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Prognostic impact of increased lymph node yield in colorectal cancer patients with synchronous liver metastasis: a population-based retrospective study of the US database and a Chinese registry

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Highlights

- This is the first study addressing the implications of the 12 LNY quality indicator on survival for CRC patients with distant metastasis based on two large population-based cohorts.
- An adequate lymphadenectomy with 12-node threshold as a guideline quality is still a critical component of high-quality surgical standard in CRC patients with distant metastases.

Abstract

Background: The National Quality Forum has endorsed at least 12 lymph node yield (LNY) as a surgical quality indicator in colorectal cancer (CRC), but the prognostic value of adequate lymphadenectomy has rarely been investigated for CRC patients with distant metastatic disease.

Methods: 4575 CRC patients with synchronous liver metastasis who underwent primary tumor resection were identified from a Chinese registry and the Surveillance, Epidemiology, and End Results (SEER) database between 2010 to 2017. Kaplan-Meier methods and Cox regression models were performed to assess the correlations between LNY and 3-year cancer specific survival (CSS). Propensity score matching (PSM) were used to confirmed the survival comparison between patients with <12 and ≥12 LNY.

Results: The retrieval of at least 12 LNY was identified in most CRC patients (SEER database, 3380/3899, 86.7%; Chinese cohort, 565/676, 83.6%). In both SEER database and Chinese cohort, the patients with LNY ≥ 12 was significantly associated with better CSS compared to patients with LNY < 12 before and after PSM, with all $P < 0.05$. After controlling for the confounders, multivariate analysis demonstrated that LNY was also an independent prognostic factor for patients with distant metastasis in both cohorts. In subgroup analysis, the CSS benefit for patients with LNY ≥ 12 was observed across most of subgroups.

Conclusions: Clinical feasibility of the 12–node threshold as a guideline quality metric of cancer care for CRC patients is necessary, and an oncologically adequate lymphadenectomy is still a critical component of high-quality surgical standard in CRC patients with distant metastases.

Keywords: Colorectal cancer; Surgical quality; Lymphadenectomy; Prognosis

1. Introduction

Colorectal cancer (CRC) is an important cause of cancer related morbidity and mortality in our population[1]. Approximately 20% of CRC patients have synchronous distant metastases at the time of diagnosis, presenting with very low survival[2]. Despite advances in multimodal care have led to improved survival outcomes of CRC patients with distant metastases, surgical treatment is still one crucial procedure for them to prolong life or at least improve quality of life.

Adequate lymphadenectomy, a proxy of quality surgery, remains a fundamental surgical principle in the resection for CRC and a principal determinant of cancer outcomes[3, 4, 5]. Moreover, lymph node yield (LNY) is an objective quantifiable marker that reflect the adequacy of surgical care in routine clinical practice[6, 7, 8]. In 2007, after considering the recommendations of various professional committees on CRC, the National Quality Forum endorsed the harvest of at least 12 LNY as a standard quality indicator and a means of improving survival. Importantly, LNY removed surgically as well as assessed pathologically governs not only accuracy of tumor staging, but also therapeutic decision-making[9, 10].

In CRC patients with distant metastatic disease, prognostic significance of adequate lymphadenectomy has rarely been investigated previously. With the use of LNY as a quality indicator of lymphadenectomy extension and a routine parameter of evaluation in early-stage CRC patients, we supposed that even in the setting of patients with distant metastatic disease, adequate resection of the primary tumor of CRC and lymphadenectomy should be practiced. To better address this issue, we performed analyses based on two international population-based databases (1) to investigate the relationship between LNY and survival outcomes and (2) to further confirm its utility of 12-node threshold as a quality indicator of the surgical management in CRC patients with distant metastatic disease.

2. Methods

2.1.Data sources

Data on CRC patients with synchronous liver metastasis (LM) were derived from the US Surveillance, Epidemiology, and End Results (SEER) and a Chinese registry

(from two Chinese tertiary centers) between January 2010 and December 2017. Individual level data on patients with incident CRC were consecutively collected in both registries. The primary tumor site was divided into three subsites according to International Classification of Diseases for Oncology (ICD-O-3) topography codes: proximal colon (C18.0, C18.1, C18.2, C18.3 and C18.4), distal colon (C18.5, C18.6, C18.7) and rectum (C19.9 and C20.9). The synchronous LM were identified by imaging or histopathological examinations. Synchronous LM refers to liver lesions found within 6 months after the diagnosis of primary CRC. Patients were excluded if they did not undergo surgery for CRC, did not have data on number of LNs retrieved and their survival status was unknown. This study was approved by the review boards (Approval No. 17-116/1439). This trial was retrospectively registered with the Clinical Trials. Unique Identifying Number (UIN) is “NCT05550701”. This work has been reported in line with the STROCSS criteria, Supplemental Digital Content 1, http://links.lww.com/JS9/A239.

