openheart

Uric acid in advanced heart failure: relation to central haemodynamics and outcome

Tania Deis ,[1] Kasper Rossing,[1] Mads Kristian Ersbøll,[1] Emil Wolsk,[2] Finn Gustafsson[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/openhrt-2022-002092).

To cite: Deis T, Rossing K, Ersbøll MK, *et al*. Uric acid in advanced heart failure: relation to central haemodynamics and outcome. *Open Heart* 2022;**9**:e002092. doi:10.1136/openhrt-2022-002092

This study was presented as an abstract at Heart Failure 2022 Congress (https://doi.org/10.1002/ejhf.2569)

Received 15 July 2022
Accepted 3 November 2022

[1]Department of Cardiology, Rigshospitalet, Copenhagen, Denmark
[2]Department of Cardiology, Herlev-Gentofte, Copenhagen, Denmark

Correspondence to
Dr Tania Deis; tania.deis@regionh.dk

ABSTRACT

Objective The role of hyperuricaemia as a prognostic maker has been established in chronic heart failure (HF) but limited information on the association between plasma uric acid (UA) levels and central haemodynamic measurements is available.

Methods A retrospective study on patients with advanced HF referred for right heart catherisation. Regression analyses were constructed to investigate the association between UA and haemodynamic variables. Cox models were created to investigate if UA was a significant predictor of adverse outcome where log1.1(UA) was used to estimate the effect on outcome associated with a 10% increase in UA levels.

Results A total of 228 patients were included (77% males, age 49±12 years, mean left ventricular ejection fraction (LVEF) of 17%±8%). Median UA was 0.48 (0.39–0.61) mmol/L. UA level was associated to pulmonary capillary wedge pressure (PCWP) and cardiac index (CI) in univariable (both p<0.001) and multivariable regression analysis (p<0.004 and p=0.025 for PCWP and CI). When constructing multivariable Cox models including PCWP, CI, central venous pressure, age, estimated glomerular filtration rate (eGFR), use of loop diuretics and LVEF, log1.1(UA) independently predicted the combined endpoint (left ventricular assist device, total artificial heart implantation, heart transplantation or all-cause mortality) (hazard ratio (HR): 1.10 (1.03–1.17), p=0.004) as well as all-cause mortality (HR: 1.15 (1.06–1.25), p=0.001).

Conclusions Elevated UA is associated with greater haemodynamic impairment in advanced HF. In adjusted Cox models (age, eGFR, LVEF and haemodynamics), UA predicts the combined endpoint and all-cause mortality in long-term follow-up.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Hyperuricaemia is a strong predictor of mortality in chronic heart failure (HF) but the exact pathophysiological link between hyperuricaemia and HF has yet to be fully clarified and the role of deranged haemodynamics is largely unknown.

WHAT THIS STUDY ADDS

⇒ We now know that an association between central haemodynamics and plasma uric acid levels exist but mechanisms beyond haemodynamic impairment explain the increased adverse outcome related to hyperuricaemia.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study brings pathophysiological insights into the world of hyperuricaemia in HF and may guide further research exploring the link between hyperuricaemia and HF.

INTRODUCTION

Heart failure (HF) is a progressive condition associated with poor quality of life[1] and high mortality.[2] It is characterised by a complex pathophysiology, including elevated ventricular filling pressure and impaired organ perfusion, affecting homeostasis and causing metabolic derangement. Hyperuricaemia refers to elevated uric acid (UA) level and is a metabolic complication frequently observed in HF. UA is the end-product of the metabolic breakdown of purines catalysed by the enzyme xanthine oxidase (XO) known to generate free oxygen radicals, and UA may be viewed as a marker of oxidative stress.[3] In HF, UA is predictive of symptom burden according to New York Heart Association (NYHA) class[4] and has been recognised as a strong independent predictor of morbidity and mortality in HF.[5–7] The exact pathophysiological link between hyperuricaemia and HF has yet to be established and it is unclear if hyperuricaemia plays a causative role in disease progression or is merely a marker associated with a poorer prognosis.

Sparse literature has been published on the association between haemodynamics and hyperuricaemia.[8 9] This paper explores the relation between UA and haemodynamic measurements in patients with advanced HF to bring insights into the pathophysiological mechanisms underlining the disease.

METHODS

Study design and patient population

Details of the study design have previously been published.[10]

This is a retrospective study on HF patients referred for non-urgent right heart catherisation (RHC) for evaluation for advanced therapy (ie, implantation of left ventricular assist device, total artificial heart implantation or heart transplantation) or as a part of assessment of advanced HF at the Department of Cardiology at Copenhagen University Hospital, Rigshospitalet from 1 January 2002 to 31 October 2020. Patients were identified through the hospital's cardiac catheterisation database, where data were extracted and linked to the hospital's echocardiography database and patients' medical records. In case of repeated RHC during the time period, only data from the first catheterisation was used. The inclusion criteria were a left ventricular ejection fraction (LVEF)<45% and a measurement of plasma UA within 14 days of the RHC. Exclusion criteria comprised congenital heart defects, young age (under 16 years), prior heart transplantation or mechanical circulatory support at the time of the haemodynamic evaluation, unstable patients requiring intensive care, dialysis or assisted ventilation. We identified 228 patients who fulfilled the criteria, and they formed the studied population.

