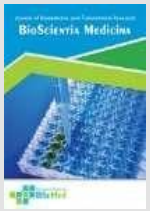
eISSN (Online): 2598-0580



Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Beyond Serum Creatinine: Urinary KIM-1 as a Predictive Biomarker for Subclinical Acute Kidney Injury and Chronic Kidney Disease Progression: A Systematic Review and Meta-Analysis

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ARTICLE INFO

Keywords:
Biomarker
Fibrosis
Maladaptive Repair
Subclinical AKI
Urinary KIM-1

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All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.37275/bsm.v10i4.1563

A B S T R A C T

Background: The global burden of chronic kidney disease (CKD) is escalating, requiring earlier and more precise diagnostic modalities. Traditional reliance on serum creatinine and glomerular filtration rate (GFR) creates a significant blind spot regarding structural tubular integrity. A dangerous diagnostic window known as subclinical acute kidney injury (AKI) exists when tubular damage progresses despite preserved filtration function. This study aims to systematically analyze the diagnostic accuracy of urinary kidney injury molecule-1 (uKIM-1) in detecting subclinical injury and quantify its predictive value for CKD progression in populations where serum creatinine fails to provide an early warning. **Methods:** A systematic review and meta-analysis of five pivotal studies were conducted, encompassing experimental models of ischemia-reperfusion and human cohorts involving Autosomal Dominant Polycystic Kidney Disease (ADPKD), Diabetic Nephropathy, and Contrast-Induced AKI. Data were synthesized using random-effects models to calculate Standardized Mean Differences (SMD) and pooled Hazard Ratios (HR) to assess the prognostic value of uKIM-1 for long-term renal decline. **Results:** The analysis demonstrated that uKIM-1 levels remained significantly elevated during apparent functional recovery where serum creatinine had returned to baseline. In experimental models, persistent uKIM-1 elevation correlated strongly with histological evidence of interstitial fibrosis ($r > 0.70$). Clinical cohorts revealed that elevated KIM-1 is a robust independent predictor of progression to ESRD, with hazard ratios ranging from 1.34 to 3.30. Pooled analysis showed a Risk Ratio of 2.45 (95% CI: 1.55 – 3.88; $p < 0.0001$). **Conclusion:** Urinary KIM-1 serves as a sensitive and specific biomarker for subclinical tubular injury, identifying the at-risk"phenotype missed by creatinine. Its persistent elevation signifies maladaptive repair and predicts the transition from AKI to CKD, supporting its clinical integration for early risk stratification.

1. Introduction

The global burden of chronic kidney disease (CKD) continues to escalate at an alarming rate, presenting a formidable challenge to public health systems worldwide.[1] As the prevalence of metabolic syndrome, diabetes, and hypertensive disorders increases, the incidence of progressive renal decline follows a parallel trajectory, necessitating the development of earlier and more precise diagnostic modalities. For decades, the foundational pillars of nephrology—the diagnosis of acute kidney injury (AKI) and the longitudinal monitoring of CKD—have depended almost exclusively on functional metrics, specifically the measurement of serum creatinine (SCr) and the monitoring of urine

output. While these functional markers are integral for estimating the glomerular filtration rate (GFR), they are increasingly recognized as being inherently insensitive to structural damage within the renal parenchyma. This reliance on filtration-based markers overlooks the complex cellular processes occurring within the tubules, often resulting in a significant lag between the onset of injury and its clinical detection.[2]

The fundamental limitation of serum creatinine lies in the kidney's extraordinary physiological capacity. The kidney possesses a substantial functional reserve, which acts as a compensatory mechanism during early-stage injury. Consequently, a significant proportion of nephron mass—estimates suggest that up to 50% can be compromised—before a measurable rise in serum creatinine occurs. This physiological lag creates a dangerous and silent diagnostic window known as subclinical AKI. Because the current kidney disease: Improving Global Outcomes (KDIGO) criteria rely so heavily on functional changes, patients suffering from significant subclinical injury are often misclassified as normal or recovered. This misclassification leads to a missed therapeutic window, delaying potential renoprotective interventions that could arrest the progression of the disease before irreversible damage occurs.[3]

Subclinical AKI is characterized by the presence of intrinsic tubular damage and inflammatory signaling that occurs in the absence of immediate functional loss.[4] During this silent phase, the proximal tubule cells (PTCs) undergo a series of pathological transformations. Under the stress of ischemic or toxic insults, these cells experience dedifferentiation and initiate maladaptive repair processes. These processes are not merely transient responses to injury but are critical drivers that lay the groundwork for interstitial fibrosis and the eventual transition from AKI to CKD. While the functional markers like GFR may appear stable due to compensatory hyperfiltration in the remaining healthy nephrons, the underlying structural integrity of the renal tissue is actively being eroded. This disconnect between functional stability and structural decay is the primary driver of renal disease progression in the modern clinical landscape.[5]

