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Clinicopathological characteristics and prognosis of colon cancer with lung metastasis without liver metastasis

A large population-based analysis

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Abstract

Distant metastasis explains the high mortality rate of colon cancer, in which lung metastasis without liver metastasis (LuM) is a rare subtype. This study is aimed to identify risk factors of LuM and LLM (lung metastasis with liver metastasis) from colon cancer, and to analyze the prognosis of patients with LuM by creating a nomogram. Patients' information were obtained from the Surveillance, Epidemiology, and End Results (SEER) database. Multivariable logistic regression analysis was used to determine the risk factors for LuM and LLM. Prognostic factors for cancer-specific survival (CSS) and overall survival (OS) were identified by multivariate Cox proportional hazards regression and nomogram models were established to predict CSS and OS. Multivariate logistic regression analysis showed that blacks, splenic flexure of colon tumor, tumor size >5 cm, T4, N3, and higher lymph node positive rate were associated with the occurrence of LuM. Meanwhile, age >65 years old, female, splenic flexure of colon, higher lymph node positive rate, and brain metastasis were independent risk factors for CSS. The C-index of the prediction model for CSS was 0.719 (95% CI: 0.691–0.747). In addition, age, primary site, tumor size, differentiation grade, N stage, and bone metastasis were significantly different between LuM and LLM. The nomograms we created were effective in predicting the survival of individuals. Furthermore, patients with LuM and LLM from colon cancer might require different follow-up intervals and examinations.

Abbreviations: CRC = colorectal cancer, CSS = cancer-specific survival, LLM = lung metastasis with liver metastasis, LuM = lung metastasis without liver metastasis, OS = overall survival, SEER = surveillance, epidemiology, and end results.

Keywords: colon cancer, liver metastasis, lung metastasis, nomogram, prognosis.

1. Introduction

Colorectal cancer (CRC) is the second deadliest cancer in the world, and nearly 900,000 people die from the disease every year.[1,2] The United States owns a high incidence and a high mortality rate of colorectal cancer, which are ranking third and second respectively.[3] Distant metastasis could well explain the high mortality rate of CRC. Approximately 22% of CRCs metastasize during the course of the disease. When distant metastasis occurs, the 5-year survival rate drops rapidly from 64.4% to 14.2%.[4] Therefore, a comprehensive understanding of the potential metastatic factors of CRC is conducive to accurate monitoring and early treatment, which has significant benefits for CRC patients' survival.

Lung is the most common extra-abdominal metastasis site from CRC, with an incidence of about 11%.[5] Studies have reported that the risk of lung metastasis varies in different locations of CRCs.[6] Rectal cancer is more prone to metastasis to extrahepatic organs due to its hemodynamic characteristics, especially to lung, which has been proven to be an independent risk factor for lung metastasis of CRC.[7] Since the venous return from the left and right hemispheres of the colon passes through the liver into the lung, most colon cancer patients with lung metastases have concomitant liver metastases. However, lung metastasis without liver metastasis (LuM) is relatively rare, and the specific mechanism of metastasis has rarely been studied.[8] Therefore, we take colon cancer as the research target.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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In this article, we analyzed the SEER database, focusing on the risk factors and prognostic factors of LuM from colon cancer. At the same time, comparing lung metastasis with liver metastasis (LLM) to LuM from colon cancer, we identified the different clinicopathologic factors between the 2 metastatic patterns, so as to facilitate the clinical guidance of accurate follow-up, supervision and timely treatment. In this way, patients with metastatic colon cancer will obtain a longer survival time.

2. Materials and Methods

2.1. Inclusion and exclusion criteria for patient selection

The Surveillance, Epidemiology, and End Results (SEER) database, sponsored by the National Cancer Institute, covers about 28% of the U.S. population and includes cancer incidence and survival data from 20 cancer regions. Since SEER only began to collect metastasis information of specific sites (liver, lung, bone, brain) in 2010, we screened all cases of postoperative colon cancer from 2010 to 2016. Because all of our case information is publicly available from the SEER database, ethical approval is not required. We included cases with colon cancer as the only primary tumor and valid follow-up data. However, cases with unclear information such as race, sex, age at diagnosis, tumor site, size, differentiation, T, N, M stage, site of metastasis, total number of lymph nodes dissected, and number of positive lymph nodes were excluded.

2.2. Factors

A total of 11 parameters were selected, including race, sex, age, tumor primary site, tumor size, grade of differentiation, T stage, N stage, lymph node positivity rate, bone metastasis, and brain metastasis. Race was divided into white, black, and other (American Indian/Native American, Asian/Pacific Islander). Age was categorized as <65 years and ≥65 years. The primary tumor site was subdivided into 7 parts according to SEER Site Recode ICD-O-3, including cecum (C180), ascending colon (C182), hepatic flexure of colon (C183), transverse colon (C184), splenic flexure of colon (C185), descending colon (C186), Sigmoid colon (C187). Tumor size was split into 3 classes at the boundary of 3 and 5 cm. Both T and N stages have been reclassified from the original data according to the eighth edition of the American Joint Committee on Cancer TNM staging system. The lymph node positivity rate, represents the ratio of the number of positive lymph nodes to the total number of dissected lymph nodes.

