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Research Paper

Cystatin C as an Early Biomarker for Acute Kidney Injury: A Systematic Review

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Abstract

Acute kidney injury (AKI) remains a major clinical problem associated with increased morbidity, mortality, prolonged hospitalization, and rising healthcare costs. Serum creatinine, the conventional biomarker used for AKI diagnosis, has several well-recognized limitations, including delayed elevation after renal injury and susceptibility to non-renal influences such as age, sex, muscle mass, and hydration status. In recent years, cystatin C has gained attention as a potentially more sensitive biomarker because of its relatively constant production rate and earlier response to changes in glomerular filtration. This systematic review aimed to evaluate the diagnostic performance and clinical applicability of cystatin C for the early detection of AKI across diverse clinical settings. A comprehensive literature search was conducted in PubMed, Scopus, and Google Scholar for studies published up to December 2025. Eligible studies included human subjects at risk of AKI, assessment of serum or urinary cystatin C, and the use of recognized AKI diagnostic criteria. Study selection and data extraction were performed using predefined eligibility criteria, and findings were synthesized narratively because of substantial methodological heterogeneity among studies. The included studies consistently indicated that cystatin C may detect AKI earlier than serum creatinine in several clinical contexts, particularly in intensive care units, cardiac surgery, and contrast-induced nephropathy. Across studies, cystatin C generally demonstrated moderate-to-high diagnostic sensitivity and specificity; however, considerable variability was observed in cutoff values, sampling time, patient characteristics, and reference standards. Several studies also reported high negative predictive value, suggesting potential utility in excluding AKI in selected populations. Nevertheless, the diagnostic performance of cystatin C appeared to be influenced by multiple confounding factors, including systemic inflammation, corticosteroid therapy, thyroid dysfunction, and fluid balance status. Overall, current evidence suggests that cystatin C is a promising biomarker for the early detection of AKI and may provide diagnostic advantages over serum creatinine in specific clinical settings. However, existing evidence predominantly supports diagnostic accuracy rather than direct improvement in patient-centered outcomes. Further large-scale prospective studies are needed to establish standardized cutoff values, clarify optimal clinical application, and determine whether cystatin C-guided strategies improve clinical outcomes.

Keywords: *Acute Kidney Injury, Cystatin C, Biomarker, Early Diagnosis, Diagnostic Accuracy, Serum Creatinine, Contrast-Induced Nephropathy*

INTRODUCTION

Acute kidney injury (AKI) is a clinical syndrome characterized by a rapid decline in renal function, leading to the accumulation of nitrogenous waste products and disturbances in fluid, electrolyte, and acid–base homeostasis. AKI affects approximately 10–15% of hospitalized patients and up to 50–60% of critically ill individuals, with mortality rates reaching 20–50% among patients requiring renal replacement therapy (Alsabri et al., 2026; Bao et al., 2011). Beyond its immediate clinical consequences, AKI is strongly associated with prolonged hospitalization, increased healthcare costs, progression to chronic kidney disease, cardiovascular complications, and long-term mortality, thereby representing a substantial global healthcare burden (Yong et al., 2017; Abadeer et al., 2021).

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For several decades, serum creatinine has remained the conventional biomarker for AKI diagnosis and monitoring. Nevertheless, serum creatinine has important limitations, particularly in the early phase of kidney injury. Serum creatinine concentrations often increase only 48–72 hours after a significant decline in glomerular filtration rate (GFR) because of delayed accumulation and distribution kinetics. Furthermore, creatinine levels are influenced by multiple non-renal factors, including age, sex, muscle mass, nutritional status, and hydration status. In critically ill patients, aggressive fluid resuscitation may further dilute serum creatinine concentrations, potentially masking early renal dysfunction and delaying diagnosis (Briguori et al., 2010; El-Sadek et al., 2019). Consequently, reliance on serum creatinine alone may limit timely recognition of AKI and reduce opportunities for early therapeutic intervention (Wenhua et al., 2013).

In recent years, cystatin C has emerged as a promising alternative biomarker for the early detection of AKI. Cystatin C is a low-molecular-weight (13-kDa) cysteine protease inhibitor produced at a relatively constant rate by all nucleated cells. Unlike serum creatinine, its production is less dependent on muscle mass, age, or sex. Cystatin C is freely filtered through the glomerulus and subsequently reabsorbed and metabolized by proximal tubular cells without substantial tubular secretion, making circulating concentrations closely associated with GFR (Budano et al., 2020; Lin et al., 2021). In addition, its shorter biological half-life may allow earlier detection of changes in renal function compared with serum creatinine, particularly in selected high-risk clinical settings (He et al., 2020).

Several previous systematic reviews and meta-analyses have investigated the diagnostic value of cystatin C for AKI detection. However, the available evidence remains heterogeneous and, in several aspects, inconclusive. Earlier reviews frequently focused on specific patient populations, such as critically ill patients, cardiac surgery cohorts, or contrast-induced nephropathy, thereby limiting broader clinical applicability. In addition, substantial variability has been reported regarding AKI definitions, timing of biomarker measurement, cutoff thresholds, specimen type (serum versus urinary cystatin C), and reference standards used across studies. Although previous reviews commonly emphasized pooled diagnostic accuracy estimates, many provided limited discussion regarding methodological heterogeneity, potential confounding factors, and the practical implications of cystatin C use in routine clinical settings.

