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ORIGINAL RESEARCH ARTICLE

Elevated urinary albumin concentration predicts worse clinical outcomes in hospitalized acute decompensated heart failure patients

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Abstract

Objective To investigate the prognostic value of elevated urinary albumin concentration (UAC) in hospitalized acute decompensated heart failure (ADHF) patients.

Methods We measured UAC at baseline in 1818 hospitalized ADHF patients who were admitted to our Heart Failure Center. All patients were followed up for a median period of 937.5 days. The primary endpoint was a composite of all-cause death or heart transplantation (HTx) or left ventricular assist device (LVAD) implantation.

Results In total, 41.5% of ADHF patients had albuminuria (UAC $\geq$ 20 mg/L). The median value of UAC was 15.5 mg/L. A total of 679 patients died or underwent HTx/LVAD during follow-up. The median UAC was significantly lower in non-HTx/LVAD survivors (14.3 mg/L) than in those who died or underwent HTx/LVAD (18.0 mg/L, $P < 0.001$). Compared with patients without albuminuria (reference, n = 1064), those with albuminuria had a 1.47-fold higher risk of all-cause death or HTx/LVAD (95% confidence interval [CI]:1.26–1.71, $P < 0.001$), with hazard ratios (HRs) of 1.42 (95% CI: 1.21–1.66) and 1.74 (95% CI: 1.33–2.26) in patients with microalbuminuria (20 mg/L $\leq$ UAC $<$ 200 mg/L, n = 617) and macroalbuminuria (UAC $\geq$ 200 mg/L, n = 137), respectively (both $P < 0.001$). After adjustment for significant clinical risk factors, the albuminuria group had a higher risk of primary adverse events than the non-albuminuria group (HR = 1.28, 95% CI: 1.09–1.50, P = 0.003), with HRs of 1.27 [95% CI: 1.07–1.49] and 1.36 [95% CI: 1.01–1.84] in patients with microalbuminuria and macroalbuminuria, respectively (P = 0.006 and P = 0.041). The adjusted risk of primary adverse events also increased with the degree of albuminuria in the test for trend (HR = 1.21, 95% CI: 1.06–1.37, P for trend = 0.004). In the subgroup analysis, albuminuria had a significantly greater prognostic value for patients with left ventricular ejection fraction $\geq$ 40%, eGFR $\geq$ 60 mL/min/1.73 m^2, BUN/creatinine ratio $\geq$ 20 or NT-proBNP $<$ 2098 pg/mL.

Conclusion The presence of albuminuria evaluated by UAC predicts adverse clinical outcomes in hospitalized ADHF patients.

Keywords Urinary albumin concentration; Acute decompensated heart failure; Albuminuria

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Introduction

The population with heart failure (HF) has been growing, placing a great burden on health care worldwide.[1–3] The overall prognosis of HF is not optimistic and should be taken seriously.[4] Moreover, renal dysfunction has been reported to be strongly related to a poor prognosis in patients with HF.[5] The frequently used parameter, estimated glomerular filtration rate (eGFR), is not sensitive enough to reflect early renal dysfunction. Instead, elevated urinary albumin excretion is a good indicator of early kidney damage and occurs in 25.3%–44% of patients with chronic HF.[6,7] Previous studies, including the GISSI-Heart Failure (GISSI-HF) trial and Candesartan in Heart Failure: Assessment of Reduction in

Mortality (CHARM) Program, reported that elevated urinary albumin excretion is a powerful and independent predictor of poor prognosis in patients with chronic HF, irrespective of the presence of hypertension (HTN) or diabetes.[6,7] Previous studies mainly investigated the urinary albumin-to-creatinine ratio (UACR) but rarely evaluated a more commonly measured parameter, that is, the urinary albumin concentration (UAC). UAC is more convenient and easily available in clinical practice. It has been demonstrated to be acceptable for population screening of albuminuria.[8–11] Therefore, it will be useful to evaluate UAC as a potential biomarker to predict the prognosis of HF. In addition, few studies have focused on the prognostic value of urinary albumin excretion in acute decompensated heart failure (ADHF), which is more unstable and has a worse prognosis than HF without decompensation. However, the results from studies in patients with chronic HF could not be extrapolated to ADHF patients. Therefore, to fill in the gaps in previous studies, we performed this real-world cohort study to evaluate the clinical significance of elevated UAC in hospitalized ADHF patients.

Material and methods

Patients

This study retrospectively recruited hospitalized ADHF patients who were admitted to the Heart Failure Center of Fuwai Hospital (Beijing, China) from January 2010 to November 2017. The diagnosis of HF was based on the following criteria according to guidelines.[4,12] For heart failure with reduced ejection fraction (HFrEF), the diagnostic criteria include the presence of symptoms and/or signs of HF and left ventricular ejection fraction (LVEF) $<$ 40%. For heart failure with middle-range ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), the diagnostic criteria include the presence of symptoms and/or signs of HF, plasma NT-proBNP level $>$ 125 pg/mL and objective evidence of the cardiac functional and structural alterations underlying HF. At least two cardiologists confirmed the patients' diagnoses. Patients were prescribed guideline-directed medical therapy if they could tolerate the medication during hospitalization and after discharge. The exclusion criteria included malignancy, prior heart transplantation (HTx) or mechanical circulatory assist devices, end-stage renal disease requiring dialysis and other severe infectious or systemic diseases (AMI, amyloidosis). Patients with complete baseline and follow-up medical records and UAC measured at admission were ultimately enrolled. This study was conducted under the principles contained in the Declaration of Helsinki and the ethical standards of the institutional and national research committee. Each participant signed informed consent forms in this study.

