

The association of the neutrophil-to-lymphocyte ratio and postoperative complications in colorectal cancer surgery: A scoping review

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ABSTRACT

Background: Surgical resection of tumours is usually performed in patients with colorectal carcinoma regardless of the disease's stage. Nonetheless, before undergoing surgery, it is important to be aware that various postoperative complications may arise. The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker related to complications following surgical operations. Hence, the present review study was undertaken to assess the association of the NLR and postoperative complications in resections of colorectal tumours.

Methods: Major electronic databases were searched to find all available existing literature. Data was extracted and processed from the eligible studies and presented in the present review.

Results: Overall, a total of 32 observational and case-control studies consisting of 9095 colorectal cancer patients were included in the review. In 27/32 of the studies, a statistically significant positive association was found between the NLR and post-operative complications. Preoperative NLR was assessed in 25/32 of the studies and postoperative NLR was assessed in 8/32 of the studies including studies in which NLR was assessed in both moments.

Conclusions: High preoperative and postoperative values of the NLR increase the risk of developing postsurgical complications. However, it is important to conduct further prospective cohort studies to verify the results and deepen knowledge in this area.

Key Words: *Colorectal cancer; postoperative complications; surgical complications; neutrophil-lymphocyte ratio; NLR*

INTRODUCTION

Colorectal cancer (CRC), also known as bowel cancer, is the third most frequent malignant disease and the second

most common cause of cancer-related death worldwide [1]. The European Society of Medical Oncology (ESMO) guidelines suggest a surgical resection of the tumour when it is classified as a carcinoma, either with or without the administration of neoadjuvant chemotherapy according to the tumour's stage [2]. Nevertheless, after a surgical operation, different complications, namely anastomotic leakage, postoperative infections and bleeding, intra-abdominal abscesses, hernias, bowel obstruction and cardiac events may occur [3,4].

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These complications have been shown to decrease rates of overall survival and even increase the risk of intra-abdominal recurrence of the disease [5-7]. Hence, preventive strategies must be undertaken in patients with a high risk of developing these complications, and in case of occurrence, therapeutic procedures must begin without delay [4]. It is thus deemed necessary to discover diagnostic tools that enable clinicians to identify patients who are at a high risk of developing postoperative complications.

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory marker, derived from dividing the number of neutrophils by the number of lymphocytes in a complete blood count, which has recently been of great interest as a prognostic biomarker in the fields of medical and surgical oncology [8]. The use of this diagnostic tool has been emerging since it is both non-invasive and cost-effective, and can be calculated through a complete blood count which is a routine examination in clinical settings, meaning that there is no need for further laboratory examinations [9]. High levels of the NLR have been found to be predictors of inflammation in different neoplastic diseases [10]. To this end, the present scoping review was undertaken to assess whether the NLR value prior to and after surgery is associated with postoperative complications following colorectal tumour dissections. An observed association would imply its use as a prognostic biomarker which would alert clinicians to start taking preventive measures earlier.

METHODS

The present scoping review was conducted in complete accordance with the PRISMA Extension for Scoping Reviews (PRISMA-ScR) guidelines [11]. Hence, it included the following critical phases: 1) specifying the research question, 2) identifying relevant literature, 3) selecting eligible literature records, 4) extracting and mapping out the data and 5) summarising and reporting the results.

Research question

The present scoping review was directed by the question "Are higher values of the neutrophil-to-lymphocyte ratio before or after colorectal cancer surgery associated with postsurgical complications, as described in existing literature?".

Search strategy

The electronic databases PubMed, Scopus and EMBASE were systematically searched for records from November 2023 until inception using a combination of keywords and Boolean operators. The keywords used were: "colorectal",

"colon", "bowel", "cancer", "carcinoma", "tumour", "neutrophil-lymphocyte ratio", "neutrophil-to-lymphocyte ratio", "NLR", "postoperative complications", "surgical complications" and "complications after surgery". The search was limited to articles written in the English language.

Using the EndNote citation manager, duplicate records were removed and in turn, the remaining citations were screened based on their titles and abstracts. Inclusion criteria were observational studies assessing the correlation of the preoperative or postoperative NLR with postsurgical complications in patients undergoing colorectal cancer surgery. The final selection was done after reading the full-text versions of the remaining records. The selection process was performed by two independent reviewers (DK and PA). No discrepancies arose between the reviewers.

