

Prognostic Value of Preoperative Serum Albumin Level in Patients with Non-Muscle-Invasive Bladder Cancer Undergoing Transurethral Resection of Bladder Tumor: Postprint

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Abstract

Objective: To determine whether preoperative serum albumin level can serve as a survival prognostic indicator in patients with non-muscle-invasive bladder cancer (NMIBC) undergoing transurethral resection of bladder tumor (TURBT). **Methods:** A total of 216 bladder cancer patients who were newly diagnosed with NMIBC and underwent TURBT in our hospital between January 2007 and April 2012, with complete clinical data and follow-up information, were included. The included patients were divided into a low serum albumin group (<40 g/L) and a normal serum albumin group (≥40 g/L) based on preoperative serum albumin level. The Kaplan-Meier model was used to evaluate survival in both groups, and Cox proportional hazards model was employed for univariate and multivariate analyses of overall survival (OS). **Results:** Among the 216 NMIBC patients, there were 82 (39%) cases in the low serum albumin group and 127 (61%) cases in the normal serum albumin group. Kaplan-Meier analysis demonstrated that the 5-year OS of the low serum albumin group was lower than that of the normal serum albumin group (P=0.017). Further multivariate Cox analysis to eliminate the influence of confounding factors revealed that preoperative serum albumin level remained an independent risk factor for 5-year OS in NMIBC patients undergoing TURBT (HR: 3.102, 95% CI: 1.200~8.020, P=0.020). **Conclusion:** NMIBC patients with low preoperative serum albumin levels had poorer 5-year OS. For NMIBC patients undergoing TURBT, preoperative serum albumin level can serve as an inexpensive, readily accessible, and simple yet effective survival prognostic indicator.

Full Text

Preamble

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Abstract

Objective To assess whether preoperative serum albumin level can serve as a survival prognostic indicator for patients with non-muscle-invasive bladder cancer (NMIBC) undergoing transurethral resection of bladder tumor (TURBT). **Methods** We retrospectively analyzed 216 patients with newly diagnosed NMIBC who underwent TURBT between January 2007 and April 2012 and had complete clinical data and follow-up information. Patients were categorized into low serum albumin group (<40 g/L) and normal serum albumin group (≥40 g/L) based on preoperative serum albumin levels. Kaplan-Meier analysis was used to evaluate survival outcomes, and univariate and multivariate Cox proportional hazard models were applied to analyze overall survival (OS). **Results** Among the 216 NMIBC patients, 82 (39%) were in the low albumin group and 127 (61%) in the normal albumin group. Kaplan-Meier analysis revealed that the 5-year OS was significantly lower in the low albumin group compared to the normal albumin group (P=0.017). After adjusting for confounding factors through multivariate Cox analysis, preoperative serum albumin level remained an independent risk factor for 5-year OS (HR: 3.102, 95% CI: 1.200–8.020, P=0.020). **Conclusion** NMIBC patients with low preoperative serum albumin levels who underwent TURBT had worse 5-year OS. Preoperative serum albumin level can serve as an inexpensive, readily available, and simple yet effective prognostic indicator for survival in NMIBC patients undergoing TURBT.

Keywords: bladder urothelial carcinoma, non-muscle-invasive bladder cancer, transurethral resection of bladder tumor, albumin, prognosis

Introduction

Bladder urothelial carcinoma (BUC) is currently the ninth most common malignant tumor worldwide and ranks second in incidence among urogenital system malignancies. The 2017 American Cancer Report indicated approximately 79,030 new bladder cancer cases in the United States, with an estimated 16,870 deaths from bladder cancer that year [1]. Approximately 80% of newly diagnosed bladder cancer cases are non-muscle-invasive bladder cancer (NMIBC), for which transurethral resection of bladder tumor (TURBT) is considered the standard treatment [2]. Current research generally accepts that postoperative pathological stage and grade serve as the primary prognostic factors for survival

in BUC patients [3-6]. However, despite comprehensive evaluation of postoperative pathological indicators to guide subsequent treatment and follow-up protocols, NMIBC patients still experience high rates of recurrence and progression, making the search for new prognostic indicators clinically significant.

