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The value of spot urinary creatinine as a marker of muscle wasting in patients with new-onset or worsening heart failure

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Abstract

Background Muscle wasting and unintentional weight loss (cachexia) have been associated with worse outcomes in heart failure (HF), but timely identification of these adverse phenomena is difficult. Spot urinary creatinine may be an easily accessible marker to assess muscle loss and cachexia. This study investigated the association of urinary creatinine with body composition changes and outcomes in patients with new-onset or worsening HF (WHF).

Methods In BIOSTAT-CHF, baseline spot urinary creatinine measurements were available in 2315 patients with new-onset or WHF in an international cohort (index cohort) and a validation cohort of 1431 similar patients from Scotland.

Results Median spot urinary creatinine concentrations were 5.2 [2.7–9.6] mmol/L in the index cohort. Median age was 69 ± 12 years and 73% were men. Lower spot urinary creatinine was associated with older age, lower height and weight, worse renal function, more severe HF, and a higher risk of >5% weight loss from baseline to 9 months (odds ratio = 1.23, 95% CI = 1.09–1.39 per log decrease; P = 0.001). Spot urinary creatinine was associated with Evans criteria of cachexia (OR = 1.26 per log decrease, 95% CI = 1.04–1.49; P = 0.016) and clustered with markers of heart failure severity in hierarchical cluster analyses. Lower urinary creatinine was associated with poorer exercise capacity and quality of life (both $P < 0.001$) and predicted a higher rate for all-cause mortality [hazard ratio (HR) = 1.27, 95% CI = 1.17–1.38 per log decrease; $P < 0.001$] and the combined endpoints HF hospitalization or all-cause mortality (HR = 1.23, 95% CI = 1.15–1.31 per log decrease; $P < 0.001$). Significance was lost after addition of the BIOSTAT risk model. Analyses of the validation cohort yielded similar findings.

Conclusions Lower spot urinary creatinine is associated with smaller body dimensions, renal dysfunction, and more severe HF in patients with new-onset/WHF. Additionally, lower spot urinary creatinine is associated with an increased risk of weight loss and a poorer exercise capacity/quality of life. Urinary creatinine could therefore be a novel, easily obtainable marker to assess (risk of) muscle wasting in HF patients.

Keywords Urinary creatinine; Muscle wasting; Weight loss; Acute heart failure

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Introduction

Unintentional weight loss or cachexia is common in heart failure (HF) and associated with adverse outcomes.[1–3] A state of cachexia may reflect underlying muscle loss (in addition to fat or bone tissue loss), which is associated with decreased exercise capacity, reduced muscle strength, and a worse outcome in patients with HF.[4,5] However, subclinical muscle wasting does not always result in lower body weight and can often go undetected.[6] Patients who are obese or of normal body weight may still have underlying muscle wasting,[6,7] and oedema may also mask underlying muscle breakdown. Concentrations of serum creatinine, produced after stable conversion of creatine largely found in skeletal muscles, are generally used to estimate glomerular filtration rate. However, provided that renal function, physical activity, and dietary protein intake remain consistent, it can also be used as a marker to reflect (peripheral) muscle catabolism.[8] Currently, 24 h creatinine excretion rate is used as a measure of muscle wasting, and recent studies have shown that lower urinary creatinine is an independent predictor of worse outcomes in the general population and in various chronic illnesses such as HF, coronary artery disease, diabetes mellitus, and chronic kidney disease.[9–14]

Even though 24 h urine collection is a reliable measure of muscle breakdown, it is a time-consuming procedure and often inconvenient for patients.[15,16] In a recent analysis of the GISSI-HF study, we showed that morning spot urinary creatinine, an inexpensive and easily accessible marker, was associated with smaller body dimensions and worse outcomes in chronic HF.[15] However, previous studies have not investigated its role in patients with acute/worsening HF (WHF). In addition, the association between spot urinary creatinine and weight loss over time has not yet been studied in patients with HF. Therefore, the aims of the current study were to investigate the value of spot urinary creatinine (as a marker of muscle wasting) in new-onset or WHF patients, to predict outcomes and to evaluate its association with weight loss. We hypothesize that lower urinary creatinine may be an easily obtainable marker to identify HF patients at risk of muscle wasting, who might ultimately benefit from interventions aimed at increasing muscle mass.

Methods

Study population

Study design and results of BIOSTAT-CHF (A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure) have been previously published.[17–19] Briefly, in the multicentre, prospective, observational study, 2516 patients with new-onset HF or WHF were enrolled. The validation cohort enrolled 1738 patients from Scotland, UK. Recruited patients were receiving oral or intravenous furosemide ≥40 mg/day or equivalents, had left ventricular ejection fraction (LVEF) ≤ 40%, or had brain natriuretic peptide (BNP) concentrations >400 pg/mL and/or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations >2000 pg/mL at the time of inclusion. Both inpatients and outpatients were enrolled, but most patients had worsening signs/symptoms of chronic HF (WHF), and the rest had new-onset HF.[17] Investigators were encouraged to initiate new evidence-based therapies or uptitrate current therapies in the first 3 months of the study, followed by a 6-month period of maintenance phase. The study was conducted according to the Declaration of Helsinki and was approved by all local and national ethical committees. All patients provided written informed consent.

Study assessments

Baseline spot urinary creatinine measurements were available in 2315 (92%) patients in the index cohort and 1431 (82%) patients in the validation cohort. The exact timing of spot urinary measurements was not specified in the study protocol. Patients missing baseline urinary creatinine were excluded (n = 201 for the index cohort and n = 307 for the validation cohort). Baseline characteristics according to included and excluded patients for index and validation cohort have been shown in Supporting Information, *Tables S1* and *S2*. Urinary samples were stored at −80°C until measurement at the clinical laboratory of University Medical Center Groningen using the Roche Cobas® analyser. Measurements of neutrophil gelatinase-associated lipocalin (NGAL) were performed at the laboratory of University Medical Center Utrecht, using a Luminex-based in-house developed and validated multiplex immunoassay (xMAP; Luminex, Austin, TX previously published).[20] N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations were measured using electrochemiluminescence on a Cobas e411 analyser (Roche Diagnostics GmbH, Mannheim, Germany).[19] All other biomarkers were measured as published previously.[19,21] Estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula. Weight was measured at baseline and at 9 months. Weight loss or weight gain was defined as difference in weight between baseline and 9 months; furthermore, weight loss or weight gain greater than 5% within 9 months was calculated (Fearon's criteria for cachexia).[22] Lastly, we used the Evans criteria for cachexia, which includes weight loss >5% from baseline to 9 months and C-reactive protein (CRP) > 5 mg/L or interleukin-6 (IL6) > 4 pg/mL, haemoglobin <7.45 mmol/L, and albumin <32 d/L.[23] The 6-min walking test was used as a measure of physical activity in the index cohort; however, this was unavailable in the validation cohort. For the index cohort, a clinical congestion

score (range from 0 to 5) was defined as the sum of jugular venous pressure (JVP) (0 to 1), extent of peripheral oedema (0, 1/3, 2/3, or 1) and orthopnoea (0 to 1), with a maximum score of 4 in the validation cohort, as orthopnoea was not assessed in this cohort.[19]

