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Prognostic value of nomogram based on pre-treatment inflammatory markers in patients with pulmonary-only synchronous metastases from colorectal cancer

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ABSTRACT

Background: The inflammatory markers were important factors affecting proliferation, invasiveness and metastasis of tumors. However, the prognostic value of inflammatory markers and related nomogram in patients with pulmonary-only synchronous metastases (POSM) from colorectal cancer has not been reported.

Materials and methods: A total of 98 POSM patients undergoing resection of colorectal cancer were included. The Kaplan-Meier survival analysis and Cox regression analysis were used to estimate the overall survival (OS) and progression-free survival (PFS). The nomogram was built based on multivariate Cox analysis model and evaluated by calibration curve, concordance index (C-index) and receiver operating characteristics (ROC).

Results: The multivariate analysis showed that neutrophil-to-lymphocyte ratio (NLR) was prognostic factor of OS (HR = 2.73, 95%CI: 1.54–4.84) and PFS (HR = 1.78, 95%CI: 1.13–2.82). Elevated alkaline phosphatase (ALP) also was predictor of poor OS (HR = 1.99, 95%CI: 1.12–3.51) and PFS (HR = 2.23, 95%CI: 1.40–3.55). The early N stage and solitary pulmonary metastases had significant survival benefit for OS, while advanced T stage was independently related with worse PFS. Nomograms were consist of above significant risk factors, with C-index of 0.742 for OS and 0.656 for PFS. The calibration curves showed non-significant deviations between predicted and actual probability of OS and PFS.

Conclusions: Pre-treatment NLR and ALP were independently associated with OS and PFS in POSM patients. The nomograms involving inflammatory markers and clinicopathological factors were practical in predicting survival, which may help to guide use of therapeutic strategy and cancer surveillance.

1. Introduction

Colorectal cancer (CRC) was the fifth most commonly diagnosed cancer and fifth leading cause of cancer-related death for Chinese, with 376,300 new cases and 191,000 deaths in 2015 [1]. The 5-year overall survival (OS) rate of CRC patients was 65% in the United States [2]. Metastatic lesions were found in 20%–25% of newly diagnosed patients, which most likely occur in the liver, followed by lung and other organs [3]. Among patients with synchronous metastases, 11.0% of patients had pulmonary metastases (PM), but only one third of those patients had pulmonary-only synchronous metastases (POSM) [4,5]. The PM patients without standard treatment had a 5-year OS rates of less than 5%, while the pulmonary resection was reported to greatly improve the 5-year OS rate to more than 50% [6,7]. However, few patients with POSM were eligible for the criteria of pulmonary resection, and prognostic factors for POSM patients have not been well defined.

Recent studies suggested that cancer-related inflammation was associated with the genesis, invasion and metastasis of tumors [8]. Thus, the peripheral blood neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and lymphocyte to monocyte ratio (LMR) can reflect the status of inflammation and immunity in patients, which have

Abbreviations: POSM, pulmonary-only synchronous metastases; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; CRC, colorectal cancer; PM, pulmonary metastases; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; CA-125, carbohydrate antigen-125; ROC, receiver operating curve; HR, hazard ratio; CI, confidence intervals; AUC, area under the curve; RFS, recurrence-free survival

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showed significant prognostic value of survival and cancer progression in many cancers, including lung cancer and breast cancer [9,10]. Moreover, the lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) were also reported as prognostic factors [11,12]. Previous research found that increased NLR was associated with poor OS and early lung-specific recurrence in patients undergoing pulmonary metastasectomy [13]. In addition, as a graphical representation of statistic model that predict clinical events via quantifying various risk factors, the nomogram of inflammatory factors was considered to be practical and reliable in patients with colorectal cancer, pancreatic cancer and so on [14,15]. However, the NLR, PLR, LMR, LDH, ALP and inflammatory nomogram have not been systematically estimated in POSM patients. Therefore, it is of great importance to investigate the effectiveness of inflammatory markers for predicting survival outcome and optimizing therapeutic strategy for high-risk POSM patients.

In this study, we retrospectively reviewed 98 patients with POSM from colorectal cancer, and estimated the prognostic role of inflammatory markers (NLR, PLR, MLR, LDH and ALP) and nomogram incorporating inflammatory markers and clinicopathological factors.

2. Methods

2.1. Patients

A database of 7207 CRC patients in the West China Hospital (Sichuan, China) from January 2010 to December 2015 was screened [16]. Patients who met the following criteria were enrolled: (1) patients received surgical resection of primary lesion, and CRC was confirmed by histopathology. (2) Patients were diagnosed with POSM. Synchronous pulmonary metastases were defined as the pulmonary tumors identified prior to or within 3 months after primary colorectal resection [17]. (3) Patients had complete clinical information of laboratory test, radiologic examination and follow-up. Patients with other metastases, infection, hematologic disease or any medication that might affect the inflammatory markers were excluded. The present study was conducted according to REMARK checklist [18].

2.2. Data extraction and follow-up

Clinical data including patients' age at diagnosis, gender, location of primary tumor, histological differentiation, T stage, N stage, PM features and treatment regimens were extracted from electronic medical records. The laboratory data including NLR, PLR, LMR, LDH, ALP, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9) and carbohydrate antigen-125 (CA-125) were collected from peripheral blood within 10 days before first treatment (surgery, chemotherapy or radiotherapy). The pathological stage of CRC patients was classified according to AJCC-TNM stage eighth edition. All patients were followed up until December 2016 or their death. The primary endpoint was overall survival (OS), which was measured from the date of pathologic diagnosis to death. And progression-free survival (PFS), the secondary endpoint, was defined as the period from pathologic diagnosis to objective tumor progression or death.

2.3. Statistical analysis

The receiver operating curve (ROC) analysis was used to calculate the optimal cut-off values of NLR, PLR, LMR, LDH and ALP based on OS. The difference of clinicalopathologic factors between NLR, PLR and LMR groups were compared using Chi squared test. The OS and PFS were estimated by the Kaplan-Meier analysis and compared by the log-rank test. The Cox proportional hazard regression model analysis was performed to obtain the hazard ratio (HR) and 95% confidence interval (CI). The proportional hazards assumptions were checked by log-minus-log plots of log[-log(time)] versus log(time), and non-intersect curves satisfy the assumption [19]. The significant predictors in univariate analysis would be further estimated by multivariate analysis through forward stepwise (Likelihood Ratio) selection, thus only the significant variables were showed with HR and 95% CI. Above statistical analyses were conducted on SPSS version 21.0 and p value of < 0.05 was defined as statistically significant.

