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*Original Article*

# Survival and risk factors in patients with liposarcoma with distant metastasis

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**Abstract:** Background: The distant metastasis in liposarcoma is not thoroughly investigated. Based on a large cohort, we attempted to evaluate the survival in liposarcoma patients with distant metastasis and to reveal the risk factors. Methods: The records of liposarcoma patients with or without distant metastasis were extracted from the Surveillance, Epidemiology, and End Result (SEER) database from 2010 to 2016. Survival was calculated by the Kaplan-Meier method. Cox hazard regression was scheduled to investigate prognostic factors for liposarcoma patients with distant metastasis. Risk factors for metastasis were identified by the logistic regression analysis. Results: A total of 227 liposarcomas with distant metastasis were identified in 4,181 patients. The 5-year survival rate for patients with and without metastasis was 12.1% (95% CI: 5.0%-19.0%) and 75.4% (95% CI: 73.6%-77.2%), respectively. Age ≥60 years (HR=1.73; 95% CI: 1.11-2.69) and surgery (HR=0.26; 95% CI: 0.17-0.41) were independent prognostic factors for patients with metastasis. The annual incidence of distant metastasis was from 3.76% to 7.3%. Liposarcoma in trunk (OR=1.69; 95% CI: 1.02-2.79), myxoid type (OR=2.65; 95% CI: 1.16-6.05), grade III (OR=2.62; 95% CI: 1.17-5.88), grade IV (OR=4.07; 95% CI: 1.84-9.00), T2 stage (OR=2.71; 95% CI: 1.15-6.40), and N1 stage (OR=9.44; 95% CI: 4.63-19.26) were associated with the development of metastasis. Homogeneous and heterogeneous factors were found for patients with different metastatic organs. Conclusions: The survival was significantly dismal in liposarcoma patients with distant metastasis. The risk and prognostic factors provide a reference to clinical screening and prevention for distant metastasis in liposarcoma.

**Keywords:** Liposarcoma, distant metastasis, mortality, prognosis

## Introduction

Soft tissue sarcomas are a rare group of malignancies, with an annual incidence of approximately 2-5 per 100,000 [1]. Among this group, liposarcomas are one of the most common types [2]. Various histologic subtypes exist for liposarcoma, such as well-differentiated, dedifferentiated, myxoid tumor, and pleomorphic [3]. A previous study revealed worse survival in patients with the dedifferentiated subtype, large tumors, and metastases [3].

Distant metastasis is widely accepted as the main reason for poor survival in patients with cancer. Various homogeneous and heterogeneous prognostic and risk factors for metastasis have been reported for different cancers [4-6]. Distant metastasis has been reported in 32.5% of patients with myxoid/round cell liposarcoma [7] and 37% of patients with liposarcoma [8]. In a retrospective review of the medical records of 148 patients with dedifferentiated liposarcoma, 29.7% were noted to have distant metastasis, and high tumor grade (odds ratio [OR], 5.05; 95% confidence interval [CI], 2.01-13.48) and local recurrence (OR, 4.46; 95% CI, 1.67-13.40) were independent risk factors for metastasis [9]. In another retrospective review, involving 441 patients with liposar-

coma in the extremities, distant metastases were noted in 12.9% of patients, most of which occurred in patients with pleomorphic liposarcoma (25 of 54 patients with this subtype) [10]. Because of difficulties obtaining a large sample size, few investigations have evaluated survival and predictive factors among patients with liposarcoma, especially those with distant metastasis.

Expanding our understanding of the prognostic and risk factors associated with metastases in various body areas is crucial for screening for metastasis and improving the survival of patients with liposarcoma. Therefore, based on a large cohort of patients from the National Cancer Institute Surveillance, Epidemiology and End Results (NCI SEER) database, we examined the survival of patients with liposarcoma who have distant metastasis, and identified risk factors associated with the occurrence of these metastases.

## Materials and methods

### *Data source and cohort selection*

Data for this study were obtained from the SEER database (https://seer.cancer.gov/data/), which was accessed with the SEER*Stat application (version 8.3.5). This database collects cancer records from 18 registries and encompasses approximately 30% of the population in the United States of America (USA). Specific metastatic sites have been recorded in the SEER database since 2010. Records of patients diagnosed with primary liposarcoma from 2010 to 2016 were extracted from the database. **Figure 1** illustrates the patient selection process. We excluded patients who met one or more of these criteria: diagnosed only at autopsy, diagnosis indicated only on the death certificate, and unknown distant metastasis status.