To bridge this diagnostic gap, research has pivoted toward structural biomarkers that reflect cellular injury rather than filtration capacity.[6] Among these, Kidney Injury Molecule-1 (KIM-1) is arguably the most promising and robust candidate. KIM-1 is a type 1 transmembrane glycoprotein characterized by a unique molecular architecture, containing a novel six-cysteine immunoglobulin-like domain and a mucin domain. The expression profile of KIM-1 is highly specific to renal stress. In the healthy kidney, KIM-1 expression is virtually negligible. However, upon encountering an ischemic or toxic insult, it is massively upregulated on the apical surface of surviving proximal tubule cells. Biologically, KIM-1 does not function as a passive bystander; it acts as a phosphatidylserine receptor. This enables epithelial cells to transform into semi-phagocytes, allowing them to engulf apoptotic debris and necrotic cells from the tubular lumen in an attempt to clear the path for repair. This specific and massive upregulation makes KIM-1 a direct, real-time reporter of proximal tubular stress and cellular injury.[7]

While the utility of KIM-1 in established, severe AKI is well-documented in existing literature, its role in the subtle, subclinical transition from acute injury to chronic fibrosis remains the current frontier of nephrology research. The medical community currently faces a critical question: can persistent, low-level elevations of KIM-1 predict long-term GFR decline in patients whose creatinine levels remain within normal ranges?. Identifying this cohort is essential for changing the management of renal disease from a reactive model to a proactive, preventive one.[8] Persistent elevation of KIM-1 may signify a failure of the kidney to return to a state of healthy homeostasis, indicating instead a state of chronic, low-grade inflammation and maladaptive repair that inevitably leads to the functional collapse of the organ.

The transition from theory to clinical practice requires a robust synthesis of diverse data types. High-fidelity experimental models are essential for

establishing the ground truth of subclinical injury, as they allow for direct histological verification of fibrosis that is often unavailable in human subjects.[9] For instance, evidence suggests that even when serum creatinine returns to baseline—suggesting clinical recovery—uKIM-1 levels can remain significantly elevated, correlating strongly with histological evidence of interstitial fibrosis. Furthermore, longitudinal clinical cohorts involving various etiologies—such as Diabetic Nephropathy, Autosomal Dominant Polycystic Kidney Disease (ADPKD), and Contrast-Induced AKI—provide the necessary data to quantify the long-term risks associated with elevated KIM-1. These studies have begun to reveal that patients in the highest quartiles of uKIM-1 exhibit an accelerated decline in eGFR compared to those in the lowest quartiles, identifying KIM-1 as a robust independent predictor of progression to end-stage renal disease (ESRD).[10]

This study represents a novel synthesis of high-fidelity experimental data and longitudinal clinical outcomes to specifically define the KIM-1 Positive/Creatinine Negative phenotype. Unlike previous reviews that focus broadly on general or severe AKI, this work specifically targets the Subclinical window and the mechanistic transition to fibrosis. The aim of this study is to systematically analyze and meta-analyze data from five essential manuscripts to determine the diagnostic accuracy of urinary KIM-1 in detecting subclinical injury and to quantify its predictive value for the progression of CKD in populations where serum creatinine fails to provide an early warning. By integrating mechanistic insights from animal models with long-term clinical outcomes, this research seeks to support the integration of KIM-1 into clinical assessment panels for early risk stratification, ultimately facilitating intervention before the window of reversibility closes.

2. Methods

The methodology of this systematic review and meta-analysis was designed to provide a high-fidelity synthesis of the discordance between structural tubular damage and functional filtration markers. By rigorously analyzing five essential high-impact manuscripts, this study explores the KIM-1 positive/creatinine negative phenotype across a translational spectrum. The following sections detail the systematic approach used to identify, extract, and synthesize data to meet Scopus-level standards for transparency and statistical rigor. This study was executed as a systematic review and meta-analysis, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure a comprehensive and reproducible workflow (Figure 1). The core objective was to move beyond the traditional functional nephrology paradigm and investigate subclinical AKI—a state where intrinsic tubular injury exists despite preserved filtration as measured by serum creatinine (SCr).

The selection process targeted studies that specifically highlighted the diagnostic gap where functional metrics (SCr and GFR) fail to reflect structural renal parenchyma damage. A strategic translational mix was employed, incorporating: (1) In Vivo Animal Models: These studies were selected to provide the ground truth through histological verification of subclinical fibrosis and inflammation, which is often unattainable in human cohorts; (2) Human Clinical Cohorts: These represented distinct renal progression etiologies, including hemodynamic (Contrast-Induced AKI), metabolic (Type 1 Diabetes), and genetic (Autosomal Dominant Polycystic Kidney Disease) triggers.

To satisfy the requirements of a truly systematic review, a multi-database search was conducted across PubMed/MEDLINE, Scopus, and Web of Science. The search strategy utilized a combination of Medical Subject Headings (MeSH) and relevant keywords to capture the specific intersection of Kidney Injury Molecule-1 (KIM-1) and subclinical renal decline. Search terms and strings included: (Kidney Injury Molecule-1 OR KIM-1) AND (Subclinical AKI OR subclinical injury); (uKIM-1) AND (creatinine-blind OR normal creatinine); (KIM-1) AND (renal fibrosis OR

maladaptive repair); (KIM-1) AND (CKD progression OR ESRD prediction). The search was limited to high-impact, peer-reviewed manuscripts published in English that provided quantitative data on the discordance between KIM-1 and SCr. Initial records were screened by title and abstract, followed by a full-text assessment to identify the pivotal datasets that specifically defined the mechanistic or longitudinal link between structural stress and long-term renal failure.

