Advances and Clinical Translation of Biomarkers in Cardiovascular-Kidney-Metabolic Syndrome: A Narrative Review

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Abstract

Cardiovascular-kidney-metabolic (CKM) syndrome, defined by the American Heart Association in 2023, emphasizes interactions among metabolic disorders, kidney disease, and cardiovascular disease, supporting multidisciplinary prevention and management. Biomarkers offer valuable information for detecting organ injury, stratifying risk, and informing clinical assessment. However, many of these markers primarily reflect single-organ processes, while emerging markers remain investigational and lack established clinical application frameworks. This narrative review summarizes current biomarkers, their clinical applications, translation prospects, and limitations. Particular attention is given to the distinction between prognostic associations and demonstrated clinical utility, alongside challenges in assay standardization and validation. The review aims to inform biomarker assessment and future research toward precision management of CKM syndrome.

Keywords: biomarkers; cardiovascular-kidney-metabolic syndrome; clinical translation; early diagnosis; risk stratification

Introduction

The concept of cardiovascular-kidney-metabolic (CKM) syndrome arises from the recognition of shared pathophysiological mechanisms across multiple organ systems. In 2011, researchers noted that various pathological conditions—including hypertension, insulin resistance, metabolic dyslipidemia, obesity, microalbuminuria, and renal dysfunction—interact and mutually influence one another, collectively facilitating disease progression. This observation led to the earlier concept of "cardio-renal-metabolic syndrome."[1] Ronco and Di Lullo subsequently synthesized bidirectional heart–kidney interactions and cardiorenal syndrome subtypes, providing an important historical foundation[2]. This earlier literature overlaps mechanistically with the contemporary CKM construct but does not necessarily use identical staging criteria or populations. The American Heart Association (AHA) defined "CKM syndrome" in 2023 as a systemic disorder resulting from pathophysiological interactions among metabolic risk factors (such as obesity and diabetes), chronic kidney disease (CKD), and cardiovascular

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disease (CVD), which culminates in multi-organ dysfunction and significantly elevates the risk of adverse cardiovascular events[3]. In current clinical practice, CKM syndrome is classified into five stages: Stage 0, characterized by the absence of any cardiovascular, renal, or metabolic risk factors; Stage 1, marked by excess or dysfunctional adiposity, including overweight/obesity, abdominal obesity, or prediabetes, without other metabolic risk factors or CKD; Stage 2, defined by established metabolic risk factors or moderate-to-high risk CKD; Stage 3, characterized by subclinical CVD or risk equivalents, including very high-risk CKD or high predicted CVD risk; and Stage 4, which includes clinical CVD in the setting of CKM risk factors, with further subdivision into Stage 4a (without kidney failure) and Stage 4b (with kidney failure)[4]. Kidney failure corresponds to an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m^2 or chronic kidney replacement therapy. CKD must additionally be classified independently by cause, GFR category, and albuminuria category[5]. These stages describe CKM burden; they do not replace organ-specific assessment. Recent population studies show that CKM abnormalities are common, although their prevalence varies with the population and staging criteria. In US adults, stage-specific CKM prevalence estimates for stages 0–4 were 10.6%, 25.9%, 49.0%, 5.4%, and 9.2%, respectively; advanced stages 3–4 accounted for 14.6%[6]. A Chinese population-based study of 33,685 adults reported corresponding estimates of 18.8%, 15.5%, 42.1%, 14.7%, and 8.9%, with 23.6% at stages 3–4[7]. These interactions provide a rationale for assessing cardiac, renal, and metabolic risk together. This review discusses biomarkers used or studied in CKM syndrome, with emphasis on early detection, risk stratification, and the evidence needed for clinical use. Biological associations are considered alongside assay limitations and evidence that testing changes clinical decisions. The integrated CKM framework and the evaluation pathway for biomarker translation are summarized in Figure 1.

Pathophysiological mechanisms of CKM syndrome

The core pathogenesis of CKM syndrome is rooted in systemic metabolic disorders, with insulin resistance and

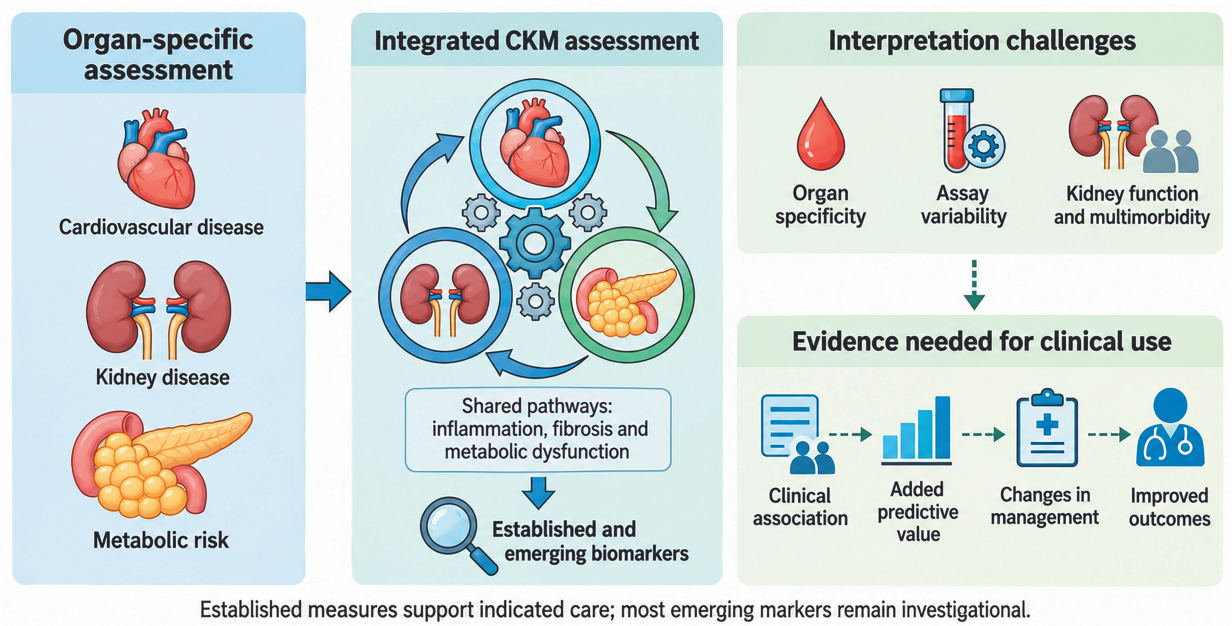


Figure 1: CKM syndrome and biomarker translation.

The cardiovascular, kidney and metabolic systems share pathways that support integrated risk assessment. Organ specificity, assay variability, kidney function and multimorbidity affect interpretation. Clinical associations require evaluation of added predictive value, effects on management and patient outcomes before they support new uses. The pathway shown is an evaluation framework, not evidence that emerging-marker testing already improves outcomes. Sources: manuscript references[3-5].

