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Prognostic Value of Lymph Node Ratio in Patients Receiving Combined Surgical Resection for Gastric Cancer Liver Metastasis: Results from Two National Centers in China

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Abstract: The purpose of this study was to evaluate the prognostic value of lymph node ratio (LNR) in patients with gastric cancer liver metastasis (GCLM) who received combined surgical resection.

A retrospective analysis of 46 patients from two hospitals was conducted. Patients were dichotomized into two groups (high LNR and low LNR) by the median value of LNR. The overall survival (OS) and recurrence-free survival (RFS) were analyzed by the Kaplan–Meier method with the log-rank test. The Cox proportional hazard model was used to carry out the subsequent multivariate analyses. And the relationship between LNR and clinicopathological characteristics was assessed.

The cut-off value defining elevated LNR was 0.347. With a median follow-up of 67.5 months, the median OS and RFS of the patients were 17 and 9.5 months, respectively. Six patients survived for >5 years after surgery. Patients with higher LNR had significantly shorter OS and RFS than those with lower LNR. In the multivariate analyses, higher LNR and multiple liver metastatic tumors were identified as the independent prognostic factors for both OS and RFS. Elevated LNR was significantly associated with advanced pN stage ($P<0.001$), larger primary tumor size ($P=0.046$), the presence of microvascular invasion ($P=0.008$), and neoadjuvant chemotherapy ($P=0.004$).

LNR may be prognostic indicator for patients with GCLM treated by synchronous surgical resection. Patients with lower LNR and single liver metastasis may gain more survival benefits from the surgical resection. Further prospective studies with reasonable study design are warranted.

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Abbreviations: CI = confidence interval, CRCLM = colorectal cancer liver metastasis, CT = computed tomography, DCF = docetaxel/cisplatin/5-fluorouracil regimen, ECF = epirubicin/cisplatin/5-fluorouracil regimen, GCLM = gastric cancer liver metastasis, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, JGCA = Japanese Gastric Cancer Association, LNR = lymph node ratio, MRI = magnetic resonance imaging, OS = overall survival, pN = pathological nodal, RFS = recurrence-free survival, SD = standard deviation.

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INTRODUCTION

Gastric cancer is the fourth most common malignant cancer and the second most killing cancer worldwide,[1,2] which is much more serious here in China.[2,3] In the past decades, the rapid development of surgical technology, chemotherapy, radiotherapy, and molecular target therapy has greatly improved the clinical prognosis of gastric cancer,[4] especially for those at early or intermediate stage. Patients with gastric cancer liver metastasis (GCLM) tend to have inferior survival outcome and are classified as stage IV according to the 7th UICC/AJCC TNM grading system and Japanese gastric cancer treatment guidelines 2010 (ver. 3).[5,6] The efficacy of operative resection for colorectal cancer liver metastasis (CRCLM) has been well established with a 5-year survival rate of 30% to 50%.[7] The role of surgical resection in GCLM and the relevant prognostic factors remain to be illusive.[8]

Lymph node (LN) status has long been regarded as an indispensable proportion of the prognosis discrimination system for patients with gastric cancer.[9] And the significance of LNs dissection is critically valued in the surgical operation protocol. Nevertheless, in GCLM patients who underwent combined resection, the impaction of LN status on the prognosis has not been well defined. Wang et al[10] just proved that pathological nodal (pN) stage was an independent prognostic factor for patients who underwent combined resection for GCLM. Lymph node ratio (LNR), calculated as the number of metastatic LNs divided by the total number of retrieved LNs, has been introduced to appraising the LN status. Prognostic value LNR has been extensively evaluated in multiple malignancies including breast cancer, pancreatic cancer, and colorectal cancer.[11–13] In 1997, Kodera et al[14] proposed LNR as a novel and significant prognostic factor for resectable stage IV gastric cancers. And the prognostic value of LNR in patients with gastric cancers has been studied in a number of studies.[15–18] However, to the best of our knowledge, no studies exploring the prognostic value of LNR exclusively in GCLM patients have been published yet.

Therefore, we retrospectively reviewed the data of gastric patients with liver metastasis who underwent simultaneous resection of the primary tumor lesion and hepatic metastases from two national medical centers in China in order to gauge the prognostic value of LNR in patients with GCLM. In this process, we also assessed the relationship between LNR and other clinicopathological factors.