### *Statistical analysis*

We examined these demographic and clinicopathologic variables: age at diagnosis (<60 years or ≥60 years); sex (female or male); race (white, black, Indian/Alaska Native, or Asian or Pacific Islander); insurance status (insured or uninsured); marital status (married or unmarried); primary tumor site (extremities, trunk, retroperitoneal/intra-abdominal, thorax, or other); histologic subtype (well-differentiated, dedifferentiated, myxoid, pleomorphic, or other); tumor grade (grade I, II, III, or IV); T stage (T1 or T2); N stage (N0 or N1); number of distant metastasis (≤1 or >1); and surgical treatment (yes or no). For the primary tumor site, tumors in the head or neck were classified as "trunk", and tumors for which the location was unclear were classified as "other". Distant metastasis was defined as at least one metastasis in the lung, bone, brain, or liver.

Pearson's chi-square test and rank-sum test were used to evaluate differences in demographic and clinicopathologic variables between patients with or without distant metastasis. The Kaplan-Meier method was used to evaluate overall survival (OS) from the time of diagnosis to the time of death (from all causes) in patients with or without distant metastasis and in patients with various sites of metastasis. Differences between survival curves were compared using the log-rank test. Prognostic factors for patients with liposarcoma who had distant metastasis were investigated using univariate and multivariate Cox regression analysis. Univariate and multivariate logistic regression analyses were used to identify risk factors for the development of distant metastasis.

SPSS 23.0 (IBM Corporation, Armonk, NY, USA) was used to perform all statistical analyses. Survival curves were generated using MedCalc 15.2.2. Two-sided $p$-values <0.05 were set as the criteria for statistically significant differences.

### *Ethics statement*

Specific patient-informed consent was not required for this study because it was an analysis of information obtained from the SEER database. Cancer is a reportable disease in every state of the USA. All analyses in this study were conducted according to the guidelines in the 1964 Helsinki Declaration and its later amendments.

## Results

### *Patient selection and characteristics*

The patient selection process and detailed diagnostic methods are illustrated in **Figure 1**. Using the inclusion criteria, we initially selected

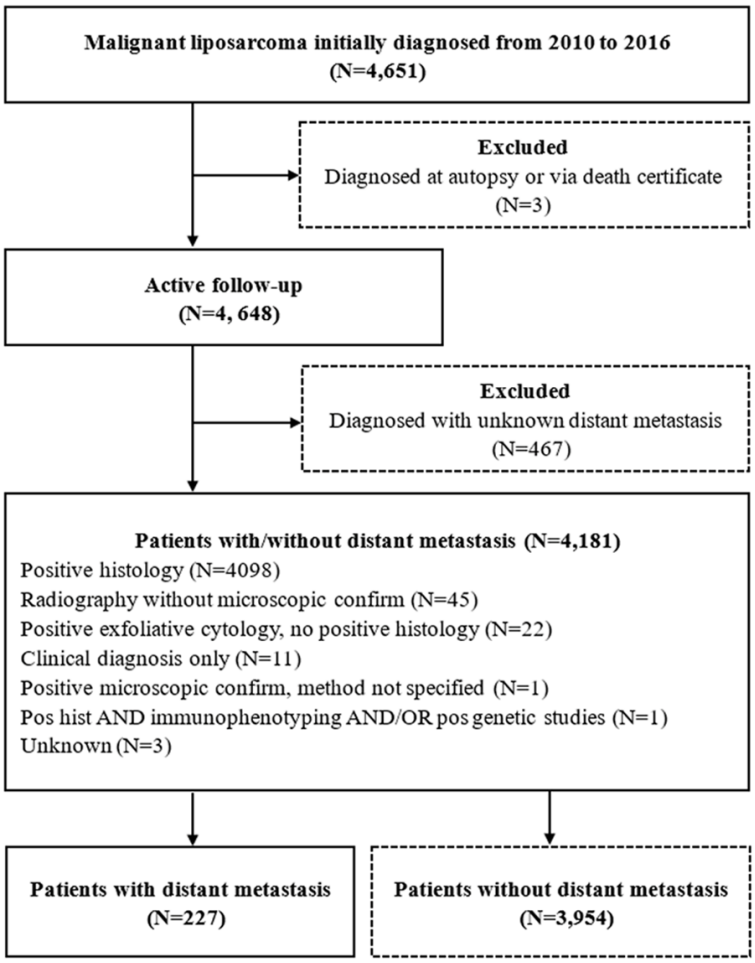


**Figure 1.** Flowchart of the patient selection for analyzing the risk factors for the morbidity and prognosis of distant metastasis in liposarcoma patients.

