

Evaluation of Serum Uric Acid as a Potential Predictive Biomarker in Pulmonary Arterial Hypertension Evaluation

Monalisa Mohapatro¹, Satya Narayan Routray², Biswakesh Panigrahy³,
Pratima Kumari Sahu⁴, Suryasnata Jena⁵

Abstract

Background: Pulmonary arterial hypertension (PAH) is a relatively rare fatal disease, confounding many cardiopulmonary diseases. Systolic pulmonary artery pressure (sPAP), measured by Transthoracic Echocardiography (TTE), can be taken as a surrogate marker for diagnosing this disease. Uric Acid (UA), a marker of oxidative stress, has been investigated as a potential predictive biomarker for risk stratification. Our study was conducted to ascertain the incidence and severity of sPAP, to evaluate the level of UA levels, and to establish a correlation.

Methods: This is an observational case-control study that included 51 cases of PAH diagnosed by sPAP ≥ 36 mm Hg, along with 51 controls. Serum UA was assayed using a spectrophotometric method. Statistical analysis was performed using Microsoft Excel and SPSS version 20.0.

Results: Cases were observed in the range of 24 to 87 years (average 48 years) with female predominance. UA levels were significantly higher in cases than in controls. Females showed slightly lower levels of UA as compared to males. Correlation analysis indicated a significant positive correlation between sPAP and uric acid levels. Receiver Operating Characteristic (ROC) analysis demonstrated that serum UA had 68% predictive accuracy for sPAP severity at a cutoff of 5.45 mg/dL.

Conclusions: The level of UA, a routine biomarker analysed in laboratories, is found to be increased in PAH patients and closely correlates with the severity of sPAP. This suggests a potential role of UA as a predictive biomarker in PAH management.

¹ Assistant Professor, Department of Biochemistry, SCB Medical College and Hospital, Cuttack, India.

² Professor, Department of Cardiology, SCB Medical College and Hospital, Cuttack, India.

³ Associate Professor, Dept of Orthopedics, PGIMER & Capital Hospital, Bhubaneswar, India.

⁴ WHO Fellow, Professor, Dept of Biochemistry, SCB Medical College and Hospital, Cuttack, India.

⁵ Undergraduate Medical Student (MBBS Program), SCB Medical College and Hospital, Cuttack, India

Correspondence:

Monalisa Mohapatro,

Department of Biochemistry, SCB Medical College and Hospital, Cuttack, India.

Email: monalisa.mohapatro@gmail.com

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Introduction

Pulmonary Arterial Hypertension (PAH) is a multifaceted pathophysiological life-threatening disorder associated with various cardiovascular and respiratory diseases. It is characterized by chronic elevation of Pulmonary Arterial Pressure (PAP) and Pulmonary Vascular Resistance (PVR) due to progressive occlusive pulmonary vasculature remodelling, ultimately leading to Right Ventricular Hypertrophy (RVH), causing cardiac failure and death. PAH is a comparatively rare disease with variable prevalence globally, ranging from 0.4 to 1.4 per 100,000 persons.¹ The disease was defined arbitrarily in First World Symposium on Pulmonary Hypertension convened in Geneva in 1973 as a mean Pulmonary Artery Pressure (mPAP) of >25mm Hg at rest by cardiac catheterization which is the gold standard having both diagnostic and prognostic utility.² In the Sixth World Symposium in 2018, PAH was estimated to be mPAP > 20 mm Hg and the severity was classified as mild (20- 40 mm Hg), moderate (41-55 mmHg) and severe (> 55 mmHg).³

The incidence and prevalence of PAH are increasing due to heightened awareness and suspicion among clinicians, increased access to echocardiograms, an ageing population, and improved quality of treatment. In a study by Malligreddy AR et al. on the current status and barriers of PAH in India, diagnostic evaluations for PAH were found to be limited. Patients and physicians were hesitant about the invasive right heart catheterization.⁴ The correct and final diagnosis of PAH is delayed from the time of presentation of non-specific symptoms of right ventricular dysfunction due to the initial exclusion of common clinical conditions. Non-invasive Transthoracic Echocardiography (TTE) plays a pivotal role as an initial screening test, detecting preclinical conditions, assessing outcomes, and monitoring the efficacy of therapeutic interventions.⁵ PAH diagnosis is suggested initially by a tricuspid regurgitant jet velocity >2.8 m/s corresponding to a systolic Pulmonary Artery Pressure (sPAP) of \approx 35mmHg.⁶

