Uric Acid As A Prognostic Biomarker In Paediatric Pulmonary Arterial Hypertension

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Background

For optimal clinical decision-making in the treatment of paediatric pulmonary arterial hypertension (PAH), it is crucial to have a reliable, non-invasive and inexpensive biomarker to monitor disease progression. Earlier studies suggest that serum uric acid could have the potential to fulfil such a role. This study aims to evaluate the association of uric acid levels, measured both at baseline and longitudinally during the course of the disease, with disease severity and outcome in children with PAH.

Methods

This study includes 81 paediatric patients diagnosed with PAH. Baseline serum uric acid values were correlated with disease severity markers and outcome. The predictive value of longitudinally collected uric acid measurements for disease severity and disease outcome was analysed using linear mixed effects modelling. Finally, the linear development of uric acid levels over time was stratified by outcome and compared.

Baseline Uric Acid Levels correlate with Disease Severity

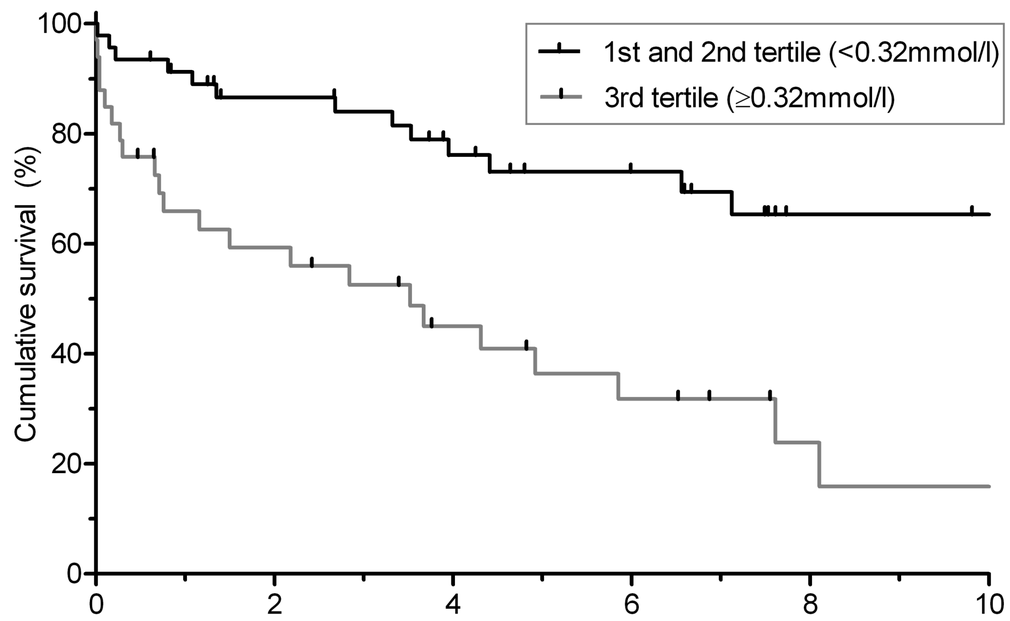
	Univariate Analysis			Adjusted for Age, Sex and Creatinine		
	n	r	*p* value	n	r	*p* value
Clinical Characteristics						
Diagnosis: IPAH/HPAH (vs.associated PAH)	81	0.04	0.714	71	0.05	0.660
Female	81	-0.10	0.381		N.A.	
Age at baseline	81	0.29	0.009		N.A	
WHO functional class	80	0.31	0.005	70	0.36	0.002
6min walking distance (>7yrs)	36	-0.28	0.094	33	-0.31	0.094
Creatinine	71	0.45	<0.001		N.A.	
N-terminal proBNP	61	0.31	0.014	54	0.27	0.050
Hemoglobin	81	0.18	0.104	71	0.15	0.233
TAPSE	54	-0.30	0.027	52	-0.26	0.067
Diuretics at diagnosis	81	0.12	0.305	71	0.17	0.165
Hemodynamic Characteristics						
Mixed venous saturation	50	-0.37	0.008	46	-0.41	0.006
Mean right atrial pressure	52	0.41	0.003	48	0.40	0.006
Mean pulmonary atrial pressure	52	0.31	0.025	48	0.21	0.159
Pulm. vascular resistance index	51	0.41	0.003	47	0.29	0.055
Systemic flow index	51	-0.02	0.875	47	0.00	0.999
Pulmonary/systemic flow index	51	-0.22	0.128	47	-0.16	0.306

Definition of abbreviations: TAPSE = tricuspid annular plane systolic excursion; N.A.= not applicable.

1 Higher baseline serum uric acid levels are associated with a worse clinical state, as reflected by a higher WHO functional class, NT-proBNP levels, mean right atrial pressure, mean pulmonary arterial pressure, pulmonary vascular resistance index, lower TAPSE, and mixed venous saturation.

Baseline Uric Acid Levels correlate with Disease Outcome

Transplantation-free survival curves stratified by uric acid levels measured at baseline



2 Patients with higher baseline serum uric acid values had a significantly (p<0.001) lower transplantation-free survival.

Changes in Uric Acid Levels over time correlate with Disease Severity and Disease Outcome

	Univariate Analysis			Adjusted for Age, Sex, Creatinine		
	n*	β/HR [95%CI]	p value	n*	β/HR [95% CI]	p value
Predictive value of UA for WHO functional class	785/80	0.09 [0.03-0.16]	0.007	762/70	0.09 [0.01-0.16]	0.028
Predictive value of UA for log NT-proBNP	751/81	0.19 [0.14-0.24]	<0.001	748/54	0.20 [0.14-0.26]	<0.001
Predictive value of UA for TAPSE Z-score	563/54	-0.46 [-0.69- -0.23]	<0.001	560/52	-0.26 [-0.53-0.01]	0.057
Predictive value of time-varying UA for death/LTx	860/81	1.78 [1.40-2.26]	<0.001	831/79	1.52 [1.13-2.04]	0.006
Predictive value of ≥50% UA increase for death/LTx	860/81	3.94 [1.51-10.27]	0.005	831/71	3.63 [1.22-10.77]	0.020

Definition of abbreviations: UA= uric acid; NTproBNP = N-terminal pro brain natriuretic peptide; TAPSE = tricuspid annular plane systolic excursion; LTx = lung-transplantation.

Linear development of uric acid levels over time stratified by survival status at end of follow-up

3 From the 81 patients there were ≥563 measurements of uric acid values and disease severity markers collected during follow-up. Analysis shows that the associations at baseline are persistent at any time point during follow-up. Transplantation-free survivors had lower baseline values and a less steeper increase of uric acid levels over time, compared to non-survivors.

Conclusion

This study demonstrates that higher serum uric acid levels are associated with disease severity and mortality in children with PAH, throughout the full course of the disease. Increases in uric acid values during follow-up correlated with worse clinical outcome. Monitoring absolute values and changes of uric acid levels provides valuable information and could help guide decisions in the management of paediatric PAH.

Declaration of interest: none

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