Received: 25 October 2017 | Revised: 30 January 2018 | Accepted: 18 March 2018

DOI: 10.1111/chd.12620

ORIGINAL ARTICLE

WILEY Congenital Heart Disease

# Risk factors for hyperuricemia in congenital heart disease patients and its relation to cardiovascular death

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## Abstract

**Introduction**: Hyperuricemia has been associated with cardiovascular risk factors but it remains controversial if uric acid is an independent predictor of cardiac mortality.

**Methods**: A total of 503 CHD patients (457 nonhypoxemic and 46 hypoxemic) and 772 control patients fulfilled inclusion criteria. Demographic, clinical, and analytical data [serum uric acid and 24h urine uric acid levels, N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), and C-reactive-protein (CRP) concentrations] were studied. Survivals curves to determine cardiac death and arterial thrombosis in CHD patients were also examined.

**Results**: Noncyanotic and cyanotic CHD patients had significant higher serum uric acid concentration (5.2 ± 1.5 vs 4.9 ± 1.3mg/dL, $P = .007$ and 6.7 ± 2.1 vs 4.9 ± 1.3mg/dL, $P < .001$, respectively) and gout (1% vs 0%, $P = .003$ and 4% vs 0%, $P < .01$, respectively) than the control population. Among CHD patients, hyperuricemic patients were significant older and with overweight, used more diuretics, were more cyanotic and had higher serum creatinine, NT-pro-BNP and CRP concentrations than nonhyperuricemic. In the multivariable analysis, the body mass index (BMI) (OR 1.09; 95% CI 1.01–1.18), cyanosis (OR 6.2; 95 CI 1.5–24.6), serum creatinine concentration (OR 49; 95% CI 44–538), and being under diuretic treatment (OR 4.5; 95% CI 1.4–14.5) proved to be risk factors for hyperuricemia in CHD patients. The Kaplan–Meier events free survival curves, during a 5.2 ± 2.7 years follow-up of up time, showed that hyperuricemic CHD patients had significant higher cardiovascular death ($P = .002$). However, after applying the Cox regression analysis uric acid levels lost its statistical significance. No significant differences were seen in relation to thrombotic events between CHD patients with and without hyperuricemia.

**Conclusions**: CHD patients, noncyanotic and cyanotic, have higher serum uric acid levels and gout than patients in the general population. BMI, renal insufficiency, cyanosis, and the use of diuretics were risk factor for hyperuricemia among CHD patients.

KEYWORDS

cardiovascular death, congenital heart disease, hyperuricemia, inflammation, thrombosis

  

## 1 | INTRODUCTION

Some studies have shown an association between serum uric acid level elevation and cardiovascular outcomes in the general population.[1–3] Despite this, the relationship between hyperuricemia and cardiovascular risk factors is controversial and conflicting and the debate focuses on whether hyperuricemia is an independent risk factor for cardiovascular disease or it is only associated with cardiovascular risk factors and cardiac death because of confounding factors. Indeed, many cardiovascular risk factors have been associated with increased serum uric acid levels such as body mass index (BMI), hyperlipidemia, arterial hypertension, and diabetes mellitus.[4,5]

Also, urate is a likely physiological substrate for myeloperoxidase and the products of their interaction have the potential role to exacerbate inflammation.[6] As matter of fact, inflammation has shown to play a role in the development and progression of a variety of cardiovascular conditions such as coronary atherosclerosis or congestive heart failure.[7,8]

Although there are several studies about hyperuricemia in cyanotic[9,10] and noncyanotic[11] congenital heart disease (CHD) patients there is no information regarding cardiovascular risk factors and cardiovascular events in these subgroups of patients.

The aim of this study is to determine which factors favor hyperuricemia in CHD patients and if it entails a risk for thrombotic events and cardiovascular death.

## 2 | METHODS

### 2.1 | Study population and clinical data

Prospective longitudinal study of CHD patients attended at our CHD unit between January 2006 and June 2017. The inclusion criteria specified patients older than 14 years with a structural congenital heart disease. On the contrary, exclusion criteria included patients with renal failure (creatinine > 2mg/dL), inflammatory disease, history of cancer, and a previous surgery or interventional cardiac procedure in the last 6 months. Clinical data were acquired from patient records and CHD was verified by echocardiography, cardiovascular magnetic resonance, and/or cardiac catheterization. Patients with more than one defect were classified according to the prevalent lesion from a clinical and/or hemodynamic point of view. Control patients were selected from of a similar socioeconomic population and a same geographical area than CHD patients were matched for age, sex, and cardiovascular risk factors to CHD patients. Patients included in the study, or their parents, gave informed consent to participate in the study and the protocol of the study was approved by the Hospital's Ethics Committee.

