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**Name of Journal:** *World Journal of Clinical Oncology*

**Manuscript NO:** 77327

**Manuscript Type:** SYSTEMATIC REVIEWS

**Neutrophil-to-Lymphocyte ratio as a prognostic factor for the survival in patients with colorectal liver metastases: a systematic review**

Papakonstantinou *et al.* NLR in colorectal liver metastases prognosis.

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## **Abstract**

### **BACKGROUND**

The inflammatory response to tumor has been proven to be closely related to the prognosis of colorectal cancer. Neutrophil to Lymphocyte Ratio (NLR) is a widely available inflammatory biomarker that may have prognostic value for patients with colorectal liver metastasis (CRLM).

### **AIM**

To assess the role of NLR as a prognostic factor of survival and tumor recurrence in patients with CRLM.

### **METHODS**

A systematic literature search of PubMed, Cochrane Library and clinicaltrials.gov was conducted by two independent researchers in order to minimize potential errors and bias. Conflicts were discussed and settled between three researchers. Studies including patients undergoing different types of medical interventions for the treatment of CRLM and evaluating the correlation between pretreatment NLR and disease-free survival (DFS) and overall survival (OS) were included in the review. Nineteen studies, involving 3,283 patients matched our inclusion criteria.

### **RESULTS**

In the studies that we included, NLR was measured before the intervention and the NLR thresholds ranged between 1.9 and 7.26. Most studies used 5 as the cut-off value. Liver metastases were treated with hepatectomy with or without chemotherapy regimens in 13 studies and with radiofrequency ablation, radioembolization, chemoembolization or solely with chemotherapy in 6 studies. High NLR was associated with decreased overall survival and disease-free survival after liver resection or other medical intervention. Moreover,

high NLR was associated with poor chemosensitivity. On the contrary, CRLM patients with low pretreatment NLR demonstrated improved OS and DFS. NLR could potentially be used as a predictive factor of survival and tumor recurrence in patients with CRLM treated with interventions of any modality, including surgery, chemotherapy and ablative techniques.

## CONCLUSION

NLR is an inflammatory biomarker that demonstrates considerable prognostic value. Elevated pretreatment NLR is associated with poor OS and DFS in patients with CRLM who are submitted to different treatments.

**Key Words:** Neutrophil-to-Lymphocyte Ratio; Colorectal liver metastasis; Prognosis; Survival

Papakonstantinou M, Fiflis S, Christodoulidis G, Giglio MC, Louri E, Mavromatidis S, Giakoustidis D, Papadopoulos VN, Giakoustidis A. Neutrophil-to-Lymphocyte ratio as a prognostic factor for the survival in patients with colorectal liver metastases: a systematic review.. *World J Clin Oncol* 2022; In press

**Core Tip:** <sup>1</sup>Colorectal cancer is the third most common cancer globally and liver is the most common site of metastasis. Even though surgery and chemotherapy are the main treatment options, prognostic markers are also essential for the progress and future management of the disease. Neutrophil-to-Lymphocyte Ratio is a promising biomarker that has been recently proposed as an indicator for the survival and recurrence of various malignancies. In our review we assess the role of NLR in the overall survival of patients with colorectal liver metastases.

## INTRODUCTION

According to GLOBOCAN 2020 Data,<sup>1</sup> colorectal cancer (CRC) is the third most frequent cancer in both men and women with an estimated 1.931.500 new cases and 935.173 deaths worldwide in 2020. The liver is the most common site of metastasis in patients with CRC since almost 50% of these patients will develop liver metastases (LM) during the course of their disease of whom 15-25% have LM at initial diagnosis. The rest 18-25% will have metachronous LM in the next 5 years.<sup>1,2</sup> The management of patients with colorectal liver metastases (CRLM) consists of different treatment options such as tumor resection, radiofrequency ablation (RFA), which can destroy the tumor by usage of high-frequency electromagnetic current and can be applied in unresectable CRLM, or microwave ablation. Other treatment options include systemic therapy, such as Irinotecan-loaded drug-eluting beads and radioembolization (RE), that administer high doses of chemotherapy and radiation respectively, and chemotherapy. The intra-arterial techniques aim specifically at the tumor's vasculature, thus minimizing systemic toxicity, and may be an option in patients not eligible for surgery or ablation.<sup>3</sup> Different treatment methods are selected depending on the patient's clinical and radiological data.<sup>4</sup> Advancements in treatment for patients with CRLM have resulted in an improved 5-year survival rates as high as 46%, however survival remains low in patients where all sites of disease are not surgically resectable.<sup>5</sup> The low 5-year overall survival (OS) and the fact that recurrences occur in more than half of the CRLM patients, highlights the need for more prognostic factors that could be easily applied in predicting OS as well as disease-free survival (DFS).<sup>6</sup>

