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Neutrophil to lymphocyte ratio in urolithiasis: a systematic review

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Abstract

Background Urolithiasis is among the most prevalent and possibly devastating diseases. It affects millions worldwide, and a cheap or rapid biomarker is required to diagnose it. Previous investigations revealed that inflammation has a role in the progression of urolithiasis patients, and an elevated neutrophil-to-lymphocyte ratio (NLR) value can be a valuable biomarker to ensure inflammation and, consequently, renal stones. This study was conducted to summarize the results of studies investigating the role of NLR in urolithiasis.

Methods We systematically searched three main databases (Scopus, PubMed, and Web of Science) up to January 1, 2023. Our study was registered in PROSPERO (CRD42024500756).

Results Ultimately, 33 studies were selected for this review article. Patients in either acute or subacute phase exhibited higher NLR levels than healthy controls. Also, patients in acute and subacute phases significantly differed regarding NLR levels. In addition, studies showed that NLR could predict sepsis and systemic inflammatory response syndrome (SIRS) among urolithiasis patients. In addition, evidence reported that NLR was helpful in the prediction of spontaneous stone passage among these patients.

Conclusion Our results support a reliable biomarker that is easily added into clinical settings to help predict urolithiasis patients' condition.

Keywords Neutrophil to lymphocyte ratio, Urolithiasis, Systematic review

Background

Urinary lithiasis is a prevalent illness progressively encountered in roughly 1 out of every ten persons worldwide with a high risk of recurrence [1–4]. Even though kidney stones are not life-threatening, they have been associated with a high risk of diabetes, cardiovascular disorders, end-stage renal failure, and chronic kidney disease. Renal stones also lead to increased morbidity, hospitalization, healthcare burden, and work absences associated with kidney disease, making stones prediction quite imperative [5–7]. Common symptoms of urinary lithiasis include acute renal colic or flank discomfort, obstructive uropathy, and infections [7–9]. Urosepsis is also a crucial indicator linking renal stones to systemic

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inflammatory response syndrome (SIRS) [10]. It is either because of urolithiasis-induced obstructive acute pyelonephritis (APN) or as a post-procedure complication mainly caused by ureteroscopic lithotripsy (URSL) or percutaneous nephrolithotomy (PCNL) [11, 12].

Numerous institutions globally have developed comprehensive guidelines on urolithiasis. Typically, the available treatment modalities encompass medical management with α -blockers, calcium channel blockers, and phosphodiesterase type 5 (PDE5) inhibitors, oral chemolysis utilizing potassium citrate, extracorporeal shock wave lithotripsy (ESWL), URSL, PCNL, and surgical interventions such as open surgery and laparoscopy, employed only when ESWL, URSL, and PCNL are deemed unlikely to succeed or when further reconstruction is warranted [13]. The latest guidelines on the medicinal and surgical care of stone disease exhibit considerable consensus, with just a few points of disagreement. Discrepancies and areas of insufficient data pertain to follow-up imaging protocols and stone monitoring, the application of a ureteral access sheath during ureteroscopy, and recommendations on miniature percutaneous nephrolithotomy [14].

It has been estimated that about 75–90% of ureteral stones fall spontaneously [15]. An accurate forecast of spontaneous passage can prevent costly therapeutic interventions or high-risk complications. Several inflammatory indicators like C-reactive protein (CRP), Procalcitonin, and cytokines were associated with the likelihood of spontaneous passage in many studies. The increase in these markers might result from ureteral stone impaction [16–19].

Renal stones vary in size, location, shape, and composition, but they are all made by similar physicochemical reactions and urine supersaturation, mainly attributed to multifactorial abnormalities in genetics and environmental factors [4, 7, 20–23]. Clinical and experimental investigations showed elevated expression of genes associated with inflammation in renal stone cases [24]. Moreover, increased circulating neutrophils have been shown to speed up the release of inflammatory mediators, potentially leading to stone formation. As a result, neutrophils may contribute to the production of kidney stones by creating a pro-inflammatory environment. A lower lymphocyte count may play a role in the inflammatory response to stones, contributing to its presentations [18].

However, several studies have found that various physiological or pathological factors such as sociodemographic characteristics, lifestyle choices, physical and mental comorbidities, and the severity of a disease could affect how neutrophil-to-lymphocyte ratio (NLR) levels are related to diseases [25–27]. Altogether, studies found that NLR is a quick and cost-effective predictor of inflammatory imbalance [28, 29].

Based on the literature, NLR has the potential to improve the treatment pathway by acting as a predictive tool. This can help in making informed therapeutic decisions, possibly reducing the need for unnecessary interventions and managing both the medical and economic burden more effectively. By allocating resources specifically to patients who require them, NLR can help tailor treatment plans and optimize cost efficiency. Therefore, this study aims to evaluate NLR as a predictor of stone formation and spontaneous passage or risk of further complications.

Material and method

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for our systematic review. This study was registered in the Prospective Register of Systematic Reviews (PROSPERO) with ID of CRD42024500756. Two reviewers individually searched three main online databases (PubMed, Web of Science, and Scopus) for all relevant articles, regardless of publication date or language. A consensus was established by group discussion where there were disputes. We conducted a literature search using the terms (“neutrophil-to-lymphocyte ratio” OR “neutrophil to lymphocyte ratio” OR “NLR”) AND (Kidney OR renal OR urinary) AND (Stone OR Calculi) to find papers on the diagnostic and prognostic utility of the NLR. Finally, on January 1, 2023, the search was refreshed. We also looked through the reference lists of the related studies to see if there were any other papers.

Study selection and data extraction

Two reviewers independently assessed relevant papers' titles, abstracts, and full texts after excluding duplicates. The following items regarded as inclusion criteria: (a) Peer-reviewed original studies; (b) Calculating the NLR by dividing the total number of neutrophils by the total number of lymphocytes; (c) Reporting peripheral blood NLR value; (d) Evaluation of the predictive and diagnostic effectiveness of the NLR in urolithiasis.

Exclusion criteria included: (a) In vitro and animal research; (b) letters; (c) case reports or case series; (d) review articles; (e) editorials; (f) studies with insufficient data.

