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Systematic Review

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A Biomarker-Centric Diagnostic Approach based on Neutrophil Percentage to Albumin Ratio (NPAR) for Diabetic UTIs

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ABSTRACT

The Neutrophil Percentage to Albumin Ratio (NPAR) was identified as a promising biomarker for identifying inflammation and renal complications in diabetic Urinary Tract Infections (UTIs). **Objective:** To evaluate the diagnostic potential of NPAR as a novel biomarker for the diagnosis and prognosis of diabetic UTIs. **Methods:** The current study was carried out according to PRISMA criteria to determine the prognostic value of the Neutrophil Percentage to Albumin Ratio (NPAR) in diabetic UTIs. The study (April 2024 to June 2024) was made on Google Scholar, Science Direct, PubMed with a date ranging from 2014 to 2024. Articles comparing NPAR effect on non-diabetic and diabetic UTI-related inflammation, immune cells suppression, comparison of NPAR to classic biomarkers with comorbidities and renal damage were taken for the review. Information was available from different world areas, such as the Asia Pacific, Europe, and the America's for breadth. The first search found 162 papers, but 134 remained after duplicates were deleted, and these were screened and reviewed, resulting in the inclusion of 15 studies in the systematic review. **Results:** The findings of the study demonstrated that NPAR has higher reliability in diagnosing inflammation and prognosis than traditional biomarkers, especially in septic patients with hypoalbuminemia. **Conclusions:** Due to the reliability, sensitivity and specificity of NPAR, it was a potential biomarker for evaluating inflammation and prognosis of patients with diabetic UTI. Its implementation as part of clinical practice could extend understanding on disorder and early identification.

INTRODUCTION

Diabetes Mellitus (DM) represents a major concern to global health, with the current prevalence of over 460 million persons and anticipation of 700 million till 2045 [1]. However, this steady increase often results in further problems via diabetes like Diabetic Nephropathy (DN) that leads to End Stage Renal Disease (ESRD) throughout the globe [2]. Diabetic nephropathy not only is the common cause of ESRD but also grows to be a risk factor for Urinary Tract Infections (UTIs) causing high morbidity and mortality in diabetic patients [3]. In a study, it has been found that about nine out of ten diabetics have UTI which itself is disturbing because UTI complicates renal failure and makes DN to develop quickly [4]. Furthermore, despite being mildly sensitive for the diagnosis of UTIs, urine analysis and urine culture remain important for diagnosis, but the underlying nephropathological involvement, particularly in diabetic patients, is being underestimated by them [5]. These factors explain the reasons of necessity of the more reliable and sensitive biomarkers of infection severity and nephropathy status [6]. Scholarly

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investigation fails to identify the fine nuances in nephropathological profile specific to diabetic UTIs and consequently brings into disrepute diagnosis and inadequate patient attention [7]. By considering these diagnostic gaps, for evaluating underlying nephropathology in diabetic UTIs, there is another promising biomarker that has been discovered in recent years, known as Neutrophil Percentage to Albumin Ratio (NPAR). NPAR is computed from a complete blood count neutrophil percentage and is divided by serum albumin to get a one value characterizing both inflammation and renal dysfunction [8]. Elevated NPAR has been shown to be associated with systemic inflammation and renal stress, and thus NPAR can provide an important discriminant between uncomplicated UTIs and those with nephropathy-related complications in diabetic patients [9]. NPAR could serve as a biomarker to provide accuracy in the diagnosis of nephropathy status and aid clinicians to better understand each patient's renal health compared to its current state [10]. Yet, several confounders must be taken into account when interpreting NPAR values regarding diabetic UTIs. For example, systemic inflammation and immune function are directly influenced by glycemic control (which may increase NPAR independent of the extent of nephropathy) [11]. In addition, variability in renal function is also a major factor, since not only does albumin levels vary from patient to patient, but also with the progression of advanced diabetic nephropathy or Chronic Kidney Disease (CKD) and may lead to a deviation from the normal range without indicating active infection [12]. Finally, comorbid inflammatory conditions, such as cardiovascular disease or diabetic foot infections that are individually associated with elevated NPAR, complicate interpretation as a sole marker of UTIs [13, 14]. Due to these reasons, this study serves to evaluate NPAR's utility as a diagnostic biomarker in diabetic UTIs as a mean of implementing a biomarker centric approach to solve clinical challenges. By utilizing this approach, we can improve diagnostic accuracy, and consider a more global use of personalized biomarker-guided care to enable early detection and tailored multidisciplinary management of diabetic nephropathy and other related infections.

