Research article

Preoperative neutrophil to lymphocyte ratio can improve disease progression prediction of non-muscle invasive bladder cancer

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Abstract

The purpose of this study was prospectively evaluate the ability of Neutrophil-to-Lymphocyte ratio (NLR) to predict disease progression in patients with non-muscle invasive bladder cancer (NMIBC). This is a continuation of our previous retrospective study that indicated the significance of NLR $>$ 2.5 criterion as a predictor of progression in patients with NMIBC. Since December 2013, all patients admitted to Bnai-Zion department for TUR-BT and agreed to participate in the study, had blood analyses for cell count and differential 24hr prior to surgery. Patients with pathological NMIBC were followed prospectively for disease progression. The end-point of the follow up was either a disease progression or the termination of the study. Kaplan-Meier curves and Cox regression were performed to assess the predictive ability of NLR $>$ 2.5 for disease progression. Our results demonstrate a significant difference ($p = 0.02$) in mean progression-free survival – (35.9 months vs 41.1 months) in the whole cohort Kaplan-Meier survival plot factored by NLR $>$ 2.5. Mean progression-free survival of NLR $>$ 2.5 stratified by stage, grade and treatment (sub-group analysis), showed statistical significance ($p = 0.035$) for those treated with intra-vesical instillation, and demonstrated a persistent trend for the rest of the stratifications - revealing that the NLR $>$ 2.5 groups always fared worse than the NLR $<$ 2.5 groups. In a univariate analysis, whole cohort Cox regression analysis for disease progression, NLR $>$ 2.5 was found significant ($p = 0.05$; HR 7.8; CI 1–61), indicating that the probability of progression is increased at least 7-fold for a person with a NLR $>$ 2.5 compared with those with NLR $<$ 2.5. In conclusion, NLR $>$ 2.5 was found to be a significant predictor of disease progression and demonstrated high hazard ratio and worse progression-free survival in patients with NMIBC, especially in those treated with intra-vesical instillation. We propose to consider the incorporation of NLR $>$ 2.5 in the next revisions of the European Organization for Research and Treatment of Cancer (EORTC) scores, given more widely available evidence.

Keywords

Neutrophil-lymphocyte ratio; NLR; NMIBC; Urothelial carcinoma; Recurrence; Bladder cancer

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1. Introduction

Bladder cancer is the most common malignancy of the urinary tract, and the 4th most common cancer in males in developed countries [1]. Upon diagnosis, the majority (∼75%) of patients with bladder cancer present with non-muscle invasive disease (NMIBC), which by definition includes the Tis, Ta and T1 pathologic stages [2]. As such, NMIBC represents a heterogeneous group of tumors with different rates of recurrence, progression and disease-related mortality. Consequently, each subgroup of NMIBC should be followed up and treated differently [3]. The main concern during treatment of NMIBC is progression to a muscle invasive stage (T2), which markedly worsens prognosis [4]. To prevent this scenario, clinical and pathological factors are commonly used to stratify patients into different risk groups. These methods, such as the EORTC (European Organization for Research and Treatment of Cancer) Risk Tables, help physicians predict the probability of progression and recurrence, and ultimately – facilitate the decision of the treatment of choice [3, 5].

However, these grouping systems are far from optimal and raise critical questions: would a probability of recurrence of 35% per year justify an aggressive treatment? Is a 15% chance of progression per one year a sufficient reason to perform a cystectomy [5]? Thus, we still lack a strong prognostic factor that could help predict the patient's specific risk rather than the group-specific risk of recurrence and progression. According to recent studies cited below, the state of the systemic inflammatory response triggered by the tumor microenvironment, alters acute phase reactants and hematologic components-including changes in serum neutrophil and lymphocyte counts, leading to relative neutrophilia and lymphocytopenia. This state of elevated Neutrophil-Lymphocyte ratio (NLR) is associated with worse disease-free and overall survival in a variety of distinct malignancies [6–8].

Among patients with bladder cancer, an elevated NLR was associated with advanced stage, increased mortality, and decreased overall survival in patients with muscle-invasive disease [9–11], along

with higher risk of recurrence and progression in NMIBC [12, 13]. Specifically, in both our retrospective studies which employed different methods of analysis, NLR $>$ 2.5 was found to be a significant predictor of recurrence and progression [12, 13]. Based on these results, and in addition to the fact that prospective data regarding the role of NLR in predicting disease recurrence and progression in NMIBC is scarce, the aim of the current study was to prospectively evaluate the role of NLR $>$ 2.5 as a predictor of disease progression in patients with primary NMIBC.