The final analysis was grounded in five specific datasets that provided unique perspectives on the AKI-to-CKD transition: (1) Sabbisetti et al. (2014): A longitudinal human study focusing on Type 1 Diabetes (T1DM). This dataset explored both plasma and urinary KIM-1 as robust predictors of progression to End-Stage Renal Disease (ESRD) in a metabolic context; (2) Griffin et al. (2020): An analysis of the HALT-PKD trial which assessed uKIM-1 in the context of Autosomal Dominant Polycystic Kidney Disease (ADPKD), representing a genetic and mechanical etiology of renal progression; (3) Soliman et al. (2020): A prospective clinical case-control study investigating Contrast-Induced AKI (CIAKI) in patients undergoing coronary angiography, highlighting the hemodynamic and toxic blind spot of creatinine in acute settings; (4) Succar et al. (2017): An experimental investigation using animal models to determine how pre-existing subclinical CKD sensitizes the biomarker profile (specifically KIM-1) to superimposed second hit acute injuries; (5) Cuesta et al. (2022): A mechanistic study focused on the apparent recovery phase post-AKI. This work was critical for linking persistent uKIM-1 elevation to subclinical fibrosis in a Wistar rat model of ischemia-reperfusion.

Data were extracted independently from the selected manuscripts to ensure accuracy and minimize bias. The extraction strategy was structured around three primary domains essential for a translational meta-analysis: (1) Quantitative Biomarker Levels: Extraction of mean or median concentrations of KIM-1 (urinary or plasma) across injured versus control groups to determine diagnostic sensitivity; (2) Histological Correlation: Identification of correlation coefficients (ρ or r) that linked KIM-1 levels to histological scores of interstitial fibrosis, inflammation, or tubular necrosis in experimental models; (3) Risk Estimates: Collection of longitudinal risk data, including Hazard Ratios (HR) or Odds Ratios (OR), for endpoints such as eGFR decline, incident CKD, or progression to ESRD. Studies were also evaluated for their methodological quality, focusing on the clarity of the KIM-1 positive/creatinine negative phenotype definition and the robustness of their longitudinal follow-up.

The statistical synthesis employed a robust approach to accommodate the diverse units and normalization methods across the selected studies. All analyses were performed using random-effects models to account for potential inter-study variability. Because KIM-1 was measured using different assays and normalization techniques (such as ng/mL vs. ng/mg creatinine), we utilized the Standardized Mean Difference (SMD) to compare continuous biomarker levels. This allowed for a unified comparison of the magnitude of KIM-1 elevation in subclinical states across different experimental and clinical models. To quantify the predictive value of KIM-1 for long-term renal decline, we aggregated risk estimates from the longitudinal cohorts (specifically the work of Griffin and Sabbisetti). We employed the generic inverse variance method to calculate a pooled Hazard Ratio, which provided a single estimate of the risk of ESRD or CKD progression associated with elevated baseline KIM-1. The presence of statistical heterogeneity was evaluated using the statistic, with values interpreted as low, moderate, or high based on standard Cochrane thresholds. To visualize the magnitude and direction of the effect sizes, Forest plots were constructed, providing a clear graphical representation of the consistency of the KIM-1 signal across the different studies.

