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Research Article

Prognostic Value of Lymphocyte-to-Monocyte Ratio and Neutrophil-to-Lymphocyte Ratio in Patients with Colorectal Cancer: "A Retrospective Cohort Study"

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Abstract

Background: In the past decade, advancements in the treatment of colorectal cancer (CRC) have greatly improved survival; nevertheless, simple biomarkers to predict responsiveness to therapy or survival that seem relevant to all medical oncology settings globally have yet to be developed. The neutrophil/lymphocyte ratio (NLR) and the lymphocyte-to-monocyte ratio (LMR) are two simple and generally accessible examples of inflammation markers based on differential white cell counts.

Methods: LMR and NLR were evaluated in 69 patients diagnosed with CRC and received different treatment approaches depending on the stage, ECOG, and treatment guidelines. The correlation between LMR and clinical pathology was retrospectively evaluated. The predicted values of NLR and compared the predicted values of LMR and NLR were also assessed.

Results: After analyzing the receiver operating characteristic (ROC) curve, the cut-off level for LMR and NLR was determined to be 2. Out of the total patients, 55 (79.7%) were classified into the high LMR group, while 14 (20.3%) were categorized into the low LMR group. Among the patients, 30 (43.5%) and 39 (56.5%) were grouped into low and high NLR groups, respectively. It was concluded that tumor markers (CEA) (p 0.031), TNM staging (p=0.016), distant metastasis (p=0.014), and disease progression (p=0.038) were significant. NLR was significant in only tumor markers (p=0.014) and tumor location (p=0.046). OS was significant.

Conclusion: The results indicate that prior to treatment, both LMR and NLR were significant independent predictors in colon cancer and that incorporating NLR/LMR alongside TNM staging may enhance prognostic evaluation in patients with colon cancer. However, the study was limited by a retrospective methodology and

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a relatively small sample size. To determine the exact cut-off values for NLR and LMR as prognostic indicators in colorectal cancer, larger-scale prospective studies involving multiple centers will be required.

Keywords: Colorectal cancer; NLR; LMR**;** Surgical resection; Adjuvant chemotherapy; Neoadjuvant chemotherapy.

Introduction

The third most prevalent disease in terms of new cases is colorectal cancer (CRC). According to GLOBOCAN 2020,931590 (10%), and the second 935,173 (9.4%) leading cause of cancer-related death worldwide in 2020 report. Because of the improvement of surgery, chemotherapy, and radiotherapy treatment, local recurrence and survival have improved in CRC patients. Abraham Virchow hypothesized the relationship between cancer and systemic inflammation in 1863 [1]. The interaction between the host and the tumor has been shown to influence cancer development [2]. It has also been hypothesized that systemic inflammation may provide vital information for prognosis.

Previous studies showed that a higher NLR had been linked to a worse prognosis for several types of cancer patients, whereas increased LMR has been linked to a better prognosis [3]. Whereas decreased lymphocytes are responsible for an inadequate immune response to the tumor, thus promoting tumor progression and metastasis [4-6].

On the other hand, monocytes can infiltrate tumors and differentiate into tumor-related macrophages. Therefore, macrophages are involved in tumor growth, infiltration, metastasis, angiogenesis, and recurrence [7,8]. As a result, LMR is assumed to represent the host's immunological response and the degree of tumor growth, and a low LMR is associated with a poor prognosis.

Furthermore, the NLR blood test, which is affordable, reliable, and routinely used, is a significant predictor of poor prognosis for colorectal cancer. The NLR is with progression and metastasis of gastric cancer, non-small-cell lung cancer, ovarian cancer, intrahepatic cholangiocarcinoma, hepatocellular carcinoma, pancreatic cancer, and CRC nasopharyngeal cancer [9].

