Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Prognostic Value of Hyperuricemia on Clinical Outcomes of Sepsis:

Sivaranjani T[1*], Mohamed Rebayudeen S M[2], Jeganathan Geetha[3], Prabakar B[4]

[1*]Junior resident in General Medicine, Karpaga Vinayaga Institute of Medical Sciences & Research Centre, Chengalpattu District, Tamil Nadu, Pin: 603308, India. Email ID: drsivavivek17@gmail.com Mob: 9566213850,

Orcid ID: 0009-0004-6821-1477

[2]Assistant Professor of General Medicine, Karpaga Vinayaga Institute of Medical Sciences &Research Centre, Chengalpattu District, Tamil Nadu, Pin: 603308, India. Email id: rebayudeen@gmail.com Mob:9629304056

Orcid ID: 0009-0004-6446-0265

[3]Associate Professor of General Medicine, Karpaga Vinayaga Institute of Medical Sciences &Research Centre, Chengalpattu District, Tamil Nadu, 603308 India. Mail ID: dr.geeths25@gmail.com Mobile No: 9840797106

Orcid ID: 0000-0002-4374-5358

[4]Professor of General Medicine, Karpaga Vinayaga Institute of Medical Sciences &Research Centre, Chengalpattu District, Tamil Nadu, 603308 India. Mail ID: prabakarvandai@gmail.com Mob No:9344641277

Cite this paper as: Sivaranjani T, Mohamed Rebayudeen S M, Jeganathan Geetha, Prabakar B, (2025) Prognostic Value of Hyperuricemia on Clinical Outcomes of Sepsis:. *Journal of Neonatal Surgery*, 14 (32s), 1979-1986.

ABSTRACT

Background: Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection. Recent studies suggest that metabolic disturbances, including hyperuricemia, may influence the clinical course of sepsis. Uric acid, an end product of purine metabolism, has pro-inflammatory properties that may exacerbate organ dysfunction in septic patients and hence used as a marker of poor prognosis in sepsis. Hyperuricemia and its potential association with poor clinical outcomes, such as acute kidney injury (AKI), need for vasopressor support, mechanical ventilation, and mortality, remains an area of growing interest. This study investigates the association between hyperuricemia and clinical outcomes in adult sepsis patients admitted to the Medical Intensive Care Unit (MICU).

Methods: This retrospective analytical study included 162 adult patients diagnosed with sepsis and admitted to the MICU of Karpaga Vinayaga Medical College Hospital, Chengalpattu, Tamil Nadu, India, between January 2024 and December 2024. Adult patients who met Sepsis-3 definition of sepsis is included in this study. Serum uric acid levels, Lactate levels, Creatinine value at the time of admission and after 24 hours of admission were noted. Serum Uric acid levels more than 7 mg/dL is considered as hyperuricemia. Patients were divided into hyperuricemia (n=107) and normouricemia (n=55) groups based on serum uric acid levels. Baseline characteristics, laboratory parameters, AKI, duration of hospital stay, need for vasopressor support, need for assisted mechanical ventilation and mortality outcomes were compared between the groups using appropriate statistical tests, including Fisher's exact test and chi-square analysis.

Results: The median age was 59.5 years, with a female predominance (60.49%). Diabetes (58.02%) and hypertension (53.09%) were the most common comorbidities. Hyperuricemia was present in 66.04% of patients, with a mean serum uric acid level of 8.24 ± 3.13 mg/dL. AKI was significantly associated with hyperuricemia ($p<0.0001$). Elevated lactate levels (>2.2 mmol/L) were found in 98.13% of hyperuricemia patients, indicating hemodynamic instability. Vasopressor support was more frequently required in the hyperuricemia group, with 38% needing two or more vasopressors versus 16.7% in the normouricemia group ($p<0.001$). Additionally, 35.51% of hyperuricemia patients required mechanical ventilation compared to 3.63% in the normouricemia group ($p<0.001$). In-hospital mortality was also significantly higher in the hyperuricemia group ($p=0.0194$), although 30-day mortality did not reach statistical significance ($p=0.2248$).

