EXPOSURE IN TIME TO SERUM URIC ACID LEVELS INFLUENCES THE RISK OF DEATH OF CKD PATIENTS

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INTRODUCTION and OBJECTIVES

Uric acid (UA) is considered a mortality risk factor in several diseases, however in CKD patients this link is still controversial, for the unavoidable cause-effect relationship between UA and GFR. In fact, in CKD high serum UA can be secondary to renal function impairment, therefore patients in the final stages of CKD may also experience high levels of UA, but their mortality could be mainly caused by the severity of renal impairment. Moreover, on the methodological side, many studies investigated this connection using only baseline UA values instead of its variation in time. In this study we tried to disentangle the UA and GFR relationships with mortality by estimating the probability of death associated to subgroups of CKD patients sharing similar exposure trajectories of UA and GFR.

Figure 1 - Diagram of the GMM model

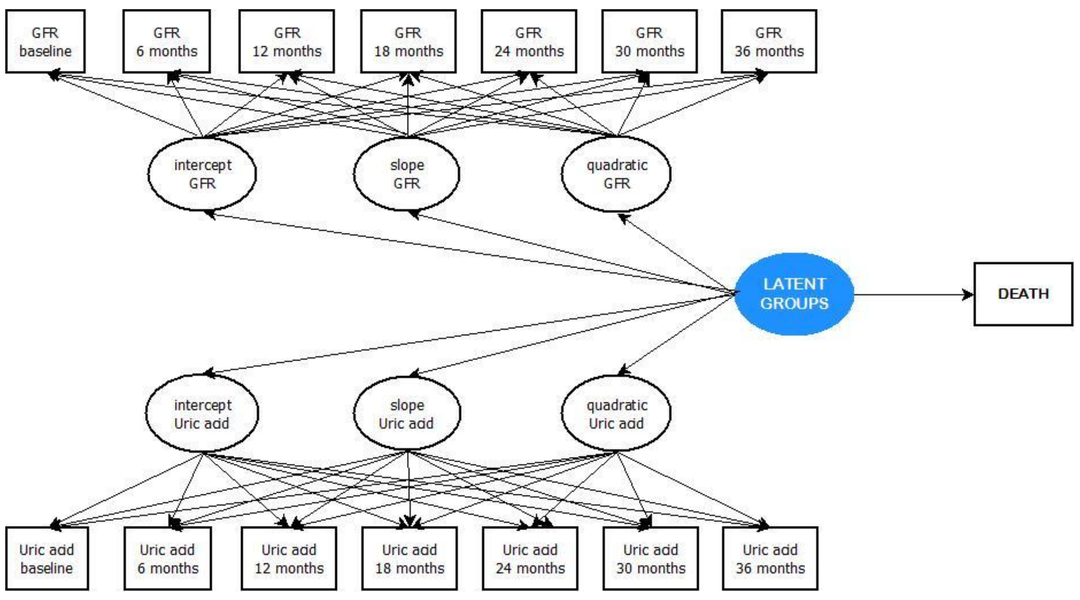

Figure 2 - Estimated trajectories of UA and GFR

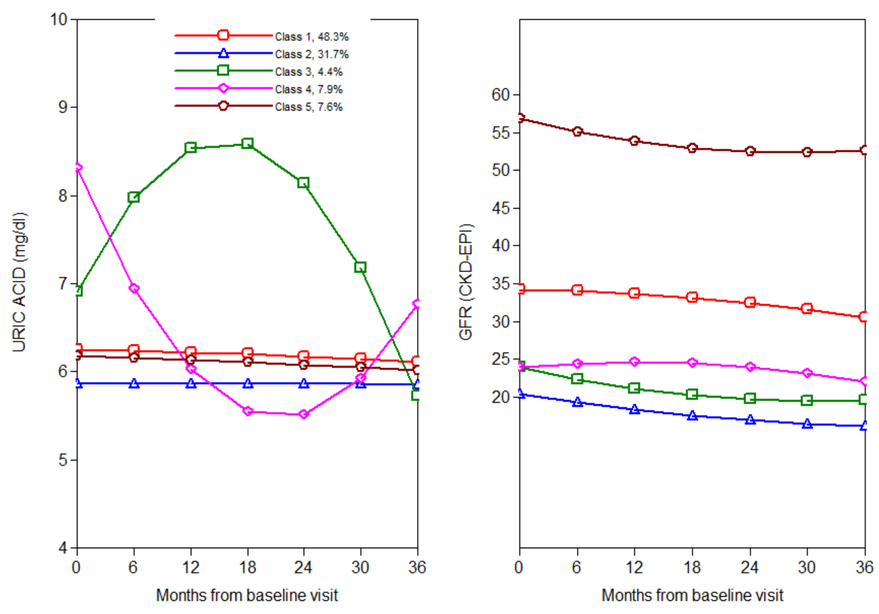

Table 1 - Predictors of trajectory membership (multinomial regression)