Methods

Data collection

A first-morning spot sample of urine on the next day after admission was provided as clinically required. Urine samples were analysed instantly in the morning and assayed for albumin with an immunoturbidimetric method (HITACHI 7180 biochemistry automatic analyser, Tokyo, Japan). Blood samples were collected in the fasting state at baseline, and routine blood tests and assessment of NT-proBNP and biochemical parameters were performed. Blood samples were collected strictly following a standard procedure and sent to the laboratory for immediate testing using standard techniques. The value of eGFR was calculated by the Modification of Diet in Renal Disease (MDRD) equation modified for the Chinese population.[13] We performed echocardiography in all the patients during hospitalization. Measurement of cardiac structures and the LVEF was performed by commercially available ultrasound systems according to the established method by echocardiologists. We defined the patients as having HFrEF when EF $<$ 40%, HFmrEF when 40% $\leq$ EF $<$ 50% and HFpEF when EF $\geq$ 50%.[4,12] We defined patients as having microalbuminuria when 20 mg/L $\leq$ UAC $<$ 200 mg/L and macroalbuminuria when UAC $\geq$ 200 mg/L.[14]

Follow-up and primary endpoints

The primary endpoint was a composite of all-cause death or HTx or left ventricular assist device (LVAD) implantation. When HTx or LVAD occurred, the endpoint event was counted. Then, the patients were not followed up for death to avoid a competing risk for the endpoints. Follow-ups were performed either by telephone or clinical outpatient visits at the 3rd month, 6th month, 12th month and every 6 months thereafter, according to our regular procedures. We obtained information about the adverse events of death or HTx/LVAD from the medical records, the patients themselves, their families or their affiliated hospitals.

Statistical analyses

Distributions of continuous data were tested with the Kolmogorov–Smirnov test. Data with skewed distribution are expressed as the median (interquartile range). Categorical variables are expressed as numbers, *n* (proportions, %). For continuous variables with a skewed distribution, the Mann–Whitney *U* test was performed for comparison of each pair of groups. For categorical variables, the χ^2 test was used for comparison. The relationship between UAC and eGFR was assessed using Spearman's correlation test and linear regression analysis. Survival curves for the adverse events of all-cause death/HTx/LVAD were plotted using the Kaplan–Meier method. Survival curves were compared

between two or three groups with the log-rank test, as appropriate. Restricted cubic spline multivariable Cox regression analysis was performed to evaluate the relationship between UAC as a continuous parameter and adverse endpoint events. The prognostic value of UAC in predicting adverse events was tested by Cox regression model, entering UAC as a categorical variable according to the degree of albuminuria. First, univariate Cox proportional hazards regression analysis was performed to identify the predictors of all-cause death/HTx/LVAD. Variables with significant *P*-values ($P < 0.05$) were retained in the final multivariable Cox regression model. Then, multivariable Cox regression analysis with the forward LR method was performed. The median value of NT-proBNP was chosen as the cut-off point for grouping in the subgroup analysis. All statistical analyses and plots were performed using SPSS (Version 24; IBM), Excel (Office 2016) or R language Version 4.0.3 (www.r-project.org). All tests were two-sided, with a significance level of 5%.

Results

Baseline clinical characteristics

A total of 1818 eligible ADHF patients were ultimately enrolled in this study (*Figure 1*). The median age of the patients was 57 years old, and the percentage of male patients was 72.4%. The percentage of ischaemic HF was 29.4%. A total of 41.5% of ADHF patients had albuminuria, with 33.9% having microalbuminuria and 7.5% having macroalbuminuria. The median value of UAC was 15.5 mg/L.

We divided patients into two groups based on the UAC value: the normal group (UAC $<$ 20 mg/L) and the albuminuria group (UAC $\geq$ 20 mg/L). The clinical characteristics of the whole population and the subgroups are shown in *Table 1*. The patients with albuminuria tended to have a higher percentage of New York Heart Association (NYHA) Class IV and a lower percentage of NYHA Classes I and II, a higher level of blood pressure (both systolic blood pressure [SBP] and diastolic blood pressure [DBP]), heart rate, plasma NT-proBNP, serum total bilirubin (TB), fasting blood glucose (FBG), glycated haemoglobin A1C (HbA1C), serum creatinine, blood urea nitrogen (BUN) and blood uric acid (UA) at admission but a lower level of serum albumin and eGFR. The percentages of HTN and diabetes mellitus (DM) were also higher in the albuminuria group. Other parameters, including age, HF classification according to the LVEF and ischaemic aetiology, left ventricular diameter in diastole (LVDD), LVEF, haemoglobin and lipid profile, were not different between the two groups.

Figure 1 Study flowchart. A total of 1818 acute decompensated heart failure patients were ultimately enrolled in this study according to the flowchart. UAC, urinary albumin concentration.