2. Materials and Methods

2.1. Study design and procedures

This was a single center, prospective cohort study. Recruited patients were pathologically confirmed to harbor non-invasive BC stages – Ta, T1 and Tis, after undergoing trans-urethral resection of bladder tumor (TUR-BT). Tumors were graded and staged according to the 2004 WHO grading system [14]. Pre-operative NLR was recorded using the admission's (usually 24 hr prior to surgery) complete blood count (CBC) with differential. Follow up invitations were sent out every three months for urine cytology, upper tract imaging, cystoscopy and treatment based on the American Urological Association (AUA) guidelines [15], which were either 'No Treatment', 'Mitomycin C (MMC)' or 'Bacillus Calmette–Guérin (BCG)' intra-vesical treatments. We point out that given the nature of a prospective study design, an intervention that might affect the variables is not desirable, and hence the treatment was chosen solely according to best practice guidelines and not according to our assumption that NLR may play a role. The end-point of the follow up was either a disease progression or the termination of the study. Disease progression was defined according to the International Bladder Cancer Group consensus definition for progression in NMIBC, in the presence of an increase in T category from CIS or Ta to T1 (lamina propria invasion), development of $\geq$ T2 or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high [16]. Some degree of non-compliance to the follow up and treatment was expected, and so the last date of follow-up was recorded for missing and deceased patients. This study was based on the principles of Helsinki and was approved by the institutional review board.

2.2. Objectives

A primary objective of the current study was to evaluate the ability of NLR $>$ 2.5 to predict NMIBC progression after trans-urethral resection of bladder tumor (TUR-BT). Secondary objectives were to evaluate the effect of NLR $>$ 2.5 on disease progression, when stratified by different variables including the pathologic Grade (high and low), Stage (Ta, T1) and the Intra-Vesical Treatment (Yes or No). These objectives were set in advance, and were meant to test the hypothesis that a prediction of disease progression by NLR $>$ 2.5 can be produced prospectively, and not only retrospectively [12, 13].

2.3. Participants

Eligible patients were $\geq$ 18 years with pathologically confirmed NMIBC who underwent TUR-BT since December 2013. An inclusive approach was taken in order to examine broad and general effect of NLR, not only on some naïve or carefully chosen groups. Key exclusion criteria were: T2 Stage, hematologic malignancies, acute infections, and patients without preoperative NLR. All pathological grades were included.

2.4. Statistical Analysis

Clinical features between groups were evaluated using the chi-square test. Disease progression was treated as time-dependent variable, and estimated rates were calculated using the Kaplan-Meier method and compared using the log-rank test. The analysis was first performed for the whole cohort, and next stratified by Stage groups (Ta or T1), Grade groups (Low Grade, High Grade) and Treatment Groups (received intravesical treatment, or did not receive treatment). Next, a multivariate Cox regression analysis was performed to account for covariance with the other significant variables (Stage & Grade) and confirm whether the NLR $>$ 2.5 is truly significant. The results are presented as hazard ratios along with their 95% confidence intervals. A 2-sided p value of $<$ 0.05 was considered statistically significant. Data were analyzed using IBM SPSS v25.0.

3. Results

Between December 2013 and October 2016, 113 patients were recruited to the study. The cohort included 96 men and 17 women with a median age of 72 years (IQR 63, 81) with a confirmed pathological diagnosis of NMIBC. Only 11 patients (10%) had a disease progression during the study, occurring at a median time of 8 months (IQR 6, 11), while the median follow-up time for patients without disease progression was 13 months (IQR 7, 20).

The median NLR was 2.69 (IQR 1.9, 4.35) including 67 patients (59%) who have had NLR $>$ 2.5. Table 1 shows an analysis of differences in clinical features between groups divided by progression. Table 2 shows an analysis of differences in clinical features between groups divided by NLR-2.5.

Similar to our retrospective study, NLR ($>$ 2.5) was correlated significantly with disease progression ($p = 0.025$) but also with age (69 vs 77 years, $p = 0.001$), and stage ($p = 0.016$). When stratifying the correlation between NLR $>$ 2.5 and disease progression by treatment (i.e. received or did not receive intra-vesical treatment), NLR correlates specifically with the treated group ($p = 0.042$).

