ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/cardiosci.2023-96729

Serum Uric Acid is Associated with Right Heart Failure in Patients with Heart Failure with Reduced Ejection Fraction: A Cross-Sectional Study

Serum Ürik Asit Seviyesi, Düşük Ejeksiyon Fraksiyonlu Kalp Yetersizliği Hastalarında Sağ Kalp Yetersizliği ile İlişkilidir: Kesitsel Çalışma

Rengin Çetin GÜVENÇ[a], Abdurrahman NASER[b]

[a]Department of Cardiology, İstanbul Okan University Faculty of Medicine, İstanbul, Türkiye
[b]Clinic of Cardiology, VM Medical Park Pendik Hospital, İstanbul, Türkiye

ABSTRACT Objective: Serum uric acid (UA), which is the final product of purine metabolism, is a predictor of left-sided heart failure (HF), as well as being a marker of outcomes and survival in patients with heart failure with reduced ejection fraction (HFrEF). Right-sided HF may or may not accompany HFrEF, but is associated with worse prognosis and increased morbidity and mortality when present. All available data for the association between RHF and UA are derived from patients with pulmonary arterial hypertension, and virtually no data is available for patients with HFrEF. Our aim was to understand the relationships between UA, echocardiographic markers of right ventricular systolic function and RHF in patients with HFrEF. **Material and Methods:** A total of 45 patients with an ejection fraction <40% and signs of HF were included. Patients were divided into tertiles according to serum UA concentration. RHF was defined according to the modified Interagency Registry for Mechanically Assisted Circulatory Support criteria. **Results:** Compared to patients within the lowest UA tertile, patients within the 3rd tertile had a significantly higher incidence of RHF (50.0% vs. 0.0%, Bonferroni-corrected p=0.009) and a significantly lower tricuspid annular plane systolic excursion (20.5±4.4 vs. 16.1±4.4, p=0.02). After adjusting for relevant clinical, demographic, laboratory and echocardiographic variables, serum UA remained a significant predictor of RHF [odds ratio: 2.89, 95% confidence interval (CI): 1.21-6.91, p=0.017]. For serum UA, the c-statistic for determination of RHF was 0.83 (95% CI: 0.71-0.96). **Conclusion:** Serum UA is associated with the occurrence of RHF in patients with HFrEF.

Keywords: Heart failure with reduced ejection fraction; right heart failure; echocardiography; uric acid

ÖZET Amaç: Pürin metabolizmasının nihai ürünü olan ürik asit (ÜA), sol taraflı kalp yetersizliğinin bir prediktörü ve düşük ejeksiyon fraksiyonlu kalp yetersizliğinde (DEFKY) sonlanım ve sağkalımın bir göstergesidir. Sağ taraflı kalp yetersizliği (SğKY) sol kalp yetersizliği ile beraber görülebilir veya görülmeyebilir, ancak görüldüğü taktirde kötü prognoz ve artmış morbidite ve mortalite ile ilişkilidir. SğKY ve ÜA arasındaki ilişkiyi araştıran çalışmaların tamamı pulmoner hipertansiyonlu hastalar üzerinde yapılmıştır ve DEFKY'li hasta grubunda olası bir ilişkiyi gösteren veri yoktur. Bu çalışmada amacımız, DEF-KY'li hastalarda serum ÜA, sağ ventrikül fonksiyonunun ekokardiyografik göstergeleri ve SğKY arasındaki ilişki araştırılmaktır. **Gereç ve Yöntemler:** Ejeksiyon fraksiyonunun 40%'ın altında olduğu ve kalp yetersizliği bulguları olan 45 DEFKY hastası çalışmaya dahil edilmiştir. Hastalar serum ÜA seviyelerine göre üç eşit gruba ayrılmışlardır. SğKY'nin tanımlanması için, modifiye edilmiş "Interagency Registry for Mechanically Assisted Circulatory Support" kriterleri kullanılmıştır. **Bulgular:** En düşük ÜA grubu ile karşılaştırıldığında, 3. gruptaki hastalarsa SğKY sıklığı anlamlı olarak daha fazla bulunmuştur (50.0% - 0.0%, Bonferroni-düzeltilmiş p=0.009) ve aynı grupta triküspit düzlem sistolik hareketi anlamlı olarak azdır (20.5 ± 4.4 - 16.1 ± 4.4, p=0.02). Klinik, demografik, laboratuvar ve ekokardiyografik değişkenler istatistiksel olarak düzeltildikten sonra dahi, serum ÜA düzeyi SğKY için istatistiksel olarak anlamlı bir öngördürücü olmuştur (OO:2.89, 95%GA:1.21 – 6.91, p=0.017). SğKY'nin belirlenmesi için serum ÜA'nın c-istatistiği 0.83'tür (95%GA: 0.71 – 0.96). **Sonuç:** Serum ÜA, DEFKY hastalarında SğKY ile ilişkili bulunmuştur.

Anahtar Kelimeler: Düşük ejeksiyon fraksiyonlu kalp yetersizliği; sağ kalp yetersizliği; ekokardiyografi; ürik asit

Correspondence: Rengin Çetin GÜVENÇ
Department of Cardiology, İstanbul Okan University Faculty of Medicine, İstanbul, Türkiye
E-mail: rcguvenc1@gmail.com

Peer review under responsibility of Turkiye Klinikleri Cardiovascular Sciences.

