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RESEARCH ARTICLE

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The prognostic value of neutrophil-to-lymphocyte ratio in colorectal cancer: A systematic review

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BACKGROUND AND OBJECTIVES: The detection of a simple and reliable prognostic biomarker for colorectal cancer (CRC) outcomes remains a significant challenge. The use of neutrophil-to-lymphocyte ratio (NLR), has been reported to predict surgical and survival outcomes. The aim of our review was to assess the predictive value of pre-operative NLR in predicting post-operative outcomes in CRC.

METHODS: A systematic review of the available studies on NLR in CRC was performed. Primarily, we assessed its ability to predict survival outcomes, and highlight values that would help adjuvant therapy choices.

RESULTS: 19 studies comprising 10 259 patients were included. Eleven and eight studies reported on patients with localized CRC and colorectal liver metastasis, respectively. Five-year survival for those with localized CRC was 77.2% in patients with a "low" pre-operative NLR versus 50.8% in those with a "high" pre-operative NLR value. Alternatively, for patients with colorectal liver metastasis, patients with a "high" pre-operative NLR value had a 5-year survival of 27%.

CONCLUSION: Elevated pre-operative NLR>5 is associated with poorer long-term survival in both patients with localized CRC and those with liver metastasis. NLR is a useful biomarker in delineating those patients with poorer prognosis and whom may benefit from adjuvant therapies.

KEYWORDS
colorectal cancer, neutrophil-to-lymphocyte ratio, survival, surgical outcomes

1 | INTRODUCTION

Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies and represents the fourth most common cause of cancer-related mortality globally.[1,2] However, in recent years, overall mortality rates have decreased significantly due to improved medical therapies and surgical techniques, combined with the introduction of multidisciplinary team management in dedicated specialist centers and earlier diagnosis through focused screening programmes.[3,4] CRC represents a heterogeneous spectrum of disease and the predictive (staging) models, such as the Tumor Nodal Metastasis (TNM) system or Dukes classification, are not always sufficient to guide management.[5,6] Therefore, there is a need to explore other potential markers that could help clinicians further when stratifying patients' therapeutic needs.

In recent decades, the link between inflammation and the development of cancer has been better delineated.[7] First described by Virchow in 1863,[8] numerous studies have demonstrated that cancer-associated inflammation affects different stages of cancer development and progression.[7,9] The link between chronic inflammation and susceptibility to CRC has been best reported in patients with chronic inflammatory bowel disease (IBD).[10] IBD is recognized as a risk for conversion to CRC, with the risk increasing by 0.5-1% each year.[7,11] Furthermore, it has been found that some anti-inflammatory drugs, such as Cyclooxygenase-2 (COX2) inhibitors and steroids, can reduce the incidence and progression, as well as the mortality, of CRC.[9] On account of this, several prognostic scores, such as Glasgow Prognostic Score (GPS) and the Prognostic Nutritional Index (PNI), which use circulating inflammatory biomarkers, have been formulated to predict outcomes in colon cancer.[12–14]

More recently, there have been several publications citing the role of NLR as a valuable predictor of post-operative complications, recurrence and long-term survival in different kinds of visceral cancer. Appealing factors regarding this biomarker are that it is simple, cheap, and widely available.[15–17] There are numerous studies from the last decade that demonstrate that increased NLR rates are associated with poor overall and disease-specific survival, as well as decreased time to recurrence.[18–20] A recent study indicates that NLR can be used in both the pre-operative and post-operative period to accurately predict long-term survival in patients with Stage II/III colorectal cancer who have undergone surgical resection.[21]

There is accumulating evidence showing that cancer-triggered inflammation plays a crucial role in colorectal carcinogenesis. Furthermore, several studies have suggested that systemic inflammatory (bio)markers are potential surrogate markers for predicting time to recurrence and long-term survival. In this context, we sought to systematically review the existing evidence available, in order to assess the value of NLR at predicting clinical and survival outcomes.

2 | METHODS

A systematic review was conducted according to the guidelines and recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist (PRISMA).[22] Institutional review board approval was not required.