2.3. Statistical analysis

Continuous variables were presented as mean ± standard deviations. Univariate analyses and multivariate logistic regression analyses were performed between patients without any metastasis (M0) and with LuM to identify the risk factors. The Pearson's chi-square test and *t* test were used in univariate analysis. Subsequently, univariate and multivariate COX proportional hazard regression analyses were used to determine prognostic factors for tumor-specific survival (CSS) and overall survival (OS) of LuM. Based on the above results, 2 nomograms were created to predict CCS and OS, respectively, and evaluated using calibration curves and consistency indices. Finally, we further conducted univariate and logistic multivariate regression analyses between patients with LLM and patients with LuM to explore the associations and differences between the 2 types of lung metastases. All statistical analyses were implemented using R software (version 3.6.2; www.r-project.org). A P value <.05 was identified to be statistically significant, and all P values were 2-tailed.

3. Results

3.1. Demographics and characteristics of patients with M0 and LuM

Based on our inclusion and exclusion criteria, 56,295 patients without any metastasis (M0) and 488 patients with LuM were finally screened. Since the SEER database primarily collected cancer data from the United States, it was predominantly black and white, with little data for other racial groups. However, whites accounted for a higher proportion of patients than blacks in both M0 and LuM, at more than 70%. The sigmoid colon was the most common site of origin, accounting for 27.60% and 32.99% of M0 and LuM, respectively, followed by cecum and ascending colon. Most of the patients with M0 were in T3 (56.80%), while T1, T2, and T4 were relatively few (11.40%, 16.38%, and 15.42%, respectively). However, although T3 (55.53%) was dominant in patients with LuM, T4 in LuM (40.16%) were significantly more than that in M0 (15.42%). In terms of N stage, there was a noticeable difference between patients with M0 and LuM. N0 stage constituted more than half of the patients with M0 (61.14%), while the majority of LuM patients were N2 stage. The demographic and clinical histopathological characteristics of patients with M0 and LuM are shown in Table 1. Univariate analysis showed that LuM was associated with race (P < .001), primary site (P = .008), tumor size (P < .001), grade (P < .001), T stage (P < .001), N stage (P < .001), and lymph node positive rate (P < .001). Further logistic multivariate regression indicated that LuM was more likely to occur in blacks (OR = 1.405; 95% CI: 1.087–1.794; P = .008), sigmoid colon (OR = 1.671; 95% CI: 1.293–2.169; P < .001), tumor size >5 cm (OR = 1.443; 95% CI: 1.094–1.928; P = .011), T4 (OR = 8.601; 95% CI: 3.986–22.484; P < .001), N2 (OR = 2.94; 95% CI: 2.099–4.116; P < .001), and higher lymph node positive rate (OR = 4.973; 95% CI: 3.047–8.021; P < .001) (Fig. 1).

3.2. Establishment and validation of the nomogram model for patient with LuM

To explore factors influencing the prognosis of LuM patients, we performed univariate and multivariate Cox proportional hazard regression analyses with CSS and OS as final outcomes, respectively. In the univariate analysis, age, primary site, N stage, lymph node positive rate, bone metastasis and brain metastasis were significantly different in CSS and OS. Gender was only associated with CSS, whereas race was correlated with OS. Multivariate analysis showed that male might be a beneficial factor in CSS compared to female, while race was not significantly different with OS. Primary tumors in the ascending colon, transverse colon, and splenic regions of the colon, patients with age >65, higher rate of lymph node positive, and combined brain metastasis were common risk factors for both CSS and OS (Tables 2 and 3). Based on these results, we developed 2 nomogram models to predict 1-, 3-, and 5-years CSS (Fig. 2) and OS (Fig. 3), respectively. The C-index for the CSS-predicted nomogram model was 0.719 (95% CI: 0.691–0.747) and for the OS-predicted nomogram model was 0.700 (95% CI: 0.671–0.728). The calibration curves for CSS and OS at 1-, 3-, and 5-years presented the comparison between the prediction probability of the models and the actual observation results. The prediction curves were all close to the 45° line, indicating that the models had predictive performance (Fig. 4).

3.3. Risk factors for LLM and LuM

We also screened 950 colon cancer patients with LLM following the same inclusion and exclusion criteria. According to the data in Table 4, more than half of the LLM patients were ≤65 years old (57.47%), and there was little difference

Table 1

: Univariate analysis of patients with LuM.