Conclusion: Hyperuricemia in sepsis is significantly associated with worse clinical outcomes, including acute kidney injury, need for multiple vasopressors, assisted mechanical ventilation, and increased in-hospital mortality. Serum uric acid may serve as a useful biomarker for risk stratification in septic patients.

Keywords: *Hyperuricemia, Sepsis, Septic shock, Mechanical ventilation, Vasopressor support, Mortality, AKI, Duration of stay.*

1. INTRODUCTION

Sepsis is defined as a life-threating organ dysfunction caused by an infection or suspected infection with an increase in the Sequential Organ Failure Assessment (SOFA) score ≥ 2 [1]. According to the Sepsis-3 criteria, septic shock is defined as persistent hypotension that necessities vasopressor initiation to maintain a mean arterial pressure (MAP) of 65 mm Hg or greater with a serum lactate level greater than 2 mmol/L after at least 30 mL/kg of crystalloid fluid resuscitation [1]. Sepsis-related mortality has been reported to reach up to 50%, among several case series [2-5]. Sepsis remains one of the challenging medical conditions in intensive care unit (ICUs), causing more than 30% of the short-term ICU mortality in ICUs [6]. The early identification of sepsis and timely appropriate management can prevent severe complications and progression to septic shock [7]. Uric acid is the final product of purine catabolism by xanthine oxidase in liver cells, accounting for more than 50% of the total antioxidant activity in the blood, and it delays cell senescence through its antioxidant effect [8-10]. Approximately two-thirds of uric acid is excreted by the kidney, and the rest is excreted by the gastrointestinal tract. In addition, some uric acid is degraded in the body after reaction with oxidants or peroxynitrite[11]. Hyperuricemia is defined as the accumulation of serum uric acid beyond its solubility point in water and develops due to uric acid over production, under secretion, or both [12]. The changes in the level of serum Uric acid are affected by oxidative stress and provide evidence of impaired plasma antioxidant capacity in severe sepsis [13]. Normal levels of blood uric acid are typically 3.4–7.2 mg/dL for men and 2.4–6.1 mg/dL for women. Since the last century, elevated uric acid levels have been noted to be associated with atherosclerosis [14–18], hypertension, hyperinsulinemia [19,20], and chronic kidney disease [21], chronic heart failure [22,23] and obstructive pulmonary disease [24,25]. Majority of intensive care unit patients undergo ischemic reperfusion injury and inflammation to varying degrees during their hospitalization. Uric acid may be a factor playing a role in these processes since it has both oxidant and antioxidant properties. Since high levels of oxyradicals and lower antioxidant levels in patients with sepsis are believed to result in multiorgan failure, the measurement of uric acid levels could be possibly used as a marker of oxidative stress in patients with sepsis. Hence, we retrospectively analysed patients admitted to Medical Intensive Care Unit (MICU) with sepsis to see if there is any significance of serum uric acid with respect to the morbidity and mortality rate, because of its low cost and readily available in our basic laboratory panel. We hypothesized that elevated uric acid levels at the early hours of sepsis can predict an increased risk of morbidities as a single test.

2. MATERIALS AND METHODS

2.1 Study Design : We retrospectively analysed patients with sepsis admitted to the intensive care unit (ICU) of our Hospital between January and December 2024. We followed them for a maximum of 30 days, after their first day of hospitalization.

2.2 Enrollment criteria: Patients were included if they were at least 18 years of age and met the Sepsis-3 definition of sepsis (having an infection or suspected infection with an increase in Sequential Organ Failure Assessment (SOFA) score ≥ 2) [1]. Patients were excluded if they were <18 years old, pregnant females, patients from an outside facility that have already been in the MICU for more than 24 hours, had no uric acid data within 24 h of admission, had a history of gout, CKD, Malignancy or were on allopurinol or on hemodialysis, diuretics. During the course of the study, all patients continued to receive standard of care for their illnesses by the MICU team.

