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ORIGINAL ARTICLE

Hyperuricemia in Cardiac Rehabilitation Patients: Prevalence and Association with Functional Improvement and Left Ventricular Ejection Fraction

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Abstract

Introduction The role of uric acid (UA) and Hyper Uricemia (HU) in cardiac rehabilitation (CR) patients have been very little studied.

Aim To evaluate the prevalence of HU and if it is associated to the functional improvement obtained or the left ventricular Ejection Fraction (EF) in CR patients after Acute or Chronic Coronary Syndrome (ACS and CCS respectively).

Methods We enrol 411 patients (62.4 ± 10.2 years; males 79.8%) enrolled in the CR program at Niguarda Hospital (Milan) from January 2012 to May 2023. HU was defined both as the classic cut-off (> 6 for females, > 7 mg/dL for males) and with the newly identified one by the URRAH study (> 5.1 for females, > 5.6 mg/dL for males). All patients performed a 6MWT and an echocardiography at the beginning and at the end of CR program.

Results Mean UA values were within the normal range (5.6 ± 1.4 mg/dL) with 19.5% (classic cut-off) HU patients with an increase to 47.4% with the newer one. Linear regression analysis showed no role for UA in determining functional improvement, while UA and hyperuricemia (classic cut-off) were associated to admission and discharge EF. The same was not with the URRAH cut-off.

Conclusions HU is as frequent in CR patients as in those with ACS and CCS. UA didn't correlate with functional recovery while it is associated with admission and discharge EF as also is for HU (classic cut-off). Whit the URRAH cut-off HU prevalence increases significantly, however, it doesn't show any significant association with EF.

Keywords Uric Acid · Cardiac rehabilitation · Functional improvement · 6-minute walking test · Ejection fraction

1 Introduction

In Acute Coronary Syndrome (ACS) the advances in diagnosis and treatment strongly reduce the in-hospital and short-term mortality and complication. The same reduction was not observed on long-term outcome and many patients, despite a good control in CardioVascular (CV) risk factors, generating the need for a better secondary CV prevention [1]. Cardiac Rehabilitation (CR) programs are the places where this can be done together with patients disease awareness and engagement (more important as the hospital stay became shorter) as well as drug therapies refinement and tailoring [2, 3].

Uric acid (UA) and HyperUricemia (HU) are novel CV risk factors on which many papers have been published in latest years. UA and HU have been related to many CV diseases related to the atherosclerotic process (ACS and Chronic Coronary Syndrome—CCS—[3], stroke [4] and peripheral artery disease [5]) but also in other CV disease such as heart failure (HF) [6] and atrial fibrillation [7].

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HU prevalence progressively increases from healthy subjects to patients with single CV risk factors to metabolic syndrome patients reaching the higher values in patients that already experienced a CV events [8].

Despite CR had a strong indication for ACS and CCS patients, only few patients (20–50%) are referred [9]. Since more frequently referred patients are the one with multiple CV events, multiple cardiac and non-cardiac comorbidities and with the lowest control in CV risk factors [10], a higher prevalence of HU could be hypothesized in CR patients. Furthermore, newer and lower HU cut-off were published in recent years since they better correlate with CV events [11] and, obviously, if clinically adopted this will lead to a further increase of the HU prevalence.

The role of UA in CR program has been very little studied. In fact, no data have been published on the prevalence of HU in CR patients nor with the classic nor with the newer cut-off. Furthermore, only few studies evaluated the variation of UA during CR [12–17], and only one assessed the possible role of baseline UA as a determinant of functional improvement during CR [18].

Left ventricular Ejection Fraction (EF) is a strong predictor of prognosis not only in HF patients but also in subjects with ACS and CCS. In fact, it represents an outcome of interest during the CR programs. The associations between UA and EF have already been investigated but mainly in HF patients and only rarely in ACS/CCS subjects [19–21].

So, the aim of our study was to evaluate the HU prevalence in patients enrolled in a CR program after an ACS or a recent coronary revascularization in the context of a CCS. Prevalence of HU has been assessed both with the classic cut-off and the newly one identified by the URRAH study. Furthermore, we want to assess if UA levels or the presence of HU are significantly associated with functional improvement during CR and admission and discharge EF.

2 Methods

2.1 Study Population

This study has a longitudinal and observational design. The cohort is composed by 411 patients, who attended the outpatient CR program at the Niguarda Hospital from January 2015 until May 2023. Inclusion criteria are being recruited for a CR program for a recent (< 12 months) hospitalization for ACS or for CCS that leads to coronary revascularization (both programmed or from the emergency department).

Exclusion criteria were all non-ACS and CCS heart diseases (dilated or hypertrophic cardiomyopathy and peripheral artery disease), the presence of neurological, pneumological or orthopaedic diseases impairing prolonged physical activity as well as the absence of serum UA value at CR admission. Furthermore, individuals with a premature interruption of CR program were not considered in the analysis.