Quality assessment

Two authors independently assessed the quality of the studies included using the Newcastle-Ottawa Scale (NOS) [30]. The NOS is commonly utilized to assess methodological quality in observational studies. This scale comprises three sections: selection, comparability, and exposure, totaling a possible score of 0 to 9. The criteria of exposure section are as follows: (1) non-response

Table 1 Characteristics of included studies

First author	Sample size	Study design	Year of publication	Country	Mean age (y)	Male	Cut off the value of NLR	Outcome
Uyeturk [40]	209	Retrospective	2014	Turkey	NA	NA	NA	NLR was significantly higher in patients with kidney stones compared to controls ($p = 0.0021$).
Lim [65]	73	Retrospective	2015	Korea	57	19.17%	NA	Septic shock was predicted by increased NLR with an OR of 3.83 (95% CI: 0.75–5.14, $p = 0.037$)
Sen [59]	487	Retrospective	2016	Turkey	44.0 ± 2.5 for patients with sepsis	66.94%	2.5	NLR's AUC for predicting postoperative sepsis was 0.588. Postoperative sepsis was significantly more common in the NLR at 2.50 or above. There is a relation between culture findings and NLR, showing OR of 1.42 (95% CI 1.13–1.77) with $p = 0.003$ for preoperative urinary culture, OR of 1.35 (95% CI 1.08–1.69) with $p = 0.008$ for postoperative urinary culture, OR of 0.89 (95% CI 0.56–1.42) with $p = 0.627$ for renal pelvis urine culture and OR of 1.09 (95% CI 0.86–1.37) with $p = 0.487$ for stone culture.
Lee [28]	131	Retrospective	2017	Korea	52.6 (38.7–61.0)	68.1%	2.3	Low NLR (< 2.3) (OR = 9.03, 95% CI = 2.125–38.353, $p = 0.003$) was associated with SSP in patients with stones less than 1.0 cm in size.
Jung [60]	64	Retrospective	2017	Korea	65.43 and 61.74 years in the non-sepsis group and sepsis group	18.75%	NA	NLR was higher in the sepsis group than in the non-sepsis one (18.67 ± 12.68 and 10.90 ± 8.68, respectively, $p = 0.014$). NLR had an OR of 1.092 (95% CI 1.006–1.142) with a $p = 0.03$.
Cetinkaya [57]	192	Retrospective	2017	Turkey	47.3 ± 15.1	68.2%	NA	In total 192 patients; the mean preoperative NLR was 2.6 ± 1.5, with 2.4 ± 1.4 in the non-SIRS group (78.7% of patients), and 3.1 ± 1.9 in the SIRS group ($p = 0.018$).
Tang [11]	717	Retrospective	2017	China	52.5 (11.9) years for SIRS group and 51.9 (12.7) years for non-SIRS group	62.9%	NA	Patients with kidney stones had greater NLR (2.31 ± 1.70 vs. 1.61 ± 0.56) and dNLR (1.59 ± 0.98 vs. 1.22 ± 0.40) than the healthy controls ($p < 0.001$). Based on AUC values of 0.648 (95% CI 0.604–0.692), 0.625 (95% CI 0.58–0.67) with $P < 0.001$, ROC curve analysis indicated that NLR and dNLR had restricted relevance for the identification of individuals with kidney stones, respectively.
Gokhan [38]	122	Prospective observational case-control	2018	Turkey	38.65 ± 12.16 in patient group, 36.81 ± 9.52 in control group	52.45%	4.06	NLR was found to be substantially higher in patients (4.06 ± 2.41) than in controls (1.53 ± 0.59) with $p < 0.001$.
Gao [58]	194	Retrospective	2019	China	49.01 (13.19) group	48.7%	NA	OR of 1.291 for NLR (95% CI 0.886–1.882, $p = 0.184$) was associated with sepsis. With a $p = 0.082$, NLR was 2.90 (3.52) in sepsis (+) stone patients and 2.08 (0.95) in sepsis (-) ones. With $p = 0.261$, NLR was found to be 2.23 (1.72) in total 194 patients, 2.37 (2.24) in stone patients, and 2.09 (0.94) in non-stone ones.
Abou heidar [30]	619	Retrospective	2019	Lebanon	46.8 ± 15.4	71.4%	NA	NLR Q3 (2.87–4.87) had 2.99 (95% CI = 1.78–5.03) odds of failure for SSP after multivariate assessment and 2.96 (95% CI = 1.80–5.49) after bootstrapping, while NLR Q4 (> 4.87) had 3.68 (95% CI = 2.15–6.32) and 3.63 odds (95% CI = 2.04–6.69). The c-statistic for the NLR model was 0.782 ± 0.019 (95% CI = 0.745–0.818) on the ROC curve
Sasmaz [41]	275	prospective, double-centered	2019	Turkey	41.0 ± 14.9	61.1%	NA	There is a very weak linear relationship between the NLR levels and the Visual Analog Scale score which is represented renal colic pain ($r = 0.220$, $p < 0.001$).

Table 1 (continued)

First author	Sam-ple size	Study design	Year of publication	Country	Mean age (y)	Male	Cut off the value of NLR	Outcome
Algün and Sinanoğlu [42]	191	Retrospective	2019	Turkey	40.30 ± 13.96	51.3%	2.16	Patients with stones had significantly lower NLR levels ($n = 94$, 2.68 ± 1.86) than those without stones ($n = 97$, 4.04 ± 3.67) with $p = 0.009$. For stone positive patients, the NLR cutoff value was 2.16 (sensitivity: 59.57, specificity: 61.86, ROC: 0.610 (95% CI: 0.530–0.689)); and had statistically meaningful association with stone status ($p = 0.003$).
Xu [52]	556	Retrospective	2019	China	52	59.5%	2.9	NLR has a predictive value for post-PCNL SIRS with cutoff value of 2.9, AUC of 0.669 (95%CI = 0.629–0.708, $p < 0.01$), and OR of 2.476 (95%CI = 1.471–4.167, $p < 0.01$). They reported that NLR was 2.13 (1.64–2.86) in all of the patients.
Sonmez [44]	126	Case-control	2019	Turkey	46.11 ± 16.9 in patient group, 43.63 ± 6.4 in control group	59.7 in patient group, 56.4 in control group	NA	There was no significant change in the NLR between the urolithiasis group (2.96 ± 2.61) and the control group (2.38 ± 1.38 , $p = 0.7$), no noticeable changes between patients with nephrolithiasis and ureterolithiasis ($n = 56.6\%$, 2.8 ± 2.2 vs. $n = 43.4\%$, 3.1 ± 2.5 , $p = 0.55$), between patients with stone size > 15 mm ($n = 37$) and stone size < 15 mm ($n = 39$) (3.06 ± 2.2 vs. 2.84 ± 2 , $p = 0.71$), and between 37 stone patients with renal colic and 39 stone patients who did not (2.99 ± 2.39 vs. 2.92 ± 2.1 , $p = 0.9$).
Hazar [46]	110	Prospective	2019	Turkey	36.57 ± 9.34	80.90%	NA	No significant statistical difference was found in NLR value between those with impacted ureteral stone and non-impacted ones ($n = 51$, 3.02 ± 1.80 and $n = 59$, 2.80 ± 2.03 , respectively, $p = 0.543$). NLR level was (2.90 ± 1.92) in the whole patients.
Demirtaş [62]	519	Retrospective	2020	Turkey	46	63.39%	2.21	NLR was 3.295 (1.46–12.85) in fever (+) patients and 2.050 (0.35–32.4) in fever (–) patients with $p < 0.001$. NLR had a 2.21 cutoff value with 86% sensitivity, 55.2% specificity, and 0.733 AUC for prediction
Selvi [31]	280	Prospective, observational, multicenter	2020	Turkey	44 (35–54)	54.28%	1.96	SSP rate was 2 times greater with NLR < 1.96 (Sensitivity = 69.2%, Specificity = 64.2%, AUC = 0.729, and $p = 0.030$).
Cilesiz [34]	87	Prospective observational	2020	Turkey	40 (20–60)	74.71%	NA	The NLR amounts in passed stone groups (2.9 ± 1.7) did not differ significantly from those in the no passage group (2.8 ± 1.7) ($p = 0.821$). In a univariate assessment of spontaneous passing in 5–10 mm distal ureteral stones, NLR was shown to have 1.03 odd ratios (95% CI: 0.74 – 1.43, $p = 0.855$).
Abou Heidar [29]	450	Retrospective	2021	Lebanon	44.5 (32–57)	75.5%	3.14	The NLR ≥ 3.14 had the odds for SSP failure (OR = 6.00, 95% CI = 3.8 – 11.00).
Mao [32]	21,106	Cross-sectional	2021	USA	20–39 years, 40–59 years and 60+ years	48.4%	1.72	NLR was exclusively related to the prevalence of renal stones and the quantity of stones passed (NLR > 1.72 vs. NLR ≤ 1.72 , OR = 1.18, 95% CI: 1.03–1.36, $p = 0.019$).
Cilesiz [33]	87	Prospective observational case-control	2021	Turkey	40 (20–60)	74.71%	NA	NLR was found to be significantly higher in patients (29.6% female) with renal colic and a single ureteral stone measuring 5–10 mm (2.8 ± 1.7) than the healthy participants (2.0 ± 0.3) ($p = 0.009$).
Barua [39]	399	Prospective	2021	India	47.0 (15.0–98.0)	85.21%	NA	NLR reported 2.6 (0.6–16.6) in urolithiasis patients and 2.3 (1.2–3.3) in healthy patients with $p = 0.076$. In a binary multiple logistic regression analysis, NLR had an OR of 0.438 (95% CI 0.004, 0.398, $p = 0.006$), indicating that it was substantially related to urinary stone disease prediction. Also, multivariable analysis showed 0.055 OR (0.004, 0.758) with a $p = 0.030$ for NLR.

