Original Article

Pretreatment neutrophil-to-lymphocyte ratio predicts worse survival outcomes and advanced tumor staging in patients undergoing radical cystectomy for bladder cancer

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Abstract *Background:* An elevated neutrophil-to-lymphocyte ratio (NLR) has been associated with adverse outcomes in various malignancies. However, its role in prognosticating urothelial bladder cancer (UCB) is not fully validated.

Methods: We retrospectively reviewed 84 patients undergoing radical cystectomy (RC) for UCB from January 2002 to June 2012. NLR was computed (median: 5 days) prior to surgery. No patients received neoadjuvant chemotherapy. NLR was analyzed as a continuous variable and a cut-off point of 2.7 was obtained, with a statistical receiver operating characteristics of 0.74. Kaplan—Meier curves, multivariate Cox proportional hazard and logistics regression models were used to predict NLR association with survival outcomes.

Results: The median follow-up period was 30.1 months (range: 3.2—161.7) owing to high recurrence rate and subsequent mortalities, compared to the median 64.7 months in patients alive at the end of study period. NLR ≥ 2.7 was associated with worse survival outcomes (5-year disease-specific survival: 22% *vs* 58% p = 0.017 CI: 1.193—6.009; 5- year overall survival: 23% *vs* 60% p = 0.008 CI: 1.322—6.147). Furthermore, on multivariate analyses, higher NLR was independently associated with higher recurrence rate (p = 0.007, 6.999, 95% CI: 1.712—28.606), higher T staging (p = 0.021, HR = 3.49, 95% CI: 1.212—9.990) and lymph node involvement (p = 0.009, HR = 4.534, 95% CI: 1.465—14.034).

Conclusion: This study suggests that NLR can be an inexpensive novel factor for patients risk stratification pre-operatively. This improves patient counseling and identifies patients who may benefit from multimodal treatment.

1. Introduction

Radical cystectomy (RC) with pelvic lymph node dissection (PLND) remains the standard treatment for muscle-invasive urothelial cancer of the bladder (UCB) [1,2], and a strong recommendation for patients with non-muscle-invasive disease with high risk of progression [3]. However, despite such aggressive curative surgeries, survival remained dismal over the decades [4]. Approximately 50% of patients will eventually develop recurrence or metastasis [5], and 5-year survival ranges from 26% to 64% [1,6].

Adding to the challenge in managing UCB is the lack of pre-operative risk stratification. While most predictive models are based on pathological data, this information is insufficient to provide detailed prognosis for pre-operative decision making [7,8]. Upstaging of RC on final histology was reported as high as 50% [9]. Given the high recurrence rate and surgical morbidities, newer prognostic factors should be considered to provide a better risk stratification for more informed patient counseling and patient selection for surgery.

On the other hand, there has been increasing evidence supporting the role of inflammation in cancer development and progression [10], and the neutrophil-to-lymphocyte ratio (NLR) has been identified as a marker of tumor activity [11]. A higher NLR has been associated with poorer disease specific and overall survival in gastric, hepatic, non-small cell and cervical cancer [12–14]. This evidence can be relevant in prognosticating UCB, given that inflammation appears to be an important role in the pathogenesis and progression of UCB [10].

Through this paper, we aim to determine the prognostic value of NLR in patients undergoing radical cystectomy for UCB, in particularly looking at the disease specific survival, overall survival and recurrence rate. This will allow us to better identify more suitable candidates for RC or other neoadjuvant or adjuvant therapies.

2. Materials and methods

Following Institutional Review Board approval (CIRB reference number: 2009/1027/D), we retrospectively reviewed our institutional database and identified 108 patients that underwent RC for UCB, between January 2002 to June 2012. Eight patients were excluded from the studies due to incomplete datasets. Given the small number and heterogeneity of neoadjuvant chemotherapeutic drugs and regimes, we excluded 16 patients who received neoadjuvant treatments prior to the definitive surgeries. All patients had histological proven UCB via transurethral resection of bladder tumor (TURBT). We have excluded patients who underwent surgeries for UCB after June 2012 due to the short subsequent follow-up time, which will affect the interpretation of the survival outcomes and recurrence rates.

All patients had undergone staging scans with computed tomographies of the thorax, abdomen and pelvis to confirm the extent of disease. Magnetic resonance imagings were used as adjunct as deemed necessary by the surgeons.

Hematological and biochemical blood results were collected at a median of 5 days (range 1–16) prior to operation. All patients were cleared of any infection or active inflammation at the time of examination. We defined leukocytosis as total white blood cell counts $\geq 12 \times 10^9$/L, anemia as hemoglobin <12.5 g/dL for women and <13.5 g/dL for men. NLR was analyzed as a continuous variable and a cut-off point of 2.7 was obtained, with a statistical receiver operating characteristics (ROC) of 0.74 (Area under curve).

3. Outcome measures

All patients underwent RC and bilateral standard pelvic lymphadenectomies and achieve clear margins on final histology. Post-operatively, all patients were reviewed outpatient within 4 weeks after discharge. Given the retrospective nature of this study, follow-ups were not consistently standardized. However, in our institution's follow-up protocol, we recommended quarterly for the first 2 years post-operatively, semiannually for the subsequent 3 years and yearly follow-ups onwards. Evaluations included history and physical examination, urine cytology, repeated computed tomography scans of the thorax, abdomen and pelvis and cystoscopies to monitor for disease recurrence. Primary outcomes were disease-specific and overall survivals, and secondary outcome was recurrence rate. The time to recurrence, disease-specific and overall survivals were measured from the time of RC.

Statistical analyses were performed using IBM SPSS Statistics 20.0. The relationship between clinicopathological features and preoperative NLR was calculated with chi-square and Wilcoxon tests as appropriate. Survival curves were measured using Kaplan–Meier, with comparisons between patients with NLR <2.7 and ≥ 2.7 performed using log rank test. Univariate and multivariate Cox proportional hazard regression models were used to find associations between NLR and survival outcomes, after adjusting for clinicopathologic factors. Univariate and multivariate logistic regression models were used to predict recurrence rate. All tests were two-sided with $p < 0.05$ considered to be statistically significant.