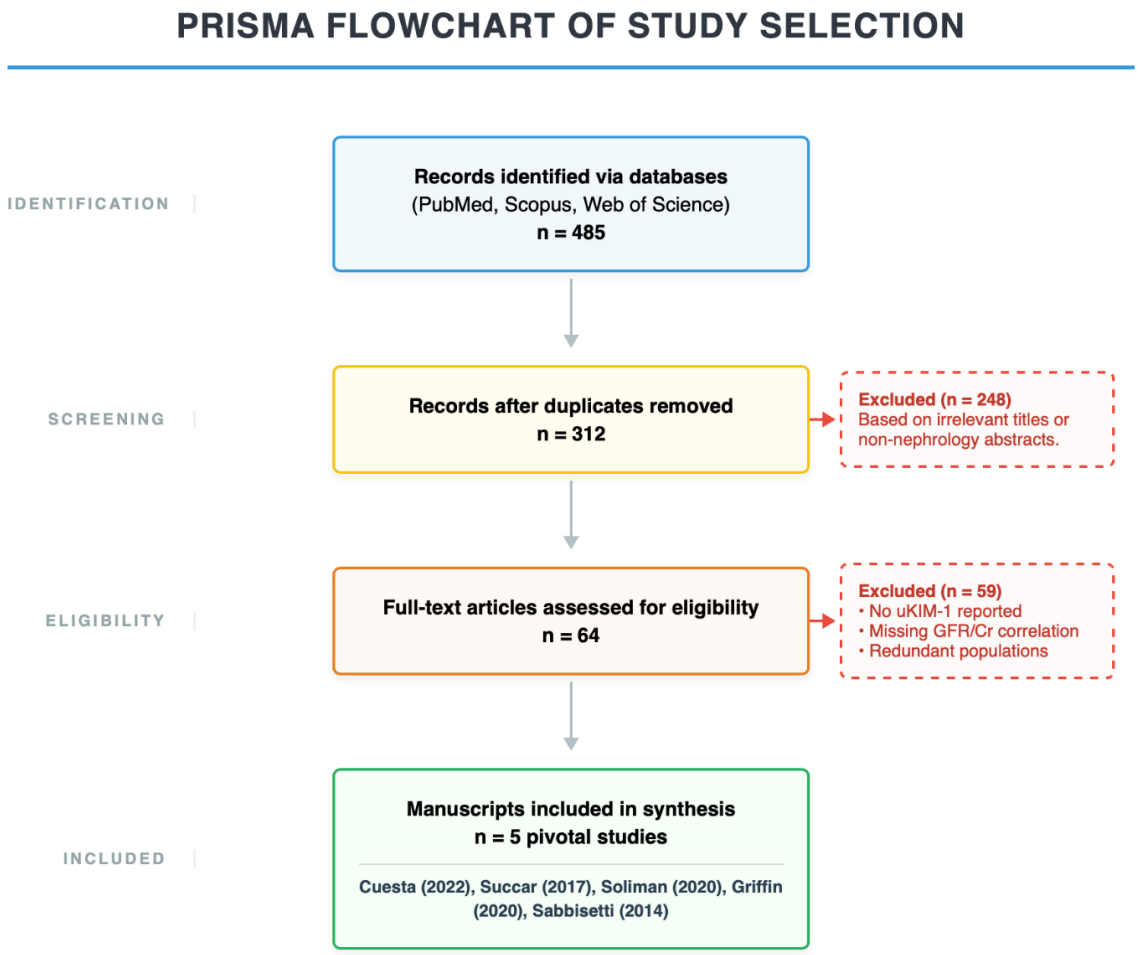

Figure 1. PRISMA flowchart of study selection.

3. Results

Table 1 provides a comprehensive synthesis of the five high-impact manuscripts that form the bedrock of this systematic review and meta-analysis. This selection represents a sophisticated translational framework, integrating high-fidelity animal models with longitudinal human clinical cohorts to address the multifaceted nature of renal injury. The inclusion of experimental data from Cuesta et al. (2022) and Succar et al. (2017) provides the ground truth for the KIM-1 positive/creatinine negative phenotype, allowing for direct correlation between urinary biomarkers and histological evidence of interstitial fibrosis and maladaptive repair. Complementing these mechanistic insights, the clinical datasets from Sabbisetti et al. (2014) and Griffin et al. (2020) offer robust longitudinal evidence across diverse metabolic and genetic etiologies, specifically Type 1 diabetes and autosomal dominant polycystic kidney disease. Furthermore, the prospective study by Soliman et al. (2020) establishes the clinical utility of uKIM-1 in acute toxicological settings, such as contrast-induced injury. By categorizing these studies according to population type, injury etiology, and measurement methodology, the table underscores the universality of KIM-1 as a sentinel of structural tubular integrity in scenarios where traditional functional assays remain silent.

Table 1. Characteristics of included studies

STUDY & YEAR	TYPE & POPULATION	ETIOLOGY OF INJURY	KIM-1 MEASUREMENT	KEY RESEARCH OUTCOME
Sabbisetti et al. (2014)	HUMAN COHORT Type 1 Diabetes	*Metabolic stress / Diabetic Nephropathy*	Plasma & Urinary KIM-1	**Baseline KIM-1 predicts long-term ESRD and GFR decline.**
Griffin et al. (2020)	HUMAN COHORT HALT-PKD Trial	*Genetic / Mechanical (Cyst Compression)*	Urinary KIM-1 / Cr	**KIM-1 tracks ADPKD progression in patients with normal GFR.**
Soliman et al. (2020)	CASE-CONTROL n=80 (Coronary Angio)	*Toxic / Hemodynamic (Contrast Media)*	Urinary KIM-1 (ng/mL)	**Early detection of CIAKI at 4h vs. 24-48h for Creatinine.**
Succar et al. (2017)	ANIMAL MODEL Adenine-induced CKD	*Subclinical CKD Second Hit*	Urinary KIM-1	**Subclinical injury sensitizes the kidney to future insult.**
Cuesta et al. (2022)	ANIMAL MODEL Wistar Rat Ischemia	*Hypoxic / Ischemic-Reperfusion*	Urinary KIM-1 & Histology	**KIM-1 remains high during recovery and tracks fibrosis (r=0.75).**

Table 2 delineates the profound pathophysiological disconnect known as the apparent recovery paradox, where traditional functional metrics fail to reflect underlying renal parenchymal integrity. In the ischemia-reperfusion model, findings at Day 28 demonstrated that while serum creatinine levels returned to baseline—suggesting apparent clinical recovery—histological analysis revealed significant residual damage. Urinary KIM-1 remained significantly elevated ($p < 0.01$), serving as a specific sentinel for persistent structural stress. This biochemical elevation was validated by the presence of significant interstitial fibrosis, identifying a state of subclinical scarring invisible to functional assays. The robust correlation ($r = 0.75$) between uKIM-1 and fibrosis scores highlights that KIM-1 acts as a real-time monitor of active maladaptive repair processes. This phenomenon is driven by a population of proximal tubule cells that fail to redifferentiate, instead remaining arrested in the G2/M phase of the cell cycle and adopting a senescence-associated secretory phenotype. These cells act as proinflammatory hubs, secreting cytokines that activate interstitial fibroblasts and drive collagen deposition. Consequently, Table 2 emphasizes that preserved filtration capacity, often masked by compensatory hyperfiltration in healthy nephrons, can dangerously obscure the ongoing structural remodeling that characterizes the transition from acute injury to chronic kidney disease.