At admission data regarding classic CV risk factors (familiar history, hypertension, Diabetes Mellitus - DM, smoking habit and dyslipidaemia), CV medical history (previous revascularization, stroke or Transitory Ischaemic Attack—TIA, Peripheral Artery Disease—PAD, atrial fibrillation), comorbidities (Chronic Kidney Disease – CKD – defined as a Glomerula Filtration Rate—GFR— < 60 mL/min) and drug therapies (β-blockers, lipid-lowering, antiplatelet and antihypertensive) were collected. Data from the recent index hospitalization were also collected: coronary vessels revascularized and number of vessels involved, lipid profile, renal function, glucose, peak high-sensitivity troponin T (hs-TnT) and MB-isoform of Creatin Kinase (CK-MB), left ventricular Ejection Fraction (EF) and UA. In ACS subjects UA was registered only if obtained at least after 7 days after hospitalization in order to avoid acute changes [3].

HU was defined both as the classic cut-off (> 6 mg/dL for females, > 7 mg/dL for males) and with the newly identified one by the URRAH study (> 5.1 mg/dL for females, > 5.6 mg/dL for males) [11]. A further values of LDL cholesterol, tryglicerides and glucose were repeated at the end of the CR.

During the physical examination height and weight (with the calculation of Body Mass Index—BMI), Systolic and Diastolic Blood Pressure (SBP and DBP respectively) and Heart Rate (HR) were collected.

A 6-Minute Walking Test (6MWT) was performed both at admission and at discharge. The differences between the meter walked at discharge and the one at admission (Δ6MWT, both as absolute values and as percentage) were considered proxy for functional improvement granted by the program and were used for the analysis.

Finally, at the end of CR all the patients underwent an echocardiography with EF collection.

2.2 Cardiac Rehabilitation Program

The CR program at Niguarda hospital is based on an outpatient regime. Patients access the program daily for a total of 25 access. The mainstay of the rehabilitation program is the physical training, which is predominantly aerobic and is divided into two phases: endurance on the exercise bike and free-body exercises (with physiotherapist). The two sequential phases last 45 mins each, with 15 mins of rest between them. The intensity of the endurance phase is tailored to the assessments at admission and the functional improvement demonstrated throughout the program. Nonetheless, for all patients, a progressive increase in workload is planned over the course of the program.

CR program included meeting with psychologist (to support the patient in changing lifestyle and in controlling emotional feelings), dietologist (to educate about nutritional

habits [1]) and cardiologist in order to explain disease and therapies with the final aim to increase patients engagement [2].

2.3 6-minute Walking Test

Six-minute walking test reflects the functional capacity of the patient and was conducted following specific guidelines by a trained physiotherapist [22]. It was performed in the hospital along a corridor, free of obstacle, straight and flat; each patient walked 30 m forth and back, for a total of 60 m every lap. 10 min' rest were mandatory before the test was performed. Over final walked distance, also HR and oxygen saturation were detected continuously and registered every minute.

2.4 Statistical Analysis

Statistical analyses were performed via IBM® SPSS Statistics and a p value lower than 0.05 was considered significant.

Continue variables were expressed as mean value ± standard deviation, whereas categorical variables were reported as relative frequencies and percentages. Paired Student *t* test was used for normally distributed variables which have both admissions and discharge's values.

The study population was divided into hyperuricemic and control group (with both cut-off) and the differences were assessed by unpaired Student *t* test and χ^2 *(Chi-square) test* for normally distributed variables and categorical variables, respectively.

We performed linear regression model with Δ6MWT, admission and discharge EF as dependent variables and with age, sec, BMI, GFR and diuretic use as covariates. UA, HU (classic cut-off) and HU (URRAH cut-off) were further inserted into the models.

3 Results

3.1 Population Characteristics

Admission and discharge characteristics of the enrolled population are shown in Table 1. Mean age was 62.4 ± 10.2 years and males represent the 79.8% of the population. Among CV risk factors, dyslipidaemia was the most represented present one (72.0%) followed by arterial hypertension (66.2%) and obesity/overweight (61.1%) while DM and active smoking regards to 21.9% and 27.5% of the population, respectively.

Twenty percent of the patients had a previous revascularization but also other non-cardiological atherosclerotic diseases were well represented with 8.4% of the patients having PAD and 12.8% a previous stroke or TIA. Atrial fibrillation was present in 9.0% and CKD in 17.9% of the population.

Regarding the index hospitalization for ACS/CCS, in half of the patient the patients one coronary artery was involved (50.8%), mainly the left anterior descending one (66.4%). Almost all the patients were discharged on beta-blockers, statins and renin-angiotensin system inhibitors.

SBP, DBP and HR were well controlled at the beginning of the CR and further improves before discharge. The same applies also to triglycerides (from 126.8 ± 60.2 to 116.7 ± 61.8 mg/dL, $p < 0.001$) and LDL cholesterol (from 105.7 ± 38.5 to 68.6 ± 24.3 mg/dL, $p < 0.001$) while there were no differences for glucose values.