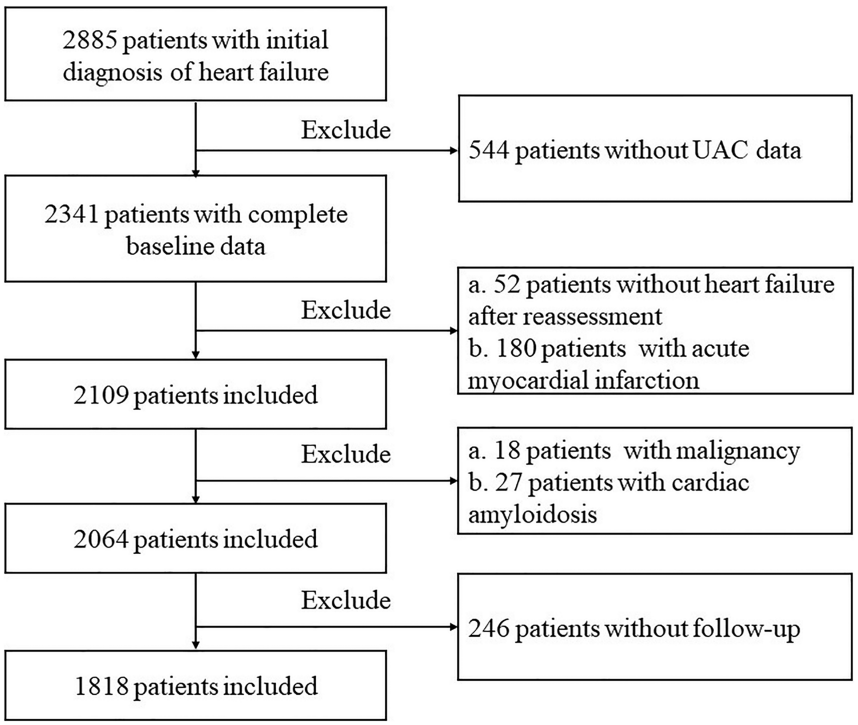


Table 1 Baseline clinical characteristics of the normal and albuminuria groups

Parameters	Total (n = 1818)	Normal (n = 1064)	Albuminuria (n = 754)	P
Age, y	57(45,68)	57.5(46,67)	57(45,69)	0.885
Male, *n* (%)	1316 (72.4)	791 (74.3)	525 (69.6)	0.027
NYHA class				<0.001
I, *n* (%)	49 (2.7)	44 (4.1)	5 (0.7)	
II, *n* (%)	410 (22.6)	257 (24.2)	153 (20.3)	
III, *n* (%)	909 (50.0)	527 (49.5)	382 (50.7)	
IV, *n* (%)	450 (24.8)	236 (22.2)	214 (28.4)	
Hypertension, *n* (%)	883 (48.6)	458 (43.0)	425 (56.4)	<0.001
Diabetes mellitus, *n* (%)	542 (29.8)	273 (25.7)	269 (35.7)	<0.001
Atrial fibrillation/flutter, *n* (%)	651 (35.8)	368 (34.6)	283 (37.5)	0.197
HF classification				0.924
HFrEF, *n* (%)	1046 (57.5)	612 (57.5)	434 (57.6)	
HFmrEF, *n* (%)	300 (16.5)	173 (16.3)	127 (16.8)	
HFpEF, *n* (%)	472 (26.0)	279 (26.2)	193 (25.6)	
Ischaemic HF, *n* (%)	535 (29.4)	313 (29.4)	222 (29.4)	0.991
Heart rate, beats/min	78 (69,91)	77 (68,90)	80 (70,93)	<0.001
SBP, mm Hg	118 (104,131)	116 (102,130)	120 (106,137)	<0.001
DBP, mm Hg	70 (63,80)	70 (61,80)	72 (65,83)	<0.001
BMI, kg/m^2	24.2 (21.7,27.1)	24.2 (21.6,26.8)	24.4 (21.9,27.7)	0.159
UAC, mg/L	15.5 (6.7,42.2)	8.0 (4.1,12.9)	56.3 (30.8,134.3)	<0.001
Plasma NT-proBNP, pg/mL	2097.9 (857.5,4873.5)	1660.6 (724.2,3931.0)	2799.0 (1180.0,6564.8)	<0.001
Haemoglobin, g/L	140.0 (125.0,154.0)	141.0 (127.0,152.0)	140.0 (122.0–156.0)	0.601
Serum albumin, g/L	40.2 (36.8,43.5)	41.0 (37.9,44.1)	39.0 (35.4,42.6)	<0.001
TB, μmol/L	20.5 (14.3,31.5)	19.8 (14.0,29.2)	22.5 (14.6,35.4)	<0.001
FBG, mmol/L	5.2 (4.6,6.1)	5.1 (4.6,5.9)	5.3 (4.7,6.5)	<0.001
Serum creatinine, μmol/L	93.0 (77.3,113.2)	90.3 (74.9,107.9)	98.5 (80.9,125.0)	<0.001
eGFR, mL/min/1.73 m^2	90.7 (70.2,112.7)	94.6 (76.0,116.3)	84.3 (62.5,106.9)	<0.001
eGFR ≥ 60 mL/min/1.73 m^2, *n* (%)	1,529 (84.1)	942 (88.5)	587 (77.9)	<0.001
BUN, mmol/L	7.5 (5.8,9.9)	7.3 (5.5,9.3)	8.0 (6.2,11.1)	<0.001
BUN/creatinine ratio (mg/dL/mg/dL)	20.0 (16.0,24.4)	20.1 (16.2,24.4)	19.9 (16.0,24.8)	0.968
UA, μmol/L	457.1 (363.8,571.0)	443.0 (348.9,552.7)	482.6 (386.1,600.4)	<0.001
TG, mmol/L	1.29 (0.95–1.80)	1.30 (0.96,1.78)	1.28 (0.95,1.82)	0.673
TC, mmol/L	3.98 (3.27,4.75)	4.01(3.33,4.75)	3.93 (3.17,4.77)	0.191
LDL-C, mmol/L	2.45 (1.93,3.08)	2.44 (1.96,3.08)	2.46 (1.89,3.10)	0.735
HbA1C, %	6.2 (5.8,7.0)	6.1(5.7,6.7)	6.4 (5.9,7.3)	<0.001
LVDD, mm	63 (54,71)	63 (54,70)	62 (54–71)	0.947
LVEF, %	36 (28,50.0)	36 (28,50)	35 (27–50)	0.198
ACEi/ARB, *n* (%)	1,059 (58.3)	632 (59.4)	427 (56.6)	0.238
β-Blocker, *n* (%)	1,612 (88.7)	945 (88.8)	667 (88.5)	0.814
MRA, *n* (%)	1,381 (76.0)	826 (77.6)	555 (73.6)	0.048
Diuretic, *n* (%)	1709 (94.0)	993 (93.3)	716 (95.0)	0.148

ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1C, glycated haemoglobin A1C; HF, heart failure; HFmrEF, heart failure with middle-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LDL-C, low-density lipoprotein cholesterol; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TB, total bilirubin; UA, serum uric acid; TC, total cholesterol; TG, triglyceride; UAC, urinary albumin concentration.

