



The Prognostic Value of Neutrophil-to-lymphocyte Ratio in Bladder Cancer

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Abstract

In the last decade, cumulative evidence suggests that systemic inflammation is closely related to oncologic outcomes in patients with cancer. This has been demonstrated by a strong correlation between the degree of systemic inflammatory response and poor oncologic outcomes in a variety of malignancies. Several systemic inflammatory markers have been studied and, of those, neutrophil-to-lymphocyte ratio (NLR) is one of the most widely used inflammatory markers. Although elevated pretreatment NLR has been reported as a useful marker associated with poor oncologic outcome in many cancers, its prognostic value in bladder cancer remains inconsistent. Therefore, this study was designed to evaluate the prognostic significance of NLR in patients with bladder cancer by reviewing published studies.

Keywords: Neutrophil-to-lymphocyte Ratio; Systemic inflammation; Bladder cancer

Introduction

There is a large amount of evidence that the host inflammatory response plays an important role in the development and progression of cancer [1-3]. In particular, the systemic inflammatory response, which is measured by surrogate blood-based parameters such as C-reactive protein or circulating inflammatory blood cells, plays an important role in the progression of various solid tumors [4-6]. Among these markers of systemic inflammatory response, neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the neutrophil count by the lymphocyte count, has recently gained considerable attention as a biomarker in a variety of malignancies. In recent years several studies have shown that elevated NLR has a prognostic value in patients with various localized and advanced cancers, including gastrointestinal, liver, lung, breast, ovaries, and urological cancers [4,5,7-11]. In the case of bladder cancer, there are conflicting evidences as to the prognostic value of NLR in patients with localized or metastatic disease receiving chemotherapy.

In this paper, we conducted a review of publications which evaluated the usefulness of NLR in relation to oncologic outcomes in bladder cancer.

NLR

NLR is a widely available marker obtained from peripheral complete blood cell counts because cell separation has been widely applied. Although the exact mechanisms behind the poor prognostic impact of an elevated NLR remain to be clarified, this association may relate to increased neutrophil-dependent inflammation and decreased lymphocyte-mediated tumor response [12,13]. Neutrophils have been shown to contribute to enhanced angiogenesis and tumor cell intravasation. In addition, circulating neutrophils have been found to produce inflammatory mediators, such as tumor necrosis factor and interleukin, which promote tumor cell proliferation and angiogenesis [14,15]. Lymphocytes are involved in cytotoxic cell death and cytokine production, which inhibits proliferation and metastasis of tumor cells [16]. The presence of lymphocytes in a tumor is associated with better responses to cytotoxic treatment and a more favorable prognosis in cancer patients [17]. NLR reflects the balance between innate (neutrophils) and adaptive (lymphocytes) immune responses. Although it seems that several leukocyte parameters from peripheral blood (e.g, neutrophil, lymphocyte, and total leukocyte counts) are linked with poor oncologic outcomes [18,19], NLR has been demonstrated to be superior to other markers. For example, it was the best predictor of short- and long-term mortality in breast cancer patients [11]. Based on the background information described above, the prognostic value of NLR has also been demonstrated in urologic cancers including prostate cancer, kidney cancer, and urothelial cancer in bladder or upper urinary tract [4,9,13,20-33].

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Table 1: Clinical studies on the prognostic value of NLR in non-metastatic bladder cancer.

Author	Year	Patients No.	Cut-off value	Treatment	Conclusion
Gondo et al.[32]	2012	189	2.5	RC	Elevated NLR (>2.5) was associated with CSS
Demirtas et al.[34]	2013	201	2.5	RC	Elevated NLR (>2.5) was not associated with OS
Krane et al.[31]	2013	68	2.5	RC	Elevated NLR (≥ 2.5) was associated with OS, CSS, and extravesical disease.
Hermanns et al.[30]	2014	424	3.0	RC	Elevated NLR (>3.0) was associated with pathological advanced disease. Elevated NLR (>3.0) was associated with OS, CSS, and RFS
Potretzke et al.[29]	2014	102	continuous	RC	Elevated NLR was associated with pathological upstaging after RC
Viers et al.[28]	2014	899	2.7	RC	Elevated NLR (≥ 2.7) was associated with adverse pathologic finding Elevated NLR (≥ 2.6) was associated with OS, CSS, and RFS
Mano et al.[25]	2015	107	2.41 (for PFS) 2.43 (for RFS)	TURB	Elevated NLR (>2.41) showed more pT1 tumors and was associated with PFS Elevated NLR (>2.43) was associated with RFS
Kang et al.[35]	2015	385	2.1 (preoperative) 2.0 (postoperative)	RC	Elevated NLR (postoperative ≥ 2.0) was associated with OS and CSS Perioperative elevated NLR (2.1 \rightarrow 2.0) was associated with OS and CSS
Morizawa et al.[36]	2016	110	2.6	RC	Elevated NLR (≥ 2.6) was associated with OS, CSS, and RFS

