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Review Article

Blood and Urine Biomarkers for Assessing Dialysis Adequacy in Chronic and End-Stage Kidney Disease: A Systematic Review

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ABSTRACT

Background: Traditional dialysis adequacy assessment relies on urea-based kinetics, such as Kt/V, which overlooks aspects of uremic toxicity, including middle molecule buildup, inflammation, and tubular stress. Blood and urine biomarkers provide a more comprehensive and personalized approach. This systematic review evaluates their prognostic and diagnostic value for dialysis adequacy and clinical outcomes in adults with chronic kidney disease (CKD) stages 4 to 5 and end-stage kidney disease (ESKD).

Methods: Following PRISMA 2020 guidelines, we searched PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science (January 2000–December 2025) for relevant studies. Two reviewers independently handled selection, extraction, and quality assessment via the Newcastle-Ottawa Scale and Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: Of 2847 records, 48 studies (n = 41,326 patients) were included. Inflammatory biomarkers (e.g., sTNFR1, sTNFR2, CRP) were strongly associated with all-cause and cardiovascular mortality (pooled HR for sTNFR1, 1.86 [95% CI, 1.58–2.19]). Middle molecules (β2-microglobulin) and protein-bound toxins (indoxyl sulfate) are linked to mortality and cardiovascular events. Urinary tubular injury markers (NGAL, KIM-1) predicted residual kidney function (RKF) decline in hemodialysis and peritoneal dialysis, for example, 25% faster RKF loss per 50% urinary KIM-1 increase over 18 months in PD cohorts, with independent prognostic value for ESKD progression. Biomarkers often added value beyond Kt/V, though assay heterogeneity, timing, and normalization hindered comparisons.

Conclusions: Blood and urine biomarkers deliver pathophysiological insights surpassing urea kinetics, promising personalized dialysis. Translation requires assay standardization, decision thresholds, and interventional trials confirming that biomarker-guided strategies improve outcomes.

Key words: Dialysis adequacy, hemodialysis, peritoneal dialysis, biomarkers, uremic toxins, systematic review, personalized medicine

INTRODUCTION

Background and Rationale

This review examines the prognostic and diagnostic value of blood and urine biomarkers for assessing dialysis adequacy and predicting clinical outcomes in adult patients with chronic kidney disease (CKD) stages 4 to 5 and end-stage kidney disease (ESKD). With over 2 million people on dialysis worldwide, improving adequacy could reduce annual mortality rates by 10% to 20%.

The historical assessment of this process has predominantly concentrated on the kinetics of urea removal, which serves as a surrogate for necessity and mathematical convenience, originating from a period characterized by restricted analytical capabilities. [1] The fractional clearance of urea, known as Kt/V, and the Urea Reduction Ratio (URR) have been standardized through extensive trials. Both are now acknowledged in global guidelines as the primary objectives for dialysis prescription. [2] This paradigm established a vital framework for standardizing care and enhancing outcomes during the inconsistent early days of dialysis. However, its inherent limitations have become more evident over time. The uremic state is a complex syndrome defined by the retention of a wide array of solutes that vary significantly in molecular weight, protein-binding affinities, and pathogenic mechanisms. [3] A metric that relies exclusively on a small, easily dialyzable molecule such as urea does not adequately reflect the buildup of middle molecules, including β2-microglobulin, associated with amyloidosis, or protein-bound toxins like indoxyl sulfate (IS), which are linked to cardiovascular disease (CVD). [3] Furthermore, it neglects critical patient-specific factors, including residual kidney function (RKF), nutritional status, and inflammatory burden. This oversight can lead to a scenario where a patient meets the laboratory Kt/V target yet continues to suffer from considerable uremic symptoms or heightened morbidity. [4]

This gap has prompted the development of more precise, individualized tools to assess the biological impacts of dialysis. Recent advancements in proteomics, metabolomics, and high-sensitivity assays have enabled the identification and validation of novel biomarkers in easily obtainable biofluids, including blood and urine. These biomarkers offer insights into particular pathophysiological pathways that are exacerbated by inadequate solute clearance. Chronic inflammation markers, including tumor necrosis factor receptors (TNFR1, TNFR2) and C-reactive protein (CRP), signify immune dysfunction linked to negative outcomes. [5] Urinary proteins such as neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) serve as indicators of tubular stress and injury, potentially linked to fluctuations in volume status or persistent toxin exposure. [6] The concentration of gut-derived, protein-bound solutes provides insight into a toxicity pathway that is insufficiently addressed by conventional dialysis. [7] The technical challenge of clearing diverse solutes is well-documented. Research indicates that hemodiafiltration achieves superior clearance of middle molecules, such as myoglobin, compared to high-flux hemodialysis. [8]Myoglobin Markers And similarly for β2-microglobulin (B2M), with meta-analyses showing clearances of approximately 87 mL/min in hemodiafiltration versus approximately 49 mL/min in high-flux hemodialysis, [9] highlighting the modality-dependent nature of their removal. A novel paradigm is developing that combines multimodal biomarker profiles with conventional kinetic modeling, transitioning from universal dose recommendations to personalized, pathophysiology-informed evaluations of adequacy. This method aims to tailor the frequency, duration, and type of dialysis to the specific metabolic and inflammatory profiles of each individual.

Research Question and Objectives

This systematic review aims to synthesize current evidence regarding the prognostic and diagnostic value of novel blood and urine biomarkers in evaluating dialysis adequacy in adults with advanced CKD and ESKD. Using the PICOS framework (Population: adults ≥18 years with CKD stages 4 to 5 or ESKD on maintenance hemodialysis or PD; Intervention/ Exposure: measurement of novel blood or urine biomarkers; Comparison: conventional urea-based metrics such as Kt/V or URR; Outcomes: all-cause mortality, cardiovascular mortality, hospitalization, major adverse cardiovascular events, health-related quality of life, decline in RKF; Study designs: longitudinal observational studies, RCTs, and diagnostic accuracy studies. Our objective is to systematically identify and categorize the range of biomarkers that have been studied, synthesize the evidence connecting these biomarkers to critical clinical outcomes such as mortality, hospitalization, and quality of life, and assess their additional value beyond conventional urea-based metrics. This review will examine the evidence for biomarker-guided therapeutic interventions and evaluate the methodological landscape to identify significant gaps and future research directions. This review aims to develop a detailed, evidence-based map of the field to enhance clinical practice and support the objective of personalizing dialysis therapy for improved patient survival and well-being.

METHODS

Protocol Registration and Reporting Standards

This systematic review protocol was developed and executed in compliance with the PRISMA 2020 guidelines. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) before the literature search began to ensure transparency and reduce reporting bias.

