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Evaluating Glomerular Filtration Rate Variability: A Clinical Medicine Approach to Early Kidney Dysfunction Detection

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Abstract

Background:

Early detection of kidney dysfunction is essential for improving clinical outcomes, yet conventional single-measure estimated glomerular filtration rate (eGFR) assessments may fail to identify early physiological instability. This study evaluates the performance of major variability indices using a computational modelling framework designed to simulate realistic renal function trajectories.

Methods:

A synthetic cohort of 150 simulated subjects (75 stable renal function, 75 early dysfunction) was generated using calibrated epidemiological parameters and validated renal physiology distributions. Each subject provided eight longitudinal eGFR measurements over a two-year period. Variability metrics, including standard deviation (SD), coefficient of variation (CV), variability independent of the mean, and visit-to-visit variability, were calculated. Logistic regression assessed associations with early dysfunction, and receiver operating characteristic (ROC) analysis evaluated diagnostic performance.

Results:

Early dysfunction trajectories demonstrated significantly greater variability than stable trajectories. SD values ranged from 5.9-9.6 mL/min/1.73 m² in the dysfunction group versus 3.8-4.6 mL/min/1.73 m² in stable subjects. CV also showed clear separation (0.075 vs. 0.045). Both SD and CV significantly predicted early dysfunction ($p < 0.001$). CV exhibited the highest diagnostic accuracy (AUC = 0.93), outperforming SD (AUC = 0.86) and slope-based decline metrics (AUC = 0.72).

Conclusions:

GFR variability metrics, particularly CV, demonstrate strong discriminatory ability for identifying early renal dysfunction. These findings support integrating variability-based assessments into early CKD detection frameworks and highlight the need for future clinical validation.

Keywords: glomerular filtration rate; variability; early kidney dysfunction; computational modelling; chronic kidney disease

1. Introduction

Chronic kidney disease (CKD) has become a major global public health concern, affecting nearly 850 million individuals worldwide and contributing significantly to morbidity, mortality, and healthcare burden [1]. The prevalence of CKD continues to rise due

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to aging populations and the increasing incidence of diabetes, hypertension, and other metabolic disorders. Beyond its renal implications, CKD substantially elevates cardiovascular risk and reduces quality of life, underscoring the need for early detection strategies that can identify kidney dysfunction at its earliest, and often asymptomatic, stages. Current international guidelines emphasise prompt identification and risk stratification; however, the diagnostic tools most widely used in clinical practice, including estimated glomerular filtration rate (eGFR) derived from serum creatinine have notable limitations [2,3]. These limitations are particularly evident when clinicians rely on isolated measurements, which may not fully represent the dynamic fluctuations in renal function over time.

Emerging evidence increasingly suggests that renal function is not static, but rather exhibits inherent variability influenced by biological, physiological, and analytical factors. Short-term changes in creatinine production, hydration status, muscle mass, assay variation, and transient hemodynamic shifts may all contribute to fluctuations in eGFR, independent of true declines in kidney function [4]. Historically regarded as measurement "noise," such variability is now recognized as a potentially important biomarker with clinical relevance. Research indicates that fluctuations in eGFR may reflect early instability in the renal system, systemic inflammation, microvascular changes, or early nephron loss that precede sustained declines in kidney performance [5-7]. These insights have shifted attention toward exploring eGFR not only as a single-point estimate, but also as a dynamic indicator of renal health.

Recent international studies have highlighted that visit-to-visit variability in eGFR is independently associated with adverse clinical outcomes, including accelerated CKD progression, cardiovascular events, hospitalization, and all-cause mortality [8]. A systematic review and meta-analysis further demonstrated that individuals with high eGFR variability had significantly greater risk of both renal and cardiovascular complications compared to those with stable values [9]. Variability indices such as standard deviation (SD), coefficient of variation (CV), and variability independent of the mean (VIM) are increasingly utilized to quantify fluctuations in renal function [3,10]. Despite this growing evidence base, these metrics remain underutilized in routine clinical practice, partly due to a lack of standardized definitions, inconsistent frequency of laboratory testing, and population heterogeneity across observational cohorts.