Tumors-activated neutrophils enhance angiogenesis and immunosuppression, tumor cell migration, invasion, and metastasis, according to several relevant in vitro and in vivo investigations. As a result, it became vital to learn about the processes that control neutrophil biology and function in the setting of the tumor microenvironment [10]. This study aimed to determine the predictive value of NLRs and LMRs in colorectal cancer patients. TNM's current edition determined the tumor stage (eight editions in 2017). Histological confirmation of colorectal cancer was typically acquired through a lower gastrointestinal tract endoscopy or a surgical specimen. In addition, computed tomography was used to perform systemic staging. Tumors are classified histologically based on differentiation grade, immunohistochemistry, and molecular components for MMR deficiency, RAS, and BRAF mutation.

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The inclusion criteria were pathological confirmed CRC, no previous anti-inflammatory therapy, and no acute infection. The exclusion criteria were: incomplete clinicopathological and follow-up date and presence of hematological disorders.

Different treatment approaches were selected in the study group. Surgical resection, adjuvant or neoadjuvant chemotherapy, and pre/post-operative radiation are options for treating localized diseases. On the other hand, unresectable metastatic CRC varies, including monotherapy, dual chemotherapy, immunotherapy, and biological agents. The therapeutic anti-tumor effect or post-surgery effect was evaluated. The total lesion clearance, including the lymph node, was regarded as a complete response (CR). A partial response (PR) is defined as a decrease in the sum of the longest diameter of lesions by at least 30%. Stable disease (SD) has neither enough regression nor enough growth to be classified as progressive disease (PD), as measured by the longest diameter after therapy commenced. Progressive disease (PD) is defined as a 20% increase in the sum of the longest diameter of measures lesion compared to the least sum LD observed since therapy began or the emergence of one or more lesions [5].

Methods

Medical records from patients diagnosed with CRC at NMC oncology center (UAE, Abu Dhabi) were analyzed retrospectively (2015-2019). Patients with CRC having histologically proven CRC were included in the study. Patients with medical records lacking a complete blood count and clinicopathological and follow-up information were excluded from the study. To guarantee that the WBC reflected the typical basal value, patients with a co-occurring hematological condition or a known chronic inflammatory disease were also removed from the research. On the basis of endoscopy histopathological and radiographic evidence, CRC recurrence was identified.

Assessment of LMR and NLR

Prior to initiating any treatment, blood samples were collected from the patients at the time of diagnosis. The pre-treatment blood sample was used to calculate the LMR by dividing the absolute lymphocyte count by the absolute monocyte count. In addition, the NLR was determined by dividing the absolute neutrophil count and absolute lymphocyte count, both obtained from the pre-treatment blood sample.

Follow-up data

Patients were monitored for a period of 2-5 years through various means such as measuring carcinoembryonic antigen, physical examination, colonoscopy, and radiological imaging including CT-scan of chest, abdomen, and pelvis, as well as Positron emission tomography scans. Recurrence of the tumor was classified as local or distant based on pathological evidence and confirmed through the aforementioned techniques. Local recurrence was defined as the spread of the tumor in the surgical anastomosis region, while distant recurrence referred to the spread of the tumor in other parts of the body.

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Statistical analysis

The IBM SPSS software was used to conduct the statistical study. Receiver operating characteristic (ROC) curve analysis was used to find the optimal cut-off values for LMR and NLR to stratify patients. To ascertain the relationship between LMR, NLR, and the factors, clinical-pathological variables were analyzed using the X^2 or Fisher's exact test or Mann-Whitney U test, as applicable. Analyses of the relevance of various prognostic indicators were also conducted. The OS and PFS were estimated using the Kaplan-Meier technique, and comparison was done using the Log-rank test. The COX proportional hazards model was used to calculate the univariate and multivariate hazard ratios (HRs) for the research parameters with a 95% confidence interval (CI). A p-value of 0.05 or less was regarded as significant.