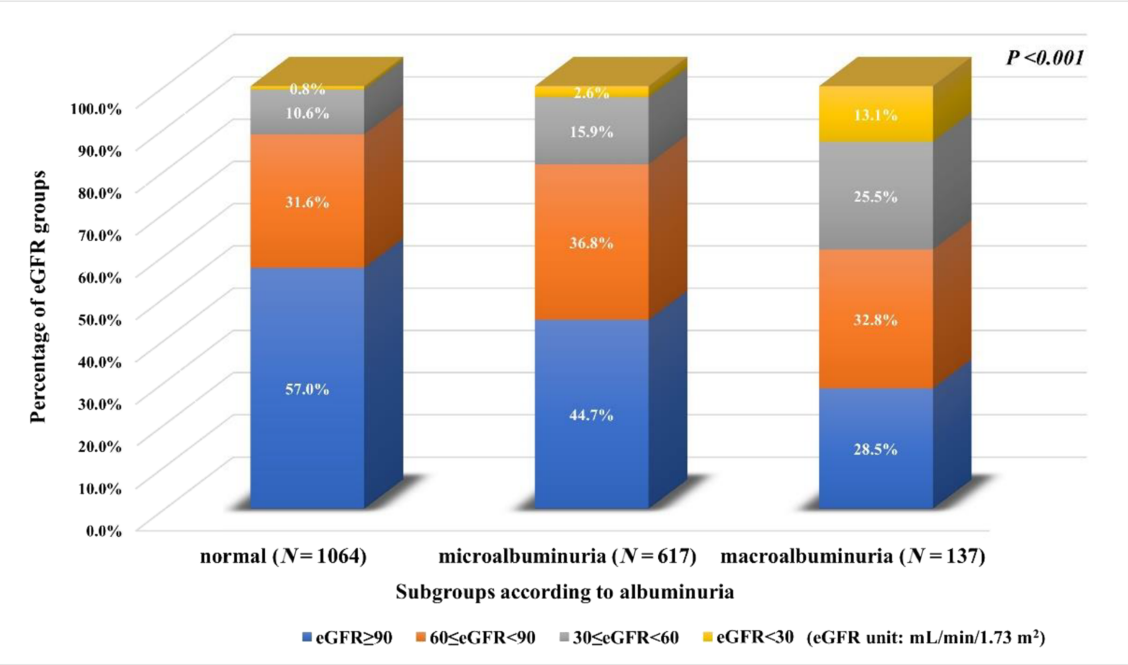
Relationship between albuminuria and eGFR

As UAC is an early marker of kidney damage, it was valuable to investigate the relationship between UAC and eGFR. The values of UAC and eGFR had a significant inverse linear relationship (Spearman's coefficient of correlation, r = −0.176, $P < 0.001$). The linear regression analysis also confirmed their inverse correlation (unstandardized coefficients β = −0.431 [95% confidence interval [CI]: −0.560, −0.303], $P < 0.001$). Categorical data analysis showed that the distributions of renal function classifications according to eGFR were significantly different among the normal, microalbuminuria and macroalbuminuria groups. The percentages of patients with renal dysfunction increased in the microalbuminuria and macroalbuminuria groups (*Figure 2*).

The prognostic value of albuminuria in ADHF patients

The median follow-up time was 937.5 days (interquartile range: 365–1450 days). In all, 679 patients died or underwent HTx/LVAD during the follow-up period. Compared with non-HTx/LVAD survivors (n = 1139), they were older and leaner

Figure 2 The relationship between eGFR and albuminuria. Distribution of patients classified according to eGFR among subgroups. The distributions of renal function classifications according to eGFR were significantly different among the normal, microalbuminuria and macroalbuminuria groups. The percentages of patients with renal dysfunction increased in the microalbuminuria and macroalbuminuria groups. eGFR, estimated glomerular filtration rate.



and had higher levels of NT-proBNP, UAC, serum creatinine, BUN, BUN/creatinine ratio, serum UA, TB and HbA1C but lower levels of SBP and DBP, haemoglobin, serum albumin and eGFR. They also tended to have larger LVDD and lower LVEF. In addition, they had a less frequent history of HTN and more frequent atrial fibrillation/flutter, ischaemic aetiology, HFrEF classification and NYHA Class IV. β-Blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEis/ARBs) were prescribed more frequently to non-HTx/LVAD survivors; the opposite was true for diuretics (*Table 2*).

The median UAC was significantly lower among the non-HTx/LVAD survivors (14.3 mg/L) than among those who died or underwent HTx/LVAD (18.0 mg/L, $P < 0.001$). Similarly, the percentages of microalbuminuria and macroalbuminuria were higher in patients who died or underwent HTx/LVAD.

Kaplan–Meier plots demonstrated the cumulative event rates for subgroups. The risk of primary adverse events (all-cause death or HTx/LVAD) was significantly higher over time for the ADHF patients with albuminuria during the follow-up period than for those without albuminuria ($P < 0.001$) (*Figure 3A,B*). Pairwise comparisons using the log-rank test showed that the risk of primary adverse events was not significantly different between the microalbuminuria and macroalbuminuria groups ($P = 0.14$, *Figure 3B*).

Compared with patients with normal UAC (reference, $n = 1064$), those with albuminuria had a risk of all-cause death or HTx/LVAD that was 1.47-fold higher (95% CI: 1.26–1.71, $P < 0.001$). We further divided the albuminuria patients into microalbuminuria ($n = 617$) and macroalbuminuria groups ($n = 137$). The risks of all-cause death or HTx/LVAD were 1.42-fold (95% CI: 1.21–1.66) and 1.74-fold (95% CI: 1.33–2.26) higher for patients with microalbuminuria and macroalbuminuria (both $P < 0.001$), respectively. The trend towards an increased risk of adverse events was significant as patients progressed from a normal condition to having microalbuminuria and macroalbuminuria (HR = 1.35 [1.21–1.51], P for trend < 0.001) (*Table 3*).

A multivariable Cox regression model recruited all the demographic and clinical variables at the time of urine collection, which had significant relationships with primary adverse events with $P < 0.05$ when analysed in the univariate Cox regression model, including age, history of HTN, presence of atrial fibrillation/flutter, NYHA class, heart rate, SBP, BMI, haemoglobin, serum albumin, TB, serum creatinine, eGFR, BUN/creatinine ratio, UA, NT-proBNP, LVDD, LVEF and prescription of ACEI/ARB, β-blockers or diuretics. Due to collinearity, BUN and serum creatinine were not included in the regression model after the BUN/creatinine ratio was included. After adjustment for these significant clinical risk factors, the albuminuria group (UAC ≥ 20 mg/L) had a higher

Table 2 Comparison of clinical characteristics between the non-HTx/LVAD survivors and patients who died or underwent HTx/LVAD

