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A TRIPARTITE BIOMARKER PANEL OF SYSTEMIC INFLAMMATION, IMMUNE ACTIVATION, AND TUBULAR INJURY (IL-6, suPAR, KIM-1) PREDICTS MORTALITY AND CARDIOVASCULAR OUTCOMES IN END-STAGE RENAL DISEASE

TROČLANI BIOMARKERNI PANEL SISTEMSKE INFLAMACIJE, IMUNOLOŠKE AKTIVACIJE I TUBULARNOG OŠTEĆENJA (IL-6, suPAR, KIM-1) PRI PREDVIĐANJU MORTALITETA I KARDIOVASKULARNIH ISHODA KOD TERMINALNE BUBREŽNE INSUFICIJENCIJE

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Summary

Background: The high mortality in end-stage renal disease (ESRD) is driven by a confluence of inflammatory, cardiovascular, and persistent tubulointerstitial injury pathways. We hypothesised that a multi-domain biomarker panel combining Interleukin-6 (IL-6, inflammation), soluble urokinase plasminogen activator receptor (suPAR, immune activation), and Kidney Injury Molecule-1 (KIM-1, tubular injury) would provide superior prognostic value for fatal and non-fatal outcomes.

Methods: We performed a prospective cohort study of 538 prevalent haemodialysis patients. Serum IL-6, suPAR, and KIM-1 were measured at baseline. The primary endpoint was a composite of all-cause mortality and major adverse cardiovascular events (MACE). Secondary endpoints were cardiovascular mortality and heart failure hospitalisations. Cox proportional hazards models and C-statistics were used for analysis.

Results: Over a median follow-up of 36 months, 192 patients (35.7%) experienced the primary composite endpoint. In fully adjusted models, each biomarker independently predicted the primary endpoint: IL-6 (HR 1.85, 95% CI 1.51–2.26), suPAR (HR 2.15, 95% CI 1.70–2.73), and KIM-1 (HR 1.67, 95% CI 1.35–2.06). A model containing all three biomarkers demonstrated

Kratak sadržaj

Uvod: Visoka stopa mortaliteta kod terminalne bubrežne bolesti (ESRD) je rezultat istovremenog delovanja inflamatornih, kardiovaskularnih i perzistentnih tubulointersticijalnih mehanizama oštećenja. Pretpostavili smo da bi multidomenski biomarkerni panel koji kombinuje interleukin-6 (IL-6, inflamacija), rastvorivi receptor aktivatora urokinaznog plazminogena (suPAR, imunološka aktivacija) i molekul oštećenja bubrega-1 (KIM-1, tubularno ošteć enje) mogao da pruži superiornu prognostičku vrednost za fatalne i nefatalne ishode.

Metode: Sproveli smo prospektivnu kohortnu studiju na 538 pacijenata na hroničnoj hemodijalizi. Serumske koncentracije IL-6, suPAR i KIM-1 su određene na početku studije. Primarni ishod bio je kompozitni ishod ukupnog mortaliteta i velikih neželjenih kardiovaskularnih događaja (MACE). Sekundarni ishodi su bili kardiovaskularni mortalitet i hospitalizacije zbog srčane insuficijencije. Za analizu su korišćeni Cox modeli proporcionalnih hazarda i C-statistika.

Rezultati: Tokom medijane praćenja od 36 meseci, 192 pacijenta (35,7%) su doživela primarni kompozitni ishod. U potpuno prilagođenim modelima, svaki biomarker je nezavisno predviđao primarni ishod: IL-6 (HR 1,85; 95% CI 1,51–2,26), suPAR (HR 2,15; 95% CI 1,70–2,73) i KIM-1 (HR 1,67; 95% CI 1,35–2,06). Model koji je

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significantly improved discrimination (C-index 0.81) over models with any single biomarker (C-indices 0.71–0.74) or a clinical model alone (C-index 0.67; p<0.001). Patients in the highest-risk category (all three biomarkers in the top tertiles) had a 6.8-fold increased risk (HR 6.80, 95% CI 3.85–12.02) for the primary endpoint.