Received: 11 Apr 2023 ***Received in revised form:*** 30 Aug 2023 ***Accepted:*** 07 Sep 2023 ***Available online:*** 15 Sep 2023

2146-9032 / Copyright © 2023 by Türkiye Klinikleri. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Uric acid (UA) is the end product of purine metabolism and is formed when xanthine is oxidized to UA by xanthine oxidase (XO), an enzyme that also plays an important role in the formation of superoxide and peroxynitrite radicals.[1,2] A wealth of evidence suggests that increased UA is associated with an increased risk of cardiovascular diseases, particularly heart failure (HF), poor left ventricular function, worse outcomes and increased mortality in patients with established HF.[3-7] It has been suggested that increased blood UA serves as a biomarker for increased XO activity and thus over-production of harmful free radicals such as superoxide anion or peroxynitrites, providing a causal basis for the association of UA with poor prognosis in HF.[8,9]

Right ventricular dysfunction (RVD) and right heart failure (RHF) are common in patients with HF and both are important determinants of prognosis and survival.[10] Given that there is a strong association between UA and left ventricular function, a reasonable assumption would be that there should also be a relationship between UA and right ventricular (RV) function since the harmful effects of an increased XO activity should affect the myocardium globally. However, save for a few studies on patients with pulmonary hypertension, there is surprisingly scarce data on the link between high UA and right ventricular failure/right ventricular hypertrophy and virtually no data exists for patients with HF.

As such, the purpose of this present analysis was to study the associations between UA, RVD and RHF, and to understand the predictive ability of UA for RHF in patients with HF.

MATERIAL AND METHODS

For the present analysis, data from a previous study that collected data on patients with HF with reduced ejection fraction were used.[11] Briefly, HF patients with a left ventricular ejection fraction <40% and over 18 years who admitted to the cardiology outpatient clinics in the study center were consecutively included to this former study. For this particular analysis, patients with acutely decompensated HF at the time of enrolment, patients with de novo HF, patients on allopurinol or febuxostat and those with pulmonary hypertension secondary to an etiology other than left ventricular dysfunction were excluded. Out of the initial 55 patients, 10 were excluded due to aforementioned criteria and the final analysis included 45 patients. Figure 1 summarizes study design and workflow. Patients' demographic and clinical data were collected by direct interviews or by using the institutional electronic medical database. All patients underwent a detailed physical examination and transthoracic echocardiography following enrolment to the study.

The study was conducted according to 1975 Declaration of Helsinki and its subsequent revisions, and all patients gave their informed consent prior to enrolment to the study. The study was approved by a İstinye University Clinical Research Ethics Committee (date: June 23, 2021, no: (2017-KAEK-120)/2/2021.G-97). The data was collected as part of another study, so no further ethics committee approval was sought for the present analysis.

ECHOCARDIOGRAPHIC EXAMINATION

All echocardiographic examinations were done using an echocardiography platform (Affiniti 50, Philips Healthcare, Andover MA) equipped with a S4-2 sector array transducer. All measurements were done according to the relevant international guidelines. For patients in sinus rhythm, 3 consecutive cycles were recorded and an average of 3 measurements was accepted as the final result. For patients in atrial fibrillation, an average of ten measurements was used. RV minor and major dimensions, as well as RV end-diastolic and end-systolic diameters were measured from the apical 4-chamber view. RV fractional are change (RVFAC) is calculated by subtracting the RV end-diastolic area from the RV end-systolic area and dividing the remaining number to RV end-diastolic area. Tricuspid annular plane systolic excursion (TAPSE) is measured using M-mode by placing the cursor to the lateral tricuspid annulus. Likewise, peak velocity of the systolic motion of the lateral tricuspid annulus (St) was measured by placing the pulsed-wave Doppler cursor in the tissue-Doppler imaging mode. Estimated systolic pulmonary artery pressure (sPAP) was calculated using the modified Bernoulli equation and the right atrial pressure was estimated

