Огляд

Review

НИРКИ KIDNEYS

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Hematologic Alterations In Renal Disease: Pathological Mechanisms And Clinical Correlates

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Abstract

Hematologic abnormalities are common and clinically significant complications of renal disease, contributing to increased morbidity, mortality, and reduced quality of life. Anaemia, iron dysregulation, platelet dysfunction, and immune abnormalities arise from complex interactions between impaired kidney function, chronic inflammation, and disrupted haematopoiesis. Advances in molecular and clinical research have expanded understanding of these processes and reshaped therapeutic strategies. This review aims to synthesise current evidence on hematologic alterations in renal disease, focusing on underlying pathological mechanisms and their clinical correlates, while highlighting emerging biomarkers and therapeutic innovations. A narrative review of recent experimental, translational, and clinical literature was conducted, with emphasis on studies published between 2021 and 2025. Key areas examined include anaemia pathophysiology, iron metabolism disorders, platelet and coagulation abnormalities, immune cell dysfunction, disease-specific hematologic complications, prognostic biomarkers, and novel therapeutic approaches. Renal disease disrupts the kidney-bone marrow-immune axis, leading to impaired erythropoietin production, inflammation-driven iron sequestration, reduced erythrocyte lifespan, platelet dysfunction, and immune dysregulation. These abnormalities contribute to cardiovascular disease, infection susceptibility, thrombotic and bleeding risks, and progression of kidney dysfunction. Emerging therapies, particularly hypoxia-inducible factor-based agents and strategies targeting inflammatory and iron-regulatory pathways, offer mechanism-based alternatives to traditional treatments. Hematologic biomarkers such as anaemia severity and leukocyte-derived indices show promise for prognostic stratification. Hematologic alterations in renal disease reflect interconnected pathophysiological processes with significant clinical implications. Integrating mechanistic insights, biomarker-driven risk assessment, and precision therapeutic strategies is essential to improving outcomes and advancing holistic management of patients with renal disease.

Keywords: Chronic kidney disease; Anaemia; Iron metabolism; Hematologic biomarkers

1. Introduction

Chronic kidney disease (CKD) is a significant issue of international public health concern, with a growing percentage of the adult population being affected and causing a significant burden to cardiovascular morbidity, lowered quality of life and early mortality. In addition to the gradual decline of the renal excretory function, CKD is typified by a set of systemic complications, of which hematologic abnormalities are most abundant and

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clinically relevant. Early changes in haemostasis, platelet dysfunction, and inflammation-induced changes in haemostasis are also observed in the onset of renal disease and are exacerbated as the kidney progresses, highlighting the strong physiological interdependence between the hematopoietic system and the kidney [1,2].

The most commonly investigated hematologic presentation of CKD is anaemia, which continues to be a key factor that dictates patient outcomes. Its incidence is rising gradually with the deterioration of glomerular filtration rate, which is a manifestation of a defect in erythropoietin synthesis, iron dysregulation, chronic inflammation, and survival of red blood cells. Notably, anaemia in CKD is not only a laboratory finding, but also a clinical issue that is linked with left ventricular hypertrophy, heart failure, impaired cognition, fatigue, and increased renal disease progression rate [1]. Even after decades of therapeutic intervention, the ideal management of anaemia related to CKD remains a developing issue, with new information on the complex pathophysiology of the condition and long-term safety concerns of current therapies.

The process of inflammation is also becoming a common denominator between hematologic and renal dysfunction. CKD is currently perceived as a chronic inflammatory condition, which is featured by the incessant immune response, the overproduction of cytokines and oxidative stress. These inflammatory events are known to cause functional iron deficiency by mediating iron sequestration by hepcidin, inhibit erythroid progenitor, platelet dysfunction, and endothelial homeostasis. Bibliometric reviews of the current trends in CKD research reveal an increase in the focus on inflammation as the major factor of disease progression and systemic complications, such as hematologic dysfunction [3]. This paradigm shift has extended the conceptual base of renal anaemia and the associated hematologic changes beyond the simplistic models of hormone deficiency.

Further examples of the hematologic complications of renal disease include platelet abnormalities. Qualitative platelet dysfunction often occurs in patients with CKD, which is clinically manifested by a high probability of bleeding, especially at the advanced stages of the disease. Ironically, increased thrombotic risk is also linked to CKD, caused by platelet hyperreactivity, endothelial dysfunction, and dysregulated coagulation processes. These conflicting haemostatic dispositions both coexist and change with the disease stages and clinical situations, making risk stratification and management difficult [2]. The acknowledgement of this duality has led to a revived study into the biology of platelets, abnormalities in coagulation and how these abnormalities are integrated into the overall inflammatory environment of CKD.

The therapy of anaemia in CKD has been extensively developed during the last 20 years. The use of erythropoiesis-stimulating agents (ESAs) has transformed the way anaemia is treated by minimising the need to rely on transfusion and enhancing quality of life. Nevertheless, cardiovascular risk, thromboembolic, and optimal haemoglobin targets have cast doubt on the zeal to pursue aggressive ESA therapy. As a reaction to this, recent years have seen a rise in the number of new therapeutic classes, which resemble physiological erythropoietic regulation more closely. A new area of particularly promising development is hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which activate endogenous erythropoietin production and at the same time increase iron utilisation and decrease hepcidin levels [4].