2.1 | Search strategy

An electronic search for relevant publications was performed using the following resources: PubMed, Embase, and the Cochrane collaboration database from January 2005 to April 2016. The following search terms and headings were used: "colorectal cancer, neutrophil-to-lymphocyte ratio," "colorectal cancer inflammatory markers," "neutrophil-to-lymphocyte ratio," "prognosis," "outcome," "survival," and "recurrence." All titles were initially screened, and appropriate abstracts were reviewed. Each of the relevant publication reference sections and Google scholar were also screened for other applicable publications. Only studies published in peer-review journals were included. The last date of search was 30th June 2016.

2.2 | Inclusion criteria

To be included in the analysis, the studies had to meet the following criteria: a) the diagnosis of colorectal cancer must be pathologically confirmed (colorectal cancer or colorectal liver metastasis); b) correlation of pre-treatment (surgery) NLR with overall survival must be reported; c) patients must have resectable disease; d) studies must have a clear research methodology; e) articles thought to incorporate data published previously were used once only.

2.3 | Exclusion criteria

Studies were excluded from analysis if: a) they did not report specifically on histologically confirmed colorectal cancer; b) they did not specifically report NLR with relevant cut-off values; c) they did not report on survival outcomes; d) they reported overlapping data among authors; e) they reported data regarding other cancers from which colorectal cancer group could not be separated; f) they reported abstracts, letters, editorials, expert opinions, reviews, case reports, or case series with less than ten patients; g) they were written in any language other than English; or h) they reported on non-human research.

2.4 | Data extraction

Two reviewers (AH, RW) independently reviewed the available literature according to the above predefined search strategy and criteria. Each reviewer extracted the following data variables: title and reference details (first author, journal, year, and country), study population characteristics (number in study, gender, and age), disease characteristics (location of the colorectal neoplasm, tumor differentiation), preoperative NLR and outcome data (survival in months; 3- and 5-year overall survival). Any disagreement between the two reviewers was settled by an independent third reviewer (MK).

All data were recorded independently by both literature reviewers in separate databases and were compared at the end of the reviewing process to limit selection bias. The database was also reviewed by a third person (MK). Duplicates were removed and any disparities were clarified.

2.5 | Outcomes of interest

Within this systematic review patients designated as having "high" pre-operative NLR values from individual studies were compared and analyzed as were those with "low" NLR values. Details with regard to different NLR values used in each study were also provided.

The following outcomes were used to compare the effectiveness of pre-treatment NLR (cut-off values of ≤5 and >5) in predicting survival outcomes for colorectal cancer patients:

- Primary outcome:
  - Survival outcomes: 3- and 5-year survival rates as well as overall survival. (Overall survival was defined as the duration of time between the last treatment and the death of the patient or the last follow-up).
- Secondary outcome:
  - Histopathological differentiation of colorectal cancer (well, moderate or poor).

2.6 | Analysis and assessment of methodological quality of studies

Descriptive statistics were used to report the characteristics of all eligible studies, describing the specifics of CRC, pre-operative NLR cut-off values, total patient numbers, median age, and follow-up and survival

data. The Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized cohort studies was applied to assess the overall quality of each included study. An NOS score of ≥6 indicated high quality studies. Details of the scoring of each included study are shown in Table 1

3 | RESULTS

3.1 | Eligible studies

A total of 1 596 articles were initially identified using the aforementioned search strategy. Fifty articles were deemed eligible for full-text screening, and 19 publications met the inclusion criteria for systematic review. Of the 31 publications excluded, eighteen did not report data on overall survival, five included patients with non-resectable disease, and eight were case reports/series, letters to the editor or systematic reviews (Fig. 1). Of the 19 studies included, eleven involved patients with localized colorectal cancer, and eight involved patients with colorectal cancer with liver metastases. The sample size of the included studies ranged from 92 to 5 336 patients. All studies were retrospective, spanning a time period of 19 years (1995-2014), and had good geographical distribution and representation. Seven studies were from China, five from the United Kingdom, and one each from Taiwan, Austria, Japan, South Korea, Canada, the United States, and Poland. Nine of the studies had more than 200 patients, with only two having less than 100 patients.