EF significantly improves (from 53.8 ± 8.6 to 55.9 ± 7.9 %, $p < 0.001$, absolute Δ 2.1 ± 4.8%) as well as 6MWT distance (from 465.8 ± 100.3 to 574.3 ± 110.8 meters, $p < 0.001$) with an absolute increase of 114.3 ± 74.9 m (relative increase 19.7 ± 12.1%).

3.2 Hyperuricemia Versus Normouricemia Patients

Mean UA values (Table 1) were within the normal range (5.6 ± 1.4 mg/dL) with 19.5% that had HU with the classic cut-off (> 6 mg/dL for females, > 7 mg/dL for males) while this number increases to 47.4% with the newer one (> 5.1 mg/dL for females, > 5.6 mg/dL for males).

When patients with HU (defined with the classic cut-off) were compared to those who present normal UA values (table 2) they were older, had more frequently PAD (15.1 vs 6.9%, $p = 0.023$) and CKD (38.7 vs 13.0%, $p < 0.001$), with lower GFR values (67.8 ± 20.5 vs 81.9 ± 19.7 vs, $p < 0.001$). They had higher triglycerides (143.3 ± 78.9 vs 123.0 ± 54.3, $p = 0.009$) with lower EF (51.7 ± 12.2 vs 54.4 ± 7.5 %, $p = 0.020$, Fig. 1A) at admission and at discharge (53.2 ± 11.0 vs 56.5 ± 6.9 %, Fig. 1B) but no differences in Δ (1.6 ± 5.0 vs 2.2 ± 4.7, $p = 0.368$). Finally, although there was not a significant difference in meter walked at 6-MWT ad admission or discharge, the increase in functional ability was lower, both absolute (97.2 ± 63.3 vs 118.4 ± 76.9 meters, $p = 0.030$) and percentage (16.9 ± 10.4 vs 20.4 ± 12.3 %, $p = 0.028$).

With the newer cut-off (Table 3), over what already described for the classic one, HU subjects also present a higher BMI (27.7 ± 4.3 vs 26.6 ± 3.7, $p = 0.006$) and higher prevalence of hypertension (74.4 vs 58.8 %, $p < 0.001$), as well as previous stroke/TIA (16.7 vs 9.2 %, $p = 0.027$). However, differences in triglycerides, EF and functional improvement are no longer significant (absolute: 107.8 ± 78.4 vs 120.4 ± 71.2 meters, $p = 0.101$; percentage 18.6 ± 11.5 vs 20.7 ± 12.5 %, $p = 0.099$).

Table 1 Whole population characteristics at admission and at discharge

	CR admission	CR discharge	P value
Number	411	–	–
Age (years)	62.4 ± 10.2	–	–
Male gender (n, %)	328 (79.8)	–	–
CV risk factors and previous diseases			
Smoke (n, %)	113 (27.5)	–	–
Familiar history of CV disease (n, %)	172 (41.8)	–	–
Body Mass Index (kg/m^2)	27.2 ± 4.0	–	–
Overweight or obesity (n, %)	250 (61.1)	–	–
Diabetes (n, %)	90 (21.9)	–	–
Dyslipidaemia (n, %)	296 (72.0)	–	–
Hypertension (n, %)	272 (66.2)	–	–
Peripheral Artery Disease (n, %)	33 (8.4)	–	–
Previous stroke/TIA (n, %)	50 (12.8)	–	–
Previous PCI (n, %)	76 (18.5)	–	–
Previous CABG (n, %)	6 (1.5)		
Critical coronary lesions			
LAD (n, %)	235 (66.4)	–	–
RC (n, %)	147 (41.2)		
CX (n, %)	119 (33.3)		
LM (n, %)	19 (5.3)		
Number of coronary arteries involved			
1 (n, %)	182 (50.8)	–	–
2 (n, %)	102 (28.5)		
3 (n, %)	48 (13.4)		
Atrial fibrillation	37 (9)	–	–
CKD (eGFR < 60 mL/min) (n, %)	70 (17.9)	–	–
CV drug therapies			
Beta-blockers (n, %)	375 (95.7)	–	–
Statins (n, %)	394 (98.5)	–	–
Ezetimibe (n, %)	133 (39.2)	–	–
Double antiplatelet therapy (n, %)	268 (66.2)	–	–
ACE-inhibitors or ARB (n, %)	325 (79.1)	–	–
Calcium Channel Blockers (n, %)	17 (4.1)	–	–
Diuretics (n, %)	20 (4.9)	–	–
Clinical parameter			
SBP (mmHg)	124.6 ± 16.0	114.9 ± 11.5	< 0.001
DBP (mmHg)	74.2 ± 9.2	66.5 ± 8.8	< 0.001
HR (bpm)	64.0 ± 9.6	61.3 ± 8.0	< 0.001
Biochemical data			
Peak CK-MB (mcg/L)	182.2 ± 526.3	–	–
Peak hs-TnT (ng/L)	3250.9 ± 4216.9	–	–
Triglycerides (mg/dL)	126.8 ± 60.2	116.7 ± 61.8	< 0.001
LDL cholesterol (mg/dL)	105.7 ± 38.5	68.6 ± 24.3	< 0.001
Glucose (mg/dL)	105.5 ± 32.0	114.6 ± 32.9	0.764
eGFR MDRD (ml/min/1.73 m^2)	79.1 ± 20.6	–	–
Uric acid (mg/dL)	5.6 ± 1.4	–	–
Hyperuricemia (> 6 mg/dL for females, > 7 mg/dL for males) (n, %)	80 (19.5)	–	–
Hyperuricemia (> 5.1 mg/dL for females, > 5.6 mg/dL for males) (n, %)	195 (47.4)	–	–

