

INPLASY

Prognostic value of neutrophil-to-lymphocyte ratio in non-muscle-invasive bladder cancer patients with intravesical Bacillus Calmette-Guérin immunotherapy: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 July 2024 and was last updated on 14 July 2024.

INTRODUCTION

Review question / Objective Although previous studies have reported the relationship between NLR and survival outcomes in NMIBC patients, there is currently a lack of a comprehensive meta-analysis on NMIBC patients with intravesical BCG immunotherapy. Considering that patients receiving intravesical BCG immunotherapy after TURBT represent independent treatment types, and several studies have reported that NLR levels can predict the efficacy of intravesical BCG therapy and disease relapse progression in NMIBC patients receiving intravesical BCG immunotherapy. Based on these previous findings, this meta-analysis aimed to systematically evaluate the relationship between NLR and the prognostic value of postoperative intravesical BCG immunotherapy in NMIBC patients.

Condition being studied Bladder cancer (BCa) is one of the most commonly diagnosed malignancies worldwide, and the most common

malignancy of the urologic system, with approximately 573,000 new cases and 213,000 deaths. On the basis of the depth of tumor invasion, BCa is classified as non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Approximately 70% of the patients with BCa present with disease limited to the mucosa (stage Ta, carcinoma in situ [CIS]) or submucosa (stage T1). The gold standard for the treatment of NMIBC is transurethral resection of the bladder tumor (TURBT) followed by intravesical instillation therapy, and then undergoing a second surgery when it is necessary. Bacillus Calmette-Guérin (BCG) has been shown to be the most effective intravesical immunotherapy for preventing recurrence of NMIBC by inducing an immune response in the bladder to attack cancer cells. Although the prognosis for NMIBC is favorable, with a 5-year overall survival (OS) rate of approximately 90%, 30-80% case of recurrences and 45% case progressions to muscle invasion were observed within 5 years in patients with NMIBC. Therefore, predicting BCG failure, tumor recurrence and progression may promote timely

radical cystectomy or combination therapy and improve the survival rate of patients. Currently, the European Organization for Research and Treatment of Cancer (EORTC) model is widely utilized to assess the risk of recurrence and progression of NMIBC treated with intravesical BCG immunotherapy. The accuracy of EORTC model needs to be improved, in spite of the fact that this scoring system is useful in clinical practice. Consequently, new predictors are needed to improve the risk classification and prediction of recurrence and progression of NMIBC.

Several studies have suggested that some inflammatory markers may be associated with the prognostic assessment of intravesical BCG immunotherapy for NMIBC. The neutrophil-to-lymphocyte ratio (NLR), as a biomarker for assessing inflammatory status, is easily obtainable in clinical practice. Many systematic reviews and meta-analyses have effectively integrated the findings of multiple studies, generating valuable insights into the complex relationships between NLR and solid tumors (e. g., breast cancer, cervical cancer, esophageal cancer, colorectal cancer, prostate cancer, and pancreatic cancer). Collective evidence consistently suggests a noteworthy correlation, suggesting that elevated NLR levels are significantly associated with poor prognosis in patients who develop these specific cancer types. Furthermore, NLR levels have been found to independently predict the prognosis of BCa. In a meta-analysis of 17 studies reported by Xingxing Tang et al, an elevated NLR was a predictor for poor clinical outcome in patients with bladder cancer, including OS, recurrence-free survival (RFS), progression-free survival (PFS) and cancer-specific survival (CSS). In another meta-analysis of six studies, it was confirmed that an elevated NLR predicted worse RFS and PFS in NMIBC patients treated with TURBT.

METHODS

Search strategy In order to collect the studies for the purpose of the study, we searched in PubMed, the Cochrane Library, Web of Science, and Embase, for the literature published from inception to May 14, 2024, with no language limitations. The search terms included combinations of the suggested words by Medical Subject Heading (MeSH) and other related words. Search query in PubMed was performed as follows for the indicated discipline: (((Neutrophil-to-Lymphocyte Ratio[Title/Abstract]) OR (Neutrophil to Lymphocyte Ratio[Title/Abstract])) OR (NLR[Title/Abstract])) AND (((((((Non-Muscle Invasive Bladder Neoplasms[MeSH Terms]) OR (Non Muscle Invasive Bladder Neoplasms[Title/

Abstract])) OR (NMIBC[Title/Abstract])) OR (Non-Muscle-Invasive Bladder Cancer[Title/Abstract])) OR (Bladder Cancer, Non-Muscle-Invasive[Title/Abstract])) OR (Bladder Cancers, Non-Muscle-Invasive[Title/Abstract])) OR (Cancer, Non-Muscle-Invasive Bladder[Title/Abstract])) OR (Cancers, Non-Muscle-Invasive Bladder[Title/Abstract])) OR (Non-Muscle Invasive Bladder Cancer[Title/Abstract])) AND (((((Bacillus Calmette-Guerin[Title/Abstract]) OR (Bacillus Calmette Guerin[Title/Abstract])) OR (Bacillus Calmette-Guérin[Title/Abstract])) OR (Bacillus Calmette Guérin[Title/Abstract])) OR (BCG[Title/Abstract])). In addition, the references cited in the captured articles were manually examined to identify any additional relevant research.