Moreover, recent studies published after earlier reviews have expanded the available evidence regarding the comparative performance of serum and urinary cystatin C, the influence of clinical heterogeneity, and the potential value of combining cystatin C with other biomarkers for AKI detection. Despite these developments, an updated synthesis integrating these findings across diverse clinical contexts remains limited. Therefore, a more comprehensive and context-specific evaluation of the current evidence is warranted.

The present systematic review aims to evaluate the diagnostic performance and potential clinical utility of cystatin C for the early detection of AKI across different clinical settings and patient populations. Specifically, this review addresses the following questions: (1) How does the diagnostic performance of cystatin C compare with serum creatinine for early AKI detection? (2) How do serum and urinary cystatin C perform across different patient populations and clinical settings? (3) What clinical and methodological factors influence the diagnostic performance of cystatin C, including timing of measurement and study heterogeneity? and (4) What evidence supports the potential utility of combining cystatin C with other biomarkers for AKI detection? By addressing these questions, this review aims to provide a structured and evidence-based interpretation of current findings while identifying important areas for future prospective investigation.

LITERATURE REVIEW

Several systematic reviews and meta-analyses have previously evaluated the role of cystatin C in the early detection of acute kidney injury (AKI). Nevertheless, important methodological and clinical limitations remain within the existing body of evidence. Many earlier reviews focused primarily on specific patient groups or clinical settings, such as cardiac surgery, contrast-induced nephropathy, intensive care units, or pediatric populations, which may limit the generalizability of their findings across broader and more heterogeneous clinical contexts (Alsabri et al., 2026; Bao et al., 2011; Pirgakis et al., 2014). In addition, substantial variation has been reported regarding AKI diagnostic criteria, timing of biomarker assessment, specimen type (serum versus urinary cystatin C), cutoff thresholds, and reference standards, making direct comparison between studies challenging.

Previous studies have also demonstrated inconsistent findings concerning the diagnostic performance of cystatin C. This variability may be partly explained by multiple clinical and methodological factors capable of influencing cystatin C concentrations independently of renal function. Reported confounding factors include systemic inflammation, corticosteroid therapy, thyroid dysfunction, fluid balance alterations, and pre-existing kidney disease, all of which may contribute to heterogeneity in sensitivity and specificity estimates across studies (Yong et al., 2017; Dunstone, 2017). Moreover, diagnostic performance appears to vary according to patient characteristics and clinical setting, with some studies reporting stronger predictive performance in relatively homogeneous populations, such as cardiac surgery cohorts, compared with critically ill patients with complex systemic conditions.

Comparative evidence between cystatin C and other emerging AKI biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and interleukin-18 (IL-18), remains limited and heterogeneous (Pei et al., 2020; Ahmad et al., 2021). These biomarkers reflect different pathophysiological mechanisms of kidney injury. While cystatin C primarily reflects changes in glomerular filtration rate, biomarkers such as NGAL and KIM-1 are more strongly associated with tubular injury. Consequently, the relative diagnostic value of cystatin C may differ according to the underlying mechanism, severity, and timing of kidney injury.

Although several studies have demonstrated that cystatin C may identify AKI earlier than serum creatinine, the clinical implications of earlier biomarker detection remain insufficiently established. Most currently available studies emphasize diagnostic accuracy measures rather than clinically meaningful outcomes such as mortality reduction, decreased need for renal replacement therapy, shorter hospitalization, or improved therapeutic decision-making (Ho et al., 2015; van den Eynde et al., 2022). Therefore, improved diagnostic sensitivity should not automatically be interpreted as evidence of superior clinical effectiveness.

In addition to diagnostic considerations, issues related to implementation and healthcare utilization remain underexplored. Compared with serum creatinine testing, cystatin C measurement may involve higher laboratory costs and limited availability in certain healthcare settings. However, relatively few studies have comprehensively evaluated its cost-effectiveness, feasibility for routine clinical implementation, or potential impact on healthcare resource utilization and patient management strategies (Li et al., 2015).

Given these limitations, a more updated and context-specific synthesis of the available evidence remains necessary. The present systematic review aims to evaluate the diagnostic performance and potential clinical utility of cystatin C for early AKI detection across diverse clinical settings and patient populations. Specifically, this review examines: (1) the diagnostic performance of serum and urinary cystatin C; (2) variations in diagnostic findings across different clinical contexts; (3) factors contributing to heterogeneity in biomarker performance; and (4) current evidence regarding the combined use of cystatin C with other biomarkers for AKI detection. Rather

than focusing solely on pooled diagnostic estimates, this review provides a structured narrative synthesis intended to support a more clinically contextualized interpretation of cystatin C use in contemporary practice.

