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ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC CANCER

Blood Neutrophil-to-Lymphocyte Ratio Predicts Survival in Patients with Colorectal Liver Metastases Treated with Systemic Chemotherapy

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ABSTRACT

Background. Whether neutrophil-to-lymphocyte ratio (NLR) predicts survival of patients with colorectal liver metastases (CLM) treated with systemic chemotherapy remains unclear.

Methods. Clinicopathologic data were reviewed for patients with CLM treated with chemotherapy and resection ($n = 200$) or chemotherapy only ($n = 90$). Univariate and multivariate analyses for prognostic factors were performed. In the resection group, whether chemotherapy normalizes high NLR and the effect of NLR normalization on survival were evaluated.

Results. In the resection group, patients with preoperative NLR > 5 had a worse 5-year survival rate than patients with NLR ≤ 5 (19% vs. 43%; $P = 0.009$), and NLR > 5 was the only independent preoperative predictor of worse survival ($P = 0.016$; hazard ratio [HR] = 2.22; 95% confidence interval [95% CI], 1.16–4.25). In the nonresection group, patients with prechemotherapy NLR > 5 had a worse 3-year survival rate than patients with NLR ≤ 5 (0% vs. 23%; $P = 0.0002$), and NLR > 5 was the only independent predictor of worse survival ($P = 0.001$; HR = 2.91; 95% CI, 1.54–5.50). In the resection group, chemotherapy normalized high NLR in 17 of 25 patients, and these 17 patients had better survival than the 8 patients with high NLR both before chemotherapy and before surgery ($P = 0.021$).

Conclusion. NLR independently predicts survival in patients with CLM treated with chemotherapy followed by resection or chemotherapy only. When chemotherapy normalizes high NLR, improved survival is expected.

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Several prognostic factors have been identified for patients with colorectal liver metastases (CLM) undergoing hepatic resection.[1–4] These include patient age, primary tumor stage, disease-free interval (DFI), carcinoembryonic antigen (CEA) level, tumor size, tumor number, whether the CLM are bilateral, and surgical margin status. However, clinical risk scores based on these prognostic factors were not validated in recent studies of patients undergoing hepatic resection.[1–3,5–8]

Unfortunately, few patients with CLM are eligible for hepatic resection, and prognostic factors for patients treated solely with chemotherapy are not well defined.[9] Further, with the increasing use of preoperative chemotherapy in both resectable and unresectable CLM, the population of patients who can benefit from hepatic resection has also changed. Adam et al. showed that 12.5% of patients with initially unresectable CLM had their disease converted to resectable by chemotherapy and that the 5-year survival rate after hepatic resection in these patients was 33%.[10] These results suggest that we cannot predict the outcome of patients with CLM before chemotherapy. The prognostic factors proposed to date may have limited usefulness in patients who receive preoperative chemotherapy.

Recently, high serum C-reactive protein level (CRP), high neutrophil-to-lymphocyte ratio (NLR), and weak histologic lymphocyte infiltration around the tumor have been reported to be associated with poor prognosis in patients with CLM.[7,11–13] A recent study by Malik et al. showed that only

the host inflammatory response, defined as NLR > 5 or CRP > 10 mg/l, and tumor number independently predicted disease-free and overall survival after resection of CLM.[7] The inflammatory response suggested by CRP or NLR is useful because it can be easily measured by preoperative blood sampling. Although preoperative NLR has been shown to be associated with outcomes after the resection of primary tumor or liver metastases, its usefulness has not been well demonstrated in patients with CLM treated with chemotherapy. Malik et al. found that preoperative chemotherapy for CLM did not normalize high NLR; however, the number of patients in that study who received preoperative chemotherapy was small, and the authors did not show detailed results regarding the degree to which high NLR was normalized by chemotherapy.[7,13] Therefore, it remains to be confirmed whether prechemotherapy NLR is a useful prognostic factor in patients with CLM.

