

Characteristics and prognosis of primary malignant melanoma of the esophagus

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Abstract

Primary malignant melanoma of esophagus (PMME) is a rare malignant tumor of esophagus. This study aimed to investigate the clinic pathologic characteristics and analyze the factors that might affect the prognosis of PMME patients.

A total of 20 PMME patients who underwent surgical treatment in our hospital from 1975 to 2017 were analyzed. The clinical data, surgical and pathologic features of all patients were collected.

For 20 PMME patients, the average age was 57.3 ± 10.7 years, and the male patients account for 75%. Most of the tumors (95%) were located in the middle and lower of the esophagus. There were 7 patients with primary tumor invasion beyond the muscular layer (T3 + T4) and 10 patients with lymph node metastasis (LNM). The median survival time of 20 patients was 12 months, and the 1-year and 5-year survival rates were 50% and 16.9%, respectively. The probability of LNM in tumors confined to submucosa (T1) and myometrium (T2) was lower than that in tumors with deeper invasion (T3, T4) ($P = .035$). Multivariate analysis showed that tumor node metastasis (TNM) staging was the independent prognostic factor for survival of PMME patients (hazard ratio [95% confidence interval], 4.15 [1.36–12.67]; $P = .012$).

For PMME patients, tumors with deeper invasion were more likely to have LNM, and TNM staging was an independent predictor of prognosis for survival. Early detection of the disease and radical resection of the tumor are critical for better survival of the PMME patients.

Abbreviations: LNM = lymph node metastasis, OS = overall survival, PMME = primary malignant melanoma of esophagus, TNM = tumor node metastasis, UICC = Union for International Cancer Control.

Keywords: esophagus, lymph node metastasis, myometrium, primary malignant melanoma of esophagus, submucosa

1. Introduction

Primary malignant melanoma of esophagus (PMME) is an extremely rare and aggressive disease, which comprises only 0.1% to 0.2% of all tumors of esophagus.^[1–3] PMME has the characteristics of high degree of malignancy, high rate of

recurrence and metastasis, and poor prognosis. The 5-year survival rate was about 4% to 37%.^[2–4] PMME may be induced by melanosis increased along the basal cell layer,^[5] and its clinical symptoms are not easy to distinguish from other esophageal malignant tumors. Some scholars believe that hyperplastic epithelium or chronic esophagitis leading to melanocytosis in the basal layer of the epithelium may be an important cause of the disease.^[6,7]

The main treatment of PMME is still radical resection of tumor. However, due to its rarity, the optimal adjuvant therapies for PMME have not yet been established.^[8] One study has reported the risk of recurrence was extremely high after an initial staging operation, which might indicate the importance of adjuvant therapy and the aggressive characteristics of PMME.^[9] Better understanding of the clinical and pathologic features of the disease will help to improve the effectiveness of diagnosis and treatment. Therefore, in this study, the clinical data of 20 PMME patients, who underwent surgical treatment in the Department of Thoracic Surgery, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College from 1975 to 2017, were collected to analyze the potential factors that might affect the prognosis of PMME patients.

2. Materials and methods

2.1. Patients

The present study was approved by the Institutional Review Board of our hospital, and it conformed to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all individuals before surgery. A total of 20 PMME patients,

Editor: YX Sun.

HC and QF contributed equally to this study and thus shared the co-first authorship.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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How to cite this article: Chen H, Fu Q, Sun K. Characteristics and prognosis of primary malignant melanoma of the esophagus. *Medicine* 2020;99:28(e20957).

Received: 19 January 2020 / Received in final form: 8 May 2020 / Accepted: 12 May 2020

<http://dx.doi.org/10.1097/MD.00000000000020957>

who diagnosed and underwent surgical treatment in our hospital from 1975 to 2017 (3 cases from 1975 to 1997 and 17 cases from 1998 to 2017), were retrospectively analyzed. All patients were confirmed to be PMME by postoperative pathologic examination, with no history of melanoma in the skin or other parts of the patient before surgery. If patients only received radiotherapy and chemotherapy in our hospital without surgical treatment or had incomplete clinical data were excluded.