Conclusion: The combination of IL-6, suPAR, and KIM-1 – reflecting systemic inflammation, innate immunity, and residual tubular damage – creates a powerful, integrative prognostic tool that significantly improves risk stratification for mortality and cardiovascular events in ESRD.

Keywords: end-stage renal disease, haemodialysis, biomarkers, interleukin-6, soluble urokinase plasminogen activator receptor, kidney injury molecule-1, prognosis, cardiovascular disease

uključivao sva tri biomarkera je pokazao značajno bolju diskriminaciju (C-indeks 0,81) u poređenju sa modelima sa pojedinačnim biomarkerima (C-indeksi 0,71–0,74) ili samo kliničkim modelom (C-indeks 0,67; p<0,001). Pacijenti u kategoriji najvišeg rizika (sva tri biomarkera u najvišim tercilima) su imali 6,8 puta veći rizik (HR 6,80; 95% CI 3,85–12,02) za primarni ishod.

Zaključak: Kombinacija IL-6, suPAR i KIM-1 – koja odražava sistemsku inflamaciju, urođeni imunitet i rezidualno tubularno oštećenje – predstavlja snažan, integrativni prognostički alat koji značajno unapređuje stratifikaciju rizika za mortalitet i kardiovaskularne događaje kod bolesnika sa ESRD.

Ključne reči: terminalna bubrežna bolest, hemodijaliza, biomarkeri, interleukin-6, rastvorljivi receptor aktivatora urokinaznog plazminogena, molekul oštećenja bubrega-1, prognoza, kardiovaskularna bolest

Introduction

End-stage renal disease (ESRD) is associated with an exceptionally elevated risk of death, with cardiovascular complications accounting for the majority of mortality. Importantly, this risk is not adequately explained by conventional cardiovascular risk factors. Increasing evidence indicates that the excess mortality burden arises from the interaction of several non-traditional mechanisms, most notably chronic systemic inflammation, disturbances in immune regulation, and the cumulative effects of sustained tubular damage (1, 2).

Biomarkers reflecting these biological pathways have individually demonstrated associations with adverse clinical outcomes. Interleukin-6 (IL-6) is a multifunctional cytokine that plays a pivotal role in the inflammatory milieu characteristic of ESRD, contributing to hepatic acute-phase protein synthesis, myocardial hypertrophy, and endothelial dysfunction (3, 4). Soluble urokinase plasminogen activator receptor (suPAR) extends beyond its role as an inflammatory indicator and functions as an active mediator of immune signalling. Released from activated immune cells, suPAR has been implicated in podocyte injury, vascular atherosclerosis, and endothelial impairment through integrin-dependent pathways (5, 6). Kidney Injury Molecule-1 (KIM-1) is a transmembrane protein that is released into the circulation following proximal tubular epithelial injury and serves as a sensitive indicator of ongoing tubulointerstitial damage (7, 8). In patients with ESRD, elevated circulating KIM-1 levels may reflect persistent renal parenchymal injury and maladaptive repair responses, processes closely linked to fibrosis and unfavourable clinical outcomes (9, 10).

Although previous investigations have assessed IL-6 (11), suPAR (12), or KIM-1 (13), individually, the prognostic value of their combined assessment – representing an integrated evaluation of inflammatory activity, immune dysfunction, and tissue injury – has not yet been explored. We therefore hypothesise that these biomarkers capture complementary yet interconnected pathophysiological processes and that their combined use will provide superior prognostic performance compared with any single biomarker or conventional clinical model in predicting mortality and cardiovascular events among patients undergoing haemodialysis.

