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RESEARCH ARTICLE

Albuminuria in transthyretin cardiac amyloidosis: Prevalence, progression and prognostic importance

Adam Ioannou[1], Muhammad U. Rauf[1], Rishi K. Patel[1], Yousuf Razvi[1], Aldostefano Porcari[1,2], Ana Martinez-Naharro[1], Lucia Venneri[1], Francesco Bandera[3], Ruta Virsinskaite[1], Tushar Kotecha[1], Dan Knight[1], Aviva Petrie[4], Carol Whelan[1], Ashutosh Wechalekar[1], Helen Lachmann[1], Philip N. Hawkins[1], Scott D. Solomon[5], Julian D. Gillmore[1†], and Marianna Fontana[1*†]

[1]National Amyloidosis Centre, University College London, Royal Free Campus, London, UK; [2]Center for Diagnosis and Treatment of Cardiomyopathies, Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano-Isontina (ASUGI), University of Trieste, Trieste, Italy; [3]Cardiology University Department, IRCCS Policlinico San Donato, Milan, Italy; [4]University College London, London, UK; and [5]Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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Aims Transthyretin cardiac amyloidosis (ATTR-CA) is an infiltrative cardiomyopathy that commonly presents with concomitant chronic kidney disease. Albuminuria is common in heart failure and associated with worse outcomes, but its prevalence and relationship to outcome in ATTR-CA remains unclear.

Methods and results A total of 1181 patients with ATTR-CA were studied (mean age 78.1 ± 7.9 years; 1022 [86.5%] male; median estimated glomerular filtration rate 59 ml/min/1.73m^2 [interquartile range: 47–74]). Albuminuria was present in 563 (47.7%) patients (499 [88.6%] with microalbuminuria and 64 [11.4%] with macroalbuminuria). Patients with albuminuria had a more severe cardiac phenotype evidenced by higher serum cardiac biomarkers (median N-terminal pro-B-type natriuretic peptide [NT-proBNP]: 4027 ng/L [2173–6889] vs. 1851 ng/L [997–3209], $p < 0.001$; median troponin T: 69 ng/L [46–101] vs. 48 ng/L [34–68], $p < 0.001$) and worse echocardiographic indices of systolic (longitudinal strain: −10.0 ± 3.6% vs. −11.6 ± 3.8%, $p < 0.001$) and diastolic function (E/e′: 17.5 ± 6.4 vs. 16.4 ± 6.7, $p < 0.001$) than those with a normal urinary albumin to creatinine ratio (UACR). Microalbuminuria and macroalbuminuria were independently associated with mortality in the overall population (hazard ratio [HR] 1.47, 95% confidence interval [CI] 1.13–1.92, $p = 0.005$ and HR 1.87, 95% CI 1.15–3.05, $p = 0.012$, respectively). In a subgroup of patients ($n = 349$) without concomitant hypertension, diabetes mellitus or chronic kidney disease, albuminuria was also associated with mortality (HR 2.98, 95% CI 1.72–5.17, $p < 0.001$). At 12 months, 330 patients had a repeat UACR measurement; those in whom UACR increased by 30% or more ($n = 148$, 44.8%) had an increased risk of mortality (HR 1.84, 95% CI 1.06–3.19, $p = 0.030$).

Conclusions Albuminuria is common in patients with ATTR-CA, and more prevalent in those with a more severe cardiac phenotype. Albuminuria at diagnosis and a significant increase in UACR during follow-up are associated with mortality.

*Corresponding author. National Amyloidosis Centre, University College London, Royal Free Hospital, Rowland Hill Street, London. NW3 2PF, UK. Tel: +44 20 74332764, Fax: +44 20 74332803, Email: m.fontana@ucl.ac.uk
†Contributed equally as joint last authors.

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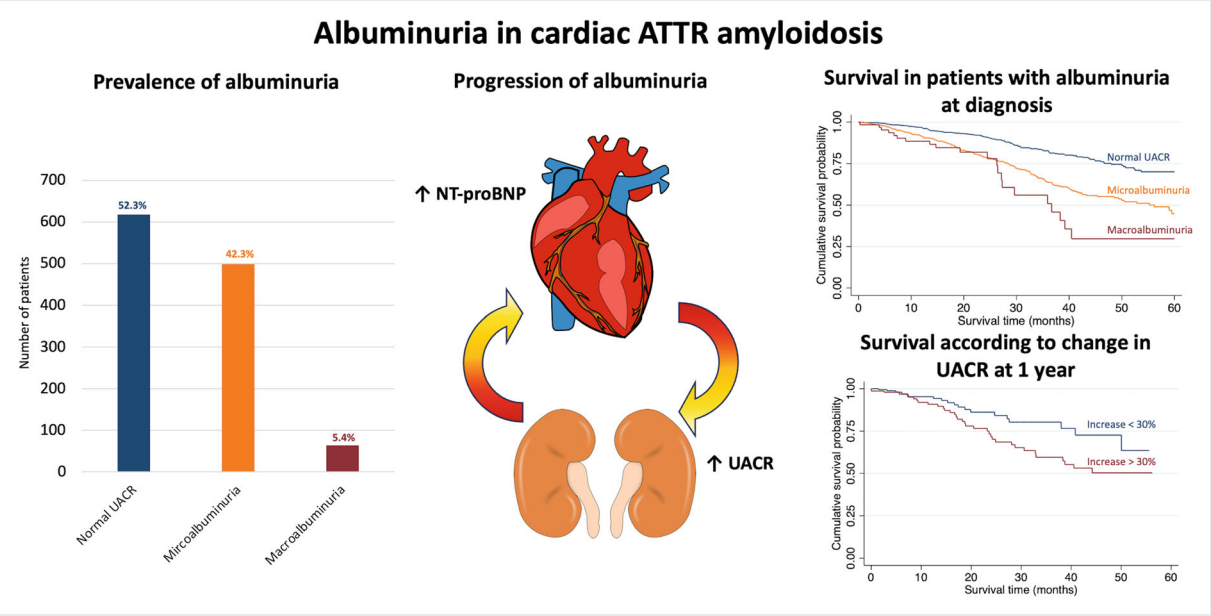
Graphical Abstract



Albuminuria in transthyretin cardiac amyloidosis. ATTR, transthyretin amyloidosis; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UACR, urinary albumin to creatinine ratio.