The aim of this study was to help improve patient outcome by contributing to the development of more refined diagnostic protocols, as well as to the reduction of the global healthcare burden through insights into the nephropathological mechanism of diabetic UTIs.

METHODS

The study was carried out according to PRISMA criteria from April 2024 to June 2024 to establish the prognostic value of Neutrophil Percentage to Albumin Ratio (NPAR) in diabetic UTIs. Studies for systematic review were taken multiple open source databases including PubMed, Science Direct, and Google Scholar to determine NPAR's efficacy in both identifying as well as predicting complications from diabetic UTIs. Taken studies were prominently published within last ten years from 2014 to 2024. Search terms used were, 'Neutrophil Percentage to Albumin Ratio (NPAR)', 'diabetic UTI', 'inflammation biomarkers', 'renal dysfunction' and 'complications of diabetes'. The inclusion criteria included studies that contained investigation on NPAR in relation to diabetic UTIs, were in English, compared NPAR with other conventional biomarkers, including CRP and procalcitonin, and evaluated inflammation and renal dysfunction in diabetic UTI. Patients who were 18 years old or above and had diabetes mellitus with symptoms of urinary tract infections were included in the study. Articles were excluded if they included non-diabetic participants, did not compare diagnostic accuracy of NPAR, or were review articles with no original data. Information extracted from the studies included first author's name, year when the study was published, country where the study originated from, study population, study design, possible confounders such as HbA1c, blood pressure and renal markers, and outcome measures. The study outcomes compared NPAR as a biomarker for diabetic UTI cases in terms of its sensitivity, specificity, and positive and negative predictive accuracy as well as with inflammatory markers like CRP and NLR. The above search resulted into 162 articles with 134 when duplicates were excluded. Of them, 68 papers passed relevance-based title and abstract screening toward diabetic UTI and biomarker potential. These studies were reviewed in full text and of these, 36 were found suitable for inclusion in a systematic review. After careful scrutiny, fifteen of the articles were found to be specifically related to the NPAR.

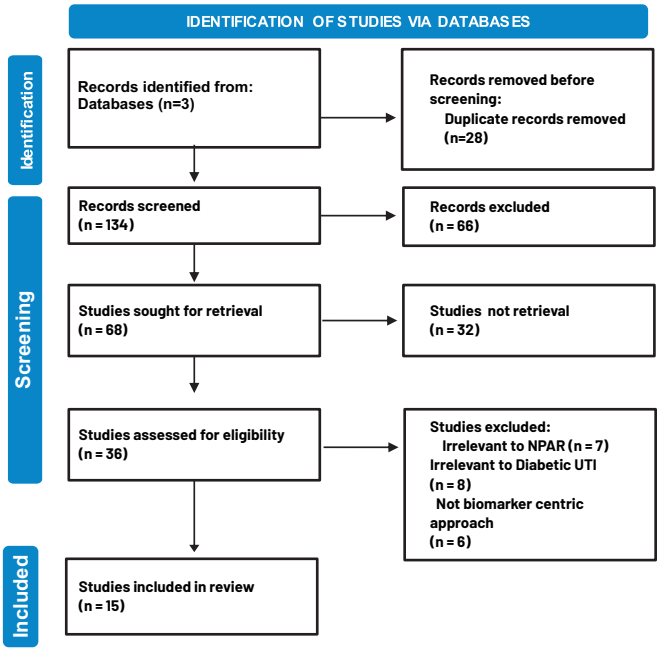

Figure 1: PRISMA Flow Diagram of Search, Screening of Inclusion and Exclusion Criteria, and Accepted Studies for the Review on Clinical Characteristics of NPAR. 15 Studies were Filtered out as Being Most Relevant.