2.3 Data collection and Definitions: We gathered information regarding age, sex, BMI, concomitant diseases, immunosuppression, site of infection, length of hospital stay, complete blood count, lactate levels, uric acid levels on admission, creatinine levels on admission and after 24 hours of admission, SOFA score, need for vasopressor support, need for assisted mechanical ventilation from medical records. The baseline uric acid level was defined as the serum uric acid level collected from patients within 24 h of ICU admission. Based on baseline Uric acid levels, Patients were divided into hyperuricemia and non-hyperuricemia groups. Hyperuricemia in general is defined as a serum urate level of >7mg/dL in men and >6mg/dL in women. For our study, we defined hyperuricemia as a uric acid level ≥7mg/dL in both males and females. We defined Acute Kidney Injury (AKI) as an absolute ≥0.3mg/dL increase in serum creatinine over a 48-hour period from the baseline creatinine based on the Acute Kidney Injury Network (AKIN) definition [26]. We used as the baseline creatinine value as the patients' creatinine value at the time of initial presentation to the MICU.

2.4 Clinical outcomes: The primary end point was the correlation between hyperuricemia in patients presenting with sepsis and the mortality in ICU. Main outcomes included Length of Stay, Acute Kidney Injury, the need for assisted mechanical ventilation (AMV), and the need for vasopressor support (norepinephrine, epinephrine, vasopressin, dopamine, or phenylephrine), as well as mortality in the 28-day follow-up after the first day of admission to the ICU.

2.5 Statistical analysis: All data were collected, tabulated, and statistically analyzed using SPSS 28.0. Quantitative data were expressed as mean ± SD. These data were analyzed by applying chi-square test (expected frequency >5) and Fischer exact test (expected frequency <5) with 95% confidence interval. A p-value < 0.05 was considered statistically significant. For the qualitative data, they were expressed in the form of number and percentage and then analyzed by applying $\chi 2$ for comparison between two independent qualitative variables that were normally distributed.

3. RESULTS

3.1. Baseline Characteristics.

A total of 162 adult patients with sepsis admitted to the MICU at Karpaga Vinayaga Medical College hospital in Chengalpattu, Tamilnadu, India, who met inclusion criteria were included in the study. Among these, 107 were in Hyperuricemia group, while 55 were in the non- hyperuricemia group. The median age was 59.5 years. The most prevalent co morbidities were diabetes and hypertension however they are not statistically significant (see Table 1) Overall there are 39.51%(n=64) males and 60.49%(n=98) females and 43.21% of the enrolled patient population were ≥65 years of age. Also to note was that 25.31% of the overall patient population had a body mass index (BMI) ≥30. The BMI distribution in the overall population is given in Table 1. Main comorbidities and risk factors for sepsis were also included, with Type 2 Diabetes mellitus being the most frequent with 94 (58.02%) cases followed by systemic hypertension 86(53.09%) and cardiovascular disease 54 (33.33%)

Five infection sites were identified, with pulmonary (n=52, 32.1%) being the most common, followed by urinary tract (n=48, 29.63%), bacteremia (n=20, 12.35%), soft tissue infections (n=16, 9.88%), abdominal infections (n=8, 4.94%) and others (n=18, 11.11%).

3.2. Acute Kidney Injury

Amongst 162 patients, 107 (66.04%) had the primary end point of hyperuricemia. The mean serum uric acid level was 8.24 ± 3.13SD mg/dL (see Table 2). The probability of having hyperuricemia along with AKI is about 95.32% and without AKI is about 4.68%. The mean serum creatinine value at the time of admission was 2.3 ± 1.5SD mg/dL (see Table 2). Meanwhile the probability of having a uric acid value <7mg/dL along with AKI is 58.18% and without AKI about 41.82%. These probabilities are statistically significant with a p value of <0.0001.

3.3. Severity of Illness.

Elevated lactic acid levels can be used as a marker for indicating impaired tissue oxygenation, leading to increased anaerobic metabolism and suggesting the presence of hemodynamic instability resulting in lack of appropriate organ perfusion. In our lab elevated lactic acid level was considered as any level >2.2mmol/L. The mean lactate level of our study population was 3.6 ± 2.9 SD mmol/L (see Table 2). Of the patients with hyperuricemia 98.13% had an elevated lactic acid level, which is statistically significant.