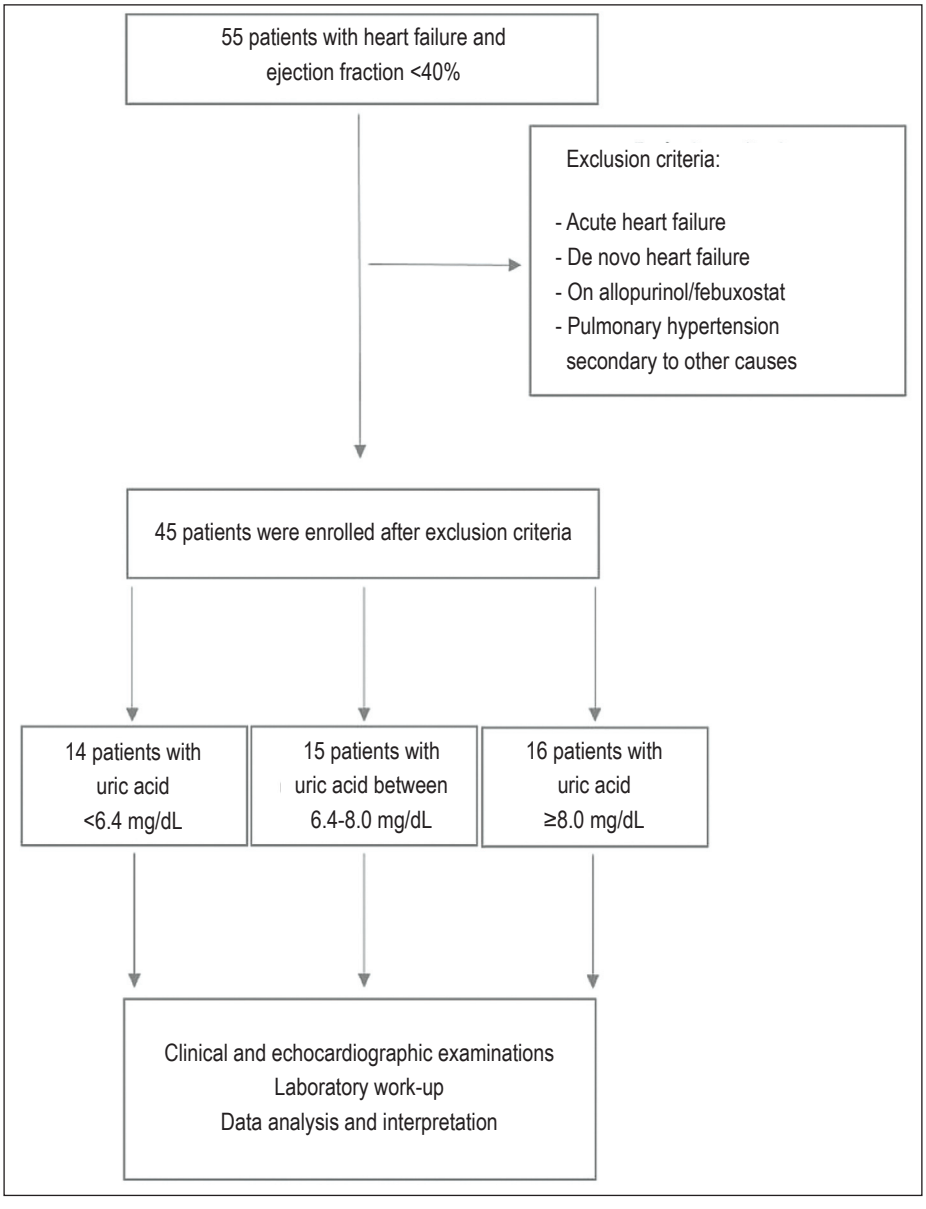

FIGURE 1: Flow chart summarizing the study design and analyses.

using the inferior vena cava diameters recorded at rest and during the sniff test.

DEFINITIONS

A modified version of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria, which we have proposed in a previous study, was used to define RHF for the purposes of the present study due to a lack of other standardized criteria for the definition of RHF.[11,12] Per this definition, a patient was accepted to have RHF if both criteria were present:

i) There is examination evidence or echocardiographic findings compatible with elevated central venous pressure,

ii) Clinical or laboratory evidence compatible with elevated central venous pressure. Briefly, clinical and examinations manifestations of elevated central venous pressure included jugular venous dis-

tention, 2+ or more bilateral pretibial edema, ascites or palpable hepatomegaly, while laboratory manifestations were total bilirubin ≥2.0 mg/dL or creatinine ≥2.0 mg/dL in the absence of an alternative explanation. A dilated inferior vena cava (≥2.1 cm) that was not compressible with inspiration was considered as echocardiographic evidence for elevated central venous pressure. Individual echocardiographic parameters (TAPSE, St, and RVFAC) were used to determine RV systolic function.

LABORATORY ANALYSIS

Blood samples were collected on the morning of echocardiographic examination, and a 20-gauze needle was used to withdraw blood while the patients was in the sitting position. Overnight fasting was not mandatory before sample collection. All collected samples were transferred to the institutional laboratory within 30 minutes of collection. Serum UA concentration was measured with colorimetric method using an autoanalyzer (Abbott Architect Plus ci8200, Abbott Labs, Chicago, USA) and compatible reagents (Archem Health Ind, Türkiye). All other measurements were done according to conventional methods.

STATISTICAL ANALYSIS

Continuous variables were presented as mean±standard deviation or as median and interquartile range, depending on the patterns of distribution. Patterns of distribution were analyzed using visual inspection of the Q-Q plots and with using Shapiro-Wilk test. Categorical variables were given as percentages. For continuous variables, differences between tertiles were analyzed with one-way analysis of variance or with Kruskal-Wallis tests. Levene test was used to check for the equality of variances. Post-hoc analyses were done using Tukey's HSD, Games-Howell or Dwass-Steel-Critchlow-Fligner tests, depending on the patterns of distribution and equality of variances. Univariate logistic regression models were used to determine demographic, clinical, laboratory and echocardiographic predictors of RHF and parameters with a p value ≤0.10 on univariate analyses were included to multivariate models. Three multivariate logistic regression models were constructed to determine independent predictors of RHF. First model included demographic and clinical parameters, while the second one included laboratory parameters in addition to parameters included in the first model and the third one included echocardiographic parameters on top of the variables included in the second model. Laboratory and echocardiographic parameters that were used to define RHF were excluded from models. A backwards selection criterion was used to determine predictors of RHF in all three logistic regression models. Finally, a receiver-operator curve was drawn to calculate the predictive value of UA to determine RHF, and to find the threshold value with the highest accuracy to detect RHF. For all comparisons, a two-sided p value of less than 0.05 was accepted as statistically significant, and Bonferroni corrections were done for necessary comparisons. All statistical analyses were done with Jamovi 2.2 for Windows (The Jamovi project 2021, retrieved from https://www.jamovi.org) and SPSS 25.0 (IBM Inc., USA) statistical packages.