The physicochemical definition of hyperuricemia is a true serum urate level above 7mg/dL. Therefore, hyperuricemia was established as a serum uric acid level >7.0mg/dL in men and > 6mg/dL in women.[12] Arterial hypertension was defined

**TABLE 1** Demographic, clinical, and analytical data in congenital heart disease patients with and without cyanosis and the control population

| | Noncyanotic CHD | Control | *P** | Cyanotic CHD | Control | *P** | Total CHD | Control | *P** |
|---|---|---|---|---|---|---|---|---|---|
| Patients (*n*) | 457 | 772 | | 46 | 772 | | 503 | 772 | |
| Age (years) | 34 ± 14 | 34 ± 13 | .886 | 40 ± 12 | 34 ± 13 | 0.107 | 35 ± 14 | 34 ± 13 | 0.842 |
| Sex (male) | 255 (56) | 389 (50) | .083 | 22 (48) | 389 (50) | .982 | 277 (55) | 389 (50) | 0.096 |
| Arterial hypertension (*n*) | 66 (14) | 103 (13) | .951 | 3 (6) | 103 (13) | .227 | 69 (14) | 103 (13) | 0.991 |
| Dyslipidemia (*n*) | 54 (12) | 119 (15) | .115 | 4 (9) | 119 (15) | .275 | 58 (12) | 119 (15) | 0.115 |
| Diabetes mellitus (*n*) | 21 (5) | 22 (3) | .556 | 2 (4) | 22 (3) | .665 | 23 (5) | 22 (3) | 0.276 |
| Gout (*n*) | 5 (1) | 0 (0) | .003 | 2 (4) | 0 (0) | <.001 | 7 (1) | 0 (0) | 0.001 |
| Uric acid treatment (*n*) | 16 (3) | 7 (1) | .001 | 4 (9) | 7 (1) | <.001 | 20 (4) | 7 (1) | <0.001 |
| Serum creatinine (mg/dL) | 0.9 (0.8–1.0) | 0.7 (0.6–0.9) | <.001 | 1.0 (0.8–1.2) | 0.7 (0.6–0.9) | <.001 | 0.9 (0.8–1.0) | 0.7 (0.6–0.9) | <0.001 |
| Serum uric acid (mg/dL) | 5.2 ± 1.5 | 4.9 ± 1.3 | .007 | 6.7 ± 2.1 | 4.9 ± 1.3 | <.001 | 5.3 ± 1.6 | 4.9 ± 1.3 | <0.001 |
| Diuretics (*n*) | 52 (11) | 32 (4) | <.001 | 24 (52) | 32 (4) | <.001 | 76 (15) | 32 (4) | <0.001 |
| Oral anticoagulation (*n*) | 56 (12) | 3 (0.4) | <.001 | 19 (41) | 3 (0.4) | <.001 | 75 (15) | 3 (0.4) | <0.001 |

Abbreviations: CHD, congenital heart disease; *n*, number of patients. The data are expressed as mean ± standard deviation, median and quartiles (25;75) and as number and percentage. *Categorical variables are evaluated by the Pearson chi-square test, continuous data with normal distribution are compared by Student's *t* test, and continuous data without normal distribution by Mann–Whitney test.