Many studies have examined the prognostic role of neutrophil to lymphocyte ratio (NLR) in CRLM patients. NLR is a widely available, low-cost prognostic index<sup>1</sup> that is calculated by dividing the number of neutrophils by the number of lymphocytes and reflects the inflammatory response of the patient against the tumor, which is correlated with tumor development and poor outcomes.<sup>7,8</sup> Neutrophils play a role in cancer development and metastases, while lymphocytes mediate an immune response against the malignancy, consequently an elevated NLR value could indicate a protumorigenic status.

In this systematic review we investigated the association between NLR and the prognosis of CRLM in patients treated with interventions of any modality including surgery, chemotherapy and ablative techniques.<sup>9,10</sup> High NLR has been associated with poor survival in CRLM patients in Tang's *et al* systematic review and metaanalysis which included 8 studies and Haram's *et al* systematic review which included 8 studies too. In this systematic review we investigated the association between NLR and the prognosis of CRLM in patients treated with interventions of any modality including surgery, chemotherapy and ablative techniques.<sup>9,10</sup> High NLR has been associated with poor survival in CRLM patients in Tang's *et al* systematic review and metaanalysis which included 8 studies and Haram's *et al* systematic review which included 8 studies too.<sup>11,12</sup> Our systematic review includes 19 studies thus making the analysis' results more robust. It consists of 12 studies including 2.442 patients treated surgically, 6 studies including 641 patients treated with RFA or RE or solely chemotherapy and 1 study (Kishi *et al*) including 200 patients treated surgically and 90 different patients treated with RFA. We studied the different impact of pretreatment NLR as a prognostic factor depending on the medical intervention and we present the analysis' results in two categories. The first category included 2.642 patients that were treated surgically and the second category included 731 patients that were treated with ablative techniques or solely chemotherapy. All the studies that we included demonstrate that CRLM patients with low pretreatment NLR present better survival and disease-free survival in comparison to high pretreatment NLR patients regardless of the medical intervention that they were submitted to.

## **MATERIALS AND METHODS**

### Data extraction and risk of bias

A systematic literature search of PubMed and the Cochrane Library was performed using the following search terms: "Neutrophil to Lymphocyte Ratio and liver metastas\* and survival", "NLR and liver metastas\* and survival", "NLR and liver metastasis and prognostic factor", "NLR and liver metastas\*" and "NLR". The same search strategy

was used for the trial registry "ClinicalTrials.gov" in order to minimize publication bias by identifying unpublished studies.

The titles of the articles were screened and relevant abstracts were assessed for eligibility. After excluding duplicates, eligible articles were further evaluated and then the references of those studies were also checked. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart is shown in Figure 1.

In order to minimize possible errors and bias, two independent researchers blindly reviewed the literature and extracted data using the method of completely independent data extraction. After that, any potential differences were cleared up through discussion between them and a third reviewer.

The following data were extracted from each study: 1) patients' clinicopathological characteristics, 2) the treatment modalities used to treat CRLM, 3) the median survival, 3-year and 5-year overall survival, 3-year and 5-year disease-free survival 4) the univariate and multivariate analysis outcomes.

#### Inclusion and exclusion criteria

In order to be included in the analysis, the studies must meet all of the following criteria: 1) include patients older than 18 years of age diagnosed with CRLM, 2) define NLR as the absolute number of neutrophils divided by the absolute number of lymphocytes in the peripheral blood, 3) clearly stated pretreatment NLR values and NLR thresholds, 4) analyzing the correlation between pretreatment NLR value and OS outcome and/or DFS,

The following exclusion criteria were applied: 1) not specifically reported colorectal metastasis to the liver, 2) patients with liver metastases originating from outside the colorectum 3) pre-clinical studies, 4) studies published in a language other than English.

#### Definitions

NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes in the peripheral blood.



Overall Survival (OS)<sup>4</sup> was defined as the time between treatment (hepatectomy, RFA, RE, chemotherapy) and death or last follow-up.

Disease Free Survival (DFS) was defined as the time between the treatment and the first detection of disease recurrence, including local tumor recurrence, intrahepatic recurrence and extrahepatic metastases.

<sup>1</sup> Progression Free Survival (PFS) was defined as the duration between primary tumor resection and disease progression.