Introduction

Transthyretin cardiac amyloidosis (ATTR-CA) is an increasingly recognised cause of heart failure, and is a progressive and ultimately fatal cardiomyopathy. The underlying disease process is characterized by the deposition of misfolded transthyretin in the form of amyloid fibrils within the myocardial extracellular space, which disrupt cardiac structure and function.[1,2] The sporadic, non-inherited, wild-type (wtATTR-CA) is a condition of older, predominantly male individuals; while the hereditary form (hATTR-CA) can present earlier in life with a varying clinical phenotype, often comprising of both restrictive cardiomyopathy and polyneuropathy.[3,4]

In the setting of heart failure, chronic kidney disease (CKD) is frequent and characterized by albuminuria and reduced glomerular filtration rate (GFR). Albuminuria and reduced GFR are prognostic for heart failure hospitalizations and cardiovascular mortality, and remain independent predictors even after adjusting for comorbidities such as diabetes mellitus and hypertension.[5–8] Although both parameters indicate the extent of renal dysfunction, creatinine-based estimated GFR (eGFR) is most widely used as a focal metric in assessing renal and cardiovascular risk.[9] This premise extends to ATTR-CA, and is most notably demonstrated in a well-established staging system that combines eGFR with N-terminal pro-B-type natriuretic peptide (NT-proBNP) to accurately stratify patients into prognostic categories.[10]

While changes in eGFR may be due to changes in true GFR or serum creatinine levels, which can be influenced by extra-renal factors such as skeletal muscle mass, albuminuria directly reflects morphological glomerular damage.[9] Hence, albuminuria represents an early marker of renal dysfunction that can even precede a reduction in eGFR. These differences, in part, explain why the presence and magnitude of albuminuria confers a strong predictor of adverse events irrespective of eGFR, with even high-normal albuminuria conferring an increased risk of both incident heart failure and heart failure progression.[11] However, despite the indisputable link between heart failure and renal function, the significance of albuminuria in patients with ATTR-CA is yet to be characterized.

The aims of this study were to assess: (i) the prevalence of albuminuria in patients with ATTR-CA; (ii) the clinical characteristics and biomarker profile associated with albuminuria; (iii) the changes in urinary albumin to creatinine ratio (UACR) over time; and (iv) the association between albuminuria and prognosis.

Methods

The National Amyloidosis Centre (NAC) is the single specialist centre funded by the United Kingdom (UK) National Health Service for the diagnosis and management of amyloidosis. Consecutive patients diagnosed with ATTR-CA between 2017 and 2023, and in whom a UACR was measured at diagnosis were included.

The diagnosis of ATTR-CA was established on the basis of presence of symptoms of heart failure together with a characteristic amyloid echocardiogram and either direct endomyocardial biopsy proof of ATTR amyloid or presence of ATTR amyloid in an extra-cardiac biopsy along with cardiac uptake on ^{99m}technetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy, or grade 2–3 cardiac uptake on ^{99m}Tc-DPD scintigraphy

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in the absence of biochemical evidence of a plasma cell dyscrasia. All patients underwent genetic sequencing of the *TTR* gene and provided written consent for their data to be retrospectively analysed and published, in line with the Declaration of Helsinki and approval from the Royal Free Hospital ethics committee (REC 21/PR/0620).

Microalbuminuria was defined as UACR >30 mg/g, and macroalbuminuria was defined as an UACR >300 mg/g.[12] A significant increase in UACR at 1 year of follow-up was defined as an increase of ≥30%. Therefore, patients were classed as having a stable UACR if the increase was <30% or an increased UACR if the increase was ≥30%.[13]

Statistical analysis

Statistical analysis was performed using Stata (StataCorp LLC, Stata Statistical Software: Release 17, College Station, TX, USA). All continuous variables were tested for normality (Shapiro–Wilk test) and presented as mean ± standard deviation if the distribution was normal or median (interquartile range) otherwise. The independent samples *t*-test was used to compare means if the data were normally distributed in each group, or its non-parametric equivalent (Mann–Whitney U test) was used to compare the distributions of the two groups. One-way analysis of variance (ANOVA) if the data were normally distributed in each group was used to compare means in more than two groups; or its non-parametric equivalent (Kruskal–Wallis test) was used to compare the distributions of multiple groups. A significant result in these analyses was followed by post-hoc Bonferroni corrected pairwise comparisons to establish where differences lay. Levene's test was used to check the homogeneity of variance in the *t*-test and ANOVA. Categorical data are presented as absolute numbers and frequencies and compared using the chi-square test.

The relationship between baseline UACR and changes in various biomarkers were estimated by preforming a linear regression analysis with the outcome variable being the 12-month value and the explanatory variables being the baseline value of that variable and the group (where albuminuria = 1 and normal UACR = 0). The estimated regression coefficient for the group in the regression analysis represented the estimated difference in means at 12 months after adjusting for the baseline value. A similar analysis was used to assess the effect of an increased UACR at 12 months on the 12-month value of each of the various biomarkers after adjusting for the relevant baseline value. The assumptions of these regression analyses were checked by a study of the residuals.