Parameters	Non-HTx/LVAD survivor(n = 1139)	Death or HTx/LVAD (n = 679)	P
Age, y	56(44,66)	60(48,71)	<0.001
Male, *n* (%)	822 (72.2)	494 (72.8)	0.787
NYHA class			<0.001
I, *n* (%)	45 (4.0)	4 (0.6)	
II, *n* (%)	331 (29.1)	79 (11.6)	
III, *n* (%)	576 (50.6)	333 (49.0)	
IV, *n* (%)	187 (16.4)	263 (38.7)	
Hypertension, *n* (%)	591(51.9)	292(43.0)	<0.001
Diabetes mellitus, *n* (%)	336 (29.5)	206 (30.3)	0.705
Atrial fibrillation/flutter, *n* (%)	386 (33.9)	265 (39.0)	0.027
HF classification			<0.001
HFrEF, *n* (%)	609 (53.5)	437 (64.4)	
HFmrEF, *n* (%)	213(18.7)	87 (12.8)	
HFpEF, *n* (%)	317 (27.8)	155 (22.8)	
Ischaemic HF, *n* (%)	308 (27.0)	227 (33.4)	0.004
Heart rate, beats/min	79 (69,93)	78 (68,88)	0.014
SBP, mm Hg	120 (110,134)	111 (98,125)	<0.001
DBP, mm Hg	72 (65,82)	69 (60,77)	<0.001
BMI, kg/m^2	24.8 (22.5,27.8)	23.3 (20.6,26.0)	<0.001
UAC, mg/L	14.3 (6.5,35.1)	18.0 (7.5,57.1)	<0.001
UAC grouping			<0.001
Normal group, *n* (%)	713 (62.6)	351 (51.7)	
Microalbuminuria group, *n* (%)	355 (31.2)	262 (38.6)	
Macroalbuminuria group, *n* (%)	71 (6.2)	66 (9.7)	
Plasma NT-proBNP, pg/mL	1503.0 (649.0,3472.0)	3576.9 (1643.0,7000.0)	<0.001
Haemoglobin, g/L	143 (128,156)	136 (120,151)	<0.001
Serum albumin, g/L	40.9 (37.6,44.2)	39.0 (35.3,42.5)	<0.001
TB, μmol/L	18.8 (13.5,27.3)	25.7 (16.3,40.4)	<0.001
FBG, mmol/L	5.2 (4.7,6.2)	5.2 (4.6,6.0)	0.249
Serum creatinine, μmol/L	89.6 (75.6,107.9)	100.0 (80.9,127.3)	<0.001
eGFR, mL/min/1.73 m^2	94.1(75.6,115.5)	82.9 (61.9,105.5)	<0.001
eGFR grouping			<0.001
eGFR < 60 mL/min/1.73 m^2, *n* (%)	133 (11.7)	156 (23.0)	
eGFR ≥ 60 mL/min/1.73 m^2, *n* (%)	1006 (88.3)	523 (77.0)	
BUN, mmol/L	7.2 (5.5,9.1)	8.2 (6.3,12.3)	<0.001
BUN/creatinine ratio (mg/dL/mg/dL)	19.4 (15.7,23.7)	21.1 (17.0,25.8)	<0.001
UA, μmol/L	442.0 (358.4,549.3)	486.3 (379.3,599.2)	<0.001
HbA1C, %	6.1 (5.7,6.9)	6.3 (5.9,7.1)	0.001
LVDD, mm	62 (53,69)	65 (55,74)	<0.001
LVEF, %	38 (30,52)	33 (26,48)	<0.001
ACEI/ARB, *n* (%)	762 (66.9)	297 (43.7)	<0.001
β-blocker, *n* (%)	1031(90.5)	581 (85.6)	0.001
MRA, *n* (%)	861 (75.6)	520 (76.6)	0.633
Diuretic, *n* (%)	1052 (92.4)	657 (96.8)	<0.001

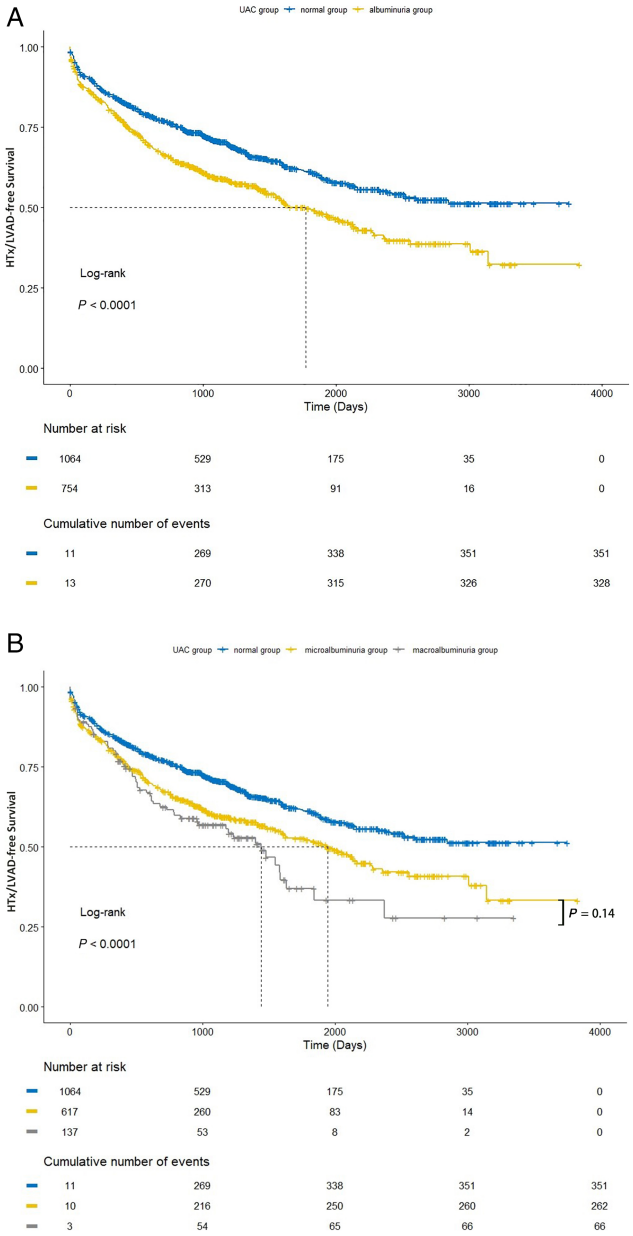
ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1C, glycated haemoglobin A1C; HF, heart failure; HFmrEF, heart failure with middle-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplantation; LDL-C, low-density lipoprotein cholesterol; LVAD, left ventricular assist device; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TB, total bilirubin; UA, serum uric acid; TC, total cholesterol; TG, triglyceride; UAC, urinary albumin concentration.

adjusted risk of primary adverse events than the normal group (HR = 1.28 [95% CI: 1.09–1.50], P = 0.003). The adjusted risks of all-cause death or HTx/LVAD were 1.27-fold [95% CI: 1.0–1.49] and 1.36-fold [95% CI: 1.01–1.84] higher for patients with microalbuminuria and macroalbuminuria, respectively (P = 0.006 and P = 0.041), with a significant trend towards an increased event risk (HR = 1.21 [1.06–1.37], P for trend = 0.004 after adjustment) (*Table 3*). Restricted cubic spline multivariable Cox regression analysis also demonstrated that UAC ≥ 20 mg/L was a constant and independent predictor of an increased risk of all-cause death or HTx/LVAD after adjustment for significant clinical parameters (*Figure 4*, linear P = 0.006, nonlinear P = 0.0053).

