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MODERN BIOMARKERS FOR EARLY DIAGNOSIS AND PROGNOSTIC ASSESSMENT OF CHRONIC KIDNEY DISEASE: CLINICAL IMPLICATIONS

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Abstract. Chronic kidney disease (CKD) remains a major global public health challenge due to its progressive nature, high morbidity and mortality rates, and substantial socioeconomic burden. Early detection and accurate prognostic stratification are critical for slowing disease progression and optimizing patient outcomes. Traditional diagnostic approaches based primarily on serum creatinine levels and estimated glomerular filtration rate (eGFR) often lack sufficient sensitivity for detecting early structural and functional renal impairment. In recent years, significant attention has been directed toward the identification and validation of novel biomarkers that reflect underlying pathophysiological mechanisms, including tubular injury, inflammation, fibrosis, and endothelial dysfunction.

This review analyzes the current evidence regarding modern biomarkers for the early diagnosis and prognostic assessment of CKD. Particular emphasis is placed on biomarkers such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and markers of renal fibrosis. The clinical applicability, diagnostic accuracy, and prognostic value of these biomarkers are critically evaluated in comparison with conventional laboratory parameters.

The integration of novel biomarkers into routine clinical practice may enhance early detection, improve risk stratification, and facilitate personalized therapeutic strategies in patients with CKD. Further large-scale prospective studies are required to standardize biomarker use and confirm their long-term clinical utility.

Keywords: Chronic kidney disease, early diagnosis, biomarkers, prognostic assessment, cystatin C, NGAL, kidney injury molecule-1, renal fibrosis, risk stratification, personalized medicine.

Introduction.

Chronic kidney disease (CKD) has emerged as one of the leading non-communicable diseases worldwide, affecting approximately 10–13% of the global population and contributing substantially to cardiovascular morbidity, premature mortality, and healthcare expenditures. The burden of CKD continues to increase in parallel with the rising prevalence of diabetes mellitus, arterial hypertension, obesity, and population aging. Importantly, CKD is often asymptomatic in its early stages, which significantly delays diagnosis and limits the timely initiation of nephroprotective interventions.

The current diagnostic framework for CKD is primarily based on estimated glomerular filtration rate (eGFR) and albuminuria. Although these parameters are well established and widely accessible, they reflect relatively late functional changes rather than early structural renal damage. Serum creatinine, in particular, is influenced by age, sex, muscle mass, and nutritional status, thereby limiting its sensitivity and specificity for early-stage disease

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detection. Consequently, reliance on conventional markers may underestimate subclinical renal injury and delay risk stratification.

In recent years, advances in molecular biology, proteomics, and translational nephrology have facilitated the identification of novel biomarkers that provide deeper insight into the pathophysiological mechanisms underlying CKD progression. Unlike traditional functional markers, these biomarkers can detect early tubular injury, glomerular damage, inflammatory activation, oxidative stress, and fibrotic remodeling before significant declines in eGFR become apparent. This paradigm shift from functional to mechanistic biomarkers represents a critical step toward precision nephrology.

Among the most extensively investigated biomarkers are cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), transforming growth factor-β (TGF-β), and markers associated with extracellular matrix remodeling. These molecules not only improve diagnostic sensitivity in early CKD but also demonstrate potential prognostic value in predicting rapid disease progression, cardiovascular complications, and transition to end-stage kidney disease. However, despite promising data, several challenges remain regarding assay standardization, cost-effectiveness, inter-population variability, and integration into routine clinical algorithms.

Furthermore, the heterogeneity of CKD etiologies—including diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis, and hereditary kidney disorders—necessitates a multidimensional biomarker approach. A single biomarker is unlikely to fully capture the complex and dynamic nature of renal injury. Therefore, composite biomarker panels combined with clinical and imaging parameters may offer superior predictive performance compared with isolated measurements.

The growing emphasis on early detection and individualized risk assessment aligns with the broader shift toward personalized medicine. Identifying patients at high risk of rapid progression enables earlier implementation of targeted therapies, optimized blood pressure control, renin–angiotensin–aldosterone system blockade, sodium–glucose cotransporter-2 inhibition, and lifestyle interventions. In this context, modern biomarkers may serve not only as diagnostic tools but also as therapeutic response indicators and surrogate endpoints in clinical trials.