All mortality data were obtained via the UK Office of National Statistics. The mortality endpoint was defined as time to death from baseline for all deceased patients and time to censor date (23 March 2023) from baseline among the remainder. Follow-up was restricted to ≤60 months, after which patients were censored due to the majority of events occurring in the first 60 months, and a low number of patients at risk after 60 months.

Survival was evaluated using Cox proportional hazards regression analysis, providing estimated hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was checked and confirmed. UACR was log transformed and its association with mortality explored first as a continuous variable. The optimal cut-point was established using time-dependent receiver operating characteristic curves followed by the Youden method. The association between UACR and mortality was then explored as a dichotomous variable. Additional analyses specified a priori were carried out in the following subgroups: patients who did not have concomitant hypertension, diabetes mellitus or CKD stage 3–5, patients with a left ventricular ejection fraction (LVEF) ≤40%, patients with a LVEF >40%, patients with wtATTR-CA and patients with hATTR-CA. Significant results were followed by a sensitivity analysis whereby patients were censored at the start date of disease-modifying therapy and clinical trials to account for their impact on survival.

The likelihood ratio test was used to evaluate the contribution of adding UACR to a multivariable model comprising covariates known to contribute to albuminuria (diabetes mellitus and hypertension) and the NAC disease stage. Harrell's c-statistics were calculated to measure the discriminatory ability of each model. In order to compare c-statistics of the two models, we randomly divided our data set into a test and validation cohort (1:1). The models were fitted to the test cohort and the c-statistics compared in the validation cohort using a *t*-test after creating Jackknife standard errors.[14]

The association between a significant increase in UACR and mortality was assessed, and considering the smaller sample size of patients with a follow-up UACR, internal validation of the Cox proportional hazards regression model was achieved by performing a bootstrapping procedure with 500 repeats, affording a comparison of the percentile and bias-corrected methods to ensure the results were unbiased. Kaplan–Meier curves were constructed with statistical significance being assessed with a log-rank test. Statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics

During the study period, 1316 patients were diagnosed with ATTR-CA, of whom 1181 patients had a UACR measurement at diagnosis. The characteristics of patients with a UACR at baseline and those without are displayed in online supplementary *Table S1*. The population comprised of 901 (76.3%) with wtATTR-CA, and 280 (23.7%) with hATTR-CA. The mean age of the population was 78.1 ± 7.9 years and 1022 (86.5%) were male. The median NT-proBNP was 2690 ng/L (1405–5040), median eGFR was 59 ml/min/1.73 m^2 (47–74), and most of the population had NAC stage 1 (50.3%) and stage 2 (34.1%) biomarkers. During follow up, 214 (18.1%) patients were enrolled into clinical trials and 132 (11.2%) were prescribed disease-modifying therapy (patisiran, $n = 73$; tafamidis, $n = 52$; inotersen, $n = 7$).

The prevalence of microalbuminuria and macroalbuminuria was 499 (42.3%) and 64 (5.4%), respectively. Patients with albuminuria were older, had a higher prevalence of atrial fibrillation, diabetes mellitus and stroke/transient ischaemic attack (TIA) than patients with a normal UACR. Patients with albuminuria had a more severe cardiac phenotype evidenced by a higher NAC disease stage (a greater proportion of patients had NAC stage 3 [severe] disease), median NT-proBNP (4027 ng/L [2173-6889] vs 1851 ng/L [997-3209], $p < 0.001$), median troponin (69 ng/L [46-101] vs 48 ng/L [34-68], $p < 0.001$), lower LVEF (46.4 ± 11.0 vs 50.2 ± 9.3, $p < 0.001$) and worse longitudinal strain (−10.0 ± 3.6% vs −11.6 ± 3.8%, $p < 0.001$) than those with a normal UACR. Furthermore, a greater proportion of patients with albuminuria had a LVEF ≤40%. Patients with microalbuminuria and macroalbuminuria had higher biomarkers suggestive of hepatic congestion (elevated bilirubin, alkaline phosphatase and gamma-glutamyl transferase) than those with a normal UACR. Furthermore, patients

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with microalbuminuria and macroalbuminuria had a higher prevalence of CKD stage 3–5, lower median eGFR and higher urea than those with a normal UACR (*Table 1*).

In 349 patients who did not have concomitant hypertension, diabetes mellitus or CKD stage 3–5, 116 (33.2%) patients had albuminuria. These patients were older, had a higher prevalence of atrial fibrillation and stroke/TIA and had a more severe cardiac phenotype evidenced by a higher median NT-proBNP, median troponin, lower LVEF and worse longitudinal strain, and had higher biomarkers suggestive of hepatic congestion than those with a normal UACR (online supplementary *Table S2*). Similar results were also observed in a subgroup of patients who did not have concomitant cardiovascular disease or cardiovascular risk factors (online supplementary *Table S3*).

Follow-up

At 12 months, 330 patients had repeat serum biochemistry and UACR measurements, of whom 154 (46.7%) had a normal UACR at baseline, and 176 (53.3%) had albuminuria at baseline. There were no significant differences in baseline characteristics between patients who attended a 1-year follow-up appointment and had repeat UACR measurements and those who did not (online supplementary *Table S4* and *Figure S1*). Patients with albuminuria at baseline experienced a greater decline in eGFR than patients with a normal UACR, whereby the difference in mean eGFR (adjusted for baseline eGFR) between the two groups was −2.8 ml/min/1.73 m^2 (95% CI −5.4 to −2.6, $p = 0.031$). The difference in mean NT-proBNP at 12 months was not significantly different between the two groups.