RESEARCH METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to enhance methodological transparency, reproducibility, and reporting quality. The review process consisted of study identification, screening, eligibility assessment, data extraction, and narrative synthesis of findings.

A quantitative meta-analysis was not performed because of substantial heterogeneity across the included studies, particularly regarding patient populations, clinical settings, AKI definitions, cystatin C specimen types, timing of biomarker assessment, and diagnostic cutoff thresholds. Therefore, a narrative synthesis approach was considered more appropriate to provide a context-specific interpretation of the available evidence while preserving methodological consistency across heterogeneous studies. The overall study selection process is summarized in Figure 1 using the PRISMA 2020 flow diagram.

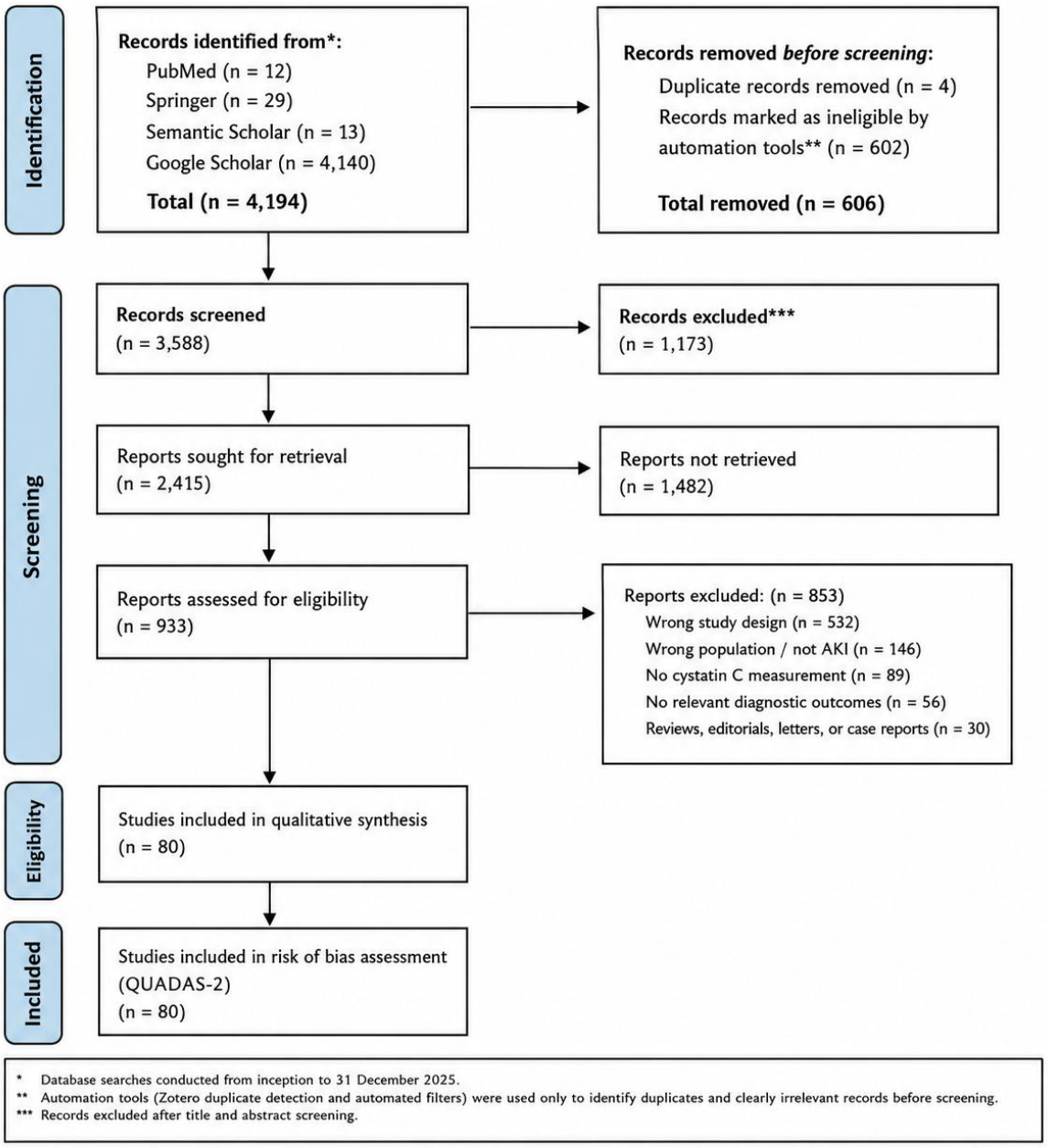

Figure 1. PRISMA Flow Diagram

Eligibility Criteria

Studies were selected according to predefined inclusion and exclusion criteria. Eligible studies included original human diagnostic studies evaluating serum, plasma, or urinary cystatin C for the early detection, diagnosis, or prediction of acute kidney injury (AKI). Included studies were required to report at least one diagnostic performance parameter, including sensitivity, specificity, area under the receiver operating characteristic curve (AUC), predictive values, or diagnostic odds ratio.