RESULTS

Mean age of the study sample was 63.2±14.2 years, and 12 (26.7%) patients were female. Out of 45 patients, 28 (62.2%) patients had either NYHA class 3 or 4 HF, 35 (77.8%) patients had ischemic cardiomyopathy and mean left ventricular ejection fraction was 28.6%±6.9%. A diagnosis of RHF was established in 12 (26.7%) patients. Mean UA concentration was 7.37±2.11 mg/dL. Patients were divided into three tertiles for analyses. Patients within the first tertile (n=14) had a UA concentration <6.4 mg/dL, while those within the second tertile (n=15) had an UA concentration ranging from 6.4 mg/dL to 8.0 mg/dL and patients within the third tertile (n=16) had an UA concentration ≥8.0 mg/dL.

Table 1 summarizes clinical and laboratory characteristics of patients within the UA tertiles. Compared to patients within the first tertile, those within the third tertile had lower blood pressure, a higher incidence of chronic kidney disease, had worse functional class and had a higher mean N-terminal pro B-type natriuretic peptide (NT-proBNP) concentration. Patients within the highest UA tertile also had a

TABLE 1: Demographic, clinical and laboratory characteristics of the patients within the uric acid tertiles.

Characteristic	1st tertile (n=14)	2nd tertile (n=15)	3rd tertile (n=16)	p value
Age (years)	65.4±14.9	63.1±15.8	61.4±12.6	0.75
Gender (female %)	5 (35.7%)	2 (13.3%)	5 (31.3%)	0.38
Body mass index (kg/m^2)	27.8±4.3	29.3±2.8*	27.6±3.7	0.39
Systolic BP (mmHg)	132.0±16.3	116.0±13.9	118.0±22.2	0.04
Diastolic BP (mmHg)	80.0±7.1	73.1±8.1	69.8±10.7**	0.01
Heart rate (beats/min)	68.9±18.0	75.5±11.5	80.3±12.4	0.10
Smoking	1 (7.1%)	4 (26.7%)	2 (12.5%)	0.35
Diabetes	8 (57.1%)	7 (46.7%)	7 (43.8%)	0.75
Chronic kidney disease	0 (0.0%)	3 (20%)	6 (37.5%)	0.04
NYHA class				
- Class I-II	9 (64.3%)	4 (26.7%)	4 (33.3%)	0.048
- Class III-IV	5 (35.7%)	11 (73.3%)	12 (66.7%)	
Duration of heart failure (years)	3.0 (2.1-4.0)	4.0 (2.5-6.5)	5.0 (2.8-6.0)	0.50
Aetiology				
- Ischemic	10 (71.4%)	14 (93.3%)	11 (68.8%)	0.21
- Dilated	4 (28.6%)	1 (6.7%)	5 (31.2%)	
Rhythm				
- Sinus/pacemaker	14 (92.9%)	12 (80.0%)	13 (81.2%)	0.67
- Atrial fibrillation	1 (7.1%)	3 (20.0%)	3 (18.8%)	
Medications				
- ACEi/ARBs	11 (78.7%)	9 (60.0%)	8 (50.0%)	0.27
- Sacubitril/valsartan	3 (21.4%)	3 (20.0%)	8 (50.0%)	0.06
- β-blockers	13 (92.9%)	15 (100.0%)	15 (93.8%)	0.76
- MRAs	7 (50.0%)	7 (46.7%)	11 (68.8%)	0.41
- Furosemide	6 (42.9%)	10 (66.7%)	10 (62.5%)	0.39
Hemoglobin (g/dL)	12.4±1.9	13.0±2.2	12.4±2.0	0.71
White blood cell count (10^3/mm^3)	7.5±1.7	7.3±1.7	7.4±2.2	0.96
Creatinine (mg/dL)	0.95±0.27	1.25±0.45	1.34±0.41*	0.02
Albumin (g/dL)	3.94±0.58	4.23±0.54	3.81±0.46	0.11
Total bilirubin (mg/dL)	0.62±0.25	0.81±0.42	1.21±0.88	0.09
Alanine aminotransferase (U/L)	19.0 (16.0-23.0)	22.0 (13.3-24.8)	19.5 (15.3-29.3)	0.95
Aspartate aminotransferase (U/L)	21.0 (15.0-28.0)	22.0 (15.8-33.0)	23.0 (18.3-24.0)	0.76
Uric acid (mg/dL)	5.1 (4.8-5.7)	7.3 (7.0-7.6)	9.0 (8.1-9.9)	<0.001
N-terminal pro-BNP (pg/mL)	895.0 (458.0-2936.0)	2524.0 (326.0-4956.0)	3401.0 (2247.0-5663.0)*	0.03

*p<0.05; **p<0.01; BP: Blood pressure; NYHA: New York Heart Association; ACEi: Angiotensin converting enzyme inhibitors; ARB: angiotensin receptor blocker; MRA: Mineralocorticoid receptor blocker; BNP: B-type natriuretic peptide.

more pronounced reduction in left ventricular ejection fraction, as well as a higher mean mitral E/mean e' ratio and lower TAPSE as compared to those with the first tertile (Table 2). Notably, there were no significant differences between groups in terms of peak tricuspid regurgitation velocity or estimated systolic pulmonary artery pressure.

