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CLINICAL RESEARCH
Heart failure and cardiomyopathies

Albuminuria as a marker of systemic congestion in patients with heart failure

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See the editorial comment for this article 'Rethinking albuminuria as a marker to drive treatment in congestive heart failure', by N.R. Pugliese *et al.*, https://doi.org/10.1093/eurheartj/ehac612.

Abstract

Aims Albuminuria is common in patients with heart failure and associated with worse outcomes. The underlying pathophysiological mechanism of albuminuria in heart failure is still incompletely understood. The association of clinical characteristics and biomarker profile with albuminuria in patients with heart failure with both reduced and preserved ejection fractions were evaluated.

Methods and results Two thousand three hundred and fifteen patients included in the index cohort of BIOSTAT-CHF were evaluated and findings were validated in the independent BIOSTAT-CHF validation cohort (1431 patients). Micro-albuminuria and macro-albuminuria were defined as urinary albumin–creatinine ratio (UACR) >30 mg/gCr and >300 mg/gCr in spot urines, respectively. The prevalence of micro- and macro-albuminuria was 35.4% and 10.0%, respectively. Patients with albuminuria had more severe heart failure, as indicated by inclusion during admission, higher New York Heart Association functional class, more clinical signs and symptoms of congestion, and higher concentrations of biomarkers related to congestion, such as biologically active adrenomedullin, cancer antigen 125, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (all $P < 0.001$). The presence of albuminuria was associated with increased risk of mortality and heart failure (re)hospitalization in both cohorts. The strongest independent association with log UACR was found for log NT-proBNP (standardized regression coefficient 0.438, 95% confidence interval 0.35–0.53, $P < 0.001$). Hierarchical clustering analysis demonstrated that UACR clusters with markers of congestion and less with indices of renal function. The validation cohort yielded similar findings.

Conclusion In patients with new-onset or worsening heart failure, albuminuria is consistently associated with clinical, echocardiographic, and circulating biomarkers of congestion.

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Structured Graphical Abstract

Key Question

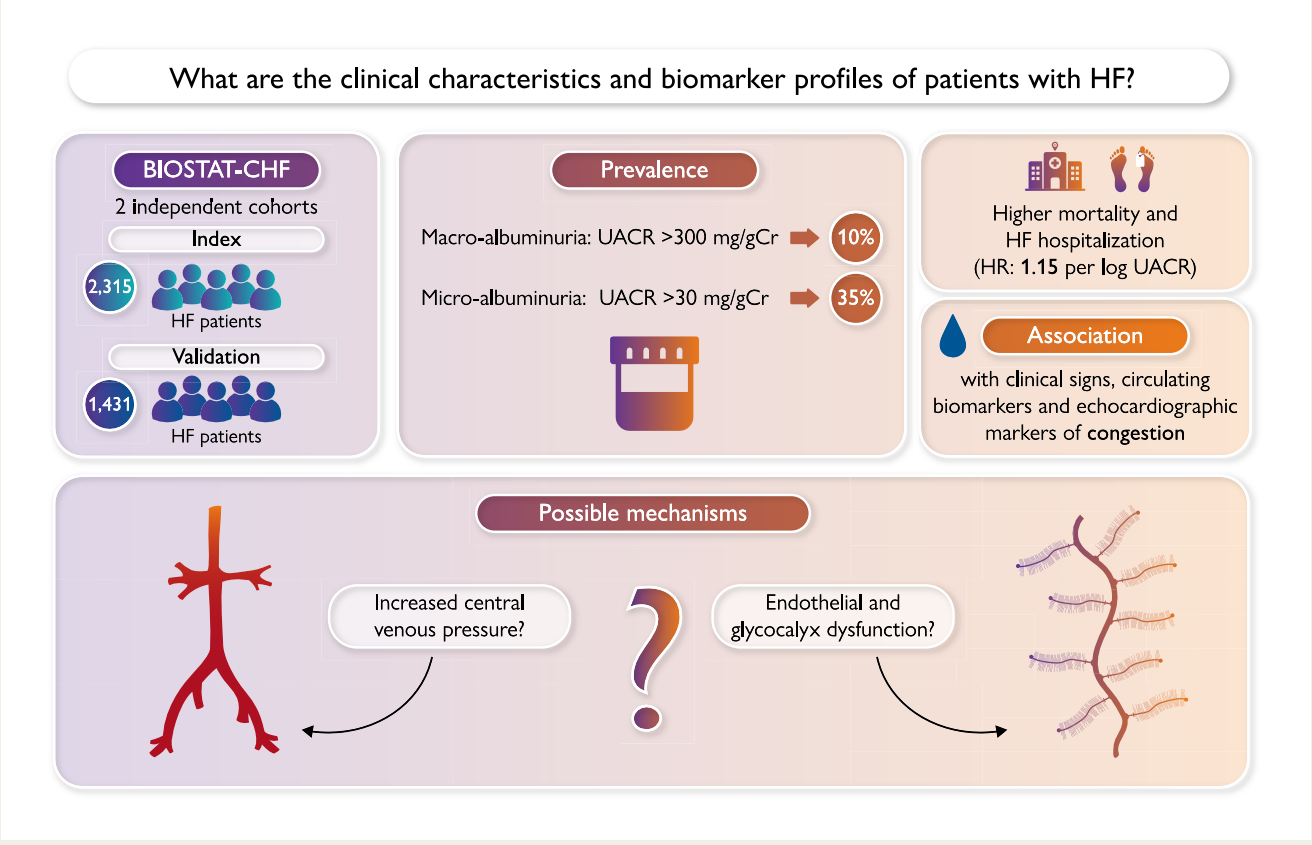
What are the causes and the prognostic relevance of albuminuria in heart failure (HF)?

Key Finding

Albuminuria was common in patients with heart failure (~10% macroalbuminuria, ~35% microalbuminuria). Albuminuria was associated with worse outcomes and with clinical, circulating, and echocardiographic markers of congestion

Take Home Message

In patients with HF, albuminuria is associated with markers of congestion, even after adjustment for common comorbidities that are known to result in albuminuria, such as hypertension and diabetes, and with worse clinical outcomes.



Graphical summary of the main findings of the current study. Prevalence and hazard ratio are based on the index cohort. HF, heart failure; UACR, urinary albumin–creatinine ratio; HR, hazard ratio. Created with BioRender.com.

Keywords Albuminuria • Congestion • Cardiorenal interaction • Biomarkers • Central venous pressure

Introduction

Under normal circumstances, only 0.008% of plasma albumin is filtered by the glomeruli.[1] Leakage through the glomerular membrane, caused by damage to (one of the layers of) the glomerular endothelial membrane will cause more albumin to pass through the glomeruli, leading to albuminuria.[1] This is a disease mechanism which is well described in hypertensive and diabetic kidney disease and is usually related to intraglomerular hypertension.[2,3] In patients with chronic heart failure, the presence of albuminuria is a strong prognostic indicator of adverse events, such as mortality and heart failure hospitalization, even after correction for diabetes, hypertension, and concomitant renal disease.[4,5] While its prognostic value is well recognized, the underlying mechanisms of albuminuria in heart failure are incompletely understood. First, albuminuria could be the result of renin–angiotensin–aldosterone (RAAS) system activation, as angiotensin may directly cause podocyte injury.[6] Secondly, albuminuria might be the result of endothelial dysfunction, manifesting in both the peripheral vessels and the glomeruli. Third, albuminuria could be the result of increased renal venous pressure. Two studies from the same group indicated that when renal

venous pressure was increased this led to albuminuria, while external pressure on the kidney parenchyma did not lead to albuminuria.[7,8] Lastly, albuminuria could be an indicator of comorbidities which frequently occur alongside heart failure, such as diabetes and hypertension.[9–11] In addition, its differential relevance in heart failure with reduced (HFrEF) and preserved ejection fraction (HFpEF) has not been described. We, therefore, aimed to study the clinical characteristics and biomarker profile associated with albuminuria, in addition to previously described clinical outcomes, in patients with heart failure with both reduced and preserved ejection fraction.