2.2. Data collection and follow-up

The clinical data of all patients were collected from the medical record database of our hospital, including age, sex, symptoms, tumor family history, operative time, postoperative complications, tumor location, endoscopic and radiographic examination, tumor size, tumor node metastasis (TNM) staging, and others. For all patients, the follow-ups were performed by telephone and outpatient medical record system, and the complete follow-up data should include survival status, cause of death, and time of death. The median follow-up time was 15.5 months.

2.3. Diagnostic evaluation

For all patients, clinical and pathologic stages were reassessed according to the 8th edition of the Union for International Cancer Control (UICC) TNM classification system.^[10] The tumor histology was reviewed and confirmed by 2 independent pathologists. To evaluate the accuracy of preoperative staging, the comparison between the clinical stage and pathologic stage was studied.

2.4. Statistical methods

All statistical analyses were performed with the SPSS version 22 (IBM Corp, Armonk, NY). Data were presented as mean \pm standard deviations. The factors with a value $P < .1$ were included in the multivariate logistic regression model. Survival

curves were constructed using the Kaplan–Meier method, which was also used for univariate analysis. Variables with a value $P < .1$ were included in the Cox proportional hazards model. For all statistical analyses, $P < .05$ was considered statistically significant difference.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the 20 PMME patients are summarized in Table 1. The average age of 20 patients with PMME was 57.3 ± 10.7 years (range, 37–73 years), and 75% (15/20) patients were males. Among them, 15 (75%) patients presented with dysphagia, 4 (20%) patients showed bellyache, and 1 (5%) patient was diagnosed during physical examination.

One patient could not be obtained the preoperative esophagoscopy and biopsy results. Therefore, the preoperative results of esophagoscopy were recorded in 19 patients, including ulcerative mass ($n = 3$), cauliflower-like mass ($n = 2$), polypoid mass ($n = 1$), and protuberant mass ($n = 13$). Mucosal erosion, rupture, or bleeding was observed on the surface of 15 cases, but melanin deposition was found in only 8 cases. Eleven patients were diagnosed as PMME by preoperative esophagoscopy biopsy, the accurate preoperative diagnosis rate was 57.9% (11/19). Eight patients failed to obtain accurate preoperative diagnosis, including 3 cases of squamous cell carcinoma, 2 cases of adenocarcinoma, and 3 case of malignant tumor (Fig. 1).

3.2. Surgical and pathologic features

The surgical and pathologic features of the 20 PMME patients are summarized in Table 2. All patients underwent subtotal esophagectomy and esophagogastrostomy plus systemic mediastinal and abdominal lymph node dissection. Before operation, all patients were performed with the esophagoscopy, cardiopulmo-

Table 1
Clinical characteristics of the PMME patients.

No.	Sex	Age, yr	Family history	Chief complaint	Esophagoscopy	Esophagoscopy biopsy	Survival time, mo	Alive
1	Female	46	No	Bellyache	No record	No record	204	No
2	Male	57	No	Bellyache	Cauliflower-like mass	Malignant tumor	7	No
3	Male	43	No	Dysphagia	Protuberant mass	Squamous cell carcinoma	8	No
4	Female	41	No	Dysphagia	Protuberant mass	Adenocarcinoma	5	No
5	Male	60	No	Bellyache	Cauliflower-like mass	Melanoma	8	No
6	Male	55	No	Dysphagia	Protuberant mass	Squamous cell carcinoma	2	No
7	Female	43	No	Dysphagia	Protuberant mass	Melanoma	7	No
8	Female	67	No	Bellyache	Protuberant mass	Melanoma	47	No
9	Male	63	No	Dysphagia	Polypoid mass	Melanoma	25	No
10	Male	73	No	Dysphagia	Protuberant mass	Melanoma	7	No
11	Male	70	Yes	Dysphagia	Ulcerative mass	Squamous cell carcinoma	65	Yes
12	Male	71	Yes	Dysphagia	Protuberant mass	Melanoma	46	No
13	Female	52	No	Dysphagia	Protuberant mass	Adenocarcinoma	55	Yes
14	Male	54	No	Dysphagia	Protuberant mass	Melanoma	48	No
15	Male	37	No	Dysphagia	Protuberant mass	Melanoma	12	No
16	Male	63	Yes	Dysphagia	Protuberant mass	Melanoma	26	No
17	Male	58	No	Dysphagia	Ulcerative mass	Malignant tumor	6	No
18	Male	65	No	Physical examination	Protuberant mass	Melanoma	20	Yes
19	Male	67	Yes	Dysphagia	Ulcerative mass	Melanoma	12	No
20	Male	60	No	Dysphagia	Protuberant mass	Malignant tumor	19	No

LNM = lymph node metastasis, PMME = primary malignant melanoma of esophagus, TNM = tumor node metastasis.

