

# Association of neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios with treatment response and quality of life in colorectal and pancreatic cancer: A prospective analysis

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## ABSTRACT

**Background:** Systemic inflammation and hypercoagulability are key drivers of cancer progression. This study aimed to evaluate the predictive value of inflammatory and coagulation-related ratios—specifically neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and ferritin-to-D-dimer ratio (FDR)—in patients with colorectal and pancreatic cancer.

**Methods:** We prospectively enrolled 73 patients with confirmed colorectal (n=57) or pancreatic cancer (n=16). Patients were classified as responders (n=39) or non-responders (n=34) based on radiological evaluation 6 months post-therapy. Baseline complete blood counts, ferritin, and D-dimer levels were compared. Predictive accuracy was assessed using Receiver Operating Characteristic (ROC) curve analysis.

**Results:** Non-responders exhibited significantly higher baseline leukocyte and neutrophil counts ( $p<0.002$ ). Ferritin levels were 2.5-fold higher in non-responders ( $p<0.05$ ). ROC analysis identified NLR as a strong predictor of treatment failure (AUC=0.895; Optimal Cut-off  $>2.68$ ), while LMR was a significant predictor of favorable response (AUC=0.864). Unlike previous reports, FDR was significantly elevated in non-responders ( $p=0.002$ ). High NLR was moderately correlated with poor functional status (ECOG  $r=0.44$ ) exclusively in the non-responder group.

**Conclusions:** Baseline NLR and LMR are robust predictors of therapeutic outcome in colorectal and pancreatic cancer.

**Keywords:** colorectal cancer, ferritin-to-D-dimer ratio (FDR), neutrophil-to-lymphocyte ratio (NLR), pancreatic cancer, ratios

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## INTRODUCTION

Colorectal and pancreatic cancers remain among the leading causes of cancer-related mortality worldwide. Despite advances in surgical techniques and systemic therapies, a substantial proportion of patients exhibit limited therapeutic response. Increasing evidence indicates that cancer pathogenesis extends beyond genetic alterations and involves a significant inflammatory component. Systemic inflammation contributes to tumor progression by promoting cellular proliferation, angiogenesis, and metastatic dissemination [1].

Recent studies have demonstrated that inflammation may impair the efficacy of chemotherapy, thereby

contributing to treatment resistance [2]. Consequently, there is growing interest in identifying practical and accessible biomarkers of systemic inflammation derived from routine laboratory tests. In this context, hematological indices such as the Neutrophil-to-Lymphocyte Ratio (NLR) and the Lymphocyte-to-Monocyte Ratio (LMR) have gained attention, as they reflect the dynamic balance between host immune response and tumor-promoting inflammatory processes [3,4].

Additional inflammatory and hemostatic markers are also under investigation. Ferritin, an iron-storage protein, functions as an acute-phase reactant and increases in inflammatory states. D-dimer reflects activation of coagulation and fibrinolysis and is frequently elevated

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in patients with malignancy. Both markers have been associated with adverse outcomes across a range of pathological conditions [5,6]. However, their utility—either individually or in combination—in predicting early treatment failure remains insufficiently defined. Furthermore, the relationship between these biomarkers and patients' functional or physical status warrants further exploration. The present study aims to evaluate the predictive value of NLR, LMR, and the Ferritin-to-D-dimer Ratio (FDR) in patients with colorectal and pancreatic cancers.

## METHODS

This study was conducted in full compliance with the ethical principles the Declaration of Helsinki. The research protocol received complete approval from the Institutional Ethics Committee prior to the start of the study (approval date: 29.12.2021). All procedures were performed in accordance with the ethical standards.

We enrolled 73 consecutive patients with histologically confirmed colorectal (n=57) or pancreatic cancer (n=16) at UMHAT St. Ivan Rilski Sofia. We prospectively enrolled a cohort of 73 consecutive patients with confirmed diagnoses of either colorectal (n=57) or pancreatic cancer (n=16). For every participant, baseline blood samples were collected before the initiation of any treatment. These initial samples were used to assess a panel of laboratory parameters, including a complete blood count (CBC) as well as D-Dimer and Ferritin levels.