Methods

Patient population

For the present study, we used the index and validation cohort of BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure). The trial design has been published before.[12] In brief, BIOSTAT-CHF was a European, multicentre clinical study executed in 11 different countries, consisting of 2516 patients in the index cohort. Patients were included after presentation with either new-onset or worsening heart failure, which was defined as left ventricular ejection fraction (LVEF) ≤40% or B-type natriuretic peptide (BNP) >400 pg/mL or N-terminal pro-B-type natriuretic peptide (NT-proBNP) >2000 pg/mL. Patients were encouraged to be uptitrated to recommended treatment doses of betablockers and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs).

Data were validated in the independent BIOSTAT-CHF validation cohort consisting of 1738 patients with heart failure from Scotland, United Kingdom.

All patients enrolled in BIOSTAT-CHF provided written informed consent to participate in the study and BIOSTAT-CHF was conducted in concordance with the Declaration of Helsinki, national ethics and legal requirements, as well as relevant EU legislation.

Biomarkers

Spot urinary samples were collected at the baseline visit. Samples were frozen in −80°C and thawed prior to analyses. Standard urinary chemistry measurements for albumin, creatinine, sodium, potassium, urea, and uric acid were performed in the laboratory of the University Medical Center Groningen, using routine clinical chemistry measurement on a Roche Cobas® analyser.

At baseline, a total of 2315 patients in the index cohort and 1431 patients in the validation cohort had urinary samples available. Micro-albuminuria was defined as an urinary albumin–creatinine ratio (UACR) >30 mg/gCr, while macro-albuminuria was defined as an UACR >300 mg/gCr.[3]

Statistical analysis

Patients were divided in groups based on normo-, micro-, or macro-albuminuria, respectively. Normally distributed continuous data are presented as means and standard deviation, not normally distributed data as medians and 25th until 75th percentile, and categorical variables as percentages and frequencies. Intergroup differences were tested using one-way ANOVA for normally distributed continuous data, whereas skewed data were analysed using χ^2 test or Kruskal–Wallis test depending on whether the data were nominal or continuous. Whether variables were parametric or non-parametric was assessed visually using Q–Q plots. When Q–Q plots were inconclusive, a histogram was created. When the histogram was also inconclusive, the variable was deemed to be non-parametric. In a subgroup analysis, HFpEF was defined as an LVEF ≥50% and HFrEF was defined as an LVEF <40%, per the most recent European Society of Cardiology (ESC) heart failure guidelines.[13]

Associations of UACR were analysed using univariable and multivariable regression analyses, in which all variables with $P < 0.10$ in univariable analysis were included in the multivariable analysis and subjected to the backward elimination method. The assumption of normality was checked with the use of Q–Q plots, the assumption of linearity was checked using scatter plots and independence of residuals was analysed using residual time series plots. Moreover, we checked the assumption of homoscedasticity with the use of fitted value vs. residual plots. If the assumption was not met, log transformation was performed to ensure homoscedasticity. The models obtained using stepwise backward selection were validated by repeating the variable selection using least absolute shrinkage and selection operator (LASSO) regression. First, variables with more than 15% missingness were excluded from the analysis, second LASSO regression was performed using the R package glmnet.[14] Alpha was set to 1 and the optimal penalization parameter (lambda) was obtained using 10-fold cross-validation. To derive the most parsimonious model, the lambda within 1 standard error of the minimum lambda was used. Variables selected with LASSO regression were then used in a linear regression model to obtain their coefficients. The coefficients of determination (R^2) have been calculated for all regression models.

A Cox regression analysis was used to investigate the association of UACR with clinical endpoints of mortality and heart failure hospitalization, first in a univariable model, secondly corrected for known causes of albuminuria (i.e. renal disease, diabetes mellitus, and hypertension), and lastly corrected for the BIOSTAT-CHF risk model, which consists of the strongest predictors of each clinical outcome.[15] Proportional hazards assumption of the Cox regression models were checked by the use of Schoenfeld residuals in R, with the use of the Survival and Survminer package to test and plot the Schoenfeld residuals.

The dendrograms were built using hierarchical clustering based on Euclidean distance, which has the benefit of using real-valued vectors, as compared with Spearman's correlation, which uses ranked variables. The optimal number of clusters was decided in a supervised manner and based on clinical experience. The current number of clusters is 9. Any number of clusters of 7 or higher puts UACR in between the congestion cluster. A similar approach was used in the validation cohort. All variables were standardized prior to analysis. Aside from urinary and plasma biomarkers, a clinical congestion score was added to the dendrogram. This congestion score was modified from the validated Ambrosy score[16] and constructed by assigning points based on clinical findings: 1 point for orthopnoea, 1 point for jugular vein distention and, respectively, 1/3, 2/3, or 1 point for peripheral oedema until the ankle, below the knee and above the knee, for a maximum of 3 points.[17] A two-sided P-value of <0.05 was considered to be significant.

Results

Baseline characteristics

The prevalence of macro-albuminuria and micro-albuminuria was 242 (10.0%) and 819 (35.4%), respectively, in the index cohort. Baseline characteristics based on these groups are depicted in *Table 1*. In summary, patients with micro- or macro-albuminuria had more severe heart failure indicated by inclusion during admission, more frequent New York Heart Association (NYHA) functional class of III or IV, higher blood pressures and heart rate, more clinical signs of congestion, and higher plasma concentrations of congestion-related biomarkers, such as NT-proBNP, biologically active adrenomedullin (bio-ADM), and cancer antigen 125 (CA-125) (all $P < 0.001$).

