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Novel Biomarkers for Kidney Disease: New Frontiers in Early Diagnosis and Monitoring

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Abstract: Kidney diseases pose a significant threat to global public health, with early diagnosis and accurate monitoring being crucial for improving patient outcomes. However, traditional kidney disease markers such as serum creatinine and blood urea nitrogen have limitations in sensitivity and specificity. In recent years, rapid advancements in molecular biology and proteomics have led to the discovery of a series of novel biomarkers that are gradually being applied in clinical practice. This review examines novel kidney disease biomarkers, including cystatin C (Cys-C), neutrophil gelatinase-associated lipocalin (NGAL), and kidney injury molecule-1 (KIM-1). These markers not only reflect kidney injury earlier and more accurately but may also provide important bases for kidney disease classification, severity assessment, and prognosis prediction. Additionally, this paper explores the potential of multi-marker combined detection strategies in improving diagnostic accuracy. Although these novel markers show immense potential, they still face challenges such as standardization and cost-effectiveness before widespread clinical application. Future research should focus on optimizing detection methods, establishing clinical decision thresholds, and evaluating the value of these markers in personalized medicine, thereby paving new paths for precise diagnosis and treatment of kidney diseases.

Keywords: Kidney Disease; Biomarkers; Early Diagnosis; Disease Monitoring; Personalized Medicine.

1. Introduction

Kidney diseases represent a serious threat to global public health, with incidence and mortality rates rising worldwide[1]. The World Health Organization estimates that chronic kidney disease (CKD) affects approximately 10% of the global population, while acute kidney injury (AKI) occurs in up to 20% of hospitalized patients [2]. These diseases not only severely impact patients' quality of life but also impose a substantial economic burden on healthcare systems. Early diagnosis and accurate monitoring play crucial roles in kidney disease management. Traditionally, clinicians have primarily relied on indicators such as serum creatinine, blood urea nitrogen, and proteinuria to assess kidney function[3]. However, these markers have significant limitations: they often show abnormalities only after substantial kidney function impairment, failing to reflect early or mild kidney injury [4]. For instance, serum creatinine levels only rise significantly when glomerular filtration rate decreases by more than 50% [5]. This lag may result in missed opportunities for optimal treatment, affecting patient prognosis.

In recent years, with the rapid development of molecular biology, proteomics, and metabolomics, a series of novel biomarkers have been discovered and are gradually being applied in clinical practice[6]. These new markers not only reflect kidney injury earlier and more accurately but may also provide important bases for kidney disease classification, severity assessment, and prognosis prediction [7]. For example, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) can be detected within hours of acute kidney injury onset, days ahead of traditional markers [8].

However, these novel markers still face challenges such as standardization, cost-effectiveness, and clinical interpretation before widespread clinical application. Moreover, due to the complexity and heterogeneity of kidney diseases, a single marker may struggle to comprehensively reflect disease status, leading to increased attention on multi-marker combined detection strategies[9].

This review aims to summarize recent important advances in kidney disease biomarker research, focusing on several representative novel markers. We will discuss their application prospects in early diagnosis and disease monitoring, and explore the potential advantages of multi-marker combined detection strategies. Simultaneously, we will analyze the limitations in current research and future development directions, providing new insights for precise diagnosis and treatment of kidney diseases.

2. Limitations of Traditional Kidney Disease Markers

In clinical practice of kidney disease diagnosis and monitoring, traditional markers such as serum creatinine (SCr), blood urea nitrogen (BUN), proteinuria, and estimated glomerular filtration rate (eGFR) have long played important roles. These indicators are widely used due to their simple detection and low cost, but they show significant deficiencies in early diagnosis and precise assessment of kidney injury.

Serum creatinine, as the most commonly used indicator for assessing kidney function, primarily reflects glomerular filtration function. It is a product of muscle metabolism, mainly excreted through glomerular filtration. Although SCr correlates well with glomerular filtration rate, its levels are influenced by various factors such as age, gender, and muscle mass. More importantly, SCr only rises significantly when kidney function is impaired by more than 50%, meaning it cannot reflect early kidney injury [10]. In cases of acute kidney injury (AKI), changes in SCr may take 24-48 hours to be detected, and this delay may result in missing the optimal treatment window.

Blood urea nitrogen, as an end product of protein metabolism, is also used to assess renal excretory function. However, BUN levels are not only affected by kidney function but also change due to diet, liver function, and the use of certain medications. These multiple influencing factors reduce the specificity and sensitivity of BUN as a kidney function indicator. BUN only rises significantly when kidney function is severely impaired, limiting its application in early diagnosis.