The etio-pathogenesis of PH is a complex myriad of genetics and metabolomics generating a lot of circulating biomarkers like BNP, N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP), Troponins (T, I), Inflammatory markers (C-Reactive Protein [CRP]), cytokines (Interleukin [IL]-6, IL-8, IL-10) etc.⁷ In a meta-analysis by Smits AJ et al, IL-6 and Uric Acid (UA) were found to have significant predictive value with low risk of bias.⁸ Thus, there is increased interest in the exploration of the potential utility of non-invasive serum biomarkers for faster

diagnosis and initiation of treatment before the development of right heart failure that might help in improving the overall survival and quality of life.

Significant positive correlation between UA and the severity of idiopathic PAH was first elaborated as an independent risk factor for poor prognosis of survival by Nageya et al in 1999.⁹ Zhou Y et al observed that dynamic UA concentration can help in assessing the severity and predict prognosis in connective tissue disease associated PAH.¹⁰ In a study done by Yan L et al for the prognostic impact of hyperuricemia on long term mortality of PAH, it was found that elevated levels of circulating UA at baseline significantly correlated with increased severity and increased risk of 5-year mortality.¹¹ These findings were also corroborated by Luo J et al which established that UA can be used as a practical and economic biomarker for risk stratification and therapeutic response in PAH.¹² Thus hyperuricemia closely correlates with symptom severity and high mortality in PAH. Further research is required to establish UA as an independent risk factor of prognosis in PAH.

This study was conducted to identify serum UA as a potential predictive marker of sPAP, which can be clinically utilised in patients with PAH.

Methods

The present study was an observational case-control study conducted at the Post Graduate Department of Biochemistry in collaboration with the Department of Cardiology for a period of 9 months from August 2023 to April 2024.

Inclusion Criteria

51 cases of pulmonary artery hypertension diagnosed by sPAP \geq 36 mm Hg attending the Outpatient Department (OPD) of the Department of Cardiology of the tertiary care centre were included for the study. Sampling was done by simple random sampling. The sample size was calculated using a 95% confidence level, a 5% margin of error, and a Prevalence of PAH of 1.4%, as provided by calculator.net. An equal number of age-, sex-, and socioeconomic status-matched healthy volunteers served as controls.

Exclusion Criteria

Patients having renal function disorders, being obese, and on medications that can affect UA were excluded from this study. Patients with metabolic disorders, diabetes mellitus, and hypertension, critically ill patients, or those with other co-morbidities were excluded from the study. Patients unwilling to provide consent for the study were also excluded.

Biochemical Analysis

After obtaining written informed consent from patients, 3 mL of fasting venous blood was collected and centrifuged to separate serum. Samples were kept at -20°C until analysis. Serum UA was assayed by the spectrophotometric method using reagent kits in an auto analyzer (BS-390 MISPA Clinia auto analyzer by AGAPPE / TBA 1200FR).

Statistical Analysis

For quantitative data, statistical analysis was performed using Microsoft Excel and SPSS version 20.0 (IBM Inc., Chicago, Illinois). Results were expressed as Mean and Standard Deviation for continuous variables and as percentages for categorical variables. Data were compared using an independent-samples t-test. The correlation was assessed using Pearson’s correlation coefficient. Bar graphs and scatter plots were done. A p-value of < 0.05 was considered statistically significant.

Ethics Statement

The study was approved by the Institutional Ethics Committee, SCB Medical College and Hospital, Cuttack, Odisha. (1525/ 16.08.2023)

Results

The present study of 51 PAH patients observed ages ranging from 24 to 87 years (48.07 ± 16.75), whereas controls were 50.35 ± 17.20 years; the difference was not statistically significant. ($p = 0.5$) PAH patients had a female predominance of 55% (28 cases) as compared to males, 45% (23 cases).

sPAP in PAH patients was found to be significantly higher at 53.27 ± 11.42 mm Hg compared to controls (sPAP of 28.6 ± 3.6 mm Hg), which was found to be statistically significant (p -value = 0.0001). The levels of UA in patients with PAH (6.11 ± 2.17 mg/dL) were significantly higher than in controls (3.9 ± 1.36 mg/dL; $p < 0.0001$). Male PAH patients 6.4 ± 2.3 mg/dL; females 5.9 ± 2.1 mg/dL. [Table 1, Figure 1]