Since patients were not required to have symptoms of advanced HF at the time of the RHC, some patients were classified as NYHA II. These patients were included, as they had recently experienced advanced HF symptoms and/or their HF condition was considered so severe that it justified referral for evaluation for advanced therapies. All patients were considered to have an element of chronic HF, but some patients could be in the state of worsening HF with decompensation during the time of their RHC.

Patient and public involvement

Patients or members of the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research (not appropriate or possible).

Alcohol consumption

Information was retrieved from the patients' medical records. High alcohol consumption was defined as more or equal to 14 units/week for women and 21 units/week for men according to the Danish Health Authority's guidelines 2010 (the limits of appropriate alcohol intake in the national guidelines are not universally accepted).

Haemodynamic evaluation

The invasive protocol followed the department's routine diagnostic procedure. Four different experienced physicians performed all the haemodynamic evaluations in the cardiac catheterisation laboratory using a Swan-Ganz catheter. Appropriate zeroing and calibration of the pressure transducer were performed before measurements. The catheter was inserted in the femoral vein or the internal jugular vein where correct placement was confirmed by fluoroscopy and by visualisation of pressure curves on a monitor.

Patients underwent RHC with determination of central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), pulmonary artery systolic pressure, pulmonary artery diastolic pressure, mean pulmonary artery pressure, right ventricular systolic pressure, right ventricular diastolic pressure, cardiac output (CO) using thermodilution technique, heart rate (HR), systolic blood pressure and diastolic blood pressure. Arterial blood pressure was measured noninvasively using a semiautomatic inflatable blood pressure cuff.

Derived variables were calculated as follows: Cardiac Index (CI) was determined as CO divided by the body surface area (BSA). BSA was determined using the DuBois method. MAP was estimated using the formula $MAP = \frac{(2 \times DBP) + SBP}{3}$.

Blood samples

Laboratory tests were collected within 2 days of the RHC except plasma UA where measurements within 14 days of the procedure were included. Estimated glomerular filtration rate (eGFR) was estimated using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula.[11] The following values for UA were defined by our laboratory as; upper normal limit for women: 0.40 mmol/L (~6.7 mg/dL) (age 50–125 years) and upper normal limit for men: 0.48 mmol/L (~8.1 mg/dL) (age 18–125 years).

Statistical analysis

All continuous variables were reported as mean±SD except N-terminal pro-B-type natriuretic peptide (NT-proBNP) and UA, which were reported as median with IQR as they were non-normally distributed. Categorical variables were reported as numbers and/or percentages.

Regression models were constructed to test the association between UA and central haemodynamics and other relevant variables known to impact UA levels. A multivariable model was constructed using statistically significant variables from univariable models and analysed using forward analysis. UA was log transformed for a better model fit. Data are presented backtransformed in table 2.

End of follow-up was set to 31 October 2020. Events were defined as following: death from all causes, left ventricular assist device implantation, total artificial heart implantation or heart transplantation. Kaplan-Meier survival curves were plotted, dividing patients into normal and high UA levels (according to gender-specific cut-off values) and presented with a rank p value. Cox proportional hazards models was used to estimate the ability of UA to predict (1) all-cause mortality and (2) the combined endpoint of all-cause mortality, left ventricular assist device, total artificial heart or heart transplantation and presented as estimated HRs with 95% CI. Since plasma levels of UA has a relatively narrow range, we used

log1.1(UA) ($log1.1 = \frac{log10(UA)}{log10(1.1)}$) to estimate the effect on outcome associated with a 10% increase in UA levels. The interaction effect of gender on log1.1(UA)'s ability to predict outcome was tested.

Model assumptions for all models were assessed including proportional hazard for Cox regression analyses and lack of collinearity by tolerance and variance inflation factor and assumptions were met. Two-sided p values were used, and a p<0.05 was considered statistically significant. Statistical analyses were performed using SPSS (V.25, IBM) and R.

RESULTS

Clinical characteristics

A total of 228 patients formed the study population. Their characteristics are presented in table 1.

The cohort was of relatively young age (49±12 years) and was dominated by men (77%). They had a severely reduced LVEF (17±8) and most patients were in NYHA class III or IV (67%). Almost one-third (29%) had ischaemic HF aetiology and two-thirds non-ischaemic aetiology (71%). Median UA was 0.48 (0.39–0.61) mmol/L. The average time between UA measurements and RHC was 2.6 days.