Abbreviations: CKM, cardiovascular-kidney-metabolic.

adipose tissue dysfunction acting as pivotal initiating factors. At the organismal level, insulin resistance and abnormal lipid metabolism are both hallmarks of cardiac and renal injury, serving as key drivers of disease progression while mutually reinforcing each other to form a vicious cycle. Insulin resistance is characterized by the reduced sensitivity of target tissues to the biological effects of insulin, resulting in decreased glucose uptake and utilization efficiency, which triggers compensatory hyperinsulinemia. Hyperinsulinemia promotes renal sodium reabsorption, activates the sympathetic nervous system, and stimulates vascular smooth muscle proliferation, while insulin resistance impairs insulin-mediated suppression of lipolysis[8]. Dysfunctional adipose tissue, particularly in the context of visceral fat deposition, further exacerbates insulin resistance through the release of free fatty acids, lipotoxic substances, and other factors[9], thereby forming a vicious cycle of mutual causation and amplification between the two. Consequently, metabolic disorders lead to multi-organ damage through multiple intertwined pathways. Under conditions of insulin resistance and obesity, a significant number of macrophages infiltrate adipose tissue and show a shift toward pro-inflammatory phenotypes. These immune cells, along with the adipocytes themselves, continuously release inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), sustaining chronic low-grade systemic inflammation. Interleukin-6 further stimulates the liver to synthesize C-reactive protein, thereby amplifying systemic inflammatory responses and collectively contributing to atherosclerosis, endothelial dysfunction, and myocardial remodeling[10,11].

Conversely, metabolic disorders can promote mitochondrial DNA (mtDNA) damage and mitochondrial dysfunction, which impair cellular energy metabolism, reduce oxidative phosphorylation efficiency, and lead to excessive production of reactive oxygen species (ROS)[12]. Simultaneously, metabolic substrates such as hyperglycemia and free fatty acids activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, serving as another significant source of ROS[13]. When excessive ROS exceed the cellular antioxidant defense capacity, they directly attack proteins, lipids, and DNA, resulting in cellular dysfunction, aging, or death. This phenomenon serves as the direct molecular basis for damage to target organs such as the heart, kidneys, and blood vessels.

Additionally, cellular injury and stress induced by metabolic disorders can strongly activate the renin-angiotensin-aldosterone system (RAAS), with its overactivation acting as a central hub linking hypertension, cardio-renal damage, and metabolic disorders. Increased angiotensin II (Ang II) production triggers systemic vasoconstriction and elevates blood pressure, while Ang II selectively constricts the efferent arterioles of the glomerulus, leading to elevated intraglomerular pressure. While this may provide short-term compensation, prolonged exposure can lead to decompensation, resulting in glomerulosclerosis, proteinuria, and ischemic injury to the renal medulla. Concurrently, increased aldosterone secretion enhances water and sodium reabsorption, elevating blood volume and cardiac workload, which ultimately contributes to heart failure. Beyond hemodynamic effects, both Ang II and aldosterone serve as potent pro-fibrotic factors. Experimental studies have linked aldosterone signaling to cardiac fibroblast activation and renal inflammation and fibrosis[14,15]. Within the overall RAAS regulatory network, angiotensin-(1–7), an active peptide derived from angiotensin II, exerts biological effects via binding to the Mas receptor. It effectively counteracts Ang II-mediated vasoconstriction and pro-inflammatory signaling, offsetting partial pathological injury induced by excessive RAAS activation. Recent experimental evidence has demonstrated vasoprotective crosstalk between Mas and endothelin receptors, which jointly maintain vascular homeostasis[16]. Beyond canonical signaling pathways, epigenetic mechanisms also modulate the shared pathological processes underlying cardiorenal injury and metabolic disorders. Aberrant DNA methylation and chromatin modifications in human renal tissues are closely associated with the development of kidney disease, whereas abnormal histone acetylation has been strongly linked to insulin resistance and activation of inflammatory signaling[17,18]. Nevertheless, the specific regulatory roles and clinical relevance of these protective pathways and epigenetic mechanisms in the initiation and progression of human CKM remain to be further elucidated. Furthermore, activation of the RAAS can exacerbate upstream metabolic disorders through various molecular mechanisms. Primarily, it upregulates NADPH

oxidase activity, leading to excessive generation of ROS and triggering widespread oxidative stress[19]. In the context of oxidative stress, Ang II directly activates the mechanistic target of rapamycin (mTOR)/ribosomal protein S6 kinase 1 (S6K1) signaling pathway, disrupting the normal phosphorylation of insulin receptor substrate-1 (IRS-1) in systemic tissues, thereby inducing insulin resistance[20]. Locally in the pancreas, Ang II can directly impair the function and survival of pancreatic β-cells by inducing endoplasmic reticulum stress, mitochondrial dysfunction, and inflammatory responses, which leads to defects in insulin secretion[21,22]. Injured tissues release chemokines such as monocyte chemoattractant protein-1 (MCP-1), which recruits macrophages to infiltrate and polarize into pro-inflammatory phenotypes. These cells subsequently release increased amounts of ROS and inflammatory factors, amplifying local inflammation[23-25]. Activated immune cells can also migrate through circulation to distant organs, propagating the inflammatory state and promoting fibrosis, allowing local injury to affect other tissues[26]. Furthermore, dysfunctional cells can release exosomes carrying specific microRNAs, proteins, and lipids, which, upon entering target cells, can inhibit insulin signaling or promote fibrosis, thereby propagating insulin resistance and fibrotic signals between organs[27].

These interconnected pathological processes ultimately lead to damage in target organs such as the heart and kidneys. This damage constitutes a chronic inflammatory state, characterized by the release of large amounts of pro-inflammatory cytokines that impair the normal metabolic functions of adipose tissue, liver, and skeletal muscle, while also inducing oxidative stress. Collectively, these effects drive insulin resistance and metabolic disorders. In summary, these intertwined and mutually reinforcing effects create a self-perpetuating and progressively worsening CKM vicious cycle[3,19].

Classification and recent research advances in biomarkers of CKM syndrome

Traditional markers

In the study of CKM syndrome, traditional single-system biomarkers have gained renewed significance. They not only function as “sentinels” for organ-specific damage but also serve as “bridges” linking the cardiac, renal, and metabolic systems through shared pathophysiological pathways.

Cardiovascular system biomarkers: injury assessment and prognosis

High-sensitivity cardiac troponin (hs-cTn) assays measure cardiac troponin I or T; concentrations above the assay-specific 99th percentile indicate myocardial injury. Chronic renal insufficiency, insulin resistance, hyperglycemia, and associated chronic low-grade inflammation can contribute to sustained stress or micro-injury in myocardial cells, resulting in a gradual and mild elevation of hs-cTn levels[28,29]. Consequently, a progressive upward trend in hs-cTn is associated with future adverse cardiovascular events and the risk of all-cause mortality. Elevated baseline hs-cTn in CKD reflects chronic myocardial injury, structural heart disease, and cardiorenal stress, as well as altered clearance; it should not be attributed solely to reduced renal clearance[30]. Troponin identifies myocardial injury but does not establish its cause. In advanced CKD, serial changes, assay-specific thresholds, symptoms, and other clinical findings are therefore more informative than an isolated elevation[31].

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is primarily synthesized and released by ventricular cardiomyocytes in response to mechanical stretch or increased pressure load, and is widely used in the diagnosis and evaluation of heart failure[32]. Furthermore, higher NT-proBNP was associated with all-cause mortality in a small cohort of patients with CKD stages 3–5. In patients with pre-existing renal dysfunction undergoing cardiac surgery, postoperative NT-proBNP and the postoperative-to-preoperative ratio were associated with acute kidney injury[33,34]. NT-proBNP reflects cardiac wall stress, with concentrations also affected by kidney function, age, atrial fibrillation, obesity, acute illness, and volume status; it should not be interpreted as a direct measure of kidney function. In advanced CKD, interpretation requires attention to clinical findings, changes over time, and the thresholds used by the assay and clinical pathway. Figure 2

summarizes the interpretation of cardiac biomarkers in CKM syndrome and the clinical factors that affect their concentrations.

