Author's response to reviews

Title: A cross-sectional analysis of the relationship between uric acid and coronary atherosclerosis in patients with suspected coronary artery disease in China

Authors:

yujiao sun (sunnuyjiaomy08@sina.cn)
xin yu (1442665097@qq.com)
ying zhi (448590615@qq.com)
song geng (418334319@qq.com)
hua li (1694651910@qq.com)
ting liu (250170204@qq.com)
ke xu (375479902@qq.com)
ling chen (965441808@qq.com)
chunwei wu (10857296@qq.com)
guoxian qi (qigx2011@hotmail.com)

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Author's response to reviews: see over
Dear editors,

**MS: 9191593421054725 - A cross-sectional analysis of the relationship between uric acid and coronary atherosclerosis in patients with suspected coronary artery disease in China**

First of all thanks very much for the reviewers and editors to give me the opportunity to modify the paper. Now, I have finished modification according to the opinions provided by reviewers, and submitted the revised manuscript. In the revised manuscript, the modify content were marked by red front. In the covering letter, I will answer the specific comments of the reviewers and explaining point-by-point

Thanks very much for giving us the opportunity to revise the paper again, If you have any question, please feel free to contact us.

**Here are answers to questions.**

**Comment 1.**

**Reviewer: Takafumi Okura**

**Reviewer's report:**

1) Why did authors exclude the patients who had known CAD or myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting? These patients were identified as high risk patients with coronary arteriosclerosis.

The title of the paper is “A cross-sectional analysis of the relationship between uric acid and coronary atherosclerosis in patients with suspected coronary artery disease in China”. In this study, we assessed the association between UA and coronary atherosclerosis in patients with suspected CAD who underwent 256-detector-row coronary computed tomographic angiography (CCTA).

We mainly want to explore the relationship between uric acid and early coronary atherosclerosis. Patients with known CAD may implement lifestyle modifications and drugs intervention to some extent, the real relationship between uric acid and coronary atherosclerosis may be influenced by those confounding factors; the low accuracy of coronary CT image analysis may occur in patients with percutaneous coronary intervention or coronary artery bypass grafting. So, we exclude the patients who had known CAD or myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting according to the purpose and the characteristics of patients in the study.

2) Uric acid level is influenced by age, sex and renal function. If authors have renal function data, they should include renal function (creatinine et al) in simple
and multiple analyses.

We have creatinine data, we have added the data in the paper. Please see the red words in tables.

3) Why did authors define coronary lesions $\geq 50$ and $70\%$ as significant and severe stenosis, respectively?

The definition of significant and severe stenosis of the coronary artery were different in different study. Some studies defined coronary lesions $\geq 50$ and $75\%$ as significant and severe stenosis, but some studies defined coronary lesions $\geq 50$ and $70\%$ as significant and severe stenosis (JACC 2011;58:2533-40, Atherosclerosis 2011; 219: 573-578, et al.). Because patients with suspected CAD were enrolled in the study, the degree of lesion was relatively less severe, so we define coronary lesions $\geq 50$ and $70\%$ as significant and severe stenosis according to our data.

3) Please show the representative view of calcified, non-calcified and mixed plaque.

I added the picture in the paper(fig 2).

4) In discussion, the LIFE study showed that the beneficial effects observed with losartan did not contribute to decreasing UA level. Is it true?

I change the words, I think it is more apt to express the opinion. “The LIFE study showed an association between UA and cardiovascular events in hypertensive women, the unique results may be due in part to the specific feature of reduction of UA by losartan, but it did not mean that the beneficial effects observed with losartan were contributed to decreasing UA levels.” Please see red words.

Comment 2.

Reviewer: Angelo Gaffo

Reviewer's report:

Major compulsory
- The title describes the study as cross sectional, and I agree with that from reviewing the methods. However, the methods start by calling the study “prospective”. Probably the prospective element was in how the patients were recruited but I would correct the methods section.

This is our carelessness, I deleted the word “prospective” in the method.

- What was the rationale for excluding patients with known CAD from this
analysis?

The title of the paper is “A cross-sectional analysis of the relationship between uric acid and coronary atherosclerosis in patients with suspected coronary artery disease in China”. In this study, we assessed the association between UA and coronary atherosclerosis in patients with suspected CAD who underwent 256-detector-row coronary computed tomographic angiography (CCTA).

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-It is unclear at different moments which analyses are done using quartiles for the whole population or sex-specific quartiles. I would review the verbage throughout the manuscript to make this as clear as possible.