Patients with any albuminuria in the index cohort were less likely to be on ACE-inhibitor or ARB [63.2% (macro-) and 69.0% (micro-) vs. 75.8% (normo-albuminuria), $P < 0.001$], while they were on higher doses of loop diuretics [114 ± 141 (macro-) and 101 ± 120 (micro-) vs. 85 ± 116 mg of furosemide or equivalent daily (normo-albuminuria), $P < 0.001$]. No differences in medical treatment between those with

Table 1 Baseline characteristics according to normo-, micro-, and macro-albuminuria

	Index cohort				Validation cohort			
	Macro (UACR >300 mg/gCr)	Micro (UACR 30–300 mg/gCr)	Normal (UACR <30 mg/gCr)	*P*-value	Macro (UACR >300 mg/gCr)	Micro (UACR 30–300 mg/gCr)	Normal (UACR <30 mg/gCr)	*P*-value
N	242 (10.0%)	819 (35.4%)	1254 (54.2%)		112 (7.0%)	446 (31.2%)	873 (61.0%)	
Demographics								
Age (years)	69.75 (11.26)	70.44 (12.17)	67.69 (11.79)**	<0.001	74.5 (10.8)	76.1 (9.5)	72.2 (10.7)**	<0.001
Female sex, *n* (%)	56 (23.1)	240 (29.3)	323 (25.8)	0.083	30 (26.8)	136 (30.5)	286 (32.8)	0.368
Duration of heart failure (years)	2.12 (3.38)	4.16 (6.37)	2.38 (4.69)*	0.088	2.95 (4.82)	3.25 (4.26)	3.56 (4.73)	0.280
Inpatient hospitalization, *n* (%)	168 (69.4)	596 (72.8)	786 (62.7)**	<0.001	69 (61.6)	278 (62.3)	374 (42.8)**	<0.001
NYHA class, *n* (%)			**	<0.001				<0.001
I	4 (1.7)	9 (1.1)	39 (3.2)		0 (0.0)	2 (0.4)	13 (1.5)	
II	57 (23.9)	242 (30.6)	508 (41.7)		33 (29.5)	152 (34.1)	420 (48.2)	
III	140 (58.8)	411 (51.9)	568 (46.7)		55 (49.1)	200 (44.8)	361 (41.4)	
IV	37 (15.5)	130 (16.4)	102 (8.4)		24 (21.4)	92 (20.6)	78 (8.9)	
Systolic blood pressure (mmHg)	131.32 (22.60)**	126.50 (23.40)	122.51 (20.80)**	<0.001	141.09 (25.68)**	127.44 (21.99)	123.42 (20.77)**	<0.001
Diastolic blood pressure (mmHg)	76.16 (13.70)	75.71 (14.66)	74.17 (12.50)*	0.013	74.96 (14.55)**	69.81 (13.45)	68.19 (11.83)*	<0.001
Heart rate (bpm)	80.42 (18.40)	82.82 (20.70)	77.82 (18.59)**	<0.001	76.43 (17.25)	75.57 (17.95)	72.10 (15.27)**	<0.001
Weight (kg)	83.16 (17.38)	81.25 (18.58)	81.72 (18.11)	0.361	83.13 (20.26)	81.79 (19.71)	82.79 (20.11)	0.651
BMI (kg/m^2)	28.5 (5.0)	27.8 (5.6)	28.8 (5.3)	0.191	29.0 (6.2)	28.8 (6.4)	29.2 (6.3)	0.357
Waist hip ratio					1.01 (0.10)*	0.98 (0.09)	0.97 (0.09)	0.002
Medication								
ACE-inhibitors or ARB, *n* (%)	153 (63.2)	565 (69.0)	950 (75.8)**	<0.001	78 (69.6)	311 (69.7)	634 (72.6)	0.493
Beta-blockers, *n* (%)	201 (83.1)	667 (81.4)	1056 (84.2)	0.258	73 (65.2)	334 (74.9)	631 (72.3)	0.116
Mineralocorticoid receptor antagonists, *n* (%)	107 (44.2)	407 (49.7)	727 (58.0)**	<0.001	38 (33.9)	142 (31.8)	295 (33.8)	0.764
Loop diuretic dose (mg furosemide or equivalent)	114 (141)	101 (120)	85 (116)**	<0.001	86 (67)**	78 (53)	62 (43)**	<0.001
Medical history, n (%)								
Myocardial infarction	109 (45.0)**	288 (35.2)	487 (38.8)	0.016	52 (46.4)	223 (50.0)	442 (50.7)	0.696
Atrial fibrillation	107 (44.2)*	419 (51.2)	519 (41.4)**	<0.001	59 (52.7)	241 (54.5)	343 (39.6)**	<0.001
Stroke	28 (11.6)	82 (10.0)	102 (8.1)	0.136	21 (18.8)	98 (22.2)	147 (17.0)*	0.076

Continued

Table 1 *Continued*

	Index cohort				Validation cohort			
	Macro (UACR >300 mg/gCr)	**Micro (UACR 30–300 mg/gCr)**	**Normal (UACR <30 mg/gCr)**	***P*-value**	**Macro (UACR >300 mg/gCr)**	**Micro (UACR 30–300 mg/gCr)**	**Normal (UACR <30 mg/gCr)**	***P*-value**
Peripheral arterial disease	42 (17.4)	110 (13.4)	107 (8.5)**	<0.001	37 (33.3)	108 (24.9)	182 (21.4)	0.014
Hypertension	192 (79.3)**	534 (65.2)	729 (58.1)**	<0.001	82 (73.2)	285 (64.3)	458 (52.7)**	<0.001
Current smoking	35 (14.5)	118 (14.4)	178 (14.2)	0.751	17 (15.3)	48 (10.9)	121 (13.9)	0.424
Diabetes mellitus	137 (56.6)**	280 (34.2)	347 (27.7)**	<0.001	55 (49.5)	175 (39.5)	236 (27.2)**	<0.001
COPD	44 (18.2)	150 (18.3)	208 (16.6)	0.561	22 (19.6)	82 (18.6)	143 (16.6)	0.533
Renal disease	114 (47.1)**	247 (30.2)	283 (22.6)**	<0.001	70 (62.5)	237 (53.6)	336 (39.3)**	<0.001
Clinical profile								
Bibasilar rales/crackles, *n* (%)	117 (49.4)	372 (46.2)	418 (34.5)**	<0.001	51 (46.8)	209 (48.3)	250 (29.9)**	<0.001
Peripheral oedema, *n* (%)			**	<0.001	*		**	<0.001
Not present	66 (30.8)	218 (31.5)	493 (48.3)		26 (24.1)	133 (32.1)	351 (45.3)	
Ankle	69 (32.2)	201 (29.0)	304 (29.8)		35 (32.4)	136 (32.9)	230 (29.7)	
Below knee	53 (24.8)	208 (30.0)	176 (17.3)		30 (27.8)	116 (28.0)	163 (21.1)	
Above knee	26 (12.1)	66 (9.5)	47 (4.6)		17 (15.7)	29 (7.0)	30 (3.9)	
Jugular venous distention, *n* (%)	67 (38.5)	213 (37.6)	230 (26.3)**	<0.001	43 (41.3)	136 (34.3)	195 (25.8)**	<0.001
Haepatomegaly, *n* (%)	46 (19.1)	132 (16.2)	150 (12.0)**	0.002	8 (8.1)	21 (5.0)	23 (2.9)*	0.017
Orthopnoea, *n* (%)	93 (38.4)	330 (40.4)	382 (30.5)**	<0.001				
VAS dyspnoea score	40.71 (21.30)*	47.89 (22.87)	48.49 (22.30)	0.077	2.36 (0.80)	2.32 (0.85)	2.02 (0.83)**	<0.001
Chest X-ray, n (%)								
Congestion present	48 (30.6)	200 (35.1)	194 (24.5)**	<0.001				
Cardio thorax ratio >0.5	114 (72.6)	406 (71.5)	501 (63.3)**	0.002				
Echo parameters								
LVEF (%)	32.32 (10.45)	31.26 (11.72)	30.66 (9.71)	0.083	43.20 (15.61)	40.47 (13.39)	39.66 (13.21)	0.076
LVEDD (mm)	60.75 (10.24)	60.32 (10.25)	61.59 (9.55)**	0.028	53.97 (8.40)	55.19 (9.67)	55.28 (9.10)	0.436
Intraventricular septal thickness (mm)	11.30 (2.66)**	10.69 (2.62)	10.47 (2.36)	<0.001	13.39 (2.90)*	12.51 (3.07)	12.17 (4.37)	0.041
Posterior wall thickness (mm)	11 (9, 12)**	10 (9, 12.00)	10 (9, 11)	0.001	12 (10,14)*	11 (10, 13)	11 (9, 13)	0.002
Left atrial diameter (mm)	48.55 (7.29)	47.85 (8.60)	46.90 (7.77)*	0.010	46.53 (6.20)	46.96 (7.85)	44.40 (6.94)**	<0.001
Mitral regurgitation, *n* (%)	114 (49.1)	377 (49.1)	556 (46.3)	0.433	38 (34.5)	160 (37.4)	243 (29.3)**	0.012
E/A ratio	1.50 (0.99, 2.48)	1.50 (0.80, 2.40)	1.10 (0.72, 2.07)**	0.005	1.10 (0.76, 2.10)	1.10 (0.80, 1.87)	0.90 (0.70, 1.20)**	<0.001

