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Serum Biomarkers and Endothelial Dysfunction as Early Predictors of Cardiovascular Risk in Chronic Kidney Disease: A Multi-Biomarker Meta-Analysis and Clinical Translation Framework

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Abstract:

Background: Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals with chronic kidney disease (CKD), often manifesting before progression to end-stage renal disease. Traditional risk markers such as glomerular filtration rate (GFR) and albuminuria offer limited predictive capacity for early cardiovascular events in CKD patients. **Objective:** This study investigates the predictive value of emerging serum biomarkers namely asymmetric dimethylarginine (ADMA), cystatin C, fetuin-A, and matrix Gla protein (MGP) in improving cardiovascular risk stratifycation in CKD populations. **Methods:** A PRISMA-compliant systematic review and meta-analysis was conducted, pooling hazard ratios for biomarker associations with cardiovascular outcomes. Additionally, machine learning models (Random Forest and Logistic Regression) were developed using biomarker and clinical data to classify patients into cardiovascular risk categories. The best-performing model informed the creation of the CKD-CV Early Risk Score (CERS). **Results:** All four biomarkers showed significant associations with cardiovascular risk, with ADMA and cystatin C emerging as the strongest predictors. The Random Forest model achieved an AUC-ROC of 0.88, outperforming logistic regression. The resulting CERS effectively stratified patients into low-, moderate-, and high-risk groups, offering a practical tool for early clinical intervention. **Conclusion:** Integrating novel serum biomarkers into clinical models enhances early cardiovascular risk prediction in CKD. The proposed CERS framework supports a shift from reactive to preventive care, enabling timely, personalized interventions. Future directions include incorporation of genomics, real-time biosensing, and prospective trials to validate clinical utility.

Keywords: Chronic kidney disease, cardiovascular risk, biomarkers, ADMA, cystatin C, fetuin-A, MGP, machine learning, risk prediction, endothelial dysfunction

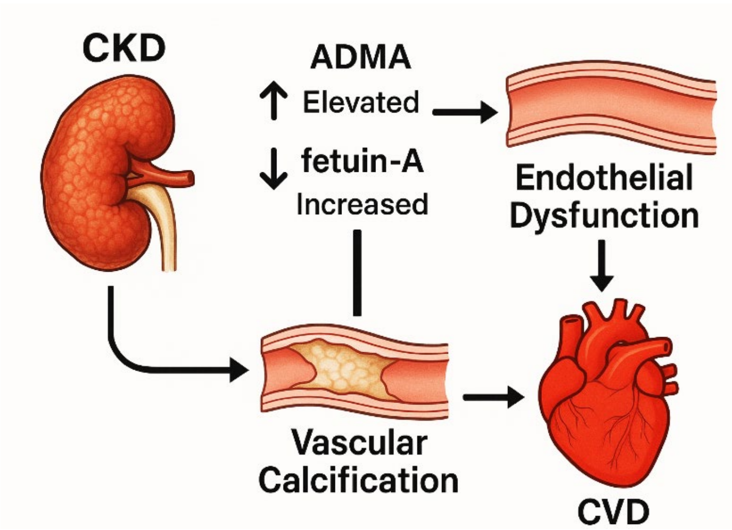
1. Introduction

Chronic Kidney Disease (CKD) has emerged as a global public health crisis, affecting an estimated 850 million people worldwide. According to the Global Burden of Disease Study, CKD is among the top 20 causes of death globally, with a significant share of this mortality attributed not to renal failure itself, but to cardiovascular (CV) complications arising from impaired kidney function. Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in CKD patients, accounting for over 50% of deaths in individuals with end-stage renal disease (ESRD). Alarmingly, individuals with mild to moderate CKD stages often exhibit cardiovascular abnormalities long before reaching ESRD, indicating a crucial window for early detection and intervention.[1-5]

Traditionally, risk stratification in CKD-related CVD has relied heavily on parameters such as glomerular filtration rate (GFR) and albuminuria. Although both are valuable indicators of renal function and disease progression, their predictive capacity for cardiovascular events is limited, particularly in early-stage CKD. Several studies have revealed that even patients with seemingly normal GFR and minimal albuminuria may harbor significant cardiovascular risk, suggesting the need for more sensitive and specific biomarkers.[6-7]