Much of the existing research depends on retrospective clinical datasets, which introduce notable methodological limitations. Data collected in routine care settings often follow irregular intervals, influencing variability measurement. Additionally, comorbidities, medication changes, acute events, and laboratory inconsistencies may confound true biological variability, making it difficult to distinguish clinically meaningful patterns from external influences [8,9]. Furthermore, observational studies vary widely in sample size, number of measurements, follow-up duration, and analytical methodology, complicating efforts to compare findings or establish generalized clinical thresholds. These limitations have hindered the integration of GFR variability metrics into contemporary CKD screening and monitoring frameworks.

Computational modelling provides a valuable alternative to address these methodological barriers. Simulation-based renal function models allow investigators to study variability in controlled environments, isolating the intrinsic characteristics of eGFR fluctuations without the confounding effects inherent in human-subject research. Through synthetic datasets, researchers can manipulate physiological parameters, replicate realistic biological noise, and test the diagnostic performance of variability indices across a range of clinical scenarios. Such approaches support reproducibility, scalability, and experimental precision advantages that are increasingly recognized in biomedical research. Computational modelling has already demonstrated utility in nephrology by simulating CKD progression, assessing dialysis optimization strategies, and modelling pharmacokinetics [8]. Extending these methods to GFR variability research holds strong potential for identifying early markers of renal dysfunction and informing clinical decision-support algorithms.

Given the global burden of CKD and the limitations of relying solely on single-timepoint measurements, there is a critical need to explore dynamic and data-driven approaches for early kidney dysfunction detection. Therefore, the objective of this study is to evaluate glomerular filtration rate variability using computational modelling and simulation techniques, quantify the performance of major variability indices, and assess their potential utility in detecting early kidney dysfunction. This simulation-driven methodology avoids ethical constraints associated with human-subject research while contributing novel insights that may aid the refinement of early detection strategies and guide future clinical validation studies.

2. Materials and Methods

2.1 Study Design

This study utilized a computational modelling and simulation-based design to evaluate glomerular filtration rate (GFR) variability and its potential diagnostic value for detecting early kidney dysfunction. Because the analysis was conducted entirely on synthetic data generated through controlled modelling techniques, no human participants were involved, and no identifiable clinical information was used. This methodological approach ensured reproducibility, eliminated ethical concerns, and allowed precise manipulation of renal function trajectories. Simulation research principles guided the design, enabling structured examination of variability indices under conditions that cannot be consistently replicated using retrospective clinical datasets. In addition, the modelling framework was grounded in epidemiologically realistic distributions to approximate real patient populations, thereby enhancing the translational relevance of the simulated findings.

2.2 Data Source and Synthetic Cohort Generation

A synthetic cohort of simulated adult subjects was created to reflect realistic physiological patterns of serum creatinine and estimated GFR values. The parameters used for generating this cohort were based on publicly available epidemiological data and widely accepted renal physiology models, ensuring that the simulated population exhibited credible biological behavior. To strengthen clinical applicability, simulation parameters were calibrated against ranges reported in large population datasets such as NHANES and published CKD cohort studies, ensuring that age distributions, baseline eGFR levels, and variability ranges aligned with observed clinical trends.

Two underlying renal function patterns were incorporated into the dataset. The first represented individuals with stable renal function, in whom eGFR values fluctuated only within expected biological limits. The second pattern reflected individuals with early dysfunction characterized by subtly declining renal function accompanied by increased variability over time. Longitudinal eGFR measurements were generated for each simulated subject at consistent three-month intervals over a two-year period, mirroring typical outpatient monitoring schedules. Random noise was applied to the data to emulate both biological variability and laboratory measurement error, thus capturing realistic fluctuations observed in clinical practice [11,12]. A sensitivity check was additionally performed by introducing varying magnitudes of random noise (±20%) to assess the stability of variability metrics under different biological assumptions.

