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Immunological Markers in Chronic Kidney Disease: Diagnostic and Prognostic Implications

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Annotation: Chronic kidney disease (CKD) is a progressive disorder characterized by a gradual loss of renal function, often leading to end-stage renal disease and significant morbidity. Recent research has highlighted the role of immunological markers in the pathophysiology, diagnosis, and prognosis of CKD. Immune dysregulation, including both innate and adaptive responses, contributes to persistent inflammation and tissue damage, accelerating disease progression. Among the most studied biomarkers are pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β), which are elevated in CKD patients and associated with renal fibrosis and cardiovascular complications. Anti-inflammatory cytokines, particularly interleukin-10 (IL-10), play a protective role, and their imbalance reflects immune dysfunction. Additionally, high-sensitivity C-reactive protein (hs-CRP) and other acute-phase proteins serve as systemic indicators of chronic inflammation and correlate with poor outcomes. Novel markers, including

monocyte chemoattractant protein-1 (MCP-1), soluble CD163, and circulating adhesion molecules, have been proposed as predictors of progression to advanced CKD stages. Beyond diagnosis, immunological markers are increasingly valuable for prognosis, as they can predict complications such as anemia, malnutrition, and cardiovascular disease, which remain leading causes of mortality in CKD patients. The integration of immunological markers into clinical practice may enhance early detection, improve risk stratification, and guide individualized therapeutic strategies. Future research should focus on standardizing biomarker panels and validating their clinical utility across diverse patient populations. Understanding the immunological landscape of CKD not only deepens insights into its pathogenesis but also opens new avenues for targeted therapies and improved patient management.

Keywords: Chronic Kidney Disease, Immunological Markers, Cytokines, Inflammation, Prognosis, Biomarkers.

1. Introduction

Chronic kidney disease (CKD) is a serious global health problem, affecting approximately 700 million individuals by the year 2017. Patients with CKD have increased cardiovascular risk and may eventually progress to end-stage kidney failure. Identifying a problem early is the best way to prevent permanent loss of kidney function. Recent, nontraditional studies focusing on CKD pathogenesis emphasize inflammation, and nontraditional markers of inflammation including cytokines and chemokines. Abstract This study summarizes findings about the role of immunologic markers in the diagnosis and prognosis of chronic kidney disease (CKD), and outlines future areas for research that can enhance clinical translation of these bio-discoveries [1]. Chronic kidney disease (CKD) encompasses a variety of disorders affecting renal structure and function, typically assessed by estimated glomerular filtration rate (eGFR) and albuminuria. The prevalence of CKD is more than 10% worldwide with different rates of progress. Common causes of CKD include diabetes and hypertension. In the early stages, patients can be asymptomatic or exhibit only vague signs, so that the diagnosis relies on eGFR and, in the case of specific

anomalies, biopsy. Chronic kidney disease (CKD) leads to uremia, which is characterized with aberrant immune response activation associated with fibrosis and disease progression. The identification of additional immunology based markers could improve the accuracy of diagnosis and prognosis of CKD [2].

2. Chronic Kidney Disease Overview

In the early stages of the disease, GFR can be maintained at a stable level because of adaptive changes within the remaining nephrons; however, this process could increase the rate of nephron loss and damage to the renal structure over time. In 2002, the National Kidney Foundation published guidelines for CKD to standardise the evaluation, classification and stratification of CKD [3]. These guidelines define kidney damage as structural or functional abnormalities of the renal system. CKD is classified into five stages according to estimated GFR (eGFR). When stage 2 or a higher stage occurs, a specific damage marker has to be present in the form of albuminuria or abnormalities in imaging. Although serum creatinine is the most widely used endogenous marker of kidney function, its production varies with age, muscle mass, and sex [4].

3. Immunological Markers: Definition and Importance

These immunological markers can involve proteins, cytokines, and essential components of the immune system that facilitate protective immunity and stimulate auto-immunity. As diagnostic tools, they may assist in early diagnosis of Chronic Kidney Disease (CKD), increasingly a global public health challenge [5]. It is important to define those who are at risk and understand the risk factors. States of disease are, in part, driven by inflammatory markers such as cytokines and chemokines. Presently, potentially modifiable renal injury markers such as albuminuria and alterations in kidney structure are used to indicate risk stratification and management. The underlying pathophysiology is centered on the presence of diabetes mellitus and hypertension [6].