Studies were also required to apply recognized AKI diagnostic criteria, including Kidney-Disease: Improving Global Outcomes (KDIGO), Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE), or Acute Kidney Injury Network (AKIN) definitions. Eligible study designs included prospective cohort studies, retrospective cohort studies, case-control studies, and cross-sectional diagnostic accuracy studies. Randomized controlled trials were included only when relevant diagnostic performance data for cystatin C were available. Systematic reviews and meta-analyses

were excluded from the primary evidence synthesis to avoid duplication of evidence; however, their reference lists were screened manually to identify potentially relevant studies.
Studies were excluded if they:

1. focused exclusively on chronic kidney disease without AKI assessment;
2. involved animal or in vitro experiments;
3. did not report sufficient diagnostic outcome data;
4. were conference abstracts without accessible full-text articles; or
5. consisted of editorials, narrative reviews, letters, expert opinions, case reports, or small case series with insufficient methodological detail.

Search Strategy

A comprehensive literature search was conducted using multiple electronic databases, including PubMed, Springer, Semantic Scholar, and Google Scholar. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to acute kidney injury, cystatin C, diagnostic biomarkers, and early detection. Boolean operators ("AND" and "OR") were applied to optimize both search sensitivity and specificity.

The search included studies published in English from database inception until December 2025. Additional manual searches were performed by screening the reference lists of eligible studies and relevant review articles to identify potentially missed publications. For Google Scholar, only the first 200 results sorted by relevance were screened because unrestricted searches may produce excessive retrieval volume and limited reproducibility. Duplicate records identified across databases were removed before title and abstract screening. A detailed summary of the search strategy and database retrieval process is presented in Table 1.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Critically ill patients" OR "ICU patients" OR "High-risk hospitalized adults and children" OR "Post-operative cardiothoracic patients") AND ("Cystatin C measurement" OR "Serum cystatin C" OR "Plasma cystatin C" OR "Urinary cystatin C") AND ("Serum creatinine" OR "NGAL (neutrophil gelatinase-associated lipocalin)" OR "Novel AKI biomarker" OR "RIFLE / KDIGO / AKIN criteria") AND ("Early detection of acute kidney injury" OR "Diagnostic accuracy (sensitivity, specificity, AUC)" OR "Earlier timing of AKI diagnosis" OR "Prediction of AKI before creatinine rise")*	12
Semantic Scholar	*("Critically ill patients" OR "ICU patients" OR "High-risk hospitalized adults and children" OR "Post-operative cardiothoracic patients") AND ("Cystatin C measurement" OR "Serum cystatin C" OR "Plasma cystatin C" OR "Urinary cystatin C") AND ("Serum creatinine" OR "NGAL (neutrophil gelatinase-associated lipocalin)" OR "Novel AKI biomarker" OR "RIFLE / KDIGO / AKIN criteria") AND ("Early detection of acute kidney injury" OR "Diagnostic accuracy (sensitivity, specificity, AUC)" OR "Earlier timing of AKI diagnosis" OR "Prediction of AKI before creatinine rise")*	13
Springer	*("Critically ill patients" OR "ICU patients" OR "High-risk hospitalized adults and children" OR "Post-operative cardiothoracic patients") AND ("Cystatin C measurement" OR "Serum cystatin C" OR "Plasma cystatin C" OR "Urinary cystatin C") AND ("Serum creatinine" OR "NGAL (neutrophil gelatinase-associated lipocalin)" OR "Novel AKI biomarker" OR "RIFLE / KDIGO / AKIN criteria") AND ("Early detection of acute kidney injury" OR*	29

Database	Keywords	Hits
	"Diagnostic accuracy (sensitivity, specificity, AUC)" OR "Earlier timing of AKI diagnosis" OR "Prediction of AKI before creatinine rise")	
Google Scholar	*("Critically ill patients" OR "ICU patients" OR "High-risk hospitalized adults and children" OR "Post-operative cardiothoracic patients") AND ("Cystatin C measurement" OR "Serum cystatin C" OR "Plasma cystatin C" OR "Urinary cystatin C") AND ("Serum creatinine" OR "NGAL (neutrophil gelatinase-associated lipocalin)" OR "Novel AKI biomarker" OR "RIFLE / KDIGO / AKIN criteria") AND ("Early detection of acute kidney injury" OR "Diagnostic accuracy (sensitivity, specificity, AUC)" OR "Earlier timing of AKI diagnosis" OR "Prediction of AKI before creatinine rise")*	4,140

Study Selection Process

Study selection was performed in multiple stages according to PRISMA 2020 recommendations. Initially, all retrieved records were screened based on titles and abstracts to identify potentially eligible studies. Duplicate records and clearly irrelevant articles were removed during this stage. To improve screening efficiency, duplicate detection and preliminary record management were assisted using reference management software. Automated exclusion was limited to duplicate identification and clearly irrelevant records based on predefined screening criteria, followed by manual reviewer verification to minimize selection bias.

