

Prognostic value of serum uric acid in patients with acute heart failure

A meta-analysis

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Abstract

Background: Conflicting results have been reported on the prognostic significance of serum uric acid (SUA) in patients with acute heart failure (AHF). This meta-analysis aimed to determine the prognostic significance of SUA level in patients with AHF.

Methods: We made a comprehensive literature search in Pubmed and Embase databases from inception to April 6, 2018. All available observational studies or post hoc analysis of randomized controlled trial that evaluated the prognostic value of SUA level in patients with AHF were eligible. Outcome of interests were all-cause mortality and the combined endpoint of death or readmission. Prognostic values of SUA level were summarized as higher vs lower SUA category or per 1 mg/ml SUA rise.

Results: Ten studies involving 12,854 AHF patients were identified and analyzed. AHF patients with the highest SUA level had an increased risk of all-cause mortality (risk ratio [RR] 1.43; 95% confidence intervals [CI] 1.31–1.56) and combined endpoint of death or readmission (RR 1.68; 95% CI 1.33–2.13) after adjusting potential variables. In addition, per 1 mg/ml SUA rise significantly increased by 11% and 12% higher risk all-cause mortality and combined endpoint of death or readmission, respectively. A leave out 1 study sensitivity analysis confirmed the reliability of the pooling effect sizes.

Conclusion: This meta-analysis indicates that elevated SUA level independently predicts all-cause mortality and the combined endpoint of death or readmission in AHF patients. Measurement of SUA level may improve risk stratification of adverse outcomes in these patients.

Abbreviations: AHF = acute heart failure, CI = confidence intervals, NOS = Newcastle–Ottawa Scale, RR = risk ratios, SUA = serum uric acid.

Keywords: all-cause mortality, major adverse cardiac events, meta-analysis, uric acid

1. Introduction

Heart failure is a worldwide public health concern. Acute heart failure (AHF) is a complex heterogeneous clinical syndrome.^[1] Despite the advance of medical care, AHF is still associated with high death and readmission rate.^[2] Therefore, early identification of AHF patients with poor prognosis is still an unmet need for better guide treatment. Accurate prediction of adverse outcomes of heart failure patients is an ongoing challenge.

Biomarkers can be used to refine the risk classification of AHF patients. Uric acid is a product of the metabolic breakdown of purine nucleotides.^[3] Serum uric acid (SUA) is under investiga-

tion as prognostic biomarker in heart failure patients.^[4,5] Previous 2 meta-analyses^[6,7] have demonstrated that a higher level of SUA was a strong and independent predictor of all-cause mortality in patients with heart failure. However, this conclusion was mainly built on chronic heart failure patients and the strength of the prognostic value of SUA in AHF patients remains controversial. Nevertheless, magnitude of the reported prognostic value varied considerably.

Several new studies investigating the prognostic significance of SUA in AHF patients have been published, which instigated our efforts to conduct a focused meta-analysis. Therefore, we aimed to evaluate the prognostic value of SUA level among AHF patients in terms of all-cause mortality and the combined endpoint of death or readmission by performing a meta-analysis.

2. Materials and methods

2.1. Literature search

We made a comprehensive literature search in Pubmed and Embase databases from inception to April 6, 2018. Our search strategy included the following combined keywords:

“uric acid” OR “urate” OR “hyperuricemia” AND “acute heart failure” OR “congestive heart failure” AND “mortality” OR “death” OR “hospitalization” OR “major adverse cardiovascular events” AND “prognostic”. References of relevant articles were manually reviewed to ensure identification of any additional studies. No language restrictions were imposed. Ethical approval was not necessary due to the current study only applied the study-level data.

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2.2. Study selection

Two authors independently selected the eligible studies according to the following criteria:

1. Original full-text observational studies or post hoc analyses of randomized controlled trials;
2. reported the prognostic value of all-cause mortality or death combined readmission associated with SUA level in AHF patients;
3. provided multivariate adjusted hazard ratios (HR), risk ratio (RR) or odds ratios (OR) with their corresponding 95% confidence intervals (CI) for the prognostic measures;
4. follow-up duration no less than 3 months.