The cohort was divided into two groups according to high (women>0.40 mmol/L, men>0.48 mmol/L) or normal UA levels, where 132 patients (58%) had high UA levels and 96 patients (42%) had normal UA levels. Compared with patients with normal UA levels patients with high UA had lower eGFR (70±24 mL/min/1.73 m^2 vs 82±26, p=0.001) and were more often prescribed loop diuretics (93% vs 84%, p=*0.034*). Sixty patients (74%) with normal UA levels were on high doses of loop diuretics (defined as more or equal to 80 mg furosemide) and 100 patients (82%) with high UA levels were on high doses of loop diuretics (p=0.178). There were no differences between groups in standard of care HF medication or inotropic support (dopamine, dobutamine, milrinone or norepinephrine) at the time of the haemodynamic evaluation nor in use of metolazone, allopurinol or colchicine. Further, there were no statistically significant differences in age, sex, LVEF, body mass index (BMI), medical history of diabetes mellitus or alcohol consumption between the two groups.

Patients with high UA had higher PCWP (22±8 vs 19±8, p=0.010), higher CVP (19±8 vs 10±5, p<0.001) as well as lower CI (2.3±0.6 vs 2.5±0.7, p=0.012) compared with patients with normal UA. There were no differences in MAP (p=0.518) or HR (p=0.774).

Association between UA and different haemodynamic and clinical variables

A significant association was found between UA and the haemodynamic parameters CVP (p<0.001), PCWP (p<0.001) and CI (p<0.001) (figure 1) as well as eGFR (p<0.001), LVEF (p=0.009) and sex (p<0.001) in univariable analysis. MAP (p=0.846), allopurinol (p=0.195), haemoglobin (p=0.291), age (p=0.474), high alcohol consumption (p=0.761), loop diuretics (p=0.052) and BMI (p=0.055) were not statistically significantly associated with UA.

In a multivariable analysis including all significant variables from the univariable analysis, PCWP (p=0.004), CI (p=0.025), eGFR (p<0.001) and sex (p<0.001) was found to be significantly associated with UA. CVP and LVEF did not reach statistical significance in the multivariable analysis (table 2). There were no signs of multicollinearity in the multivariable analysis.

UA and outcome

Mean follow-up time for the cohort was 9 years. One patient was lost to follow-up. At the end of the study, 87 patients (38%) had died, 44 (19%) had an LVAD implanted and 76 (33%) had received a heart transplantation. LVAD implantation was used as destination therapy or bridge-to-transplantation, and 22 out of 44 patients who had an LVAD implantation were later transplanted. Of the patients alive at follow-up, 70 (50%) were alive with an LVAD or a heart transplant, whereas 70 (50%) were alive without.

The results of the univariable and multivariable Cox regression models are presented in table 3. In univariable analysis, log1.1(UA) predicted the combined endpoint of all-cause mortality, left ventricular assist device implantation, total artificial heart implantation or heart transplantation (HR 1.17, 95% CI 0.10 to 1.24, p<0.001) and all-cause mortality (HR 1.14, 95% CI 1.07 to 1.21, p<0.001).

In multivariable Cox models adjusted for the haemodynamic parameters CI, CVP and PCWP, log 1.1(UA) remained independently associated with the combined endpoint (HR 1.12, 95% CI 1.05 to 1.19, p<0.001) and all-cause mortality (HR 1.12, 95% CI 1.05 to 1.20; p<0.001). When further adjusting for age, eGFR, use of loop diuretics and LVEF in the multivariable models, log1.1(UA) remained an independent predictor of the combined endpoint (HR 1.10, 95% CI 1.03 to 1.17, p=0.004) and all-cause mortality (HR 1.15, 95% CI 1.06 to 1.25, p=0.001). Further adjusting for use of allopurinol (sensitivity analysis, online supplemental file) did not impact the ability of log1.1(UA) to predict the combined endpoint (HR 1.10, 95% CI 1.03 to 1.17, p=0.003) or all-cause mortality (HR 1.16, 95% CI 1.06 to 1.26, p=0.001).

There was no interaction effect of gender on log1.1(UA)'s ability to predict freedom from the combined endpoint (p=0.192) and all-cause mortality (p=0.962) in univariable Cox models.

A Kaplan-Meier curve demonstrated significant differences between patients with high UA levels and normal UA levels for the combined endpoint (log rank p<0.001) and all-cause mortality (log rank p=0.034) (figure 2).

