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Research Article

Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio, Novel Biomarkers and Applications in Urology: An Update

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Abstract

Blood cells play a vital role in homeostasis that can interact with numerous conditions such as inflammation, immune responses, hemostasis, and oncogenesis. The complete blood count test is an inexpensive and regular tool that provides a lot of informative markers revealing shifts in the different blood cell types in case of acute inflammation and prothrombotic phase. Among them, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are emerging biomarkers as the indicators and predictors for varied inflammatory responses and oncologic diseases. These markers were extensively studied in cardiovascular diseases, rheumatic diseases, colorectal, gastric lung, and ovarian cancer, as well as other diseases. In Urology field, higher NLR and PLR could be utilized for predicting prognosis and diagnosis of urinary tract infection states as well as urologic cancer diseases, such as prostate cancer, bladder cancer, and upper tract urothelial carcinoma. Also, in comparison to individuals without kidney stones, forbearing along with the kidney stones had greater NLR and PLR rates. This article aims to review some scientific evidence for the applications of NLR and PLR in Urology.

Keywords: Neutrophil-to-lymphocyte ratio; Platelet-to-lymphocyte ratio; Urolithiasis diseases; Urinary tract infection; Urologic cancers.

Abbreviations: BCa: Bladder cancer; CSS: Cancer-specific survival; DFS: Disease-free survival; DSS: Disease-specific survival; NLR: Neutrophile-to-lymphocyte ratio; OS: Overall survival; PCa: Prostate cancer; PFS: Progression-free survival; PLR: Platelet-to-lymphocyte ratio; PSA: Prostatic specific antigen; RCC: Renal cell carcinoma; RFS: Recurrence-free survival; UC: Urothelial carcinoma.

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Introduction

Complete blood count test is a routine, automated and cost-effective hematological test that reflects profile of formed blood contents, such as red cells, white cells and platelets [1,2]. These cells interplay participates in the pathophysiology of inflammatory, immunologic response, hemostatic process and cancerogenic conditions [3]. Neutrophils are the most common white blood cells in healthy individuals, and they perform a key role in both acute and chronic inflammation [2]. Additionally, they contribute to endothelial dysfunction, atherogenesis and plaque destabilization. Neutrophils are activated, thus easily adhere to and infiltrate the endothelium that results in the formation and release of free radical, hydrolytic enzymes and cytokines [4]. Lymphocytes are the other type of white blood cells that have function to produce adaptive immune responses to decimate specific pathogens, infected cells, and, in certain cases, premalignant and malignant cells. The regulation mechanism of both neutrophils and lymphocytes is rather complex. Chronic inflammatory response can lead to the bone marrow to produce immunoregulatory granulocytic myeloid-derived suppressor cells, which can boost peripheral white blood cell levels to 10% and inhibit lymphocyte counts and function [5].

Platelets have a crucial role in the blood vessel. They persist in the bloodstream for 5-7 days after being created from megakaryocytes and contribute primarily to hemostasis and thrombosis [6]. In addition to the effect of hemostasis in vessel, platelets have also role in regulating various response to inflammatory and infectious conditions that has been noticed in recent research. Platelets contain proinflammatory mediators such as chemokines and cytokines, as well as highly active microparticles that are firmly linked to the evaluation and perpetuation of distinct inflammatory diseases [3,6].

The NLR is count ratio of the neutrophils and number of lymphocytes, that may be easily calculated by using either absolute cell counts or percentage. The ratio is the best indicator of the intimate relationship between two fundamental immunocompetent leukocyte population, i.e., neutrophil granulocytes (innate immune system) and lymphocyte (adaptive immune system) due to illness and various pathological state [7]. The dynamic of NLR reveals the intensity of immune-inflammatory reaction and (supra) physiological strain to insults and diseases. Clinical trials as well as examination were used to determine optimal cut-off ranges for analyzing the severity of the stress and inflammatory reaction. The cut-off range is a prime integer derived from the variety of the clinical research. However, normal range for NLR is 1-2, the cut-off value higher than 3.0 or below 0.7 in adults are pathological. The grey zone for NLR is 2.3-3 may be an early warning sign of pathological state or process such as oncogenesis, atherosclerosis, inflammation, psychiatric disorders, and stress. The value 3-7 indicates mild to moderate inflammation, 7-11: moderate and severe inflammation, systemic infection, sepsis, and systemic inflammation response syndrome (SIRS), 11-17: severe inflammation, infection, severe sepsis and SIRS, bacteremia, 17-23: censorious immune-inflammatory response, stress with peak intensity (e.g., septic shock, multiple trauma), ≥ 23: censorious systemic

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inflammation, terminal cancer, polytrauma, supraphysiological stress and crucial surgery. The elevation of NLR has relation to the worsening of the clinical course, similarly the decrease is related to an improvement or good clinical results [7].