Table 1 (continued)

	CR admission	CR discharge	P value
Echocardiography			
LVEF (%)	53.8 ± 8.6	55.9 ± 7.9	< 0.001
Δ LVEF (%)	–	2.1 ± 4.8	–
6-MWT			
6MWT (mt)	465.8 ± 100.3	574.3 ± 110.8	< 0.001
Δ6MWT absolute (mt)	–	114.3 ± 74.9	–
Δ6MWT percentage (%)	–	19.7 ± 12.1	–

CR, Cardiac Rehabilitation; *CV*, Cardiovascular; *TIA*, Transitory Ischemic Attack; *PCI*, Percutaneous Coronary Intervention; *CABG*, Coronary Artery By-pass Graft; *LAD*, Left Anterior Descendant; *LM*, Left Main; *RC*, Right coronary; *CX*, Circumflex coronary; *CKD*, Chronic Kidney Disease; *eGFR*, estimed Glomerular Filtration Rate; *ACE*, Angiotensin Converting Enzyme; *ARB*, Angiotensin Receptor Inhibitors; *SBP*, Systolic Blood Pressure; *DBP*, Diastolic Blood Pressure; *CK-MB*, Creatin Kinase MB isoform; *hs-TnT*, high sensitivity Troponin T; *LDL*, Low Density Lipoprotein; *HR*, Heart Rate; *LVEF*, Left Ventricular Ejection Fraction; *6MWT*, Six Minute Walk Test

3.3 Linear Regression Multivariable Analysis

Nor UA nor HU (classic and URRAH cut-off) were associated with functional improvement (Δ6MWT) in the multivariable model (supplementary table 1).

Instead, UA and HU (classic cut-off) were significantly associated with admission EF (UA: β = 0.16, 95% CI from − 0.28 to − 0.05, p = 0.048; HU: β = − 0.35, 95% CI from − 0.62 to − 0.08, p = 0.012, Table 4) and discharge EF (UA: β = − 0.18, 95% CI from − 0.30 to − 0.07, p = 0.001; HU: β = − 0.43, 95% CI from − 0.71 to − 0.16, p = 0.021, Table 5). On the contrary, when the URRAH cut-off was used to define hyperuricemia there was not a significant association with nor admission nor discharge EF (admission EF: β = − 0.16, 95% CI from − 0.38 to 0.06, p = 0.153; discharge EF: β = − 0.19, 95% CI from − 0.41 to 0.02, p = 0.084, Tables 4 and 5).

4 Discussion

The main results of our study is that the prevalence of HU in CR patients is 19.5% (with the classic cut-off) similar to what has been founded in in ACS (23%) [3] and CCS hospitalized patients (22.9%) [23]. As already mentioned, patients that are normally referred to CR are the one with multiple CV events, multiple cardiac and non-cardiac comorbidities and the one with uncontrolled risk factor and the need for therapies optimization [10]. Even if this may suggest the possibility to find a higher prevalence of HU, our study didn't confirm this speculation.

The second point is that, when the newer and lower URRAH cut-off was used, HU prevalence significantly increases to 47.4% of the population. This new cut-off is of importance since UA begins to negatively impact the CV system at lower values than the classical one that is, conversely, principally related to UA crystal deposition, and so, to articular and kidney gout. As obvious, the lower we move the cut-off, the higher will be the prevalence of hyperuricemia (in our study raises from 19.5 to 47.4%). Nevertheless, this could be of interest if a clinical and a therapeutic benefit is determined by this re-classification. This matter is still under investigation as the last trial on hypouricemic agents (ALL-HEART study [24]) suggests that treating asymptomatic HU does not yield a substantial benefit on subsequent CV events in secondary prevention patients. As discussed elsewhere [25], this trial has strong limitation and other trials (evaluating also febuxostat and not only allopurinol, enrolling also recent ACS and not only CCS, selecting only UA overproduction patients) are needed before definitive conclusions can be drawn.

Another result of our study deserved to be mentioned, i.e. the fact that HU was not associated with functional improvement (Δ6MWT). Only one previous study evaluate this association [18] founding a direct correlation between elevated UA levels and a higher Δ6MWT in a population of patients who underwent CR after heart surgery. However, the correlation was found only in the subpopulation aged over 65 years. 47% of the subjects of this study underwent valve surgery with no coronary artery disease, so a completely different cohort in comparison to ours.

