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Review

# The pretreatment lymphocyte to monocyte ratio predicts clinical outcome for patients with urological cancers: A meta-analysis

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ABSTRACT

*Background:* The lymphocyte to monocyte ratio (LMR), a novel systematic biomarker of inflammation, has been reported to be associated with the progression and prognosis of many malignant cancers. However, the relationship between LMR and survival outcome of urological cancers (UCs) remains controversial. Herein, we conducted a meta-analysis to identify the prognostic value of pretreatment LMR in patients with UCs.

*Methods:* A literature search was performed in PubMed, Web of Science, Embase, Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, and CINAHL databases up to July 2018. The pooled hazard ratios (HRs) and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated to evaluate the association of LMR with survival outcome and clinicopathological characteristics in UCs.

*Results:* A total of 17 articles containing 5552 patients were included in our study. The synthesized analysis showed that elevated pretreatment LMR level could predict favorable overall survival (OS) of UCs patients (pooled HR = 0.82, 95%CI: 0.77-0.87). Additionally, the decreased LMR level was correlated with tumor stage (OR = 1.72, 95%CI: 1.15–2.55), lymph node metastasis (OR = 1.46, 95%CI:1.06-1.99), grade (OR = 1.79, 95%CI:1.41–2.27), tumor size (OR = 2.21, 95%CI:1.81–2.68) and necrosis (OR = 1.71, 95%CI:1.36–2.16).

*Conclusion:* The high pretreatment LMR was associated with favorable prognosis, and could be a potential prognostic biomarker in patients with UCs.

## 1. Introduction

Urological cancers (UCs), which include cancers of the kidney, bladder, prostate and urinary tract, put a huge burden on human healthcare [1,2]. Renal cell carcinoma (RCC) constitutes approximately 2–3% of all adult tumors, with an increasing incidence of 2%–4% per year worldwide [3]. Bladder cancer (BCa) is the ninth most common cancer in the world, especially frequently in males [4]. Prostate cancer (PCa) remains the most prevalent carcinoma in males [5]. Though urinary tract urothelial carcinoma (UTUC) accounts for only 5–10% of all UCs, its progression is aggressive [6]. In spite of tremendous advanced therapies and techniques for UCs including chemotherapy and molecular therapy, the prognosis of UC patients continues to be unsatisfactory, partly due to the high recurrence and metastasis rate [7]. So far, clinical guidelines for the treatment of UCs are mainly based on pathological staging. Nevertheless, the current staging system is still insufficient to support treatment selection and prognosis assessment of UCs [8]. Therefore, a supplementary predictive biomarker would facilitate UCs treatment greatly.

A growing amount of evidences suggested that the outcomes of UC patients were determined not only by tumour features, but also by patient-related factors such as the systematic inflammatory status. Several inflammatory biomarkers such as C-reactive protein and albumin have been reported to be independent prognostic indicators in UCs [9]. It also has been well recognized that systematic inflammatory response is correlated with the alteration of hematologic components, including lymphocyte-to-monocyte ratio (LMR), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). Numerous researches have illustrated the close association between LMR, NLR, PLR and the survival outcome in various types of tumors including colorectal cancer, hepatocellular carcinoma, ovarian cancer and so on [10–14]. These biomarkers are simple, inexpensive and could be examined routinely in clinical setting, thereby providing physicians with objective information to evaluate patient outcomes.

Previous studies have evaluated the prognostic value of LMR in UCs, including RCC, BCa and UTUC. However, these articles have moderate limitations because of relatively small sample sizes and inconsistent results. Therefore, we gathered the available clinical researches and

