Review Article

Prognostic Significance of the Lymphocyte-to-Monocyte Ratio in Bladder Cancer Undergoing Radical Cystectomy: A Meta-Analysis of 5638 Individuals

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Introduction

A growing number of studies have explored the association between the pretreatment lymphocyte-to-monocyte ratio (LMR) and survival outcomes in various cancers. However, its prognostic significance on bladder cancer remains inconsistent. The aim of this meta-analysis was to evaluate the prognostic value of pretreatment LMR in bladder cancer.

Methods

The MEDLINE, EMBASE, Cochrane Library, and CNKI databases were comprehensively searched for relevant studies. A meta-analysis of overall survival (OS), recurrence-free survival (RFS), or cancer-specific survival (CSS) clinicopathological features was conducted.

Results

Nine studies containing 5,638 cancer patients were analyzed in this meta-analysis. Patients with high LMR tended to have favourable OS (HR: 0.63, 95% CI: 0.50-0.80, \( P < 0.001 \)), RFS (HR: 0.59, 95% CI: 0.38-0.91, \( P = 0.017 \)), and CSS (HR: 0.76, 95% CI: 0.70-0.83, \( P < 0.001 \)). Moreover, low LMR was highly correlated with age (≥60), differentiation (low), T stage (III-IV), lymph node metastasis (yes), and concomitant Cis (yes).

Conclusion

Pretreatment LMR might be a useful predictor of survival outcomes in patients with bladder cancer.

1. Introduction

Bladder cancer is one of the most common urinary malignancies and represents approximately 90%-95% of urothelial carcinomas [1]. There was an estimated 76,960 newly diagnosed cases (58,950 men and 18,010 women) in the USA in 2016 [2]. Although the accuracy of current diagnostic methods has greatly improved, the 5-year overall survival (OS) remains unsatisfying, especially for metastatic bladder cancer [1, 2]. Furthermore, bladder cancer has a high recurrence rate (50%), and 15-40% of cases develop into a muscle-invasive form of the disease [3, 4]. Therefore, a reliable and readily accessible preoperative prognostic biomarker is required to determine the optimal therapeutic strategies.

A growing number of studies have shown that inflammation has been closely involved in tumorigenesis and cancer progression and also has been found to correlate with the prognosis [5]. Based on the accumulating evidence, inflammation-based models, such as the C-reactive protein/albumin ratio, albumin-to-globulin ratio (AGR), inflammation-based index (IBI), and neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR) have been developed to predict oncological outcomes in a variety of human cancers [6–9]. The lymphocyte-to-monocyte ratio (LMR) has been associated with worse prognoses in various cancers such as hepatocellular carcinoma, colorectal cancer, and lung adenocarcinoma [10–12]. However, because of the inconsistent results, whether LMR is associated with the prognosis in the bladder remains controversial [13–15]. Therefore, this study was conducted to evaluate the prognostic value of LMR and analyze the relationships between LMR and clinicopathological parameters in patients with bladder cancer.

2. Materials and Methods

2.1. Search Strategies. The MEDLINE, EMBASE, Cochrane Library, and CNKI databases were comprehensively searched up to September 20th, 2018. Studies focused on the correlation
of LMR and bladder cancer were taken into retrieved. Studies were selected using the following keywords: "bladder cancer," "bladder carcinoma," "bladder adenocarcinoma," "bladder tumor," "bladder neoplasms," "transitional cell carcinoma," "ureteral neoplasms," or "urethral neoplasms" and "LMR," "lymphocyte to monocyte ratio," "lymphocyte monocyte ratio," or "lymphocyte-to-monocyte ratio." The references of retrieved studies were also checked to avoid missing relevant studies. For the detailed search strategies, please refer to the supplementary material file (available here).

2.2. Selection Criteria. The criteria for inclusion were as follows: (1) studies focused on bladder cancer patients, (2) studies that evaluated the prognostic value of LMR, (3) a reported cut-off value for LMR, and (3) available hazard ratios (HRs) with 95% CIs for OS, RFS, or CSS. Articles were included if they were duplicate publications or reviews, data was not usable, or the studies were only performed on animals.