Table 1 (continued)

First author	Sam-ple size	Study design	Year of publication	Country	Mean age (y)	Male	Cut off the value of NLR	Outcome
Karsli [43]	192	Retrospective	2021	Turkey	47.2 ± 14.11 (11–82)	68.22%	NA	NLR reported significantly higher in staghorn stones (2.91 ± 2.10) when compared to single calyx, pelvis, and two calyces stones (2.23 ± 0.85, 2.20 ± 1.26, 2.06 ± 0.88, respectively, $p = 0.015$). The mean NLR was measured as 2.25 ± 1.29 (0.93–11.89).
Cetinkaya and Alatlil [45]	73	Retrospective	2021	Turkey	45.45 ± 14.37	60.27%	NA	NLR was reported 6.71 (3.92–11.11) in the renal infarction group ($n = 8$) and 4.21 (2.23–6.19) in the urolithiasis group ($n = 65$) which had no meaningful relation with $p = 0.154$
Kocan [47]	244	Retrospective	2021	Turkey	50.5 years for those with prostate stones and 40.1 years for those without prostate stones	100%	NA	The NLR was 2.3 (2.5 ± 1.2) for those who had a prostate stone (40.98%) and 2.0 (2.2 ± 1.1) for those who did not have a prostate stone (59.02%), with $p = 0.045$. As a result, a high NLR can be regarded as a known risk for prostate stone formation
Peng [51]	365	Retrospective	2021	China	53.9 ± 11.1	63.3%	2.16	NLR was considered as an independent predictor of post-PCNL SIRS with AUC of 0.734 (95%CI = 0.683–0.776, $p < 0.01$) and OR of 2.406 for 2.16 or more level of NLR (95%CI = 1.153–5.021, $p = 0.019$). With $p < 0.001$, the NLR in the whole patients was 2.16 ± 0.71, in the SIRS group ($n = 108$) was 2.55 ± 0.61, and in the non-SIRS group ($n = 257$) was 1.99 ± 0.68. The total NLR value was 2.34 (1.86–2.76), with 2.25 (1.83–2.68) NLR in non-SIRS patients following PCNL and 2.75 (2.22–3.80) NLR in SIRS patients, with $p = 0.001$, showing a significant relation between them
Akdeniz [54]	228	Retrospective	2021	Turkey	48.5	66.66%	NA	Higher NLR was associated with an increased frequency of infection-induced SIRS after PCNL. The preoperative NLR measured at 1.9 ± 0.8 in patients with sepsis, at 2.0 ± 1.4 in patients without sepsis, and at 2.0 ± 1.3 in all patients, with $p = 0.737$. According to the ROC curve, the NLR under 72.2 could indicate sepsis following PCNL (sensitivity: 80.5% and specificity: 33.3%)
Sichani [55]	152	Prospective observational	2021	Iran	52.1 ± 13.4	62.5%	NA	The SIRS group had a higher preoperative NLR of 2.5 (1.0) than the non-SIRS group with a preoperative NLR of 2.0 (0.9) ($p < 0.001$). Preoperative NLR was associated with SIRS with an OR of 1.721 (95%CI 1.116–2.653, $p = 0.014$) and AUC of 0.652.
Tang [56]	717	Retrospective	2021	China	52.5 (11.9) years for SIRS group and 51.9 (12.7) years for non-SIRS group	62.9%	?	With $p < 0.001$, NLR was 2.6 (1.1) in the urosepsis-developed group and 2.0 (0.9) in the urosepsis-undevloped group with an OR of 1.604 (95%CI 1.135–2.266, $p = 0.007$) and AUC of 0.682.
Lu [62]	53	Retrospective	2021	Taiwan	59.91 (10.99)	56.6%	5	NLR > 5 had a crude -OR of 9.33 (1.04–84.02) with $p = 0.046$ and an adjusted OR of 5.82 (0.58–58.46) with $p = 0.135$ in a logistic regression study of risk factors for fever in these patients. Furthermore, a crude OR of 1.22 (0.89–1.69) for NLR ($p = 0.217$) and a crude OR of 8.43 (1.00–71.13) with $p = 0.050$ and an adjusted OR of 3.78 (0.41–34.89) with $p = 0.241$ for NLR > 5 were observed in an ordinal logistic regression analysis.

Table 1 (continued)

First author	Sam-ple size	Study design	Year of publication	Country	Mean age (y)	Male	Cut off the value of NLR	Outcome
Bairanran [63]	369	Retrospective	2021	China	54.9 ± 11.3 in the SIRS group, and 51.1 ± 12.7 in non-SIRS group	68.29%	2.61	SIRS was substantially more common in patients with NLR > 2.61 (sensitivity: 67.4% (95% CI 0.513–0.805), specificity: 61.0% (95% CI 0.555–0.663) than in other patients (RR = 4.932, $p = 0.040$).
Yoo [64]	115	Multicenter retrospective	2021	Korea	65	26.1%	3.0	Preoperative NLR ≥ 3.0 was independently associated predictor of postoperative SIRS with an OR of 2.706 (95% CI 1.039–7.049) and $p = 0.042$.

rate; (2) Same method of ascertainment for controls and cases; (3) Ascertainment of exposure. The criterion of comparability section is as follows: Comparability of controls and cases. The criteria of selection section are as follows: (1) Definition of Controls; (2) Selection of Controls; (3) Representativeness of the cases; (4) Is the case definition adequate?

In case of any disagreements, a third author acted as a mediator to come to an agreement.