The widening clinical use of HIF-PHIs has led to a wider reassessment of the paradigm of anaemia management in CKD. Network meta-analyses and systematic reviews have shown that these agents are effective in raising haemoglobin in dialysis and non-dialysis populations with specific mechanistic benefits relative to conventional ESAs [4]. These innovations have been met with a wealth of expert consensus efforts, such as the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference, which highlighted the importance of an anaemia management approach that is tailored to patient heterogeneity, comorbidity and safety data changes [5].

Regardless of these treatment developments, the hematologic defects in renal disease are not confined to anaemia. The changes in iron metabolism, platelet activity, immune cell activity, and coagulation pathways all contribute to patient outcomes and therapeutic responses. These abnormalities are interconnected, and it is important to note that an integrated systems-based approach to the hematologic changes in renal disease is warranted. Instead of being singular complications, these alterations are a reflection of a broken kidney-bone marrow-immune axis, which is affected by inflammation, metabolic malfunctions, and therapeutic interventions.

This review summarises the existing information on hematologic changes in renal disease, with a priority on underlying pathologic processes and their clinical parallels. Among the critical areas are anaemia, iron regulation, platelet and coagulation disorders, immune cell dysfunction, and hematologic complications peculiar to renal pathologies, as well as the new biomarkers and treatment options. Incorporating mechanistic knowledge with clinical information, this review offers a multifaceted framework of hematologic dysfunction in renal disease and reveals the way forward in research and clinical practise in this fast-growing area.

2. Kidney-Bone Marrow Axis: Physiological Overview

The bone marrow and the kidney are interrelated with closely regulated endocrine, metabolic and immunologic processes that sustain erythropoiesis, iron and systemic homeostasis. Many of the hematologic abnormalities found in the range of kidney dysfunction are caused by disruption of this bidirectional axis in renal disease.

2.1 Renal Contributions to Haematopoiesis

One of the key roles of the kidney in haematopoiesis is the production of erythropoietin (EPO), a glycoprotein hormone that is secreted by the renal cortex and the outer medulla by specialised interstitial fibroblast-like cells. Under physiological conditions, these erythropoietin-producing cells (EPCs) react to tissue hypoxia by the

hypoxia-inducible factor (HIF)-dependent oxygen-sensing pathways that strictly control the transcription of the EPO gene [6]. In normoxia, the prolyl hydroxylase domain enzymes stimulate the degradation of HIF, but in hypoxia, HIF- subunits are stabilised, and transcriptional activation of erythropoietic genes occurs.

Recent experimental and translational research studies have shown that chronic kidney injury results in phenotypic remodelling of EPCs, which trans-differentiate to myofibroblast-like cells with a reduced EPO-producing ability [7]. This pathological plasticity is directly related to renal fibrosis and defective erythropoiesis and is involved in the maintenance of anaemia in chronic kidney disease. Notably, the EPC dysfunction can be partially reversed under some hypoxic or drug conditions, which underscores the therapeutic implication of the HIF pathway targeting [8].

The kidney is also important in the homeostasis of systemic iron, besides the production of EPO. Decreased clearance by the kidney and upregulation of hepcidin through inflammation disrupts iron mobilisation through the hepcidin-ferroportin axis and causes iron-limited erythropoiesis in the presence of sufficient iron stores. Inhibition of hepcidin activity or increased ferroportin-mediated iron export has become a potential therapy to achieve effective erythropoiesis in renal disease [9].

Additionally, the vitamin D renal activation plays a role in an indirect effect on haematopoiesis, through immune responses and inflammatory signalling. Immune dysregulation and heightened inflammatory load have been linked to vitamin D deficiency in kidney disease, worsening anaemia, and reduced responsiveness to erythropoietic stimuli.

2.2 Hematologic System Influence on Renal Homeostasis

The hematologic system has a reciprocal effect on the renal structure and functioning in terms of oxygen supply, immune control and haemostatic regulation. Sufficient red blood cell bulk and deformability are necessary to sustain renal microvascular perfusion and tissue oxygenation, especially in the hypoxia-prone renal medulla. Intrarenal hypoxia may thus be worsened by anaemia and erythrocyte dysfunction to increase fibrotic remodelling and functional loss.

Renal homeostasis is also influenced by immune cells and platelets, which are involved in the process of inflammatory and reparative reactions. Platelets engage in a dynamic interaction with leukocytes and endothelial cells, which releases cytokines, growth factors and microparticles that regulate vascular integrity and immune activation. Exposure of blood to artificial membranes in renal disease and haemodialysis may increase platelet activation and inflammatory signalling, which may cause endothelial dysfunction and microvascular damage [10].

Together, these interactions highlight the kidney-bone marrow axis as a complicated, two-way network where renal failure disrupts haematopoiesis, and hematologic changes provide feedback to affect the renal perfusion, inflammation, and repair. This physiological crosstalk understanding presents an important paradigm in the interpretation of hematologic abnormalities in renal disease and in designing specific therapeutic interventions. Figure 1 schematically represents the two-way interactions between the renal activity, haematopoiesis and immune regulation.