A significant p-value correlation with CIS was found but is irrelevant as only 3 patients had a primary CIS. There's a discrepancy between the literature and our data regarding the known incidence rates of concomitant CIS. A possible explanation can either be attributed to chance, or the notion that many patients with concomitant CIS are diagnosed already in T2 stage, and thus were not included in this study.

Whole cohort Kaplan-Meier survival plot factored by NLR $>$ 2.5 was then performed and showed a significant difference ($p =$ 0.02) in mean progression-free survival-(35.9 months vs 41.1 months, Fig. 1). Mean progression-free survival of NLR $>$ 2.5 stratified by stage, grade and treatment (sub-group analysis), showed statistical significance ($p = 0.035$) for the 'treatment' group only, though a persistent trend was demonstrated for the rest of the stratifications in overall comparisons-Stage ($p = 0.067$), Grade ($p = 0.054$), in the sense that the NLR $>$ 2.5 groups always fared worse than the NLR $<$ 2.5 groups–i.e. shorter time to disease progression. We believe that given a larger cohort per sub-groups such as treatment type or pathological stage, a statistical significance is probable (Fig. 2-4).

In a univariate analysis, whole cohort NLR2.5 Cox regression for disease progression, NLR $>$ 2.5 was found significant ($p = 0.05$)

Table 1. Patient and tumor characteristics of the study cohort stratified by disease progression

		Patient Groups						p-Value
		No Disease Progression			Disease Progression			
		Count	Row %	Median (IQR)	Count	Row %	Median (IQR)	
Age		102	90.3%	72 (63, 80)	11	9.7%	83 (73, 87)	0.077
Sex	Female	16	94.1%		1	5.9%		0.561
	Male	86	89.6%		10	10.4%		
Grade	1	73	94.8%		4	5.2%		0.019
	2	1	50.0%		1	50.0%		
	3	28	82.4%		6	17.6%		
Stage	Ta	77	93.9%		5	6.1%		0.034
	T1	25	80.6%		6	19.4%		
CIS	No	99	90.0%		11	10.0%		0.564
	Yes	3	100.0%		0	0.0%		
Number of Tumors	Single Tumor	31	88.6%		4	11.4%		0.684
	2-7 Tumors	71	91.0%		7	9.0%		
	8 or More	0	0.0%		0	0.0%		
Tumor Diameter	<30 mm	68	89.5%		8	10.5%		0.684
	30 mm or more	34	91.9%		3	8.1%		
Past TCC	No	71	88.8%		9	11.3%		0.397
	Yes	31	93.9%		2	6.1%		
WBC		102	90.3%	7.8 (6.75, 9.87)	11	9.7%	8.0 (5.69, 9.41)	0.370
NLR		102	90.3%	2.63 (1.86, 4.5)	11	9.7%	2.83 (2.60, 2.67)	0.627
NLR 2.5	Below 2.5	45	97.8%		1	2.2%		0.025
	Above 2.5	57	85.1%		10	14.9%		
Treatment	No Treatment	38	86.4%		6	13.6%		0.264
	Intra-Vesical Treatment	64	92.8%		5	7.2%		

Table 2. Patient and tumor characteristics of the study cohort stratified by neutrophil-to-lymphocyte ratio (NLR)

		Patient Groups						*p*-Value
		Below 2.5			Above 2.5			
		Count	Row %	Median (IQR)	Count	Row N %	Median (IQR)	
Age		46	40.7%	69 (59, 75)	67	59.3%	77 (70, 83)	0.001
Disease Progression	No	45	44.1%		57	55.9%		0.025
	Yes	1	9.1%		10	90.9%		
Sex	Female	6	35.3%		11	64.7%		0.622
	Male	40	41.7%		56	58.3%		
Grade	1	34	44.2%		43	55.8%		0.339
	2	0	0.0%		2	100.0%		
	3	12	35.3%		22	64.7%		
Stage	Ta	39	47.6%		43	52.4%		0.016
	T1	7	22.6%		24	77.4%		
CIS	No	43	39.1%		67	60.9%		0.034
	Yes	3	100.0%		0	0.0%		
Number of Tumors	Single Tumor	13	37.1%		22	62.9%		0.605
	2-7 Tumors	33	42.3%		45	57.7%		
	8 or More	0	0.0%		0	0.0%		
Tumor Diameter	<30mm	30	39.5%		46	60.5%		0.702
	30mm or more	16	43.2%		21	56.8%		
Past TCC	No	31	38.8%		49	61.3%		0.509
	Yes	15	45.5%		18	54.5%		
WBC		46	40.7%	7.59 (6.26, 8.6)	67	59.3%	8.86 (6.94, 10.5)	0.013
Treatment	No Treatment	16	36.4%		28	63.6%		0.453
	Intra-Vesical Treatment	30	43.5%		39	56.5%		