Subsequently, full-text articles were independently assessed according to the predefined inclusion and exclusion criteria. Any disagreements during the screening and eligibility assessment process were resolved through discussion and consensus among the reviewers. A total of 4,194 records were initially identified across all databases. After duplicate removal, title and abstract screening, and full-text eligibility assessment, 80 studies were included in the final narrative synthesis. The detailed study selection workflow is presented in Figure 1.

Data Extraction

Data extraction was conducted systematically using a standardized extraction framework developed before the review process. Extracted variables included study characteristics (author, publication year, country, study design, sample size, and patient population), clinical setting, AKI diagnostic criteria, and cystatin C measurement characteristics. Additional variables included specimen type (serum, plasma, or urinary cystatin C), assay methods, timing of biomarker measurement, and diagnostic cutoff values. Diagnostic performance outcomes extracted from eligible studies included sensitivity, specificity, area under the curve (AUC), predictive values, and diagnostic odds ratios, where available.

Comparative findings involving serum creatinine and other biomarkers, including neutrophil gelatinase-associated lipocalin (NGAL), were also recorded. Factors potentially contributing to heterogeneity, such as age, baseline renal function, inflammatory status, corticosteroid exposure, thyroid dysfunction, and clinical setting, were documented to support contextual interpretation of the findings.

Risk of Bias Assessment

The methodological quality of the included diagnostic studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. This instrument evaluates four principal domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for potential risk of bias, while the first three domains were additionally evaluated for concerns regarding applicability.

Each study was categorized as having low, high, or unclear risk of bias according to QUADAS-2 guidance. The results of the risk-of-bias assessment were summarized in tabular and graphical formats to improve methodological transparency and reporting clarity.

Overall, most included studies demonstrated low-to-moderate risk of bias. However, several studies presented methodological concerns related to patient selection procedures, variability in diagnostic cutoff thresholds, and inconsistencies in timing between cystatin C measurement and AKI diagnosis.

FINDINGS AND DISCUSSION

Study Characteristics

A total of 80 studies were included in the final narrative synthesis following the PRISMA-based selection process presented in Figure 1. The included studies represented diverse patient populations and clinical settings, including critically ill patients in intensive care units (ICUs), cardiac surgery cohorts, patients undergoing coronary interventions, emergency care populations, pediatric patients, and neonatal populations. Sample sizes varied considerably across studies, ranging from small single-center cohorts with fewer than 50 participants to large multicenter studies involving more than 15,000 patients, reflecting substantial heterogeneity in study design and population characteristics.

Most studies applied standardized AKI definitions based on KDIGO, RIFLE, or AKIN criteria, although variability remained regarding diagnostic thresholds, timing of assessment, and reference standards. Serum cystatin C was the most frequently evaluated biomarker, whereas urinary cystatin C was examined less consistently and was predominantly assessed in postoperative or tubular injury–related settings. Considerable variability was also observed in assay methods, cutoff values, and timing of biomarker measurement, all of which may have contributed to differences in reported diagnostic performance across studies.

Overall Diagnostic Performance

Across the included studies, cystatin C generally demonstrated moderate-to-high diagnostic performance for early AKI detection. Previous meta-analyses reported pooled sensitivity values ranging from 78% to 86% and specificity values between 79% and 82%, with area under the curve (AUC) estimates generally ranging from 0.85 to 0.89 (Bao et al., 2011; Yong et al., 2017). These pooled estimates are discussed descriptively in the present review and were not recalculated as part of a new quantitative meta-analysis.

Individual studies demonstrated variable diagnostic performance across different clinical settings. Reported diagnostic odds ratios ranged from approximately 21 to 27.7, suggesting that cystatin C may provide clinically meaningful discrimination between patients with and without AKI in selected populations. Nevertheless, substantial heterogeneity was identified across studies because of differences in patient populations, timing of biomarker assessment, AKI definitions, and diagnostic thresholds. Therefore, interpretation of diagnostic performance should remain context-specific rather than generalized uniformly across all clinical scenarios.

Timing of AKI Detection

One of the most consistent findings across the included studies was the earlier elevation of cystatin C compared with serum creatinine following renal injury. Several studies reported that cystatin C may identify renal dysfunction approximately 12–48 hours earlier than conventional creatinine-based assessment (Abadeer et al., 2021; Briguori et al., 2010; El-Sadek et al., 2019). In cardiac surgery populations, cystatin C elevations were reported as early as 8 hours postoperatively, whereas serum creatinine frequently peaked approximately 24–48 hours later

(Abadeer et al., 2021). Similarly, studies conducted in ICU settings suggested that cystatin C may predict AKI development before creatinine-based diagnostic criteria were fulfilled (Royakkers et al., 2010; Sawhney et al., 2018). Comparable temporal findings were also observed in neonatal populations (El-Sadek et al., 2019).

Although these findings suggest a temporal diagnostic advantage, earlier biomarker elevation should not automatically be interpreted as evidence of improved clinical outcomes. Most studies primarily evaluated diagnostic timing and diagnostic accuracy rather than outcome-based endpoints such as mortality reduction, avoidance of renal replacement therapy, or shortened hospitalization duration.