MATERIALS AND METHODS

Patients and Treatment

From January 1998 to December 2013, a total of 50 patients underwent combined surgical resection of both the liver metastases and primary gastric cancer in Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Hospital. We retrospectively collected their demographic and clinicopathologcial data from the medical records. Eligibility criteria included: (1) the primary gastric cancer and the liver metastatic lesions should be removed in the same operation; (2) histologically confirmed R0 resection; (3) diagnosis of gastric adenocarcinoma should be confirmed by pathological examination of the resected specimen; (4) liver metastasis from the gastric adenocarcinoma should be pathologically confirmed. Exclusion criteria included: (1) evidence of peritoneal metastases or other extrahepatic metastases before or during the operation; (2) primary gastric cancer with direct infiltration to the liver; (3) patients lost to follow-up. After screening the potential eligible patients, one patient was excluded because of the positive surgical margin (R1 resection); another patient was excluded because the pathological examination of the specimen proved to be gastric neuroendocrine cancer; two patients were excluded as they were lost to follow-up. Thus, a total of 37 patients from Cancer Hospital, Chinese Academy of Medical Sciences and 9 patients from Peking Union Medical College Hospital were finally enrolled into our study (Figure 1). Patients' informed consent was not required owing to the retrospective nature of the study.

Pathologic data were retrieved from the medical records. In the two medical institutions, pathological examinations of the specimen were performed with adherence to the General Rules of the Japanese Gastric Cancer Association (JGCA)[5] and to the current NCCN guideline.

Operation

Preoperative evaluation of the tumor status was conducted by gastroscopy, ultrasonography, computed tomography (CT), and (or) magnetic resonance imaging (MRI). After comprehensive assessment of patients' general health and tumor status, potentially curative surgical resection was attempted in cases in which primary lesion and liver metastases were assessed to be safely resectable. Combined resection of the gastric tumor and liver metastases along with the D2 lymphadenectomies were performed. All of the patients underwent radical subtotal or total gastrectomies, depending on the tumor location and intraoperative verification of tumor-free resection margins, as well as D2 lymphadenectomies.[19] The methods of reconstruction after distal gastrectomy include Billroth I, II, or Roux-en-Y. The surgical procedure of hepatectomy was classified as anatomic resection (segmentectomy and lobectomy) or nonanatomic resection with negative margin width of at least 1 cm.

Follow-Up

The follow-ups of the patients were carried out by face-to-face or telephone interview on 1, 3, 6, 12 month(s) within the first year after the operation and every 6 months thereafter. In the process, information of physical examination, x-ray of chest, abdominal ultrasonography, and gastroscopy were collected. CT and (or) MRI were performed every 6 months, or when there was a suspicion of tumor recurrence or distant metastasis. Overall survival (OS) was measured from the date of surgery to May 2015 or death. Recurrence-free survival (RFS) was calculated from the date of surgery to May 2015 or the time of detection of tumor recurrence.

Statistical Analysis

Continuous data were expressed as mean $\pm$ standard deviation (SD) or median (range). Categorical data were presented as frequencies. Chi-square test or Fisher's exact test (categorical variables) and Student's *t* test (continuous variables) were used to analyze differences between the subgroups. Cumulative OS and RFS were estimated according to the Kaplan–Meier method with the log-rank test. Significant factors identified in the univariate analysis were taken into the Cox proportional hazards model. All P values were two tailed and $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS 11.5 statistical software package (SPSS Inc., Chicago, IL).

RESULTS

Clinicopathological Features of the Studied Patients

The baseline characteristics of eligible patients are summarized in Table 1. There were 37 men and 9 women as patients with a median age of 59 (range = 38–79) years. The primary gastric cancer was located at the proximal portion of stomach in 15 (15/46, 32.6%) patients, at the stomach body in 14 (14/46, 30.4%) patients, and at the distal portion of stomach in 17 (17/46, 37.0%) patients. Twenty-two of the 46 (22/46, 47.8%) patients had solitary liver metastasis whereas 24 of them (24/46, 52.2%) had multiple liver metastases. R0 resection was achieved in all of