Conversely, 6 studies evaluated the relationship in the opposite direction, looking for the effects of cardiac rehabilitation on UA serum levels. Unfortunately, since we didn't have a second UA value, we cannot add new information on this topic. However, all the study published were on very few patients (n = 26–90) showing heterogeneous results with 2 of them in favour of a decrease of UA after CR [14, 15] while 2 of them showed no significant difference [13, 17]. The only one with an appropriate number of patients (n = 693) showed the absence of a significant differences in UA before and after CR [12]. Finally, one study showed an

Table 2 Characteristics of the population enrolled when divided according to the presence/absence of hyperuricemia with the classic cut-off

	Classic cut-off (6 mg/dL for female and 7 mg/dL for males)		
	Normal UA	Hyperuricemia	P value
Number	331	80	–
Age	61.9 ± 10.0	64.5 ± 10.5	0.039
Male gender (n, %)	264 (79.8)	64 (80.0)	0.961
CV risk factors and previous diseases			
Smoke (n, %)	93 (28.1)	20 (25.0)	0.879
Familiar history of CV disease (n, %)	141 (42.6)	31 (38.8)	0.109
Body Mass Index (kg/m^2)	27.1 ± 3.9	27.6 ± 4.5	0.261
Overweight or obesity (n, %)	199 (60.3)	51 (64.6)	0.486
Diabetes (n, %)	72 (21.8)	18 (22.5)	0.885
Dyslipidaemia (n, %)	245 (74.0)	51 (63.7)	0.066
Hypertension (n, %)	212 (64.0)	60 (75.0)	0.063
Peripheral Artery Disease (n, %)	22 (6.9)	11 (15.1)	0.023
Previous stroke/TIA (n, %)	37 (11.6)	13 (17.8)	0.151
Previous PCI (n, %)	56 (16.9)	20 (25.0)	0.079
Previous CABG (n, %)	4 (1.2)	2 (2.5)	0.134
Critical coronary lesions			
LAD (n, %)	189 (64.3)	46 (76.7)	0.064
RC (n, %)	123 (41.6)	24 (39.3)	
CX (n, %)	99 (33.4)	20 (32.8)	
LM (n, %)	15 (5.1)	4 (6.6)	
Number of coronary arteries involved			
1 (n, %)	155 (52.2)	27 (44.3)	0.799
2 (n, %)	83 (27.9)	19 (31.1)	
3 (n, %)	38 (12.8)	10 (16.4)	
Atrial fibrillation	28 (8.4)	9 (11.3)	0.467
CKD (eGFR < 60 mL/min) (n, %)	41 (13.0)	29 (38.7)	< .001
CV drug therapy			
Beta-blockers (n, %)	300 (90.6)	75 (93.8)	0.376
Statins (n, %)	318 (98.5)	76 (98.7)	0.699
Ezetimibe (n, %)	107 (38.9)	26 (40.6)	0.866
Dual antiplatelet therapy (n, %)	223 (68.2)	45 (57.7)	0.211
ACE inhibitors or ARB (n, %)	260 (78.5)	65 (81.3)	0.594
Calcium Channel Blockers (n, %)	16 (4.8)	1 (1.3)	0.149
Diuretics (n, %)	13 (3.9)	7 (8.8)	0.072
Clinical parameter			
SBP at admission (mmHg)	124.4 ± 15.9	125.5 ± 16.4	0.593
DBP at admission (mmHg)	74.0 ± 8.8	74.9 ± 10.6	0.466
HR at admission (bpm)	63.9 ± 9.6	64.0 ± 9.6	0.976
Biochemical data			
Peak CK-MB (mcg/L)	184.0 ± 572.2	173.5 ± 175.2	0.933
Peak hs-TnT (ng/L)	3216.5 ± 4300.8	3437.8 ± 3789.0	0.789
Triglycerides at admission (mg/dL)	123.0 ± 54.3	143.3 ± 78.9	0.009
LDL cholesterol at admission (mg/dL)	109.2 ± 37.9	91.4 ± 38.0	< 0.001
Glucose at admission (mg/dL)	106.4 ± 33.5	101.7 ± 24.4	0.275
eGFR MDRD (ml/min/1.73 m^2)	81.9 ± 19.7	67.8 ± 20.5	< 0.001
Echocardiography			
LVEF at admission (%)	54.4 ± 7.5	51.7 ± 12.2	0.020
LVEF at discharge (%)	56.6 ± 6.9	53.2 ± 11.0	0.001
ΔLVEF (%)	2.2 ± 4.7	1.6 ± 5.0	0.368

Table 2 (continued)

	Classic cut-off (6 mg/dL for female and 7 mg/dL for males)		
	Normal UA	Hyperuricemia	P value
6-MWT			
6MWT at admission (mt)	467.9 ± 105.5	456.7 ± 74.5	0.370
6MWT at discharge (mt)	579.2 ± 114.4	553.8 ± 92.2	0.079
Δ6MWT absolute (mt)	118.4 ± 76.9	97.2 ± 63.3	0.030
Δ6MWT percentage (%)	20.4 ± 12.3	16.9 ± 10.4	0.028