Proteinuria detection plays an important role in assessing glomerular filtration membrane integrity, especially in the early diagnosis of certain kidney diseases (such as diabetic nephropathy). However, proteinuria levels can be affected by various temporary factors (such as intense exercise, fever, etc.), and it cannot reflect changes in tubular function. Moreover, accurate quantitative detection requires 24-hour urine collection, and this cumbersome operation to some extent limits its clinical application.

Estimated glomerular filtration rate (eGFR) is a comprehensive indicator calculated based on factors such as serum creatinine, age, and gender, which can more accurately assess kidney function than using SCr alone. eGFR plays an important role in the staging and monitoring of chronic kidney disease (CKD). However, the accuracy of eGFR may be affected in certain special populations (such as the elderly, extremely obese or thin individuals). Additionally, in the early stages of AKI, eGFR may not be sensitive enough to timely reflect acute changes in kidney function.

These limitations of traditional markers highlight the necessity of seeking new, more sensitive and specific biomarkers. Ideal kidney disease biomarkers should have the following characteristics: ability to reflect kidney injury early, specificity to the kidney, not significantly affected by other organ functions or external factors, and ability to accurately reflect disease severity and prognosis.

3. Novel Kidney Disease Biomarkers

Novel biomarkers not only reflect kidney injury earlier and more accurately but may also provide important bases for kidney disease classification, severity assessment, and prognosis prediction.

Cystatin C (Cys-C) is a low-molecular-weight protein produced by all nucleated cells and freely filtered through the glomeruli. Compared to traditional serum creatinine, Cys-C has significant advantages. It is not affected by muscle mass, age, or gender, and is more sensitive to early declines in kidney function [11]. Cys-C performs better than serum creatinine, especially in assessing kidney function in the elderly. This makes Cys-C show unique value in early diagnosis of chronic kidney disease (CKD) and assessment of cardiovascular disease risk. However, Cys-C levels may be affected by factors such as thyroid function and glucocorticoid use, which needs to be considered in clinical interpretation. Moreover, the relatively high detection cost also limits its widespread application to some extent.

Neutrophil Gelatinase-Associated Lipocalin (NGAL) is another novel marker receiving much attention. As an acute-phase protein, NGAL expression increases significantly after tubular injury. NGAL's greatest advantage lies in its rapid responsiveness: it can be detected to rise within 2-6 hours after acute kidney injury occurs, which is 24-48 hours earlier than traditional markers [12]. NGAL is highly sensitive to ischemic and toxic kidney injury and can be detected in urine and blood, giving it unique advantages in early diagnosis of acute kidney injury (AKI) and predicting AKI severity. However, it should be noted that NGAL may also rise in infection and inflammatory states, requiring consideration of the patient's overall condition in clinical interpretation.

Kidney Injury Molecule-1 (KIM-1) is a transmembrane glycoprotein that is barely expressed in normal kidneys but significantly increases in expression after tubular epithelial cell injury. The high specificity of KIM-1 makes it one of the ideal kidney injury markers [13]. It is particularly sensitive to proximal tubular injury and can stably exist in urine, characteristics that make KIM-1 perform excellently in early diagnosis of acute tubular necrosis and monitoring kidney injury caused by nephrotoxic drugs. However, since KIM-1 mainly reflects tubular injury, its sensitivity to glomerular diseases is relatively low, which needs to be noted in application.

Liver-type Fatty Acid-Binding Protein (L-FABP) is an intracellular lipid carrier protein expressed in renal proximal tubules. L-FABP is highly sensitive to hypoxia and oxidative stress, with increased expression in various kidney diseases[14]. This makes L-FABP potentially valuable in early diagnosis of acute kidney injury and monitoring the progression of chronic kidney disease. L-FABP can be detected in urine, providing the possibility for non-invasive monitoring. However, L-FABP levels may also be affected by liver disease, which needs to be considered in clinical applications.

Interleukin-18 (IL-18) is a pro-inflammatory cytokine that increases in release after tubular injury. IL-18 can be detected to rise early after AKI occurs and is particularly sensitive to ischemic kidney injury [15]. This gives IL-18 unique advantages in early diagnosis and prediction of acute kidney injury, as well as assessment of rejection reactions after kidney transplantation. However, since IL-18 may also rise in other inflammatory states, its clinical interpretation needs to be combined with the patient's overall condition.