Accurate pathological staging and grading can only be obtained postoperatively, and currently there are no reliable preoperative prognostic indicators. Identifying new preoperative prognostic markers would be valuable for clinical practice. Patients' systemic nutritional status significantly impacts their survival. Albumin is a major component of human serum proteins and is commonly used to assess nutritional status. Previous studies have shown that patients with high-grade malignant tumors often have serum albumin levels below normal thresholds [7]. Preoperative or pre-chemotherapy serum albumin levels hold important prognostic value for cancer patients [8]. Increasing attention has been focused on patients' preoperative nutritional status, particularly the predictive value of preoperative serum albumin levels for survival outcomes in BUC patients [9]. However, most relevant studies have focused on the prognostic impact of preoperative serum albumin levels in patients undergoing radical cystectomy, with relatively limited evidence regarding its impact on NMIBC patients receiving TURBT. Therefore, this study aimed to evaluate the prognostic value of preoperative serum albumin levels in newly diagnosed NMIBC patients treated with TURBT.

1.1 Study Population and Grouping

This retrospective study was conducted by searching the electronic medical record system of Nanfang Hospital between January 2007 and April 2012. A total of 427 adult patients with a clinical diagnosis of bladder cancer and detailed clinical and follow-up data were identified. Patients were then strictly screened according to inclusion and exclusion criteria.

1.1.1 Inclusion Criteria

- (1) Adult patients receiving first-time treatment;
- (2) Patients who completed preoperative examinations without surgical contraindications;
- (3) Patients who underwent TURBT;
- (4) Surgery performed using a continuous irrigation transurethral 30° resectoscope with F27 outer sheath plus a Gyrus Medical bipolar plasma resection system;
- (5) Surgery performed by senior clinical physicians qualified and experienced in such procedures;
- (6) Complete resection of all visible tumors during surgery;
- (7) Patients requiring a second TURBT if muscle layer was not included in postoperative pathology;
- (8) Postoperative pathology confirming non-muscle-invasive bladder urothelial carcinoma.

1.1.2 Exclusion Criteria

- (1) Recurrent patients;
- (2) Patients who received neoadjuvant radiotherapy,

chemotherapy, or intravesical instillation therapy before surgery; (3) Patients requiring conversion to open surgery during TURBT; (4) Patients who underwent partial cystectomy or radical cystectomy; (5) Palliative surgery cases; (6) Postoperative pathology showing non-urothelial carcinoma or muscle-invasive bladder cancer.

1.1.3 Grouping After screening, 216 patients were included in the study. Based on preoperative serum albumin levels and according to our hospital laboratory standards, patients were divided into low serum albumin group (<40 g/L) and normal serum albumin group (≥40 g/L). Among patients with available preoperative serum albumin data, 82 (39%) were classified into the low albumin group and 127 (61%) into the normal albumin group.

1.2 Data Collection

General patient information, postoperative pathology, and preoperative laboratory data were collected from individual medical records, while postoperative follow-up data were obtained from medical record systems and telephone follow-up results. All patients underwent routine preoperative laboratory examinations. Postoperative pathological specimens were diagnosed, staged, and graded by multiple pathologists from the Department of Pathology at Nanfang Hospital.

1.2.1 Study Variables Epidemiological indicators included age, gender, smoking status, Karnofsky score, and ASA score. Postoperative pathological indicators included tumor number, pathological T stage, and tumor grade. Preoperative laboratory indicators included hemoglobin concentration, neutrophil count, lymphocyte count, platelet count, serum albumin level, serum globulin level, and serum creatinine level. Additionally, creatinine clearance rate was calculated using the Cockcroft-Gault formula for chronic kidney disease (CKD) staging.

1.2.2 Postoperative Treatment and Follow-up Patients routinely received postoperative intravesical chemotherapy with epirubicin 50 mg (first instillation within 24 hours post-surgery, then weekly for 8 consecutive times, followed by monthly for 10 consecutive times). Follow-up was conducted every 3 months for the first 2 years, every 6 months in the third and fourth years, and annually thereafter. Patient survival and death status were followed up until the fifth postoperative year.

1.3 Statistical Analysis

All data were analyzed using SPSS 20.0 software. Chi-square test, Mann-Whitney U test, and t-test were used for intergroup comparisons between low and normal serum albumin groups. Kaplan-Meier model was used to evaluate patient survival, with Log-rank test for group comparisons. Univariate and

multivariate Cox survival analyses were used to determine hazard ratios (HR) for overall survival (OS). $P < 0.05$ was considered statistically significant for all analyses.