At 12 months, 182 (55.2%) patients had a stable UACR (defined as an increase in UACR <30%) and 148 (44.8%) had an increased UACR (defined as an increase in UACR ≥30%). Those with an increased UACR at 12 months had a significantly higher prevalence of ischaemic heart disease, higher median troponin T and higher median bilirubin, than those with a stable UACR at baseline (online supplementary *Table S5*). While demographics, cardiac function and heart failure treatments were not different between the two groups, patients who experienced an increase in UACR had a greater increase in NT-proBNP than in those with a stable UACR, whereby the difference in mean NT-proBNP (adjusted for baseline NT-proBNP) between the two groups was 764 ng/L (95% CI 50.6–1477, $p = 0.036$). The difference in mean eGFR (adjusted for baseline eGFR) was not significantly different between the two groups.

Survival

Compared to patients with a normal UACR in which the rate of death was 6.3 (95% CI 5.2–7.7) per 100 person-years, the rate of death was 13.4 (95% CI 11.3–15.7) deaths per 100 person-years in those with microalbuminuria, and 56.1 (95% CI 43.2–71.7) deaths per 100 person-years in those with macroalbuminuria (*Figure 1A*).

In the overall study population, UACR assessed as a continuous variable was associated with mortality (log UACR: HR 1.98, 95% CI 1.60–2.44, $p < 0.001$). The Youden method identified 26.6 mg/g as the optimal cut-point (sensitivity: 68.6%, specificity: 57.9%), and when assessed as a dichotomous variable, UACR >27 mg/g was associated with a two-fold higher risk of mortality (HR 2.01, 95% CI 1.56–2.58, $p < 0.001$). Microalbuminuria (UACR >30 mg/g) and macroalbuminuria (UACR >300 mg/g) were both associated with an increased risk of mortality. Even within the subgroup of patients with a normal UACR, those with a high-normal UACR (>10 mg/g) had an increased risk of mortality compared to those with a low-normal UACR (≤10 mg/g) (HR 1.63, 95% CI 1.08–2.47, $p = 0.021$). Microalbuminuria and macroalbuminuria remained independently associated with an increased risk of mortality after adjusting for the presence of diabetes mellitus and hypertension, and also adjusting for the NAC disease stage (HRs adjusted for diabetes mellitus, hypertension and NAC stage; microalbuminuria vs. normal UACR: HR 1.47, 95% CI 1.13–1.92, $p = 0.005$; macroalbuminuria vs. normal UACR: HR 1.87, 95% CI 1.15–3.05, $p = 0.012$). The likelihood ratio test demonstrated that the addition of albuminuria to the multivariable model comprising the presence of diabetes mellitus and hypertension and the NAC disease stage significantly improved the goodness-of-fit of the model ($\chi^2 = 24.12$, $p < 0.001$) and significantly improved the discriminatory ability of the classification (Harrell's c-statistic: 0.725 95% CI 0.685–0.765 vs. 0.708 95% CI 0.666–0.749, $p = 0.029$) (*Table 2*). These findings were confirmed by a sensitivity analysis, whereby patients were censored at the start date of disease-modifying therapy and clinical trials (HRs adjusted for diabetes mellitus, hypertension and NAC stage; microalbuminuria vs. normal UACR: HR 1.38, 95% CI 1.02–1.86, $p = 0.034$; macroalbuminuria vs. normal UACR: HR 1.76, 95% CI 1.06–2.92, $p = 0.029$).

Albuminuria was associated with an increased risk of mortality in patients with NAC stage 1 or 2 disease, but not in those with NAC stage 3 disease, however assessment in this subgroup was limited by the small sample size (*Figure 2*). Albuminuria was also associated with an increased risk of mortality in patients with an eGFR ≥60 ml/min/1.73 m^2 or an eGFR between 30 and 59 ml/min/1.73 m^2, but not in those with an eGFR <30 ml/min/1.73 m^2, however assessment in this subgroup was limited by the small sample size (*Figure 3*). Albuminuria was also associated with increased rates of mortality regardless of LVEF and genotype (online supplementary *Table S6*).

In a subgroup of 349 patients who did not have concomitant hypertension, diabetes mellitus or CKD stage 3–5, there were 4.0 (95% CI 2.6–5.9) deaths per 100 person-years in those with a normal UACR and 10.9 (95% CI 7.4–16.0) deaths per 100 person-years in those with albuminuria. Albuminuria was associated with almost a three-fold higher risk of mortality (HR 2.98, 95% CI 1.72–5.17, $p < 0.001$), and this was confirmed by a sensitivity analysis, whereby patients were censored at the start date of disease-modifying therapy and clinical trials (HR 3.70, 95% CI 1.96–6.98, $p < 0.001$) (*Figure 1B*).

In a subgroup of patients with repeat UACR measurements at 12 months, those with a stable UACR (defined as an increase <30%) had a death rate of 7.7 (95% CI 4.7–11.9) deaths per 100 person-years; and those with an increased UACR (defined as an increase ≥30%) had a death rate of 14.9 (95% CI 10.4–20.7) deaths per 100 person-years. An increase in UACR ≥30% at 12 months was associated with an 84% higher risk of mortality

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Table 1 Baseline characteristics, blood biomarkers and echocardiographic parameters for the whole transthyretin cardiac amyloidosis population, and in patients with a normal urinary albumin to creatinine ratio, microalbuminuria and macroalbuminuria