4,651 patients diagnosed with malignant liposarcoma in 2010 to 2016. After excluding 3 patients diagnosed only at autopsy or on the death certificate and 467 patients whose metastasis status was unclear, we selected 3,954 patients without distant metastasis and 227 patients with distant metastasis for inclusion in this study.

Demographic and clinical characteristics of the included patients are summarized in **Table 1**. The cohort exhibited a male predominance (58.7% of all patients), and 79.4% of patients were white. The primary tumor was located in the extremities in 44.2% of patients, the trunk in 28.5% of patients, and the retroperitoneum or intra-abdominal cavity in 19.9% of patients. The most common histologic subtypes were well-differentiated (34.8%), myxoid (19.9%), and dedifferentiated (19.0%) liposarcomas. Most patients were diagnosed at grade I (46.0%) and stage N0 (94.3%). Tumor size was relatively large, with 82.2% of patients diagnosed at stage T2. Surgery was performed in 90.6% of included patients.

*Survival and prognostic factors*

Of the 227 patients with distant metastasis, 37 had metastases involving more than one site. Details of the total metastases and metastases at each site are summarized in **Table 1**. Lungs were the most common site (n=87, 38.3%), followed by liver (n=51, 22.5%), bones (n=50, 22.0%), and brain (n=7, 3.1%). In patients with a single metastatic site, the tumor was located in the lungs in 56 patients, liver in 30 patients, bones in 26 patients, and brain in 3 patients.

By the time of last follow-up, 662 patients had died. Mean OS was 21.4 months (95% CI, 17.9-24.9) in patients with distant metastasis and 68.0 months (95% CI, 67.0-69.0) in patients without distant metastases. Mean OS varied according to metastatic site in patients with a single metastasis: lungs, 15.0 months (95% CI, 9.7-21.2); liver, 24.2 months (95% CI, 14.2-34.2); bones, 22.3 months (95% CI, 17.2-27.4); and brain, 3.3 months (95% CI, 0.7-5.9). Mean OS for patients with multiple metastases was 9.3 months (95% CI, 5.9-12.6). For patients with distant metastasis, 1- and 5-year survival rates were 47.8% (95% CI, 40.9%-54.6%) and 12.1% (95% CI, 5.0%-19.0%), respectively. For patients without distant metastasis, 1- and 5-year survival rates were 92.6% (95% CI, 91.7%-93.4%) and 75.4% (95% CI, 73.6%-77.2%), respectively. Kaplan–Meier curves for patients with or without distant metastasis are shown in **Figure 2**.

**Table 2** depicts the results of Cox regression analyses for survival. For all patients with distant metastasis, univariate analysis revealed

**Table 1.** Characteristics of the liposarcoma with distant metastasis at diagnosis in the SEER dataset from 2010 to 2016

