Prognostic Significance of Inflammatory Markers in Oncology: Evaluating Neutrophil-to-Lymphocyte Ratio in Mediastinal Germ Cell Tumors and Colorectal Cancer with Liver-Only Metastases

Ph.D. Thesis

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Introduction:

The neutrophil-to-lymphocyte ratio (NLR) has emerged as a significant prognostic biomarker in cancer research. Derived from routine blood tests, NLR reflects the balance between systemic inflammation (neutrophils) and immune response (lymphocytes).
Elevated NLR has been associated with poor outcomes in various cancers due to its indication of an inflammatory tumor microenvironment, which facilitates tumor progression and metastasis. Numerous studies have established that elevated NLR is consistently associated with poorer OS and PFS across a broad spectrum of cancers, including gastrointestinal, lung, breast, and urological malignancies.
Templeton et al. (2014) conducted a comprehensive meta-analysis, demonstrating that high NLR predicted reduced OS and PFS across 60 studies covering diverse cancers. [1] The biological background behind the mechanism was studied by Galdiero et al. And was concluded that an elevated NLR reflects a systemic inflammatory state driven by neutrophils, which secrete pro-tumorigenic factors like vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs). This inflammatory microenvironment suppresses cytotoxic lymphocytes, reducing anti-tumor immunity and promotes tumor growth, angiogenesis, and metastasis. Conversely, low lymphocyte counts indicate a weakened adaptive immune response, further compromising the host's ability to control tumor progression. The dual role of neutrophils and lymphocytes makes NLR a compelling and accessible biomarker for cancer prognosis. [2] But unfortunately this general biomarker has its own disadvantages for instance NLR thresholds for prognostic classification vary significantly between studies and cancer types, complicating its clinical implementation. For example, while some studies use a cut-off of 3, others consider 5 as the threshold for high risk. The prognostic significance of NLR also varies by tumor type, stage, and treatment modality. For instance, NLR is a stronger predictor in metastatic settings compared to localized disease. [1] But regardless of its limitations the simplicity and cost-effectiveness of measuring NLR make it an attractive biomarker for clinical use. It can aid in risk stratification, guiding treatment decisions, and monitoring therapeutic responses.

My thesis work explores two specific applications of the use of NLR one of which in Mediastinal Germ Cell tumors (MGCT), a rare tumor subtype, to predict disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) across different histological types and disease stages and the application of NLR and SII in CRLM, with a focus on rectal liver metastases (RLM) and colon liver metastases (CLM), to evaluate their influence on relapse-free survival (RFS) and OS following metastasectomy.

Main Research Questions

1.: How does the neutrophil-to-lymphocyte ratio (NLR) influence survival outcomes in primary mediastinal germ cell tumors (MGCT), and what are the differences between seminomas and nonseminomas in this regard?

2.: What was the role of systemic immune-inflammation index (SII) in rectal liver- only metastases (RLM), and how did its prognostic value compare to that of NLR?

3.: In what way did high NLR and SII emerge as favorable prognostic markers in rectal liver metastases (RLM), and how does this finding contrast with their prognostic roles in colon liver metastases (CLM)?

4.: What evidence supports the integration of inflammatory markers like NLR into clinical decision-making for tailoring treatments in high-risk nonseminomatous MGCT and rectal liver metastases (RLM)?

5.: How do the findings of these studies challenge traditional assumptions about the prognostic roles of inflammatory markers in cancer and highlight the need for cancer-type-specific prognostic models?

Methods

Our Mediastinal Germ cell tumor study was aimed to investigate the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in patients with primary mediastinal germ cell tumors (MGCT). The research was conducted as a retrospective cohort study spanning two decades (1998–2018) and focused on identifying correlations between NLR and survival outcomes such as disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS). The study included 59 patients diagnosed with MGCT, divided into seminomas (S) and nonseminomas (NS) based on histology. Patients were further categorized by disease stage (localized or disseminated). Inclusion criteria ensured the availability of complete clinical data, treatment details, and NLR measurements. Patients with confounding inflammatory or hematologic disorders were excluded.

The NLR values were calculated at the time of diagnosis using routine complete blood counts, with a predefined cut-off value used for stratification. Patients underwent standard treatment protocols, including neoadjuvant BEP (bleomycin, etoposide, cisplatin) chemotherapy, surgical resection, or a combination. The study recorded treatment responses to evaluate their association with survival outcomes. For statistical analysis Kaplan-Meier curves and Cox proportional hazards models were employed to assess the relationship between NLR and survival metrics. Subgroup analyses were conducted to compare outcomes between seminomas and nonseminomas.