Baseline characteristics	Overall population ($n = 1181$)	Normal UACR (UACR <30 mg/g) ($n = 618$, 52.3%)	Microalbuminuria (UACR 30–300 mg/g) ($n = 499$, 42.3%)	Macroalbuminuria (UACR <300 mg/g) ($n = 64$, 5.4%)	*p*-value
Age (years)	78.1 ± 7.9	77.0 ± 8.3*	79.3 ± 7.4	79.3 ± 7.1	<0.001
Male sex	1022 (86.5%)	530 (85.8%)	437 (87.6%)	55 (85.9%)	0.670
Ethnicity					0.340
Caucasian	970 (82.1%)	509 (82.4%)	412 (82.6%)	49 (76.6%)	
Afro-Caribbean	189 (16.0%)	97 (15.7%)	77 (15.4%)	15 (23.4%)	
Asian	16 (1.4%)	7 (1.1%)	9 (1.8%)	0 (0.0%)	
Other	6 (0.5%)	5 (0.8%)	1 (0.2%)	0 (0.0%)	
wtATTR	901 (76.3%)	461 (74.6%)	395 (79.2%)	45 (70.3%)	0.105
hATTR	280 (23.7%)	157 (25.4%)	104 (20.8%)	19 (29.7%)	0.105
AF/flutter	566 (47.9%)	245 (39.6%)*	287 (57.5%)	34 (53.1%)	<0.001
IHD	226 (19.1%)	113 (18.3%)	101 (20.2%)	12 (18.8%)	0.709
Diabetes mellitus	183 (15.5%)	77 (12.5%)*	95 (19.0%)	11 (17.2%)	0.010
Hypertension	426 (36.1%)	221 (35.8%)	182 (36.5%)	23 (35.9%)	0.970
Stroke/TIA	122 (10.3%)	52 (8.4%)†	56 (11.2%)‡	14 (21.9%)	0.002
Blood biomarkers					
NAC stage					<0.001
1	594 (50.3%)	411 (66.5%)*†	171 (34.3%)‡	12 (18.8%)	
2	403 (34.1%)	158 (25.6%)*	216 (43.3%)	29 (45.3%)	
3	184 (15.6%)	49 (7.9%)*	112 (22.4%)	23 (35.9%)	
NT-proBNP (ng/L)	2690 (1405–5040)	1851 (997–3209)*†	3958 (2136–6679)	5294 (3004–7750)	<0.001
Troponin-T (ng/L)	57 (38–83)	48 (34–68)*†	68 (46–99)	74 (50–114)	<0.001
CKD stage 3–5	593 (50.2%)	245 (39.6%)*†	303 (60.7%)	45 (70.3%)	<0.001
eGFR (ml/min/1.73 m^2)	59 (47–74)	65 (53–78)*†	55 (43–69)	50 (38–62)	<0.001
Serum creatinine (μmol/L)	104 (87–127)	97 (83–115)*†	112 (93–138)	118 (101–150)	<0.001
Serum urea (mmol/L)	8.5 (6.6–11.2)	7.6 (6.1–9.7)*†	9.6 (7.1–12.5)	9.6 (7.4–12.7)	<0.001
Serum total bilirubin (μmol/L)	13 (9–18)	11 (8–15)*†	15 (10–22)	17 (9–22)	<0.001
Alanine transaminase (IU/L)	25 (20–33)	24 (19–31)*	26 (20–36)	24 (18–38)	0.019
Alkaline phosphatase (IU/L)	94 (76–124)	86 (71–107)*†	110 (84–144)	111 (82–140)	<0.001
GGT (IU/L)	65 (32–132)	46 (26–94)*†	97 (46–190)	95 (41–204)	<0.001
Albumin (g/L)	44 (42–46)	44 (42–46)*†	44 (42–46)	43 (40–45)	0.001
Echocardiographic parameters					
IVSd (mm)	16.9 ± 2.6	16.8 ± 2.6	17.1 ± 2.6	16.8 ± 2.3	0.093
PWTd (mm)	16.4 ± 2.7	16.2 ± 2.8	16.6 ± 2.6	16.4 ± 2.4	0.052
LVEF (%)	48.4 ± 10.3	50.2 ± 9.3*	46.3 ± 11.0	47.2 ± 10.5	<0.001
LVEF ≤40%	258 (21.8%)	99 (16.0%)*	144 (28.9%)	15 (23.4%)	<0.001
Longitudinal strain (%)	−10.9 ± 3.8	−11.6 ± 3.8*	−10.0 ± 3.6	−10.3 ± 3.4	<0.001
Average E/e′	16.9 ± 6.6	−16.4 ± 6.7*	17.6 ± 6.4	16.8 ± 6.3	<0.001
Heart failure treatment					
Beta-blocker	608 (51.5%)	291 (47.1%)*	282 (56.5%)	35 (54.7%)	0.006
ACEi/ARB	605 (51.2%)	305 (49.4%)	264 (52.9%)	36 (56.3%)	0.354
ARNI	25 (2.1%)	18 (2.9%)	6 (1.2%)	1 (1.6%)	0.136
MRA	364 (30.8%)	190 (30.7%)	158 (31.7%)	16 (25.0%)	0.553
SGLT2 inhibitor	64 (5.4%)	33 (5.3%)	28 (5.6%)	3 (4.7%)	0.946

ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; hATTR, hereditary transthyretin amyloidosis; hATTR-CA, hereditary transthyretin cardiac amyloidosis; IHD, ischaemic heart disease; IVSd, interventricular septal thickness in diastole; GGT, gamma-glutamyl transferase; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NAC, National Amyloidosis Centre; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PWTd, posterior wall thickness in diastole; SGLT2, sodium–glucose cotransporter 2; TIA, transient ischaemic attack; UACR, urinary albumin to creatinine ratio, wtATTR, wild-type transthyretin amyloidosis.