The goal of this study was to evaluate whether NLR before chemotherapy or hepatic resection predicts the survival of patients with isolated CLM treated with systemic chemotherapy followed by resection or systemic chemotherapy alone. In addition, we evaluated whether chemotherapy normalizes high NLR and the effect of NLR normalization on survival.

METHODS

This study was approved by our institutional review board (IRB DR08–0143), which waived the requirement for informed consent. We selected two groups of patients with liver-only metastases from colorectal cancer—those who underwent preoperative chemotherapy followed by hepatic resection and those who underwent chemotherapy only.

For the resection group, we identified 340 patients at our institution who underwent curative resection of CLM after preoperative chemotherapy between September 1997 and June 2007 from our prospectively collected database on hepatic resection. Chemotherapy regimens consisted of a fluoropyrimidine plus irinotecan or oxaliplatin, and no patient received other chemotherapy within 6 months before the preoperative chemotherapy. Because we wished to focus on the effect of NLR in patients with liver-only metastases, 35 patients were excluded because hepatic resection preceded resection of primary tumors ($n = 23$) or because patients had synchronous resection of primary tumors at the time of hepatectomy ($n = 12$). Three patients who were lost to follow-up were also excluded. Of the remaining 302 patients, the 200 patients who had NLR measurements available both before preoperative chemotherapy and between preoperative chemotherapy and hepatic resection were included.

For the nonresection group, we identified 93 patients who were treated with chemotherapy after resection of primary tumors but who did not undergo hepatic resection for unresectable liver-only CLM between September 1997 and June 2007. As in the resection group, chemotherapy regimens consisted of a fluoropyrimidine plus irinotecan or oxaliplatin. Of these 93 patients, three patients who were lost to follow-up were excluded. The remaining 90 patients who were treated with chemotherapy for liver-only CLM were included in the study.

In all 290 patients, the following factors were reviewed: status of lymph node metastasis of primary lesion, DFI, CEA level, tumor (CLM) number and size (diameter of the largest nodule), and NLR. DFI was defined as the period from the date of resection of the primary tumor to the date of diagnosis of CLM. NLR was calculated as neutrophil count divided by lymphocyte count, and no patient had clinical signs of sepsis at the time of blood sampling for NLR. NLR > 5 was defined as high, in accordance with the practice in previous studies.[7,13,14]

For patients in the resection group, tumor number and size, CEA level, and NLR were evaluated both before chemotherapy and before surgery. Tumor number and size were determined before chemotherapy and before surgery on the basis of radiologic findings and after surgery on the basis of pathologic findings. Type of hepatic resection and surgical margin status were also reviewed. Hemihepatectomy and extended hemihepatectomy were considered to be major hepatectomy; all other procedures were considered to be minor hepatectomy. Positive surgical margin was defined as the presence of exposed tumor along the line of transection, presence of tumor cells at the line of transection detected by histologic examination, or microscopic margins of <1 mm.[15]

Univariate and multivariate analyses were performed to identify prognostic predictors available before chemotherapy or hepatic resection. In addition, the number of patients in the resection group who experienced normalization of NLR as a result of chemotherapy and how such normalization affected outcome were analyzed.

Continuous data were expressed as median and range and compared by the Mann-Whitney *U*-test. The primary endpoint was overall survival. For analyses of the entire patient cohort and the nonresection group, survival was calculated from the date of initiation of chemotherapy. For analysis of patients in the resection group, survival was calculated from the date of surgery. Survival curves were made by the Kaplan-Meier method and compared by the log-rank test. Univariate and multivariate analyses to identify prognostic predictors were performed by Cox proportional hazard regression models. Variables with $P < 0.10$ on univariate analysis were entered into multivariate analyses. $P < 0.05$ was considered statistically significant in all analyses.

