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Cardiorenal Nexus in ATTR-Amyloidosis: Beyond eGFR—Leveraging Albuminuria for Enhanced Risk Stratification

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Abstract

Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) leads to progressive heart failure and renal congestion. Existing risk models, such as the National Amyloidosis Centre (NAC) staging system, rely on the estimated glomerular filtration rate (eGFR), which typically identifies organ damage only at advanced stages. In this study, the urine albumin-to-creatinine ratio (UACR) was evaluated as an early marker of systemic disease and its predictive value for disease progression before a decline in eGFR was assessed.

Methods

In this longitudinal study, 124 patients with ATTR-CM were evaluated using the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 Risk Matrix. A statistical model was developed to examine the direct and indirect relationships of baseline UACR and eGFR with subsequent NAC stage and follow-up eGFR.

Results

The cohort (median age, 80.2 years; 88.7% male) had a median baseline eGFR of 61.2 mL/min/1.73 m^2 and a wide range of UACR values. Generalised structural equation modelling indicated that baseline UACR was not directly associated with follow-up eGFR ($p = 0.971$) but was positively associated with subsequent NAC stage ($p = 0.068$). Follow-up eGFR exhibited a strong correlation with NAC stage ($p < 0.001$). At a preserved eGFR of 60 mL/min/1.73 m^2, increasing the UACR from 30 to 400 mg/g reduced the probability of remaining in NAC Stage I from 76.6% to 41.3%, whereas the likelihood of progression to NAC Stage II increased from 23.2% to 56.7%.

Conclusions

UACR serves as a sensitive early indicator of systemic disease in ATTR-CM. Incorporating UACR alongside eGFR facilitates earlier detection of subclinical cardiac and renal involvement, potentially improving risk stratification and supporting more timely therapeutic intervention before irreversible organ damage occurs.

1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a progressive systemic disease characterised by the accumulation of abnormal amyloid proteins in the heart muscle, resulting in increased ventricular

stiffness and, ultimately, heart failure. Advances in non-invasive imaging and the development of disease-modifying therapies have contributed to an increase in ATTR-CM diagnosis, making accurate and early risk assessment increasingly important. Clinical management has traditionally emphasised cardiac staging, particularly through the National Amyloidosis Centre (NAC) staging system [1], which incorporates N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the estimated glomerular filtration rate (eGFR). However, this approach often fails to capture the extent of renal involvement in affected patients.

The kidney and heart are closely linked through the cardiorenal axis, whereby cardiac dysfunction leads to renal venous congestion and impaired renal perfusion, whereas kidney injury exacerbates cardiac strain through volume overload, vascular dysfunction and inflammation. In ATTR-CM, elevated right-sided heart pressure can impair the filtering system of the kidney, resulting in urinary protein excretion before measurable declines in filtration function. Accordingly, the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [2] for primary care (Step 4) recommend that kidney risk assessment incorporate both measures of filtration function (eGFR) and markers of structural kidney damage, such as the urine albumin-to-creatinine ratio (UACR).

Current cardiac staging models rely primarily on eGFR, a late marker of kidney dysfunction that declines only after irreversible nephron loss. In contrast, albuminuria—quantified as the UACR—captures earlier structural injury that often precedes eGFR decline [3, 4]. Consequently, many patients with early-stage ATTR-CM may be misclassified as ‘low risk’ simply because their filtration rate (eGFR) remains preserved, despite notable venous congestion and ongoing glomerular damage.

The aim of this study was to address the diagnostic gap by applying the KDIGO 2024 Risk Matrix to a well-characterised cohort of patients with ATTR-CM. It is hypothesised that UACR serves as a sensitive early indicator of overall disease burden and predicts future progression—as measured by the NAC staging system—independent of baseline eGFR. The trajectory from early structural renal damage to moderate disease burden and subsequent functional decline was also delineated using a generalised structural equation model.