Although novel biomarkers provide new tools for early diagnosis and precise monitoring of kidney diseases, their clinical application still faces challenges such as standardization, cost-effectiveness, and large-scale validation. Future research needs to further clarify the performance characteristics of these markers in different types and stages of kidney diseases, establish unified detection standards and reference ranges, and explore their application value in personalized medicine.

4. Application of Novel Markers in Different Types of Kidney Diseases

As research on novel biomarkers deepens, their application value in various kidney diseases is gradually emerging. From acute kidney injury to chronic kidney disease, from diabetic nephropathy to kidney transplantation, these markers are changing our understanding of kidney disease diagnosis and monitoring.

In the diagnosis and management of acute kidney injury (AKI), novel biomarkers show significant advantages. Traditionally, AKI diagnosis mainly relied on the rise of serum creatinine, but this change usually lags behind actual kidney injury by 24-48 hours. In contrast, neutrophil gelatinase-associated lipocalin (NGAL) can be detected to rise within 2-6 hours after AKI occurs [16]. This early diagnostic capability provides a valuable time window for timely intervention. Similarly, urinary levels of kidney injury

molecule-1 (KIM-1) are closely related to the severity and duration of AKI and can be used to predict kidney function recovery[17]. Interleukin-18 (IL-18) shows significant elevation in AKI patients after cardiac surgery, becoming a potential early warning indicator [18](as shown in Figure 1). The combined use of these markers may further improve the accuracy and timeliness of AKI diagnosis.

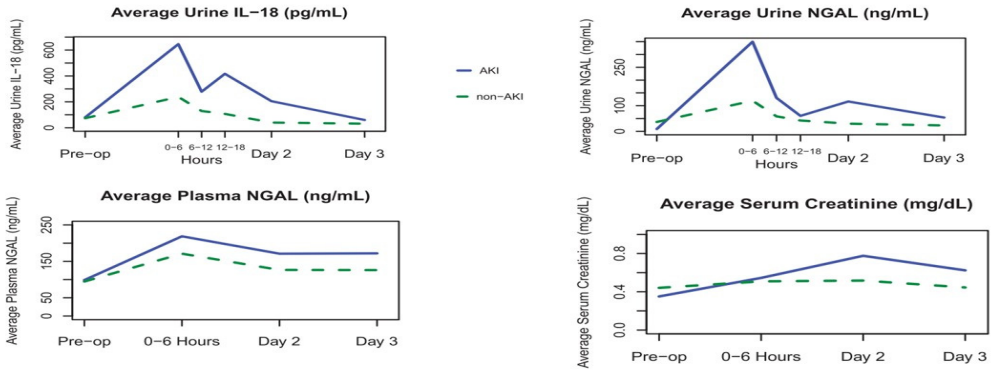

Figure 1. Distribution of urinary IL-18, urinary NGAL, and plasma NGAL in AKI patients after cardiac surgery [15]

In the field of chronic kidney disease (CKD), novel markers play important roles in early diagnosis and progression monitoring. The combination of cystatin C (Cys-C) and estimated glomerular filtration rate (eGFR) significantly improves the accuracy of early CKD diagnosis [19]. Urinary levels of liver-type fatty acid-binding protein (L-FABP) are closely related to CKD progression rate, providing a new tool for predicting kidney function decline [20](as shown in Figure 2). Moreover, serum NGAL levels correlate with CKD staging, reflecting disease severity [21]. The application of these markers not only aids in early diagnosis of CKD but also provides new bases for individualized treatment and prognosis assessment.