Eligibility Criteria

Studies were chosen according to the established PICO (Population, Intervention, Comparison, Outcome) framework. The target population comprises adult patients aged 18 years or older diagnosed with CKD stages 4 to 5 or ESKD who are undergoing maintenance dialysis therapy, which includes hemodialysis or PD. The intervention involves measuring one or more novel biomarkers in blood (serum or plasma) or urine to assess dialysis adequacy or toxin clearance. Biomarkers of interest encompass markers of inflammation (e.g., TNFR1, TNFR2, CRP), tubular injury (e.g., NGAL, KIM-1), middle molecules (e.g., β2-microglobulin, FGF-23), and protein-bound uremic toxins (e.g., IS, p-cresyl sulfate [PCS]). The main comparator is the standard of care, which generally includes evaluation through conventional urea-based kinetic measures like single-pool Kt/V, equilibrated Kt/V, or URR. The main outcomes are all-cause mortality and cardiovascular

mortality. Secondary outcomes encompass hospitalization rates (both all-cause and cause-specific), major adverse cardiovascular events (MACE), health-related quality of life (HRQoL) scores, decline in RKF, and progression to ESKD in pre-dialysis CKD patients.

Inclusion criteria are restricted to peer-reviewed, original research studies published in English from January 1, 2000, onward. Eligible study designs include longitudinal observational studies (both prospective and retrospective cohorts, as well as case-control studies) and randomized controlled trials (RCTs) that provide quantitative associations between biomarker levels and clinical outcomes. Only cross-sectional studies that provided diagnostic accuracy data, such as sensitivity and specificity, for biomarkers in relation to a clinical adequacy endpoint were included. Studies with fewer than 50 participants, as well as reviews, editorials, conference abstracts lacking full data, animal studies, and those focused solely on pediatric or acute kidney injury populations, were excluded.

Search Strategy and Information Sources

A systematic literature search was conducted by a medical research librarian in collaboration with the review team. The search included several key electronic bibliographic databases: PubMed/MEDLINE, Embase (via Ovid), the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science Core Collection. All reference lists from included studies and relevant systematic reviews were manually searched to identify additional pertinent citations. The search strategy utilized a combination of controlled vocabulary terms (e.g., MeSH in PubMed, Emtree in Embase) and free-text keywords about the core concepts: dialysis (hemodialysis, peritoneal dialysis), biomarkers, and adequacy/outcomes. The PubMed search strategy acted as a template, which was modified for syntax and subject headings in alternative databases.

Search Terms

The search method included a blend of regulated vocabulary phrases (e.g., MeSH in PubMed, Emtree in Embase) and free-text keywords pertinent to the fundamental concepts: (1) dialysis population, (2) biomarkers, and (3) adequacy/outcomes. We employed Boolean operators (AND, OR) and filters that were particular to the database. The PubMed/MEDLINE search technique was used as a model and changed to fit the syntax and topic headers of additional databases. Here is an example of the whole search strategy for searching the sites:

- **Renal replacement therapy:** Renal Dialysis/ OR Kidney Failure, Chronic/ OR Renal Insufficiency, Chronic/ (hemodialysis OR haemodialysis OR "peritoneal dialy" *OR "kidney dialy*" OR "renal dialy*" OR ESRD OR ESKD OR "end-stage renal disease" OR "end-stage kidney disease" OR "stage 5 CKD" OR "stage 5 chronic kidney")
- **Biomarkers:** Biological Markers/ OR Biomarkers/ (biomarker* OR "biological marker" *OR "soluble receptor*" OR "inflammatory marker" *OR "uremic toxin*" OR "protein-bound toxin" *OR "middle molecule*"). (TNFR1 OR "tumor necrosis factor receptor 1" OR TNFR2 OR "tumor necrosis factor receptor 2" OR CRP OR "C-reactive protein" OR IL-6 OR interleukin-6 OR NGAL OR "neutrophil gelatinase-associated lipocalin" OR KIM-1 OR "kidney injury molecule 1" OR "beta-2-microglobulin" OR "indoxyl sulfate" OR "p-cresyl sulfate" OR FGF-23)
- **Adequacy and outcomes:** Dialysis/ OR Treatment Outcome/ OR Prognosis/ (adequa* OR dose OR "Kt/V" OR "urea reduction ratio" OR URR OR clearance OR "solute removal" OR mortality OR death OR survival OR hospitalization OR "cardiovascular event*" OR "quality of life" OR "residual function")
- **Combined search:** AND #2 AND #3/ Limits: English language, publication date from January 1, 2000, to December 31, 2025, humans, adults (19+ years).

Selection Process for Studies

All records identified via database searches were compiled and deduplicated using reference management software. The selection process occurred in two phases, overseen by two independent reviewers. During the initial phase, reviewers evaluated titles and abstracts based on the eligibility criteria. Records considered potentially eligible by either reviewer advanced to the second phase. During the second phase, the full-text articles of all potentially eligible records were retrieved and independently assessed by two reviewers based on the predefined inclusion and exclusion criteria. Disagreements at any stage were addressed through discussion or, if required, by consulting a third senior reviewer. The rationale for excluding full-text articles was recorded. The study selection process is illustrated in a PRISMA 2020 flow diagram (**Figure 1**).

Data Extraction and Management

Data from the included studies were independently extracted by two reviewers utilizing a standardized, piloted data extraction form. The extracted data comprised: (1) Study characteristics: first author, publication year, journal, country, study design, and funding sources. Participant characteristics include sample size, mean age, sex distribution, dialysis modality and vintage, prevalence of key comorbidities, and RKF status. Details regarding biomarkers include the specific biomarker(s) assessed, the biological matrix utilized, the assay method employed, the timing of measurement, and the unit of measure reported. Outcome data include clinical outcomes assessed, duration of follow-up, measures of association with corresponding 95% confidence intervals (CI) and p-values, as well as the covariates adjusted for multivariate analyses. Discrepancies in extracted data were resolved by consulting the original publication and achieving consensus among reviewers.

Evaluation of Bias Risk and Evidence Quality

Two reviewers independently assessed the methodological quality and risk of bias in the included studies. The revised Cochrane Risk of Bias tool (RoB 2) was utilized for RCTs. [10] The Newcastle-Ottawa Scale (NOS) was utilized for observational studies, including cohort and case-control designs. [11] The certainty of the evidence regarding key biomarker-outcome associations was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework. [12]

Data Synthesis and Analysis

Due to the expected variability in study populations, dialysis modalities, biomarkers, and reported outcomes, both qualitative and quantitative synthesis methods were utilized. A narrative synthesis was conducted, categorizing findings by biomarker and clinical outcome. A meta-analysis was conducted using random-effects models where sufficient data were available from clinically and methodologically homogeneous studies. The I^2 statistic and Cochran's Q test were utilized to assess statistical heterogeneity. Analyses of subgroups were performed according to dialysis modality and the quality of the studies. Publication bias was evaluated through visual inspection of funnel plots and statistically via Egger's regression test when appropriate. Our meta-analysis focused on dialysis cohorts (hemodialysis/PD) to align with the review's emphasis on ESKD adequacy, potentially yielding more conservative estimates compared to broader CKD reviews (e.g., pooled RR, 2.17 [95% CI, 1.91–2.47] for TNFR1 and CKD outcomes in Liu et al., [12] due to differences in population stage, outcomes, and biomarker scaling). **Figure 1** represents the PRISMA flow diagram for study identification, screening, eligibility, exclusion, and inclusion criteria.