Continued

Table 1 *Continued*

	Index cohort				Validation cohort			
	Macro (UACR >300 mg/gCr)	**Micro (UACR 30–300 mg/gCr)**	**Normal (UACR <30 mg/gCr)**	***P*-value**	**Macro (UACR >300 mg/gCr)**	**Micro (UACR 30–300 mg/gCr)**	**Normal (UACR <30 mg/gCr)**	***P*-value**
Inferior caval vein diameter >2.1 cm, *n* (%)					25 (22.5)	113 (25.9)	133 (15.6)**	<0.001
Tricuspid regurgitation gradient (mmHg)					40.70 (16.52)	36.83 (14.48)	33.17 (11.57)**	<0.001
Laboratory values								
Haemoglobin (g/dL)	12.90 (11.40, 14.20)	13.20 (11.76, 14.50)	13.40 (12.10, 14.60)**	<0.001	12.50 (11.07, 13.93)*	13.00 (11.50, 14.40)	13.40 (12.20, 14.70)**	<0.001
Serum creatinine (μmol/L)	123.76 (97.24, 169.00)**	106.08 (87.00, 133.00)	97.24 (80.33, 121.16)**	<0.001	121.00 (89.75, 169.00)**	103.00 (83.00, 135.00)	94.00 (79.00, 117.00)**	<0.001
eGFR (mL/min/1.73 m^2)	39.1 (28.0, 52.8)**	48.1 (35.9, 66.5)	55.3 (40.0, 72.5)**	<0.001	39.8 (28.2, 56.1)**	48.8 (34.1, 65.6)	55.8 (41.2, 74.1)**	<0.001
Serum urea (mmol/L)	14.90 (9.30, 24.15)**	11.85 (8.10, 18.65)	10.35 (7.10, 16.42)**	<0.001	10.10 (7.77, 15.05)	9.40 (7.10, 13.50)	8.00 (6.30, 10.40)**	<0.001
Fractional excretion of urea (%)	25.2 (16.2, 36.9)	26.6 (16.8, 36.2)	25.4 (16.5, 36.4)	0.721	31.2 (26.5, 37.0)	30.4 (24.7, 36.9)	30.5 (25.1, 36.4)	0.434
Serum albumin (g/L)	30.40 (9.37)	31.34 (8.78)	33.23 (8.55)**	<0.001	36.21 (6.39)	37.32 (6.08)	39.02 (5.68)**	<0.001
ALAT (U/L)	22.00 (15.00, 31.00)*	24.35 (16.00, 37.76)	26.00 (18.00, 38.75)	0.001	21.00 (16.00, 31.75)	22.00 (16.00, 33.00)	22.00 (17.00, 32.00)	0.569
Alkaline phosphatase (μg/L)	111.75 (66.28)	106.96 (70.28)	96.40 (55.22)**	0.006	123.56 (64.43)	111.54 (71.87)	95.68 (44.45)**	<0.001
Gamma-GT (U/L)	63.00 (29.00, 125.00)	63.00 (31.88, 120.00)	46.00 (25.29, 94.00)**	0.001	81.00 (41.75, 146.75)**	51.00 (31.00, 105.50)	40.00 (24.00, 76.00)**	<0.001
Total bilirubin (pmol/L)	29.47 (156.81)	20.32 (21.89)	17.15 (13.49)**	0.049	14.03 (9.99)	14.28 (9.62)	11.35 (6.78)**	<0.001
NT-proBNP (ng/L)	5045 (2358, 11823)**	3891 (1721, 7516)	1936 (872, 3885)**	<0.001	3957 (1487, 8885)**	2369 (994, 5230)	855 (336, 2137)**	<0.001
Bio-ADM (pg/mL)	45.2 (27.6, 69.6)	40.1 (26.5, 67.5)	28.5 (20.6, 43.0)**	<0.001	41.7 (26.3, 66)**	31.80 (21.0, 50.3)	23.9 (16.8, 35.2)**	<0.001
Glucose (mmol/L)	7.33 (5.66, 10.20)**	6.49 (5.50, 7.99)	6.05 (5.27, 7.40)**	<0.001	7.40 (5.80, 9.60)	6.60 (5.40, 9.40)	6.00 (5.20, 8.00)**	<0.001
Aldosterone (pg/mL)	82.00 (38.00, 177.25)	84.50 (41.00, 183.05)	103.00 (48.00, 211.13)**	0.001				
Renin (IU/mL)	65.43 (22.09, 173.34)	83.52 (25.24, 230.04)	101.61 (32.22, 305.14)**	<0.001				
GDF-15 (pg/mL)	3923 (2373, 6328)*	3623 (2149, 5942)	2189 (1441, 3475)**	<0.001	4826 (2992, 7358)**	3486 (2332, 5598)	2344 (1611, 3764)**	<0.001
FGF-23 (RU/mL)	460.30 (180.13, 1301.75)	331.89 (149.59, 847.95)	162.25 (100.99, 324.44)	<0.001				
CA-125 (U/mL)	69 (22, 205)	58 (21, 149)	28 (14, 105)**	<0.001	56 (25, 159)**	37 (17, 92)	20 (12, 41)**	<0.001

For differences between groups: * $P < 0.05$ compared with micro-albuminuria, ** $P < 0.01$ compared with micro-albuminuria.
UACR, urinary albumin-to-creatinine ratio; NYHA, New York Heart Association; BMI, body mass index; ACE, angiotensin converter enzyme; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; VAS, visual analogue scale; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; ALAT, alanine transferase; gamma-GT, gamma-glutamyltransferase; NT pro-BNP, N-terminal pro-B-type natriuretic peptide; bio-ADM, biologically active adrenomedullin; GDF-15, growth differentiation factor 15; FGF-23, fibroblast growth factor 23; CA-125, cancer antigen 125.

