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Predictive and Prognostic Role of Neutrophil to Lymphocyte Ratio in Rectal Cancer: A Case Control Study with Propensity Score Analysis

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Rezumat

Rolul predictiv și prognostic al raportului dintre neutrofile și limfocite în cancerul rectal: un studiu de caz și control cu analiza scorului de propensitate

Introducere: Raportul dintre neutrofile şi limfocite (NLR) este promovat ca un marker care reflectă răspunsul inflamator anti-tumoral. În acest studiu, ne propunem să evaluăm dacă NLR în momentul diagnosticării poate prezice răspunsul la terapia neoadjuvantă şi supraviețuirea pe termen lung într-o cohortă de pacienți cu neoplasm rectal.
Metode: Acesta este un studiu caz-control pe pacienți cu neoplasm rectal cărora li s-a efectuat un tratament oncologic standard şi li s-a prelevat NLR în fiecare etapă a tratamentului multimodal. Curba ROC a fost utilizată pentru a stabili valoarea limită a NLR la diagnostic. Au fost comparate două grupuri (NLR ridicat şi scăzut). Analiza Kaplan Meier de supraviețuire globală (OS) şi fără boală (DFS) a fost efectuată comparativ între două grupuri de pacienți: NLR scăzut şi ridicat. Testele Pearson şi Log Rank au fost utilizate pentru a stabili semnificația statistică. A fost efectuată potrivirea scorului de propensie (PSM) şi toate variabilele au fost comparate din nou pe subgrupurile potrivite.
Rezultate: Au fost incluși o sută de pacienți şi 54 au fost comparați din nou după PSM. NLR la diagnostic nu s-a corelat cu gradul de regresie tumorală (p=0,77). NLR ridicat la diagnostic (NLR > 2,58) nu a fost asociat în mod semnificativ cu OS mai scurtă (p=0,096) sau DFS (p=0,128). Rezultate similare au fost obținute după PSM, cu excepția cazului în care au fost comparate subgrupurile din stadiul

III, unde NLR mai mare a fost asociat cu o DFS mai scurtă (p=0,04), în timp ce rezultatele pentru OS au fost la limita (p=0,05).
Concluzii: În general, un NLR preterapeutic ridicat (> 2,58) nu prezice supraviețuirea sau răspunsul la terapia neoadjuvantă la pacienții cu cancer rectal. Cu toate acestea, un NLR mai mare poate fi asociat cu supraviețuire fără boală mai scurtă în cancerul colorectal avansat.

Cuvinte cheie: cancer rectal, rata neutrofile limfocite, inflamație, supraviețuire, radioterapie

Abstract
Background: Neutrophil to lymphocyte ratio (NLR) is promoted as a marker reflecting the anti-tumoral inflammatory response. Herein, we aim to assess whether NLR at the time of diagnosis can predict response to neoadjuvant therapy and long-term survival in a matched cohort of rectal cancer patients.
Methods: This is a case control study on rectal cancer patients who underwent standard oncological treatment and had NLR sampled at each stage. ROC curve was used to establish the cut off value of NLR at diagnosis. Two groups (high and low NLR) were compared. Kaplan Meier overall and disease-free survival (DFS) analysis was done comparatively between two groups of patients: low and high NLR. Pearson and Log Rank tests were used to establish statistical significance. Propensity score matching (PSM) was performed, and all variables were compared again on the matched subgroups.
Results: One hundred patients were included and 54 were compared again after PSM. NLR at diagnosis did not correlate with tumor regression grade (p=0.77). High NLR at diagnosis (NLR > 2.58) was not found to be significantly associated with worse overall survival (p=0.096) or DFS (p=0.128). Similar results were achieved after PSM, except when stage III subgroups were compared, where higher NLR was associated with worse DFS (p=0.04), while results for OS were borderline (p=0.05).
Conclusions: Overall, a pretherapeutic high NLR (> 2.58) was not found to predict survival or response do neoadjuvant therapy in patients with rectal cancer. However, a higher NLR may be associated with worse outcomes in advanced colorectal cancer.