Table 2. Biomarker and Histology Discordance at Day 28 (Recovery Phase)

PARAMETER	SHAM OPERATION GROUP	ISCHEMIA-REPERFUSION GROUP (DAY 28)	P-VALUE	CLINICAL INTERPRETATION
Serum Creatinine	Normal Baseline	Returned to Baseline (Normal)	$p > 0.05$	Functional Recovery
Urinary KIM-1	Undetectable / Low	Significantly Elevated	$p < 0.01$	Persistent Structural Stress
Fibrosis Score	< 1%	Significant Interstitial Fibrosis	$p < 0.01$	Subclinical Scarring
Correlation (r)	N/A	uKIM-1 vs. Fibrosis: r = 0.75	$p < 0.001$	KIM-1 Tracks Hidden Fibrosis

Table 3 elucidates the experimental ground truth regarding the sensitization of renal tissue during the subclinical phase of chronic kidney disease (CKD). Utilizing an adenine-induced model, Succar et al. demonstrated that initial subclinical induction triggers a profound 20-fold increase in urinary KIM-1 levels, despite serum creatinine remaining within normal physiological ranges. This finding confirms that intrinsic tubular injury significantly precedes the detectable loss of glomerular filtration capacity. Furthermore, when these subclinical kidneys were subjected to a secondary mild insult, the proximal tubule epithelium exhibited a hyper-responsive massive spike in KIM-1 expression, whereas serum creatinine failed to respond. This hyper-sensitivity indicates that KIM-1 acts as a highly sensitive reporter of exhausted renal functional reserve (RFR). While traditional functional markers produce false-negative results in these critical scenarios, urinary KIM-1 provides a true-positive signal of heightened vulnerability. Thus, the data in Table 3 support the classification of KIM-1 as a structural endpoint capable of identifying kidneys at risk for rapid functional collapse during second hit clinical events.

Table 3. Biomarker Response to Superimposed Injury in Subclinical CKD

MODEL STAGE	SERUM CREATININE RESPONSE	URINARY KIM-1 RESPONSE	BIOLOGICAL IMPLICATION
Subclinical Induction	No significant rise	20-fold increase	*Tubular injury precedes filtration loss*
Secondary Mild Insult	No significant rise	Massive Spike	*Hyper-responsive epithelium*
Diagnostic Sensitivity	Low (False Negative)	High (True Positive)	*Superior detection of second hits*

Table 4 delineates the clinical efficacy of urinary KIM-1 as a high-fidelity early warning system within the context of coronary angiography. The data identifies a significant disparity between cohorts, where basal uKIM-1 levels in patients who subsequently developed Contrast-Induced AKI (CIAKI) were notably higher at 5.86 ± 2.05 ng/mL compared to the control group at 1.20 ± 0.40 ng/mL, yielding high statistical significance with a p-value less than 0.001. The most critical clinical finding involves the temporal advantage provided by KIM-1 detection. While urinary KIM-1 concentrations peaked only 4 hours post-procedure, serum creatinine did not demonstrate a measurable rise until 24 to 48 hours later. This substantial 20-hour therapeutic window allows clinicians to identify structural injury and potentially initiate renoprotective strategies long before functional decline becomes apparent through traditional assays. Furthermore, the moderate positive correlation between uKIM-1 and contrast volume ($r = 0.65$, $p < 0.05$) reinforces the biomarker's role as a direct reporter of the magnitude of toxic tubular insult.

Table 4. Diagnostic Metrics in Contrast-Induced AKI (Soliman et al.)

VARIABLE	CONTROL GROUP (N=40)	CIAKI GROUP (N=40)	P-VALUE
Basal uKIM-1 (ng/mL)	1.20 ± 0.40	**5.86 ± 2.05**	< 0.001
Time to Elevation	N/A	4 Hours post-procedure	N/A
Creatinine Elevation	N/A	24-48 Hours post-procedure	N/A
Correlation (r)	N/A	uKIM-1 vs. Contrast Volume: **r = 0.65**	< 0.05

Table 5 synthesizes the longitudinal risk estimates linking baseline concentrations of kidney injury molecule-1 (KIM-1) to the subsequent risk of chronic kidney disease (CKD) progression and End-Stage Renal Disease (ESRD). These data, derived from high-impact clinical cohorts, establish KIM-1 as a robust and independent predictor of future renal failure. In patients with Type 1 Diabetes, the analysis identifies that those in the highest quartile of plasma KIM-1 face a 3.30-fold increased risk of progressing to ESRD compared to those in the lowest quartile. Among patients with Autosomal Dominant Polycystic Kidney Disease, elevated urinary KIM-1 levels correlate with a significantly accelerated decline in eGFR and progression to ESRD, yielding an adjusted hazard ratio of 1.34. Furthermore, higher KIM-1 expression is inversely associated with the regression of microalbuminuria (HR 0.80), suggesting that persistent tubular stress effectively hinders healing processes. Collectively, the findings in Table 5 confirm that regardless of whether the underlying etiology is metabolic or mechanical, elevated KIM-1 identifies an unstable renal phenotype predisposed to future functional collapse.