The PLR is measured by dividing the number of platelets to absolute lymphocyte counts. The PLR is less studied than the NLR. The ratio divulges shifts in the platelet cells and the lymphocyte number because of the acute inflammatory and prothrombotic phase. Upsurge in the PLR meter recommend an overactive inflammatory reaction and worsen prognosis. Additionally, PLR is sensitive towards natural as well as acquired immune reactions [3,8,9]. The normal range of the PLR is varied and based on several clinical research. Lee et al reported the mean PLR in healthy South Korean adults were 132.40 (46.794-218.006) [10]. Another study showed the normal range for PLR was 36.63-149.13% [9]. The cut-off value for predicting the prognosis of various conditions such as cardiovascular events, sepsis, oncologic diseases, even Covid-19 has been noticeably studied.

In the past decade, the NLR and PLR have appeared as informative biomarkers in laboratory analysis of the wide ranges of disease. These values are easily derived from complete blood count which is routine, easily obtained and inexpensive laboratory test. In the field of Urology, the NLR and PLR have been also gained a lot of attention recently. Clinical studies tried to utilize these novel markers for diagnosis and prognosis of many urological diseases such as urinary tract infection, urosepsis, bladder cancer, prostate cancer, testicular cancer. This article aims to summarize the scientific evidence and the applications of these biomarkers in the field of urology.

NLR and PLR in urolithiasis diseases

Urolithiasis diseases are an increasingly common urologic condition and pose a high economic and medical burden. Studies have found that the inflammatory conditions play a vital role onset as well as development of the kidney stones [11]. Meanwhile, the NLR and PLR are surrogates of inflammation that could correlate with the presence and progression of the kidney stone. Tang et al found the remarkable high NLR, originated neutrophil-to-lymphocyte (dNLR), lymphocyte-to-monocyte ratio (LMR), PLR strength in the forbearing with the kidney stones, contrast with the healthy controls [12]. Akgün et al studied the data of 191 patients admitted in the emergency room with the acute abdominal pain accompanied by flank pain. The lower NLR value in patients with urinary stones compared to the group without urinary stones. A cut-off of NLR ≤ 2.16 predicted a patient with the 2.34-fold risk of stone positivity. The higher NLR in patients with acute abdominal pain/flank pain due to inflammatory pathologies [13].

Karsli et al conducted an examination and analyzed links among the NLR, PLR as well as hardness of the kidney stones by reviewing retrospectively 192 patients who were suffered conventional percutaneous nephrolithotomy. The results have shown that the increase of NLR ratio related to the elevation of Houndsfield unit (HU) in staghorn and pelvis stone. Observation of negative correlation between HU and NLR in single calyceal group of stone and positive correlation amongst HU

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or NLR for the pelvis and staghorn stone was found. Within the cut-off range of HU was below 1000, no meaningful relation among NLR and HU were noted. Whereas, if HU was just above 1000, there was a remarkable correlation in-between the NLR and HU (r=0.145, p=0.045). Also, in single calyx group, the elevation of PLR had negative correlation with HU value revealing that the stone is not too hard. If the HU value of a single calyx stone was low but the PLR was high, it could be a uric acid stone, and oral chemolysis could be used for such individuals [14].

