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ORIGINAL ARTICLE

The prognostic value of the neutrophil-to-lymphocyte ratio in patients with testicular cancer

La valeur pronostique du rapport neutrophiles/lymphocytes chez les patients atteints de cancer des testicules

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Testicular cancer;
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Tumor marker;
Liquid biopsy

Abstract
Objectives. — To evaluate the potential prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in testicular cancer.
Materials and methods. — 80 patients with testicular cancer treated at our institution from 2005 to 2018 were retrospectively reviewed. Age, tumor markers, stage and histotype at final pathology, eventual medical treatment, tumor recurrence and follow-up data were extracted. The NLR was retrospectively calculated from blood tests. Data were analyzed by medians comparison, linear correlation, univariate and multivariate Cox regression and survival curve analysis.
Results. — Population's median age was 33 years and median follow-up was 40.5 months. Overall, the median NLR was significantly reduced after orchiectomy (2.2 [1.55—3.09] vs. 1.77 [1.34—2.46], M—W $P < 0.001$). Post-orchiectomy NLR was higher in patients who had disease recurrence (2.51;IQ 1.84—3.74 vs 1.59; IQ 1.10—2.24; M—W $P = 0.001$), regardless of disease's stage: HR = 1,85 (95% CI 0,99—3,46) and HR = 1,91 (95% CI 0,96—3,78) for stage disease I or stage II, respectively. After stratification of patients by post-orchiectomy NLR (optimal cut-off: 2.255), patients with lower NLR had significantly longer recurrence-free survival (107.7 months [95% CI

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97,7—119,2] vs. 57.65 months [95% CI 48,2—81,1], $P < 0.001$). Univariable and multivariable Cox proportional hazard analyses, showed post-orchiectomy NLR, histotype at final pathology and disseminated disease at diagnosis as predictors of recurrence.
Conclusion. — NLR is a simple and wildly available biomarker. Higher post-orchiectomy NLR was found independently correlated to higher risk of recurrence, regardless of disease stage, which could potentially lead to a worse prognosis.

MOTS CLÉS
Cancer des testicules ;
Rapport neutrophiles/lymphocytes ;
Inflammation ;
Marqueur tumoral ;
Biopsie liquide

Résumé
Objectifs. — Évaluer la valeur pronostique potentielle du rapport neutrophiles/lymphocytes (NLR) dans le cancer du testicule.
Matériaux et méthodes. — Quatre-vingt patients atteints de cancer du testicule traités dans notre établissement de 2005 à 2018 ont été revus rétrospectivement. L'âge, les marqueurs tumoraux, le stade et l'histotype à la pathologie finale, le traitement médical éventuel, la récidive tumorale et les données de suivi ont été extraits. La NLR a été calculée rétrospectivement à partir de tests sanguins. Les données ont été analysées par comparaison des médianes, corrélation linéaire, régression univariée et multivariée de Cox et analyse de la courbe de survie.
Résultats. — L'âge médian de la population était de 33 ans et le suivi médian de 40,5 mois. Globalement, le NLR médian était significativement réduit après orchidectomie (2,2 [1,55—3,09] contre 1,77 [1,34—2,46], M—W $p < 0,001$). La NLR post-orchidectomie était plus élevée chez les patients récidivants (2,51; QI 1,84—3,74 contre 1,59; IQ 1,10—2,24; MW $p = 0,001$), quel que soit le stade de la maladie: HR = 1,85 (IC 95 % 0,99—3,46) et HR = 1,91 (IC 95 % 0,96—3,78) pour le stade de la maladie I ou le stade $\geq$ II, respectivement. Après stratification des patients par NLR après orchidectomie (seuil optimal: 2,255), les patients avec un NLR inférieur présentaient une survie sans récidive significativement plus longue (107,7 mois [IC 95 % 97,7—119,2] par rapport à 57,65 mois [IC 95 %]. 48,2—81,1, $p < 0,001$). Des analyses de risque proportionnel de Cox univariées et multivariées ont montré une NLR post-orchidectomie, un histotype lors de la pathologie finale et une maladie disséminée au diagnostic en tant que facteurs prédictifs de la récurrence.
Conclusion. — La NLR est un biomarqueur simple et extrêmement disponible. Une NLR plus élevée après une orchidectomie a été trouvée indépendamment corrélée à un risque plus élevé de récurrence, quel que soit le stade de la maladie, ce qui pourrait potentiellement conduire à un pire pronostic.

