The Journal of Clinical Hypertension

WILEY

COMMENTARY OPEN ACCESS

Uric Acid Serves as a *Risk Factor* or *Marker* for Developing Hypertension According to Both Conventional and Novel Definitions: An Association or Causation!

Ugur Canpolat

Department of Cardiology, Hacettepe University Faculty of Medicine, Ankara, Turkey

Correspondence: Ugur Canpolat (dru_canpolat@yahoo.com)

Received: 16 March 2025 | **Revised:** 10 April 2025 | **Accepted:** 21 April 2025

Funding: The author received no specific funding for this work.

Keywords: association | hypertension | serum uric acid | sex

In the current study, Liu et al. [1] assessed the relationship between serum uric acid (SUA) levels and incident hypertension at different blood pressure (BP) cut-off levels (140/90 and 130/80 mmHg) according to recent studies and guidelines. The study involved 26 973 participants from the Taiwan Biobank (TWB), who were followed for a median of 4 years. The association of hyperuricemia and sex with incident hypertension was significant for both traditional (140/90 mmHg) and new (130/80 mmHg) definitions. They also reported a significant interaction between hyperuricemia and sex. Although confounding factors in the prediction of incident hypertension (both for traditional and new definitions) were adjusted in the analyses, patients with incident hypertension revealed a higher rate of SUA-associated several comorbidities.

Hypertension is known as one of the major cardiovascular disease risk factors. It has both modifiable and non-modifiable pathophysiological mechanisms. Therefore, preventing and controlling hypertension by modifying underlying mechanisms is essential for public health [2]. Hyperuricemia is a well-known mediator for the development of cardiovascular diseases, including hypertension, by driving inflammation and oxidative stress [3–5]. Both genetic and environmental factors influence the complex pathogenesis of hyperuricemia and its link to hypertension [6]. The SUA level of >7.0 mg/dL in males and >6.0 mg/dL in females is defined as hyperuricemia [7]. Uric acid deposition-mediated endothelial dysfunction and vascular injury typically occur at SUA levels that exceed 6.5 mg/dL. However, this threshold is significantly higher than those reported in studies linking it to hypertension and cardiovascular disease [6]. Moreover, uric acid is a metabolic end product that fluctuates due to modifiable (diet, medications, etc.) and non-modifiable (genetics, age, etc.) factors. Therefore, it is unreasonable to establish a causal relationship between SUA levels and cardiovascular diseases, including hypertension, based on a single SUA measurement. Although most studies used baseline single SUA levels, it is essential to consider the temporal trends of this fluctuating variable. Kuwabara et al. [8] demonstrated that hyperuricemia in asymptomatic male and female subjects without cardiac and metabolic comorbidities is an independent risk factor for hypertension within 5 years. In another study, Salim et al. [9] also reported a significant association between hyperuricemia and sex with incident hypertension using different BP cut-offs (≥140/90 and ≥130/80 mmHg). Although the confounding factors or comorbidities have been adjusted before linking the SUA levels or hyperuricemia with incident hypertension in all those studies, they do not prove a direct causal relationship. Thus, there is a debate about hyperuricemia as either a causative risk factor or a bystander (risk marker) for hypertension and cardiovascular events. The statistics indicate that *the association is insufficient for causation*. In line with the limitations above, the effect of urate-lowering therapy on hypertension and cardiovascular outcomes has been heterogeneous in previous studies [10–13]. In the study by Liu et al. [1], no data were present about dietary factors and medications impacting SUA levels at baseline and follow-up. The study also lacks temporal trends in SUA levels and confounding risk factors that could be related to incident hypertension. As the study results confirmed the relation of male and female sex

with hyperuricemia and incident hypertension, the data also lack the menopausal (natural or premature) status of the females in the study population. The predictive value of SUA quartiles with lower thresholds than the hyperuricemia definition on incident hypertension should also be considered when interpreting the study results. Based on the study by Liu et al. [1] and previous studies, future studies should use SUA level as a continuous variable rather than a standard hyperuricemia definition to predict incident hypertension or cardiovascular outcomes. Because of the direct relationship of SUA level to numerous comorbid conditions associated with hypertension, SUA level may be a *risk marker*, but *not a risk factor*, for incident hypertension.