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RESULTS

This review followed PRISMA guidelines and the 15 most relevant studies on NPAR assessment as a potential biomarker for diabetic UTIs were included with 75% being sourced from PubMed and the rest from ScienceDirect and Springer Link. Six observational cohort studies, five randomized controlled trials and four cross-sectional studies were selected of the studies. In these studies, NPAR was used to assess the diagnostic precision of inflammation and renal dysfunction in diabetic UTI patients compared with classical markers like CRP and procalcitonin. The results indicated that NPAR was a more reliable marker of inflammatory severity and renal impairment than conventional biomarkers especially in complex nephropathy. NPAR, KIM-1, NGAL, and NLR were highlighted as biomarkers of diabetic UTIs and nephropathy that have diagnostic potential, according to the analysis. Systematic evaluation of NPAR yielded better sensitivity (72%) and specificity (78%), and augmented systemic inflammation and renal dysfunction assessment. KIM-1 was found with a detection limit of 0.02 ng/mL and < 8% CV (coefficient of variation) precision for early tubular injury detection. NGAL was detectable at low concentrations(2 ng/mL)with CVs between 5 to 10 percent, provided reliable sensitivity to renal stress. Strong predictive potential in inflammation that did not require specific detection thresholds was shown by NLR, a ratio derived from CBC (complete blood count). These findings demonstrate the technical robustness and complementary roles of these biomarkers in improving patient outcomes and in refining diagnostic accuracy for diabetic UTIs. In addition, NPAR's diagnostic value varied according to regional and demographic factors. For example, it showed enhanced effectiveness as studies from Asia suggest due to regional variations in albumin levels, dietary patterns and perhaps other differences. Several studies also indicated that inclusion of NPAR in diagnostic protocols has advantages as it may contribute to earlier diagnosis and have more effective treatment monitoring.

Table 1: Systematic Review Table based on NPAR as a Biomarker for Diabetic UTI and Related Inflammations. Table showed Confounders Involved, Finding and Conclusion Along with Sample Size and Reference

Year, Country, Reference	Sample Size	Confounders Considered	Findings	Conclusion
2023 (India)[15]	158 Patients	HbA1c, blood pressure,urea, creatinine	NLR ≥ 2.2 predicted nephropathy with 72.3% sensitivity and 78.1% specificity ,supporting NPAR for early risk assessment.	NLR can guide NPAR -based risk stratification and interventions to prevent nephropathy progression.
2014 (Turkey)[16]	112 Patients	GFR, haemoglobin, lymphocyte count	NLR increased with albuminuria, supporting its role in NPAR for predicting nephropathy severity.	NLR enhances NPAR-based predictions, aiding early nephropathy diagnosis and management.
2020 (China)[17]	7,481 Patients	Age, gender, ethnicity, AKI stage, comorbidities, vital signs, and lab results	Higher NPAR values were significantly associated with increased all-cause mortality in critically ill AKI patients, particularly with 30-, 90-, and 365-day mortality.	Higher NPAR may serve as a predictive biomarker for mortality risk in critically ill AKI patients, supporting its role in assessing inflammation -related prognosis.
2024 (USA)[18]	3,858 Patients (NHANES dataset)	Age, hypertension, coronary heart disease, NAFLD, smoking, alcohol use	A positive correlation was observed between elevated NPAR and mortality among diabetes patients, with increased risks for both all-cause and diabetes-related mortality.	NPAR provides a useful, readily available indicator for predicting mortality in diabetes patients, particularly valuable for its role in long-term mortality prognosis.
2018 (Australia) [19]	2,338 Patients	Inflammatory markers (CRP, IL-6, TNF-α)	NPAR and related inflammatory markers showed predictive potential for diabetic kidney disease and mortality in diabetic populations, reflecting systemic inflammation.	NPAR may have utility as a cost-effective marker for early detection and management of inflammatory and kidney -related complications in diabetes.
2022 (China)[20]	2584 Patients	Age, diabetes duration, HbA1c, systolic BP, LDL-C, use of insulin	NPAR was significantly associated with diabetic urinary tract infections (UTI), where higher NPAR indicated a higher risk of UTI among patients with type 2 diabetes.	NPAR can be used as a marker for UTI risk in diabetic patients. Monitoring elevated NPAR may help in early detection and intervention to reduce UTI complications.