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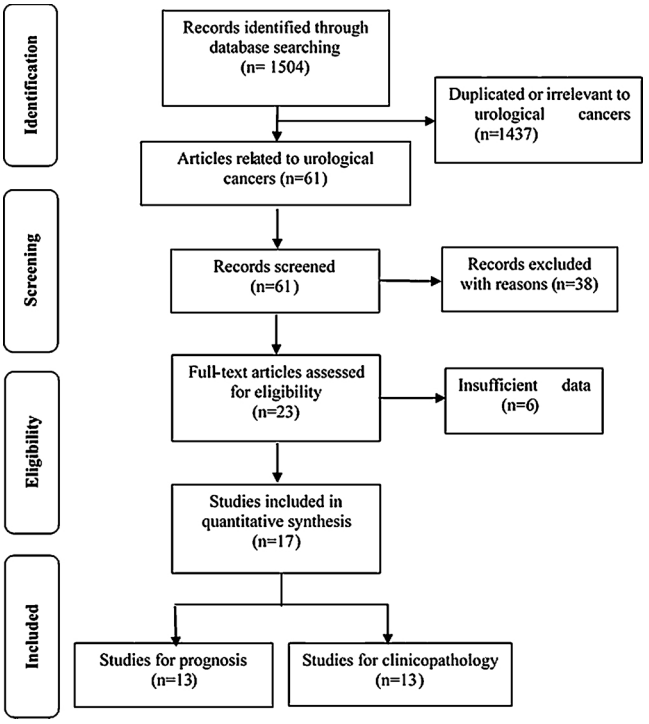


**Fig. 1.** The flow chart of the process for the study selection.

performed a systematic meta-analysis to assess the prognostic and clinicopathological roles of LMR in UCs.

## 2. Materials and methods

### 2.1. Search strategy

A comprehensive literature research was performed in PubMed, Web of Science, Embase, Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, and CINAHL databases, up to July 2018, by using the following key words: ('lymphocyte to monocyte ratio' or 'LMR') and ('urological cancers' or 'prostate cancer' or 'bladder cancer' or 'renal cell carcinoma' or 'urinary tract cancer') and ('prognosis' or 'survival' or 'characteristic'). Additionally, relevant studies of references were also manually retrieved for potential eligibility.

### 2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) clinical studies evaluating the relationship between the LMR level and overall survival outcome or clinicopathological parameters of urological cancers; (2) hazard ratio (HR) with 95% confidence interval could be obtained from articles directly or survival curves indirectly; (3) articles published in English; (4) available full-text articles.

Exclusion criteria: (1) articles without sufficient data; (2) articles with small sample size and low quality; (3) duplicate publication; (4) reviews, letters, conference abstracts.

### 2.3. Data extraction and quality assessment

The following variables were extracted by two investigators (Menglan Li and Qianyun Deng): (1) the first author's name, publication year, region, type of urological cancer, sample size, disease stage, number of patients, median age, follow-up duration, cut-off value of LMR, survival outcome. (2) clinicopathological characteristics including the tumor stage, lymph node metastasis, TNM stage, grade, tumor size, tumor necrosis. (3) HRs with 95%CI from multivariate analysis or survival curves. The quality assessment was conducted according to the Newcastle–Ottawa Quality Assessment Scale (NOS) assessment tool [15].

### 2.4. Statistical analysis

HRs and ORs with corresponding 95% CIs were pooled to estimate the relationship between the LMR and survival outcomes or clinicopathological features of UCs patients respectively. HRs with 95% CIs were extracted from the original articles directly or estimated by Kaplan–Meier curves using Engauge Digitizer version 4.1 indirectly. Statistical heterogeneity among studies was examined using Cochrane's Q test. The fixed-eff ;ect model was used to calculate pooled results in the absence of heterogeneity ($I^2 < 50\%$ or $p > 0.1$). Otherwise, a random-eff ;ect model was selected. Sensitivity analyses were conducted to determine the stability of results. Begger's and Egger's tests with funnel plots were used to test publication bias when more than 6 literatures were embraced. All of the above analyses were performed on STATA 12.0 (Stata, College, TX, USA).