All studies reported survival outcomes following surgical resection of colorectal cancer and/or radiofrequency ablation (RFA) of colorectal liver metastasis. In all studies NLR was calculated using pre-treatment WBC differentiated counts. In our systematic review, patients were designated as having "high" and "low" NLR values due to significant variation between studies regarding the actual NLR value used. All eligible studies were assessed for methodological quality by the two reviewers independently. The Newcastle-Ottawa Quality Assessment Scale (NOS) was applied to assess the overall quality of each included study. The numbers, characteristics, and quality of all the studies are outlined in Tables 1 and 2.

3.2 | Study details

A total of 10 259 patients were included in this review, of whom 8 688 (84.7%) had colorectal specific disease, and the remaining 1 571 (15.3%) of whom had colorectal liver metastasis. Across all studies, the male gender was more common (Tables 1 and 2). Eight studies used an NLR "cut-off" value of 5, with the largest study (Li et al) using a cut-off value of 2.72.[23]

3.2.1 | Colorectal-specific disease

Eleven studies reported 8 688 patients diagnosed with colorectal-specific disease, for which primary colorectal resection was performed. The mean (range) age of this cohort was 62 (22-92). All studies were published between 2010 and 2016 and had a mean Newcastle-Ottawa Score (NOS) of 5.45, indicating moderate methodological quality, with 6 of the 11 studies having an NOS of 6. The largest series reported on 5 336 patients.[23] The male-to-female ratio was 1.5:1. The primary lesion was located in the colon in 52.2% of cases (n = 4 536), and in the rectum in 46.1% (n = 4 007). Three of the eleven studies used five as the NLR

TABLE 1 Patient demographics and study specifics for localized colorectal cancer

Study (Surname et al)	Year	Journal	Country	Retrospective or prospective	Number of patients	Gender (M/F)	Median age (range)	NOS score
Liu et al[31]	2010	Journal of Gastrointestinal Cancer	China	Retrospective	123	74/49	61 yrs (28-81)	5
Hung et al[32]	2011	International Journal of Colorectal Disease	Taiwan	Retrospective	1040	561/479	65 yrs	6
Absenger et al[28]	2013	Anticancer research	Austria	Retrospective	504	293/211	65 yrs (27-95)	6
Shen et al[33]	2014	Radiation oncology	China	Retrospective	199	149/50	55 yrs (22-76)	6
Nagasaki et al[34]	2015	Digestive Surgery	Japan	Retrospective	201	140/61	60 yrs (28-81)	5
Kwon et al[22]	2012	Biomarkers	Korea	Retrospective	200	123/77	64 yrs (26-83)	6
Carruthers et al[35]	2012	Colorectal Dis	UK	Retrospective	115	75/40	63.8 yrs (32.3-81.1)	4
Ying et al[2]	2014	Medical Oncology	China	Retrospective	205	144/61	60 yrs	6
Choi et al[36]	2015	Annals of surgical oncology	Canada	Retrospective	549	296/253	68.7 yrs (28.3-92.6)	5
Zou et al[37]	2016	Oncology Letters	China	Retrospective	216	137/79	50 yrs	6
Li et al[38]	2016	International Journal of Cancer	China	Retrospective	5,336	3167/ 2169	59 yrs (51-66)	5

NOS: Newcastle-ottawa quality assessment scale.

