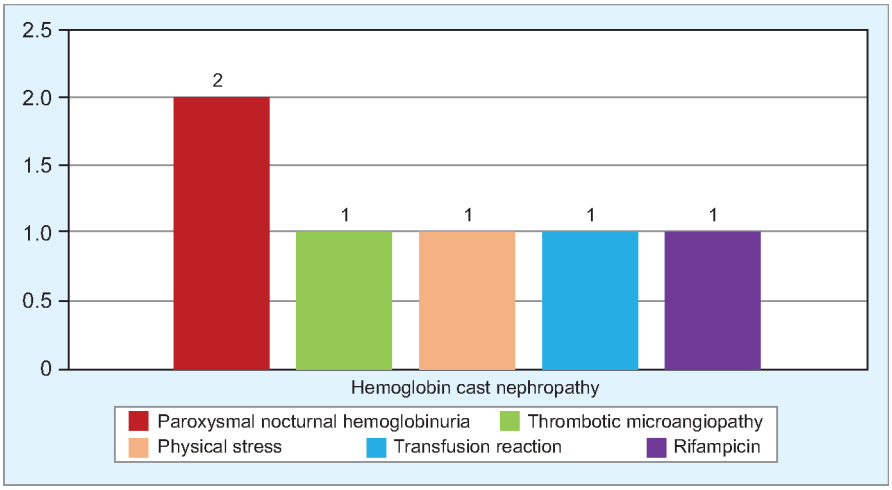

Fig. 3: Etiology of hemoglobin cast nephropathy in study population ($n = 6$)

hospitalization were also documented. Renal biopsy samples were examined under light microscopy using hematoxylin and eosin, Periodic acid–Schiff, trichrome, Periodic acid–Schiff methenamine, and Prussian blue stains. Myoglobin and hemoglobin immunohistochemistry (IHC) were performed on the intratubular pigmented cast. The etiology of rhabdomyolysis and hemolysis was determined by clinical history and laboratory findings. Supportive treatment was provided to all patients, and hemodialysis (HD) was provided to those who required it. The definition of AKI followed the criteria established by the KDIGO guidelines published in 2012.[10] Recovery of renal function was defined as a decline in the serum creatinine to the normal range. Patients were followed for a minimum of 1 year, with renal function tests and urine albumin-to-creatinine ratio measured at 3, 6, and 12 months.

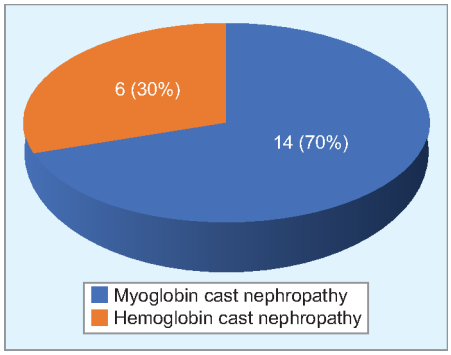

Fig. 1: Types of pigment nephropathy in the study population ($n = 20$)

Statistical Analysis

Mean ± standard deviation is used for normally distributed data, while median with interquartile range (IQR) is used for data that are not normally distributed. Frequencies and percentages are used to present categorical variables.

Results

Out of a total of 481 acute kidney injury cases diagnosed between June 2022 and May 2025, 20 (4.1%) patients with either rhabdomyolysis or hemolysis were included in the analysis. All 20 cases showed histological evidence of pigment nephropathy on tissue biopsy. The mean age was 27.75 years (range: 13–52), with a male-to-female ratio of 18:2. Urine was positive for pigments in 50% of patients, and 50% had oliguria. The average peak serum creatinine was 12.09 mg/dL (range: 0.84–22.3). Other clinical data are presented in Table 1. Rhabdomyolysis was identified in 14 (70%) and hemolysis in 6 patients (30%) (Fig. 1). Cause of rhabdomyolysis were postacute gastroenteritis, persistent hypokalemia (4), infection (3), strenuous exercise (2), physical trauma (2), inflammatory myositis (1), quetiapine and chlorpromazine induced neuroleptic malignant syndrome (1) and heat stroke (Fig. 2).[1] One patient with biopsy-proven inflammatory myositis had