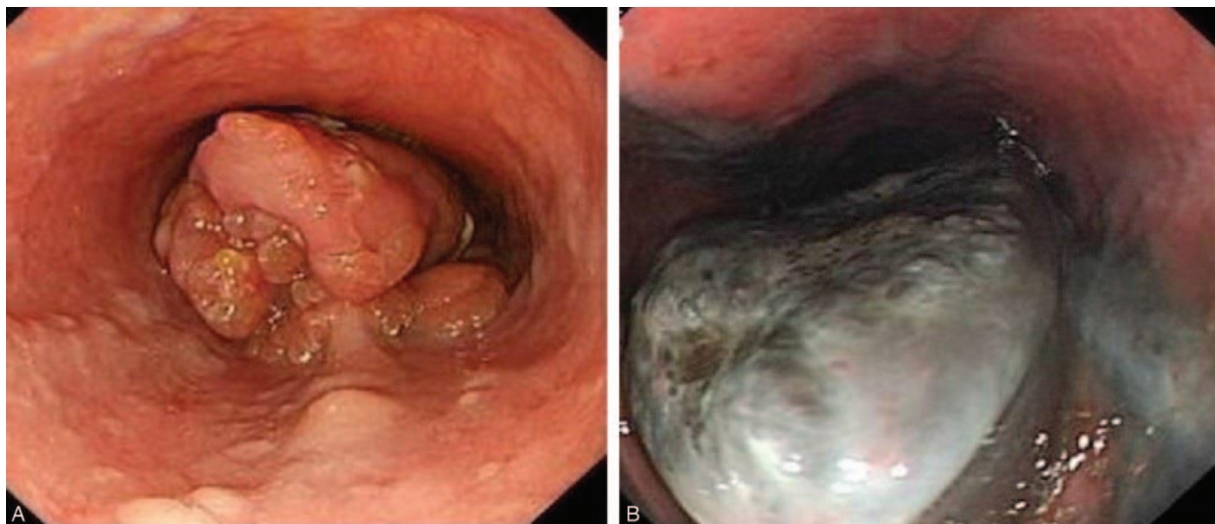


Figure 1. (A) Esophagoscopy revealed the ulcerative mass at 31 to 38 cm from the incisor, covered with a large amount of dirt and white moss. (B) Esophagoscopy revealed a protuberant mass 26 to 30 cm from the incisor, the mucous membrane was congested, rough, erosive, and pigmented.

nary function, upper gastrointestinal angiography, chest and abdomen computed tomography. It was confirmed that there was no obvious contraindication of operation. Among them, 2 patients underwent radical resection of cervical-thoracic-abdominal three incisions, 1 patient underwent radical resection with laparoscopy and right posterolateral thoracotomy, and 17 patients underwent radical resection with left thoracotomy. The esophagus and stomach were fully freed by blunt dissection. Then cutoff the left gastric vessels and preserve the gastroepiploic vascular arch. Finally, the diseased esophagus was removed and esophagogastrostomy was performed. Mediastinal and upper abdominal lymph node dissection was necessary, and cervical lymph nodes were also

needed to be dissected if a triple-incision approach (cervical-thoracic-abdominal) of radical resection was performed.

The average operative time was 229.3 ± 86.4 minutes, and the average intraoperative blood loss was 245 ± 157.2 mL. The average diameter of the tumor was 5.4 ± 2.0 cm. After operation, all patients were treated with parenteral nutrition, anti-infection, inhibition of gastric acid, and others. The patient's diet was gradually restored, and body temperature, drainage volume, and white blood cell count were also closely monitored. There were 7 patients with postoperative complications, and the total incidence of complications was 35% (7/20). Among them, 1 patient died of severe sepsis and respiratory failure caused by

Table 2
Surgery and pathologic features of the PMME patients.