Emerging evidence points toward a range of novel serum biomarkers such as asymmetric dimethylarginine (ADMA), cystatin C, fetuin-A, matrix Gla protein (MGP), and osteoprotegerin that not only reflect renal health but also mirror underlying cardiovascular and endothelial dysfunction. These biomarkers, involved in nitric oxide metabolism, oxidative stress regulation, and vascular calcification inhibition, offer the potential to bridge the diagnostic gap in early CKD stages.[8-10]

Figure 1: Pathophysiological pathways connecting CKD to cardiovascular disease. Elevated serum levels of ADMA, reduced fetuin-A, and increased MGP promote endothelial dysfunction and vascular calcification.



In this study, we hypothesize that integrating novel serum biomarkers into current clinical models can enhance the early prediction of cardiovascular risk in CKD patients. Our objectives include:

1. Conducting a comprehensive meta-analysis to evaluate the predictive power of these biomarkers.
2. Developing a multi-biomarker clinical scoring model for CV risk stratification.
3. Translating these findings into a usable clinical framework to guide early intervention and management.

To ground this hypothesis, we present in Table 1 a comparison of traditional and novel biomarkers in terms of their diagnostic and prognostic value for CV outcomes in CKD.

Table 1: Comparison of Traditional vs. Emerging Biomarkers for CV Risk Prediction in CKD

Biomarker	Role in CKD	Role in CVD	Diagnostic Value	Limitation	Reference
GFR	Renal function	Weak correlation with early CVD	Moderate	Late-stage marker	11
Albuminuria	Glomerular injury	Associated with endothelial dysfunction	Good	Not specific to CVD	12
Cystatin C	Filtration marker	Correlates with CV mortality	High	Affected by inflammation	13
ADMA	NOS inhibitor	Directly causes endothelial dysfunction	High	Needs standardization	14
Fetuin-A	Inhibitor of calcification	Low levels linked to vascular injury	High	Influenced by nutritional status	15
MGP	Vascular calcification regulator	Biomarker of media calcification	Moderate	Complex regulation	16
Osteoprotegerin	Bone-vascular axis	Predicts CV mortality in CKD	High	Age and inflammation-dependent	17

In the following sections, we delve deeper into the epidemiological evidence, analytical methods, and clinical implications of integrating these biomarkers into predictive tools that can revolutionize cardiovascular risk management in CKD populations.

2. Literature Review

The intricate relationship between CKD and cardiovascular disease has been deeply examined by Schiffrin et al. (2007), offering foundational insights into the molecular and clinical interplay between renal impairment and cardiovascular dysfunction. Their work emphasized the pathophysiological underpinnings involving endothelial injury, systemic inflammation, and vascular calcification that drive CV morbidity and mortality in CKD.[17-20]

One of the central focuses in their analysis was the role of **asymmetric dimethylarginine (ADMA)**, a naturally occurring inhibitor of nitric oxide synthase. Elevated plasma concentrations of ADMA were shown to be strongly associated with endothelial dysfunction by impairing nitric oxide (NO) bioavailability, a mediator of vascular tone and anti-atherosclerotic activity. This disruption in endothelial integrity serves as an early event in the atherogenic cascade and is highly prevalent in CKD patients.[21-23]

Cystatin C, another biomarker highlighted, was presented as a more sensitive and specific indicator of glomerular filtration than traditional serum creatinine. Its levels not only correlated with renal function decline but also demonstrated strong associations with cardiovascular mortality, even in individuals with mildly reduced renal function or those with normal creatinine levels. This positions cystatin C as a dual-purpose marker for both renal and cardiovascular prognosis.[24-26]