Setting-Specific Diagnostic Performance

The diagnostic performance of cystatin C varied substantially across clinical settings. Several studies reported relatively high diagnostic accuracy in contrast-induced nephropathy, with AUC values ranging from approximately 0.92 to 0.93 (Lin et al., 2021; He et al., 2020). Strong diagnostic performance was also reported in selected pediatric populations, with AUC values ranging from approximately 0.85 to 0.88 (Yang et al., 2021).

In contrast, findings from cardiac surgery and ICU populations were more heterogeneous. In cardiac surgery cohorts, reported AUC values ranged from 0.69 to 0.87 depending on timing of measurement, patient characteristics, and methodological differences between studies (Peng et al., 2024). Similarly, ICU studies generally demonstrated moderate diagnostic performance, with AUC values ranging from approximately 0.72 to 0.81 (Shi et al., 2024).

This variability likely reflects differences in AKI pathophysiology, severity of illness, inflammatory status, fluid balance, and comorbid conditions across patient populations. Consequently, the diagnostic performance of cystatin C should be interpreted as highly context-dependent.

Comparison with Serum Creatinine

Many included studies reported earlier or higher diagnostic performance for cystatin C compared with serum creatinine in AKI detection. For example, in patients with acute myocardial infarction, cystatin C demonstrated higher reported AUC values than serum creatinine (Pei et al., 2020). Similarly, studies in critically ill neonates demonstrated substantially lower diagnostic performance for serum creatinine compared with cystatin C (El-Sadek et al., 2019).

Several ICU-based studies additionally suggested improved sensitivity and earlier AKI detection using cystatin C relative to conventional creatinine-based assessment (Ahmad et al., 2021). However, the magnitude of diagnostic superiority varied considerably across studies and was influenced by patient characteristics, timing of biomarker measurement, and the reference standards used for AKI diagnosis.

These findings support the potential utility of cystatin C as an earlier indicator of renal dysfunction. Nevertheless, the current evidence does not support universal replacement of serum creatinine in all clinical settings, particularly given the substantial heterogeneity of findings and the influence of non-renal confounding factors.

Comparison with Other Biomarkers

Comparisons between cystatin C and other emerging biomarkers demonstrated variable findings across clinical settings. In contrast-induced nephropathy, several studies reported higher diagnostic performance for cystatin C compared with neutrophil gelatinase-associated lipocalin (NGAL) (He et al., 2020). Conversely, in pediatric cardiac surgery populations, NGAL frequently demonstrated superior early diagnostic performance, likely reflecting its stronger association with

tubular injury processes (van den Eynde et al., 2022).

In heterogeneous ICU populations, cystatin C generally demonstrated diagnostic performance comparable to other biomarkers, including NGAL and kidney injury molecule-1 (KIM-1) (Shi et al., 2024; Klein et al., 2018). These findings indicate that no single biomarker consistently outperforms all others across all clinical contexts. Instead, biomarker performance appears to depend on the predominant pathophysiological mechanism and timing of kidney injury assessment.

Serum versus Urinary Cystatin C

Most included studies suggested that serum cystatin C demonstrated more consistent overall diagnostic performance than urinary cystatin C. Earlier studies and meta-analyses reported relatively stable AUC estimates for serum cystatin C, whereas urinary cystatin C demonstrated greater variability across clinical settings (Bao et al., 2011; Yong et al., 2017).

However, urinary cystatin C demonstrated strong diagnostic performance in selected postoperative populations associated predominantly with tubular injury. For example, studies in vascular surgery populations reported excellent early postoperative diagnostic discrimination using urinary cystatin C measurements (Pirgakis et al., 2014). These findings suggest that the clinical utility of urinary cystatin C may depend heavily on the timing of assessment and the underlying mechanism of kidney injury.

Combination with Other Biomarkers

Several studies suggested that combining cystatin C with additional biomarkers or clinical parameters may improve diagnostic performance compared with single-marker approaches. Combined assessment using cystatin C and NGAL demonstrated improved early AKI detection in patients with liver cirrhosis (Pei, 2019). Similarly, combining cystatin C with renal resistive index measurements demonstrated high discriminatory performance in critically ill pregnant patients (Tian et al., 2022).

Other studies reported that integrating cystatin C with established clinical criteria, including RIFLE classification systems, improved diagnostic discrimination compared with isolated biomarker assessment (Magro & Vattimo, 2013). Nevertheless, substantial methodological variability across studies limited direct comparison and prevented definitive conclusions regarding optimal multimarker strategies.

Performance-Modifying Factors and Clinical Interpretation

Several factors were identified as potential modifiers of cystatin C performance. Clinical setting appeared to be a major determinant, with more consistent diagnostic performance observed in relatively homogeneous populations compared with critically ill ICU cohorts. Pre-existing chronic kidney disease also appeared to influence biomarker accuracy and may reduce discriminatory performance in patients with impaired baseline renal function (Lin et al., 2021; He et al., 2020).