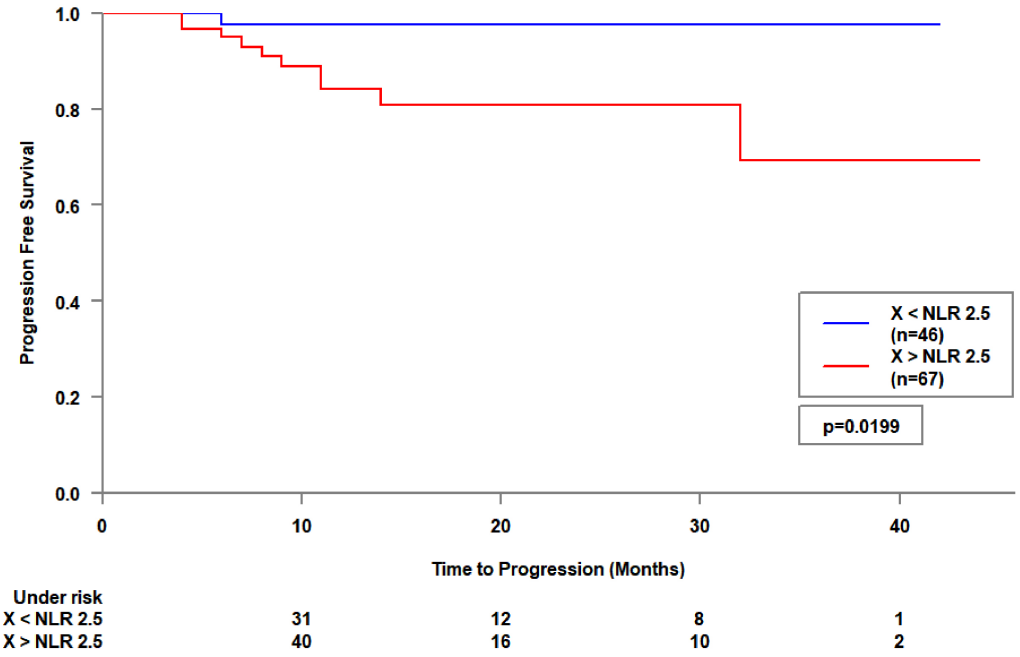

Fig. 1. Whole cohort survival analysis, Kaplan-Meier estimates of progression-free survival stratified NLR 2.5.

with Hazard ratio of 7.8 (CI 1–61), indicating that the probability of recurrence is increased at least 7-fold for a patient with NLR $>$ 2.5, compared with NLR $<$ 2.5 in this whole cohort analysis.

A multivariate Cox model (backwards, conditional) was then performed to account for covariance with Stage and Grade. While NLR $>$ 2.5 was not found significant ($p = 0.059$) in this model, it is by a narrow margin, and is attributed to the small number of patients in the 'disease progression' group. Stage is entirely removed from the regression model, whereas the Grade is retained ($p = 0.046$, HR 1.8, CI 1.011 – 3.458).

4. Discussion

The main advantage of this study is its prospective nature, which to the best of our knowledge, is one of the few to deal with NLR as a predictor for NMIBC. Upon diagnosis, NMIBC is initially treated with complete TUR-BT, after which an adjuvant therapy is considered. Based on clinical and pathological factors, patients can be assigned to risk groups, such as the EORTC Score for the assessment of disease recurrence and progression [5]. However, these predictive tools are far from optimal for the individual patient, and raise the key questions: what is the progression probability cutoff that justifies cystectomy? How aggressive an intra-vesical treatment should be with a 35% risk of recurrence per year? To be able to answer these questions in a more evidence-based manner, new and novel predictors are a necessity.