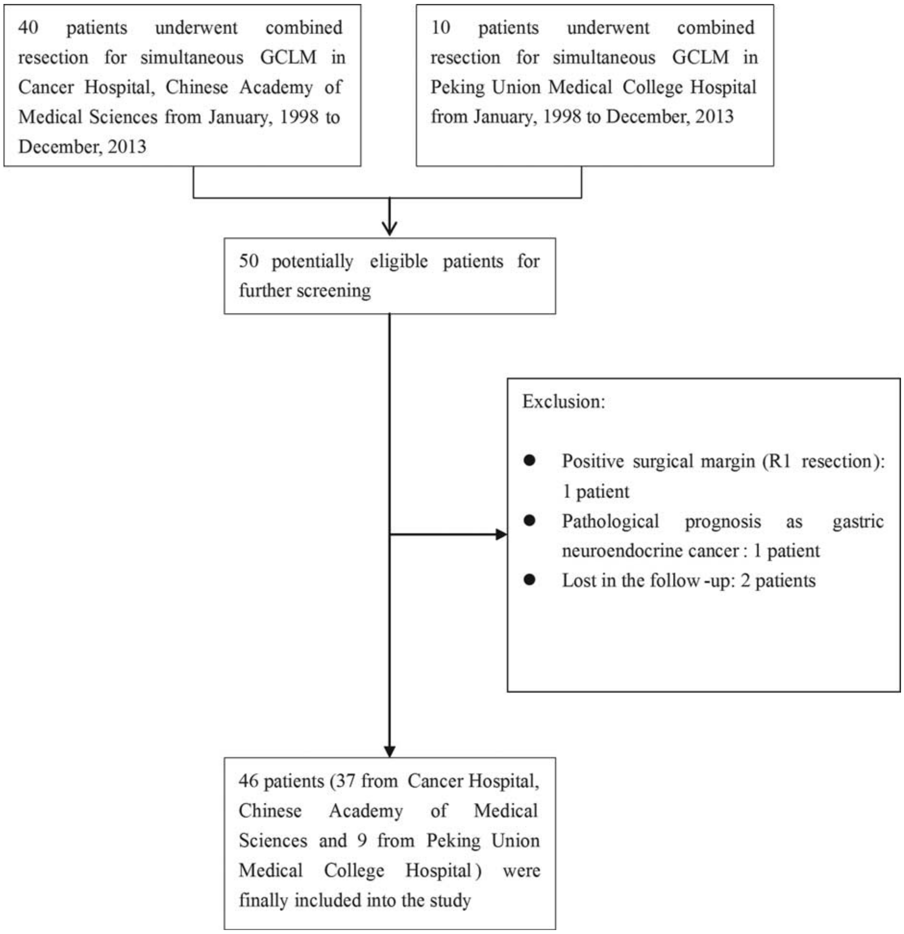

FIGURE 1. The flowchart describing the selection of the patients.

the patients. Because of the retrospective nature of the study, we could only get access to the human epidermal growth factor receptor-2 (HER-2) status in 36 patients. The number of retrieved LNs were $\geq$ 16 in 30 patients (30/46, 65.2%). The number of patients at pN0, pN1, pN2, and pN3 were 6 (13.1%), 8 (17.4%), 10 (21.7%), and 22 (47.8%), respectively. Ten of them (10/46, 21.7%) underwent neoadjuvant chemotherapy before the operation. The postoperative adjuvant chemotherapy was performed in all of the patients. The detailed regiments and number of chemotherapy cycles were specifically designed by the oncologists with adherence to the current clinical guidelines (e.g., docetaxel/cisplatin/5-fluorouracil (DCF) regimen and epirubicin/cisplatin/5-fluorouracil (ECF) regimen). None of the patients died within 30 days after the operation.

Relationship Between LNR and Other Clinicopathological Parameters

We adopted the median value of LNR (0.347) as the cut-off value defining elevated level of LNR. There were 23 patients in the high LNR group and 23 patients in the low LNR group. A comparison between the clinicopathological features in each group is shown in Table 2. Patients in the high LNR group predisposed to be featured with advanced pN stage ($P < 0.001$, Table 2), larger primary tumor size ($P = 0.046$, Table 2), and presence of microvascular invasion ($P = 0.008$, Table 2) when compared with those in the low LNR group. Of note, majority of the patients who underwent preoperative neoadjuvant chemotherapy were classified in the low LNR group ($P = 0.004$, Table 2). No significant associations were detected between LNR and other clinicopathological characteristics including the Lauren's classification and HER-2 status.

Survival Outcome

With a median follow-up duration of 67.5 months (range = 18–202 months), the median OS of the patients was 17 months (range = 2–147 months). Six patients survived for >5 years. The 1-, 3-, and 5-year OS rates were 65.2%, 36.9%, and 10.9%, respectively. The median RFS of the patients was 9.5 months (range = 1–147 months). The 1-, 3-, and 5-year RFS rates were 39.1%, 13.0%, and 10.9%, respectively. Causes of mortality in all of the patients were tumor recurrence. Six (6/46, 10.9%) of the studied patients survived in the last follow-up and two (2/46, 4.3%) of them survived without tumor recurrence. With regard to the 44 patients who experienced the tumor recurrence, liver was the most common site involved by the recurrence (32/44, 72.7%). None of the patients underwent a second resection. Chemotherapy based on the clinical guidelines was performed in all of the 44 patients with regard to the postoperative tumor recurrence.