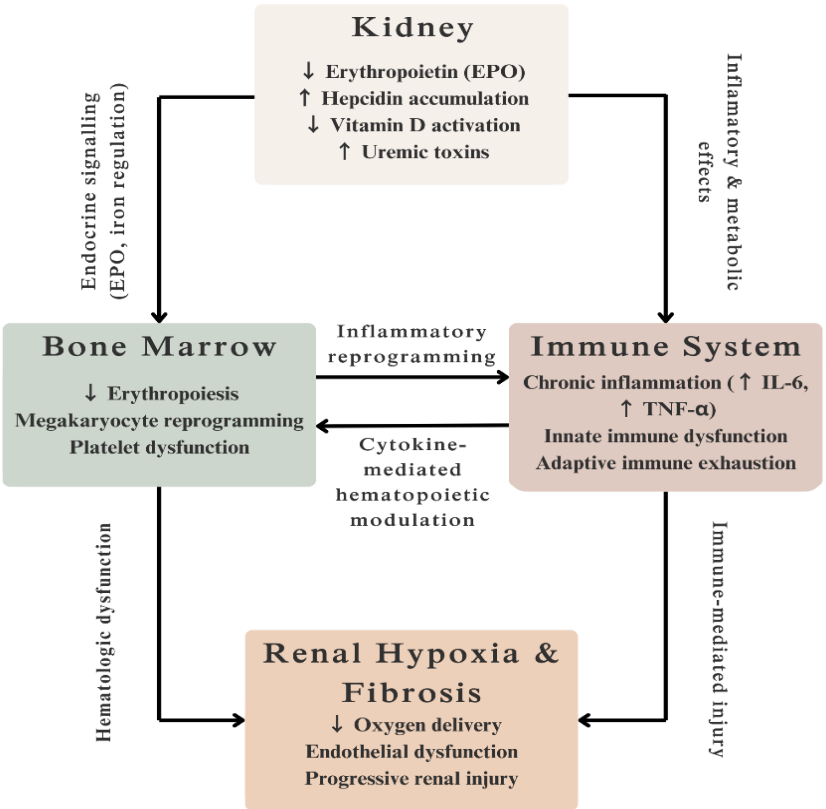

Figure 1. The Kidney-Bone Marrow-Immune Axis in Renal Disease

3. Anaemia in Renal Disease

Anaemia is one of the most frequent as well as clinically significant complications of renal disease, and the result of a combination of endocrine dysfunction, iron dysregulation, inflammation, and metabolic derangements. Its existence is linked to unfavourable cardiovascular consequences, poor quality of life, and rapid renal failure, and it is a major therapeutic opportunity in acute and chronic kidney disorders [11,12].

3.1 Pathophysiological Mechanisms

The pathophysiology of anaemia in renal disease is the deficiency of erythropoietin (EPO), which is caused by the injury-induced inability of the renal erythropoietin-producing cells. This defect is increased in chronic renal kidney disease (CKD) by EPO resistance, which results from inflammation, iron trapping, and suppression of erythroid progenitor responsiveness by the uremic milieu [11,12].

The iron deficiency is very widespread and comes in both absolute and functional types. Absolute iron deficiency indicates actual iron store depletion, whereas functional iron deficiency involves the inability to mobilise iron, though ferritin levels are sufficient or high. The latter is largely regulated by the upregulation of hepcidin mediated by inflammation that prevents the export of iron by ferroportin on macrophage and enterocytes, limiting the supply of iron for erythropoiesis [11].

The anaemia mediated by inflammation further enhances the hepcidin impairment by cytokine signalling, especially through interleukin-6 mediated hepcidin expression. This state of inflammation inhibits the growth of erythroid progenitor cells and leads to decreased responsiveness to the erythropoiesis-stimulating agents (ESAs) [12]. Simultaneously, uremic toxin build-up causes erythrocytes to die earlier, which is driven by oxidative stress, membrane instability, and eryptosis and is becoming increasingly recognised as a significant cause of the severity of anaemia in end-stage CKD [13].

Nutritional deficiencies, including vitamin B12 and folate insufficiency, although less common, may coexist and further exacerbate anaemia, particularly in patients with advanced disease, dietary restrictions, or gastrointestinal malabsorption [11]. The multifactorial mechanisms contributing to anaemia in renal disease are summarised in Table 1.

Table 1. Pathophysiological Mechanisms of Anaemia in Renal Disease

Mechanism	Biological Basis	Key Mediators	Clinical Consequences
EPO deficiency	Loss/dysfunction of renal EPO-producing cells	↓ EPO, HIF dysregulation	Normocytic normochromic anaemia
EPO resistance	Inflammation, uraemia	IL-6, TNF-α	ESA hyporesponsiveness
Absolute iron deficiency	Depleted iron stores	↓ Ferritin, ↓ TSAT	Microcytosis, fatigue
Functional iron deficiency	Iron sequestration	Hepcidin, ferroportin blockade	Iron-restricted erythropoiesis
Reduced RBC lifespan	Oxidative stress, eryptosis	Uremic toxins	Worsening anaemia

3.2 Anaemia in Acute Kidney Injury versus Chronic Kidney Disease

Although anaemia is a characteristic of CKD, it is also present in acute kidney injury (AKI), albeit in different temporal and mechanistic patterns. In AKI, anaemia commonly serves as an indicator of acute inflammation, haemodilution, blood loss and temporary inhibition of erythropoiesis. Notably, in this case, anaemia can be reversed by restoration of renal activity in EPO production, which makes it potentially reversible [11].