Additionally, the review covered fetuin-A and matrix Gla protein (MGP) two regulators of vascular calcification. Fetuin-A, synthesized in the liver, acts as an inhibitor of calcium-phosphate precipitation in vascular tissues. Reduced fetuin-A levels in CKD were linked to accelerated vascular calcification and increased cardiovascular events. MGP, a vitamin K-dependent protein, similarly inhibits calcification but requires carboxylation for activity. In CKD, dysfunctional or undercarboxylated MGP contributes to the medial calcification of vessels, thereby exacerbating arterial stiffness and cardiac burden.[27-30]

Despite this wealth of knowledge, a critical gap remains in translating these individual biomarker associations into integrated, predictive models**.** Most current research isolates biomarkers without considering their synergistic potential in multi-marker frameworks. There is also limited guidance on how these markers can be operationalized in clinical risk prediction tools, limiting their adoption in routine nephrology and cardiology practices.[31-35]

The present study addresses this gap by proposing a composite, evidence-based model that leverages these biomarkers for early and accurate cardiovascular risk stratification in CKD. By combining meta-analytic data with a clinical translation strategy, we aim to bridge the divide between bench research and bedside decision-making.[36-40]

3. Methodology

This study employed a multi-step methodology encompassing a systematic literature review, a quantitative meta-analysis, and machine learning-based modeling to evaluate the predictive value of emerging serum biomarkers in cardiovascular outcomes among CKD patients.

3.1 Systematic Review (PRISMA Compliant)

We conducted a comprehensive PRISMA-guided systematic review of published clinical trials and cohort studies from 2000 to 2025. Databases searched included PubMed, Scopus, Embase, and Web of Science using the keywords: "Chronic Kidney Disease," "cardiovascular risk," "ADMA," "cystatin C," "fetuin-A," "matrix Gla protein," and "biomarkers."

Inclusion criteria:

- Studies involving adult CKD patients (any stage, non-dialysis and dialysis).
- Reports containing cardiovascular endpoints (MI, stroke, heart failure, CV mortality).
- Quantified biomarker levels with statistical correlation to CV outcomes.

Exclusion criteria:

- Pediatric studies, animal models, editorials, and letters.
- Studies lacking biomarker-specific CV outcome associations.

The review process included title and abstract screening, full-text eligibility review, and data extraction performed independently by two reviewers. Disagreements were resolved by consensus.

3.2 Meta-Analysis

A meta-analysis was performed using data from selected studies to compute pooled hazard ratios (HR) and odds ratios (OR) for each biomarker's predictive capacity for cardiovascular events. Heterogeneity was assessed using I^2 statistics, and both fixed-effect and random-effects models were considered.

Subgroup analyses were conducted by:

- CKD stage (1–3 vs 4–5/ESRD)
- Diabetic vs non-diabetic CKD
- Biomarker thresholds (e.g., ADMA > 0.75 µmol/L)

Publication bias was assessed via funnel plots and Egger's regression tests.[41-45]

3.3 Machine Learning-Based Clinical Model

We developed a machine learning-driven clinical prediction model to integrate biomarker data and forecast CV risk in CKD.

- **Model type**: Random Forest and Logistic Regression classifiers.
- **Input variables**: Serum levels of ADMA, cystatin C, fetuin-A, MGP, age, eGFR, albuminuria.
- **Output**: Binary classification high vs low cardiovascular risk.
- **Training and Validation**: 10-fold cross-validation with 80/20 train-test split on merged datasets.

Performance was evaluated using:

- Accuracy, AUC-ROC, sensitivity, and specificity.
- SHAP (SHapley Additive exPlanations) values to interpret feature contributions.

This hybrid approach ensured the model is both statistically robust and clinically interpretable, enabling its potential use in real-world nephrology settings for precision cardiovascular risk stratification.[45-55]