RESULTS

Profiles

In the hepatic resection group ($n = 200$), the median patient age was 57 years (range, 23–86 years), and 132 patients (66%) were male. Preoperative chemotherapy regimens consisted of a fluoropyrimidine and one of the following: irinotecan ($n = 75$), irinotecan with bevacizumab ($n = 20$), oxaliplatin ($n = 35$), oxaliplatin with bevacizumab ($n = 59$), and irinotecan and oxaliplatin ($n = 11$). The median number of chemotherapy cycles was four (range, 2–23), and the median interval between the last dose of chemotherapy and hepatic resection was 42 days (range, 14–174 days).

In the nonresection group ($n = 90$), the median patient age was 56 years (range, 26–81 years), and 61 patients (68%) were male. Chemotherapy regimens consisted of a fluoropyrimidine and one of the following: irinotecan ($n = 40$), irinotecan with bevacizumab ($n = 8$); oxaliplatin ($n = 10$), oxaliplatin with bevacizumab ($n = 17$), and irinotecan and oxaliplatin ($n = 15$). The median number of first-line chemotherapy cycles was six (range, 1–26).

Changes in Clinicopathologic Features After Chemotherapy in the Resection Group

In the resection group, CEA level, tumor number, and tumor size were statistically significantly decreased after chemotherapy. Specifically, median (range) values before chemotherapy and before surgery were as follows: CEA level: 8.5 (1.0–4513.4) ng/ml, 2.8 (1.0–670.7) ng/ml, $P < 0.001$; tumor number: 2.5 (1–32), 2.0 (0–15), $P < 0.001$; and tumor size: 3.4 (.5–19.0) cm, 2.4 (.0–16.5) cm, $P < 0.001$.

In addition, tumor number was larger at pathologic examination than by preoperative radiologic assessment (median [range], mean: 2.0 [1–24], 3.5 vs. 2.0 [0–15], 2.8; $P < 0.001$). Likewise, tumor size was larger on pathologic examination than on preoperative radiologic assessment (median [range], mean; 2.5 [.5–17.0], 3.5 cm vs. 2.4 [.0–16.5], 3.0 cm; $P < 0.001$).

Prognostic Factors for All Patients

For the entire study group of 290 patients, the median follow-up time from the date of initiation of chemotherapy was 29 months (range, 3–105 months). Cumulative 1-, 3-, and 5-year survival rates were 91%, 63%, and 34%, respectively.

Thirty-nine patients (13%) had NLR > 5 before chemotherapy. Cumulative 1-, 3-, and 5-year survival rates were 77%, 47%, and 26%, respectively, in the patients with NLR > 5 before chemotherapy and 92%, 65%, and 36%, respectively, in the patients with NLR ≤ 5 before chemotherapy ($P = 0.017$) (Fig. 1).

The results of univariate and multivariate analysis for the predictors of survival in all 290 patients are listed in Table 1. On univariate analysis, predictors of worse survival were male sex, DFI <1 year, CEA level >200 ng/ml, multiple tumors, tumor size >5 cm, no resection, and NLR > 5. Of these factors, male sex, no resection, and NLR > 5 remained independent predictors of worse survival on multivariate analysis.

Prognostic Factors for the Resection Group

For the 200 patients who underwent hepatic resection, the median follow-up period after hepatic resection was 28 months (range, 2–102 months). Cumulative 1-, 3-, and 5-year survival rates were 96%, 68%, and 41%, respectively.

Twenty patients (10%) had NLR > 5 before surgery. Cumulative 1-, 3-, and 5-year survival rates were 100%, 38%, and 19%, respectively, in the patients with NLR > 5 before surgery and 96%, 70%, and 43%, respectively, in the patients with NLR ≤ 5 before surgery ($P = 0.009$) (Fig. 2). NLR before chemotherapy did not predict survival (5-year survival rate, NLR > 5 vs. ≤ 5, 42% vs. 41%, $P = 0.324$).