Right HF was seen in none of the patients within the first tertile, while 26.6% (n=4) patients within the second and 50% (n=8) patients within the third tertile had RHF (p=0.007). Compared to patients within the first tertile, patients within the third tertile had a statistically significant increase in the incidence of RHF (p=0.009) (Figure 2). While RHF was also numerically more common in patients within the second tertile, this finding was not statistically significant (p=0.30).

Table 3 summarizes the results of the prediction models. In Model 1, which encompasses demographic and clinical univariate predictors of RHF,

TABLE 2: Echocardiographic characteristics of patients within the uric acid tertiles.

Characteristic	1st tertile (n=14)	2nd tertile (n=15)	3rd tertile (n=16)	p value
LV end-diastolic volume (mL)	211.0±39.9	223.0±45.4	275.0±95.3*	0.03
LV end-systolic volume (mL)	144.0±32.2	160.0±44.5	209.0±81.7*	0.01
LV ejection fraction (%)	31.7±6.3	29.2±7.2	25.3±6.0*	0.04
Left atrial volume (mL)	120.0±20.9	123.0±26.3	142.0±54.6	0.60
Degree of mitral regurgitation				
- Mild-moderate	14 (100.0%)	14 (93.3%)	13 (81.2%)	0.31
- Severe	0 (0.0%)	1 (6.7%)	3 (18.8%)	
Mitral E wave (cm/s)	80.5±23.8	92.5±24.5	97.4±21.1	0.14
Mitral A wave (cm/s)	74.7±22.9	65.7±29.4	53.6±31.8	0.18
Mitral E/A ratio	1.07 (0.81-1.39)	1.30 (0.92-1.73)	2.02 (1.28-3.41)*	0.04
Lateral e' wave (cm/s)	6.9±2.3	7.5±2.1	7.0±2.3	0.75
Septal e' wave (cm/s)	5.1±1.5	5.1±1.7	4.6±1.3	0.54
E/mean e' ratio	14.1±4.5	16.1±6.4	18.2±6.5	0.17
RV short-axis diameter (mm)	39.7±4.8	44.9±5.2*	42.7±5.9	0.04
RV long-axis diameter (mm)	78.4±7.7	83.7±8.9	84.4±7.5	0.11
TR velocity (m/s)	2.99±0.22	3.14±0.42	3.20±0.34	0.24
Inferior vena cava diameter (mm)	20.6±4.1	22.8±5.3	22.3±6.8	0.53
Estimated systolic PAP (mmHg)	36.4±5.4	41.9±12.5	44.1±9.9	0.10
Degree of tricuspid regurgitation				
- Mild-moderate	12 (85.7%)	9 (60.0%)	11 (68.7%)	0.32
- Severe	2 (14.3%)	6 (40.0%)	5 (31.3%)	
Tricuspid E/A ratio	1.26±0.33	1.29±0.58	1.16±0.57	0.45
Tricuspid E/lateral e' ratio	9.0±2.9	10.8±5.8	10.3±3.7	0.41
Tricuspid annular systolic excursion (mm)	20.5±4.4	17.3±4.5	16.1±4.4*	0.02
Tricuspid s' velocity (cm/s)	12.8±2.4	10.6±3.6	10.2±3.3	0.06
RV fractional area change (%)	34.7±4.8	28.5±10.5	29.2±8.9	0.11
Right heart failure (%)	0 (0.0%)	4 (26.6%)	8 (50.0%)**	0.007

*p<0.05; **p<0.01; LV: Left ventricle; RV: Right ventricle; TR: Tricuspid regurgitation; PAP: Pulmonary artery pressure.

only systolic blood pressure and the presence of chronic renal disease were significant predictors of RHF. When laboratory results, including UA, were added to the parameters in Model 1; only UA and NT-proBNP predicted the occurrence of RHF while clinical variables were not associated with RHF. The association between UA and RHF remained statistically significant after the addition of echocardiographic variables, including parameters associated with RV systolic function (Model 3). Interestingly, the only echocardiographic parameter that showed a statistically significant association with RHF was the presence of severe tricuspid regurgitation, and conventional parameters of RV systolic function or RV afterload were not associated with RHF (Table 3).

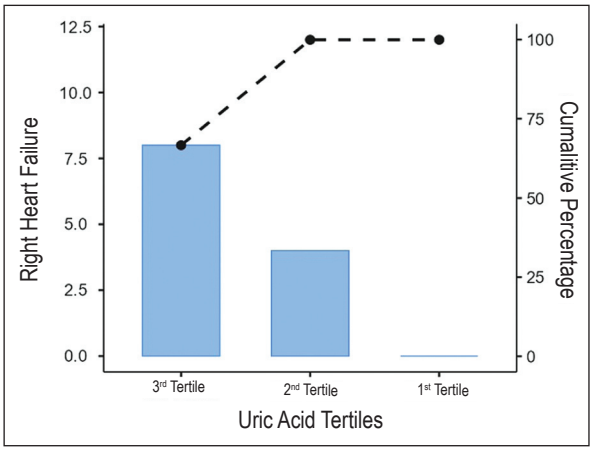

FIGURE 2: Pareto chart summarizing the incidence of right heart failure in the study sample. Bars show the number of cases with right heart failure in each tertile, and the dashed line shows the cumulative incidence of right heart failure in the study sample.

TABLE 3: Univariate and multivariate predictors of right heart failure in the study sample. Three different models were used for determining the independent predictors, with Model 1 included demographic and clinical variables, Model 2 included laboratory variables in addition to the variables introduced in Model 1 and Model 3 including echocardiographic variables on top of the variables introduced in Model 2.