2. Methods

A retrospective longitudinal analysis was conducted in 124 patients enrolled in a prospective cardiac amyloidosis study at the Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna. The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Medical University of Vienna (EK No. 1918/2019) and written informed consent was obtained from all participants before enrollment. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

According to current recommendations, ATTR-CM was diagnosed in patients who showed myocardial radiotracer uptake (Perugini grade ≥ 2) on [99mTc]Tc-DPD scintigraphy without detectable monoclonal

protein, as confirmed by serum and urine immunofixation electrophoresis and serum free light chain analysis. All patients diagnosed with ATTR-CM were offered *TTR* gene sequencing and all consented to genetic testing.

Clinical, biochemical and renal parameters were collected at baseline and follow-up visits. Structural kidney damage was assessed using the UACR, whereas renal filtration function was assessed using the eGFR.

The analysis was conducted in two stages. First, descriptive statistics and cross-tabulation analyses were used to characterise the distribution of KDIGO 2024 renal risk categories and to explore statistical associations between renal markers and clinical staging. These analyses provided a preliminary assessment of the hypothesised relationship among albuminuria, eGFR and NAC stage and served as an initial evaluation of UACR as a potential early indicator of subsequent clinical deterioration, as reflected by NAC stage.

Second, to formally evaluate the hypothesised trajectory in which UACR reflects early renal injury that contributes to subsequent functional decline and clinical severity, as measured by NAC stage, a generalised structural equation model (GSEM) was constructed. The model included baseline log-transformed UACR and baseline log-transformed eGFR as early renal predictors, follow-up log-transformed eGFR as an intermediate functional outcome and follow-up NAC stage (Gillmore staging; ordinal) as the final clinical endpoint. The ordinal NAC outcome was modelled using a probit link function. Direct and indirect (mediated) effects of baseline UACR on follow-up NAC stage were estimated using non-linear combinations of coefficients. Model fit was assessed using log-likelihood, Akaike information criterion and Bayesian information criterion. Figure 1 illustrates how the clinical rationale underlying the study was translated into the statistical framework of the analyses.

The figure depicts a simplified structural model examining how early renal injury may be associated with subsequent clinical status in ATTR-CM. Baseline log-transformed UACR reflects structural kidney damage at the initial assessment and is directly associated with the final clinical endpoint—the follow-up NAC stage—suggesting that early glomerular injury predicts later disease severity independently of changes in renal filtration function. Baseline log-transformed UACR also affects follow-up log-transformed eGFR, representing a pathway through which structural kidney damage may contribute to subsequent functional decline. Follow-up log-transformed eGFR then contributes to the follow-up NAC stage, reflecting the well-established relationship between renal filtration function and clinical staging in ATTR-CM. Together, these pathways quantify the direct and indirect (mediated) effects of baseline UACR on subsequent clinical deterioration, providing a coherent framework for evaluating whether UACR serves as an early predictor of disease severity in patients with ATTR-CM.

Cardiac disease severity was assessed using the NAC (Gillmore) staging system, with Stages I–III treated as an ordinal outcome in both the descriptive analyses and the structural equation model.

For the descriptive and cross-tabulation analyses, renal status was categorised according to the KDIGO 2024 Risk Matrix (Step 4), which integrates measures of renal filtration and structural kidney damage. Renal filtration was classified using the standard G categories (G1 ≥ 90 mL/min/1.73 m^2 to G5 < 15 mL/min/1.73 m^2), whereas structural kidney damage was classified using the A-stages (A1 < 30 mg/g; A2 30–299 mg/g; and A3 ≥ 300 mg/g). These classifications enabled patients to be mapped onto the KDIGO heatmap to visualise the distribution of renal risk (Online Supplementary Material).