The exclusion criteria were:

1. enrollment of chronic heart failure patients;
2. reported the unadjusted risk estimates;
3. when multiple publications from the same studied patients, we selected the longest follow-up articles.

2.3. Data extraction and quality assessment

Two authors independently extracted the following data from each study: first author's surname, publication year, study design, study location, sample size, patient age and gender, cutoff value of SUA, event number, duration of follow-up, multivariate adjusted risk estimate for prognostic outcomes, and adjustment for variables. The study quality of the selected studies was assessed using the Newcastle–Ottawa Scale for the cohort studies.^[8] Studies with 7 or more points were considered as good quality. Any discrepancies in data extraction and quality assessment were resolved by discussion.

2.4. Statistical analysis

All the meta-analyses were conducted using STATA12.0 software (Stata Corporation, College Station, TX). Data analyses were performed using the most fully adjusted risk estimate for the higher vs the lower SUA level or each 1 mg/ml SUA rise. For analyzing SUA as continuous value, we recalculated risk estimate by 1 mg/ml SUA rise using the following formula: $RR1 = \exp(\ln(RRSD)/SD)$. The pooled summary was expressed as RR and 95% CI. To explore the heterogeneity across studies, we applied the Cochran Q statistic (significance level of $P < .10$) and I^2 statistics (significance level of 50%). A random effects model was used when the significant heterogeneity among studies was found. Otherwise, we selected a fixed-effect model. Publication bias was assessed using the Begg rank correlation^[9] and Egger linear regression test^[10] when the number of analyzed studies was more than ten.^[11] To investigate the influence of any single study on the pooling summary, sensitivity analysis was performed by removing individual study at each turn.

3. Results

3.1. Search results and studies characteristics

Figure 1 shows the study selection process. The electronic literature search produced 732 potential citations. Of these, 246 records were screened after duplicated articles removed. We excluded 192 obvious irrelevant articles after reviewed the titles and abstracts thus retrieved 54 full-text articles for a detailed assessment. Forty-three studies were further removed mainly

because the studied populations were not restricted in AHF patients. No additional studies were identified from the hand search. Thus, 10 studies^[12–21] finally met our predefined inclusion criteria.

Baseline characteristics of these 10 studies are presented in Table 1. A total of 12,854 AHF patients were identified and analyzed. The mean/median age of the patients ranged from 68.2 to 82 years. All the selected studies were retrospective analysis. The sample size of the included studies ranged between 167 and 8246. The duration of follow-up ranged from 3 to 27.5 months. Of these studies, 2 reported the risk estimate by both categorical and continuous SUA level, 2 reported the risk estimate by categorical SUA level, and 5 reported data as continuous SUA level. For methodological quality assessment, the NOS of these studies ranged from 5 to 7 points.

3.2. All-cause mortality

Three studies^[12–14] reported the all-cause mortality outcome by categorical SUA level and 4 studies^[13,14,17,22] provided data by continuous SUA level. As shown in Figure 2A, elevated SUA level was associated with an increased risk of all-cause mortality (RR 1.43; 95% CI 1.31–1.56) in a fixed-effect model. There was no significant heterogeneity across studies ($I^2 = 0\%$; $P = .550$). In addition, each 1 mg/dl rise in SUA level, the pooled RR of all-cause mortality was 1.11 (95% CI 1.08–1.14; Fig. 2B). Heterogeneity was not significant among studies ($I^2 = 41.8\%$; $P = .161$). Sensitivity analysis suggested that individual study could not significantly influence the overall pooled risk summary (data not shown).

3.3. Combined endpoint of death or readmission

Three studies^[12,18,21] reported the combined endpoint of death or readmission events by categorical SUA level analysis and four studies^[15,16,20,21] reported this outcome by continuous SUA level analysis. As shown in Figure 3A, elevated SUA level was associated with an increased risk of the combined endpoint of death or readmission (RR 1.68; 95% CI 1.33–2.13) in a fixed-effect model, without statistical significant heterogeneity among studies ($I^2 = 36.7\%$; $P = .192$). Moreover, each 1 mg/dl rise in SUA level increased by 12% (RR 1.12; 95% CI 1.07–1.17; Fig. 3B) risk of the combined endpoint of death or readmission. No statistically significant heterogeneity ($I^2 = 0\%$; $P = .747$) was found across these studies. Sensitivity analysis by removal of 2 studies^[15,20] with short-term (3months) following duration, the pooled RR of the combined endpoint of death or readmission was 1.12 (95% CI 1.06–1.18) for each 1 mg/dl rise in SUA level.