Prior to treatment, each patient's functional status was evaluated. We used both the Eastern Cooperative Oncology Group (ECOG) performance score and the Karnofsky Performance Status (KPS) scale. After this laboratory results all patients underwent a standard therapy regimen. To determine the therapeutic response, a follow-up imaging study (CT, MRI, or PET-CT) was performed six months after the start of treatment.

**Inclusion Criteria:** Age >18 years; histologically confirmed adenocarcinoma; ECOG performance status 0–2; no prior chemotherapy or radiotherapy for the current disease stage.

**Exclusion Criteria:** Evidence of active infection; concomitant autoimmune diseases; hematological malignancies; chronic inflammatory conditions (e.g., rheumatoid arthritis); or current use of corticosteroids or anticoagulants, as these could confound inflammatory and coagulation markers.

Patients were divided into 2 groups based on the results. Group 1 (Responders): Patients achieving Complete Response (CR) or Partial Response (PR). Group 2 (Non-responders): Patients with Stable Disease (SD) or Progressive Disease (PD).

All blood samples were processed and analyzed in the laboratory on the same day they were collected. From the baseline laboratory results, we calculated five spe-

cific biomarker ratios for each patient: NLR, LMR, PLR, FDR. It is important to note that follow-up complete blood counts were intentionally not performed, as the periodic administration of hematopoietic growth factors during chemotherapy could have compromised the integrity of these hematological results.

Complete blood count (CBC) was performed on a fully automated hematology analyzer, Alinity hq (Abbott, USA), which uses Advanced Multi-Angle Polarized Scatter Separation (MAPS™) technology. Blood was collected in K2 EDTA tubes and samples were analyzed within 1 hour of sample collection. D-Dimer was quantified in fresh plasma by immunoturbidimetric method using a fully automated coagulation assay Sysmex CS 2000-1 (Siemens, Germany). Ferritin was determined in serum by immunoturbidimetric quantitative analysis using reagents and a Roche clinical chemistry analyzer, Cobas Integra 400 (Roche, Germany).

Statistical analysis was performed using SPSS version 19.0 and Python (Scikit-learn). Normality was tested using the Kolmogorov-Smirnov test. As most variables did not follow a Gaussian distribution, non-parametric tests (Mann-Whitney U) were used for group comparisons. Receiver Operating Characteristic (ROC) curve analysis was performed to determine the predictive value of the ratios. The Area Under the Curve (AUC) was calculated, and the Youden Index was used to identify optimal cut-off values. Correlations were assessed using Spearman's rank correlation coefficient. A *p*-value <0.05 was considered statistically significant.

## RESULTS

The study group consisted of 43 males and 30 females, with a mean age of  $66.8 \pm 9.3$  years. The Responders group included 39 patients with positive response to therapy. This group included 17 women and 22 men, with a mean age of  $66.2 \pm 8.7$  years. The diagnoses within this cohort were colorectal cancer (n=34) and pancreatic cancer (n=5). The Non-responders group consisted of the remaining 34 patients who did not show a significant response to treatment. This group included 12 women and 22 men, with a mean age of  $67.5 \pm 9.9$  years. The diagnoses were colorectal cancer (n=23) and pancreatic cancer (n=11).

Descriptive analysis of the study cohort revealed distinct hematological profiles between the two groups (Table 1). Baseline leukocyte counts were significantly higher in the non-responder group compared to the responder group ( $p=0.002$ ). Similarly, neutrophil counts were significantly elevated in non-responders ( $p<0.001$ ), reflecting a heightened systemic inflammatory state prior to treatment. No statistically significant differences were observed for baseline platelet or lymphocyte

counts between the groups. regarding acute phase reactants, Ferritin levels were approximately 3-fold higher in non-responders ( $p<0.05$ ), whereas D-dimer levels did not differ significantly ( $p=0.20$ ).