Results

Patient's characteristics

The study included a total of 69 patients. The median age at the time of diagnosis was 51 years. Males outnumbered females, with 59 males diagnosed with CRC vs 10 females. Most patients were diagnosed with left colon cancer, whereas 32 were diagnosed with stage 3 colorectal cancer and 31 with stage 4 colorectal cancer (Table 1).

Patient traits compared on the basis of cut-off numbers

A total of 69 patients were involved; 14 were placed in the low-LMR (LMR=2) group, and 55 were placed in the high-LMR (LMR > 2) group. Similarly, 39 patients were given a high NLR, and 69 were given a low NLR (NLR=2). Table 2 compares the baseline patient characteristics of the high- and low-LMR groups and Table 3 compares the baseline patient characteristics of the high- and low-NLR groups. Concerning patient age, gender, and primary tumor site, both groups were relatively balanced. The stage, distant metastasis, progression, and tumor markers (CEA) between the low- and high-LMR groups did, however, differ significantly (all P=0.05). The NLR group, on the other hand, was only significant in terms of the location and tumor marker (CEA).

Survival outcome

The overall survival rate at three years and five years was 86.04 %and 75.28 %, respectively. Meanwhile, PFS was 57.0% in and 47.5% in the third year (Table 3-4).

Discussion

There is a significant link between inflammation and cancer, and certain types of peripheral inflammatory cells, like neutrophils and lymphocytes, are considered a prognostic indicator for different types of cancer [13-15]. The study included a total of 69 patients.

The median age at the time of diagnosis was 51 years. Males outnumbered females, with 59 males diagnosed with CRC vs ten females. Most patients were diagnosed with left colon cancer, whereas 32 were diagnosed with stage 3 colorectal cancer and 31 with stage 4 colorectal cancer.

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Parameters		N	Percentages %
Gender	Male	59	85.5
	Female	10	14.5
Location	Right-side	10	14.5
	Left side	34	49.3
	Rectum	25	36.2
TNM stage	1	0	0
	2	6	8.7
	3	32	46.4
	4	31	44.9
Mutation	Wild	26	37.7
	Mutant	17	24.6
	MMS	1	1.4
Distant metastasis	Yes	34	49.3
	No	35	50.7
LMR status	LMR <=2	14	20.3
	LMR >2	55	79.7
NLR status	NLR <=2	30	43.5
	NLR >2	39	56.5
Tx	Chemotherapy	15	21.7
	Chemotherapy/radiotherapy	12	17.4
	Chemotherapy/radiotherapy/surgery	17	24.6
	Surgery alone	1	1.4
	Chemotherapy/surgery	24	34.8
Final outcome	Complete response	33	47.8
	Partial response	5	7.2
	Stable disease	15	21.7
	Progressive disease	9	13
	Regression	5	7.2
		2	2.9
Recurrence	Yes	23	33.3
	No	46	66.7

Table 1: The clinical characteristic of the study groups.

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LMR<=2			LMR>2	
Age	Mean	Standard Deviation	Mean	Standard Deviation
	52.36	12.67	51	9.29
CEA	490.02	689.24	43.32	166.11
Variables	LMR<2		LMR>2	P value
Gender	Male	13	46	0.348
	Female	1	9	
Tumor location	Right	2	8	0.393
	Left	9	25	
	Rectum	3	22	
TNM Stage*	II	0	6	0.016
	III	3	29	
	IV	11	20	
Distant metastasis	Yes	11	23	0.014
	No	3	32	
Treatment	Chemo	4	11	0.768
	Chemo/Radio	2	10	
	Chemo/radio/surgery	2	15	
	Surgery	0	1	
	Chemo/surgery	6	18	
Progression	Yes	8	15	0.038
	No	6	40	
Recurrence	Yes	3	7	0.326
	No	11	48	

Table 2: Pre-treatment lymphocyte-to-monocyte ratio (LMR) stratified univariate comparison of baseline clinical characteristics of patients with newly diagnosed colorectal cancer. Tumor (T), Nodes (N), and Metastases (M)*.