The prognostic value of albuminuria in subgroups

We further analysed the prognostic value of albuminuria evaluated by UAC in subgroups. The presence of albuminuria predicted a consistently higher risk of all-cause death or HTx/LVAD, irrespective of age strata (≥65 years vs. < 65 years), sex, the presence of HTN or DM, NYHA class

Figure 3 Kaplan–Meier analysis for HTx/LVAD-free survival. (A) Kaplan–Meier survival plot according to normal and albuminuria groups. Kaplan–Meier analysis showed a significantly higher risk of all-cause death or HTx/LVAD over time in the HF patients with albuminuria during the follow-up period. (B) Kaplan–Meier survival plot according to normal, microalbuminuria and macroalbuminuria groups. Kaplan–Meier analysis showed a significantly higher risk of all-cause death or HTx/LVAD over time in the HF patients with microalbuminuria or macroalbuminuria during the follow-up period. The risk of all-cause death or HTx/LVAD was not significantly different between the microalbuminuria and macroalbuminuria groups. HF,heart failure; HTx,heart transplantation; LVAD, left ventricular assist device; UAC, urinary albumin concentration.



(III/IV vs. I/II) and ischaemic aetiology. However, albuminuria predicted a higher risk of all-cause death or HTx/LVAD in patients with LVEF $\geq$ 40%, eGFR $\geq$ 60 mL/min/1.73 m^2, BUN/creatinine ratio $\geq$ 20 or NT-proBNP $<$ 2098 pg/mL but not in patients with LVEF $<$ 40%, eGFR $<$ 60 mL/min/1.73 m^2, BUN/creatinine ratio $<$ 20 and NT-proBNP $\geq$ 2098 pg/mL (*Figure 5*).

Discussion

In this study, we found that 41.5% of ADHF patients had albuminuria, with 33.9% having microalbuminuria and 7.5% having macroalbuminuria. The presence of albuminuria independently predicted a higher risk of all-cause death or HTx/LVAD in hospitalized ADHF patients, especially patients

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Table 3 Univariate and multivariable Cox regression analyses to evaluate elevated urinary albumin concentrations as prognostic markers for all-cause death or heart transplantation

	Univariate analysis			Multivariable analysis		
Variables	HR	95% CI	*P*	HR	95% CI	*P*
Albuminuria vs. normal UAC	1.47	1.26–1.71	<0.001	1.28	1.09-1.50	0.003
Microalbuminuria vs. normal UAC	1.42	1.21–1.66	<0.001	1.27	1.07-1.49	0.006
Macroalbuminuria vs. normal UAC	1.74	1.33–2.26	<0.001	1.36	1.01-1.84	0.041
Macroalbuminuria vs microalbuminuria	1.23	0.93-1.61	0.14	-	-	-
	HR	95% CI	*P* for trend	HR	95% CI	*P* for trend
From normal UAC to macroalbuminuria	1.35	1.21–1.51	<0.001	1.21	1.06–1.37	0.004

Adjusted by age, history of HTN, presence of atrial fibrillation/flutter, NYHA class, heart rate, SBP, BMI, haemoglobin, serum albumin, TB, serum creatinine, eGFR, BUN/creatinine ratio, UA, NT-proBNP, LVDD, LVEF and prescription of ACEI/ARB, β-blockers or diuretics.
Grouping according to UAC: normal, UAC < 20 mg/L; microalbuminuria, 20 mg/L ≤ UAC < 200 mg/L; macroalbuminuria, UAC ≥ 200 mg/L.
ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; HR, hazard ratio; HTN, hypertension; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TB, total bilirubin; UA, serum uric acid; UAC, urinary albumin concentration.

Figure 4 RCS multivariable Cox regression analysis for the HR for all-cause death or HTx/LVAD after adjustment [95% CI]. UAC ≥ 20 mg/L was a constant predictor of an increased risk of all-cause death or HTx/LVAD in patients with acute decompensated heart failure ($P < 0.0001$). Variables included in the model included age, history of HTN, presence of atrial fibrillation/flutter, NYHA class, heart rate, SBP, BMI, hemoglobin, serum albumin, TB, eGFR, BUN/creatinine ratio, UA, NT-proBNP, LVDD, LVEF and prescriptions for ACEI/ARB, β-blockers or diuretics. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker; BMI, body mass index; BUN, blood urea nitrogen; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTN, hypertension; HTx, heart transplantation; LVAD, left ventricular assist device; LVDD, left ventricular diameter in diastole; LVEF, left ventricular ejection fraction; NT-proBNP, amino-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; RCS, restricted cubic spline; SBP, systolic blood pressure; TB, total bilirubin; UA, serum uric acid; UAC, urinary albumin concentration.