2.2 Variable and outcome of interest

The primary outcome was cancer specific survival (CSS), which was defined as the time interval from the synchronous LM diagnosis until cancer specific death or the end of follow-up in Chinese registry, and the CSS was defined using the SEER cause-of-death codes in SEER registry[11]. The primary independent variable was the number of LNY evaluated. In addition, demographic and clinical information about patients (age, sex), lymph node ratio [LNR], the number of positive lymph nodes divided by the total lymph node yield, tumor (primary tumor site, tumor grade, histology types, the American Joint Committee on Cancer [AJCC] TNM stage and preoperative carcinoembryonic antigen [CEA]), surgical strategy (only primary site resection, both primary site and metastasis resection), and outcome variables (follow-up time and survival status). Pathological tumor stage was characterized according to the 7th edition of the AJCC TNM staging system.

2.3 Statistical analysis

Patients were grouped by the suggested lymph node number of 12 according to the National Comprehensive Cancer Network (NCCN) guideline[6]. Descriptive

statistics were presented as median (inter quartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Categorical variables were compared using the Chi-square test. Survival analyses were performed using the Kaplan-Meier (KM) method and differences between groups were assessed with the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression model for calculating hazard ratio (HR) with its 95% confidence interval (CI). The baseline characteristics between two groups were matched by the propensity score matching (PSM) using the nearest-neighbor method with a caliper of 0.20 (Ratio 1:3) to reduce selection bias[12, 13]. The balance in covariates was assessed by using the standardized mean difference (SMD) approach. If the SMD is greater than 10%, this is usually considered a meaningful imbalance in the factors between the two groups. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using R software (version 4.0.4; http://www.r-project.org).

3. Results

3.1.Patient and tumor characteristics

A total of 3899 patients in SEER database and 676 patients in Chinese registry who met the eligibility criteria were included in this study. The baseline characteristics are shown in Table 1. Of these patients, the proportion of males was higher than that of in both SEER cohort (56.3%) and Chinese cohort (65.2%). Most resected primary tumors were located in distal colon (SEER, 49.9%; Chinese registry, 43.5%), were of stage T3-T4 (SEER, 96.3%; Chinese registry, 94.1%), and were declared node positive (SEER, 84.9%; Chinese registry, 74.6%). Additionally, 24.9% and 58.9% of patients in SEER cohort and Chinese cohort underwent metastases resection respectively.

In terms of the count of LNY, the median LNY in surgical specimens was 17 (IQR 12-23) and 18 (IQR 13-26) in SEER database and Chinses registry, respectively. The retrieval of at least 12 LNY was identified in most patients (SEER, 86.7%; Chinese registry, 83.6%). Also, the proportion of LNY≥12 with respect to different tumor sites showed that the proximal colon was higher than the distal colon and rectum in both cohorts (Table 2). Similar results are observed for the mean and

median of LNY (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/A240).

3.2.Baseline covariates after PSM

We used the PSM to balance baseline covariates between subgroups of patients with LNY < 12 and LNY ≥ 12. The baseline characteristics of eligible patients in the pre-matched and post-matched cohorts were listed in Table 2. In SEER and Chinese cohorts, 1550 patients in the LNY ≥ 12 subgroup were matched with 519 patients in the LNY < 12 subgroup and 299 patients in the LNY ≥ 12 subgroup were matched with 108 patients in the LNY < 12 subgroup, respectively. The matching process eliminated some significant differences that existed between two subgroups. After PSM adjustment, the SMD for all characteristics was less than 0.1, indicating that the population in the LNY < 12 vs. LNY ≥ 12 groups were subsequently comparable (Supplementary Figure 1, Supplemental Digital Content 3, http://links.lww.com/JS9/A241).

3.3.Survival analyses

In SEER cohort, both before and after PSM, survival analysis showed that patients with LNY ≥ 12 was significantly associated with better CSS (all log-rank P < 0.001) compared to patients with LNY < 12. A consistent trend was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Figure 1). All of the clinicopathological and surgery related variables were included in the univariate analysis. As shown in Table 3, LNY, LNR, age, sex, primary tumor site, grade, histology type, AJCC M stage, preoperative CEA and metastasectomy were potential prognostic factors for CSS (all P < 0.05). Next, variables that tended to be significant (P < 0.05) in univariate analysis were included in a multivariate Cox proportional hazards regression model. After controlling for other prognostic factors, patients with LNY ≥ 12 were still associated with better CSS (HR = 0.38; 95% CI, 0.33-0.44; P < 0.001), patients with higher LNR were still associated with worse CSS (HR = 2.26; 95% CI, 1.80-2.84; P < 0.001) and patients who underwent metastases resection were associated with decreased relative risk of death (HR = 0.56; 95% CI, 0.45-0.69; P < 0.001).