3.4. Publication bias

The number of analyzed studies in the outcomes was small; therefore, we did not perform a funnel plot, Begg rank or Egger test to examine publication bias.

4. Discussion

The main findings of this meta-analysis suggested that high SUA level independently predicted all-cause mortality and the combined endpoint of death or readmission in AHF patients. AHF patients with hyperuricemia were associated with a 43% and 68% higher risk of all-cause mortality and the combined endpoint of death or readmission. Furthermore, per 1 mg/ml SUA

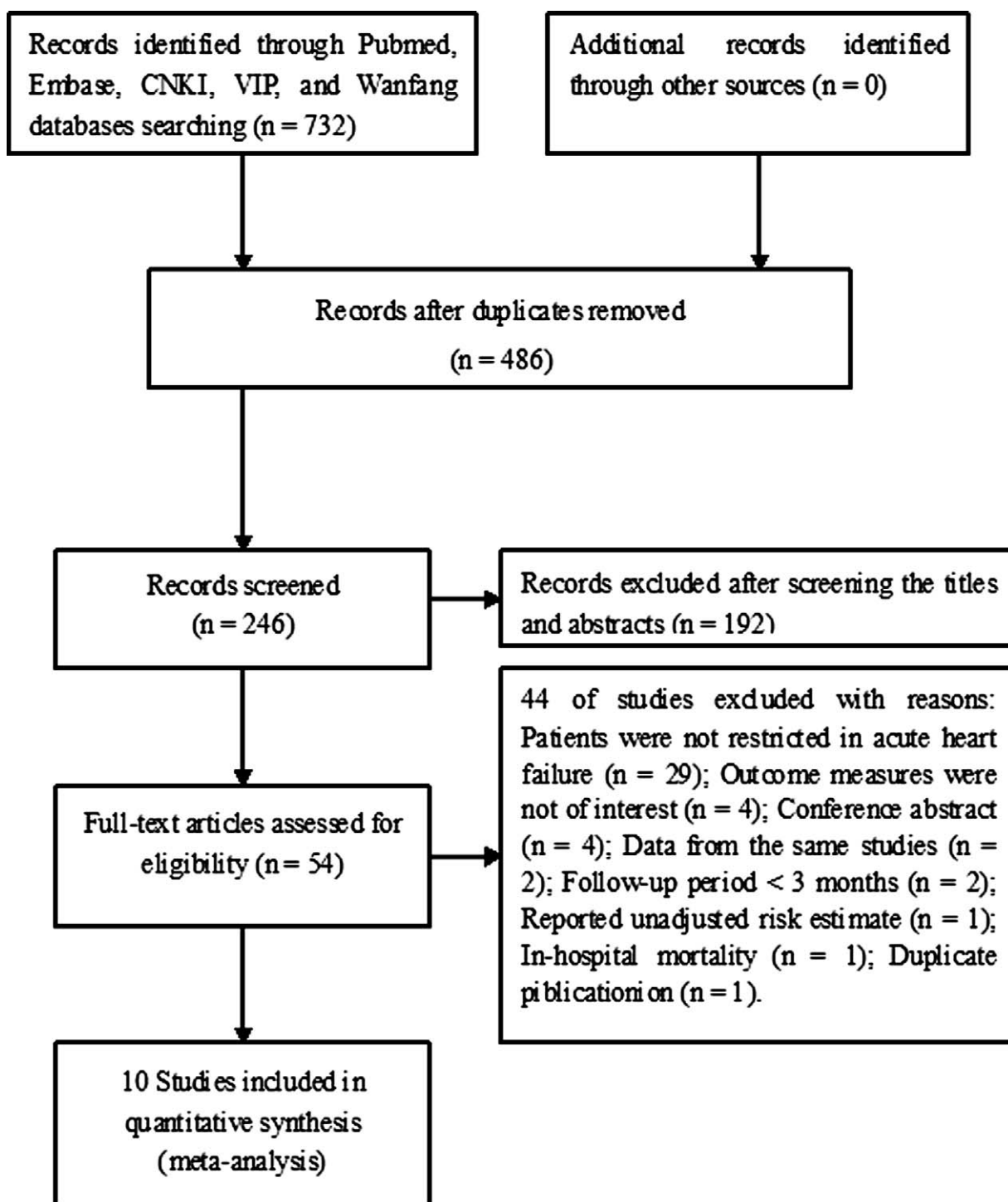


Figure 1. Flow chart of studies selection process.