The results of univariate and multivariate analysis for the predictors of survival are provided in Table 2. On univariate analysis, predictors of worse survival were concomitant radiofrequency ablation (RFA), multiple tumors in the pathologic specimen, and preoperative NLR > 5. Male sex and positive surgical margins were marginally statistically significant predictors of worse survival. On multivariate analysis that used variables

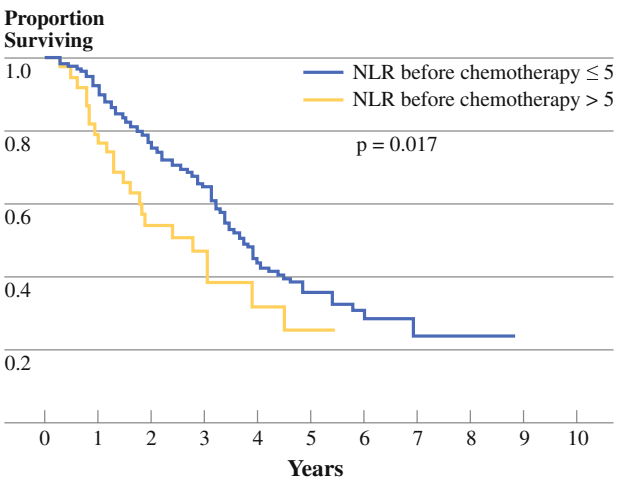

FIG. 1 Survival of all patients according to NLR before chemotherapy

TABLE 1 Univariate and multivariate analysis of prognostic predictors in 290 patients

Variable	N	1-y survival (%)	3-y survival (%)	5-y survival (%)	Median survival (mo)	Univariate analysis			Multivariate analysis		
						P value	HR	95% CI	*P* value	HR	95% CI
Sex											
Male	193	90	60	28	41	0.015	1.6	1.1–2.3	0.029	1.6	1.1–2.3
Female	97	93	68	50	56						
Age (year)											
>60	103	90	66	34	48	0.581	0.9	0.6–1.3			
≤60	187	91	61	34	42						
Lymph node metastasis of primary tumor											
Positive	215	90	58	37	42	0.461	1.2	0.8–1.8			
Negative	37	93	76	26	48						
DFI (y)											
<1	230	88	57	30	39	<0.001	2.6	1.5–4.5	.139	1.6	0.9–3.0
≥1	60	100	86	54	65						
CEA (ng/ml)[a]											
>200	43	86	38%	22	26	0.003	1.9	1.2–2.8	0.969	1.0	0.6–1.6
≤200	240	91	67	37	47						
Tumor number[a]											
Multiple	272	90	58	29	40	<0.001	2.9	1.6–5.1	.057	1.8	1.0–3.2
Solitary	87	95	81	63	NA						
Tumor size (cm)[a]											
>5	81	88	58	27	38	0.010	1.4	0.9–2.0	0.111	1.4	0.9–2.0
≤5	199	92	64	39	47						
Treatment											
No Hx	90	74	20	12	18	<0.001	5.3	3.8–7.5	<0.001	4.7	3.2–7.1
Hx	200	98	81	44	54						
NLR[a]											
>5	39	77	47	26	34	0.019	1.7	1.1–2.7	0.005	2.0	1.3–3.3
≤5	251	92	65	36	45						

HR hazard ratio, *95% CI* 95% confidence interval, *NA* not available, *DFI* disease-free interval, *CEA* carcinoembryonic antigen, *Hx* hepatic resection, *NLR* neutrophil-to-lymphocyte ratio

[a] Measured before chemotherapy

available before surgery (sex, NLR), only NLR > 5 was an independent predictor of worse survival (Table 2). On multivariate analysis that used variables available after surgery (sex, RFA, multiple tumors, surgical margin status, NLR), concomitant RFA, positive surgical margin, and NLR > 5 were independent predictors of worse survival (Table 2).

Prognostic Factors for the Nonresection Group

For the 90 patients who did not undergo hepatic resection, the median follow-up period after the initiation of chemotherapy was 16 months (range, 3–99 months). Two patients (2%) had no radiologic evidence of disease after follow-up of 99 and 55 months, respectively. Cumulative 1-, 3-, and 5-year survival rates were 74%, 20%, and 12%, respectively.