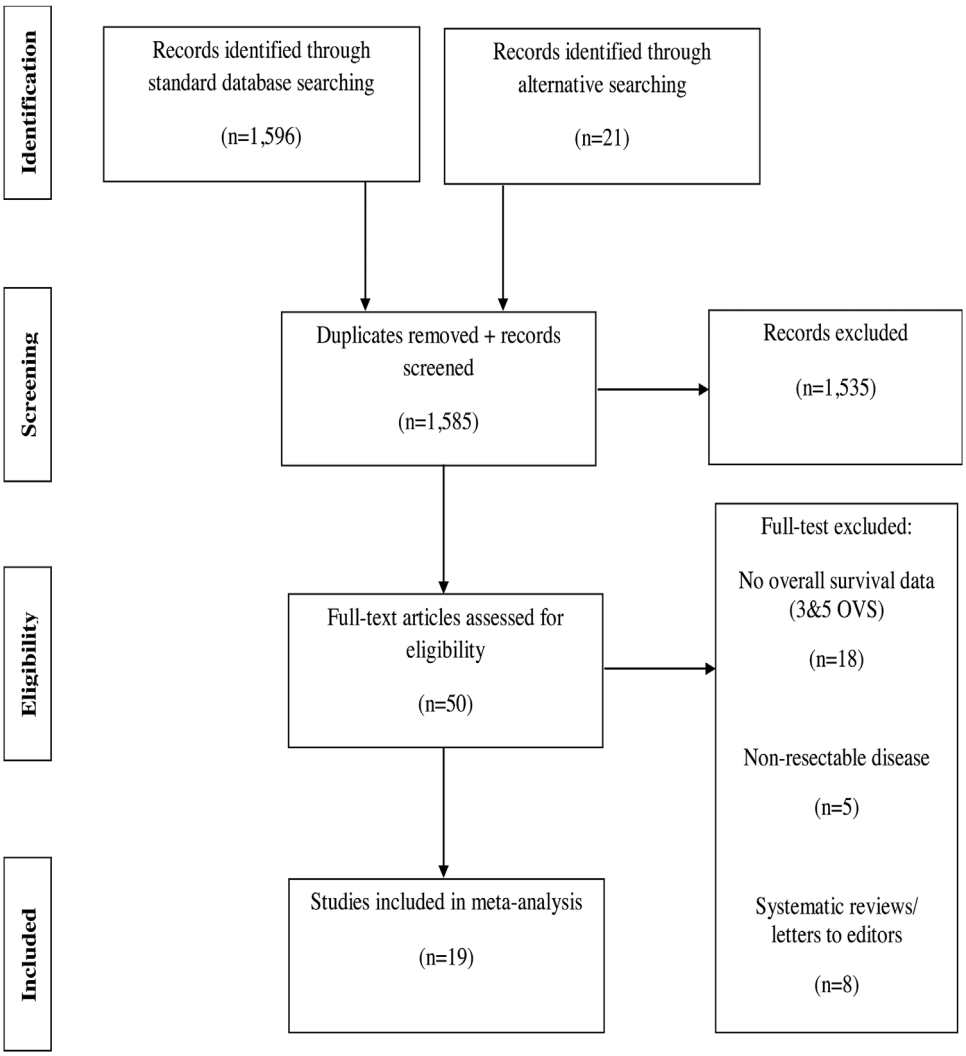

FIGURE 1 PRISMA flowchart of the included studies

cut-off, with the remaining eight studies using a cut-off value between 2 and 5. Nine studies reported on median follow-up time, and this averaged 45.95 (1-136) months, as shown in Table 3. The median overall survival was reported in four studies. Two studies reported a 3-year overall survival, while a 5-year overall survival was reported in nine studies. In the four studies reporting median overall survival one found no difference in survival between those in the "high" NLR group and those in the "low" group.[24] However, two studies using an NLR cut-off value of 4 and 5 found a statistically significant difference in median overall survival time between the "high" and "low" NLR groups.[20,25] The other study reporting median overall survival (Ying et al) did not distinguish survival between the two groups.[2] The largest study by Li et al, with more than 5 000 patients, found that having a "high" NLR was an independent prognostic factor for poorer disease free survival with a hazard ratio of >1.5 ($P < 0.001$).

3.2.2 | 3- and 5-year survival rates

Of the two studies reporting 3-year survival rates, only one study reported on the rates between the "high" and "low" groups,[24] and this noted that 61.8% of patients with a high NLR survived for 3 years, compared to 77.8% of the group with the "low" NLR. Nine of the eleven studies reported on 5-year survival rates. Of these, eight described the difference in rates observed between high and low NLR groups. The overall 5-year survival rate among those in the "high" NLR group was 50.8% compared to 77.22% in the "low" NLR group. Two of the eight studies had a cut-off NLR value of 5.[26,27] The mean 5-year survival rate between these two studies was 76.6% in patients with an NLR of <5, and 53.5% in those with an NLR of >5. Of the other six studies that had an NLR cut-off value of between 2 and 5, the mean 5-year survival rate was 77.4% in patients with an NLR of <5 and 49.9% in those with an NLR of >5.