Materials and Methods

Study design and population

Between January 2022 and June 2025, we enrolled 538 adult patients (≥18 years) on maintenance haemodialysis for >90 days. Patients with active infection, malignancy, or autoimmune or inflammatory diseases at baseline were excluded to minimise acute inflammatory states that could disproportionately influence circulating biomarker levels. Individuals with recent hospitalisation or acute cardiovascular events were also excluded to avoid short-term perturbations in systemic inflammation and immune activation unrelated to chronic ESRD status. In addition, patients with incomplete clinical data or insufficient serum samples were excluded to preserve analytical robustness and avoid bias introduced by missing covariates. Active infection at baseline was defined a priori as any of the following occurring at the time of enrolment or within 14 days before blood sampling: (1) receipt of systemic antimicrobial therapy (antibiotic, antiviral, or antifungal) initiated for a suspected or confirmed infection; (2) infection-related hospitalisation or emergency department visit with a primary diagnosis of infection; or (3) clinician-diagnosed infection documented in the medical record accompanied by compatible clinical features (e.g., fever ≥38.0°C, localised infectious symptoms/

signs) and supportive laboratory evidence (e.g., leucocytosis/leukopenia or elevated CRP). Patients with an estimated life expectancy of less than six months were excluded to ensure sufficient follow-up time for outcome assessment and to avoid confounding from terminal or rapidly progressive conditions that may disproportionately drive short-term mortality independent of chronic ESRD-related pathophysiology.

The Medical Centre Institutional Review Board approved the study protocol, and all participants provided written informed consent.

Biomarker measurements

Pre-dialysis venous blood samples were collected at baseline under standardised conditions. Serum was separated, aliquoted, and stored at -80 °C until batch analysis.

- IL-6 was quantified using a high-sensitivity electrochemiluminescence immunoassay (Meso Scale Discovery, Rockville, MD). Lower limit of detection (LLoD): 0.1 pg/mL; inter-assay CV: <8%.
- suPAR was measured using the suPARnostic® AUTO Flex ELISA (ViroGates, Copenhagen, Denmark). LLoD: 0.1 ng/mL; inter-assay CV: <10%.
- KIM-1 was measured using a commercially available quantitative sandwich enzyme immunoassay (R&D Systems, Minneapolis, MN). LLoD: 0.009 ng/mL; inter-assay CV: <7%.

All serum samples were stored at -80 °C and analysed in multiple assay runs due to logistical constraints. To minimise batch-related variability, samples were randomly allocated across assay runs, and identical assay kits, protocols, and calibration procedures were used throughout. Laboratory personnel were blinded to clinical outcomes. Batch effects were evaluated by inspecting biomarker distributions across runs and were addressed by including batch identifiers as covariates in sensitivity analyses; results were materially unchanged, indicating that batch-related variability did not meaningfully influence the observed associations. Inter-assay coefficients of variation were within the ranges specified by the manufacturers.

To minimise biological variability, blood samples for biomarker measurements were collected immediately before a scheduled haemodialysis session using a standardised pre-dialysis protocol. All patients were clinically stable at the time of sampling, with no evidence of acute intercurrent illness; individuals with fever or active infection were excluded according to predefined criteria. Pre-dialysis sampling was chosen to avoid acute effects of ultrafiltration, hemodynamic shifts, and dialysis-related inflammatory responses that could influence circulating levels of suPAR and IL-6. This standardised timing and clinical screening were intended to ensure that measured biomarker concentrations reflected baseline inflammatory and immune activation status rather than transient dialysis-related or acute physiological perturbations.

Clinical data and outcomes

Baseline demographic characteristics, clinical variables, and laboratory measurements were extracted from the electronic health record system. The primary composite outcome was defined as the time to the first event of either all-cause death or a major adverse cardiovascular event (MACE), including non-fatal myocardial infarction, non-fatal ischemic stroke, or hospitalisation due to unstable angina or coronary revascularisation. Secondary outcomes comprised: (1) cardiovascular-related mortality and (2) hospitalisation for heart failure. All outcome events were reviewed and adjudicated by an independent clinical endpoints committee blinded to biomarker measurements, which applied pre-specified adjudication criteria.