Results

Search results and included studies

In total, 615 items were found in the manual search of the article citation and three main databases. Among them, 33 papers were included in our study. The characteristics of the included studies are illustrated in Table 1. The PRISMA flow diagram, indicating the process of screening the studies, is shown in Fig. 1. The results of the quality assessments are displayed in Supplementary Table 1. In our assessment, all studies received a score ≥ 7.

NLR and spontaneous stone passage

Parameters predicting spontaneous stone passage (SSP) have been widely studied; however, stone size and location are the only two considered in clinical practice [16]. Seven studies have investigated the predictive role of NLR for SSP [31–37].

Lee et al. (Korea, 2017) evaluated NLR as an SSP predictor for the first time, using the data from 131 patients with ureter stones ≤ 10 mm in size. Results of multivariate analysis showed low NLR (< 2.3) was associated with SSP in patients with stones less than 1.0 cm (OR = 9.03, 95% CI = 2.125–38.353, $p = 0.003$). The total median NLR was 2.18 (1.31–4.38). The median NLR in patients who passed their stones spontaneously ($n = 90$) was significantly lower than those without SSP [2.04 (1.20–3.92) versus 3.67 (1.78–5.83) with $p = 0.025$] [31].

In a retrospective study on 450 patients with a single ureteral stone ≤ 10 mm in length, width, and depth, Abou Heidar et al. (Lebanon, 2021) reported that the NLR ≥ 3.14 had an association with SSP failure (OR = 6.00, 95% CI = 3.8–11.00). This level of NLR was seen in 141 patients who failed SSP ($n = 207$) and among 73 patients with SSP ($n = 243$) with $p < 0.001$ [32].

Another study by Abou Heidar et al. (Lebanon, 2019) reported that they measured NLR in 619 patients with ureteral stone (with a median size of 5 ± 2 mm) and classified into four NLR quartiles Q1 (< 1.90), Q2 (1.90–2.87), Q3 (2.87–4.87), and Q4 (> 4.87). Patients with higher NLR in the Q4 group were older and more likely to have hypertension and diabetes mellitus than those with NLR Q1. The results revealed that NLR Q3 (2.87–4.87) could predict failure for SSP with an OR of 2.96 (95% CI = 1.80–5.49). Similarly, NLR Q4 (> 4.87) could predict

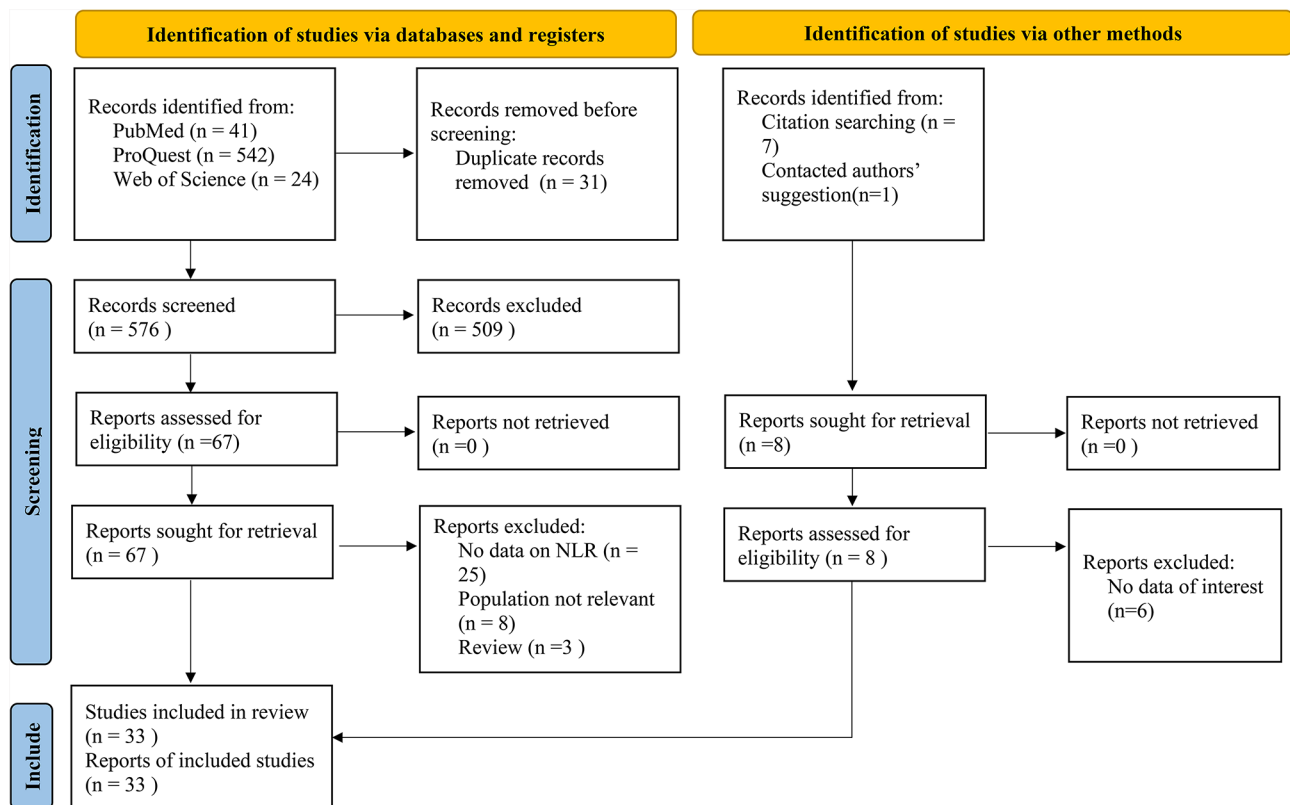


Fig. 1 PRISMA 2020 Flow diagram for new systematic reviews, which includes searches of databases, registers, and other sources (Thirty-three)

failure for SSP with an OR of 3.68 (95% CI = 2.15–6.32). Patients were more likely to be hospitalized and fail SSP ($p < 0.0001$) as their NLR was raised [33].

Moreover, Selvi et al. (Turkey, 2020) found a relationship between duration until stone passage and NLR. Two hundred eighty adult patients were included in this study. Solitary unilateral ureteral stones (≤ 10 mm in diameter) were divided into upper and lower stone groups. In patients who experienced SSP, upper ($n = 68$) and lower ($n = 108$) ureteral stone patients had NLR of 1.62 (1.08–2.08) and 1.58 (1.12–2.09), respectively, compared to those who did not have a SSP ($n = 50$), 2.29 (1.85–2.78), and ($n = 54$), 2.29 (1.58–2.79), respectively. Overall, patients with SSP ($n = 176$) had lower levels of NLR compared to the other group (1.59 (1.12–2.09), vs. 2.29 (1.76–2.78), $p < 0.001$). According to multivariate analysis and ROC analysis, the SSP rate was twice higher with $NLR < 1.96$ (Sensitivity = 69.2%, Specificity = 64.2%, AUC = 0.729, and $p = 0.030$). Moreover, this study indicated a correlation between Framingham's risk score and NLR ($\rho = 0.195$, $p = 0.001$) [34].

Furthermore, Mao et al. (the USA, 2021), after assessing a relationship between NLR and the prevalence of kidney stones and the number of stones passed, showed NLR was exclusively related to the prevalence of renal stones and the number of stones passed ($NLR > 1.72$ vs.