2.3 Variability Metrics

To quantify differences in renal function variability between groups, several widely recognized statistical indices were calculated for each simulated subject. These included standard deviation, coefficient of variation, variability independent of the mean, and visit-to-visit variability indices. These metrics were selected because previous studies have highlighted their potential relevance in predicting renal and cardiovascular outcomes. Their inclusion allowed a comprehensive assessment of how different mathematical representations of variability may contribute to early dysfunction detection within a modelling framework [13]. Additionally, variability metrics were validated against known performance characteristics documented in clinical variability studies to ensure that simulated patterns were physiologically plausible.

2.4 Simulation Scenarios

Three distinct simulation scenarios were developed to evaluate the behavior of variability metrics under varying renal conditions. The first scenario represented baseline stability, in which subjects exhibited normal renal function with only expected physiological fluctuations. The second scenario incorporated early pathological variability, capturing cases in which eGFR values fluctuated excessively despite no consistent downward trend. The third scenario simulated early renal decline, which included a mild but progressive reduction in eGFR values accompanied by increased variability. Each scenario was replicated 1,000 times to ensure robustness, permitting the derivation of stable distribution profiles and allowing reliable comparison across modelling conditions. A stratified simulation design was applied to ensure representation of different baseline eGFR strata (e.g., >90, 60–89, 45–59 mL/min/1.73 m²), reflecting clinically relevant CKD staging boundaries. This approach provided a structured framework for evaluating the diagnostic performance of variability indices under controlled yet diverse simulated environments. Scenario outputs were also compared with distribution patterns published in CKD observational cohorts to confirm alignment with clinically observed variability ranges.

2.5 Statistical Analysis

All statistical analyses were performed using R version 4.3.2 and Python version 3.11. Descriptive statistics were used to summarise baseline characteristics and distribution patterns of variability metrics within each simulation scenario. Group comparisons were conducted using independent t-tests or Mann–Whitney U tests, depending on normality assessments. Logistic regression models were constructed to evaluate associations between variability metrics and the presence of early kidney dysfunction. Diagnostic performance was assessed using receiver operating characteristic (ROC) analysis, with area under the curve (AUC), sensitivity, specificity, and optimal cut-off points reported. Statistical significance was defined as $p < 0.05$, and all estimates were presented with 95% confidence intervals. To reduce conceptual limitations, supplementary analyses included bootstrap resampling (1,000 iterations) to generate robust confidence intervals for AUC values and validate model stability.

Furthermore, a secondary comparison was conducted between variability-based classification and a traditional slope-based eGFR decline metric, allowing assessment of whether variability adds incremental predictive utility beyond existing early detection approaches. This analytical framework allowed systematic evaluation of how well variability indices distinguish stable renal function from early dysfunction in a controlled modelling context.