TABLE 1. Baseline Clinicopathological Features of the Patients Involved in This Study

Variable	Value
Age (years)	59 (38–79)*
Gender (man/woman)	37 (80.4%)/9 (19.6%)†
Primary tumor location	
Proximal	15 (32.6%)†
Body	14 (30.4%)†
Distal	17 (37.0%)†
Primary tumor size (cm) ± SD	5.5 ± 2.8‡
Depth of tumor	
T2	5 (10.9%)†
T3	18 (39.1%)†
T4	23 (50.0%)†
Cell differentiation	
Moderate	17 (37.0%)†
Low	29 (63.0%)†
LNs retrieved	
≥16	30 (65.2%)†
<16	16 (34.8%)†
pN	
N0	6 (13.1%)†
N1	8 (17.4%)†
N2	10 (21.7%)†
N3	22 (47.8%)†
LNR	0.347 (0–1)†
Microvascular invasion	
Present	23 (50.0%)†
Absent	23 (50.0%)†
Lauren's classification	
Intestinal type	33 (71.7%)†
Diffuse type	10 (21.7%)†
Mixed type	3 (6.6%)†
HER-2	
−	21 (45.7%)†
+	6 (13.0%)†
++	4 (8.7%)†
+++	5 (10.9%)†
Not known	10 (21.7%)†
Liver metastatic tumor location	
Left Lobe	25 (54.3%)†
Right Lobe	13 (28.3%)†
Bilateral	8 (17.4%)†
Liver metastatic tumor size (cm)	1.5 (0.3–8)*
No. of liver metastatic tumors	
Solitary	22 (47.8%)†
Multiple	24 (52.2%)†
Intraoperative blood transfusion	
Present	23 (50.0%)†
Absent	23 (50.0%)†
Neoadjuvant chemotherapy	
Present	10 (21.7%)†
Absent	36 (78.3%)†

HER-2 = human epidermal growth factor receptor-2, LN = lymph node, LNR = lymph node ratio, No. = number.
*Median (range).
†Number (percentage).
‡Mean ± standard deviation (SD).

Prognostic Factors

Kaplan–Meier survival analysis revealed that the OS and RFS of patients in the high LNR group were significantly shorter than that of those in the low LNR group (median OS: 11 months vs. 32 months, $P < 0.001$; median RFS: 6 months vs. 19 months, $P < 0.001$, Tables 3 and 4, Figure 2A and B). High LNR ($P < 0.001$, Table 3, Figure 2A), advanced pN category ($P = 0.001$, Table 3), and multiple liver metastases ($P = 0.010$, Table 3, Figure 2C) were conversely correlated with the OS in the univarate analysis. Above-mentioned three factors were enrolled into the subsequent multivariate cox hazard model analysis. High LNR (hazard ratio (HR) = 3.357, 95% confidence interval (CI) = 1.411–7.987, $P = 0.006$, Table 3) and multiple liver metastatic tumors (HR = 3.347, 95% CI = 1.586–7.066, $P = 0.002$, Table 3) were identified as independent prognostic factors for OS. In the univariate analysis towards RFS, high LNR ($P < 0.001$, Table 4, Figure 2B), presence of microvascular invasion ($P = 0.033$, Table 4), advanced pN category ($P = 0.001$, Table 4), and multiple liver metastases ($P = 0.013$, Table 4, Figure 2D) were recognized to be statistically significant. In the multivariate analysis, high LNR (HR = 3.175, 95% CI = 1.255–8.031, $P = 0.015$, Table 4) and multiple liver metastatic tumors (HR = 2.987, 95% CI = 1.513–5.898, $P = 0.002$, Table 4) were proved to be the independent prognostic factors for RFS.

The Number of Identified Risk Factors Further Distinguished Patients With Different Risk of Recurrence

We further evaluated the prognosis of patients according to the number of independent risk factors (i.e., LNR and multiple liver metastases). Varied outcomes in OS and RFS stratified by different number of risk factors are shown in Figure 3. Patients with two risk factors had significantly shorter OS and RFS than those with one risk factor (median OS: 9 months vs. 17 months, $P = 0.001$, Figure 3A; median RFS: 4 months vs. 10 months, $P = 0.001$, Figure 3B), as well as those with no risk factors (median OS: 9 months vs. 35 months, $P < 0.001$, Figure 3A; median RFS: 4 months vs. 29 months, $P < 0.001$, Figure 3B). And patients with one risk factor had significantly worse survival outcomes than those with no risk factors (median OS: 17 months vs. 35 months, $P = 0.006$, Figure 3A; median RFS: 10 months vs. 29 months, $P = 0.006$, Figure 3B).