Data extraction and qualitative synthesis

Data regarding the study's design, the number of enrolled patients, the stage and position of the tumour, the surgical methods used, the value of the NLR, the postsurgical complications and the statistical figures indicating association, were extracted from each included study by two independent reviewers (DK and PA). The extracted data was processed and is presented in the present review article using descriptive statistics.

RESULTS

The online database search retrieved a total of 325 citations and one additional citation was retrieved from ResearchGate. Following the removal of duplicates, a total of 182 citations remained, amongst which 64 citations didn't meet the inclusion criteria during screening and thus, were excluded from the review. Amongst the remaining 118 records, 79 were found to be irrelevant to the research question, 6 were found to be review articles and 1 was found to be a commentary after assessing their full texts. Consequently, a total of 32 studies were included in this scoping review. Figure 1 presents a diagram summarising the search strategy and the inclusion process.

Studies reporting the association of the NLR with postsurgical complications have been summarised in Table 1. The postsurgical complications studied in the included records have been summarised in Table 2.

Overall, a total of 9095 colorectal cancer patients were included in all of the studies, and the studies reported infection, anastomotic leakage, ileus, bowel obstruction, bleeding, pelvic collection, flap necrosis, cardiac, gastric and urinary events as postoperative complications. 23/32 of the studies were retrospective cohort, 6/32 were prospective cohort, 2/32 were cross-

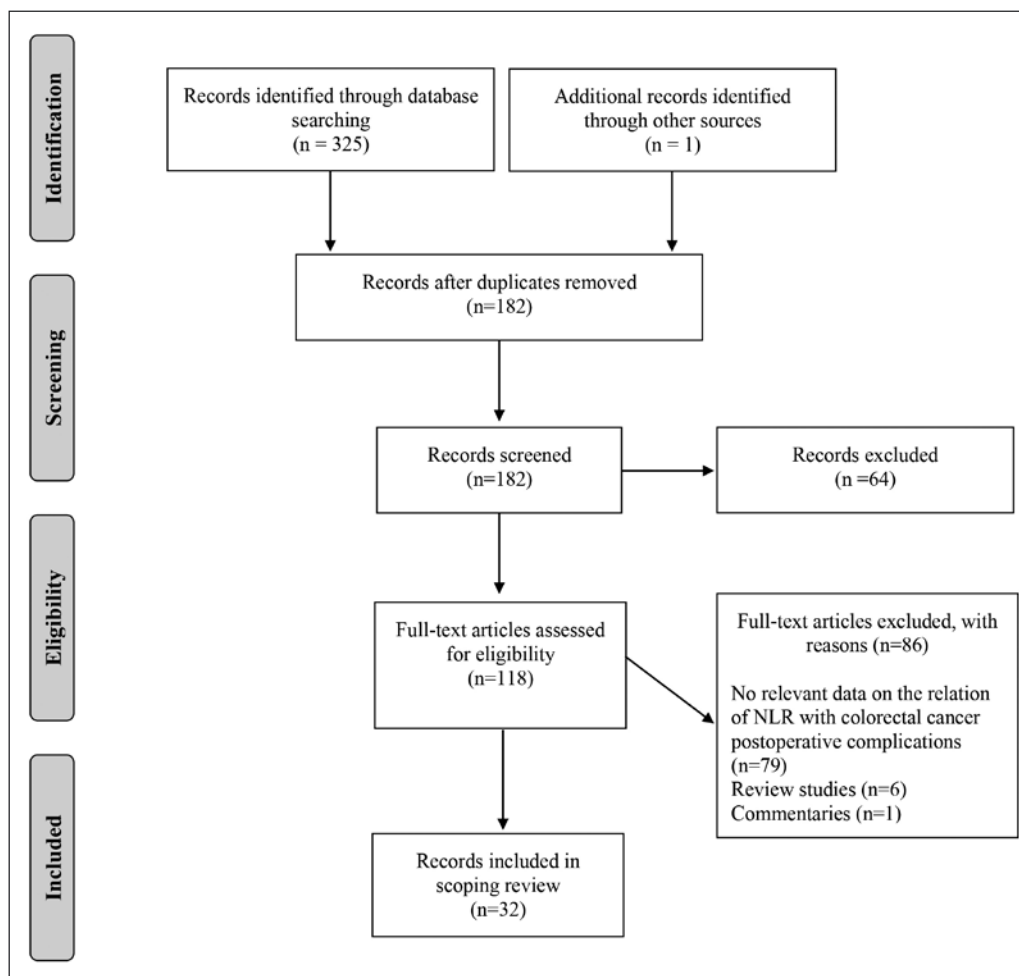


FIGURE 1. PRISMA diagram of the search strategy and inclusion process.