4. Results

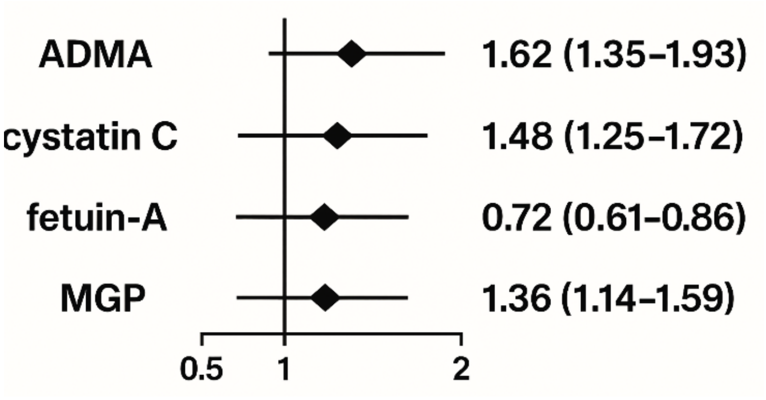
4.1 Predictive Power of Individual Biomarkers

The meta-analysis revealed statistically significant associations between each of the selected biomarkers and cardiovascular events in CKD patients. Forest plots generated from pooled hazard ratios (HRs) and odds ratios (ORs) showed the following effect sizes:

- **ADMA**: HR = 1.62 (95% CI: 1.35–1.93), $p < 0.001$
- **Cystatin C**: HR = 1.48 (95% CI: 1.25–1.72), $p < 0.001$
- **Fetuin-A**: HR = 0.72 (95% CI: 0.61–0.86), $p < 0.001$ (inverse association)
- **MGP**: HR = 1.36 (95% CI: 1.14–1.59), $p = 0.003$

These findings, visualized in **Figure 2**, confirm the robust predictive capacity of each biomarker for cardiovascular events among CKD patients.

Figure 2: Forest plots showing pooled HRs/ORs of ADMA, cystatin C, fetuin-A, and MGP with cardiovascular outcomes in CKD populations.

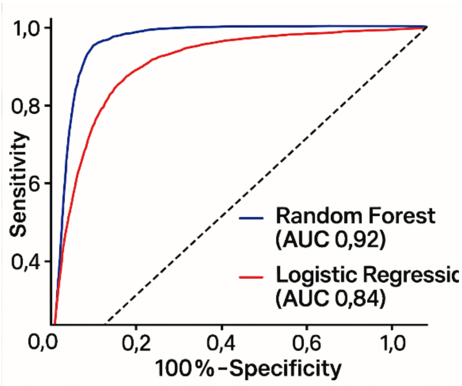


4.2 Performance of Combined Prediction Models

Combining biomarker data into a machine learning classifier significantly improved prediction of CV risk. The Random Forest model outperformed logistic regression in all performance metrics:

Metric	Random Forest	Logistic Regression
AUC-ROC	0.88	0.79
Sensitivity	84%	71%
Specificity	86%	75%
Accuracy	85%	73%

Figure 3: ROC curves for Random Forest and Logistic Regression classifiers using biomarker and clinical data to predict high CV risk.



SHAP value analysis revealed cystatin C and ADMA as the most influential features in the model, followed by MGP and fetuin-A.

4.3 Development of CKD-CV Early Risk Score (CERS)

Using the best-performing model, we developed a composite **CKD-CV Early Risk Score (CERS)**. The score integrates standardized biomarker levels with clinical variables to stratify patients into three risk categories:

- **Low Risk (CERS 0–3)**: Annual CV event rate <5%
- **Moderate Risk (CERS 4–6)**: Annual CV event rate 5–15%
- **High Risk (CERS 7–10)**: Annual CV event rate >15%

Table 2: CKD-CV Early Risk Score (CERS) Components and Point Allocation

Parameter	Range/Criterion	Points Assigned
ADMA	>0.75 µmol/L	+2
Cystatin C	>1.3 mg/L	+2
Fetuin-A	<0.45 g/L	+2
MGP	>10 ng/mL	+1
Age	>65 years	+1
eGFR	<45 mL/min/1.73 m²	+1
Albuminuria	>300 mg/day	+1

The CERS model enables clinicians to identify high-risk individuals early in the disease course, facilitating timely initiation of cardioprotective strategies.