$NLR \leq 1.72$, OR = 1.18, 95% CI: 1.03–1.36, $p = 0.019$) by multivariate logistic regression of it. This cross-sectional research evaluated 21,106 adult participants (51.6% female) from 2007 to 2014. Between them, 1864 patients reported a history of kidney stones (292 in the no-stones-passed group, 1,462 in the stones passed 1–5 times group, and 110 in the stones passed > 5 times group), and 19,242 were in the no-stone group. According to this study, the NLR amounts (2.18 ± 1.94 , 2.30 ± 1.19 , 2.35 ± 1.30 , and 2.52 ± 1.31) rose in the no stone, no stones passed, stones passed 1–5 times, and stones passed > 5 times groups. On the same side, 61.2% of non-stone former, 66.1% of no stone pass, 69.7% of stone pass 1–5 times, and 70.9% of stone pass > 5 times patients had NLR above 1.72 ($p < 0.001$), so the proportion of individuals with the $NLR > 1.72$ was elevated in each consecutive group [35].

On the other hand, Cilesiz et al. (Turkey, 2021), in a prospective observational case-control study, concluded that NLR did not play a role in predicting SSP. In the case group, 54 patients (29.6% female) with renal colic and a single ureteral stone were included. At the same time, 33 healthy participants were in the control group. NLR was significantly higher in the case group (2.8 ± 1.7) than the control (2.0 ± 0.3) group ($p = 0.009$). After the following, 55.5% could pass ureteral stones, but 45% could not. The NLR value demonstrated no statistically significant

difference between the two groups with (2.9 ± 1.7) and without (2.8 ± 1.7) passages ($p = 0.821$) [36].

In another prospective observational study, Cile-siz et al. (Turkey, 2020) aimed to show the relationship between NLR and SSP in patients with renal colic and a single distal ureteral stone (5–10 mm in diameter) with no indications for interventional therapy undergoing medical treatment. The case group had 54 patients, and the control group had 33 healthy participants. NLR was found to be 2.8 ± 1.7 in the case group and 2.0 ± 0.3 in the control group ($p = 0.009$). Finally, the stone was passed by 55.5% of patients. NLR levels in the passed stone group (2.9 ± 1.7) did not differ significantly from those in the no passage group (2.8 ± 1.7) ($p = 0.821$). In a univariate assessment of spontaneous passing of 5–10 mm distal ureteral stones, NLR was shown to have 1.03 odd ratios (95% CI: 0.74–1.43, $p = 0.855$). As a result, this research found that NLR had no significant association with SSP [37].

Final comment

Most patients presenting to the emergency department with renal calculi are in terrible pain [38]. Altogether, we found NLR could significantly help clinicians predict SSP or stone retention and consequent adverse outcomes.

NLR and stone formation and presentations

Globally, kidney stone disease's frequency and recurrence rates are rising [7, 39]. However, the effectiveness of medical treatments and the specific therapy plan will differ based on an individual's risk factors and the composition of the stone [40]. Urolithiasis management must, therefore, emphasize preventative measures and timely diagnosis [7]. In this regard, ten studies investigated the value of NLR in stone status and renal colic pain [41–50].

Gökhan et al. (Turkey, 2018) indicated that NLR was diagnostically suitable for detecting renal colic in 75 patients (45% female) who came to the emergency unit compared to 47 healthy volunteers. NLR was found to be substantially higher in renal colic patients (4.06 ± 2.41) than in controls (1.53 ± 0.59) with $p < 0.001$. It was discovered that patients with urinary stone diseases had a significantly higher NLR mean value than patients without it ($n = 51$, 5.44 ± 2.09 vs. $n = 24$, 2.00 ± 0.91) with $p < 0.001$ [41].

Additionally, NLR levels were shown to be significantly higher in individuals with kidney stones by Barua et al. (India, 2021). With a $p = 0.076$, NLR reported 2.6 (0.6–16.6) in the 358 urolithiasis patients (15.1% female) and 2.3 (1.2–3.3) in 41 healthy (12.2% female) patients. In a binary multiple logistic regression analysis, NLR had an OR of 0.438 (95% CI 0.004, 0.398, $p = 0.006$), indicating that it was substantially related to urinary stone disease prediction. Also, multivariable analysis showed an OR

of 0.055 (95%CI=0.004, 0.758) with a $p = 0.030$ for NLR [42].

Besides, Uyeturk et al. (Turkey, 2014) noted that the NLR was significantly elevated in patients with kidney stones compared to controls ($p = 0.021$) during the investigation of subcutaneous and perirenal tissue thickness and stone diameter in 147 patients with renal stone disease in comparison to 62 healthy subjects [43]. In comparison, Sasmaz and Kirpat (Turkey, 2019) found a fragile linear relationship between the NLR levels and the Visual Analog Scale score, which represented renal colic pain ($r = 0.220$, $p < 0.001$) in a prospective, double-centered study of 275 patients [44].

Akgün and Sinanoğlu (Turkey, 2019) findings revealed that NLR could be a logical way to differentiate pain caused by urinary stone disease from pain mediated by an inflammatory process. They analyzed retrospectively 191 patients referred to the ED with acute abdominal and flank pain. There was a statistically significant difference in the NLR of stone patients without gender discrimination ($p < 0.01$). Patients with stones had significantly lower NLR levels ($n = 94$, 2.68 ± 1.86) than those without stones ($n = 97$, 4.04 ± 3.67) with $p = 0.009$. For stone-positive patients, the NLR cutoff value was 2.16 (sensitivity: 59.57, specificity: 61.86, ROC: 0.610 (95% CI: 0.530–0.689)); and had a statistically meaningful association with stone status ($p = 0.003$). The probability of a stone being positive is 2.34 times higher when the NLR value is less than 2.16. Moreover, NLR had an OR of 2.390 (95% CI: 1.337–4.272). Also, the NLR after imaging tests in patients with stones was (2.45 ± 1.41) in the kidney, (3.28 ± 2.60) in the proximal ureter, and (2.52 ± 1.65) in the distal ureter; thus, there was no high correlation between the anatomic location of the urinary stone and the NLR values ($p = 0.667$) [45].

In contrast, NLR was reported significantly higher in staghorn stones (2.91 ± 2.10) when compared to the single calyx, pelvis, and two calyces' stones (2.23 ± 0.85 , 2.20 ± 1.26 , 2.06 ± 0.88 , respectively, $p = 0.015$) by Karşlı et al. (Turkey, 2021) in a retrospective study on 192 patients who underwent conventional percutaneous nephrolithotomy (PCNL). The location of the stones was grouped as the pelvis ($n = 64$), single calyx ($n = 14$), two calyces ($n = 93$), and staghorn ($n = 21$), and the mean NLR was measured as 2.25 ± 1.29 (0.93–11.89). In the Spearman correlation test, despite the single and two calyceal stone groups ($r = -0.363$, $p = 0.10$, and $r = -0.012$, $p = 0.91$, respectively), the Hounsfield Unit (HU) as a value for stone formation, and NLR, had a positive correlation with pelvis and staghorn stones ($r = 0.318$, $p = 0.008$, and $r = 0.266$, $p = 0.163$, respectively). Moreover, by presuming a random amount above 1000 for HU's cutoff value, they found a positive correlation between NLR and HU ($r = 0.145$, $p = 0.045$). Meanwhile, for HU below 1000,

no significant correlation between NLR and HU was reported ($r=0.266$, $p=0.171$) [46].