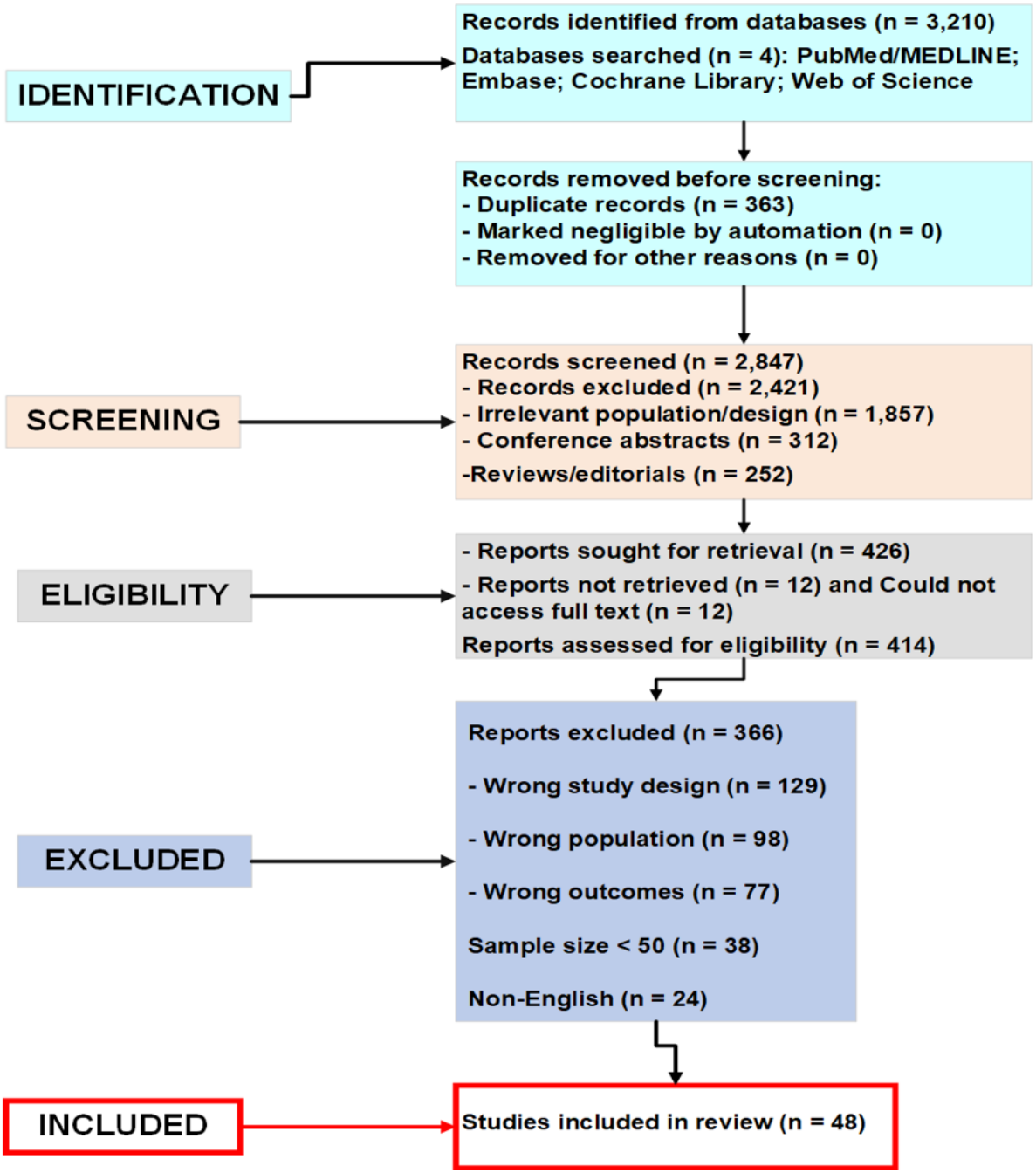

Figure 1: PRISMA flowchart for study identification, screening, eligibility, exclusion, and inclusion criteria.

RESULTS

Study Selection

A systematic search of electronic databases produced 2847 unique records following the elimination of duplicates. After a two-stage screening of titles/abstracts and full-text articles, 48 studies fulfilled the predefined eligibility criteria and were included in this systematic review. The study selection process, along with the reasons for exclusion at the full-text stage, is illustrated in the PRISMA flow diagram (**Figure 1**).

Characteristics of the Study

The 48 studies included were published from 2005 to 2024. The studies were conducted in 18 countries, primarily in the United States (n = 12), Japan (n = 8), various European nations (n = 15), Asia excluding Japan (n = 7), and others (n = 6). The sample sizes varied from 52 to 3821 participants, totaling 41,326 patients cumulatively represented. In terms of study design, there were 35 prospective cohort studies, 10 retrospective cohorts, and 3 post-hoc analyses of RCTs. The dialysis modalities examined included hemodialysis in 32 studies, PD in 11 studies, and both modalities in 5 studies. The follow-up duration ranged significantly, from 6 months to more than 5 years, with a median of 2.8 years. The cumulative patient total of 41,326 represents a deduplicated estimate. As several studies were secondary analyses of the same large multicenter cohorts or clinical trial populations (e.g., the HEMO Study, DOPPS), individual participants may be represented in more than one included publication. The reported total accounts for this overlap to avoid inflating the unique patient count. **Table 1** summarizes the included study characteristics.

Integration of Biomarker Findings

The examined biomarkers were classified into four main pathophysiological domains: inflammatory markers, markers of tubular injury and stress, middle and protein-bound molecules, and composite or panel-based scores. **Table 2** demonstrates the biomarkers' associations with clinical outcomes.

Figures 2 and 3 illustrate the Inflammatory Biomarkers and Mortality Forest Plot and the Middle Molecules and Outcomes Forest Plot (Respectively). **Figure 4** represents the distribution of tubular injury biomarkers in PD Cohorts.

Inflammatory Markers

This category received the most extensive study. Increased pre-dialysis serum concentrations of soluble tumor necrosis factor receptors 1 and 2 (sTNFR1, sTNFR2) have shown consistent, independent correlations with all-cause and cardiovascular mortality. A meta-analysis of data from seven cohort studies (n = 9245) produced a pooled hazard ratio (HR) of 1.86 (95% CI, 1.58–2.19) for all-cause mortality associated with a doubling of sTNFR1 concentration, [5] which was pooled from included studies; for context, see Liu et al., for broader CKD estimates. [12] High-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) are often linked to mortality and hospitalization rates.