DISCUSSION

To the best of our knowledge, the present study, involving a total of 46 patients from two national medical centers with a time range of 16 years, was the first multicenter study evaluating the prognostic value of LNR in patients presenting as gastric cancer and synchronous hepatic metastasis. The results exhibited LNR <0.347 and solitary liver metastasis independently predicted superior OS and RFS. The prognostic discrimination efficacy of the number of the identified risk factors further upheld the robustness of our results.

Liver is the most frequent site of distant metastasis from gastric cancer with a reported incidence of 4% to 14%.[20] However, only a small number of studies evaluating the simultaneous resection for GCLM[10,21–25] have ever been reported. Some authors claimed that surgical resection may render survival benefits, relieved symptoms, and enhanced life quality.[8] In our study, the median OS of the patients was 17 months (range = 2–147 months) and the median RFS of the patients was 9.5 months (range = 1–147 months), which was in accordance with some

TABLE 2. Comparison of Clinicopathological Features Between Patients in High LNR Group and Low LNR Group

Variable	Value		*P*
	High LNR (n = 23)	Low LNR (n = 23)	
Age (years)	58.5 ± 9.3*	61.5 ± 11.1*	0.326
Gender (man/woman)	19/4	18/5	1.000
Primary tumor location			0.753
Proximal	8	7	
Body and distal	15	16	
Primary tumor size (cm)	6.3 ± 3.4*	4.6 ± 1.7*	**0.046**
Depth of tumor invasion			0.140
T2 and T3	9	14	
T4	14	9	
Cell differentiation			0.359
Moderate	7	10	
Low	16	13	
LNs retrieved			1.000
≥16	15	15	
<16	8	8	
N stage			**<0.001**
N0, N1, N2	4	20	
N3	19	3	
Microvascular invasion			**0.008**
Present	16	7	
Absent	7	16	
Lauren's classification			1.000
Intestinal type	16	17	
Diffuse type	5	5	
Mixed type	2	1	
HER-2			0.908
−	11	10	
+	3	3	
++	3	1	
+++	3	2	
Liver metastatic tumor location			0.697
Unilateral	18	20	
Bilateral	5	3	
Liver metastatic tumor size (cm)	1.9 ± 1.4*	2.3 ± 2.0*	0.406
No. of liver metastatic tumors			0.555
Solitary	10	12	
Multiple	13	11	
Intraoperative blood transfusion			0.768
Present	11	12	
Absent	12	11	
Neoadjuvant chemotherapy			**0.004**
Present	1	9	
Absent	22	14	

HER-2 = human epidermal growth factor receptor-2, LN = lymph node, LNR = lymph node ratio, No. = number.

Significant results were expressed in bold.

*Mean ± standard deviation(SD).

previous reports. It was noted that patients with LNR <0.347 and solitary liver metastasis gained a median OS of 35 months and a median RFS of 29 months, which suggested that this subgroup might benefit from the combined resection. Future studies are warranted to validate the role of LNR-based criteria selecting the candidates receiving synchronous resection.

The presence of tumor involving locoregional LNs has long been established as an essential prognostic factor in most solid malignances. With regard to the biological significance of LN involvement in the course of cancer progression, some experts considered LNs as the first line of defense against stepwise systematic spreading.[13] GCLM is classified as stage IV by the UICC/AJCC TNM grading system.[9] LN status is not incorporated into the definition of stage IV now. Thus, remarkable heterogeneity of the LN burden status may be observed in patients at stage IV. Hindered by issues such as poor body condition, extensive locoregional tumor invasion, or extrahepatic metastases, only 10% to 20% of patients with GCLM are eligible for combined surgical treatment.[8,26,27] Partially because of the low resectable rate of GCLM, the wholesome information of LN status is hardly collected. Therefore, fairly little relevant clinical evidences regarding the prognostic value of LN burden in GCLM are available. Previous studies examining the prognostic value of LNR in gastric cancer patients chiefly focused on patients at stage II or III,[15] in which the impaction of LN burden on the clinical outcome was relatively definite. It was postulated that resection of regional LNs might reset the ''cancer-friendly'' immunological balance, resulting in an improvement of patients' prognosis.[13] Therefore, we hypothesized that LNR, which provided information about retrieved LNs as well as the metastatic LNs, may be a surrogate of the LN burden and a prognostic factor in GCLM patients.

