Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

The prognostic impact of uric acid in patients with severely decompensated acute heart failure

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ARTICLE INFO

Article history:
Received 26 February 2016
Received in revised form 12 April 2016
Accepted 18 April 2016
Available online xxx

Keywords:
Uric acid
Renal failure
Loop diuretics
Acute heart failure syndrome

ABSTRACT

Background: The serum level of uric acid (UA) is a well-known prognostic factor for heart failure (HF) patients. However, the prognostic impact of hyperuricemia and the factors that induce hyperuricemia in acute HF (AHF) patients are not well understood.

Methods and results: Eight hundred eighty-nine AHF patients were enrolled in this study. The patients were assigned into a low UA group (UA $\leq$ 7.0 mg/dl, n = 495) or a high UA group (UA $>$ 7.0 mg/dl, n = 394) according to their UA level on admission. A Kaplan–Meier curve showed that the survival rate of the low UA group was significantly higher than that of the high UA group. A multivariate Cox regression model identified that a high UA level (HR: 1.192, 95%CI 1.112–1.277) was an independent predictor of 180-day mortality. A multivariate logistic regression model for a high serum UA level on admission indicated that chronic kidney disease (CKD) (OR: 2.030, 95%CI: 1.298–3.176, p = 0.002) and the administration of loop diuretics before admission (OR: 1.556, 95%CI: 1.010–2.397, p = 0.045) were independent factors. The prognosis, including all-cause death and HF events, was significantly poorer among patients who had a high UA level who had previously used loop diuretics and among CKD patients with a high UA level than among other patients.

Conclusions: The serum UA level was an independent predictor in patients who were hospitalized during an emergent situation for AHF. An elevated serum UA level on admission was associated with the presence of CKD and the use of loop diuretics. These factors were also associated with adverse outcomes in hyperuricemic patients with AHF.

Introduction

The serum levels of uric acid (UA) are an important risk factor for several adult lifestyle-related diseases that are etiologically attributed to atherosclerosis, including hypertension, diabetes mellitus, and metabolic syndrome [1,2]. Furthermore, they can predict a worse outcome in patients with chronic kidney disease (CKD), and cardiovascular disease (including coronary artery disease and stroke) [3–5].

Previous studies have shown that elevated levels of serum UA are also associated with adverse clinical outcomes in patients with chronic heart failure (HF) [6–9]. Tamariz et al. reported the results of a meta-analysis from six clinical trials that included a total of 1456 HF patients. They noted that the degree of serum UA level had a linear association with adverse outcomes, and that a UA level of >7 mg/dl was an independent predictor of all-cause mortality [7]. Moreover, Kim et al. reported that serum UA was the only predictor of the prognosis in patients with non-ischemic diastolic cardiomyopathy and that it was a better prognostic factor than the N-terminal pro B-type natriuretic peptide (BNP) level [8]. In fact, serum UA has been adopted as one of the predictive markers for the

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http://dx.doi.org/10.1016/j.jjcc.2016.04.013
0914-5087/

major HF scoring systems, such as the Seattle Heart Failure Model and the SENIORS mortality risk model [9,10].

As mentioned above, most researchers only investigated the serum level of UA in chronic HF or HF patients with a preserved ejection fraction [11,12], with relatively few examining the levels in patients with acute HF (AHF) [13,14]. Furthermore, no study has been conducted in Japanese populations. In addition, whether the elevated levels of serum UA are associated with atherosclerotic factors in AHF patients is unclear. Thus, it is necessary to determine the factors that induce hyperuricemia in AHF patients and to investigate the impact of hyperuricemia on their prognosis. We therefore investigated the prognostic impact of the serum UA level and the factors that induce hyperuricemia in Japanese patients who were admitted to an intensive care unit (ICU) with AHF.

Methods

Subjects

Eight hundred eighty-nine patients who were admitted to the ICU at Nippon Medical School Chiba Hokusoh Hospital between January 2000 and December 2014 and who underwent the measurement of serum UA were enrolled in this study. AHF was defined as either new-onset HF or the decompensation of chronic HF with symptoms sufficient to warrant hospitalization [15]. HF was diagnosed according to the Framingham criteria for a clinical diagnosis of HF, based on the fulfillment of two major criteria or one major and two minor criteria [16]. All of the patients had a New York Heart Association (NYHA) functional class of either III or IV. Based on the European Society of Cardiology guidelines for the diagnosis of AHF, an abnormal electrocardiogram result or the presence of pulmonary edema on a chest X-ray and a BNP level of $\geq$100 pg/ml are required to diagnose AHF [17]. The treating physician in the emergency department diagnosed AHF based on these criteria within 30 min of admission by filling out a form. The patients who met one of the following criteria were admitted to the ICU: (1) patients who needed high projectile oxygen inhalation (including mechanical support) to treat orthopnea; (2) patients who needed inotrope or mechanical support due to low blood pressure; and (3) the patients who needed the various types of diuretics to improve general or lung edema. All the patients in the present study received either diuretics or vasodilators for the treatment of AHF after admission. Patients with HF caused by acute coronary syndrome, overflow in regular hemodialysis or end-stage kidney disease, pulmonary hypertension or right-sided HF, and non-Japanese patients were excluded from the study. All of the data were retrospectively retrieved from hospital medical records.