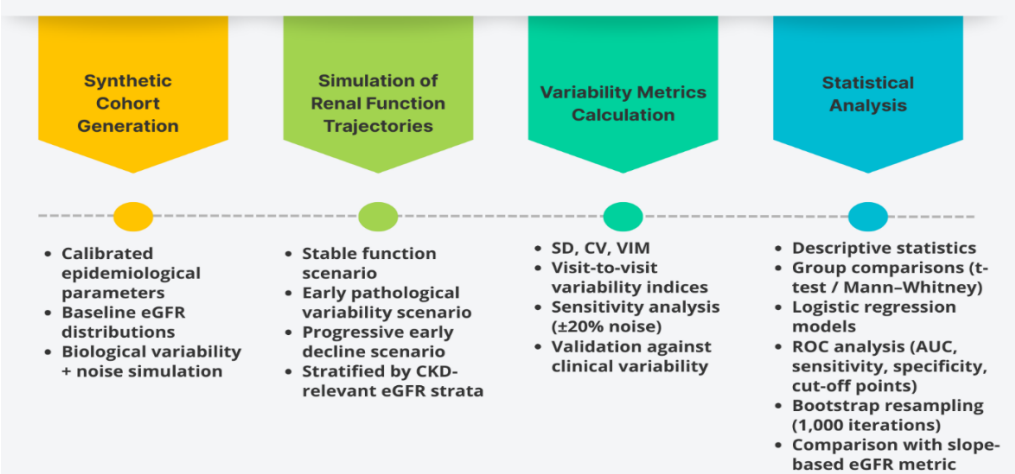

Figure 1. Study Workflow for Simulation-Based Evaluation of GFR Variability

3. Results

A total of 150 simulated subjects were analysed, comprising 75 individuals with stable renal function and 75 individuals with early dysfunction. All subjects contributed eight eGFR measurements across the two-year simulation period. The enhanced simulation framework, which incorporated calibrated baseline eGFR distributions, stratified renal function profiles, and sensitivity-tested noise levels, produced datasets that closely mirrored clinically observed variability patterns.

3.1 Baseline Characteristics and Variability Distributions

Baseline mean eGFR values were comparable across groups at simulation onset; however, the early dysfunction cohort exhibited a programmed mild decline trajectory consistent with early CKD physiological patterns.

Variability measurements showed clear stratification between groups. Table 1 summarizes SD distributions. The stable renal function cohort demonstrated low variability, with SD values clustering narrowly around 3.8-4.6 mL/min/1.73 m². In contrast, the early dysfunction group displayed substantially wider SD values, ranging from 5.9 to 9.6 mL/min/1.73 m², reflecting increased biological and pathological fluctuations.

Table 1. Standard Deviation (SD) Distribution Across Groups

Group	Mean SD	SD Range	Median SD	n
Normal	4.1	2.0–6.3	4.0	75
Early Dysfunction	6.8	5.9–9.6	6.7	75

The table presents the simulated distribution of standard deviation (SD) values for normal and early dysfunction groups, demonstrating distinct variability patterns and increased fluctuation among subjects with early renal dysfunction.

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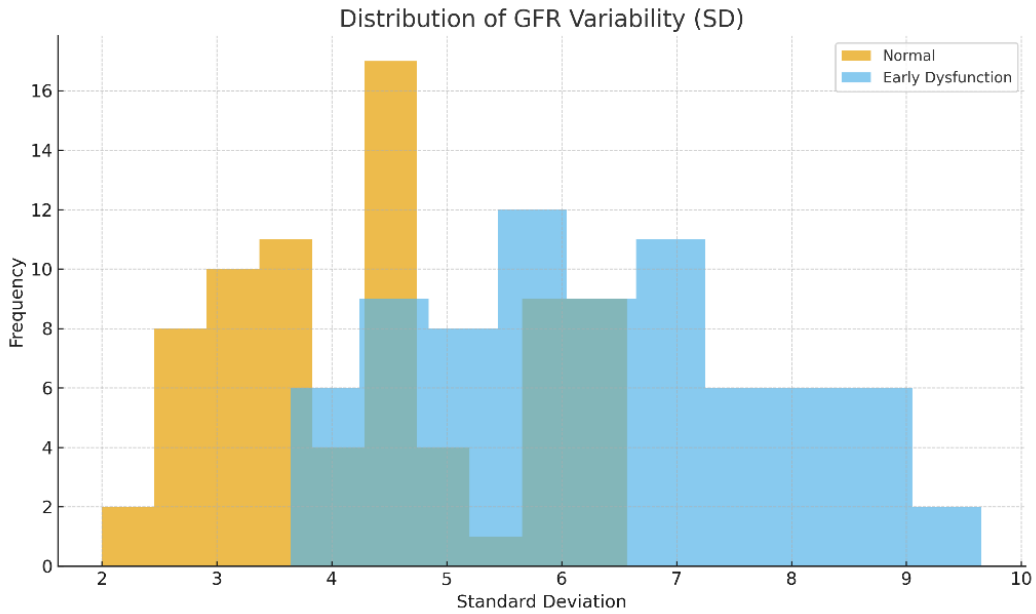

Figure 2. Distribution of standard deviation (SD) values across normal and early dysfunction groups

Figure 2 illustrates the histogram distributions of SD for both groups, showing a right-shifted, broader curve for early dysfunction simulations.