According to the results of multivariate Cox analysis, the nomograms were established by "rms" package in R version 3.5.3 (http://www.r-project.org/) with endpoints of 1-year, 3-year and 5-year OS and PFS. The Harrell's concordance index (C-index) and ROC analysis were used to estimate the discriminative performance of nomogram. Larger C-index represents higher probability of concordance, whereas C-index of 0.5 indicates accidental consistence. The calibration curves were measured by bootstrapping validation with 1000 resamples, which could quantify predictive accuracy of nomograms. The difference between predicted survival and actual survival was tested by the Hosmer-Lemeshow test. These analyses were conducted using R version 3.5.3, and a value of $p < 0.05$ suggested statistically significant.

3. Results

3.1. Cut-off values of inflammatory markers

The areas under the curve (AUCs) of NLR, PLR, LMR, LDH and ALP were 0.622 (95%CI: 0.508–0.736, p = 0.037), 0.548 (95%CI: 0.432–0.664, p = 0.414), 0.521 (95%CI: 0.405–0.637, p = 0.722), 0.605 (95%CI: 0.429–0.717, p = 0.075) and 0.615 (95%CI: 0.524–0.766, p = 0.046) in ROC analysis for overall survival, respectively. The optimal cut-off value was 3 for NLR, 162 for PLR, 4.3 for LMR, 212 (U/L) for LDH and 79 (U/L) for ALP based on maximum sum of specificity and sensitivity. Serum CEA ≥ 3.4 (ng/ml), CA19-9 ≥ 22 (U/ml) and CA-125 ≥ 35 (U/ml) were considered as elevated-level groups according to reference value of examinations.

3.2. Baseline characteristics of patients

A total of 7207 CRC patients were assessed for inclusion, and 1058 (14.7%) patients had synchronous metastases. Among them 361 (34.1%) cases had pulmonary lesions, and pulmonary-only metastases were present in 125 patients. Sixteen patients without key data of inflammatory markers, 5 patients with infection, 4 patients with hematologic disease and 2 patients lost to follow-up were excluded. Finally, 98 POSM patients were enrolled in present study. There were 65 (66.3%) male and 33 (33.7%) female with median age at diagnosis of 60 years old (range 26–83 years). In terms of PM, median diameter of the largest lung tumor was 1.6 cm (range 0.2–5.4 cm). And 21 (21.4%) patients suffered from solitary nodules, whereas 77 (78.6%) patients had multiple tumors. Pulmonary resection was performed by video assisted thoracic surgery (VATS). The adjuvant therapies included intensity-modulated radiation therapy (IMRT) and 5-FU based chemotherapy (FOLFOX, FOLFIRI or XELOX). Targeted therapy contained Erbitux/cetuximab and Avastin/bevacizumab. The clinicopathological characteristics grouped by NLR, PLR and LMR were showed in Table 1. Significant differences were found in the distribution of primary tumor location between high and low groups (all $p < 0.05$). Compared with low-level LMR group, there were more patients had unilateral PM in high-level LMR group (p = 0.034). More patients underwent adjuvant chemotherapy in low-level LMR group (p = 0.034).

3.3. Univariate analysis of inflammatory markers

The results of univariate analysis were summarized in Table 2. No patient was lost to follow-up. The median period of follow-up was 24 months (range 4–75 months). On the last follow-up, 50 (51.0%) patients were died in this study. The cumulative 1-year, 3-year and 5-year OS rates were 73.5%, 49.3% and 35.6%, respectively. There were 78 (79.6%) patients had evidence of cancer progression. Eighteen, 39

Table 1
Baseline characteristics of patients.