Patients with hATTR-CA had the following mutations: p.(Val142Ile) $n = 160$; p.(Thr80Ala) $n = 69$; p.(Ile127Val) $n = 11$; p.(Val50Met) $n = 10$; p.(Ser77Tyr) $n = 6$; p.(Gly26Ser) $n = 5$; p.(Glu62Asp) $n = 3$; p.(Ser43Asn) $n = 2$; p.(Tyr134Cys) $n = 2$; p.(Arg54Gly) $n = 1$; p.(Asp58Val) $n = 1$; p.(Glu109Lys) $n = 1$; p.(Glu112Lys) $n = 1$; p.(Gly67Arg) $n = 1$; p.(Gly67Glu) $n = 1$; p.(Gly67Val) $n = 1$; p.(Gly73Ala) $n = 1$; p.(Gly73Glu) $n = 1$; p.(Ile88Leu) $n = 1$; p.(Ser70Arg) $n = 1$; p.(Tyr89Phe) $n = 1$.

P-values for pairwise comparison: *$p < 0.05$ normal UACR vs. microalbuminuria, †$p < 0.05$ normal UACR vs. macroalbuminuria, ‡microalbuminuria vs. macroalbuminuria.

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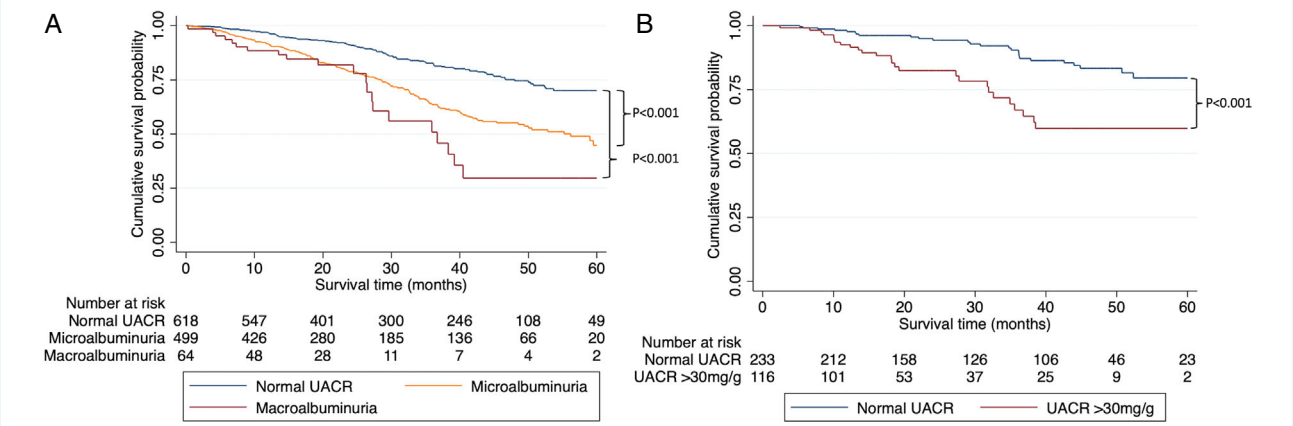

Figure 1 (*A*) Kaplan–Meier curves demonstrating the association between albuminuria and survival in the overall population. (*B*) Kaplan–Meier curves demonstrating the association between albuminuria and survival in the pre-specified subgroup of patients without hypertension, diabetes mellitus or chronic kidney disease stage 3–5. UACR, urinary albumin to creatinine ratio.

Table 2 Univariable and multivariable analysis of mortality risk associated with microalbuminuria and macroalbuminuria at the time of diagnosis

	Univariable		Multivariable		Multivariable	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Diabetes mellitus	1.40 (1.05–1.88)	0.024	1.38 (1.02–4.43)	0.036	1.33 (0.99–1.80)	0.062
Hypertension	1.24 (0.98–1.58)	0.075	1.12 (0.88–1.43)	0.353	1.13 (0.89–1.45)	0.322
NAC stage 1	Ref		Ref		Ref	
NAC stage 2	3.28 (2.46–4.38)	<0.001	3.32 (2.49–4.43)	<0.001	2.88 (2.13–3.90)	<0.001
NAC stage 3	4.64 (3.33–6.47)	<0.001	4.53 (3.24–6.32)	<0.001	3.75 (2.63–5.33)	<0.001
Normal UACR	Ref		–	–	Ref	
Microalbuminuria	2.22 (1.72–2.84	<0.001	–	–	1.47 (1.13–1.92)	0.005
Macroalbuminuria	3.36 (2.09–5.39)	<0.001	–	–	1.87 (1.15–3.05)	0.012
Harrell's c-statistic	–	–	0.708 (0.666–0.749)	<0.001	0.725 (0.685–0.765)	<0.001

CI, confidence interval; HR, hazard ratio; NAC, National Amyloidosis Centre; UACR, urinary albumin to creatinine ratio.

(HR 1.84, 95% CI 1.06–3.19, $p = 0.030$), and the bootstrapped results indicated that the coefficients remained constant across the resamples, suggesting robustness in the association between an increase in UACR ≥30% and mortality (*Figure 4*).

Discussion

This is the first study to comprehensively evaluate the importance of albuminuria in a large population of patients with ATTR-CA, and demonstrated that: (i) almost half the patients with ATTR-CA had albuminuria; (ii) patients with albuminuria had more severe cardiac disease than those with a normal UACR; (iii) albuminuria at diagnosis was independently associated with an increased risk of mortality; and (iv) at 12 months almost half the patients with serial measurements had a significant increase in UACR, and a significant increase in UACR was associated with an increased risk of mortality (*Graphical Abstract*).

