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Correspondence

Letter to the Editor: When Claiming a U-shaped Association between Uric Acid Levels and Major Adverse Cardiac Events, Perhaps Show the Evidence?

Ivo Abraham [1,2,3]

[1]Center for Health Outcomes and PharmacoEconomic Research, College of Pharmacy, University of Arizona, Tucson, AZ, USA
[2]Department of Pharmacy Practice and Science, College of Pharmacy, University of Arizona, Tucson, AZ, USA
[3]Department of Family and Community Medicine, College of Medicine, University of Arizona, Tucson, AZ, USA

▸ See the article "Uric Acid Level Has a U-shaped Association with Clinical Outcomes in Patients with Vasospastic Angina" in volume 32 on page 1275.

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Address for Correspondence:
Ivo Abraham, PhD
Center for Health Outcomes and PharmacoEconomic Research, College of Pharmacy, University of Arizona, Drachman Hall B-306H, 1295 N. Martin Ave., Tucson, AZ 85721, USA.
E-mail: abraham@pharmacy.arizona.edu

ORCID iDs
Ivo Abraham
https://orcid.org/0000-0003-0490-4421

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A study of 818 patients with vasospastic angina (VSA) categorized according to tertiles of serum uric acid (sUA) level aimed to evaluate the association between sUA and major adverse cardiac effects (MACEs).[1] At a rate of 17.1%, patients in the second tertile group (sUA = 4.9–5.9 mg/dL) showed a significantly lower risk of MACE compared to the 24.6% patients in the first tertile group (sUA ≤ 4.8 mg/dL) (hazard ratio [HR], 1.52; 95% confidence interval [CI], 1.02–2.26; $P = 0.040$). Compared to the 22.5% rate in the third group (sUA ≥ 6.0 mg/dL), the second group showed, in the authors' words, a "tendency," though non-significant, of lower risk (HR, 1.44; 95% CI, 0.98–2.13; $P = 0.067$).

By foregoing the continuous mg/dL scale of sUA level for the discrete tertile-based categorization, the association evaluated is no longer with sUA level (mg/dL) but with tertile group membership (I–III). Per Table 2, a simple 3 × 2 contingency analysis of group membership by MACE (non-)occurrence yields a statistically non-significant $\chi^2 = 4.91$ ($P = 0.086$), indicating that group membership and MACE (non-)occurrence are independent events.

Validity-wise, do the categorization cut-off values correspond to indications from animal or human studies? In other words, is there evidence that 4.9 and 6.0 mg/dL are physiologically and clinically defensible marks; not in general, but in relation to MACE? With continuous sUA data, a logistic model of MACE as a function of sUA level, controlling for potential confounders, would have answered the question as to whether sUA level is a risk factor for MACE.

With the contingency analysis telling us that, overall, the three groups did not differ in MACE rates, the Kaplan-Meier curves and associate log-rank tests (Fig. 2A-C) compare the pace at which (the statistically equivalent) MACE events occurred in each group. Fig. 2A indicates that patients in group II who experienced a MACE did so relatively later than patients in groups I and III. Fig. 2B conveys that this was more pronounced when focusing on the pure VSA patients but not, as Fig. 2C reports, on mixed-angina patients. Together, the three figures confirm that, in the end, all three groups are likely to end with statistically similar probabilities of experiencing MACE.

The title claims the existence of a U-shaped association. This is the only mention of such association in the entire paper and no graphical or statistical evidence is presented. A line plot of the MACE incidence rates (24.6%, 17.1%, and 22.5% against a 0%–100% Y-axis) would show a slightly declining line between groups I and II, and a slightly inclining line to group III. The HRs imply a negative slope coefficient significantly different from zero for the first line, and a nominally but not statistically significant positive slope coefficient for the second line — certainly not a U but at best a nearly straight line with a slight inflection. While the details are beyond the statistical scope of this Correspondence, data can be fitted to functions specifying curves that model the phenomena — in this case, sUA group membership and MACE incidence. No statistical evidence of curve-fitting is presented. We attempted to estimate both linear and hyperbolic regression curves for what is, essentially, a flattened V-curve (if such letter exists). The fit was poor because the exercise was underpowered (n = 3).

The statistical analyses were done at the aggregate level of MACE incidence rates for patient groupings; not at the patient level as observed or non-observed MACE for each patient. This makes claims of an association between sUA levels and MACE, and the shape of such association, impossible. The question whether there is an association between tertile-based sUA group membership and MACE was answered: there is none, except that those patients in group II with MACE experienced it relatively later. As to the shape and predictive association of sUA in terms of MACE, these questions remain open.

REFERENCES

1. Gwag HB, Yang JH, Park TK, Song YB, Hahn JY, Choi JH, et al. Uric acid level has a U-shaped association with clinical outcomes in patients with vasospastic angina. *J Korean Med Sci* 2017;32(8):1275-80.
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