NLR<=2			NLR>2		p-value
Age	Mean	Standard Deviation	Mean	Standard Deviation	
	49	9.93	52.79	9.87	0.653
CEA	19.27	52.39	226.25	494.26	0.014

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Table 3: The pre-treatment neutrophil-to-Lymphocyte ratio (NLR) stratified univariate comparison of baseline clinical characteristics of patients with newly diagnosed colorectal cancer.

Variables	Univariate			Multivariate	
	HR (95% CI)		P value	HR (95% CI)	P value
Age	0.99 (94.64-102.91)		0.537		
Gender	Male	1	0.276		
	Female	2.25 (52.27-970.42			
Tumor location	Right	0.62 (13.28-289.06)	0.592		
	Left	1.29 (54.09-308.89)			
	Rectum	1			
TNM stage	≤ 3	1	0.000	15.01 (0.78-289.79)	0.073
	4	6.49 (238.63-1763.27)		1	
Mutation	Mutant	1	0.152	1	0.011
	wild	2.09 (76.16-575-0.5)		6.54 (1.54-27.743)	
Distant metastasis	Yes	7.38 (249.33-2184.24)	0.000	56.845 (1.927-1676.574)	0.004
	No	1		1	
Treatment	Chemo alone	3.64 (129.02-1027.74)	0.011	7.60 (1.42-40.60)	0.049
	Chemo/surgery	1		1	
	Chemo/Radio	1.59 (53.28-476.30)		6.70 (0.99-45.49)	
	Chemo/radio/surgery	0.11 (1.35-91.65)		1.17 (0.08-16.80)	

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	Surgery alone	0.00 (0.00-0.00)		0.00 (0.00-0.00)	
LMR group	≤ 2	3.86 (158.64-940.76)	0.003	16.75 (2.50-112.13)	0.004
	> 2	1		1	
NLR Group	≤ 2	1	0.503	2.52 (0.71-8.99)	0.152
	> 2	1.33 (57.74-306.15)		1	

Table 4: Univariate and multivariate analysis of variables associated with PFS of patients newly diagnosed.

Parameters of the study included gender, location, TNM stage, mutation, distant metastasis, LMR status, NLR status, Tx, final outcome, and recurrence of the respondents. It was found that 44.9% of the respondents were at the 4th stage of TNM, whereas 46.4% were at the 3rd stage (Figure 1). The mutation found was 37.7% for the wild, 24.6% for the mutant, and 1.4% for MMS. Patients. A previous study evaluated the relationship between KRAS mutation and lymphocyte/inflammatory expression. It concluded that there had been no significant association between KRAS mutation and elevated lymphocyte/inflammation protein [7]. Genetic changes that cause neoplasia trigger the intrinsic pathway, while inflammation can raise the likelihood of cancer development through the extrinsic pathway [17].

In the past few years, noteworthy advancements and revelations in cancer genomics have occurred. However, the clinical usefulness of gene expression-based arrays or analyzing germline single-nucleotide polymorphisms to determine prognosis or anticipate therapy response remains restricted, even for prevalent malignancies like breast and lung cancers [18,19]. As an illustration, Wacholder, et al., [18] found that adding ten prevalent genetic variants associated with breast cancer only slightly enhanced current risk-assessment models among 411,000 patients. This yielded minimal alterations to the anticipated risk of breast cancer for most women based on the presently accessible genetic data.

Additionally, these tests are costly and primarily utilized in developed countries, limiting use in under-resourced communities. For a biomarker to be helpful, it must be both precise and consistent, and easily accessible. While there has been a strong emphasis on molecular assessments of tumors to predict outcomes, the prognostic significance of the body's response to cancer has not received adequate attention. These findings suggest a need to reconsider the current approach [20].