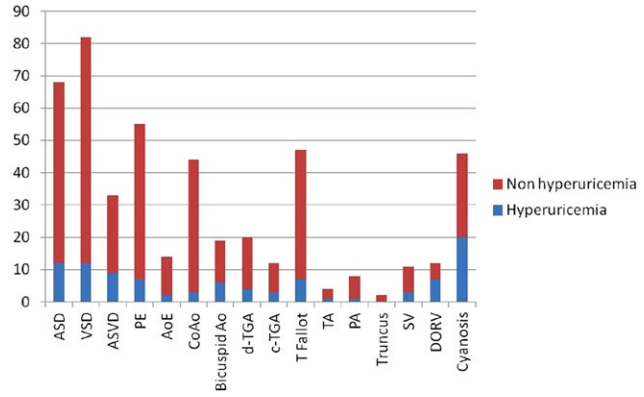


**FIGURE 1** Bar graph illustrating the most frequent types of congenital heart disease patients and the number of patients with and without hyperuricemia. Hyperuricemia was established as a serum uric acid level >7.0mg/dL in men and >6mg/dL in women. Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; AVSD, atrioventricular septal defect; PS, pulmonary stenosis; AoS, aortic stenosis; CoAo, coarctation of the aorta; Bicuspid Ao, bicuspid aorta; d-TGA, dextro-transposition of the great arteries; c-TGA, corrected-transposition of the great arteries; TA, tricuspid atresia; PA, pulmonary atresia; Truncus, truncus arteriosus; SV, single ventricle; DORV, double outlet right ventricle. Cyanotic CHD group was made up of 3 patients with atrial septal defect (ASD), 6 patients with ventricular septal defect (VSD), 6 patients with atrioventricular septal defect (AVSD), 1 patient with tetralogy of Fallot, 3 patients with dextro-transposition of the great arteries (d-TGA), 5 patients with congenital corrected transposition of the great arteries (cc-TGA), 3 patients with tricuspid atresia, 5 patients with pulmonary atresia, 6 patients with single ventricle, 6 patients with double outlet right ventricle, 1 patient with Ebstein anomaly, and 1 patient with pulmonary arteriovenous fistula [Colour figure can be viewed at wileyonlinelibrary.com]

when systolic blood pressure was >130mm Hg, diastolic blood pressure was >80mm Hg or the patient was receiving medication for hypertension; diabetes mellitus when fasting blood glucose levels was >126mg/dL or the patient was treated with oral anti-diabetic agents or insulin. Dyslipidemia if the patient was under any lipid lowering treatment. Patients were defined as hypoxemic if hemoglobin oxygen saturation was <93%. Body weight and height were measured with the patients wearing light clothes and barefoot and body mass index (BMI) were determined as weight (kg)/[height (m) × height (m)]. The left ventricular ejection fraction (LVEF) in CHD patients was calculated by echocardiography using Simpson's biplane method.[13]

## 2.2 | Blood collection

Blood samples were collected for subsequent laboratory analysis after an overnight fast of at least 10h, and during the 24-h urine collection CHD patients were recommended to have the usual diet and drink fluids, avoiding drinking alcohol or doing exercise strenuously. All blood samples were processed immediately after sampling.

**TABLE 2** Demographic, clinical, and analytical data in male congenital heart disease patients

| | Male CHD patients | | |
|---|---|---|---|
| | Hyperuricemia | Nonhyperuricemia | *P** |
| CHD patients (*n*) | 53 | 224 | |
| Age (years) | 38 ± 12 | 33 ± 12 | .013 |
| BMI (kg/m$^2$) | 27 ± 6 | 23 ± 5 | .002 |
| NYHA (functional class) | 1.6 ± 0.8 | 1.2 ± 0.5 | .011 |
| Gout (*n*) | 4 (7) | 1 (0.4) | <.001 |
| Uric acid treatment (*n*) | 7 (13) | 3 (1) | <.001 |
| Arterial hypertension (*n*) | 9 (17) | 38 (17) | .841 |
| Diabetes mellitus (*n*) | 3 (6) | 9 (4) | .731 |
| Cyanosis (*n*) | 11 (21) | 13 (6) | .001 |
| Serum glucose (mg/dL) | 97 ± 13 | 96 ± 11 | .673 |
| Hemoglobin (mg/dL) | 16 (15–16) | 15 (14–16) | .166 |
| Platelets (mg/dL) | 209 ± 71 | 232 ± 124 | .211 |
| Creatinine (mg/dL) | 1.0 (0.9–1.2) | 1.0 (0.8–1.1) | <.001 |
| Total cholesterol (mg/dL) | 176 ± 42 | 157 ± 36 | .001 |
| LDLc (mg/dL) | 104 ± 35 | 90 ± 30 | .005 |
| ESR (mm/h) | 9 ± 6 | 7 ± 8 | .300 |
| CRP (mg/dL) | 0.2 (0.1–0.5) | 0.1 (0.1–0.3) | .011 |
| ALT (U/L) | 26 (19–39) | 19 (15–28) | .002 |
| AST (U/L) | 26 (22–33) | 24 (19–29) | .032 |
| NT-pro-BNP (pg/mL) | 72 (17–396) | 44 (13–107) | .112 |
| 24 hour urine uric acid (mg/24h) | 586 ± 321 | 596 ± 637 | .931 |
| Aspirin (*n*) | 9 (17) | 19 (8) | .145 |
| Oral anticoagulation (*n*) | 15 (28) | 33 (15) | .012 |
| Beta-blockers (*n*) | 17 (32) | 31 (14) | .001 |
| ACE inhibitors/ARBs (*n*) | 13 (23) | 39 (17) | .614 |
| Diuretics (*n*) | 16 (30) | 28 (12) | .001 |
| Ventricular function (%) | 48 ± 10 | 47 ± 15 | .884 |
| Thrombotic events (*n*) | 2 (4) | 7 (3) | .811 |
| Cardiovascular death (*n*) | 5 (9) | 12 (5) | .266 |