2.3. Data Extraction and Quality Assessment. Data extraction and quality evaluation were independently operated by two investigators. Any discrepancies between the two investigators were resolved by discussion until reaching a consensus. General information was gathered as follows: the first authors’ name, year of publication, age, geographical regions, number of patients, distribution of gender, sample size, tumor stage, differentiation, lymph node metastasis, distant metastasis, treatment type, tumor size, cut-off values, survival outcome, follow-up period, and concomitant Cis (carcinoma in situ).

The methodological quality of included studies was independently assessed according to the Newcastle-Ottawa Scale (NOS) [16], which included three primary domains: Selection, Comparability, and Outcome. Studies with an NOS score of ≥6 were deemed high-quality studies.

2.4. Statistical Analysis. We used Stata 13.0 statistical software (Stata, College Station) to estimate HRs for OS, RFS, and CSS and odds ratios (ORs) for clinicopathological parameters. As for prognostic variables (e.g., OS, DFS, and RFS), the hazard ratio (HR) and corresponding 95% confidence interval (CI) were directly extracted from published studies. Otherwise, they were indirectly calculated from survival curves if only survival curves were available in some studies. The heterogeneity among studies was assessed using Cochran’s Q test and Higgins I² statistic; the fixed effect model was used in case of the absence of significant heterogeneity (P > 0.10 or/and I² < 50%); otherwise, the random effect model was chosen. We then performed subgroup analyses to examine the potential source of heterogeneity. To validate the robustness of the pooled results, sensitivity analyses were performed by removing each study. Publication bias was evaluated using Egger’s test. All P values were two-sided, and the difference was considered significant when the P value was less than 0.05.

3. Results

3.1. Study Characteristics. A total of 123 records were initially retrieved from four common databases (Figure 1). Meanwhile, 2 articles were identified through references. After the removal of duplicates, 96 articles remained for further evaluation. As shown in Figure 1, after screening titles and abstracts, 76 duplicate articles were excluded. The remaining articles were carefully evaluated by evaluating the full texts, and 11 articles were excluded. Finally, a total of 9 studies were included in the meta-analysis [13–15, 19–24].

Table 1 displays the characteristics of included studies. All included studies were retrospective cohort trials and released from years 2014 to 2018. These studies were carried out in six countries, including Lebanon, UK, China, Japan, Austria, and Poland. The treatments were surgery and mixed methods. Cut-off values of LMR ranged from 1.8 to 4. All cases in the eligible studies were classified into two groups (high and low). Eight studies reported the association between LMR and OS, and 3 studies reported RFS and CSS. NOS scores of all the studies were at least 6 or more (Table 1).

4. Meta-Analysis

4.1. Impact of LMR on OS. Eight studies, including 5,368 patients, were included in this meta-analysis of OS. The pooled results showed significant differences in OS among the higher LMR groups and lower LMR groups (HR: 0.63, 95% CI: 0.50-0.80, P < 0.001, Figure 2). To further explore the prognostic value of LMR in bladder cancer, subgroup analysis based on the main features was performed. Results for subgroup analyses are shown in Table 2. The results indicated that elevated LMR significantly predicted favourable OS in patient mixed stages (HR = 0.63; 95% CI = 0.49-0.80; P < 0.001). Pooled HRs for OS were stratified by the cut-off value for LMR. The result showed that patients with LMR ≥ 3 had significantly increased OS (HR: 0.56, 95% CI: 0.35-0.88, P = 0.011). However, no prognostic value was observed in patients with LMR < 3 (HR: 0.65, 95% CI: 0.41-1.04, P = 0.075). Moreover, the ethnicity, treatment, and analysis method also did not affect the significant predictive value of LMR in bladder cancer patients.