CV, cardiovascular; *TIA*, transitory ischemic attack; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery by-pass graft; *LAD*, left anterior descendant; *LM*, left main; *RC*, right coronary; *CX*, circumflex coronary; *CKD*, chronic kidney disease; *eGFR*, estimed glomerular filtration rate; *ACE*, angiotensin converting enzyme; *ARB*, angiotensin receptor inhibitors; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *CK-MB*, creatin kinase MB isoform; *hs-TnT*, high sensitivity Troponin T; *LDL*, low density lipoprotein; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *6MWT*, six minute walk test

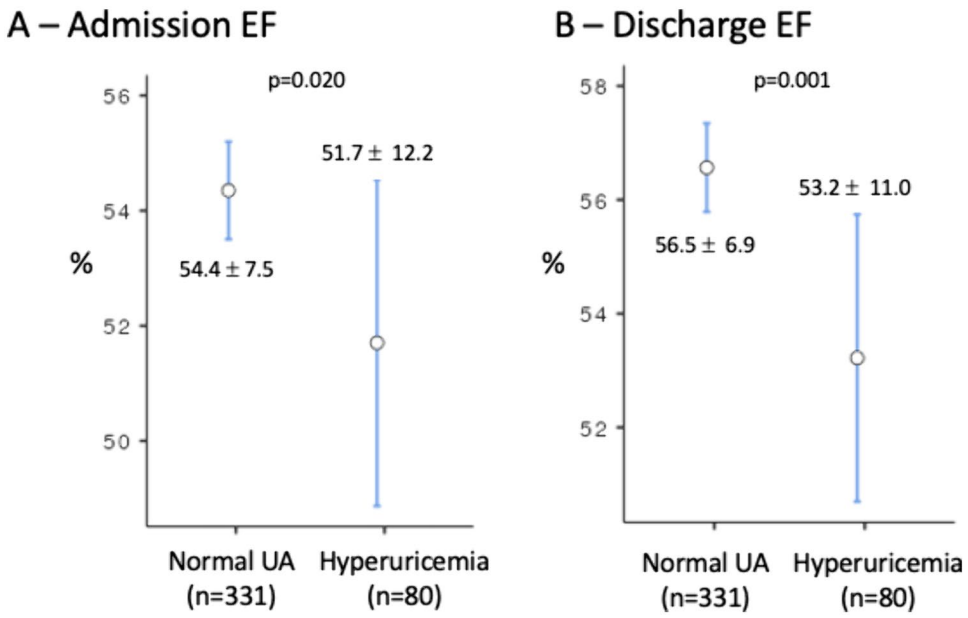

Fig. 1 Admission (**A**) and discharge (**B**) left ventricular ejection fraction in hypeuricemic patients compared to normouricemic one defined with the classic cut0off

increase in UA during CR [16]. However, none of the cited studies described baseline hypouricemic agents nor if this were started or dosage were increased during the CR.

Differences in these studies results are probably driven by three factors: (1) population (only ACS patients or also CCS patients); (2) time of CR initiation after the index events; (3) pro-oxidant and anti-oxidant properties of UA.

Regarding the latter it is well established that oxidoreductive impairment plays a crucial role in CV diseases. Whether UA stands as a scavenger mechanism or may worsen the balance is still disputed. The origin of this dualism lies in the final biochemical transformation of hypoxanthine in UA; this passage could be catalyzed by two different enzymes, xanthine-dehydrogenase (XDH) and xanthine-oxidase (XO). The balance between these two enzymes will define whether UA help to reduce the oxidative state or worsen it. Some authors suggest that an ischemic drive may facilitate the conversion from XDH to XO and therefore may enhance the production of reactive oxygen species [26].

Another point of our study deserved to be mentioned, i.e. the relationship between UA and EF. Our results are in line with the few studied already published, mostly focused on HF, in which a significant association was found [19–21, 27]. The association was confirmed also in CCS [20, 28] and ACS patients [3].

Regarding the mechanism that could link UA to EF, all the cited studies are cross-sectional doesn't give us the opportunity to draw definite conclusion on the direction of the associations found. So, it could be possible that UA can determine an EF reduction but also that a reduced EF is able to determine an increase in UA. Data in favour of both hypotheses have been published.