Table 1 Baseline characteristics

	Total N (n=228)	Normal UA (n=96)	High UA (n=132)	P value
Age	228 49±12	49±12	50±13	0.515
Male sex	228 175 (77%)	73 (76%)	102 (77%)	0.828
BMI	227 26.1±4.8	25.7±4.8	26.4±4.8	0.285
NYHA class III or IV	215 143 (67%)	56 (61 %)	87 (71%)	0.130
LVEF	228 17±8	18±8	17±7	0.070
Ischaemic aetiology	228 67 (29%)	29 (30%)	67 (29%)	0.816
Atrial fibrillation/flutter	223 79 (35%)	26 (28%)	53 (41%)	0.061
Diabetes mellitus (type 1 or 2)	226 39 (17%)	16 (17%)	23 (17%)	0.470
High alcohol consumption (≥ 14/21 units/week)	206 20 (10 %)	8 (9.5%)	12 (10%)	0.706
Device therapy	228			
None	144 (63%)	59 (62 %)	85 (64%)	0.650
ICD	40 (18%)	19 (20%)	21 (16%)	0.447
Pacemaker	3 (1%)	2 (2%)	1 (1%)	0.386
CRT-P	7 (3%)	2 (2%)	5 (4%)	0.461
CRT-D	34 (15%)	14 (15%)	20 (15%)	0.905
Medication	227			
ACE-I, ARNI or ARB	183 (81%)	78 (81%)	105 (80%)	0.836
BB	153 (67%)	59 (62%)	94 (72%)	0.102
MRA	159 (70%)	69 (72%)	90 (69%)	0.606
Loop diuretics	203 (89%)	81 (84%)	122 (93%)	**0.034**
SGLT-2i	2 (1%)	1 (1%)	1 (1%)	0.789
Metolazone	5 (2%)	0	5 (4%)	0.053
Allopurinol	18 (8%)	11 (12%)	7 (5%)	0.092
Colchicin	9 (4%)	1 (1%)	8 (6%)	0.053
Inotropy	22 (10%)	8 (8%)	14 (11%)	0.566
Blood samples				
eGFR (mL/min/1.73 m^2)	214 75±25	82±26	70±24	**0.001**
Uric acid (mmol/l) (IQR)	228 0.48 (0.39–0.61)	0.38 (0.33–0.43)	0.58 (0.50–0.67)	**<0.001**
NTpro-BNP (pg/mL) (IQR)	101 2285 (983–4851)	1739 (751–4939)	2755 (1105–4698)	0.756
Resting haemodynamic parameters				
HR	36 82±22	81±25	82±20	0.774
SBP	182 102±17	102±18	101±17	0.669
DBP	181 65±11	65±12	64±11	0.507
MAP	181 77±12	78±12	77±11	0.518
CVP	223 11±5	10±5	12±6	**<0.001**
CI	225 2.4±0.7	2.5±0.7	2.3±0.6	**0.012**
PCWP	226 21±8	19±8	22±8	**0.010**
PAPi	222 2.3 ± 1.5	2.3±1.6	2.3±1.5	0.900

N defines the number of patients with obtained information in the category. Categorical variables are reported as numbers (n) and valid percentages (%) and compared using X^2 test. Continuous data are reported as mean±SD and compared using Student's t-test, except UA and NTpro-BNP, which is reported as mean (IQR) and compared using Mann-Whitney U test.
ACE-I, ACE inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; BB, beta blockers; BMI, body mass index; CI, Cardiac Index; CRT, cardiac resynchronisation therapy; CVP, central venous pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; MAP, mean arterial blood pressure; MRA, mineralocorticoid receptor antagonists, sodium-glucose cotransporter-2; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PAPI, Pulmonary Artery Pulsatility Index; PCWP, Pulmonary Capillary Wedge Pressure; SBP, systolic blood pressure; SGLT-2, sodium-glucose cotransporter 2.

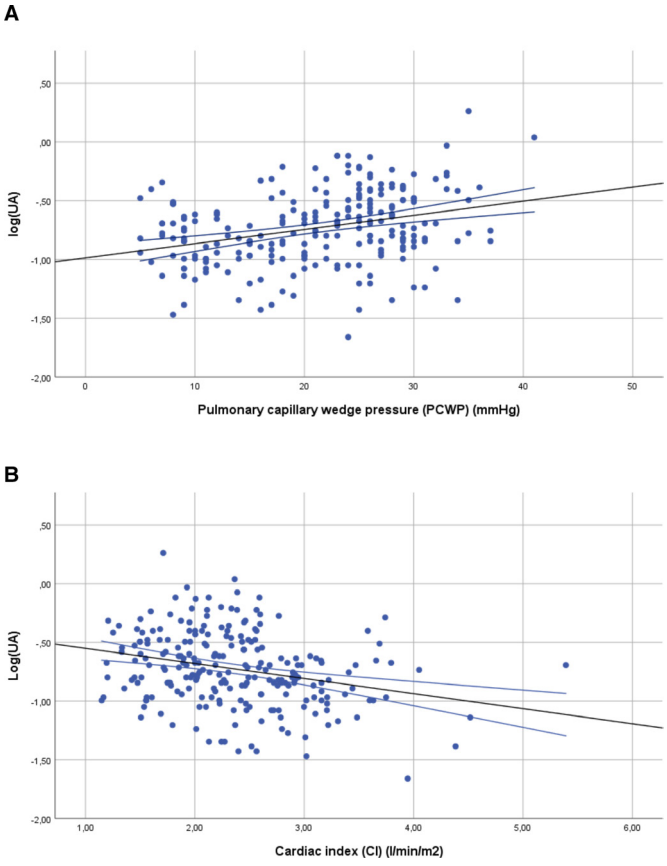

Figure 1 (A, B) The association between the natural logarithm of uric acid (UA) and pulmonary capillary wedge pressure (PCWP) and CI.