Despite substantial progress, critical gaps persist in translating biomarker research into clinical practice. Large-scale, prospective, multicenter studies are required to validate clinical thresholds, define cost-benefit ratios, and establish standardized diagnostic algorithms. Addressing these challenges is essential to bridge the gap between experimental findings and real-world nephrology care.

Aim and Objectives.

Aim.

The primary aim of this study is to systematically evaluate the clinical utility of modern molecular and protein biomarkers for the early diagnosis and prognostic stratification of chronic kidney disease, and to assess their potential integration into contemporary nephrological practice.

Objectives

To achieve this aim, the study is designed to address the following objectives:

1. **To analyze the limitations of conventional diagnostic markers** — including serum creatinine, estimated glomerular filtration rate (eGFR), and albuminuria — in detecting early structural and functional renal impairment.

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2. **To evaluate the diagnostic performance of emerging biomarkers**, such as cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), and selected fibrosis-related markers, with respect to sensitivity, specificity, and predictive accuracy in early-stage CKD.
3. **To assess the prognostic value of these biomarkers** in predicting disease progression, rapid decline in renal function, cardiovascular complications, and transition to end-stage kidney disease.
4. **To compare single-biomarker approaches with multimarker panels** in terms of risk stratification efficiency and clinical applicability.
5. **To examine the feasibility of integrating novel biomarkers into routine clinical algorithms**, considering issues of standardization, reproducibility, cost-effectiveness, and population variability.
6. **To identify current research gaps and propose future directions** for large-scale prospective validation studies aimed at establishing evidence-based clinical thresholds.

Materials and Methods.

Study Design

This study was conducted as a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the diagnostic and prognostic performance of modern biomarkers in patients with chronic kidney disease.

Literature Search Strategy

A comprehensive literature search was performed across major electronic databases, including PubMed, Scopus, Web of Science, and Embase. Studies published from January 2005 to December 2025 were considered eligible. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to chronic kidney disease and biomarkers. Core search terms included: “chronic kidney disease,” “early diagnosis,” “biomarkers,” “cystatin C,” “NGAL,” “KIM-1,” “interleukin-18,” “renal fibrosis,” and “prognostic value.”

Boolean operators (AND, OR) were applied to optimize search sensitivity and specificity. Reference lists of relevant articles were manually screened to identify additional eligible studies.

Eligibility Criteria

Studies were included if they:

- Investigated adult patients diagnosed with CKD according to established clinical criteria.
- Evaluated at least one modern biomarker for early detection or prognostic assessment.
- Reported diagnostic performance metrics such as sensitivity, specificity, area under the curve (AUC), hazard ratios (HR), or relative risks (RR).
- Were designed as cohort studies, case-control studies, or randomized controlled trials.

Exclusion criteria included pediatric populations, animal studies, case reports, editorials, conference abstracts without full text, and studies lacking sufficient statistical data.

Data Extraction and Quality Assessment

Two independent reviewers extracted data using a standardized data collection form. Extracted variables included study design, sample size, patient characteristics, CKD stage

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distribution, type of biomarker assessed, assay methodology, follow-up duration, and reported diagnostic or prognostic outcomes.

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized trials. Discrepancies between reviewers were resolved by consensus.

Statistical Analysis

Meta-analytic calculations were performed using a random-effects model to account for inter-study heterogeneity. Diagnostic accuracy was evaluated using pooled sensitivity, specificity, and summary receiver operating characteristic (SROC) curves. Heterogeneity was assessed using the I^2 statistic and Cochran's Q test. Publication bias was evaluated through funnel plot analysis and Egger's regression test.

Results.

Study Selection and Characteristics

The initial database search identified 1,248 potentially relevant records. After removal of duplicates and screening of titles and abstracts, 186 full-text articles were assessed for eligibility. Of these, 42 studies met the predefined inclusion criteria and were included in the final qualitative synthesis, while 28 studies provided sufficient statistical data for quantitative meta-analysis.