UA could increase due to many conditions that are present when EF reduce such as an increased purine

Table 3 characteristics of the population enrolled when divided according to the presence/absence of hyperuricemia with the URRAH cut-off

	URRAH cut-off (5.1 mg/dL for female and 5.6 mg/dL for males)		
	Normal UA	Hyperuricemia	P value
Number	216	195	–
Age	61.4 ± 9.7	63.5 ± 10.5	0.037
Male gender (n, %)	168 (77.8)	160 (82.1)	0.281
CV risk factors and previous diseases			
Smoke (n, %)	62 (28.7)	51 (26.2)	0.572
Familiar history of CV disease (n, %)	97 (44.9)	75 (38.5)	0.253
Body Mass Index (kg/m^2)	26.6 ± 3.7	27.7 ± 4.3	0.006
Overweight or obesity (n, %)	122 (56.7)	128 (66.0)	0.056
Diabetes (n, %)	45 (20.8)	45 (23.1)	0.583
Dyslipidaemia (n, %)	155 (71.8)	141 (72.3)	0.902
Hypertension (n, %)	127 (58.8)	145 (74.4)	< 0.001
Peripheral Artery Disease (n, %)	10 (4.9)	23 (12.4)	0.007
Previous stroke/TIA (n, %)	19 (9.2)	31 (16.7)	0.027
Previous PCI (n, %)	32 (14.8)	44 (22.6)	0.081
Previous CABG (n, %)	3 (1.4)	3 (1.5)	0.141
Critical coronary lesions			
LAD (n, %)	125 (64.4)	110 (68.8)	0.392
RC (n, %)	77 (39.5)	70 (43.2)	
CX (n, %)	67 (34.3)	52 (32.1)	
LM (n, %)	9 (4.6)	10 (6.2)	
Number of coronary arteries involved			
1 (n, %)	105 (53.6)	77 (47.5)	0.211
2 (n, %)	47 (24.0)	55 (34.0)	
3 (n, %)	29 (14.8)	19 (11.7)	
Atrial fibrillation	20 (9.2)	17 (8.7)	0.848
CKD (eGFR < 60 mL/min) (n, %)	25 (12.1)	45 (24.6)	0.001
CV drug therapy			
Beta-blockers (n, %)	199 (92.1)	176 (90.3)	0.791
Statins (n, %)	208 (98.6)	185 (98.4)	0.242
Ezetimibe (n, %)	69 (38.8)	64 (39.8)	0.559
Dual antiplatelet therapy (n, %)	150 (70.4)	118 (61.5)	0.163
ACE inhibitors or ARB (n, %)	166 (76.9)	159 (81.5)	0.243
Calcium Channel Blockers (n, %)	11 (5.1)	6 (3.1)	0.305
Diuretics (n, %)	7 (3.2)	13 (6.7)	0.107
Clinical parameter			
SBP at admission (mmHg)	123.6 ± 15.7	125.7 ± 16.3	0.201
DBP at admission (mmHg)	74.0 ± 8.6	74.4 ± 9.8	0.699
HR at admission (bpm)	64.4 ± 9.8	63.4 ± 9.3	0.320
Biochemical data			
Peak CK-MB (mcg/L)	248.8 ± 725.6	114.6 ± 131.4	0.145
Peak hs-TnT (ng/L)	3166.3 ± 4358.4	3374.2 ± 4025.6	0.734
Triglycerides at admission (mg/dL)	123.0 ± 58.7	131.1 ± 61.7	0.184
LDL cholesterol at admission (mg/dL)	109.2 ± 37.9	101.9 ± 39.0	0.063
Glucose at admission (mg/dL)	108.4 ± 37.3	102.1 ± 24.1	0.065
eGFR MDRD (ml/min/1.73 m^2)	83.8 ± 19.7	73.9 ± 20.3	< 0.001
Echocardiography			
LVEF at admission (%)	54.4 ± 7.7	53.3 ± 9.6	0.221
LVEF at discharge (%)	56.6 ± 6.9	55.1 ± 9.0	0.062
ΔLVEF (%)	2.1 ± 4.8	2.1 ± 4.7	0.916

Table 3 (continued)

	URRAH cut-off (5.1 mg/dL for female and 5.6 mg/dL for males)		
	Normal UA	Hyperuricemia	P value
6-MWT			
6MWT at admission (mt)	475.6 ± 108.9	454.9 ± 88.7	0.037
6MWT at discharge (mt)	587.5 ± 114.0	559.9 ± 105.6	0.015
Δ6MWT absolute (mt)	120.4 ± 71.2	107.8 ± 78.4	0.101
Δ6MWT percentage (%)	20.7 ± 12.5	18.6 ± 11.5	0.099

CV, Cardiovascular; *TIA*, transitory ischemic attack; *PCI*, percutaneous coronary intervention; *CABG*, coronary artery by-pass graft; *LAD*, left anterior descendant; *LM*, left main; *RC*, right coronary; *CX*, circumflex coronary; *CKD*, chronic kidney disease; *eGFR*, estimed glomerular filtration rate; *ACE*, angiotensin converting enzyme; *ARB*, angiotensin receptor inhibitors; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *CK-MB*, creatin kinase MB isoform; *hs-TnT*, high sensitivity Troponin T; *LDL*, low density lipoprotein; *HR*, heart rate; *LVEF*, left ventricular ejection fraction; *6MWT*, six minute walk test

Table 4 Linear regression multivariable analysis with admission EF as the dependent variables