Renal system markers: kidney injury and cardiovascular risk

eGFR and the urinary albumin-to-creatinine ratio (UACR) are standard measures for evaluating renal function and injury. Elevated UACR not only signifies impairment of the glomerular filtration barrier but also reflects systemic vascular endothelial dysfunction and increased permeability. In states of metabolic disorder, chronic inflammation, oxidative stress, and activation of the RAAS can occur. These pathophysiological processes synergistically compromise the structure and function of both the heart and kidneys, resulting in abnormal eGFR and UACR changes. Notably, abnormalities in UACR may precede alterations in eGFR, although nonalbuminuric CKD also occurs. The study by Gunzler et al.[35] demonstrated that in patients with diabetic kidney disease, an increase in UACR occurs prior to a significant decline in eGFR. As the disease advances, characteristic changes manifest as a sharp rise in UACR accompanied by a progressive decline in eGFR, indicating that UACR serves as a sensitive marker for the early prediction of renal function deterioration. Furthermore, both reduced eGFR and elevated UACR are independent risk factors for all-cause and cardiovascular mortality. The coexistence of these two conditions is associated with greater patient risk. The study by Ninomiya et al.[36] demonstrated that reduced eGFR and elevated UACR jointly identify patients at higher cardiovascular and renal risk. Both measures should therefore be assessed when estimating kidney and cardiovascular risk in CKM syndrome.

Uric acid is a commonly measured clinical parameter. Experimental research has described mechanisms linking hyperuricemia with cardiovascular and kidney injury, but the benefit of urate lowering must be assessed in

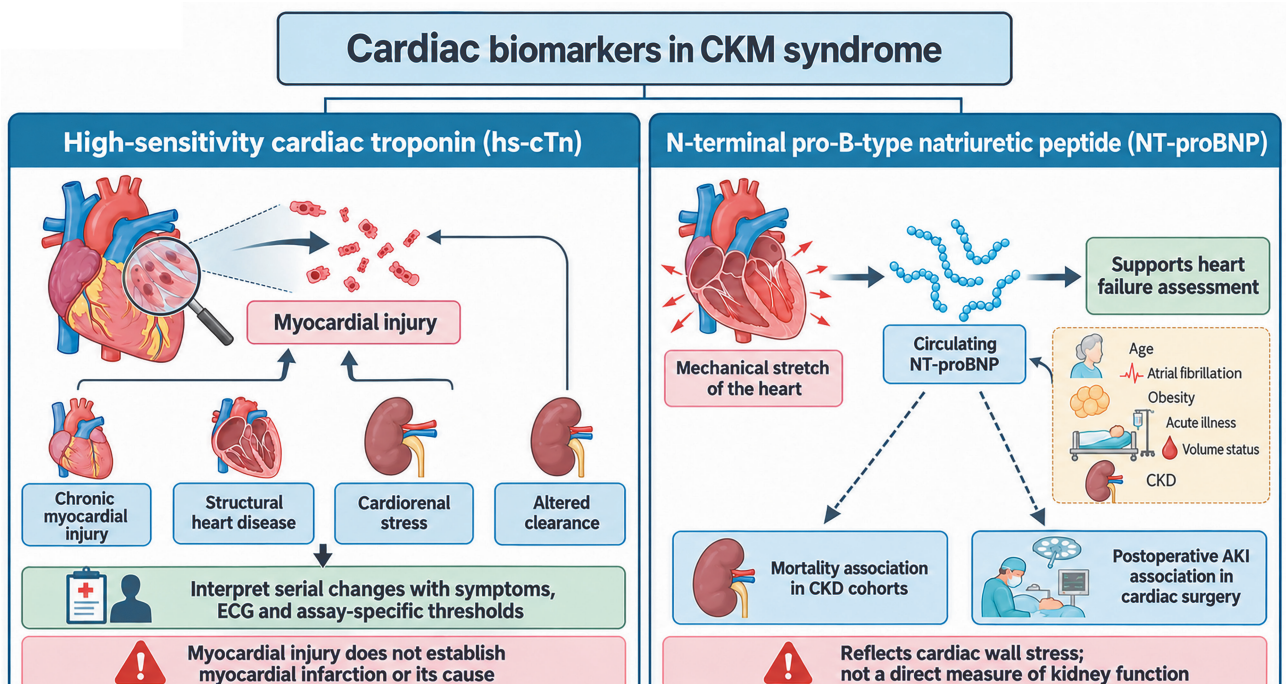


Figure 2: Cardiac biomarker interpretation in CKM syndrome.

hs-cTn identifies myocardial injury but does not determine its cause or establish myocardial infarction. Chronic injury, structural heart disease and cardiorenal stress contribute to elevation; altered clearance affects circulating concentrations. Serial measurements require clinical and assay-specific interpretation. NT-proBNP supports heart failure assessment, but kidney dysfunction and other factors affect concentrations. Dashed links denote observational associations in the stated settings, not treatment effects or direct measures of kidney function. Sources: manuscript references[28-34].

Abbreviations: CKM, cardiovascular-kidney-metabolic; hs-cTn, high-sensitivity cardiac troponin; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CKD, chronic kidney disease; AKI, acute kidney injury; ECG, electrocardiogram.

clinical trials. The process of purine metabolism generates ROS through xanthine oxidase (XO)-mediated uric acid production. A high-uric-acid environment can activate NADPH oxidase in endothelial cells, further amplifying ROS generation[37,38]. Uric acid also activates the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome in immune cells, promoting the release of pro-inflammatory factors and triggering chronic low-grade inflammation[39]. Furthermore, a bidirectional vicious cycle exists between insulin resistance and hyperuricemia. Insulin resistance upregulates the expression of urate transporter 1 (URAT1) and glucose transporter 9 (GLUT9) in renal tubules and activates sodium-hydrogen exchangers (NHE), leading to increased uric acid reabsorption and decreased excretion, thereby elevating serum uric acid levels[40,41]. Simultaneously, insulin resistance enhances lipolysis and the release of free fatty acids in the body. Uric acid can provide additional clinical context, but these mechanisms do not establish that urate lowering prevents CKM events. In the Controlled Trial of Slowing of Kidney Disease Progression From the Inhibition of Xanthine Oxidase (CKD-FIX), allopurinol did not slow eGFR decline in 369 randomized participants (363 analyzed)[42]; urate-lowering treatment should follow established indications.

Cystatin C is a low-molecular-weight, alkaline, non-glycosylated single-chain protein that serves as a highly sensitive biomarker for evaluating glomerular filtration function. Cystatin C is less dependent on muscle mass than creatinine, but is affected by age, adiposity, inflammation, thyroid dysfunction, corticosteroids, and smoking[5,43]. Previous studies have shown that elevated serum cystatin C levels are associated with an increased risk of CVDs, including hypertension, stroke, and coronary heart disease, independent of normal creatinine levels or estimated eGFR values[44-46]. Cystatin C may therefore help refine kidney function and risk assessment in selected patients. When available, combined creatinine–cystatin C equations improve GFR estimation and clinical risk assessment.

Neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) are tubular injury markers studied mainly in acute kidney injury and CKD. Their urine or plasma concentrations depend on the assay, sampling context, inflammation, and kidney function. In a Chronic Renal Insufficiency Cohort (CRIC) analysis of 2,466 participants, urinary tubular injury markers did not improve prediction of CKD progression beyond an established clinical model including eGFR and albuminuria[47]. Accordingly, routine CKM screening or treatment selection using these markers remains investigational. Figure 3 summarizes the roles and interpretation limits of kidney markers in CKM assessment.