Fourteen patients (16%) had NLR > 5 before chemotherapy. Cumulative 1-, 3-, and 5-year survival rates were 40%, 8%, and 0%, respectively, in the patients with NLR > 5 before chemotherapy and 78%, 40%, and 23%, respectively, in the patients with NLR ≤ 5 before chemotherapy ($P = 0.0002$) (Fig. 3).

The results of univariate and multivariate analysis for the predictors of survival are listed in Table 3. Univariate analysis revealed that NLR > 5 was a predictor of worse survival. Male sex was a marginally statistically significant predictor of worse survival. NLR > 5 remained an independent predictor of worse survival on multivariate analysis.

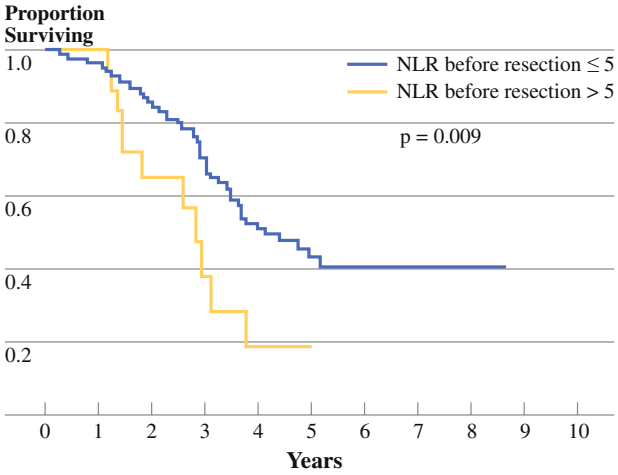

FIG. 2 Survival of patients who underwent hepatic resection according to NLR after chemotherapy but before resection

Influence of Preoperative Chemotherapy on NLR in Patients in the Resection Group

In the resection group, 25 patients (12.5%) had NLR > 5 before chemotherapy, and 17 of these patients (68%) had NLR ≤ 5 before surgery. In contrast, 175 patients had NLR ≤ 5 before chemotherapy, and 12 of these patients (6.9%) had NLR > 5 before surgery. Cumulative 1-, 3-, and 5-year survival rates of the 17 patients with improved NLR were 94%, 63%, and 50%, respectively, similar to the corresponding rates in the 163 patients with NLR ≤ 5 both before chemotherapy and before surgery (96%, 73%, and 43%, respectively, $P = .991$) and better than those in the 8 patients with NLR > 5 both before chemotherapy and before surgery ($P = .021$) (Fig. 4).

DISCUSSION

The present study showed that high NLR (NLR > 5) independently predicted worse survival in patients with CLM treated with chemotherapy followed by hepatic resection or chemotherapy only. Although the patients included in the resection and nonresection groups were different, especially with respect to tumor burden, we evaluated the prognostic predictors in the whole group as well as in each subgroup because resectability of CLM cannot always be predicted before preoperative chemotherapy. In multivariate analysis of all patients, NLR > 5 was shown to be an independent predictor of worse survival, along with male sex and absence of hepatic resection, and neither tumor size nor tumor number predicted survival. This result suggests either that high NLR indicates aggressive tumor biology associated with poor outcomes that cannot be estimated on the basis of previously proposed risk factors, including tumor size and tumor number, or that high NLR may indicate impaired host immune response to the tumor. A pathologic study by Canna et al. showed that increased infiltration of $CD4^+$ T lymphocytes within colorectal cancer was associated with lower CRP and better prognosis.[16]