Variables	Parameters	NLR		p	PLR	PLR	p	LMR	LMR	p
		< 3 (%)	≥3 (%)		< 162 (%)	≥162 (%)		< 4.3 (%)	≥4.3 (%)	
Age (year)	< 60	31 (51.7)	16 (42.1)		29 (43.9)	18 (56.3)		21 (45.7)	26 (50.0)	
	≥60	29 (45.3)	22 (57.9)	0.356	37 (56.1)	14 (43.7)	0.253	25 (54.3)	26 (50.0)	0.667
Gender	Male	39 (65.0)	26 (68.4)		44 (66.7)	21 (65.6)		12 (26.1)	21 (40.4)	
	Female	21 (35.0)	12 (31.6)	0.727	22 (33.3)	11 (34.4)	0.918	34 (80.9)	31 (59.6)	0.135
Primary tumor	Colon	17 (28.3)	26 (68.4)		22 (33.3)	21 (65.6)		25 (54.3)	18 (34.6)	
	Rectum	43 (71.7)	12 (31.6)	< 0.001*	44 (66.7)	11 (34.4)	0.003*	21 (45.7)	34 (65.4)	0.049*
Histology	Well-Moderate	40 (66.7)	23 (60.5)		39 (59.1)	24 (75.0)		29 (63.0)	34 (65.4)	
	Poor	20 (33.3)	15 (39.5)	0.536	27 (40.9)	8 (25.0)	0.335	17 (37.0)	18 (34.6)	0.809
T classification	T2-T3	28 (46.7)	18 (47.4)		31 (47.0)	15 (46.9)		22 (47.8)	24 (46.2)	
	T4	32 (53.3)	20 (52.6)	0.946	35 (53.0)	17 (53.1)	0.993	24 (52.2)	28 (53.8)	0.869
N classification	N0	15 (25.0)	7 (18.4)		15 (22.7)	7 (21.9)		11 (23.9)	10 (19.2)	
	N1-N2	45 (75.0)	31 (81.6)	0.447	51 (77.3)	25 (78.1)	0.707	35 (76.1)	42 (80.8)	0.573
Pulmonary metastases	Solitary	14 (23.3)	7 (18.4)		15 (22.7)	8 (25.0)		6 (13.0)	15 (28.8)	
	Multiple	46 (76.7)	31 (81.6)	0.792	51 (77.3)	24 (75.0)	0.803	40 (87.0)	37 (71.2)	0.057
Pulmonary lesions	Unilateral	19 (31.7)	8 (21.1)		19 (28.8)	8 (25.0)		8 (17.4)	19 (36.5)	
	Bilateral	41 (68.3)	30 (78.9)	0.252	47 (71.2)	24 (75.0)	0.694	38 (82.6)	33 (63.5)	0.034*
Maximum tumor size	< 2 cm	39 (65.0)	27 (71.1)		45 (68.2)	21 (65.6)		31 (67.4)	35 (76.1)	
	≥2 cm	21 (35.0)	11 (28.9)	0.543	21 (31.8)	11 (34.4)	0.800	15 (32.6)	17 (36.9)	0.993
Preoperative therapy	No	47 (78.3)	28 (73.7)		53 (80.3)	22 (68.8)		35 (76.1)	40 (76.9)	
	Yes	13 (21.7)	10 (26.3)	0.597	13 (19.7)	10 (31.2)	0.206	11 (23.9)	12 (23.1)	0.992
Adjuvant chemotherapy	No	6 (10.0)	10 (26.3)		8 (12.1)	8 (25.0)		10 (21.7)	6 (11.5)	
	Yes	54 (90.0)	28 (73.7)	0.033*	58 (87.9)	24 (75.0)	0.106	36 (78.3)	46 (88.5)	0.173
Adjuvant radiotherapy	No	38 (63.3)	29 (76.3)		43 (65.2)	24 (75.0)		33 (71.7)	34 (65.4)	
	Yes	22 (36.7)	9 (23.7)	0.178	23 (34.8)	8 (25.0)	0.326	13 (28.3)	18 (34.6)	0.500
Pulmonary resection	No	51 (85.0)	31 (81.6)		57 (86.4)	25 (78.1)		39 (84.8)	43 (82.7)	
	Yes	9 (15.0)	7 (18.4)	0.655	9 (13.6)	7 (21.9)	0.301	7 (15.2)	9 (17.3)	0.780
Targeted therapy	No	50 (83.3)	29 (76.3)		55 (83.3)	24 (75.0)		39 (84.8)	42 (80.8)	
	Yes	10 (16.7)	9 (23.7)	0.392	11 (16.7)	8 (25.0)	0.328	7 (15.2)	10 (19.2)	0.967

NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, LMR lymphocyte-monocyte ratio, LDH lactate dehydrogenase, ALP alkaline phosphatase.
* Statistically significant $p < 0.05$.

and 15 patients developed local recurrence, PM progression and new distant metastases. The cumulative 1-year, 3-year and 5-year PFS rates were 41.8%, 17.6% and 15.9%, respectively.

Patients with elevated NLR showed significantly worse 5-year OS and 3-year PFS than low NLR group. The univariate HR and 95%CI was 2.60 (1.48–4.56, p = 0.001) for OS and 1.63 (1.04–2.56, p = 0.035) for PFS. The result also reflected additional OS benefiting from low PLR with HR of 1.81 (95%CI: 1.02–3.20, p = 0.041). However, the PLR failed to have significant prognostic value of PFS. As for LMR, neither the OS nor the PFS showed any statistical difference. Both elevated LDH and ALP were associated with poor OS. The HR and 95%CI was 2.18 (1.17–4.05, p = 0.014) of LDH groups and 1.80 (1.03–3.15, p = 0.038) of ALP groups. Regarding the PFS, significant differences were not found in LDH groups. Only ALP predicted the PFS with HR of 1.99 (95%CI: 1.27–3.14, p = 0.003). The results of Kaplan-Meier survival curves were showed in Fig. 1 and Fig. 2.

3.4. Univariate analysis of clinicopathologic factors

In terms of OS, the location of primary tumor (p = 0.004), N stage (p = 0.022), PM number (p = 0.019) and pulmonary lesions (p = 0.024) were found statistically significant. In addition, T stage (p = 0.007) and N stage (p = 0.020) showed significant prognostic effects on PFS. Our results indicated the elevated CA19-9 was considerably related with worse OS (HR = 2.06, 95%CI: 1.03–4.15, p = 0.042). There was significant difference of OS between high and normal CA-125 groups (p = 0.004), but few patients with CA-125 ≥ 35 affected the validity of result.

3.5. Multivariate analysis of prognostic factors

The results supported that NLR (HR = 2.73, 95%CI: 1.54–4.84, p = 0.001), ALP (HR = 1.99, 95%CI: 1.12–3.51, p = 0.018), N stage (HR = 2.38, 95%CI: 1.06–5.35, p = 0.037) and PM (solitary vs. multiple, HR = 2.92, 95%CI: 1.29–6.58, p = 0.010) were independent predictors of OS (Table 3). With regard to PFS, NLR ≥ 3 (HR = 1.78, 95%CI: 1.13–2.82, p = 0.014), ALP ≥ 79 (HR = 2.23, 95%CI: 1.40–3.55, p = 0.001) and advanced T stage (HR = 1.99, 95%CI: 1.26–3.16, p = 0.003) were independently associated with worse PFS (Table 3).

3.6. Predictive accuracy of nomogram

According to the multivariate analysis, independent risk factors were involved in nomograms, including T stage, N stage, pulmonary metastases, NLR and ALP (Fig. 3). Each scale was corresponding to different points, then estimated probabilities of death and cancer progression could be calculated by total points. The C indexes of nomogram were 0.742 (95%CI: 0.680–0.804) for OS and 0.656 (95%CI: 0.595–0.717) for PFS. Moreover, the nomogram achieved AUC of 0.715 (95%CI: 0.615–815, p < 0.001) in 5-year OS and 0.760 (95%CI: 0.648–0.872, p < 0.001) in 5-year PFS, which were significantly higher than T stage and N stage (Fig. 4). The calibration curves and Hosmer-Lemeshow test (OS: P = 0.661, PFS: P = 0.952) showed non-significant deviations between predicted probability and actual observation (Fig. 5).