Variable		No metastasis (n = 56295)	LuM (n = 488)	P value
Race	White	43,613 (78.15%)	347 (71.11%)	<.001
	Black	6846 (12.27%)	78 (15.98%)	
	Other	5348 (9.58%)	63 (12.91%)	
Sex	Female	28,818 (51.64%)	259 (53.07%)	.558
	Male	26,989 (48.36%)	229 (46.93%)	
Age	≤65	24,370 (43.67%)	235 (48.16%)	.052
	>65	31,437 (56.33%)	253 (51.84%)	
Primary site	Cecum	13,830 (24.78%)	99 (20.29%)	.008
	Ascending colon	12782 (22.90%)	93 (19.06%)	
	Hepatic flexure of colon	2690 (4.82%)	26 (5.33%)	
	Transverse colon	5629 (10.09%)	47 (9.63%)	
	Splenic flexure of colon	1882 (3.37%)	24 (4.92%)	
	Descending colon	3592 (6.44%)	38 (7.79%)	
	Sigmoid colon	15,402 (27.60%)	161 (32.99%)	
Tumor size	≤3	16,419 (29.42%)	70 (14.34%)	<.001
	3–5	20,024 (35.88%)	182 (37.30%)	
	>5	19,364 (34.70%)	236 (48.36%)	
Grade	Well	4545 (8.14%)	29 (5.94%)	<.001
	Moderate	40,518 (72.60%)	317 (64.96%)	
	Poor	8814 (15.79%)	121 (24.80%)	
	Undifferentiated	1930 (3.46%)	21 (4.30%)	
T stage	T1	6361 (11.40%)	6 (1.23%)	<.001
	T2	9142 (16.38%)	15 (3.07%)	
	T3	31,698 (56.80%)	271 (55.53%)	
	T4	8606 (15.42%)	196 (40.16%)	
N stage	N0	34,121 (61.14%)	108 (22.13%)	<.001
	N1	14,292 (25.61%)	167 (34.22%)	
	N2	7394 (13.25%)	213 (43.65%)	
Lymph node positive ratio		0.08 ± 0.16	0.26 ± 0.28	<.001
Bone metastasis	No		469 (96.11%)	
	Yes		19 (3.89%)	
Brain metastasis	No		477 (97.75%)	
	Yes		11 (2.25%)	

LuM = lung metastasis without liver metastasis.

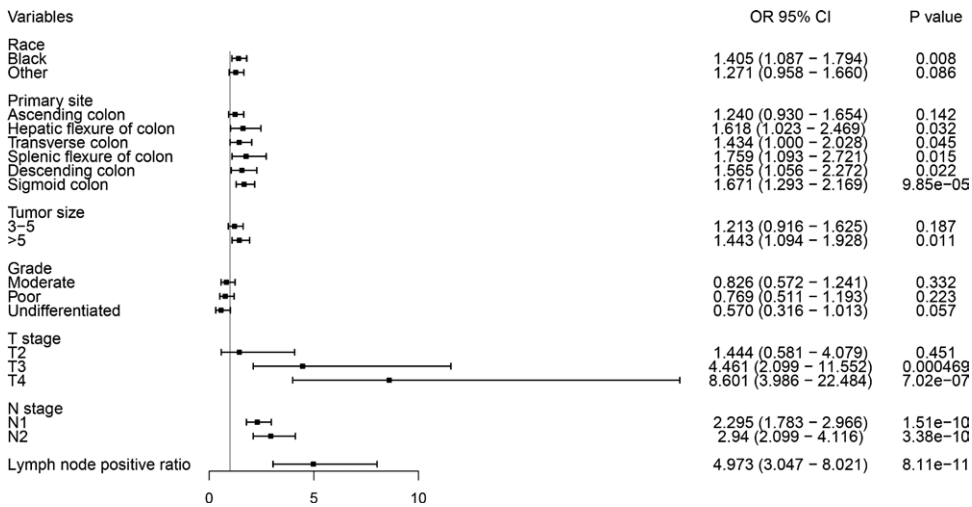

Figure 1 The forest plot exhibited the result of the multivariate analysis between M0 and LuM. LuM = lung metastasis without liver metastasis, M0 = metastasis.

between the 2 groups of age in the LuM patients (≤65 vs >65 years old = 235 vs 253). In terms of the distribution of different tumor sizes, only 8.53% of patients in LLM had a primary lesion ≤3 cm, compared to 14.34% in LuM, which was nearly twice as many as in LLM. In the univariate analysis of LLM and LuM, 11 variables including race, sex, age, primary site, tumor size, grade, T stage, N stage, lymph node positive rate, bone metastasis, and brain metastasis were analyzed one by one, and eventually 8 variables (age, primary site, tumor size, grade, T stage, N stage, lymph node positive rate and bone metastasis) were significantly different between the 2 metastatic patterns. The results of the multivariate analysis incorporating these 8 parameters showed that patients who were elderly and had primary sites in the hepatic flexure of colon

Table 2

: Univariate and multivariable Cox proportional hazards regression for CSS among patients with LuM.