rise significantly increased by 11% all-cause mortality and 12% combined endpoint of death or readmission risk.

The prognostic significance of hyperuricemia on mortality and readmission has been widely investigated both in patients with AHF and chronic heart failure. In line with our meta-analysis, 2 previous meta-analyses have summarized that hyperuricaemia (SUA > 6.5 mg/dl) was associated with approximately 2.1-fold higher risk of all-cause mortality in both acute and chronic heart failure patients. However, most of the selected studies enrolling

chronic heart failure patients. By contrast, our meta-analysis focused on AHF patients who required intensive care. AHF patients with hyperuricemia were associated with a 43% greater risk of all-cause mortality. Uric acid level at admission was an independent predictor of readmission or all-cause death during a 30 day period after discharge in acutely decompensated heart failure.^[23] In addition, hyperuricemia was associated with increased all-cause mortality and the composite endpoint in patients hospitalized for worsening chronic heart failure.^[24]

Table 1

Baseline characteristics of the included studies.

Author/year	Region	Study type	Sample size (% male)	Age (years)	LVEF (%)	Creatinine (mg/dl)	SUA cutoff	Sample timing	Event number HR/OR (95% CI)	Follow-up (mean)	Variables adjusted	NOS score
Pascual-Figal 2007 ^[1,2]	Spain	Retrospective	212 (71)	69.6±11	31±8	1.3±0.6	7 mg/dl (M) 6 mg/dl (W)	Discharge	Death or HF readmission:100; 1.64 (1.06–2.55); Total death:48	20.4 months	Age, sex, diuretics, creatinine clearance, LVEF, NYHA, ACEI or ARB, β-blocker, and urea	7
Almonda 2009 ^[3]	Spain	Retrospective	560 (54.8)	73.6±10.4	NP	1.15±0.5	7.7 mg/dl; Per 1 mg/dl rise	Admission	Total death:165; 1.45 (1.03–2.05); 1.08 (1.01–1.15)	27.5 months	Age, gender, previous admission for acute HF, NYHA, valvular etiology, SBP, diuretics, Charlson index, LVEF, eGFR, serum sodium and hemoglobin	7
Novack 2010 ^[4]	Israel	Retrospective	8246 (62.2)	75.6±11.8	NP	NP	6.5 mg/dl; Per 1 mg/dl rise #	Admission	Total death:2365; 1.42 (1.30–1.56); 1.11 (1.08–1.14)	12 months	Age, sex, DM, AF, COPD, dyslipidemia, hypertension, dementia, Charlson index, history of MI or bypass surgery, RBC, WBC, hematocrit, urea, eGFR, sodium, potassium, albumin, and medications	8
Park 2010 ^[15]	Korea	Retrospective	183 (39.4)	69±13	42.1±16.5	1.36±0.86	Per 1 mg/dl rise	Admission	MACES:28; 1.11 (1.01–1.23)	3 months	Age, NT-ProBNP, creatinine clearance, no ACEIs or ARB	6
Kim 2015 ^[16]	Korea	Retrospective	232 (45.7)	72.3±12.5	37.1±14.5	1.33±0.88	Per 1 mg/dl rise	Admission	Death or HF readmission:77; 1.18 (0.999–1.252); Total death:794	24 months	Multivariate adjustment	6
Huang 2016 ^[17]	Taiwan	Retrospective	1835 (68)	75±13	53.8±21	NP	Per 1 mg/dl increase #	Admission	1.10 (1.02–1.18)	27.1 months	Age, gender, PASP, hemoglobin, eGFR, sodium, medications, and NT-proBNP	7
Palazzuoli 2017 ^[8]	Italy	Post hoc analysis	324 (64.5)	82 (79–85)	NP	1.20 (0.91–1.64)	7 mg/dl (M) 6 mg/dl (W)	Admission	Death or HF readmission: 262; 1.24 (0.81–1.90) reduced LVEF; 2.75 (1.52–5.00) preserved LVEF;	6 months	Age, gender, hypertension, anemia, DM, blood urea nitrogen, CAD and AF	7
Okazaki 2017 ^[9]	Japan	Retrospective	394 (76.1)	72 (62–79)	32 (23–45)	1.37 (1.05–1.90)	Per 1 mg/dl rise	Admission	Total death:NP; 1.27 (1.12–1.44)	12 months	Age, gender, eGFR, BNP, sodium, CRP, and hemoglobin	7
Wu 2017 ^[20]	China	Retrospective	167 (38.2)	68.2±12.2	43.1±17.2	1.59±1.06	Per 1 mg/dl rise	Admission	Death or HF readmission:37; 1.13 (1.01–1.26)	3 months	Age, NT-ProBNP, creatinine clearance, no ACEIs or ARB, and diuretics	6
Córo 2018 ^[21]	Italy	Retrospective	196 (64.5)	77 (69–83)	35 (25–45)	1.5±1.0	>8.4 vs vs < 6.1; Per 1 mg/dl rise	Discharge	Death or HF readmission:122; 1.84 (1.16–2.93); 1.10 (1.04–1.17)	27 months	Male gender, COPD, previous af, congestion score, SpO2 < 90%, sodium at discharge, furosemide, and no ACEI/ARB at discharge	7