sectional and 1/32 was a case-control study. In 27/32 of the studies a statistically significant positive association was found between the NLR and post-operative complications, with an alpha-level of 0.05. More specifically, preoperative NLR was assessed in 25/32 of the studies, out of which 21/25 found a positive association with postoperative complications and postoperative NLR was assessed in 8/32 of the studies, out of which 6/8 found a positive association with postoperative complications. Two records studied both preoperative and postoperative NLR. In one of the studies it turned out that an increase of the change of NLR (1st postoperative day value-preoperative value) was associated with higher risk of developing infection [26]. The NLR cut-off level varied from 2.08 to 8.00 amongst all the studies. The most common postoperative complications studied were anastomotic leakage followed by infection. Nevertheless, it is worth mentioning that some studies found a lack of association of anastomotic leakage with preoperative (6.3% of the studies) and postoperative

(3.1% of the studies) NLR, whereas no study found a lack of association of postsurgical infection with preoperative or postoperative NLR.

DISCUSSION

As seen in this review, the preoperative and postoperative values of the NLR can predict the risk of developing anastomotic leakage, infections, bleeding, intra-abdominal abscesses, hernias, bowel obstruction, ileus and cardiac events following colorectal cancer surgery. A previous meta-analysis conducted in 2019 concluded that the preoperative NLR may be effective in predicting the prognosis of colorectal cancer patients who underwent curative tumour resection [44]. Moreover, other studies have discovered that the NLR can generally predict prognosis and survival in patients with colorectal cancer [45,46]. However, the present scoping review explored the topic in more depth, concluding that different postsurgical complications may also be predicted using the NLR.

TABLE 1. Characteristics of studies reporting association of the neutrophil-to-lymphocyte ratio and postsurgical complications.

Study (Author, Year, Country)	Type of study	Participants (N)	Tumour stage	Tumour position	Surgery type	Measured NLR (Preoperative/postoperative)	NLR cut-off	Postsurgical complications	Association of NLR and postsurgical complication	p-value
Alsaisf et al., 2021, Ireland [12]	Retrospective cohort	198	Stage II and III	Left colon (non-rectal): 41.3% Right colon: 36.2% Rectum: 22.5%	Laparoscopic: 80% Laparotomic: 20%	Preoperative	NLR>3.92	Ileus, Infection, Anastomotic leakage and Cardiac events	Odds ratio Ileus: 1.5 Infection: 2.4 Anastomotic leakage: 4.8 Cardiac events: 1.8	Ileus: 0.52 Infection: 0.17 Anastomotic leakage: 0.05 Cardiac events: 0.20
Caputo et al., 2016, Italy [13]	Retrospective cohort	87	Stage II and III	Rectum	Laparoscopic: 87.4% Laparotomic: 8.1% Robotic: 4.5%	Preoperative after neoadjuvant therapy	NLR≥3.8	Not mentioned	Positive association - chi-squared test performed	0.03
Cooper et al., 2021, United Kingdom [14]	Retrospective cohort	131	Unknown	Unknown	Unknown	Preoperative	Mean cut-off: NLR>5.4	Infection	Positive association - Mann-Whitney U test performed	0.026
De Leon et al., 2019, Mexico [15]	Cross-sectional cohort	54	Stage II, III and IV	Rectum	Unknown	Preoperative	Not mentioned	Not mentioned	Positive association	0.02
Egan et al., 2015, United Kingdom [16]	Case-control	Complications: 54 Controls: 161 Total: 215	Unknown	Unknown	Unknown	Preoperative and postoperative	Not mentioned	Infection: 68.5% Anastomotic leakage: 31.5%	Ratio-of means (complication vs controls) Preoperative: 1.5 Postoperative: 1.2	Preoperative: 0.0002 Postoperative: 0.065
Escobar et al., 2022, Mexico [17]	Prospective cohort	158	Stage II: 22.6% Stage III: 44.3% Stage IV: 33.1%	Left colon (non-rectal): 26.3% Right colon: 25.4% Rectum: 48.3%	Laparoscopic: 16.2% Laparotomic: 83.8%	Preoperative	NLR≥2.6	Infection and anastomotic leakage	Odds ratio: 2.24	0.02
Fuss et al., 2022, Ukraine [18]	Retrospective cohort	234	T1/T2: 34.2% T3/T4: 65.8%	Left colon (non-rectal): 32.5% Right colon: 65.8% Rectum: 1.7%	Laparoscopic: 87.5% Laparotomic: 12.5%	Preoperative	NLR≥3	Infection and anastomotic leakage	Positive association	0.04
Gallarín et al., 2017, Spain [19]	Retrospective cohort	292	Stage I, II and III	Unknown	Unknown	Preoperative	NLR≥5	Anastomotic leakage	Odds ratio: 1.9	<0.05
Gohil et al., 2013, United Kingdom [20]	Retrospective cohort	196	Unknown	Unknown	Unknown	Preoperative	Not mentioned	Anastomotic leakage	No association	