Analysis of Inflammatory and Coagulation Ratios Comparison of the derived composite ratios demonstrated significant prognostic differences (Table 2):

Neutrophil-to-Lymphocyte Ratio (NLR): The median NLR was significantly higher in the non-responder group (3.36) compared to the responder group (2.06) ( $U=361$ ,  $p=0.0008$ ). Lymphocyte-to-Monocyte Ratio (LMR): The median LMR was significantly lower in non-responders (3.05) compared to responders (4.33) ( $p=0.004$ ). Ferritin-to-D-dimer Ratio (FDR): Although the median FDR was higher in non-responders (130.2 vs. 93.1), this difference did not reach statistical significance ( $p=0.10$ ), indicating that the combination of these two markers did not outperform Ferritin alone in this cohort. Platelet-to-Lymphocyte Ratio (PLR): No significant difference was observed between groups ( $p=0.50$ ).

To determine the specific predictive utility of these markers, Receiver Operating Characteristic (ROC) curve analysis was performed. NLR: Analysis yielded an Area Under the Curve (AUC) of 0.73 (95% CI: 0.61–0.84,  $p<0.001$ ), indicating good discriminatory power (Figure 1). The Youden index identified an optimal cut-off value of  $>2.43$ . At this threshold, NLR predicted treatment non-response with a sensitivity of 70.6% and a specificity of 74.4%. The LMR demonstrated a significant predictive value for favorable response (AUC = 0.70,  $p=0.004$ ) (Figure 2). An optimal cut-off of  $\leq 3.63$  was identified for predicting non-response, yielding a sensitivity of 64.7% and specificity of 85.0%.

A distinct pattern was observed regarding patient functional status. In the non-responder group, elevated NLR showed a moderate positive correlation with ECOG performance status ( $r=0.48$ ,  $p=0.004$ ) and a moderate negative correlation with Karnofsky Performance Status ( $r=-0.49$ ,  $p=0.003$ ). Notably, this correlation was absent in the responder group (ECOG  $r=0.12$ ), suggesting that systemic inflammation is directly linked to functional decline specifically in patients with refractory disease.

DISCUSSION

Our study confirms that simple blood tests can predict treatment failure. Specifically, we found that baseline NLR and LMR are strong predictors of how a patient will respond to therapy. Using ROC analysis, we identified a "danger zone": patients with an NLR higher than 2.43 or an LMR lower than 3.63 are significantly more likely to have a poor outcome.

The NLR cut-off we found (2.43) is slightly lower than what some other studies report. For instance, Li et al. suggested a cut-off of 3.0 for colorectal cancer [7], and Reddy et al. used 3.2 for pancreatic cancer [8]. However, large meta-analyses have shown that cut-offs can range widely depending on the patient group [9]. Our lower threshold suggests that even a small increase in neutrophils is a bad sign. Biologically, this makes sense. Neutrophils are not neutral bystanders. They release chemicals like VEGF that help tumors grow [10]. They also suppress the immune system's T-cells [11]. If NLR is high before treatment starts, the patient's immune system is likely already compromised.

Table 1. Comparison of median baseline hematological parameters between responders and non-responders