Furthermore, multivariate analysis in the resection and nonresection subgroups showed that high NLR was the only factor among the factors that are available before treatment that predicted survival. It was notable that none of the five factors included in the clinical risk score (lymph node metastasis, DFI < 1 year, CEA > 200 ng/ml, tumor size > 5 cm, multiple tumors) predicted survival.[2] Although the reliability of a clinical risk score proposed on the basis of a single-institution study may be affected by patient selection bias, failure of clinical risk scores to predict prognosis was also reported in several recent studies at other high-volume centers.[6,7] Therefore, it seems reasonable to conclude that scores based only on the classic clinicopathologic factors have limited ability to predict survival in patients with CLM. Another problem with clinical risk scores is that in most studies, there is no clear discrimination between tumor number and tumor size estimated preoperatively on the basis of radiologic findings and tumor number and tumor size defined postoperatively on the basis of pathologic evaluation. In other words, tumor number and tumor size may be underestimated on preoperative evaluation. Recent studies showed that the sensitivity of contrast-enhanced computed tomography in the detection of CLM was only 60% to 73%.[17–19] The present study also revealed that in the resection group, tumor number was lower and tumor size was smaller on preoperative assessment than on pathologic examination. Our results showed that NLR is a better prognostic predictor than tumor number and tumor size, regardless of whether they are assessed radiologically or pathologically.

In the analysis for the resection group that used the variables available postoperatively, concomitant RFA and positive surgical margins were the only independent predictors besides high NLR. We previously reported that the combination of RFA with resection was associated with a higher risk of intrahepatic tumor recurrence and worse survival.[20] Positive surgical margin is also an indicator of incomplete resection. Therefore, the current analysis of patients who underwent hepatic resection suggests the importance of complete resection of CLM, although incomplete resection may occur, especially in patients with multiple or bilobar metastases.[15,21] To achieve complete resection, two-stage hepatectomy in combination with portal vein embolization is a better option than concomitant RFA.[22–24]

In contrast to Malik et al., who found that neoadjuvant chemotherapy did not normalize a high NLR, we found

TABLE 2 Univariate and multivariate analysis of prognostic predictors in the 200 patients who underwent hepatic resection

Variable	N	3 yr survival (%)	5 yr survival (%)	Median survival (m)	Univariate analysis			Multivariate analysis (preoperative factors)			Multivariate analysis (postoperative factors)		
					P value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI
Sex					0.055	1.7	1.0–3.0	0.07	1.7	1.0–2.9	0.131	1.5	0.9–2.7
Male	132	64	35	42									
Female	68	76	53	NA									
Age (y)					0.739	1.1	0.7–1.8						
>60	80	66	34	45									
≤60	120	68	43	45									
DFI (y)					0.202	1.5	0.8–2.6						
≤1	140	64	39	44									
>1	60	78	45	59									
Lymph node metastasis of primary tumor					0.702	0.9	0.5–1.6						
Positive	140	69	46	57									
Negative	53	71	30	44									
Hepatectomy					0.191	1.5	0.83– 2.54						
Major	138	66	37	44									
Minor	62	73	50	53									
Concomitant RFA					0.003	2.0	1.3–3.3				0.021	1.9	1.1–3.2
Yes	64	59	26	37									
No	136	72	51	62									
CEA (ng/mL)[a]					0.144	2.4	0.7–7.6						
>200	4	75	0	37									
≤200	196	68	42	48									
Tumor number													
Preoperative[a]					0.117	1.6	0.9–2.9						
Multiple	140	64	36	44									
Solitary	60	78	57	NA									
Pathology					0.040	2.0	1.0–3.8				0.427	1.3	0.7–2.7
Multiple	147	63	34	44									
Solitary	53	83	61	NA									
Tumor size (cm)													
Preoperative[a]					0.497	1.3	.7–2.4						
>5	27	66	37	44									
≤5	167	70	42	49									
Pathology					0.807	1.1	.6–1.9						
>5	35	71	44	45									
≤5	165	67	45	48									
Surgical margin					0.068	1.9	1.0–3.9				0.031	2.3	1.1–4.7
Positive	20	37	15	33									
Negative	180	71	43	48									
NLR[a]					0.011	2.3	1.2–4.4	.016	2.2	1.2–4.3	0.048	2.0	1.0–3.8
>5	20	40	19	34									
≤5	180	71	43	49									

