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Urinary Phenylpyruvate-to-Taurine Ratio as a Metabolic Signature for Distinguishing C3GN from MPGN Based on IVDr NMR Metabolomics

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Objectives : C3 glomerulopathy (C3GN) and membranoproliferative glomerulonephritis (MPGN) share histological features, but growing evidence highlights their distinct pathophysiology and prognosis. To better characterize these differences, we applied urinary metabolomics to identify disease-specific metabolic signatures.
Methods : We used in vitro diagnostics research nuclear magnetic resonance (IVDr NMR) spectroscopy, a standardized and high-throughput technique, to quantify urinary metabolites. Urine samples were collected at the time of kidney biopsy from 6 C3GN patients, 32 MPGN patients, and 23 donor controls. Metabolite concentrations were $\log_2$-transformed and compared between groups using ranked ANCOVA, adjusting for age, sex, body mass index, hypertension, diabetes, serum creatinine (sCr), and smoking status. The disease classification performance of metabolite-inclusive models was assessed using the area under the curve (AUC), along with integrated discrimination improvement (IDI) and net reclassification improvement (NRI).
Results : Among the 61 urinary metabolites, phenylpyruvate tended to be lowest in MPGN, while taurine showed the greatest reduction in C3GN, though these trends did not reach statistical significance. In pairwise comparison, the phenylpyruvate-to-taurine ratio was significantly higher in C3GN patients than in MPGN (2.92-fold, P = 0.042). Incorporating the phenylpyruvate-to-taurine ratio into the classification model improved the distinction between C3GN and MPGN beyond clinical variables alone. The model incorporating this ratio with all clinical variables achieved an AUC of 0.89 [IDI 0.16 (P = 0.09) and NRI 1.10 (P = 0.001)] compared to the same model without it (AUC 0.81). Furthermore, the phenylpyruvate-to-taurine ratio showed a significant positive correlation with sCr and urine protein-to-creatinine ratio in MPGN patients, with similar but non-significant trends in C3GN.
Conclusions : The urine phenylpyruvate-to-taurine ratio enhances the differentiation of C3GN and MPGN, highlighting the potential of urinary metabolomics as a complementary approach for disease classification. This finding suggests possible disruptions in phenylalanine and sulfur amino acid metabolism in C3GN, warranting further investigation.

figure - ratio.png

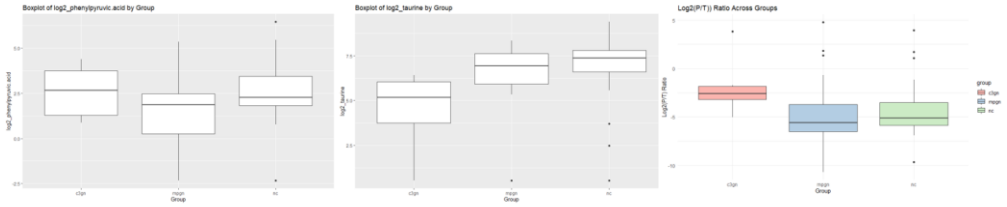

figure - ratio.png

		AUC	DeLong *p*	IDI (95% CI)	IDI *p*	Categorical NRI	NRI *p*	Continuous NRI	NRI *p*
Base	Age + Sex + HTN + DM	0.7188	-	-	-	-	-	-	-
Model 1	Age + Sex + HTN + DM **+ Cr**	0.7292	0.66	0.00 (-0.03, 0.02)	0.94	NA	NA	0.33 (-0.50, 1.16)	0.43
Model 2	Age + Sex + HTN + DM + **Cr + BMI + Smoking**	**0.8125**	0.12	0.07 (0.00, 0.13)	0.04*	0.33 (-0.04, 0.71)	0.08	0.58 (-0.24, 1.41)	0.17
Model 3	Age + Sex + HTN + DM **+ log2(P/T)**	**0.8125**	0.27	0.07 (-0.04, 0.20)	0.19	0.30 (-0.08, 0.68)	0.12	0.52 (-0.31, 1.35)	0.22
Model 4	Age + Sex + HTN + DM + **Cr + log2(P/T)**	**0.8594**	0.13	0.15 (-0.03, 0.35)	0.10	0.33 (-0.04, 0.71)	0.08	1.04 (0.36, 1.72)	0.003*
Model 5	Age + Sex + HTN + DM + **Cr + BMI + Smoking + log2(P/T)**	**0.8906**	**0.18**	**0.16 (-0.03, 0.36)**	**0.09**	**0 (-0.46, 0.46)**	**1**	**1.10 (0.43, 1.78)**	**0.001***

* P/T ratio represents the urinary phenylpyruvate-to-taurine ratio.
* Models incorporating metabolites (Models 3, 4, and 5) were compared with their respective counterpart models without metabolites (Base, Model 1, and Model 2, respectively).
* Net reclassification improvement (NRI) was assessed using a cutoff value of 0.4, where an NRI below 0.4 indicates an increased risk classification for C3GN.