Original Study

Preoperative Anemia and Low Hemoglobin Level Are Associated With Worse Clinical Outcomes in Patients With Bladder Cancer Undergoing Radical Cystectomy: A Meta-Analysis

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Abstract

A meta-analysis was performed to synthesize currently available evidence and determine the association between preoperative anemia/hemoglobin level and prognosis of patients undergoing radical cystectomy. Seventeen studies were included, and the results showed that preoperative anemia and low hemoglobin level are associated with increased all-cause mortality, cancer-specific mortality, and disease recurrence.

Purpose: The aim of this study was to determine the effect of preoperative anemia status and hemoglobin level on clinical outcomes in patients with bladder cancer undergoing radical cystectomy. **Materials and Methods:** A systematic review of literature with meta-analyses of predefined outcomes based on a search of PubMed and EMBASE was performed. Hazard ratios (HRs) measuring the association between preoperative anemia/hemoglobin and all-cause mortality, cancer-specific mortality, and disease recurrence were calculated with random effects model. Study heterogeneities were quantified by I^2 tests. Publication bias was assessed with funnel plots. **Results:** A total of 17 studies evaluating the impact of preoperative anemia status (categorical, 11 studies) and hemoglobin level (continuous, 7 studies) on clinical outcomes were included. The cutoff value of anemia varied among studies (10.5-13.5 g/dL for male, 10.5-13.4 g/dL for female). Meta-analyses showed that compared with non-anemia, anemia was associated with increased all-cause mortality (HR, 1.75; 95% confidence interval [CI], 1.48-2.05; $P < .00001$; $I^2 = 30\%$), cancer-specific mortality (HR, 1.80; 95% CI, 1.45-2.25; $P < .00001$; $I^2 = 26\%$), and disease recurrence (HR, 1.37; 95% CI, 1.16-1.62; $P = .0002$; $I^2 = 9\%$). Meta-analyses showed that higher level of hemoglobin was associated with decreased all-cause mortality (HR, 0.90; 95% CI, 0.87-0.92; $P < .00001$; $I^2 = 13\%$), cancer-specific mortality (HR, 0.90; 95% CI, 0.85-0.95; $P = .0003$; $I^2 = 61\%$), and disease recurrence (HR, 0.95; 95% CI, 0.91-0.99; $P = .01$; $I^2 = 53\%$). No obvious publication bias was observed. **Conclusions:** Preoperative anemia and low hemoglobin level are associated with earlier recurrence and shorter survival of patients with bladder cancer undergoing radical cystectomy. However, well-designed prospective studies with large sample size and limited confounding factors are needed to confirm and update our findings.

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Introduction

Bladder cancer is a major health problem in the United States. In 2016, an estimated 76,960 new cases of bladder cancer will be diagnosed, and 14,880 patients will die from the disease.[1] Level 1 evidence supports the use of neoadjuvant chemotherapy (NAC) and radical cystectomy (RC) with pelvic lymph node dissection (PLND) for patients with muscle-invasive bladder cancer (MIBC).[2] However, the 5-year survival rate after RC only ranges from 40% to 60%.[3] Treatment decision-making for MIBC is of great significance but sometimes challenging. More specifically, clinical, radiologic, and pre-RC pathologic information has significant accuracy limitations and currently is a limitation for optimal clinical decision making.[4-6] There is still a glaring need to identify other potential prognostic markers, in particular, preoperative ones, to improve the stratification of patients with MIBC.

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Recently, there has been increasing interest in the prognostic role of hematologic biomarkers in patients undergoing RC. Neutrophil-lymphocyte ratio has been widely reported as an efficient biomarker to predict oncologic outcomes in patients undergoing RC for bladder cancer.[7-9] Other biomarkers, including lymphocyte-monocyte ratio, lymphocyte-monocyte ratio, and platelet count, have also been reported.[10-12] Most of the biomarkers focused on the leukocytes, and the prognostic role of hemoglobin have not been clearly defined. Anemia and low hemoglobin level are quite common in patients with malignant tumors, including bladder cancer.[13-15] Although the number of studies exploring the prognostic role of anemia and hemoglobin level has been increasing, the results are inconsistent and often based on small samples.[16-32] Here, we performed a meta-analysis to pool currently available evidence on this topic and further define the prognostic role of anemia status and hemoglobin level in patients with MIBC undergoing RC.

