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A Systematic Review on Exploring the Role of Uric Acid in Predicting New-Onset Renal Damage in Lupus Nephritis

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Authors' contributions

This work was carried out in collaboration among all authors. Author IM did the major input to the article from generating the PICO Idea and research question, data analysis, data collection, correction and proofreading tables and figure, from abstract to conclusion. Author OO participated articles search through data bases, data collection, analysis, proofreading for errors in data and drafted the introduction and method section. Author PP contributed on data collection, articles searches, remove duplication by endnote app, proof reading process for errors, tables and methods part. Author PC participated in arranging data, proofreading of data, double checking the reference citation, collecting the DOI of reference, proofreading results section. Author SM proof reading the removed duplication, data collection, articles search, checking subheading, arranging size of text in the research, discussion drafted. Author AM contributed in analysis of data, drafted discussion part, providing suggestions and feedbacks. Author AK collection of data, figure drafting, reference editing, checking for errors, arranging tables in discussion part, drafted discussion. Author CO arranging data, collection articles, drafted conclusion, proofreading data, generate feedbacks and remove anything irrelevant. Author HDK data analysis, drafted abstract, proofreading data, double checking the criteria being applied correctly, drafted limitation part. Author SK did the title modification, reviewing manuscript, reviewing citation, participated in results part, conclusion and limitation parts, ensuring grammar proofreading, ensuring correct subheading sequences, ensuring correct guidelines was met. All authors read and approved the final manuscript.

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Systematic Review Article

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ABSTRACT

Background: Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) that can lead to significant renal damage if not detected and managed early. Hyperuricemia has been proposed as a potential predictive biomarker for renal outcomes in LN. However, gender-specific cut-off values for uric acid and the optimal timing of uric acid testing following LN diagnosis remain unclear.
Methodology: A systematic review was conducted to investigate the utility of hyperuricemia in predicting new-onset renal damage in LN. We searched five prominent databases (PubMed, Medline, Direct Science, Google Scholar, and BMC) for articles published in English within the past decade. Only studies involving participants over 18 years of age with biopsy-proven LN were included in this review.
Results: Ten research papers, encompassing a total of 1,674 patients diagnosed with biopsy-proven LN, were identified. The majority of these papers reported a positive correlation between hyperuricemia and LN, predominantly in female patients. An average follow-up duration of two years was found to have the highest specificity for uric acid as a predictor, with cut-off ranges varying from >4.9 mg/dl to >9.39 mg/dl
Conclusion: This systematic review highlights the potential significance of hyperuricemia as a predictive biomarker for new-onset renal damage in LN. Gender-specific cut-off values for uric acid could enhance the accuracy of prognostic assessment. Uric acid testing, which is affordable and widely accessible across various healthcare settings, may aid in achieving early identification of patients at risk of renal deterioration after LN diagnosis. Further prospective studies are warranted to validate these findings and establish standardized guidelines for incorporating uric acid testing into the clinical management of LN patients.

Keywords: Systemic lupus erythematosus; renal damage; predictor; lupus nephritis; uric acid.

1. INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune system dysfunction, leading to organ damage. The etiology of SLE remains unknown, and the disease manifests with various clinical presentations. Females are more prevalent across all ethnicities, with gender ratios varying from 2:1 to 15:1. The peak age of occurrence in female's ranges from the third to seventh decades, while males typically experience a later peak incidence in the fifth to seventh decades [1]. Renal involvement is a major concern, and despite treatment, the five-year survival rate for SLE patients with renal complications remains low [2]. Hyperuricemia has been associated with active lupus nephritis (LN), peripheral neuropathy, and cerebral infarction [3]. LN affects approximately 60% of SLE patients, and despite treatment, around 30% of these patients continue to experience varying degrees of renal impairment [4].

Traditional biomarkers used to diagnose LN include urinalysis, protein creatinine ratio, 24-hour urine collection for proteinuria, and serum creatinine with glomerular filtration rate estimation. Serological markers such as elevated anti-ds DNA levels and decreased C3 and C4 levels are also important indicators of active LN [5]. Renal biopsy remains the gold standard for diagnosing lupus nephritis, and it aids in classifying LN into six different histopathological findings.