An increased NLR and decreased LMR indicate that the body's inflammatory response is tilting towards promoting tumor cell growth and cancer spread while weakening anti-tumor defenses, resulting in

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unfavorable outcomes. Since NLR and LMR can be easily measured through routine blood tests, they may serve as useful additional tools in assessing the clinicopathology of patients. Recent research has highlighted the close connection between inflammation and cancer through intrinsic and extrinsic pathways (Figure 2). 50.7% of the total respondents were found to have distant metastasis. Recent studies have shown systemic inflammation promotes tumor progression and metastasis by inhibiting apoptosis, angiogenesis, and damaging DNA [20].

Leukocyte count, monocyte count, platelet count, and ratios such as NLR, LMR, and PLR are hematological measures used to assess systemic inflammation. Recent studies have indicated that these measures can act as independent prognostic indicators for patients diagnosed with non-small cell lung, gastric, and breast cancer [20]. It can be concluded that 79.7% had LMR>2, and 20.3% had LMR<2. LMR may be a useful prognostic marker in patients with colon cancer. It was also found that 56.5% of total respondents were with NLR>2, and 43.6% were with NLR<2 (Figure 3).

The predictive ability of NLR and LMR in individuals diagnosed with colorectal cancer and comparison of effectiveness as prognostic markers were assessed and it was found that LMR was notably linked to disease-free survival (DFS) among colon cancer patients with neoadjuvant chemotherapy (NAC).

These results suggest that LMR could be a valuable criterion in determining the necessity for adjuvant chemotherapy with active regimens. While many studies have investigated the prognostic significance of NLR or LMR in colon cancer, most have used varying ROC curve-determined cut-off values for these markers.

In a recent meta-analysis, Ethier, et al., examined the correlation between NLR and breast cancer prognosis. However, to date, no meta-analysis has been conducted on the association between LMR and colon cancer prognosis in the Gulf region. Additionally, most studies that have explored the predictive value of NLR or LMR in colorectal cancer have focused on respectable cases [1,16] with only a few studies examining the prognostic significance in metastatic colon cancer. Regarding the Tx factors of the respondents, it was found that 34.8% were undergoing chemotherapy/surgery, 1.4% with surgery alone, 24.6% with chemotherapy/radiotherapy/surgery, 17.4% with chemotherapy/radiotherapy, and 21.7% with chemotherapy alone.

In patients with metastatic colorectal cancer, (mCRC) not received prior treatment, a high LMR level before undergoing FOLFOX chemotherapy is an independent favorable prognostic factor for both progression-free survival (PFS) and overall survival (OS). Moreover, alterations in LMR before and after chemotherapy appear to be indicative of the benefits of such treatment [27]. In patients undergoing chemotherapy, patients with consistently high LMR levels (high-high subgroup), patients with an increase in LMR (low-high subgroup), and patients with a decrease in LMR (high-low subgroup) have shown superior outcomes in PFS and OS

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compared to patients with consistently low LMR levels (low-low subgroup).

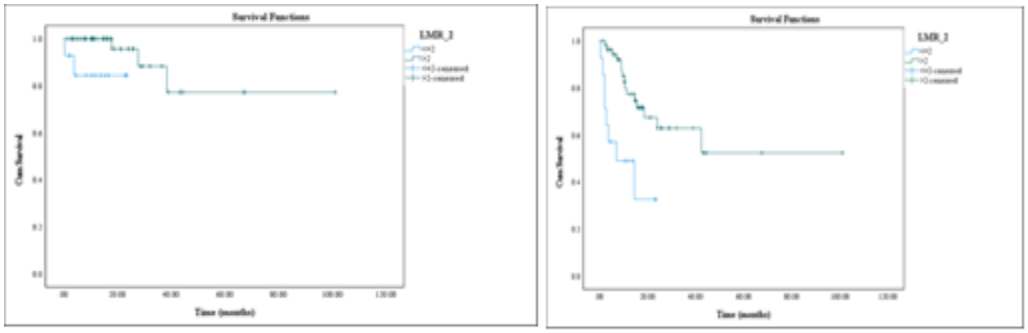

Figure 1: Kaplan-Meier curves: the low LMR group had significantly worse PFS and OS (p=0.001, P=0.019).