4. Discussion

Previous studies have proved that tumor-related immune response has important effect on tumor progression [20]. Chronic inflammation can cause genotoxic stress, which may induce cancer cell proliferation, increase angiogenesis and tissue infiltration that favors the spread of tumor [21]. Several inflammatory markers, such as NLR, PLR and LMR, have been suggested as independent prognostic factors in nonmetastatic and metastatic CRC as well as colorectal liver metastases [22,23].

Table 2
Univariate Cox analysis of factors associated with survival.

Variables	Parameters	n	Overall survival (%)					Progression-free survival (%)				
			3-year	5-year	P^1	HR (95% CI)	P^2	1-year	3-year	P^1	HR (95% CI)	P^2
Overall	–	98	49.3	35.6	–	–	–	41.8	17.6	–	–	–
Age (year)	< 60	47	13.6	40.6		1		38.3	13.2		1	
	≥60	51	54.9	33.7	0.738	0.91 (0.52–1.59)	0.740	45.1	21.2	0.381	0.83 (0.53–1.29)	0.398
Gender	Male	65	47.5	32.4		1		40.0	14.9		1	
	Female	33	47.7	47.7	0.727	0.90 (0.49–1.65)	0.730	45.5	22.6	0.390	0.82 (0.51–1.32)	0.407
Primary tumor	Colon	43	35.5	26.6		1		37.2	14.9		1	
	Rectum	55	60.1	42.9	0.003*	0.44 (0.25–0.77)	0.004*	45.5	18.8	0.129	0.72 (0.46–1.12)	0.145
Histology	Well-Moderate	63	48.5	33.7		1		34.9	14.5		1	
	Poor	35	45.7	40.0	0.991	1.00 (0.56–1.79)	0.991	51.3	24.2	0.052	0.63 (0.39–1.03)	0.063
T stage	T2-T3	46	62.5	43.2		1		54.3	25.6		1	
	T4	52	31.6	–	0.050	1.75 (0.99–3.12)	0.056	30.8	9.7	0.004*	1.87 (1.19–2.96)	0.007*
N stage	N0	22	69.3	46.2		1		50.0	38.9		1	
	N1-N2	76	43.5	33.8	0.016*	2.56 (1.15–5.71)	0.022*	35.5	11.7	0.014*	2.05 (1.12–3.74)	0.020*
Pulmonary metastases	Solitary	21	67.5	60.0		1		52.4	37.5		1	
	Multiple	77	41.6	26.9	0.014*	2.63 (1.18–5.87)	0.019*	39.0	11.8	0.071	1.67 (0.93–2.99)	0.084
Pulmonary lesions	Unilateral	27	68.2	56.0		1		51.9	28.8		1	
	Bilateral	71	41.7	26.6	0.019*	2.23 (1.11–4.48)	0.024*	40.8	13.0	0.257	1.33 (0.80–2.21)	0.275
Maximum tumor size	< 2 cm	66	56.3	43.7		1		42.4	22.3		1	
	≥2 cm	32	36.9	27.7	0.357	1.31 (0.74–2.31)	0.363	40.6	7.4	0.201	1.34 (0.84–2.13)	0.219
Preoperative therapy	No	75	54.0	39.9		1		48.0	17.7		1	
	Yes	23	33.5	–	0.048*	1.82 (0.99–3.36)	0.055	30.4	17.4	0.493	1.19 (0.71–2.00)	0.509
Adjuvant chemotherapy	No	16	49.2	49.2		1		31.3	–		1	
	Yes	82	54.1	37.6	0.099	0.53 (0.25–1.15)	0.110	43.9	20.8	0.113	0.64 (0.36–1.14)	0.130
Adjuvant radiotherapy	No	67	47.3	43.3		1		40.3	23.2		1	
	Yes	31	50.3	27.9	0.586	0.85 (0.47–1.53)	0.591	45.2	8.7	0.777	1.07 (0.67–1.70)	0.785
Pulmonary resection	No	82	46.9	31.5		1		39.0	17.7		1	
	Yes	16	61.9	46.4	0.332	0.69 (0.32–1.48)	0.339	43.8	18.8	0.548	0.84 (0.46–1.52)	0.562
Targeted therapy	No	79	48.9	33.1		1		40.5	16.5		1	
	Yes	19	50.2	50.2	0.500	0.77 (0.36–1.68)	0.506	42.1	21.1	0.514	0.83 (0.47–1.48)	0.529
NLR	< 3	60	60.3	42.5		1		45.0	26.1		1	
	≥3	38	31.2	18.7	< 0.001*	2.60 (1.48–4.56)	0.001*	36.8	3.8	0.027*	1.63 (1.04–2.56)	0.035*
PLR	< 162	66	56.1	44.4		1		43.9	17.2		1	
	≥162	32	34.4	28.5	0.036*	1.81 (1.02–3.20)	0.041*	37.5	19.1	0.138	1.28 (0.80–2.05)	0.306
LMR	< 4.3	46	40.5	23.6		1		43.5	14.3		1	
	≥4.3	52	51.1	47.1	0.056	0.59 (0.34–1.03)	0.062	40.4	20.1	0.551	0.88 (0.56–1.37)	0.566
LDH (U/L)	< 212	77	54.4	37.2		1		42.9	19.2		1	
	≥212	21	30.9	30.9	0.011*	2.18 (1.17–4.05)	0.014*	38.1	11.9	0.296	1.31 (0.77–2.22)	0.314
ALP (U/L)	< 79	58	53.8	47.0		1		51.7	25.9		1	
	≥79	40	38.3	23.9	0.034*	1.80 (1.03–3.15)	0.038*	27.5	5.8	0.002*	1.99 (1.27–3.14)	0.003*
CEA[a] (ng/ml)	< 3.4	27	55.3	33.5		1		44.4	25.9		1	
	≥3.4	64	51.8	39.0	0.594	1.19 (0.63–2.23)	0.559	40.6	16.8	0.221	1.37 (0.81–2.29)	0.239
CA19-9[b] (U/ml)	< 22	35	64.4	58.5		1		48.6	27.2		1	
	≥22	38	42.8	27.7	0.036*	2.06 (1.03–4.15)	0.042*	36.8	12.1	0.097	1.53 (0.91–2.60)	0.112
CA-125[c] (U/ml)	< 35	53	55.4	48.7		1		43.4	214		1	
	≥35	7	–	–	0.004*	3.53 (1.39–8.95)	0.008*	14.3	–	0.149	1.77 (0.78–3.99)	0.171

HR hazard ratio, CI confidence interval, NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, LMR lymphocyte-monocyte ratio, LDH lactate dehydrogenase, ALP alkaline phosphatase, CEA carcinoembryonic antigen, CA19-9 carbohydrate antigen 19-9, CA-125 carbohydrate antigen-125.