In our study, the results exhibited that GCLM patients with elevated LNR seemed to have more clinicopathologic factors related to advanced diseases including advanced pN stage, lager primary tumor size, and presence of microvascular invasion. Lower LNR values were also more often observed among patients who underwent preoperative neoadjuvant chemotherapy. It is considered that neoadjuvant chemotherapy may influence the total harvested number of LNs as well as the number of metastatic LNs. As LNR was calculated as the number of metastatic LNs divided by the total number of retrieved LNs, the influence of neoadjuvant chemotherapy on LNR awaited to be addressed. Because of the relatively small sample size of our study, further studies with larger sample size and proper study design are needed to determine the exact influence of neoadjuvant chemotherapy on the LNR after surgery. In the multivariate analysis, LNR weighed over the above-mentioned clinicopathological factors and was proved to be the independent prognostic factor. These further strengthened the prognostic value of LNR in patients with GCLM receiving the combined resection.

Numerous cut-off points of LNR have been proposed in previous studies.[14,16,17] In the present study, we determined the cut-off value (0.347) as the median value of LNR. The heterogeneity in establishing cut-off values to categorize different groups may be influenced by multiple factors including sample size, expertise of the pathologists, and the different average number of harvested LNs in these various studies.[28] More well-designed studies with sufficient sample size are warranted to further establish the accuracy of the cut-off value.

Besides LNR, our study also unveiled that patients with multiple liver metastases had significantly shorter OS and RFS than those with solitary ones. Multiple liver metastases may partially reflect greater systematic tumor burden. The number of liver metastases has been proposed to be significantly related to the survival outcome in previous studies.[5,27] Our findings were consistent with other authors who indicated that patients with

TABLE 3. Univariate and Multivariate Analysis of the Overall Survival

			Univariate Analysis	Multivariate Analysis		
Variable	**No.**	**Median OS (months)**	***P***	**HR**	**95% CI**	***P***
Age (years)			0.859			
≥60	22	15				
<60	24	18				
Gender			0.707			
Man	37	17				
Woman	9	17				
Primary tumor location			0.260			
Proximal	15	17				
Body and distal	31	17				
Primary tumor size (cm)			0.853			
≥5	28	15				
<5	18	17				
Depth of tumor			0.293			
T2, T3	23	20				
T4	23	17				
Cell differentiation			0.187			
Moderate	17	26				
Low	29	15				
LNs retrieved			0.413			
≥16	30	15				
<16	16	18				
pN			**0.001**	2.021	0.876–4.661	0.099
N0–N2	24	31				
N3	22	10				
LNR			**<0.001**	**3.357**	**1.411–7.987**	**0.006**
≥0.347	23	11				
<0.347	23	32				
Microvascular invasion			0.066			
Present	23	15				
Absent	23	30				
Lauren's classification			0.693			
Intestinal type	33	17				
Diffuse type	10	18				
Mixed type	3	17				
HER-2			0.777			
−	21	18				
+	6	17				
++	4	9				
+++	5	9				
Liver metastatic tumor location			0.421			
Unilateral	38	17				
Bilateral	8	15				
Liver metastatic tumor size (cm)			0.589			
≥3	12	13				
<3	34	18				
No. of liver metastatic tumors			**0.010**	**3.347**	**1.586–7.066**	**0.002**
Solitary	22	27				
Multiple	24	11				
Neoadjuvant chemotherapy			0.118			
Present	10	32				
Absent	36	15				
Intraoperative blood transfusion			0.450			
Present	23	17				
Absent	23	17				

Significant results were expressed in bold.
CI = confidence interval, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, LN = lymph node, LNR = lymph node ratio, No. = number, OS = overall survival.

