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Confounders of uric acid level for assessing cardiovascular outcomes

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We read the article entitled *Serum uric acid as a prognostic marker in the setting of advanced vascular disease: a prospective study in the elderly* by Stolfo, *et al*.[1] with great interest. The authors evaluated the association of serum uric acid (SUA) levels with adverse cardiovascular events and deaths in an elderly population affected by advanced atherosclerosis. They founded meaningful association between SUA levels and of cardiovascular events and cancer related death. We believe that these findings will lead for further studies on uric acid.

Recent studies have shown that hyperuricemia may damage endothelial function and increases the cardiovascular event risk.[2] Thus, investigation of the association between uric acid and cardiovascular events may contribute to understand the underlying mechanism. However SUA level may be affected by several factors and its exclusion is very difficult. In this well designed study, the authors had compared groups for traditional cardiovascular risk parameters such as hypertension, dyslipidemia, and diabetes mellitus, etc. Beyond these, alcohol consumption or hypothyroidism are well known confounders for uric acid level so it would have been better if the authors had compared these parameters too.[3,4]

Most diuretics elevate the SUA level and in this study the authors have shown that high SUA group has increased diuretic use.[1] In our daily practice, we use diuretics frequently in hypertension and congestive heart failure patients. Thus, it is possible that high SUA group may have lower ejection fraction rates. Poor outcomes are directly associated with left ventricle systolic dysfunction.[5] If the authors had mentioned about ejection fraction rates, a more comprehensive assessment would be possible.

In conclusion this article enlightens the relationship between uric acid and poor cardiovascular outcomes. However new studies with more detailed risk factors assessment and using all echocardiographic parameters may contribute to our knowledge in this area.

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Author's reply

We read with great interest the letter of Dogan, *et al*. regarding the confounders of uric acid for assessing cardiovascular outcomes. The comment is related to the original article published in the Journal by Di Stolfo, *et al*.[1], which

was a prospective study regarding role of serum uric acid (SUA) as a marker for cardiovascular events in a population affected by peripheral artery disease. Dogan, *et al*. underlined as additional confounders than classical cardiovascular risk factors for SUA levels analysis could be represented by hypothyroidism and alcohol assumption. We agree completely with the comment; as not reported in the aforementioned article, alcohol consumption and thyroid dysfunction was not considered among confounders. Nevertheless patient's data were collected by our *Multidisciplinary Clinic for Advanced Atherosclerosis Database*, a well built self-made software, with a sharp definition of each patient clinical and biohumoral status, allowing further extrapolation for population study. We have not a clear and reliable measure of alcohol consumption for each patient; anyway, we encouraged all patients to contain alcohol intake among one to two glass of red wine for day, corresponding to 10–20 g daily, according to cardiovascular disease prevention guidelines.[2] Furthermore, we have not noticed any case of alcohol abuse, together with a high level of compliance to prescription.

Thyroid function was evaluated by thyroid-stimulating hormone (TSH) assessment in 107 of 276 patients (reference range 0.4–4 mUI/mL); there was no difference between SUA groups (Table 1). Among them, only seven patients were affected by mild hypothyroidism, well distributed in both groups (three patients in the low SUA group and four patients in the high SUA group, without any correlation between SUA levels and TSH), and three patients affected by hyperthyroidism, with equal distribution among groups (one patient in the low group and two patients in the high group).

In addition Dogan, *et al*. questioned about diuretics consumption as marker of heart failure and lower ejection fraction, related to poorer outcome. Once again, as we collected echocardiographic parameters in each patient, we had already analyzed left ventricle ejection fraction distribution in both SUA groups, without finding a clear difference (Table 1). From this point of view, a limit of our study (yet not a declared end-point, as our population was selected for peripheral artery disease) was the missing collection of diastolic function parameters and cardiac biohumoral characterization (i.e., brain natriuretic peptide), since from literature approximately half of heart failure patients have preserved ejection fraction.[3] However, although diuretics consumption was higher in High SUA group, we calculated hazard ratio for cardiovascular events adjusting for this factor; consequently, even if it would be intended as marker of heart failure congestion, the last one would be weighted in multivariate Cox proportional analysis.

Table 1. Left ventricle ejection fraction and TSH levels in SUA groups.

	Total (n = 276)	Low SUA level	High SUA level	P
TSH, mUI/mL	2.06 ± 2.18	2.08 ± 2.1 (59 patients)	2.05 ± 2.3 (48 patients)	0.9
LVEF, %	58.6 ± 5.8	58.5 ± 6.3	58.7 ± 5.2	0.7

LVEF: left ventricular ejection fraction; SUA: serum uric acid; TSH: thyroid-stimulating hormone.

In conclusion, we agree with Dogan, *et al*. that further well designed studies are needed to better clarify pathophysiological role of serum uric acid in different clinical setting such as heart failure.

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