Table 1. Socio-demographic and Investigative characteristics of pulmonary arterial hypertension patients and controls

Parameter	PAH Patients (n = 51)	Controls (n = 51)	P-value
Age, years	48.07 ± 16.75	50.35 ± 17.20	0.5
Gender, n (%)			
Male	23 (45%)		1.00
Female	28 (55%)		
sPAP, mmHg	53.27 ± 11.42	28.6 ± 3.6	0.0001
Serum uric acid, mg/dL	6.11 ± 2.14	3.9 ± 1.36	0.0001
Male	6.4 ± 2.3	-	
Female	5.9 ± 2.1	-	

sPAP: systolic Pulmonary Arterial Pressure.

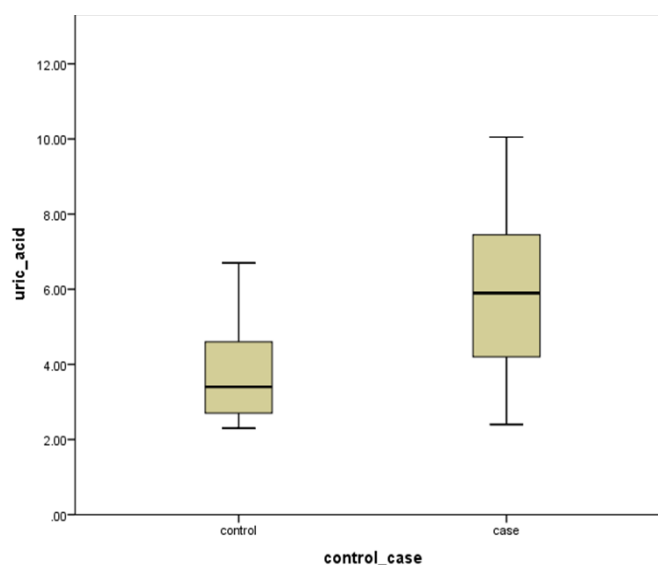


Figure 1. Box-plot diagram showing the levels of uric acid in controls and cases.

Serum UA levels were analyzed according to the severity of PAH, categorized by the levels of peak sPAP. In patients with mild PAH (sPAP: 36-50 mmHg) the serum UA levels was 6.23 ± 2.35 mg/dL, in cases of moderate PAH (sPAP: 50-70 mmHg), UA levels slightly decreased to 6.23 ± 1.76 mg/dL and in severe PH cases (sPAP > 70 mmHg) showed a decrease in UA levels to 5.34 ± 2.16 mg/dL. Analysis of the correlation between serum UA

levels and peak systolic sPAP in patients with PAH yielded correlation coefficients (r) and associated p-values, indicating the strength and significance of these associations. Notably, there is a significant positive correlation between sPAP and UA levels ($r = 0.470$, $p = 0.001$), suggesting an association with PAH severity. [Table 2, Figure 2]

Table 2. Comparison of Serum Uric Acid level as per severity in pulmonary arterial hypertension patients.

Severity (level of sPAP)	No of cases (n)	Uric acid (in mg/dL)
Mild(36-50 mmHg)	28	6.23 ± 2.35
Moderate (50- 70 mmHg)	16	6.23 ± 1.76
Severe (> 70 mmHg)	7	5.34 ± 2.16

sPAP: systolic Pulmonary artery pressure

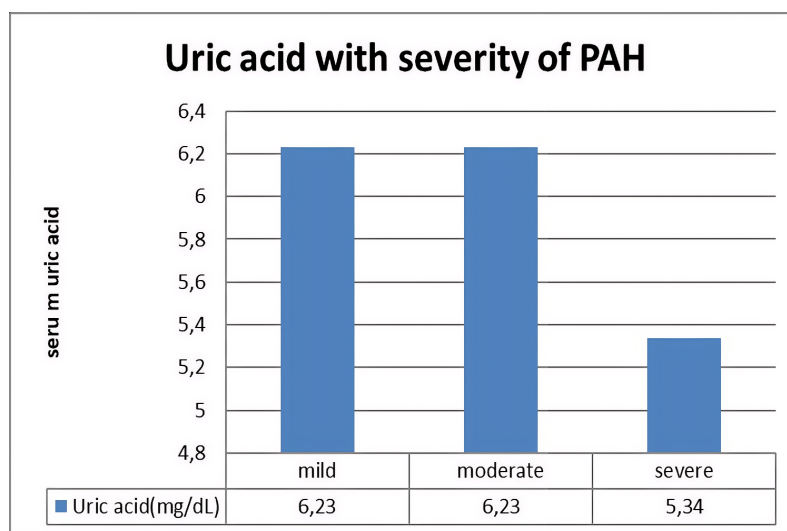


Figure 2. Comparision of uric acid as per the severity of pulmonary hypertension patients.