| Characteristics | Total distant metastasis | | | | | | Metastasis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Not | % | Yes | % | $\chi^2$ | *P*-value | Lung | Liver | Bone | Brain |
| Sex | | | | | 1.48 | 0.224 | | | | |
| Male | 2,312 | 94.21% | 142 | 5.79% | | | 58 | 26 | 28 | 5 |
| Female | 1,642 | 95.08% | 85 | 4.92% | | | 29 | 25 | 22 | 2 |
| Age (year) | | | | | 4.49 | 0.034 | | | | |
| <60 | 1,993 | 95.31% | 98 | 4.69% | | | 39 | 19 | 28 | 3 |
| ≥60 | 1,961 | 93.83% | 129 | 6.17% | | | 48 | 32 | 22 | 4 |
| Race | | | | | 3.86 | 0.425 | | | | |
| White | 3,137 | 94.49% | 183 | 5.51% | | | 70 | 36 | 43 | 4 |
| Black | 360 | 94.49% | 21 | 5.51% | | | 9 | 5 | 2 | 2 |
| IA | 35 | 97.22% | 1 | 2.78% | | | 0 | 1 | 0 | 0 |
| API | 365 | 94.32% | 22 | 5.68% | | | 8 | 9 | 5 | 1 |
| Unknown | 57 | 100.00% | 0 | 0.00% | | | 0 | 0 | 0 | 0 |
| Insurance recode | | | | | 6.95 | 0.031 | | | | |
| Insured | 3,737 | 94.70% | 209 | 5.30% | | | 81 | 46 | 44 | 5 |
| Uninsured | 121 | 89.63% | 14 | 10.37% | | | 6 | 5 | 5 | 2 |
| Unknown | 96 | 96.00% | 4 | 4.00% | | | 0 | 0 | 1 | 0 |
| Marital status | | | | | 5.06 | 0.080 | | | | |
| Married | 2,320 | 94.89% | 125 | 5.11% | | | 45 | 26 | 26 | 2 |
| Unmarried | 1,375 | 93.66% | 93 | 6.34% | | | 39 | 22 | 22 | 5 |
| Unknown | 259 | 96.64% | 9 | 3.36% | | | 3 | 3 | 2 | 0 |
| Year of diagnosis | | | | | 10.99 | 0.089 | | | | |
| 2010 | 492 | 96.09% | 20 | 3.91% | | | 9 | 3 | 2 | 1 |
| 2011 | 538 | 96.24% | 21 | 3.76% | | | 9 | 9 | 5 | 0 |
| 2012 | 551 | 93.71% | 37 | 6.29% | | | 9 | 4 | 9 | 0 |
| 2013 | 540 | 94.74% | 30 | 5.26% | | | 11 | 5 | 6 | 1 |
| 2014 | 598 | 94.62% | 34 | 5.38% | | | 17 | 7 | 12 | 2 |
| 2015 | 587 | 94.52% | 34 | 5.48% | | | 13 | 6 | 8 | 3 |
| 2016 | 648 | 92.70% | 51 | 7.30% | | | 19 | 17 | 8 | 0 |
| Primary site | | | | | 46.42 | <0.001 | | | | |
| Extremities | 1,846 | 96.75% | 62 | 3.25% | | | 24 | 10 | 20 | 0 |
| Trunk | 1,192 | 93.05% | 89 | 6.95% | | | 36 | 17 | 17 | 3 |
| RIA | 831 | 93.16% | 61 | 6.84% | | | 17 | 20 | 5 | 2 |
| Thorax | 26 | 89.66% | 3 | 10.34% | | | 2 | 0 | 2 | 1 |
| Others | 59 | 83.10% | 12 | 16.90% | | | 8 | 4 | 6 | 1 |
| Histology | | | | | 91.08 | <0.001 | | | | |
| Well-differentiated | 1,453 | 98.58% | 21 | 1.42% | | | 7 | 5 | 4 | 1 |
| De-differentiated | 795 | 89.73% | 91 | 10.27% | | | 35 | 16 | 11 | 0 |
| Myxoid | 828 | 94.20% | 51 | 5.80% | | | 14 | 10 | 16 | 2 |
| Pleomorphic | 257 | 92.11% | 22 | 7.89% | | | 13 | 4 | 5 | 2 |
| Others | 113 | 93.39% | 8 | 6.61% | | | 3 | 3 | 3 | 0 |
| Unknown | 508 | 93.73% | 34 | 6.27% | | | 15 | 13 | 11 | 2 |
| Grade | | | | | 145.87 | <0.001 | | | | |
| Grade I | 1,894 | 98.54% | 28 | 1.46% | | | 12 | 7 | 5 | 3 |
| Grade II | 518 | 95.22% | 26 | 4.78% | | | 2 | 4 | 9 | 0 |
| Grade III | 556 | 92.67% | 44 | 7.33% | | | 10 | 14 | 11 | 0 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Grade IV | 496 | 88.10% | 67 | 11.90% | | | 33 | 9 | 10 | 2 |
| Unknown | 490 | 88.77% | 62 | 11.23% | | | 30 | 17 | 15 | 2 |
| T stage | | | | | 52.29 | <0.001 | | | | |
| T1 | 427 | 97.49% | 11 | 2.51% | | | 3 | 2 | 2 | 0 |
| T2 | 3,263 | 94.97% | 173 | 5.03% | | | 66 | 37 | 36 | 3 |
| Unknown | 264 | 85.99% | 43 | 14.01% | | | 18 | 12 | 12 | 4 |
| N stage | | | | | 197.65 | <0.001 | | | | |
| N0 | 3,772 | 95.66% | 171 | 4.34% | | | 58 | 38 | 35 | 4 |
| N1 | 41 | 62.12% | 25 | 37.88% | | | 10 | 9 | 9 | 1 |
| Unknown | 141 | 81.98% | 31 | 18.02% | | | 19 | 4 | 6 | 2 |
| Number of Met | | | | | 650.24 | <0.001 | | | | |
| ≤1 | 3954 | 95.42% | 190 | 4.58% | | | 55 | 30 | 26 | 3 |
| >1 | 0 | 0 | 37 | 100% | | | 32 | 21 | 24 | 4 |
| Vital status | | | | | 362.70 | <0.001 | | | | |
| Alive | 3,292 | 97.86% | 72 | 2.14% | | | 20 | 15 | 10 | 0 |
| Dead | 662 | 81.03% | 155 | 18.97% | | | 67 | 36 | 40 | 7 |
| Surg (prim) | | | | | 402.17 | <0.001 | | | | |
| None | 280 | 72.54% | 106 | 27.46% | | | 57 | 26 | 24 | 5 |
| Yes | 3,667 | 96.81% | 121 | 3.19% | | | 30 | 25 | 26 | 2 |
| Unknown | 7 | 100.00% | 0 | 0.00% | | | 0 | 0 | 0 | 0 |