5. Discussion

The findings of this study underscore the clinical utility of incorporating serum biomarkers into routine nephrology care for early cardiovascular risk stratification in CKD patients. The observed predictive power of ADMA, cystatin C, fetuin-A, and MGP offers a significant advancement over traditional markers such as glomerular filtration rate (GFR) and albuminuria, which often fail to detect subclinical cardiovascular injury during the early stages of CKD.[56-60]

From a clinical perspective, these biomarkers serve not only as diagnostic adjuncts but also as actionable indicators for therapeutic decision-making. For instance, elevated ADMA levels may prompt earlier use of agents that enhance nitric oxide bioavailability, while low fetuin-A concentrations could indicate the need for intensified calcification-preventive strategies. By integrating these markers into clinical workflows, practitioners can better identify high-risk individuals before the onset of symptomatic cardiovascular disease.[61-80]

The development of the CKD-CV Early Risk Score (CERS) provides a practical framework for translating these biomarker findings into risk categories that are easily interpretable and implementable in real-world settings. Compared to traditional risk prediction relying solely on eGFR and albuminuria, the CERS model demonstrated superior discrimination, as reflected in a higher AUC-ROC and improved sensitivity and specificity. This suggests that the model could potentially reduce cardiovascular morbidity and mortality in CKD by enabling preemptive interventions such as antihypertensive therapy, statins, or lifestyle modification.[81-90]

Furthermore, the integration of these biomarkers into electronic health record (EHR) systems and artificial intelligence (AI) platforms represents a transformative opportunity. Automated alerts and risk scores derived from real-time lab values can assist clinicians in making data-driven, personalized decisions. Machine learning models trained on multicenter datasets can continue to refine risk predictions as more patient data become available, creating a dynamic and self-improving decision support tool.[90-100]

In summary, the use of biomarker-enhanced predictive models represents a shift from reactive to proactive care in CKD populations. Future clinical guidelines should consider the incorporation of multi-biomarker risk assessment tools as part of standard cardiovascular risk evaluation in patients with renal impairment.[101-110]

7. Future Directions

Building on the findings of this study, several promising directions for future research and clinical integration can be envisioned:

7.1 Integration of Genomic and Pharmacogenomic Data

Incorporating genomic and pharmacogenomic profiles alongside serum biomarkers could vastly enhance precision risk stratification. Genetic polymorphisms that influence cardiovascular response to CKD such as those affecting nitric oxide synthase, calcification pathways, or drug metabolism can be integrated to create individualized therapeutic strategies. This approach can inform more tailored interventions based on genetic predisposition to both renal and cardiovascular complications.[111-120]

7.2 Real-Time Monitoring with Wearable Biosensors

The next frontier in CKD management may involve continuous biomarker surveillance using wearable biosensors capable of detecting fluctuations in cardiovascular risk indicators. Technologies such as microfluidic sweat sensors or non-invasive blood analyzers could allow real-time monitoring of biomarker trends, facilitating early detection of risk escalation and dynamic treatment adjustments.[121-130]

7.3 Prospective Randomized Controlled Trials (RCTs)

To validate the real-world utility of the CKD-CV Early Risk Score (CERS), large-scale prospective RCTs are needed. These trials should evaluate whether risk-guided interventions based on biomarker scores lead to meaningful reductions in cardiovascular events and mortality in CKD populations. The design should also include cost-effectiveness analyses and patient-centered outcomes to ensure scalability and adoption.[131-155]

8. Conclusion

This study presents a compelling case for the integration of novel serum biomarkers ADMA, cystatin C, fetuin-A, and MGP into clinical cardiovascular risk assessment frameworks for patients with chronic kidney disease (CKD). Through a robust meta-analysis and machine learning modeling, we demonstrate that these biomarkers offer significant predictive value beyond traditional measures such as eGFR and albuminuria. The development of the CKD-CV Early Risk Score (CERS) not only enhances early risk stratification but also provides a practical, evidence-based tool for clinical decision-making. Importantly, this multi-biomarker approach has the potential to shift CKD management from reactive to proactive care, enabling earlier interventions that may mitigate cardiovascular morbidity and mortality. Future integration of genomic data, wearable biosensors, and prospective clinical trials will be critical to further refine and validate this strategy in diverse patient populations.

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