Duration of stay in the MICU helps indirectly identify the degree of severity of illness of the ICU patients. We found that overall, 82.72% of our enrolled patients were still in the MICU and not transferred to a lower level of care at the end of 72 hours. The probability of having hyperuricemia and still being in the MICU at the end of 72 hours and more than 7 days was 32.10% and 30.86%, respectively, while the probability of having a uric acid level <7mg/dL and being in the MICU at the end of 72 hours and more than 7 days was 16.67% and 3.09%, respectively, which is statistically significant.

3.4. In hospital and 30 days mortality.

In this study, there is a significant correlation between In hospital mortality and higher uric acid levels. In hospital mortality (overall n=24, 14.81%) is significantly higher in the hyperuricemia group (n=21, 87.5%) than those in the normal uric acid level group (n=3, 12.5%), with p value of 0.0194 which is statistically significant, while 30 days mortality (overall n=12, 7.40%) in the hyperuricemia group (n=10, 83.33%) and normal uric acid level group (n=2, 16.67%) are not statistically significant (p value= 0.2248)

3.5. Need for vasopressor support.

In our study, the need for vasopressor support was significantly higher in the hyperuricemia group compared to the normouricemia group. The proportion of patients requiring 2 or more vasopressors was significantly higher in the hyperuricemia group (38/100 = 38%) compared to the normouricemia group (3/18 = 16.7%). Notably, 18 patients in the hyperuricemia group required 3 vasopressors, while none in the normouricemia group did. This difference was statistically significant (p <0.001, Fisher's exact value test), suggesting a strong association between hyperuricemia and the need for escalating vasopressor support.

3.6. Need for Assisted Mechanical Ventilation.

Among the 162 patients included in the study, 40(24.69%) required assisted mechanical ventilation. A significantly higher proportion of patients in the hyperuricemia group required ventilatory support compared to the normouricemia group. Specifically, 38 out of 107 patients (35.51%) with hyperuricemia required mechanical ventilation, while only 2 out of 55 patients (3.63%) in the normouricemia group did. This difference was statistically significant (p<0.001, Fisher's exact test), indicating a strong association between hyperuricemia and the increased need for mechanical ventilation in patients with sepsis.

Table 1. Baseline Characteristics

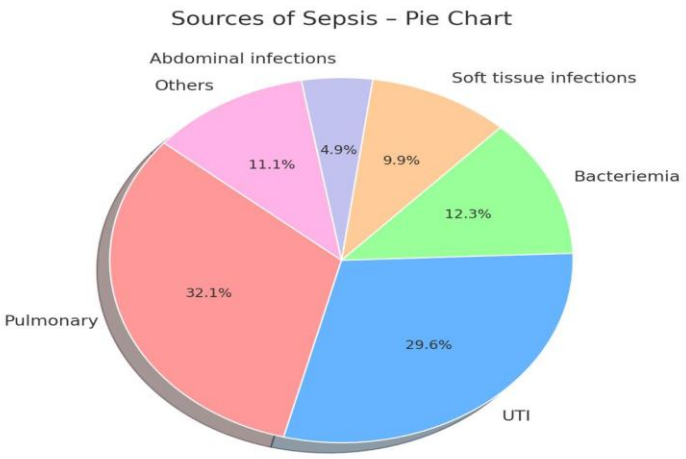
Characteristics	Overall N %	Uric Acid		p value
		High N %	Normal N %	
Age				
<30 years old	12 (7.40%)	6 (5.61%)	6 (10.91%)	0.1731
30-65 years old	80 (49.38%)	52 (48.59%)	28(50.91%)	
>65 years old	70 (43.21%)	49 (45.79%)	21 (38.18%)	
Sex				
Males	64 (39.51%)	46 (42.99%)	18 (32.73%)	0.2057
Females	98 (60.49%)	61 (57.01%)	37 (67.27%)	
BMI				
18.5-24.9	70 (43.21%)	49 (45.79%)	21 (38.18%)	0.3176
25-29.9	51(31.48%)	33 (30.84%)	18 (32.73%)	
>30	41 (25.31%)	25 (23.37%)	16 (29.09%)	
Comorbidities				
Diabetes	94 (58.02%)	63 (58.88%)	31 (56.36%)	0.7587
Hypertension	86 (53.09%)	57 (53.27%)	29 (52.73%)	0.9477
Cardiac Disease	54 (33.33%)	36 (33.64%)	18 (32.73%)	0.9065
Pulmonary Disease	31 (19.14%)	19 (17.76%)	12 (21.82%)	0.5338