Statistical analysis

Biomarker levels were log-transformed to approximate normal distributions. Spearman's rank correlation assessed inter-biomarker relationships. Cox proportional hazards regression models were built sequentially: Model A (Clinical Model): adjusted for age, sex, diabetes mellitus, systolic blood pressure, serum albumin, and history of CVD. Model B-D: Clinical Model + one biomarker (IL-6, suPAR, or KIM-1). Model E: Clinical Model + all three biomarkers. Model discrimination was compared using Harrell's C-index. Improvement in model performance with the addition of biomarkers was assessed using the integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) (14). We also performed risk stratification by categorising patients into tertiles (T1–T3) for each biomarker and creating combined risk groups. A two-sided p-value <0.05 was considered significant. Analyses were performed using R version 4.2.0.

In addition to discrimination, model calibration was evaluated for the final tripartite biomarker model. Calibration was assessed by comparing predicted versus observed event probabilities at a predefined follow-up time using calibration plots derived from grouped risk estimates. Observed risks were estimated using Kaplan–Meier methods within deciles of predicted risk. This approach was chosen to appropriately account for censoring in time-to-event data and to assess agreement between predicted and observed outcomes.

Results

Baseline characteristics and biomarker levels

The study cohort comprised 538 haemodialysis patients. The mean age was 61.5±13.2 years, 56.1% were male, 44.2% had diabetes, and 38.7% had a prior history of cardiovascular disease. Median biomarker levels were: IL-6: 7.2 pg/mL (IQR 4.1–12.8), suPAR: 8.1 ng/mL (IQR 5.5–12.0), KIM-1: 1.15 ng/mL (IQR 0.781.89). IL-6 and suPAR were moderately correlated ($\rho=0.47$, $p<0.001$), while correlations of KIM-1 with IL-6 ($\rho=0.31$, $p<0.001$) and suPAR ($\rho=0.28$, $p<0.001$) were weaker.

Primary composite endpoint: all-cause mortality or MACE

Over a median follow-up of 36.0 months (IQR 28.5–38.0), 192 patients (35.7%) reached the primary endpoint (116 deaths, 76 non-fatal MACE).

All three biomarkers remained independent predictors in the fully adjusted tripartite model (Model E, *Table I*). The C-index for Model E (0.81) was significantly higher than for Models A–D ($p<0.001$ for all pairwise comparisons). The addition of the three-biomarker panel to the clinical model yielded a significant NRI of 0.41 (95% CI 0.27–0.55) and an IDI of 0.102 (95% CI 0.068–0.145).

Table I Association of individual and combined biomarkers with the primary composite endpoint (all-cause mortality or MACE).

Model	Variables Included	Hazard Ratio (HR) per 1-log increase	95% CI for HR	P-value	Model C-index
A	Clinical Model Only (Age, Sex, DM, SBP, Albumin, CVD Hx)	-	-	-	0.67
B	Clinical Model + IL-6	1.85	1.51–2.26	<0.001	0.74
C	Clinical Model + suPAR	2.15	1.70–2.73	<0.001	0.75
D	Clinical Model + KIM-1	1.67	1.35–2.06	<0.001	0.71
E*	Clinical Model + IL-6 + suPAR + KIM-1				0.81
	- IL-6	1.58	1.28–1.95	<0.001	
	- suPAR	1.92	1.49–2.47	<0.001	
	- KIM-1	1.38	1.11–1.72	0.004	

*Adjusted HR for each biomarker in the full tripartite model
DM, diabetes Mellitus; SBP, systolic blood pressure; CVD Hx: history of cardiovascular disease.

Table II Tisk of primary composite endpoint by number of elevated biomarkers (in top tertile, T3).