TABLE 4. Univariate and Multivariate Analysis of the Recurrence-Free Survival

			Univariate Analysis	Multivariate Analysis		
Variable	**No.**	**Median RFS (months)**	***P***	**HR**	**95% CI**	***P***
Age (years)			0.738			
≥60	22	9				
<60	24	9				
Gender			0.712			
Man	37	10				
Woman	9	8				
Primary tumor location			0.189			
Proximal	15	10				
Body and distal	31	9				
Primary tumor size (cm)			0.874			
≥5	28	8				
<5	18	10				
Depth of tumor			0.263			
T2, T3	23	11				
T4	23	8				
Cell differentiation			0.220			
Moderate	17	11				
Low	29	9				
LNs retrieved			0.313			
≥16	30	9				
<16	16	10				
pN			**0.001**	2.000	0.887–4.508	0.095
N0–N2	24	13				
N3	22	5				
LNR			**<0.001**	**3.175**	**1.255–8.031**	**0.015**
≥0.347	23	6				
<0.347	23	19				
Microvascular invasion			**0.033**	1.335	0.679–2.626	0.402
Present	23	8				
Absent	23	13				
Lauren's classification			0.844			
Intestinal type	33	10				
Diffuse type	10	6				
Mixed type	3	9				
HER-2			0.699			
−	21	9				
+	6	10				
++	4	8				
+++	5	6				
Liver metastatic tumor location			0.110			
Unilateral	38	10				
Bilateral	8	5				
Liver metastatic tumor size (cm)			0.532			
≥3	12	5				
<3	34	9				
No. of liver metastatic tumors			**0.013**	**2.987**	**1.513–5.898**	**0.002**
Solitary	22	12				
Multiple	24	5				
Neoadjuvant chemotherapy			0.078			
Present	10	13				
Absent	36	8				
Intraoperative blood transfusion			0.244			
Present	23	9				
Absent	23	10				

Significant results were expressed in bold.

CI = confidence interval, HER-2 = human epidermal growth factor receptor-2, HR = hazard ratio, LN = lymph node, LNR = lymph node ratio, No. = number, RFS = recurrence-free survival.