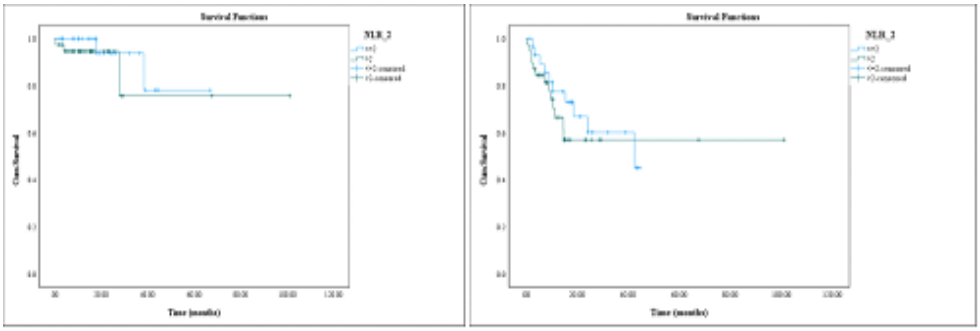

Figure 2: Kaplan-Meier curves: There was no significant difference in PFS (p=0.502) and OS (p=0.433) between patients with low and high LMR.

These findings indicate that variations in LMR before and after chemotherapy could serve as a predictive indicator for the potential benefits of such treatment [22-24]. Chan et al. investigated 150 breast cancer patients with neoadjuvant chemotherapy (NAC) and found that patients with elevated LMR levels and low NLR levels exhibited favorable DFS outcomes [11]. In 199 non-smokers with advanced lung adenocarcinoma getting gefitinib or conventional chemotherapy as first-line therapy, new research assessed the prognostic effect of the NLR. Among chemotherapy-naïve patients with metastatic colorectal cancer (mCRC) receiving FOLFOX treatment, patients with high pre-treatment NLR levels experienced a decrease in NLR after treatment and demonstrated longer OS compared to NLR levels remained elevated in some patients (20.7 vs 7.9 months, P<0.001). Similarly, patients with low pre-treatment NLR levels maintaining low NLR levels after treatment had longer OS than patients with increased NLR levels after treatment (26.4 vs 18.9 months, P<0.001). These results suggest that changes in LMR before and after chemotherapy may indicate chemotherapy

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benefits in this patient population [23]. Outcomes showed that 7.2%, 13.0%, 21.7%, 7.2%, and 47.8% had regression, progressive, stable, partial, and complete responses, respectively. A recurrence rate was found in 33.3% of the total respondents. This meta-analysis indicates that the LMR may be a good predictor of the outcome of patients with colon cancer. It also suggests that active regimens should be considered before the disease progresses. Although few studies have investigated the link between LMR and the prognosis of colorectal cancer, it is widely believed that this LMR can predict cancer's response to chemotherapy. In a study conducted by Lin et al, they reported that patients with high levels of LMR and low NLR were more likely to have good DFS. Lymphocytes play essential roles in developing systemic inflammatory responses and evaluating tumor-infiltrating lymphocytes [24]. These cells are known to have an improved prognosis in patients with certain types of cancer. As a potential limitation, this study is a single-center retrospective study with small sample size. Thus, additional prospective multinational studies are required to evaluate the advantages and disadvantages of the results.