**Table 1**
Characteristics of the included studies.

| Author | Year | Region | Tumor type | Sample size | Stage | Age(range) | Follow-up (months) | Cutoff value | Survival outcome | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| Zhang et al. [16] | 2015 | China | BCa | 124 | Mixed | 65(30-78) | NR | 4.0 | OS | 7 |
| Lee et al. [29] | 2015 | UK | BCa | 226 | Mixed | 75(65-81) | NR | 1.8 | NR | 7 |
| Temraz et al. [17] | 2014 | Lebanon | BCa | 68 | Mixed | 65(43-88) | 24 | 2.81 | OS | 6 |
| Xia et al. [30] | 2016 | China | RCC | 985 | Nonmetastatic | 55(21-81) | 58(3-60) | 4.0 | NR | 8 |
| Hutterer et al. [18] | 2014 | Austria | RCC | 678 | Nonmetastatic | 65(22-80) | 44(0-130) | 3.0 | OS | 8 |
| Chang[1] et al. [19] | 2015 | China | RCC | 441 | Mixed | 56(46-63) | 66(63-69) | 4.44 | OS | 7 |
| Chang[2] et al. [20] | 2015 | China | RCC | 430 | Nonmetastatic | 56(46-63) | 66(63-70) | 3.25 | OS | 7 |
| Gu[1] et al. [21] | 2016 | China | RCC | 145 | Metastatic | 56(47-63) | NR | 3.0 | OS | 6 |
| Hutterer et al. [22] | 2015 | Austria | UTUC | 182 | Nonmetastatic | 69(32-89) | NR | 2.0 | OS | 6 |
| Gu[2] et al. [23] | 2016 | China | RCC | 103 | Mixed | 56(16-79) | 19.9(10.8-35.1) | 3.11 | OS | 7 |
| RAJWA et al. [24] | 2018 | Poland | BCa | 144 | Mixed | NR | 14(7-40) | 2.44 | OS | 7 |
| Peng et al. [25] | 2017 | China | RCC | 1360 | Mixed | 55(14-87) | 67(2-108) | 4.295 | OS | 8 |
| Zhang et al. [26] | 2017 | China | UTUC | 100 | Mixed | 60.3(30-85) | 45.83(1-151) | 3.0 | OS | 6 |
| Song et al. [32] | 2016 | China | UTUC | 140 | Mixed | 67(39-81) | 45(11-108) | 3.6 | NR | 7 |
| Fukuda et al. [27] | 2018 | Japan | RCC | 152 | Metastatic | 64.0(61.5–64.8) | 14 | 3.23 | OS | 7 |
| Gu[3] et al. [28] | 2016 | China | RCC | 161 | Metastatic | 56 (17–83) | NR | 3.23 | OS | 8 |
| Altan et al. [33] | 2017 | Turkey | UTUC | 113 | Nonmetastatic | 63.7(52.6-74.8) | 34 (3-186) | 2.9 | NR | 6 |

RCC: renal cell carcinoma; BCa: bladder cancer; UTUC: urinary tract urothelial carcinoma; OS: overall survival; NR: not reported; NOS, newcastle–Ottawa scale.