LCA group	n (%)	Prob. of death	Significant predictors (RRR;p)
1	535 (48.3)	0.099	Reference
2	351 (31.7)	0.244	Age (1.191; <0.001) Haemoglobin (0.835; 0.002) Phosphates (2.049; <0.001) Proteinuria (2.699; <0.001) Xanthine oxidase inhibitors (0.657; 0.034)
3	49 (4.4)	0.192	Haemoglobin (0.821; 0.009) Xanthine oxidase inhibitors (2.116; 0.037) Diuretics (2.770; 0.026)
4	88 (7.9)	0.172	Phosphates (1.910; 0.006) Xanthine oxidase inhibitors (2.073; 0.002)
5	84 (7.6)	0.028	Age (0.731; <0.001) Haemoglobin (1.331; 0.037) Phosphates (0.520; 0.052) Proteinuria (0.312; 0.002) Xanthine oxidase inhibitors and Diuretics (4.159; 0.001)

METHODS

Patients enrolled in the PIRP Project were included in the study if they fulfilled the following criteria: entering PIRP between 1.01.2004 and 31.12.2009; being followed-up for at least 5 years (3 years to evaluate the UA and CKD exposure and the following 2 years to evaluate the distal outcome, which was observed until 31.12.2014); having at least 4 visits spaced out multiples of 6 months ± 45 days from the baseline visit in the 3 years of exposure assessment; having at least 3 valid UA measurements in their available visits.
Parallel Growth Mixture Modeling (GMM) was used to find unobservable groups of patients who shared similar trajectories of UA while controlling for their GFR trajectories. The risk of death of each group was computed using the BCH method. Multivariate multinomial regression was used to find which factors among age, gender, haemoglobin, phosphates, proteinuria, CV events, treatment with xanthine oxidase inhibitors and treatment with diuretics predicted group membership.

RESULTS and CONCLUSIONS

Patients entering the study were 1107, of which 65.4% males. At baseline, UA was 6.34 1.7 mg/dl and GFR (CKD-EPI) was 30.8 14.1 ml/min/1.73 m^2, with 49.3% patients classified in stage 4 and 29.4% in stage 3b. In the 2-years follow-up, death occurred for 14.5% of patients. Among the several GMM models that were tried, we chose the one with quadratic curves and five latent groups, for its better fit to the data and clinical suitability (Fig.1). Groups 1, 2 and 5 summed up 87.7% of patients and showed very similar trajectories of UA (slightly decreasing around 6 mg/dl) and trajectories of GFR nearly parallel at very different values (Fig.2). Groups 3 and 4 representing 12.3% of patients had instead similar trajectories of GFR (around 25 ml/min/1.73 m^2) and very different trajectories of UA, one steeply increasing in the first three semesters and then decreasing, the other following a specular path. The relative risk ratio (RRR) to be classified in these two latter groups was significantly higher for patients who were treated with xanthine oxidase inhibitors (Tab.1).

The estimated probability of death in the 2 years following the trajectories was highest in group 2 and lowest in group 5; patients in these groups had opposite clinical characteristics explaining their difference in mortality. Patients in groups 3 and 4 had a slightly over-average mortality, that could be explained by the exposure to high uremic levels and to relatively low GFR levels.

In conclusion, by taking into account the exposure over time to uric acid (and not only its baseline values), we identified subgroups of patients with distinct trajectories and probabilities of death. Although levels of GFR stand as the main driver for the risk of death, an association between exposure to UA and risk of death can be highlighted as well in some subsets of patients. Patients whose exposure and plasma levels of UA, even when high at baseline, are reduced in time due to therapeutic interventions (groups 3 and 4) had a risk of death only slightly higher than the average.

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