Uric acid has emerged as a potential indicator for endothelial dysfunction and renal disease [2]. It is synthesized in the liver by breaking down purine compounds obtained from the diet and produced endogenously, and subsequently eliminated through the kidneys and intestine. Notably, around 20% of LN patients advance to end-stage renal disease (ESRD) within ten years after initial presentation, necessitating renal replacement treatment [6]. A strong correlation has been established between LN and hyperuricemia, with uric acid recognized as a risk factor for renal

complications [7]. Hyperuricemia is a significant predictor of a negative renal prognosis [8].

The aim of this systematic review is to underscore the importance of hyperuricemia as a predictor for renal disease progression in lupus nephritis, while considering gender-specific cut-off values. Additionally, we sought to determine the average timing for uric acid testing following the diagnosis of lupus nephritis. Our secondary endpoints included investigating the association between uric acid levels and blood pressure values, as well as its correlation with other blood parameters such as C3 levels and glomerular filtration rate (GFR). Overall, this systematic review provides valuable insights into the predictive role of hyperuricemia in renal progression among lupus nephritis patients

2. MATERIALS AND METHODS

The present systemic review adhered to the guidelines outlined in the Preferred Reporting Items for Systemic Review and Meta-Analysis (PRISMA) 2020 [9]. We searched using the terms "uric acid," lupus nephritis," and renal damage" through PubMed, Medline, Science Direct, and Google Scholar. Furthermore, we searched for the relevant literature observation (cohort, case-control, and cross-sectional) studies published from January 2013 to January 2023. Searching teams were ((("Lupus Nephritis/blood"[Mesh] OR "Lupus Nephritis/ prevention and control"[Mesh])) AND ("Uric Acid/blood)) AND "Renal Insufficiency /blood"[Mesh] OR "Renal Insufficiency/prevention and control"[Mesh]). See Table 1 which shows the search strategies summary and number of identified researches.

2.1 Inclusion and Exclusion Criteria

We included the articles published in the last ten years, written in English (or if the full text was translated into English), and with participants that were 18 years of age or older with biopsy-proven LN. The selection criteria exclude review articles, letters to the editor, non-biopsy-proven LN, and pregnancy.

2.2 Selection Process and Quality Assessment of the Studies

We selected articles and transferred them to Endnote and then removed duplicated papers. Inclusion and exclusion criteria were applied to all articles to create a shortlist. The next step was to apply the assessment tools we used, which were the Newcastle-Ottawa scale (case-control, cross-section, and cohort) and the Assessment of Multiple Systematic Review (AMSTAR), for systematic review and meta-analysis.

2.3 Data Collection Process

After the articles were shortlisted and finalized for this systematic review, all information and the resulting outcomes were assessed. IM and her colleagues extracted the data and retrieved outcomes that were assessed using an extraction questionnaire.

Table 1. Shows the search strategies for different databases and the number of identified research papers

Search strategy	Database use	Number of papers
((("Lupus Nephritis/blood"[Mesh] OR "Lupus Nephritis/prevention and control"[Mesh])) AND ("Uric Acid/blood"[Majr:NoExp])) AND "Renal Insufficiency/blood"[Mesh] OR "Renal Insufficiency/prevention and control"[Mesh])	PubMed (Mesh)	592
Uric acid AND Lupus nephritis OR lupus nephritis AND new onset renal damage	Medline	43
Uric acid AND Lupus nephritis OR lupus nephritis AND new onset renal damage	Science Direct	107
Uric acid AND Lupus nephritis OR lupus nephritis AND new onset renal damage	BMC	101
Total number of research identified		843
The total number after removing duplicated		648

3. RESULTS

3.1 Study Identification and Selection

A total of 8,223 articles were identified by searching through databases. There were 1,500 duplicated articles removed before the screening stage. By looking over the abstract titles and obtaining the full texts, 6,723 articles were screened; of those 373 were shortlisted. Ten articles were selected for this systematic review after assessment tools and inclusion and exclusion criteria were applied. Fig. 1 shows the identification and selection process in a PRISMA flowchart.

All the studies were assessed by different types of assessment tools/quality appraisal. Table 2 shows the summary of all the articles that met the satisfied criteria.