In Chinese cohort, survival analysis also showed that patients with LNY ≥ 12 was significantly associated with better CSS (all log-rank $P < 0.001$) compared to patients LNY < 12 both before and after PSM. The same relationship was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Figure 2). Univariable Cox regression model suggested that LNY, LNR, grade, histology type, AJCC M stage, preoperative CEA and metastasectomy were all associated with CSS (all $P < 0.05$). After controlling for other prognostic factors, multivariate analysis further demonstrated that patients with LNY ≥ 12 were still associated with better CSS (HR = 0.61; 95% CI, 0.45-0.82; $P = 0.001$), patients with higher LNR were still associated with worse CSS (HR = 4.02; 95% CI, 2.11-7.66; $P < 0.001$) and patients who underwent metastases resection were still associated with decreased relative risk of death (HR = 0.44; 95% CI, 0.33-0.58; $P < 0.001$).

In addition, we used PSM to balance the baseline covariates between the LNY < 12 and LNY ≥ 12 subgroups of overall patients in the two registries (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/JS9/A240), and also compared the CSS curves of the overall patients. Survival analysis also showed that patients with LNY ≥ 12 was significantly associated with better CSS (all log-rank $P < 0.05$) compared to patients LNY < 12 both before and after PSM. The same relationship was observed when only patients with AJCC M1a or M1b stages were included in the analysis (Supplementary Figure 2, Supplemental Digital Content 4, http://links.lww.com/JS9/A242).

3.4.Subgroup survival analysis

In SEER cohort, the CSS benefit for patients with LNY ≥ 12 was observed across most, but not all, subgroups (Figure 3). In particular, patients with mucinous/signet histology and those with AJCC T1-T2 stage did not have a clear benefit. In Chinese cohort, the results showed that the CSS superiority of the patients with LNY ≥ 12 over the patients with LNY < 12 in the majority of subgroups, except in the subgroups of patients with mucinous/signet histology, female, and those with AJCC T1-T2 stage (Figure 4).

In addition, we performed a separate analysis for the effect of LNY on prognosis

at different primary tumor sites. In both registries, the CSS benefit for patients with LNY ≥ 12 was observed in the proximal and distal colon, but not in the rectum (Supplementary Figure 3, Supplemental Digital Content 5, http://links.lww.com/JS9/A243).

4. Discussion

In this international population-based study, we have explored practice outcomes related to LNY for CRC patients in stage IV treated with primary tumor resection and lymphadenectomy and to further validate its role of 12-node threshold as a quality indicator of surgical care. In our findings, patients in stage IV with more than 12 LNY exhibited significant improved survival, indicating that the LNY considered as a powerful indicator for survival prediction and a quality indicator of surgical care in clinical practice. To our knowledge, this is the first study addressing the implications of the 12 LNY quality indicator on survival in patients with stage IV CRC based on two large cohorts.

Reassuringly, we found that most CRC patients had at least 12 LNY harvested at time of primary tumor resection, which reflects an increased understanding of the importance of this metric as a critical principle of oncologic resection for CRC with efforts led by both surgeons and pathologists[8]. In concordant with the existing literature, our finding presented that resections of proximal colon tumors were more likely to reach a 12 LNY threshold compared to distal colon and rectum tumors, typically attributed to the longer size of right sided specimens and thereby a higher LNY[14, 15, 16]. It is no surprise that more resected colorectal mesenteric tissue contribute to increased LNY, and variant lymphatic anatomy may also be another possible explanation[17]. In addition, the decrease in the number of LNY was due to the use of neoadjuvant chemoradiotherapy for rectal cancer patients[18, 19, 20].

For CRC patients in stage IV with resectable metastases, a 5-year overall survival of 60% can be achieved when surgery is feasible[21]. For those with initially non-resectable metastasis, current guides suggested that systemic chemotherapy should be administrated first to achieve secondary resection[22]. In this study, our analysis suggested that metastasectomy was an independent prognostic factor for

survival, which was similar to the results of previous studies[23, 24]. However, whether metastasectomy should be performed simultaneously with primary cancer or should be delayed remains controversial[25, 26]. Thus, large scale and multicenter prospective randomized studies are needed to compare both strategies in the future.

There are many reasons to explain that patients with distant metastasis influence the retrieval of LNY at the time of primary tumor resection. Surgeons may adjust the planned lymphadenectomy because of patient healthy status and complexity in practice. Increased technical difficulty regarding surgery for patients in stage IV is often expressed by surgeons, particularly the elderly who are considered to be high-risk operative candidates secondary to any life-threatening comorbidities, which then alter to perform less extensive mesenteric resections. Our results also demonstrated that patients in stage IV with LNY ≥ 12 had a better survival, predicting a better prognostic correlation with appropriate lymphadenectomy. Thus, an oncologically adequate lymphadenectomy is still a critical component of high-quality surgical care even in CRC patients with stage IV disease.

Whether the total LNY should be used as an ideal quality measure for CRC had been immensely investigated. Evidence suggested that non-metastatic CRC patients, particularly in stage II disease, with a reduced LNY had a worse prognosis[27]. Accurate determination of nodal status is crucial to accomplish adequate staging and an inadequate LNY assessed may result in stage migration, with attendant prognostic and possibly therapeutic impacts. Meanwhile, studies have consistently shown that increased LNY is associated with improvement in survival[28, 29, 30], even in rectal cancer patients treated with neoadjuvant chemoradiotherapy[20]. The main mechanism underlying the association between a higher LNY and better survival remains unknown. Some researchers contended that there were two aspects of cancer immunity exerted by tumor-draining lymph nodes, namely antitumor immunity and tolerance for cancer, and that the balance of cancer immunity inclines toward tolerance as the cancer advances[31]. Therefore, resection of regional lymph nodes, despite them not being metastatic nodes, may reset this ‘cancer-friendly’ immunological balance, resulting in an improvement of patient prognosis.