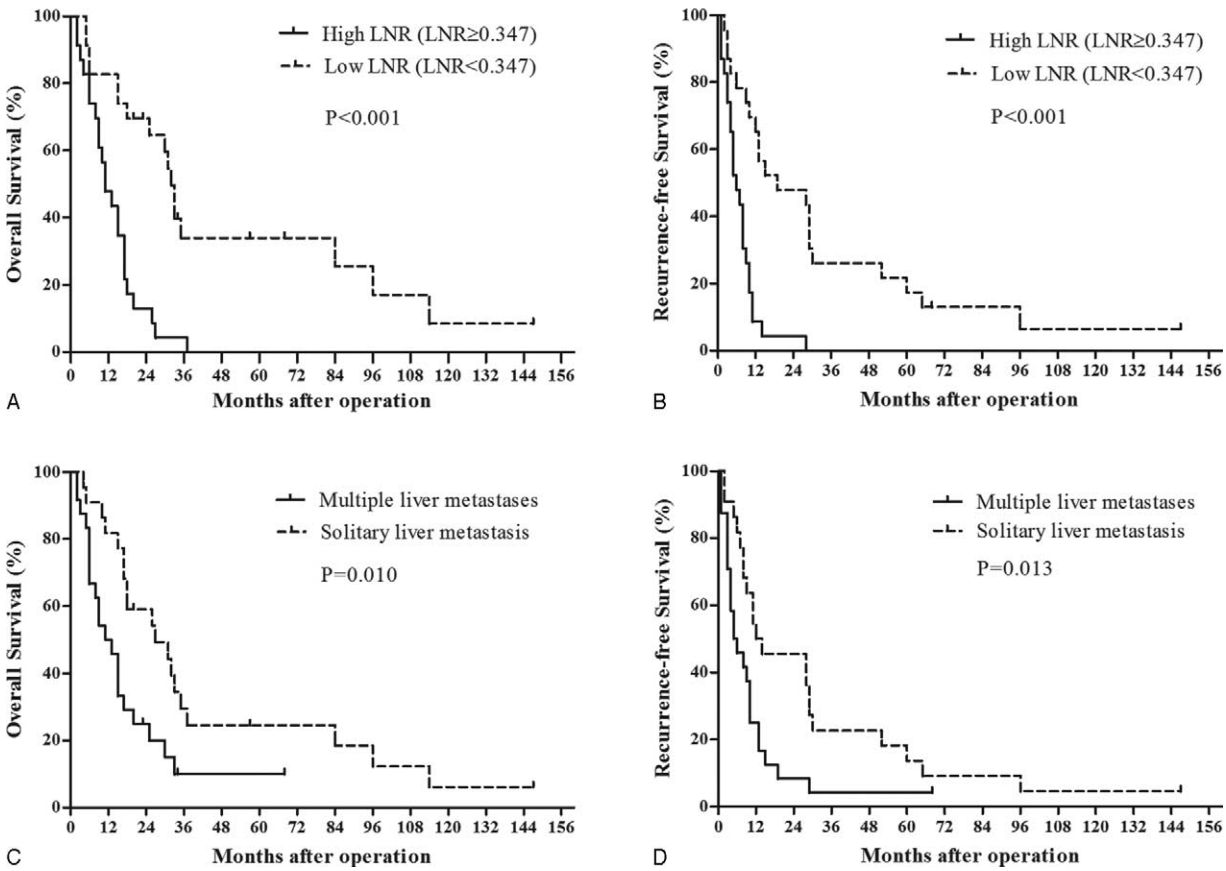

FIGURE 2. Kaplan–Meier survival analysis of OS (A) and RFS (B) according to lymph node ratio (LNR). Kaplan–Meier survival analysis of OS (C) and RFS (D) according to number of liver metastases. LNR = lymph node ratio, OS = overall survival, RFS = recurrence-free survival.

solitary liver metastasis from gastric cancer might have greater priority to receive the combined surgical operation.[24]

Of note, there were some limitations of our study. First of all, performed in a retrospective setting, the study was susceptive to some biases such as recalling bias and selection bias. But our results may have some implications for the design of the study in the future. Secondly, some studies categorized the gastric cancer patients into four groups according to LNR, which could be compared with the predicative value of AJCC pN categories (pN0–pN3) at a more specific level. To our regret, the sample size of the study population was relatively small, which hindered us from performing subsequent analysis. Thirdly, surgeon's evaluation of patient's general status and the extent of the disease may influence the treatment decision making process. The retrospective nature of our work hampered the further evaluation of these parameters. Additionally,

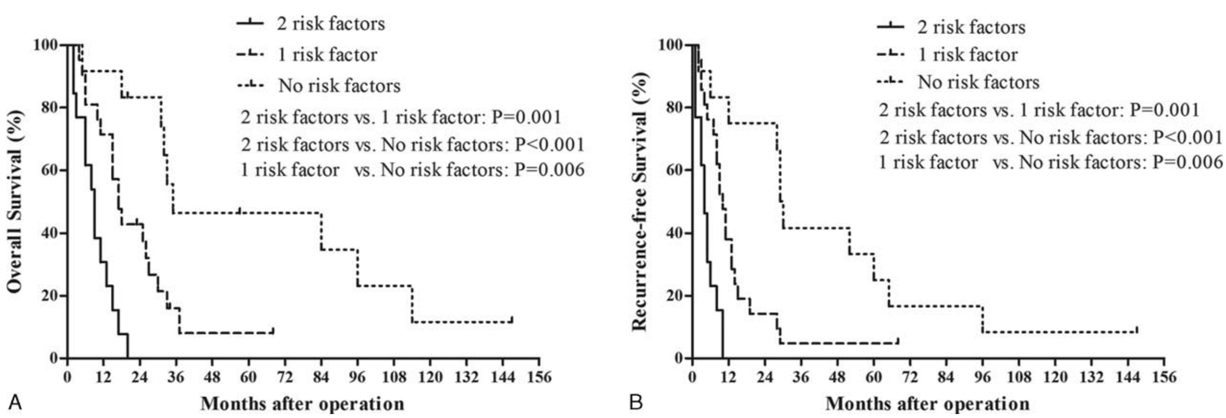

FIGURE 3. OS (A) and RFS (B) stratified by number of independent risk factors. OS = overall survival, RFS = recurrence-free survival.

because of the retrospective nature of our study, some of the patients received the treatments >10 years ago. In that time, the notion of neoadjuvant chemotherapy was not emphasized in China. These may partially explain the relatively low percentage (10/46, 21.7%) of patients who underwent neoadjuvant chemotherapy especially for those patients with multiple liver metastases in our study. Though being adherent to the evidence-based clinical guidelines, the regiments, duration, and cycles of chemotherapies may be adjusted with the individual condition. Thus, impaction of neoadjuvant and adjuvant therapies on the clinical outcome could not be fully explored.

In conclusion, LNR, which was significantly associated with pN category, microvascular invasion, primary tumor size, and neoadjuvant chemotherapy, was a potent and independent prognostic factor for gastric cancer patients with synchronous liver metastasis who underwent combined surgical resection. Patients with lower LNR and solitary liver metastasis may gain more survival benefits from synchronous resection of the gastric cancer and liver metastasis. The follow-up strategy should also be adjusted accordingly. And further well-designed studies with adequate sample size are warranted to validate the prognostic value of LNR.

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