Introduction

Testicular cancer is a relatively rare disease, typically affecting the young male, representing the 1% of the neoplasms of the gender and the 5% of the urological tumors [1,2].

Nevertheless, the rate of disease recurrences in the industrialized countries has progressively risen during the last decades [3—6].

It is known that the systemic inflammation processes play an important role in many aspects related to cancer, such as tumor growth, disease progression, clinical presentation and prognosis [7].

Multiple mechanisms have been suggested and numerous markers of systemic inflammation have been described,including the C-reactive protein, the platelets or leucocytes counts and the NLR [8].

Previous reports found the NLR a poor prognostic factor in either non-urological (colorectal, pancreatic, breast and hepatic) [9—12] or urological cancers (renal, prostatic, urothelial and penile)[13—16]. In a recent meta-analysis, Wei et al. reported high NLR values after analysing 17 studies including 3159 patients affected by urological tumors and concluded NLR could be a prognostic biomarker in urological cancers [17].

Unfortunately, Wei et al. did not include studies on testicular cancer in their meta-analysis.

In this scenario, to give a contribution in the field, we conceived the present retrospective study. The study purpose was to evaluate the NLR as a prognostic biomarker in patients with testicular cancer.

Materials and methods

Data of patients diagnosed with testicular cancer who underwent radical orchiectomy in our Institution between January 2005 and December 2018 were retrospectively extracted. Radical orchiectomy had been performed according to the guidelines recommendations [11]. Patients with conditions, which could affect to NLR (such as other malignancies, active/chronic infection, immunosuppressive diseases, systemic inflammatory conditions, the use of immunosuppressant agents and renal and/or hepatic disfunction) were excluded from the study.

The patients' demographic and clinical data and complete blood count (CBC) were extracted. Pre-orchiectomy, the CBC was performed 5 to 7 days before the surgery; post-orchiectomy, the CBC was performed 30 days postoperation. Specifically for the purpose of the study, the NLR was calculated by dividing the absolute neutrophils count by the absolute lymphocytes count. Lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG) were determined pre- and post-orchiectomy too.

Patients' classification according prognostic groups was also gathered, following guidelines criteria suggestions [1,18]. Pathological variables, including histology, tumor size and stage (based on the 2009 TNM classification of the International Union Against Cancer) [19] were collected, together with subsequent eventual chemotherapy (as adjuvant or primary treatment), recurrence and follow-up. Tumor features suggesting occult metastatic disease [20] (seminomas: tumor size > 4 cm and rete testis invasion; non-seminomas: vascular/lymphatic invasion, proliferation rate > 70%, and percentage of embryonal carcinoma > 50%) were collected.

Adjuvant chemotherapy was administered to all patients with occult metastatic risk factors. Upfront chemotherapy was given to those patients with disseminated disease (defined as cN+ or cM+) at the time of diagnosis. The chemotherapy regimens were chosen according ESMO guidelines recommendations [21].

Patients who had recurrence were treated with salvage chemotherapy using the cisplatin + etoposide + isofosfamide (VIP/PEI) regimen or with salvage chemotherapy plus retroperitoneal lymphadenectomy, depending on whether the tumor was seminomatous or non seminomatous, following guidelines recommendations [21].

The oncological follow-up was performed by physical examination, tumor markers monitoring, abdominopelvic computed tomography (CT) and chest X-ray or CT-scan, according to the current guidelines [1].

Statistical analysis: descriptive analysis was performed calculating medians and quartiles (1Q-3Q) or means and standard deviations, as appropriate, for continuous variables, and frequencies and proportions for categorical ones. Recurrence-free survival (RFS) was defined as the time interval between the treatment's beginning and the onset of the disease's recurrence. NLR was evaluated as a continuous variable, calculating the HR [22] adjusted by disease's stage.

Pearson correlation coefficient was used to assess the correlation between pre- and post-orchiectomy NLR and pre- and post-orchiectomy tumor markers.

Receiver operating characteristic (ROC) curve analysis was drawn for relapse events. To identify the optimal cut-off values of the NLR to predict relapse, we used sensibility and 1-specificity tables according to the minimum description length principle method [23].

The Kaplan–Meier method was used to calculate the recurrence-free survival (RFS). The log-rank test was used for intergroup comparisons of NLR with respect to RFS. We performed a univariable Cox Regression analysis with each factor potentially related to recurrence. The significant factors at univariable analysis were included in a multivariable model. *P*-value < 0.05 indicated statistical significance.

Table 1 Summary of characteristics of the study population.

