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Hyperuricemia Treatment Reduces ESKD Risk and Mortality in CKD Patients: A Causal Inference Analysis Using the G-Formula Approach

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Objectives : Hyperuricemia is recognized as an independent predictor of chronic kidney disease (CKD), but the role of treating it in CKD, especially when asymptomatic, remains under debate. The g-formula, valuable for epidemiological causal inference, allows estimation of effects in complex scenarios with time-varying factors and feedback loops among covariates. We used the g-formula to assess the impact of treating hyperuricemia in CKD patients using urate-lowering agents (ULAs).
Methods : Employing the g-formula, we analyzed data from 28,660 CKD patients to build regression models, evaluating relationships among time-varying covariates: serum urate (UA), creatinine, and ULA prescription status, measured every 6 months. We also adjusted for time-invariant factors like diabetes and hypertension. Our focus was the impact of various strategies for managing hyperuricemia (always treating, treating if UA ≥ 7mg/dL, 9mg/dL, or 10mg/dL, or never treating) on end-stage kidney disease (ESKD) and all-cause mortality, supported by 1,000 bootstrap replicates for 95% confidence intervals (CIs).
Results : Of the cohort, 6,571 patients had been prescribed allopurinol, febuxostat, or benzbromarone. Our findings reveal that any level of hyperuricemia treatment decreased ESKD and all-cause mortality risks compared to no treatment. Lower ULA thresholds were linked to dose-responsive relative risk (RR) reductions, particularly at 7mg/dL [RR reductions of -3.8% for ESKD (95% CI: -4.7% to -3.0%), and -2.8% for mortality (95% CI: -3.2% to -2.4%)]. Compared to the natural course, initiating treatment ≥9mg/dL or 10mg/dL, or not treating at all, significantly increased ESKD (RR of 1.006, 1.013, and 1.022 respectively) and mortality (RR of 1.003, 1.008, and 1.014 respectively), with a protective effect observed only at the 7mg/dL threshold (RR 0.983).
Conclusions : Our study demonstrates that treating hyperuricemia in CKD patients significantly reduces the risk of ESKD and mortality. This suggests potential harm in not treating hyperuricemia at urate levels of 9mg/dL or higher.

figure-1.png

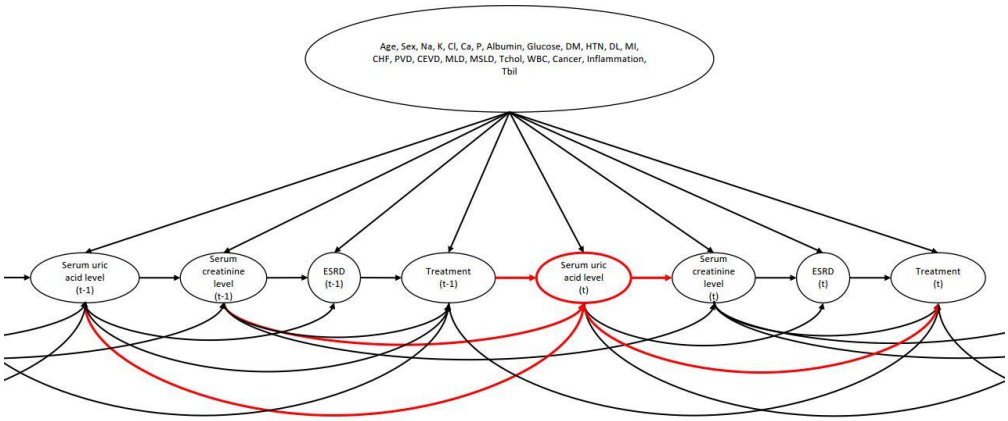

figure-1.png

Outcome	Intervention	Risk	RR	RR reduction	95% CIs of RR reduction	modified RR [a]
ESRD	**Natural course**	0.1730	0.9784	-2.2%	-2.7% , -1.7%	**1.0000**
	Never treat	0.1768	**1.0000**	0.0%	0.0% , 0.0%	1.0220
	Treat if serum uric acid level ≥10	0.1754	0.9918	-0.8%	-1.0% , -0.6%	1.0139
	Treat if serum uric acid level ≥9	0.1742	0.9854	-1.5%	-1.8% , -1.1%	1.0069
	Treat if serum uric acid level ≥7	0.1700	0.9617	-3.8%	-4.7% , -3.0%	0.9827
	Always treat	0.1607	0.9090	-9.1%	-11.0% , -7.3%	0.9289
Mortality	**Natural course**	0.2542	0.9862	-1.4%	-1.6% , -1.2%	**1.0000**
	Never treat	0.2578	**1.0000**	0.0%	0.0% , 0.0%	1.0142
	Treat if serum uric acid level ≥10	0.2564	0.9945	-0.5%	-0.6% , -0.5%	1.0087
	Treat if serum uric acid level ≥9	0.2552	0.9902	-1.0%	-1.1% , -0.8%	1.0039
	Treat if serum uric acid level ≥7	0.2506	0.9720	-2.8%	-3.2% , -2.4%	0.9820
	Always treat	0.2370	0.9195	-8.1%	-9.0% , -7.0%	0.9323

a. To estimate the modified relative risks (RRs), the risk observed in the natural course—derived from actual patient data—served as the reference for both outcomes. The 95% confidence intervals (CIs) for the modified RRs are not included here.
RR; relative risk, CI; confidential interval