Metabolic and inflammatory markers: common pathways in systemic pathogenesis

Glycated hemoglobin (HbA1c) is an established measure of long-term glycemic control used in diabetes management. The chronic hyperglycemia it represents constitutes a common pathophysiological basis for damage to the heart, kidneys, and metabolic organs. Associations between HbA1c and cardiovascular risk vary across populations and study designs; a value of 5.5% should not be treated as a universal CKM risk threshold[48]. Additionally, HbA1c is a strong predictor of the progression of diabetic kidney disease, and its fluctuations serve as an independent risk factor for this progression[49]. Improved glycemic control can delay the progression of microalbuminuria[50]. Glycemic management remains part of CKM care, with targets individualized to the patient's comorbidities and risk of hypoglycemia. In advanced CKD, anemia, altered erythrocyte lifespan, transfusion, and erythropoiesis-stimulating therapy can distort HbA1c; interpret it alongside measured glucose.

After hepatic conjugation, bilirubin is secreted into the intestine where it is deconjugated and reduced by bacterial bilirubin reductase (BilR) to urobilinogen. Urobilin is formed by subsequent oxidation[51]. Some urobilinogen is reabsorbed and may be excreted by the kidneys. In a small human study, plasma urobilin was positively associated with insulin resistance and adiposity[52]. The finding is exploratory and has not established a prognostic role in CKM syndrome. Associations of low bilirubin with mortality or heart failure[53-55] should not be transferred to increased urobilin.

High-sensitivity C-reactive protein (hs-CRP) and IL-6 are among the most commonly measured clinical inflammatory

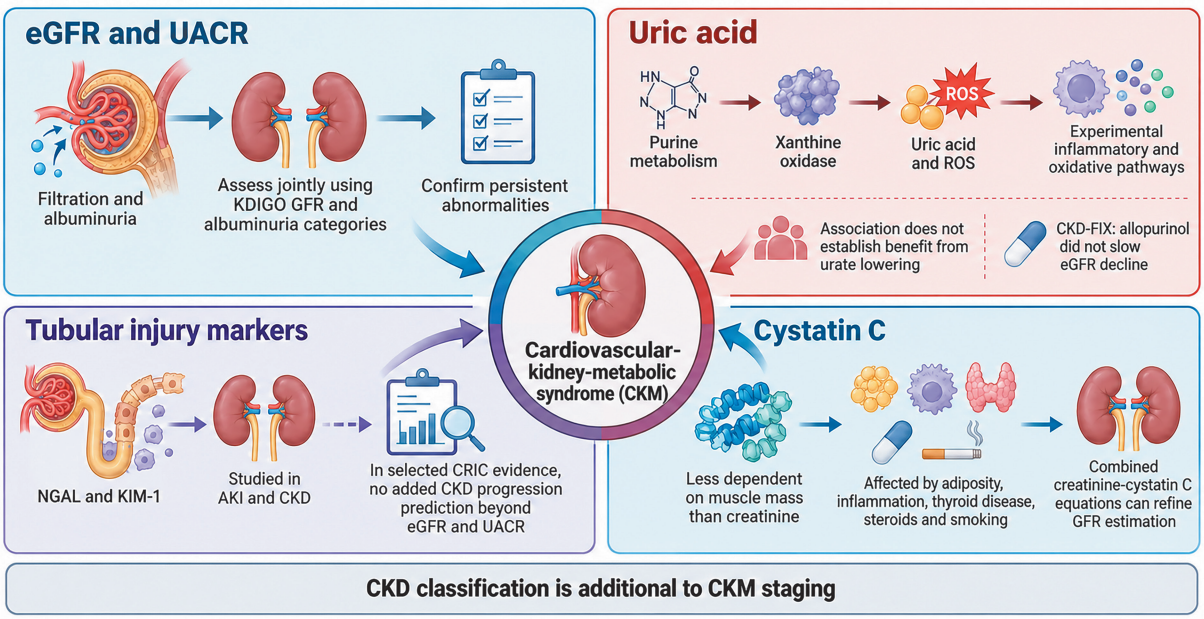


Figure 3: Kidney markers and their roles in CKM assessment.

eGFR and UACR should be assessed jointly, with persistent abnormalities confirmed and CKD classified independently of CKM stage. Cystatin C can refine GFR estimation, particularly in combined equations, but has non-GFR determinants. Selected urinary tubular injury markers did not improve CKD progression prediction beyond the clinical model in the cited CRIC analysis. Experimental urate pathways do not establish clinical benefit from urate lowering; CKD-FIX did not demonstrate slower eGFR decline with allopurinol. Icons and arrows summarize assessment themes and are not quantitative causal models. Sources: manuscript references[5,35-43,47].

Abbreviations: CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; GFR, glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; AKI, acute kidney injury; CRIC, Chronic Renal Insufficiency Cohort; ROS, reactive oxygen species; CKD-FIX, Controlled Trial of Slowing of Kidney Disease Progression From the Inhibition of Xanthine Oxidase.

markers. The primary pathological characteristic of CKM syndrome is chronic, persistent low-grade inflammation. Inflammatory markers have therefore been studied for their prognostic value. Previous studies have shown that hs-CRP and IL-6 are associated with inflammatory pathways involved in renal fibrosis, atherosclerotic plaque formation, and metabolic disorders by inducing insulin resistance[56-58]. In advanced CKD, chronic inflammation and concurrent infection or acute illness complicate interpretation. An elevated result may reflect a concurrent inflammatory illness rather than progression of CKM injury. Figure 4 summarizes metabolic and inflammatory markers and their interpretation in CKM syndrome.

Emerging biomarkers and calculated metabolic indices

Emerging biomarkers

In the study of CKM syndrome, emerging biomarkers primarily focus on key pathological processes such as inflammation, fibrosis, metabolic disorders, and organ-specific damage. Studies of these markers examine whether the underlying processes also provide information relevant to early injury or prognosis.

Remnant cholesterol (RC) refers to the total cholesterol content in triglyceride-rich lipoproteins and their metabolic remnants found in human plasma. It represents the fraction of cholesterol remaining in total plasma cholesterol after excluding low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). RC is commonly calculated as total cholesterol–LDL-C–HDL-C, with all concentrations expressed in the same units. Cholesterol-rich remnant particles can enter the arterial wall and contribute to macrophage foam-cell formation. This process subsequently promotes the development of atherosclerotic plaques, driving atherosclerosis in vital organs such as the heart and kidneys, and results in adverse cardiovascular events, including coronary heart disease and renal