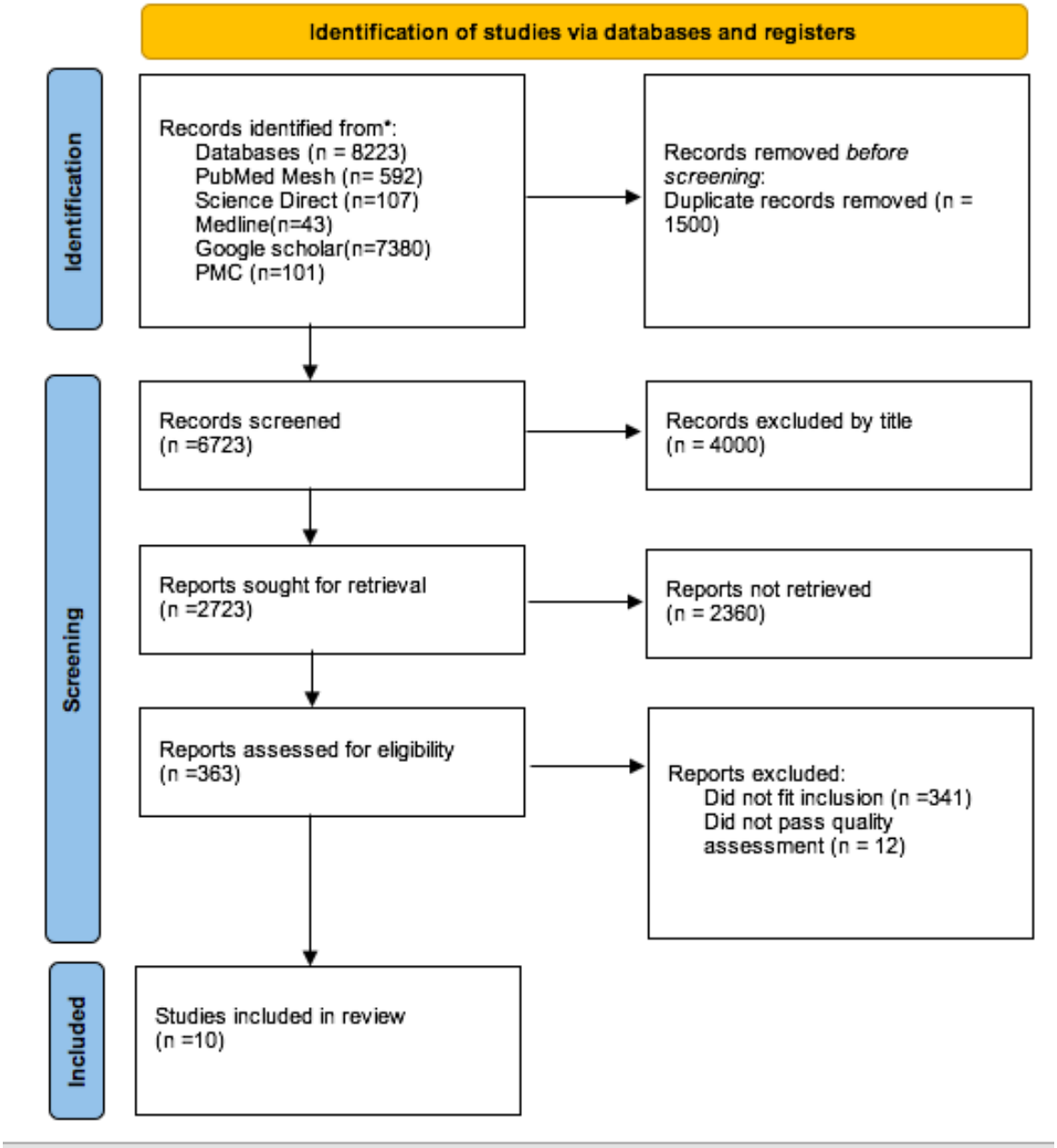

Fig. 1. PRISMA flowchart shows article selection and identification process

Table 2. Results of Newcastle Ottawa tool for observational studies

Year& study	Selection				Comparability		Outcome			Overall
Lopeset et al. [4].	-	-	*	*	*	*	*	*	*	8
Elnady et al. [5]	*	-	-	*	*	*	*	*	*	7
Hafez et al. [10].	-	*	*	*	*	-	*	*	-	7
Park et al. [11]	*	*	*	*	*	*	*	*	-	8
Xie T et al . [12]	*	*	*	*	*	*	-	-	*	8
Ryom Oh et al. [13]	*	*	*	*	*	*	*	*	*	9
Liu et al. [14]	-	*	*	*	*	*	*	*	*	9
Tang et al. [15]	-	*	-	*	*	-	*	*	*	7
Han et al. [16]	-	*	*	*	*	*	*	*	*	9
Okba et al. [17]	*	*	*	*	*	*	*	*	-	9

* *Newcastle Ottawa tool accepted score (>=70%: minimum scores of 6 out 9).*

3.2 Outcomes Measured

The first outcome extracted from the final papers was the role of uric acid in predicting the new onset of renal damage in LN. The second outcome suggested that hyperuricemia is an independent factor for women but not for men. A decreased uric acid level of less than 6.5 mg/dl was observed to indicate a favorable renal outcome progression. Additionally, other biomarkers such as proteinuria, lower levels of C3, and thrombocytopenia were found to be predictive of the early onset of renal damage in LN patients.

3.3 Study Characteristics

We analyzed ten research papers with a total of 1,674 patients diagnosed with LN. All the studies were cohort, case-control, and cross-sectional observation studies. All the studies that mentioned biopsy- proven LN were included, which was the gold standard for diagnosis of LN. One study was a case control followed by a prospective cohort that mentioned that the LN renal biopsy was done for only 18 out of 24 patients; the remaining seven refused the biopsy procedure. A few studies compared hyperuricemia in SLE with no LN and SLE with LN, which reported a positive correlation between both LN and SLE disease activities. Studies also mentioned women are more at risk for hyperuricemia due to multiple factors. These factors include renal excretion rate and postmenopausal or premenopausal status linked to estrogenic level. This was not seen in the male gender. Table 3 below shows the summary of the characters of all the studies and their results.