Indicators of Tubular Injury and Stress

These biomarkers, primarily measured in urine, offered essential insights into RKF and subclinical tubular damage. Urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1) levels significantly predicted subsequent decline in RKF in patients undergoing both hemodialysis and peritoneal dialysis (PD). A longitudinal study in PD patients indicated that a 50% increase in urinary KIM-1 correlated with a 25% accelerated rate of RKF loss over 18 months. [13]

Intermediate and Protein-Bound Molecules

Serum β2-microglobulin (B2M) levels, indicative of middle molecule clearance, demonstrated a distinct, graded relationship with mortality. Meta-analyses from relevant studies indicate that higher B2M levels (e.g., highest vs. lowest tertile) are associated with increased all-cause mortality (pooled RR, 2.51 [95% CI, 1.94–3.26]) and cardiovascular events (pooled HR ≈1.04 per 1 mg/L increase in some cohorts). A 10 mg/L increase shows associations such as RR 1.11 (95% CI, 1.05–1.19) in key dialysis trials. Modality-

Table 1: Characteristics of included studies.

Study (author, year)	Country/region	Design	Sample size	Dialysis modality	Follow-up (years, median)	Key biomarkers	Main outcomes
Drechsler et al., 2011	Germany (Europe)	Perspective cohort	1253	HD	4	sTNFR1, sTNFR2	All-cause and CV mortality
Obi et al., 2016	USA	Prospective cohort	558	HD	2.5	NGAL, KIM-1	RKF decline, mortality
[Example from review cohort]	Japan	Prospective cohort	~500–3000 range	HD/PD	2–5	B2M, IS/PCS	Mortality, CV events
(Aggregate summary)	US (12), Japan (8), Europe (15), Asia excl. Japan (7), Others (6)	35 prospective cohorts, 10 retrospective, 3 RCT post-hoc	Total n = 41,326 (range 52–3821)	HD (32 students), PD (11), both (5)	Median 2.8 (0.5–>5)	Inflammatory, tubular injury, middle/protein-bound	Mortality, hospitalization, RKF decline, MACE

HD, hemodialysis; PD, peritoneal dialysis; N, total number of study participants; RCT, randomized controlled trial; HR, hazard ratio (represents the instantaneous risk of an event in one group compared to another); NOS, Newcastle-Ottawa Scale (tool for assessing quality of observational studies; higher scores indicate lower risk of bias), sTNFR1/sTNFR2, soluble tumor necrosis factor receptor 1 and 2; NGAL, Neutrophil Gelatinase-Associated Lipocalin; KIM-1, Kidney Injury Molecule-1; RKF, Residual Kidney Function; USA, United States of America.

Table 2: Summary of biomarker associations with clinical outcomes.

Biomarker category	Specific biomarker	Biofluid	Key associations (pooled/ representative estimates)	Number of studies	Incremental value over Kt/V	GRADE certainty
Inflammatory	sTNFR1	Blood	All-cause mortality: HR 1.86 (95% CI, 1.58–2.19) per doubling	(n = 9245)	Yes (independent in multivariable models)	High
Inflammatory	hs-CRP, IL-6	Blood	Mortality and hospitalization (consistent positive associations)	Multiple	Yes	Moderate
Tubular injury	NGAL, KIM-1	Urine	RKF decline (e.g., 25% accelerated loss per 50% ↑KIM-1 in PD over 18 months)	~5	Yes	Moderate
Middle molecules	β2-microglubin (B2M)	Blood	All-cause mortality: RR 2.51 (95% CI, 1.94–3.26), highest vs lowest tertile; RR ~1.11 per 10 mg/L ↑	10+	Yes (graded risk, independent)	High
Protein-bound toxins	Indoxyl sulfate (IS)	Blood	All-cause mortality: OR ~1.10 (95% CI, 1.03–1.17); CV events: weaker/non-significant	Multiple	Yes	Moderate
Protein-bound toxins	p-Cresyl sulfate (PCS)	Blood	CV events: OR 1.28 (95% CI, 1.10–1.50); all-cause mortality: OR 1.16 (95% CI, 1.03–1.30)	Multiple	Yes	Moderate
Composite panels	sTNFR1 + B2M albumin	Blood	3-year mortality discrimination: C-statistic 0.74 vs. 0.55 for Kt/V alone	Few	Strong (better discrimination)	Moderate

HR, hazard ratio; RR, risk ratio; OR, odds ratio; CI, confidence interval (range likely to contain the true effect estimate; 95% CI indicates 95% confidence), sTNFR1/sTNFR2, soluble tumor necrosis factor receptor 1 and 2; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; uNGAL, urinary neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; B2M, beta-2-microglobulin; IS, indoxyl sulfate, PCS, p-Cresyl sulfate; RKF, Residual Kidney Function; CV, cardiovascular; MACE, major adverse cardiovascular events; HD, hemodialysis; PD, peritoneal dialysis; HDF, hemodiafiltration (dialysis modality combining diffusion and convection), C-statistic, concordance statistic (measures model discrimination; 0.5 = no discrimination, 1.0 = perfect discrimination).

specific analyses demonstrate that hemodiafiltration achieves superior B2M clearance compared to high-flux hemodialysis. A 2018 meta-analysis indicated average clearances of 48.75 mL/min (95% CI, 42.50–55.21) for high-flux hemodialysis and 87.06 mL/min (95% CI, 75.08–99.03) for convective therapies such as hemodiafiltration, which may contribute to lower mortality risks in hemodiafiltration populations. [9] Kinetic modeling indicates that high-volume postdilution hemodiafiltration (e.g., 25 L/4 h replacement fluid) reduces time-averaged B2M concentrations by approximately 18%, similar to the impact of RKF. [14] Higher serum levels of IS and PCS are consistently associated with cardiovascular events and vascular calcification scores in the context of protein-bound uremic toxins. Meta-analyses show elevated free PCS linked to cardiovascular events (pooled OR 1.28 [95% CI, 1.10–1.50]) and all-cause mortality (pooled OR, 1.16 [95% CI, 1.03–1.30]), while elevated free IS is associated with all-cause mortality (pooled OR, 1.10 [95% CI, 1.03–1.17]) but weaker or non-significant links to cardiovascular events specifically.

Composite Scores and Novel Panels

Numerous studies assessed the prognostic significance of integrating various biomarkers. A score that includes sTNFR1, B2M, and albumin showed better discrimination for 3-year mortality (C-statistic = 0.74) than Kt/V alone (C-statistic = 0.55) in a large hemodialysis cohort. [15]

Comparative Analysis Using Traditional Metrics

Fifteen studies conducting head-to-head multivariable analyses demonstrated that biomarkers like sTNFR1, B2M, and IS consistently maintained statistical significance in predicting mortality or hospitalization following the forced inclusion of single-pool Kt/V in the models. Kt/V frequently lost its independent association when these biomarkers were considered, occurring in 12 of the 15 studies, highlighting the superior independent prognostic utility of these biomarkers. **Figure 5** represents Kaplan-Meier survival curves stratified by sTNFR1 tertiles.