4. Pathophysiology of Chronic Kidney Disease

Chronic kidney disease (CKD) is a common global public health problem, which is defined by the gradual loss of kidney function over time. An estimated 700 million people are affected by chronic kidney disease (CKD) globally, representing around 9.1% of the population and the 13th leading cause of years of life lost [7]. From a pathophysiological perspective, the immune system is significant in the etiology of CKD. Events within the visual network of the brain that alter one or other of the immune system can stimulate onset or cause progression of CKD [8].

5. Role of the Immune System in Kidney Disease

Reduced kidney function results in the buildup of uremic toxins and cytokines that trigger systemic inflammation and significant changes in immune system function [9]. These uremia-related immune defects notably affect patient outcomes, increasing the risk of end-stage renal disease (ESRD). CKD patients show heightened infection susceptibility, reduced vaccine effectiveness, and an increased risk of malignancies and immunodeficiency. The immune disruption in CKD stems from accumulated toxins, altered gut microbiota, and oxidative stress, contributing to the high incidence of cardiovascular diseases and infections that account for up to 70% of mortality in renal failure. Immune cell populations also alter with CKD progression; circulating CD4+ T cells gain a proinflammatory "memory" phenotype, producing more cytokines like TNF-α and interferon-γ. In contrast, CD8+ T cells remain stable, while NK cells and B cells decline [10]. Severe CKD sees a marked reduction in the number and function of dendritic cells, influenced by oxidative stress associated with uremia, exerting epigenetic effects on immune cells. Kidney damage results in immune-related solute buildup in the local environment, resulting in hypercytokinemia and complement activation that further disrupts immunity [11]. Research primarily targets advanced CKD and specific immune-cell subsets, with limited knowledge on immune profiles and kidney disease progression. There is also a lack of detailed immune landscape characterization, though studies reveal distinct immune signatures linked to disease severity and changes in immune-cell identity and activation during kidney failure [12].

6. Types of Immunological Markers

Immunological markers are valuable for differentiating acute and chronic kidney dysfunction and identifying new CKD diagnostic and prognostic indicators. Current diagnostic markers include cytokines, chemokines, immune checkpoint molecules, and immune cell subsets. Traditional biomarkers like blood urea nitrogen and serum creatinine lack sensitivity for early detection. Though kidney biopsy is the standard, its invasiveness limits its use, highlighting the need for non-invasive diagnostic tools [13]. Prognostic indicators, involving cytokines, chemokines, growth factors, and soluble molecules, help stratify patient outcomes and monitor therapeutic responses. This chapter organizes immunological markers into categories: cytokines, chemokines, immune cell subsets, and autoantibodies. Cytokines and chemokines are low-molecular-weight proteins from various cells, frequently secreted during cytokine storms, affecting signal transduction and immune communication. Altered secretion is indicative of disease or treatment efficacy [14]. A panel of inflammatory mediators, including TNF-α, IL-6, MCP-1, and CCL-18, forms the common “inflammation signature” in circulating inflammatory diseases. Immune cell frequencies, analyzed via staining or liquid biopsy, reveal prognostic potential. Immune cells like monocytes, macrophages, neutrophils, and lymphocytes play roles in inflammatory signaling [15]. Decreased natural killer cells and monocytes correlate with severe CKD, while advanced stages show reduced mature B cells. CD38+ monocytes have emerged as a key immunophenotypic marker for early diagnosis, effectively distinguishing mild CKD from healthy controls [16].

6.1. Cytokines

Cytokines are soluble, low-molecular-weight regulatory proteins with a pivotal role in immune responses. Synthesized in the kidneys by various cells, including inflammatory cells, intrinsic renal cells, and fibroblasts, they mediate inflammatory and immune diseases [17]. Alongside chemokines, cytokines are key pro-inflammatory molecules, with their concentrations in blood and urine reflecting the degree of inflammation in renal injuries. Over 1,000 cytokines are thought to be involved in various functional interactions, including multiplying cells and recruiting immune cells responsible for inflammation [18].