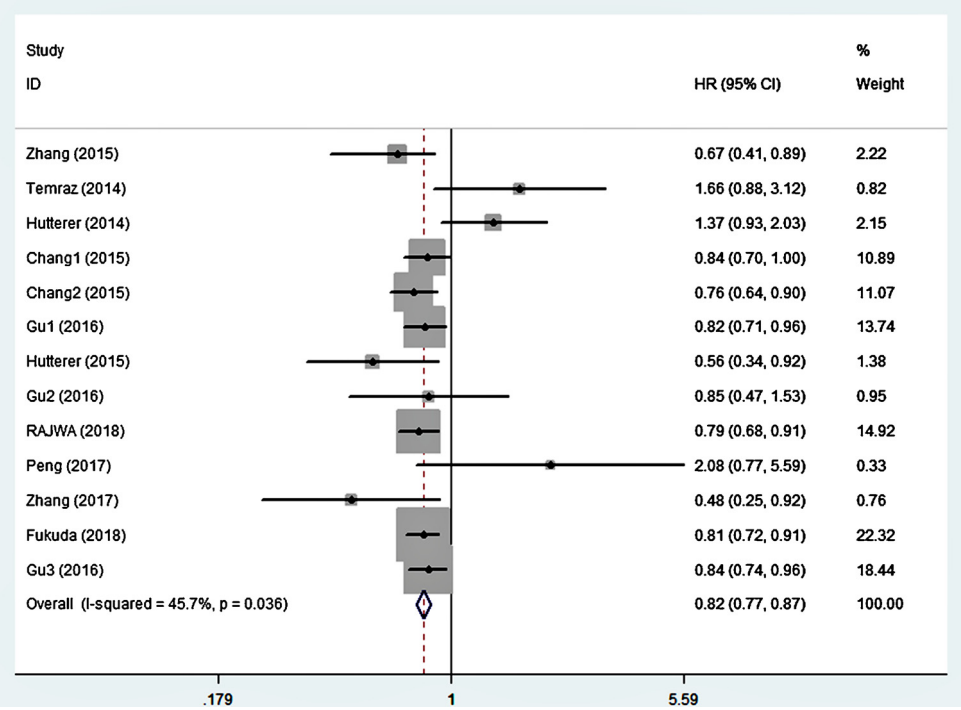


**Fig. 2.** The forest plot of the relationship between the LMR and OS in urological cancers.

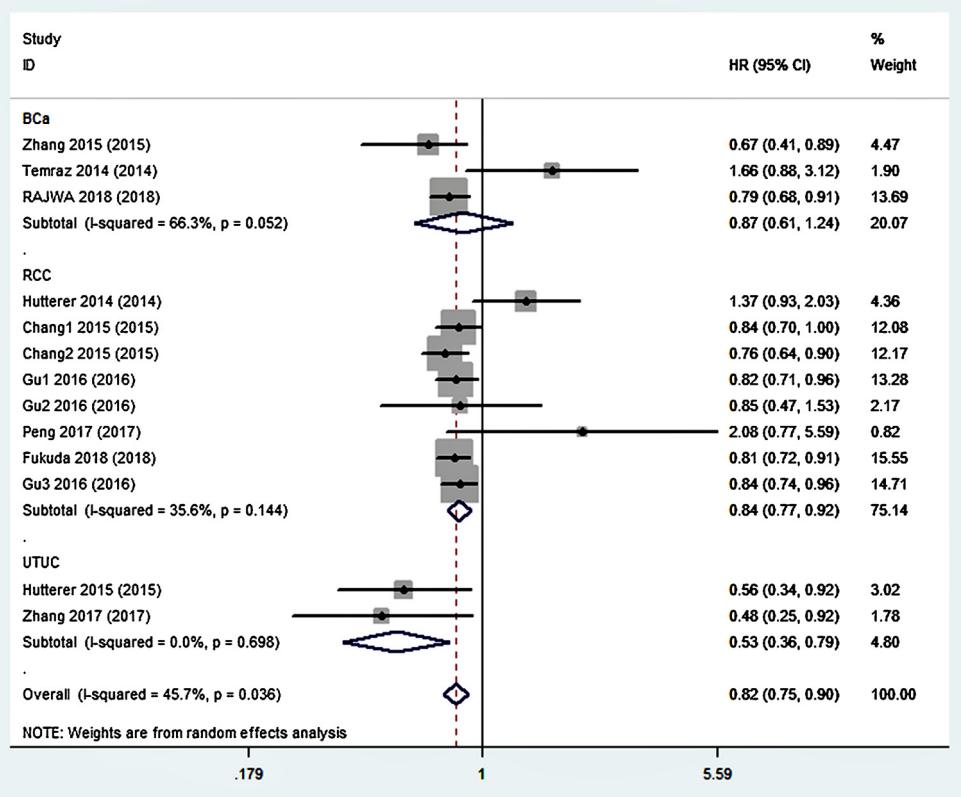


**Fig. 3.** Forest plots of the association between the LMR and OS in diff ;erent types of urological cancers.

## 3. Results

### 3.1. Study search and characteristics

The flow diagram of study selection is presented in Fig. 1. A total of 1504 articles were recruited initially from PubMed, Web of Science, Embase Cochrane Library, Cochrane Central Register of Controlled Trials, Scopus, and CINAHL databases, of which 1437 articles duplicated or irrelevant to urological cancers were removed. After screening the titles and abstracts of these studies, 38 articles including1 letter, 3 meta-analysis, 7 conference abstracts and 27 not related to the LMR were excluded. Subsequently, the remaining 23 full text articles were