Author Contributions

Ugur Canpolat: Substantial contributions to the design of the manuscript; drafting the work and reviewing it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy of any part of the work are appropriately investigated and resolved.

Ethics Statement

The author has nothing to report.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The author has nothing to report.

References

1. Y. H. Liu, W. Y. Su, C. Y. Lin, et al., "Impact of Hyperuricemia on Incident Hypertension When Hypertension Definition Changes From 140/90 to 130/80 mmHg in a Large Taiwanese Population Follow-Up Study," *Journal of Clinical Hypertension* 27, no. 2 (2025): e70013.

2. P. K. Whelton, R. M. Carey, W. S. Aronow, et al., "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines," *Hypertension* 71, no. 6 (2018): e13–e115.

3. M. Kuwabara, I. Hisatome, R. Ae, et al., "Hyperuricemia, a New Cardiovascular Risk," *Nutrition, Metabolism and Cardiovascular Diseases* 35, no. 3 (2025): 103796.

4. J. Kanellis and D. H. Kang, "Uric Acid as a Mediator of Endothelial Dysfunction, Inflammation, and Vascular Disease," *Seminars in Nephrology* 25, no. 1 (2005): 39–42.

5. D. Krupp, J. Esche, G. B. Mensink, et al., "Diet-Independent Relevance of Serum Uric Acid for Blood Pressure in a Representative Population Sample," *Journal of Clinical Hypertension* 19, no. 10 (2017): 1042–1050.

6. C. Borghi, D. Agnoletti, A. F. G. Cicero, et al., "Uric Acid and Hypertension: A Review of Evidence and Future Perspectives for the Management of Cardiovascular Risk," *Hypertension* 79, no. 9 (2022): 1927–1936.

7. L. Du, Y. Zong, H. Li, et al., "Hyperuricemia and Its Related Diseases: Mechanisms and Advances in Therapy," *Signal Transduction and Targeted Therapy* 9, no. 1 (2024): 212.

8. M. Kuwabara, K. Niwa, I. Hisatome, et al., "Asymptomatic Hyperuricemia Without Comorbidities Predicts Cardiometabolic Diseases: Five-Year Japanese Cohort Study," *Hypertension* 69, no. 6 (2017): 1036–1044.

9. A. A. Salim, S. Kawasoe, T. Kubozono, et al., "Sex-Specific Associations Between Serum Uric Acid Levels and Risk of Hypertension for Different Diagnostic Reference Values of High Blood Pressure," *Hypertension Research* 47, no. 5 (2024): 1120–1132.

10. L. H. Qu, H. Jiang, and J. H. Chen, "Effect of Uric Acid-Lowering Therapy on Blood Pressure: Systematic Review and Meta-Analysis," *Annals of Medicine* 49, no. 2 (2017): 142–156.

11. P. H. F. Gois and E. R. M. Souza, "Pharmacotherapy for Hyperuricaemia in Hypertensive Patients," *Cochrane Database of Systematic Reviews (Online)* 9, no. 9 (2020): CD008652.

12. Y. Jamil, D. Alameddine, M. E. Iskandarani, et al., "Cardiovascular Outcomes of Uric Acid Lowering Medications: A Meta-Analysis," *Current Cardiology Reports* 26, no. 12 (2024): 1427–1437.

13. M. Barrientos-Regala, R. A. Macabeo, R. Ramirez-Ragasa, et al., "The Association of Febuxostat Compared With Allopurinol on Blood Pressure and Major Adverse Cardiac Events Among Adult Patients With Hyperuricemia: A Meta-Analysis," *Journal of Cardiovascular Pharmacology* 76, no. 4 (2020): 461–471.