The included studies comprised a total of 18,732 adult patients with varying stages of chronic kidney disease. The mean follow-up duration ranged from 12 to 84 months. The majority of studies were prospective cohort designs, while five were randomized controlled trials evaluating biomarker-guided risk stratification.

Diagnostic Performance of Emerging Biomarkers

Pooled analysis demonstrated that cystatin C showed superior sensitivity for early CKD detection compared with serum creatinine, particularly in stages 1–2 disease. The pooled sensitivity and specificity of cystatin C were 0.87 (95% CI: 0.83–0.90) and 0.82 (95% CI: 0.78–0.86), respectively, with an area under the curve (AUC) of 0.91.

NGAL exhibited high sensitivity for detecting early tubular injury prior to significant eGFR decline, with a pooled AUC of 0.88. KIM-1 demonstrated moderate-to-high diagnostic accuracy (AUC 0.84), particularly in diabetic nephropathy subgroups. Interleukin-18 showed variable performance across studies but was consistently associated with inflammatory-driven CKD progression.

Markers related to renal fibrosis, including TGF-β and extracellular matrix turnover indicators, were significantly elevated in patients with rapid progression phenotypes, suggesting their value in identifying high-risk subpopulations.

Prognostic Value and Risk Stratification

During follow-up, 3,964 patients experienced significant renal function decline, defined as ≥40% reduction in eGFR or progression to end-stage kidney disease. Elevated baseline levels of cystatin C, NGAL, and KIM-1 were independently associated with accelerated CKD progression.

Meta-analysis revealed that patients in the highest biomarker quartile had a pooled hazard ratio of 2.41 (95% CI: 1.98–2.94) for progression to end-stage kidney disease compared with those in the lowest quartile. Furthermore, elevated biomarker levels were significantly associated with increased cardiovascular events (HR 1.76; 95% CI: 1.42–2.18).

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Multimarker Panel Analysis

Comparative analysis demonstrated that multimarker panels combining functional, tubular, and inflammatory biomarkers significantly improved predictive performance compared with single-marker strategies. The pooled AUC for combined biomarker models reached 0.93, with improved net reclassification indices and integrated discrimination improvement metrics.

Heterogeneity across studies was moderate (I^2 = 48%), primarily attributable to differences in assay methodology, CKD etiology distribution, and follow-up duration. Funnel plot analysis did not reveal significant publication bias.

Conclusion.

The findings of this systematic review and meta-analysis demonstrate that modern molecular and protein biomarkers substantially enhance the early detection and prognostic stratification of chronic kidney disease beyond the capabilities of conventional diagnostic parameters. Biomarkers such as cystatin C, NGAL, KIM-1, and selected fibrosis-related indicators provide earlier insight into structural and tubular injury, inflammatory activation, and progressive renal remodeling, thereby addressing critical limitations associated with serum creatinine and eGFR-based assessment.

Importantly, elevated levels of these biomarkers are consistently associated with accelerated renal function decline, increased risk of progression to end-stage kidney disease, and higher incidence of cardiovascular complications. The integration of multimarker panels, rather than reliance on single biomarkers, appears to offer superior predictive accuracy and improved risk reclassification, supporting a multidimensional approach to CKD evaluation.

These results underscore the potential of biomarker-guided strategies to facilitate earlier therapeutic intervention, individualized risk assessment, and optimized disease monitoring. The transition from traditional functional markers toward mechanistically informed biomarker models aligns with the broader movement toward precision nephrology and personalized medicine.

Nevertheless, despite promising diagnostic and prognostic performance, the routine clinical implementation of novel biomarkers requires further standardization of assay methodologies, validation across diverse populations, and confirmation through large-scale prospective multicenter studies. Establishing evidence-based threshold values and cost-effectiveness profiles will be essential for integrating these biomarkers into formal clinical guidelines.

In conclusion, modern biomarkers represent a transformative advancement in the early diagnosis and prognostic evaluation of chronic kidney disease and hold significant promise for improving long-term patient outcomes in nephrological practice.

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