Key words: rectal cancer, neutrophil to lymphocyte ratio, inflammation, survival, radiotherapy

Introduction

Inflammation is a key factor governing tumorigenesis and cancer progression. In the tumor microenvironment cancer cells constantly interact with the surrounding inflammatory biomarkers and this interaction is a subject of important research having both diagnostic and therapeutic implications. The possibility of using biomarkers of inflammation to predict antitumoral immune response, cancer progression and patient survival has been proposed in various studies (1-7).

One simple test which could highlight the balance between pro-tumoral and anti-tumoral inflammatory responses is represented by the ratio between peripheral neutrophils and lymphocytes (NLR). It is thought that tumorigenesis triggers recruitment of myeloid-derived suppressor cells (MDSCs) and causes a shift in neutrophil phenotype to a pro-tumoral subfamily (e.g., N2 neutrophils), which results in an overall increase in neutrophils in the tumor microenvironment and peripheral blood (8,9).

The emergence of NLR as a potential

prognostic marker in cancer has become a hot topic because it can be easily calculated in peripheral blood and thus, a plethora of studies on various types of cancer have been published analyzing if a high NLR is associated with worse survival (2,3,6-21). The normal values of NLR have been reported between 0.78 and 3.53 (22); however, the cut off value varies considerably between studies. Despite the amount of data supporting NLR as a prognostic marker, it is rarely used in clinical practice to guide clinical decision. More so, a recent umbrella review of 204 meta-analyses on NLR and cancer prognosis showed that only 29% of current data has strong evidence favoring NLR (10). For rectal cancer, NLR is proposed not only as an indicator of survival but also as a predictive marker of tumor response to neoadjuvant therapy.

In this study we aimed to analyze the predictive role of NLR in a cohort of patients diagnosed with rectal cancer that had a full course of treatment including neoadjuvant therapy, surgery, and long-term follow-up. Response to neoadjuvant radio-chemotherapy, overall survival and disease-free survival were compared between patients with low and high NLR, before and after propensity score matching.

Material and Methods

Design and Setting

This is a retrospective case control study on patients diagnosed with rectal cancer who underwent long course neoadjuvant therapy, curative surgery, followed by adjuvant therapy, if indicated, and regular oncological follow-up at our institution. All stages of diagnosis, management and follow-up were done at our institution. All surgeries were performed by one senior colorectal surgeon between 2016 and 2021. Patient consent was waived by our Institutions` Ethics Committee as the research did not pose any risks to the patients and data was anonymized. The STROBE checklist v4 (23) for cohort studies was adhered to.

Inclusion and Exclusion Criteria

Only patients fully managed at our institution from diagnosis to surgery, followed by standard cancer follow-up were included in order to ensure standardized sampling of NLR at specific intervals: diagnosis, after neoadjuvant therapy, pre- and postoperative and during outpatient follow-up at 1 year. Only patients which had NLR sampling at least at diagnosis and after neoadjuvant therapy were included. To reduce confounding bias, patients with concomitant hematological, autoimmune or systemic inflammatory diseases were excluded.

Data Extraction

An Excel database was created including age at diagnosis, sex, ASA grading, comorbidities that could influence immune response (including autoimmune or systemic inflammatory diseases), clinical staging, NLR at diagnosis, type of neoadjuvant therapy including dose and type of concomitant chemotherapy, NLR before surgery, type of surgery, postoperative complications, NLR at 30 days postoperatively, type and duration of adjuvant therapy, NLR at 1 year follow-up, date of recurrence, type of recurrence, date of death. Data on recurrences was extracted from patients' electronic records (medical notes, scan reports) and, where necessary, patients were called to request missing information. The extracted data on recurrences were double checked by a colorectal surgery specialist (SM) to ensure recurrences were correctly attributed. Date of death was extracted from our local populational registry or via phone calls.

Data Analysis

The Excel database was transferred to IBM SPSS v26.0 software. ROC (Receiver Operating Characteristic) curve was used to establish the cut off value of T1-NLR in our cohort of patients. Kaplan Meier overall and disease-free survival (DFS) analysis was

done comparatively between two groups of patients: low and high NLR. Survival analysis was also performed separately for stages II and III. Stage IV patients were not analyzed separately due to the small number of cases. Pearson and Log Rank tests were used to establish statistical significance. A statistically significant difference was defined as a p value less than 0.05.