HR hazard ratio, *95% CI* 95% confidence interval, *NA* not available, *DFI* disease-free interval, *CEA* carcinoembryonic antigen, *Hx* hepatic resection, *NLR* neutrophil-to-lymphocyte ratio

[a] Measured before hepatic resection

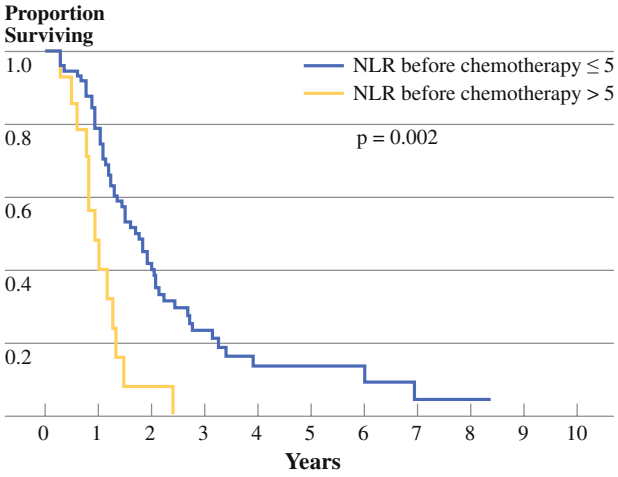

FIG. 3 Survival of patients who did not undergo hepatic resection according to NLR before chemotherapy

that high NLR reverted to normal after preoperative chemotherapy in 17 patients (68%).[7,13] The survival of these 17 patients was similar to that of patients with NLR ≤ 5 both before chemotherapy and before surgery. The survival of the 17 patients with normalized NLR also was better than that of the patients whose NLR remained high.

Perhaps because of the high rate of conversion from high NLR to low NLR in our data set, high NLR before chemotherapy was not associated with worse survival in the resection group. We did not assess the rate of conversion from NLR > 5 to NLR ≤ 5 after chemotherapy in the nonresection group because most patients in that group were shifted to second-line chemotherapy after evidence of disease progression without a chemotherapy-free interval required to accurately ascertain the NLR. Further prospective studies are needed to evaluate the relative contributions of NLR normalization to the improved survival in patients who undergo hepatic resection.

Although we demonstrated the usefulness of NLR as a prognostic factor, it would not be appropriate to conclude that hepatic resection should be withheld only because preoperative NLR is high. In addition, there is a possibility that inflammatory response was underestimated in the present study. First, the proportion of patients with high NLR before hepatic resection in the resection group was 10% (20 of 200), lower than the 18% (78 of 440) reported

TABLE 3 Univariate and multivariate analysis of prognostic factors in the 90 patients who underwent chemotherapy without hepatic resection

Variable	N	1 yr survival (%)	3 yr survival (%)	5 yr survival (%)	Median survival (m)	Univariate analysis			Multivariate analysis		
						P value	HR	95% CI	*P* value	HR	95% CI
Sex											
Male	61	72	15	8	16	0.080	1.6	0.9–2.7	0.152	1.5	0.9–2.5
Female	29	75	29	22	22						
Age (y)											
>60	23	70	15	15	20	0.721	1.1	0.7–1.9			
≤60	67	74	22	11	18						
Lymph node metastasis of primary tumor											
Positive	75	73	18	11	18	0.860	1.7	0.6–2.0			
Negative	14	71	26	17	18						
CEA (ng/mL)[a]											
>200	27	77	16	11	16	0.902	1.0	0.6–1.7			
≤200	63	69	21	12	18						
Tumor number[a]											
Multiple	85	74	18	10	18	0.216	2.5	0.6–1.5			
Solitary	5	53	53	53	NA						
Tumor size (cm)[a]											
>5	30	66	13	13	15	0.165	1.4	0.9–2.4			
≤5	59	76	24	12	19						
NLR[a]											
>5	14	40	0	0	11	<0.001	3.1	1.7–5.9	0.001	2.9	1.5–5.5
≤5	76	78	23	14	21						