In addition to these literatures, several studies suggested that the number of lymph nodes present in a given patient reflects, at least in part, the underlying tumor-host interaction. Tumor factors may stimulate reactive lymph nodes to grow, making them more visible to be detected by surgeons and pathologists, and tumor antigens may stimulate germinal centers resulting in an increase in the number of lymph nodes[32]. This also partly explains our previous findings that why lymph nodes were more likely to be detected in younger patients compared to older patients, because increasing age is associated with a decline in immune competence[15]. LNY may therefore be a marker for tumor-host immunologic interactions, which may ultimately predict disease progression. Further studies exploring the mechanism underlying the relationship between LNY and cancer immunity may identify novel therapeutic targets and should be pursued.

There are some limitations in our study. First, the present study had its selection bias due to its retrospective nature. Second, similar to other national databases, the present cohort cannot provide more detailed information on individual surgeon, pathologist and hospital related factors which also can affect surgical outcomes and LNY[33]. Third, recurrence would more likely be one primary endpoint in this study, but SEER lacked the recurrence data and thus could not be analyzed, CSS instead. Most notably, information regarding the use of chemotherapy was not available to the authors, raising additional concerns related to the possible impact of neoadjuvant and adjuvant therapy on survival. Although alternative statistical strategy applied to the present study, such as PSM, may have helped minimize confounding, these limitations should be kept in mind while interpreting our study. Indeed, very few quality indicators are “perfect,” the aim of our study remains to better elucidate an already set benchmark, especially when it is used as a standard for surgical quality assessment across the CRC patients in stage IV.

5. Conclusion

In conclusion, adequate LNY (12-node threshold) was achieved in the majority of primary tumor resections for CRC patients in stage IV, and the 12-node threshold was predictive of CSS for patients with distant metastases. Therefore, we support the

clinical feasibility of the 12–node threshold as both a guideline quality metric of cancer care for CRC patients in stage IV. Meanwhile, institutions should continue to promote safe, high quality, surgical care by experienced teams, with the goal of appropriate lymphadenectomy as part of comprehensive multidisciplinary cancer management.

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Competing interests

The authors declare that they have no conflict of interest.

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Figure 1. Cox adjusted survival curves stratified by the LNY among patients in SEER database before and after PSM. (a) All patients in stage IV before PSM; (b) Patients in stage M1a before PSM; (c) Patients in stage M1b before PSM; (d) All patients in stage IV after PSM; (e) Patients in stage M1a after PSM; (f) Patients in stage M1b after PSM.

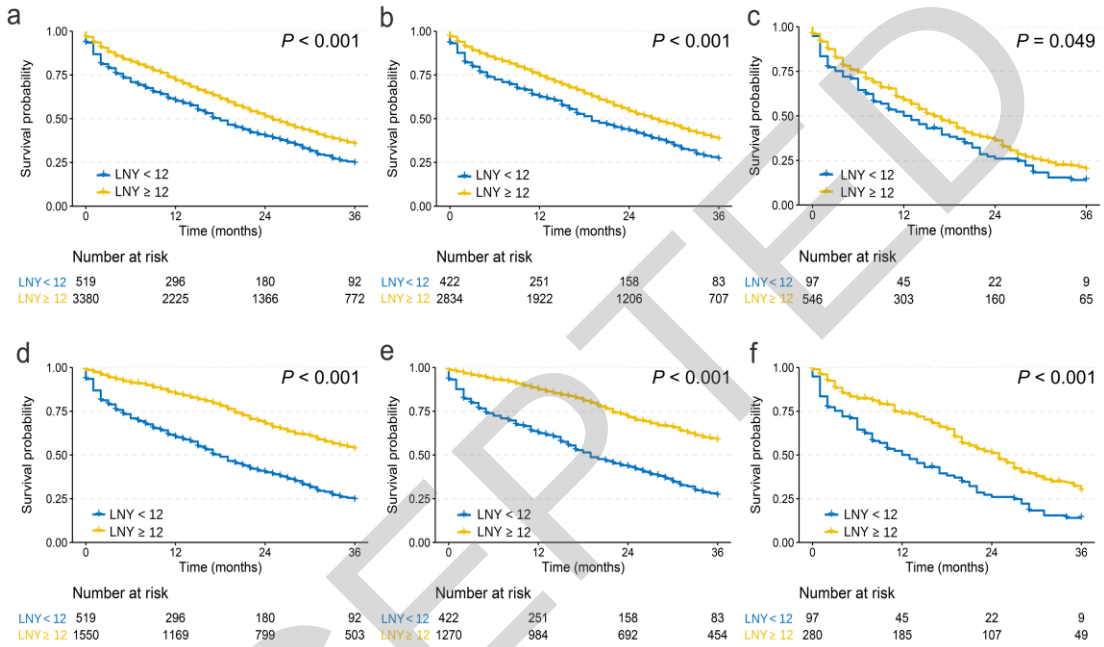

Figure 2. Cox adjusted survival curves stratified by the LNY among patients in Chinese registry before and after PSM. (a) All patients in stage IV before PSM; (b) Patients in stage M1a before PSM; (c) Patients in stage M1b before PSM; (d) All patients in stage IV after PSM; (e) Patients in stage M1a after PSM; (f) Patients in stage M1b after PSM.