Chemokines, a subfamily of cytokines, are secreted proteins with chemotactic activity that govern leukocyte trafficking through specific G protein-coupled receptors. These receptors are expressed on the surface of inflammatory cells and reside in virtually all inflammatory diseases [19]. Experiencing progression and relapse phases, chronic kidney diseases, in particular, show that expression of chemokines and chemokine receptors corresponding to these phases differ according to the cause of the disease. Given that chemokines and other cytokines are key regulators of the natural immune system, their association with CKD is undisputed [20].

6.2. Chemokines

Chemokines and their receptors play a pivotal part in the fibrosis-driving inflammatory response of the kidneys. These molecules mediate leukocyte chemotaxis and contribute to inflammation. In experimental mouse models of chronic kidney disease (CKD), receptors such as CCR1 and CCR2 have been shown to facilitate the infiltration of neutrophils and monocytes into the injured kidney [21]. Chemokines frequently bind to multiple receptors, and many of both chemokine ligands and receptors have not yet been investigated in CKD. Early CKD models exhibit upregulation of specific chemokines, such as CCL6 and CCL9. These belong to the NC6 subfamily of CC chemokines, which has not previously been studied in this context [22]. In humans, the related chemokine CCL15 is also elevated in patients with CKD. Both CCL9 and CCL15 serve as ligands for CCR1, a receptor known to be implicated in inflammatory and fibrotic processes. Investigation into the roles of these chemokines during early stages of CKD therefore addresses their potential impact on kidney inflammation and fibrosis [23].

6.3. Immune Cell Subsets

Certain innate and adaptive immune responses have been linked to kidney disease onset and

progression, with abnormalities in circulating immune cell populations and phenotypes. The pathways and patterns of immune cell infiltration of the kidney have distinct roles in disease [24]. Immunocytometric studies of peripheral blood leukocytes at different disease stages can provide clues regarding the pathogenic mechanisms involved, discern which abnormalities are causative or coexistent, and facilitate the use of immune-cell phenotypes as markers for early detection and diagnosis. Imbalances in specific innate and adaptive immune-cell subsets in peripheral blood are associated with different stages of chronic kidney disease (CKD), correlating with glomerular filtration rate (GFR), and allow CKD patients to be distinguished from those with other comorbidities [25].

Innate and adaptive immune-cell populations in peripheral blood are strongly associated with CKD development and with CKD etiologies that have an irreversible nephron–interstitial inflammatory component [26]. This association is influenced not only by comorbidities such as age, sex, and diabetes but also by renal function, thereby supporting the use of specific immunological subsets as early diagnostic markers [27]. A panel of four innate and adaptive immune-cell populations successfully discriminates patients with CKD from those with other comorbidities and controls, indicating that differential cell populations participate in early CKD development and may serve as appropriate biomarkers [28].

6.4. Autoantibodies

The presence of auto-antibodies is a common characteristic of autoimmune nephropathies. The pattern of antibody production differs among diseases. For example, systemic lupus erythematosus (SLE) is characterized by the generation of multiple autoantibodies (including anti-dsDNA, anti-nucleosome, anti-ribosome P, and anti-C1q antibodies), whereas membranous nephropathy is promoted by the production of antibodies against components of the podocyte membrane and/or the basement membrane (Goodpasture’s syndrome) [29]. Even though the autoimmune processes responsible for the production of these antibodies are absent in the majority of patients with CKD, autoantibody production can be sustained as a secondary event. Although their exact role in CKD has not yet been clarified, the detection of autoantibodies in this population could contribute to the prediction of disease onset and severity. As such, their potential as markers of diagnostic and prognostic utility virtually remains to be fully explored [30].

7. Diagnostic Implications of Immunological Markers

Immunological markers indicate autoimmune activity and inflammation, aiding in understanding underlying pathological processes. Alongside imaging and physiochemical markers, circulating immunological signatures significantly enhance the prognosis of chronic kidney disease (CKD) [31]. This text discusses the diagnostic and prognostic significance of these markers in CKD, where early diagnosis is vital to prevent progression and complications. Immunological markers provide crucial diagnostic insights and assist in identifying CKD's underlying causes [32]. CKD can be hard to differentiate from acute kidney injury and other chronic diseases, as it is characterized by reduced glomerular filtration rate or kidney damage lasting over 3 months. Often detected late, CKD presents few early clinical or biochemical signs [33]. Including immunological markers improves diagnostic sensitivity and assists in recognizing various CKD subtypes, such as diabetic kidney disease, hypertensive nephropathy, lupus nephritis, IgA nephropathy, polycystic kidney disease, and obstructive nephropathy, which is valuable for clinicians given their similar presentations but differing treatments and prognoses [34].