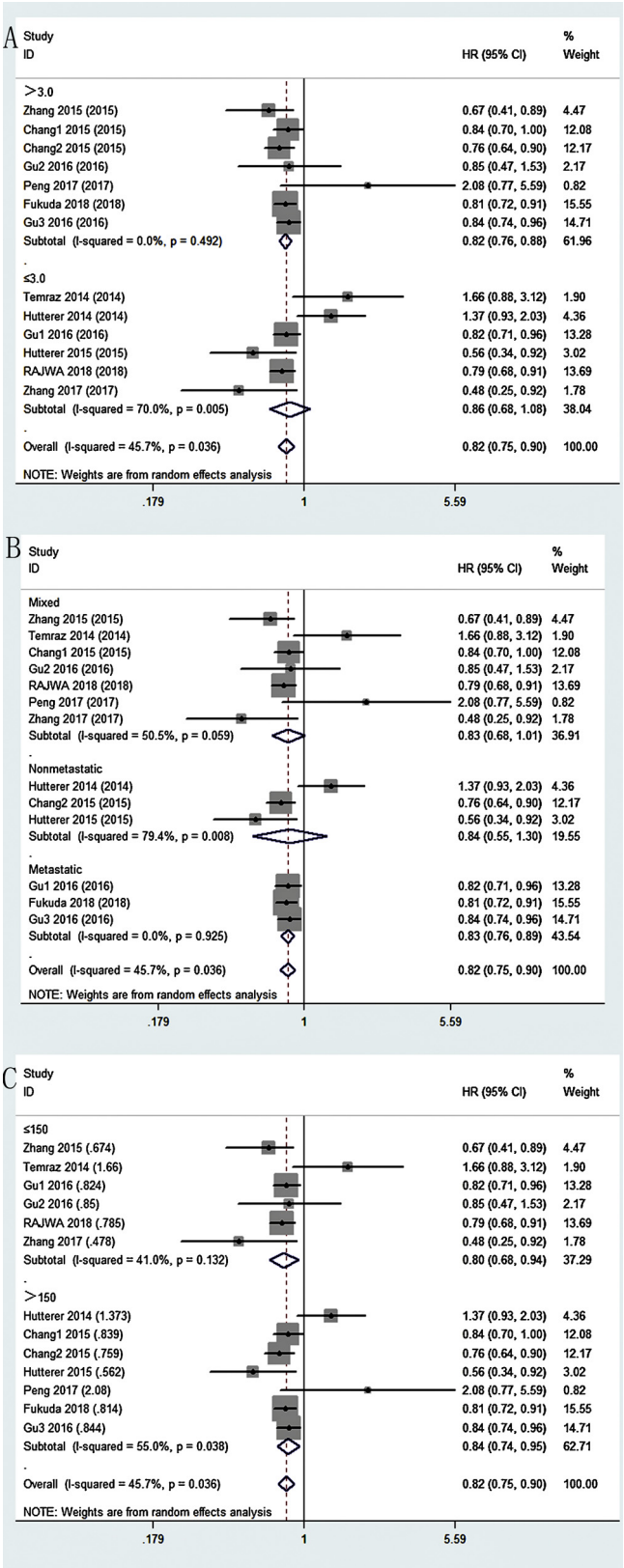


**Fig. 4.** Forest plots of the association between the LMR and OS in diff ;erent subgroups. (A) The cut-off value of LMRs. (B) The disease stage. (C) The sample size.

assessed for eligibility, and 6 studies without sufficient data were also excluded. As a result, 17 articles, comprising 5552 patients, were eventually included in present meta-analysis. Of the 17 included studies, 13 were related to prognosis [16–28] and 13 to clinicopathology [16–19,21,22,26,28–32]. Among these literatures, a cohort of 10 studies were from China [16,19,21,23,25,26,28,30–33] and 7 from the other countries [17,18,22,24,27,29,33]. The detail information of each study is presented in Table 1.

### 3.2. Associations between the LMR and overall survival

A fixed-effect model was chosen to analyze the pooled HR and its corresponding 95%CI with OS among studies due to the moderate but not statistically significant level of heterogeneity (overall $I^2$ = 45.7% in Fig. 2). As shown in Fig. 2, the elevated LMR level was significantly correlated with the increased OS of patients with UCs (pooled HR = 0.82, 95%CI: 0.77-0.87, p < 0.001). Afterwards, we conducted analyses based on the type of UCs (Fig. 3). There were 8 studies that investigated the LMR and OS of RCC patients, and the pooled HR was 0.84 (95%CI: 0.77-0.92) with slight heterogeneity ($I^2$ = 35.6%). The pooled HR of 2 articles related to UTUC was 0.53 (95%CI: 0.36-0.79) with no heterogeneity ($I^2$ = 0.0%). Other 3 researches assessed LMR in BCa patients, whose merged data was 0.87 (95%CI: 0.61–1.24, $I^2$ = 66.3%).