On the other hand, Sonmez et al. (Turkey, 2019) indicated there was no significant change in the NLR between the urolithiasis group ($n=76$, 2.96 ± 2.61) and the control group ($n=50$, 2.38 ± 1.38 , $p=0.7$), between patients with nephrolithiasis and ureterolithiasis ($n=56.6\%$, 2.8 ± 2.2 vs. $n=43.4\%$, 3.1 ± 2.5 , $p=0.55$), patients with stone size >15 mm ($n=37$) and <15 mm ($n=39$) (3.06 ± 2.2 vs. 2.84 ± 2 , $p=0.71$), and 37 stone patients with renal colic and 39 who did not (2.99 ± 2.39 vs. 2.92 ± 2.1 , $p=0.9$). Although the neutrophil count was more significant in this trial than in the control group ($p=0.002$), the NLR value did not differ substantially [47].

According to the ROC curve, NLR levels did not have potential diagnostic efficacy in discriminating between the renal infarction and urolithiasis groups ($p=0.175$), as well in the study by Çetinkaya and Alatli (Turkey, 2021). They reported that NLR was 6.71 (3.92–11.11) in the renal infarction group ($n=8$) and 4.21 (2.23–6.19) in the urolithiasis group ($n=65$) ($p=0.154$) [48].

Along with this, no significant statistical difference was found in NLR value between those with impacted ureteral stones and non-impacted ones ($n=51$, 3.02 ± 1.80 and $n=59$, 2.80 ± 2.03 , respectively, $p=0.543$) in the study of patients with a single ureteral stone conducted by Hazar et al. (Turkey, 2019). NLR level was (2.90 ± 1.92) in the whole patients [49].

Koçan (Turkey, 2021) assessed the clinical and demographic differences between 244 clinically diagnosed significant kidney stones men with and without prostate stones. The NLR was 2.3 (2.5 ± 1.2) for those who had a prostate stone (40.98%) and 2.0 (2.2 ± 1.1) for those who did not have a prostate stone (59.02%), with $p=0.045$. In this study, a high NLR can be considered a known risk for prostate cancer formation [50].

Final comment

A single event does not cause renal failure, but recurring renal calculi can harm tubular epithelial cells, resulting in functional loss of renal parenchyma [38]. After the studies above are assessed, we are to report whether NLR could be beneficial in detecting stone-related patients.

NLR and sepsis

Urosepsis is a potentially fatal condition that affects between 0.1% and 4.7% of patients following a ureteroscopic surgery or PCNL [51–53]. Concerning this critical event, sixteen studies investigated NLR as a predictor of SIRS, fever, and sepsis after PCNL, fURS, or semi-rigid ureteroscopy [18, 54–68].

Peng et al. (China, 2021) explored the utility of NLR in predicting SIRS after PCNL. The study found NLR as an independent predictor of post-PCNL SIRS with

AUC of 0.734 (95%CI=0.683–0.776, $p<0.01$) on the ROC curve and OR of 2.406 for 2.16 or more level of NLR (95%CI=1.153–5.021, $p=0.019$), revealed by multivariate analysis. With $p<0.001$, the NLR in the whole patients was 2.16 ± 0.71 , in the SIRS group ($n=108$) was 2.55 ± 0.61 , and in the non-SIRS group ($n=257$) was 1.99 ± 0.68 . However, it did not differ based on gender in the SIRS group ($p=0.618$), which was 2.61 ± 0.65 in male SIRS patients ($n=55$) and 2.49 ± 0.62 in female SIRS patients ($n=53$) [54].

Similarly, Xu et al. (China, 2019) found NLR has a predictive value for post-PCNL SIRS with a cutoff value of 2.9, AUC of 0.669 (95%CI=0.629–0.708, $p<0.01$), and OR of 2.476 (95%CI=1.471–4.167, $p<0.01$). They reported that NLR was 2.13 (1.64–2.86) in the 556 patients (40.5% female) who experienced this procedure and vastly different in the SIRS group ($n=123$, 2.66 (1.91–4.02)) compared to the non-SIRS group ($n=433$, 2.04 (1.58–2.70)) with $p<0.01$ [55].

SIRS and metabolic syndrome (MetS) after PCNL were also evaluated by Tang et al. (China, 2017) in 513 nephrolithiasis patients and 204 healthy controls to see whether NLR or derived NLR (dNLR) may predict them or not. The study found kidney stones patients had greater NLR (2.31 ± 1.70 vs. 1.61 ± 0.56) and dNLR (1.59 ± 0.98 vs. 1.22 ± 0.40) than the healthy controls ($p<0.001$). Based on AUC values of 0.648 (95% CI 0.604–0.692) and 0.625 (95%CI 0.58–0.67) with $P<0.001$, ROC curve analysis indicated that NLR and dNLR had restricted relevance for the identification of individuals with kidney stones, respectively. NLR and dNLR in SIRS (+) kidney stone patients were 3.42 ± 2.42 and 2.23 ± 1.38 , and in SIRS (-) was 1.70 ± 0.50 and 1.25 ± 0.33 , respectively. NLR and dNLR in MetS (+) were 3.03 ± 2.00 and 2.16 ± 1.50 , and in MetS (-) were 2.17 ± 1.61 and 1.49 ± 0.80 with all $p<0.001$. Furthermore, there was a positive correlation between NLR, dNLR, MetS, and post-PCNL SIRS ($p<0.05$) in Spearman correlation analysis, and significant correlations between MetS and NLR, dNLR in this analysis, as well as post-PCNL SIRS and NLR, dNLR. Moreover, multivariate analysis revealed that NLR with SIRS had a hazard ratio of 6.743 (95% CI 3.947–11.518) with $p<0.001$ and with MetS had a hazard ratio of 0.943 (95% CI 0.762–1.168) with $p=0.593$. In addition, dNLR with SIRS had a 7.844 Hazard ratio (95% CI 4.257–14.455) with $p<0.001$, and MetS had a 1.893 Hazard ratio (95% CI 1.277–0.861) with $p=0.225$. Tang and colleagues concluded that a higher NLR level before surgery was an independent and negative predictor of MetS comorbidities and post-PCNL SIRS [18].

In contrast to Tang et al. results in identifying kidney stone patients, Haoran et al. (China, 2020) found AUCs of 0.730 and 0.717 for NLR and dNLR, respectively, for predicting individuals with nephrolithiasis. In this study,

Patients with renal stones ($n=513$) had greater NLR and dNLR values than those without ($n=204$). Similar to the findings of the study above about post-PCNL SIRS, the ROC curves of Haoran and colleagues' study for NLR and dNLR showed AUC of 0.831 and 0.813, using post-PCNL SIRS as the end-point. Multivariate analysis demonstrated that NLR and dNLR were independently related to SIRS after PCNL [56].