Variable		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Race	White	1		—	—
	Black	0.739 (0.534–1.022)	.067	—	—
	Other	1.027 (0.727–1.451)	.880	—	—
Sex	Female	1		1	
	Male	0.790 (0.623–0.993)	.044	0.735 (0.578–0.935)	.012
Age	≤65	1		1	
	>65	1.800 (1.430–2.267)	<.001	2.137 (1.661–2.750)	<.001
Primary site	Cecum	1		1	
	Ascending colon	1.518 (1.072–2.149)	.019	1.580 (1.111–2.247)	.011
	Hepatic flexure of colon	1.347 (0.807–2.249)	.255	1.589 (0.938–2.692)	.085
	Transverse colon	1.787 (1.175–2.718)	.007	2.041 (1.327–3.139)	.001
	Splenic flexure of colon	1.730 (1.024–2.924)	.041	2.163 (1.269–3.687)	.005
	Descending colon	0.668 (0.386–1.155)	.148	0.933 (0.535–1.630)	.809
	Sigmoid colon	0.838 (0.604–1.162)	.290	0.940 (0.668–1.322)	.722
Tumor size	≤3	1		—	—
	3–5	0.987 (0.692–1.408)	.942	—	—
	>5	1.059 (0.750–1.494)	.745	—	—
Grade	Well	1		—	—
	Moderate	0.808 (0.491–1.329)	.400	—	—
	Poor	1.489 (0.886–2.503)	.133	—	—
	Undifferentiated	1.302 (0.649–2.610)	.458	—	—
T stage	T1	1		—	—
	T2	0.364 (0.081–1.629)	.186	—	—
	T3	0.970 (0.309–3.045)	.959	—	—
	T4	1.547 (0.492–4.865)	.456	—	—
N stage	N0	1		1	
	N1	1.343 (0.954–1.891)	.091	1.057 (0.734–1.512)	.764
	N2	1.860 (1.345–2.570)	<.001	0.775 (0.487–1.233)	.282
Lymph node positive ratio		4.227 (2.907–6.147)	<.001	8.529	<.001
Bone metastasis	No	1		1	
	Yes	2.170 (1.309–3.599)	.003	1.404 (0.836–2.359)	.200
Brain metastasis	No	1		1	
	Yes	3.210 (1.699–6.064)	<.001	3.720 (1.941–7.128)	<.001

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, LuM = lung metastasis without liver metastasis.

and transverse colon were prone to LuM. In contrast, patients whose primary tumor size ≥3 cm, moderately differentiated, and developing bone metastases were more likely to have LLM (Fig. 5).

4. Discussion

Patients with lung metastasis from CRC has a superior outcome comparing with those developing other metastases.[9] Early detection of lung metastasis can give full play of lung metastasectomy's advantages and then achieve a satisfactory prognosis.[10] The data displayed that radical lung metastasectomy can even improve the 5-year survival rate to more than 50%.[11] Moreover, the identification of high-risk groups is the key to early and accurate diagnosis and the formulation of individualized treatment plans. It can ensure that the metastatic population is not missed and the overuse of medical detection devices is avoided. In this article, we have identified several factors, based on the SEER database, that are associated with the development of LuM from colon cancer. In patients with colon cancer carrying these high-risk factors, both preoperative screening and postoperative follow-up protocols should be individually tailored. In recent years, the value of routine preoperative chest CT among CRC patients has been questioned. The American Society of Clinical Oncology and European Society for Medical Oncology guidelines merely recommend preoperative chest CT for colon cancer to assess the extent of disease extension as grade IIB.[12] However, there is no equivalent study for patients with colon cancer to guide the examination of chest under different conditions. In this paper, we quantify the risk of LuM, providing a rationale for performing chest CT examinations in high-risk clinical populations, which is equally instructive for postoperative follow-up guidance. Current guidelines recommend chest and abdominal CT scans every 6 to 12 months,[13] However, in clinical practice, more attention is paid to the abdominal examination since the liver is the most common site of distant metastasis. For example, the abdominal CT is reviewed every 6 months, whereas the chest CT may only be reviewed once a year. Therefore, for these high-risk populations, more emphasis should be place on chest CT scan.

Due to the individual differences between colon cancer patients, the TNM staging system may not be accurate enough to predict survival. Nomogram is a graphical representation of a statistical prediction model that combines important prognostic factors to generate numerical probabilities of clinical events such as OS, thus achieving a more scientific, effective and accurate prediction without bias based on clinical experience. In this study, we integrated several factors that might affect prognosis and constructed prediction nomogram models to understand the predicted survival of individuals.

Age is a prognostic factor for several tumors,[14–17] and also an independent predictor of lung metastasis from colon cancer in our article. Yet the effect of gender on colon cancer prognosis is still in dispute. Most studies have shown that among colon cancer patients, women have longer OS and CSS,[18,19] while the life expectancy of women was originally longer than that of men,[20] which as a confounding factor influencing survival outcome was not excluded in those researches. However, a range of studies indicated that gender was not a prognostic factor for colon cancer.[21] Some have even found that female individuals havd a

Table 3

: Univariate and multivariable Cox proportional hazards regression for OS among patients with LuM.