To further reduce bias from confounding variables and selection bias, propensity score analysis (PSM) was performed using XLSTAT software. Matching control patients in the low NLR group were selected according to propensity scores, in a 1:1 ratio, determined by Mahalanobis distances, with patients in the high NLR group, based on seven covariates including age, sex, cTNM, Dworak regression grade and tumor volume.

Results

Patient Characteristics

A total of 100 patients were included in the study (*Fig. 1*), with 71% males (n=71) and 29% females (n=29). Mean age was 64.2 years old. With regards to tumor staging, 65% (n=65, 38) of patients were stage III according to the 8th edition of AJCC colorectal cancer staging (24), while 27% (n=27) were stage II and 8% (n=8) were stage IV. The majority (60.4%) of tumors were low grade adenocarcinomas. Anterior resection was performed in 54% (n=54) of cases, while abdominoperineal resection was done in 35% (n=35) of cases. 11% (n=11) of patients had multiorgan resection including uterus, ovaries, prostate or bladder due to local invasion. The cut off value of NLR was set at 2.58, at which it showed the highest sensitivity and specificity according to the ROC curve analysis. *Table 1* summarizes the clinicopathological variables which were compared between the two studied groups (low and high NLR) using chi-squared test. Higher NLR values were not significantly correlated with none of the studied variables. The mean NLR in ypT0-2N0 was 2,91±1,56 and 2,68±1,41 in the ypT3-4/N+, the difference being insignificant (p=0.43). Similarly, the mean NLR in Dworak 0-2 was 2,80 ± 1,50 and 2,71 ± 1,34 in Dworak 3-4, without reaching statistical significance (p=0.77).

Figure 1. STROBE flow diagram

After propensity score matching, 27 patients with high NLR were compared to 27 patients with low NLR in a similar fashion. Results are depicted in *Table 2*. Similarly to the overall cohort, higher NLR (>2.58) was not correlated with any of the studied variables.

NLR Predictor of Recurrence?

Low and high NLR at diagnosis (T1) were compared in terms of five-year survival curves. The five-year overall survival (OS) rate was 62.3% in patients with low NLR and 37.7% in patients with high NLR; the difference in survival did not reach statistical significance according to the Log Rank test (p=0.098) (*Fig. 2*). Similarly, disease free survival was 62.8% in patients with low NLR and 37.2% in patients with high NLR (p=0.134, Log Rank test) (*Fig. 3*). OS and DFS were analyzed again after PSM on 54 patients (27 with low NLR vs 27 with high NLR). In each category, there was a difference of survival rates between the two groups, however the survival curves were not significantly different (*Figs. 2* and *3*).

At diagnosis (T1) the mean NLR value was 2.77 ± 1.47, increasing at 4.84 ± 2.52 after neoadjuvant therapy (T2), reaching a peak at 6.32 ± 6.99 postoperatively (T3), after which it decreased to a mean of 3.81 ± 2.21 at one year postoperatively (T4). By using ROC curve analysis, the cut off value of the difference between NLR at T3 and T1 was established at 1.70. Patients were further divided into two

Table 1. Clinicopathological variables in patients with low and high NLR.