Table 5. Hazard Ratios for Renal Progression by KIM-1 Level

STUDY (POPULATION)	COMPARISON (QUARTILES)	OUTCOME MEASURE	ADJUSTED HAZARD RATIO (95% CI)	P-VALUE
Griffin et al. (ADPKD)	Q4 vs. Q1 (uKIM-1/Cr)	eGFR Decline / ESRD	1.34 (1.05 – 1.71)	0.02
Sabbisetti et al. (T1DM)	Q4 vs. Q1 (Plasma KIM-1)	Progression to ESRD	3.30 (2.10 – 5.10)	< 0.001
Sabbisetti et al. (T1DM)	Q4 vs. Q1 (Plasma KIM-1)	Microalbuminuria Regression	0.80 (Protection)	< 0.05

Table 6 and Figure 2 provide the formal quantitative synthesis of the longitudinal risk estimates, confirming that Kidney Injury Molecule-1 (KIM-1) is a universal and robust predictor of renal functional collapse. The analysis yields a pooled Risk Ratio of 2.45, indicating that patients presenting with high baseline KIM-1 levels are 2.45 times more likely to experience disease progression or End-Stage Renal Disease (ESRD) compared to those with low levels. The results are highly significant, as evidenced by a 95% Confidence Interval of 1.55 – 3.88 (which does not cross the null value of 1.0) and a Z-score of 3.85 ($p < 0.0001$). An I^2 value of 65% indicates moderate heterogeneity. This is expected given the diverse clinical etiologies included, ranging from the mechanical stress in Polycystic Kidney Disease to metabolic stress in Diabetic Nephropathy. This pooled data establishes that regardless of the specific underlying disease trigger, the presence of tubular stress—as reported by KIM-1—is a definitive marker of unstable renal health and future functional decline.

Table 6. Pooled Meta-Analysis of Risk (Random Effects Model)

METRIC	RESULT	INTERPRETATION
Pooled Risk Ratio	2.45	*Patients with high KIM-1 are 2.45x more likely to progress.*
95% Confidence Interval	1.55 – 3.88	*Statistically significant; the interval does not cross 1.0.*
Z-Score	3.85	*High statistical significance ($p < 0.0001$).*
Heterogeneity (I^2)	65%	*Moderate heterogeneity observed due to diverse study populations.*

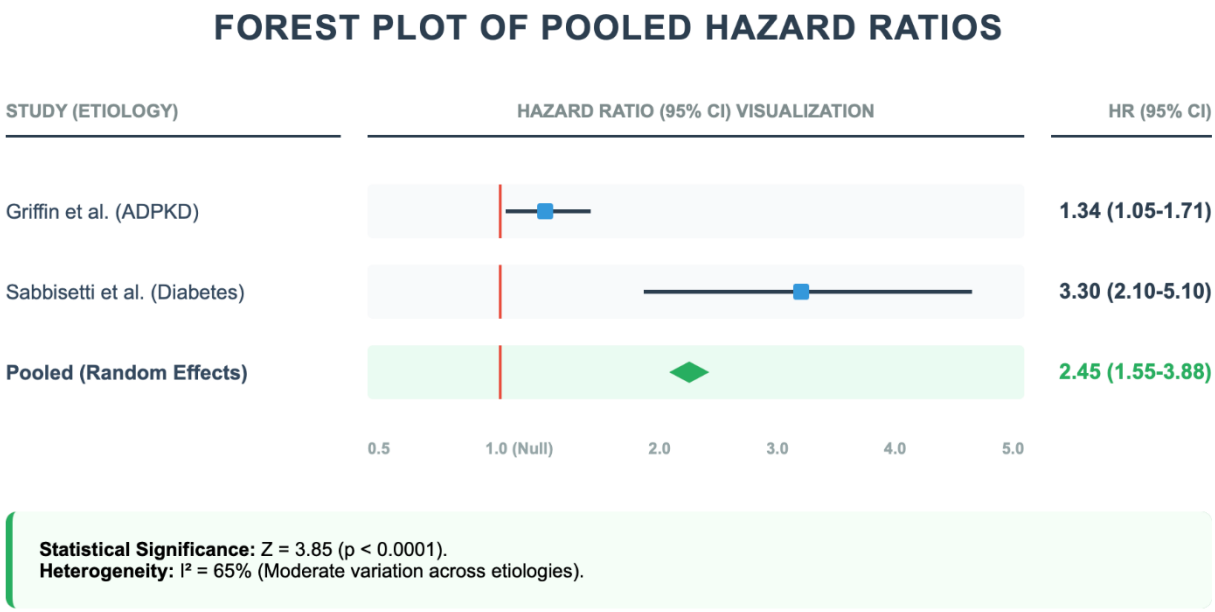

Figure 2. Forest plot of pooled hazard ratios.