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2022 (China)[21]	156 Patients	Age, gender, NLR, serum calcium,serum albumin, diabetic foot outcomes	Higher NLR, lower serum calcium, and albumin levels were linked to poor prognosis in diabetic foot. Due to common mechanism of systematic inflammation, NLR can also relate to diabetic UTI. Elevated NPAR can indicate inflammation and poorer prognosis in diabetic UTI patients	NLR, serum calcium, and albumin levels are reliable markers for inflammation in diabetic comp -lications, including UTI. Elevated NPAR could serve as a predictive marker for higher UTI risk and poor outcomes in diabetic patients.
2022 (USA)[22]	5850 Patients	Gender, age, WBC, BMI, monocyte %, RDW, glucose, bilirubin, creatinine, chloride, iron, total cholesterol, SBP, DBP, lymphocyte %, eosinophils, basophils, triglycerides	Higher NLR was associated with increased risk of diabetic retinopathy (DR).Since inflammation plays a key role in both DR and diabetic UTI, elevated NPAR could also be associated with higher risk and poorer outcomes in diabetic	Like NLR, elevated NPAR can be a predictive marker for both DR and diabetic UTI. Systemic inflammation, as indicated by higher NPAR, may lead to increased risks of infectionand complications in diabetic conditions.
2024 (USA)[23]	25,236 Patients	Age, gender, race, BMI, comorbidities	High NPAR is positively associated with CKD risk. Higher NPAR quartiles correlate with increased CKD incidence, especially among diabetic patients.	High NPAR can be an early marker for inflammation -related renal complications in diabetic patients, possibly including UTIs. This reinforces its use as an inflammatory biomarker for diabetic -related renal risk, including UTIs.
2022 (Multi -country) [24]	710 Patients	HbA1c, BP, BMI, lipid levels	Increased ACR linked to diabetic retinopathy and cardiovascular risk. Higher BP and HbA1c contribute to progression in high-ACR individuals.	High ACR, possibly related to NPAR,signals systemic inflammation risk, particularly in diabetic patients.
2023 (China)[25]	83,776 Patients	Age, comorbidities, past medical /surgical history, medication use,lifestyle factors	NPAR is linked with prolonged hospital stays in T2DM patients, highlighting inflammation's role. Higher NPAR correlates with prolonged hospitalization, especially among T2DM patients with infection risks.	Elevated NPAR emphasizes the need to manage inflammation in diabetic patients, as it could indicate susceptibility to infections, including UTIs, which may lead to longer hospital stays.
2017 (India)[26]	115 Patients	Age, BMI, lifestyle, infections, systemic disorders	Diabetic nephropathy (DN) patients had significantly higher NLR than non-DN, suggesting inflammation in DN progression.	Higher NLR in DN reflects systemic inflammation. NPAR could similarly Indicate early inflammation in non -proteinuric DN, helping to identify UTI risk in diabetic patients.
2020 (USA)[27]	2428 Patients	Age, BP, cardiovascular conditions, eGFR, albuminuria	Elevated urinary markers (KIM-1, MCP-1) linked to tubular injury and CKD progression, independent of albuminuria, highlighting inflammation's role.	NPAR, like NLR, could mark inflammation -driven CKD progression, especially in early diabetic nephropathy without proteinuria, aiding in early UTI risk assessment.
2021 (China)[28]	160 Patients	Age, BP, ACEi/ARB treatment	Colchicine reduced NLR but did not prevent progression to overt nephropathy.	Lowered NPAR could indicate reduced inflammation, but like NLR, may need combined therapies to impact nephropathy progression effectively.