No.	Surgery time, min	Blood loss, mL	Complication	Location	Size, cm	T stage	LNM	LNM area	N stage	TNM stage
1	180	300	No	Mid	5	T2	0		N0	IIA
2	210	600	No	Lower	7	T4a	2	Upper abdominal	N1	IIIB
3	270	400	No	Lower	9	T1b	0		N0	IB
4	120	400	No	Lower	7	T4a	7	Upper abdominal	N3	IVA
5	135	300	No	Lower	6	T3	1	Upper abdominal	N1	IIIB
6	140	300	Bronchopleural fistula + sepsis + respiratory failure	Mid	4.5	T1b	0		N0	IB
7	190	200	No	Mid	3.5	T1b	0		N0	IB
8	195	200	Arrhythmia	upper	2.7	T1b	0		N0	IB
9	210	200	Arrhythmia	Mid	4	T1b	1	Upper abdominal	N1	IIB
10	240	600	hydrothorax + arrhythmia	Lower	8	T3	2	Upper abdominal	N1	IIIB
11	230	200	Arrhythmia	Lower	7.5	T3	0		N0	IIA
12	230	100	Arrhythmia	Lower	7	T1b	9	Mid-lower diastinal + Upper abdominal	N3	IVA
13	290	100	No	Lower	3	T1b	1		N1	IIB
14	160	100	No	Lower	4.2	T1b	0		N0	IB
15	270	100	No	Mid	4	T1b	1	Upper mediastinal	N1	IIB
16	230	100	No	Mid	4.3	T1b	0		N0	IB
17	186	200	No	Lower	7.5	T3	1	Upper abdominal	N1	IIIB
18	440	100	Bronchopleural fistula	Mid	1.7	T1a	0		N0	IB
19	450	100	No	Lower	7	T2	0		N0	IIA
20	210	300	No	Lower	6	T4a	1	Upper abdominal	N1	IIIB

LNM = lymph node metastasis, PMME = primary malignant melanoma of esophagus, TNM = tumor node metastasis.

Table 3**Univariate and multivariate logistic regression analysis of predictive factors of LNM.**

Variables		Univariate analysis	Multivariate analysis		
		P value	P value	OR	95% CI
Sex	Female vs male	.608			
Age	>60 vs ≤60	.365			
Family history	Yes vs no	.284			
T stage	T1 + T2 vs T3 + T4	.035	.035	13.5	1.197–152.211
Tumor location	Lower vs upper + middle	.079	.569		

CI = confidence interval, LNM = lymph node metastasis, OR = odds ratio.

bronchopleural fistula, 5 patients had arrhythmia, and 1 patient had bronchopleural fistula after operation.

Most of the tumors (19/20, 95%) were located in the middle (7/20, 35%) and lower (12/20, 60%) of the esophagus, only 1 case was located in the upper esophagus. Lymph node metastasis (LNM) was observed in 10 cases (50%). Pathologic examination showed that the lesions were confined to the mucous layer (T1a) in 1 case (5%), and the tumor invaded the submucous layer (T1b) in 10 cases (50%); the tumors extended to deep muscular layer (T2), fibrous membrane (T3), and extraserous membrane (T4a) in 2 cases (10%), 4 cases (20%), and 3 cases (15%), respectively. It was worth noting that in patients with LNM, the probability of LNM in tumors confined to submucosa (T1) and myometrium (T2) was significant lower than that in tumors with deeper invasion (T3, T4) (T1 + T2 vs T3 + T4, 30.8% vs 85.7%; $P = .035$; Table 3). In addition, 1 patient with the tumor located in the middle of the esophagus had upper mediastinal LNM, and the rest of the metastatic lymph nodes were located in the middle and lower mediastinal group and upper abdominal group, which had nothing to do with the location of the primary tumor ($P = .569$; Table 3).