Table 2 linear regression, standardized regression coefficient per log increase urinary albumin-to-creatinine ratio

	Index cohort			Validation cohort		
Variable	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**
Log NT pro-BNP	0.438 (0.35–0.53)	9.676	<0.001	0.486 (0.39–0.58)	9.689	<0.001
Log urinary KIM-1	0.327 (0.23–0.42)	6.915	<0.001			
Log plasma urea	0.373 (0.27–0.48)	6.9	<0.001			
Log fractional excretion of urea	0.346 (0.24–0.45)	6.68	<0.001			
Hx of diabetes mellitus	0.536 (0.37–0.7)	6.351	<0.001	0.474 (0.30–0.65)	5.218	<0.001
Systolic blood pressure	0.252 (0.17–0.33)	6.136	<0.001	0.410 (0.33–0.49)	9.940	<0.001
Log bio-ADM	0.265 (0.18–0.35)	6.197	<0.001	0.150 (0.05–0.25)	2.892	0.004
Log Y-GT				0.201 (0.12–0.29)	4.654	<0.001
Log renin	−0.228 (−0.31 to -0.14)	−5.228	<0.001			
VAS dyspnoea score				0.146 (0.06–0.23)	3.281	0.001
Body mass index				−0.110 (−0.2 to -0.02)	−2.38	0.017
Heart rate				0.10 (0.02–0.18)	2.323	0.019
Log urinary NGAL	0.139 (0.05–0.23)	3.066	0.002			
Log serum creatinine				0.094 (0–0.19)	1.997	0.046
Peripheral oedema above knees				0.389 (0.01–0.77)	2.011	0.045
	Adjusted R^2: 0.2844 *N = 1645*			*Adjusted R^2: 0.2882* *N = 1471*		

NT pro-BNP, N-terminal pro-B-type natriuretic peptide; KIM-1, kidney injury marker-1; Hx, medical history; bio-ADM, biologically active adrenomedullin; Y-GT, gamma-glutamyltransferase; VAS, visual analogue scale; NGAL, neutrophil gelatinase-associated lipocalin.

and without albuminuria were seen in the validation cohort, with the exception of loop diuretic doses.

Echo parameters that provide assessment of right-sided pressures and volume (only available in the validation cohort) suggested that pulmonary pressures were higher in patients with albuminuria (peak tricuspid regurgitation gradient 40.7 mmHg, 36.4 mmHg, and 33.2 mmHg for macro-, micro, and normo-albuminuria, respectively, $P < 0.001$) and inferior caval vein diameter >2.1 cm (22.5%, 25.9%, and 15.6% for macro-, micro, and normo-albuminuria, respectively, $P < 0.001$).

Linear and logistic regression analysis

From multivariable linear regression, the strongest associations with log UACR were found for log NT-proBNP (standardized regression coefficient 0.438, (95% CI: 0.35 – 0.53)), log urinary KIM-1 (standardized regression coefficient 0.327), log plasma urea, log fractional excretion of urea, a history of diabetes mellitus, systolic blood pressure, log bio-ADM, and log renin (all $P < 0.001$) (*Table 2*). Multivariable linear regression in the validation cohort yielded similar results regarding NT-proBNP, history of diabetes mellitus, systolic blood pressure and bio-ADM. Yet, several differences were also observed, in part driven by the inclusion of different variables in the index and validation cohorts due to availability (*Table 2*). The adjusted R^2 of the multivariable regression models for the index and validation cohorts were 0.284 and 0.288, respectively. Outcomes of univariable regression analysis performed prior to multivariable regression can be found in Supplementary *Table S1*. To account for the possibility that a higher NT-proBNP was the result of poorer renal clearance, the presence of an interaction was tested between log NT-proBNP and estimated glomerular filtration rate (eGFR) for the association with log UACR, which was not significant (P for interaction = 0.260). In order to differentiate between congestion and heart failure severity, linear regression was performed in subsets of NYHA functional class (I/II, III, and IV). In all NYHA classes the strongest association with log UACR was found for log NT-proBNP (see Supplementary material online, *Table S2A and B*).

The independent associations of log UACR in multivariable linear regression analysis in HFrEF and HFpEF were similar (*Table 3* and *4*).

To further validate our findings from the linear regression analyses, the variable selection was repeated using LASSO, which gave very similar variables to include in the final model for the complete cohort and the HFrEF subgroups (see Supplementary material online, *Table S3A and B*). However, for the HFpEF subgroup, slightly different variables were selected (see Supplementary material online, *Table S3C*). The regression models build with the variables selected using LASSO can be found in Supplementary material online, *Tables S4*. In all these models, log NT-proBNP showed the strongest independent association with log UACR.

As a history of diabetes was a major factor associated with log UACR in all subgroups, linear regression analyses were repeated in those with

Table 3 Linear regression analysis for log urinary albumin–creatinine ratio in heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction in the index cohort

	HFrEF (LVEF <40%)			HFpEF (LVEF ≥50%)		
Variable	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**
Log NT-proBNP	0.414 (0.3–0.52))	7.355	<0.001	0.568 (0.2–0.93)	3.092	0.003
Log plasma urea	0.42 (0.28–0.56)	6.052	<0.001			
Log urinary KIM-1	0.371 (0.25–0.49)	5.949	<0.001	0.393 (0.09–0.69)	2.594	0.011
Systolic blood pressure	0.285 (0.18–0.39)	5.296	<0.001			
Log fractional excretion of urea	0.334 (0.21–0.46)	5.097	<0.001			
Log bio-ADM	0.242 (0.13–0.35)	4.301	<0.001			
Serum creatinine				0.46 (0.22–0.7)	3.793	<0.001
Log renin	−0.186 (−0.29–0.08)	−3.362	0.001	−0.49 (−0.81–0.17)	−3.053	0.003
Log plasma CA-125				0.588 (0.19–0.99)	2.92	0.004
History of diabetes mellitus	0.379 (0.15–0.6)	3.303	0.001	0.96 (0.37–1.55)	3.253	0.002
Log urinary uromodulin	−0.163 (−0.27–0.06)	−3.083	0.002	−0.348 (−0.63–0.06)	−2.414	0.018
Log urinary NGAL	0.147 (0.03–0.26)	2.523	0.012			
Plasma glucose	0.112 (0.01–0.24)	2.211	0.027			
Beta-blocker use				0.707 (0.13–1.28)	2.428	0.017
	Adjusted R^2: 0.2771 *N = 11031*			*Adjusted R^2: 0.432* *N = 113*		

NT pro-BNP, N-terminal pro-B-type natriuretic peptide; KIM-1, kidney injury marker-1; bio-ADM, biologically active adrenomedullin; NGAL, neutrophil gelatinase-associated lipocalin.