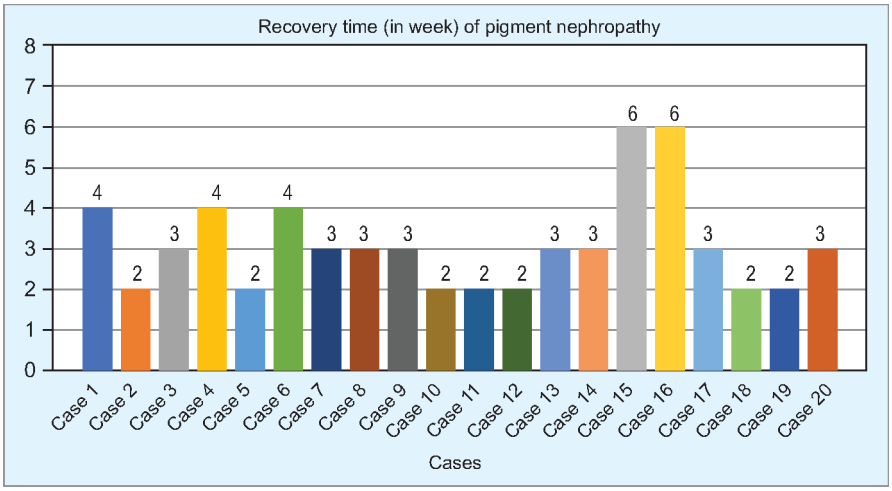

Fig. 4: Recovery time of renal function of patients with pigment nephropathy (n = 20)

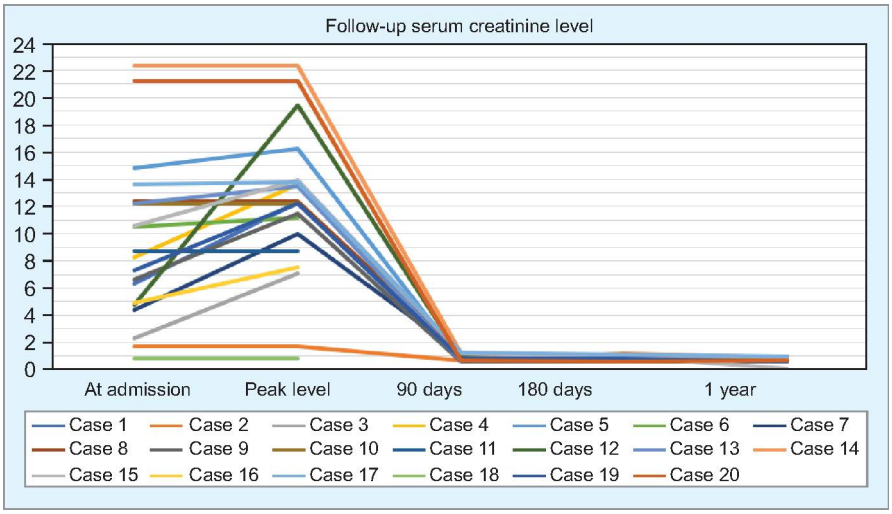

Fig. 5: Serum creatinine level of patients with pigment nephropathy at admission and on follow-up (n = 20)

experienced two prior episodes of recurrent acute kidney injury (AKI) over the past 12 years. Another patient had been on quetiapine (50 mg twice daily) and chlorpromazine (100 mg once daily) for the previous 2 years. The etiologies of hemolysis were paroxysmal nocturnal hemoglobinuria (2), thrombotic microangiopathy (1), transfusion reaction (1), rifampicin (1), and physical stress (Fig. 3).[1] Two patients with paroxysmal nocturnal hemoglobinuria had diffuse intense blue staining on Perl's Prussian Blue technique, indicating hemosiderin deposition. One patient showed histological evidence of thrombotic microangiopathy in addition to pigment nephropathy. In the case of rifampicin-induced hemolysis, the patient had been on daily therapy for 10 days. Another patient developed hemolysis due to physical stress from running. Kidney biopsy showed acute tubular injury with sloughed off epithelial cells, interstitial edema, and pigment casts in all 20 patients. None of the biopsies demonstrated significant glomerulosclerosis, interstitial fibrosis, or tubular atrophy. The majority of patients (85%) required hemodialysis during hospitalization, with a mean of six sessions (range: 3–17). Three patients (15%) did not require dialysis; these included one case each of myoglobin cast nephropathy, paroxysmal nocturnal hemoglobinuria, and thrombotic microangiopathy. The average duration of hospital stay was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6) (Fig. 4). All patients survived the acute phase and achieved complete renal recovery with normalization of serum creatinine. Of the 20 patients, 13 completed at least 1 year of follow-up, four were lost to follow-up, and three remain under observation. At the 1-year mark, all 13 had normal serum creatinine; 12 patients had normal urine albumin-to-creatinine ratios (A1) except one had microalbuminuria (A2). None of the patients went into chronic kidney disease (CKD) (Fig. 5).