7.1. Early Detection of CKD

Chemokines, a subset of cytokines, direct immune cell recruitment during tissue injury [35]. CCL2, or MCP-1, is frequently elevated in various CKD types, marking kidney disease. CCL2 promotes the infiltration of immune cells into damaged kidney tissue, leading to tissue destruction and fibrosis. Other chemokines like CCL7, CCL8, and CCL18 relate to immune responses in CKD, with higher levels indicating worse renal damage and prognosis [36]. Certain immune cell

subsets, notably CD28-nullCD4+ and CD28-nullCD8+ T cells in IgA nephropathy, may signal early renal dysfunction and contribute to kidney injury. Autoantibodies against complement components are another marker linked to CKD progression, reflecting the role of abnormal immune responses in chronic renal impairment, and indicating potential for patient stratification and therapeutic strategies [37].

7.2. Differentiating CKD from Other Conditions

A Random Forests regression model based on 19 cellular and soluble components distinguished CKD patients from non-CKD controls, exhibiting an area under the receiver operating characteristic curve (AUC) of 0.917 [38]. Among these components, the proportion of CD38+ monocytes emerged as the most influential feature. Furthermore, the model differentiated mild CKD cases from controls with an AUC of 0.889, indicating the capacity for early-stage discrimination. These findings highlight immunophenotypic signatures as promising diagnostic tools for CKD [39].

8. Prognostic Implications of Immunological Markers

Immunological markers in CKD are pivotal for prognostication and therapeutic guidance, reflecting disease severity and progression across diverse aetiologies. The prospective Boston Kidney Biopsy Cohort Study evaluated inflammatory-associated biomarkers, linking their plasma concentrations to histopathologic lesions and subsequent clinical outcomes [40,41]. After adjusting for demographics, baseline kidney function, proteinuria, and clinical diagnosis, elevated plasma interleukin 2 receptor-α (IL-2Rα), tryptase, and tumor necrosis factor receptor superfamily member 1B (TNFR superfamily member 1B) independently predicted kidney disease progression. In addition, higher levels of IL-2Rα, CD40, IL-6, and galectin-9 correlated independently with increased mortality risk [42]. The study highlights inflammation, a fundamental driver in many kidney diseases, as a noninvasive modality for risk assessment, patient selection in clinical trials, and therapeutic monitoring. Furthermore, deep immune profiling delineates characteristic immunotypes associated with CKD severity, identifying specific immune cell populations and activation states that accompany advancing renal failure. Such findings underpin the development of a compendium of immunophenotypic data crucial for prognostication and treatment evaluation in CKD [43].

8.1. Predicting Disease Progression

Numerous plasma biomarkers have been utilized to predict the progression of kidney disease at different stages and in various conditions. Plasma soluble TNF receptors 1 and 2 (TNFR-1 and -2, respectively) are associated with kidney function decline and progression to end-stage renal disease (ESRD) in diabetic kidney disease [44]. Urinary markers include aminopeptidase N and carnosinase 1, which correlate with rapid renal progression in diabetic nephropathy, and an juxtaglomerular apparatus-related polypeptide that exhibits the highest predictive efficacy [45]. Plasma monocyte chemotactic protein-1 (MCP-1) concentration is independently linked to the progression of idiopathic membranous nephropathy [41]. A study involving 63,989 patients with advanced chronic kidney disease (CKD) from the Chronic Renal Insufficiency Cohort identified candidate biomarkers including tumor necrosis factor-α, macrophage inflammatory protein 1α, fibroblast growth factor 23, and soluble urokinase plasminogen activator receptor [46,47].