Serum UA measurements and the definition of hyperuricemia

Serum samples were obtained from all 889 patients on the day of admission, within 30 min, from 354 patients who were admitted from May 2011 to December 2014, and within 24 h from 535 patients who were admitted from January 2000 to April 2011. If it was difficult to examine the blood samples on the day of sampling, they were cooled to 2–10 °C. An absorptiometry kit (Sekisui Medical Company, Tokyo, Japan) was used to measure the UA level based on the hydrogen peroxide produced in the chemical reaction that occurs when UA is combined with uricase. In the present study, a UA level of >7.0 mg/dl was defined as high, according to the Japanese guidelines [18].

Procedure

The patients were divided into two groups, consisting of a low UA group (UA $\leq$ 7.0 mg/dl; n = 495) and a high UA group (UA > 7.0 mg/dl; n = 394) according to their serum UA level on admission. We compared the patients' characteristics including their age, sex, gender, the presence of *de novo* or recurrent HF, the clinical scenario classification [19], the etiology of HF, risk factors for atherosclerosis (diabetes mellitus, hypertension, dyslipidemia, smoking, and obesity), vital signs, arterial blood gas, laboratory data, the medications taken before admission, and the outcome. The significant factors indicating elevated serum UA on admission were determined by the multivariate logistic regression model. The prognostic value for 180-day mortality was evaluated using a Cox regression hazard model and a Kaplan–Meier curve.

Statistical analysis

All of the data were statistically analyzed using the SPSS 21.0 software program (SPSS Japan Institute, Tokyo, Japan). All of the numerical data were expressed as medians (range or 25–75% interquartile range), depending on normality. Normality was assessed using the Shapiro–Wilk W test. An unpaired Student's t-test or the Mann–Whitney U test was used to compare two groups. Comparisons of all proportions were made using a chi-squared analysis. Values of p less than 0.05 were considered to indicate statistical significance.

The prognostic value of an elevated UA level on admission (UA > 7.0 mg/dl) in comparison to non-elevated UA levels (UA $\leq$ 7.0 mg/dl) as a referent was assessed using a Cox regression hazard model. A Cox regression analysis was performed to determine the HR for 180-day mortality and HF events. The factors with p-values of <0.05 in the univariate analysis were included in a multivariate analysis to determine the factors that were independently associated with high UA (>7.0 mg/dl) on admission. The survival rates in the two groups were analyzed using Kaplan–Meier curves, and the log-rank test was used to calculate the statistical significance of differences.

Ethics review board

The institutional review board at Nippon Medical School Chiba Hokusoh Hospital approved the study protocol.

Results

The mean serum UA level of the whole population was 6.8 mg/dl; 44.3% of the patients had hyperuricemia (UA > 7.0 mg/dl). The relationship between the patient characteristics and the UA level on admission are shown in Table 1. Male subjects accounted for 64.4% of the whole study population, which had a median age of 74 years. The patients in the high UA group were more likely to be male than those in the low UA group and patients in the high UA group were significantly younger than those in low UA group. Regarding the atherosclerotic risk factors, the patients in the high UA group were more likely to be obese, have a history of smoking, and to have other risk factors than those in the low UA group. The total bilirubin, serum potassium, blood urea, creatinine and BNP levels were significantly higher, and the hemoglobin, arterial PCO_2, and HCO_3^- levels were significantly lower in the high UA group than in the low UA group. The population of patients with chronic kidney disease (CKD) was higher and the left ventricular ejection fraction (LVEF) on echocardiography was significantly lower in the high UA group than in the low UA group. A significantly higher number of patients in the high UA group were administered loop diuretics, calcium channel blockers, and statins before hospitalization. The length of ICU hospitalization was significantly longer, and in-hospital mortality rate was significantly higher in the high UA group. The Kaplan–Meier curves for the serum UA levels are shown in

Please cite this article in press as: Okazaki H, et al. The prognostic impact of uric acid in patients with severely decompensated acute heart failure. J Cardiol (2016), http://dx.doi.org/10.1016/j.jjcc.2016.04.013