[1] The p value for log-rank test.

[2] The p value for HR in Cox analysis.

[a] 91 were available.

[b] 73 were available.

[c] 60 were available.

* Statistically significant $p < 0.05$.

Considering the convenience and non-invasive property, peripheral inflammatory markers have great research potential and value. However, patients with POSM are relatively uncommon due to the discrete metastatic process that mostly involving the liver firstly, the lungs secondly and other locations finally [4,5]. Thus compared with colorectal liver metastases, the prognostic effect of inflammatory factors in POSM patients has not been fully estimated. In present study, we indicated that pre-treatment inflammatory markers were also independent predictors of survival for the first time in CRC patients with POSM.

It found that numerous neutrophils would infiltrate in cancerous tissue, and peripheral neutrophils were also significantly higher in cancer patients than healthy adults [24]. In tumor microenvironment, neutrophils can be classified into N1 and N2 phenotype by TGF-beta signaling [25]. The N2 phenotype of neutrophils can produce vascular endothelial growth factor (VEGF) and metalloproteinases to promote tumor angiogenesis, invasiveness and metastasis [26]. By contrast, lymphocytes play an important part in antitumor immunity [27]. Thus the elevated NLR indicated relative increase of neutrophils and decrease of lymphocytes, thereby was associated with enhanced risk of tumor progression and worse survival. Previously, NLR was suggested as prognostic factor for OS and recurrence-free survival (RFS), but only independent predictor of RFS [13]. Our results supported that pre-treatment NLR was feasible to independently predict OS and PFS of POSM patients. The difference of results may be attributed to the patients' characteristics and treatment regimens. Previous study included patients with pulmonary metastases only or combined with liver metastases, and all patients received pulmonary metastasectomy [13].

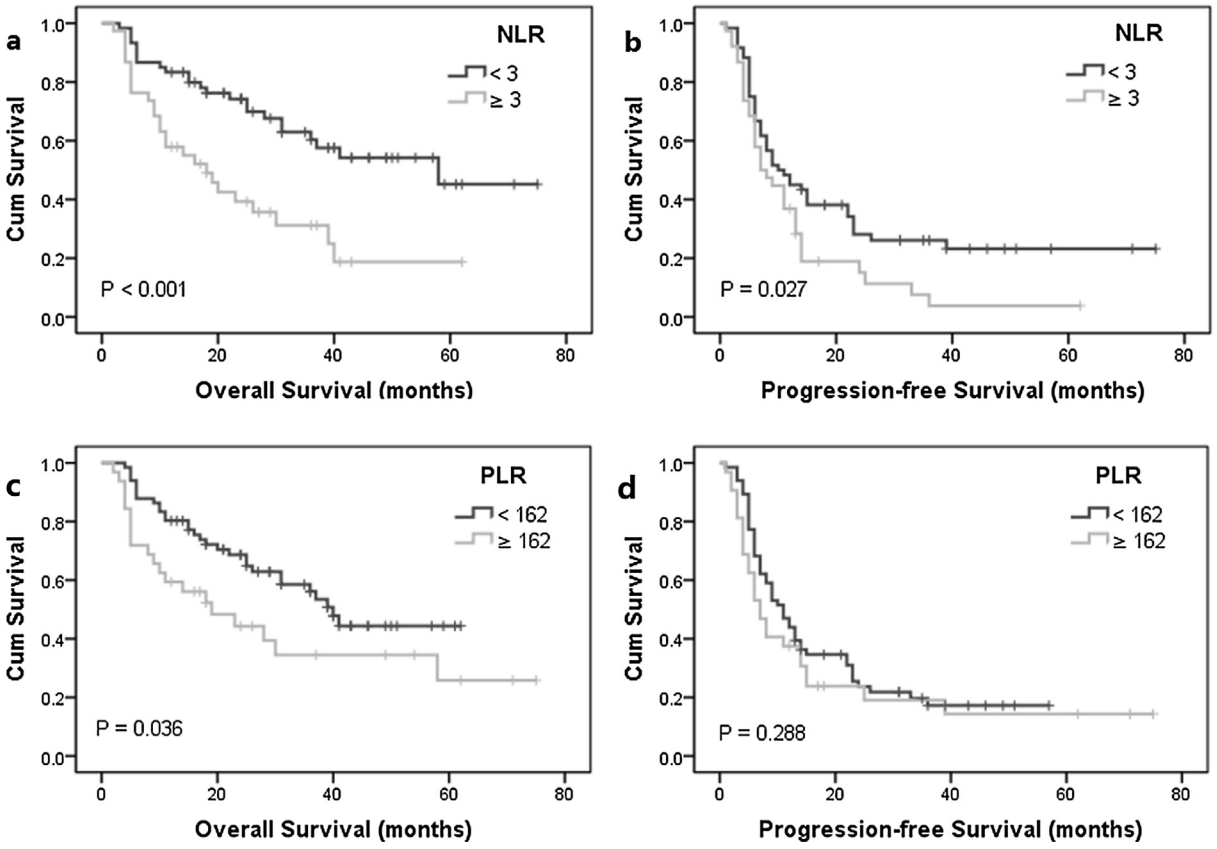

Fig. 1. Kaplan-Meier curves of OS (a) and PFS (b) for NLR. Kaplan-Meier curves of OS (c) and PFS (d) for PLR.