4. DISCUSSION

Lupus nephritis (LN) pathogenesis involves an inflammatory response triggered by an overactive immune system [13]. Hyperuricemia is a potential predictor of prognosis in LN, suggesting its significance in assessing renal activity. Several factors influence uric acid levels, including gender and age. Females tend to have higher uric acid levels due to multiple hypotheses, one of which suggests the estrogen effect on urate excretion, leading to higher uric acid levels in premenopausal SLE patients compared to healthy premenopausal individuals [18,19].

In the study conducted by Ryom Oh et al., 578 patients with biopsy-proven LN were included, with 86.0% being female [13]. The crude analysis revealed an association between serum uric acid levels and the progression of LN. During the median follow-up period of 6 years, fifty-one patients (8.8%) experienced LN progression. A significant association was found between uric acid levels and LN progression in females, with a hazard ratio (HR) of 1.158 (95% confidence interval [CI] = 1.018–1.317, $p < 0.028$). However, no association was found in males [18]. One study reported no association between gender and poor renal outcomes [13]. In contrast, Han et al. reported that females with LN and high uric acid would have an increased risk of renal damage, unlike males, who exhibited a nonlinear pattern [16]. It is challenging to establish a consistent positive or negative correlation between gender, as the natural disease tends to be predominantly female.

In a study of 89 patients with biopsy-proven LN, follow-up assessments conducted at 0 months, 6 months, 12 months, and 7 years showed a significant association ($p < 0.02$) between uric acid levels at the one-year follow-up (using a cut-off value of < 6.05 mg/dl), as documented by Lopes et al [4]. These findings suggest that uric acid blood level tests hold sustainable value in determining renal outcomes and indicate that