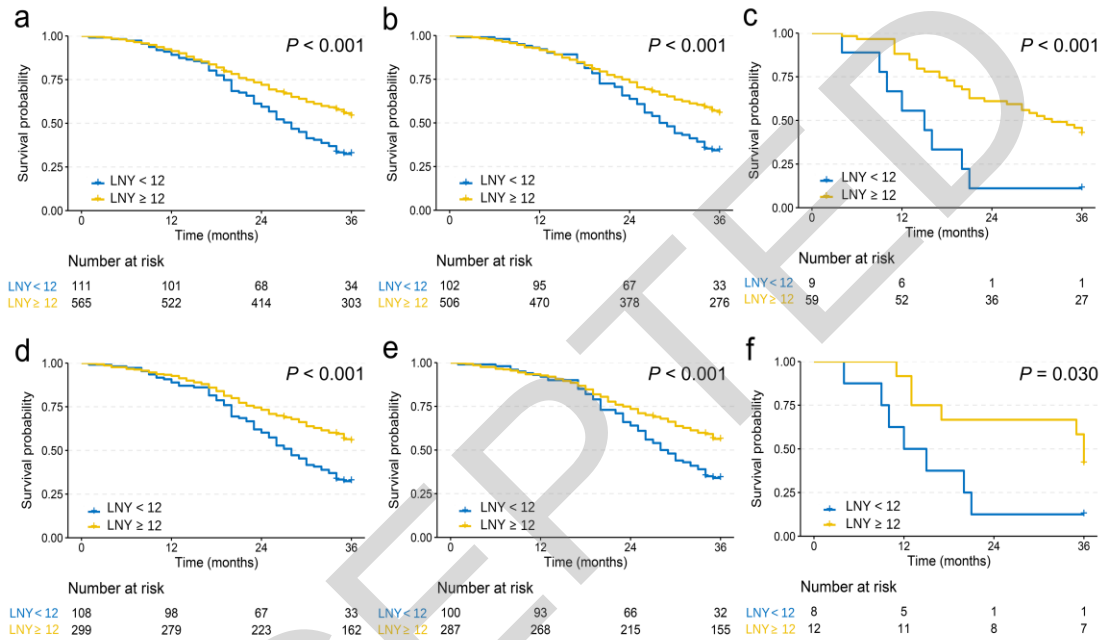

Figure 3. Subgroup analysis of survival in SEER database according to the LNY stratification.