On the contrary, anaemia in CKD develops over time and becomes more and more refractory with the progression of renal damage. The presence of chronic inflammation, ongoing hepcidin increase, ongoing EPO deficiency and progressive uremic toxin exposure sets up a vicious cycle of erythropoietic failure. These persistent causes distinguish between the CKD-related anaemia and the more temporary hematologic changes that are witnessed in AKI [12,14].

3.3 Clinical Consequences

The clinical effect of anaemia in renal disease goes far beyond a decrease in haemoglobin. Chronic anaemia is a contributor to left ventricular hypertrophy, adverse cardiac remodelling and heightened risk of heart failure, in large part because of compensatory rises in cardiac output and chronic tissue hypoxia [12].

The most notable outcomes are neurocognitive impairment, fatigue, and decreased exercise tolerance, which significantly reduce the quality of life of patients. Besides, anaemia has been found to increase the rate of progression of renal disease per se, possibly by enhancing fibrotic processes caused by hypoxia and increased inflammatory signalling in the kidney [11].

3.4 Diagnostic and Therapeutic Considerations

The diagnosis of anaemia in renal disease involves hematologic and iron biomarkers (serum ferritin, transferrin saturation (TSAT), and reticulocyte haemoglobin content) to make accurate diagnoses.

These parameters help in the differentiation of the phenotypes of iron deficiency and inform a therapeutic decision [14].

ESAs have traditionally served as the basis of anaemia treatment in CKD, but their application is still a contentious topic because it is claimed to increase cardiovascular risk, thromboembolism, and accelerate malignancy at elevated haemoglobin levels [12]. Modern KDIGO practises focus on patient-centred treatment objectives and careful dose adjustment [14].

These novel treatments, especially hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), are a paradigm shift in the treatment of anaemia. These agents enhance endogenous production of EPO and enhance iron utilisation by inhibiting hepcidin. They have been shown to be effective in large randomised trials and meta-analyses in both dialysis and non-dialysis CKD groups, and long-term safety profiles are still being evaluated [15–18].

4. Disorders of Iron Metabolism

Iron metabolism disorders are the core of the pathogenesis of anaemia in renal disease and form an important point of inflammation, erythropoiesis, and therapeutic responsiveness. Dysregulated iron management in chronic kidney disease (CKD) is associated with iron-restricted erythropoiesis, inefficient reaction to erythropoiesis-stimulating agents, and the complication of treatment [19].

4.1 Iron Handling in Renal Dysfunction

Hepcidin is the overall controller of systemic iron homeostasis, which is central to iron dysregulation in renal disease. The circulating hepcidin concentrations have been increased in CKD by decreased renal clearance and increased hepatic overproduction caused by inflammation. High levels of hepcidin inhibit the export of iron via ferroportin on enterocytes and macrophages, reducing the absorption of dietary iron and reducing the availability of iron to erythropoiesis [20,21].

Simultaneously, macrophage-mediated iron recycling is affected. In a physiological state, the macrophages absorb the iron in senescent erythrocytes and emit it into the bloodstream. Sustained hepcidin signalling in renal disease confines iron stores in macrophages, decreases plasma iron despite a sufficient or exaggerated total body iron stores. This dysfunctional sequestration will lead to functional iron deficiency and will further propagate anaemia in even patients under iron supplementation [9,21].

4.2 Clinical Phenotypes

Iron-restricted erythropoiesis is the most common clinical presentation of iron dysregulation in renal disease, which is characterised by low saturation of transferrin with normal or excessive ferritin levels. This type of iron deficiency is a manifestation of functional and not absolute iron deficiency, and is especially prevalent in patients with advanced CKD and systemic inflammation [19,20].

On the other hand, iron overload can occur in certain groups of patients, especially those who are in the transfusion-dependent group or those who received repeated intravenous iron treatment. Overload with iron deposition may increase oxidative stress, worsen immune response and may cause cardiovascular and hepatic complications. Striking a balance between iron replacement and overload risk is one of the most significant clinical challenges in the management of long-term anaemia [19]. Distinct iron phenotypes observed in renal disease and their therapeutic implications are outlined in Table 2.

Table 2. Iron Dysregulation in Renal Disease: Phenotypes and Therapeutic Implications

Iron Phenotype	Ferritin	TSAT	Hepcidin	Typical CKD Stage	Preferred Therapy
Absolute iron deficiency	Low	Low	Normal/Low	Early CKD	Oral or IV iron
Functional iron deficiency	Normal/High	Low	High	Advanced CKD	IV iron, HIF-PHI
Iron overload	High	High	Variable	Dialysis/Transfusion	Reduce iron exposure

4.3 Therapeutic Strategies

Oral and intravenous iron preparations are employed in the treatment of iron deficiency in renal disease, and the choice is determined by the disease progression, inflammatory load, and response to treatment. The gastrointestinal absorption, hepcidin-mediated blockade, and intolerance of oral iron therapy are frequently constrained, especially in patients with advanced CKD. Iron in its intravenous form is more assured in delivering iron, but it should be closely monitored to prevent iron overload and adverse reactions [19].