The GSEM analysis used the renal variables in their original continuous form. Both eGFR and UACR were log-transformed to account for highly skewed distributions and to preserve the full information contained in the measurements. Baseline log-transformed UACR and baseline log-transformed eGFR served as early renal predictors, follow-up log-transformed eGFR as an intermediate functional outcome and follow-up NAC stage as the final ordinal endpoint. This approach enabled the estimation of the direct and indirect (mediated) effects of baseline UACR on subsequent clinical severity.

3. Results

Baseline Cohort Profile

Table 1 summarises the baseline characteristics of the study cohort.

Table 1
Baseline Characteristics of the Study Cohort

Parameter	Value/Medien
Total Number of Patients (N)	124
Male, n (%)	110(88.7%)
Female (%)	14(11.3%)
Age (Years)	80.2(75.4–84.1)
BMI (kg/m2)	25.4(24.8–25.9)
Serum Creatinine(mg/dL)	1.16(0.98–1.38)
NT-proBNP(pg/ml)	2450(1120–4890)
eGFR(ml/min/1.73m2)	61.2(44.5–78.3)
UACR (mg/g)	18.4(8.2–84.5)
NAC Stages I/II/III (%)	58%/31%/11%

The cohort consisted predominantly of men (88.7%) and had a median age of 80 years, consistent with the reported epidemiology of transthyretin amyloidosis. Cardiac disease severity was substantial, as reflected by elevated NT-proBNP concentrations and the distribution of NAC stages, with 58% of patients classified as Stage I, 31% as Stage II and 11% as Stage III.

Renal impairment was also evident. The median eGFR was 61 mL/min/1.73 m^2 and UACR values showed substantial variability, with many patients exhibiting albuminuria.

Together, the cohort exhibited both functional and structural indicators of renal abnormalities at baseline, providing an appropriate clinical context for evaluating the prognostic role of albuminuria in subsequent disease progression.

Longitudinal Analysis

GSEM

GSEM identified a pattern of association linking early structural renal injury to subsequent functional decline and clinical severity. As shown in Table 2, baseline UACR was not directly associated with follow-up eGFR (β = −0.0013, $p = 0.971$), whereas baseline eGFR remained a strong positive determinant of subsequent kidney function (β = 0.5673, $p < 0.001$). This pattern indicates that albuminuria does not produce immediate measurable functional loss but rather reflects early glomerular injury whose clinical implications become apparent over time through downstream pathways.

In the ordinal NAC-stage equation (Table 2), follow-up eGFR showed a large inverse association with NAC stage (β = −5.53, $p < 0.001$), indicating that lower renal filtration function was associated with greater systemic disease burden. Baseline UACR remained positively associated with NAC stage (β = 0.365, $p = 0.068$), suggesting a trend towards higher NAC stages with increasing albuminuria, even after adjustment for follow-up renal function. Although this association did not reach conventional statistical significance, its direction and magnitude were consistent with the proposed role of UACR as an early marker of renal injury.

Table 2
Results of the Generalised Structural Equation Model With a Probit Link for the Ordinal NAC Stage

Model Component	Coefficient (β)	SE	z	*p*-value	95% CI
Equation 1: Log-transformed follow-up eGFR					
Log-transformed baseline UACR	−0.0013	0.0362	−0.04	0.971	−0.0723 to 0.0697
Log-transformed baseline eGFR	0.5673	0.0808	7.02		0.4089 to 0.7257
Constant	1.6923	0.3598	4.70		0.9871 to 2.3975
Equation 2: Follow-up NAC stage (ordinal)					
Log-transformed follow-up eGFR	−5.5285	0.9050	−6.11		−7.3023 to −3.7547
Log-transformed baseline UACR	0.3651	0.1998	1.83	0.068	−0.0264 to 0.7567
Cutpoints (ordinal NAC stage)					
Cutpoint 1	−20.6674	3.5089	—	—	−27.5445 to −13.7902
Cutpoint 2	−18.3996	3.1829	—	—	−24.6380 to −12.1612
Residual variance					
var(e. log-transformed follow-up eGFR)	0.1071	0.0171	—	—	0.0782 to 0.1466

Taken together, the GSEM results support the hypothesised framework in which baseline UACR reflects early structural renal injury, follow-up eGFR reflects subsequent renal functional decline and NAC stage reflects overall disease severity. By modelling these variables simultaneously, the GSEM suggests that albuminuria may provide early prognostic information that is propagated through later renal and multisystem deterioration.