### 3.3. Subgroup analysis

To explain the heterogeneity in OS, we further performed subgroup analyses based on the LMR cut-off value, disease stage and sample size. As shown in Fig. 4, the heterogeneity mainly existed in cut-off value ≤ 3.0 group (HR = 0.86, 95%CI: 0.68–1.08, $I^2$ = 70%) and mixed/non-metastatic group (HR = 0.83, 95%CI: 0.68–1.01, $I^2$ = 50.5%; HR = 0.84, 95%CI: 0.55–1.30, $I^2$ = 79.4%) and sample size > 150 (HR = 0.84, 95%CI:0.74-0.95, $I^2$ = 55%), while there was no heterogeneity in studies with cutoff value > 3.0 (HR = 0.82, 95%CI: 0.76-0.88, $I^2$ = 0.0%), metastatic group (HR = 0.83, 95%CI: 0.76-0.89, $I^2$ = 0.0%) and sample size ≤ 150 (HR = 0.80, 95%CI: 0.68-0.94, $I^2$ = 41%)(Table 2).

### 3.4. Associations between the LMR and clinicopathological characteristics

To further explore the impact of the LMR on clinicopathological characteristics in UCs, a total of 13 articles consisting of 3793 patients were recruited for analysis (Table 3). The pooled OR results indicated that the low LMR was significantly correlated with the advanced tumor stage (OR = 1.72, 95%CI: 1.15–2.55), lymph node metastasis (OR = 1.46, 95%CI:1.06-1.99), grade (OR = 1.79, 95%CI: 1.41–2.27), tumor size (OR = 2.21, 95%CI: 1.81–2.68) and necrosis (OR = 1.71, 95%CI: 1.36–2.16), whereas no significant relationship was observed with age, smoking history and TNM stage.

### 3.5. Sensitivity analysis and publication bias

Sensitivity analysis was conducted to evaluate the reliability and stability of the results by omitting each study orderly to assess the influence on the pooled HR for OS. The result of Fig. 5 showed that there was no significant alteration after removing any articles. Then, we evaluated the potential publication bias with Begger's (Fig. 6) and Egger's test, and the p value was 1.0 and 0.475 respectively, indicating that no significant publication bias existed.

## 4. Discussion

The hypothesis that the systemic inflammatory biomarkers based on circulating cells, particularly the lymphocyte to monocyte ratio (LMR), reliably predict the prognosis of UCs patients has attracted much attention over the past decades. Nevertheless, the mechanism responsible for the relationship between the LMR and outcomes of UCs remained elusive. Accumulating evidence indicated that infiltration of

**Table 2**
Subgroup analyses of pooled hazard ratios for OS.

| Subgroup | Studies (n) | Pooled HR (95%CI) | P value | Heterogeneity | | Effects model |
|---|---|---|---|---|---|---|
| | | | | $I^2$ (%) | P value | |
| LMR cut-off value | | | | | | |
| ≤3.0 | 6 | 0.86(0.68-1.08) | 0.186 | 70 | 0.005 | Random |
| >3.0 | 7 | 0.82(0.76-0.88) | < 0.001 | 0 | 0.492 | Random |
| Stage | | | | | | |
| Mixed | 7 | 0.83(0.68-1.01) | 0.062 | 50.5% | 0.059 | Random |
| Non-metastatic | 3 | 0.84(0.55-1.30) | 0.041 | 79.4% | 0.008 | Random |
| Metastatic | 3 | 0.83(0.76-0.89) | < 0.001 | 0 | 0.925 | Random |
| Sample size | | | | | | |
| ≤150 | 6 | 0.80(0.68-0.94) | 0.007 | 41 | 0.132 | Random |
| >150 | 7 | 0.84(0.74-0.95) | 0.006 | 55 | 0.038 | Random |