ACEI = angiotensin converting enzyme inhibitors, AF = atrial fibrillation, ARB = angiotensin receptor blockers, BMI = body mass index, BNP = B-type natriuretic peptide, CAD = coronary artery disease, CI = confidence interval, CKD = chronic kidney disease, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, HF = heart failure, HR = hazard ratio, OR = odds ratio, HYP = hypertension, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NOS = Newcastle–Ottawa Scale, NT-proBNP = N-terminal pro-hormone brain natriuretic peptide, PAD = peripheral arterial disease, PASP = pulmonary artery systolic pressure, RAS = renin-angiotensin system, SBP = systolic blood pressure.

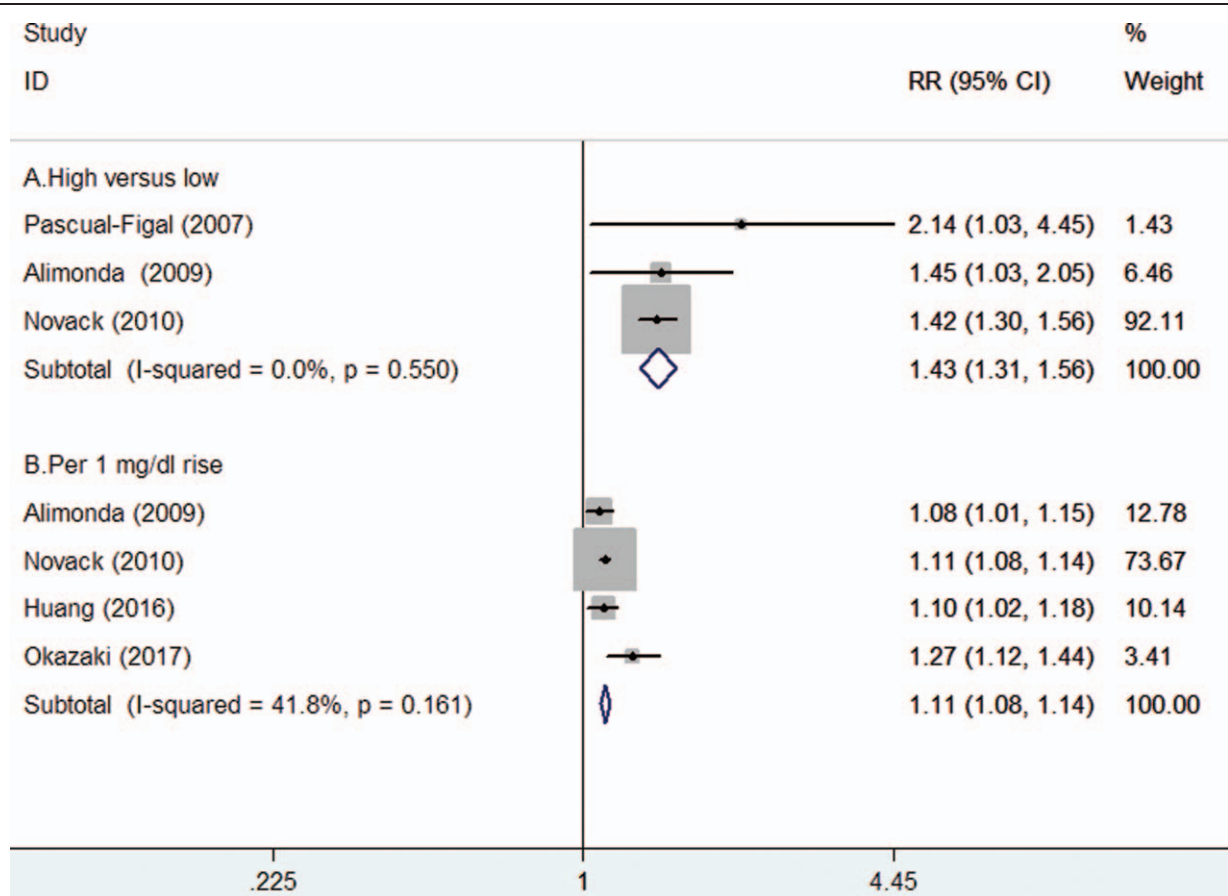


Figure 2. Forest plots showing pooled RR with 95% CI of all-cause mortality for the higher vs lower serum uric acid level (A) and per 1 mg/dl serum uric acid rise (B).

Left ventricular ejection fraction (LVEF) of AHF may be an important confounder for the prognostic value of SUA. In patients with preserved LVEF, concomitant hyperuricemia was significantly associated with the combined endpoint of death or readmission but not in those with reduced LVEF.^[18] The reduced LVEF reflects a severe condition of heart failure. The impact of hyperuricemia on the prognosis was more pronounced in preserved LVEF than reduced LVEF. However, due to insufficient data, we could not conduct subgroup analysis according to the LVEF.

Patients admitted to hospital with heart failure commonly have some degree of renal dysfunction.^[25] Worsening renal function is one of the most important prognostic variables in heart failure patients.^[26] The impaired renal clearance and upregulation of xanthine oxygenase can be responsible for elevated uric acid level.^[27] Ischemic renal dysfunction rather than xanthine oxidoreductase activity may be the predominant factor for elevated uric acid level in AHF.^[15]