To facilitate interpretation of the GSEM findings, predicted probabilities of assignment to each NAC stage were generated for an individual with preserved renal function (eGFR = 60 mL/min/1.73 m^2) across a range of UACR values (Table 3). Holding the eGFR constant at 60 isolates the effect of albuminuria, translating the model coefficients into clinically interpretable risk gradients.

Across increasing UACR values, the probability of remaining in NAC Stage I decreases steadily (from 0.766 at 30 mg/g to 0.413 at 400 mg/g), whereas the probability of being in NAC Stage II increases (from 0.232 to 0.567). The probability of NAC Stage III, although low overall, also rises (from 0.001 to

0.020). This graded shift towards higher NAC stages is consistent with the positive association between baseline UACR and systemic disease burden observed within the GSEM.

These predicted probabilities reinforce the conceptual framework in which albuminuria functions as an early structural marker of renal injury. Even at a preserved eGFR, elevated UACR is associated with a greater likelihood of systemic involvement, supporting the view that albuminuria provides early prognostic information before measurable functional decline occurs.

By translating model-derived associations into predicted absolute probabilities, Table 3 enhances the interpretability of the findings and strengthens the evidence for the proposed relationship between UACR and NAC stage.

Table 3. Predicted Probabilities of NAC Stages for an Individual With Preserved Renal Function (eGFR = 60 mL/min/1.73 m^2) Across Selected UACR Values

UACR (mg/g)	Probability of NAC Stage I	Probability of NAC Stage II	Probability of NAC Stage III
30	0.766	0.232	0.001
100	0.613	0.382	0.005
400	0.413	0.567	0.020

4. Discussion

To our knowledge, this is the first study to evaluate the role of UACR at baseline and during follow-up in patients with ATTR-CM. The findings offer a new perspective by showing that UACR is an early and independent marker of overall disease burden, predicting a progression to higher NAC stages before filtration problems appear.

These findings are further clarified by the predicted probabilities derived from the GSEM, which translate the statistical associations into clinically interpretable risk gradients.

The predicted probabilities derived from the GSEM provide clinically interpretable insights into the relationship between albuminuria and NAC stage in ATTR-CM. Even when renal function was held constant, increasing UACR values were associated with a shift towards higher NAC stages, indicating greater multisystem involvement. For example, at an eGFR of 60 mL/min/1.73 m^2, the probability of remaining in NAC Stage I decreased from 77% at a UACR of 30 mg/g to 41% at a UACR of 400 mg/g, whereas the predicted probability of NAC Stage II more than doubled. Although the predicted probability of NAC Stage III remained low, it increased 20-fold across the same range of UACR values. These gradients translate statistical associations into clinically interpretable probabilities, suggesting that albuminuria provides prognostic information well before measurable functional decline occurs. The

findings are consistent with the proposed role of UACR as an early marker of structural renal injury and support its potential utility in risk stratification in patients with ATTR-CM.

Previous studies have validated the NAC staging system using standard clinical measures [1] and others have shown that chronic kidney disease greatly increases the risk of mortality in patients with ATTR-CM [8]. However, the relationship between early renal injury and subsequent cardiac disease severity has not been fully characterised. Traditionally, ATTR-CM care has focused mainly on eGFR to assess renal disease development or even mortality risk [1, 9].

In this study, the cohort had a median eGFR of 61.2 mL/min/1.73 m^2, whereas UACR values were frequently elevated and varied widely. These findings suggest that assessments based solely on eGFR can be misleading, as our baseline group showed.