Table 4 Linear regression analysis for log urinary albumin–creatinine ratio in heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction in the validation cohort

	HFrEF (LVEF <40%)			HFpEF (LVEF ≥50%)		
Variable	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**	**Standardized regression coefficient (95% CI)**	***T*-value**	***P*-value**
Log NT-proBNP	0.557 (0.42–0.69)	8.168	<0.001	0.639 (0.51–0.77)	9.576	<0.001
Systolic blood pressure	0.036 (0.23–0.49)	5.522	<0.001	0.326 (0.2–0.45)	5.025	<0.001
Log bilirubin	0.237 (0.1–0.37)	3.512	<0.001			
History of diabetes Mellitus	0.43 (0.16–0.7)	3.101	0.002	0.468 (0.19–0.75)	3.28	0.001
Log bio-ADM				0.178 (0.04–0.31)	2.584	0.01
VAS dyspnoea score	0.17 (0.03–0.31)	2.422	0.016			
Log gamma-GT	0.141 (0.01–0.27)	2.089	0.037			
	Adjusted R^2: 0.275 *N = 444*			*Adjusted R^2: 0.286* *N = 296*		

NT pro-BNP, N-terminal pro-B-type natriuretic peptide; gamma-GT, gamma-glutamyltransferase; GDF-15, growth differentiation factor-15; VAS, visual analogue scale.

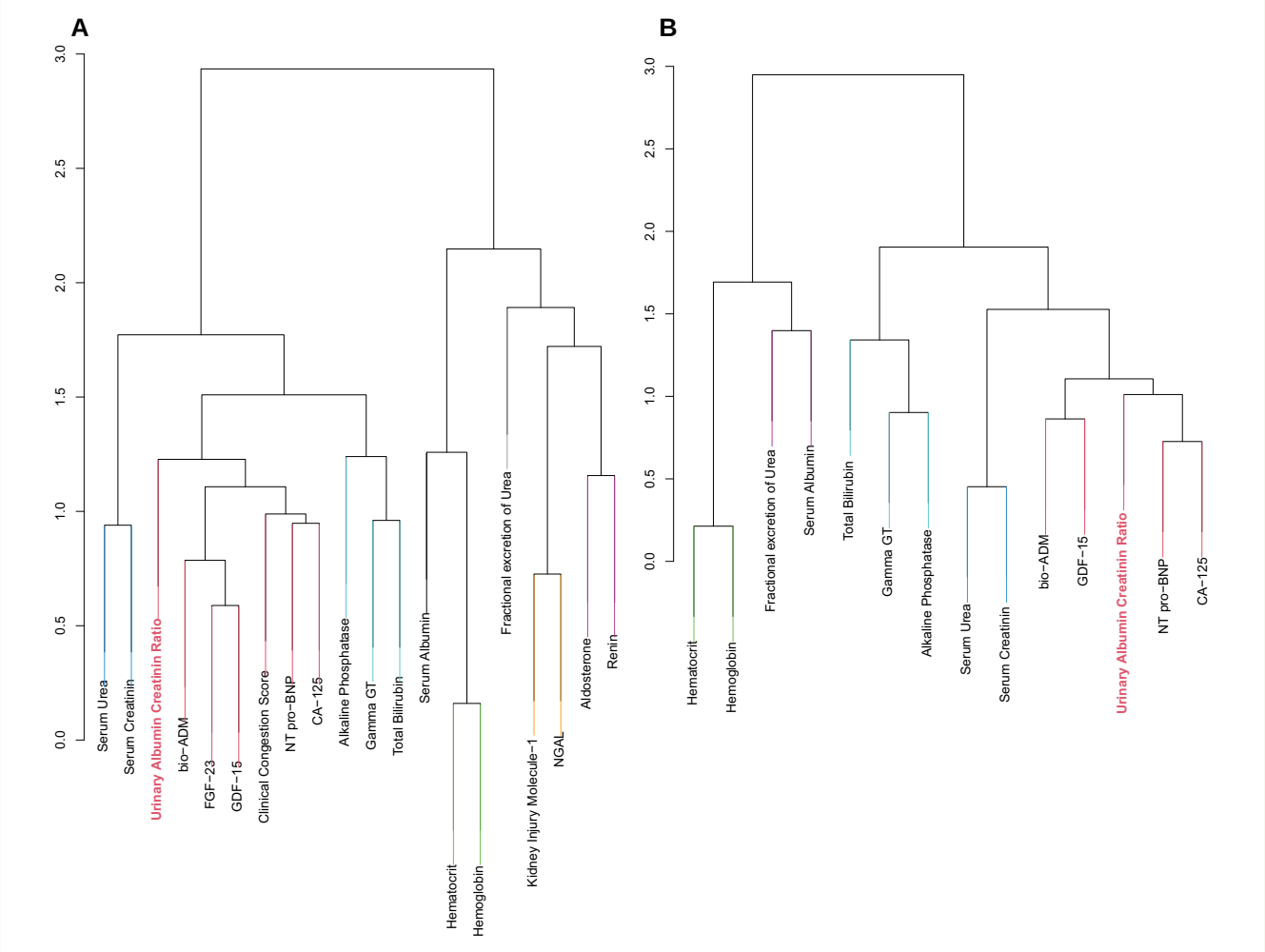


Figure 1 Dendrogram displaying hierarchical clustering based on Euclidean distance in the index (*A*) and validation cohort (*B*). bio-ADM, biologically active adrenomedullin; FGF-23, fibroblast growth factor 23; GDF-15, growth differentiation factor 15; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CA-125, cancer antigen 125; gamma-GT, gamma-glutamyltransferase; NGAL, neutrophil gelatinase-associated lipocalin.

and without a history of diabetes mellitus (see Supplementary material online, *Table S5*). Again, associations found were similar in both subgroups, and NT-proBNP and systolic blood pressure remained the strongest associations.

Sensitivity analyses using multivariable logistic regression for associations of any vs. no albuminuria showed similar results (see Supplementary material online, *Table S6*).

Hierarchical cluster analysis of urinary albumin–creatinine ratio and other biomarkers

Figure 1A shows a dendrogram based on Euclidean distance positioning. Urinary albumin–creatinine ratio clearly clusters with biomarkers of congestion, as well as the clinical congestion score. Other clusters that can be appreciated are a 'glomerular cluster' of serum creatinine and serum urea, a renal injury cluster of urinary kidney injury molecule-1 (KIM-1) and urinary neutrophil gelatinase-associated lipocalin (NGAL), a hepatic cluster of alkaline phosphatase, gamma-glutamyltransferase, and total bilirubin, and a RAAS cluster of aldosterone and renin. Very similar clusters were found in the validation cohort (*Figure 1B*).

Cox regression analysis

Kaplan–Meier survival curves showed that the presence of any albuminuria was associated with a higher risk of mortality and heart failure (re) hospitalization (index cohort *Figure 2A* and validation cohort *Figure 2B*, log-rank *P* for both <0.001). Multivariable Cox regression analyses showed that log UACR was independently associated with mortality in both the index and validation cohort and was independently associated with the combined endpoint of death or heart failure hospitalization in the validation cohort (*Table 5*). To account for potential differences in biology between patients with HFpEF or HFrEF, an interaction term was added to the Cox regression model. There, however, was no significant interaction on outcome (index: likelihood ratio rest $P = 0.452$, $P = 0.2316$ for mortality and the combined endpoint, respectively; validation: likelihood ratio rest $P = 0.978$, $P = 0.5455$ for mortality and the combined endpoint, respectively)'.