3.3 | Tumor differentiation

Seven studies reported on the level of differentiation of colorectal cancer. All seven publications found that levels of differentiation were likely to be poorer with higher NLR values. However, only three studies showed a statistically significant correlation between NLR and tumor grade.[2,23,28] The time to recurrence rate was only reported in one study.[23] There were

TABLE 2 Patient demographics and study specifics for colorectal cancer and liver metastatic disease

Study (Surname et al)	Year	Journal	Country	Retrospective or prospective	Number of patients	Gender (M/F)	Median age (range)	NOS score
Halazun et al[39]	2008	European journal of surgical oncology	UK	Retrospective	440	289/151	64 yrs (32-88)	6
Kishi et al[40]	2009	Annals of surgical oncology	USA	Retrospective	200	132/68	57 yrs (23-86)	7
Zhang et al[41]	2012	International journal of hyperthermia	China	Retrospective	92	51/41	59 yrs (43-78)	6
Zeman et al[42]	2013	Polish Journal of Surgery	NS	Retrospective	130	70/60	60 yrs (33-82)	4
Chang et al[43]	2014	Medical oncology	China	Retrospective	98	56/42	62 yrs (28-92)	4
Neofytou et al[44]	2014	Medical oncology	UK	Retrospective	140	88/52	70 yrs	6
Giakoustidis et al[45]	2015	Journal of surgical oncology	UK	Retrospective	169	104/65	70 yrs	6
Neal et al[46]	2015	Medical oncology	UK	Retrospective	302	192/110	66 yrs (26-85)	6

NOS: Newcastle-ottawa quality assessment scale.

insufficient data available from the eligible studies to examine NLR value and the incidence of surgical complications, anastomotic leak rate, procedure related mortality, or length of hospital stay.

3.4 | Tumor stage

Ten studies reported on the relationship between NLR and tumor stage. Four studies reported on tumor stage only,[23,26,29,30] compared to five which reported full TNM staging.[2,24,27,28,31] The final study reported only that T4 tumors were significantly associated with NLR >4 without giving details on other tumor stages.[20] Of the studies reporting T stage only, three out of the four studies[23,26,29] found a statistically significant correlation between "high" NLR values and Stage III/IV disease compared to Stage I/II disease. The fourth study showed a similar correlation but this was not found to be statistically significant ($P = 0.28$).[30] Three of the five studies[2,28,31] reporting full TNM stage found a statistically significant correlation between "high" NLR values and increasing stage of disease. The fourth study involving 123 patients found some correlation between NLR and Stage III disease but this was not significant ($P = 0.188$),[24] and the fifth study by Kwon et al found no correlation ($P = 0.921$).[27]

3.4.1 | Liver metastatic disease

Eight studies reported on patients with colorectal cancer and liver metastases. All patients underwent liver resection ± ablation therapy with or without chemotherapy. All patients had also undergone resection of the primary lesion. These studies were published between 2008 and 2015, and had a mean Newcastle-Otawa Score (NOS) of 5.62, indicating moderate methodological quality, with 5 of the 8 studies having an NOS of 6. Five studies used an NLR cut-off value of 5, while two studies used a cut-off value of 2.5, and the remaining one used 2.4. In total, there were 1 571 patients across the eight studies, with study size ranging from 92 to 440 patients. The largest series reported on 440 patients.[32] The mean (range) age among the studies was 63.5 (23-92) years. Male-to-female ratio was 1.66:1.

Site of primary colonic lesion was only reported in two studies,[33,34] and in these studies the primary lesion was located in the colon in 51.6% of cases ($n = 223$), and in the rectum in 48.4% ($n = 209$). Two studies reported the hepatic distribution of liver metastasis, with bilobar disease in 111 patients.[35,36] All eight studies reported on median follow-up time, and this averaged 31.95 (1-156) months. Seven of the eight studies reported a 3-year overall survival, while 5-year overall survival was reported in all studies. Three studies reported median overall survival. This was found to be 55 months across the three studies in the "high" NLR group. In two of these studies, where the NLR cut-off values were 2.4 and 2.5, the median overall survival time in the "low" NLR group was not assessed,[35,36] and in the third, which had an NLR cut-off of 5, the median overall time was 45 months.[37] The fourth study to report median overall survival time was by Zeman et al,[33] and showed 56 months in those undergoing resection, but this was not specified with regard to an NLR cut-off value.