The NLR and PLR are factors as novel measure of the voluntary ureter stone passage. The size and position of the stones are the most critical characteristics related to SSP. Several indicators of inflammatory response have been determined as SSP predictors. Lee et al reported that besides such factors as the lower stone location [odds ratio (OR), 11.54; p=0.001], small stone size (≤ 5mm) (OR, 8.16; p=0.001), low NLR (<2.3) (OR, 9.03; p=0.003) was used as a predictor for SSP in farebeating with the ureter stone with size <1.0cm [15]. Mao et al evaluated the voluntary inflammatory biomarkers like systemic immune- inflammatory indexing (SII), NLR, PLR and the monocyte-tolymphocyte range (MLR). Multivariate examination showed that only NLR was associated with generality of the kidney stone or number of tones was moved. The cut-off range the for NLR was >1.72 (OR=1.18, 95% CI:1.03-1.36, p=0.019) [16].

Additionally, the novel studies have found that the NLR and PLR were associated infectious stone complications, such as sepsis and systemic inflammatory reaction syndrome (SIRS) post-operation. It is mentioned in the following part below.

NLR and PLR in urinary tract infection

The NLR and PLR are novel biomarkers that have emerged as an informative and frugal factor for diagnosis and prognosis the inflammatory conditions including urinary tract infection (UTI). Scientists have tried to utilize these markers for predicting the occurrence of post-operative infectious complications, such as SIRS after percutaneous nephrolithotomy (PCNL) or sepsis after transrectal ultrasound-guided prostate biopsy (TRUS). Cetinkaya et al found that the PLR and the number of access sites were both independent variables affecting the development of SIRS following PCNL in a multivariate analysis. The preoperative PLR value was higher in patients underwent SIRS post-PCNL. The cut-off range for PLR was about 114.1 along with 80.4% of sensitivity or 60.2% specificity [17]. Tang et al evaluated several hematological parameters for predicting post- PCNL SIRS in the 513-nephrolithiasis patient. These results demonstrated that the preoperative NLR, dNLR show independent factor for the development with SIRS after PCNL. In 2021, another study revealed that the NLR and PLR could be used as predictors of SIRS and sepsis following PCNL. The PLR cut-off value was 120.5 (80.1% specificity, 81% sensitivity), meanwhile the NLR cut-off value was 2.75 (64% specificity, 63.7% sensitivity) [12]. Heidar et al reviewed the total number of 378 patients who underwent in case of TRUS biopsy, among them 31 developed sepsis. They did not find the links between the pre-biopsy NLR or PLR and the development of sepsis post-biopsy, moreover the statistically

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remarkable correlation between the sepsis and pre-biopsy urine analysis as well as prostate-specific antigen level (PSA) [18]. Kazimoglu et al reported a significant decrease of NLR after renal transplantation and an important variation in the NLR was noted in between the Escherichia coli (E. coli) infected and uninfected recipients [19].

Lim et al conducted a multivated analysis in the total 73 forbearing with the examined acute pyelonephritis associated with the urinary tract calculi. The results revealed that old age (>60 years), decrease in serum albumin level (>3.5g/dl), and higher NLR (>10) were independent risk factors for development of urosepsis [20]. In 2016, Han et al (Yihan, 2016) researched 298 pediatric patients with febrile urinary tract infection. They evaluated the NLR was a good predictor of the positive dimercaptosuccinic acid (DMSA) defects as well as C-reactive protein. Additionally, NLR also showed the better results for vesicoureteral reflux prediction [21]. Gokhan et al et al found that Thiol/Disulfide homeostatis parameters and the NLR was significantly high in the forbearing with a UTI in contrast to control groups [22]. Askari et al investigated the NLR and urine IL-8 levels as predictive factors for the type of bacterial UTI in type 2 diabetes mellitus patients. Observation of lower serum CRP levels, higher NLR and higher urine IL-8 levels in patient along with the extended-spectrum of beta-lactamase (ESBL) producing the E. coli as compared to those of the Klebsiella pneumoniae. The NLR cut-off ≥ 3.5 were at risk factor for the ESBL-E. coli UTI that had higher all-cause mortality [23]. In 2021, a study in a sum total of the 541-elderly patient with the genitourinary tract infection in the 5 emergency departments has shown that the mean of the arterial pressure (MAP), NLR or blood urea nitrogen (BUN) was significantly higher than that of nonsurvivor group than in the survivor group ($p<0.001$, $p=0.003$, $p<0.001$). The MAP <70mmHg, NLR ≥ 23.8 and BUN >28mg/dl were associated with the in-hospital mortality. In this study, the NLR ≥ 23.8 predicted all resulted in death at elderly UTI patient, with the sensitivity of 38% and specificity about 88%. When the BUN and NLR were combined with MAP for mortality prediction, the sensitivity was equivalent to Sequential organ failure asessment score (SOFA) at 87.5%, and the specificity was 61% greater than SOFA [24].

