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Orijinal Makale

Can Systemic Inflammatory Index (SII) and MELD Score Predict Survival in Liver Metastatic Colorectal Cancer?

Sistemik Inflamatuar Index (SII) ve MELD Skoru Karaciğer Metastatik Kolorektal Kanserde Sağ Kalımı Öngörebilir mi ?

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ABSTRACT

Aim: In this study, it was aimed to investigate whether the blood neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and model for end-stage liver disease (MELD) score at the time of liver metastasis in colorectal cancers (CRC) predict overall survival (OS) and their prognostic roles.

Materials and Methods: 1250 colorectal cancer patients followed up in our oncology center between 2015-2020 were retrospectively screened and 203 patients with liver metastatic colorectal cancer (LMCRC) were included in the study. Blood NLR, PLR and MELD scores at the time of liver metastasis were calculated retrospectively .

Results: Liver specific OS (LSOS) was 22 months (95% CI: 16.82-27.18) in patients with an NLR ratio of 2.5 or less, while it was 10 months (95% CI: 6.59-13.41) in patients with an NLR rate above 2.5 (p=0.004). LSOS was 19 months (95% CI: 14.33-23.36) in patients with a PLR rate of 150 or less, and 10 months (95% CI: 5.52-14.47) in patients with a PLR rate above 150 (p=0.0042). There was a negative correlation between MELD score and LSOS (r.-0.152, p=0.031). In the multivariate regression analysis, high NLR rate was found to be an independent prognostic factor for LSOS (HR:95% CI:1.08-1.98).

Conclusion: In this study, it was shown that higher NLR, PLR and MELD scores are associated with worse survival in LMCRC. NLR was revealed to be an independent prognostic factor for LSOS. Closer follow-up may be an option in patients with high SII and MELD scores when liver metastasis develops.

Keywords: NLR; PLR; MELD Score; Liver Metastatic Colorectal Cancer; Overall Survival.

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ÖZ

Amaç: Bu çalışmada kolorektal kanserlerde (CRC) karaciğer metastazı geliştiği andaki kan nötrofil lenfosit oranı (NLR), platelet lenfosit oranı (PLR) ve model for end-stage liver disease (MELD) skorunun genel sağ kalımı (OS) predikte edip etmediği ve prognositik rollerinin araştırılması amaçlanmıştır.

Gereç ve Yöntemler: Onkoloji merkezimizde 2015-2020 yılları arasında takip edilen 1250 kolorektal kanser tanılı hasta retrospektif olarak tarandı ve 203 karaciğer metastatic kolorektal kanserli (LMCRC) hasta çalışmaya dahil edildi. Karaciğer metastazı geliştiği andaki kan NLR, PLR ve MELD skorları retrospektif olarak hesaplandı.

Bulgular: NLR oranı 2.5 ve altında olan hastalarda liver specific OS (LSOS) 22 ay (95% C.I: 16.82-27.18) iken, 2.5 üzerinde olanlarda ise 10 ay idi (95% C.I:6.59-13.41) (p=0.004). PLR oranı 150 ve altında olan hastalarda LSOS 19 ay (95% C.I: 14.33-23.36), 150'nin üzerinde olanlarda ise 10 ay idi (95% C.I:5.52-14.47) (p=0.0042). MELD skoru ile LSOS arasında negatif bir korelasyon vardı (r.-0.152, p=0.031). Multivariate regresyon analizinde yüksek NLR oranı LSOS açısından bağımsız prognostic faktör olarak saptandı (HR:95% CI:1.08-1.98).

Sonuç: Bu çalışmada yüksek NLR, PLR ve MELD skorunun LMCRC'de daha kötü bir sağ kalımla ilişkili olduğu gösterildi. NLR'nin LSOS için bağımsız prognostik bir faktör olduğu ortaya konuldu. Karaciğer metastazı geliştiği anda bakılan SII ve MELD skoru yüksek olan hastalarda daha yakın bir takip seçenek olabilir.

Anahtar Kelimeler: NLR; PLR; MELD Skoru; Karaciğer Metastatik Kolorektal Kanser; Genel Sağ Kalım.

Introduction

Colorectal cancers (CRC) are one of the most common malignancies among all. The liver is the most common area of metastasis, with 40% of the patients present as de-novo metastatic, while synchronous and metachronous liver metastases can be seen in approximately 20% of each [1,2]. Despite all the advances in treatment approaches, long-term overall survival (OS) results in liver metastatic colorectal cancer (LMCRC) patients are not satisfactory enough yet, and non-invasive markers that predict survival in these patients are gaining even more importance.