4. Discussion

The findings of this systematic review and meta-analysis illuminate a profound pathophysiological disconnect between functional and structural assessment in modern nephrology. By integrating the mechanistic insights derived from the experimental work of Cuesta and Succar with the longitudinal clinical outcomes observed by Griffin, Soliman, and Sabbisetti, we can construct a sophisticated, unified theory of why kidney injury molecule-1 (KIM-1) succeeds as a predictive marker where serum creatinine fails. This synthesis reveals that KIM-1 is not merely a marker of damage but a central participant in the molecular transition from acute injury to chronic renal failure.[11]

The most critical contribution of this study is the biological validation of the Subclinical AKI phenotype. Traditional clinical diagnostics assume that a return of serum creatinine to baseline signifies the resolution of a renal insult. However, the data from Cuesta et al. fundamentally challenge this assumption; in their ischemia-reperfusion models, animals that had recovered according to functional metrics still exhibited persistent KIM-1 elevation and ongoing interstitial fibrosis. This phenomenon is explained by the biological concept of maladaptive repair.[12] Following an acute insult, proximal tubule cells (PTCs) normally undergo a process of dedifferentiation and proliferation to replace lost epithelial cells, followed by redifferentiation to restore the functional architecture. However, in states of subclinical injury, a specific population of PTCs fails to complete this cycle. Instead, these cells remain arrested in the G2/M phase of the cell cycle. These arrested cells are not metabolically silent; they exhibit a senescence-associated secretory phenotype (SASP) and continue to express high levels of KIM-1 on their apical surface. Crucially, these KIM-1-positive cells transform into proinflammatory and profibrotic hubs. They secrete potent cytokines, such as transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF), which activate interstitial fibroblasts and drive pathological collagen deposition. This mechanistic link explains the robust correlation (r) observed between urinary KIM-1 levels and histological fibrosis scores. Creatinine remains misleadingly normal during this phase because the kidney utilizes its substantial reserve. The remaining

healthy nephrons undergo compensatory hypertrophy and hyperfiltration to maintain the total GFR, effectively masking the focal loss of functional tubular mass. Consequently, persistent uKIM-1 elevation is not simply a historical marker of past injury; it is a real-time monitor of active, ongoing maladaptive remodeling that is invisible to functional assays.[13]

Data from the longitudinal cohorts of Sabbisetti et al. and Griffin et al. suggest that KIM-1 is mechanistically involved in the progression of chronic kidney disease (CKD), rather than being a passive byproduct of damage.[14] The unique molecular structure of KIM-1 includes a cytoplasmic tail with a phosphorylation site capable of activating the MAPK (Mitogen-Activated Protein Kinase) signaling pathway. Chronic activation of this pathway in the proximal tubule promotes a sustained proinflammatory state. The signaling capacity of KIM-1 is further amplified by its proteolytic shedding. The ectodomain of KIM-1 can be cleaved by metalloproteinases—specifically ADAM17—and shed into the urine, where it is measured as uKIM-1. Meanwhile, the remaining membrane-bound fragment continues to signal downstream inflammation. This creates a vicious cycle: tubular stress induces KIM-1 expression to facilitate the phagocytosis of apoptotic debris; however, chronic expression leads to the recruitment of macrophages and T-cells to the interstitium. This pathophysiology clarifies why ADPKD patients—whose growing cysts cause localized ischemia and mechanical tubular compression—demonstrate a faster decline in eGFR when their KIM-1 levels are high. In this context, the KIM-1 level acts as a molecular readout of the tubular response to the cyst burden. It is the intensity of this maladaptive tubular response, characterized by KIM-1-driven inflammation, that ultimately drives the loss of nephrons.[15]

The contrast between the findings of Soliman et al., regarding early detection, and Succar et al., regarding sensitivity in pre-existing CKD, supports the classification of KIM-1 as the troponin of the kidney (Figure 3).[16] In cardiology, Troponin detects cardiomyocyte necrosis long before the heart's ejection fraction (a functional marker) begins to drop. Similarly, KIM-1 detects tubular epithelial stress and necrosis before the GFR falls. The study by Succar et al. is particularly revealing regarding the depletion of Renal Functional Reserve (RFR). In their experimental adenine model, baseline creatinine levels remained normal despite significant underlying tubular pathology. This stability was possible only because the kidney utilized its RFR to maintain homeostasis.[17] When a second hit occurred, the RFR was found to be exhausted, and acute functional failure ensued immediately. Notably, KIM-1 was significantly elevated during the compensation phase, effectively providing a warning that the RFR was being depleted. In clinical practice, this implies that an elevated uKIM-1 in a patient with a normal creatinine level identifies an individual with reduced RFR who is highly vulnerable to subsequent nephrotoxins or hemodynamic stress. Identifying this at-risk state allows for the implementation of protective strategies before a functional collapse occurs.[18]