Discussion

The present study shows that patients with heart failure who had albuminuria showed more signs and symptoms of (systemic) congestion at

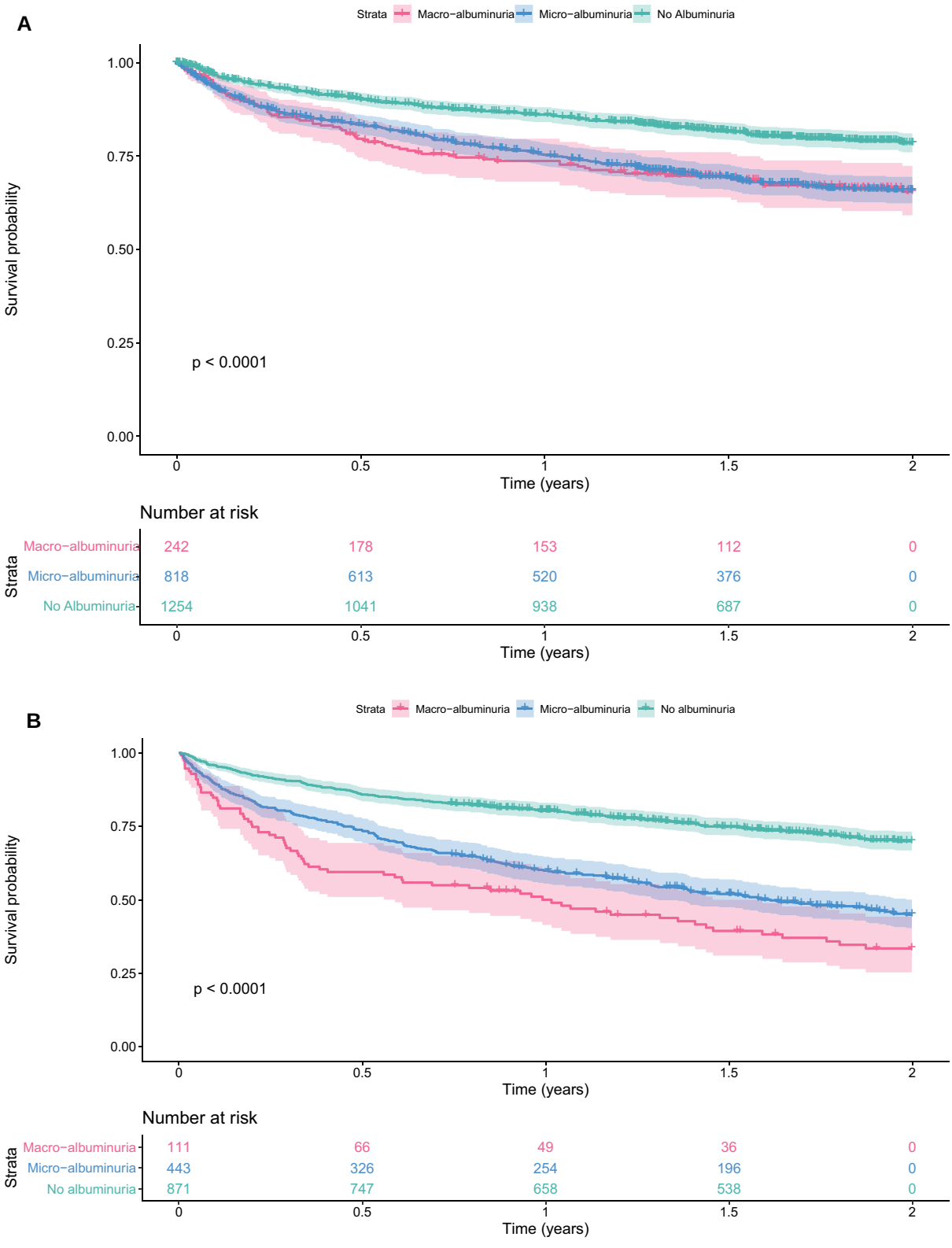


Figure 2 Survival analyses, proportion free from mortality or heart failure hospitalization in the index (*A*) and validation cohort (*B*).

baseline, compared with those who did not have albuminuria. Even after adjustment for several kidney markers, such as urinary NGAL and KIM-1, the strongest association with log UACR was found for plasma NT-proBNP, in multivariable regression analysis. In addition, the correlation between NT-proBNP and UACR was independent of glomerular filtration and remained present across all NYHA functional

Table 5 Cox regression

	Index cohort			Validation cohort		
	Hazard ratio	(95% confidence interval)	*P*-value	Hazard ratio	(95% confidence interval)	*P*-value
2-year mortality						
Univariate	1.148	1.104–1.193	<0.001	1.330	1.257–1.407	<0.001
Serum creatinine, age,History of DM and NT-proBNP	1.061	1.009–1.116	0.02	1.214	1.140–1.293	<0.001
BIOSTAT-CHF risk model[a]	1.059	1.012–1.107	0.013	1.134	1.066–1.206	<0.001
Combined endpoint of HF hospitalization or mortality						
Univariate	1.118	1.084–1.153	<0.001	1.296	1.237–1.359	<0.001
Serum creatinine, age, History of DM and NT-proBNP	1.037	0.999–1.079	0.066	1.198	1.138–1.262	<0.001
BIOSTAT-CHF risk model[b]	1.031	0.995–1.067	0.091	1.201	1.143–1.263	<0.001

DM, diabetes mellitus; NT pro-BNP, N-terminal pro-B-type natriuretic peptide.
[a]Variables included in the BIOSTAT risk model for 2-year mortality: age, blood urea nitrogen, NT pro-BNP, haemoglobin, and failure to prescribe a beta-blocker.
[b]Variables included in the BIOSTAT risk model for the combined endpoint of HF hospitalization or mortality: age, previous HF hospitalization, peripheral oedema, systolic blood pressure, NT pro-BNP, haemoglobin, high-density lipoprotein, sodium, and use of beta-blockers.

classes. Other markers and clinical parameters reflective of congestion, such as bio-ADM and peripheral oedema, were also associated with a higher UACR. Lastly, in hierarchical cluster analysis UACR clustered with established and novel markers of congestion, as well as with the clinical congestion score, rather than with glomerular and tubular markers such as creatinine, NGAL, and KIM-1 (*Structured Graphical Abstract*). Taken together, these findings suggest that in patients with heart failure the extent of albuminuria is more related to the severity of congestion than to markers of intrinsic renal disease.