Ferric citrate has become a two-in-one agent that is able to enhance iron parameters and manage hyperphosphatemia in non-dialysis-dependent CKD. Its effectiveness in haemoglobin and iron index increases, and other pleiotropic effects on fibroblast growth factor 23 and platelet parameters, are supported by meta-analysis evidence of its efficacy [22,23].

Since the interaction between iron metabolism and inflammation is a close process, the aspects of safety should be treated with primary importance. The application of iron supplementation in active infection or a more intense inflammatory response can contribute to an increase in oxidative stress and microbial proliferation. To this end, new therapeutic approaches are directed more towards upstream regulation of the hepcidin-ferroportin axis to restore physiologic iron

trafficking, but not merely increasing iron delivery [9,21].

5. Platelet Abnormalities and Haemostatic Dysfunction

Renal disease is characterised by platelet dysfunction and haemostatic derangements that are the result of an intricate interplay of uraemia, inflammation, endothelial damage, and bone marrow signalling changes. These malformations lead to the paradoxical presence of bleeding diathesis with the increased thrombotic risk in patients with chronic kidney disease (CKD) and associated renal pathologies [2,24].

5.1 Platelet Quantitative and Qualitative Defects

Qualitative defects of Uremic platelets dysfunction are more characteristic than overt thrombocytopenia. The accumulation of uremic toxins alters platelet adhesion, platelet activation and platelet aggregation by disrupting intracellular signalling pathways, calcium flux and expression or function of major glycoprotein receptors. Such abnormalities impair primary haemostasis and are the basis of the high bleeding predisposition in advanced CKD [2].

In addition to uraemia, it is now becoming evident that platelet impairment in CKD begins with bone marrow reorganisation and megakaryocyte reprogramming. Renal dysfunction signals (inflammatory and metabolic) change Megakaryopoiesis and generate platelets with reduced functional potential and proinflammatory phenotypes. The mechanism is a paradigm-shifting process connecting the hematopoietic dysregulation that renal disease causes directly to circulating platelet abnormalities [25].

Dialysis also alters platelet biology by exposing blood to unnatural surfaces and shear stress. Haemodialysis has been linked to platelet activation, degranulation and consumption, which cause the reduction of platelet quality and increased turnover. Such effects depend on membrane biocompatibility and dialysis modality, and help bring interindividual differences in bleeding and thrombotic complications [26].

5.2 Coagulation Abnormalities

Renal disease also interferes with the coagulation cascade by affecting the synthesis, clearance, and activity of coagulation factors in addition to platelet dysfunction. The decreased clearance of procoagulant factors by the kidney, hepatic synthetic changes and inflammation, provide a disproportionate haemostatic state. The standard coagulation assays might not be sensitive enough to these subtle variations, and hence they have limited predictive power in clinical practise [27].

The dysfunction of the endothelium is a prime cause of abnormal coagulation in CKD. The activation of endothelium facilitates the liberation of von Willebrand factor, intensification of platelet-vessel wall communication, and a prothrombotic condition. Parallel to this, dysfunctional nitric oxide and prostacyclin signalling also increase platelet activation and vascular inflammation [24,28].

5.3 Clinical Manifestations

Platelet and haemostatic changes in renal disease have an opposite clinical manifestation. On the one hand, patients develop a bleeding diathesis, which is manifested as mucocutaneous bleeding, gastrointestinal bleeding, and bleeding problems during procedures. Such events can mainly be explained by the dysfunction of platelets and the absence of primary haemostasis.

Conversely, CKD is also becoming known as a prothrombotic condition, and there are high risks of venous thromboembolism, cardiovascular disease, and access thrombosis. This tendency toward thrombosis is fuelled by chronic inflammation, endothelial damage, platelet hyperreactivity, and dysregulation of coagulation pathways, especially in nephrotic syndrome, in which depletion of endogenous anticoagulant proteins also increases the risk [24,28].

Taken together, these results contribute to the importance of risk stratification and careful decision-making in therapeutic practice in patients with renal disease when it comes to bleeding and thrombotic risks. Table 3 outlines the range of haemostatic abnormalities and associated clinical implications in renal disease.

Table 3. Haemostatic Abnormalities and Clinical Manifestations in Renal Disease

Abnormality	Underlying Mechanism	Clinical Manifestation	Predominant Risk
Platelet dysfunction	Uremic toxins, megakaryocyte reprogramming	Mucocutaneous bleeding	Bleeding
Endothelial activation	Chronic inflammation	Microvascular injury	Thrombosis
Coagulation imbalance	Altered factor clearance	Venous thromboembolism	Thrombosis
Dialysis-related changes	Bioincompatibility	Access thrombosis/bleeding	Mixed

6. Leukocyte and Immune Cell Alterations

Chronic kidney disease (CKD) is becoming a condition of immune dysregulation that is typified by both immune activation and immune deficiency. The changes in leukocyte counts, phenotype, and activity impair host defence and promote persistent inflammation, which leads to an increase in infection vulnerability, cardiovascular disease, and progressive renal damage [29].