Table 2. Clinical Characteristics at Admission N=162

Variables	Mean + SD
Respiratory rate (bpm)	24.8 ± 5.4
Pulse (bpm)	106.2 ± 19.2
Temperature (Farenheit)	98.2 ± 2.4
Systolic Blood Pressure (mmHg)	90.4 ± 21.2
Mean arterial pressure (mmHg)	66.3 ± 17.6
Glasscow coma scale score	13.3 ± 1.2
Serum Uric Acid levels (mg/dL)	8.24 ± 3.13
Serum Lactate levels (mmol/L)	3.6 ± 2.9
Serum creatinine levels (mg/dL)	2.3 ± 1.5

Table 3. Primary and Secondary Outcomes.

Variables	Overall N %	Uric Acid		p value
		High N%	Normal N%	
Primary Outcomes				
In hospital Mortality	24 (14.81%)	21 (87.5%)	3 (12.5%)	0.0194
30 days Mortality	12 (7.40%)	10 (83.33%)	2 (16.67%)	0.2248
Secondary Outcomes				
Hospital stay in MICU				
< 3 days	28 (17.28%)	5 (4.67%)	23 (41.82%)	<0.0001
3 – 7 days	79 (48.77%)	52 (48.60%)	27 (49.09%)	
>7 days	55 (33.95%)	50 (46.73%)	5 (9.09%)	
Elevated Lactate levels	142(87.65%)	105(64.81%)	37(22.84%)	<0.0001
Development of AKI	134 (82.71%)	102 (95.32%)	32 (58.18%)	<0.0001
Need for Vasopressors	118 (72.84%)	100 (84.74%)	18 (15.25%)	<0.0001
Single support	77 (65.25%)	62 (80.52%)	15 (19.48%)	
Dual support	23 (19.49%)	20 (86.96%)	3 (13.04%)	
Triple support	18 (15.25%)	18 (100%)	0	
Need for Assisted Mechanical Ventilation	40 (24.69%)	38 (35.51%)	2 (3.63%)	<0.0001



4. DISCUSSION

This retrospective analytical study evaluated the association between hyperuricemia and clinical outcomes in adult patients with sepsis admitted to the MICU. Our findings demonstrate a significant correlation between elevated serum uric acid levels and adverse clinical outcomes, including acute kidney injury, increased need for vasopressor support, mechanical ventilation, and higher in-hospital mortality.

The prevalence of hyperuricemia in our sepsis cohort was 66.04%, aligning with existing literature that describes hyperuricemia as a common metabolic disturbance in critical illness due to increased catabolism, renal dysfunction, and impaired clearance of uric acid [27]. We observed a strong association between hyperuricemia and acute kidney injury (AKI), with a statistically significant difference ($p<0.0001$). This supports previous findings that uric acid has nephrotoxic properties, contributing to renal vasoconstriction, oxidative stress, and inflammation, which may exacerbate AKI in septic patients [28,29].

Our results also indicate a significant association between hyperuricemia and hemodynamic instability. Patients with hyperuricemia were more likely to require multiple vasopressors, with 38% requiring two or more agents compared to 16.7% in the normouricemia group ($p<0.001$). Moreover, 18 patients in the hyperuricemia group required three vasopressors, whereas none in the normouricemia group did. This trend may reflect the impact of hyperuricemia on vascular tone and endothelial dysfunction, which have been implicated in reduced vasopressor responsiveness [30].

Another important finding is the association between hyperuricemia and respiratory failure. A striking 35.51% of patients in the hyperuricemia group required assisted mechanical ventilation, compared to just 3.63% in the normouricemia group ($p<0.001$). This suggests that elevated uric acid may be a marker of more severe disease with systemic involvement, possibly due to its link with increased proinflammatory cytokine activity and tissue hypoxia [31].