Abbreviations: CHD, congenital heart disease; *n*, number of patients; BMI, body mass index; NYHA, New York Heart Association; LDLc, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-pro-BNP, NT-pro-brain natriuretic peptide; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers. The data are expressed as mean ± standard deviation, median, and quartiles (25;75) and as number and percentage. *Categoricalvariables are evaluated by the Pearson chi-square test, continuous data with normal distribution are compared by Student's *t* test, and continuous data without normal distribution by Mann–Whitney test.

**TABLE 3** Demographic, clinical, and analytical data in female congenital heart disease patients

| | Female CHD patients | | |
|---|---|---|---|
| | Hyperuricemia | Nonhyperuricemia | P* |
| CHD patients (*n*) | 33 | 193 | |
| Age (years) | 46 ± 17 | 34 ± 14 | <.001 |
| BMI (kg/m$^2$) | 27 ± 7 | 24 ± 5 | .069 |
| NYHA (functional class) | 1.8 ± 0.8 | 1.2 ± 0.5 | .004 |
| Gout (*n*) | 1 (3) | 1 (0.5) | .142 |
| Uric acid treatment (*n*) | 6 (18) | 4 (2) | <.001 |
| Arterial hypertension (*n*) | 4 (12) | 18 (9) | .632 |
| Diabetes mellitus (*n*) | 5 (15) | 6 (3) | .015 |
| Cyanosis (*n*) | 9 (27) | 13 (7) | <.001 |
| Serum glucose (mg/dL) | 96 ± 26 | 93 ± 10 | .503 |
| Hemoglobin (mg/dL) | 14 (13–15) | 14 (13–14) | .046 |
| Platelets (mg/dL) | 228 ± 73 | 235 ± 64 | .596 |
| Creatinine (mg/dL) | 1.0 (0.9–1.2) | 0.8 (0.7–0.9) | <.001 |
| Total cholesterol (mg/dL) | 168 ± 45 | 169 ± 40 | .861 |
| LDLc (mg/dL) | 98 ± 38 | 97 ± 32 | .981 |
| ESR (mm/h) | 13 ± 14 | 14 ± 13 | .886 |
| CRP (mg/dL) | 0.7 (0.2–1.5) | 0.2 (0.1–0.4) | <.001 |
| ALT (U/L) | 15 (12–23) | 15 (12–23) | .531 |
| AST (U/L) | 21 (18–28) | 19 (17–23) | .039 |
| NT-pro-BNP (pg/mL) | 278 (93–1569) | 90 (37–261) | <.001 |
| 24 hour urine uric acid (mg/24h) | 383 ± 200 | 410 ± 172 | .518 |
| Aspirin (*n*) | 4 (12) | 19 (10) | .660 |
| Oral anticoagulation (*n*) | 11 (33) | 16 (8) | <.001 |
| Beta-blockers (*n*) | 9 (27) | 19 (10) | .003 |
| ACE inhibitors/ARBs (*n*) | 4 (12) | 23 (12) | .275 |
| Diuretics (*n*) | 18 (54) | 16 (8) | <.001 |
| Ventricular function (%) | 48 ± 5 | 59 ± 11 | .225 |
| Thrombotic events (*n*) | 1 (3) | 5 (3) | .888 |
| Cardiovascular death (*n*) | 5(15) | 3 (2) | <.001 |

Abbreviations: CHD, congenital heart disease; *n*, number of patients; BMI, body mass index; NYHA, New York Heart Association; LDLc, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-pro-BNP, NT-pro-brain natriuretic peptide; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers. The data are expressed as mean ± standard deviation, median, and quartiles (25;75) and as number and percentage. *Categorical variables are evaluated by the Pearson chi-square test, continuous data with normal distribution are compared by Student's *t* test, and continuous data without normal distribution by Mann–Whitney test.