Discussion

Acute kidney injury is a serious complication of heme pigment-induced kidney injury.[9] It was first described by Meyer-Betz in 1911.[11] Prevalence of AKI in rhabdomyolysis varies from 10 to 50%, and contributes up to one-fourth of AKI.[12,13] In our study, about 4.1% of AKI is contributed by rhabdomyolysis or hemolysis. Pigment nephropathy is most commonly caused by rhabdomyolysis, hemolysis, and bile pigment accumulation. The breakdown of striated muscle in rhabdomyolysis releases myoglobin, a 17.8-kDa heme pigment, into the bloodstream. This condition typically arises following prolonged, intense, or unaccustomed physical activity, especially in hot and humid environments where muscle energy production is compromised due to an imbalance between supply and demand. The mechanism of pigment-induced kidney injury is complex and involves several interrelated processes, including renal vasoconstriction, direct toxicity to proximal tubular epithelial cells, and obstruction of distal tubules by pigment cast formation. In acidic urine, heme pigments readily bind with Tamm-Horsfall protein, promoting the formation of obstructive casts within the distal tubules.[2,6] Rhabdomyolysis causes can be grouped into three categories: traumatic (such as crush injuries, physical trauma, or prolonged immobilization), nontraumatic exertional (including intense physical activity, eccentric exercise, hyperthermia, or underlying metabolic and muscular disorders), and nontraumatic nonexertional (such as drug or toxin exposure, infections, or electrolyte imbalances). In the present study, rhabdomyolysis was observed in approximately 14 patients (70%) and was attributed to various causes, including persistent hypokalemia following diarrhea (4), infections (3), strenuous exercise (2), physical trauma (2), inflammatory myositis (1), neuroleptic malignant syndrome induced by quetiapine and chlorpromazine (1), and heat stroke.[1] Consistent with established classifications, our study observed cases of rhabdomyolysis arising from all three major etiological categories. Rhabdomyolysis results in the leakage of myoglobin, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) into the blood. Although serum myoglobin levels rise early following muscle injury, its rapid and variable metabolism limits its diagnostic sensitivity.[13] Therefore, serum CPK is considered the most sensitive enzymatic marker for detecting muscle injury. Though the threshold for serum CPK to predict the risk of AKI has not been outlined, levels above 5000 U/L are generally

considered to be associated with an increased risk.[14] In contrast, only eight patients (57.1%) in our cohort exhibited such elevated levels. Among the remaining six patients, four had CPK levels ranging from 936 to 3640 IU/L, while two had normal serum CPK levels. Notably, pigment nephropathy was also observed in patients with normal CPK values in the present study. Therefore, a high index of suspicion is essential for timely and accurate diagnosis of pigment nephropathy, regardless of CPK levels.

The second leading cause of pigment nephropathy is intravascular hemolysis. The important causes of intravascular hemolysis are paroxysmal nocturnal hemoglobinuria (PNH), hemoglobinopathies, malaria, transfusion reaction, prosthetic heart valves, and drugs.[4,15,16] Intravascular hemolysis releases hemoglobin into the plasma. When plasma hemoglobin levels exceed the binding capacity of haptoglobin, the concentration of free plasma hemoglobin increases. Free hemoglobin then dissociates into dimeric hemoglobin, which further breaks down into heme and globin. Free heme can pass through the glomerulus and may cause kidney injury. Studies on novel biomarkers have highlighted the role of free iron-mediated kidney injury and identified it as a significant mechanism underlying AKI in patients undergoing cardiopulmonary bypass.[17] Hemolysis was observed in six patients (30%) in our study and was attributed to various causes: paroxysmal nocturnal hemoglobinuria (two patients), thrombotic microangiopathy (1), transfusion reaction (1), rifampicin-induced hemolysis (1), and physical exertion (Fig. 3).[1] Both patients with paroxysmal nocturnal hemoglobinuria exhibited diffuse, intense blue staining with Perl's Prussian Blue stain, indicating hemosiderin deposition. In one patient, pigment nephropathy was caused by hemolysis associated with thrombotic microangiopathy. Rifampicin-induced hemolysis leading to pigment nephropathy was observed in a patient on daily therapy for 10 days. Another patient experienced severe hemolysis following intense running and developed hemoglobin cast nephropathy. Other studies have also reported hemolysis associated with PNH, blood transfusion, and rifampicin therapy.[3–5] Envenomation, poisoning, malaria, infections, and sepsis are common etiologies for both rhabdomyolysis and hemolysis.[6,16] However, in our study, we did not identify envenomation or poisoning as a cause of pigment nephropathy, conditions that are more commonly reported in the southern regions of India. There are no significant histological differences in pigment nephropathy caused by rhabdomyolysis versus hemolysis, except for the presence of hemosiderin deposition in cases of hemoglobin cast nephropathy.[3] In our study, all kidney biopsies showed severe acute tubular necrosis with granular pigment casts. Therefore, it is morphologically challenging to distinguish the underlying cause of pigment nephropathy. Immunohistochemistry for myoglobin and hemoglobin remains the only reliable method for differentiating between myoglobin-induced and hemoglobin-induced kidney injury.