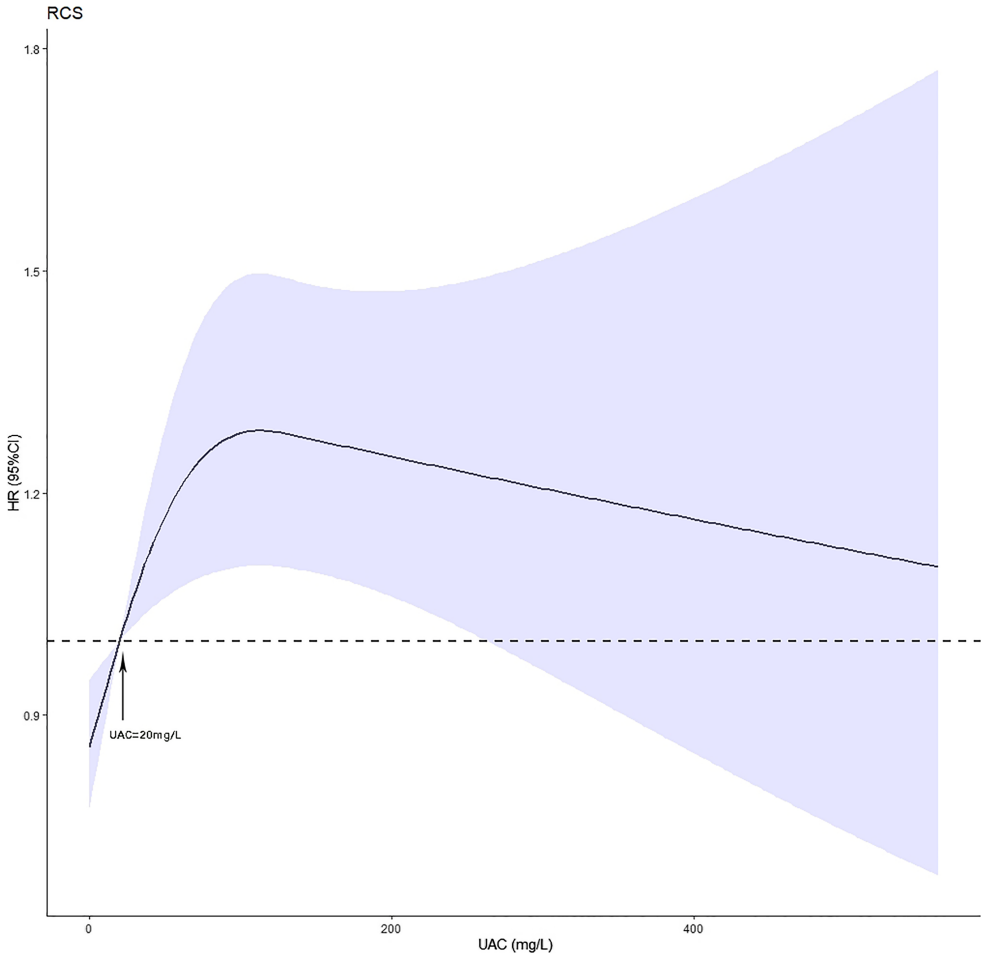
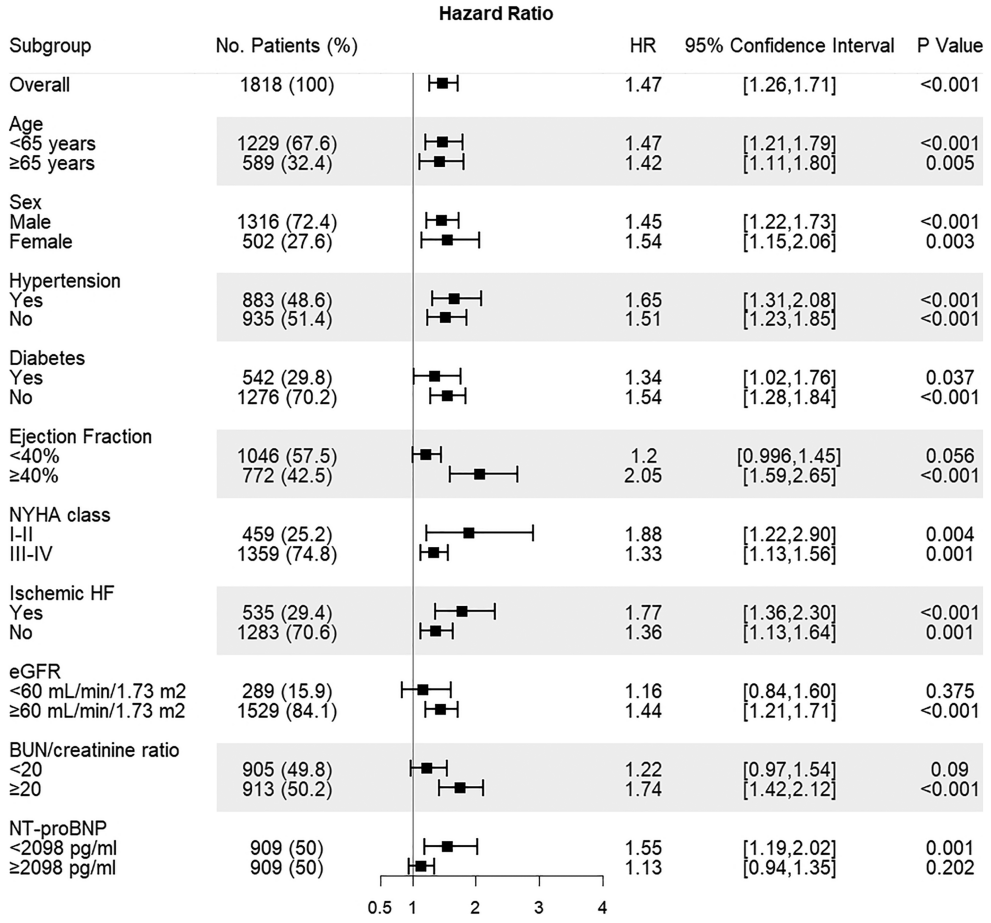


Figure 5 Subgroup analysis for prognostic value of albuminuria in HF patients. The prognostic value of albuminuria had greater significance in patients with left ventricular ejection fraction ≥ 40%, eGFR ≥ 60 mL/min/1.73 m2 , BUN/creatinine ratio ≥ 20 or NT-proBNP < 2098 pg/mL. BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HF, heart failure; NT-proBNP, amino-terminal pro-brain natriuretic peptide; UAC, urinary albumin concentration.



with HFpEF and HFmrEF, eGFR ≥ 60 mL/min/1.73 m^2, BUN/creatinine ratio ≥ 20 or NT-proBNP < 2098 pg/mL.