Variable		Univariate analysis		Multivariate analysis	
		HR (95%CI)	*P* value	HR (95%CI)	*P* value
Race	White	1		1	
	Black	0.708 (0.517–0.969)	.031	0.807 (0.584–1.115)	.194
	Other	0.987 (0.702–1.386)	.938	0.975 (0.688–1.383)	.889
Sex	Female	1		—	—
	Male	0.802 (0.643–1.000)	.050	—	—
Age	≤65	1		1	
	>65	1.839 (1.471–2.298)	<.001	1.999 (1.572–2.541)	<.001
Primary site	Cecum	1		1	
	Ascending colon	1.535 (1.094–2.153)	.013	1.559 (1.107–2.193)	.011
	Hepatic flexure of colon	1.366 (0.829–2.252)	.222	1.514 (0.909–2.523)	.111
	Transverse colon	1.711 (1.129–2.593)	.011	1.896 (1.231–2.918)	.004
	Splenic flexure of colon	1.755 (1.053–2.926)	.031	2.227 (1.324–3.746)	.003
	Descending colon	0.732 (0.440–1.218)	.230	0.955 (0.569–1.602)	.862
	Sigmoid colon	0.869 (0.634–1.190)	.381	0.981 (0.706–1.361)	.906
Tumor size	≤3	1		—	—
	3–5	0.945 (0.672–1.330)	.747	—	—
	>5	1.018 (0.732–1.415)	.915	—	—
Grade	Well	1		—	—
	Moderate	0.821 (0.512–1.315)	.411	—	—
	Poor	1.437 (0.876–2.357)	.151	—	—
	Undifferentiated	1.314 (0.682–2.531)	.414	—	—
T stage	T1	1		—	—
	T2	0.347 (0.093–1.294)	.115	—	—
	T3	0.800 (0.296–2.159)	.660	—	—
	T4	1.193 (0.441–3.227)	.729	—	—
N stage	N0	1		1	
	N1	1.165 (0.849–1.600)	.344	0.939 (0.672–1.313)	.714
	N2	1.606 (1.191–2.166)	.002	0.665 (0.431–1.028)	.066
Lymph node positive ratio		3.667 (2.540–5.295)	<.001	8.075 (4.552–14.328)	<.001
Bone metastasis	No	1		1	
	Yes	2.039 (1.231–3.378)	.006	1.341 (0.800–2.247)	.266
Brain metastasis	No	1		1	
	Yes	2.989 (1.585–5.640)	.001	3.367 (1.758–6.448)	<.001

CI = confidence interval, HR = hazard ratio, LuM = lung metastasis without liver metastasis, OS = overall survival.

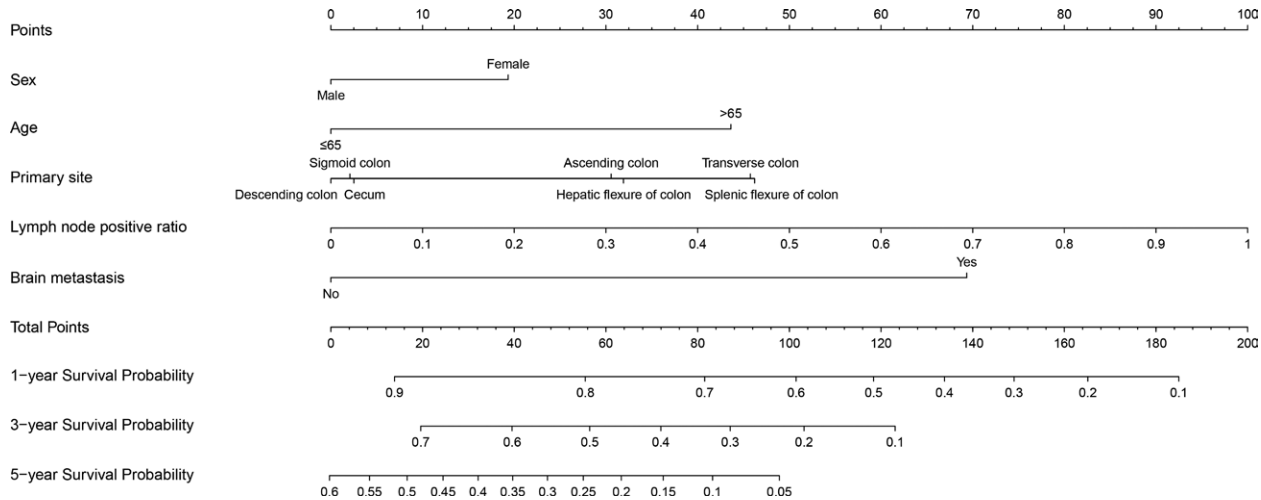

Figure 2 Nomogram for predicting 1-, 3-, and 5-yr OS in patients with colon cancer with LuM. LuM = lung metastasis without liver metastasis, OS = overall survival.

worse survival prognosis as well.[22] In our analysis, for patients with colon cancer with LuM, women had a worse CSS rate than men. But there was no significant difference of gender in OS, which could be explained by the impact of underlying disease. Therefore, more studies are required to verify the effect of gender on prognosis. It is known that different parts of the primitive intestinal tube develop into different parts of the colorectum during embryonic development.[23] Studies have pointed out significant differences in the epidemiology, pathology, and genetics between the left and right colons.[24–26] In our study, the results revealed that colon cancer with LuM, whose primary tumors were located in the hepatic flexure of colon, ascending colon, and transverse colon (right colon) had an inferior prognosis than those located in sigmoid and descending colon (left colon),