On analysis of the Receiver Operating Characteristic curve (ROC) for serum UA by plotting false positives (1-specificity) in X-axis and true positives (sensitivity) in Y-axis to ascertain the predictive accuracy of our parameters for Severe Pulmonary Arterial Hypertension, the Area Under the Curve (AUC) for UA was 0.680 with a 95 % confidence interval 0.563- 0.796. The cutoff value for serum UA was 5.45 mg/dL, with 77.8% sensitivity and 65.6% specificity. [Table 3, Figure 3]

Discussion

PAH is a chronic progressive fatal disease characterized by increased precapillary pulmonary hypertension and elevated pulmonary vascular resistance, presenting with non-specific symptoms like dyspnea and ultimately leading to right heart failure and death.¹³ The global incidence and prevalence of PAH vary widely worldwide as a rare complication of various heterogeneous disorders, with an approximate incidence of 1 %.¹⁴

Table 3. Diagnostic accuracy of uric acid with pulmonary hypertension.

AUC (Area Under Curve)	(95 % CI)	Cut-off	Sensitivity	Specificity
0.680	(0.563- 0.796)	5.45	77.8%	65.6%

In our study, cases of PAH were observed across a range of ages from 24 to 87 years, with a mean age of 49 years. There is a female discrepancy (55%) reported, similar to other studies, with a greater incidence of PAH in females but better outcomes labelled as ‘estrogen paradox’.¹

Serum UA, the final product of purine metabolism, has been implicated as a surrogate marker and an indicator of impaired oxidative stress and redox balance, which are involved in the pathobiochemistry of various cardiovascular disorders, and has also

been a significant predictor of PAH.¹⁵ In our study, the levels of serum UA in PAH cases (6.11 ± 2.14 mg/dL) were higher than those of controls (3.9 ± 1.36 mg/dL), which was statistically significant (p value < 0.0001) and showed a significant positive correlation with sPAP ($r = 0.470$, $p = 0.001$). Females had slightly lower levels of UA (5.9 ± 2.1 mg/dL) than males (6.4 ± 2.3 mg/dL). On comparing the severity of PAH, the level of UA showed a decreasing trend of 6.23 ± 2.35 mg/dL in mild PAH, 6.23 ± 1.76 mg/dL in moderate PAH, and 5.34 ± 2.16 mg/dL in severe PAH.

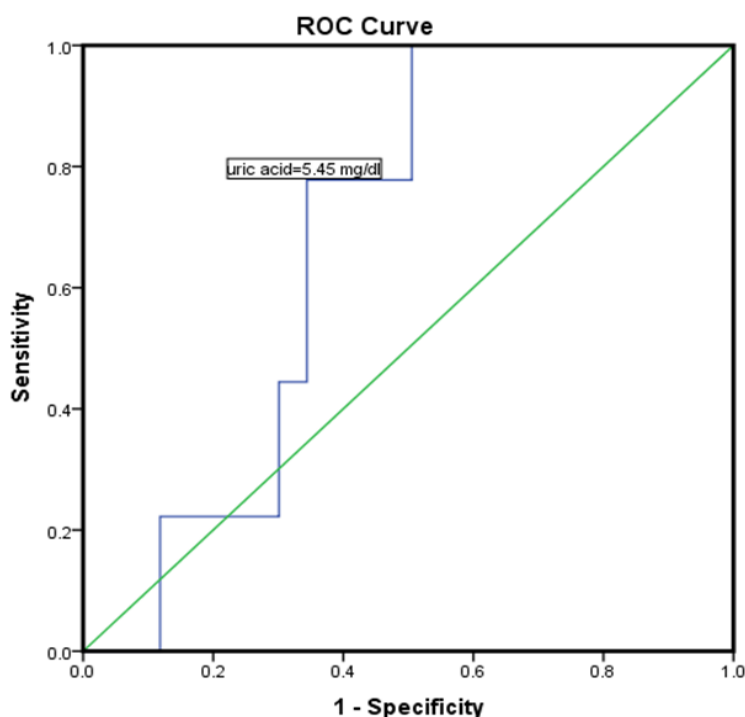


Figure 3. Comparison of uric acid as per the severity of pulmonary hypertension patients.