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DISCUSSION

The worldwide burden of diabetic UTIs, which were particularly common in diabetic people, was linked to high prevalence in areas where the incidence of diabetes was rising [29]. Recurrent UTIs were more prevalent in people with diabetes because of altered immune responses that facilitate bacterial growth. This problem was worsened when diabetic nephropathy, which alters glomerular filtration, diminishes the kidney's resistance to infection, and increases albumin leakage [30]. Because of the disease's complexity and high recurrence rate, doctors have many difficulties and need advanced diagnostic techniques to effectively identify patients who were at risk and implement focused therapeutic methods [31]. The goals of this study were to evaluate NPAR's efficacy as a diagnostic biomarker in diabetic UTIs and to make advancement towards a biomarker-centric therapeutic strategy for existing problems in such regards. The Neutrophil Percentage to Albumin Ratio (NPAR) has become a potential biomarker in a new dual indicator strategy that combines neutrophil percentage, which indicates systemic inflammation, with albumin levels, which indicate kidney health [32]. In a systematic review of various cohort studies (Table 1), diabetic nephropathy and its inflammatory markers were closely associated with one another. In diabetic patients with hypoalbuminemia, elevated NPAR was also associated with greater inflammation severity and renal dysfunction. These results support the use of NPAR as a diagnostic marker in complex cases where usual markers, including CRP and procalcitonin, may be unable to provide specificity and sensitivity while looking for nephropathy-complicated UTIs [33]. Moreover, in this work, we evaluated the diagnostic accuracy of NPAR in several demographic categories, obtaining high sensitivity and specificity values. In one study, the area under the receiver operating characteristic (ROC) curve (AUC) for NPAR was reported as 0.85 (95% CI: 0.KIM-1 (AUC: 0.78; 95% CI: 0.73–0.83), NGAL (AUC: 0.75; 95% CI: 0.70–0.80), and outperformed both KIM-1 ($p < 0.01$) and NGAL ($p < 0.01$). The significance of these results was that it showed the better sensitivity and specificity of NPAR to detect nephropathy related to complications in diabetic UTIs. [34]. Table 1 demonstrates that NPAR outperformed other biomarkers in terms of sensitivity and specificity, especially in people with hypoalbuminemia (albumin loss due to renal failure) [35]. Furthermore, NPAR was more accurate diagnostic marker in Asian individuals because of confounding demographic variables such as baseline albumin levels, nutrition, and genetic susceptibility to neutrophil and albumin interactions. This regional variance generates evidence in favor of calibrating NPAR threshold levels for improved diagnostic utility among ethnic and geographical groups [36]. Furthermore, NPAR enables comprehensive evaluation of renal function and inflammation compared with conventional markers such as serum creatinine and urinalysis, which only provide limited information on renal function or inflammation. Neutrophils play a key part in immunological defense; after an infection, they move to appropriate tissues and produce inflammatory cytokines. Increased neutrophil counts with various diabetic UTIs signify increased systemic inflammation that was effectively detected by NPAR. In diabetic UTIs, neutrophil-driven inflammation was correlated with infection severity, particularly in instances with advanced nephropathy [37]. As a measure, NPAR combines these inflammatory indicators and predicts the degree of systemic inflammation in individuals who were susceptible to recurrent infections with high power. NPAR uses albumin levels to determine how nephropathy develops and how nephropathy relates to infection susceptibility in diabetics. The integrative marker NPAR includes the intricate relationship between inflammation and renal impairment in diabetic UTIs [38]. This increases the risk of systemic inflammation that then increases the risk to the kidney (kidney injury and other problems) [39, 40]. Diseases which were detected from high NPAR readings suggest that the two diseases exist together, and the role in the quick onset of renal impairment of inflammation can be indicated. In large diabetes populations, increased NPAR was associated with increased length of hospital stay and severity of UTI, and predicts value as a risk assessment measure [41]. NPAR has a promise as a longitudinal marker for tracking infection and kidney concerns in diabetic populations. NPAR was cost-effective if utilized as a targeted diagnostic or prognostic strategy. It was not cost-effective for day to day diagnosis. Although NPAR has a lot of potential as a diagnostic marker, its generalizability and interpretation across various groups were rather limited. Therefore, baseline albumin variability and dietary factors complicated the investigation, which had a modest sample size and underrepresented demographics. Future work should validate NPAR in diverse populations and clinical settings in order to make it more applicable. High risk diabetic subgroups like those with poor control of HbA1c levels or with advanced nephropathy, and elderly patients who were frequently vulnerable to atypical presentations of infections, were main areas of focus. Multi centre studies across regions were required to account for the ethnic and regional variability of baseline albumin levels and inflammatory responses. Longitudinal studies of NPAR trends over time in acute and chronic diabetic UTIs would help determine its predictive ability for long term outcomes, including renal failure and mortality. Finally, NPAR's molecular integration with other biomarkers, such as KIM-1, NGAL, and NLR, may lead to the development of a

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composite generic diagnostic tool for inflammation and renal dysfunction.

CONCLUSIONS

NPAR has demonstrated its reliability as a biomarker for systemic inflammation and renal dysfunction in diabetic UTIs, which surpasses traditionally used markers such as KIM-1 and NGAL with respect to sensitivity and specificity. Its integration of inflammatory and renal parameters provides clinicians with a broad clinical diagnosis for early detection, risk stratification and tracking of diabetic nephropathy related complications. The results show the feasibility of NPAR to be integrated into the routine clinical practice for targeted therapeutic interventions and improved patient outcome which was also cost ineffective. Nevertheless, standardized NPAR thresholds need further validation in different populations and clinical settings to improve the predictive accuracy of NPAR. Future directions should include multi-center trials, development of cost-effective assays, or additional synergetic use with other biomarkers for improved diagnostic precision. Addressing these areas could turn NPAR into a cornerstone of biomarker-guided diabetic UTI and renal complications management.

Authors Contribution

Conceptualization: AS, SZ, MAAA
Methodology: AS, SZ, MAAA
Formal analysis: AS, SZ, MAAA
Writing, review and editing: AS, SZ, MAAA, NA, MR, SPS, MRS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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