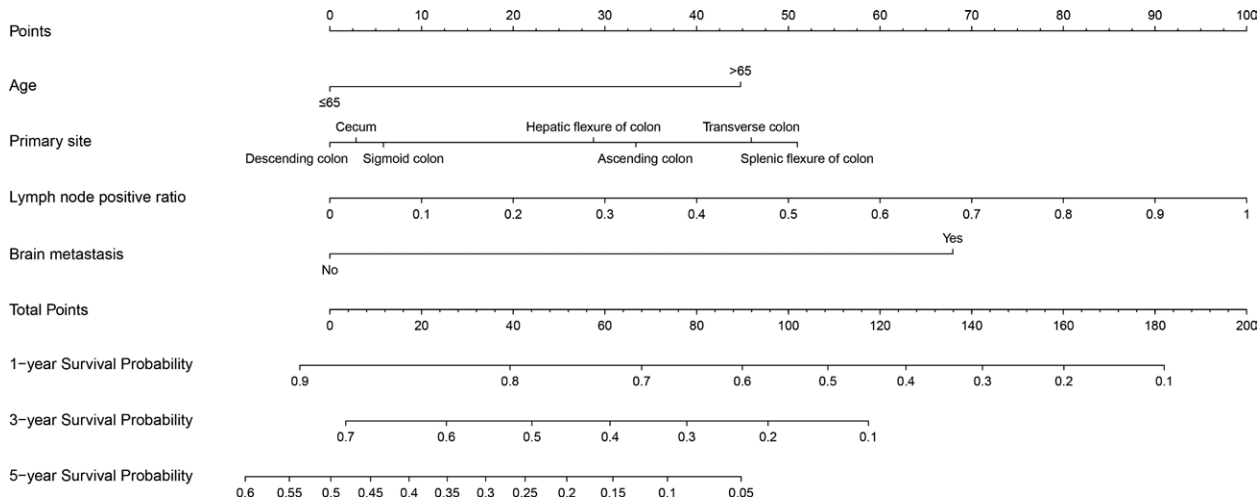

Figure 3 Nomogram for predicting 1-, 3-, and 5-yr CSS in patients with colon cancer with LuM. CSS = cancer-specific survival, LuM = lung metastasis without liver metastasis.

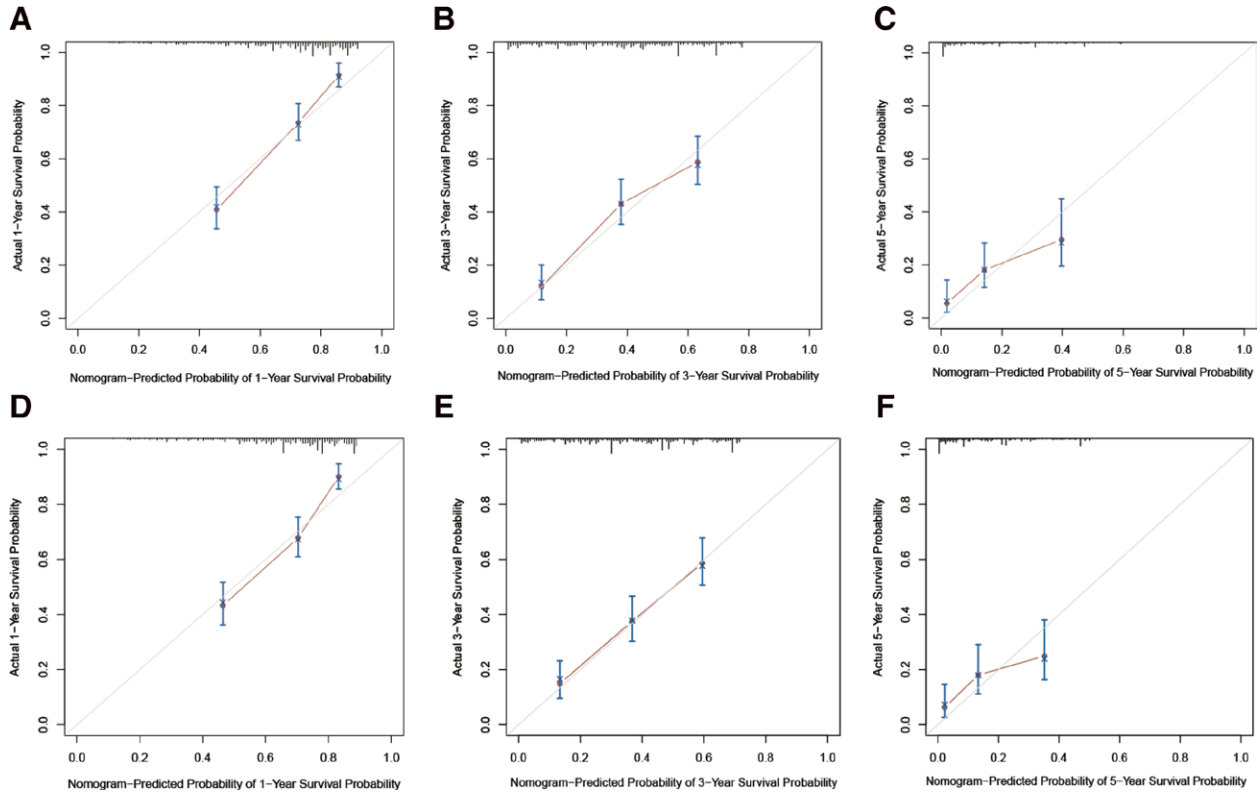

Figure 4 Calibration curves for the nomogram. The calibration curves for predicting 1-, 3-, and 5-yr (A–C) CSS nomogram, and (D–F) OS nomogram, respectively. The horizontal axis was the survival rate predicted by the nomogram model and the vertical axis was the actual survival rate. The closer the solid line was to the dashed line indicated the more accurate prediction of the model. OS = overall survival.