TABLE 1. Characteristics of studies reporting association of the neutrophil-to-lymphocyte ratio and postsurgical complications (continued).

Study (Author, Year, Country)	Type of study	Participants (N)	Tumour stage	Tumour position	Surgery type	Measured NLR (Preoperative/postoperative)	NLR cut-off	Postsurgical complications	Association of NLR and postsurgical complication	p-value
Hu et al., 2023, Canada [21]	Retrospective cohort	534	N0 stage: 57% Lymph node spread: 43%	Unknown	Laparoscopic: 27% Laparotomic: 73%	Preoperative	Not mentioned	Not mentioned	No association	-
Jones et al., 2018, United Kingdom [22]	Prospective cohort	314	T1/T2: 34% T3/T4: 66%	Rectum	Unknown	Preoperative and postoperative	NLR > 4	Anastomotic leakage, Infection, Pelvic collection and Flap necrosis	Positive association	< 0.01
Josse et al., 2016, Canada [23]	Retrospective cohort	583	Stage I or in-situ: 37% Stage II: 31% Stage III: 26% Stage IV: 6%	Colon: 62% Rectum: 38%	Laparoscopic: 48% Laparotomic: 52%	Preoperative	NLR ≥ 2.3	Infection: 41% Gastric and urinary: 16.4% Cardiac events: 16.4% Anastomotic leakage: 12.9% Bleeding: 12.8%	Odds ratio: 2.52	0.009
Kim et al., South Korea [24]	Retrospective cohort	405	Unknown	Rectum	Unknown	Postoperative (day 5)	NLR ≥ 8	Anastomotic leakage	Odds ratio: 2.997	< 0.001
Kumar et al., India [25]	Prospective cohort	17	Unknown	Unknown	Unknown	Postoperative (day 3)	Not mentioned	Anastomotic leakage	Positive association	< 0.05
Matsuda et al., 2014, Japan [26]	Retrospective cohort	364	Unknown	Unknown	Laparoscopic	Change in NLR (Postoperative day 1 - preoperative)		Infection	Odds ratio: 1.20	0.031
Meliti et al., 2021, Tunisia [27]	Retrospective cohort	55	Unknown	Left colon (non-rectal): 22% Right colon: 43% Rectum: 35%	Unknown	Preoperative	NLR ≥ 5	Infection: 48% Anastomotic leakage: 26% Abdominal collection: 17% Bleeding: 4.5% Ileus: 4.5%	Positive association	0.01
Mik et al., 2018, Poland [28]	Prospective cohort	724	Stage I: 17.7% Stage II: 35.4% Stage III: 36.3% Stage IV: 10.6%	Left colon (non-rectal): 31.9% Right colon: 26% Rectum: 42.1%	Laparotomic	Postoperative (day 4)	NLR ≥ 6.5	Anastomotic leakage	Positive association	0.0012

TABLE 1. Characteristics of studies reporting association of the neutrophil-to-lymphocyte ratio and postoperative complications (continued).