	Before PSM			
Variables	**N (%)**	**NLR<2.58 (n=56)**	**NLR≥2.58 (n=44)**	**p**
Sex			0.611	
M	71 (71%)	38 (30%)	33 (41%)	
F	29 (29%)	18 (15%)	11 (14%)	
Age			0.064	
≤60	65 (65%)	37 (37%)	28 (28%)	
>60	35 (35%)	19 (19%)	16 (16%)	
Immune related comorbidities				
Cardiovascular diseases	34 (34%)	16 (16%)	18 (18%)	0.21
Chronic Kidney Disease	13 (13%)	8 (8%)	5 (5%)	0.7
Diabetes	11 (11%)	6 (6%)	5 (5%)	1
Allergies	9 (9%)	5 (5%)	4 (4%)	1
Clinical staging				0.787
II	27 (27%)	14 (14%)	13 (13%)	
III	65 (65%)	38 (38%)	27 (27%)	
IV	8 (8%)	4 (4%)	4 (4%)	
Differentiation Grade				0.792
G1	22 (32.4%)	12 (17.6%)	10 (14.7%)	
G2	41 (60.3%)	23 (33.8%)	18 (26.5%)	
G3	5 (7.4%)	2 (2.9%)	3 (4.4%)	
Type of operation				0.276
Low Anterior Resection	54 (54%)	34 (34%)	20 (20%)	
APR	35 (35%)	16 (16%)	19 (19%)	
Multiorgan Resection	11 (11%)	6 (6%)	5 (5%)	
Postoperative complications				0.455
Yes	11 (11.0%)	5 (5.0%)	6 (6.0%)	
No	89 (89.0%)	51 (51.0%)	38 (38.0%)	
ypTNM				0.578
ypT0-2 N0	39 (39.4%)	20 (20.2%)	19 (19.2%)	
ypT3-4 or N+	60 (60.6%)	36 (35.4%)	25 (25.3)	
Tumour regression grade				0.095
D0-D2	68 (74.7%)	38 (41.8%)	30 (33.0%)	
D3-D4	23 (25.3%)	12 (13.2%)	11 (12.1%)	
Adjuvant therapy	49 (49%)	25 (25%)	23 (23%)	0.548
Recurrence in the first year				0.285
Yes	14 (14.0%)	6 (6.0%)	8 (8.0%)	
No	86 (86.0%)	50 (50.0%)	36 (36.0%)	

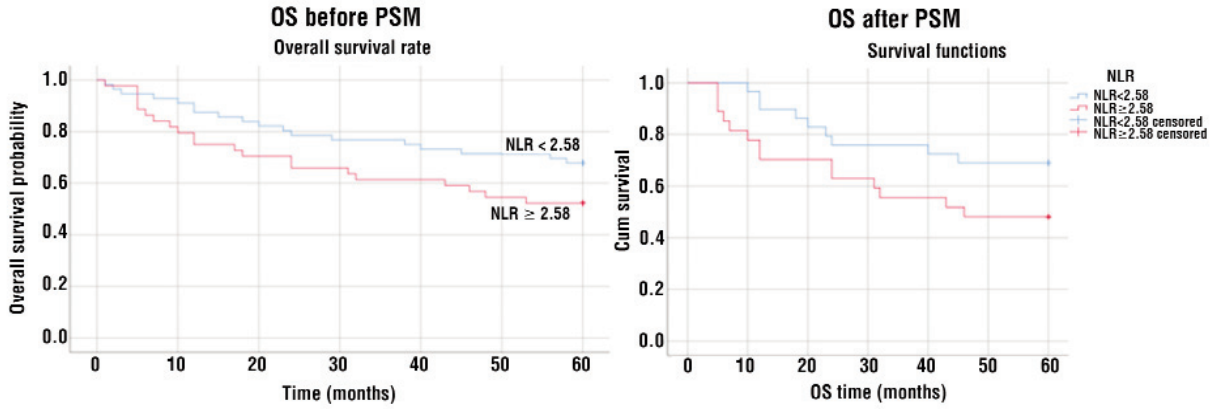

Figure 2. OS in patients with high and low NLR before and after PSM

Table 2. Comparative analysis after propensity score matching

	After PSM			
Variables	**N (%)**	**NLR<2.58 (n=27)**	**NLR≥2.58 (n=27)**	**p**
Sex			0.209	
M	40 (75.0%)	20 (74.1%)	20 (74.1%)	
F	14 (25.0%)	7 (25.9%)	7 (25.9%)	
Age			0.420	
≤60	35 (64.3%)	16 (59.3%)	19 (70.4%)	
>60	19 (35.7%)	11 (40.7%)	8 (29.6%)	
Clinical staging				0.571
II	11 (23.2%)	7 (25.9%)	5 (18.5%)	
III	39 (71.4%)	18(66.7%)	21(77.8%)	
IV	3 (5.4%)	2 (7.4%)	1 (3.7%)	
Differentiation Grade				0.762
G1	10 (31.4%)	4 (26.7%)	6 (33.3%)	
G2	21 (62.9%)	11 (73.3%)	10 (55.6%)	
G3	2 (5.7%)	0 (0.0%)	2 (11.1%)	
Type of operation				0.310
Low Anterior Resection	31 (58.9%)	17 (63.0%)	14 (51.9%)	
APR	19 (33.9%)	9 (33.3%)	10 (37.0%)	
Multiorgan Resection	4 (7.1%)	1 (3.7%)	3 (11.1%)	
ypTNM				0.704
ypT0-2 N0	19 (33.9%)	9 (33.3%)	10 (37.0%)	
ypT3-4 or N+	35 (66.1%)	18 (66.7%)	17 (63.0%)	
Tumor regresion score				1.00
D0-D2	39 (71.4%)	19 (70.4%)	20 (74.1%)	
D3-D4	15 (28.6%)	8 (29.6%)	7 (25.9%)	