In recent years, there have been many studies showing that inflammation-based blood parameters predict survival in patients with CRC [3,4,5]. The roles of systemic inflammatory response in tumor progression and metastasis steps are known [6]. The host immune response to malignancy is a critical tool, causing systemic inflammation associated with altered blood markers due to overexpression of proinflammatory cytokines and signaling molecules [7]. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), which are the most frequently used systemic inflammatory blood markers in clinical practice, are easily applicable and inexpensive parameters that show this systemic inflammation. It has been shown that high NLR and PLR values are associated with tumor aggressiveness and poor prognosis [8,9].

The Model for end-stage liver disease (MELD) score is essentially a chronic liver disease severity scoring system that uses a patient's laboratory values such as serum bilirubin, serum creatinine, and international normalized ratio (INR) to predict 90-day survival [10]. The MELD score has also proven useful in other clinical situations and is most commonly used to prioritize candidates awaiting liver transplantation [11,12]. Previous studies have shown that MELD has a good predictive value , especially in hepatocellular cancer (HCC) or in patients with primary or secondary liver tumors scheduled for surgery [13,14]. Data on the prognostic and predictive use of the MELD score in LMCRC patients are limited. Therefore, this study aimed to investigate the prognostic significance of systemic inflammatory indexes (SII) and MELD score for OS after liver metastasis in LMCRC .

Materials and Methods

Patients

In this study, 1250 colorectal cancer patients followed in our oncology center between 2015 and 2020 were retrospectively screened. Of these patients, 203 patients who met the inclusion criteria were included in the study. Patients over the age of 18 who were diagnosed with LMCRC were included in the study. Patients with secondary malignancy, patients under 18 years of age, patients with additional comorbidities and conditions that may affect systemic inflammatory markers such as active

infection and steroid use were excluded from the study. In addition to demographic data of all patients, complete blood count and biochemistry parameters at the time of diagnosis of liver metastasis were recorded.

Blood Parameters

NLR and PLR were calculated with the formula: Neutrophil count (/µL) / Lymphocyte count (/µL) and Platelet count (109/L) / Lymphocyte count (/µL). The cut-off values for NLR and PLR were taken as 2.5 and 150, respectively (3,15). MELD score is calculated using the patient's serum bilirubin, serum creatinine and PT/INR. It is calculated according to the following formula: MELD = 3.78 × ln [serum bilirubin (mg/dL)] + 11.2 × ln [INR] + 9.57 × ln [serum creatinine (mg/dL)] + 6.43. When using the MELD score, the cut-off value was taken as 10 (16).

Statistical Method

Statistical analyzes were performed with SPSS 25.0 software (SPSS, Chicago, IL, USA). Mann Whitney U test for comparison of non-parametric data and Student T test was used to compare parametric data. Chi-square or Fisher's Exact test was used to compare categorical data. Kaplan–Meier method was used for survival analysis and Log-Rank test was performed for comparisons between groups. Predictive factors affecting overall survival were determined by multivariate analysis with the Cox proportional hazards model. p value <0.05 was considered as statistically significant. The primary endpoint was LSOS .

Results

Of the 203 patients included in the study, 132 (65%) were male, with a median age at diagnosis of 60 (IQR 52-68). Patients' demographic data are summarized in Table-1. The overall survival of the patients was 18 months (95% CI: 9-30), while the OS (liver-specific OS) after development of liver metastasis was 15 months (95% CI: 6-28). Liver specific OS (LSOS) was 22 months (95% CI: 16.82-27.18) in patients with an NLR ratio of 2.5 and below, while it was 10 months (95% CI: 6.59-13.41) in patients with an NLR above 2.5, which was statistically significant (p=0.004). LSOS was 19 months (95% CI: 14.33-23.36) in patients with a PLR ratio of 150 and below, and 10 months (95% CI:5.52-14.47) in patients with a PLR ratio above 150, which was statistically significant (p=0.0042). There was a negative correlation between MELD score and LSOS (r.-0.152, p=0.031). LSOS was 16 months (95% CI: 12.94-19.05) in patients with a MELD score of 10 and below, and 4 months (95% CI: 0-12.76) in those with a MELD score of 10, although there was a numerical difference, it did not reach statistical significance (p=0.24). When multivariate regression analysis was performed, high NLR rate was found to be an independent prognostic factor for LSOS (HR:95% CI:1.08-1.98).

Table 1: Baseline Characteristics of the Patients

Variables	N	Percent %
Age (years)	60 (IQR 52-68)	
Gender		
Male	132	65%
Female	71	35%
Location		
Right sided colon	33	16.3%
Left sided colon and rectum	162	79.8%
Transvers colon	8	3.9%

Discussion

In this presented study, the relationship between survival after liver metastasis development and SII and MELD scores in patients with CRC was examined. A negative correlation was found between LSOS and NLR, PLR and MELD scores, and NLR was shown to be an independent prognostic factor.