**TABLE 4** Demographic, clinical, and analytical data in congenital heart disease patients

| | Total of CHD patients | | |
|---|---|---|---|
| | Hyperuricemia | Nonhyperuricemia | P* |
| CHD patients (*n*) | 86 | 417 | |
| Age (years) | 41 ± 14 | 33 ± 14 | <.001 |
| Sex (male) | 53 (62) | 224 (54) | .187 |
| BMI (kg/m$^2$) | 27 ± 6 | 24 ± 5 | .001 |
| NYHA (functional class) | 1.6 ± 0.8 | 1.2 ± 0.5 | <.001 |
| Gout (*n*) | 5 (6) | 2 (0.5) | <.001 |
| Uric acid treatment (*n*) | 13 (15) | 7 (2) | <.001 |
| Arterial hypertension (*n*) | 13 (15) | 56 (13) | .584 |
| Diabetes mellitus (*n*) | 8 (9) | 15 (4) | .105 |
| Cyanosis (*n*) | 26 (30) | 20 (5) | <.001 |
| Serum glucose (mg/dL) | 96 ± 19 | 95 ± 11 | .371 |
| Hemoglobin (mg/dL) | 15 (14–16) | 14 (13–14) | .010 |
| Platelets (mg/dL) | 216 ± 72 | 233 ± 101 | .157 |
| Creatinine (mg/dL) | 1.0 (0.9;1.2) | 0.8 (0.7;1.0) | <.001 |
| Total cholesterol (mg/dL) | 172 ± 43 | 162 ± 38 | .039 |
| LDLc (mg/dL) | 101 ± 3.6 | 93 ± 31 | .057 |
| ESR (mm/h) | 11 ± 11 | 10 ± 11 | .532 |
| CRP (mg/dL) | 0.3 (0.1–0.7) | 0.1 (0.1–0.4) | <.001 |
| ALT (U/L) | 21 (14–37) | 17 (13–23) | .002 |
| AST (U/L) | 25 (20–32) | 21 (18–26) | <.001 |
| NT-pro-BNP (pg/mL) | 110 (41;641) | 62(19;168) | <.001 |
| 24 hour urine uric acid (mg/24h) | 510 ± 297 | 517 ± 501 | .908 |
| Aspirin (*n*) | 12 (14) | 33 (8) | .165 |
| Oral anticoagulation (*n*) | 26 (30) | 49 (12) | <.001 |
| Beta-blockers (*n*) | 26 (30) | 50 (12) | <.001 |
| ACE inhibitors/ARBs (*n*) | 17 (20) | 62 (15) | .890 |
| Diuretics (*n*) | 34 (39) | 44 (11) | <.001 |
| Ventricular function (%) | 48 ± 9 | 53 ± 14 | .249 |
| Thrombotic events (*n*) | 3 (3) | 12 (3) | .762 |
| Cardiovascular death (*n*) | 10 (12) | 15 (4) | .002 |

Abbreviations: CHD, congenital heart disease; *n*, number of patients; BMI, body mass index; NYHA, New York Heart Association; LDLc, low-density lipoprotein cholesterol; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-pro-BNP, NT-pro-brain natriuretic peptide; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers. The data are expressed as mean ± standard deviation, median, and quartiles (25;75) and as number and percentage. *Categorical variables are evaluated by the Pearson chi-square test, continuous data with normal distribution are compared by Student's *t* test, and continuous data without normal distribution by Mann–Whitney test.