3.4.2 | 3- and 5-year survival rates

Seven of the eight studies reported data on 3-year overall survival. Of these, two did not distinguish between "high" and "low" NLR groups.[33,38] The overall 3-year survival rate among those two studies was 69.5%. Of the five other studies reporting 3-year survival rates with high/low NLR, the mean 3-year overall survival rate in the "high" NLR group was 45.1%, compared to 64.74% in the "low" NLR group. When we examined 3-year overall survival rates in the studies using 5 as the NLR cut-off value, we found it to be much lower at 29.7% in the "high" (>5) NLR group.[34,37,39] All of these studies showed statistically significant differences in 3-year survival rates between the high and low NLR groups. All eight of the studies reported on 5-year overall survival rates, but similarly, two studies did not disclose rates for the "high" and "low" NLR groups,[33,38] with an average 5-year overall survival rate between them of 42.2%. The other six studies showed statistically

TABLE 3 Tumour characteristics, NLR cut-off values, and survival outcomes for localized colorectal cancer patients

Study (Surname et al)	Number of patients	Primary site	Tumour differentiation	NLR cut-off	Follow-up (months)	Median survival (months)	3-year overall survival	5-year overall survival	Recurrence rate
Liu et al[31]	123	123 rectal	99 (80.5%) well&moderate	2	NR	55	(NLR<2) 77.8%	(NLR<2) 55.6%	NR
			24 (19.5%) poor				(NLR>2) 61.8%	(NLR>2) 37.5%	
Hung et al[32]	1040	A*	161 (15.5%) well	5	74.5 (45.9-136.8)		NR	(high NLR) 63.5%	NR
			823 (79.1%) moderate					(normal NLR) 78.5%	
			52 (5%) poor						
Absenger et al[28]	504	504 colon	NR	4	45 (1-108)	(NLR<4) 101.3	NR	NR	NR
						(NLR>4) 83.4			
Shen et al[33]	199	199 rectal	NR	2.8	31 (1-84)	NR	NR	(NLR<2.8) 0.717	NR
								(NLR>2.8) 0.437	
Nagasaki et al[34]	201	201 rectal	NR	3	51.2 (3.6-120.1)	NR	NR	(NLR<3) 92.5%	NR
								(NLR>3) 80.5%	
Kwon et al[22]	200	104 colon	103 (51.5%) well	5	33.6	NR	NR	median	NR
		96 rectal	81 (40.5%) moderate					5-yr OS rate = 71.4% (NLR<5 = 74.8%, NLR>5 = 43.5%)	
			8 (4%) poor						
			8 (4%) mucinous						
Carruthers et al[35]	115	115 rectal	NR	5	37.1	(high NLR) 18.8	NR	NR	NR
						(low NLR) 54.4			
Ying et al[2]	205	140 colon	47 (22.9%) poor	3.12	NR	26(14.5-60)	NR	(NLR>3.12) 25%	NR
		65 rectal						(NLR<3.12) 75%	
Choi et al[36]	549	468 colon	101 (18.4%) well	2.6	48 (0-124.8)	NR	NR	(NLR>2.6) 71%	NR
		81 rectal	418 (76.1%) moderate					(NLR<2.6) 85%	
			29 (5.3%) poor						
Zou et al[37]	216	113 colon	31 (14.4%) well	4.98	38	NR	76%	(NLR>4.98) 42%	NR
		103 rectal	126 (58.3%) moderate					(NLR<4.98) 84.7%	
			59 (27.3%) poor						
Li et al[38]	5 336	2 167 colon	4190 (78.5%) well&moderate	2.72	55.2	NR	NR	79.20%	25.3%
		3 024 rectal	371 (6.95%) poor						
			775 (14.5%) unknown						

*A**, 243 cecum and ascending colon, 212 transverse colon, 138 descending colon, 447 sigmoid colon.
NLR, neutrophil to lymphocyte ratio; NR, not reported; RFA, radiofrequency ablation.

significant differences between the "high" and "low" NLR groups, with means across the studies of 47.6% and 27%, respectively. Four of these studies used an NLR cut-off value of 5 and found that patients with an NLR of >5 had an overall 5-year survival rate of just 17.25%.