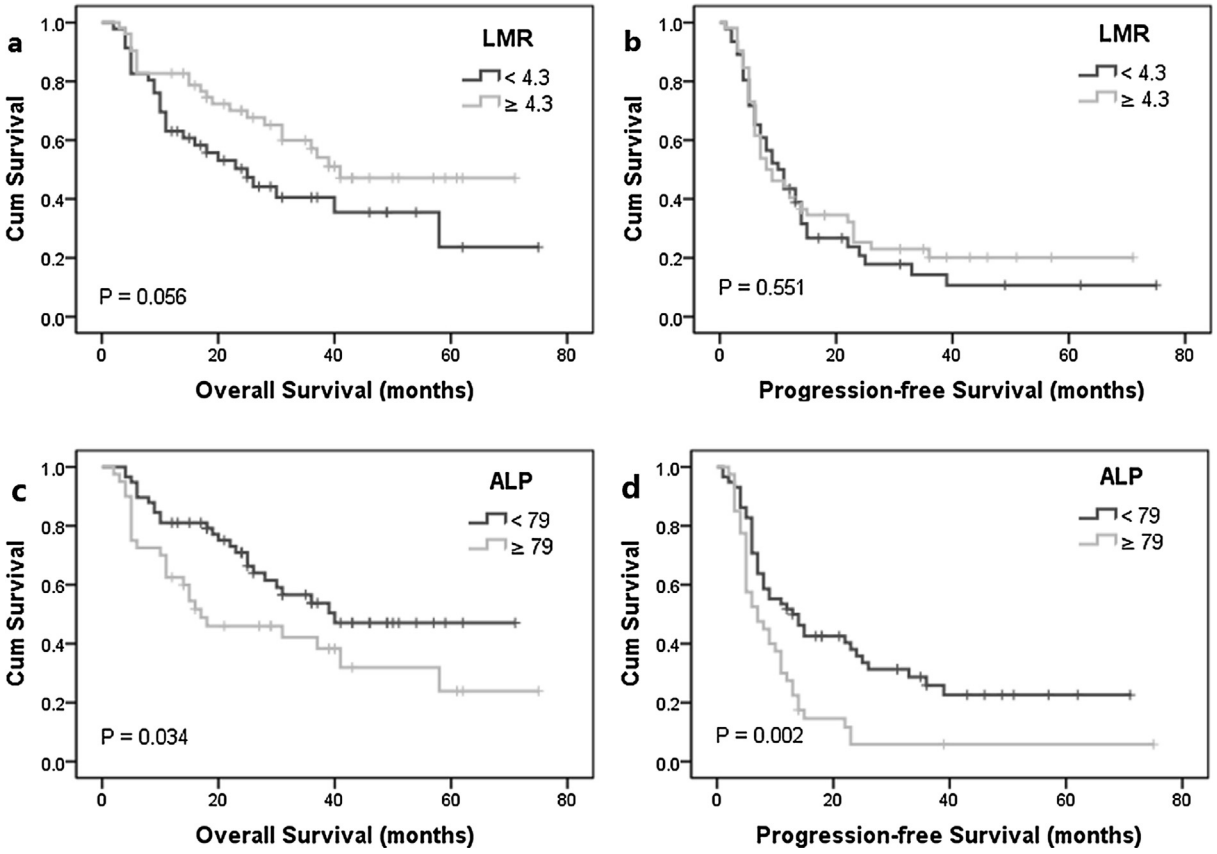

Fig. 2. Kaplan-Meier curves of OS (a) and PFS (b) for LDH. Kaplan-Meier curves of OS (c) and PFS (d) for ALP.

Table 3
Multivariate Cox analysis of factors associated with survival.

Variables	Parameters	Overall survival		Progression-free survival	
		HR (95% CI)	*p*	HR (95% CI)	*p*
Primary tumor	Colon vs. Rectum	–	0.053		
T stage	T2-T3 vs. T4			1.99 (1.26–3.16)	0.003*
N stage	N0 vs. N1-N2	2.38 (1.06–5.35)	0.037*	–	0.203
Pulmonary metastases	Solitary vs. Multiple	2.92 (1.29–6.58)	0.010*		
Pulmonary lesions	Unilateral vs. Bilateral	–	0.774		
NLR	< 3 vs. ≥3	2.73 (1.54–4.84)	0.001*	1.78 (1.13–2.82)	0.014*
PLR	< 162 vs. ≥ 162	–	0.094		
LDH	< 212 vs. ≥ 212	–	0.788		
ALP	< 79 vs. ≥79	1.99 (1.12–3.51)	0.018*	2.23 (1.40–3.55)	0.001*

HR hazard ratio, CI confidence interval, NLR neutrophil-lymphocyte ratio, PLR platelet-lymphocyte ratio, LDH lactate dehydrogenase, ALP alkaline phosphatase.
* Statistically significant $p < 0.05$.