Serum creatinine (normal values: 0.51–0.95mg/dL), uric acid (2.6–6.0mg/dL), total cholesterol (20–220mg/dL), low-density lipoprotein-cholesterol (LDLc) (0–155mg/dL), C-reactive protein (CRP) (0–0.5mg/dL), aspartate aminotransferase (AST) (5–31 U/L), alanine aminotransferase (ALT) (0–34 U/L), and 24-h proteinuria (250–750mg/24 h) were measured by spectrophotometry with an Olympus AU 2700 equipment (Olympus Diagnostic, Hamburg, Germany). The low-density lipoprotein cholesterol (in mg/dL) was determined with the Friedewald formula (LDLc = total cholesterol – [HDLc + triglycerides/5]). Complete blood counts were performed on a Coulter LH 750 (Beckman Coulter, Fullerton, California) analyzer to determine, hemoglobin concentration (12.0–17.0g/dL), platelet count (150–400^10$^3$/μL) and the erythrocyte sedimentation rate (ESR) (0–20mm/h). Hemoglobin oxygen saturation was assessed by pulse oximeter (Pulsox 300i, Konica Minolta Sensing Inc. Osaka, Japan).

### 2.3 | Outcomes

Clinical follow-up data in CHD patients were obtained from medial history, telephone interviews or the National Health Service computer system. Cardiovascular death included death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes.[14] Ischemic stroke was defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue and myocardial infarction when there was evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.[14]

### 2.4 | Statistical analysis

Quantitative variables were expressed as mean ± standard deviation or median and quartiles (25;75). Qualitative variables were expressed in percentages. A normal distribution was tested using the Kolmogorov–Sirmov test. Possible associations between categorical variables were evaluated by using the Pearson chi-square test. Continuous data were compared by Student's *t* test or Mann–Whitney test for variables with or without normal distribution, respectively. A one-way analysis of variance (ANOVA) was used to test the equality of three or more means at one time by using variances. Binary logistic regression analysis was performed to compare CHD patients without and with hyperuricemia (males with serum uric acid >7mg/dL and females with serum uric acid >6mg/dL) obtaining crude and stratified data. The results were expressed as odds ratios (ORs) with their 95% confidence intervals (CIs). The survival curves were estimated by the Kaplan–Meier method and the results were compared by the log-rank test. Cox regression analysis was used to investigate the effect of several variables upon the time cardiovascular death occurred. A *P* value less than .05 was considered statically significant. Data analysis was carried out using SPSS 19.0 (SPSS, Chicago, Illinois).

## 3 | RESULTS

About 564 CHD patients were asked to participate in the study and 503 (457 noncyanotic and 46 cyanotic) and 772 control patients fulfilled inclusion criteria. Among CHD patients 2 patients were excluded due to chronic renal disease, 6 patients because of inflammatory diseases, 11 patients due to a history of tumors, 2 for having previous surgeries in the last 6 months, and 40 patients because they did not give prior authorization for analytical extraction or blood samples were not drawn despite authorization.

Table 1 shows demographic, clinical, and analytical data in noncyanotic and cyanotic CHD patients and the control population. Basal hemoglobin oxygen saturation in cyanotic CHD patients was 84% ± 8%. Figure 1 shows the most frequent types of CHD in our series and the number of patients with and without hyperuricemia. After applying the ANOVA test no significant differences were seen between the serum uric acid concentrations and the 24h urine acid levels in the different types of CHD. Table 2 compares demographic, clinical and analytical data of male CHD patients with and without hyperuricemia, Table 3 does the same with female patients and Table 4 with the total population of CHD patients. Table 5 shows the results of the binary logistic regression analysis (with crude and adjusted data) of CHD patients with and without hyperuricemia. In it BMI, cyanosis, serum creatinine concentration, and diuretic treatment obtained statistical significance as risk factors for hyperuricemia in CHD patients.

Cardiac mortality occurred in 25 out of 503 (5%) CHD patients. Follow-up time was of 5.2 ± 2.7 years. 15 (4%) cardiac deaths occurred in the group without hyperuricemia and 10 (12%) cardiac deaths occurred in the group with hyperuricemia (*P* = .002) (Table 4). The Kaplan–Meier events free survival curve (Figure 2) showed statistical significance between patients with high and low serum uric acid levels (*P* = .002). Nonetheless, after applying the Cox regression analysis uric acid levels lost its statistical significance (Table 6). In relation to arterial thrombotic events 14 patients had strokes and 1 patient had a myocardial infarction with no significant differences between CHD patients with and without hyperuricemia (Table 4). Similarly, the Kaplan–Meier survival curve showed no significance in relation to arterial thrombosis regardless of uric acid levels.