Statistical analysis

Baseline characteristics were summarized according to quartiles of urinary creatinine for the index and validation cohort. Categorical variables were summarized as frequency (percentages) and continuous variables as mean ± standard deviation or as median [inter-quartile range] based on normal/skewed distribution. Differences between quartiles of spot urinary creatinine were tested for significance using Fisher's exact test for categorical variables, Kruskal–Wallis test for continuous skewed variables, and analysis of variance (ANOVA) for continuous normally distributed variables. Trends over quartiles were tested with Cochran–Armitage trend test for categorical variables, Jonckheere–Terpstra for non-normally distributed variables, and linear regression model for normally distributed variables. Non-normally distributed variables were log transformed or standardized for further analyses where necessary. The association of baseline clinical variables with baseline urinary creatinine concentrations and percentage change in weight were investigated in univariable and multivariable linear regression models. Transformations were verified using multifractional polynomials. All variables with a P-value < 0.10 in univariable analyses were included in the multivariable models. Multivariable regression models were constructed via backward elimination and validated using 1000 replicate bootstrap re-sampling. The correlation heatmaps and dendrograms were constructed using the ggplot2, reshape2, fastcluster, Hmisc, and sparcl packages in R. The association between spot urinary creatinine and weight loss was investigated using a univariable logistic regression model. The association of spot urinary creatinine concentrations with endpoints all-cause mortality and the combined endpoint all-cause mortality and first occurrence of HF rehospitalisation was assessed using Cox regression hazards proportional analysis. Proportional hazards assumptions were checked using log–log plots and Schoenfeld residuals. Models were adjusted for body mass index (BMI), age, sex, eGFR, and loop diuretic doses at baseline. Following this, the outcome analyses were adjusted for the respective previously published models for all-cause mortality, and the combined endpoint of all-cause mortality and heart failure hospitalization.[24] Kaplan–Meier curves were used to investigate prognostic ability of urinary creatinine concentrations and weight loss for the endpoints. Differences between groups were tested using a log-rank test. A two-tailed P value < 0.05 was considered statistically significant. All analyses were performed using R: a Language and Environment for Statistical Computing, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics index cohort

Baseline characteristics of the index cohort according to urinary creatinine quartiles are shown in *Table 1*. Briefly, mean age was 69 (±12) years, 73% (1696) of the patients were men, 60% had a NYHA class III/IV, and mean LVEF was 31% (±9.9%). Median urinary creatinine concentrations were 5.2 [2.7–9.6] mmol/L in the index cohort. Lower urinary creatinine concentrations were associated with older age and smaller body dimensions (lower height, weight and BMI at baseline and at 9 months, $P < 0.001$) (*Table 1*). Patients in the lowest urinary creatinine quartile were more likely to have severe HF (worse NYHA class and higher NT-proBNP concentrations, $P < 0.001$), signs and symptoms of congestion such as oedema, orthopnoea, rales, elevated JVP, hepatomegaly, elevated clinical congestion score (all $P < 0.032$), and poorer renal function (low eGFR and high BUN concentrations, all $P < 0.001$) (*Table 1*). There was no significant difference in loop diuretic use and LVEF across the quartiles; however, patients with lower urinary creatinine did require higher doses of loop diuretics. These patients also had a higher urinary sodium-to-creatinine ratio ($P < 0.001$) (*Table 1*). Men had higher urinary creatinine concentrations compared with women ($P < 0.001$) (*Table 1*). Patients from the lowest creatinine quartile were significantly more likely to have >5% weight loss over a period of 9 months ($P < 0.001$) (*Table 1*, *Figure 1*). Interestingly, patients with lower urinary creatinine concentrations had a significantly lower exercise capacity, as assessed by the 6-min walking test ($P < 0.001$), and experienced a poorer quality of life as assessed by the EuroQol five dimension visual analogue scale (EQ-5D VAS) and Kansas City Cardiomyopathy Questionnaire (KCCQ) ($P < 0.001$) (*Table 1*). Not only urinary creatinine but also weight loss was an independent predictor of lower exercise capacity.

Baseline predictors of urinary creatinine concentrations and hierarchical cluster analysis

Predictors of urinary creatinine concentrations in the index cohort are presented in *Table 2*. In a multivariable linear regression model, lower spot urinary creatinine was associated with higher plasma NT-proBNP, female sex, lower diastolic blood pressure, lower plasma sodium, and was borderline non-significant for oedema and orthopnoea ($r^2 = 0.06$) (*Table 2*). The results of hierarchical clustering of variables and a

Table 1 Baseline characteristics according to quartiles of urinary creatinine for the index cohort