The UA quartiles specific information for the whole population or sex-specific quartiles have been added in the result of the study. Please see red words. The UA quartiles for the whole population or sex-specific quartiles are marked below the figures in the study.

-The discussion does not flow well, in my opinion. Starts with a summary of the results, which is good but then the authors dwell in why they used CCTA and not CAG which I find unnecessary. Later, I find very little in the actual meaning and implications of their results. I appreciate their contrast with prior published data and would add data published also using IMT measurement by US and its association with uric acid levels.

In the discussion, we think it may be necessary to illustrate why we used CCTA and not CAG. Because some people think CAG is the best choice to assess the coronary artery lesion, so we illustrate the benefit of CCTA in discussion of the study. I added data published also using IMT measurement by US and its association with UA in the discussion. Please see red words.

-Please review the paper, mainly the discussion, for English grammar and syntax. Many table titles also need to be reviewed. Some sections in tables lack capitalization and others are misspelled (“Muitivariate”)
I modified the grammar and syntax, table titles, capitalization and misspelled.

**Minor essential**
- The verbage where the patient exclusions are described is confusing. Please consider writing this paragraph (in “Study population”) more clearly. A CONSORT type diagram might be helpful. Also, how where the excluded patients different from the included population?

I write the diagram of the path of patients enrollment to describe the inclusion and exclusion criteria, it might be more clearly(fig.1). The excluded patients are not within the field of the study, or the excluded patients may influence the results of the study. So in order to reflect the real relationship between UA and and coronary atherosclerosis in patients with suspected CAD, we excluded these confounding patients.

- Is always useful in these uric acid epidemiology studies to have a brief description of the uric acid measurement method. Was it uniform throughout the study enrollment period?

I added the section in the paper. The contents of uric acid were measured with enzyme kinetics in all enrolled patients, and it was uniform throughout the study period.

- The statistical modeling section is brief: was goodness of fit for the data measures? Where the final variable tested for collinearity or interaction? How missing data (if any) was treated?

The goodness of fit was not performed in the study. Univariable and multivariable logistic regression were used to assess the association of UA with coronary atherosclerosis, the variables was adjusted in multivariable analysis. In the study, there is no missing data in enrolled patients.

- The fact that uric acid quartile progression was correlated with the proportion of CACS of 0 but also >10 in some analyses seems contradictory. Do I understand the results well? How would this apparent contradiction be explained?

We think that they are not contradictory, the UA quartile progression was positively correlated with the CACS of 0, The proportion of a CACS of 0 in total, in men, and in women was lowest in the fourth quartile; but the UA quartile progression was negatively correlated with the CACS >10, the proportion of CACS >10 in total, in men, and in women was highest in the fourth quartile. All in all, the relationship between UA quartile progression and the proportion of CACS of 0 and >10 in the analyse which suggested the non-calcification composition is highest(CACS=0) and calcification composition is lowest(CACS >10) in the first UA quartile, and the
non-calcification composition is lowest (CACS=0) and calcification composition is highest (CACS >10) in the four UA quartile. So their conclusions are consistent that the calcification composition increased and non-calcification composition decreased with UA.

-I find quite interesting that, mainly in women, the urate quartiles fell almost entirely below the accepted hyperuricemia thresholds (<404) lending support to the hypothesis that this might be an unimportant concept for associations other than gout.

This is true that the level of UA is significantly lower in women than men in the study. I think the difference was caused by gender differences. The level of UA was significantly associated with coronary atherosclerosis in women, but not men in the study. In the study we did not adopt the hyperuricemia as the cutoff point, the uniform standard of hyperuricemia thresholds (<404) might not apply to women.

Discretionary

- The authors might consider adding a line to their tables and graphs in how to convert international to metric units (divide by 59.48) to help readers that (like me) live and think in metric units.

We have added it. Please see red words under the table1.

- Where the two experienced radiologists and cardiologist reviewing the images paper authors (can identify by initials).

Please see the section of Author’s contribution.

- Although I appreciate the attempt to be throughout with results reporting, the number of tables + figures might be excessive for this type of paper. The authors might consider consolidating some tables (mainly those with negative results = men) or leaving some only as supplementary material.

I try to consolidating some figures. But it is difficult for us to consolidating some tables.

Sincerely Yours,
Sunyujiao
Department of Cardiology, Department of Cardiology of Aging,
First Affiliated Hospital
China Medical University