In the current study, we prospectively assessed the predictive value of an isolated NLR value in a group of NMIBC patients. The main finding for the whole cohort includes a statistically significant association between high NLR ($>$ 2.5) and increased probability of progression, especially among patients that have been treated with an intra-vesical treatment (BCG or MMC) – a finding that manifests in shorter time to disease progression. This was demonstrated both when treating progression as an outcome, or as a time-dependent variable. In addition, high NLR was consistently found to be associated with worse outcomes in all sub-groups (Stage, Grade, and Treatment) although significance was demonstrated only for the treatment sub-group. We believe that given a larger cohort per sub-group, a statistical significance is probable. Nevertheless, the trend is clear– patients with higher NLR presented with worse progression-free survival in each stratification.

It is important to point out that the current gold-standard for disease progression prediction are the EORTC risk tables, which were never designed to be used when intra-vesical treatment with BCG is chosen, as was clearly stated in the published EORTC guidelines [5]. This limitation of the EORTC signifies our finding that NLR $>$2.5 is specifically significant for the 'Treatment' subgroup, that includes the BCG intra-vesical treatment. The Spanish CUETO scoring model does account for the BCG instillation treatment, but similarly does not account for any inflammatory or hematologic marker like NLR that can potentially benefit it.

While the pathophysiology is not yet clear, it has been suggested that the relative neutrophilia increases the number of inflammatory markers that include pro-angiogenic factors (VEGF), growth factors (CXCL8), proteases and anti-apoptotic markers (NF-kB) – all of which support tumor growth and progression. In addition, the lymphocytopenia is suggested to repress cell-mediated immune response, thus worsening the prognosis [17].

Pretreatment NLR is readily available, and higher values have been shown to correlate with higher stage tumors and adverse treatment outcomes in a wide variety of cancers including malignancies of the gastrointestinal and genitourinary tracts, including urothelial carcinoma of the bladder [6, 7, 12, 13].