3.5 | Recurrence/tumor differentiation

The recurrence rate was reported in four publications and was found to be associated with higher NLR levels as shown in Table 4.[32,35,36,39] Only two studies reported data on NLR and the level of tumor differentiation, but neither found a statistically significant difference between NLR groups with regard to degree of differentiation.[38,39] Zeman et al reported four incidences of 30-day mortality, but did not correlate these with NLR levels.[33] Among the other studies, there were insufficient data with regard to surgical morbidity and length of hospital stay. Only one study by Zhang et al within this group reported on the correlation between pre-operative NLR and the primary tumor stage,[39] and found that there was no statistically significant correlation between a "high" NLR value and increasing tumour stage (Stage II vs III; $P = 0.298$).

4 | DISCUSSION

Our systematic review demonstrated that elevated NLR was associated with poorer long-term survival in both patients with

TABLE 4 Tumour characteristics, NLR cut-off values, and survival outcomes for patients with colorectal cancer and liver metastasis

Study (Surname et al)	Number of patients	Primary site	Tumour differentiation	NLR Cut-off	Follow-up (months)	Median survival (months)	3-year overall survival	5-year overall survival	Recurrence rate
Halazun et al[39]	440	NR	NR	5	24 (11-97)	NR	NR	(NLR>5) 22%	52%
								(NLR<5) 43%	
Kishi et al[40]	200	NR	NR	5	28 (2-102)	(NLR>5) 34	(NLR>5) 38%	(NLR>5) 19%	NR
						(NLR<5) 45	(NLR<5) 70%	(NLR<5) 43%	
Zhang et al[41]	92	NR	45 (48.9%) well and moderate	5	27.1 (5-62)	NR	(NLR>5) 14.3%	(NLR>5) 9.5%	78.3%
			47 (51.1%) poor				(NLR<5) 38.7%	(NLR<5) 26%	
Zeman et al[42]	130	70 colon	NR	5	resection group = 44 (6-156)	(resection group) 56	(resection group) 64.5%	(resection group) 46.6%	NR
		60 rectal			RFA group = 26 (2-67)		(RFA group) 33%	(RFA group) 9.5%	
								(NLR >5) 0%	
Chang et al[43]	98	NR	32 (32.7%) well	2.5	avarage = 35.2 ± 21.89 months	NR	74.5%	37.7%	NR
			53 (54.1%) medium						
			13 (13.3%) poor						
Neofytou et al[44]	140	NR	NR	2.4	33 (1-103)	(NLR>2.4) 55	(for entire group) 72%	(for entire group) 57%	67.9%
						(NLR>2.4) not reached	(NLR>2.4) 65%	(NLR>2.4) 42%	
							(NLR<2.4) 78%	(NLR<2.4) 69%	
Giakoustidis et al[45]	169	NR	NR	2.5	34.6	(NLR>2.5) 75	(for entire group) 77%	(for entire group) 64%	68%
						(NLR>2.5) not reached	(NLR>2.5) 71%	(NLR>2.5) 51%	
							(NLR<2.5) 82%	(NLR<2.5) 74%	
Neal et al[46]	302	153 colon	NR	5	29.7 (4-96)	NR	(NLR>5) 37.2%	(NLR>5) 18.5%	NR
		149 rectal					(NLR<5) 55%	(NLR<5) 30.6%	

NLR, neutrophil to lymphocyte ratio; NR, not reported; RFA, radiofrequency ablation.

localized colorectal cancer (CRC) and those with colorectal liver metastasis (CLM). The mean 5-year survival rate for those with localized CRC was 77.2% in patients with a "high" NLR cut-off value, in comparison to 50.8% in those with a low NLR value. Alternatively, patients with CLM and a "high" NLR value had a 5-year overall survival rate of 27%. This highlights the usefulness of a simple, inexpensive biomarker that correlates the inflammatory state associated with colorectal cancer to its impact on survival.