## **RESULTS**

NLR as a predictor of survival after hepatectomy with neoadjuvant or adjuvant chemotherapy

Eleven studies assessed the prognostic significance of NLR for patients undergoing hepatectomy for CRLM after neoadjuvant chemotherapy. Details on patient demographics and the different NLR thresholds are given in Table 2. Five studies that included 902 patients in total, used 5 as the cut-off value for the NLR. Elevated NLR was significantly associated with worse OS.<sup>13-17</sup> Peng *et al* used 4.63 as the NLR threshold in 59 patients who received neoadjuvant chemotherapy yielded the same results.<sup>18</sup> Elevated NLR was also significantly correlated with poor OS when the threshold was 1.9, 2.3, 2.4, 2.5, 2.6 or 7.26.<sup>19-23</sup>

Ninety-eight patients in 3 studies received only adjuvant chemotherapy after metastasectomy. Elevated NLR was associated with significantly worse DFS.<sup>19,24,25</sup> The OS was also significantly shorter with elevated preoperative NLR in two of the studies.<sup>19,24</sup> However, the NLR cut-off value was different in each cohort (4.1, 1.94 and 5).<sup>19,24,25</sup> Further information on the OS and DFS, the tumor characteristics as well as the results of univariate and multivariate analyses for the studies mentioned above are shown in Tables 3 and 4.

Non surgical methods (RFA, RE, only chemotherapy)



Five studies included 494 patients that were submitted to RFA or RE or intraarterial therapy and they investigated the correlation between NLR and OS or DFS.

Chang *et al* and Zhang *et al* included 190 patients with CRLM without concomitant metastases outside of the liver. Patients were treated with RFA and both studies showed that preoperative high NLR (>2.5) was associated with worse OS and DFS.[26,27](#) Weiner *et al* and Tohme *et al* enrolled 235 patients, 100 of whom had extrahepatic metastases and an unspecified number of patients had unresected primary CRC both of which affect NLR and its correlation to OS. All of the patients were submitted to RE and high NLR was significantly associated with reduced OS.[28,29](#) The fifth study investigated the correlation between NLR and OS in CRLM patients with unresectable CRC that were treated with Irinotecan drug-eluting beads against a control group and high NLR was significantly associated with reduced OS.[30](#)

Two studies included 145 patients with unresectable or potentially resectable liver-only metastases from colorectal cancer and all of them were treated with primary tumor resection followed by chemotherapy. Both studies revealed that high NLR was significantly associated with worse survival and that prolonged survival was anticipated when NLR was normalized after chemotherapy. Wu *et al* demonstrated that the normalization of high NLR was significantly associated with better PFS.[15,31](#)

More details of patient demographics, medical treatments provided to the patients and survival outcomes are given in Tables 5, 6 and 7.

## **DISCUSSION**

Many studies have shown the significance of elevated NLR as a prognostic marker in various cancers and the role of NLR in predicting survival remains unanimous across diverse studies that included different cancer types, disease stages and sites.[32](#) In the studies we analyzed, the NLR cut-off values were determined either by using receiver operating curve analysis that assigned patients in high and low NLR groups or arbitrarily by the authors based on previous studies or the decision making for the

threshold was not mentioned. At the moment there is no perfect cut-off value that could be used for all the CRLM patients as the NLR is greatly affected by chemotherapy regimens, other inflammatory conditions and the tumor burden of each patient. The most frequently used cut-off value in CRLM patients is 2.5 and 5 but further research needs to be done in order to establish the ideal NLR threshold.

#### Association between NLR - inflammation - cancer

NLR is an inexpensive and easily calculated marker <sup>7</sup> by dividing the total count of neutrophils by the total count of lymphocytes in peripheral blood as measured in a complete blood count (CBC) exam.<sup>11,12</sup> NLR is also immediately available since a CBC exam is part of routine exams in patients with cancer.

The association between high NLR and worse prognosis in CRLM patients is complicated and is being rigorously studied. Inflammation plays a significant role in tumor initiation, promotion and progression through pro-inflammatory cytokines, growth factors, chemokines and pro-angiogenic factors. Neutrophils promote tumorigenesis through several mechanisms. They induce DNA damage and mutations by producing toxic substances such as reactive nitrogen species (RNS), they promote neoangiogenesis and tumor progression by releasing MMP-9 followed by the release of vascular endothelial growth factor (VEGF). Moreover, neutrophils release a granule protein, called Arg-1, which restricts CD3-cell mediated T cell activation, thus establishing an immunosuppressive microenvironment that contributes to cancer growth. Therefore, a high count of neutrophils could indicate worse prognosis in patients with cancer.<sup>33,34</sup> On the contrary, a low count of lymphocytes is associated with poorer tumor infiltration and insufficient cell immunity and therefore with worse prognosis in patients with cancer.<sup>32</sup> Consequently, high NLR as a result of increased neutrophils and/or decreased lymphocytes could be an indicator of poor host against tumor response and poor prognosis.