DISCUSSION

In the current study investigating the relation between central haemodynamics and UA levels, an association between UA and left sided filling pressure (PCWP) was demonstrated, as was the case for CI in multivariable regression models. We further found that UA was a strong independent predictor of all-cause mortality and the combined endpoint of all-cause mortality, left ventricular assist device, total artificial heart or heart transplantation in multivariable Cox hazard models.

Hyperuricaemia is commonly observed in HF and has been established as an independent predictor of increased risk of HF hospitalisations and death by several studies.[5–7] Not only is hyperuricaemia a predictor of poor prognosis in HF populations, studies have showed that UA predicts incident HF with both preserved[12] and reduced ejection fraction.[13–16] There also seems to be a concentration–effect relationship between UA levels and risk of incident HF, and Huang *et al* showed in a meta-analysis, that for every 1 mg/dL increase in UA, the odds of developing HF increase by 19%.[7]

In agreement, we found UA to be a strong predictor of adverse outcome in our adjusted Cox models, where a 10% increase in plasma UA was associated with a 10% increased risk of the combined endpoint and a 15% increased risk of all-cause mortality.

Although UA's prognostic value has been established in HF, the exact mechanisms behind the relation of UA levels and outcome have yet to be fully clarified. UA is mainly excreted by the kidneys and renal impairment (frequently observed in HF) as well as diuretic-induced

Table 2 Linear regression models—association between UA and haemodynamic and clinical variables

	Univariable analysis		Multivariable analysis			
Variables	**Unstandardised β (CI)**	**P value**	**Unstandardised β (CI)**	**P value**	**Tolerance**	**VIF**
CVP	1.018 (1.011 to 1.026)	**<0.001**				
PCWP	1.012 (1.007 to 1.017)	**<0.001**	1.007 (1.002 to 1.013)	**0.004**	0.837	1.194
CI	0.883 (0.827 to 0.929)	**<0.001**	0.933 (0.876 to 0.991)	**0.025**	0.828	1.208
MAP	1.000 (0.996 to 1.004	0.846				
Allopurinol	0.906 (0.778 to 0.950)	0.195				
Loop diuretics	1.140 (0.999 to 1.301)	0.052				
eGFR	0.996 (0.995 to 0.998)	**<0.001**	0.997 (0.995 to 0.998)	**<0.001**	0.966	1.035
Haemoglobin	1.019 (0.984 to 1.056)	0.291				
LVEF	0.993 (0.988 to 0.998)	**0.009**				
BMI	1.001 (1.000 to 1.017)	0.055				
Diabetes mellitus	1.001 (0.997 to 1.001)	0.587				
Male sex	1.240 (1.131 to 1.136)	**<0.001**	1.208 (1.103 to 1.322)	**<0.001**	0.977	1.023
Age	1.001 (0.998 to 1.005)	0.474				
High alcohol consumption	0.988 (0.913 to 1.069)	0.761				

The overall multivariable regression models were significant with p<0.001, R^2 0.254.
Bold values indicate statistical significans.
BMI, body mass index; CI, Cardiac Index; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; UA, uric acid; VIF, variance inflation factor.

Table 3 Cox proportional hazard models estimating the association between log1.1(uric acid) and the risk of the combined endpoint and all-cause mortality in patients with chronic heart failure

	Combined endpoint		All-cause mortality	
	HR with CI	P value	HR with CI	P value
Unadjusted Cox regression				
Uric acid**	**1.17 (1.10 to 1.24)**	***<0.001***	**1.14 (1.07 to 1.21)**	***<0.001***
Adjusted Cox regression				
Model 1				
Uric acid**	**1.12 (1.05 to 1.19)**	***<0.001***	**1.12 (1.05 to 1.20)**	***<0.001***
CI	0.76 (0.58 to 1.01)	0.056	0.92 (0.65 to 1.23)	0.628
CVP	1.00 (0.97 to 1.04)	0.814	1.06 (1.01 to 1.12)	*0.027*
PCWP	1.04 (1.01 to 1.07)	*0.003*	0.99 (0.95 to 1.02)	0.415
Model 2				
Uric acid**	**1.10 (1.03 to 1.17)**	***0.004***	**1.15 (1.06 to 1.25)**	***0.001***
CI	0.77 (0.57 to 1.04)	0.092	0.88 (0.59 to 1.13)	0.533
CVP	1.00 (0.96 to 1.04)	0.892	1.04 (0.97 to 1.11)	0.141
PCWP	1.04 (1.01 to 1.08)	*0.006*	1.00 (0.96 to 1.04)	0.937
Age	1.00 (0.98 to 1.01)	0.639	1.05 (1.02 to 1.08)	*<0.001*
eGFR	0.99 (0.98 to 1.00)	*0.008*	1.00 (0.98 to 1.01)	0.807
Use of loop diuretics	1.21 (0.65 to 2.25)	0.544	0.46 (0.21 to 0.99)	*0.047*
LVEF	0.99 (0.96 to 1.01)	0.302	1.02 (0.99 to 1.05)	0.212