Our CRLM study was a retrospective study aimed to evaluate the prognostic utility of NLR and the systemic immune-inflammation index (SII) in rectal liver-only metastases (RLM). The study included 170 patients (103 with RLM and 67 with colon liver metastases [CLM]) treated between 2001 and 2018. It sought to identify differences in NLR and SII's predictive power between RLM and CLM patients. Eligibility criteria included patients with confirmed liver-only metastases undergoing metastasectomy. Preoperative chemotherapy or targeted therapy regimens were recorded to account for their influence on inflammatory markers. Patients with mixed primary cancers or systemic inflammatory conditions were excluded to ensure homogeneity.

NLR and SII were derived from routine preoperative blood tests. NLR was calculated as the ratio of absolute neutrophil count to lymphocyte count, while SII incorporated platelet count alongside neutrophils and lymphocytes. For statistical analysis survival metrics, including relapse-free survival (RFS) and OS, were analyzed using multivariate Cox regression models. Hazard ratios were calculated to determine the prognostic significance of high versus low NLR/SII. Kaplan-Meier survival curves illustrated differences between subgroups.

Results

Our Mediastinal Germ cell tumor study found that elevated NLR was significantly associated with worse survival outcomes, particularly in NS patients. Objective response rates (complete or partial) emerged as independent predictors of OS, suggesting a potential role for integrating NLR into prognostic models for MGCT. On the contrary our CRLM study we found that high NLR and SII were independently associated with longer RFS and OS in RLM patients, contrary to expectations based on previous CRLM studies.

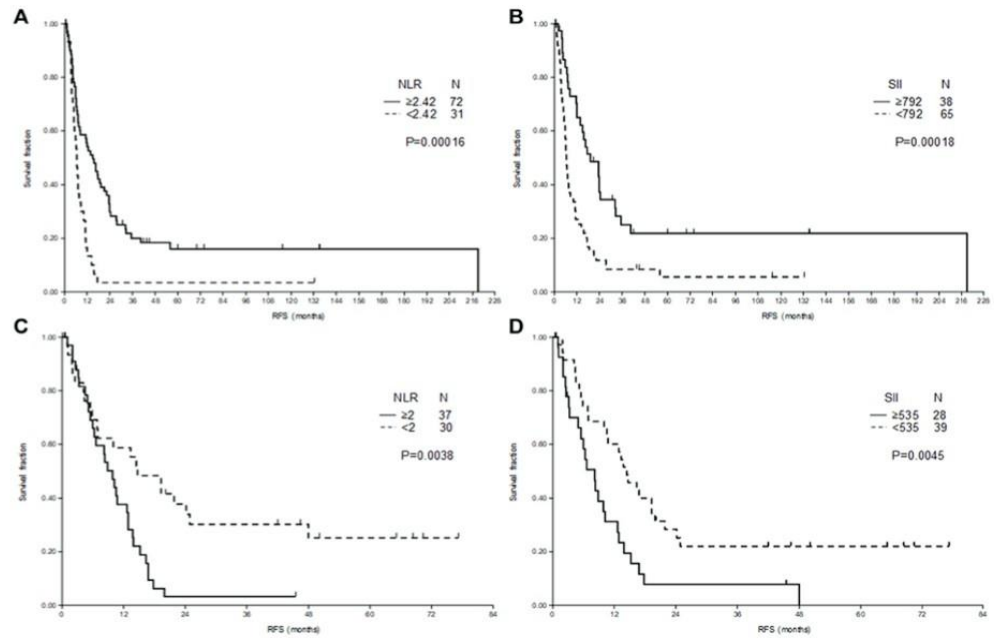

FIGURE 1 | Relapse-free survival (RFS) after liver metastasectomy of patients with rectal cancer **(A,B)** and colon cancer **(C,D)** according to neutrophil-to-lymphocyte ratio (NLR) **(A,C)** and systemic immune-inflammation index (SII) **(B,D)**.