Materials and Methods

Literature Search

This meta-analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[33] A systematic search of the literature was conducted on May 13, 2016 using the PubMed and EMBASE database. The following search strategy was employed to both PubMed and EMBASE: (*radical cystectomy*) *AND* (*anemia OR hemoglobin OR hematocrit OR transfusion OR blood cell OR hematology*). No restrictions on publication type, publication language, or publication year were applied. Cited references from the selected articles were manually searched and assessed.

Study Selection

Original research studies that met the following criteria were included: (1) had the cohort of patients with bladder cancer underwent standard RC with curative intent; (2) evaluated the relationship between preoperative anemia status (categorical variable) or hemoglobin level (continuous variable) and prognostic outcomes; (3) reported at least 1 of the outcomes of interest, which were determined as all-cause mortality (ACM), cancer-specific mortality (CSM), and disease recurrence (DR); (4) used the Cox proportional hazards model and provided the hazard ratios (HRs) for ACM, CSM, and DR; (5) provided the 95% confidence intervals (CIs) or *P*-value with the HRs. Risk ratio or relative risk was considered the same as HR. If multiple studies had a duplicate patient cohort, only the study with the largest sample size was included for the same outcome. If multiple studies had a duplicate patient cohort as well as the same sample size, only the study with the longest follow-up time was included for the same outcome. However, if multiple studies with duplicate patient cohort had different outcomes of interest, they were included for analysis separately for each outcome.

Data Extraction

The following information was collected from each included study: first author, year of publication, the country in which the study was conducted, study design, anemia cutoff value, number of patients, patients' age, patients' gender, preoperative hemoglobin level, number of patients who received NAC, number of patients who received adjuvant chemotherapy (AC), number of patients who received other therapies, follow-up time, pathologic type, pathologic stage, number of patients with positive lymph nodes, number of patients with positive surgical margin, number of patients with lymphovascular invasion, urinary diversion type, number of patients with perioperative blood transfusion, and HRs for the outcomes of interest (ACM, CSM, DR). For HRs, if both univariable Cox regression and multivariable Cox regression were provided, data from multivariable Cox regression was extracted, otherwise, data from univariable Cox regression was used.

Quality Assessment

The quality of the included cohort studies was assessed using the Newcastle-Ottawa Scale (NOS).[34] The NOS assesses the quality of studies by examining 3 aspects of the study design: patient selection, comparability of the study groups, and assessment of outcomes. A score of 0 to 9 may be given to individual studies. Studies achieving a score of 7 or more indicate a high quality.

Statistical Analysis and Meta-Analysis

HRs and 95% CIs were pooled to assess the effect of anemia and hemoglobin level on the survival outcomes of patients with bladder cancer. Because anemia status (anemia vs. non-anemia) is a categorical variable and the hemoglobin level is a continuous variable, 2 separate meta-analyses were carried out, one on anemia status and another one on hemoglobin level. For the purpose of clear description, the first one was referred to as anemia meta-analysis and the latter one as hemoglobin meta-analysis in our manuscript.

The meta-analyses were performed using Review Manager 5.3 (The Cochrane Collaboration). Random-effect model was used. Statistical heterogeneity was quantified using the inconsistency (I^2) statistic. Publication bias was assessed using the funnel plot. This test presumes that in the absence of publication bias, larger studies (sample size in y-axis) will be plotted near the average (effect size in x-axis), and smaller studies will be spread symmetrically around the average, ideally shaping a funnel. All the *P*-values were 2-sided, and $P < .05$ was considered statistically significant.

Sensitivity and Subgroup Analysis

Sensitivity analyses were performed for the anemia meta-analysis on ACM, which had the largest number of included studies. We excluded one study at a time and calculated the pooled HRs from the remaining studies to explore the robustness of the result.

Subgroup analyses were also performed for the anemia meta-analysis on ACM to explore the cause of heterogeneity. Subgroup analyses were specified according to the following factors: (1) study quality (high quality vs. low quality), (2) sample size ($\geq$ 500 vs. $<$ 500), and region (Asia vs. non-Asia).

Results

Literature Search

Figure 1 shows the flow diagram of the selection of studies. A total of 1222 references were identified in the preliminary search. After excluding 209 duplicate publications, 1013 references were identified for screening. By reviewing the titles and abstracts, 899 references were excluded and 114 studies were identified for full-text review. After reading the full-text, 97 studies were excluded. Finally,