Bold values indicate statistical signifcance.
*HR for a 10% increase in uric acid.
CI, Cardiac Index; CVP, central venous pressure; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure.

impaired UA excretion can lead to plasma UA accumulation. However, several studies have shown that hyperuricaemia remains a strong predictor of worse outcome even after adjusting for renal function and loop diuretics. Our study is in line with these findings, as we found that the risk of worse outcome with higher UA persisted after adjustment for renal function and diuretic use. Hyperuricaemia may also be a result of increased UA production due to upregulated XO activity.[17] XO can produce free oxygen radicals (ROS) that can lead to oxidative stress-related cardiac and vascular tissue injury and contribute to the pathophysiology of cardiac remodelling and HF.[18] However, use of UA-lowering agents by XO inhibition has been investigated and neither the OPT-CHF study (oxypurinol compared with placebo for class III-IV NYHA congestive heart failure)[19] (oxypurinol) nor the EXACT study[20](effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients) (allopurinol) showed significant benefit of pharmacological lowering of UA levels. In a small group of CHF patient, UA was lowered by Benzbromarone, a uricosuric treatment without XO inhibition, but it had no effect on either LVEF, BNP, echocardiographic measurements or NYHA class,[21] indicating that lowering UA in itself may not have a beneficial role in CHF pathophysiology. Whether there is potential effect of lowering UA still needs to be fully elucidated and more work is needed to test the clinical efficacy of pharmacological therapies lowering UA before any final conclusions can be made. In the current study, allopurinol was used in 8% of the patients, with no significant difference in the proportion of patients presenting with normal (treated) versus abnormal levels of UA. The low number of patients treated with allopurinol precludes robust analyses of the importance of uricosuric treatment in this study but adding allopurinol treatment to the Cox regression analyses did not change the association between UA and survival significantly.

Deranged haemodynamics characterise advanced HF, but sparse attention has been given to haemodynamics in research on hyperuricaemia in HF populations. Only a few, smaller studies have been published showing an association (not causality) between deranged haemodynamics and hyperuricaemia. More than a decade ago Hoeper *et al*[8] presented a short report on the relation between haemodynamics and UA levels on 36 HF patients referred for heart transplantation. They showed that UA was significantly associated to PCWP but not CVP or CI in multivariate regression analysis. Amin *et al*[9] also explored the relationship between UA and haemodynamics investigating 50 patients with a Swan-Ganz catheter and they found similar results. In our cohorts of 228 patients, we also found a strong association between UA and left sided filling pressure. However, in contrast to the

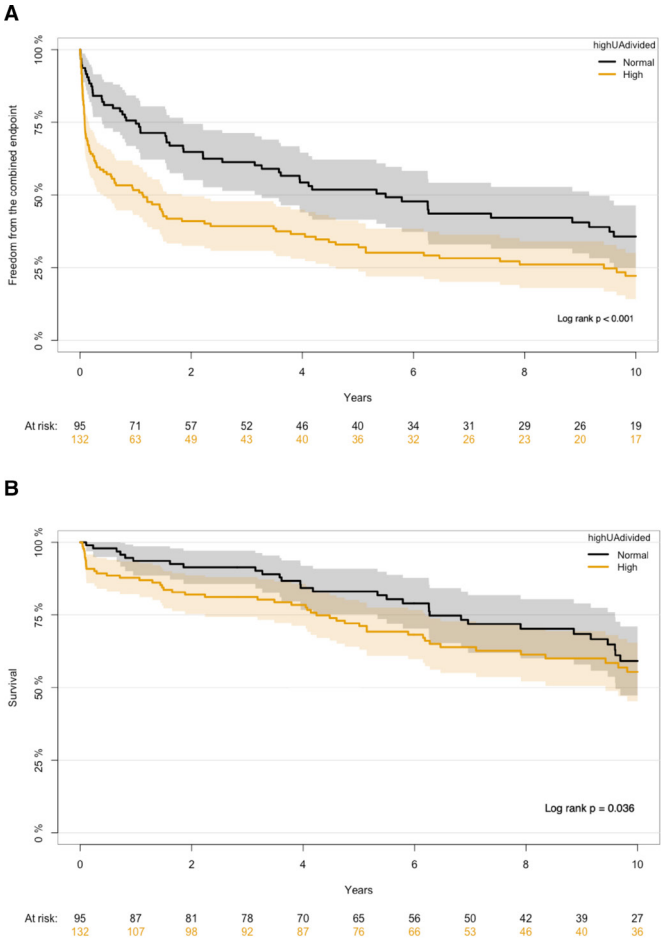

Figure 2 Kaplan-Meier curves. Normal uric acid (UA) level (black): Uric acid less or equal to 40 mmol/L (female) or 0.48 mmol/L (male). High UA (yellow) level: Uric acid more than 40 mmol/L (female) or 0.48 mmol/L (male). UA, uric acid.

two above-mentioned studies, we also found a significant association between UA and CI. The discrepancies could possibly be explained by a greater power in the current study, since we investigated a larger number of patients than in prior studies.