4.2. Impact of LMR on RFS and CSS. Three studies with 4,536 patients investigated the association between LMR and RFS. The pooled HR was 0.59, which indicated that elevated LMR was significantly associated with favourable RFS (Figure 3). There were three studies with a total of 4,459 patients investigating the predictive value of LMR for CSS. As shown in Figure 4, a statistically significant difference was observed between the higher LMR groups and the lower LMR groups (HR: 0.76, 95% CI: 0.70-0.83, P < 0.001). The result revealed that patients with a high LMR had a significantly favourable CSS compared with those with a low LMR.

4.3. Associations between LMR and Clinicopathological Parameters. Meta-analyses for the association between LMR and clinicopathological parameters were conducted, and the results are presented in Table 3. Compared with high LMR, low LMR was highly correlated with age (≥60 vs. <60; OR = 2.07, 95% CI: 1.22-3.50, P = 0.007), differentiation (low vs. moderate/high; OR = 1.60, 95% CI: 1.10-2.32, P = 0.01), T stage (III-IV vs. I-II; OR = 1.13, 95% CI: 1.01-1.28,
4.4. Sensitivity Analysis and Publication Bias. A sensitivity analysis was performed by omitting the enrolled studies in turn to investigate the stability of the results. The results indicated that the pooled results were relatively reliable and steady (Figure 5).

No obvious publication bias was found among studies (Figure 6), which were also demonstrated in Egger’s test for OS ($P > |t| = 0.055$).

5. Discussion

Recently, more and more studies focused on the correlation between inflammation and cancers revealed that tumor initiation, progression, and metastasis were affected by host systemic inflammatory response as well as tumor microenvironment [5, 25, 26]. To the best of our knowledge, our study is the first and most comprehensive meta-analysis that systematically analyzed the prognostic value of pretreatment LMR in bladder cancer survivors. A prognostic effect for LMR on OS, RFS, and CSS was found after pooling the results. Therefore, LMR could serve as biomarker for the prognosis of bladder cancer patients. Additionally, the correlations between LMR and clinicopathological parameters were evaluated. Low LMR was highly correlated with age ($\geq 60$), differentiation (low), T stage (III-IV), lymph node metastasis (yes), and concomitant Cis (yes). LMR, as a composite inflammatory-based prognostic system, has shown great prognostic value in multiple cancers. However, the underlying molecular mechanisms have not been adequately illuminated. Lymphocytes play a major role in suppressing cancer cell proliferation and migration [27]. Tumor-infiltrating lymphocytes (TILs) are vital components of the antitumor immune microenvironment and are involved in several stages of tumor progression [28, 29]. Cytotoxic lymphocytes, mainly cytotoxic T cells, are essential for eliminating residual cancer cells and are being applied in immunotherapy [30, 31]. Monocytes are thought to have an impact on tumorigenesis through differentiation to tumor-associated macrophages (TAMs). TAMs are recruited to the