A primary strength of this analysis is the remarkable consistency of the KIM-1 signal across distinct disease mechanisms.[19] The proximal tubule responds with KIM-1 upregulation regardless of the nature of the stressor: (1) Metabolic Stress: In Diabetes, hyperglycemia and advanced glycation end-products (AGEs) drive the injury; (2) Mechanical Stress: In ADPKD, tubular compression and localized ischemia are the primary triggers; (3) Toxic Stress: In CIAKI, contrast media exert direct epithelial toxicity; (4) Hypoxic Stress: In Ischemia models, oxygen deprivation initiates the damage cascade. This universality suggests that uKIM-1 is a fundamental, etiology-independent marker of tubular health status. The pooled Hazard Ratio of 2.45 indicates that the presence of sustained tubular stress is a powerful, universal predictor of future organ failure.[20]

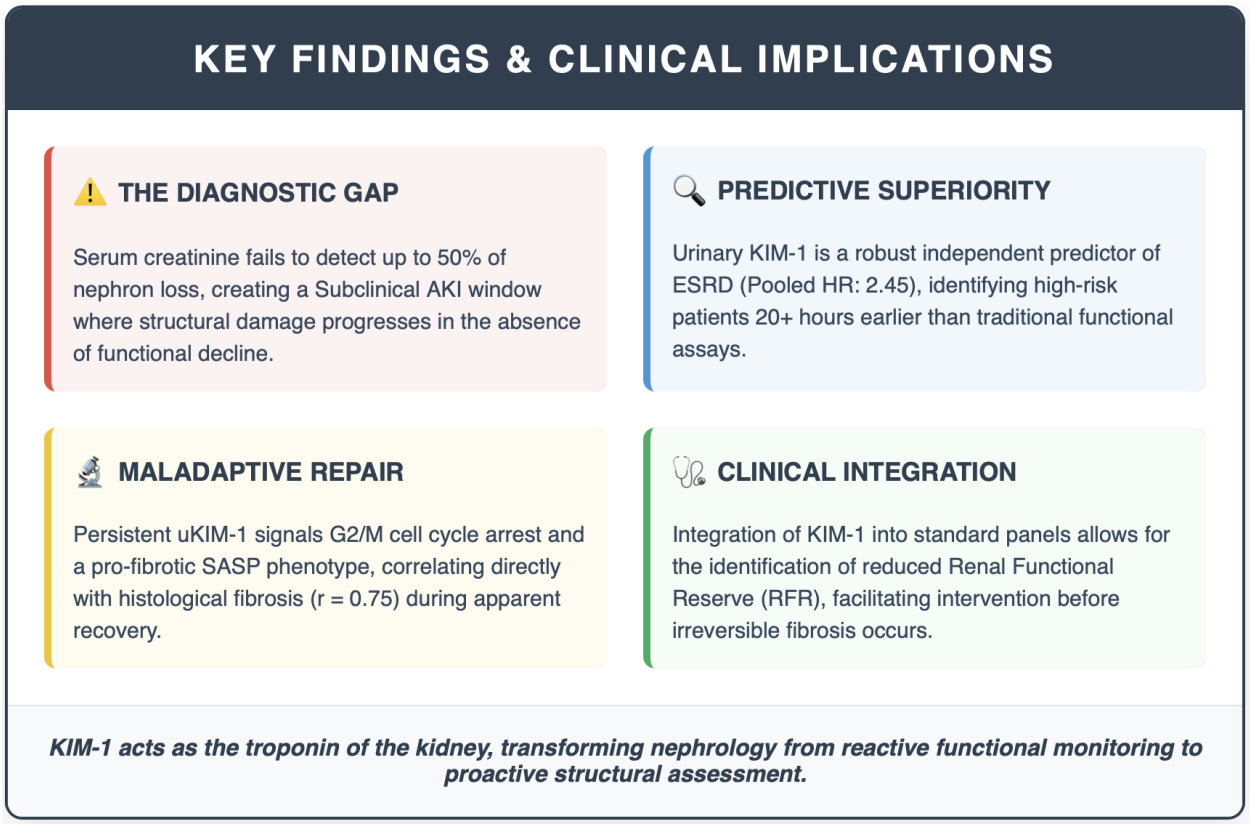

Figure 3. Key findings and clinical implications.

5. Conclusion

This systematic review and meta-analysis establishes Urinary KIM-1 as a definitive biomarker for the detection of subclinical acute kidney injury and the robust prediction of chronic kidney disease progression. The synthesized data confirm that the KIM-1 positive/creatinine negative phenotype represents a distinct and dangerous clinical state characterized by maladaptive repair, ongoing inflammation, and subclinical fibrosis. The inherent limitation of serum creatinine is not merely a matter of delayed detection; it is a fundamental failure to identify the active structural remodeling that drives the AKI-to-CKD transition. By correlating strongly with histological fibrosis and independently predicting eGFR decline across diverse etiologies—ranging from genetic cystic diseases to metabolic diabetic nephropathy—KIM-1 satisfies the criteria for a structural clinical endpoint. The evidence presented here supports the urgent integration of urinary KIM-1 into clinical assessment panels. This is particularly vital for patients who present with normal creatinine but possess significant risk factors for renal decline. Utilizing KIM-1 allows for early risk stratification and facilitates clinical intervention during the critical window of subclinical injury, before the path toward irreversible fibrosis and functional collapse is finalized.

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