In addition, inflammatory conditions, corticosteroid exposure, thyroid dysfunction, fluid balance abnormalities, and demographic characteristics may independently influence cystatin C concentrations and contribute to heterogeneity across studies (Jou-Valencia et al., 2024; Munir et al., 2025). Timing of biomarker assessment also appeared critical, with several studies reporting optimal diagnostic performance when cystatin C was measured within approximately 6–24 hours following renal insult (Yong et al., 2017).

Taken together, the available evidence suggests that cystatin C may provide clinically useful early diagnostic information for AKI detection in selected populations. However, substantial

heterogeneity across studies indicates that cystatin C interpretation should remain integrated with broader clinical assessment rather than used as a standalone determinant of kidney injury.

Discussion

The findings of this systematic review suggest that cystatin C may provide clinically useful diagnostic information for the early detection of acute kidney injury across several clinical settings. Previous studies and meta-analyses have consistently reported moderate-to-high diagnostic performance for cystatin C, with pooled AUC estimates generally exceeding 0.80 (Bao et al., 2011). However, these findings should be interpreted cautiously because substantial heterogeneity was observed across patient populations, study methodologies, assay techniques, and timing of biomarker measurement (Pei et al., 2020).

One of the most consistently reported observations was the earlier elevation of cystatin C relative to serum creatinine following renal injury. Physiologically, cystatin C has a shorter half-life and more rapid equilibration following changes in glomerular filtration rate, potentially allowing earlier recognition of impaired renal function. Several studies reported that cystatin C elevations may occur approximately 12–48 hours earlier than creatinine-based AKI diagnosis (Abadeer et al., 2021; Briguori et al., 2010; El-Sadek et al., 2019). This temporal advantage was particularly evident in postoperative cardiac surgery populations and contrast-induced nephropathy settings, where the timing of renal insult is relatively well defined.

Nevertheless, earlier biomarker detection should not automatically be interpreted as evidence of improved clinical outcomes. Most included studies primarily evaluated diagnostic accuracy and timing rather than clinically meaningful endpoints such as mortality reduction, dialysis avoidance, shortened hospitalization, or improved therapeutic response. Therefore, the current evidence supports the diagnostic utility of cystatin C but remains insufficient to establish direct clinical effectiveness.

The diagnostic performance of cystatin C also varied substantially according to clinical setting. Higher diagnostic accuracy was frequently reported in contrast-induced nephropathy populations, possibly because of the relatively predictable timing of renal injury and lower degree of confounding factors (Lin et al., 2021; He et al., 2020). In contrast, studies conducted in ICU and cardiac surgery populations demonstrated more heterogeneous findings, likely reflecting the multifactorial nature of AKI in critically ill patients.

Several non-renal factors may additionally influence cystatin C concentrations independently of kidney function, including thyroid dysfunction, corticosteroid therapy, inflammatory states, and baseline chronic kidney disease (Jou-Valencia et al., 2024; Munir et al., 2025). These factors should be carefully considered when interpreting cystatin C values in complex clinical settings.

Comparisons with other emerging biomarkers further demonstrated that biomarker performance depends strongly on the underlying mechanism of kidney injury. In contrast-induced nephropathy, cystatin C frequently demonstrated higher diagnostic performance than NGAL (He et al., 2020; Ho et al., 2015). Conversely, NGAL often demonstrated stronger predictive performance in cardiac surgery populations, likely because NGAL primarily reflects tubular injury, whereas cystatin C more closely reflects glomerular filtration changes. These findings suggest that cystatin C may provide complementary rather than universally superior diagnostic information.

The distinction between serum and urinary cystatin C also appears clinically important. Most included studies demonstrated more consistent diagnostic performance for serum cystatin C, whereas urinary cystatin C produced more variable findings across clinical settings. Nevertheless, urinary cystatin C demonstrated promising diagnostic performance in selected postoperative populations when measurements were obtained during periods of peak tubular injury (Pirgakis et

al., 2014).

Several studies additionally suggested that combining cystatin C with other biomarkers or clinical parameters may improve overall diagnostic discrimination. Multimarker approaches integrating NGAL, renal resistive index, or established clinical scoring systems demonstrated encouraging findings in selected populations (Pei, 2019). However, methodological variability across studies currently limits definitive conclusions regarding optimal biomarker integration strategies.

Despite these limitations, cystatin C may offer several practical advantages over serum creatinine. Its relative independence from muscle mass and reduced susceptibility to fluid dilution may improve reliability in critically ill populations receiving aggressive fluid resuscitation. Furthermore, several studies reported high negative predictive values, suggesting potential usefulness in excluding AKI among low-to-moderate risk populations.

However, important implementation challenges remain, including higher laboratory costs, variability in assay methods, lack of standardized cutoff values, and limited accessibility in certain healthcare settings. Moreover, the absence of large prospective outcome-based studies continues to limit understanding regarding whether cystatin C-guided clinical management improves patient prognosis or healthcare utilization.

Future studies should prioritize standardization of measurement protocols, harmonization of clinically applicable cutoff thresholds, and prospective evaluation of outcome-based clinical utility. Additional investigation into multimarker approaches and integration with clinical decision-support systems may further clarify the role of cystatin C in personalized AKI detection strategies.