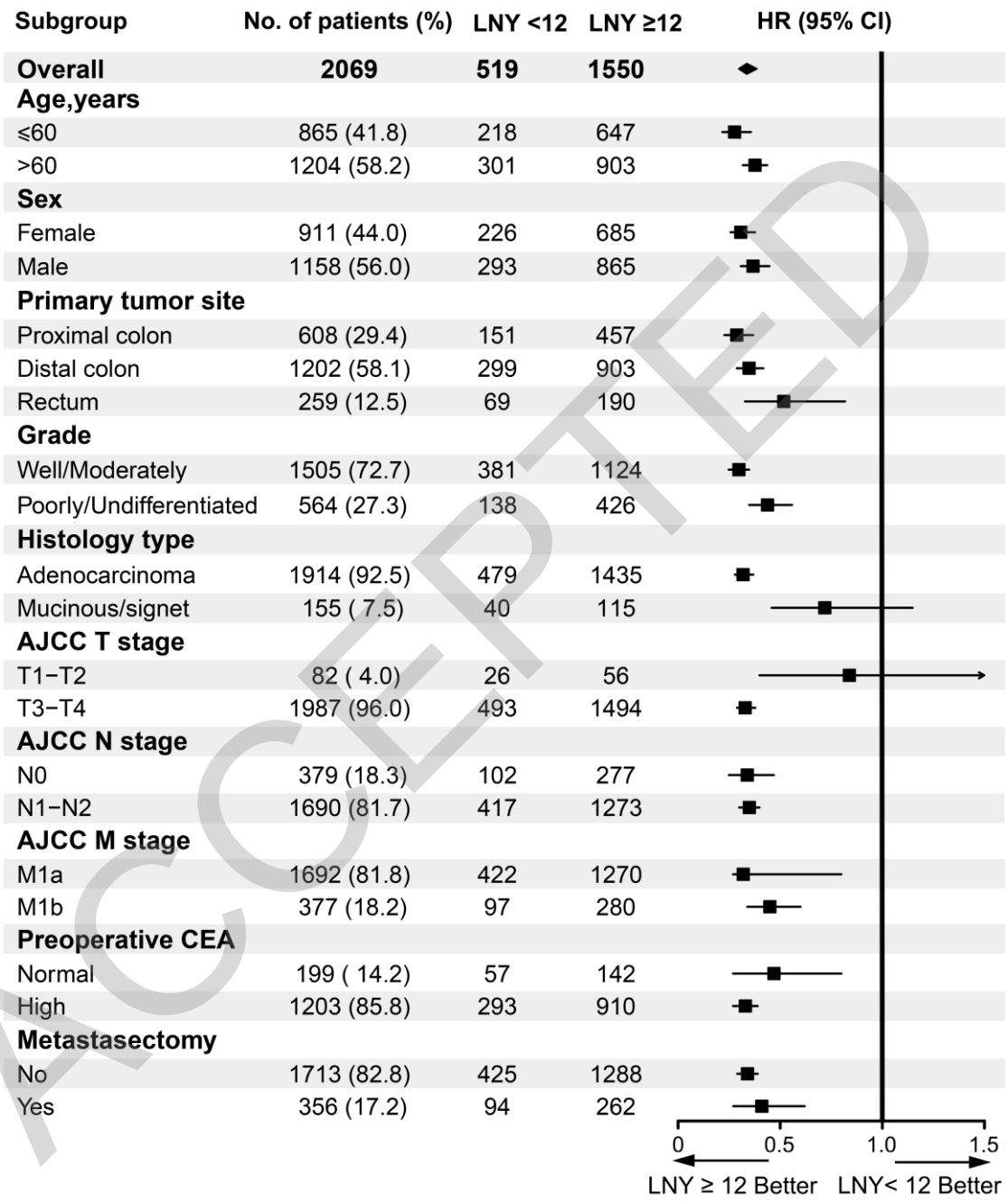

Figure 4. Subgroup analysis of survival in Chinese registry according to the LNY stratification.