Study (Author, Year, Country)	Type of study	Participants (N)	Tumour stage	Tumour position	Surgery type	Measured NLR (Preoperative/postoperative)	NLR cut-off	Postsurgical complications	Association of NLR and postsurgical complication	p-value
Mikayata et al., 2016, Japan [29]	Retrospective cohort	261	Stage II and III	Rectum	Unknown	Preoperative	Not mentioned	Anastomotic leakage, Infection, and Bowel obstruction	Odds ratio Infection: 4 Anastomotic leakage: 8.66 Bowel obstruction: 3.86	Infection: 0.004 Anastomotic leakage: <0.001 Bowel obstruction: 0.007
Mikayata et al., 2017, Japan [30]	Retrospective cohort	260	In-situ: 11% Stage I: 30% Stage II: 31% Stage III: 28%	Rectum	Unknown	Preoperative	NLR ≥ 2.21	Anastomotic leakage, Infection, and Bowel obstruction	Odds ratio Infection: 3.65 Anastomotic leakage: 4.51 Bowel obstruction: 2.06	Infection: 0.0138 Anastomotic leakage: 0.0329 Bowel obstruction: 0.1842
Mohri et al., 2014, Japan [31]	Retrospective cohort	186	Unknown	Unknown	Unknown	Preoperative	NLR > 3	Infection	Positive association	<0.05
Morimoto et al., 2021, Japan [32]	Retrospective cohort	208	T1/T2: 27.8% T3/T4: 72.1%	Colon: 86.1% Rectum: 13.9%	Laparoscopic: 60% Laparotomic: 40%	Preoperative	NLR ≥ 2.7	Anastomotic leakage	Positive association	<0.05
Nakao et al., 2016, Japan [33]	Retrospective cohort	76	Unknown	Unknown	Laparoscopic	Preoperative	NLR ≥ 3.2	Not mentioned	No association	-
Paliogiannis et al., 2020, Italy [34]	Retrospective cohort	1432	In-situ: 0.9% Stage I: 16.9% Stage II: 32.8% Stage III: 36.7% Stage IV: 11.7% Unknown: 1%	Left colon (non-rectal): 34% Right colon: 38.4% Rectum: 27.6%	Laparoscopic: 26% Laparotomic: 74%	Postoperative (day 4)	NLR ≥ 6.5	Anastomotic leakage	Odds ratio: 1.068	0.004
Pantoja-Pachajoa et al., 2021, Argentina [35]	Retrospective cohort	116	Stage I: 23.3% Stage II: 60.3% Stage III: 15.5% Stage IV: 0.9%	Left colon (non-rectal): 53% Right colon: 31% Rectum: 16%	Laparoscopic: 44% Laparotomic: 56%	Postoperative (day 1-5)	Not mentioned	Anastomotic leakage	No association	-

TABLE 1. Characteristics of studies reporting association of the neutrophil-to-lymphocyte ratio and postsurgical complications (continued).

Study (Author, Year, Country)	Type of study	Participants (N)	Tumour stage	Tumour position	Surgery type	Measured NLR (Preoperative/postoperative)	NLR cut-off	Postsurgical complications	Association of NLR and postsurgical complication	p-value
Sagawa et.al., 2017, Japan [36]	Retrospective cohort	351	Unknown	Colon: 70.7% Rectum: 29.3%	Laparoscopic: Laparotomic:	Preoperative	NLR>4	Infection	Odds ratio: 3.24	0.01
Tan et.al., 2022, China [37]	Retrospective cohort	306	Stage I, II, III	Rectal	Laparotomic	Preoperative	NLR>6.54	Anastomotic leakage	Positive association	< 0.001
Vieira et.al., 2019, Spain [38]	Prospective cohort	221	Unknown	Rectal	Unknown	Preoperative	NLR>5	Anastomotic leakage	Positive association	0.001
Yalav et.al., 2020, Turkey [39]	Retrospective cohort	279	Stage I, II and III	Colon	Laparotomic: Laparoscopic:	Preoperative	NLR>2.08	Infection, Internal abscess, Evisceration, Ileus, Anastomotic leakage	-	Infection: 0.456 Internal abscess: 0.034 Evisceration: 0.574 Ileus: 0.05 Anastomotic Leakage: 0.426
Yano et.al., 2017, Japan [40]	Retrospective cohort	188	Unknown	Colon: 62.7% Rectum: 37.3%	Unknown	Preoperative	NLR>3	Infection, Ileus, Bleeding	Positive association	<0.05
Yuliandar et.al., 2020, Indonesia [41]	Cross-sectional cohort	54	Unknown	Sigmoid colon	Laparotomic	Preoperative	NLR>6.06	Anastomotic leakage	No association	0.518
Zeman et.al., 2020, Poland [42]	Retrospective cohort	392	Stage III	Sigmoid colon	Laparotomic	Preoperative	NLR>5	Anastomotic leakage	OR= 2.98	0.033
Zhang et.al., 2022, Germany [43]	Prospective cohort	204	Stage II and III	Colon	Unknown	Postoperative	NLR>4.95	Anastomotic leakage	Positive association	0.001

TABLE 2. Postsurgical complications studied in included records.