Table 3. The characters of all studies that were included in this study

Author and year of publications	Type of Study	Purpose of the study	Number of participants	Country	Results	Conclusion
Lopes et al., [4].	Prospective cohort.	The potential of serum uric acid as a predictor for long-term renal outcomes was assessed by identifying its optimal level	80	Brazil	At 12 months, serum uric acid was found to be significant (P value = 0.02), and unlike the initial and six months, it was unable to separate the good or poor long-term renal outcome in LP. The uric acid value at 12 months had an accuracy of 0.76, and the cutoff was 6.05 mg/dL. In SLE patients with active LN, uric acid levels were found to be higher compared to two control groups (P value < 0.005). A threshold of 0.41 mmol/L was identified as being related to serum uric acid and lupus nephritis onset.	Elevated serum uric acid levels at 12 months were linked to new-onset lupus nephritis and renal damage. However, serum uric acid levels below 6.05 mg/dL at the same time point were associated with a favorable long-term renal outcome in LN. Monitoring serum uric acid could be valuable in assessing renal involvement and predicting lupus nephritis prognosis.
Elnady et al. [5].	The case-control study followed by a prospective cohort	The relationship of uric acid levels in Systemic Lupus Erythematosus (SLE) with	89	Saudi Arabia	Uric acid levels were high in SLE patients with active LN compared to two groups with a P value <0.005. A threshold of 0.41 mmol/L was identified as related	Both the new onset of lupus nephritis and the new onset of renal damage were found to be associated with elevated serum uric acid levels.

Author and year of publications	Type of Study	Purpose of the study	Number of participants	Country	Results	Conclusion
		active Lupus Nephritis (LN) and inactive LN was analyzed in comparison to healthy control groups for the new onset of renal damage in lupus nephritis.			to serum uric acid and lupus nephritis onset.	
Hafez et al. [10].	Cross-sectional study.	The study aimed to find a connection between uric acid levels, the occurrence of LN, and SLE progression with normal kidney function	60	Egypt	Uric acid was found to be able to serve as a prognostic factor for developing LN in SLE patients. The sensitivity and specificity were 83.3% and 70%, respectively.	A relationship has been observed between uric acid and the development of LN in patients with normal renal function tests. Furthermore, uric acid has been linked with LN activity and a chronic status of LN.
Park et al. [11].	Prospective longitudinal cohort.	The impact of uric acid on long-term outcomes of patients with biopsy-proven LN was studied	137	Korea	The progression of chronic kidney disease CKD in patients with LN was found to be influenced by uric acid levels of more than 7 mg/dl	In patients with LN, chronic kidney disease (CKD) was found to be influenced by uric acid, which played the role of an independent progenitor
Xie T et al. [12].	Prospective cohort.	The association of uric acid and	177	China	In LN patients with hyperuricemia, elevated	Worse progression was indicated in patients with LN who had hyperuricemia.

Author and year of publications	Type of Study	Purpose of the study	Number of participants	Country	Results	Conclusion
		renal damage in LN was evaluated.			levels of hypertension, urea, and creatinine were observed. However, the positive rate of anti-U1RNP antibody was decreased, leading to a decrease in the glomerular filtration rate	
Ryom Oh et al. [13]	Retrospective cohort.	To understand the roles of gender impacting uric acid and the progression of LN, the impact of gender on uric acid levels and LN progression was investigated	578	Korea	the male gender had a higher level than the female. A 1 mg/dl increase was associated with a 15.1% higher risk for the progression of LN	In women, the uric acid level was identified as an independent factor. On the other hand, it was not found in men.
Liu et al. [14].	Retrospective cohort.	The relationship between hyperuricemia and early detection, treatment, and the subtype of LN was evaluated	177	China	CKD patients had a higher prevalence of hyperuricemia than patients with LN.	Renal underexcretion is the most common subtype in stage 1–3 CKD.

Author and year of publications	Type of Study	Purpose of the study	Number of participants	Country	Results	Conclusion
Tang et al., [15].	Cross-sectional study.	Treatment for LN and progression factors were assessed.	173	China	Uric acid and C3 were found to be sensitive to the development of new renal lesions	Elevated levels of uric acid value in the female gender were also found to be associated with an increased risk for renal progression
Han et al. [16].	Retrospective observational study and meta-analysis.	The linked effect between uric acid and LN was investigated	123	China	Out of 123 LP biopsies, 110 proved that 89.4% of LN patients had high uric acid levels, as found using the Cox proportional hazard regression model	The machine assessment to predict the progression of LN was found to have the potential to predict progression
Okba et al., [17].	Prospective cohort.	The level of hyperuricemia was assessed concerning the prognosis of LN	80	Egypt	Hyperuricemia was found to be associated with increased activities of SLE and proteinuria with a P value less than 0.001	A relationship between hyperuricemia and the new onset of renal damage in LN was observed