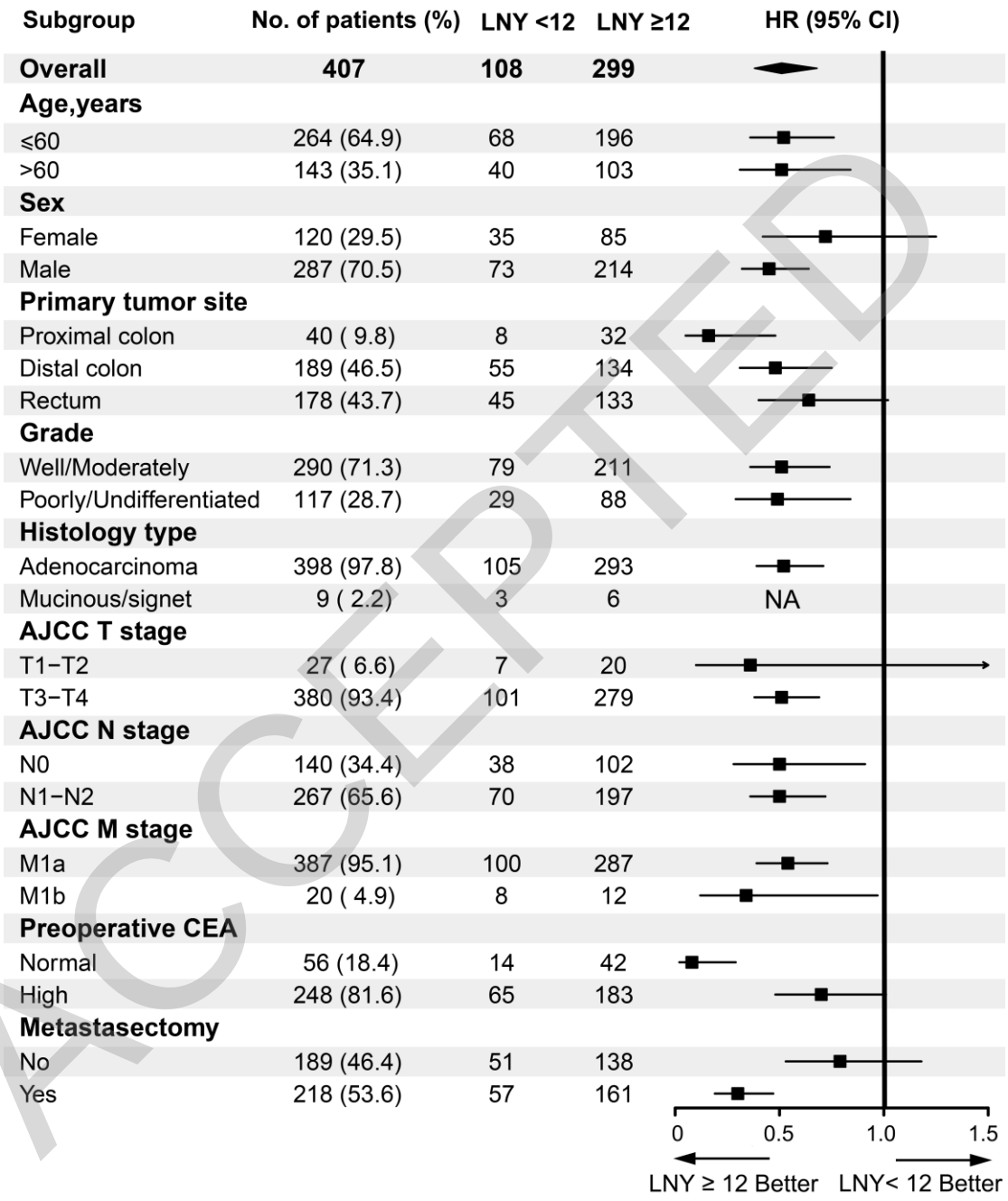

Table 1. Clinicopathological characteristics of CRC patients in stage IV in SEER database and Chinese registry.

Characteristics	**SEER Database No. (%)**	**Chinese Registry No. (%)**
Total	3899	676
LNY, median [IQR]	17 [13, 23]	18 [13,26]
LNR, median [IQR]	0.18 [0.05, 0.42]	0.11 [0,0.29]
Age, years		
≤60	1791 (45.9)	406 (60.1)
> 60	2108 (54.1)	270 (39.9)
Sex		
Female	1704 (43.7)	235 (34.8)
Male	2195 (56.3)	441 (65.2)
Primary tumor site		
Proximal colon	1549 (39.7)	133 (19.7)
Distal colon	1947 (49.9)	294 (43.5)
Rectum	403 (10.3)	249 (36.8)
Grade		
Well/Moderately	2863 (73.4)	493 (72.9)
Poorly/Undifferentiated	1036 (26.6)	183 (27.1)
Histology type		
Adenocarcinoma	3627 (93.0)	660 (97.6)
Mucinous/signet	272 (7.0)	16 (2.4)
AJCC T stage		
T1-T2	145 (3.7)	40 (5.9)
T3-T4	3754 (96.3)	636 (94.1)
AJCC N stage		
N0	587 (15.1)	172 (25.4)
N1-N2	3312 (84.9)	504 (74.6)
AJCC M stage		
M1a	3256 (83.5)	608 (89.9)
M1b	643 (16.5)	68 (10.1)
Preoperative CEA		
Normal	574 (14.7)	129 (19.1)
High	2198 (56.4)	415 (61.4)
Unknown	1127 (28.9)	132 (19.5)
Metastasectomy		
No	2928 (75.1)	278 (41.1)
Yes	971 (24.9)	398 (58.9)

AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; LNY, lymph node yield; CEA, carcinoembryonic antigen; IQR, interquartile range; LNR, lymph node ratio

Table 2. Association between LNY and clinicopathological characteristics in CRC patients in stage IV in SEER database and Chinese registry.

Characteristics	SEER Database						Chinese Registry					
	Before PSM			After PSM			Before PSM			After PSM		
	LNY< 12	LNY≥ 12	*P*	LNY< 12	LNY ≥ 12	*P*	LNY< 12	LNY≥ 12	*P*	LNY< 12	LNY≥ 12	*P*
No. of patients	519	3380		519	1,550		111	565		108	299	
Age, years			0.060			0.957			0.697			0.715
≤60	218 (42.0)	1573 (46.5)		218 (42.0)	647 (41.7)		69 (62.2)	337 (59.6)		68 (63.0)	196 (65.6)	
Sex			0.976			0.836			0.649			0.513
Female	226 (43.5)	1478 (43.7)		226 (43.5)	685 (44.2)		36 (32.4)	199 (35.2)		35 (32.4)	85 (28.4)	
Primary tumor site			<0.001			0.826			0.001			0.436
Proximal colon	151 (29.1)	1398 (41.3)		151 (29.1)	457 (29.5)		8 (7.2)	125 (22.1)		8 (7.4)	32 (10.7)	
Distal colon	299 (57.6)	1648 (48.8)		299 (57.6)	903 (58.3)		56 (50.5)	238 (42.1)		55 (50.9)	134 (44.8)	
Rectum	69 (13.3)	334 (9.9)		69 (13.3)	190 (12.2)		47 (42.3)	202 (35.8)		45 (41.7)	133 (44.5)	
Grade			1.000			0.735			0.898			0.701
Well/Moderately	381 (73.4)	2482 (73.4)		381 (73.4)	1,124 (72.5		82 (73.9)	411 (72.7)		79 (73.1)	211 (70.6)	