Results

The median age of the 216 patients was 60.0 years (interquartile range: 47.0–70.8 years); 176 (81.5%) were male and 40 (18.5%) female. Karnofsky scores were 90 in 165 cases and < 90 in 51 cases. ASA scores were 1–2 in 204 cases and 3–5 in 12 cases. Tumor multiplicity: 156 patients had single tumors and 60 had multiple tumors. Pathological T stage: Ta in 182 cases and T1 in 34 cases. Tumor grade: low grade in 185 cases and high grade in 31 cases. Preoperative hemoglobin was 133.77 ± 21.27 g/L, and serum albumin was 40.71 ± 4.31 g/L. Other clinical indicators are shown in Table 1 .

Patients in the low serum albumin group were significantly older than those in the normal albumin group ($P = 0.001$). No significant differences were observed between groups in gender, smoking status, Karnofsky score, ASA score, pathological T stage, tumor grade, platelet count, or serum globulin level ($P > 0.05$). However, hemoglobin concentration, neutrophil count, lymphocyte count, and serum albumin level were significantly higher in the normal albumin group compared to the low albumin group ($P < 0.05$), while more patients in the low serum albumin group had higher CKD stages ($P = 0.001$, Table 1).

2.2 Univariate Analysis of Overall Survival

The follow-up endpoint was the fifth postoperative year, with a median follow-up time of 60 months (interquartile range: 48–60 months). During follow-up, 27 patients died, with mortality rates of 19.5% (16/82) in the low albumin group and 8.7% (11/127) in the normal albumin group. In the low albumin group, 1 patient died from bladder cancer metastasis after recurrence and radical cystectomy, 3 died from bladder cancer progression after recurrence and systemic chemotherapy, 3 died from bladder cancer after recurrence and progression with treatment abandonment, 2 died from other malignant tumors, 1 died from systemic infection, 1 died from “cachexia,” and 5 had unknown causes of death. In the normal albumin group, 2 patients died from bladder cancer metastasis after recurrence and radical cystectomy, 2 died from bladder cancer progression after recurrence and systemic chemotherapy, 2 died from bladder cancer after recurrence and progression with treatment abandonment, 1 died from other malignant tumors, 3 died from cardiovascular or cerebrovascular accidents, and 1 died from “cachexia.” Kaplan-Meier analysis and Log-rank test showed that the 5-year OS was significantly lower in the low albumin group compared to the normal albumin group ($P = 0.017$) [Figure 1: see original paper].

Univariate Cox survival analysis revealed that preoperative serum albumin level was significantly associated with OS. Additionally, among demographic and clinicopathological variables, age, Karnofsky score, ASA score, tumor number,

pathological T stage, and tumor grade were significantly associated with OS. Among laboratory variables, hemoglobin concentration, serum albumin level, and CKD stage were significantly associated with OS.

2.3 Multivariate Analysis of Overall Survival

All variables with potential prognostic value were included in multivariate Cox survival analysis to determine whether preoperative serum albumin level was an independent prognostic factor for bladder urothelial carcinoma (Table 2). The data in Table 2 show that preoperative serum albumin level (HR: 2.851, 95% CI: 1.083-7.507; $P=0.034$), age (HR: 3.585, 95% CI: 1.398-9.191; $P=0.008$), Karnofsky score (HR: 3.511, 95% CI: 1.483-8.314; $P=0.004$), and pathological T stage (HR: 6.690, 95% CI: 2.693-16.617; $P<0.001$) remained independent prognostic factors for overall survival in multivariate analysis.

Discussion

BUC is a clinically common malignant tumor with high recurrence rates [1], and TURBT is the standard treatment for NMIBC patients [2]. In recent years, several novel preoperative prognostic factors for bladder urothelial carcinoma have been identified, such as vascular endothelial growth factor (VEGF) [10], hyaluronidase [11], and sarcopenia rate [12-13]. However, most of these markers have limitations in clinical application, particularly regarding high testing costs. Serum albumin, in contrast, is a routine preoperative examination item that offers convenient and cost-effective testing.

Previous studies have demonstrated that hypoalbuminemia is a poor prognostic factor in patients requiring surgical treatment [14], and low preoperative serum albumin levels predict poor outcomes in BUC patients [15-17]. However, few reports have examined whether preoperative serum albumin levels affect prognosis in newly diagnosed NMIBC patients undergoing TURBT. Therefore, this study incorporated variables from three aspects—general patient condition, postoperative pathology, and preoperative laboratory indicators—to evaluate 5-year OS prognosis, focusing on the prognostic value of preoperative serum albumin levels in newly diagnosed NMIBC patients treated with TURBT.