Risk Group	IL-6	suPAR	KIM-1	Number of patients	Event rates per 100 person-years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Low risk	T1/T2	T1/T2	T1/T2	197	5.2	1.00 (Reference)	1.00 (Reference)
Intermediate risk	T3	T1/T2	T1/T2	58	9.8	1.98 (1.10–3.55)	1.72 (0.95–3.12)
	T1/T2	T3	T1/T2	62	10.8	2.24 (1.28–3.92)	1.99 (1.13–3.51)
	T1/T2	T1/T2	T3	54	9.9	1.99 (1.10–3.60)	1.65 (0.91–3.01)
High risk	T3	T3	T1/T2	41	18.7	4.71 (2.78–7.98)	3.85 (2.25–6.59)
	T3	T1/T2	T3	38	18.4	4.62 (2.70–7.92)	3.65 (2.11–6.31)
	T1/T2	T3	T3	35	18.1	4.53 (2.61–7.87)	3.78 (2.16–6.62)
Very high risk	T3	T3	T3	53	28.3	8.95 (5.68–14.11)	6.80 (3.85–12.02)

Adjusted for age, sex, diabetes, systolic BP, albumin, and history of CVD.

Risk stratification by combined biomarker tertiles

Tertiles of each biomarker stratified patients. The risk increased progressively with the number of elevated biomarkers (presented as high-risk tertile, T3)

As shown in *Table II*, the »Very high risk« group (all three biomarkers in T3) had an adjusted hazard ratio of 6.80 (95% CI 3.85-12.02) compared to the »Low risk« group.

Secondary endpoints

Similar patterns were observed for the secondary endpoints. The tripartite panel significantly improved prediction for cardiovascular mortality (C-index 0.83) and heart failure hospitalisations (C-index 0.78).

Discussion

This study demonstrates, for the first time, that a tripartite biomarker panel integrating IL-6, suPAR, and KIM-1 provides powerful and synergistic prognostic information for major clinical outcomes in ESRD, substantially outperforming established clinical factors and single-biomarker approaches.

Our findings confirm and extend the known roles of individual biomarkers. IL-6's association with mortality reinforces its position as a master regulator of the uremic inflammatory milieu (3, 15). The robust and independent association observed for suPAR highlights the central involvement of dysregulated innate immune activation and its direct pathogenic influence on both the vascular system and the kidneys (5, 16, 17). The independent prognostic contribution of circulating KIM-1 is particularly noteworthy. Although KIM-1 is well established as a urinary biomarker of acute kidney injury (7), its predictive value in the circulation among patients with ESRD suggests that ongoing, low-grade tubulointerstitial damage, a fundamental driver of chronic kidney disease progression (18), continues to confer substantial risk even after dialysis initiation. This effect may be mediated through persistent systemic inflammation and profibrotic signalling pathways (19, 20).

The observed synergy among these biomarkers likely reflects their involvement in interconnected pathogenic pathways (21). For example, inflammatory signalling mediated by IL-6 can enhance suPAR expression in activated immune cells (22) while immune activation and pro-inflammatory cytokines can further aggravate tubular epithelial injury (23). In turn, mediators released from damaged renal tubules may amplify systemic inflammatory responses (24, 25). This bidirectional biological interplay provides a mechanistic rationale for the superior risk discrimination achieved by the combined biomarker panel, as reflected by the marked improvement in the C-index (0.81).

Systematic evaluations of prognostic models in patients with chronic dialysis have demonstrated that traditional clinical models generally exhibit C-statistics of 0.71–0.75 when externally validated in independent cohorts, indicating modest discrimination (26). This moderate performance is consistent with findings from broader systematic reviews of mortality prediction models in kidney failure populations, in which none of the existing clinical models have demonstrated sufficient performance to be recommended for routine guideline use, reflecting both methodological limitations and modest predictive power.

In contrast, the tripartite biomarker model's C-index of 0.81 represents a substantial improvement over these established benchmarks. This level of discrimina tion is comparable to, or exceeds, that of recent biomarker-enriched models that integrate inflammatory or immune parameters.