Variables	N = 80
Age (years)	33 (28.25–39)
Pre-orchiectomy tumor markers	
hCG (mIU/mL)	1.7 (1.2–18.24)
AFP (ng/mL)	2.46 (1.89–12.47)
LDH (U/l)	234 (172–387.25)
Post-orchiectomy tumor markers	
hCG (mIU/mL)	1.2 (1.2–1.75)
AFP (ng/mL)	2 (1.3–3.53)
LDH (U/L)	158 (141–183)
Pre-orchiectomy absolute neutrophils (10^3/uL)	4500 (3625–6740)
Pre-orchiectomy absolute lymphocytes (10^3/uL)	2020 (1520–2500)
Pre-NLR	2.2 (1.55–3.09)
Post-NLR	1.77 (1.34–2.46)
Pathology	
Seminoma	50 (62.5)
No-seminoma	22 (27.5)
Mixt	8 (10)
Stage	
IS	20 (25)
IA	22 (27.5)
IB	10 (12.5)
II	19 (23.75)
III	9 (11.25)
Mean size (cm)	4.1 (3–7)
Rete testis invasion	34 (42.5)
Lymph/vascular invasion	42 (52.5)
N+	20 (25)
Pulmonary M1	6 (7.5)
Non-pulmonary M1	3 (3.75)

SD: standard deviation, pre-NLR: pre-orchiectomy NLR, post-NLR: post-orchiectomy NLR, LDH: lactate dehydrogenase, AFP: alpha-fetoprotein, hCG: human chorionic gonadotropin. Data are presented as median and interquartile range, and absolute value (%).

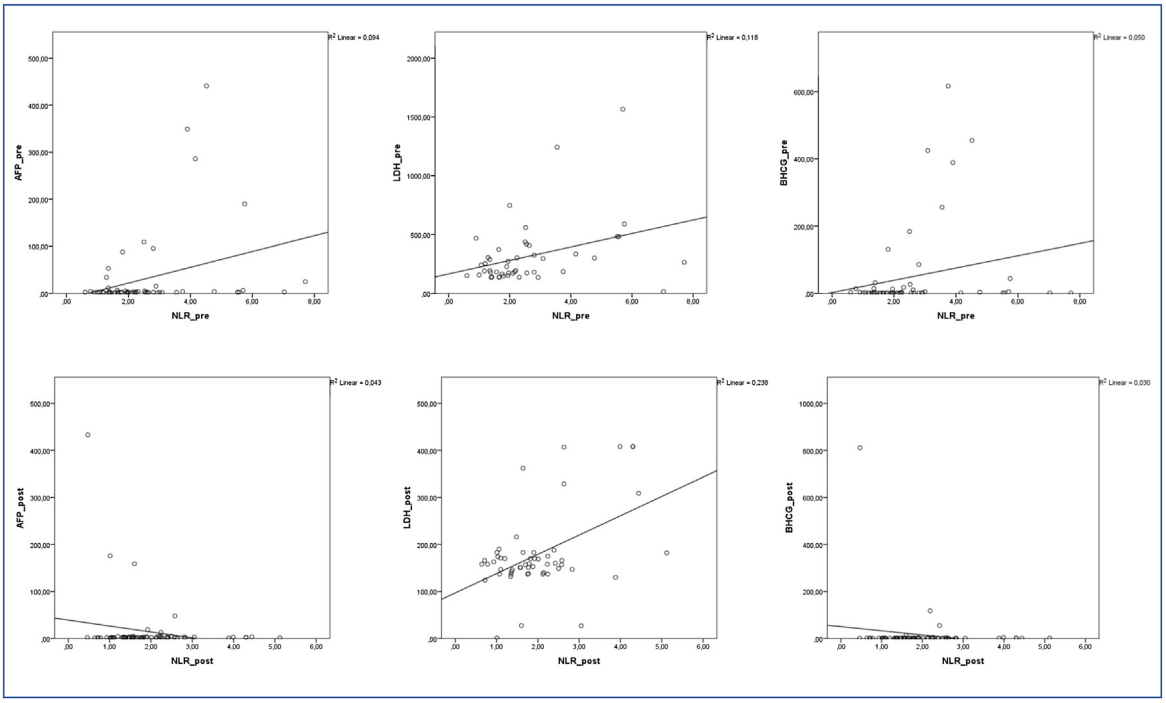

Figure 1. Scatterplots showing the absence of correlation between NLR and conventional tumor markers.

Statistical analysis was performed using IBM© SPSS® Statistics v21.