In the overall population of patients with ATTR-CA, almost half had albuminuria at diagnosis, the majority of whom had microalbuminuria (88.6%), while around one-tenth had macroalbuminuria (11.4%). Albuminuria is common in patients with heart failure of different aetiologies; however, the prevalence varies depending on the presence of comorbidities and degree of systolic and diastolic failure. The Gruppo Italiano per lo Studio della Sopravvivenza nell'Inufficienza Cardiaca heart failure trial[8] and Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity[7] trial enrolled heart failure patients regardless of LVEF, and post-hoc analyses revealed that one-quarter (26.1%) and just over one-third (37.2%) of the study populations had concomitant diabetes mellitus, and the prevalence of albuminuria was 25.3% and 41.6%, respectively. The treatment of preserved cardiac function heart failure with an aldosterone antagonist trial enrolled heart failure patients with a preserved ejection fraction, and a post-hoc analysis revealed that nearly half (43.8%) the study population had concomitant diabetes mellitus, and a similar

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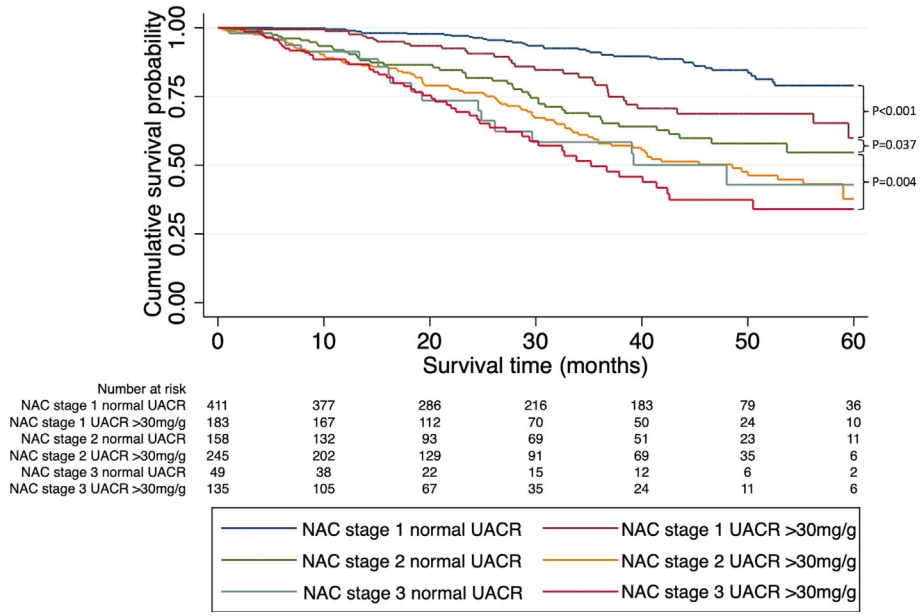

Figure 2 Kaplan–Meier curve demonstrating the effect of the National Amyloidosis Centre (NAC) disease stage and albuminuria on survival. UACR, urinary albumin to creatinine ratio.

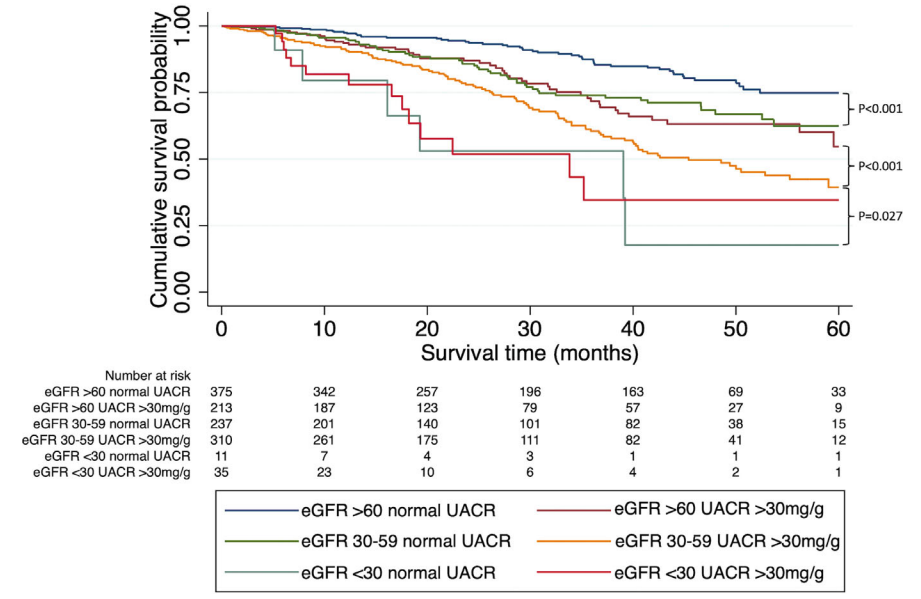

Figure 3 Kaplan–Meier curve demonstrating the effect of chronic kidney disease stage and albuminuria on survival. eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio.

proportion had albuminuria (48.5%).[15] In contrast, only 15.5% of the current study population had concomitant diabetes mellitus, but nearly half (47.7%) had albuminuria. Within the subgroup of patients who did not have hypertension, diabetes mellitus or CKD stage 3–5, over one-third (33.2%) had albuminuria, suggesting that in the context of ATTR-CA, albuminuria occurs independently of concomitant comorbidities. These data also suggest that albuminuria is more common in patients with ATTR-CA than in patients with heart failure of different aetiologies. However, it is noteworthy that patients with ATTR-CA are generally older than the those enrolled into previous heart failure trials, and hence, there could be other confounding factors that have contributed to the higher prevalence of albuminuria observed in this cohort of patients.