Variables[a]	Q1	Q2	Q3	Q4	*P*-value
N	579	586	588	562	
Urinary creatinine (mmol/L)	1.8 [1.3–2.2]	3.7 [3.2–4.5]	7.0 [6.0–8.3]	13.0 [11.0–16.5]	
Demographics					
Men (% (*n*))	66.0 (382)	71.7 (420)	75.2 (442)	80.4 (452)	<**0.001**
Age (years)	70.2 ± 12.0	70.9 ± 11.4	68.5 ± 11.7	65.8 ± 12.0	<**0.001**
NYHA class (% (*n*))					<**0.001**
I	2.1 (12)	2.6 (15)	1.5 (9)	2.8 (16)	
II	29.0 (168)	31.4 (184)	36.4 (214)	42.9 (241)	
III	49.9 (289)	51.2 (300)	48.3 (284)	43.8 (246)	
IV	17.6 (102)	11.9 (70)	9.7 (57)	7.1 (40)	
LVEF (%)	31.3 ± 10.9	31.6 ± 10.8	31.1 ± 10.5	30.2 ± 10.0	0.067
Anthropometrics					
Weight (kg) at baseline	78.9 ± 17.9	80.9 ± 18.0	82.3 ± 18.1	84.9 ± 18.3	<**0.001**
Weight (kg) at 9 months	78.7 ± 17.3	80.8 ± 17.2	83.1 ± 19.4	86.0 ± 19.4	<**0.001**
Change in weight (kg)	−0.9 ± 8.5	−0.4 ± 8.5	0.4 ± 9.2	0.3 ± 10.4	**0.025**
>5% weight loss (% (*n*))	26.3 (104)	24.1 (100)	19.3 (89)	16.9 (78)	<**0.001**
>5% weight gain (% (*n*))	18.0 (71)	21.7 (90)	20.8 (96)	18.2 (84)	0.918
Height (cm)	169.5 ± 9.2	170.7 ± 9.4	171.2 ± 8.6	172.3 ± 9.1	<**0.001**
BMI (kg/m^2) at baseline	27.3 ± 5.5	27.7 ± 5.4	28.0 ± 5.3	28.5 ± 5.2	<**0.001**
BMI (kg/m^2) at 9 months	27.2 ± 5.3	27.6 ± 5.3	28.2 ± 5.9	28.8 ± 5.7	<**0.001**
Change in BMI (kg/m^2)	−0.3 ± 2.8	−0.1 ± 2.9	0.2 ± 3.2	0.1 ± 3.4	**0.012**
Clinical profile at baseline					
SBP (mmHg)	123 ± 22	124 ± 23	125 ± 22	128 ± 20	<**0.001**
DBP (mmHg)	73 ± 13	74 ± 13.9	75 ± 13	78 ± 13	<**0.001**
HR (b.p.m.)	81 ± 20	80 ± 20	79 ± 19	80 ± 19	0.286
Peripheral oedema above ankle (% (*n*))	37.4 (186)	34.5 (167)	26.5 (130)	20.4 (93)	<**0.001**
Orthopnoea (% (*n*))	42.2 (244)	38.1 (222)	31.6 (186)	27.3 (153)	<**0.001**
Rales >1/3 upper lung fields (% (*n*))	21.0 (70)	23.3 (79)	15.6 (45)	16.1 (37)	**0.032**
Elevated JVP (% (*n*))	43.8 (171)	37.6 (147)	25.7 (96)	25.8 (96)	<**0.001**
Hepatomegaly (% (*n*))	17.5 (101)	16.8 (98)	12.4 (73)	10.0 (56)	<**0.001**
Clinical congestion score	1.3 [0.3–2.0]	1.0 [0–1.7]	0.3 [0–1.3]	0.0 [0–1.3]	<**0.001**
6MWT (m)	180 [0–325]	150 [0–340]	249 [50–360]	300 [160–387]	<**0.001**
KCCQ	43 [27–59]	44 [27–64]	48 [34–67]	56 [41–71]	<**0.001**
EQ 5 D VAS	50 [40–65]	55 [40–70]	50 [40–70]	60 [45–70]	<**0.001**
Medical history, (% (*n*))					
NYHA class prior to decompensation/worsening HF					**0.001**
I	6.4 (37)	10.2 (60)	8.7 (51)	10.1 (57)	
II	47.7 (276)	42.5 (249)	46.8 (275)	46.6 (262)	
III	31.4 (182)	31.9 (187)	29.6 (174)	24.9 (140)	
IV	3.1 (18)	3.4 (20)	3.1 (18)	3.2 (18)	
Previous HF hospitalization	37.5 (217)	31.6 (185)	31.1 (183)	25.1 (141)	<**0.001**
Hypertension	61.1 (354)	65.5 (384)	61.4 (361)	63.3 (356)	0.790
Atrial fibrillation	48.2 (279)	49.0 (287)	44.6 (262)	38.6 (217)	<**0.001**
Myocardial infarction	39.2 (227)	37.9 (222)	38.9 (229)	36.7 (206)	0.473
PCI	21.6 (125)	20.6 (121)	24.7 (145)	20.1 (113)	0.976
CABG	20.6 (119)	19.3 (113)	16.3 (96)	12.8 (72)	<**0.001**
Pacemaker	7.1 (41)	8.9 (52)	8.0 (47)	5.5 (31)	0.262
ICD	10.2 (59)	6.7 (39)	9.0 (53)	5.5 (31)	**0.022**

(*Continues*)

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Table 1 (continued)

Variables[a]	Q1	Q2	Q3	Q4	*P*-value
Biventricular pacer (CRT) and ICD	8.5 (49)	7.5 (44)	5.3 (31)	6.0 (34)	**0.043**
Diabetes mellitus	30.4 (176)	40.8 (239)	32.1 (189)	28.5 (160)	0.104
COPD	18.0 (104)	21.5 (126)	16.2 (95)	13.7 (77)	**0.011**
Peripheral artery disease	12.4 (72)	12.8 (75)	11.1 (65)	8.4 (47)	**0.018**
Medication history, (% (*n*)) at baseline					
Loop diuretics	99.7 (577)	100.0 (586)	99.5 (585)	99.1 (557)	0.082
Loop diuretic doses (40 mg of furosemide equivalents)	60 [40–125]	45 [40–124]	40 [40–80]	40 [40–75]	<**0.001**
ACEi/ARB	69.1 (400)	67.1 (393)	75.2 (442)	77.0 (433)	<**0.001**
% on target dose	11.7 (68)	12.1 (71)	13.8 (81)	16.0 (90)	**0.023**
Beta-blockers	80.5 (466)	81.6 (478)	83.3 (490)	87.2 (490)	**0.002**
% on target dose	7.1 (41)	5.6 (33)	5.3 (31)	3.9 (22)	**0.021**
MRA	50.6 (293)	52.6 (308)	55.3 (325)	56.0 (315)	**0.041**
Digoxin	20.9 (121)	18.8 (110)	18.0 (106)	19.0 (107)	0.385
Plasma biomarkers at baseline					
Haemoglobin (g/dL)	13.1 [11.7–14.4]	12.8 [11.6–14]	13.4 [12.0–14.6]	13.8 [12.5–14.8]	<**0.001**
Sodium (mmol/L)	139 [136–142]	139 [136–141]	140 [137–142]	140 [138–142]	<**0.001**
Potassium (mmol/L)	4.2 [3.9–4.5]	4.2 [3.9–4.5]	4.3 [3.9–4.7]	4.3 [3.9–4.6]	**0.005**
Creatinine (μmol/L)	104 [84–133]	110 [88–146]	101 [83–126]	96 [80–114]	<**0.001**
BUN (mmol/L)	12.5 [8.0–20.7]	12.0 [8.1–20.8]	11.1 [7.4–16.6]	8.9 [6.5–13.2]	<**0.001**
eGFR (mL/min/1.73 m^2)	54.8 [42.3–75.1]	54.7 [37.2–75.5]	60.9 [45.5–79.1]	68.1 [52.4–83.7]	<**0.001**
Albumin (g/L)	32 [26–39]	32 [26–37]	33 [27–38]	34 [29–39]	<**0.001**
NT-proBNP (ng/L)	3756 [1471–8122]	3034 [1429–6652]	2476 [1205–4845]	1713 [748–3830]	<**0.001**
NGAL (ng/mL)	66.0 [39.5–105.5]	69.3 [43.7–111.3]	59.9 [35.8–94.5]	50.3 [33.1–75.0]	<**0.001**
Urinary sodium/creatinine ratio	43 [28–68]	18 [12–25]	9 [6–14]	5 [3–7]	<**0.001**