NLR: Neutrophil-To-Lymphocyte Ratio; TURB: Transurethral Resection of Bladder Tumor; RC: Radical Cystectomy; OS: Overall Survival; CSS: Cancer-Specific Survival; RFS: Recurrence-Free Survival; PFS: Progression-Free Survival

NLR in Non-Metastatic and Localized Bladder Cancer

Recently, several studies suggested that elevated NLR can be an independent prognostic factor in non-metastatic bladder cancer for a variety of poor oncological outcomes including adverse pathologic features, recurrence, progression and survival after surgical treatment (Table 1). Although one study reported no significant association between elevated NLR and OS [34], most studies have demonstrated that it is an independent prognostic factor predicting recurrence-free survival (RFS), progression-free survival (PFS), overall survival (OS), and cancer-specific survival (CSS) [25,28-32,35,36]. Most studies have shown that NLR has a prognostic value in the preoperative setting. A very recent study showed that not only preoperative NLR but also early postoperative NLR can be a valuable predictor of oncologic outcomes in patients who underwent radical cystectomy for bladder cancer [35]. Above mentioned studies on the prognostic value of NLR have been focused on patients with muscle invasive tumor following radical cystectomy. These studies demonstrated a significant association between an elevated NLR and poor oncologic outcomes as well as adverse pathologic features including larger tumor size, pathological upstaging to pT3 disease, and lymph node involvement after radical cystectomy [28-32,35,36]. Interestingly, one recent study reported that elevated preoperative NLR was associated with more pT1 tumors after transurethral resection of bladder tumor and was a prognostic factor predicting recurrence and disease progression [25].

Table 2: Clinical studies on the prognostic value of NLR in metastatic and advanced bladder cancer.

Author	Year	Patients No.	Cut-off value	Chemotherapy	Conclusion
Bambury et al.[27]	2015	129	continuous	Pemetrexed (2nd)	Elevated NLR was associated with OS
Rossi et al.[24]	2015	292	3.0	Platinum based and others	Elevated NLR (>3.0) during chemotherapy is associated with OS and PFS
Santoni et al.[23]	2015	298	3.0	Platinum based and others	Decreased NLR (≤ 3.0) was associated with OS and PFS
Taguchi et al.[22]	2015	185	3.0	Platinum based and others	Elevated NLR (≥ 3.0) was associated with OS and CSS

NLR: Neutrophil-To-Lymphocyte Ratio; OS: Overall Survival; CSS: Cancer-Specific Survival; PFS: Progression-Free Survival

NLR in Metastatic and Advanced Bladder Cancer

As above mentioned, the prognostic value of NLR in patients with bladder cancer following radical cystectomy has been demonstrated in several studies. However, few studies investigated the usefulness of NLR as a prognostic factor for oncological outcomes in patients with advanced or metastatic bladder cancer treated with chemotherapy. Four studies recently reported the use of the NLR in predicting survival and response in patients receiving chemotherapy in this setting [22-24,27]. One study reported that significantly decreased NLR was associated with OS and PFS [23], whereas the remaining 3 studies have demonstrated that elevated NLR was an independent predictor of poor oncologic outcomes in terms of PFS, OS and CSS [22,24,27]. Most studies in bladder cancer treated with chemotherapy have also shown that NLR has a prognostic value in the pre-therapy setting [22,23,27]. However, one study reported that a persistently elevated NLR during chemotherapy is an independent predictive factor for patients with advanced urothelial cancer [24]. In that study, the pre-therapy NLR was not a predictor of PFS but only of OS, whereas the follow-up NLR was a predictor of both PFS and OS.

Conclusion

Elevated NLR is significantly associated with poor oncologic outcomes in terms of recurrence, clinical progression, and death in patients with bladder cancer. The NLR is a potentially valuable marker

for future risk assessment of disease and counseling of patients with bladder cancer. However, there is no uniform cut-off value for the general population or for a specific condition including bladder cancer. In addition, it is not yet clear as to the best time (e.g., pre- or post- or during treatment) to measure the NLR for the accurate prediction of oncological outcomes. To facilitate the utilization of NLR for predicting oncologic outcomes of bladder cancer in clinical practice, further prospective studies with larger populations are needed.

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