groups: those who had a NLR increase more than 1.7 times between the time of diagnosis (T1) and after neoadjuvant therapy and surgery (T3); and those who had a NLR increase less than 1.7 times. The overall survival of the two subgroups was compared using the Log Rank test and it did not show a significant difference (p=0.059) (*Fig. 4*).

When comparing survival curves based on staging (stage II and stage III), we found that, in stage II, high NLR values were not associated with worse OS (p=0.28) or DFS (p=0.41). The results were similar before and after PSM (*Figs. 5* and *6*). For stage III, before PSM, high NLR did not predict a worse OS (p=0.18) or DFS (p=0.19) however, after PSM,

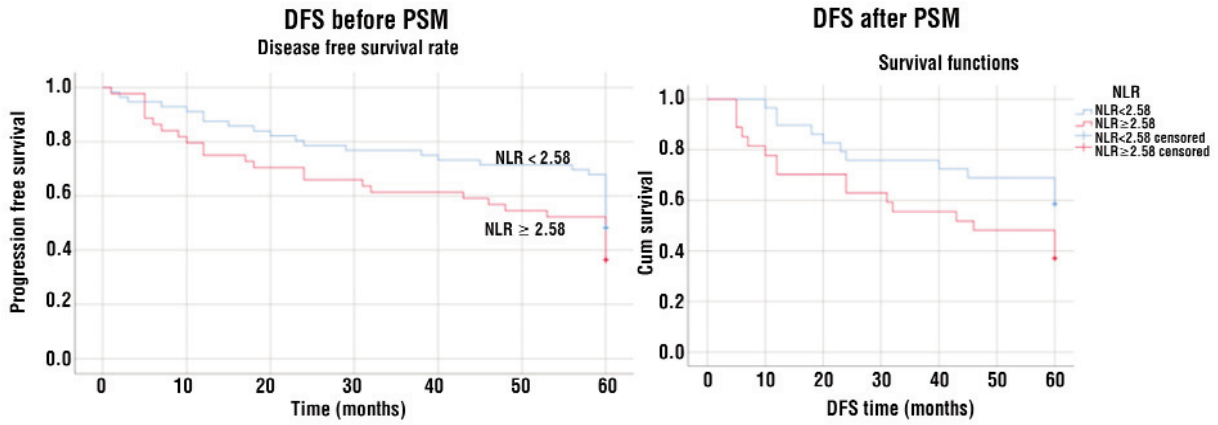

Figure 3. DFS in patients with high and low NLR before and after PSM

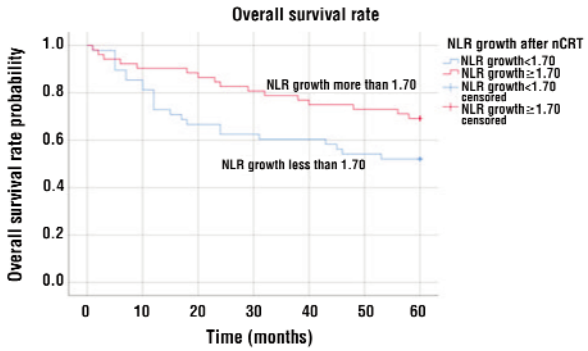

Figure 4. OS in patients with an increase of more and less than 1.7 times (cut off value) between T1 and T3

higher NLR were associated with worse DFS (p=0.04) and borderline worse OS (p=0.05), according to Log Rank test (*Figs. 7* and *8*).