[a]Categorical variables were presented as (% (numbers)) and continuous variables were presented as mean ± standard deviation or median [interquartile range] as appropriate.
6MWT, 6 min walking test; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; BUN, blood urea nitrogen; CABG, coronary artery bypass graft surgery; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EQ-5D VAS, EuroQol five dimension visual analogue scale; HF, heart failure; HR, heart rate; ICD, implantable cardioverter defibrillator; JVP, jugular venous pressure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NGAL, neutrophil gelatinase-associated lipocalin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

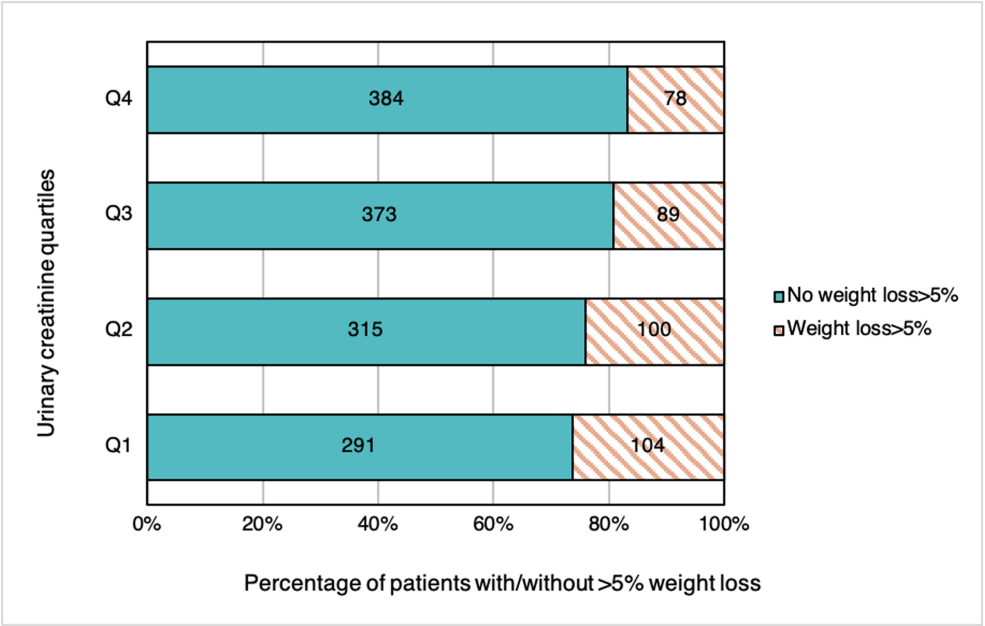

Figure 1 Percentage of patients with or without more than 5% weight loss (in 9 months) per quartile of urinary creatinine (index cohort).

Table 2 Multivariable linear regression model for predictors of baseline log urinary creatinine for the index cohort[a]

Variable	Beta coefficient	*T* value	*P*-value
DBP	0.095	3.654	<**0.001**
Plasma sodium	0.075	2.667	**0.008**
Plasma BUN	−0.050	−1.786	0.074
Peripheral oedema above ankle	−0.109	−1.788	0.074
Orthopnoea	−0.110	−1.885	0.060
Plasma NT-proBNP	−0.068	−2.356	**0.019**
Female sex	−0.207	−3.366	**0.001**

BUN, blood urea nitrogen; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide.
[a]r^2 = 0.06, continuous variables are presented per standard deviation.

correlation heatmap for the index cohort are presented in *Figures 2* and *3*, respectively. In a hierarchical cluster analysis (*Figure 2*), urinary creatinine clustered with NT-proBNP and troponin T. Interestingly, urinary creatinine did not cluster with BMI or albumin. The heatmap (*Figure 3*) illustrates that urinary creatinine concentrations are most strongly correlated with FGF23 (Spearman's rho: −0.25, $P < 0.001$), GDF-15 (Spearman's rho: −0.24, $P < 0.001$), and NT-proBNP (Spearman's rho: −0.24, $P < 0.001$).

Urinary creatinine and weight loss

Lower urinary creatinine was a significant predictor of weight loss at 9 months [odds ratio (OR) = 1.14, 95% CI = 1.03–1.27 per log decrease; $P = 0.015$], and especially a risk of more than 5% weight loss in 9 months (OR = 1.23, 95% CI = 1.09–1.39 per log decrease; $P = 0.001$) (*Table 3*). Lower urinary creatinine was also a significant predictor of a more stringent definition of cachexia (Evans' criteria), which incorporates abnormal biochemistry (OR = 1.26 per log decrease, 95% CI = 1.04–1.49; $P = 0.016$) (*Table 3*). As shown in Supporting Information, *Table S3*, in a multivariable model of weight loss including BMI, NT-proBNP, and urinary creatinine, urinary creatinine was non-significant ($P = 0.064$).