Table 1: Characteristics of the studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Follow-up (months)</th>
<th>Treatment</th>
<th>No. of patients</th>
<th>Stage</th>
<th>Cut-off value</th>
<th>Survival analysis</th>
<th>Analysis</th>
<th>Confounding factors adjusted for</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temraz</td>
<td>2014</td>
<td>Lebanon</td>
<td>Caucasian</td>
<td>24</td>
<td>Mixed</td>
<td>68</td>
<td>Mixed</td>
<td>2.81</td>
<td>OS/RFS</td>
<td>UV</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Lee</td>
<td>2015</td>
<td>UK</td>
<td>Caucasian</td>
<td>NA</td>
<td>Surgery</td>
<td>226</td>
<td>Early</td>
<td>1.8</td>
<td>OS</td>
<td>MV</td>
<td>Age, grade, tumor size, NLR, PLR</td>
<td>7</td>
</tr>
<tr>
<td>Zhang</td>
<td>2015</td>
<td>China</td>
<td>Asian</td>
<td>50.8</td>
<td>Mixed</td>
<td>124</td>
<td>Mixed</td>
<td>4</td>
<td>OS</td>
<td>MV</td>
<td>Age, sex, BMI, AC, concomitant Cis, T stage, LNM, DM, PLR</td>
<td>8</td>
</tr>
<tr>
<td>Yoshida</td>
<td>2015</td>
<td>Japan</td>
<td>Asian</td>
<td>72 (27.6-111.6)</td>
<td>Mixed</td>
<td>181</td>
<td>Mixed</td>
<td>3.51</td>
<td>OS</td>
<td>MV</td>
<td>T stage, N stage, grade, LVI, margin, AC, LVI</td>
<td>7</td>
</tr>
<tr>
<td>Lucca</td>
<td>2016</td>
<td>Austria</td>
<td>Caucasian</td>
<td>NA</td>
<td>Surgery</td>
<td>310</td>
<td>Early</td>
<td>3.3</td>
<td>OS</td>
<td>MV</td>
<td>T stage, grade, concomitant Cis, LVI, NLR, PLR, GPS, PNI</td>
<td>6</td>
</tr>
<tr>
<td>D’Andrea</td>
<td>2017</td>
<td>Austria</td>
<td>Caucasian</td>
<td>42.4 (18.3-85.1)</td>
<td>Surgery</td>
<td>4198</td>
<td>Mixed</td>
<td>3.5</td>
<td>OS/RFS/CSS</td>
<td>MV</td>
<td>Gender, age, margin, concomitant Cis, LNM, LVI, AC, NLR</td>
<td>8</td>
</tr>
<tr>
<td>Miyake</td>
<td>2017</td>
<td>Japan</td>
<td>Asian</td>
<td>22 (10-64)</td>
<td>Mixed</td>
<td>117</td>
<td>Mixed</td>
<td>3.3</td>
<td>OS/CSS</td>
<td>UV</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Rajwa</td>
<td>2018</td>
<td>Poland</td>
<td>Caucasian</td>
<td>14 (7-40)</td>
<td>Surgery</td>
<td>144</td>
<td>Mixed</td>
<td>2.44</td>
<td>OS/CSS</td>
<td>MV</td>
<td>T stage, LNM, grade, tumor necrosis, NLR, PLR</td>
<td>8</td>
</tr>
<tr>
<td>Wang</td>
<td>2018</td>
<td>China</td>
<td>Asian</td>
<td>NA</td>
<td>Mixed</td>
<td>270</td>
<td>Early</td>
<td>4</td>
<td>RFS</td>
<td>UV</td>
<td>NA</td>
<td>7</td>
</tr>
</tbody>
</table>