CONCLUSIONS

This systematic review suggests that cystatin C may serve as a clinically useful biomarker for the early detection of acute kidney injury across several patient populations and clinical settings. Available evidence indicates moderate-to-high diagnostic performance, particularly in settings where early renal dysfunction can be identified before conventional creatinine-based changes become apparent.

One of the principal findings across the included studies was the earlier elevation of cystatin C compared with serum creatinine following renal injury. Several studies reported that cystatin C may identify AKI approximately 12–48 hours earlier than conventional creatinine-based assessment, particularly in contrast-induced nephropathy and postoperative settings. Nevertheless, although earlier detection may facilitate earlier recognition of renal dysfunction, current evidence remains insufficient to confirm whether this temporal advantage consistently improves patient-centered outcomes or therapeutic effectiveness.

The diagnostic performance of cystatin C appeared to be strongly influenced by clinical context. More consistent diagnostic accuracy was observed in relatively homogeneous populations, such as contrast-induced nephropathy and selected pediatric cohorts, whereas greater variability was reported in critically ill ICU and cardiac surgery populations. These differences likely reflect variations in AKI pathophysiology, inflammatory status, fluid balance, baseline kidney function, and other confounding clinical factors.

Although many studies reported improved diagnostic performance compared with serum creatinine, the available evidence does not support universal replacement of creatinine-based assessment. Instead, cystatin C may be most appropriately used as a complementary biomarker integrated with broader clinical evaluation and, potentially, multimarker diagnostic approaches.

Several practical limitations continue to affect the implementation of cystatin C in routine clinical practice, including variability in assay methods, lack of universally standardized cutoff values, higher laboratory costs, and limited accessibility in some healthcare settings. Furthermore,

much of the currently available evidence focuses primarily on diagnostic accuracy rather than prospective outcome-based evaluation.

Overall, the present review highlights the context-dependent diagnostic performance of cystatin C, the importance of timing in biomarker assessment, and the potential value of integrating glomerular filtration biomarkers with other indicators of tubular injury. Future large-scale prospective studies are needed to standardize measurement approaches, validate clinically applicable thresholds, and evaluate whether cystatin C-guided strategies improve patient-centered outcomes and healthcare utilization.

LIMITATIONS AND FUTURE RESEARCH

Several limitations should be considered when interpreting the findings of this systematic review. First, substantial heterogeneity was identified across the included studies regarding patient populations, clinical settings, study designs, assay methodologies, timing of biomarker assessment, and AKI diagnostic criteria. Variability in the implementation of KDIGO, RIFLE, and AKIN definitions, as well as differences in cystatin C cutoff thresholds, may have influenced reported diagnostic performance and limited direct comparability between studies.

Second, most included studies primarily focused on diagnostic accuracy outcomes rather than patient-centered clinical endpoints. Although cystatin C frequently demonstrated earlier detection of AKI compared with serum creatinine, current evidence remains insufficient to determine whether this earlier identification consistently improves clinically meaningful outcomes such as mortality reduction, decreased need for renal replacement therapy, shortened hospitalization, improved renal recovery, or long-term prognosis.

Third, several non-renal factors that may influence cystatin C concentrations were not consistently controlled across studies. These factors include systemic inflammation, thyroid dysfunction, corticosteroid exposure, fluid balance abnormalities, and pre-existing chronic kidney disease. Such confounding variables may contribute to heterogeneity in diagnostic performance and complicate the interpretation of cystatin C values, particularly in critically ill populations.

Fourth, many included studies were conducted in selected high-risk populations, including cardiac surgery cohorts, ICU patients, and contrast-induced nephropathy settings. Consequently, the generalizability of the current findings to broader patient populations and low-resource healthcare environments remains uncertain. In addition, publication bias cannot be excluded because studies reporting positive diagnostic findings may have been more likely to be published.

Another important limitation of the present review is the use of narrative synthesis rather than formal quantitative meta-analysis. Because substantial methodological heterogeneity existed across the included studies, pooled statistical analysis was considered inappropriate. Therefore, the conclusions of this review should be interpreted as a descriptive synthesis of the available evidence rather than newly generated pooled estimates.

Future research should prioritize large-scale prospective multicenter studies evaluating the role of cystatin C across diverse patient populations and healthcare settings. Standardization of assay methodologies, timing of biomarker measurement, and clinically applicable cutoff values will be essential to improve consistency and facilitate broader implementation in clinical practice.

In addition, future investigations should extend beyond diagnostic accuracy assessment and evaluate the impact of cystatin C-guided clinical management on clinically relevant outcomes, including mortality, progression of kidney disease, requirement for renal replacement therapy, duration of hospitalization, healthcare costs, and long-term renal recovery.

Further research should also explore multimarker diagnostic strategies integrating cystatin C with biomarkers of tubular injury, inflammatory markers, and clinical decision-support systems. Such approaches may improve individualized risk stratification and optimize early AKI detection

in heterogeneous clinical populations.

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