Parameter	Admission EF					
	Uric acid		Hyperuricemia (classic cut-off)		Hyperuricemia (URRAH cut-off)	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
Uric acid (mg/dL)	− 0.16 (− 0.28; − 0.05)	0.048	–	–	–	–
Hyperuricemia classic cut-off (yes vs no)	–	–	− 0.35 (− 0.62; − 0.08)	0.012	–	–
Hyperuricemia URRAH cut-off (yes vs no)	–	–	–	–	− 0.16 (− 0.38; 0.06)	0.153
Age (years)	0.06 (− 0.05; 0.18)	0.289	0.06 (− 0.05; 0.18)	0.287	0.06 (− 0.05; 0.18)	0.297
Sex (female vs male)	0.21 (− 0.06; 0.49)	0.134	0.30 (0.03; 0.57)	0.032	0.29 (0.02; 0.56)	0.036
BMI (kg/m^2)	0.02 (− 0.09; 0.12)	0.764	0.01 (− 0.11; 0.11)	0.995	0.01 (− 0.11; 0.11)	0.969
GFR (mL/min)	0.01 (− 0.11; 0.13)	0.846	0.02 (− 0.09; 0.14)	0.689	0.04 (− 0.08; 0.16)	0.493
Diuretics use (yes vs no)	− 0.07 (− 0.54; 0.40)	0.765	− 0.08 (− 0.55; 0.39)	0.736	− 0.10 (− 0.57; 0.37)	0.679

EF, ejection fraction; *BMI*, Body Mass Index; GFR, glomerular filtration rate

Table 5 Linear regression multivariable analysis with discharge EF as the dependent variables

Parameter	Discharge EF					
	Uric acid		Hyperuricemia (classic cut-off)		Hyperuricemia (URRAH cut-off)	
	β (95 % CI)	P value	β (95 % CI)	P value	β (95 % CI)	P value
Uric acid (mg/dL)	− 0.18 (− 0.30; − 0.07)	0.001	–	–	–	–
Hyperuricemia classic cut-off (yes vs no)	–	–	− 0.43 (− 0.71; − 0.16)	0.021	–	–
Hyperuricemia URRAH cut-off (yes vs no)	–	–	–	–	− 0.19 (− 0.41; 0.02)	0.084
Age (years)	0.01 (− 0.02; 0.21)	0.102	0.09 (− 0.02; 0.21)	0.107	0.09 (− 0.02; 0.21)	0.111
Sex (female vs male)	0.24 (− 0.03; 0.51)	0.078	0.34 (0.08; 0.60)	0.011	0.33 (0.06; 0.59)	0.015
BMI (kg/m^2)	0.04 (− 0.06; 0.15)	0.421	0.02 (− 0.08; 0.13)	0.67	0.03 (− 0.07; 0.14)	0.565
GFR (mL/min)	0.05 (− 0.06; 0.18)	0.367	0.06 (− 0.05; 0.18)	0.302	0.09 (− 0.03; 0.21)	0.149
Diuretics use (yes vs no)	− 0.57 (− 1.14; − 0.01)	0.049	− 0.57 (− 1.13; 0.01)	0.051	− 0.62 (− 1.19; − 0.04)	0.035

EF, ejection fraction; *BMI*, Body Mass Index; *GFR*, glomerular filtration rate

degradation determined by hypoxia and tissue catabolism [29], increase in xanthine-oxidase activity during HF [30, 31], diuretics use (common in the settings of reduced EF) and acute kidney failure that could complicate an ACS or an HF hospitalization.

On the contrary UA could determine a decrease in EF due to an increase local inflammation, angiotensin release and increase in oxidative stress. However, longitudinal data are needed in order to give a definitive direction to this strong and important association.

Coming back to the cut-off issue, the absence of a significant association between UA and EF with the URRAH cut-off, in the absence of longitudinal studies, raise the hypothesis that higher values are needed for UA in order to damage left ventricular systolic function or that, on the opposite direction, when EF reduce UA increase in a significant very manner.

Furthermore, our patients are in a late stage of atherosclerotic disease (already with at least one CV events) and it is also possible that UA is more able to damage endothelium and arteries in a first phase when they are still healthy. When the disease progress to a more advanced stage higher values are needed to further determine a damage because the effect of lower values can be overshadowed by the other CV risk factors (aging process, previous ACS or revascularization for a CCS and comorbidities).

The results of our study are influenced by some limitations, the first of which is the cross-sectional nature of the study. As already mentioned, because of this, the direction of the observed association could not be determined. Secondly, ours is a monocentric study and so generalizability could be influenced by local patients' selection and procedures. Furthermore, the lack of a second uric acid dosage (at discharge) didn't provide us any information on its changes determined by the CR. Finally, the use of allopurinol or febuxostat was not reported.

5 Conclusions

HU is as frequent in CR patients as in those with ACS and CCS. UA didn't correlate with functional recovery (Δ6MWT) while it presents significant association with admission and discharge left ventricular EF as also is for HU evaluated with the classic cut-off. When the lower URRAH cut-off was used prevalence increases significantly, however, it doesn't show any significant association with EF.

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Declarations

Conflict of Interest The authors declare they have no conflict of interest.

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