The link between chronic inflammation and the risk of developing cancer was initially recognized around a century ago when Rudolf Virchow noted the presence of leukocytes in tumor tissue.[7,8] This relationship has been examined recently and the results reveal that chronic inflammation plays a critical role in both the acceleration of tumor cells' proliferation and metastasis.[2,7] Additionally, it also is involved in the suppression of immune response and patient tolerance to cytotoxic treatment.[2,7,9] Over 20% of all human cancer cases are estimated to be associated with chronic inflammation.[40] The association between length of chronic inflammation and susceptibility to CRC has been investigated in depth in recent decades. This has largely been through looking at the conversion to CRC in patients with chronic inflammatory bowel disease (IBD), such as Ulcerative colitis and Crohn's.[10] In fact, IBD represents the third-highest risk factor for CRC, after Familial Adenomatous Polyposis (FAP) and Hereditary Nonpolyposis Colorectal Cancer Syndrome (HNPCC).[11] Though this risk is well understood, the actual molecular biology and genetics interplay are still being researched in depth.[41]

Interestingly, the risk of CRC has been found to be reduced remarkably in patients who are in regular receipt of anti-inflammatory drugs. Despite the increased incidence of cardiovascular events and gastrointestinal side effects, regular use of Cyclooxygenase-2 inhibitors and other NSAIDs have been found to reduce not only the incidence, but also the progression to metastasis and overall mortality from CRC.[9,42]

As a result of the inflammatory carcinogenesis interplay, various inflammatory-based biomarkers have been investigated. These include GPS, serum albumin, C-reactive protein (CRP), and Cytokines such as interleukins and tumor necrosis factor-α (TNF-α), although several of these suggested biomarkers are associated with issues of availability, and cost.[7] In contrast, several studies highlight that NLR is a simple, cheap and easily-accessible biomarker that has a potential role in the prediction of CRC outcomes.[27,43,44] Certain abnormalities in peripheral blood cell count, such as lymphopenia, neutrophilia, and thrombocytosis, are classically associated with systemic inflammatory response and progression of cancer cells.[45,46] Neutrophils are an important component of peripheral blood, and have the ability to promote the development of tumors, due to their effect on tumor-related angiogenesis. As well as this, they are a primary source of circulating angiogenesis-regulating chemokines, growth factors, and proteases.[19] Lymphocytes, in turn, have potent antitumor qualities, and they play an important role in cancer immune-surveillance. Therefore, a decrease in lymphocyte count is postulated to be correlated with a poor prognosis in cancer patients.[43,47,48] Elevated NLR, as highlighted in this review, indicates a poorer prognosis in CRC, as has been already shown in other cancers, such as oesophageal, gastric, and ovarian cancers.[49–51] However, a specific cut-off value of NLR and its impact on long-term survival has yet to be conclusively noted.

This review highlights the significant heterogeneity that still remains in the management of CRC (both surgical and medical). Patients included have undergone different therapeutic interventions, including the conduction of open or laparoscopic resection procedures, administration of different chemotherapy regimens, use of biologics, and the variable role of percutaneos radiofrequency ablation (RFA) in colorectal liver metastasis. Additionally, the overwhelming majority of the involved studies examining this area are retrospective, which may increase the possibility of bias. Furthermore, there is a need for better correlation between NLR and tumor differentiation. Despite these limitations, this review is the most up-to-date analysis examining the prognostic role of NLR in patients with CRC. It is a powerful review as it includes studies comprised of more than 10 000 patients. It also clearly highlights that the interplay between inflammation and carcinogenesis needs further evaluation, and that NLR is a potential risk-stratifying tool for management of CRC. However, further prospective studies examining specific cut-off values and their value in predicting surgical/survival outcomes are required.

5 | CONCLUSION

The use of routine NLR calculation prior to CRC resection should be calculated in order to help delineate those patients with a "high" value who are likely to have poorer cancer prognosis. It is a simple, inexpensive test which is a potential surrogate marker for outcomes in CRC. It may help to identify patients in the multi-disciplinary setting who have poorer prognosis and could benefit from anti-tumor therapies.

6 | SUMMARY

A systematic review examining the use of Neutrophil-Lymphocyte Ratio in operable colorectal cancer with or without liver metastases. Elevated pre-operative NLR is associated with poorer long-term survival in both patients with localized colorectal cancer and those with liver metastasis.

POTENTIAL CONFLICTS OF INTEREST

Nothing to disclose.

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SYNOPSIS

A systematic review examining the use of Neutrophil-Lymphocyte Ratio in operable colorectal cancer with or without liver metastases. Elevated pre-operative NLR is associated with poorer long-term survival in both patients with localized colorectal cancer and those with liver metastasis.