Also, after this procedure, 29 patients with SIRS following PCNL and 199 patients without SIRS were evaluated with NLR for post-PCNL SIRS by Akdeniz et al. (Turkey, 2021). Both groups had negative preoperative urine cultures. The total NLR value was 2.34 (1.86–2.76), with 2.25 (1.83–2.68) NLR in non-SIRS and 2.75 (2.22–3.80) NLR in SIRS patients, with $p=0.001$, showing a significant relation between them [57].

Additionally, Sichani et al. (Iran, 2021) saw that higher NLR was associated with an increased frequency of infection-induced SIRS after PCNL. The preoperative NLR measured at 1.9 ± 0.8 in patients with sepsis ($n=26$), at 2.0 ± 1.4 in patients without sepsis ($n=126$), and at 2.0 ± 1.3 in all patients, with $p=0.737$. According to the ROC curve, the NLR under 72.2 could indicate sepsis following PCNL (sensitivity: 80.5% and specificity: 33.3%) [58].

Furthermore, higher preoperative NLR accounted for one of the most important predictors of SIRS after PCNL in Tang et al. (China, 2021) investigation. The SIRS group had a preoperative NLR of 2.5 (1.0), while the non-SIRS group had a preoperative NLR of 2.0 (0.9), with a $p<0.001$ difference. Also, multivariate logistic regression and ROC curve analysis revealed that preoperative NLR was associated with SIRS with an OR of 1.721 (95%CI 1.116–2.653, $p=0.014$) and AUC of 0.652 [59].

On the other hand, inconsequential preoperative NLR for the prediction of SIRS after PCNL was found in a multivariate analysis by Cetinkaya et al. (Turkey, 2017). In the total of 192 patients (31.8% female), the mean preoperative NLR was 2.6 ± 1.5 , with 2.4 ± 1.4 in the non-SIRS group (78.7% of patients) and 3.1 ± 1.9 in the SIRS group ($p=0.018$). Although preoperative NLR was shown to have substantial intergroup differences in univariate analysis ($p=0.018$), it did not in multivariate one [60].

Along with SIRS, Tang and his colleagues assess the predictive value of NLR in sepsis after PCNL. With $p<0.001$, NLR was 2.6 (1.1) in the urosepsis-developed group and 2.0 (0.9) in the urosepsis-undeveloped group with an OR of 1.604 (95%CI 1.135–2.266, $p=0.007$) and AUC of 0.682. According to the research, higher preoperative NLR is among the most critical urosepsis predictors following PCNL [59].

In predicting sepsis after PCNL, Gao et al. (China, 2019) found an OR of 1.291 for NLR (95%CI 0.886–1.882, $p=0.184$) in a univariate logistic regression analysis of

variables linked to sepsis. Meaningfully, with a $p=0.082$, NLR was 2.90 (3.52) in sepsis (+) stone patients ($n=34$) and 2.08 (0.95) in sepsis (-) stone patients ($n=63$). However, with $p=0.261$, NLR was found to be 2.23 (1.72) in total of 194 patients, 2.37 (2.24) in stone patients ($n=97$), and 2.09 (0.94) in non-stone patients ($n=97$) [61].

To weigh up the predictive role of NLR in 487 renal stone patients, Sen et al. (Turkey, 2016) expressed that in patients undergoing PCNL, preoperative NLR was found to be a potential additional predictor of bacteremia and sepsis following PCNL. According to the ROC analysis, NLR's AUC for predicting postoperative sepsis was 0.588. The analysis set a 2.50 NLR threshold. Postoperative sepsis was significantly more common in the NLR at 2.50 or above ($n=168$) group than in the $\text{NLR}<2.50$ group ($p=0.006$). Additionally, Urinary culture results were compared to NLR. Positive urinary culture preoperatively and postoperatively was linked to a greater NLR ($p=0.039$ and $p=0.003$, respectively). The univariate analysis reported NLR in (+) preoperative urinary culture was 2.79 ± 1.80 versus 2.25 ± 0.94 in the (-) group with $p=0.001$, 2.70 ± 1.57 versus 2.25 ± 0.98 in (+) versus (-) postoperative urinary culture group respectively with $p=0.004$, 2.19 ± 0.96 versus 2.30 ± 1.07 in (+) versus (-) renal pelvis urine culture group respectively with $p=0.629$ and 2.39 ± 0.97 versus 2.28 ± 1.07 in (+) versus (-) stone culture group respectively with $p=0.487$. Details of a multivariate analysis that looked into the possibility of a link between culture findings and NLR showed OR of 1.42 (95%CI 1.13–1.77) with $p=0.003$ for preoperative urinary culture OR of 1.35 (95%CI 1.08–1.69) with $p=0.008$ for postoperative urinary culture, OR of 0.89 (95%CI 0.56–1.42) with $p=0.627$ for renal pelvis urine culture and OR of 1.09 (95%CI 0.86–1.37) with $p=0.487$ for stone culture [62].

Besides, Elevated NLR linkage with a higher risk of sepsis after PCNL or semi-rigid ureterorenoscopy in patients with obstructive APN due to urinary calculi was found in Jung et al. (Korea, 2017) study of 64 patients. In this study, there was a greater NLR in the sepsis group than in the non-sepsis group (18.67 ± 12.68 and 10.90 ± 8.68 , respectively, $p=0.014$). In multivariate analysis of independent factors for sepsis in all patients, NLR had an OR of 1.092 (95%CI 1.006–1.142) with a $p=0.03$ [63].

In addition to SIRS and sepsis, post-PCNL fever was also evaluated. Demirtaş et al. (Turkey, 2020) concluded that when risk factors for fever are ruled out, NLR seems to be a simple and inexpensive diagnostic marker for predicting postoperative fever in PCNL patients. Findings revealed NLR was 3.295 (1.46–12.85) in fever (+) patients ($n=50$) and 2.050 (0.35–32.4) in fever (-) patients ($n=469$) with $p<0.001$. Based on ROC curve analysis, NLR had a 2.21 cutoff value with 86% sensitivity, 55.2% specificity, and 0.733 AUC for prediction [64].

Increased NLR was linked to a higher incidence of fever, but unlike Demirtas and colleagues, the link was not statistically significant in Lu et al. (Taiwan, 2021) study in patients (43.4% female) receiving miniaturized PCNL. $\text{NLR} < 5$ was found in 96.55% of non-fever patients ($n = 29$) and 75% of fever patients ($n = 24$) in this study ($p = 0.038$). $\text{NLR} > 5$ had a crude -OR of 9.33 (1.04–84.02) with $p = 0.046$ and an adjusted OR of 5.82 (0.58–58.46) with $p = 0.135$ in a logistic regression study of risk factors for fever in these patients. Furthermore, a crude OR of 1.22 (0.89–1.69) for NLR ($p = 0.217$) and a crude OR of 8.43 (1.00–71.13) with $p = 0.050$ and an adjusted OR of 3.78 (0.41–34.89) with $p = 0.241$ for $\text{NLR} > 5$ were observed in an ordinal logistic regression analysis. Additionally, with $p = 0.091$, NLR under five was seen in 95.24% of non-fever patients ($n = 21$), 100% of mild fever patients ($n = 8$, $37.5 < \text{temp} < 38$) patients, and 75% of fever patients ($n = 24$) [65].