					)					
Histology type			0.542			0.905			0.201	0.932
Adenocarcinoma	479 (92.3)	3148 (93.1)		479 (92.3)	1,435 (92.6)		106 (95.5)	554 (98.1)	105 (97.2)	293 (98.0)
AJCC T stage			0.122			0.2000			0.395	1.0000
T3-T4	493 (95.0)	3261 (96.5)		493 (95.0)	1,494 (96.4)		102 (91.9)	534 (94.5)	101 (93.5)	279 (93.3)
AJCC N stage			0.002			0.399			0.014	0.934
N1-N2	417 (80.3)	2895 (85.7)		417 (80.3)	1,273 (82.1)		72 (64.9)	432 (76.5)	70 (64.8)	197 (65.9)
AJCC M stage			0.166			0.8000			0.5665	0.2555
M1a	422 (81.3)	2834 (83.8)		422 (81.3)	1,270 (81.9)		102 (91.9)	506 (89.6)	100 (92.6)	287 (96.0)
Preoperative CEA			0.015			0.427			0.020	0.896
Normal	57 (11.0)	517 (15.3)		57 (11.0)	142 (9.2)		14 (12.6)	115 (20.3)	14 (13.0)	42 (14.1)
High	293 (56.5)	1905 (56.4)		293 (56.5)	910 (58.7)		66 (59.5)	349 (61.8)	65 (60.1)	183 (61.2)
Unkno	169	958		169	498		31	101	29	74

wn	(32.5)	(28.3)		(32.5)	(32.1)		(27.9)	(17.9)		(26.9)	(24.7)	
Metastasectomy			<0.001			0.573			0.148			0.938
Yes	94 (18.1)	877 (25.9)		94 (18.1)	262 (16.9)		58 (52.3)	340 (60.2)		57 (52.8)	161 (53.8)	

AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; LNY, lymph node yield; CEA, carcinoembryonic antigen; PSM, propensity score matching

Table 3. Multivariate cox analyses for cancer specific survival in CRC patients in stage IV in SEER database and Chinese registry after propensity score matching.

Variable	Cateology	SEER Database				Chinese Registry			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
LNY	≥ 12 versus < 12	0.40 (0.35 - 0.46)	< 0.001	0.38 (0.33 - 0.44)	< 0.001	0.54 (0.41 - 0.72)	< 0.001	0.61 (0.45 - 0.82)	0.001
LNR	—	4.40 (3.56 - 5.45)	< 0.001	2.26 (1.80 - 2.84)	< 0.001	6.84 (4.17 - 11.23)	< 0.001	4.02 (2.11 - 7.66)	< 0.001
Age, years	> 60 versus ≤ 60	1.89 (1.65 - 2.17)	< 0.001	1.71 (1.49 - 1.97)	< 0.001	1.24 (0.94 - 1.64)	0.141		
Sex	Male versus Female	0.87 (0.77 - 0.99)	0.036	0.86 (0.76 - 0.98)	0.025	1.02 (0.75 - 1.37)	0.934		
Primary tumor site	Distal versus Proximal colon	0.66 (0.57 - 0.76)	< 0.001	0.81 (0.70 - 0.94)	0.004	0.66 (0.42 - 1.03)	0.072		
	Rectum versus Proximal colon	0.49 (0.39 - 0.62)	< 0.001	0.72 (0.56 - 0.91)	0.007	0.71 (0.46 - 1.12)	0.144		
Grade	Poorly/Undifferentiated versus Well/Moderately	2.33 (2.04 - 2.66)	< 0.001	2.10 (1.83 - 2.41)	< 0.001	1.40 (1.05 - 1.87)	0.021	1.09 (0.80 - 1.50)	0.584
Histology type	Mucinous/signet versus Adenocarcinoma	1.90 (1.55 - 2.34)	< 0.001	1.65 (1.34 - 2.04)	< 0.001	4.46 (2.19 - 9.09)	< 0.001	5.27 (2.46 - 11.32)	< 0.001

AJCC T stage	T3-T4 versus T1-T2	1.03 (0.74 - 1.43)	0.872			3.01 (1.34 - 6.78)	0.008	2.22 (0.98 - 5.03)	0.056
AJCC N stage	N1-N2 versus N0	1.16 (0.98 - 1.37)	0.092			1.88 (1.37 - 2.58)	<0.001	1.11 (0.75 - 1.64)	0.618
AJCC M stage	M1b versus M1a	1.92 (1.66 - 2.23)	<0.001	1.93 (1.66 - 2.24)	<0.001	1.91 (1.11 - 3.28)	0.021	1.28 (0.72 - 2.26)	0.403
Preoperative CEA	High versus Normal	1.82 (1.38 - 2.38)	<0.001	2.18 (1.66 - 2.87)	<0.001	1.75 (1.09 - 2.80)	0.023	1.57 (0.97 - 2.53)	0.068
Metastasectomy	Yes versus No	0.49 (0.40 - 0.61)	<0.001	0.56 (0.45 - 0.69)	<0.001	0.38 (0.29 - 0.51)	<0.001	0.44 (0.33 - 0.58)	<0.001

AJCC, American Joint Committee on Cancer; SEER, Surveillance, Epidemiology, and End Results; LNY, lymph node yield; LNR, lymph node ratio; HR, Hazard ratio; CEA, carcinoembryonic antigen; CI, confidence interval