3.3. Survival and predictors for survival

The median survival time of 20 patients was 12 months, and the 1-year and 5-year survival rates were 50% and 16.9%, respectively. After excluding the patients who died of serious complications during the perioperative period, the log-rank

analysis was performed in the other 19 patients. The results showed that the postoperative overall survival (OS) time in patients with TNM stages III and IV was significantly shorter than that in patients with stages I and II ($P = .005$; Fig. 2). This study also showed that patients with LNM had shorter OS time than that of patients without LNM (LNM+ vs LNM-, 10 vs 9, $P = .095$; Fig. 3). Multivariate analysis of the possible factors affecting postoperative survival showed that TNM staging was the independent prognostic factor for OS of PMME patients (hazard ratio [95% confidence interval], 4.15 [1.362–12.673]; $P = .012$; Table 4).

4. Discussion

In the present study, the clinical, pathologic and prognostic data of 20 patients with PMME were summarized to analyze the relationship between the depth of tumor invasion and LNM, and explore the survival related factors of PMME patients. These findings demonstrated that tumors with deeper invasion were more likely to have LNM, and TNM staging was an independent predictor of prognosis in patients with PMME.

Considering PMME only accounts for 0.5% of all malignant melanoma, patients with suspected PMME need to exclude metastatic malignant melanoma. It has been reported that all patients with metastatic melanoma had a history of cutaneous malignant melanoma, and the interval between primary cutaneous melanoma and esophageal metastases was 11 to 62 months. And in the diagnosis of esophageal metastasis, it is often

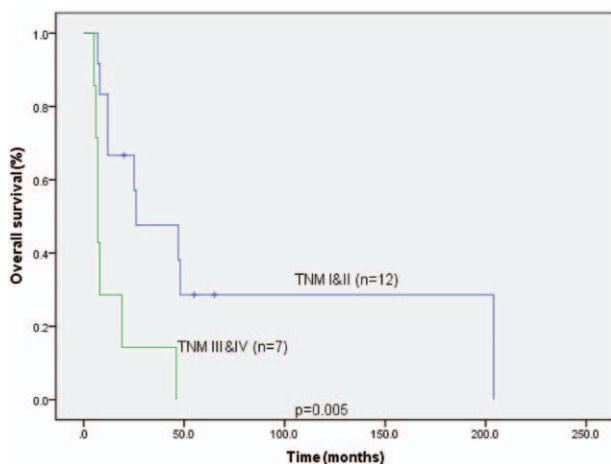


Figure 2. Tumor node metastasis (TNM) stage was associated with overall survival (OS) of primary malignant melanoma of esophagus (PMME) patients. Kaplan–Meier survival curves of stage I-II vs stage III-IV patients. The P -value was calculated by log-rank test.

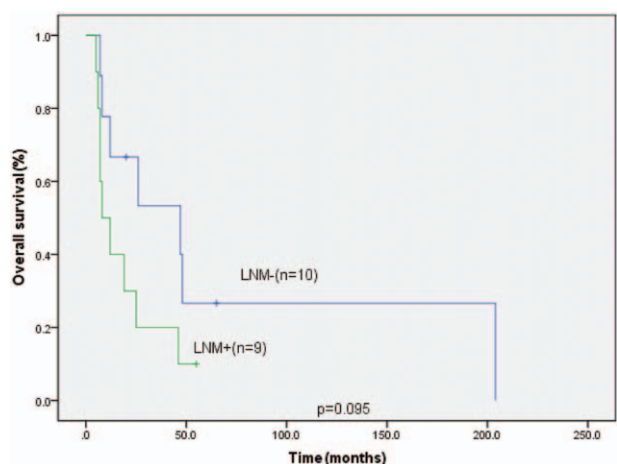


Figure 3. Association of lymph node metastasis (LNM) and survival of primary malignant melanoma of esophagus (PMME) patients. Kaplan–Meier curves of node metastasis involvement status.

Table 4**Univariate and multivariate analyses of predictive factors for postoperative survival.**

Variables		Univariate analysis	Multivariate analysis		
		P value	P value	HR	95% CI
Sex	Female vs male	.286			
Age	>60 vs ≤60	.454			
Family history	Yes vs no	.454			
Tumor location	Lower vs upper + middle	.494			
LNM	Yes vs no	.095	.981		
T stage	T1 + T2 vs T3 + T4	.1			
TNM stage	I + II vs III + IV	.005	.012	4.155	1.362–12.673
Chief complaint	Bellyache vs dysphagia vs physical examination	.595			
Esophagoscopy	Cauliflower-like mass vs protuberant mass vs polypoid mass vs ulcerative mass	.455			
Esophagoscopy biopsy	Malignant tumor vs squamous cell carcinoma vs adenocarcinoma vs melanoma	.188			