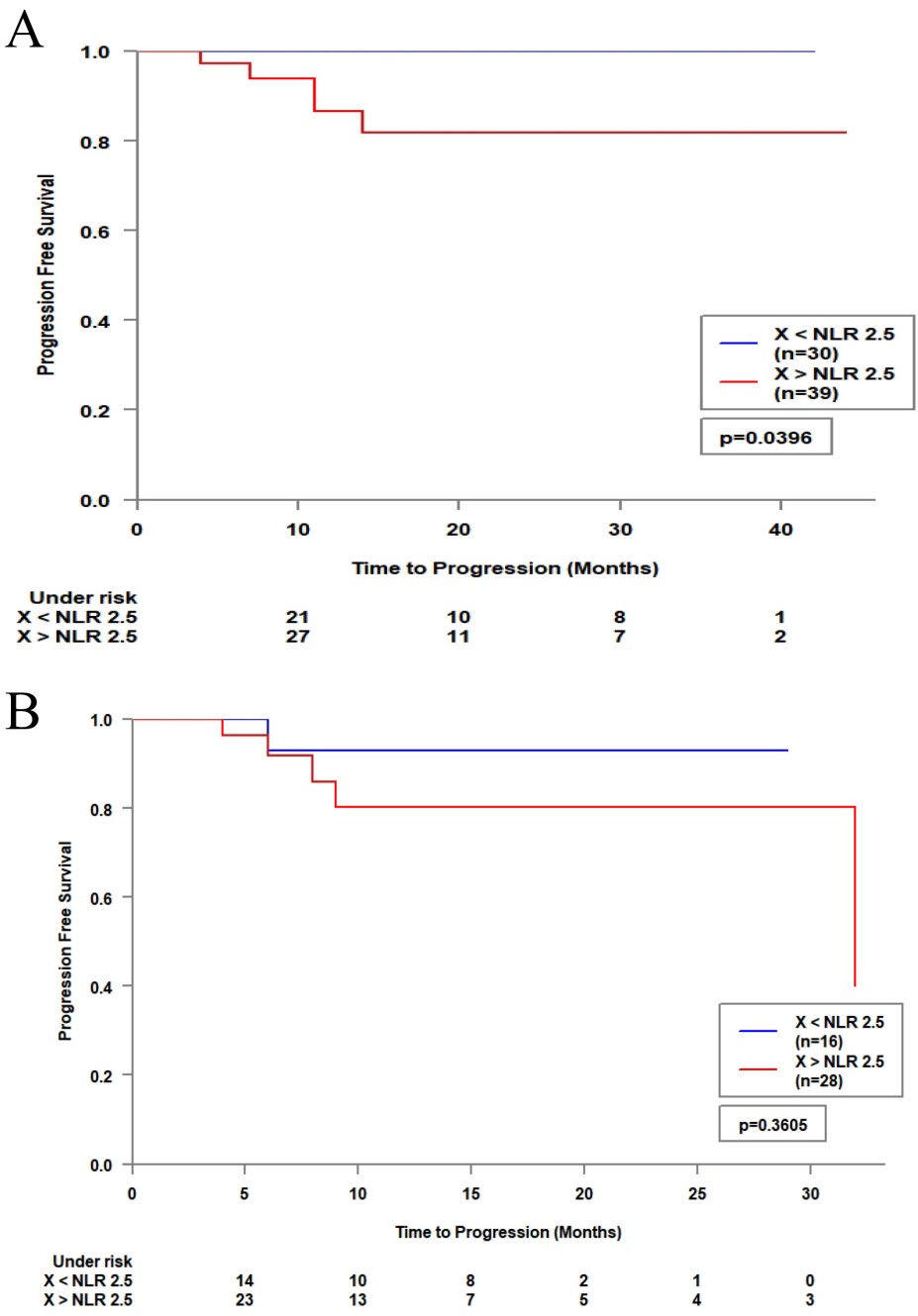

Fig. 2. Survival analysis for treatment sub-groups. (A) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for those treated with intra-vesical treatment. (B) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for untreated patients. Overall comparisons between subgroups: $p = 0.035$.

Focusing on bladder cancer, several previous studies have evaluated the predictive value of NLR, most of which were conducted on patients undergoing radical cystectomy [9, 18–20]. Based on these studies, NLR may be used in the pre-operative setting to predict tumor invasiveness, or in the post-operative setting, together with pathologic tumor characteristics, to predict outcome. Can et al., found a correlation between muscle invasive disease in TUR-BT specimens and preoperative NLR > 2.57, patient age, female gender and platelet count, and suggested using NLR > 2.57 in a risk formula which may assist in deciding which patients may benefit from early cystectomy [18]. Similarly, Krane et al., found that patients with a NLR > 2.5 had a significantly higher likelihood of extravesical disease at radical cystectomy, suggesting that they may benefit from neoadjuvant chemotherapy [21]. Finally, Viers et al., found an association between higher pre-operative NLR and significantly increased risk of extravesical tumor extension and lymph node involvement, in a large group of bladder cancer patients undergoing radical cystectomy [9].

To date, only two prospective studies on the matter have been published, after initiation of the current study. Favilla *et al.*, fur-