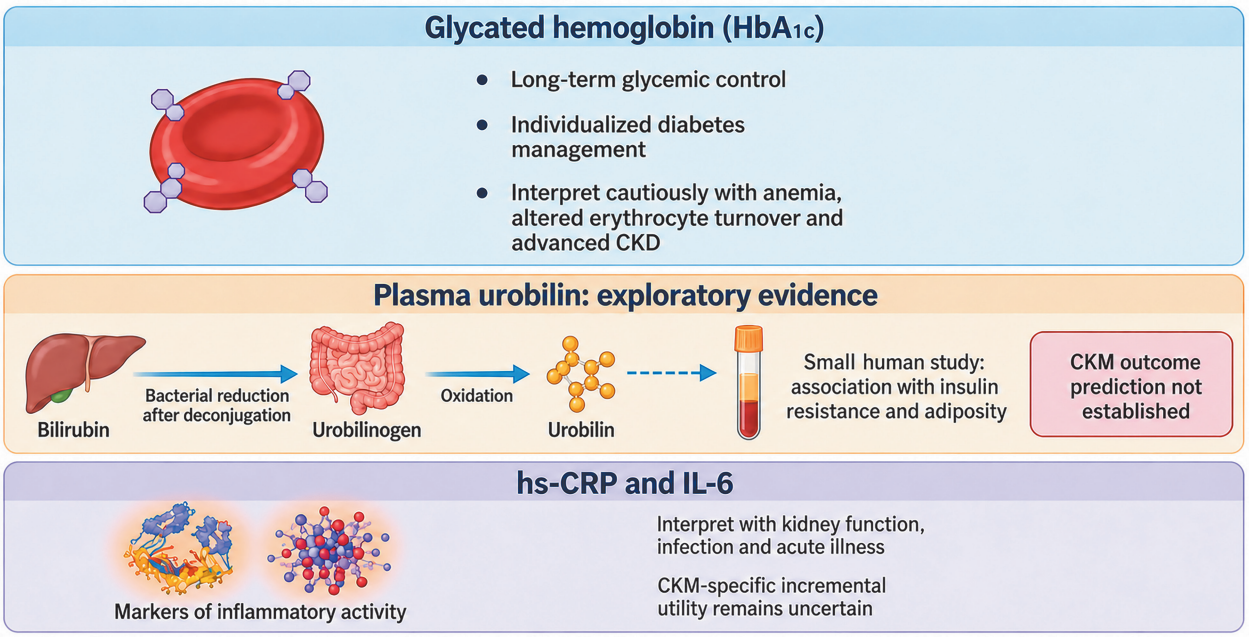


Figure 4: Metabolic and inflammatory markers in CKM syndrome.

HbA1c reflects long-term glycemia and supports individualized diabetes management; advanced CKD and altered erythrocyte turnover can complicate interpretation. Intestinal bilirubin bioconversion yields urobilinogen, followed by oxidation to urobilin. Molecular icons are schematic and do not depict exact chemical structures. The small human plasma-urobilin study reports associations with insulin resistance and adiposity, not established CKM outcome prediction. Inflammatory-marker interpretation requires attention to kidney function and concurrent illness. Clinical-use statements are presented as parallel considerations, not organ-specific causal effects. Sources: manuscript references[48-52,56-58].
Abbreviations: CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6.

ischemia[59-61]. Notably, in diabetic patients, elevated baseline RC levels are associated with the progression of diabetic nephropathy[62]. These findings support studying RC as a measure of residual lipid risk in CKM syndrome. Its added value beyond conventional lipids and the thresholds relevant to treatment still need to be established.

Both soluble suppression of tumorigenicity 2 (sST2) and galectin-3 are emerging biomarkers that are associated with fibrosis and inflammatory remodeling but are not specific measurements of myocardial fibrosis. sST2 competitively binds with interleukin-33 (IL-33), thereby disrupting cardioprotective signaling and promoting cardiomyocyte hypertrophy, increased myocardial fibrosis, and apoptosis. The persistent activation of the IL-33/ST2 signaling pathway also contributes to renal tubular injury and interstitial fibrosis[63,64]. Galectin-3, secreted by macrophages, can be induced during the early stages of tissue damage and inflammation. It not only binds directly to fibroblasts, promoting their proliferation and differentiation into myofibroblasts, but also stimulates collagen synthesis[65]. Additionally, galectin-3 acts as a key activator of the transforming growth factor-β (TGF-β)/Smad signaling pathway by enhancing the expression and activation of TGF-β, thereby significantly driving extracellular matrix deposition and tissue fibrosis[66,67]. These findings link the pathways to cardiac and renal remodeling, but circulating concentrations do not directly measure the extent of myocardial fibrosis. Both markers can be affected by extracardiac inflammation and fibrosis, and galectin-3 is influenced by kidney function. Their value depends on whether they add information to the clinical assessment already available.

Leptin is a peptide hormone secreted by white adipose tissue in humans, linking adipose tissue dysfunction, CVDs, and renal injury. In pathological conditions such as obesity and heart failure, the body often develops hyperleptinemia and leptin resistance. A study[68] utilizing rats as an experimental model demonstrated that leptin reduced ventricular myocyte shortening without a significant change in calcium-transient amplitude. Experimental studies suggest that adverse renal effects

of leptin involve the promotion of glomerular fibrosis progression. Leptin not only activates the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway by increasing TGF-β expression but also enhances the production of inflammatory cytokines, including MCP-1 and TNF-α in the kidneys[69,70]. These experimental findings suggest a role in glomerular injury. Leptin is consequently being studied as a marker of adipose dysfunction and CKM progression. Sex, fat mass, leptin resistance, and kidney function affect its concentration and complicate the choice of a clinical cutoff.

Growth differentiation factor-15 (GDF-15) is a cytokine that is highly expressed during cellular stress and binds with high affinity to the glial cell line-derived neurotrophic factor family receptor alpha-like (GFRAL) receptor in regions such as the hindbrain. This interaction recruits and activates the rearranged during transfection (RET) co-receptor tyrosine kinase, collectively forming the GDF-15–GFRAL–RET ternary signaling complex. By activating protective signaling pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), GDF-15 has shown effects on metabolic regulation and organ injury in experimental models[71]. Plasma levels of GDF-15 are significantly associated with the severity of heart failure, renal injury, and adverse prognosis. Furthermore, elevated GDF-15 levels are associated with mortality in patients with diabetic nephropathy complicated by cardiac conditions[72,73]. Circulating GDF-15 also rises with age, kidney dysfunction, inflammation, and malignancy. A high value therefore needs to be interpreted against these competing explanations; a threshold for CKM treatment decisions has not been established.

Soluble urokinase-type plasminogen activator receptor (suPAR) is associated with chronic inflammation and immune activation. Experimental studies indicate that suPAR can bind to the receptor for advanced glycation end products (RAGE) and αVβ3-integrin on the surfaces of podocytes. This binding activates the corresponding Src phosphorylation pathway, leading to podocyte cytoskeletal rearrangement and foot process effacement, which ultimately results in proteinuria and glomerulosclerosis[74]. The pathway is a candidate for further investigation, but inhibiting it has not been shown to improve human CKM outcomes. Differences between assays and the effects of kidney function and inflammation also complicate interpretation.

Klotho protein is a product encoded by an aging-suppressing gene, first identified by researchers in mouse models. It is classified as a type I transmembrane glycoprotein, primarily synthesized in the renal distal tubules, and exists in two main forms: membrane-bound Klotho (m-Klotho) and soluble Klotho (s-Klotho). Experimental studies have described anti-aging, anti-inflammatory, antioxidant, anti-fibrotic properties, and the improvement of metabolic homeostasis. m-Klotho is predominantly expressed in the distal tubular epithelial cells of the kidney, while s-Klotho is the primary active form found in circulation. The study conducted by Rotondi et al.[75] demonstrated that serum s-Klotho levels were significantly reduced as early as stage 2 CKD, although associations across studies are inconsistent and another study linked higher soluble Klotho to rapid decline in diabetic kidney disease[76]. It is not yet clear whether soluble Klotho detects injury earlier than cystatin C or UACR. Klotho remains a candidate marker of kidney injury, with inconsistent clinical associations and limited agreement between assays. These problems need to be resolved before reference ranges can support routine use.