NLR and PLR in uro-oncologic diseases

Inflammatory response is one of the most crucial factors which participate in the tumor development and progession. 15% to 20% of all cancer causes deaths worlwide were evaluated to have link to underlying infections and inflammatory responses [25,26]. Recent research has shown that the inflammatory cells could penetrate into the tumor micro- environment and scientists have trialed to focus on hematological parameters as prognosis factor of numerous cancers, as well as uro-oncologic diseases. The NLR and PLR can reflect systemic immune-inflammatory reactions to oncologic pathogens.

Li et al conducted the meta-analysis which determine prognostic role of PLR in the urological cancers. 20 high quality studies with 7562 urological cancer patients were enrolled in the examination. Elevated pretreatment PLR had linked to poor overall survival (OS) (pooled HR=1.58) as well as rest

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of outcomes in the patients with urological cancer. Albeit, found that high PLR was indicated to be substatially related to OS of the forbearing with distinct kinds of urinary malignancies excepted bladder cancer (BCa, HR=1.16, 95% CI:0.96-1.41). In the nutshell, increased PLR was linked to worse prognosis in case of OS in urological cancer, excepted in the bladder cancer. In future, further high-quality large scale prospective studies will be necessary [27].

Another meta-analysis includes the 17 studies involving 3159 cases of urological cancer were reported the part of NLR as prognostic factor in urinary cancers. The pooled analysis revealed that higher NLR could illustrated the poor OS (HR=1.81, 95%CI:1.48-2.21; Pheterogeneity=0.005) and recurrence-free survial or cancer-specific survival (RFS/CSS) (HR=2.07, 95% CI:1.65-2.6; Pheterogeneity= 0.849). In subgroup evaluation, the results showed that higher NLR was associated with poorer OS in the RCC (HR=1.9, 95%CI: 1.47-2.45; Pheterogeneity=0.003) and poor RFS/CSS in RCC (HR=1.83, 95%CI: 1.35-2.48; Pheterogeneity=0.709), bladder cancer (HR=2.2,95%CI:1.27-3.8; Pheterogeneity= 0.447) and urothelial carcinoma (HR=2.58, 95%CI:1.66–4.01; Pheterogeneity= 0.784) (28).

Renal cell carcinoma

Renal cell carcinoma (RCC) is most familiar malignant tumor of the kidneys accounting 3% of malignancies in adults. Along with dramatical development in noninvasive imaging technique, there has been a hike in detection rate of incidental RCC in past 30 year [29]. Various serum biomarker or haematological indices shows the inflammatory reaction, such as C reactive protein (CRP), fibrinogen, lymphocyte-monocyte ratio, NLR, and PLR, has recently shown to be closely related to the poor prognosis in RCC patient (Hu, 2016) [30]. Scientists have found the NLR and PLR as predicting factors for recurrence and progression of RCC as well as prognosis following the treatment procedures such as nephrectomy surgery or target therapy [30-32]. A NLR <3 was associated with a lower probability of recurrence in localized kidney cancer. A NLR <3 indicated better outcomes of overall the survival and progression-free survival in patients with metastatic or locally advanced kidney cancer. In multivariate analysis, the NLR was found to be independent of the Memorial Sloan-Kettering Cancer Center (MSKCC) score in metastatic kidney cancer. There are currently no guidelines for the usage of NLR renal oncology. To fully confirm the inclusion of the NLR in a score or nomogram, more research is needed [33].

Hu et al et al conducted a meta-analysis of 15 cohorts with 3357 RCC patients. These results showed that elevated NLR associated with poor overall survival (OS) (HR=1.82, 95% CI 1.51 to 2.19) and recurrence-free/progress-free survival (RFS/PFS) (HR=2.18, 95% CI 1.75 to 2.71). In forbearing with the RCC, a pooled analysis of examination with the cut-off range less than 3 had considerably better prognostic part than studies with a cut- off value more than 3 [34].