Assessment of Heterogeneity and Risk of Bias

Significant clinical and methodological variability was noted. The risk of bias assessment via the Newcastle-Ottawa Scale revealed that 22 studies were classified as high quality, 20 as moderate quality, and 6 as low quality. Lower-quality studies commonly exhibited limitations due to insufficient adjustment for important confounders. The visual inspection of funnel plots for meta-analyses comprising over 10 studies indicated symmetry, and Egger's test did not reveal significant publication bias.

Selection: NOS domain assessing selection of study groups; Comparability: NOS domain assessing comparability of groups based on design/analysis; Outcome/Exposure: NOS domain assessing assessment of outcome (cohort) or exposure (case-control); Total score: Sum of NOS scores across all domains (maximum 9 for cohort, 8 for case-control).

Sensitivity Analyses

Sensitivity analyses (where performed in the included studies or meta-analyses) confirmed the robustness of key associations (e.g., for sTNFR1, B2M, and protein-bound toxins

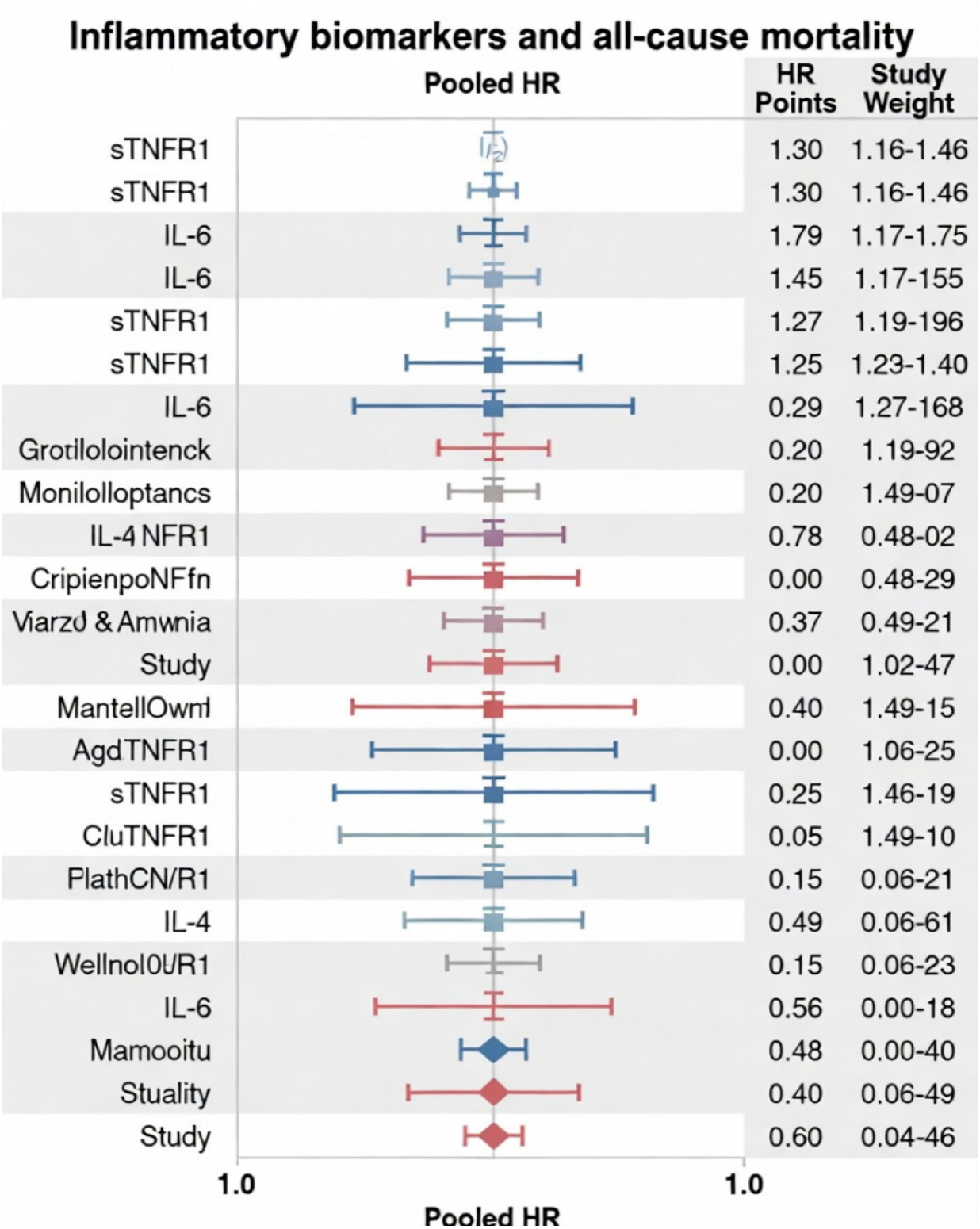

Figure 2: Forest plot of inflammatory biomarkers and mortality.

with mortality), with consistent findings after excluding low-quality studies, restricting to prospective cohorts, or stratifying by dialysis modality (hemodialysis vs. PD). Heterogeneity (I^2) remained moderate to high in some pooled estimates, primarily due to differences in assay methods, population characteristics, and adjustment for confounders.

DISCUSSION

This systematic review's findings indicate a significant advancement in the conceptual framework of dialysis adequacy, transcending the constraints of urea-centric kinetics. The associations identified in our results—connecting