The strong correlation between hyperuricemia and elevated serum lactate further supports this hypothesis, as both markers reflect impaired oxygen delivery and metabolic stress.

Mortality data from our study show that in-hospital mortality was significantly higher in the hyperuricemia group (87.5% of deaths; $p=0.0194$), consistent with findings from prior studies associating uric acid with poor outcomes in sepsis and critically ill patients [31,32].

However, 30-day mortality did not show a statistically significant difference between groups ($p=0.2248$), which may be attributed to sample size limitations or post-discharge factors not captured in the study.

Despite these findings, there are several limitations to consider. This was a single-center retrospective study, limiting the generalizability of results. Additionally, causality cannot be inferred from associations, and potential confounding variables—such as the timing of sepsis onset, fluid resuscitation status, and baseline renal function—may influence the outcomes. Nevertheless, the strength of the observed associations suggests that serum uric acid could serve as a valuable biomarker in the early risk stratification of septic patients.

5. CONCLUSION

This retrospective analytical study demonstrates a significant association between hyperuricemia and adverse clinical outcomes in patients with sepsis. Elevated serum uric acid levels were correlated with increased severity of illness, prolonged ICU stay, higher need for vasopressor support and increased mortality. These findings suggest that hyperuricemia may serve as a useful prognostic marker in the early identification of high-risk septic patients. However, further prospective studies are warranted to explore the casual relationship and to evaluate whether therapeutic modulation of serum uric acid levels could improve sepsis outcomes.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

REFERENCES

[1] Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.-D.;

[2] Lakshmikanth CL, Jacob SP, Chaithra VH, de Castro-Faria-Neto HC, Marathe GK. Sepsis: in search of cure. Inflamm Res. 2016; 65(8):587-602.

[3] Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther. 2012;10(6):701-706.

[4] Ma J, Chen C, Barth AS, Cheadle C, Guan X, Gao L. Lysosome and cytoskeleton pathways are robustly enriched in the blood of septic patients: a meta-analysis of transcriptomic data. Mediators Inflamm. 2015;2015:984825.

[5] Rossaint J, Zarbock A. Pathogenesis of multiple organ failure in sepsis. Crit Rev Immunol. 2015;35(4):277-291.

[6] Liu, V.; Escobar, G.J.; Greene, J.D.; Soule, J.; Whippy, A.; Angus, D.C.; Iwashyna, T.J. Hospital deaths in patients with sepsis from 2 independent cohorts. JAMA 2014, 312, 90–92. [CrossRef] [PubMed]

[7] Evans, L.; Rhodes, A.; Alhazzani, W.; Antonelli, M.; Coopersmith, C.M.; French, C.; Machado, F.R.; Mcintyre, L.; Ostermann, M.; Prescott, H.C.; et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021, 47, 1181–1247. [CrossRef] [PubMed]

[8] Fox, I. H. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism* 30, 616–634 (1981).

[9] Maxwell, S. R. *et al.* Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. *Eur. J. Clin. Invest.* 27, 484–490 (1997).

[10] Perlstein, T. S. *et al.* Uric acid and the state of the intrarenal renin–angiotensin system in humans. *Kidney Int.* 66, 1465–1470 (2004).

[11] W. Doehner, N. Schoene, M. Rauchhaus et al., "Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies," *Circulation*, vol. 105, no. 22, pp. 2619–2624, 2002.

[12] N. L. Edwards, "The role of hyperuricemia and gout in kidney and cardiovascular disease," *Cleveland Clinic Journal of Medicine*, vol. 75, no. 5, pp. 13–16, 2008.

[13] Mantzarlis K, Tsolaki V, Zakynthinos E. Role of oxidative stress and mitochondrial dysfunction in sepsis and potential therapies. Oxid Med Cell Longev 2017; 2017:5985209.