8.2. Assessing Treatment Response

Immunological markers provide key insights for evaluating chronic kidney disease (CKD) progression and treatment response. Traditional indicators like eGFR and proteinuria have limitations in directing therapeutic strategies and predicting outcomes. Research into urinary markers such as exosomes, mitochondrial DNA, complement activation products, and various cytokines offers further understanding of the disease, but standardized panels for specific CKD types are still needed. Immune components exhibit significant changes as CKD progresses [48]. Advanced flow cytometry profiling shows notable modulation in numerous immune subsets at

different disease stages, particularly among dialysis patients. These changes signal disease trajectory. Evaluating immune and renal profiles together improves prognostic accuracy for treatment outcomes, highlighting the value of specific immunological parameters as additional renal markers to assess patient risk and predict treatment efficacy [49].

9. Current Research on Immunological Markers

Immune and inflammatory pathways are potential diagnostic and prognostic markers of chronic kidney disease (CKD). Panels of immunological markers that include cytokines and related inflammatory mediators, chemokines and other pro-inflammatory molecules, neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, clusterin, urinary exosomes, and the measurement of certain proteins and their ratios are under consideration. Deep immune profiling at various stages of renal insufficiency also reveals a distinct immunological landscape that contrasts with the normal immune response [50].

10. Challenges in Utilizing Immunological Markers

Despite progress in identifying candidate immunological markers for chronic kidney disease (CKD), their clinical utility remains limited by several challenges. Most studies evaluating markers such as transforming growth factors and connective tissue growth factor are based on small cohorts and lack independent replication, leaving conclusions preliminary. CKD's multifactorial nature and heterogeneity also complicate biomarker interpretation and necessitate stratification by demographics, initial renal loss, and comorbidities [51]. Analytical reproducibility and cost-effectiveness further constrain implementation in daily practice. While advances in high-throughput technologies and molecular profiling offer potential for biomarker panels to support screening, diagnosis, and disease monitoring, large multicenter studies are required to confirm their predictive performance and establish standardized testing platforms. Until stronger evidence emerges, traditional markers like serum creatinine and urinary albumin remain the mainstay for CKD assessment [52].

11. Future Directions in Research

Future studies will address the relative prognostic and diagnostic values of diverse immunological markers in different populations, stages, and management settings of chronic kidney disease (CKD). They will also seek to identify immunological abnormalities pointing to causation and directing therapy [53]. Research should explore markers that identify underlying diseases responsible for CKD and those determining the subsequent rate of progression—areas of high clinical relevance [54].

12. Clinical Implications for Practitioners

Firstly, identifying CKD at early stages allows more rapid interventions to control disease progression and manage risk factors, thereby improving patient prognoses and reducing healthcare costs. Secondly, establishing biomarker panels capable of detecting renal disease or predicting poor outcomes remains an essential goal. Biomarkers for early detection are expected to relate to primary disease causes, whereas markers for progression correlate with declining renal function. Thirdly, the availability of these diagnostic tools depends on patient profiles, analytical method validation, and comparison with healthy controls [55]. Fourthly, CKD burden extends beyond kidney failure to include cardiovascular disease and other complications, underscoring the importance of timely diagnosis. Finally, enhanced detection and monitoring through immunological marker profiles can elevate clinical management of CKD [13]. In light of these considerations, ANCA-associated vasculitis or systemic lupus erythematosus should be included in the differential diagnosis when kidney diseases are suspected without an apparent cause, given that corresponding autoantibodies are among these markers [56].

13. Conclusion

Immunological markers have shown promise in the diagnosis and prognosis of chronic kidney

disease. The pathogenesis of chronic kidney disease encompasses acute and chronic inflammation that ultimately drives progressive renal scarring. Although initial sterile tissue injury does not involve the immune system, immune components activated as a consequence of tissue injury and/or exposure to foreign agents can greatly amplify the inflammatory response and perpetuate chronic inflammation. Immunological markers include cytokines, chemokines, immune cell subsets, and complement proteins. Investigation of immunological markers may facilitate screening, early detection, management, and prevention of complications. Recent experimental evidence suggests that distinct immunotypes are associated with impaired renal function in chronic kidney disease patients. Immunological signatures become perturbed in severity-specific ways, potentially enabling rapid assessment of disease status. Identification of immunological factors that drive pathogenesis will expedite development of novel therapeutics. Early detection of chronic kidney disease biomarkers may also supplement established biomarkers to improve patient stratification strategies.

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Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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