6.1 Innate Immune Dysregulation

The impaired neutrophil and monocyte functions are the main cause of innate immune dysfunction in the case of renal disease. The neutrophils in CKD have lower chemotaxis, poor phagocytosis and generation of reactive oxygen species, which reduces antibacterial defence. These malformations are explained by uremic toxins deposition, oxidative stress and chronic inflammatory signalling [29].

Monocytes have a paradoxical phenotype, which is characterised by chronic activation and production of proinflammatory cytokines. This prolonged stimulation facilitates systemic inflammation and endothelial dysfunction without being converted to productive clearance of pathogens. Increased inflammatory indices, such as composite leukocyte-derived markers, have been independently linked with decreased survival in CKD, highlighting the clinical importance of innate immune dysregulation [30].

6.2 Adaptive Immune Abnormalities

Renal disease leads to a significant change in adaptive immunity, lymphopenia and functional T cell exhaustion are important phenomena. These are decreased thymic production, enhanced apoptosis, and persistent antigenic stimulation that lead to the depletion of naïve T-cells and defective cellular immune responses. Such defects impair immune surveillance and lead to impaired immune responses to infections and immunisations [29,31].

The B-cell dysfunction also impairs the adaptive immunity in CKD. Disturbed B-cell development, defective memory B-cell development and defective antibody production are some factors leading to poor vaccine-induced immunity. The attenuated humoral response has been shown in systematic reviews of SARS-CoV-2 vaccination in CKD and dialysis patients, but partial protection is frequently obtained with booster vaccination [31,32].

6.3 Clinical Implications

Immune dysregulation in renal disease has significant clinical effects. Bacterial and viral infections are major causes of hospitalisation and death among patients with CKD, who are more prone to them. Poor vaccine responsiveness requires specific immunisation measures, such as booster vaccination and post-vaccination serologic surveillance [32,33].

In addition to the risk of infection, chronic immune stimulation is a cause of cardiovascular morbidity and fibrosis of the kidney. Proinflammatory leukocyte subsets facilitate endothelial injury, vascular remodelling and atherosclerosis, whereas persistent cytokine signalling increases fibrotic processes in the kidney. Immune dysregulation is further emphasised as a key factor of long-term outcomes in CKD by the association between systemic inflammatory markers and survival [30]. The downstream clinical consequences of immune and hematologic dysregulation in renal disease are summarised in Figure 2.

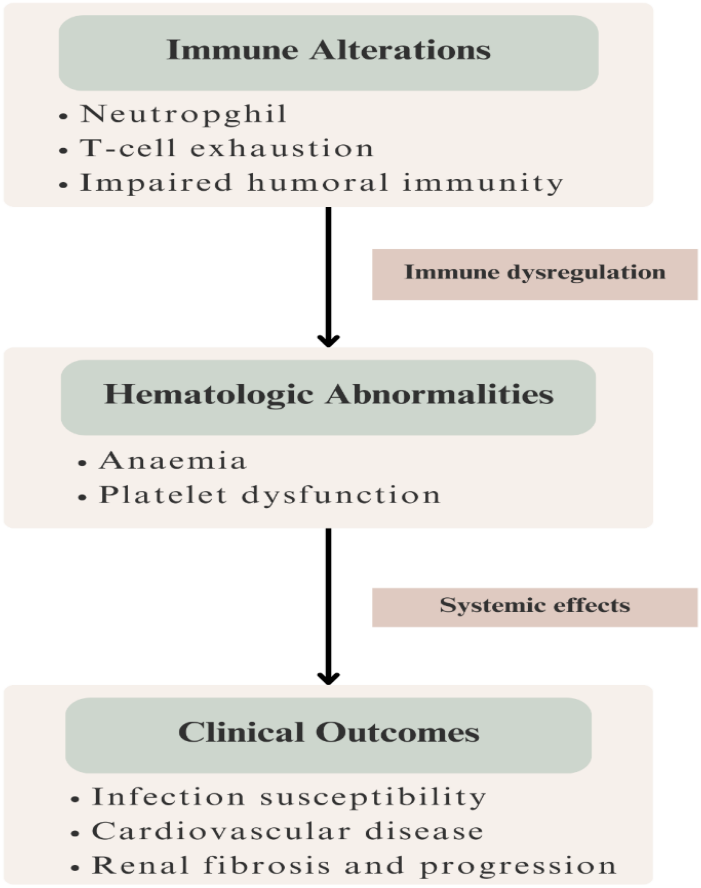

Figure 2. Clinical Consequences of Immune and Hematologic Dysregulation in Renal Disease

7. Hematologic Complications Specific to Renal Pathologies

Discrete pathologies of the kidney are linked to specific renal-related hematologic complications, which indicate disease-related processes, treatment exposures, and changes in haemostatic balance. Examples of clinical situations in which hematologic abnormalities play a significant role in morbidity and therapeutic decision making include nephrotic syndrome, dialysis dependence and renal transplantation.