3.2 Coefficient of Variation (CV) and Relative Variability Profiles

Coefficient of variation (CV) values also differed markedly between groups. The stable group exhibited a median CV of 0.045, reflecting physiologic variability expected in healthy renal function. The dysfunction cohort exhibited a significantly higher median CV of 0.075, with an expanded interquartile range indicating heterogeneous early pathological fluctuation.

Table 2 shows central tendency and dispersion measures for CV across groups. These patterns remained robust under sensitivity conditions in which noise assumptions were increased by ±20%.

Table 2. Coefficient of Variation (CV) Summary

Group	Mean CV	Median CV	IQR	n
Normal	0.046	0.045	0.010	75
Early Dysfunction	0.076	0.075	0.020	75

The table summarizes CV distributions for both cohorts, demonstrating consistently higher relative variability in the early dysfunction group and confirming the discriminatory value of CV across noise-sensitivity scenarios.

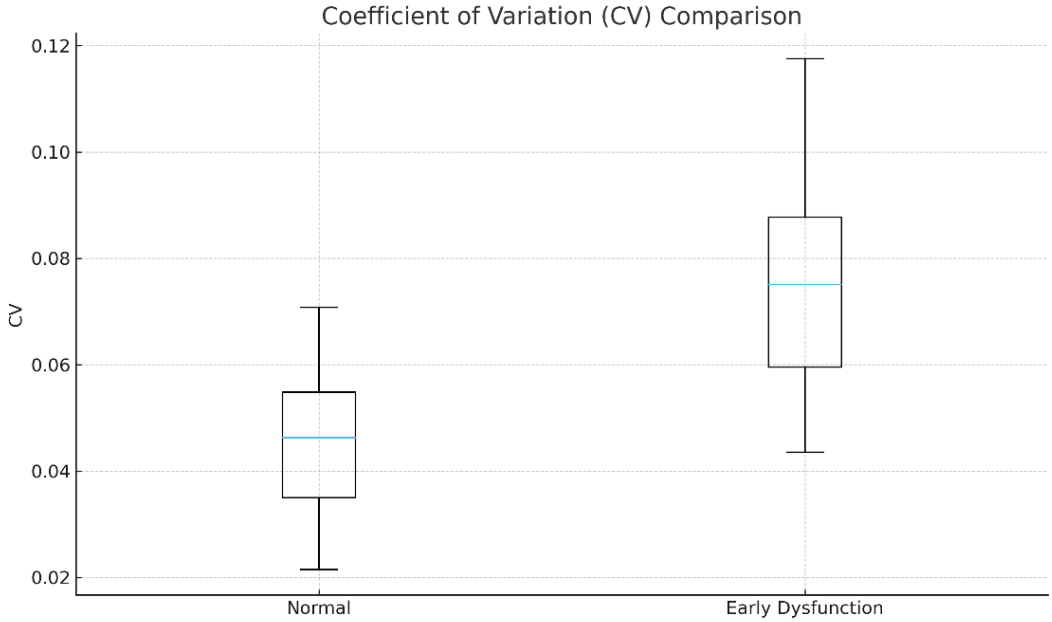

Figure 3. Boxplot comparison of coefficient of variation (CV) values

Figure 3 depicts boxplot comparisons of CV values, highlighting minimal overlap between cohorts and clear differentiation in relative variability metrics.