Urinary creatinine and outcomes

During a median follow-up of 21 months (16–27 months), out of 2315 patients, 61 (26.4%) died and 950 (41.0%) experienced the combined endpoint mortality and/or HF hospitalization. In a univariable Cox regression model, lower urinary creatinine was significantly associated with higher all-cause mortality [hazard ratio (HR = 1.27, 95% CI = 1.17–1.38 per log decrease; $P < 0.001$] and the combined endpoint of all-cause mortality and HF hospitalization (HR = 1.23, 95% CI = 1.15–1.31 per log decrease; $P < 0.001$) (*Table 4*, *Figure 4*). The associations remained significant even after adjusting for BMI, age, sex, eGFR, and baseline loop diuretic dose. The association was, however, attenuated after additional adjustment for the BIOSTAT risk model (*Table 4*). Lastly, a decrease in weight from baseline to 9 months and >5% weight loss predicted a higher risk of combined endpoint (Supporting

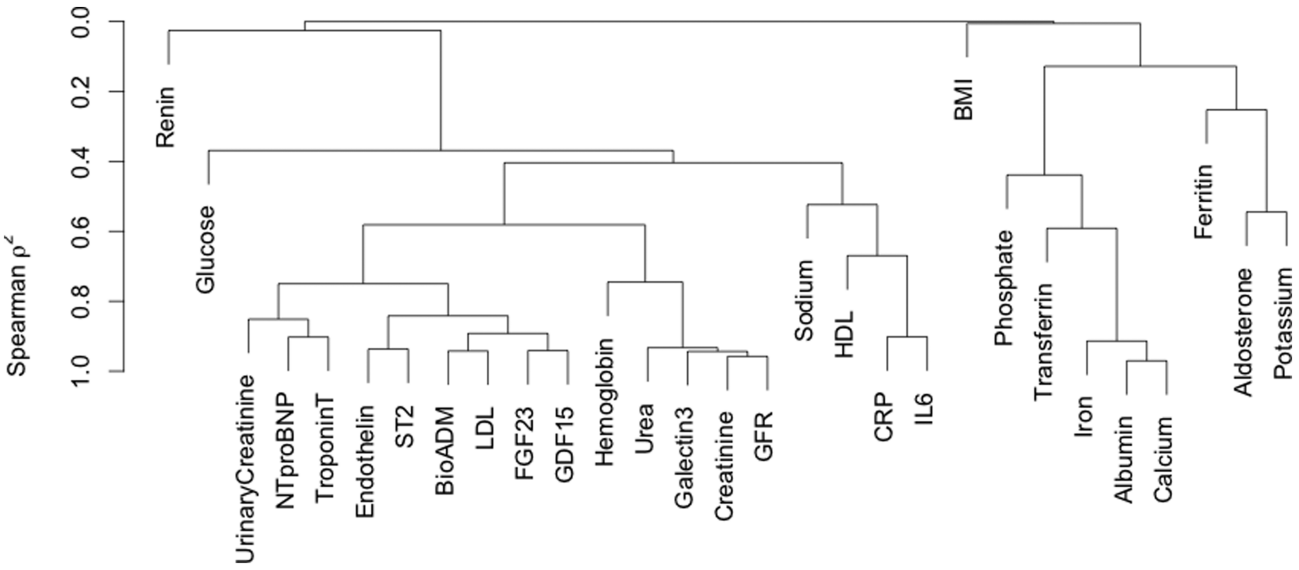

Figure 2 Biomarker position of spot urinary creatinine depicted in hierarchical cluster analysis (index cohort). Abbreviations: Bio-ADM, biologically active adrenomedullin; BMI, body mass index; CRP, C-reactive protein; FGF23, fibroblast growth factor 23; GDF15, growth differentiation factor 15; GFR, glomerular filtration rate; HDL, high density lipoprotein; IL6, interleukin-6; LDL, low density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Information, *Figures S1* and *S2*). This, however, did not remain significant after adjustment for urinary creatinine (P = 0.105) or after adjustment for the BIOSTAT risk model (P = 0.522).

Validation cohort

Median urinary creatinine was 3.9 (2.1–7.2) mmol/L. Mean age was 75 ± 11 years, 68.4% (979) of the patients were men, and mean LVEF was 41 ± 13. Patients with lower urinary creatinine had lower height, weight, and BMI (all $P < 0.008$) and were more often women ($P < 0.001$). Patients in this group had more severe HF [worse NYHA class, higher NT-proBNP concentrations, more rales (all $P < 0.021$)], and higher urinary sodium/creatinine ratio ($P < 0.001$) (Supporting Information, *Table S4*). In a multivariable model, per log decrease in urinary creatinine was associated with lower height, weight, and plasma sodium (Supporting Information, *Table S5*). In hierarchical cluster analysis (Supporting Information, *Figure S3*), urinary creatinine clustered with potassium and was part of a greater cluster that included albumin and BMI. The heatmap (Supporting Information, *Figure S4*) showed that urinary creatinine was correlated with NT-proBNP (Spearman's rho: −0.13, $P < 0.001$) and sodium (Spearman's rho: 0.12, $P < 0.001$). Lower urinary creatinine was associated with a greater risk of all-cause mortality (HR = 1.13, 95% CI = 1.01–1.27 per log decrease; P = 0.039) and the combined endpoint (HR = 1.16, 95% CI = 1.05–1.28 per log decrease; P = 0.004, Supporting Information, *Figure S5*), even after adjusting for BMI, age, sex, eGFR, and loop diuretic dose but was attenuated after adjusting for BIOSTAT risk score (Supporting Information, *Table S6*).

Discussion

In this study, we showed that in patients with new-onset/worsening HF, lower spot urinary creatinine concentrations were associated with smaller body dimensions, renal dysfunction, and more advanced HF. Furthermore, lower urinary creatinine was associated with an increased risk of weight loss and adverse outcomes in patients with new-onset/worsening HF. These findings were validated in an external cohort yielding similar findings.