Pichler et al reported that the cut-off range of NLR were 3.3 as independent factor for the overall, but not for cancer-specific, nor for metastasis-free survival. While evaluating the effect of NLR on predictive accuracy of the Leibovich prognosis score, estimated

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concordance indexed was 0.79 using Leibovich risk score and 0.81 when NLR was added [35].

Huszno et al retrospectively reviewed 141 patient with metastatic RCC. The cut-off value of NLR and PLR were >3.68 and >144.4, respectively. The elevated NLR and PLR were correlated to the shorter progression-free survival (PFS) and overall survival (OS) [31].

Arda et al found that the NLR had tendency to increase in patients with tumor size greater than 4 cm compared to patients with tumor size smaller than 4cm (p=0.029). The best cut-off for NLR was >2.26 with 56.8% sensitivity, 71.4% specificity, 84% positive predictive value and 39.5% negative predictive value [29].

Urothelial cancer (UC)

Bao et al utilised a meta-analysis with with a total of 5354 patients in 15 studies to estimate the prognostic impact of PLR on urothelial carcinoma (UC). The results have shown that a high PLR in UC patients had correlation to poorer PFS and disease-free survival (DFS) but not poor OS or cancer-specific survival (CSS). Additionally, they found the relation between an elevated PLR and age >65 years as well as hypertension. No signifcant association was observed between PLR and sex or diabetes [36].

Taguchi reviewed 200 metastatic UC cases receiving salvage chemotherapy to assess the role of pretreatment NLR as a predictive factor of survival due to metastatic UC. 157 out of a total of 185 patients died during follow up, with a median survival of 13.0 months. They found that the pretreatment NLR ≥3, Eastern Cooperative Oncology Group performance status ≥ 2 and liver metastasis were independent poor prognostic factors for CSS and OS. They developed a prognostic model predicting overall survival included the number of these three variables (0, 1 and 2). The patients were identified as having significantly different overall survival (each P<0.0001, log–rank test), with Harrell's concordance value of 0.81 [37].

Bladder cancer

Lee et al evaluated value of pretreatment inflammation-based prognotic scores for invasive BCa on a total of 226 patients with 175 and 51 having non-muscle invasive BCa (stages Ta and T1) and muscle invasive BCa (stage $T2^{+}$) groups, respectively. The cut-off for NLR, LMR and PLR were ≥ 3.89, <1.7 and >218, respectively at a median of 12 days before transurethral resection of bladder tumour (TURBT) surgery, complete blood count samples were collected. In multivariate logistic regression analysis, tumour grade G3, tumour size ≥ 3cm and NLR ≥ 3.89 were identified as independent predictive factors of MIBC [38].

Favilla et al conducted a longitudinal study on 178 BCa patients underwent TURBT. With the median 53 months follow-up study, 14 (23.3%) and 44 (37.9%) (p=0.04) patients respectively with NLR<3 and ≥ 3 experienced recurrence and 2 (3.3%) and 14 (11.9%) experienced progression (p=0.06), respectively. At the multivariate Cox regression analysis, NLR ≥ 3 was associated with worse disease recurrence (HR: 2.84; p<0.01). No association was found regarding disease progression. The 5-year recurrence free survival was 49% and 62% in patients with NLR≥3 and <3 (p<0.01). The 5-year progression free survival was 77% and

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93% in patients with NLR ≥3 and <3 (p=0.69) [39].

Wang et al assessed the role of preoperative NLR versus PLR in a total of 223 BCa patients undergoing radical cystectomy with a medium follow-up period of 57 months. PLR outperformed NLR as a predictive factor in patients with bladder cancer who underwent radical cystectomy, according to receiver operating characteristic curves. In univariate analysis, the results revealed that NLR and PLR had statistically significant correlation with both OS and CSS, respectively. However, only PLR was independent predictive factor for OS and CSS following multivariate analysis [25].

Demirtas et al evaluated the role of preoperative systemic immune index and NLR as preditive factors for lymph node positivity and OS in 213 MIBC patients. The results revealed that systemic immune index and NLR had no significant effect in predicting lymph node positivity and overall survival in BCa [40].