Whether the association is related to high filling pressure and/or inadequate perfusion leading to end-organ damage and increased cell turnover or potentially UA's proinflammatory mechanisms worsening circulatory decompensation is speculative and interpretation should be made with caution since causality still needs to be established. More work is needed investigating the link between haemodynamic derangements and hyperuricaemia to establish if there is a cause–effect relationship or if it is a question of unmeasured confounding. Future studies should test whether changes in haemodynamics is followed by changes in UA levels including data from repeated haemodynamic evaluations and UA measurements.

UA and haemodynamics are associated (in regression analysis) and while UA and haemodynamics are known to correlate with outcome independent of other factors (age, gender, etc), we cannot conclude that the two are independent of each other.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors, used to treat diabetic patients with poor glycaemic control, have proven beneficial on HF hospitalisations and cardiovascular mortality regardless of the presence of diabetes in HF patients[22] but the exact mechanism behind its cardioprotective effects is unknown. A recent study has demonstrated that dapagliflozin significantly reduce UA levels in patients with HF[23] and similar findings have been reported for empagliflozin.[24] Not only do SGLT-2 inhibitors reduce UA levels, but interestingly, it has recently been demonstrated that SGLT-2 inhibitors also have a significant effect on central haemodynamics, decreasing left sided filling pressure compared with placebo-treated controls.[25] Whether part of the treatment effect of SGLT-2 inhibitors is related to lowering left-sided filling pressure is unknown and needs to be explored further.

Study limitations

The study is limited by its retrospective design, where we cannot conclude on any cause–effect relationship. The generalisability of our results is subject to certain limitations. For instance, the study included a selected HF patient population that had an indication for RHC and was referred for evaluation at a single specialised centre, exposing the study to the possibility of selection bias.

Further, a much younger HF population than the average HF patients was investigated, thereby making these findings less generalisable to the entire HF population. Only two patients were prescribed SGLT-2 inhibitors making it impossible to evaluate the effect of SGLT-2 inhibitors in this study. No data on clinical diagnoses of gout were available so implications of repeated episodes of inflammation associated with hyperuricaemia cannot be assessed from our data.

CONCLUSION

An association between central haemodynamics and UA exist, but it is unknown if this represents a causal relationship or whether is remains a question of unmeasured confounding. Adjusting for central haemodynamics in Cox models made no significant differences and mechanisms beyond haemodynamic impairment are more likely to explain the increased adverse outcome related to hyperuricaemia.

Contributors Conception and design: FG and TD. Data extraction and data analysis: TD. All authors discussed the results and contributed to the final manuscript. All authors reviewed and approved of the final manuscript before submission. Guarantors and responsible for the overll content: FG and TD

Funding KR has received fees from Abbott, AstraZeneca, Pfizer, Novartis, Boehringer Ingelheim and Orion Pharma. FG has received research grants from the Novo Nordisk Foundation (grant no NNF20OC0060561) and reports fees from Abbott, AstraZeneca, Pfizer, Novartis, Boehringer Ingelheim, Pharmacosmos, Orion Pharma and Alnylam.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The study complies with the Declaration of Helsinki and the research protocol was approved by the local research ethics committee (3-3013-1365/1) and the Data Protection Agency (P-2020-1087). Individual patient consent was not required due to the retrospective study design.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD

Tania Deis http://orcid.org/0000-0002-1837-6538

REFERENCES

1 Lesman-Leegte I, Jaarsma T, Coyne JC, *et al*. Quality of life and depressive symptoms in the elderly: a comparison between patients with heart failure and age- and gender-matched community controls. *J Card Fail* 2009;15:17–23.
2 Stewart S, MacIntyre K, Hole DJ, *et al*. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. *Eur J Heart Fail* 2001;3:315–22.
3 Packer M. Uric acid is a biomarker of oxidative stress in the failing heart: lessons learned from trials with allopurinol and SGLT2 inhibitors. *J Card Fail* 2020;26:977–84.
4 Khan A, Shah MH, Khan S, *et al*. Serum uric acid level in the severity of congestive heart failure (CHF). *Pak J Med Sci* 2017;33:330–4.
5 Tamariz L, Harzand A, Palacio A, *et al*. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. *Congest Heart Fail* 2011;17:25–30.
6 Miao L, Guo M, Pan D, *et al*. Serum uric acid and risk of chronic heart failure: a systematic review and meta-analysis. *Front Med* 2021;8:785327.
7 Huang H, Huang B, Li Y, *et al*. Uric acid and risk of heart failure: a systematic review and meta-analysis. *Eur J Heart Fail* 2014;16:15–24.
8 Hoeper MM, Hohlfeld JM, Fabel H. Hyperuricaemia in patients with right or left heart failure. *Eur Respir J* 1999;13:682–5.
9 Amin A, Vakilian F, Maleki M. Serum uric acid levels correlate with filling pressures in systolic heart failure. *Congest Heart Fail* 2011;17:79–83.
10 Deis T, Rossing K, Gustafsson F. Aortic Pulsatility index: a new haemodynamic measure with prognostic value in advanced heart failure. *Card Fail Rev* 2022;8:e18.
11 Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–12.
12 Gu J, Fan Y-Q, Zhang H-L, *et al*. Serum uric acid is associated with incidence of heart failure with preserved ejection fraction and cardiovascular events in patients with arterial hypertension. *J Clin Hypertens* 2018;20:560–7.
13 Wu X, Jian G, Tang Y, *et al*. Asymptomatic hyperuricemia and incident congestive heart failure in elderly patients without comorbidities. *Nutr Metab Cardiovasc Dis* 2020;30:666–73.
14 Wu AH, Ghali JK, Neuberg GW, *et al*. Uric acid level and allopurinol use as risk markers of mortality and morbidity in systolic heart failure. *Am Heart J* 2010;160:928–33.
15 Krishnan E. Hyperuricemia and incident heart failure. *Circulation* 2009;2:556–62.
16 Ekundayo OJ, Dell'Italia LJ, Sanders PW, *et al*. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. *Int J Cardiol* 2010;142:279–87.
17 Filippatos GS, Ahmed MI, Gladden JD, *et al*. Hyperuricaemia, chronic kidney disease, and outcomes in heart failure: potential mechanistic insights from epidemiological data. *Eur Heart J* 2011;32:712–20.
18 Otaki Y, Watanabe T, Kinoshita D, *et al*. Association of plasma xanthine oxidoreductase activity with severity and clinical outcome in patients with chronic heart failure. *Int J Cardiol* 2017;228:151–7.
19 Hare JM, Mangal B, Brown J, *et al*. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol* 2008;51:2301–9.
20 Givertz MM, Anstrom KJ, Redfield MM, *et al*. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. *Circulation* 2015;131:1763–71.
21 Ogino K, Kato M, Furuse Y, *et al*. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail* 2010;3:73–81.
22 Zannad F, Ferreira JP, Pocock SJ, *et al*. SGLT2 inhibitors in patients with heart failure with reduced ejection fraction: a meta-analysis of the EMPEROR-Reduced and DAPA-HF trials. *Lancet* 2020;396:819–29.
23 McDowell K, Welsh P, Docherty KF, *et al*. Dapagliflozin reduces uric acid concentration, an independent predictor of adverse outcomes in DAPA-HF. *Eur J Heart Fail* 2022;24:1066–76.
24 Jensen J, Omar M, Kistorp C, *et al*. Effects of empagliflozin on estimated extracellular volume, estimated plasma volume, and measured glomerular filtration rate in patients with heart failure (Empire HF renal): a prespecified substudy of a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2021;9:106–16.
25 Omar M, Jensen J, Frederiksen PH, *et al*. Effect of Empagliflozin on Hemodynamics in Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol* 2020;76:2740–51.

Supplementary: Cox proportional hazard models estimating the association between log1.1(uric acid) and the risk of the combined endpoint and all-cause mortality in patients with chronic heart failure

	Combined endpoint		All-cause mortality	
	Hazard Ratio (HR) with confidence interval (CI)	P-value	Hazard Ratio (HR) with confidence interval (CI)	P-value
Adjusted Cox regression				
Uric acid*	**1.10 (1.03 – 1.17)**	***0.003***	**1.16 (1.06 – 1.26)**	***0.001***
CI	0.77 (0.57 – 1.04)	0.086	0.85 (0.57 – 1.28)	0.436
CVP	1.00 (0.96 – 1.04)	0.825	1.04 (0.98 – 1.10)	0.251
PCWP	1.04 (1.01 – 1.08)	*0.005*	1.00 (0.96 – 1.04)	0.943
Age	1.00 (0.98 – 1.01)	0.584	1.05 (1.02 – 1.08)	*<0.001*
eGFR	0.99 (0.98 – 1.00)	*0.008*	1.00 (0.99 – 1.01)	0.890
Use of loop diuretics	0.84 (0.45 – 1.56)	0.568	2.24 (1.04 – 4.86)	*0.041*
LVEF	0.99 (0.96 – 1.01)	0.309	1.02 (0.99 – 1.05)	0.175
Use of allopurinol	0.78 (0.48 – 1.35)	0.367	0.81 (0.28 – 1.22)	0.152

*HR for a 10% increase in uric acid
CI: Cardiac Index, CVP: Central Venous Pressure, PCWP: Pulmonary Capillary Wedge Pressure, eGFR: estimated Glomerular Filtration Rate, LVEF: Left Ventricular Ejection Fraction.