It is plausible that NLR could have an impact in clinical practice since it represents a readily-available biomarker which could potentially assist in the decision-making with prognostic significance. In the studies that we included in our literature review, patients were treated with different interventions such as surgery with or without adjuvant or neo-adjuvant chemotherapy and other patients were treated with RFA or RE or solely chemotherapy. High NLR was associated with worse OS and DFS in all of the studies.

#### Chemotherapy may affect NLR - Surgical Candidates

Colorectal liver metastases have poor prognosis if not treated appropriately. The current surgical approach when applicable is to resect the primary tumor followed by liver metastases resection 2-3 mo later with or without chemotherapy, but in certain cases there can be synchronous resection of the primary colon cancer and the hepatic metastases or the 'liver first approach'.<sup>35</sup> The role of systemic chemotherapy before or after a surgical procedure is well-established both for resectable and non-resectable disease, as it can improve overall survival.<sup>36</sup>

This systematic review points out the role of the NLR as a prognostic factor for the OS and DFS for patients with CRLM. Patients with low preoperative NLR value had better outcomes with longer OS. Similar results were presented by another systematic review which concluded that preoperative NLR calculation could contribute to the identification of patients who could benefit from adjuvant therapies.<sup>12</sup> The measurement of the NLR is cheap and easily applied with its value possibly being able to add to the management strategy for the patients.

It would be of interest if we could clarify whether different types of chemotherapy affect the NLR or vice versa. In two of the studies included, some patients received adjuvant and others neoadjuvant chemotherapy. The results showed that elevated NLR is indeed significantly associated with worse survival, but the patients who received neoadjuvant chemotherapy were not separated from the adjuvant group.<sup>14,16</sup> However, Kishi *et al* showed that preoperative chemotherapy normalized the NLR in

68% of the patients with elevated pretreatment NLR, who eventually had similar survival to those with normal pretreatment NLR.<sup>15</sup> Of note, Hand *et al* showed that overall survival was significantly shorter for the chemotherapy-naïve patients with elevated NLR, but not for those who received neoadjuvant chemotherapy.<sup>17</sup> For the latter, the OS resembled that of the patients with normal NLR. Hand *et al* did not measure the NLR after chemotherapy, but their results are consistent with the fact that neoadjuvant chemotherapy could normalize NLR. Finally, the role of chemotherapy was also investigated in Mao's *et al* study. They separated patients into four groups depending on pretreatment and presurgical NLR values. Simultaneous pretreatment and presurgical NLR > 2.3 was significantly associated with worse OS, and the authors hypothesized that high NLR may also indicate poor chemosensitivity.<sup>20</sup> Wu *et al* included patients with synchronous colorectal liver metastasis who were treated with chemotherapy after primary tumor resection. They showed that patients with normalization of NLR after one cycle of chemotherapy had better PFS than the patients that NLR remained high after chemotherapy and CRC resection. Consequently, the reduction of NLR could imply better chemosensitivity.<sup>31</sup>

#### Non Surgical candidates

To this day, hepatectomy is the “gold standard” treatment in patients with CRLM offering the longest OS, but as a matter of fact only 25% of those patients are eligible for surgery mainly because their clinical condition does not allow them to be surgical candidates or sometimes they refuse to receive surgical treatment.<sup>37</sup>

In two studies that patients were treated with RE the median OS ranged between 5.6 to 7.9 mo in the high NLR group whereas in the low NLR group 10.6 to 13 mo. Zhang *et al* and Chang *et al* included 190 patients with liver-only CRC metastases. They showed that high NLR patients present worse 5-year DFS ranging between 9.5 to 11% whereas low NLR patients present better 5-year DFS ranging between 22.6 to 26.7%.<sup>26,27</sup> Zhang *et al* also showed that high NLR is associated with worse 5-year OS (18.4%) after RFA in comparison to 41.7% in low NLR patients.



It is plausible that the studies investigating the correlation between NLR and OS or DFS in patients with unresectable tumors will demonstrate worse OS or/and DFS compared to studies done in surgically treated patients, since as mentioned before non surgical candidates present a worse clinical condition in general which affects their course of disease.