Spot urinary creatinine, weight loss, and muscle wasting in new-onset/worsening heart failure

Measurement of creatinine concentrations in a 24 h urine sample may be a useful marker to estimate muscle loss, as it is produced after stable conversion of creatine, which is mostly found in skeletal muscles.[8] The reliability of 24 h urinary creatinine excretion as a measure of muscle wasting has been investigated in several chronic illness populations[9–14] and correlated with muscle mass measured using different techniques, including bioimpedance analysis, computerized

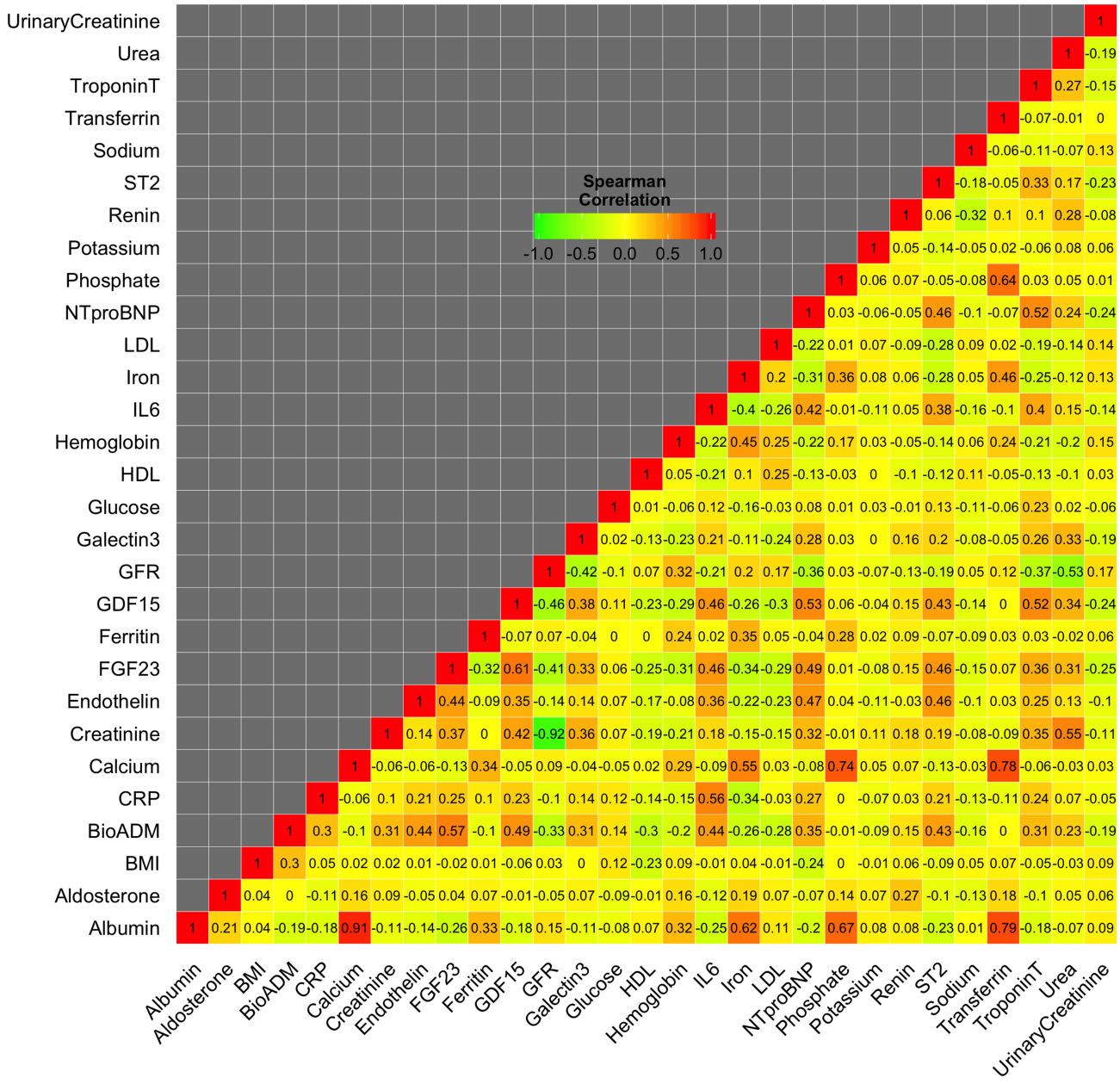

Figure 3 Biomarker position of spot urinary creatinine depicted in a correlation heatmap (index cohort). Abbreviations: Bio-ADM, biologically active adrenomedullin; BMI, body mass index; CRP, C-reactive protein; FGF23, fibroblast growth factor 23; GDF15, growth differentiation factor 15; GFR, glomerular filtration rate; HDL, high density lipoprotein; IL6, interleukin-6; LDL, low density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide.

tomography (CT), magnetic resonance imaging (MRI), and dual X-ray absorptiometry (DEXA) scans.[8,13,25,26] However, despite its value, 24 h urine collection is often considered unreliable, cumbersome, and are rarely obtained in HF patients.[15,16] In a population-based study, lower spot urinary creatinine was found to be associated with an increased risk of cardiovascular events, compared with subjects in the highest tertile, who had lower risk of developing coronary artery disease, hypertension, dyslipidaemia, and had a better renal function.[27] Furthermore, we recently demonstrated that lower urinary creatinine measured in spot urine samples was associated with smaller body dimensions and poor outcomes in chronic HF.[15] Therefore, in the current study, we propose spot urinary creatinine as an inexpensive and easily quantifiable approach to identify new onset/worsening HF patients at risk of (sub) clinical muscle wasting, as well as cachexia, who might benefit from additional interventions (if possible) to improve outcomes.

Table 3 Univariable logistic regression model for predictors of baseline log urinary creatinine for the index cohort

	Per log urinary creatinine decrease	
	OR [CI]	*P*-value
Weight loss (yes/no)	1.14 [1.03–1.27]	**0.015**
Weight loss >5%	1.23 [1.09–1.39]	**0.001**
Weight loss >10%	1.20 [1.00–1.43]	0.051
Evans' criteria for cachexia (yes/no)	1.26 [1.04–1.49]	**0.016**

Definition Evans' criteria for cachexia: weight loss>5% from baseline to 9 months and CRP > 5 mg/L or IL6 > 4 pg/mL, Hb < 7.45 mmol/L, and albumin <32 d/L.
OR, odds ratio; CI, confidence interval.

We showed that lower urinary creatinine concentrations were associated with smaller body dimensions (lower BMI, height, and weight) and an increased risk of (>5%) weight loss at 9 months. Various studies have shown that HF patients with lower BMI have an increased risk of mortality in contrast to those with a higher BMI, a phenomenon known as the obesity paradox.[7,28,29] Although the precise underlying reasons are unclear, one explanation is the fact that lower BMI may be identifying HF patients with lowered muscle mass. Cachexia and muscle wasting both have a high prevalence of 10–20% in chronic HF and are associated with worse outcomes.[1–4,6] However, the role of muscle wasting in acute/worsening HF still remains undescribed, and studies show that more than a third of these patients may exhibit muscle loss.[30,31] Consequently, timely diagnosis of these conditions may help improve outcomes. However, muscle wasting cannot be detected using weighing scales alone, as skeletal muscle mass can be replaced by age-related increase in adipose tissue, and weight can be influenced by presence of oedema and diuretic treatment.[6,10] As a result, spot urinary creatinine may be an easily accessible approach to distinguish patients with cachexia and (underlying) muscle wasting. We also found that patients with lower urinary creatinine had worse exercise capacity, as shown by a shorter distance walked during the 6-min walking test. As severe HF typically manifests with reduced exercise performance,[4] spot urinary creatinine may also help differentiate patients with reduced muscle strength in addition to muscle mass and, thus, could serve as a marker of sarcopenia.