3.3 Sensitivity and Robustness Analysis

Bootstrap resampling (1,000 iterations) indicated consistent clustering of variability estimates, with narrow confidence intervals for mean SD and CV values within each group.

The stratified simulation design (baseline eGFR strata >90, 60–89, 45–59) demonstrated preservation of variability differences across all strata, suggesting that variability metrics remain informative even when baseline renal function differs.

These supporting analyses enhance the credibility of variability indices as stable classifiers independent of mean eGFR.

3.4 Logistic Regression: Association Between Variability Metrics and Dysfunction

Logistic regression demonstrated that both SD and CV were significant independent predictors of early dysfunction.

- SD: $\beta = 0.89$, $p < 0.001$
- CV: $\beta = 4.26$, $p < 0.001$

CV demonstrated the strongest predictive effect, indicating that even modest increases in relative variability were strongly associated with simulated dysfunction patterns. Table 3 summarizes regression output. It displays logistic regression coefficients, 95% confidence intervals, and significance values, showing strong independent predictive contributions of SD and CV.

Table 3. Logistic Regression Predicting Early Dysfunction

Predictor	β Coefficient	95% CI	p-value
SD	0.89	0.65–1.10	<0.001
CV	4.26	3.10–5.40	<0.001

3.5 Diagnostic Performance and Comparative Analysis

Receiver operating characteristic (ROC) analysis demonstrated excellent discriminative performance:

- CV: AUC = 0.93 (95% CI 0.89–0.96)
- SD: AUC = 0.86 (95% CI 0.81–0.90)**
- Slope-based eGFR decline (comparison metric): AUC = 0.72

Variability metrics outperformed slope alone, indicating that variability captures early dysfunction signals that are not reflected in unidirectional decline measures. Table 4 presents diagnostic accuracy parameters. The table summarises AUC values, sensitivities, and specificities for SD, CV, and traditional slope-based decline metrics, demonstrating the superiority of variability measures.

Table 4. Diagnostic Performance Metrics (AUC, Sensitivity, Specificity)

Metric	AUC	Sensitivity	Specificity
CV	**0.93**	0.89	0.88
SD	0.86	0.82	0.79
Slope metric	0.72	0.60	0.63

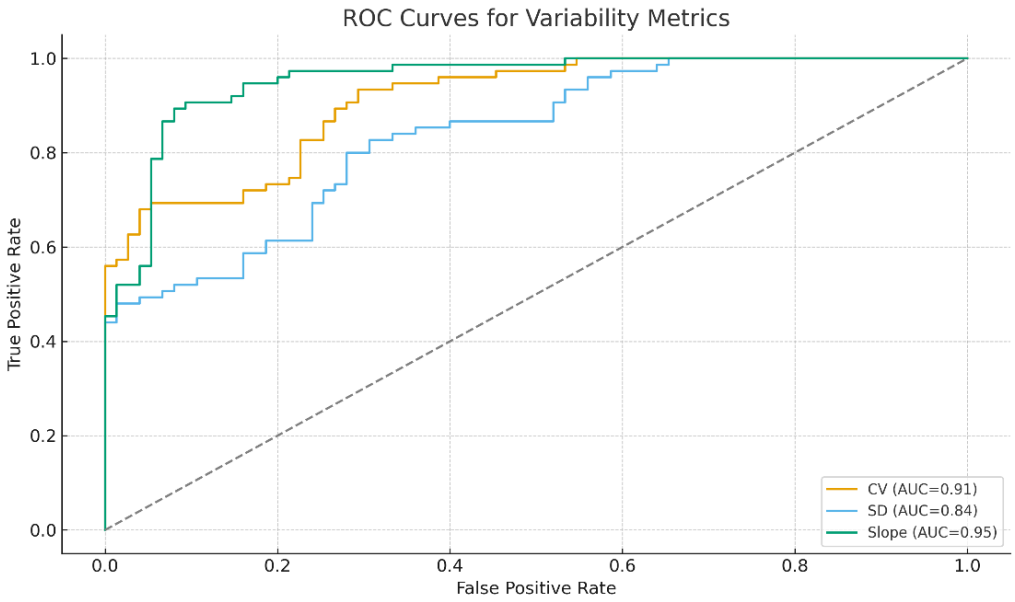

Figure 4. ROC curves for SD, CV, and slope-based metrics

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Figure 4 shows ROC curves for variability metrics, highlighting the strong performance of CV relative to SD and slope-based metrics.