	Univariate analysis		Multivariate analysis	
Characteristic	**OR (95%CI)**	**p value**	**OR (95%CI)**	**p value**
Model 1 (demographic and clinical variables)				
Systolic BP (per mmHg increase)	0.96 (0.92-0.99)	0.045	0.95 (0.91-0.99)	0.03
Diastolic BP (per mmHg increase)	0.93 (0.86-0.99)	0.047		
Chronic kidney disease (presence of)	10.00 (1.94-51.54)	0.006	13.69 (2.11-88.98)	0.006
Model 2 (clinical, demographic and laboratory variables)				
Systolic BP (per mmHg increase)	0.96 (0.92-0.99)	0.045		
Diastolic BP (per mmHg increase)	0.93 (0.86-0.99)	0.047		
Chronic kidney disease (presence of)	10.00 (1.94-51.54)	0.006		
N-terminal proBNP (per 100 pg/ml increase)	1.03 (1.01-1.05)	0.015	1.03 (1.01-1.05)	0.015
Sodium (per 1 mEq/L increase)	0.76 (0.62-0.93)	0.008		
Uric acid (per mg/dL increase)	2.13 (1.22-0.73)	0.006	2.23 (1.16-4.29)	0.016
Model 3 (clinical, demographic, laboratory and echocardiographic variables)				
Systolic BP (per mmHg increase)	0.96 (0.92-0.99)	0.045		
Diastolic BP (per mmHg increase)	0.93 (0.86-0.99)	0.047		
Chronic kidney disease (presence of)	10.00 (1.94-51.54)	0.006		
N-terminal proBNP (per 100 pg/mL increase)	1.03 (1.01-1.05)	0.015	1.03 (1.01-1.05)	0.013
Sodium (per mEq/L increase)	0.76 (0.62-0.93)	0.008		
Uric acid (per mg/dL increase)	2.13 (1.22-0.73)	0.006	2.89 (1.21-6.91)	0.017
Mitral E/e' ratio (per one unit increase)	1.16 (1.02-1.31)	0.03		
Right ventricular short axis diameter (per mm increase)	6.12 (1.35-27.70)	0.02		
Tricuspid regurgitation velocity (per m/s increase)	5.87 (0.79-43.68)	0.08		
Tricuspid regurgitation (severe)	6.30 (1.48-26.83)	0.01	12.62 (1.29-123.52)	0.029
TAPSE (per mm increase)	0.76 (0.62-0.92)	0.005		
Tricuspid s' velocity (per cm/s increase)	0.68 (0.51-0.89)	0.006		

OR: Odds ratio; CI: Confidence interval; BP: Blood pressure; BNP: B-type natriuretic peptide; TAPSE: Tricuspid annular plane systolic excursion.

Serum UA concentration had an overall 73.3% accuracy to predict RHF, with a sensitivity of 91.7% and a specificity of 67.0% for a threshold value of 7.48 mg/dL. Area under the receiver-operator curve was 0.83 (95% confidence interval: 0.71-0.96) (Figure 3).

DISCUSSION

Serum UA concentration is a strong predictor of the occurrence of HF, as well as being a determinant of outcomes in patients with established HF. To the best of our knowledge, present analysis represents the first study that associates UA with RHF and RV systolic function in patients with HF. Indeed, UA appeared to be a better determinant of RHF compared to echocardiographic indicators of RV afterload or systolic performance.

Serum UA concentration has long been associated with outcomes and survival in patients with HF.[6,7,13,14] The exact nature of this association is unclear, but it has been suggested that an elevated UA concentration reflects an increase in XO activity. XO system not only breaks down purines into UA but is also an important source of free radicals, which are detrimental to myocardial functioning and cell survival. However, this hypothesis was recently scrutinized since randomized trials with oxypurinol, allopurinol and febuxostat did not show an improvement in outcomes in patients treated with either agent.[15-17] Indeed, in case of the more selective XO

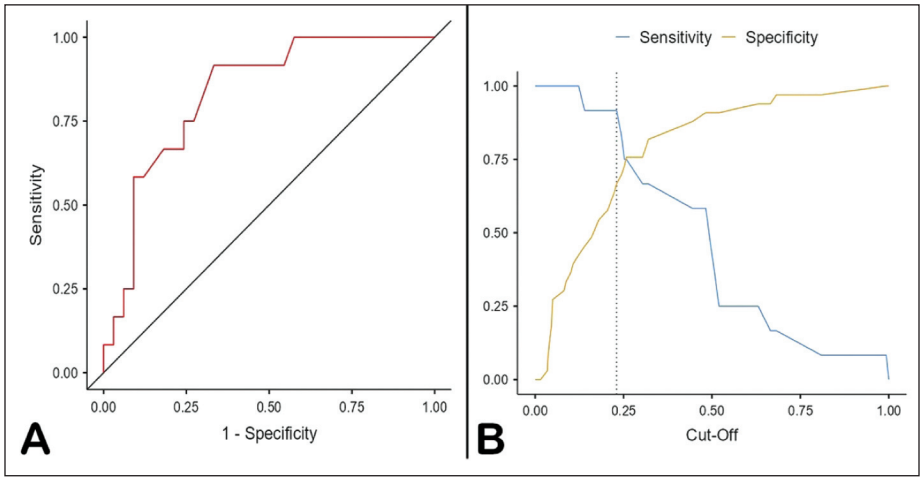

FIGURE 3: Receiver-operator curve (**panel A**) and the cut-off plot (**panel B**) showing the accuracy of serum uric acid concentration for determining right heart failure in patients with heart failure with reduced ejection fraction. The cut-off value seen in panel B (dashed vertical line) was set to 7.48 mg/dL.