7.1 Nephrotic Syndrome

Nephrotic syndrome is a paradigm hypercoagulable situation that is defined by a high risk of venous and arterial thromboembolism. Its pathophysiology is multifactorial and includes urinary depletion of anticoagulant proteins, which is dominated by antithrombin III, and increased procoagulant factors, platelet hyperreactivity, and haemoconcentration. Hypoalbuminemia also worsens hypercoagulability by changing the drug pharmacokinetics and raising the blood viscosity [34,35].

There is still clinical uncertainty on the best thromboprophylaxis in nephrotic syndrome due to the opposing thrombosis and bleeding risks. Observational evidence and cohort studies indicate that the personalised risk stratification on the basis of the severity of the disease, histologic subtype and serum albumin levels is necessary in order to inform the prophylactic anticoagulation approaches [34,36]. The present practise guidelines focus on the selective use of the agent instead of universal anticoagulation [37].

7.2 Dialysis-Associated Hematologic Changes

Dialysis causes specific hematologic issues due to recurring extracorporeal circulation and blood contact with artificial surfaces. Bioincompatibility of dialysis membranes with the blood components encourages platelet activation, complement activation and leukocyte stimulation, which leads to the development of a chronic inflammatory process that worsens anaemia and haemostatic imbalance [37].

Moreover, the loss of blood during dialysis due to circuit retention, frequent blood sampling, and access bleeding is also contributing to the development of anaemia. Dialysis could cause haemodilution that would temporarily reduce haemoglobin levels, making it difficult to assess and treat anaemia. The cumulative effects require close attention to the hematologic parameters and specific anaemia treatment plans in patients requiring dialysis [37].

7.3 Renal Transplantation

Renal transplantation has a partial corrective effect on most of the hematologic abnormalities of uraemia, but post-transplant anaemia is a common and clinically significant complication. Some of the risk factors are impaired graft functioning, iron deficiency, inflammation and decreased production of endogenous erythropoietin. Constant post-transplant anaemia has been linked to poor graft survival and a high risk of cardiovascular disease [38].

Hematologic toxicity is also caused by immunosuppressive therapies. Cytopenias may be brought about by antimetabolites, calcineurin and mammalian target of rapamycin inhibitors by suppressing bone marrow or by interfering with erythropoiesis. Post-transplant anaemia is a complex problem that needs a delicate balance in immunosuppression and reversible hematologic factors, such as iron deficiency and erythropoietin deficiency [38,39].

8. Hematologic Biomarkers as Prognostic Tools in Renal Disease

Hematologic biomarkers are easy-to-use and low-cost risk stratification tools in renal disease. In addition to the diagnostic value, hematologic parameters are becoming more prognostic factors of death, cardiovascular and kidney dysfunction development due to the strong interdependence of inflammation, immune dysregulation, and hematopoietic dysfunction.

The severity of anaemia has long been identified as an independent prognostic biomarker in chronic kidney disease (CKD), whereby low haemoglobin levels have been associated with high mortality and risks of cardiovascular disease. Even though anaemia is multifactorial, its prognostic importance may represent the cumulative disease burden, chronic inflammation, and tissue oxygenation dysfunction, which supports the relevance of systematic anaemia testing and treatment in clinical practise [40].

The neutrophil-to-lymphocyte ratio (NLR) is one of the leukocyte-derived indices that has become a strong predictor of systemic inflammation and immune imbalance. Higher NLR has continued to be linked to faster deterioration of renal functions, higher cardiovascular incidents, and overall mortality in CKD groups. The systematic review and meta-analyses endorse NLR as an independent prognostic factor, which is more effective than conventional inflammatory indicators in certain contexts because it combines both the activation of innate immunity and the suppression of adaptive immunity [41,42].

Prognostic assessment is further improved by platelet-related indices and composite inflammatory scores. Future population studies have found that integrated hematologic biomarkers, such as NLR-based and platelet-derived ones, are substantially related to patient survival in CKD, reflecting the prognostic value of regular blood parameters [30,41,42]. These results provide evidence about the possibility of individualised risk stratification with the help of multiparametric hematologic profiling.

In the future, new omics-based methods will be used to improve prognostication compared to traditional hematologic indices. A combination of transcriptomic, proteomic and metabolomic data with conventional blood markers could facilitate earlier identification of high-risk phenotype and allow precision medicine approaches to renal disease. Although these methods are still largely research-oriented, they are a logical progression of the hematologic biomarker studies into the more subtle and personalised outcome prediction.

Table 4 presents key hematologic biomarkers that have a prognostic value in renal disease.

Table 4. Hematologic Biomarkers in Renal Disease: Prognostic Utility

Biomarker	Reflects	Associated Outcomes	Clinical Utility
Haemoglobin	Anaemia severity	Mortality, CV risk	Disease monitoring
NLR	Inflammation/immune imbalance	CKD progression, mortality	Risk stratification
Platelet indices	Platelet activation	Thrombosis, inflammation	Adjunct prognostic marker
Composite inflammatory scores	Systemic inflammation	Survival	Prognostic enrichment

9. Therapeutic Advances and Future Directions

The swift progress in the hematologic dysregulation of renal disease has triggered the transition between the empiric haemoglobin-focused approaches and the mechanism-based and personalised approaches to treatment. Subsequent strategies are becoming more focused on precision medicine, which is aimed at upstream causes of anaemia, inflammation and haemostatic imbalance and incorporates hematologic endpoints into renal clinical trials.