The reported prevalence varies from 19.9% to 35% for microalbuminuria and 5.4% to 13% for macroalbuminuria in previous observational and randomized clinical trial (RCT) studies.[7,15,16] This large discrepancy might lie in the demographic and clinical differences in the participants. For example, only approximately 30% of patients were NYHA Classes III–IV, and most patients were classified as HFrEF in the GISSI-HF study.[7] In contrast, in our study, the patients had ADHF, and 50% of them had EF < 40%. Therefore, it was necessary to conduct the current study to provide more evidence to interpret the value of UAC and albuminuria. In addition, our investigation was based on the real-world observation of UAC in ADHF patients, avoiding the bias of patients' choice in RCT studies. Though we used a different testing method in ADHF patients, the prevalence of microalbuminuria and macroalbuminuria in our study was within the range of previously reported data but at a higher level, inferring that albuminuria is also a concern in hospitalized ADHF patients.

In accordance with previous studies, we found that HF patients with albuminuria were prone to meet the criteria for a severe NYHA class and have a history of HTN and DM and higher levels of SBP and serum creatinine,[6,7,15–17] indicating that co-morbidities usually accompany albuminuria. Moreover, the severity of HF is associated with the presence of albuminuria. This might be attributable to HF itself, which leads to activated neurohormonal systems, decreased renal perfusion, increased renal venous congestion, reduced tubular reabsorption of albumin and endothelial dysfunction.[18–21] Whether albuminuria is more frequent in diastolic HF is still under debate. The prevalence of albuminuria was similar among patients with HFrEF, HFmrEF and HFpEF in our study, and whereas some studies reported a higher prevalence of albuminuria in HFpEF,[6] others reported the opposite.[22]

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As both the eGFR and urine albumin excretion reflect renal damage, we explored the relationship between eGFR and UAC. We found a significant inverse linear relationship between UAC and eGFR, comparable with the relationship between UACR and eGFR in the GISSI-HF trial.[7] However, albuminuria usually leads to a decline in the eGFR and reflects a different pathophysiological mechanism. The exact correlation between them in the setting of HF still needs further investigation, especially for patients with eGFR above 60 mL/min/1.73 m^2, which accounts for 84.1% of the patients in our study and is generally not classified as renal impairment.[23]

Conducted in the real world, our study supports the concept that the presence of albuminuria independently predicts a poor prognosis in ADHF patients, regardless of urinary albumin excretion testing methods.[6,7,15,17,24] In our study, elevated UAC and albuminuria were associated with all-cause death or HTx/LVAD after adjusting for all the significant prognostic covariates. The test for the trend showed that the event risk tended to increase with increasing severity of albuminuria, further indicating the prognostic value of albuminuriain HF patients. Furthermore, it was also observed that the macroalbuminuria group had a higher risk of adverse events than the microalbuminuria group in the Kaplan–Meier analysis. However, the difference did not reach statistical significance. When UAC was further analyzed as a continuous variable, it was found that there was a nonlinear relationship between UAC and prognosis, especially when UAC was above 400 mg/L. The reason might be that there were only 30 patients with UAC $\geq$ 400 mg/L. The small sample size might yield results that do not represent the real situation. However, we could not exclude the possibility that there are underlying mechanisms explaining this phenomenon.

In addition to renal parenchymal damage, other mechanisms, such as neurohormonal activation, are also involved in albuminuria.[25] Accordingly, albuminuria can be divided into prerenal type and non-prerenal type, which can be differentiated by the BUN/creatinine ratio.[25,26] Therefore, we conducted a subgroup analysis stratified by the BUN/creatinine ratio and eGFR. We found that albuminuria had a greater predictive value for prognosis in patients with a BUN/creatinine ratio $\geq$ 20, but not in patients with an eGFR $<$ 60 mL/min/1.73 m^2. This indicated that albuminuria caused by prerenal factors had a more significant effect on the prognosis in the ADHF population, while albuminuria caused by renal parenchymal damage had no predictive value for the prognosis. One explanation is that albuminuria in patients with an elevated BUN/creatinine ratio might be caused by neurohormonal activation and is an indicator of HF progression.[25] This concept is supported by one observational study, which reported that urine albumin excretion decreased with HF compensation and in parallel with a decline in NT-proBNP.[27]

In addition, we also found that albuminuria predicted adverse events more significantly in patients with lower NT-proBNP, indicating that we should consider the influence of NT-proBNP on prognosis when evaluating albuminuria. We note that neither the GISSI-HF nor CHARM studies included NT-proBNP in the prognostic model when evaluating UACR.[7] Besides, albuminuria had a more significant prognostic value for patients with HFpEF and HFmrEF than those with HFrEF.

Our study is a retrospective observational study and therefore could not answer whether lowering albuminuria levels could improve the prognosis of HF. The usage of ACEIs/ARBs and mineralocorticoid receptor antagonists (MRAs) was not significantly different between the normal and albuminuria groups in our study. In the TOPCAT, they found that spironolactone reduced albuminuria by 39% in all participants at the 1-year visit compared with baseline and by 76% among those with macroalbuminuria in a subpopulation (n = 744). Reducing UACR by 50% was independently associated with a reduction in HF hospitalization and all-cause mortality,[15] shedding some light on targeting albuminuria in the treatment of HF. Future large prospective interventional trials are warranted to evaluate whether lowering urinary albumin might improve prognosis.

Our study had several limitations. First, it is a retrospective study, and thus, not all the patients were monitored with UAC consecutively. Nevertheless, there were noindication bias and selection bias in sampling. The reasons for missing UAC data included patient refusal. In addition, some patients were transferred from other departments, and the UAC test was therefore not performed. In addition, all patients included in this study were of Chinese ethnicity, and the results should be carefully extrapolated to the general worldwide population. Second, UAC was assessed only at baseline and not continuously measured during follow-up. As a result, we could not know whether the change in albuminuria was temporary or permanent. It is also impossible to deduce the pattern of urinary albumin change in HF patients. Third, it is a limitation that we did not obtain follow-up data on the development or worsening of renal dysfunction. Nevertheless, our population generally had preserved renal function. Patients with severe renal dysfunction account for avery small percentage, and we performed a subgroup analysis to account for this. Last, whether UAC could add incremental prognostic information to NT-proBNP or BNP needs to be assessed by a future study.

Conclusions

The clinical implication of this study is that abnormal UAC predicted a higher risk of all-cause death or HTx/LVAD in ADHF patients, providing some evidence for clinicians to interpret UAC in this specific population.

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