inhibitor febuxostat, there was an increase in cardiovascular deaths as compared to patients treated with allopurinol.[17] It has been suggested the activation of XO may be necessary in patients with HF as UA has antioxidant properties, similar to vitamin C (ascorbic acid) and may exert cytoprotective effects, and it has been suggested that more effective inhibition of XO with febuxostat leads to a loss of this cytoprotective effects mediated by UA.[18] Moreover, XO may act as a source of nitric oxide (NO) in inflammatory states, which is essential for myocardial function and cellular survival.[18,19] Thus, increased serum UA concentration and/or elevated XO activity may act as a biomarker of outcomes, similar to B-type natriuretic peptide concentration, rather than being a casual factor for myocardial damage or dysfunction.

Present findings suggest that an elevated serum concentration UA is not only indicative of poor outcomes, but is also associated with RHF in patients with HF. These findings may partly explain the link between UA and poor outcomes in HF, given that RHF per se is a marker of repeat rehospitalizations and reduced survival in patients with HF.[20] However, based on the aforementioned findings, at this time it is not reasonable to consider a causal link between UA and RV function, or to suggest that lowering UA might be a therapeutic strategy to prevent or ameliorate RHF. Instead, UA appears as an accurate biomarker of RV failure and the elevated serum concentration of UA in patients with RHF probably reflects the heightened level of oxidative stress in such patients, which might be causative of RV dysfunction or might simply reflect a more advanced disease state.

Transthoracic echocardiography is a key method to assess the failing RV, and various studies have demonstrated the prognostic impact of echocardiographic parameters that reflect RV systolic function, such as TAPSE, St or RV fractional area change, in patients with HF. While a poor RV contractility is undoubtedly associated with RHF, it should be emphasized that RHF is a clinical concept that does not equate to RV systolic dysfunction.[10,21] As such, patients with no overt RV systolic dysfunction may develop RHF in the presence of afterload mismatch or severe tricuspid regurgitation, while others with RV systolic dysfunction may not have RHF in the absence of volume overload.[10] Present findings suggest that although echocardiographic parameters of RV systolic performance were indeed associated with RHF, biomarkers such as UA or NT-proBNP had a more robust association with RHF as compared to the echocardiographic variables. While this finding may in part be explained by the relative inaccuracy of

echocardiography to characterize RV systolic performance, we consider that it largely shows the ability of biomarkers to reflect the abnormal metabolic and hemodynamic conditions associated with RHF, regardless of the RV systolic performance.

A caveat in interpreting the UA concentration in patients with HF is the concomitant use of diuretics, as diuretics reduce UA excretion from the tubules.[22] Patients with more advanced HF, especially patients with RHF, tend to use larger doses of diuretics and the latter itself is associated with a poorer prognosis. Thus, in some patients an elevated UA may simply reflect the large amounts of diuretics used by these patients.[6,23] Previous studies have found that the prognostic implications of UA persisted after adjusting the data for the diuretic dose.[4,6] Similarly, in the present analysis we did not see a difference across UA tertiles in terms of diuretic use and diuretics were not a predictor of RHF, thus suggesting that the relationship between UA and RHF was largely independent of concomitant diuretic use. However, a possible interaction cannot be safely ruled out since the sample size was relatively small and no adjustments were made for diuretic dosing. As such, in the absence of more robust data, it remains possible that diuretics may partly be responsible for the observed association between UA and RHF.

The present analysis has several advantages and disadvantages. Instead of relying on clinical judgment, we used a structured definition that incorporated clinical, laboratory and imaging markers to define RHF, thus increasing the reliability of the results. The association between UA and RHF remained robust after adjusting for a multitude of demographic, clinical, laboratory and echocardiographic variables, including parameters used to quantify RV systolic function, thus increasing the overall reliability of the present results. Nonetheless, it should be emphasized that no adjustments were made for diuretic dose. Present results were obtained from a single center using retrospective data and with a limited number of HF patients, thus restricting the statistical power of the study and introducing possible biases inherent to all retrospective analyses. While this latter constitutes the main limitation of the present study, a post-hoc analysis showed that the study had a power of 0.83 with a 95% probability of rejecting the null hypothesis. Nonetheless, present results should be considered as hypothesis-generating rather than definitive until more data emerges. The results should not be generalized to patients with HF and mildly reduced or preserved ejection fraction, or to HF patients that are on XO inhibitors.