These probable complications of nephrolithotomy are not specific to PCNL. Bai et al. (China, 2021) declared that preoperative NLR could also be utilized as a predictor of SIRS in patients with fURS. In their analysis, the postoperative SIRS group ($n = 43$, 3.90 ± 2.28) had substantially greater preoperative NLR than the postoperative non-SIRS group ($n = 326$, 2.60 ± 1.26) with $p < 0.001$. After that, multivariate logistic regression analysis revealed that preoperative NLR was an independent risk factor for SIRS after fURS ($p = 0.002$), with an OR of 1.497 (95% CI 1.156–1.938). Also, the ROC curve exhibited that the best cutoff value of preoperative NLR was 2.61 (sensitivity: 67.4% (95% CI 0.513–0.805), specificity: 61.0% (95% CI 0.555–0.663). With a $P < 0.001$ and a 95% CI of 0.706–0.852, the area under the ROC curve was computed to be 77.9%. To confirm the findings, 53 patients with fURS treatment were studied prospectively. The patients were separated into two groups based on whether their preoperative NLR value was less than 2.61 ($n = 31$) or greater than 2.61 ($n = 22$). SIRS was substantially more common in patients with $\text{NLR} > 2.61$ than in other patients ($\text{RR} = 4.932$, $p = 0.040$) [66].

Similarly, Yoo et al. (Korea, 2021), in the univariable analysis, found preoperative $\text{NLR} \geq 3.0$ against $\text{NLR} < 3.0$ was independently associated predictor of postoperative SIRS with an OR of 2.706 (95% CI 1.039–7.049) and $p = 0.042$ in patients with urolithiasis-induced obstructive acute pyelonephritis who were scheduled for flexible or semi-rigid ureteroscopic lithotripsy. However, with a $p = 0.217$, NLR was 9.6 (5.0–15.9) in the whole patients, 10.0 (5.2–17.0) in non-postoperative SIRS patients ($n = 83$), and 8.4 (4.5–14.2) in postoperative SIRS patients ($n = 32$) [67].

Also, because the septic shock was predicted by increased NLR with an OR of 3.83 (95% CI: 0.75–5.14, $p = 0.037$) in multivariate logistic regression analysis

by Lim et al. (Korea, 2015), they concluded that older patients with acute obstructive polynephritis and urinary tract calculi which have a high NLR should be managed cautiously to avoid sepsis. With $p < 0.001$, NLR was found to be 8.0 ± 6.5 in the sepsis-developed group ($n = 37$) and 18.5 ± 13.3 in the sepsis-undeveloped group ($n = 36$); thus, the sepsis group has significantly higher NLR values ($p < 0.001$) [68].

Final comment

Reviewed studies showed that NLR could predict sepsis and SIRS among patients with urolithiasis.

Discussion

Increasing evidence suggests that NLR has a role in the development and progression of inflammation in various acute and chronic diseases [27]. In recent years, NLR has emerged as a novel, easily accessible medical biomarker. An analysis of mortality-linked data from the 1999–2014 National Health and Nutrition Examination Survey in the general population of the United States revealed that higher levels of NLR were linked to increased overall mortality and also mortality caused by heart disease, chronic lower respiratory disease, influenza/pneumonia, and kidney disease [69]. To date, NLR has been extensively studied for pediatric and adult medical acute and chronic conditions. As an instance, there are studies available on internal [70, 71], autoimmune [72, 73], infectious [74–76], neurological [77, 78], cancers [79–81], urological [82, 83], orthopedics [84, 85], surgery [86–88], gynecology/obstetrics [89, 90], psychiatry [91, 92], otolaryngology [93–95], ophthalmology [96, 97], dermatology [98, 99], and emergency medicine diseases [100, 101]. Nearly all these studies highlighted that using the division of neutrophils and lymphocytes obtained on routine blood tests is a cheap and easily accessible indicator of systemic inflammation and immune response. Our study lends credence to NLR's status as a promising diagnostic and prognostic biomarker; this finding has important implications for patient triage, risk stratification, personalized treatment strategies, and allocating resources to individuals facing the most critical health issues. With all aspects considered, it seems that now is the opportunity to assign accessible, inexpensive, potentially reliable biomarkers in medical issues while saving more specific ones for more complex conditions.

Limitations

This study has some limitations which should be addressed. First of all, the majority of the included studies were retrospective designs, whose results are less reliable than prospective studies and can affect the final outcome of this systematic review. Second, most of the included studies were done in Asia, and as we know, NLR

can be affected by race and such values. So, other studies in other continents should be done to solidify the diagnostic value of NLR in urolithiasis. Third, because the number of studies included in each endpoint is limited, we could not perform a meta-analysis. In fact, there are only a limited number of published studies on this topic because NLR is really a novel biomarker. Because we did not perform a meta-analysis, the real heterogeneity and subgroup results are unavailable.

Conclusion

As discussed above, the NLR has shown to be a positive predictor of the overall inflammatory process in literature but fails to precisely predict future urinary lithiasis and SSP. Although the NLR was a positive predictor of SSP in multiple studies, the literature was not consistent enough for NLR to be used as a direct predictor of stone passage. In addition to SSP in urinary lithiasis, NLR has also been studied as a possible predictor of disease elevation to SIRS or sepsis after urinary lithiasis. These studies showed a positive correlation between NLR and peaks to a SIRS or sepsis state. The NLR is a rudimentary measure of the body's inflammatory response and, therefore, can be impacted by many factors. Patients suffering from urinary lithiasis due to an imbalance of physiochemical processes or infection can naturally present in an inflammatory state, increasing the NLR ratio. The predictive value of NLR has been shown to positively correlate with SSP and elevation of disease to SIRS or sepsis. Still, it may not hold a strong enough correlation for diagnostic value or predictability. Further testing of NLR and possible confounders in conjunction with other specific plasma contents and investigating the impact of interventions or specific treatments on NLR could move towards better predictive value. In addition, we suggest performing a meta-analysis on this topic when new articles are available.

Abbreviations

APN	Acute pyelonephritis
CRP	C-reactive protein
dNLR	Derived NLR
ESWL	Extracorporeal shock wave lithotripsy
HU	Hounsfield Unit
MetS	Metabolic syndrome
NLR	Neutrophil to lymphocyte ratio
NOS	Newcastle-Ottawa Scale
PCNL	Percutaneous nephrolithotomy
PDE5	Phosphodiesterase type 5
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
SIRS	Systemic inflammatory response syndrome
SSP	Spontaneous stone passage
URSL	Ureteroscopic lithotripsy

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12894-025-01720-y>.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

A. Gh., Sh.Kh and F. Z: conception, methodology, design, statistical analysis, and interpretation, drafted the article. A. Gh., Sh. Kh., R. R and B. L-W: collection of data and drafted the article. A. Gh, S. B, E. K, and J. C: revised the article for important intellectual content. All authors approved the final version of manuscript.

Funding

This systematic review and meta-analysis was not funded in any way.

Data availability

All data generated or analysed during this study are included in this published article.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 2 July 2023 / Accepted: 23 September 2024

Published online: 13 March 2025

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