## 4 | DISCUSSION

Prevalence of hyperuricemia in the overall population is rising[15] and factors such as aging, weight gain,[16] diet,[17] metabolic syndrome, arterial hypertension, diabetes, and dyslipidemia have been associated with higher serum uric acid levels.[18] However, after matching for age, sex, and cardiovascular risk factors and excluding dietary and genetic biases by choosing a control population of a similar socioeconomic status and a same geographic area, CHD patients still had higher serum uric acid concentrations than patient in the control group. Therefore, other factors should be taken into account, such as renal failure or diuretic treatment, to explain

why our CHD patients, both noncyanotic and cyanotic, had higher serum uric acid concentrations and a higher prevalence of gout than patients in the control group. Renal dysfunction as two-thirds of the uric acid produced in humans are excreted by the kidneys and diuretic treatment as it favors uric acid reabsorption due to volume contraction.[19]

In relation to CHD patients, and as we found when comparing CHD with the control population, hyperuricemic CHD patients used more diuretics and had higher serum creatinine concentrations, besides being older and having more overweight, than nonhyperuricemic CHD patients. On the other hand the higher incidence of oral anticoagulation and beta-blockers seen in hyperuricemic CHD patients could be explained because of the need to treat arrhythmias in patients with cardiac failure.[20,21] In fact, our hyperuricemic CHD patients had a worse NYHA functional class, significant higher NT-pro-BNP levels and higher percentage of diuretic therapy than nonhyperuricemic ones. Likewise, in our cyanotic CHD patients we found a sixfold increased risk of hyperuricemia mostly because (i) erythrocytosis, due to hypoxia, may favor an increased turnover of red blood cells and the consequent urate overproduction, (ii) an enhanced urate reabsorption as a result of renal hypoperfusion and a high filtration fraction,[22] and (iii) a more complex CHD with a higher risk of renal insufficiency and diuretic treatment.

Regarding inflammation, epidemiological studies have shown that uric acid is a risk factor for cardiovascular diseases being positively associated with proinflammatory markers. CRP is a biomarker of systemic inflammation which has been linked to hyperuricemia, cardiovascular disease, and mortality.[23,24] The link between hyperuricemia and inflammation has been examined in different vitro studies, animal models, and human studies[6,25–27] Krishnan etal.,[28] for example, found that CRP concentrations were higher among patients with greater serum urate concentrations, independent of age, sex, ethnicity, measures of obesity, or other potential confounders. Although we found significant differences in the levels of ESR and CRP between CHD patients with and without hyperuricemia both parameters lost statistical significance in the multivariate analysis.

**TABLE 5** Results of the binary logistic regression analyses of congenital heart disease patients with and without hyperuricemia

| Covariates | OR (crude) (95% CI) | OR (adjusted)* (95% CI) |
|---|---|---|
| Age (years) | 1.03 (1.02–1.05) | 0.99 (0.95–1.03) |
| Sex (male vs female) | 0.72 (0.45–1.16) | 0.67 (0.25–1.8) |
| BMI (kg/m$^2$) | 1.09 (1.04–1.14) | 1.09 (1.01–1.18) |
| NYHA functional class (grade) | 2.1 (1.4–3.1) | 0.57 (0.2–1.5) |
| Cyanosis (yes vs no) | 3.2 (1.6–6.7) | 6.2 (1.5–24.6) |
| Serum creatinine (mg/dL) | 102 (26–402) | 49 (44–538) |
| NT-pro-BNP (pg/mL) | 1.001 (1.000–1.001) | 1.00 (1.000–1.001) |
| Oral anticoagulation (yes vs no) | 2.4 (1.6–3.6) | 1.6 (0.8–3.2) |
| Diuretic treatment (yes vs no) | 5.8 (3.2–10.4) | 4.5 (1.4–14.5) |

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; NT-pro-BNP, NT-pro-brain natriuretic peptide. *Adjustments made for all factors in the table.