However, the correlation and variation of serum UA with severity could not be ascertained in our study due to the limited study period and the smaller sample size. The significant positive correlation of UA with PAH irrespective of the causative etiology in concurrence with our study has been demonstrated by various studies like Wang J et al in PAH associated connective tissue disorder¹⁶, Nagaya N et al in primary PAH patients¹¹, Luo J in PAH associated with congenital heart disease¹⁴, Simpson CE et al in systemic sclerosis related PAH¹⁷, Aghdashi M et al demonstrated increased levels of UA in PAH patients with systemic lupus erythromatosis.¹⁸ Experimental studies such as Watanabe T¹⁹, Li Q²⁰, and Savale L²¹ have also demonstrated disturbed UA me-

tabolism in PAH model rats. Clinical studies, such as Du P et al., have shown that higher levels of UA are independently associated with adverse outcomes in PAH²², and Li Wt et al. have shown that serum UA levels can be used as a non-invasive marker to evaluate the efficacy of PAH-targeted medications.²³

The findings of our study indicate that UA should be routinely assessed in patients with PAH to diagnose disease progression of severe PAH, monitor the course of treatment, and assess the efficacy of therapeutic interventions. This study corroborates that serum UA can be used as an independent biomarker for the diagnosis and risk stratification of PAH.

There are several limitations to our study. First, the sample size of this study was small, and studies with multicentre large sample sizes are required to confirm the association of UA in PAH. Furthermore, the diagnosis of PAH was made based only on systolic pulmonary arterial pressure without right heart catheterization due to the unavailability of the diagnostic procedure. Hence, further research is essential for the clinical implementation of UA as a prognostic marker in PAH.

Conclusion

In this study, we analyzed 51 cases of pulmonary hypertension and 51 age-, sex-, and socioeconomic status-matched healthy controls over a 9-month study period of using systolic pulmonary artery pressure obtained from echocardiography. We have observed that the level of UA is higher in patients with pulmonary hypertension than in controls. A significant positive correlation was found between UA and the severity of systolic pulmonary arterial hypertension. The ROC curve analysis showed a sensitivity of 68% for serum UA, indicating that it is a strong predictor of this study and supporting our findings. Hence, multicentre studies with larger sample sizes are necessary to objectively define the role of UA in pulmonary hypertension, thereby enhancing the validity of the observation.

List of Abbreviations

AUC	Area Under the Curve
BNP	Brain Natriuretic Peptide
CRP	C-Reactive Protein
IL	Interleukin
mPAP	Mean Pulmonary Arterial Pressure
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
OPD	Outpatient Department
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PVR	Pulmonary Vascular Resistance
ROC	Receiver Operating Characteristic
RVH	Right Ventricular Hypertrophy
sPAP	Systolic Pulmonary Arterial Pressure
TTE	Transthoracic Echocardiography
UA	Uric Acid

Ethical Clearance

The study was approved by the Institutional Eth-

ics Committee, SCB Medical College and Hospital, Cuttack, Odisha. (1525/ 16.08.2023).

Publication Approval

All authors are consent to the publication of this manuscript.

Authors Contributions

MM was in charge of methodology, design of the study, analysis and interpretation of data, drafting the article, revising and editing it, correspondence and making the final published version; SNR was responsible for conceptualization, data collection supervision, interpretation of clinical data, revision of article critically for important intellectual content; BP was responsible for statistical analysis and interpretation of data analysis, drafting the article; PKS was responsible for supervision of data collection, revision of analysis and revising the article; SJ was responsible for data collection and compilation of data, conducting the experiment analysis, drafting the article. All authors were responsible for the final approval of the version to be published.

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Conflict of Interest

None.

Availability of Data and Materials

Not applicable.

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Not applicable.

Generative AI and AI-Assisted Technologies in the Writing Process

Authors acknowledge that artificial intelligence (AI) tools were only used to assist in language editing and did not generate or alter the scientific content, analyses, or conclusions presented in this manuscript.

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