Although there are many studies showing that NLR is a predictive marker in CRC, data on its prognostic significance are more limited [3]. In this presented study, it has been shown that survival is much lower in LMCRC with an NLR cut-off above 2.5. (22 months vs 10 months). In a meta-analysis of 8 studies including 1685 patients in total, it was shown that high NLR rates in LMCRC were associated with worse long-term survival [3]. In another study conducted in resectable LMCRC, high NLR levels were found to be associated with poor survival [4]. Although the reasons for the correlation of high NLR with low survival cannot be clearly revealed, it is known that NLR reflects systemic inflammation [5]. Many studies have revealed the affiliation of NLR with cytokines that play an important role in carcinogenesis, such as interleukin 6, interleukin 8, and vascular epidermal growth factor [17,18]. It is also known that the inflammatory response by promoting angiogenesis and suppressing the immune response will create a favorable microenvironment that will facilitate the survival of pre-malignant cells [19]. An elevated NLR presents with high neutrophils and/or low lymphocytes. Studies have proven that lymphocytes induce tumor cell apoptosis and are inversely proportional to tumor proliferation and invasiveness [15,20]. Therefore, decreased lymphocytes may facilitate the tumor dissemination potential by causing a decrease in antitumor response [21]. In the present study, NLR was shown to be an independent prognostic factor for LSOS, in line with the data in the literature.

In the study, it was found that LSOS was lower in patients with PLR above 150 and there was a negative correlation between PLR and survival. Although not as many as NLR, there are also publications about the relationship between PLR and CRC in the literature. In a meta-analysis performed in CRC, which included non-metastatic patients, it was found that high PLR showed a worse prognosis [15]. In another study by Baranyai et al., in which patients from all stages were included and their platelet and PLR levels were examined, it was found that high platelet was an independent prognostic factor in the metastatic group, and although high PLR was negatively correlated with survival, similar to the presented study, it was an independent prognostic factor in multivariate analysis. It has been reported that it is not a factor [22]. High PLR occurs with high platelet and/or low lymphocyte levels. Platelets contribute to the development of tumor and metastasis [22]. It supports the growth of tumor cells and angiogenesis by secreting various angiogenic and tumor growth factors such as thrombospondin, platelet factor 4 (PF4), transforming growth factor beta (TGF-β) and vascular endothelial growth factor (VEGF) [23,24,25].

The MELD score, which is a chronic liver disease severity score, reflects 3-month mortality quite well. Although statistical significance could not be reached due to the small number of patients in the present study, a negative correlation was found between the MELD score and LSOS, and numerically lower survival was observed in those with a cut-off above 10. Studies that directly reflect the relationship of MELD score with CRC and LMCRM are very limited. MELD score has been investigated oncologically, especially in HCC. In a study investigating the prognostic models of scoring systems in patients with HCC, it was shown that MELD reflects the prognosis well [26]. In another study in which approximately 15000 liver metastatic cancer patients were examined, it was reported that MELD is a predictive score that reflects mortality well after metastasectomy [11]. Studies have shown that as the severity of chronic liver disease increases or hepatic fibrosis increases, there is an increase in the development of metastases in this setting. In a study by Kondo et al., liver fibrosis was shown to be a valuable prognostic factor for hepatic recurrence after curative surgical resection of CRC (27). In previous studies, suppression of hepatic fibrosis has been shown to reduce the development of metastasis. Cytokines such as TGF-β and hepatocyte growth factor are involved in the formation of fibrosis [28]. These cytokines may also increase the invasion of cancer cells and create an easier environment for metastasis [29]. Since the MELD score also indirectly reflects the severity of chronic liver disease and fibrosis, a worse prognosis occurred and LSOS decreased as the MELD score increased, which was consistent with the literature.

This study has some limitations. It was retrospective, and a prospective multicenter study would be much better in terms of evaluating inflammatory parameters and scores. Also there is a risk of bias in some results due to the small number of patients, lack of invasive methods confirming fibrosis and missing data.

Conclusion

In this study, higher SII (NLR, PLR) and MELD scores were shown to be associated with poorer survival in LMCRC. It was also revealed that NLR is an independent prognostic factor for LSOS. Closer follow-up and aggressive treatment may be an option for patients with high SII and MELD scores at the time of liver metastasis. Large prospective studies on this subject will provide better information and could reduce the possibility of bias.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest

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