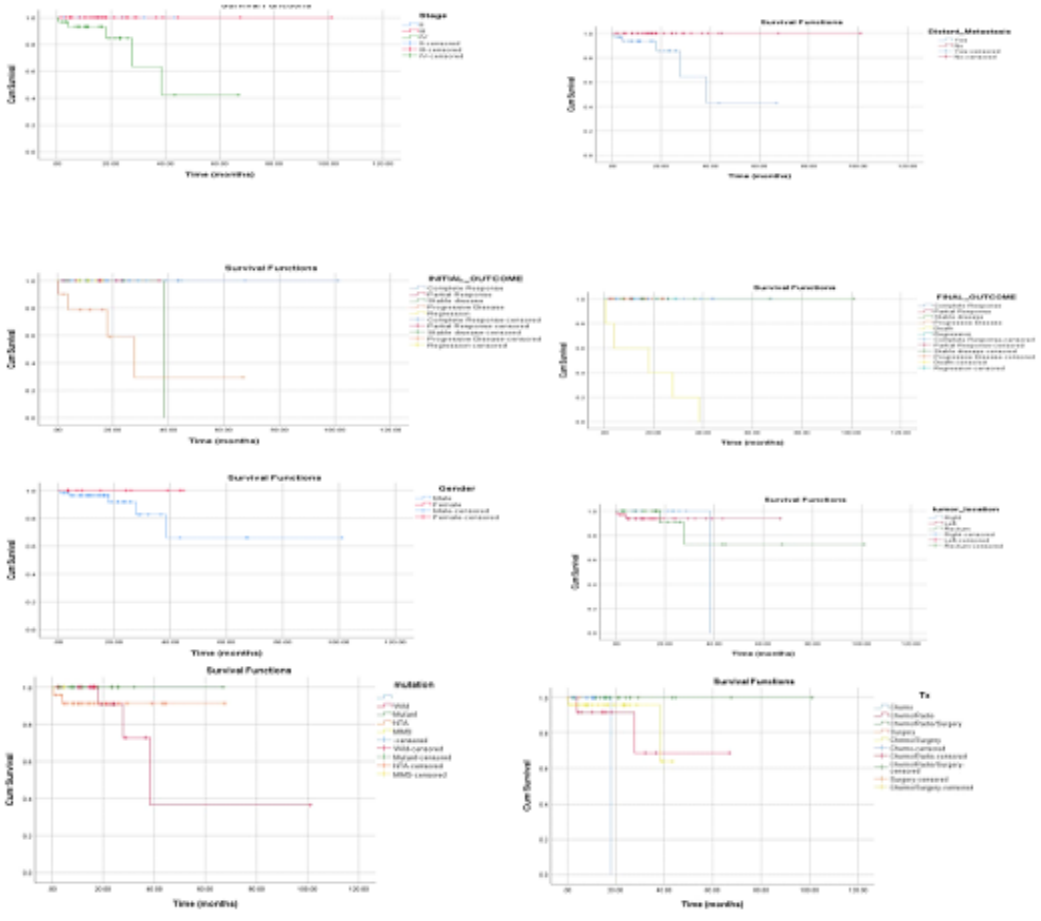

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Figure 3: Kaplan-Meier curves for correlation between clinicopathological features and OS. OS was significantly correlated with tumor staging (p=0.021), distance metastasis (p=0.008), and treatment outcome (initial treatment p=0.001), after 3 years (final outcome p=0.000). No significant relation between tumor location, genetic mutation, or treatment options.