Pigment nephropathy frequently leads to severe AKI requiring hemodialysis (HD). Currently, there is no definite treatment for pigment nephropathy. Management primarily focuses on preventing AKI in high-risk patients, particularly those with CPK levels exceeding 5000 IU/L.[14] Supportive treatment, such as adequate hydration, maintaining fluid and electrolyte balance, ensuring proper tissue perfusion, and initiating dialysis when indicated, are essential component of care. In our study, the majority of patients (85%) underwent HD, with an average of six sessions (range: 3–17). The remaining three patients (15%) did not require dialysis and showed improvement with conservative management. A study from South India by Sakthirajan et al. reported that approximately 97.8% of patients required HD during hospitalization, with a mean of 9 ± 2 sessions, findings that are broadly comparable to ours.[9] The severity of pigment nephropathy is largely influenced by the underlying disease and the promptness of preventive interventions. Severe AKI is commonly associated with prolonged hospital stays and increased morbidity. The mean peak serum creatinine level of 12.09 mg/dL and the requirement for hemodialysis in 17 patients (85%) indicate the severe nature of AKI in our cohort, which may be attributed to the severity of the underlying disease process and delayed presentation. In our study, the mean hospital stay was 15.3 days (range: 4–30), and the average time to renal recovery was 3.1 weeks (range: 2–6) (Fig. 4). Reported mortality rates in pigment nephropathy range from 3.5 to 22%, depending on several factors such as the severity of the primary illness, AKI-related complications, and the burden of prolonged hospitalization.[2,18,19] Notably, mortality is significantly higher among patients with AKI compared to those without (19.2% vs 3.6%).[9] In our cohort, all patients survived the acute phase and achieved complete renal recovery, evidenced by normalization of serum creatinine. No deaths occurred due to pigment nephropathy. The short-term prognosis of pigment nephropathy is generally favorable, with most patients achieving complete renal recovery.[7,9] However, several studies have shown an increased risk of developing CKD, even in patients who initially recover renal function. In separate cohorts, Sakthirajan et al. and Liapis et al. reported CKD development in 12% and 45% of patients, respectively.[8,9] Of the 20 patients, 13 completed at least 1 year of follow-up. Twelve had normal urine albumin-to-creatinine ratios (A1), while one had microalbuminuria (A2). None of the patients progressed to chronic kidney disease (CKD). This disparity in CKD development risk may be attributed to the shorter follow-up duration in the present study compared to others.

Overall prognosis appears favorable; however, larger studies with extended follow-up are needed to better characterize long-term outcomes in pigment nephropathy.

Limitations of the Study

The present study has several limitations, including a small sample size from a single center and the unavailability of key diagnostic markers such as urine myoglobin, serum haptoglobin, and plasma-free hemoglobin. These factors limit the generalizability of the findings. Furthermore, the short duration of follow-up restricts the ability to assess long-term outcomes.

Conclusion

Pigment nephropathy is often underrecognized cause of acute kidney injury. Total 20 patients (4.1%) were identified with pigment-induced AKI, of whom 14 (70%) had myoglobin-induced pigment nephropathy, and 6 (30%) had hemoglobin-induced pigment nephropathy. Common causes of rhabdomyolysis include hypokalemia, infection, and strenuous activity. Hemolysis was associated with paroxysmal nocturnal hemoglobinuria, thrombotic microangiopathy, transfusion reactions, rifampicin therapy, and physical exertion. Most patients (85%) required hemodialysis, with a mean hospital stay of 15.3 days. All patients survived the acute phase and achieved complete renal recovery, with normalization of serum creatinine in an average of 3.1 weeks. Of the 13 patients with a minimum of 1 year of follow-up, all had normal serum creatinine at 1 year. Twelve had normal urine albumin-to-creatinine ratios (A1), while one had improving microalbuminuria (A2). None progressed to chronic kidney disease. Despite favorable outcomes, larger studies with extended follow-up are needed to clarify long-term prognosis.

Data Availability Statement

The data sets generated and analyzed during the current study are not publicly available

due to patient confidentiality; however, they can be made available upon appropriate request to the corresponding author.

Conflict of Interest

Author do not have any competing either financial or nonfinancial interests to declare.

Informed Consent

Informed consent was obtained from all patients for the collection and utilization of their clinical and laboratory data in research and publication.

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Authors Contributions

Dr Prem Shankar Patel, Dr Prit Pal Singh, Dr Om Kumar, Dr Archana, and Dr Pinki Kumari contributed to the study's conception and design. Data acquisition and analysis were carried out by Dr Prem Shankar Patel, Dr Pinki Kumari, and Dr Archana. The initial draft of the manuscript was written by Dr Prem Shankar Patel and Dr Archana. All authors critically reviewed earlier versions and have read and approved the final manuscript.

Orcid

Prem Shankar Patel https://orcid.org/0009-0003-6480-9386

Prit Pal Singh https://orcid.org/0000-0003-4600-1693

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