Spot urinary creatinine and outcomes

In our study, we also demonstrated that patients with lower spot urinary creatinine had a higher risk of mortality or (re-) hospitalization, most likely driven by more advanced HF (higher NT-proBNP, worse renal function, and more congestion), as the association was lost after adjustment for the BIOSTAT risk model. We hypothesize that the association between urinary creatinine and heart failure severity is driven by an underlying state of wasting that affects all types of tissues, including fat, bones, and muscles. Although the HF patients in our study may have co-existent co-morbidities, the fact that NT-proBNP was associated with urinary creatinine and weight loss suggests that the state of wasting may be induced due to severe HF. This is also supported by the finding that urinary creatinine clustered with NT-proBNP, rather than markers of cachexia (such as IL6, CRP, and haemoglobin) in hierarchical cluster analyses. There are several underlying mechanisms of wasting in HF, but the general consensus is that it is caused by an anabolic-catabolic imbalance. A combination of hormonal disturbances, release of inflammatory cytokines, reduced protein synthesis, and active protein degradation all contribute to body wasting.[6] This, along with a decreased appetite, reduced physical activity, and fatigue further worsens the wasting state.[3,6] As a result, using spot urinary creatinine, we may be able to identify sicker HF patients with more advanced disease and a higher risk of wasting.

Overall, findings in the index and the validation cohort were comparable, and the small differences may be due to less severe HF in the validation cohort (lesser congestion and lower NT-proBNP concentrations). Lastly, the value of spot urinary creatinine assessment in HF has now been validated across three cohorts, showing a consistent association of lower urinary creatinine with more severe HF and poor outcomes.[15]

Table 4 Cox regression analysis of urinary creatinine for all-cause mortality and combined endpoint for the index cohort

	All-cause mortality		Combined endpoint	
Index cohort	HR [CI]	*P*-value	HR [CI]	*P*-value
Urinary creatinine per log decrease	1.27 [1.17–1.38]	<**0.001**	1.23 [1.15–1.31]	<**0.001**
Adjusted for BMI, age, sex, eGFR, and loop diuretic dose at baseline	1.20 [1.09–1.32]	<**0.001**	1.16 [1.08–1.25]	<**0.001**
Adjusted for the above with the addition of the BIOSTAT risk model[a]	1.03 [0.93–1.15]	0.550	1.01 [0.93–1.10]	0.759

Combined endpoint: age, HF hospitalization in previous year, presence of oedema, log NT-proBNP, systolic blood pressure, haemoglobin, high-density lipoprotein, sodium, and beta-blocker use at baseline.
BIOSTAT, A systems BIOlogy Study to Tailored Treatment in Chronic Heart Failure; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Variables in the BIOSTAT risk score: All-cause mortality: age, log blood urea nitrogen (BUN), log NT-proBNP, haemoglobin, and beta-blocker use at baseline.

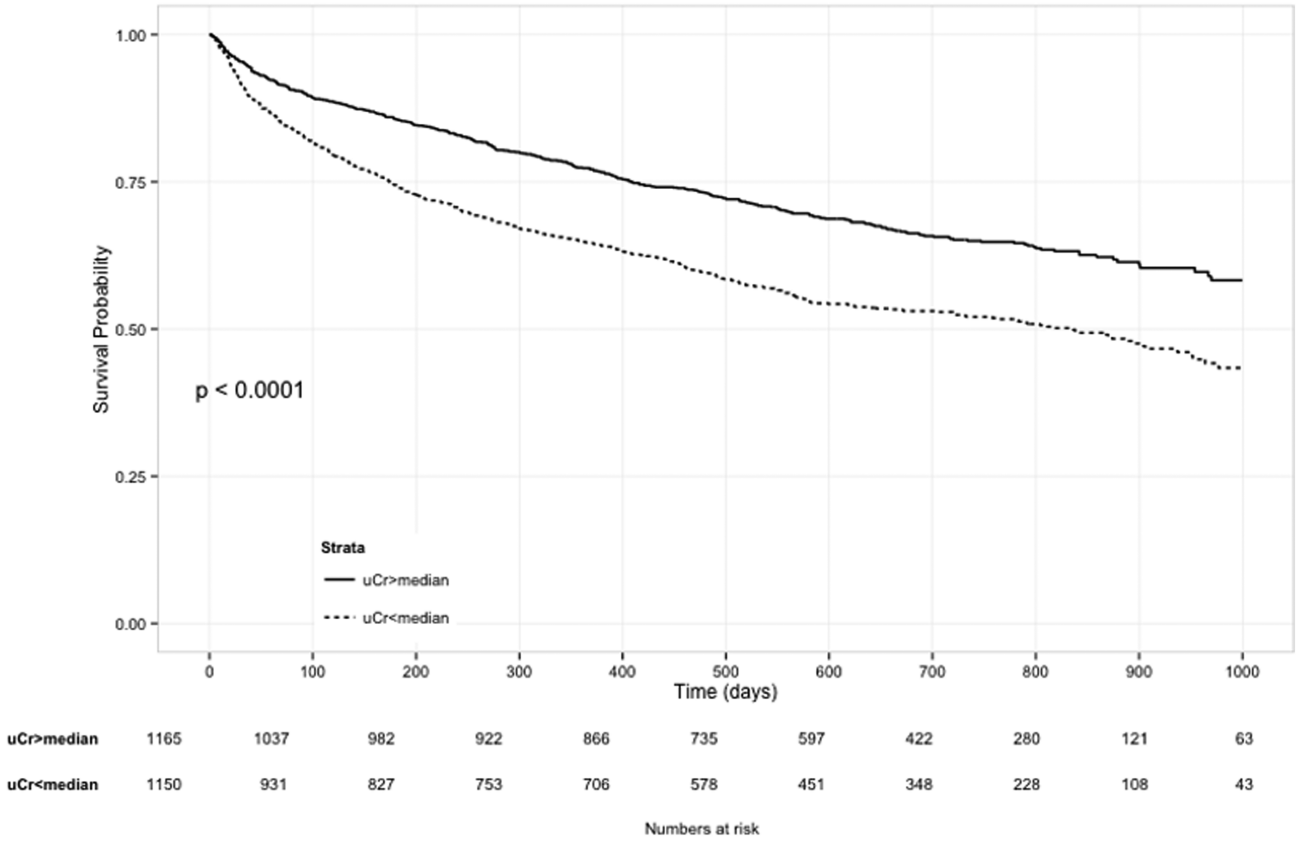

Figure 4 Kaplan Meier survival curve (index cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to urinary creatinine value (above/equal to or below the median). Abbreviations: uCR, urinary creatinine.