Abbreviations: OS: overall survival; RFS: recurrence-free survival; CSS: cancer-specific survival; MV: multivariate; Cis: carcinoma in situ; AC: adjuvant chemotherapy; NLR: neutrophil-lymphocyte ratio; PLR: platelet-lymphocyte ratio; LNM: lymph node metastasis; DM: distant metastasis; LVE: lymphovascular invasion; GPS: Glasgow prognostic score; PNI: prognostic nutritional index; PMI: psoas muscle index; NA: not available.
tumor site by obtaining the signal from tumor-derived chemotactic factors [32]. Therefore, the amount and percentage of monocytes could be representative for TAMs reflecting the tumor burden. Recent studies reported that increased infiltration of TAMs was associated with the outcome of various cancers [33, 34]. Thus, LMR may represent a balance between the antitumor immune reaction and the tumor promotion function.

There were several limitations of this study. First, the cut-off value of LMR applied in the enrolled studies was not uniform. This might have made a significant contribution to the substantial heterogeneity. Second, all of the included studies were retrospective. Third, excessive heterogeneity existed among the included studies. However, subgroup analyses showed that the heterogeneity diminished or disappeared in Caucasian patients and patients receiving surgery.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>HR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temraz (2014)</td>
<td>0.38 (0.18, 0.82)</td>
<td>7.09</td>
</tr>
<tr>
<td>Lee (2015)</td>
<td>0.70 (0.19, 2.57)</td>
<td>2.89</td>
</tr>
<tr>
<td>Zhang (2015)</td>
<td>0.67 (0.45, 0.99)</td>
<td>16.39</td>
</tr>
<tr>
<td>Yoshida (2015)</td>
<td>0.26 (0.15, 0.46)</td>
<td>10.96</td>
</tr>
<tr>
<td>Luca (2016)</td>
<td>0.44 (0.06, 3.32)</td>
<td>1.27</td>
</tr>
<tr>
<td>D’Andrea (2017)</td>
<td>0.83 (0.73, 0.95)</td>
<td>27.44</td>
</tr>
<tr>
<td>Miyake (2017)</td>
<td>0.56 (0.26, 1.23)</td>
<td>6.80</td>
</tr>
<tr>
<td>Rajwa (2018)</td>
<td>0.79 (0.69, 0.91)</td>
<td>27.15</td>
</tr>
<tr>
<td>Overall (I^2 = 65.9%, P = 0.005)</td>
<td>0.63 (0.50, 0.80)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Note: weights are from random effect analysis.
Table 3: Meta-analysis of the association between LMR and clinicopathological features of bladder cancer.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>Heterogeneity I² (%)</th>
<th>P_{I²}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (≥60 vs. &lt;60)</td>
<td>3</td>
<td>626</td>
<td>2.07 (1.22-3.50)</td>
<td>0.007</td>
<td>42</td>
<td>0.18</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>4</td>
<td>4,818</td>
<td>1.18 (0.68-2.04)</td>
<td>0.56</td>
<td>70</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking status (always/current vs. never)</td>
<td>2</td>
<td>394</td>
<td>0.95 (0.63-1.45)</td>
<td>0.82</td>
<td>0</td>
<td>0.80</td>
</tr>
<tr>
<td>Differentiation (low vs. moderate/high)</td>
<td>5</td>
<td>4,886</td>
<td>1.60 (1.10-2.32)</td>
<td>0.01</td>
<td>35</td>
<td>0.19</td>
</tr>
<tr>
<td>Tumor size (&gt;3 cm vs. &lt;3 cm)</td>
<td>2</td>
<td>496</td>
<td>1.86 (0.74-4.71)</td>
<td>0.19</td>
<td>71</td>
<td>0.06</td>
</tr>
<tr>
<td>T stage (III-IV vs. I-II)</td>
<td>3</td>
<td>4,390</td>
<td>1.13 (1.01-1.28)</td>
<td>0.04</td>
<td>0</td>
<td>0.79</td>
</tr>
<tr>
<td>Lymph node metastasis (yes vs. no)</td>
<td>3</td>
<td>4,390</td>
<td>1.22 (1.06-1.39)</td>
<td>0.005</td>
<td>0</td>
<td>0.67</td>
</tr>
<tr>
<td>Distant metastasis (yes vs. no)</td>
<td>1</td>
<td>124</td>
<td>1.46 (0.37-5.73)</td>
<td>0.59</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Multiplicity (multiple vs. solitary)</td>
<td>2</td>
<td>496</td>
<td>1.04 (0.68-1.58)</td>
<td>0.86</td>
<td>0</td>
<td>0.49</td>
</tr>
<tr>
<td>Concomitant Cis (yes vs. no)</td>
<td>2</td>
<td>4,322</td>
<td>0.88 (0.78-0.99)</td>
<td>0.03</td>
<td>0</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Cis: carcinoma in situ.
6. Conclusions

Our meta-analysis confirmed that low pretreatment LMR was associated with shorter OS, RFS, CSS, and worse clinicopathological features in patients with bladder cancer. Therefore, LMR could serve as a promising prognostic factor of bladder cancer.

Conflicts of Interest

The authors report no conflicts of interest in this work.

Authors’ Contributions

JYM, GH, and QL conceived, designed, and performed the experiments and analyzed the data. All authors contributed the reagents/materials/analysis tools and wrote the paper. Jian-ying Ma and Gang Hu contributed equally to this work.

Supplementary Materials

The search strategies of this meta-analysis. (Supplementary Materials)

References

Disease Markers