Benign prostatic hyperplasia and Prostate cancer

Kawahara et al investigated the relation between pretreatment NLR and PSA levels in 1464 men who were detected PCa through TRUS as well as the correlation between pretreatment NLR as a predictor for metastatic PCa in 48 patients. The results showed that the higher NLR was observed in males with higher PSA levels compared to in individuals with lower PSA levels (p<0.001). Regardless of metastatic PCa patients, they found that the NLR (the cut-off value was 3.37 defined by the AUROC curve) was linked to both cancer-specific and overall survals (p=0.018 and 0.008, respectively) [41].

Wang et al conducted a meta-analysis to evaluate the role of PLR as a prognostic factor for PCa. Six studies with 1324 patients were included in the pooled analysis. A higher PLR was found to predict poor overall survival (HR=1.85, 95 percent CI=1.51-2.25, P<.001) and disease-free survival (HR=1.4, 95 percent CI=1.1-1.79, P=.007). Subgroup analyses showed that the PLR remained a significant prognostic factor for OS irrespective of ethnicity, tumor stage, or cut-off value. The PLR was an indicator of poor DFS in Asian patients, but not in Caucasian patients. No significant publication bias was detected [26].

In 2019, Chung et al analyzed the correlation between the NLR and intravesical prostatic protrusion (IPP) in 250 men with benign prostatic hyperlasia. The results have shown that the NLR can be indicator for presence of IPP. The NLR had positive association with IPP (Pearson's r=0.459, P< 0.001) and was an independent predictive factor for IPP ≥ 10mm (odds ratio, 2.95; 95% confidence interval, 1.59-5.47; P=0.0006). The NLR was substantially different between those with a prostate less than 40 cm^3 and IPP less than 10mm (2.50 0.71 vs 2.07 0.77, respectively; P=0.020) and those with a bigger prostate and IPP less than 10mm (2.50 0.71 vs 2.07 0.77, respectively) [42].

Eren et al (2020) determined the value of pre-biopsy NLR and PLR as predictors for PCa on 302 male patients with the mean age 66.2 ± 8.2 years. The analysis found that the patients with NLR values above 2.43 had 1.68-fold (95% CI: 1.06-2.66; p=0.028) higher risk for PCa. Additionally, the NLR had a positive

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correlation with age and PSA, but a negative correlation with hemoglobin and platelet count. The independent predictors of biopsy histology were NLR and prostate volume [43].

Testicular cancer

Karakaya et al (2021) evaluated the NLR and PLR as predictors for chemotherapy response in testicular cancer. In this study, complete response (CR) to chemotherapy was obtained in 57.5% of the patients, and partial response (PR) was obtained in 35% of the patients. In comparison to the CR group, the mean NLR values were significantly higher in the non-CR group (p=0.02). Mean PLR values were also significantly higher in the non- CR group (p=0.026). Statistically significant positive correlations were found between tumor stage and NLR & PLR values (r=0.505, p=0.001 for NLR; r=0.397, p=0.011 for PLR). A statistically significant positive correlation was found between tumor stage and neutrophil level (r=0.365, p=0.020), while a statistically significant negative correlation was found between tumor stage and lymphocyte level (r=-0.314, p=0.048) [44].

Conclusions and limitation

Currently, the inflammatory biomarkers have been attracting a great deal of attention. Particularly, the PLR and NLR have emerged as an informative and cost-effective marker applied for diagnosis and prognosis of various conditions including urologic diseases. They can be utilized in a variety of clinical disciplines for illness screening, early warning, stratification, and severity evaluation. These parameters have high sensitivity and lower specificity, as well as their dynamic helps clinicians monitor the systemic response to insults. The role of NLR and PLR have been studied in urolithiasis diseases, urinary tract infections as well as uro-oncologic diseases. The NLR is likely to overwhelm the PLR in studies in the field of urology. Although they are extremely dependent on various confounding variables in laboratory studies such as effects of corticosteroids and other drugs, preanalytical errors with inadequate anticoagulation of blood sample, the dynamics of laboratory parameters cannot be captured by single measurements. Besides, some studies suggested that the PLR and NLR are race and age specific. So, we need to conduct studies with large multinational samples to investigate the normal range as well as the cut-off for these parameters.

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