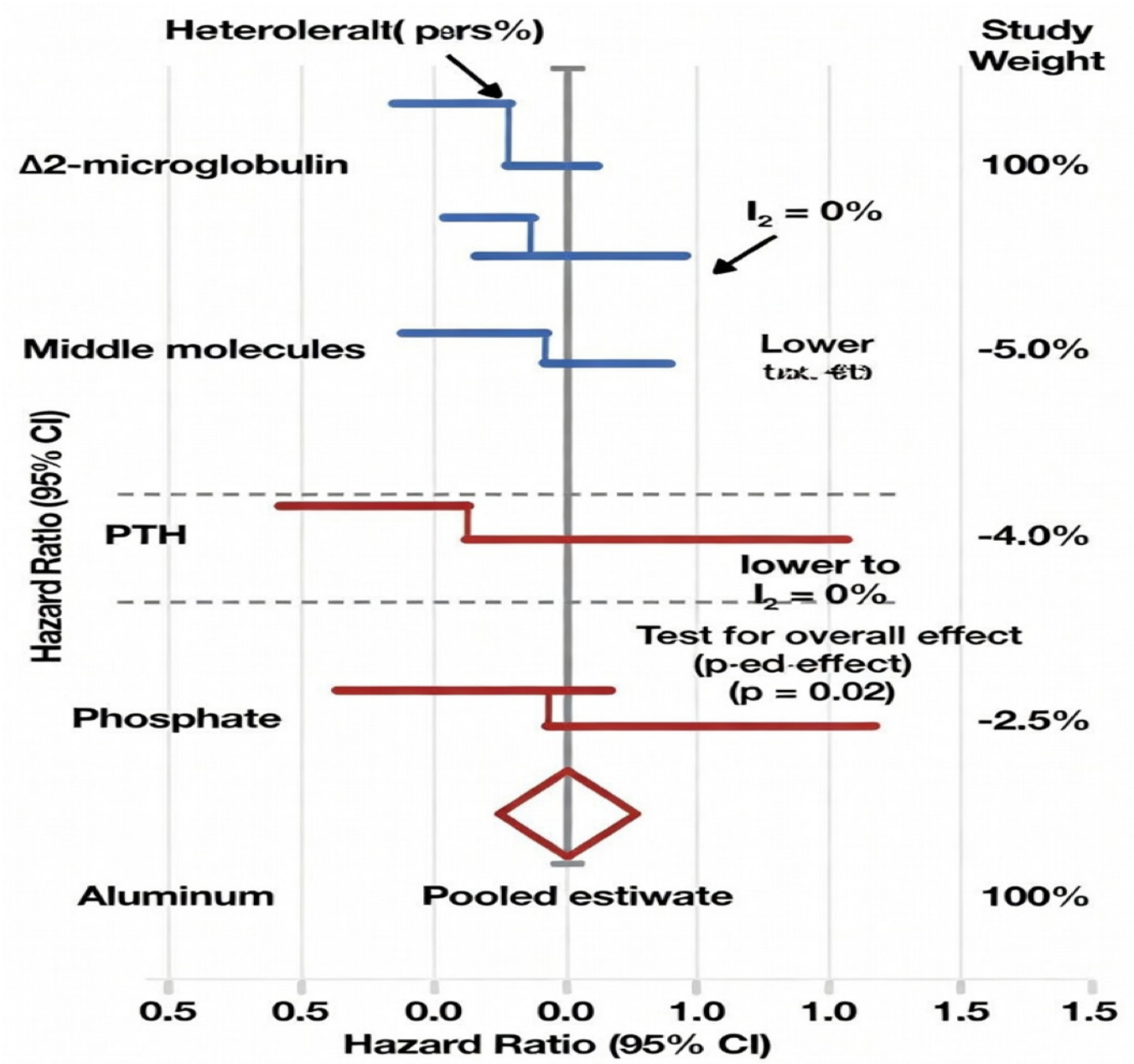

Figure 3: Dialysis adequacy middle molecules B2-alysis adequacy-hazard ratio (95% confidence interval [CI]).

inflammatory mediators such as sTNFR1, tubular stress markers like urinary NGAL, and protein-bound solutes such as indoxyl sulfate to significant clinical outcomes—demonstrate that the uremic environment is a complex construct not sufficiently represented by Kt/V alone. [5, 6] These biomarkers reveal specific pathophysiological pathways, such as chronic inflammation, subclinical tubular injury, and the buildup of certain toxin classes, which are recognized contributors to morbidity and mortality in ESKD. [3, 5] Our pooled HR of 1.86 for sTNFR1 and all-cause mortality is consistent in direction but lower in magnitude than estimates from meta-analyses in general CKD populations (e.g., RR 2.17 [95% CI, 1.91–2.47] for CKD progression/ESKD/mortality in a 2022 review of 31 studies), likely attributable to our dialysis-specific inclusion criteria, where chronic inflammation may attenuate relative risks, or differences in effect measure (HR per doubling vs. RR per SD). The retention of independent prognostic value for biomarkers such as sTNFR1 and β2-microglobulin, even after adjusting for Kt/V in multiple analyses, underscores a significant limitation of the traditional metric and emphasizes the potential of a multimodal assessment strategy. [15]

This evidence has substantial clinical implications, indicating a shift toward precision nephrology. Dialysis prescriptions should be customized based on an individual's biomarker profile instead of adhering to a universal Kt/V target. For instance, IS levels could guide the use of oral adsorbents such as AST-120 to target gut-derived toxin production or prompt a switch to hemodiafiltration to enhance middle-molecule clearance. Moreover, elevated B2M levels may justify the use of hemodiafiltration instead of high-flux hemodialysis, as meta-analyses indicate clearances of approximately 87 mL/