CI = confidence interval, HR = hazard ratio, LNM = lymph node metastasis, TNM = tumor node metastasis.

accompanied by the metastasis of other organs.^[11] In this study, the 5-year survival rate of PMME was 16.9%, which was consistent with previous reports of 4% to 37%.^[2,4] The preoperative diagnostic rate of PMME was low, and even if endoscopic biopsy was used, the preoperative diagnostic accuracy was only about 80%. When the tumor lacks melanin particles, it was easy to be confused with poorly differentiated cancer.^[12]

The PMME most commonly occurs in males, and the male-to-female ratio is 2:1, only 5 female patients were recorded in this study, which was similar to previous studies.^[9,13] In the present study, there were 8 patients who failed to obtain accurate diagnosis by endoscopic biopsy before operation, including 3 cases of squamous cell carcinoma, 2 cases of adenocarcinoma, and 3 cases of malignant tumor. It was worth noting that among the 11 patients with PMME diagnosed by endoscopic biopsy before operation, 8 cases underwent immunohistochemical examination, which also suggested that immunohistochemical examination was of great significance in the diagnosis before operation. The diagnosis of PMME depended on the immunohistochemical examination of resected specimens. Most of the classical immune markers such as MB-45, Melan-A, S100, and vimentin are positive, which was consistent with other reports.^[12]

The PMME tumors are usually located in the middle and lower 3rd of the esophagus. Some studies have shown that LNM tended to occur at the supraclavicular area, upper mediastinal area, and upper abdominal area in patients with upper, middle, lower esophageal squamous cell carcinoma, respectively.^[9,12,14,15] In this study, 10 patients had LNM, of which 1 patient had upper mediastinal LNM, and the rest were located in the mediastinal middle and lower group and the upper abdomen group, and had nothing to do with the location of the primary tumor. Previous study reported that the depth of tumor invasion is correlated with LNM in esophageal squamous cell carcinoma.^[16] In this study, it indicated the deeper the depth of invasion, the higher was the probability of LNM (T1+T2 vs T3+T4, 30.8% vs 85.7%; $P = .035$; Table 3).

The present study analyzed the potential factors that might affect the postoperative survival of patients with PMME. Previous studies have shown that LNM was an independent prognostic factor in patients with esophageal squamous cell carcinoma.^[13,17–19] Similarly, Wang et al analyzed the data of 13 PMME patients and also found that patients with LNM had a poor prognosis.^[20] The present study found that patients with LNM had shorter OS time than that of without LNM. In addition, 1 recent study has reported initial TNM stage of PMME

according to the AJCC classification for esophageal cancer was closely related to OS, indicating that TNM stage may accurately discriminate the prognosis of patients with PMME.^[9] The present study also showed that TNM staging was an independent factor affecting the postoperative survival of patients with PMME, which might suggest that early detection of the disease was essential for better survival.

There were some limitations in this study. Although the survival rate of patients with LNM was very low, there was no significant difference in multivariate analysis, which may be due to the limited sample size without enough power. The accurate and complete information on postoperative adjuvant therapy were unable to collect, which was also one of the limitations of this study. Dartmouth regimen is currently known to be effective for cutaneous malignant melanoma (dacabazine + cisplatin + dichloroethyl nitrourea + tamoxifen) with an effective rate of about 50%. However, there is no clear evidence that the regimen has the same effect in patients with PMME.^[21] Although there is no present study that adjuvant therapy can improve the OS rate of PMME, it can play a role in relieving the disease.^[12] However, to date, the present study was the largest population of PMME patients with more than 20 years span.

5. Conclusion

For PMME patients, tumors with deeper invasion were more likely to have LNM, and TNM staging was an independent predictor of prognosis for survival. Early detection of the disease and radical resection of the tumor are critical for better survival of the PMME patients.

Author contributions

Hengchi Chen and Qiang Fu performed the data analyses and wrote the manuscript, searched and reviewed the literature, drafted the manuscript, and edited the final version; Kelin Sun performed the analysis with constructive discussions and edited the final version. All authors read and approved the final manuscript.

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