Discussion

Based on the above results, NLR at diagnosis does not seem to impact the risk of disease recurrence in patients with rectal cancer. Neither disease free nor overall survival were correlated with NLR at diagnosis, although when only patients with stage III were compared, the DFS was worse in patients with

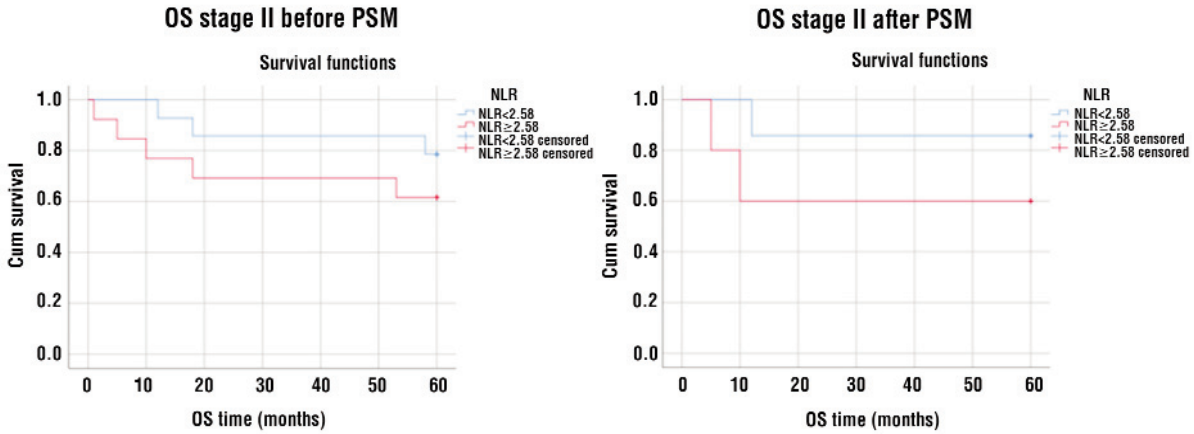

Figure 5. OS in stage II patients before and after PSM

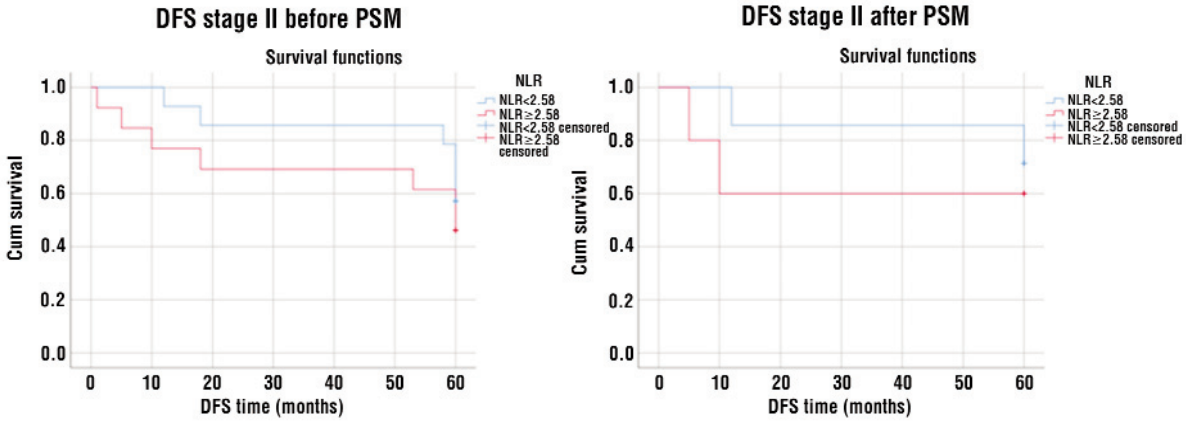

Figure 6. DFS in stage II patients before and after PSM

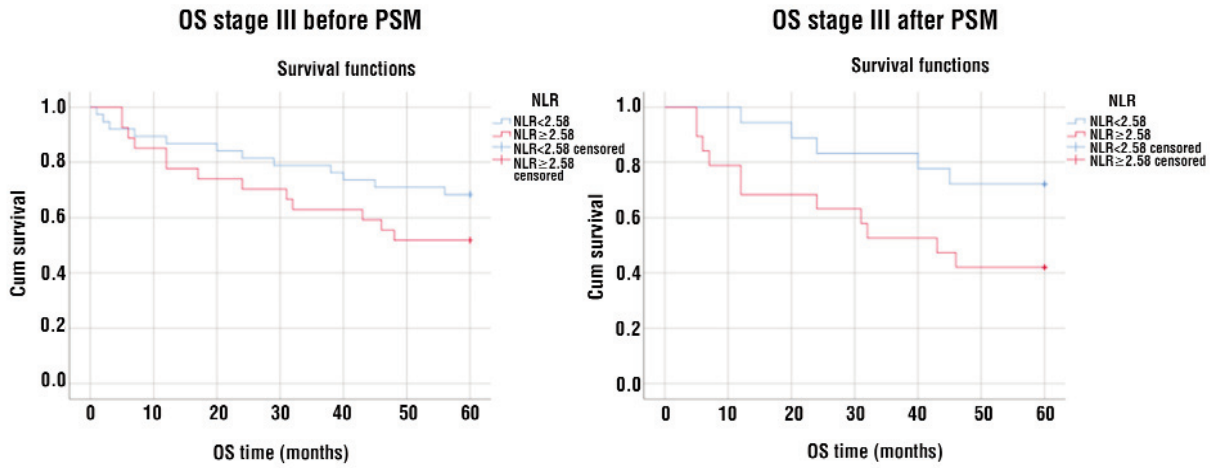

Figure 7. OS in stage III patients before and after PSM

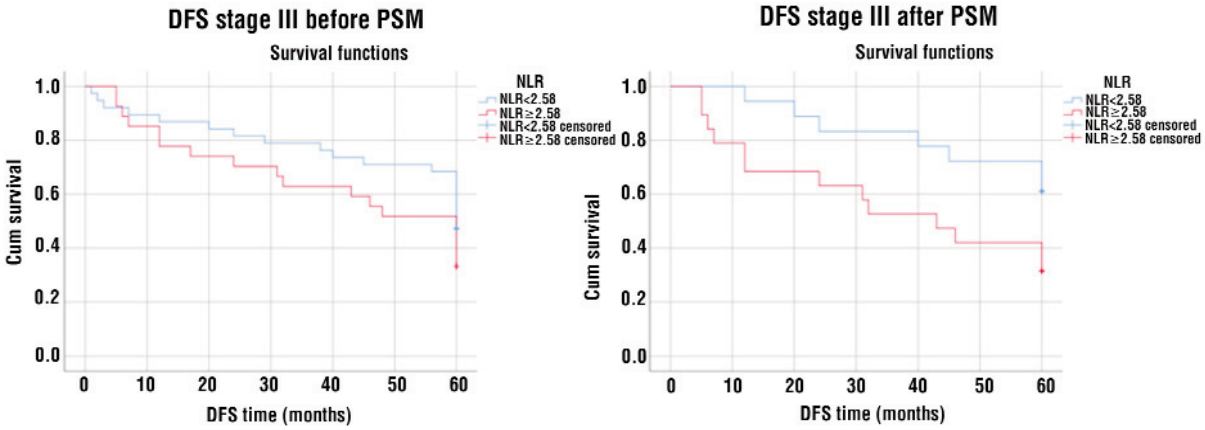

Figure 8. DFS in stage III patients before and after PSM

high NLR. These difference in results highlights the need for larger multicentric studies in order to stratify in which category of patients would NLR sampled from peripheral blood be able predict outcomes. The rate of NLR increase from T1 (diagnosis) to T3 (post-operative) does not predict overall survival, suggesting that one should not guide management considering the initial NLR, nor its fluctuations during neoadjuvant therapy. These results come to trigger more debate on this subject as they contradict previous papers which showed a correlation between high NLR and worse survival (3,4,7,13,14,25-28). At the same time, our results are in line with other studies that did not find a significant correlation (29,30). A standardized cut off value for NLR is yet to be established, as studies report various cut offs ranging from 1.95 to 4.2 (10-12), which might partially explain the difference in results.