Postoperative complication	Studies reporting association with preoperative NLR n/N (%)	Studies reporting statistically significant association with preoperative NLR n/N (%)	Studies reporting lack of association with preoperative NLR n/N (%)	Studies reporting association with postoperative NLR n/N (%)	Studies reporting statistically significant association with postoperative NLR n/N (%)	Studies reporting lack of association with postoperative NLR n/N (%)
Anastomotic leakage	15/32 (46.9%)	14/32 (43.8%)	2/32 (6.3%)	7/32 (21.9%)	6/32 (18.8%)	1/32 (3.1%)
Infection	14/32 (43.8%)	12/32 (37.5%)	0/32 (0%)	2/32 (6.3%)	1/32 (3.1%)	0/32 (0%)
Bleeding	3/32 (9.4%)	3/32 (9.4%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Ileus	4/32 (12.5%)	3/32 (9.4%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Bowel obstruction	2/32 (6.3%)	1/32 (3.1%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Cardiac events	2/32 (6.3%)	1/32 (3.1%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Gastric and urinary events	1/32 (3.1%)	1/32 (3.1%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Abdominal and pelvic collection	2/32 (6.3%)	2/32 (6.3%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Evisceration	1/32 (3.1%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)

Nowadays, with accelerated recovery being one of the most important perspectives in the field of surgery, there is a great need for non-invasive and cost-effective tools to predict postsurgical prognosis [47]. Given that at this moment, the average hospital stay in laparoscopic and laparotomic colorectal cancer surgery is only three and seven days respectively, the NLR can help surgeons predict whether there may be possible complications following a discharge and thus effectually decide whether there is a need for a longer stay in the hospital [48,49]. Also it can help surgeons decide whether the longer application of prophylactic measures, such as the use of laxatives and prophylactic antibiotics over a longer term would benefit the patient following discharge [50,51]. Furthermore, using preoperative NLR levels in patients with rectal cancer, surgeons can decide whether to place a diverting colostomy during surgery, which has been shown to significantly reduce the probability of anastomotic leakage in high risk patients [52,53].

The NLR can be measured indirectly through a full blood count prior to and after the surgical operation. Nevertheless, less firm conclusions can be drawn on the relationship of the postoperative NLR and postoperative complications, since the day that postoperative NLR was measured varied from study to study. Most studies assessed the relationship of postoperative day 1 NLR with postoperative complications, while other studies assessed postoperative day 3, day 4 and day 5 NLR.

It should also be noted that neoadjuvant chemo-

therapy may also affect the prognostic value of the preoperative NLR in predicting postoperative complications. It is known that cytostatic and cytotoxic chemotherapy can cause bone marrow suppression leading to severe neutropenia [54]. Moreover, studies have shown that some chemotherapeutic agents may also induce an increase in the lymphocyte count [55,56]. Hence, the NLR may significantly decrease following neoadjuvant therapy and so the NLR may not be very predictive for postoperative complications and a lower cut-off may be used. Indeed, in the present review, the study by Caputo et.al. that assessed the association of the NLR and postsurgical complications following neoadjuvant chemotherapy, used a lower cut-off compared to the majority of the other studies [13]. It is also worth mentioning that neoadjuvant chemotherapy by itself, can increase the risk of infections and cardiac events due to cardiotoxicity and neutropenia [57,58].

In spite of the fact that the present scoping review was conducted using the PRISMA-ScR guidelines, some limitations exist within it. First of all, the majority of the retrieved studies had a retrospective design, increasing the probability of biased results [59]. Moreover, studies were heterogeneous in design in terms of variables such as TNM stages, neoadjuvant chemoradiotherapy, laparoscopic/laparotomic method of surgery, and ages of the participants, used different cut-off values of the NLR and presented the results in different forms, making it difficult to reach more generalised and definitive conclusions

on the correlation of NLR levels with each postsurgical complication. It is also worth noting that some studies involved only a few numbers of participants, lowering their statistical effect. Finally, the literature search was limited to articles written in English, and hence articles written in different languages may have been missed in this review study.

CONCLUSIONS

Overall, as seen through this review high levels of preoperative and postoperative NLR are associated with a higher risk of developing postsurgical complications following colorectal cancer surgery. Nevertheless, more prospective cohort studies need to be conducted in the near future, in order to assess the use of the NLR as a prognostic biomarker for postoperative complication in colorectal cancer surgery. These studies should also concentrate on finding a standardised cut-off value for the NLR through which the latter can be assessed for sensitivity and specificity as a prognostic marker.

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