Regarding general patient condition, we included Karnofsky score, which has been proven in previous studies to have prognostic value for postoperative survival in BUC patients undergoing radical cystectomy [18], for preoperative physical status evaluation. Through univariate analysis, we found that age, Karnofsky score, and ASA score were all significantly associated with 5-year OS. However, after multivariate adjustment, only age and Karnofsky score remained statistically significant prognostic factors, with advanced age and low Karnofsky score predicting poor prognosis. This demonstrates that Karnofsky score has greater value than ASA score in evaluating preoperative physical status and surgical prognosis, making it suitable for clinical promotion.

In terms of postoperative pathology, univariate analysis showed that higher tumor number, pathological T stage, and tumor grade predicted worse surgical outcomes, consistent with previous research [19-21]. However, after multivariate adjustment, tumor number and tumor grade were no longer statistically significant prognostic factors, suggesting that pathological T stage has higher predictive efficacy for long-term survival in NMIBC patients after TURBT.

Regarding preoperative laboratory indicators, this study included hematological and biochemical parameters related to nutrition, immunity, coagulation, and renal function. Univariate analysis revealed that low preoperative hemoglobin, low serum albumin level, and high CKD stage predicted poor prognosis. However, after multivariate adjustment, only preoperative serum albumin level emerged as an independent prognostic indicator for survival after TURBT in NMIBC patients. The impact of preoperative serum albumin level on perioperative survival and complications has been widely recognized in clinical research [14], and our study found it also significantly affects long-term prognosis in NMIBC patients. The underlying mechanisms may include several aspects.

Albumin is a product synthesized and released by the liver, and serum albumin levels in cancer patients are known to be below normal thresholds in various cancers [7-8]. Serum albumin is a commonly used marker for assessing nutritional status, and low levels typically indicate malnutrition. Numerous studies have investigated the relationship between preoperative serum albumin levels and perioperative complications. Hollenbeck and colleagues analyzed data from the National Surgical Quality Improvement Program (NSQIP) from 1991 to 2002 and found that patients with low preoperative serum albumin levels had higher postoperative complication rates and mortality after radical cystectomy and TURBT [22-23]. Johnson et al. [24] further retrospectively analyzed NSQIP data from 2005 to 2012 and found that low serum albumin level was a strong predictor of postoperative complications, with statistically significant results even when preoperative serum albumin level was studied as a continuous variable. In all these studies, malnutrition was considered the main cause of high postoperative complication rates, as malnourished patients have weakened defense mechanisms, leading to more frequent postoperative complications and rapid cancer progression. Therefore, low serum albumin level is often associated with poor survival. We believe that low preoperative serum albumin level not only represents malnutrition but also indicates weakened patient defense mechanisms, ultimately resulting in both poor short-term and long-term outcomes.

In addition to being a nutritional status indicator, serum albumin may also be related to inflammatory response mechanisms [25]. Many studies have explored the impact of inflammatory response on bladder cancer progression, and inflammatory markers such as C-reactive protein have been found to play important roles in cancer patient mortality [26-28]. Furthermore, some studies have found that cytokines released by tumors, such as interleukin-6 (IL-6), can block albumin synthesis pathways, while elevated tumor necrosis factor-alpha (TNF-) levels can selectively inhibit albumin gene expression, ultimately reduc-

ing serum albumin levels [29]. Inflammatory factor expression occurs through three important pathways: first, cancer tissue growth and invasion can cause inflammatory reactions in surrounding tissues, stimulating human immune cells to release inflammatory factors; second, cancer cells can independently synthesize inflammatory cytokines such as IL-1, IL-6, IL-8, TNF- α , and VEGF; finally, tumor blood supply insufficiency, necrosis, or hypoxia can also lead to increased cytokines. All three mechanisms can reduce albumin production and explain why low preoperative serum albumin level can be considered a marker of systemic inflammation and a poor prognostic indicator for cancer patient survival outcomes.

In summary, this study confirms that preoperative serum albumin level, age, Karnofsky score, and pathological T stage are all closely related to survival outcomes in NMIBC patients after TURBT. Considering the important role of preoperative serum albumin in evaluating patient nutritional status and immune response, we believe preoperative serum albumin level can be used for survival prognosis assessment in NMIBC patients undergoing TURBT. Patients with low preoperative serum albumin levels (i.e., serum albumin <40 g/L) should receive more aggressive treatment and follow-up protocols.

However, our study has several limitations. First, this was a single-center, small-sample retrospective study. Second, telephone follow-up was the primary method for survival tracking, making recall bias unavoidable. Finally, different surgeons' varying experience levels may have led to different surgical outcomes. Our conclusions require confirmation through additional multicenter, large-sample cohort studies.

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