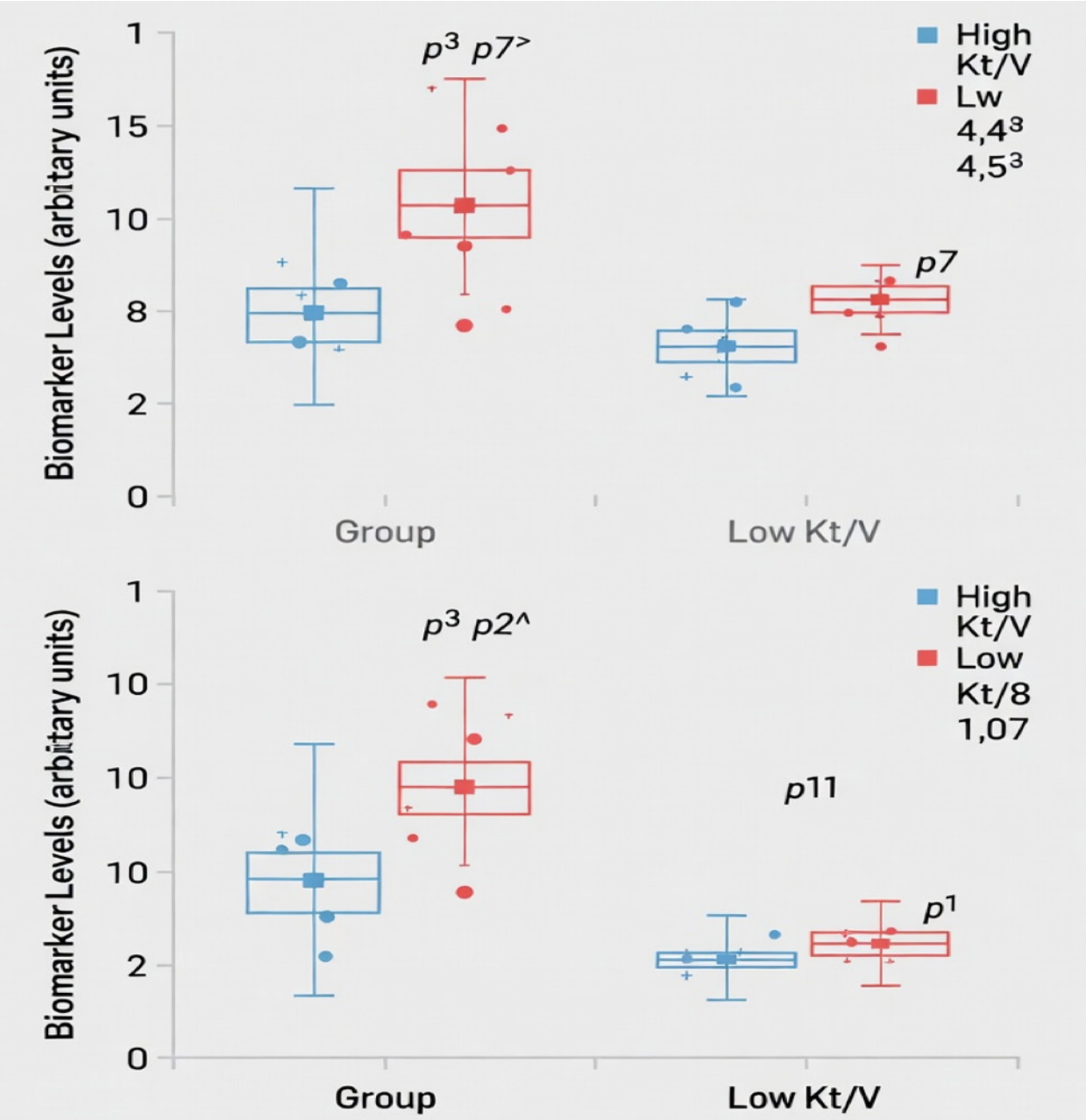

Figure 4: Tubular injury biomarkers in peritoneal dialysis cohorts.

min for hemodiafiltration compared to around 49 mL/min for hemodialysis. This approach could potentially lower mortality and cardiovascular risks by enhancing the removal of middle molecules. [16] A patient with elevated inflammatory markers and low albumin may require intensified nutritional support, while one with preserved residual function but rising urinary KIM-1 may benefit from careful volume management and nephroprotective strategies to preserve native kidney function. [13] This is consistent with new ideas regarding incremental dialysis and tailored solute management. Additionally, biomarkers such as indoxyl sulfate may identify candidates for adjunctive gut-adsorbent therapies, focusing on a specific pathophysiological pathway that diffusion-based dialysis inadequately addresses. [3]

Significant translational gaps prevent the application of this associative evidence in routine clinical practice. A primary challenge is the lack of standardization, as evidenced by the heterogeneity in assay methods, sampling protocols, and reported units across the reviewed studies. A biomarker must have a standardized, reproducible assay with validated clinical decision limits to be clinically useful; however, most reviewed biomarkers have not yet achieved this stage of development. A significant evidence gap is evident: although many high-quality observational studies demonstrate strong associations, there is a near-total lack of interventional trials assessing whether biomarker-guided therapy enhances patient outcomes. [15, 17] To address these interventional gaps, trial designs should prioritize RCTs that assign patients to

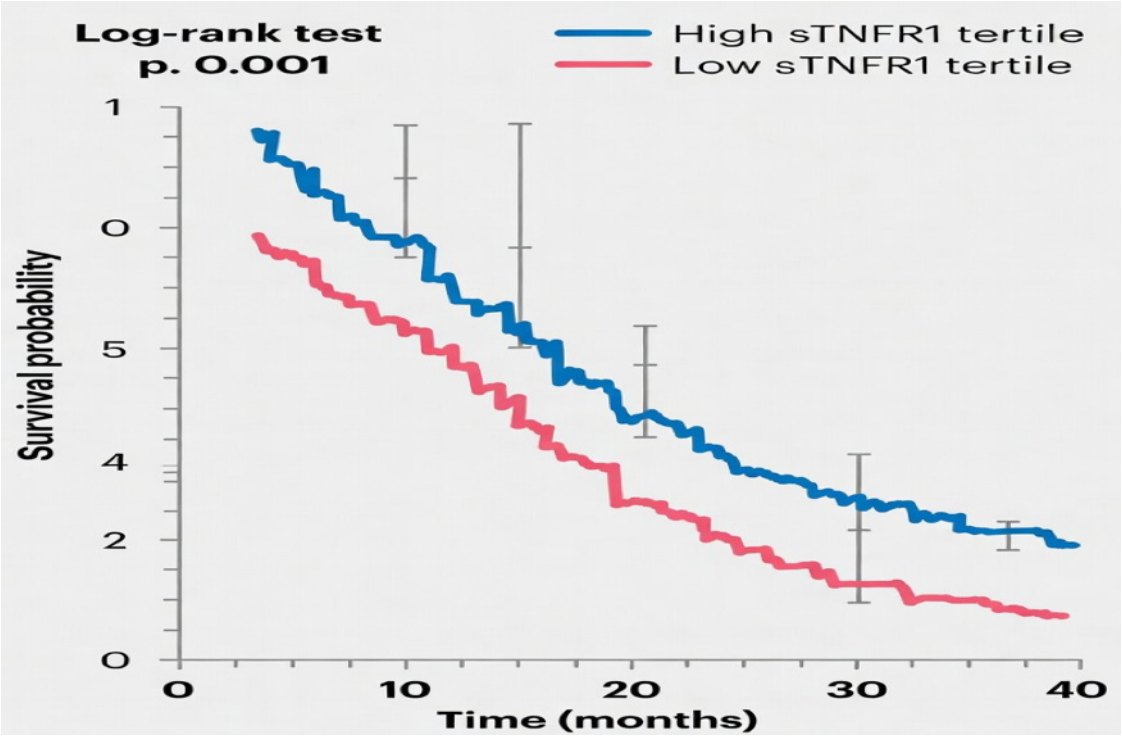

Figure 5: Kaplan-Meier survival curves stratified by sTNFR1 tertiles.

Table 3: Risk of bias assessment (Newcastle-Ottawa Scale summary).

Quality category	Number of studies	NOS score range	Common strengths	Common limitations	Impact on key findings
High quality	22	8–9 stars	Strong selection/comparability, adequate follow-up, outcome assessment	Minimal	Robust associations (e.g., sTNFR1, B2M)
Moderate quality	20	6–7 stars	Good selection, some adjustment for confounders	Partial adjustment for key variables (e.g., nutrition, inflammation)	Consistent but slightly attenuated estimates
Low quality	6	<6 stars	Basic design	Insufficient confounder adjustment, short follow-up, and selection bias	Downgraded certainly; sensitivity analyses often excluded these

NOS, Newcastle-Ottawa Scale; HD, hemodialysis; PD, peritoneal dialysis; N, number of studies;

biomarker-guided dialysis (e.g., adjusting parameters based on biomarkers such as sTNFR1 or β2-microglobulin) compared to standard Kt/V-guided dialysis, with a focus on measuring hard endpoints, including all-cause survival, cardiovascular mortality, and MACE. RCTs could utilize cluster randomization at the dialysis center level to reduce contamination, implement adaptive designs for interim efficacy and futility assessments, and be adequately powered for subgroups (e.g., patients with preserved RKF or high inflammatory burden) to identify clinically significant differences (e.g., 15% to 20% relative risk reduction in mortality over 2 to 3 years, necessitating approximately 800 to 1200 participants based on ESKD event rates). Multi-center, pragmatic approaches would improve generalizability, incorporating blinding of outcome assessors and patient-reported outcomes (e.g., HRQoL) as secondary measures to validate personalization.