Defining biomarkers of prognostication and prediction in colorectal cancer has become a hot topic in recent years given that the classic

anatomical stratification of cancer based on TNM has proven to be rudimentary. Molecular pathways, gene expression, and tumor biomarkers are now used to better stratify colorectal cancer. Another potential pathway for tumor characterization is based on the hosts' anti-tumor inflammatory response, which is an important gatekeeper against cancer progression however its magnitude and phenotype variates among patients. This variation, represented by the number of intra-tumoral CD3+/CD8+ lymphocytes, quantified in Immunoscore (1,2), is proven to impact survival and tumor response to treatment. Using the NLR, such a readily available biomarker, as a reflection of the local anti-tumor inflammatory response is appealing but debatable and yet to be standardized as studies are describing a wide range of cut off values in similar cohorts of patients.

NLR has also been reported to predict response to neoadjuvant therapy and shown to correlate with tumor downstaging according to some studies. This has been contradicted by Dudani et al. (29) and Carruthers et al. (30) who did not find any correlation between NLR and pathological response. This agrees with our results. In our cohort, a better pathological response to neoadjuvant therapy measured by Dworak grading on the specimen was not found to be linked to lower NLR values. Braun et al. (28) used a high NLR cut off of 4.09 which did show to predict a worse disease-free survival, but the cut off value was not used to assess correlation with Dworak grading, but rather they found that patients with better response (Dworak 3-4) had lower NLR values and thus concluded the NLR to be a predictor of response to neoadjuvant therapy. In our study, we used the same cut off value in all comparisons as there should be a single value that can predict outcomes if NLR is to be implemented in clinical practice.

Indeed, NLR values fluctuate during treatment, and we saw a significant increase after neoadjuvant therapy and after surgery. This is to be expected as both scenarios trigger a systemic inflammatory response and a higher circulating neutrophil count secondary to tissue necrosis associated with radiotherapy and tissue trauma associated with surgery; however, whether these fluctuations reflect future tumor behavior is yet to be proven and may be considered for future analyses, where postoperative NLR among other inflammatory markers (e.g., CRP), rather than NLR at diagnosis, are used as predictors of cancer recurrence, given that many studies (31-35) have already appraised the link between post-operative inflammatory response and cancer progression. The results of this study are limited by its retrospective nature, however both confounding and selection bias were reduced by performing PSM and analyzing all variables again, including survival, in a matched cohort of patients. Although there was a difference in survival rates between the two groups suggestive of a survival benefit for patients with low NLR, we must be cautious as the data were extracted from a small sample, and this was clarified using the Log Rank test which accepted the null hypothesis that there is no difference in survival between the two groups. Further research would be required on larger cohorts to enable a more accurate estimation of survival.

Conclusion

Overall, a pretherapeutic high NLR (> 2.58) was not found to be associated with worse survival or worse response do neoadjuvant therapy in patients with rectal cancer, although in advanced cancers there may be a link between high NLR and cancer recurrence. The data supporting NLR as a predictor and prognostic marker is abundant, but conflicting and heterogenous. Further research is required to clarify the correlation between systemic inflammation and localized antitumor inflammatory response.

Author's Contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript. Constantin Simiras, Stefan

Morarasu, Delia-Maria Simiras, Sorinel Lunca, Gabriel-Mihail Dimofte designed the study and approved the study protocol. Stefan Iacob, Wee Liam Ong, Ana Maria Musina, Natalia Velenciuc, Cristian Ene Roata included patients and collected the data. Constantin Simiras, Stefan Morarasu, Delia-Maria Simiras performed the data analysis. Stefan Morarasu performed the subgroup analysis and propensity score matching. Constantin Simiras, Stefan Morarasu, Delia-Maria Simiras wrote the manuscript. Ana Maria Musina, Natalia Velenciuc, Cristian Ene Roata, Sorinel Lunca, Gabriel-Mihail Dimofte reviewed the final manuscript.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose. The results of this study were never published or presented elsewhere.

Financial Disclosure

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