Table 4. Receiver operating characteristic (ROC) analysis of cut off uric acid related to follow-up periods

Study/ year	AUC	The best Cut-Off Points of Uric Acid	Sensitivity	Specificity	Follow-up Duration
Okba et al., [17].	Male: 0.738 Female: 0.781	Uric acid >9.1 mg/dl for males, Uric acid >5.5 mg/dl for females.	57.14%, 63.64%	100%, 88.24%	24 months
Hafez et al. [10].	0.809	Uric acid >4.9mg/dl.	83.33 %	70%	Cross-sectional study
Elnady et al. [5]	0.93 0.588	Uric acid with onset LN = uric acid >7.38 mg/dl, and uric acid along with LN predicts new renal damage = uric acid >9.36 mg/dl.	58% 43%	100% 82%	43 months
Lopeset et al., [4].	0.76	Uric acids < 6.05 mg/dL less indicated good progression	67%	89%	>7 years

lower levels of uric acid are associated with less renal injury, and short-term follow-up could predict the outcome. Similarly, another study with a one-year follow-up period reported that uric acid levels greater than 7 mg/dl were a significant predictor of the progression of chronic kidney disease (CKD) in LN patients, with a hazard ratio of 2.437 and a corresponding P value of 0.020 [13]. This supports the hypothesis that a uric acid blood test could serve as an indicator of LN progression. In addition, a baseline serum uric acid level of less than 0.52 mmol/L (9.36 mg/dl) throughout a follow-up period of 43 months may indicate the emergence of new-onset renal injury [16]. As some research suggests, various cut-off points from baseline uric acid levels post-LN diagnosis can predict renal outcomes. The comparison of all ROC analysis-based research that include uric acid cut-off values can be seen in Table 4.

Hyperuricemia has been identified as a potential predictor of prognosis in lupus nephritis (LN), suggesting its significance in assessing renal activity. Various factors, such as SLE Disease Activity Index (SLEDAI), C3 level, glomerular filtration rate (GFR), blood pressure, and urinary N-Acetyl-beta-D-Glucosaminidase (NAG) levels, have been linked to hyperuricemia in LN.

The relationship between uric acid and SLEDAI has been explored in several studies. Hafez et al. conducted a cross-sectional study with 60 patients, revealing a positive correlation between uric acid and SLEDAI score in one group ($p < 0.001$) [10]. Similarly, Obka et al. reported a positive correlation with a P value of >0.001 [2,17]. However, contrasting findings were reported by Elnady et al., who found no significant association between uric acid levels and SLEDAI [5]. It is essential to consider that not all participants in Elnady et al.'s study had biopsy-proven LN. Nevertheless, multiple observational studies have supported a positive correlation, suggesting that higher SLEDAI and increased uric acid levels may trigger a generalized inflammatory reaction affecting various body structures, including the renal system. Additionally, studies have shown that a higher SLEDAI is associated with a higher risk of renal injury, as demonstrated by the relationship between SLEDAI and creatinine [20].

Elevated uric acid has been linked to the development of new-onset renal damage in SLE [14It predominantly causes renal injury, which causes glomerular blood vessel hypertension, which eventually progresses to systemic hypertension [18]. Several studies have established hyperuricemia as a risk factor for renal damage and persistent injury. An increased incidence of hypertension in LN patients has been linked to higher uric acid levels [8]. Moreover, hypertension and low renal function at the onset of LN have been linked to a poor response to immunosuppressive treatment within the first year of diagnosis [21]. Hyperuricemia has also been associated with stages 1–3 of chronic kidney disease (CKD) in LN patients [15], and high uric acid levels have been found to be linked with an increased risk for CKD [22]. These findings support the hypothesis that higher uric acid levels correlate with an elevated risk of renal endothelial injury, leading to hypertension and overlapping with the chronic stage of kidney injury.