**Table 3**
Meta-analysis of low LMR and clinicopathological features of urologic cancers.

| Clinicopathological features | Studies (n) | Cases (n) | Pooled OR (95%CI) | Effects model | P value | Heterogeneity | |
|---|---|---|---|---|---|---|---|
| | | | | | | $I^2$(%) | P value |
| Age(≥60 vs < 60) | 11 | 3257 | 1.20 (0.87-1.66) | Random | 0.262 | 72.5 | < 0.001 |
| Smoking history(yes vs no) | 3 | 1195 | 1.13(0.52-2.49) | Random | 0.765 | 85.8 | 0.005 |
| Tumor stage(III/IV vs I/II) | 12 | 3325 | 1.72(1.15-2.55) | Random | 0.008 | 78.1 | < 0.001 |
| Lymph node metastasis (yes vs no) | 4 | 1805 | 1.46(1.06-1.99) | Fixed | 0.023 | 0 | 0.902 |
| TNM stage(III/IV vs I/II) | 3 | 1467 | 1.60(0.94-2.71) | Random | 0.084 | 59.5 | 0.085 |
| grade (high vs low) | 12 | 2805 | 1.79(1.41-2.27) | Fixed | < 0.001 | 33.5 | 0.122 |
| Tumor size(≥3 vs < 3) | 6 | 2031 | 2.21(1.81-2.68) | Fixed | < 0.001 | 0 | 0.570 |
| Tumor necrosis(yes vs no) | 7 | 1836 | 1.71(1.36-2.16) | Fixed | < 0.001 | 0 | 0.638 |

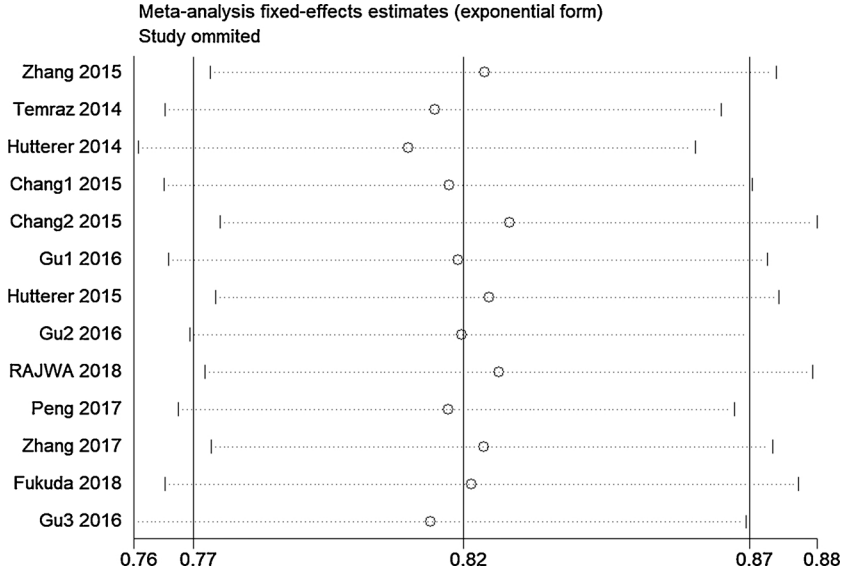


**Fig. 5.** Sensitivity analysis of included studies.

inflammatory cells in the tumor microenvironment had significant influence on tumor initiation, proliferation, angiogenesis and metastasis [34,35]. Recent studies have highlighted that lymphocytes, especially tumor-infiltrating lymphocytes (TILs), were able to secrete cytokines to trigger immune responses, to induce cytotoxic cell death and to inhibit tumor proliferation in many cancers [36–39]. A research illustrated by Fridman et al. found that a strong infiltration of TILs was correlated with a favorable survival outcome in many cancers, including urological cancers as well as colorectal, head and neck, breast, ovarian, liver and lung cancers [40]. On the other hand, monocyte has been constantly recognized as a crucial contributor to angiogenesis, which represents a central hallmark of cancers [41]. Increased monocytes could promote the secretion of proinflammatory factors such as IL-1, INF-α and suppress antitumor immune reaction [42]. The tumor associated macrophages (TAMs), derived from circulating monocytes, were reported to be associated with advanced tumor invasion and unfavorable clinical prognosis in 80% of solid tumors [43]. Based on this background, the LMR, representing a combination of circulating lymphocyte and monocyte amounts, might associate with immunity of the host, and be an effective monitor in tumor follow-up.