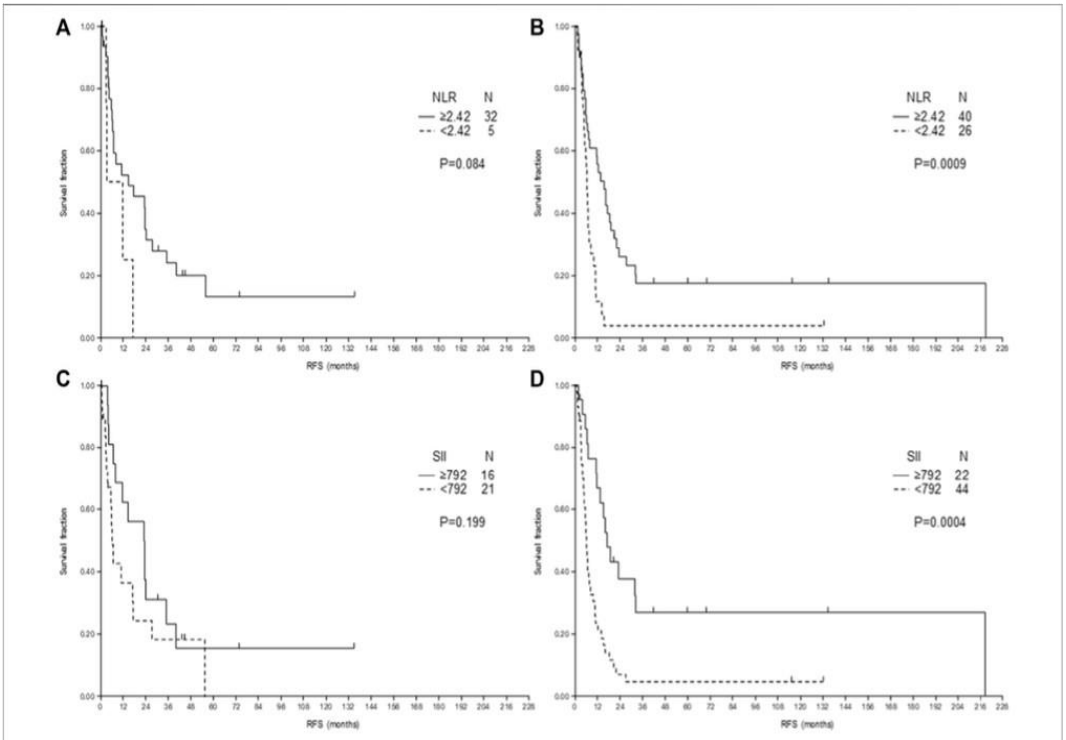

FIGURE 2 | Relapse-free survival (RFS) after liver metastasectomy of patients with rectal cancer according to neutrophil-to-lymphocyte ratio (NLR) **(A,B)** and systemic immune-inflammation index (SII) **(C,D)** and according to treatment: no treatment **(A,C)** or chemotherapy (±targeted treatment) before metastasectomy **(B,D)**.

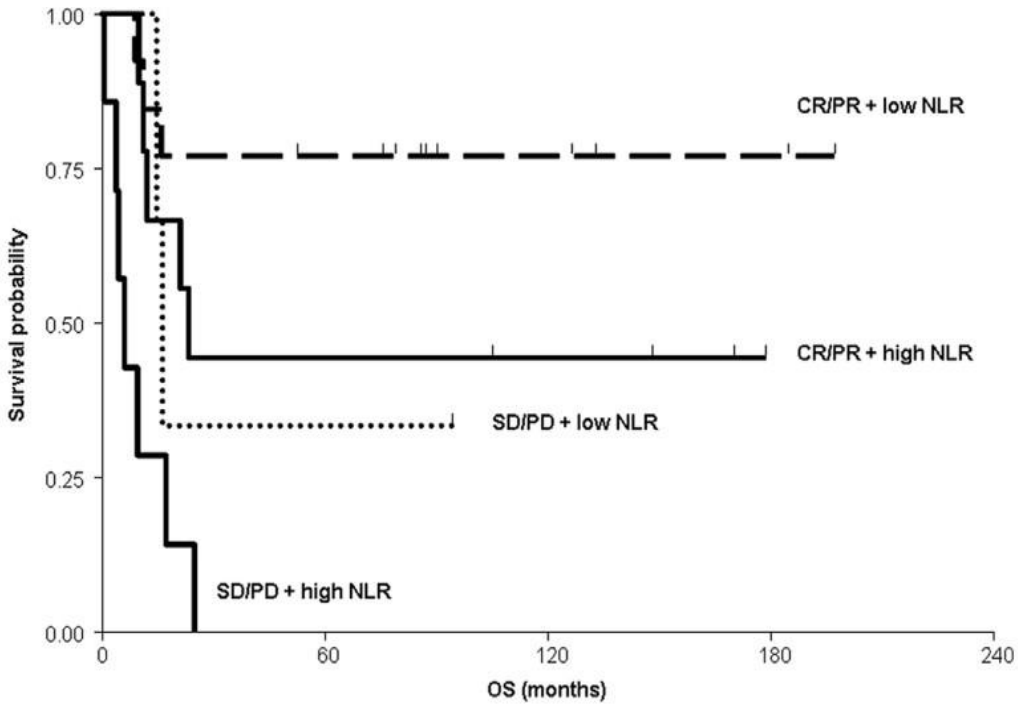

Fig. 3. Overall survival (OS) according to median neutrophil-to-lymphocyte ratio (NLR) and best response of patients with nonseminoma. Log rank test $P = 3.5 \times 10^{-4}$; survival rate at 5, 10, and 15 years for CR/PR + low NLR is uniformly 77%, for CR/PR + high NLR is uniformly 44.4%. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Discussion