Congestion

Although albuminuria is not yet an established marker of congestion in heart failure, there are several lines of evidence that support a connection between congestion and albuminuria. Firstly, ligation of the renal vein in healthy dogs resulted in albuminuria in the congested kidney after pressures of 18 mmHg were attained, while the non-congested control kidneys did not show albuminuria.[18] Central venous pressures (and with it renal venous pressure) of more than 18 mmHg are not uncommon in acute heart failure.[19,20] Importantly, after the ligation was lifted, proteinuria quickly recovered.[18] Secondly, in patients admitted for acute decompensated heart failure, the incidence of albuminuria significantly decreased after 7 days of diuretic treatment, indicating an effect of congestion relief (or reduction of central venous pressure) on albumin excretion.[21] Thirdly, in patients with the so-called 'nutcracker' syndrome, the left renal vein gets squeezed between the aorta and the superior mesenteric artery. This syndrome is typically associated with albuminuria, among other urological symptoms.[22] Similar to the nutcracker syndrome, in patients with renal vein thrombosis giving rise to occlusion of the renal vein, albuminuria is common, can be severe and is reversible after the occlusion is lifted.[23] Finally, in adult patients with congenital heart disease associated with higher (central and pulmonary) venous pressure (single ventricle Fontan, systemic right ventricle, and Eisenmenger syndrome), a higher prevalence of albuminuria is found as well. In contrast, no increase in albuminuria is found in congenital abnormalities without increased right-sided pressures, such as an aortic coarctation.[24] In addition, pulmonary hypertension is a common complication of sickle cell disease. In this patient category, the presence of albuminuria has a positive predictive value of 60% for concomitant pulmonary hypertension, further solidifying the association between increased right-sided pressures and albuminuria.[25]

The association between albuminuria and (central) venous pressure is further supported by available echocardiographic data. In the validation cohort, echo parameters related to right-sided pressure, namely vena cava inferior diameters and tricuspid regurgitation gradient, were significantly increased in patients with albuminuria, indicating increased pulmonary and central venous pressures. In logistic regression, the gradient over the tricuspid valve remained independently associated with the presence of albuminuria.

After NT-proBNP, the second strongest association with log UACR in multivariable linear regression was found for urinary KIM-1. Several animal studies have shown that clipping of the renal vein leads to increased renal interstitial pressures, with one renal congestion model in mice showing increased tubular expression of KIM-1 in the affected kidney.[18,26,27] Moreover, clipping of the vein leads to albuminuria and microscopic destruction of podocytes in these mice,[27] indicating congestion-induced damage to the glomerular membrane as well as the tubules. Importantly, our data only show correlations between congestion markers, KIM-1, and albuminuria in heart failure and therefore causality cannot be assessed.

One surprising finding is the fact that renin concentration was negatively associated with log UACR. A possible explanation for this finding could be that those with micro- or macro-albuminuria were less likely to be on ACE-inhibitor/ARB and mineralocorticoid receptor antagonist, giving rise to lower renin concentrations. This finding is further supported by the fact that ACE-inhibitor use was associated with a lower

odds ratio for UACR in logistic regression. Our findings are especially interesting in light of the fact that sacubitril/valsartan is associated with a higher incidence of albuminuria, despite a reduction in NT-proBNP and a slower decline in eGFR, in both HFrEF and HFpEF.[28,29] Importantly, however, no patients in BIOSTAT-CHF were using sacubitril/valsartan, so an influence of this drug on albuminuria could not be tested in our data.

Endothelial dysfunction

Another possible underlying mechanism explaining the relation between albuminuria and congestion could be related to endothelial dysfunction. Dysfunctional endothelial cells are associated with many cardiovascular, metabolic, and renal diseases.[30] The main symptoms of endothelial dysfunction are impaired nitric oxide production and increased vascular permeability. Impaired endothelial function in the kidneys might, therefore, result in more albuminuria.[31] Endothelial dysfunction would also explain the correlations found with congestion, as the threshold for congestion is lowered in the case of endothelial dysfunction.[32] Of particular interest is the function of the glycocalyx, which is situated on the outer border of the endothelium in both the peripheral vasculature and the glomerulus. The glycocalyx transduces stress from plasma flow, which releases mediators that in the glomerulus control podocyte function and in the peripheral vasculature regulate permeability.[1,30] It is postulated that high levels of sodium, resulting from sodium reabsorption in heart failure, structurally alter the glycocalyx, disrupting interstitial stability, which in turn diminishes interstitial protection from overt fluid overload.[33] A similar pathophysiological mechanism seems plausible for the glomerular glycocalyx.[10] In patients with sickle cell disease and pulmonary hypertension the vascular endothelial growth factor soluble fms-like tyrosine kinase-1 has been suggested to be the missing link responsible for endothelial dysfunction and thus albuminuria.[34] Endothelial dysfunction might, therefore, be an important link between congestion and albuminuria in heart failure. It is, however, important to acknowledge that the endothelium shows remarkable heterogeneity throughout the body. Endothelial phenomena observed in one part of the body may, therefore, not be easily transferable to other parts of the body.

Limitations

Limitations of this study include the *post hoc* design. Our findings are based on associations; a direct effect of central venous pressure or intrarenal congestion could not be proven. Moreover, an association with low cardiac output, the other main hallmark of heart failure aside from congestion, could not be proven as we did no measure this. However, as albuminuria was associated with a higher systolic blood pressure, rather than a lower systolic blood pressure, this association seems less likely. Similarly, it is technically possible that the inverse is true, meaning albuminuria leads to congestion, through serum hypalbuminaemia. However, hypalbuminaemia in the index cohort was very mild and not present at all in the validation cohort. Moreover, serum albumin was not associated with albuminuria in multivariable regression analyses, making it an unlikely contributor.

Additionally, no data on the timing of loop diuretic administration are present. We can, therefore, not exclude an effect of the recent administration of loop diuretics, leading to RAAS activation as a driver of albuminuria, although the total daily dose of loop diuretics was not independently associated with log UACR. Urinary albumin was only available at baseline, so no information on treatment effect or course over time could be provided.

Another important limitation is the fact that our findings cannot easily be extrapolated to the current ESC heart failure guideline recommendations of optimal medical treatment,[13] as no patients in BIOSTAT-CHF used sacubitril/valsartan or an sodium–glucose cotransporter 2 inhibitor and less than half used a mineralocorticoid receptor antagonist. The current findings should, therefore, be confirmed in contemporary databases.

While we did not find differences in independent associations of albuminuria in HFpEF and HFrEF, it is important to note that the subgroup of patients with HFpEF in both BIOSTAT-CHF cohorts is limited in number. The overall findings in the entire cohorts are, therefore, likely driven by patients with HFrEF.

Lastly, as BIOSTAT-CHF did not exclude patients based on comorbidities, our results could still be driven mainly by concomitant comorbidities, such as diabetes and hypertension.

Conclusion

In patients with new-onset or worsening heart failure, albuminuria was consistently related to clinical, echocardiographic, and circulating biomarkers of congestion.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: K.D.: Consultancy fees Abbott, Boehringer Ingelheim, AstraZeneca; F.Z.: for Actelion, Amgen, Applied Theraputics, AstraZeneca, Bayer, Boehringer, Boston Scientific, Cardior, Cellprothera, Cereno, CEVA, CVRx, G3Pharmaceutical, Merck, Novartis, NovoNordisk, Vifor-Fresenius. Founder of CardioRenal and CVCT; M.M.: personal fees of minimal amounts in the last 3 years: from Actelion as member of Data Monitoring Committeee of sponsored clinical trials; from Amgen, Livanova, Servier, and Vifor pharma as member of Executive Committees of sponsored clinical trials; from AstraZeneca, Abbott vascular, Bayer, Boheringer Ingelhelm, and Edwards Therapeutics for participation to advisory boards and/or speeches at sponsored meetings; S.D.A.: fees from Abbott, Actimed, Bayer, Boehringer Ingelheim, Cardiac Dimension, Cordio, Impulse Dynamics, Novartis, Occlutech, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Corrigendum

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