Despite the marked reduction of uric acid level, xanthine oxidase inhibitors (XOI) had no clear effect on improving clinical outcomes in the OPT-CHF study^[28] and EXACT-HF trial.^[29] However, post hoc analysis of the OPT-CHF study^[28] revealed that benefits occurred in patients with increased SUA level in a manner correlating with the degree of SUA reduction. A recently published meta-analysis^[30] showed that use of XOI could reduce total cardiovascular events but not all-cause mortality and worsening heart failure. However, this well-designed meta-analysis enrolled heterogeneous patients but not focused on the

AHF patients. Therefore, the benefits of uric acid lowering therapy should be further investigated in the specific subgroup of heart failure patients.

Our meta-analysis had a number of potential limitations. First, our meta-analysis analyzed the retrospective study-level data but not individual patients's data and the inherent limitation of the original studies could not be avoided. Second, the number of the analyzed study in individual outcomes was small, which prevented us to conduct the subgroup analysis. In addition, different follow-up duration also may make the results less reliable. Third, majority of patients enrolled in the analysis were elderly population, therefore, generalizability of the present findings to the younger patients should be with caution. Fourth, the included studies reported the various cut-off value of SUA level and we could not determine the optimal cut-off value of hyperuricemia. Finally, use of diuresis is an important prognostic factor about both hospitalization and mortality in patients with heart failure. However, this variable was not clearly defined in the individual studies. Lack of adjustment of patients' past medical history of gout, use of XOI or diuresis in the statistical model may have affected the prognostic significance of SUA.