Results

A total of 80 patients were extracted, with no patients excluded. Table 1 summarizes the characteristics of the study population. Overall, the median NLR was significantly reduced after orchiectomy (2.2 (1.55—3.09) vs. 1.77 (1.34—2.46), M—W $P < 0.001$).

No correlation was observed between NLR and conventional tumor markers (AFP and hCG) at both pre-orchiectomy (r value: 0.08 and 0.06, resectively) and post-orchiectomy (r value 0.12 and 0.07, resp.) assessments (Fig. 1).

Fifty-eight (72.5%) patients had localized disease (N0, M0) at diagnosis. Pre-orchiectomy and post-orchiectomy NLR were lower in patients with localized disease (Pre-orchiectomy: localized 1,94 IQ 1,35—2,56 vs disseminated 3,33 IQ 0,39—4,53 MW *P*-value: 0.001; Post-orchiectomy: localized 1,64 IQ 1,26—2,24 vs disseminated 2,4 IQ 1,49—3,44 MW p-value: 0.021).

Forty-seven (58.75%) patients had received chemotherapy. Pre-orchiectomy NLR was higher in patients who had adjuvant chemotherapy (2.6 1Q—3Q 1.8—3.8 vs 1,7 1Q—3Q 1.3—2.5); M—W $P = 0.007$). Such difference was not observed post-orchiectomy (1.58 1Q—3Q 1.05—2.13 vs 1.82 1Q—3Q 1.35—2.58, MW p-value = 0.190).

Median follow-up of the analyzed cohort was 40.5 months (IQ 26—72). Within the follow-up, 16 patients had recurrence. Among them, median recurrence-free survival was 8.5 months (IQ 3.3—12.0).

Post-orchiectomy NLR was higher in patients who had disease recurrence (2.51;IQ 1.84—3.74 vs 1.59; IQ 1.10—2.24; M—W $P = 0.001$). A stage disease-stratified analysis (45 stage I, 24 stage > I) showed an association between post-orchiectomy NLR and disease recurrence regardless of disease's stage: HR = 1,85 (CI95% 0,99—3,46) and HR = 1,91 (95% CI 0,96—3,78) for stage disease I or stage II, respectively.

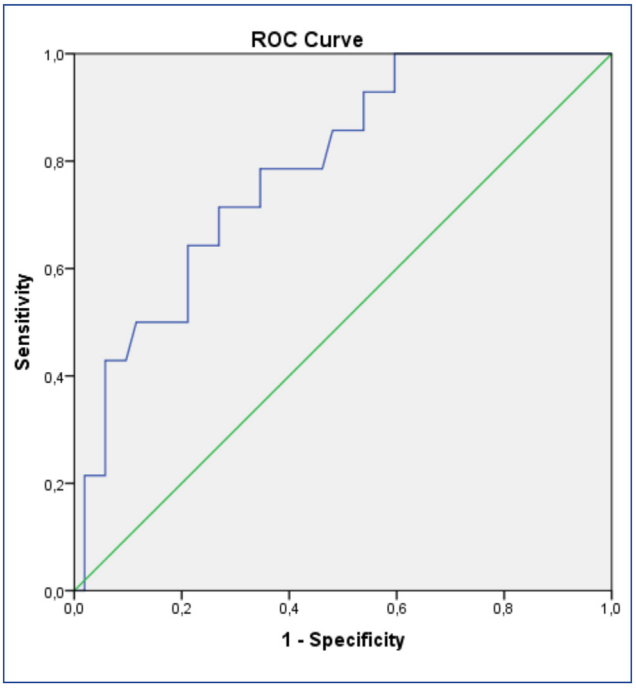

Figure 2. ROC curve for relapse according to post-orchiectomy NLR. Area under the curve: 78.7% 95% CI (0.663—0.911).