Future perspectives

Spot urinary creatinine may be used to identify patients who could benefit from exercise interventions to improve prognosis. Currently, data on the effects of exercise training in acute HF patients are still scarce, as this patient group is often excluded from trials due to severity of HF. In the EJECTION-HF trial, acute HF patients randomized to 24 weeks of supervised centre-based exercise training showed significant reduction in all-cause death (based on small number of events), but no improvement in combined endpoint of all-cause mortality or readmissions.[32] In the REHAB-HF pilot study, a 12-week rehabilitation programme focused on improving strength, balance, mobility, and endurance showed a trend towards improved physical function and decreased hospitalizations in acute HF patients.[33] Recent evidence suggests that exercise training, combined with nutritional support (e.g. protein/amino acid supplementation, preventing vitamin/mineral deficiencies), has shown considerable benefit in chronic HF patients.[6,34] Assessment of urinary creatinine at baseline and during such studies would be of great interest to illustrate an improvement of muscle mass during exercise intervention studies. Lastly, spot urinary creatinine may be incorporated in future cachexia and/or sarcopenia definitions for detecting these conditions in HF patients.

Limitations

Our study is limited by its retrospective design and all results are observational. As 24 h urinary creatinine was not measured in BIOSTAT-CHF, correlation between spot urinary creatinine and 24 h urinary creatinine measurements in this cohort is unknown. Weight at 9 months was not available in the validation cohort, and we did not use the same weighing scale for all patients. We could not distinguish in our study whether weight loss was (un)intentional, caused by fluid loss or by muscle wasting. Fluid loss caused by diuretics may partly have contributed to the association of urinary creatinine with weight loss, as patients with lower urinary creatinine concentrations had a higher urinary sodium/creatinine ratio. However, associations with outcomes remained significant even after adjusting for baseline loop diuretic doses, suggesting a larger effect of muscle loss. An

important factor to consider when using spot urinary samples to predict outcomes is that the average creatinine measured in a spot sample may be higher compared with 24 h measurement at a similar urine specific gravity. Urine osmolarity can also influence the actual measured concentrations, and we could not adjust for this.[15,16] In dilute urine (urine specific gravity ≤1.005), spot measurement and 24 h measurement had a high intraclass correlation of 98.7%. However, in concentrated urine (gravity ≥1.020), the correlation decreased to 26.8%, and values of spot samples were widely distributed.[16] As spot samples may overestimate urinary creatinine concentrations, this is likely to result in an underestimation of the mortality risk in the context of our findings. We were not able to assess the correlation of urinary creatinine with advanced body composition imaging techniques such as CT, MRI, or DEXA, as these were not available in our study. Future prospective cohort studies and functional analyses are required to corroborate our results and establish the value of spot urinary creatinine in new-onset/WHF and to investigate the effects of interventions to improve muscle mass on spot urinary creatinine concentrations.

Conclusions

Lower spot urinary creatinine is associated with smaller body dimensions, renal dysfunction, and more severe HF in patients with new-onset/WHF. Additionally, lower spot urinary creatinine is associated with an increased risk of weight loss, poorer exercise capacity, and a decreased quality of life. Urinary creatinine could therefore be a novel, easily obtainable marker to assess (risk of) muscle wasting in HF patients.

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Online supplementary material

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

Figure S1 Kaplan Meier survival curve (index cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to weight loss (yes/no)*

Figure S2 Kaplan Meier survival curve (index cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to percentage weight loss (above or below 5%)*

Figure S3 Biomarker position of spot urinary creatinine depicted in hierarchical cluster analysis (validation cohort)

Figure S4 Biomarker position of spot urinary creatinine depicted in a correlation heatmap (validation cohort)

Figure S5 Kaplan Meier survival curve (validation cohort) for combined endpoint (all-cause mortality or HF hospitalization) according to urinary creatinine value (above/equal to or below the median)

Table S1 Baseline characteristics of included and excluded patients for the index cohort

Table S2 Baseline characteristics of included and excluded patients for the validation cohort

Table S3 Multivariable linear regression model for predictors of percentage weight change from baseline (per unit increase) for the index cohort*

Table S4 Baseline characteristics according to quartiles of urinary creatinine for the validation cohort

Table S5 Multivariable linear regression model for predictors of baseline urinary creatinine for the validation cohort*

Table S6 Cox regression analysis of urinary creatinine for all-cause mortality and combined endpoint for the validation cohort

Conflict of Interest

P.P., K.W.S., K.D., and J.M.t.M. have nothing to declare. A.A.V. received consultancy fees and/or research grants from Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, GSK, Merck, Myokardia, Novacardia, Novartis, Roche diagnostics, Servier and Vifor International and personal fees from Roche. S.D.A. reports receiving fees from Abbott, Bayer, Boehringer Ingelheim, Cardiac Dimension, Impulse Dynamics, Novartis, Servier, and Vifor Pharma, and grant support from Abbott and Vifor Pharma. M.M. received consulting or speaker fees from Abbott Vascular, Amgen, AstraZeneca, Bayer, Novartis, Relypsa, Servier, Stealth Therapeutics and Trevena. C.C.L. received fees and/or research grants from Novartis, AstraZeneca and MSD. P.R. is supported RHU Fight-HF, a public grant overseen by the French National Research Agency (ANR) as part of the second 'Investissements d'Avenir' programme (reference: ANR-15-RHUS-0004), by the French PIA project 'Lorraine Université d'Excellence' (reference: ANR-15-IDEX-04-LUE). He acknowledges CRB Lorrain of Nancy CHRU for biobank handling in Nancy. P.R. reports consulting for G3P (stocks) and Idorsia; honoraria from Ablative Solutions, AstraZeneca, Bayer, Boehringer Ingelheim, Corvidia, CVRx, Fresenius, Grunenthal,

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