Fibroblast growth factor 23 (FGF23) is primarily secreted by osteocytes and has a central role in regulating phosphorus and vitamin D metabolism by forming a complex with the α-Klotho protein. Consequently, elevated levels of FGF23 are closely associated with disorders of phosphorus metabolism. Hyperphosphatemia can directly stimulate the transformation of vascular smooth muscle cells into osteoblast-like cells, thereby promoting vascular and cardiac valve calcification. This process significantly increases the risk of adverse cardiovascular events, including heart failure and arrhythmias[77]. Furthermore, experimental studies indicate that elevated FGF23 can bind to fibroblast growth factor receptor 4 (FGFR4) on cardiomyocytes, activating pro-hypertrophic signaling pathways and upregulating the expression of hypertrophy-related genes. This signaling can cause cardiomyocyte hypertrophy and ventricular thickening. In CKD, the deficiency of Klotho

protein further impairs the heart's ability to counteract hypertrophic stimuli, exacerbating the progression of myocardial hypertrophy and cardiac dysfunction[78,79]. Intact and C-terminal FGF23 assays are not interchangeable; phosphate balance, iron status, inflammation, and CKD severity affect concentrations. Because FGF23 promotes phosphate excretion, inhibiting the pathway may interfere with this compensatory response[80].

Trimethylamine N-oxide (TMAO) is a small-molecule organic compound produced with the involvement of gut microbiota, formed from microbial metabolites of dietary substrates. Experimental studies suggest that TMAO not only activates the NLRP3 inflammasome in macrophages, promoting the release of inflammatory factors, but also inhibits reverse cholesterol transport, thereby accelerating foam cell formation and the development of atherosclerotic plaques[81,82]. Furthermore, experimental work indicates that TMAO can impair endothelial nitric oxide synthase (eNOS), leading to reduced nitric oxide (NO) production and resulting in vascular endothelial dysfunction. These endothelial effects have been demonstrated experimentally[83] and should not be interpreted as proof of causal effects in patients. TMAO has also been studied in relation to hepatic and adipose signaling and metabolic disease[84]. Diet and microbial composition affect TMAO production, while reduced renal clearance can increase its concentration. This makes it difficult to determine whether an elevated value contributes to injury or mainly reflects kidney dysfunction. Figure 5 summarizes selected emerging biomarkers, distinguishing mechanistic findings from clinical associations and limitations to clinical translation.

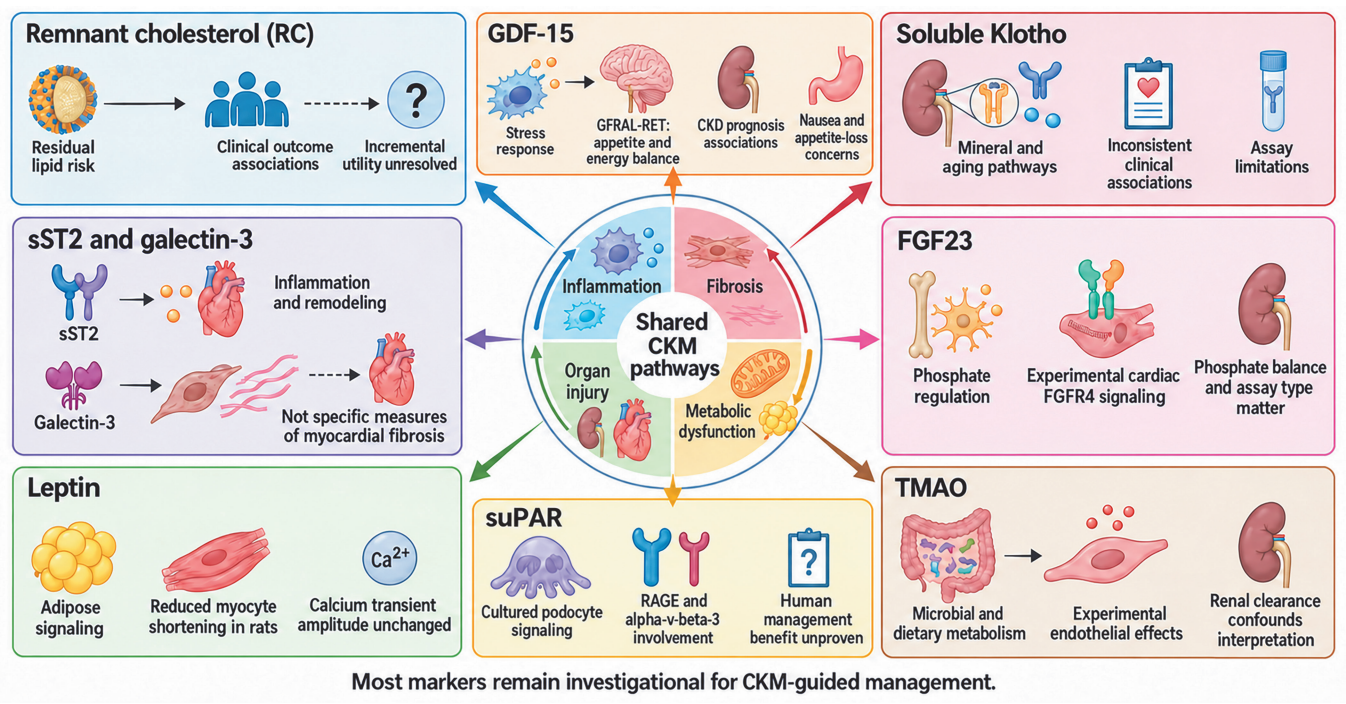


Figure 5: Emerging markers and limits of clinical translation.

Panels distinguish mechanistic findings, clinical associations and interpretation limits. Leptin reduced rat ventricular myocyte shortening without a significant change in calcium-transient amplitude. GDF-15/GFRAL–RET signaling regulates appetite; prognosis associations and agonist tolerability are separate evidence domains. suPAR findings shown concern cultured podocyte signaling. FGF23-related cardiac FGFR4 effects and TMAO endothelial effects include experimental evidence. Kidney function, assay heterogeneity and competing illnesses limit interpretation. Connecting arrows group concepts and do not establish sequential causality or biomarker-guided management benefit. Sources: manuscript references[60-69,71,73-76,79-84,90-92].

Abbreviations: CKM, cardiovascular-kidney-metabolic; CKD, chronic kidney disease; RC, remnant cholesterol; sST2, soluble suppression of tumorigenicity 2; GDF-15, growth differentiation factor-15; GFRAL, glial cell line-derived neurotrophic factor family receptor alpha-like; RET, rearranged during transfection; FGF23, fibroblast growth factor 23; FGFR4, fibroblast growth factor receptor 4; suPAR, soluble urokinase-type plasminogen activator receptor; RAGE, receptor for advanced glycation end products; alpha-v-beta-3, αVβ3-integrin; TMAO, trimethylamine N-oxide; Ca^{2+}, calcium ion.

Calculated metabolic indices

The hemoglobin glycation index (HGI) and triglyceride-glucose-body mass index (TyG-BMI) combine routinely measured variables and are calculated metabolic indices rather than molecular biomarkers. Their appeal is the use of readily available measurements, but their clinical value depends on whether the calculation adds useful information beyond those measurements.

The HGI quantifies the difference between measured HbA1c and the HbA1c value predicted based on fasting plasma glucose (FPG). HGI = observed HbA1c − predicted HbA1c, where predicted HbA1c = a + b × FPG from a population-specific regression model. HbA1c is expressed in percent; FPG must use the units employed to derive that model and be measured fasting. HGI is dependent on its component measurements and regression calibration, rather than independent of average glycemia. In prediabetic populations, a high HGI is significantly correlated with an increased risk of non-fatal cardiovascular and cerebrovascular diseases[85]. Furthermore, a higher HGI has been linked to a greater risk of developing incident CKD in the future, although HGI does not directly measure longitudinal glycemic variability and this association does not establish causality[86]. The regression equation must be calibrated to the study population. Proposed cutoffs need external validation, and associations should be reassessed after accounting for the component variables.