This analysis shows that changes in kidney structure, measured by baseline UACR, can predict later clinical disease progression, as assessed by the NAC staging system. Recent research by Ioannou et al. (2024) also found that elevated UACR is common and associated with poorer survival outcomes in cardiac amyloidosis [3]. Although previous large studies have primarily focused on survival outcomes [3], the relationship between UACR and progression across NAC stages during follow-up has not been fully characterised. To our knowledge, this study is the first to examine this relationship. These findings reveal a clinical timeline in which kidney damage serves as an early marker of overall heart and kidney decline.

Cardiac amyloidosis commonly presents as heart failure with preserved ejection fraction (HFpEF) [10]. However, studies have shown that, with disease progression, LVEF may decline, resulting in heart failure with mildly reduced ejection fraction and, in some patients, heart failure with reduced ejection fraction (HFrEF) [11, 12].

The model used in this study facilitates the early identification of clinical risk before progression to HFrEF or other adverse outcomes. In non-infiltrative HFrEF, markers such as UACR have limited sensitivity when used in isolation and are often evaluated alongside other biomarkers, including NT-proBNP, for effective risk assessment [13]. However, in this study, which included patients with ATTR-CM, UACR alone functioned as an independent risk predictor. This finding aligns with what is already known about HFpEF, in which a high UACR indicates myocardial changes independent of myocyte function, regardless of eGFR [14]. Confirming this pattern supports the hypothesis that increased myocardial stiffness elevates pressure within the kidney filters, leading to protein leakage before permanent kidney damage occurs [4].

According to the KDIGO guidelines, filtration rate (G-categories) and structural integrity (A-categories) represent distinct biological domains [2]. In ATTR-CM, this distinction may result in subclinical cardiorenal decoupling, in which substantial leakage occurs even when the eGFR remains stable. This mismatch is often overlooked because cardiac risk models frame renal impairment as a late consequence of nephron loss. However, large heart failure studies have consistently identified elevated urinary albumin as an independent predictor of adverse outcomes [15]. Recent reviews continue to

emphasise that albuminuria remains underutilised in cardiovascular risk assessments [16]. Even in the general population, high-normal albuminuria is strongly associated with incident heart failure [17]. By neglecting the UACR, clinical protocols may classify patients with early-stage ATTR-CM as 'low risk' solely on the basis of a normal eGFR.

Mechanisms of the GSEM Cascade: Congestion Versus Infiltration

A major strength of this analysis is the use of GSEM, which enables the simultaneous isolation of separate equations within a single integrated framework. In the first component of the model, baseline log-transformed UACR was not associated with follow-up log-transformed eGFR (β = −0.0013, $p = 0.971$). From a clinical perspective, this finding indicates that albuminuria was not directly associated with changes in renal function in this cohort. This observation is consistent with evidence indicating that, in ATTR-CM, renal decline is rarely caused by direct amyloid deposition within the kidney, unlike in light-chain amyloidosis, in which renal involvement is frequently observed [18). Therefore, the findings indicate that the mechanisms underlying renal stress in ATTR-CM may differ from those associated with direct renal amyloid injury.

The key finding of the model is that the prognostic power of UACR operates through a systemic pathway. Baseline log-transformed UACR remained positively associated with follow-up NAC stage (β = 0.365, $p = 0.068$). As described in established cardiorenal models, progressive myocardial amyloid deposition contributes to elevated right atrial pressures and chronic venous congestion [19,20). This fluid backpressure is transmitted directly into the renal veins, raising glomerular pressure. This elevated pressure disrupts the glomerular filtration barrier, causing protein to leak into the urine as albuminuria [19). Therefore, UACR serves as a sensitive marker of venous congestion from the heart long before eGFR begins to decline.