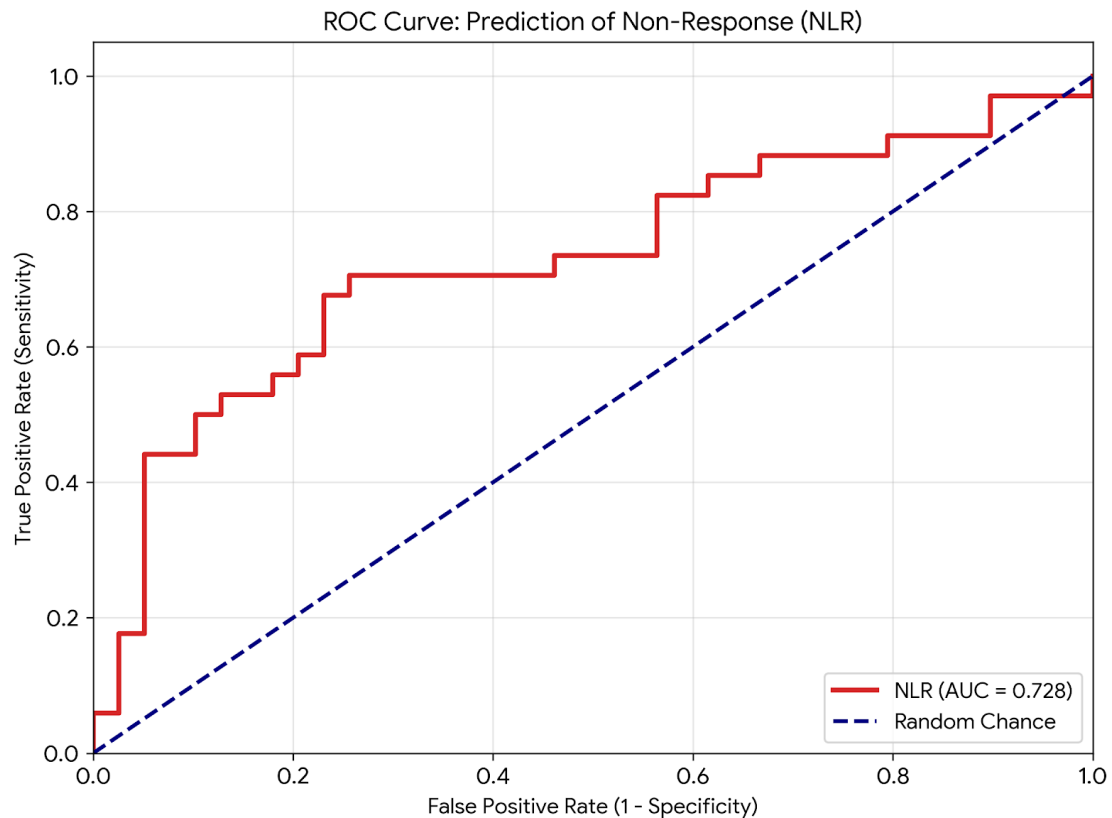
| Laboratory parameter                    | Responders (n=39) | Non- Responders (n=34) | p value         |
|-----------------------------------------|-------------------|------------------------|-----------------|
| White blood cells (x10 <sup>9</sup> /L) | 6.7 (3.1 – 13.0)  | 8.2 (4.1 – 14.2)       | < 0.05          |
| Neutrophils (x10 <sup>9</sup> /L)       | 3.6 (1.7 – 8.5)   | 5.4 (1.9 – 9.6)        | < 0.05          |
| Lymphocytes (x10 <sup>9</sup> /L)       | 2.1 (0.9 – 2.4)   | 1.9 (0.9 – 2.0)        | Non-significant |
| Monocytes (x10 <sup>9</sup> /L)         | 0.6 (0.3 – 1.2)   | 0.9 (0.4 – 1.3)        | Non-significant |
| Platelets (x10 <sup>9</sup> /L)         | 289 (125 – 527)   | 306 (160 – 664)        | Non-significant |
| Red blood cells (x10 <sup>12</sup> /L)  | 3.5 (1.1 – 3.9)   | 3.6 (1.2 – 4.0)        | Non-significant |
| Hemoglobin (g/L)                        | 126.1 ± 14.0      | 128.0 ± 15.5           | Non-significant |

Data are expressed either as median (minimum–maximum) or as mean ± standard deviation, as appropriate. A p value > 0.05 was considered statistically non-significant.