The triglyceride-glucose-body mass index (TyG-BMI) integrates two major risk factors: insulin resistance and obesity. A study[87] reported a positive association between TyG-BMI and CVD incidence in CKM stages 0–3, but superiority over established clinical models requires verified incremental performance and calibration. Moreover, an elevated TyG-BMI index has also been identified as an independent predictor of acute kidney injury in patients with heart failure[88], supporting further evaluation in this setting. TyG = ln{[fasting triglycerides (mg/dL) × fasting glucose (mg/dL)]/2}; TyG-BMI = TyG × BMI (kg/m^2). Both laboratory inputs require fasting sampling and unit consistency. Whether the index adds information beyond glucose, triglycerides, and BMI should be tested in externally validated models before it is used to guide management.

Clinical translation prospects and risk challenges of biomarkers

Clinical translation prospects of biomarkers

Biomarkers can inform CKM care by identifying organ injury and helping estimate risk. Early screening and risk stratification are two possible uses. When measured before overt clinical disease, high-risk individuals with subclinical target organ damage can be identified, supporting timely clinical assessment and established preventive interventions aimed at reducing complications such as heart failure and end-stage renal disease. For patients with established disease, serial measurements can help assess progression and treatment response. Their usefulness depends on whether a change in the result leads to a clinically justified action. Research has also identified markers of inflammation, fibrosis, and cellular stress. These markers may provide prognostic information or identify pathways worth targeting. Predictive value and benefit from pathway-directed treatment need separate evaluation. For example, GDF-15 is significantly elevated in metabolic diseases such as obesity and diabetes. GDF-15 can transmit a potent "anorexigenic" signal to the central nervous system by acting on the brainstem-specific receptor GFRAL, thereby regulating food intake and energy balance[89]. A clinical study of the GDF-15 analogue LY3463251 reported reduced appetite and food intake with modest weight loss over 12 weeks; nausea and vomiting occurred in the preceding single-dose study[90]. These results support biological activity in humans but also show the need to assess tolerability. Appetite suppression, excessive weight loss, and cachexia are particularly relevant concerns in patients with advanced disease. In experimental podocyte models, knockdown of RAGE expression or direct use of RAGE antagonists can block Src phosphorylation and downstream injurious effects induced by suPAR, but this remains experimental evidence[74]. Specific inhibition of FGFR4 has shown effects in animal experiments, but clinical benefit remains unproven and effects on phosphate handling need attention[80,91].

TMAO provides another example of a proposed therapeutic pathway. Beyond upstream strategies such as dietary modification and microbiota regulation, direct intervention

targeting TMAO production and clearance remains an investigational therapeutic approach. Future research may develop specific inhibitors to block microbial generation of its direct precursor trimethylamine (TMA) or suppress the activity of the key hepatic enzyme flavin-containing monooxygenase 3 (FMO3) responsible for its oxidation, although the benefit and wider metabolic effects of these interventions remain uncertain.

These examples suggest possible treatment pathways, but most have not reached the point of guiding CKM care. Prospective studies should test whether adding a marker to routine assessment changes management and improves patient outcomes.

Clinical translation risks and challenges of biomarkers

Several problems limit the use of new biomarkers in CKM care. First, most existing biomarkers focus on a single system, such as cardiac, renal, or metabolic functions, and may not capture injury elsewhere. Second, some biomarkers have a late detection window, becoming elevated after structural injury is already present. This limits their suitability for early screening. Age, sex, kidney function, and concurrent illness also affect biomarker concentrations. For many emerging markers, there is no agreed CKM-specific cutoff for a clinical decision. Established clinical measurements already have validated thresholds. Many are expressed in several tissues; infection or inflammation can therefore raise the result without indicating progression of CKM injury. Finally, many emerging-marker studies examine single markers without adequate comparison against validated multivariable risk models. Reproducible assays and consistent sampling are needed before results can be used across laboratories. Studies should report whether the marker improves discrimination and calibration, and whether it changes decisions at clinically relevant risk thresholds. Cost and the benefit of a marker-guided strategy then need prospective evaluation. Table 1 summarizes the biological and clinical evidence for selected biomarkers; Table 2 summarizes their incremental value, assay status, limitations, and clinical translation status.

As summarized in Table 2, established markers have defined clinical uses, whereas most emerging markers remain investigational in CKM syndrome. An association with adverse outcomes does not necessarily indicate added predictive value beyond routine assessment or justify a change in treatment.

Summary and outlook

Traditional and emerging biomarkers provide information for the early detection, precise diagnosis, and risk stratification of CKM syndrome and its complications. For established measures, this can support evidence-based interventions aimed at preventing adverse clinical events such as acute heart failure episodes and end-stage renal disease. For emerging markers, the remaining questions concern assay reliability, added predictive value, and effects on clinical decisions. First, future efforts should focus on rigorously validating their diagnostic and prognostic value in prospective, large-scale cohorts, establishing population-specific reference ranges, and addressing the standardization of detection methods. Second, given that the heart, kidneys, and metabolic organs share core pathophysiological mechanisms such as inflammation, fibrosis, and oxidative stress, future research should not examine individual biomarkers in isolation. Multicenter cohorts with diverse participants can test whether panels or multi-omics models add information beyond routine assessment. Third, externally validated panels should be evaluated in prospective management trials for clinical benefit and cost-effectiveness. Mechanistic studies remain useful for identifying treatment targets, but pathway-directed therapies require their own efficacy and safety evidence. These priorities would make it possible to judge new biomarkers by the decisions they improve, rather than by association alone.

Author contributions

Siyuan Wen is responsible for writing; Boda Zhou is responsible for revising.

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Ethics statement

Not applicable.

Table 1: Comparative biological and clinical evidence.