which was consistent with previous studies.[26,27] More notably, we found that in patients with LuM, splenic flexure of colon as the primary site was a strong predictor of poor prognosis. Possible explanations to the result might be as follows: splenic flexure colon has dual lymphatic drainage through the superior mesenteric vein and the inferior mesenteric vein, which could make it harder to surgery; splenic flexure colon cancer has a higher risk of obstruction due to its anatomical location, with increased morbidity and mortality after emergency surgery following obstruction.[28]

The correlation between lymph node metastasis and the prognosis of colon cancer is relatively clear.[29,30] Currently, there are diverse indicators assessing the status of lymph node metastasis, and the most commonly used indicator for clinical assessment of lymph node metastasis is the N stage. Nevertheless, in recent years, many studies have argued that in the current TNM system, the number of lymph nodes detected is ignored in N stage, which is considered as a potential limiting factor to predict cancer survival rate.[31] To crack the nut, many researchers have proposed other strategies to assess lymph node metastasis,

Table 4

: Univariate analysis of patients with LLM and with LuM.

Variable		LLM (n = 950)	LuM (n = 488)	*P* value
Race	White	670 (70.53%)	347 (71.11%)	.133
	Black	183 (19.26%)	78 (15.98%)	
	Other	97 (10.21%)	63 (12.91%)	
Sex	Female	452 (47.58%)	259 (53.07%)	.055
	Male	498 (52.42%)	229 (46.93%)	
Age	≤65	546 (57.47%)	235 (48.16%)	.001
	>65	404 (42.53%)	253 (51.84%)	
Primary site	Cecum	266 (28.00%)	99 (20.29%)	.025
	Ascending colon	167 (17.58%)	93 (19.06%)	
	Hepatic flexure of colon	29 (3.05%)	26 (5.33%)	
	Transverse colon	73 (7.68%)	47 (9.63%)	
	Splenic flexure of colon	43 (4.53%)	24 (4.92%)	
	Descending colon	64 (6.74%)	38 (7.79%)	
	Sigmoid colon	308 (32.42%)	161 (32.99%)	
Tumor size	≤3	81 (8.53%)	70 (14.34%)	.003
	3–5	390 (41.05%)	182 (37.30%)	
	>5	479 (50.42%)	236 (48.36%)	
Grade	Well	32 (3.37%)	29 (5.94%)	.037
	Moderate	660 (69.47%)	317 (64.96%)	
	Poor	205 (21.58%)	121 (24.80%)	
	Undifferentiated	53 (5.58%)	21 (4.30%)	
T stage	T1	2 (0.21%)	6 (1.23%)	<.001
	T2	11 (1.16%)	15 (3.07%)	
	T3	488 (51.37%)	271 (55.53%)	
	T4	449 (47.26%)	196 (40.16%)	
N stage	N0	111 (11.68%)	108 (22.13%)	<.001
	N1	358 (37.68%)	167 (34.22%)	
	N2	481 (50.63%)	213 (43.65%)	
Lymph node positive ratio		0.32 ± 0.29	0.26 ± 0.28	<.001
Bone metastasis	No	883 (92.95%)	469 (96.11%)	.023
	Yes	67 (7.05%)	19 (3.89%)	
Brain metastasis	No	932 (98.11%)	477 (97.75%)	.794
	Yes	18 (1.89%)	11 (2.25%)	

LLM = liver and lung metastases, LuM = lung metastasis without liver metastasis.

such as log ratio of lymph node positivity, lymph node positivity rate, and lymph node negativity rate.[32–34] The lymph node positive ratio is the number of positive lymph nodes to the total number which is considered as a better indicator.[35–37] Its performance is influenced by the total number of lymph nodes dissected. Moreover, it is also controversial how many lymph nodes should be dissected in all. Some scholars believe that lymph node positivity rate can only be used as a prognostic factor when the total number of lymph nodes dissected is more than 12.[36] Interestingly, it has also been maintained that the positive rate of lymph nodes without limiting the total number of lymph nodes affected the prognosis as well.[31,37] In our study, we did not set a minimum standard of the total number of lymph nodes, but our results still supported that lymph node positivity was an independent prognostic factor for patients with LuM.