Clinical Implications and Therapeutic Windows

To facilitate clinical interpretation of the path-analytical coefficients, the model-generated predicted probabilities at a fixed eGFR of 60 mL/min/1.73 m^2 exhibited a marked risk gradient. As UACR increased from 30 to 400 mg/g, the predicted probability of remaining in NAC Stage I decreased from 76.6% to 41.3%, whereas the combined predicted probability of NAC Stages II and III increased to 58.7%. These findings suggest that *not all patients with an eGFR of 60 are equivalent*, a distinction critical for timing the initiation of advanced therapeutics.

Identifying this subclinical cardiorenal progression early opens a therapeutic window in which overt cardiorenal decline may be mitigated by the early use of modern organ-protective therapies, such as SGLT2 inhibitors and mineralocorticoid receptor antagonists, which have improved heart failure and renal outcomes in large clinical trials [21,22). Importantly, the availability of highly effective amyloid-specific therapies—including stabilisers such as tafamidis [23) and emerging RNA-targeting approaches—and the use of UACR as an early structural marker ensure that disease-modifying therapies are optimised before irreversible multiorgan failure occurs.

Study Limitations and Strengths

This study has several strengths, including a longitudinal cohort with biopsy- or scintigraphy-confirmed diagnoses and the application of a GSEM capable of evaluating multivariable cascades within a single analytical framework. However, several limitations should also be acknowledged. First, the retrospective design introduces the potential for unmeasured confounding and incomplete data. Second, the sample size (N = 124), although well characterised, may have limited statistical power and the direct association between UACR and NAC stage did not reach conventional statistical significance ($p = 0.068$). Nevertheless, the risk gradients observed in the predicted probability analyses underscore a biologically coherent sequence that warrants clinical attention and further prospective validation.

This study indicates that UACR serves as an early structural marker of systemic disease burden and predicts future clinical deterioration through the NAC staging system, even when renal filtration remains preserved. The findings support the potential value of incorporating routine UACR assessment alongside eGFR to reduce diagnostic blind spots and optimize risk stratification in patients with ATTR-CM.

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Declarations

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Data availability statement

Data are available upon reasonable request. De-identified participant data will be shared upon reasonable request to the corresponding author, subject to institutional review board approval and data sharing agreements.

Competing interests

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Figures

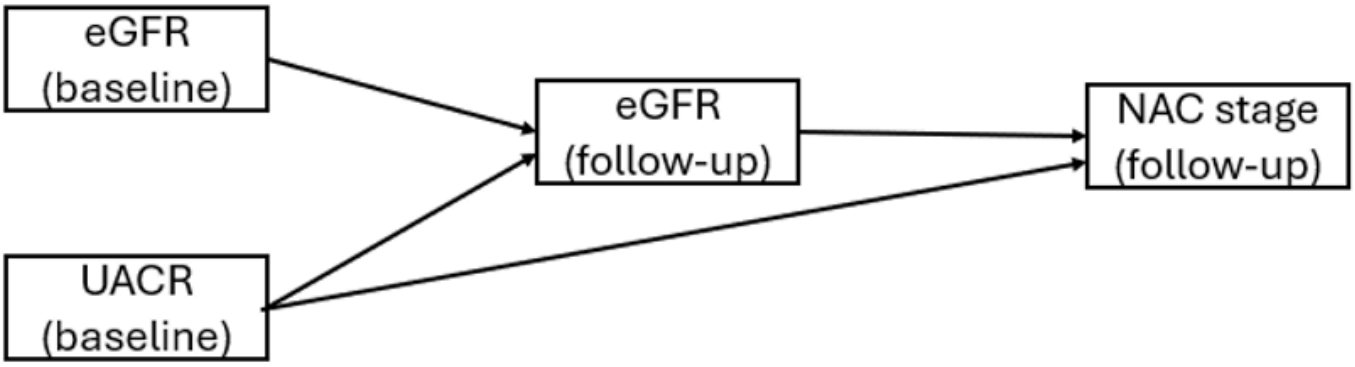


Figure 1

Conceptual and Statistical Model Linking Baseline UACR, Follow Up eGFR and NAC Stage