9.1 Precision Medicine Approaches

The goal of precision medicine in renal haematology is to individualise treatment according to individual pathophysiologic characteristics and not the treatment thresholds. Biomarker-based stratification of patients based on inflammatory biomarkers, iron regulation, erythropoietic responsiveness, and immune activation can be used to identify patient subgroups, which are most likely to respond to certain interventions. A combination of current haematologic parameters with emerging molecular biomarkers promises to improve treatment selection, reduce adverse events, and increase long-term outcomes.

The improvement of multi-omics technologies such as transcriptomics, proteomics and metabolomics should further refine the phenotyping of anaemia and coagulopathy in renal disease. These methods could help to identify high-risk patients early in their development, forecast treatment response and identify new targets in the kidney-bone marrow-immune axis.

9.2 Novel Erythropoiesis-Modulating Agents

Inhibitor of hypoxia-inducible factor prolyl hydroxylase (HIF-PHI) is a paradigm shift in the management of anaemia. These agents target several pathophysiologic aspects of renal anaemia concurrently by enhancing endogenous production of erythropoietin and optimising iron utilisation by inhibiting hepcidin. Current studies are aimed at determining their long-term safety regarding cardiovascular effects, the dosing schedule, and the use in various levels of kidney disease.

In addition to HIF-PHIs, new-generation erythropoiesis-controlling agents are under investigation that would selectively target erythroid pathways without exposing the erythroid to supraphysiologic concentrations of erythropoietin. The objectives of these approaches are physiologic regulation of erythropoiesis and minimisation of risks that are presented by conventional erythropoiesis-stimulating agents.

9.3 Anti-Inflammatory and Anti-Hepcidin Strategies

Chronic inflammatory process continues to play a key role in the production of hematologic dysfunction in renal disease, which also leads to anaemia, platelet abnormalities, and immune dysregulation. Cytokine modulation and immune-metabolic interventions are therapeutic strategies based on the inflammatory pathways that are currently being used as an adjunct to conventional anaemia treatment.

The hepcidin-ferroportin axis has been of specific interest as a way to restore physiologic iron trafficking. Potential alternatives to repeated iron supplementation are anti-hepcidin therapy, hepcidin antagonist therapy and ferroportin-enhancing therapy, especially in patients with functional iron deficiency and inflammatory burden. These measures can minimise the iron sequestration, enhance erythropoietic efficiency, and address the risks related to iron overload.

9.4 Integrating Hematologic Endpoints in Renal Trials

Traditionally, the clinical trials in renal research have been focused on hard renal and cardiovascular outcomes, and hematologic parameters are typically regarded as secondary or surrogate. The increasing appreciation of the prognostic value of the severity of anaemia, the level of inflammatory response, and platelet dysfunction encourages the use of hematologic endpoints in future trial design.

The inclusion of patient-centred hematologic outcomes, including fatigue, functional capacity, transfusion needs and bleeding or thrombosis events, could be more useful in measuring therapeutic benefit. This type of integration will be crucial in assessing the real clinical effects of new treatments as well as to support the development of comprehensive management approaches aimed at improving renal and hematologic health.

10. Conclusion

Hematologic changes are part of the pathophysiology and clinical progression of renal disease, and occur as a result of complicated and changing interactions among the kidney, bone marrow, immune system, and vascular

endothelium. Anaemia, iron dysregulation, platelet dysfunction, and immune abnormalities are complexes of interactions, which in combination are associated with morbidity, mortality, and kidney dysfunction progression in both acute and chronic conditions. Mechanistic insights have helped elucidate how disrupted haematopoiesis and haemostasis are caused by impaired erythropoietin production, inflammation-mediated iron sequestration, uremic toxicity, and immune dysregulation. These findings have redefined the clinical paradigms, demonstrated the shortcomings of conventional, haemoglobin-based methods and the necessity of overall assessment of hematologic wellbeing in patients with renal disease. Notably, the identification of the bidirectional kidney-bone marrow axis has offered a single pathway of connecting kidney injury to the systemic hematologic effects (and vice versa). Innovative approaches to therapy, especially the development of hypoxia-inducible factor-based therapies and activations of inflammatory and iron-regulatory pathways, are an opportunity to treat underlying mechanisms and not downstream effects. At the same time, the increased application of the hematologic biomarkers as prognostic indicators in the context of more sophisticated stratification of risks and individualised treatment methods. In the future, the inclusion of the principles of precision medicine and endpoints of haematology in renal studies and clinical practise will be necessary. These approaches can enhance patient-centred outcomes, minimise complications associated with treatment, and develop holistic care of renal disease. Further interdisciplinary partnership between haematology and nephrology will be the key to converting the mechanistic findings into a significant clinical value.

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