Participant or population NMIBC patients.

Intervention NMIBC patients receiving intravesical BCG immunotherapy after surgery.

Comparator None.

Study designs to be included Articles reporting on the relationship between NLR and the prognosis of NMIBC patients receiving intravesical BCG immunotherapy after surgery, the formula of NLR: $NLR = \text{neutrophil count} / \text{lymphocyte count}$.

Eligibility criteria Studies were included if they simultaneously met the following criteria: (1) articles reporting on the relationship between NLR and the prognosis of NMIBC patients receiving intravesical BCG immunotherapy after surgery, the formula of NLR: $NLR = \text{neutrophil count} / \text{lymphocyte count}$; (2) groups according to their preoperative NLR levels; (3) specific endpoints of interest, including recurrence and progression; and (4) availability of hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) or the ability to calculate them from the data presented in the articles. The exclusion criteria consisted of the following: (1) case reports, conference abstracts, editorials and reviews; (2) studies with insufficient information on NLR value and the treatment of NMIBC patients; (3) animal studies; (4) duplicates, or surveys investigating the same sample; (5) full text not being available; and (6) articles with no extractable data on the main outcomes.

Information sources PubMed, the Cochrane Library, Web of Science, and Embase.

Main outcome(s) Specific endpoints of interest, including recurrence and progression and availability of hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs) or the

ability to calculate them from the data presented in the articles.

Data management A title and abstract screening were performed by two independent investigators (JH and LL) to determine suitability of the articles. Then a more detailed examination of the potential articles was conducted through collecting the full texts. Google Translate was used if necessary to translate non-English articles. In case of any replicated publications, the study providing the most extensive information was selected. If there was a disagreement, a third party (DM) would be consulted for adjudication. Data from the articles were extracted and recorded in a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, WA) by two independent investigators (JH and LL) independently: the name of first author, the year of study publication, study region (country), number of study centers, mean or median age, sample size, tumor stage, follow-up time (months), NLR cut-off, cut-off selection, and survival outcome, HRs or ORs with 95% CIs.

Quality assessment / Risk of bias analysis Two investigators (JH and LL) involved in the quality evaluation using the Newcastle-Ottawa Scale (NOS), with a third party (DM) acting as adjudicator in case of disagreement. A higher score indicated a higher quality of the literature, showing a positive correlation between the two. Studies with scores higher than 6 were considered of high quality. Publication bias was assessed by Egger's test. $P < 0.05$ was considered statistically significant.

Strategy of data synthesis Meta-analysis was conducted using Stata 16.0 software (StataCorp). HRs and 95% CIs were computed as the combined effect size to assess the relationship between pre-treatment NRL and recurrence, progression. The Q test was used to analyze the heterogeneity among the results of the included studies. I^2 was utilized to quantitatively assess the magnitude of heterogeneity. Base on I^2 statistics, heterogeneity was categorized as high (above 75%), moderate (25% to 75%), and low (below 25%). When $I^2 > 50%$ and/or $P < 0.05$ indicated high heterogeneity, the random model was used; otherwise, the fixed model was used. Potential sources of heterogeneity were identified through subgroup analyses. If grouped data on subgroup categories were not available, they were excluded. In addition, the meta-analysis was also subjected to a sensitivity analysis in order to eliminate the effect of individual study data on survival outcomes. Publication bias was assessed by Egger's test. $P < 0.05$ was considered statistically significant.

Subgroup analysis Potential sources of heterogeneity were identified through subgroup analyses. If grouped data on subgroup categories were not available, they were excluded.

Sensitivity analysis The meta-analysis was also subjected to a sensitivity analysis in order to eliminate the effect of individual study data on survival outcomes.

Language restriction None.

Country(ies) involved China.

Keywords Non-muscle-invasive bladder cancer; Bacillus Calmette-Guérin; Neutrophil-to-lymphocyte ratio; Recurrence; Progression; Systematic review; Meta-analysis.

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