Marker	Pathway and intended use	Population or setting	Evidence and sample size	Selected performance
hs-cTn I/T	Myocardial injury; acute assessment and prognosis	CKD/HF; selected stage 3–4 settings	CRIC observational cohort, $n = 3,664$[92]	hs-cTnT mortality HR 1.62 (1.48–1.78)
NT-proBNP	Wall stress; HF diagnosis and prognosis	HF/CKD; selected stage 2–4 settings	Same CRIC cohort[92]	Mortality HR 1.92 (1.73–2.12)
eGFR and UACR	Filtration/albuminuria; CKD diagnosis and prognosis	CKD; stages 2–4	KDIGO guideline; clinical cohorts[5,36]	Risk depends on joint G/A category; no single AUC
Cystatin C/ eGFRcr-cys	Filtration; improve GFR estimation	Suspected/established CKD	Guideline and clinical interpretation literature[5,43]	Equation accuracy, not a CKM-wide diagnostic AUC
Uric acid	Purine metabolism; contextual risk association	Metabolic risk/CKD	CKD-FIX trial, $n = 369$ randomized; 363 analyzed[42]	Allopurinol did not slow eGFR decline
HbA1c	Glycemia; diagnosis and monitoring	Diabetes; mainly stages 2–4	Diabetes cohort evidence[48,49]	No universal CVD threshold of 5.5% established
hs-CRP and IL-6	Inflammation; contextual prognosis	CKD/metabolic/ inflammatory settings	Human association/ mechanistic evidence[56-58]	CKM-specific incremental performance not established in the selected evidence
RC	Derived lipid measure; residual risk association	Diabetes/CVD risk	Longitudinal cohorts[60-62]	Selected reports associate RC with outcomes; comparable AUC not reported here
sST2	Inflammation/remodeling; prognosis	CKD/HF	CRIC, $n = 3,664$[92]	Mortality HR 1.26 (1.16–1.37)
Galectin-3	Inflammation/fibrosis; prognosis research	HF/CKD	Selected experimental and clinical studies[65,67]	Added predictive value across CKM stages not established
Leptin	Adipose signaling; mechanistic/ prognostic research	Obesity/CKD and experimental models	Animal studies and clinical context[68,69]	No established cutoff for CKM decisions
GDF-15	Cell stress; prognosis research	CKD/diabetes/HF	CRIC, $n = 3,664$[92]; diabetes cohorts[73]	Mortality HR 1.61 (1.46–1.78)
suPAR	Immune activation; kidney injury research	CKD and podocyte models	Cultured podocyte experiments[74]	Mechanistic evidence; clinical utility unproven
Soluble Klotho	Aging/mineral signaling; exploratory risk assessment	CKD/diabetic kidney disease	Clinical observational studies[75,76]	Inconsistent direction of association
FGF23	Mineral metabolism; cardiovascular risk research	Especially CKD	Experimental and clinical synthesis[79,80,91]	No validated CKM-wide treatment cutoff
TMAO	Gut-derived metabolism; prognosis research	CVD/CKD/metabolic settings	Experimental and observational evidence[81,83]	CKM-specific incremental value not established
Plasma urobilin	Bilirubin metabolite; insulin resistance research	Small obesity/lean human cohort[52]	Cross-sectional study[52]	No validated CKM outcome prediction
Urinary NGAL	Tubular injury; progression research	CKD; AKI in separate settings	CRIC cohort, $n = 2,466$[47]	No improved CKD progression prediction beyond base model
Urinary KIM-1	Proximal tubular injury; progression research	CKD	Same CRIC cohort[47]	No improved prediction beyond eGFR/UACR model
HGI	Calculated glycation residual; risk research	General adult and impaired-glucose-metabolism cohorts	Longitudinal cohorts[85,86]	External calibration and incremental utility unresolved
TyG-BMI	Calculated metabolic index; risk research	CKM 0–3; ICU HF/AKI cohorts	Prospective/retrospective cohorts[87,88]	Comparative performance not quantified in this table

Note. The tables summarize selected studies. Quantitative measures are shown where specified; an unreported value does not indicate that no association exists. Mortality HRs (95% CIs) from CRIC are per one standard deviation increase in log-transformed baseline concentration; they are not treatment effects or diagnostic cutoffs. CKM stages were not uniformly assigned in older cohorts. HR = hazard ratio; CI = confidence interval; CRIC = Chronic Renal Insufficiency Cohort; AKI = acute kidney injury; HF = heart failure; AUC = area under the curve; eGFRcr-cys = creatinine–cystatin C-based eGFR; G/A = GFR/albuminuria category.

Table 2: Incremental value, assays, limitations, and translation status.

Marker	Incremental value or utility	Assay status	Main limitations	Translation status
hs-cTn I/T	Supports cardiac assessment when clinically indicated	Clinical, assay-specific reference limits	Chronic injury and CKD complicate acute interpretation	Routine for indicated myocardial injury assessment; selective prevention use
NT-proBNP	Supports cardiac assessment when clinically indicated	Clinical assays; context-dependent thresholds	Age, AF, obesity, volume status, CKD	Guideline-supported HF evaluation; selective pre-HF assessment
eGFR and UACR	Established clinical use for the stated indication	Widely available; validated equations and standardized methods	Biological variability; persistence must be confirmed	Routine; guides CKD risk and management
Cystatin C/ eGFRcr-cys	Established clinical use for the stated indication	Clinical assays; availability varies	Thyroid disease, inflammation, steroids, smoking, adiposity	Guideline-supported refinement of GFR estimation
Uric acid	Added predictive value or management benefit not established for CKM	Routine clinical chemistry	Kidney function, drugs, diet; association is not causality	Routine for indicated care; not a proven CKM prevention target
HbA1c	Established clinical use for the stated indication	Standardized clinical assays	Anemia, erythrocyte turnover, advanced CKD	Routine diabetes care; no universal CKM prognostic cutoff
hs-CRP and IL-6	Added predictive value or management benefit not established for CKM	hs-CRP widely available; IL-6 availability varies	Infection, inflammation, CKD; low organ specificity	Context-dependent clinical use; investigational CKM panel role
RC	Added predictive value or management benefit not established for CKM	Calculated from routine lipid values	LDL-C estimation and fasting status	Investigational CKM-specific thresholds and management
sST2	Added predictive value or management benefit not established for CKM	Commercial assays available in some settings	Extracardiac inflammation; context-dependent added value	Prognostic testing in some settings; CKM use investigational
Galectin-3	Added predictive value or management benefit not established for CKM	Commercial assays available in some settings	Renal function and extracardiac fibrosis	Context-dependent prognosis; not CKM-wide routine screening
Leptin	Added predictive value or management benefit not established for CKM	Research/commercial immunoassays	Sex, fat mass, resistance, CKD; no universal cutoff	Investigational
GDF-15	Added predictive value or management benefit not established for CKM	Research/clinical assay availability varies	Age, cancer, CKD, inflammation; GFRAL agonism caused nausea/emesis in human testing	Investigational CKM management
suPAR	Added predictive value or management benefit not established for CKM	Commercial/research assays	Smoking, infection, renal function, assay heterogeneity	Investigational CKM management
Soluble Klotho	Added predictive value or management benefit not established for CKM	Mainly research assays	Assay reproducibility, processing, inconsistent associations	Investigational
FGF23	Added predictive value or management benefit not established for CKM	Specialist/research assays	Intact versus C-terminal assays; iron, phosphate, CKD	Specialist use in selected mineral disorders; investigational CKM risk use
TMAO	Added predictive value or management benefit not established for CKM	Mainly research analytical assays	Diet, microbiome, renal clearance, variable concentrations	Investigational

(*continued*)

Table 2

(continued)

Marker	Incremental value or utility	Assay status	Main limitations	Translation status
Plasma urobilin	Added predictive value or management benefit not established for CKM	Research measurements; no CKM standard	Distinct from urinary urobilinogen; specimen/method variation	Exploratory
Urinary NGAL	No added prediction beyond eGFR/UACR in selected CRIC study	Clinical AKI assays in some regions; research CKD use	Infection, inflammation, urine dilution	Investigational for CKM; negative incremental CRIC result
Urinary KIM-1	No added prediction beyond eGFR/UACR in selected CRIC study	Mainly research assays	Urine dilution, normalization and heterogeneity	Investigational for CKM
HGI	Added predictive value or management benefit not established for CKM	Calculation from routine inputs	Population-specific regression; input dependence	Investigational
TyG-BMI	Added predictive value or management benefit not established for CKM	Calculation from fasting inputs	Units, fasting, population-specific cutoffs; input dependence	Investigational

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

AI statement

During the preparation of this manuscript, a generative AI tool was only used for language polishing, grammar correction and improving readability. The AI tool was not used to generate any core content of this review. All AI-suggested revisions were carefully reviewed, revised and approved by the authors. The authors take full responsibility for the originality, accuracy and integrity of the final manuscript. No AI is listed as an author.

Conflicts of interest

The authors do not have any possible conflicts of interest.

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