The mechanisms underlying tumor progression extend beyond the neutrophil-to-lymphocyte ratio (NLR). The tumor microenvironment (TME) in solid malignant tumors consists of a complex and dynamic interplay between cancer cells, the extracellular matrix (ECM), surrounding blood vessels, tumor-associated stromal cells (including various immune cells and fibroblasts), and secreted soluble factors. These interactions within the TME are crucial for driving cancer heterogeneity, clonal evolution, and the development of multidrug resistance, ultimately leading to tumor progression and metastasis. During tumor progression, cancer cells evade signals intended to restore tissue homeostasis. The angiogenic characteristics of the TME play a significant role in tumor growth. Folkman described that in situ carcinomas (measuring less than 0.5 to 1 mm in diameter) typically exhibit a non-angiogenic profile. However, as the tumor grows, the TME transitions to a hypoxic and inflammatory state, which strongly depends on angiogenesis, promoting metastatic expansion. Consequently, the TME functions as a complex network of pro- and anti-inflammatory signals that lack a stable homeostatic balance.[3]

It has long been suspected that the microenvironment of colorectal tumors—and consequently, several oncologically significant characteristics—differs from that of other tumor types. Hungarian researchers published results in 2015 showing that the baseline MDR1 activity in colorectal tumors is reduced, a feature that also sets it apart from the microenvironments of many other tumor types. [4]

Our findings align with those of Pine et al., who conducted a similar study and reported comparable results. They suggested that the longer recurrence-free survival (RFS) observed in colon cancer cases with a low neutrophil-to-lymphocyte ratio (NLR) may be attributed to the presence of tumor-infiltrating lymphocytes (TILs). Specifically, Pine et al. found that a low NLR in colorectal cancer (CRC) patients, of whom 73% had colon cancer, was significantly associated with higher levels of TILs ($p = 0.005$) at the invasive tumor margin, as well as a significantly longer disease-free survival (DFS). CD8+ TILs are believed to contribute to an antitumoral response, fostering an unfavorable tumor immune microenvironment (TIME) that ultimately results in longer RFS.[5]

Conclusion

The prognostic value of inflammatory markers like the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII) varies significantly across cancer types. In high-risk nonseminomatous mediastinal germ cell tumors (MGCT), elevated NLR is associated with poor survival, reflecting their aggressive biology and systemic inflammation, whereas seminomas maintain better outcomes regardless of NLR levels. In rectal liver-only metastases (RLM), high NLR and SII unexpectedly correlate with improved relapse-free and overall survival, contrasting their typically adverse prognostic roles in other cancers like colon liver metastases (CLM), where lower levels predict better outcomes. This discrepancy underscores the distinct tumor biology and immune environment in rectal cancer. These findings challenge traditional assumptions and emphasize the importance of cancer-type-specific models but could be explained by the different tumor microenvironment.

Future Prospectives

The simplicity and cost-effectiveness of measuring NLR and SII make them attractive for clinical use. However, standardization of thresholds and validation across diverse populations are necessary for broader implementation. Collaborative multicenter studies could address these issues and facilitate the integration of these markers into clinical guidelines. Furthermore the link between systemic inflammation and cancer progression suggests potential therapeutic opportunities. Targeting the inflammatory pathways associated with high NLR and SII could enhance treatment outcomes. For example, the use of anti-inflammatory agents or immune-modulating therapies could be explored in conjunction with conventional treatments to improve survival in high-risk patients.

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List of Abbreviations:

- **NLR**: Neutrophil-to-Lymphocyte Ratio
- **SII**: Systemic Immune-Inflammation Index
- **MGCT**: Mediastinal Germ Cell Tumor
- **S**: Seminoma
- **NS**: Nonseminoma
- **CRLM**: Colorectal Liver Metastases
- **RLM**: Rectal Liver Metastases
- **CLM**: Colon Liver Metastases
- **DFS**: Disease-Free Survival
- **PFS**: Progression-Free Survival
- **OS**: Overall Survival
- **RFS**: Relapse-Free Survival
- **BEP**: Bleomycin, Etoposide, Cisplatin (chemotherapy regimen)
- **VEGF**: Vascular Endothelial Growth Factor
- **MMPs**: Matrix Metalloproteinases
- **TME**: Tumor Microenvironment
- **TIME**: Tumor Immune Microenvironment
- **ECM**: Extracellular Matrix
- **TILs**: Tumor-Infiltrating Lymphocytes

Published Articles

Related to dissertation

Polk N, Budai B, Hitre E, Patócs A, Mersich T

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Pathol Oncol Res 28:1610315, 2022 doi: 10.3389/pore.2022.1610315

IF: 2.8 Independent citations: 23

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Magyar Sebész Társaság 65. Kongresszusa, valamint az MST Kísérletes Sebészeti Szekció XXVIII., a Coloproctológiai Szekció, a Sebészeti Endoszkópos Szekció és a Sebészeti Onkológiai Szekció csatlakozó kongresszusa, 2021