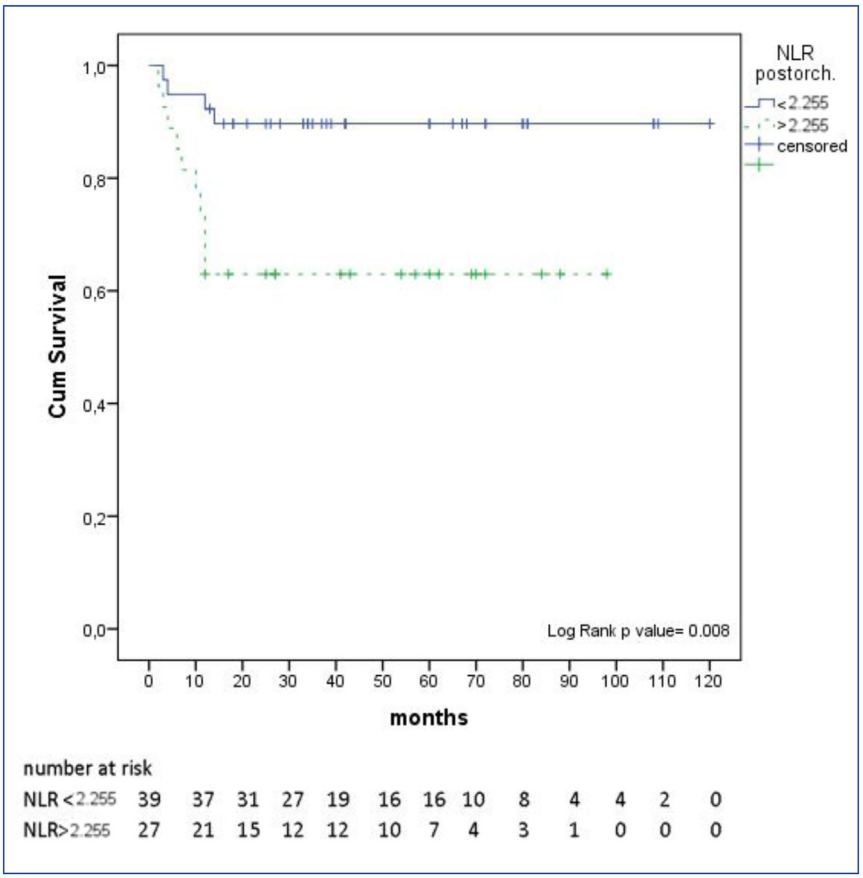

Figure 3. Recurrence-free survival of patients with post-orchiectomy NLRs below 2.255 (blue) and above 2.255 (green). A log-rank test indicated a significant difference between these two groups (107.7 months (95% CI 97,7—119,2) vs. 57.65 months (95% CI 48,2—81,1), $P < 0.001$).

At ROC curve analysis for post-orchiectomy NLR as predictor of recurrence, a NLR > 2.255 was the optimal cut-off for predicting a higher probability of recurrence, with an area under the curve of 78.7%; (95% CI = 0.663—0.911, $P = 0.001$) (Fig. 2).

Accordingly, Kaplan—Meier survival analysis showed that patients with lower post-orchiectomy NLR had significantly longer RFS (107.7 months (95% CI 97,7—119,2) vs. 57.65 months (95% CI 48,2—81,1), $P < 0.001$) (Fig. 3).

At univariable analysis, post-orchiectomy NLR > 2.255, seminoma type, AFP, LDH and disseminated disease were found predictors of recurrence and included in the multivariable analysis: post-orchiectomy NLR > 2.255 ($P = 0.022$), seminoma type ($P = 0.016$) and disseminated disease at diagnosis ($P = 0.021$) were confirmed to be independent predictors of recurrence (Table 2).

Discussion

In this report, we found that the NLR could work as a predictor of cancer relapse in patients affected by testicular cancer.

The systemic inflammation has been described to play a critical role in cancer development. It has been reported to promote either healing or growth and stimulation of metastasis [7]. Indeed, relative neutrophilia increases the inflammatory markers release, including pro-angiogenic and growth factors, proteases and anti-apoptotic factors, thus favouring tumor growth and progression[24,25].

Such neutrophilia might be due to the stimulus produced by the release of myeloid growth factors in the context of a para-neoplastic syndrome [26,27]. On the other hand, neutrophilia could more likely be secondary to a non-specific inflammatory response, favoured by the tissue destruction and subsequent cytokines release in the cancer context [28]. On the other side, the relative lymphopenia may reflect a smaller amount of CD4+ T-helper lymphocytes, leading to a suboptimal lymphocyte-mediated immune response against cancer [29].

Both the mechanisms could act together contributing to the biological aggressiveness of cancer, its progression and prognosis.

Several markers of systemic inflammation have been suggested, including the C-reactive protein, the platelets or the leucocytes counts and the NLR [8].

Previous studies reported that the NLR is a poor prognostic factor in non-urological [9—12] and urological tumors [13—16]. A recent meta-analysis reported high NLR values after analysing patients with urological tumors and suggested NLR as a prognostic biomarker for urinary cancers [17]. We thought the present study trying to contribute to the gap in the literature about the topic, as the role of the NLR is not well established in testicular cancer. Our study

Table 2 Univariate and multivariate Cox proportional models of potential risk factors for recurrence of testicular cancer patients.