#### Different NLR thresholds

Even though increased preoperative NLR is correlated with shorter OS and DFS in general, the NLR cut-off values varied between individual studies. The most commonly used threshold was 5. However, the NLR threshold ranged from 1.94 to 7.26.<sup>19,23</sup> That wide distribution could be attributed to NLR depending on many pro- and anti-inflammatory parameters and the extent of the body's inflammatory response to cancer, in other words the cancer's biology being unpredictable.<sup>7</sup> In a study where eight different cut-off values were used (2.2, 2.5, 2.6, 3, 3.5, 4, 5 and 7.26), elevated NLR was consistently associated with decreased OS, even though the results were not statistically significant for every cut-off value.<sup>23</sup> The optimal threshold is based on molecular data analyzed by computer applications, such as Cutoff Finder.<sup>38</sup> The cut-off value is calculated with various models, such as Receiver Operating Characteristics (ROC) curve analysis or Kaplan-Meier curves and proportional hazards regression.<sup>39</sup>

#### Impact on clinical practice

NLR is an easily calculated tool with a possible prognostic significance. High NLR could inform the clinicians about the worse OS and DFS that would be expected. Since worse DFS would be expected, patients with high NLR could be submitted to earlier and more frequent diagnostic imaging exams, in order to diagnose disease recurrence. Moreover, better prognosis would be anticipated in patients with low NLR since they present better OS and DFS.

Moreover, some patients are initially diagnosed with unresectable or potentially resectable CRLM. Many studies have shown that inoperable CRLM can be down-staged

to resectable CRLM after chemotherapy, but this happens in less than 35% of patients with inoperable CRLM.<sup>40</sup> Therefore, more than 65% of the patients with unresectable CRLM will not benefit from chemotherapy and it would be important to identify biomarkers that could identify chemosensitive patients. Later on, those patients would be submitted to secondary CRLM curative resection. Mao *et al* and Wu *et al* demonstrated in their studies that the normalization of NLR after chemotherapy is correlated to chemosensitivity.<sup>20,31</sup> Consequently, NLR could be used as an assisting tool in stratifying the patients as chemosensitive or chemoresistant. Chemoresistant patients would possibly benefit more from interventions such as RFA or RE rather than chemotherapy. More studies are needed to assess whether NLR can be used as an indicator of chemosensitivity or if NLR could be combined with other biomarkers to increase accuracy.

Our results clearly demonstrate that elevated NLR is associated with adverse OS and DFS. These results are significant and they are the same across heterogeneous studies that included different populations, age groups, cancer stages, chemotherapy regimens and medical interventions, which shows that NLR could be an important prognostic factor that could be used in CRLM patients. High pretreatment NLR is associated with worse outcomes independently of the treatment that the patients were submitted to.

Prospective studies are needed in order to examine whether NLR could be used as part of an algorithm for the treatment of CRLM. It could also be potentially used in combination with other biomarkers or parameters such as CEA, CA19-9, primary tumor location and primary tumor TNM stage, which have been used in other studies in order to create a novel scoring system that would improve the predictive accuracy of recurrence and survival.<sup>19,41</sup>

### Limitations

One limitation of our study is that the cut-off values were different among studies. That prevents the utilization of NLR as a tool for the management of patients in clinical practice. The timing of the blood sampling was also not consistent among the studies.

Regarding neoadjuvant chemotherapy, even though it appears to improve outcomes, there is a need for larger studies that distinguish different chemotherapy types and regimens to reach a certain conclusion. Finally, the heterogeneity of patient demographics and clinicopathological characteristics (e.g. primary tumor location and treatment, size or extent of the metastases) prevented the conduction of a meta-analysis.

<sup>1</sup> It is obvious that more research is needed in order to enhance the role of NLR as an inexpensive, independent, crucial prognostic marker. More prospective randomized trials should be designed and executed since all the articles that were available to us were retrospective except for one. In the upcoming studies the authors should clearly state the clinicopathological details of every patient, the dates of blood sampling, the primary tumor and liver metastasis characteristics and how they were treated. Ideally, all patients should have their primary colorectal tumor resected and not have extrahepatic metastasis as these raise the tumor burden of patients with CRLM and therefore affect NLR. Moreover, all of them should be treated with similar chemotherapy sessions and with interventions by surgeons of similar levels of experience and training.

## **CONCLUSION**

Neutrophil to lymphocyte ratio calculation could potentially be an assisting tool in identifying patients with colorectal liver metastases who have higher probability for poor prognosis after treatment, so that the periprocedural management could be adjusted to benefit the patient. Overall, high pretreatment NLR was significantly associated with worse OS and DFS. Larger studies could help identify a standard, widely accepted cut-off value and therefore make NLR's prognostic significance applicable in clinical practice.



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