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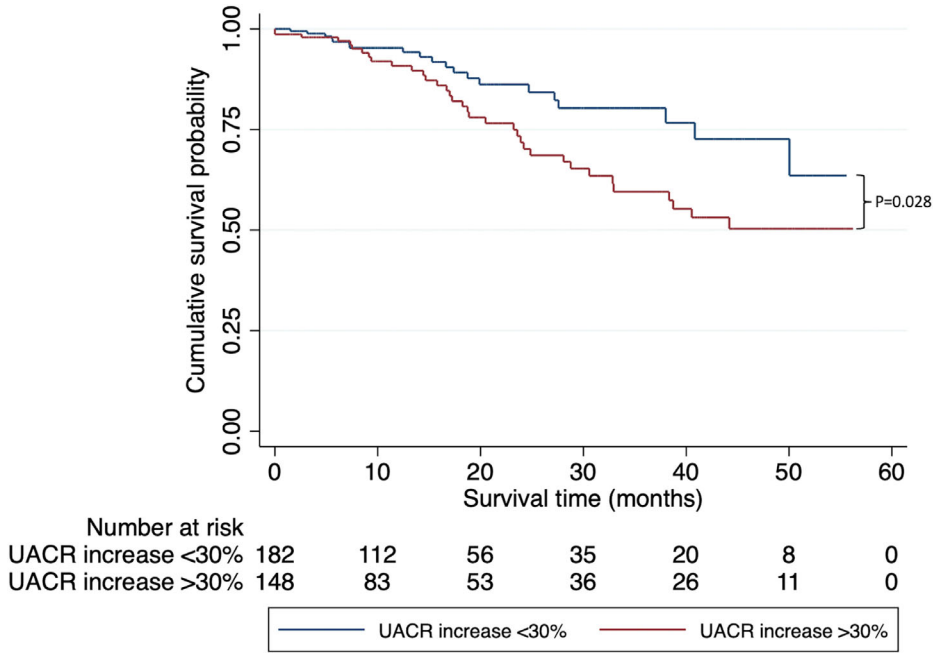

Figure 4 Kaplan–Meier curve demonstrating the effect of a significant increase in albuminuria at 12 months on survival. UACR, urinary albumin to creatinine ratio.

At the time of diagnosis, the presence of albuminuria was associated with increased mortality, and remained independently associated after adjusting for the presence of diabetes mellitus and hypertension and the NAC disease stage. This highlights the role of UACR in identifying high-risk patients and stratifying prognosis beyond the conventional biomarkers utilized in the NAC staging system (NT-proBNP and eGFR). As an early marker of renal dysfunction, albuminuria is most effective at further stratifying risk in patients with NAC stage 1 or stage 2 disease. Importantly, albuminuria remained independently associated with mortality in the cohort of patients who did not have hypertension, diabetes mellitus or CKD stage 3–5, suggesting this urinary biomarker reflects the amyloid disease burden rather than the presence or severity of other comorbidities.

Serial measurements demonstrated that almost half the patients with baseline and follow-up measurements had a significant increase in UACR at 12 months. A significant increase in UACR was associated with a significant increase in NT-proBNP, but no significant change in renal function, which suggests that changes in UACR provide incremental information compared to eGFR alone. Furthermore, a significant increase in UACR was associated with mortality, suggesting serial measurements could also be used to track changes in the underlying amyloid disease process.

The pathophysiological mechanisms responsible for albuminuria in heart failure of different aetiologies remain elusive, but in the context of ATTR amyloidosis albuminuria could potentially be compounded by the direct impact of renal ATTR amyloid fibril deposition. Multiple studies of renal biopsies in patients with p.(Val50Met) hATTR have demonstrated diffuse amyloid fibril accumulation, with heavy glomerular deposition correlating with the degree of albuminuria.[16,17] Interestingly, the presence microalbuminuria in asymptomatic p.(Val50Met) gene carriers conferred an increased risk of developing neuropathy, and once neurological signs appeared the degree of albuminuria continued to increase, suggesting that UACR measurements may represent a surrogate marker for systemic amyloid infiltration.[18]

Renin–angiotensin–aldosterone system inhibition, through use of angiotensin-converting enzyme inhibitors and the novel non-steroidal mineralocorticoid receptor antagonist (MRA) finerenone, along with sodium–glucose cotransporter 2 inhibitors (SGLT2i) have all demonstrated reno-protective properties by reducing the degree of albuminuria, whilst simultaneously reducing the risk of heart failure hospitalization and cardiovascular death in studies of patients without known ATTR-CA.[19–22] Considering the high prevalence of albuminuria in ATTR-CA, and the independent association between albuminuria and mortality, it is plausible that treatment with these medications could have a similar impact in patients with ATTR-CA, and may in part explain the reduced risk of mortality observed in ATTR-CA patients treated with MRAs.[23] While albuminuria is likely to be caused by the same mechanisms as in heart failure of different aetiologies, urinary albumin leakage may also be compounded by the direct impact of renal ATTR amyloid infiltration, which in turn, could be targeted by highly specific medications that either reduce the hepatic synthesis of transthyretin, or stabilize the transthyretin tetramer to prevent dissociation into amyloidogenic monomers.[24,25] The data presented suggest the potential role of albuminuria in tracking treatment in patients treated with MRAs, SGLT2i and possibly even ATTR amyloid specific therapies.

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Limitations

As a retrospective study we have been able to demonstrate the association between albuminuria and mortality, but are unable to prove causality. Comorbidities were ascertained from the medical records, but it is possible there may have been patients in the study population with undiagnosed diabetes mellitus and undiagnosed hypertension. The follow-up data were only available on a subset of patients and invariably introduced a survival bias, whereby the extent of differences is likely to be underestimated and rapid increases in UACR may have been associated with death prior to the 12-month follow-up timepoint. Due to the reduced number of patients with follow-up data, we were unable to assess the effect of medications on changes in UACR.

Conclusions

In summary, albuminuria is common in patients with ATTR-CA, and those with albuminuria had a more severe cardiac phenotype than those with a normal UACR. Albuminuria at diagnosis and a significant increase in UACR during follow-up are associated with mortality.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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