	Univariate			Multivariate		
	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.017	0.945—1.095	0.686			
NLR						
Pre-orchiectomy	1.263	0.947—1.685	0.064			
Post-orchiectomy	1.841	1.2—2.823	0.005	2.019	1.108—3.677	0.022
Pathology						
Seminoma		Reference				
Non-seminoma	4.486	1.530—13.152	0.006	5.931	1.390—25.315	0.016
Pre-orchiectomy Tumor markers						
AFP	1	1.000018—1.000193	0.018			0.952
LDH	1.001	1,000238—1,001488	0.007			0.625
HCG	1.001	0.997—1.006	0.578			
Disseminated disease						
No		Reference				
Yes	3.457	1.210—9.873	0.021	4.628	1.258—17.028	0.021
Tumor size	0.849	0.660—1.091	0.201			
M1 occult risk factors						
No		Reference				
Yes	1.168	0.261—5.219	0.839			
Adjuvant treatment						
No		Reference				
Chemotherapy	1.385	0.481—3.991	0.546			

CI: confidence interval, NLR: neutrophil-to-lymphocyte ratio, LDH: lactate dehydrogenase, AFP: alpha-fetoprotein, hCG: human chorionic gonadotropin. Diseminated disease: N+ and/or M1.

retrospectively analysed the features of a cohort of patients with testicular cancer and showed the potential role of the NLR in predicting cancer recurrence. Only few studies were previously published in the field.

Yuksel et al. first studied the relationship between testicular cancer and the NLR [30]. They retrospectively evaluated 36 patients with testicular cancer compared to 36 controls, concluding that the NLR could be a good complementary biomarker for the diagnosis of localized testicular cancer.

Bolat et al. retrospectively evaluated the preoperative NLRs in a group of 53 patients with testicular cancer. They analysed cancer-specific survival and progression-free survival without finding significant relationship with the NLR [31].

The authors reported a mean follow-up of 23.5 months, with 5 patients who experienced progression and 7 patients who died. The shorter follow-up and the smaller number of recurrences could explain the different finding compared to the present study. Such a low events occurrence might prevent the reliable estimation of progression-free and cancer-specific survivals.

Jankovic et al. studied in a retrospective series of 103 patients the link between the NLR and testicular cancer features. They reported that a NLR $\geq$ 4 was observed in > T1 pathological stage [32]. Our results are in line with those previously reported by Jankovich et al. Moreover, in our study we included the analysis of the value of the NLR in predicting recurrence, which is a key point in our opinion.

Fankhauser et al. retrospectively investigated the prognostic utility of several systemic inflammatory markers in 146 metastatic testicular cancer patients. The authors found that the leukocytes count, the neutrophils count, the systemic immune-inflammation index (calculated as Neutrophils $\times$ Platelets/Lymphocytes) and the NLR were independent predictors of shorter overall survival [33]. These results again do not differ from the ones reported in the present study.

More recently, Tan et al. retrospectively studied their testicular cancer cohort, reporting higher advanced disease and poorer cancer-specific survival for NLR < 3 [34], not differing with our results. We went a step further including post-orchiectomy NLR in a multivariable Cox Regression analysis, founding it an independently associated factor to testicular cancer relapse.

Although the prevalence of testicular cancer is quite low, the affected population by such a disease is typically young men, whose life expectancy and quality can be significantly influenced by chemotherapy other than cancer itself.

This study focused on a parameter scarcely studied in the available literature that could predict the cancer recurrence, with an important clinical impact.

In contrast, our study was not devoid of limitations. First, the retrospective design with inherent biases. Second, it was a single-center analysis with small sample size. The heterogeneity of the sample maybe limited the reliability of our analysis. On the other side, our results could be better generalized to testicular cancer in general.

Our preliminary report has to be validated in larger cohorts, with subgroup analyses and taking into account for potential confounders.

The conclusion drawn by the present study derived from the categorization of a parameter like the NLR should be read carefully. Indeed, from a clinical and a statistical point of view, to analyse a variable as quantitative would be recommended.

Conclusions

NLR is a simple and wildly available biomarker. Higher post-orchiectomy NLR was found independently correlated to higher risk of recurrence in testicular cancer patients, regardless of disease stage.

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Disclosure of interest

The authors declare that they have no competing interest.

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