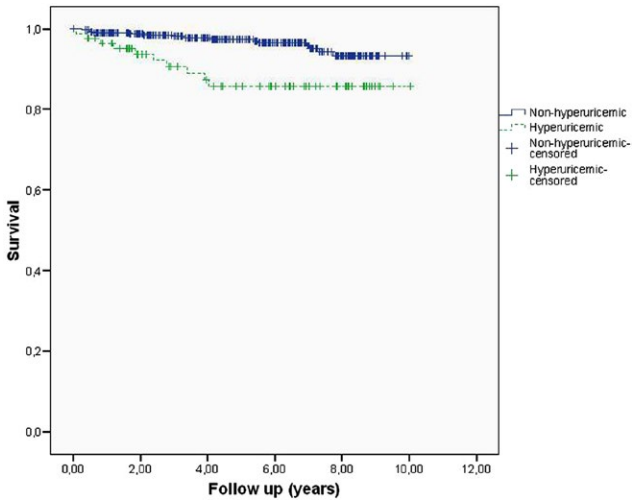


**FIGURE 2** Survival curves estimated by the Kaplan–Meier method comparing hyperuricemic (dashed line) and nonhyperuricemic (continuous line) congenital heart disease patients (log-rank test, $P = .002$) [Colour figure can be viewed at wileyonlinelibrary.com]

With respect to cardiovascular risk factors and cardiovascular death, recent data suggest that serum uric acid at high-normal level is associated with a higher incidence of events.[3] On the contrary, other authors have found no association.[2] These differences could be due to the difficulties in the assessment of the role of serum uric acid independently from other traditional risk factors and the different methodologies used in previous epidemiological studies. Although we found a worse survival between hyperuricemic CHD patients in the Kaplan–Meier analysis, hyperuricemia lost its significance in the Cox regression analysis. This may be due to the interactions of multiple factors derived from a very heterogeneous population (different types of cardiopathies, cyanosis, ventricular dysfunction, arrhythmias, right-to-left shunts, coagulation disorders or medical treatment,...) and the low frequency of cardiovascular disease among CHD patients.[29] Something similar occurred in relation to thrombotic events among our CHD patients.

In conclusion, CHD patients have higher serum uric acid levels and gout than patients in the general population. When comparing CHD with and without hyperuricemia different potential causes may explain higher serum uric acid levels such as obesity, aging, or medical conditions such as renal insufficiency, cyanosis, or the use of diuretics.

**TABLE 6** Multivariate Cox regression analyses of cardiovascular mortality in congenital heart disease patients

| Variables | Hazard ratio (95% CI) | *P* |
|---|---|---|
| Age (years) | 1.01 (0.94–1.08) | .727 |
| Sex (male vs female) | 0.39 (0.07–2.07) | .271 |
| Hyperuricemia (low vs high) | 0.45 (0.06–3.38) | .438 |
| NYHA (functional class) | 0.96 (0.27–3.38) | .952 |
| Cyanosis (yes vs no) | 2.74 (0.23–33.15) | .428 |
| Serum creatinine (mg/dL) | 4.52 (0.03–764.92) | .564 |
| LDL cholesterol (mg/dL) | 1.03 (0.95–1.11) | .446 |
| NT-pro-BNP (pg/mL) | 1.000 (1.000–1.001) | .020 |
| Oral anticoagulation (yes vs no) | 0.314 (0.038–2.58) | .281 |
| Diuretic treatment (yes vs no) | 19.22 (1.5–244.06) | .023 |

Abbreviations: CI, confidence interval; LDL, low-density lipoprotein; NT-pro-BNP, NT-pro-brain natriuretic peptide.

## ACKNOWLEDGMENT

This manuscript has not been submitted for publication nor has it been published in whole or in part elsewhere. We attest to the fact that all authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation. The authors of this manuscript have also certified that they comply with the principles of Ethical Publishing.

## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

*Design, data collection, analysis interpretation, drafting and final approval of article.*: Juan Lizandro Rodríguez-Hernández, Fayna Rodríguez-González, Marta Riaño-Ruiz, and Efrén Martínez-Quintana

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**How to cite this article:** Rodríguez-Hernández JL, Rodríguez-González F, Riaño-Ruiz M, Martínez-Quintana E. Risk factors for hyperuricemia in congenital heart disease patients and its relation to cardiovascular death. *Congenital Heart Disease*. 2018;13:655–662. https://doi.org/10.1111/chd.12620