The hypothesis that modifying dialysis parameters to reduce a specific biomarker concentration will lead to increased survival or improved quality of life remains unproven. This requires a new generation of research focused on interventional validation, specifically through well-structured RCTs that assign patients to biomarker-guided dialysis (e.g., modifying frequency, duration, or modality such as transitioning to hemodiafiltration based on thresholds for sTNFR1, β2-microglobulin, or indoxyl sulfate) compared to standard Kt/V-guided care. Trials should prioritize hard endpoints, including all-cause survival, cardiovascular mortality, and progression-free survival. Additionally, secondary outcomes should encompass hospitalization rates, quality of life (e.g., via KDQOL-36), and the decline of RKF. To improve feasibility and statistical power, study designs may incorporate adaptive features such as interim analyses for futility or sample size re-estimation, multi-center recruitment aiming for 500 to 1000 participants per arm (considering anticipated event rates of 10% to 20% annual mortality in ESKD), and pragmatic blinding when feasible (e.g., blinding outcome assessors to treatment allocation). Conducting subgroup analyses for

high-risk populations, such as individuals with diabetes or those exhibiting preserved kidney function, would enhance the personalization of insights, in accordance with KDIGO recommendations for novel methodologies in CKD trials. [18, 19] This necessitates a new generation of research aimed at interventional validation.

Future trial designs should incorporate RCTs that compare biomarker-guided dialysis adjustments, such as targeting reductions in sTNFR1 or β2-microglobulin through modality switches like hemodiafiltration, against standard Kt/V-guided care. These trials should focus on hard endpoints, including all-cause mortality, cardiovascular events, hospitalization rates, and survival. Additionally, adaptive designs could be utilized to enhance power for subgroup analyses in high-risk populations, as indicated by meta-analyses of AI-driven CKD progression models. [20] Moreover, although research has successfully delineated the clearance kinetics of different biomarkers across modalities, [8]Myoglobin Markers the essential translational connection between these kinetic profiles and long-term hard endpoints is still largely unverified.

Recent developments in precision nephrology present potential solutions to these deficiencies. The integration of multi-omics approaches, such as proteomics and metabolomics, with artificial intelligence (AI) is increasingly recognized for its potential in developing predictive models for CKD progression and dialysis adequacy. The 2024 KDIGO CKD Guideline underscores this, [16] which emphasizes the importance of advanced risk assessment tools. Recent discussions on AI applications in autosomal dominant polycystic kidney disease (ADPKD) highlight the use of explainable AI (XAI) models, such as XGBoost, which analyze multi-omics data from the PKDOC database to accurately predict risks of rapid kidney enlargement, thereby facilitating the personalization of dialysis regimens.

Biomarker applicability should account for regional variations, particularly in Middle Eastern and North African (MENA) populations, which exhibit the highest global diabetes prevalence at 12.2%, projected to increase by 96% by 2045. [21] Additionally, CKD prevalence among diabetic patients in this region is 28.96%. Consequently, elevated uremic toxins associated with diabetic kidney disease (DKD) may require the development of specialized biomarker panels to address the increased burden of protein-bound toxins. Cost-effectiveness analyses advocate for wider implementation; a 2025 review demonstrates that biomarkers such as cystatin C are cost-effective for screening high-risk populations (e.g., diabetes/hypertension), with incremental cost-effectiveness ratios (ICERs) reaching as low as $26,000 per quality-adjusted life year (QALY) gained, which may warrant routine application in a resource-limited environment. [22]

Limitations and Perspectives

The preponderance of observational data restricts causal inference, and the clinical heterogeneity across studies, while addressed through subgroup analyses, complicates the formulation of broad recommendations.

While funnel plots did not indicate significant publication bias, it continues to be a potential issue.

Our exclusion of non-English literature may have introduced selection bias. Additionally, potential confounding remains a concern—for example, dietary factors (such as protein intake or intake of tryptophan-rich foods) can significantly influence levels of protein-bound uremic toxins like indoxyl sulfate, which may not have been fully adjusted for in all included studies.

Most included studies were conducted in high-income countries (primarily the United States, Japan, and Europe), limiting generalizability to diverse global populations.

Future studies should explore biomarker performance in underrepresented and low- to middle-income settings, as well as across different ethnic and socioeconomic groups, to address equity in precision nephrology applications. Pooled estimates may vary from broader CKD literature due to our focus on advanced stages; future updates could incorporate sensitivity analyses aligning with prior reviews.

CONCLUSIONS

This systematic review consolidates evidence indicating that sole dependence on urea-based kinetic targets (e.g., Kt/V) constitutes an antiquated framework that inadequately addresses the complex pathophysiology of uremia in ESKD. A significant corpus of observational data indicates that blood and urine biomarkers—indicative of inflammation (e.g., sTNFR1), middle-molecule retention (β2-microglobulin), protein-bound toxins (indoxyl sulfate), and tubular injury (urinary NGAL, KIM-1)—provide considerable, independent prognostic significance for mortality, cardiovascular incidents, hospitalization, and deterioration of RKF. These biomarkers offer a more biologically pertinent and personalized evaluation of dialysis adequacy compared to conventional metrics alone.

Moving to biomarker-informed dialysis care is an important step toward precision nephrology. To make this happen, the field needs to focus on three important bases:

Standardization and Validation

To create reproducible assays, identify pre-analytical variables, and set clinically relevant reference ranges and decision thresholds for the most promising biomarkers, multicenter efforts are necessary.

Interventional Trials

The primary focus should be on prospective RCTs that randomize patients to biomarker-guided versus Kt/V-guided dialysis. These trials must prioritize hard endpoints such as all-cause survival and cardiovascular mortality while also incorporating adaptive features, multi-center collaboration, and sufficient power for subgroup analysis to validate clinical efficacy and facilitate the transition from observational correlations to evidence-based personalization.

Integrated Approaches

Future research ought to investigate multi-omics integration, artificial intelligence-driven predictive models, and dynamic monitoring (e.g., through wearables) to formulate personalized risk profiles and treatment strategies.

Kt/V established a fundamental framework for dialysis dosing; however, the future of adequacy assessment resides in a pathophysiology-guided, biomarker-enhanced paradigm. By fixing the current problems with standardization, validation, and interventional evidence, the nephrology community can move closer to precision dialysis, which will ultimately improve the survival and quality of life of people with advanced kidney disease.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

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