In terms of anatomy, there are 2 possible pathways for colon cancer to metastasize to the lung, one passes by the liver through the portal vein, and the other passes the vena cava through lymph nodes.[38] The former is more likely to be the mode of LLM. In this study, we found that patients with larger tumor size, worse differentiation, more lymph node metastases, combined with bone metastasis, were more likely to have LLM. It is widely accepted that individuals with these factors tend to have a high tumor primary load, high tumor aggressiveness, and high tumor survivability, and are more likely to develop multiple sites of metastasis. For individuals with risk factors for LuM, postoperative follow-up should be more frequent with chest CT, as we have discussed previously. Most guidelines recommend abdominal CT to assess the progression of abdominal disease,[23] but its sensitivity for liver metastases from colon cancer is relatively low: only 59% for a single lesion, and further decreased if the lesion is less than 1 cm.[39,40] Therefore, when patients with lung metastasis but not definite liver metastasis, have more risk factors associated with LLM, it is vital to take the presence of liver metastasis into consideration. For these patients, we recommend further evaluation with liver MR or FDG PET. If there is still no clear-cut lesion, the follow-up frequency of liver imaging should be increased.

There are certain limitations in this paper: firstly, metastatic lesions in the SEER database were not all verified by pathology, there is a possibility of false positives. Secondly, the genetic mutation status of individuals and the impact of subsequent treatment regimens on prognosis are also untold in this database.

5. Conclusion

We found that race, primary site, tumor size, differentiation, T stage, N stage, and lymph node positivity rate were independent risk factors for the development of LuM in colon cancer. Also, nomogram was established to effectively predict survival of patients with LuM. Finally, by comparing the risk factors between LuM and LLM, we propose different follow-up plans to improve the early detection rate of metastatic lesions so as to obtain the optimal opportunity for treatment and thus improving the prognosis of patients.

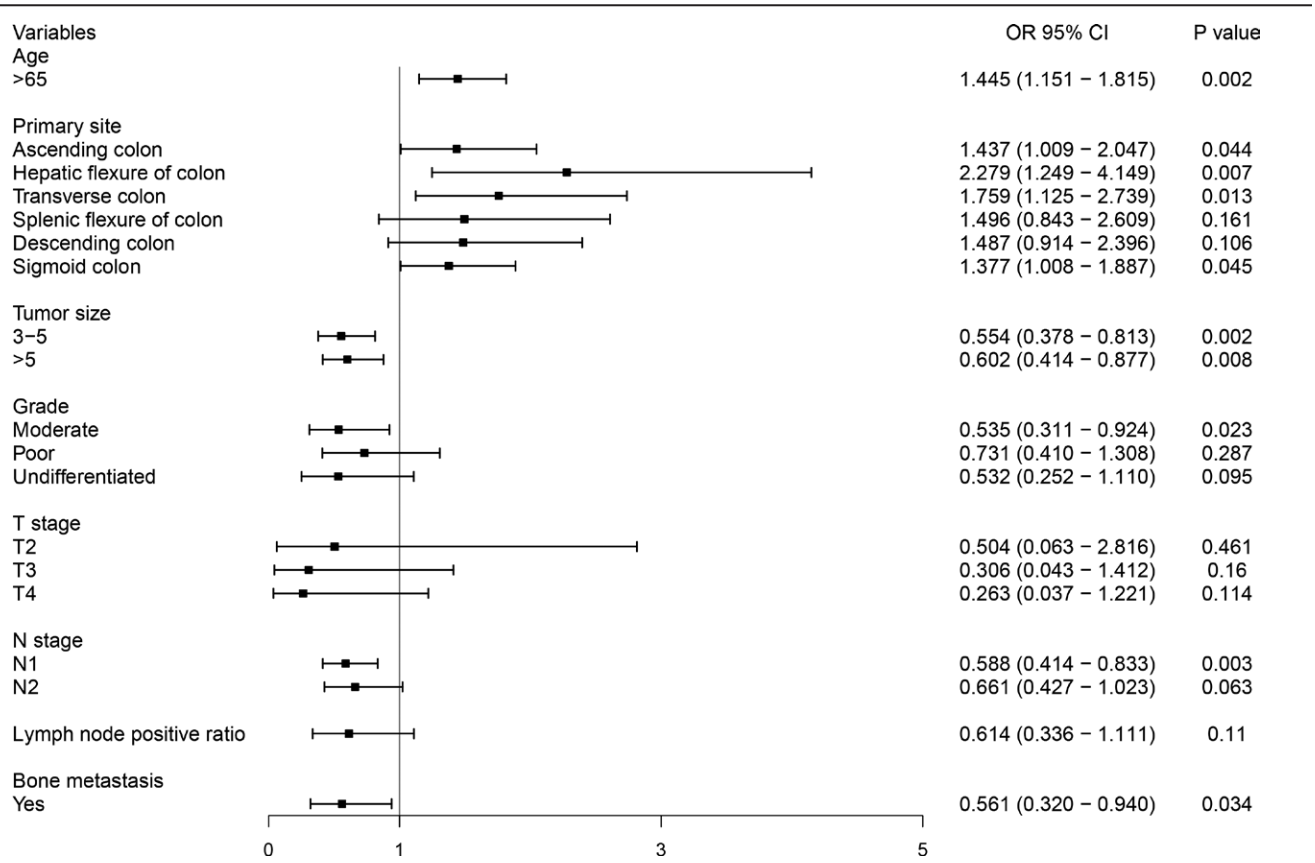

Figure 5 The forest plot for the multivariate analysis between LLM and LuM. LLM = lung metastasis with liver metastasis, LuM = lung metastasis without liver metastasis.

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