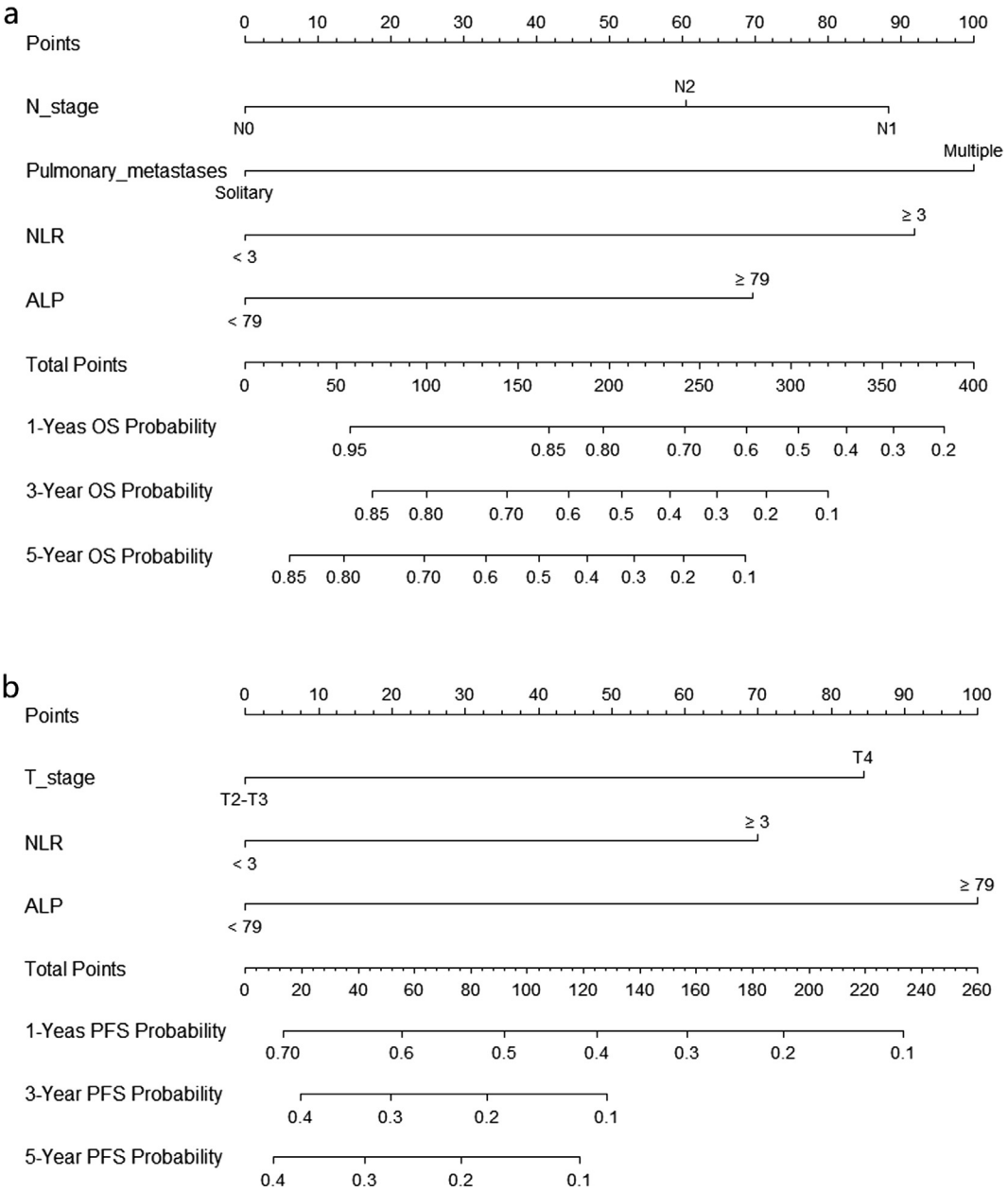

Fig. 3. Nomograms for predicting probability of 1-year, 3-year, 5-year OS (a) and PFS (b).

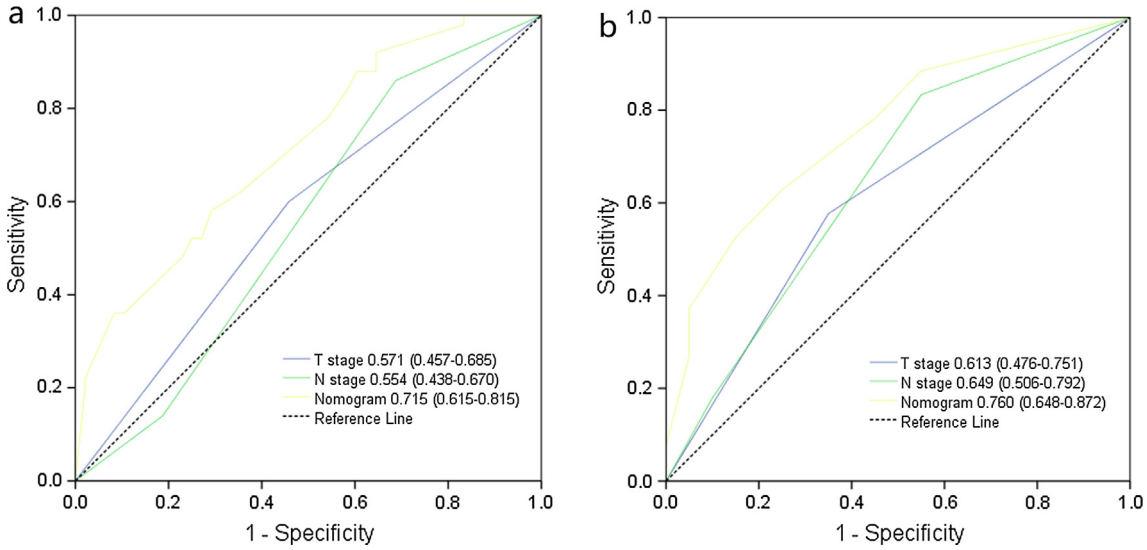

Fig. 4. Predictive performance of nomograms for 5-year OS (a) and PFS (b) were compared with T stage and N stage by ROC curves.