We speculate that the strong prognostic performance of the combined biomarker panel reflects a biologically interconnected pathway rather than parallel, independent processes. Specifically, suPAR-mediated immune activation and IL-6–driven systemic inflammation may create a pro-inflammatory and pro-oxidative milieu that sensitises renal tubular epithelial cells to injury, resulting in increased expression and release of KIM-1. Tubular injury, in turn, may promote the release of damage-associated molecular patterns (DAMPs), further activate innate immune pathways, and amplify systemic inflammatory signalling. This feed-forward loop – linking immune activation, inflammation, and tubular damage – could contribute to sustained biological stress and heightened cardiovascular and mortality risk in end-stage renal disease. While this proposed mechanism remains hypothetical and cannot be confirmed within the present observational framework, it provides a biologically plausible explanation for the synergistic prognostic value observed when these biomarkers are considered jointly.

The clinical implication is profound. The simple tertile-based stratification (*Table II*) can readily identify a »Very High Risk« subgroup comprising ~10% of the cohort but accounting for nearly 25% of all events, with a near 7-fold increased hazard. This high-risk phenotype, characterised by concurrent high inflammation, immune activation, and tubular injury, represents an ideal target population for enrolment in trials of novel anti-inflammatory therapies (e.g., IL-6 inhibitors

(27)), immunomodulatory therapies, or anti-fibrotic therapies. It also flags patients who may benefit from intensified cardiovascular surveillance and management. However, randomised controlled trials would be required to determine whether therapeutic modulation of inflammatory or immune pathways leads to meaningful reductions in cardiovascular events or mortality in patients with end-stage renal disease.

Although urinary KIM-1 is a well-established marker of proximal tubular injury, its assessment is often impractical in patients with advanced chronic kidney disease and end-stage renal disease because of absent or markedly reduced urine output. Circulating KIM-1 is biologically informative and prognostically relevant in chronic kidney disease, where plasma KIM-1 independently predicted kidney failure and mortality and improved risk stratification beyond urinary measures and traditional risk factors (28). Blood levels of KIM-1 were initially described as a marker of acute and chronic kidney injury and progression to end-stage renal disease in type 1 diabetic patients (29), and multiple studies have reported associations between plasma KIM-1 and renal outcomes across different cohorts (30). In ESRD, serum KIM-1 may originate predominantly from injured renal tubular epithelium with impaired clearance, although contributions from extra-renal expression or systemic inflammatory activation cannot be entirely excluded. Experimental and clinical data suggest that KIM-1 can be released into the circulation following sustained epithelial injury, where it may act as a marker of ongoing tissue damage rather than solely as a marker of localised urinary excretion (31). Accordingly, the use of serum KIM-1 in this study represents a pragmatic and biologically plausible approach to capture tubular injury in haemodialysis patients, while recognising that the precise sources and kinetics of circulating KIM-1 in ESRD warrant further investigation.

Our study has limitations. It is observational, precluding causal inference. The cohort is from a single region, and validation in independent, multi-ethnic populations is necessary. We measured biomarkers at a single time point; serial measurements might improve dynamic risk assessment. Despite adjustment for established clinical covariates, residual confounding remains possible. Unmeasured or incompletely captured factors – such as detailed nutritional status beyond serum albumin, specific dialysis prescription parameters (e.g., dialysate composition, treatment intensity), and volume status – may influence circulating biomarker concentrations and clinical outcomes. Although our models accounted for key demographic and clinical variables, these factors could not be fully characterised and may partially contribute to the observed associations.

Conclusion

The combination of serum IL-6, suPAR, and KIM-1 creates an integrative »risk fingerprint« that captures the multidimensional pathophysiology of ESRD. This tripartite panel significantly improves the identification of patients at the highest risk for death and cardiovascular events, enabling a more personalised and potentially mechanistic approach to risk stratification and therapeutic targeting in this vulnerable population.

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Data sharing statement

De-identified participant data and the study protocol will be made available upon reasonable request to the corresponding author, subject to a data use agreement.

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Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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