组别	例数	男/女	年龄[岁，M(Q_1～Q_3)]	ALT(U/L) M(Q_1～Q_3)	AST(U/L) M(Q_1～Q_3)	Hb(g/L) $\bar{x}\pm s$	SCr(μmol/L) $\bar{x}\pm s$	eGFR[mL/(min·1.73m²)] $\bar{x}\pm s$	尿L-FABP[μg/(g·Cr)] M(Q_1～Q_3)]
对照组	67	37/30	52(26～73)	14.3(8.1～25.3)	10.3(7.2～21.5)	136±17	66.2±14.2	103.1±18.3	5.3(3.0～6.2)
慢性肾脏病组									
CKD1期	31	17/14	49(23～68)	17.1(10.5～26.2)	14.2(9.4～23.9)	128±16[a]	63.4±16.1	101.9±8.7	9.1(5.8.～15.2)[a]
CKD2期	34	19/15	51(29～71)	16.4(9.3～24.6)	19.4(7.8～28.3)	125±21	95.2±18.7[b]	73.1±16.1[b]	23.4(14.0～46.7)[b]
CKD3期	39	23/16	52(24～73)	19.2(9.8～25.5)	18.1(8.3～27.4)	113±20[c]	131.5±29.4[c]	43.4±13.5[c]	48.0(32.1～73.5)[c]
CKD4期	24	13/11	52(31～70)	15.9(8.7～23.1)	17.1(9.5～26.6)	104±21[d]	174.0±53.6[d]	21.9±7.2[d]	75.4(53.0～105.4)[d]
CKD5期	21	11/10	53(32～75)	19.7(9.0～29.4)	18.3(8.2～27.1)	81±24[e]	673.1±365.8[e]	9.6±5.3[e]	167.1(83.2～375.9)[e]
组间比较						$P<0.01$	$P<0.01$	$P<0.01$	$P<0.01$

注：ALT：谷丙转氨酶；AST：谷草转氨酶；Hb：血红蛋白；SCr：血肌酐；eGFR：估计肾小球滤过率；L-FABP：肝型脂肪酸结合蛋白与对照组比较，[a]$P<0.05$；与CKD1期比较，[b]$P<0.01$；与CKD2期比较，c $P<0.01$；与CKD3期比较，d $P<0.01$；1与CKD4期比较，e $P<0.01$

Figure 2. Comparison of general data among CKD stages 1-5 [20]

Diabetic nephropathy (DN), as one of the leading causes of end-stage renal disease, requires particular attention to early diagnosis and progression monitoring. Traditionally, microalbuminuria was considered an early marker of DN. However, studies have found that KIM-1 may rise in the microalbuminuria stage, potentially becoming an earlier marker for DN[22]. Urinary L-FABP levels are closely related to DN progression and can be used to predict the occurrence of massive proteinuria [23]. These findings open new avenues for early intervention and individualized management of DN.

In the field of kidney transplantation, novel biomarkers show significant results in assessing transplant kidney function and predicting rejection reactions. Urinary NGAL has been found to predict delayed graft function early [24], which is of great significance for timely adjustment of immunosuppressive regimens. Elevated urinary IL-18 levels may indicate the occurrence of acute rejection[25], providing new tools for early diagnosis and treatment of rejection reactions. The application of these markers is expected to improve the success rate and long-term prognosis of kidney transplantation.

In monitoring drug-induced kidney injury, novel biomarkers also show unique advantages. KIM-1 has been recognized by the U.S. Food and Drug Administration (FDA) as a biomarker of drug-induced nephrotoxicity[26], greatly promoting its application in drug development and safety assessment. NGAL has been proven to early detect kidney injury caused by certain antibiotics and contrast agents [27], providing important safeguards for clinical medication safety.

These application examples fully demonstrate the enormous potential of novel biomarkers in improving the accuracy of kidney disease diagnosis and improving patient prognosis. They not only easily identify kidney injury but can also more accurately assess disease severity and predict prognosis.

5. Multi-Marker Combined Detection Strategy

As the understanding of the complexity and heterogeneity of kidney diseases deepens, a single biomarker may struggle to comprehensively reflect disease status, thus promoting the development of multi-marker combined detection strategies. This strategy is gradually becoming a new trend in the field of kidney disease diagnosis and monitoring.

The theoretical basis of multi-marker combined detection strategy stems from the characteristics of different biomarkers reflecting different aspects of kidney injury. For example, cystatin C mainly reflects glomerular function, while kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) more reflect tubular injury; interleukin-18 (IL-18), as an inflammatory factor, can provide information about the kidney's inflammatory state.

In the diagnosis of acute kidney injury (AKI), a study on patients after cardiac surgery showed that the combined detection of NGAL, IL-18, and KIM-1 more accurately predicted the occurrence of AKI than any single marker [28]. In predicting the progression of chronic kidney disease (CKD), the combined use of cystatin C, NGAL, and liver-type fatty acid-binding protein (L-FABP) may better predict CKD progression than using estimated glomerular filtration rate (eGFR) alone [29]. In the early diagnosis of diabetic nephropathy (DN), the combined detection of KIM-1, NGAL, and L-FABP shows potential to improve diagnostic sensitivity and specificity [30] (as shown in Figures 3 and 4). By combining these markers reflecting different physiological and pathological processes, we hope to obtain a more comprehensive and accurate assessment of kidney health status.