At present, the selection and utilization of prognostic factors were mainly based on biological behaviors of tumors such as tumor stage, grade and lymph node status [44]. However, these indicators were usually obtained after surgery or chemotherapy. In addition, these indicators couldn't evaluate the interaction between tumors and the body internal environment, and it was difficult and complicate, to identify

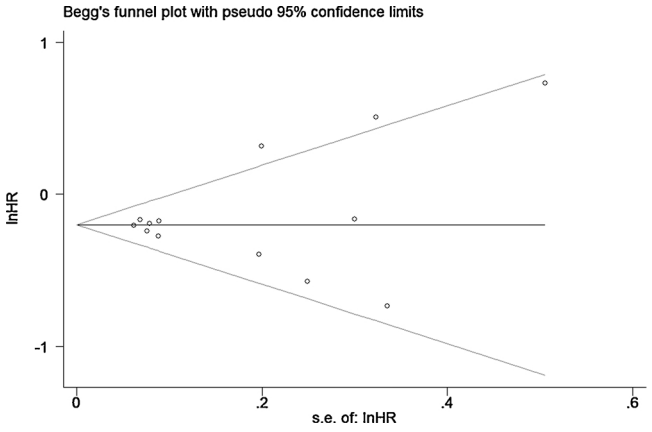


**Fig. 6.** Funnel plot of the publication bias for OS.

pathological features of tumors accurately [45,46]. From another perspective, the preoperative prognostic biomarkers such as LMR could be obtained easily and monitored routinely through peripheral blood examination. Therefore, the pretreatment LMR could be a complementary item to help doctors evaluate the prognosis of UC patients.

This is the first meta-analysis which systemically explored the relationship between the LMR and survival outcome or clinicopathological features of UC patients. The results from recruited articles revealed that high LMR was significantly correlated with favorable OS of UC patients, especially in the subtypes of RCC and UTUC. Subgroup analyses indicated that the high LMR was linked with increased OS outcome in subgroups of cut-off value > 3.0 and metastatic stage, regardless of the sample size (≤150 or > 150). In conclusion, patients with low LMR had a great possibility of advanced tumor stage, lymph node metastasis, grade, tumor size and necrosis, all of which were the indicators of worse prognosis.

There existed a moderate but not statistical significance of heterogeneity in the included studies. Though suitable effect models were used during data pooling, the source of heterogeneity was still unclear. Furthermore, sensitivity analysis also could not help to identify the source of heterogeneity. In order to explain the heterogeneity in OS, subgroup analysis was performed. The results suggested that the different cut-off values, disease stages and sample sizes might be the main origin of heterogeneity.

Nevertheless, several limitations of this study should be mentioned. Firstly, the number of articles in different cancer types (8 for RCC, 3 for BCa, 2 for UTUC, 0 for PCa) and regions (13 from Asia, 3 from Europe) were insufficient. Thus, we wish to emphasize that the results should be cautiously interpreted. Secondly, no correlation was found between the LMR and OS of BCa. This discrepancy might have been caused by relatively small sample size. Thirdly, the HRs of 2 articles were estimated by reconstructing survival curves indirectly rather than by extracting from original data [17,25]. Finally, all of the articles were retrospective design, which might contain a potential selection bias. Therefore, more prospective clinical trials should be embraced to verify the prognostic value of the LMR in UC patients.

In conclusion, this meta-analysis suggested that high preoperative LMR was associated with favorable prognosis, and could be a potential prognostic biomarker of patients with urological cancers.

## Author contribution

Conceived and designed the experiments: Menglan Li and Fang Zheng. Performed the experiments: Menglan Li and Qianyun Deng. Analyzed the data: Lei Zhang. Contributed reagents/materials/analysis tools: Siying He and Jialing Rong. Wrote the paper: Menglan Li and Fang Zheng.

## Conflicts of interest

The authors declare no conflict of interest.

## Acknowledgment

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