HR hazard ratio, *95% CI* 95% confidence interval, *NA* not available, *CEA* carcinoembryonic antigen, *NLR* neutrophil-to-lymphocyte ratio

[a] Measured before chemotherapy

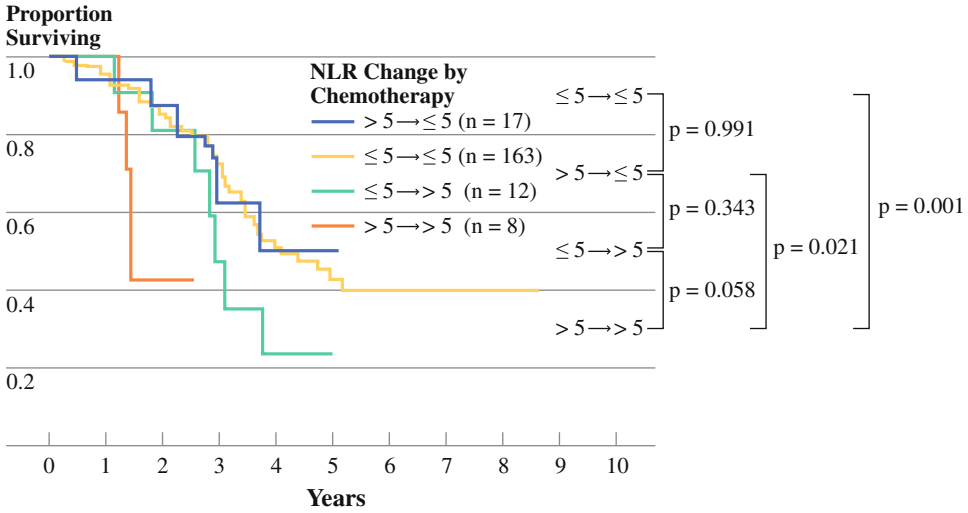

FIG. 4 Survival of patients who underwent hepatic resection according to NLR before and after preoperative chemotherapy

in the study of Halazun et al. ($P = 0.0156$).[13] In addition, the cutoffs of high NLR or CRP defined as >5 or >10 mg/l were empirical and were not validated by quantitative analyses. In the study of Malik et al., high CRP (>10 mg/l) was used in addition to NLR as an index of the presence of inflammatory response to tumor, and 24.5% of patients (137 of 423) met these criteria.[7] Patients in the resection group in our series underwent hepatic resection a median of 6 weeks after the last chemotherapy, and in 92% of cases (183 of 200), the interval was 4 weeks or more. Hence, the influence of immunosuppression by chemotherapy was minimized, but it cannot be completely ruled out. Leitch et al. reported that Glasgow prognostic score, which is based on high CRP (>10 mg/l, score 1) and hypoalbuminemia (<35 g/l, score 1), was better than NLR as a predictor of prognosis in patients with colorectal cancer.[25,26] Because CRP is not routinely measured in our institution, we could not analyze CRP or Glasgow prognostic score in the present study. Second, although high NLR is considered to reflect weak lymphocyte-mediated immune response to tumor as a result of relative lymphocytopenia, previous studies evaluating histologic infiltration of inflammatory cells around or within colorectal cancer showed that not only lymphocyte infiltration but also infiltration of macrophages, eosinophils, mast cells, and natural killer cells is associated with better prognosis.[13,16,27–29] Furthermore, there is a possibility that exclusion of one-third (102 of 300) of patients as a result of the absence of NLR data may potentially bias the results of the present study.

In conclusion, high NLR (NLR > 5) is a useful predictor of worse survival in patients with CLM treated with either chemotherapy alone or with chemotherapy followed by hepatic resection. When chemotherapy normalizes high NLR and hepatic resection is performed, survival can be expected to be similar to that of patients who have normal NLR both before chemotherapy and before surgery. Further prospective studies evaluating the inflammatory response indices, including NLR, CRP, and cytokines, in a larger numbers of patients are needed to comprehensively identify the patients with inflammatory response at high risk for poor outcomes.

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