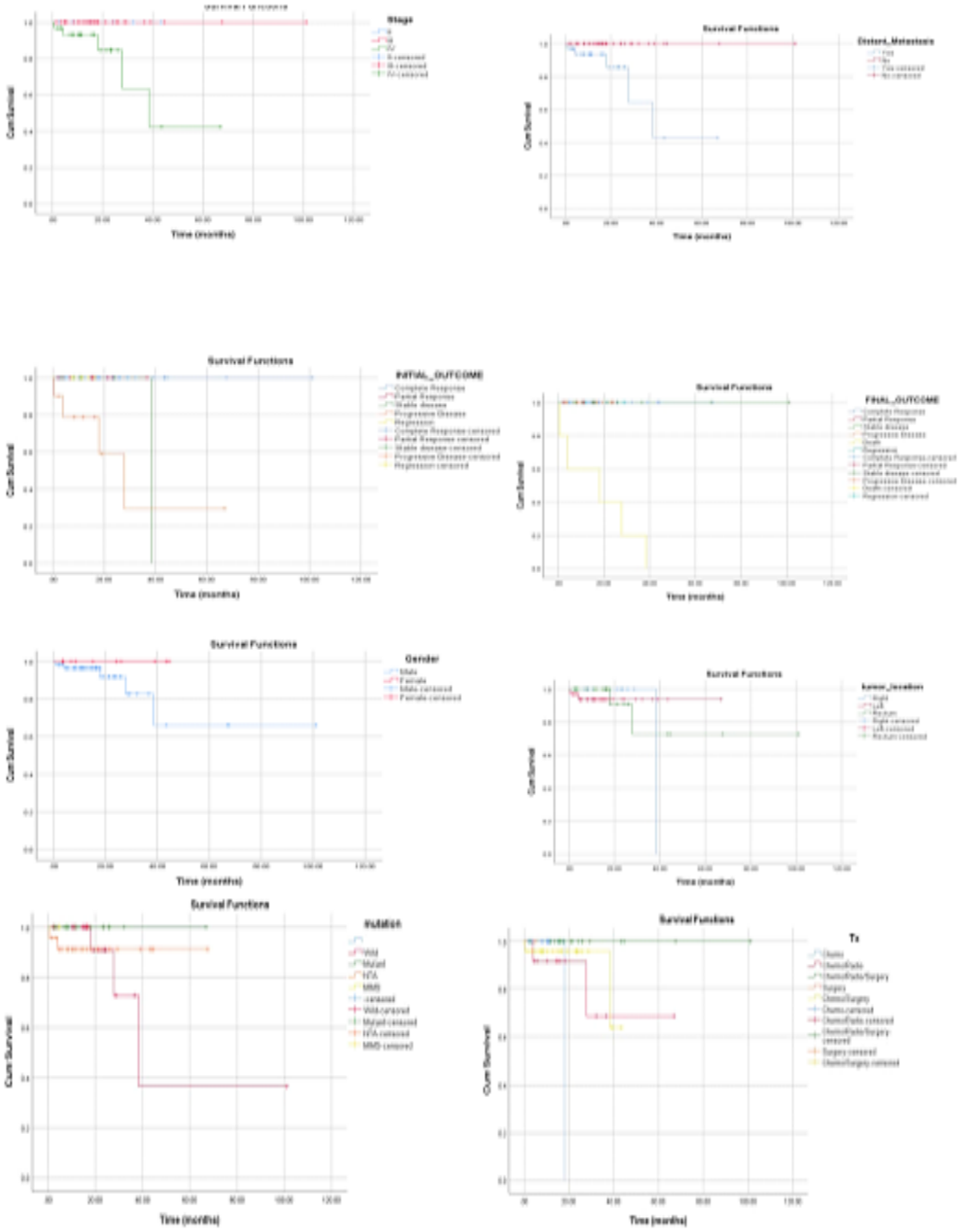

Figure 4: Kaplan-Meier curves for Co-relation between clinicopathological features and PFS. PFS was

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significantly correlated with tumor staging (p=0.000), mutation (p=0.015), distance metastasis (p=0.000), treatment type (p=0.000), treatment outcome initial treatment p=0.000), after 3 years (final outcome p=0.000). No significant relation between PFS and gender (p=0.263) or tumor location (p=0.582).

Conclusion

The conclusions suggest that LMR and NLR were independently significant predictors of colon cancer before initiating therapy. NLR and LMR were substantial predictors of colon cancer before starting the treatment of NLR MR. It might be a beneficial adjunct to TNM staging in the prognosis evaluation of colon cancer patients. The relatively small sample size and single-centered retrospective methodology used in this study are both limitations. It will be essential to conduct multicenter, extensive prospective studies to determine the exact cut-off values for NLR and LMR as colorectal cancer prognostic markers.

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