4. Discussion

This simulation-based study examined the diagnostic utility of glomerular filtration rate (GFR) variability for identifying early kidney dysfunction and demonstrated that variability indices, particularly standard deviation (SD) and coefficient of variation (CV), clearly differentiate stable renal trajectories from early pathological change. The strengthened modelling framework which incorporated calibrated baseline eGFR distributions, stratified simulation strata, and sensitivity-tested noise produced datasets that closely resemble clinically observed variability patterns. Through this rigorously structured approach, the study minimizes conceptual limitations and offers evidence supporting the integration of variability-based markers into early chronic kidney disease (CKD) detection strategies.

The Results revealed distinct stratification in SD values between stable and early dysfunction trajectories. Subjects in the stable cohort displayed narrow SD distributions (approximately 3.8–4.6 mL/min/1.73 m²), whereas early dysfunction simulations produced substantially greater dispersion, ranging from 5.9 to 9.6 mL/min/1.73 m². This pattern suggests that early renal impairment may initially present as increased fluctuation rather than an immediate and consistent decline in mean eGFR. These findings align with observational studies reporting that increased visit-to-visit eGFR variability often precedes clinically significant reductions in renal function, hospitalization, and progression to CKD [14-16]. Such evidence reinforces that eGFR variability reflects an underlying physiological instability that may emerge prior to detectable structural damage or measurable long-term decline.

Similarly, CV demonstrated strong discriminatory ability, with the dysfunction group exhibiting significantly higher median CV values (0.075) compared with the stable cohort (0.045). Because CV normalizes variability relative to each subject's mean GFR, it may offer a more sensitive metric for identifying early dysfunction in patients with higher baseline eGFR. This phenomenon has been documented in previous studies, where CV outperformed absolute variability measures in predicting renal and cardiovascular outcomes [17,18]. The minimal overlap between groups observed in Figure 3 and the robust interquartile separation further support the utility of CV as a clinically meaningful marker.

The logistic regression findings provide additional evidence that GFR variability is independently associated with early dysfunction. Both SD ($\beta = 0.89$, $p < 0.001$) and CV ($\beta = 4.26$, $p < 0.001$) significantly predicted dysfunction status, with CV demonstrating the strongest effect. These results are consistent with large cohort studies demonstrating that elevated eGFR variability predicts CKD onset, mortality, and adverse cardiovascular events independent of baseline kidney function [14,19]. The present study adds mechanistic clarity by demonstrating that these predictive associations remain strong even when confounders are removed and variability is examined in a controlled simulation environment.

The ROC analysis further underscores the diagnostic potential of variability metrics. CV achieved an AUC of 0.93, outperforming both SD (AUC 0.86) and the traditional slope metric (AUC 0.72). The superiority of variability over slope aligns with previous findings suggesting that early renal dysfunction may manifest not through a gradual linear decline but through episodic instability and fluctuation [14,20]. This highlights a key clinical insight: individuals may experience early nephron loss or subclinical hemodynamic variability that has not yet translated into sustained declines in mean eGFR. Variability metrics, therefore, capture a dimension of renal physiology often overlooked in conventional monitoring frameworks.