CONCLUSION

Patients with reduced ejection fraction HF and an elevated UA concentration were more likely to have RV dilatation, RV systolic dysfunction and RHF. Moreover, serum UA concentration appears as an accurate determinant of RHF, and an elevated UA concentration in a patient with HF and reduced ejection fraction could be interpreted as an indicator of RHF in the absence of any other apparent causes. While serum UA appears as a promising biomarker of RHF, its predictive accuracy for the development of future RHF or its usefulness in other phenotypes of HF (i.e. preserved or mildly reduced ejection fraction) is uncertain, emphasizing the need for further data addressing these topics.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Design:*** *Rengin Çetin Güvenç;* ***Control/Supervision:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Data Collection and/or Processing:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Analysis and/or Interpretation:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Literature Review:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Writing the Article:*** *Rengin Çetin Güvenç;* ***Critical Review:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***References and Fundings:*** *Rengin Çetin Güvenç, Abdurrahman Naser;* ***Materials:*** *Rengin Çetin Güvenç, Abdurrahman Naser.*

REFERENCES

1. Nishino T, Okamoto K, Eger BT, Pai EF, Nishino T. Mammalian xanthine oxidoreductase - mechanism of transition from xanthine dehydrogenase to xanthine oxidase. FEBS J. 2008;275(13):3278-89. [Crossref] [PubMed]
2. Battelli MG, Polito L, Bortolotti M, Bolognesi A. Xanthine oxidoreductase-derived reactive species: physiological and pathological effects. Oxid Med Cell Longev. 2016;2016:3527579. [Crossref] [PubMed] [PMC]
3. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol. 1995;141(7):637-44. [Crossref] [PubMed]
4. Kuo CF, See LC, Yu KH, Chou IJ, Chiou MJ, Luo SF. Significance of serum uric acid levels on the risk of all-cause and cardiovascular mortality. Rheumatology (Oxford). 2013;52(1):127-34. [Crossref] [PubMed]
5. Ekundayo OJ, Dell'Italia LJ, Sanders PW, Arnett D, Aban I, Love TE, et al. Association between hyperuricemia and incident heart failure among older adults: a propensity-matched study. Int J Cardiol. 2010;142(3):279-87. [Crossref] [PubMed] [PMC]
6. Anker SD, Doehner W, Rauchhaus M, Sharma R, Francis D, Knosalla C, et al. Uric acid and survival in chronic heart failure: validation and application in metabolic, functional, and hemodynamic staging. Circulation. 2003;107(15):1991-7. [Crossref] [PubMed]
7. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail. 2011;17(1):25-30. [Crossref] [PubMed]
8. Muiesan ML, Agabiti-Rosei C, Paini A, Salvetti M. Uric acid and cardiovascular disease: an update. Eur Cardiol. 2016;11(1):54-9. [Crossref] [PubMed] [PMC]
9. Yu W, Cheng JD. Uric acid and cardiovascular disease: an update from molecular mechanism to clinical perspective. Front Pharmacol. 2020;11:582680. [Crossref] [PubMed] [PMC]
10. Konstam MA, Kiernan MS, Bernstein D, Bozkurt B, Jacob M, Kapur NK, et al; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and Management of Right-Sided Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2018;137(20):e578-e622. [Crossref] [PubMed]
11. Naser A, Güvenç TS, Isgandarov K, Ekmekçi A, Gündüz S, Çetin Güvenç R, et al. Lack of right ventricular hypertrophy is associated with right heart failure in patients with left ventricular failure. Heart Vessels. 2022;37(10):1728-39. [Crossref] [PubMed]
12. Accessed 15 Oct 2023. [Link]
13. Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail. 2014;16(1):15-24. [Crossref] [PubMed]
14. Fujihashi T, Sakata Y, Nochioka K, Miura M, Abe R, Kasahara S, et al; CHART-2 Investigators. Prognostic impacts of serum uric acid levels in patients with chronic heart failure: insights from the CHART-2 study. ESC Heart Fail. 2021;8(2):1027-38. [Crossref] [PubMed] [PMC]
15. Hare JM, Mangal B, Brown J, Fisher C Jr, Freudenberger R, Colucci WS, et al; OPT-CHF Investigators. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. J Am Coll Cardiol. 2008;51(24):2301-9. [Crossref] [PubMed]
16. Givertz MM, Anstrom KJ, Redfield MM, Deswal A, Haddad H, Butler J, et al; NHLBI heart failure clinical research network. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients: the xanthine oxidase ınhibition for hyperuricemic heart failure patients (EXACT-HF) Study. Circulation. 2015;131(20):1763-71. [Crossref] [PubMed] [PMC]
17. White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al; CARES Investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med. 2018;378(13):1200-10. [Crossref] [PubMed]
18. Cantu-Medellin N, Kelley EE. Xanthine oxidoreductase-catalyzed reactive species generation: A process in critical need of reevaluation. Redox Biol. 2013;1(1):353-8. [Crossref] [PubMed] [PMC]
19. Umar S, van der Laarse A. Nitric oxide and nitric oxide synthase isoforms in the normal, hypertrophic, and failing heart. Mol Cell Biochem. 2010;333(1-2):191-201. [Crossref] [PubMed]
20. Rosenkranz S, Gibbs JS, Wachter R, De Marco T, Vonk-Noordegraaf A, Vachiéry JL. Left ventricular heart failure and pulmonary hypertension. Eur Heart J. 2016;37(12):942-54. [Crossref] [PubMed] [PMC]
21. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB; International Right Heart Failure Foundation Scientific Working Group. Right heart failure: toward a common language. J Heart Lung Transplant. 2014;33(2):123-6. [Crossref] [PubMed]
22. Pascual E, Perdiguero M. Gout, diuretics and the kidney. Ann Rheum Dis. 2006;65(8):981-2. [Crossref] [PubMed] [PMC]
23. Felker GM, O'Connor CM, Braunwald E; Heart Failure Clinical Research Network Investigators. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circ Heart Fail. 2009;2(1):56-62. [Crossref] [PubMed] [PMC]