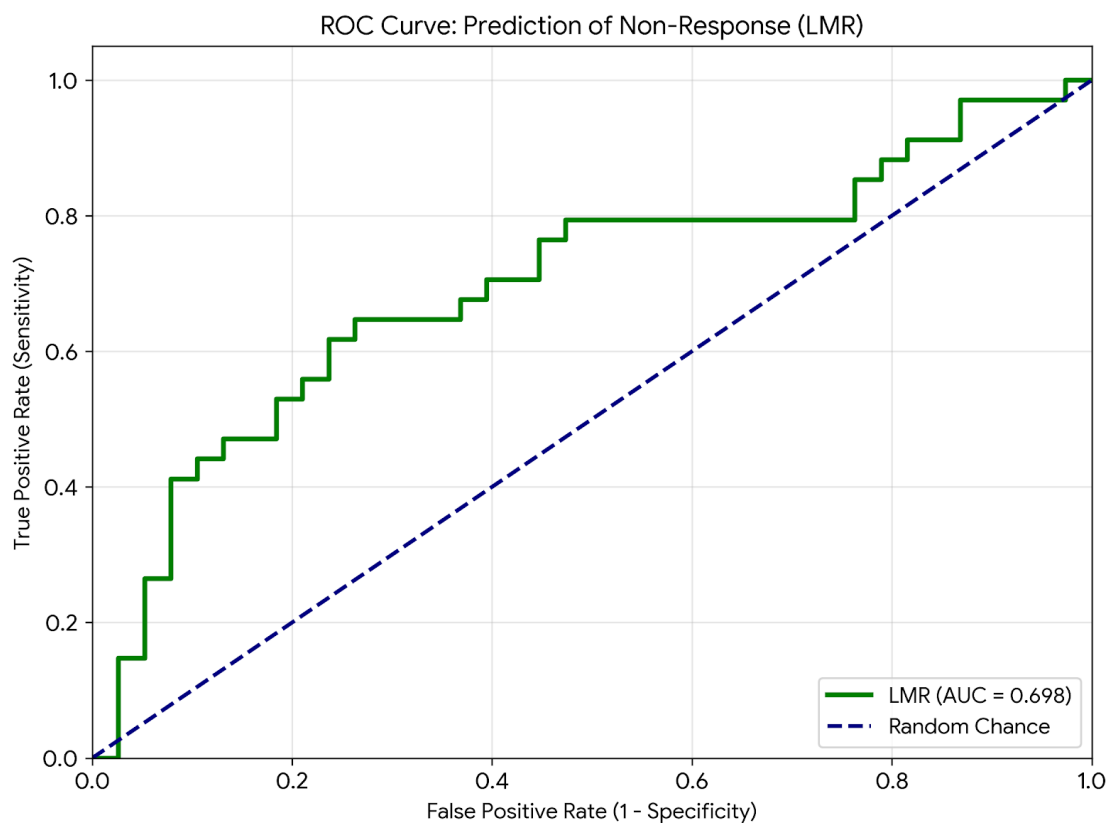
Table 2. Comparison of mean and median values for the five calculated ratios

| Composite parameter                  | Responders (n=39)                    | Non-responders (n=34)                 | p value         |
|--------------------------------------|--------------------------------------|---------------------------------------|-----------------|
| Neutrophil-to-lymphocyte ratio (NLR) | 2.16 ± 0.16<br>2.06 (0.80 – 5.60)    | 3.19 ± 1.36<br>3.36 (0.70 – 5.90)     | < 0.05          |
| Ferritin-to-D-dimer ratio (FDR)      | 177.5 ± 291.1<br>93.0 (4.5 – 1476.0) | 368.7 ± 722.4<br>130.0 (8.6 – 4017.0) | Non-significant |
| Lymphocyte-to-monocyte ratio (LMR)   | 4.80 ± 2.16<br>4.30 (2.90 – 11.90)   | 3.70 ± 2.10<br>3.10 (1.80 – 11.80)    | < 0.05          |
| Platelet-to-leukocyte ratio (PLeuR)  | 44.8 ± 13.3<br>43.7 (19.7 – 82.6)    | 40.0 ± 20.7<br>33.8 (0.4 – 92.6)      | Non-significant |
| Platelet-to-lymphocyte ratio (PLR)   | 158.7 ± 61.5<br>144.3 (70.6 – 315.7) | 184.5 ± 109.4<br>155.3 (2.5 – 452.0)  | Non-significant |

Data are expressed as as mean ± standard deviation as well as median (minimum–maximum). A p value > 0.05 was considered statistically non-significant.