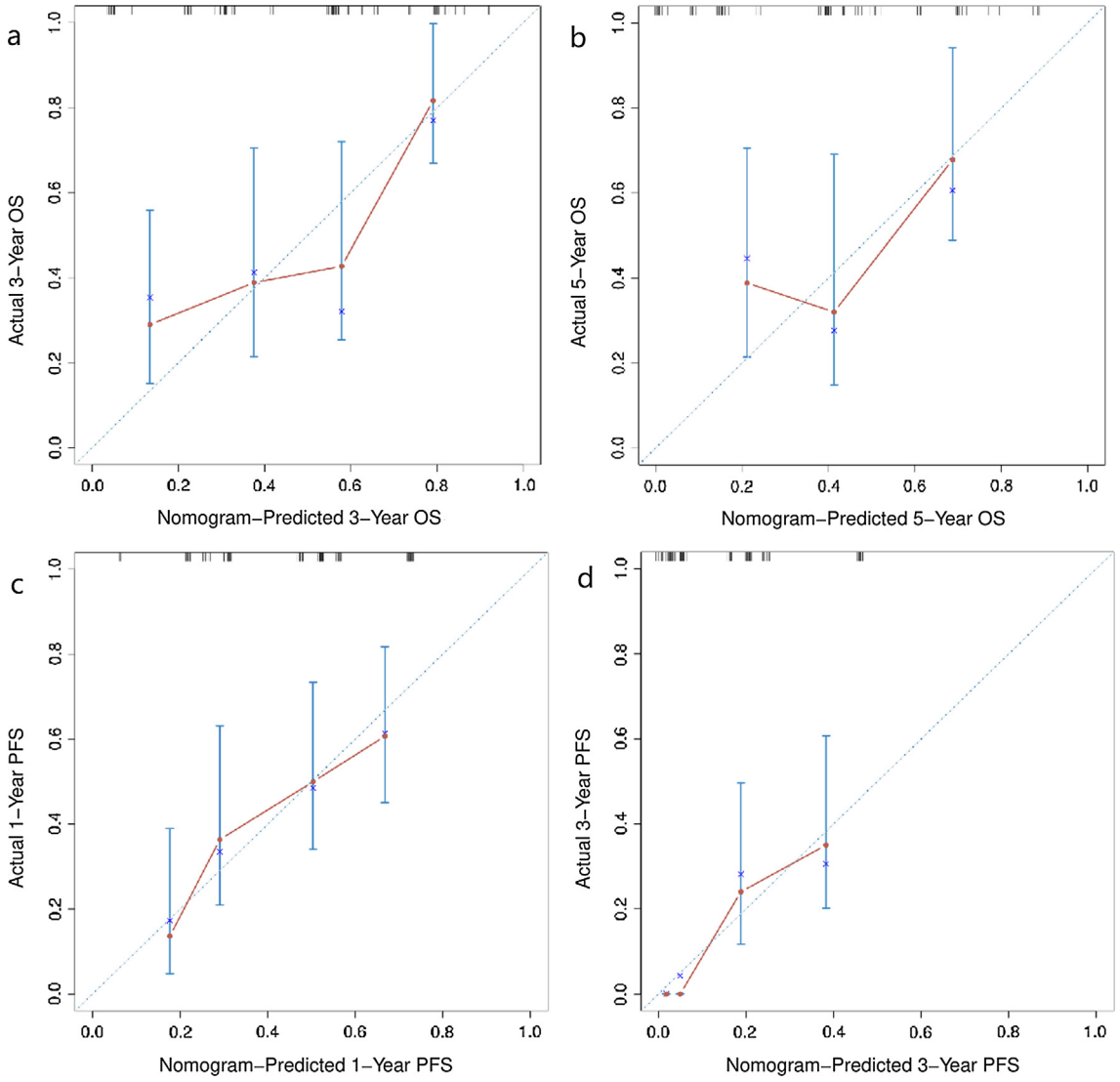

Fig. 5. The calibration curves of nomograms for 3-year OS (a), 5-year OS (b), 1-year PFS (c) and 3-year PFS (d).

However, we focused on POSM patients, and most patients didn't have pulmonary resection. Therefore, more studies should be conducted to determine whether the inflammatory markers could be applied to wider patient population or not.

Platelets were reported to promote angiogenesis via secreting VEGF, inhibit NK cells via secreting TGF-beta, and form the platelets-tumor cell complexes to help immune escape of tumor cells [28,29]. Similarly, monocytes also have important effect on tumor progression via several proinflammatory cytokines [30]. In CRC patients, some studies suggested PLR and LMR as independent predictors [3,23], while it was not agreed in other studies [31,32]. A *meta*-analysis including 32 studies concluded that LDH was inversely associated with OS but not with PFS [33]. The ALP was often discussed in bone metastatic tumors and less reported in CRC [34]. In present study, pre-treatment PLR, LMR and LDH were not independent prognostic markers in multivariate analysis, except for ALP. The inevitable heterogeneity between studies could influence the consistency of results. No final conclusion has yet been reached on the prognostic value of those inflammatory indexes, which still needs more research.

According to previous research, pulmonary metastasectomy was beneficial for PM patients with increased 5-year OS rate of 52.5% [7]. However, there existed possible selection bias due to the surgical indications that ensure technically feasible resection with tolerable risks [35]. Our results showed a tendency of improved OS in a small number of patients undergoing pulmonary resection (46.4% vs. 31.5%), whereas it was not significantly different ($p = 0.332$). There is still a lack of prospective studies to confirm the efficacy of pulmonary resection.

Pre-treatment CEA level and number of lung lesions were considered as independent risk factors affecting the survival in CRC patients received lung resection [6,36]. As a type of glycoprotein normally produced in gastrointestinal cells during embryonic development, CEA is used as a tumor marker especially for CRC. However, some advanced tumors may not cause abnormal blood elevations. Serum CEA failed to show prognostic significance in this study. However, We found that normal CA19-9 had potential survival benefit for patients. CA19-9 is also a gastrointestinal tumor marker, which was reported as independent prognostic indicator of metastatic CRC [37]. We also found that prognosis of patients with solitary PM was significantly better than those with multiple PM, and number of PM was independent predictor of OS. Therefore, it was suggested that more active intervention should be performed for POSM patients with multiple PM and elevated tumor markers.

Nomogram is an alignment diagram consisting of different lines with scale, which generates a total point to predict probability of clinical event. Nomogram transforms the complex regression model into a visual graph, which is more practical and convenient to evaluate the patients. Therefore, nomogram has received more and more attention and been suggested as an alternative standard compared with TNM staging system [38]. In this study, we established nomograms for OS and PFS by incorporating significant inflammatory markers and clinicopathological characteristics. The results of C-index, AUC and calibration curve showed the reliable discriminative performance and predictive accuracy of nomograms. Moverover, its accuracy of ROC was significantly higher than TNM staging system. The nomogram have the potential to be reliable model for predicting survival and progression in POSM patients, but it still requires more research.

There were several limitations in this study. Firstly, although there were no significant differences in Chi squared test, the various therapeutic strategies that influenced the disease development, could act as a potential confounder of prognostic analyses. Secondly, this study was limited by small sample of patients in single-center that may cause selection bias. The lack of data including tumor markers might decrease the accuracy and reliability of results. Furthermore, the present study was retrospective, thus large-scale prospective and multi-center studies were needed for better estimation.

5. Conclusions

In conclusion, pre-treatment NLR and ALP were independent prognostic factors of OS and PFS in POSM patients. Elevated level of PLR and LDH were significantly associated with worse OS but not with PFS. The nomogram act as a simple and effective model, which may help to guide use of therapeutic strategy and cancer surveillance.

Ethics approval and consent to participate

This study was approved by the institution Ethics Commission of West China Hospital of Sichuan University. The need for consent to participate was waived by Ethics Commission of West China Hospital of Sichuan University.

Data availability statement

The data were available from the corresponding author on reasonable request.

Funding Statement

The authors declare no funding.

Authors' contributions

LC collected, analyzed the data and wrote the article. XM designed the study. QL analyzed the data. YW and JY contributed to the data of medical records and follow-up. All authors revised and approved the article.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.106001.

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