Table-III

Comparison of positive rates of detection based on single indicators and multiple indicators in the DN group.

Indicators	*Number of positive cases(n)*	*Positive rate(%)*
mAlb	64	68.1
α1-MG	59	62.8
NAG	67	71.3
mAlb+α1-MG+NAG	85	90.4*

*Note: indicated P<0.05 compared to detection based on single indicator.

Figure 3. Positive detection rates based on single and multiple indicators in the DN group[31]

index	AUC(95%CI)	Youden	cut-off	Sensitivity(%)	Specificity(%)
D-D	0.703(0.598～0.794)	0.365	502.01	77.78	58.70
Kim-1	0.738(0.635～0.824)	0.404	5.69	57.78	82.61
RBP	0.785(0.678～0.864)	0.493	4.61	68.89	80.43
There combinations	0.895(0.813～0.950)	0.735	0.51	82.22	91.30

Figure 4. Diagnostic value of serum D-D, Kim-1, and urinary RBP levels for early DN [32]

However, the widespread application of multi-marker strategies in clinical practice still faces some challenges. First is the standardization issue: different laboratories and detection methods may lead to differences in results, and establishing unified detection standards and reference ranges is an important direction for future research. Second is the cost-effectiveness issue: multiple tests will undoubtedly increase medical costs. How to find a balance between improving diagnostic accuracy and controlling medical costs requires in-depth health economics assessments.

In the future, research on multi-marker combined detection strategies may develop in several directions. First is exploring individualized marker combinations to adapt to different types of kidney diseases and patient characteristics. Second is studying the clinical significance of dynamic changes in markers, rather than just focusing on levels at a single time point. Finally, combining these novel markers with traditional clinical parameters and imaging examination results may

provide a new paradigm for comprehensive assessment of kidney diseases.

In summary, multi-marker combined detection strategies represent the future development direction of kidney disease diagnosis and monitoring. They are expected to significantly improve the accuracy and timeliness of clinical decision-making. However, to truly translate this strategy into clinical practice, more large-scale, multi-center prospective studies are needed to verify its effectiveness and solve practical problems such as standardization and cost-effectiveness. With deepening research and technological progress, we have reason to expect multi-marker strategies to bring substantial clinical benefits to kidney disease patients in the near future.

6. Summary and Outlook

This review comprehensively explores the application prospects of novel kidney disease biomarkers in early diagnosis and disease monitoring, while also deeply analyzing the potential of multi-marker combined detection strategies. With the rapid development of molecular biology and proteomics, we are standing at the threshold of a new era in kidney disease diagnosis and management.

Novel biomarkers show significant advantages in sensitivity and specificity compared to traditional markers. They can not only detect kidney injury earlier but also more accurately reflect the type and degree of injury. These characteristics make novel markers show great potential in multiple areas such as early diagnosis of acute kidney injury (AKI), progression monitoring of chronic kidney disease (CKD), and early warning of diabetic nephropathy (DN). The rise of multi-marker combined detection strategies provides new ideas for solving the limitations of single markers. By combining markers reflecting different physiological and pathological processes, we hope to obtain a more comprehensive and accurate assessment of kidney health status.

Looking to the future, research on novel kidney disease biomarkers may develop in several directions:

1. Individualized marker combinations: Due to the heterogeneity of kidney diseases, future research may explore individualized marker combinations for different types of kidney diseases and patient characteristics.

2. Dynamic monitoring: Studying the dynamic changes of marker levels may provide more valuable information than measurements at a single time point. This method may better reflect disease progression and treatment effects.

3. Integration of multi-dimensional information: Combining novel biomarkers with traditional clinical parameters, imaging examination results, and genomic data may provide a new paradigm for comprehensive assessment of kidney diseases.

4. Application of new technologies: The application of emerging technologies such as nanotechnology and microfluidic chips may greatly reduce the cost of marker detection and improve the accuracy and convenience of detection.

5. Big data and artificial intelligence: Using big data analysis and artificial intelligence technology may discover new marker combinations or prediction models, further improving the accuracy of diagnosis and prognosis assessment.

Overall, research on novel kidney disease biomarkers is opening up new prospects for the diagnosis, monitoring, and management of kidney diseases. Although many challenges remain, with deepening research and technological progress, we have reason to expect these new tools to bring revolutionary changes to clinical practice in the near future.

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