[14] A. G. Ioachimescu, D.M. Brennan, B.M.Hoar, S. L.Hazen, and B. J. Hoogwerf, "Serum uric acid is an independent predictor of all-cause mortality in patients at high risk of cardiovascular disease: a Preventive Cardiology Information System (PreCIS) database cohort study," *Arthritis and Rheumatism*, vol. 58, no. 2, pp. 623–630, 2008.

[15] D. B. Corry and M. L. Tuck, "Uric acid and the vasculature," *Current Hypertension Reports*, vol. 8, no. 2, pp. 116–119, 2006.

[16] P. Patetsios, W. Rodino, W. Wisselink, D. Bryan, J. D. Kirwin, And T. F. Panetta, "Identification of uric acid in aortic aneurysms and atherosclerotic artery," *Annals of the New York Academy of Sciences*, vol. 800, pp. 243–245, 1996.

[17] J. Fang and M. H. Alderman, "Serum uric acid and cardiovascular mortality, the NHANES I epidemiologic follow up study, 1971–1992," *Journal of the American Medical Association*, vol. 283, no. 18, pp. 2404–2410, 2000.

[18] P. Verdecchia, G. Schillaci, G. Reboldi, F. Santeusanio, C. Porcellati, and P. Brunetti, "Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: the PIUMA study," *Hypertension*, vol. 36,no. 6, pp. 1072–1078, 2000.

[19] T. Nakagawa, P. Cirillo,W. Sato et al., "The conundrum of hyperuricemia, metabolic syndrome, and renal disease," *Internal and Emergency Medicine, vol. 3, no. 4, pp. 313–318, 2008.*

[20] L. G. Hunsicker, S. Adler, A. Caggiula et al., "Predictors of the progression of renal disease in the Modification of Diet in Renal Disease Study," Kidney International, vol. 51, no. 6, pp. 1908–1919, 1997.

[21] K. Iseki, S. Oshiro, M. Tozawa, C. Iseki, Y. Ikemiya, and S. Takishita, "Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects," Hypertension Research, vol. 24, no. 6, pp. 691–697, 2001.

[22] F. Leyva, S. Anker, J.W. Swan et al., "Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure,"European Heart Journal, vol. 18, no. 5, pp. 858–865, 1997.

[23] S. D. Anker, F. Leyva, P. A. Poole-Wilson, W. J. Kox, J. C. Stevenson, and A. J. S. Coats, "Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure," Heart, vol. 78, no. 1, pp. 39–43, 1997.

[24] A. Braghiroli, C. Sacco, M. Erbetta, V. Ruga, and C. F. Donner, "Overnight urinary uric acid: creatinine ratio for detection of sleep hypoxemia: Validation study in chronic obstructive pulmonary disease and obstructive sleep apnea before and after treatment with nasal continuous positive airway pressure," *American Review of Respiratory Disease*, vol. 148, no. 1, pp. 173–178, 1993.

[25] N. M. Elsayed, J. M. Nakashima, and E. M. Postlethwait, "Measurement of uric acid as a marker of oxygen tension in the lung," *Archives of Biochemistry and Biophysics*, vol. 302, no. 1, pp. 228–232, 1993.

[26] A. Khwaja, "KDIGO clinical practice guidelines for acute kidney injury," *Nephron Clinical Practice*, vol. 120, no. 4, pp. c179–c184, 2012.

[27] Watanabe S et al. "Uric acid and the kidney: novel roles in diseases of renal and cardiovascular systems." Curr Opin Nephrol Hypertens. 2011.

[28] Ejaz AA et al. "Uric acid and acute kidney injury." Semin Nephrol. 2011.

[29] Lapsia V et al. "Hyperuricemia and acute kidney injury in hospitalized patients." Kidney Int. 2012.

[30] Kanbay M et al. "Uric acid as a potential physiological trigger for the induction of hypertension." Hypertension. 2011.

[31] George J et al. "Uric acid in inflammation and the pathogenesis of disease." Rheumatology. 2006.

[32] Kim SY et al. "Association of serum uric acid level with mortality and morbidity in sepsis." Korean J Intern Med. 2013.

[33] Wu Y et al. "Association between hyperuricemia and mortality in critically ill patients: a retrospective cohort study." BMJ Open. 2021.