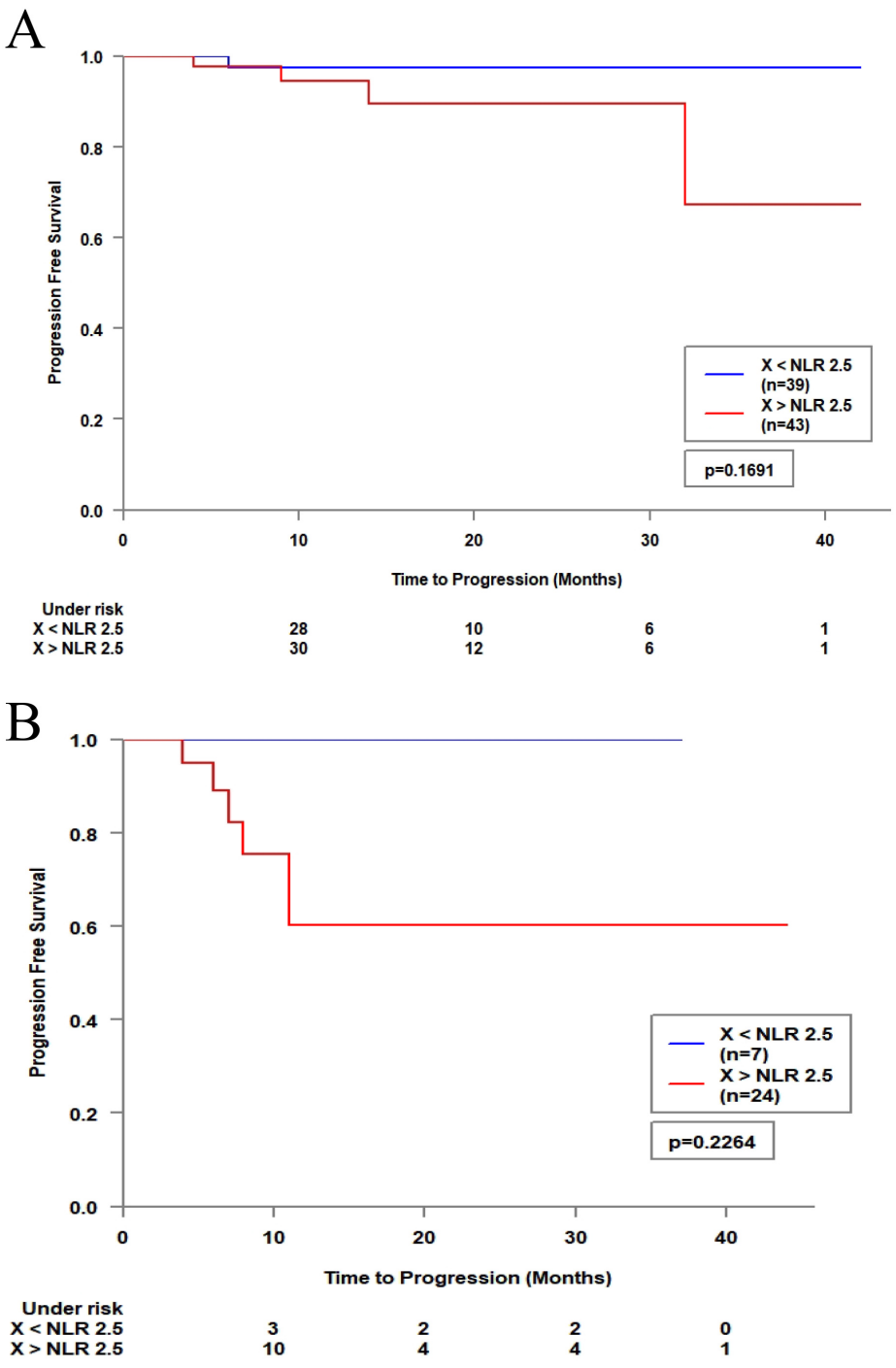

Fig. 3. Survival analysis for stage sub-groups. (A) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for Ta stage disease. (B) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for T1 stage disease. Overall comparisons between subgroups: $p = 0.067$.

ther established the predictive value of NLR on recurrence and progression but used NLR $>$ 3 as the cutoff [22]. Sebahattin et al., argued that correction for age might alter the results, so an analysis of covariance was performed (ANCOVA) to test whether age would significantly affect the relationship between NLR $>$ 2.5 and disease progression. For our data, age was not found significant ($p =$ 0.297) [23].

A prominent limitation dealing with the NLR marker is the volatility of the Neutrophil and Lymphocyte counts. While we did actively exclude patients with hematologic malignancies and with active infections, it is possible that some chronic medications or antibiotics affect the NLR value. An argument can be made that this approach might skew results, but as mentioned in the 'Materials and Methods' section – we strived to examine the effect of NLR on as many patients as possible, with the intention to generalize, and not marginalize, the utility of NLR. We believe that the inclusive cohort in this study (i.e. including a small number of possible antibiotic users) can be regarded more like a hurdle rather than a helpful