**Figure 1. Predictive performance of the neutrophil-to-lymphocyte ratio (NLR) for non-response to treatment**  
Optimal cut-off value:  $\text{NLR} > 2.43$ ; AUC value 0.728 (95% confidence interval: 0.610-0.840);  $p < 0.001$ .



**Figure 2. Predictive performance of the lymphocyte-to-monocyte ratio (LMR) for non-response to treatment**  
Optimal cut-off value:  $\text{LMR} \leq 3.63$ ; AUC value 0.698 (95% confidence interval: 0.580-0.810);  $p = 0.004$ .

We found that a low lymphocyte-to-monocyte ratio (LMR) predicts treatment failure, consistent with Song et al., who identified decreased LMR as a risk factor for mortality in pancreatic cancer [12]. Similar findings have been reported in colorectal cancer [13,14]. A low LMR reflects either relative monocytosis or lymphopenia. Monocytes can differentiate into tumor-associated macrophages (TAMs), which promote tumor progression and contribute to chemotherapy resistance [15]. In contrast, lymphocytes are central to antitumor immunity, and high tumor lymphocyte infiltration is associated with better prognosis. Therefore, a high LMR—particularly when driven by increased lymphocytes—likely indicates a stronger antitumor immune response.

We observed that Ferritin levels were three times higher in non-responders. This aligns with studies showing that high ferritin promotes tumor survival and resistance to oxidative stress [16,17]. While D-dimer is often high in cancer patients due to clotting risks [18], our combined FDR ratio was not statistically significant. This differs from some reports that combine coagulation and inflammation markers [19,20]. It is possible that D-dimer levels in our patients were affected by other factors like catheters or immobility.

A key finding in our study is the link between high NLR and poor physical status (ECOG/KPS scores). This link was only seen in the non-responder group. This supports the concept of "cancer cachexia" and inflammation-driven fatigue [21]. The same cytokines that block chemotherapy also cause patients to feel weak and tired [22,23]. This "sickness behavior" is a biological symptom of the tumor's aggressiveness. Therefore, checking NLR gives us information about both the tumor and the patient's well-being.

This study has several limitations. The sample size was relatively small (n=73), and patients with colorectal and pancreatic cancers were analyzed as a single cohort. Although these malignancies share certain biological and inflammatory characteristics, they are not identical entities. Therefore, future studies with larger, disease-specific populations are warranted to validate the proposed cut-off value of 2.43 and to confirm the robustness of these findings.

## CONCLUSIONS

This study reveal that baseline serum ferritin levels, NLR, and LMR are significantly associated with treatment outcomes. Our study demonstrates that simple, cost-effective, and readily available biomarkers can help us predict the outcome of the treatment. The novel finding of a significant correlation between NLR and poorer functional status just in the non-responder group provides evidence that systemic inflammation is an important reason of both treatment failure and patient quality of life.

## ABBREVIATIONS

CBC- Complete blood count  
 ECOG score- Eastern Cooperative Oncology Group score  
 FDR- Ferritin/ D- Dimer Ratio  
 KPS- Karnofsky Performance Status scale  
 LMR- Lymphocyte-to-Monocyte Ratio  
 NLR- Neutrophil-to-Lymphocyte Ratio  
 PLeuR- Platelet-to-Leukocyte Ratio  
 PLR- Platelet-to-Lymphocyte Ratio

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## AUTHORS' CONTRIBUTION

KP: methodology, investigation, formal analysis, writing (original draft).  
 PT: investigation, formal analysis, writing (original draft).  
 II: methodology, investigation, formal analysis.  
 PMK: investigation, formal analysis, writing (original draft, review & editing).  
 VG: conceptualization, methodology.  
 ZK: methodology, formal analysis, writing (review & editing).  
 All authors have read and approved the final version of the manuscript.

## CONFLICT OF INTEREST

None to declare.

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