5. Conclusions

AHF patients with a higher level of SUA significantly increase risk of all-cause mortality and the combined endpoint of death or readmission, even after adjustment for conventional confounding factors. Determination of SUA level may improve risk stratifica-

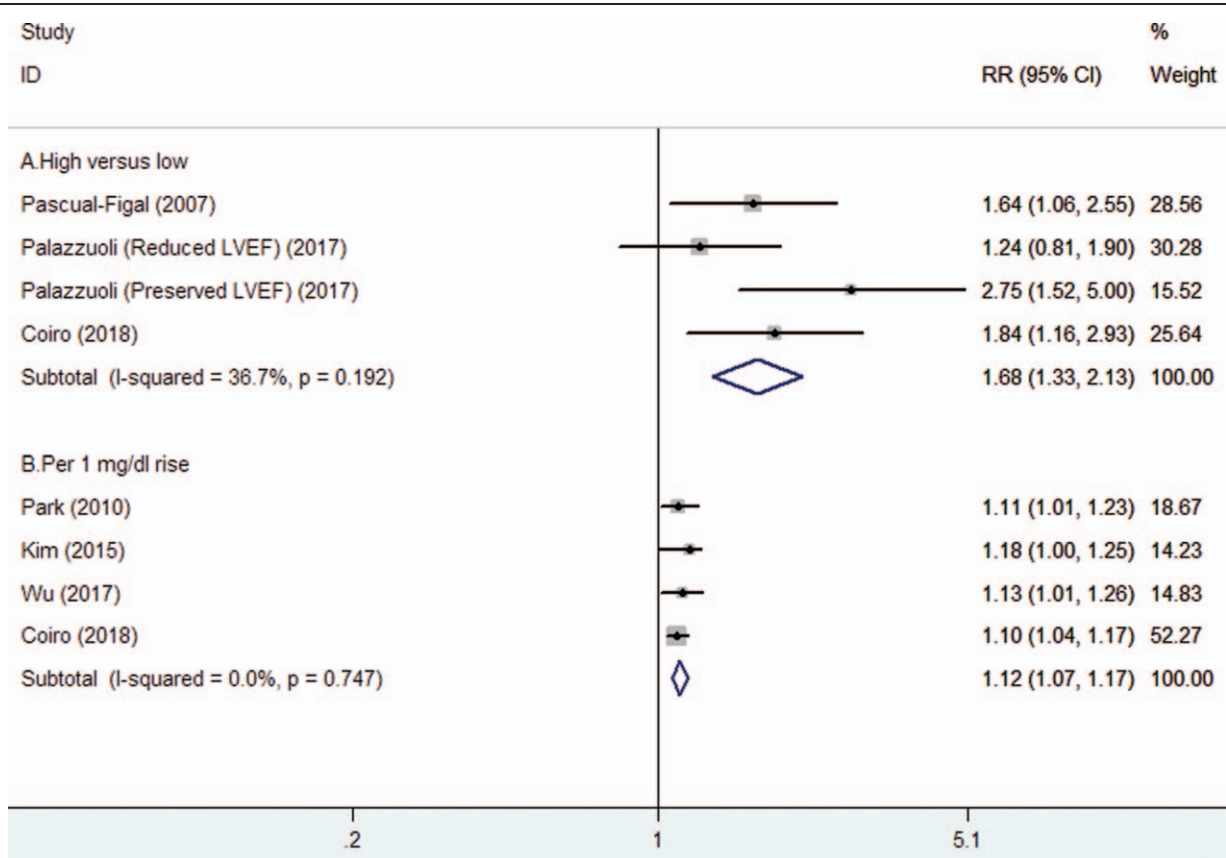


Figure 3. Forest plots showing pooled RR with 95% CI of the combined endpoint of death or readmission for the higher vs lower serum uric acid level (A) and per 1 mg/dl serum uric acid rise (B).

tion in patients with AHF. Future large randomized controlled trials are needed to evaluate whether use of xanthine oxidase-inhibitor can improve the prognosis.

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