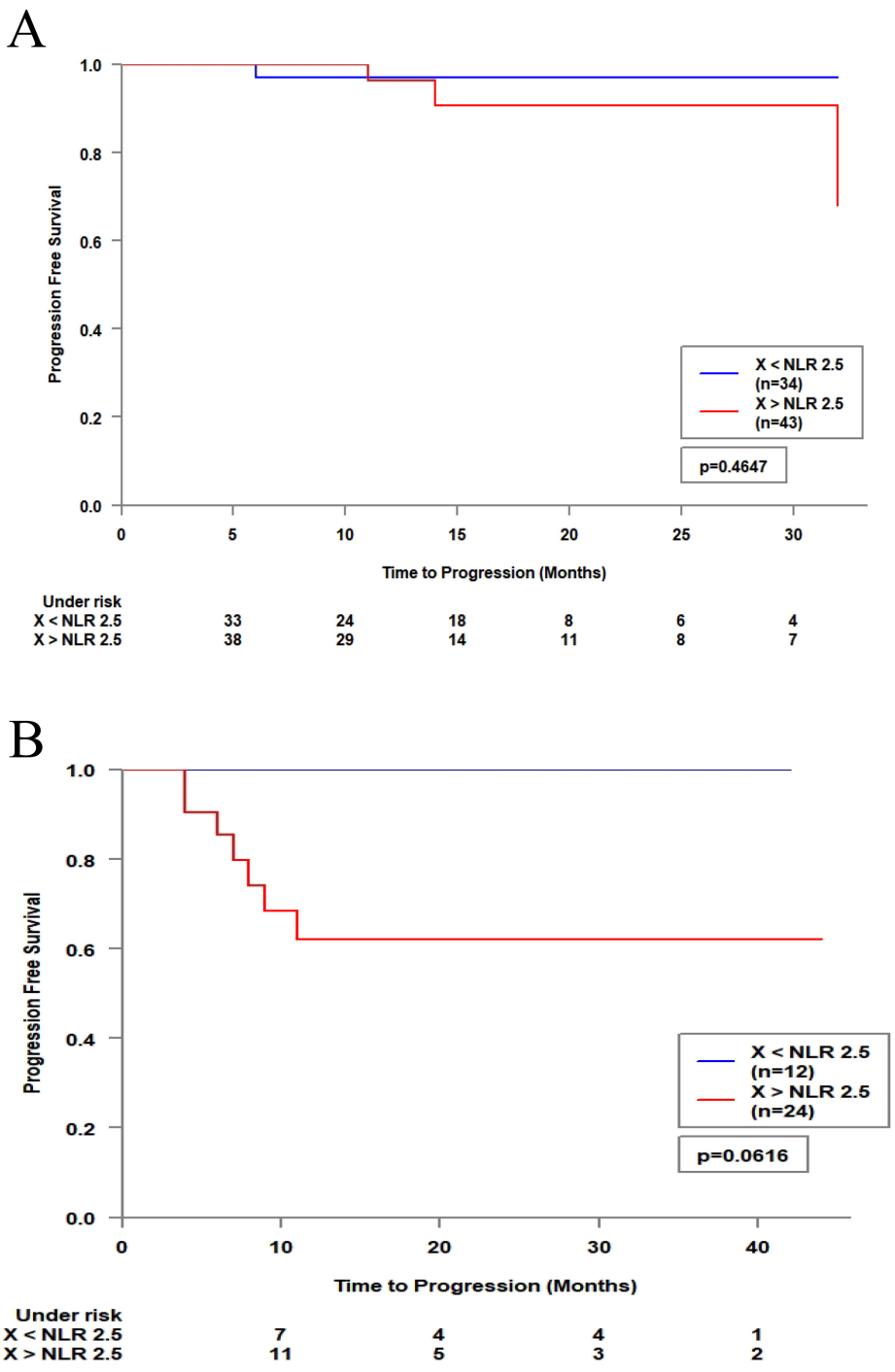

Fig. 4. Survival analysis for grade sub-groups. (A) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for low grade disease. (B) Kaplan-Meier estimates of progression-free survival stratified by NLR 2.5 for high grade disease. Overall comparisons between subgroups: $p = 0.054$.

measure, and thus the results are more meaningful. Evidence to this claim can be found in our previous publication, which dealt with a much more 'distilled' cohort [13].

5. Conclusions

NLR $>$ 2.5 was found to be a significant predictor of disease progression and demonstrated high hazard ratio and worse progression-free survival in patients with NMIBC, especially in those treated with an intra-vesical treatment. We propose to consider the incorporation of NLR $>$ 2.5 in the next revisions of the EORTC score, given more widely available evidence.

Acknowledgments

None.

Conflict of Interest

All authors declare no conflict of interest.

Statement of Human Rights

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The Study approved by the Bnai Zion Medical center Helsinki committee and the ministry of Health of Israel, Registry Number: 0049-10-BNZ

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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