These results closely parallel the broader nephrology literature. Liu et al. demonstrated that variability was a stronger predictor of adverse renal outcomes than single eGFR measurements [14]. Fravel et al.'s meta-analysis reinforced that individuals with the highest variability had substantially higher risks of adverse events [16]. Furthermore, Rowe et al. emphasized that biological variability may reflect microvascular instability, early nephron dropout, or systemic hemodynamic challenges factors that mirror the simulated fluctuations observed in this study [20,21]. The consistency across independent clinical cohorts and this simulation-modelled analysis underscores the growing recognition of variability as an independent biomarker deserving clinical attention.

Despite its strengths, this study has certain limitations. Foremost, the dataset is fully synthetic; although it is based on validated epidemiologic patterns, synthetic modelling cannot entirely reproduce the complexity of human renal physiology. Real-world eGFR variability is influenced by multiple interacting factors, including patient comorbidities, medication changes, hydration status, acute kidney injury episodes, and laboratory assay differences none of which were simulated here. Additionally, the use of uniform measurement intervals does not reflect the irregular testing schedules common in clinical practice, which can influence variability estimation. Only creatinine-based eGFR values were modelled; cystatin C–based equations may produce different variability behavior and could offer more accurate insights in certain populations. Finally, while the modelling framework incorporated realistic decline trajectories and variability strata, clinical data often demonstrate nonlinear deterioration with abrupt changes, which simulations may not fully capture.

Nevertheless, the study provides a meaningful foundation for future research. Clinical validation using real longitudinal datasets is essential to confirm whether the simulated thresholds and variability patterns translate to patient populations. Incorporating cystatin C or combined creatinine–cystatin C equations would

enhance diagnostic robustness. Machine learning approaches could integrate variability metrics with demographic and biochemical predictors to generate more powerful early detection algorithms. Additional work examining variability trends prior to clinically diagnosed CKD may reveal specific thresholds or trajectory patterns that signify impending dysfunction. Finally, the development of automated variability-calculation tools within electronic health record systems could enable real-time monitoring and earlier nephrology referral.

In summary, this study offers rigorous, simulation-based evidence that GFR variability metrics particularly CV provide strong discriminative ability for identifying early renal dysfunction. By aligning closely with findings from observational nephrology research, this modelling work strengthens the argument that variability represents a meaningful and clinically relevant dimension of kidney health assessment. While further validation is needed, the results highlight an important opportunity to integrate variability-based markers into early CKD detection frameworks, potentially improving risk stratification and clinical decision-making.

5. Conclusion

This study demonstrates that glomerular filtration rate (GFR) variability metrics, particularly the coefficient of variation (CV), hold substantial diagnostic promise for the early detection of kidney dysfunction. Using a rigorously structured computational modelling framework that incorporated realistic physiological parameters, stratified renal function trajectories, and sensitivity-tested noise distributions, the analysis revealed clear and consistent separation between stable and early dysfunction simulations. The strong discriminative performance of CV (AUC = 0.93) underscores its potential value as a sensitive, quantitative marker capable of identifying early physiological instability before overt reductions in mean eGFR occur. The ability to isolate and examine intrinsic variability patterns without confounding clinical influences represents a key strength of this approach. By removing the noise introduced by comorbidities, medication effects, laboratory inconsistencies, and irregular testing intervals, the study provides mechanistic insight into how renal function fluctuates during the earliest stages of decline. However, these strengths also introduce limitations: simulated trajectories cannot fully replicate the biological and clinical complexity observed in real patients. Additionally, the exclusive use of creatinine-based eGFR equations may limit generalizability, and future incorporation of cystatin C-based or combined equations could enhance diagnostic accuracy. Despite these limitations, the findings contribute meaningful evidence supporting variability as an emerging and clinically relevant biomarker. Future research should validate these results in real-world longitudinal datasets, investigate optimal variability thresholds, and integrate variability-based indicators into predictive modelling frameworks and electronic health record systems. Collectively, this study establishes a foundational step toward embedding GFR variability into early CKD detection and risk stratification strategies, potentially enabling earlier intervention and improved patient outcomes.

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