Studies exploring the association between uric acid and C3 levels have revealed interesting results. Ryom Oh et al. found a connection between uric acid and C3 levels, indicating that elevated uric acid activates the complement system, leading to C3 consumption via both classical and alternative pathways (P value <0.001) [13]. Furthermore, several studies have supported a significantly negative correlation between C3 and uric acid [16,18,23]. However, some studies reported no significant relationship between uric acid and C3 [4,5,17]. Notably, the study by Ryom Oh et al. had a large number of participants (578 individuals), suggesting the robustness of their findings. The activation of the complement system as a result of higher uric acid levels may contribute to the observed decrease in C3 levels.

Machine learning-based evaluation has shown potential in assessing factors related to LN, along with one urinary biomarker [15]. Moreover, urinary NAG has demonstrated a significant correlation with hyperuricemia in LN patients (P value < 0.01). This finding supports the hypothesis that higher uric acid levels are associated with elevated levels of urinary NAG, contributing to the progression of renal damage in LN patients.

A study conducted by Lopes et al. has suggested that a follow-up period of at least 12 months is crucial for distinguishing between poor long-term renal outcomes and favorable renal outcomes. Furthermore, a serum uric acid level of less than 6.05 mg/dl at the 12-month follow-up indicates a

positive long-term outcome in lupus nephritis [4]. Furthermore, Yang et al. recommend the regular monitoring of proteinuria, aiming for levels below 0.1g/24h and ideally to < 0.5g/24h, along with the imperative of maintaining Mean Arterial Pressure (MAP) below 96.5 mmHg [7]. Pakfetrat et al.'s research revealed a connection between male gender and poor renal outcomes. Additionally, their findings demonstrated that individuals with an initial creatinine (Cr) level exceeding 1.5 faced an increased risk of developing CKD (OR: 5.7, CI: 1.3–15.2, p = 0.031) [19]. A poor renal outcome is evidenced among all LN patients with a baseline uric acid level exceeding 0.52 mmol/L (>9.36 mg/dl) during a 43-month follow-up period [5]. This underscores the importance of monitoring uric acid levels in patients diagnosed with lupus nephritis, and emphasizes the necessity for consistent uric acid assessments to track renal progression.

Lupus nephritis (LN) accompanied by hyperuricemia is linked to elevated renal pathological scores compared to LN without hyperuricemia, with a significant p-value of less than 0.05; furthermore, end-stage renal disease (ESRD) or renal failure, defined by a GFR below 15 mL/min/1.73 m^2 and often accompanied by uremia symptoms, requires kidney replacement therapy like dialysis or transplantation [13]. Despite undergoing various immunotherapy treatments for lupus nephritis, a majority of patients still progress to develop chronic kidney disease and ultimately reach end-stage renal disease [11,12,19,22]. This highlights the essential significance of implementing prompt preventive measures and maintaining ongoing monitoring of uric acid levels from the point of SLE diagnosis.

5. CONCLUSION

This comprehensive systemic review aims to highlight the significant implications of uric acid levels in predicting renal damage and progression in LN. The findings underscore the importance of closely monitoring uric acid levels during follow-up, ranging from one year up to an average of 2 years, to assess the prediction of renal outcomes. Additionally, the study delves into the association between uric acid and other clinical parameters such as C3 levels, glomerular filtration rate, and blood pressure. Therefore, during regular follow-up visits, C3 and C4 levels, along with one significant urinary biomarker, should be monitored, in addition to renal function and blood pressure monitor. These valuable insights enhance our understanding of the role of uric acid in the progression of LN.

While this review provides essential insights, further research should focus on establishing the cut-off value of uric acid in LN with chronic kidney disease and explore the effects of immunological therapy on uric acid levels in patients diagnosed with LN. Such investigations will advance our knowledge and may lead to more targeted and effective interventions for LN patients in the future.

6. LIMITATION

This study had a few limitations, such as confounding factors from alcohol, diet, and drugs. Such factors are hard to control in observational studies and, as a result, they may influence uric acid levels. Furthermore, a few centers of selected studies had participants from only one ethnic background, indicating a lack of generalization of the findings to a broader population. Overall, our recommendation for future research is to conduct a large-scale study with a more diverse pool of patients to ensure adequate representation of both genders. This will help in obtaining more robust and generalizable results that can be applicable to a wider population.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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