Abbreviations: SEER: Surveillance, Epidemiology, and End Result; Met = Metastases. RIA: Retroperitoneal/intra-abdominal; IA: Indian/Alaska Native; API: Asian or Pacific Islander; Surg (prim): surgery for primary tumor.

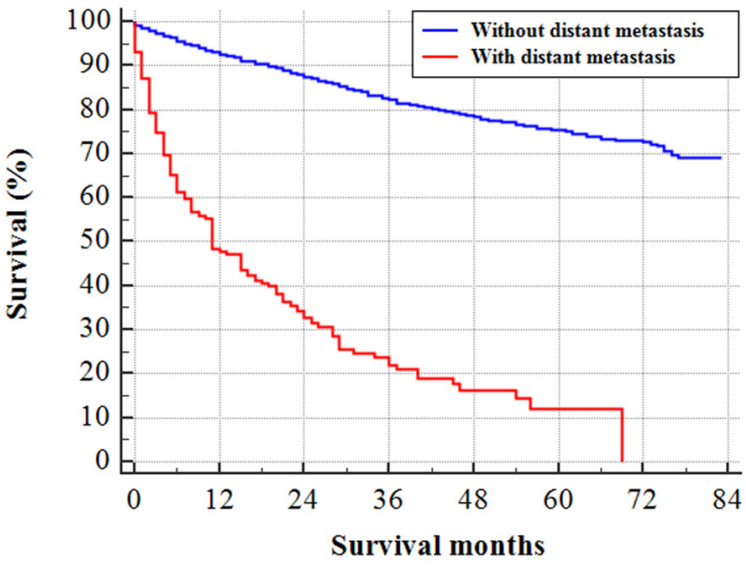


**Figure 2.** Kaplan-Meier curves of overall survival for liposarcoma patients diagnosed with or without bone metastasis.

that retroperitoneal or intra-abdominal metastasis, "other" site metastasis, and multiple metastases were associated with worse survival, whereas surgery for the primary tumor was associated with improved survival. In multivariate analysis, age >60 years (hazard ratio [HR], 1.73; 95% CI, 1.11-2.69; P=0.015) and surgery (HR, 0.26; 95% CI, 0.17-0.41; P<0.001) were independent prognostic factors associated with improved survival. The results of Cox regression analysis for survival of patients with metastasis to the lungs, liver, bones, or brain are shown in the Supplementary Materials. No independent prognostic factors were identified for patients with brain metastasis, likely because of the limited number of patients with metastasis in this location. Surgery was a protective factor associated with improved OS for all other metastatic sites (lungs, liver, and bones).

*Risk factors for distant metastasis*

The mean annual incidence of distant metastasis was 5.4%, ranging from 3.8% in 2011 to 7.3% in 2016. The results of logistic regression analysis are shown in **Table 3**. In univariate analysis, risk factors for the development of metastasis in all patients were age ≥60 years; uninsured status; primary tumor in the trunk,

**Table 2.** The prognostic factors for total liposarcoma patients with distant metastasis diagnosed between 2010 and 2016 by Cox regression

| Subject characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | *P-value* | HR (95% CI) | *P-value* |
| Sex | | | | |
| Male | 1.00 (Reference) | | 1.00 (Reference) | |
| Female | 0.91 (0.66-1.27) | 0.592 | 0.74 (0.49-1.12) | 0.159 |
| Age (year) | | | | |
| <60 | 1.00 (Reference) | | 1.00 (Reference) | |
| ≥60 | 1.33 (0.96-1.84) | 0.082 | 1.73 (1.11-2.69) | 0.015 |
| Race | | | | |
| White | 1.00 (Reference) | | | |
| Black | 1.26 (0.75-2.13) | 0.385 | NA | NA |
| AI | 4.66 (0.64-33.87) | 0.128 | NA | NA |
| API | 0.96 (0.54-1.70) | 0.878 | NA | NA |
| Insurance recode | | | | |
| Insured | 1.00 (Reference) | | | |
| Uninsured | 1.30 (0.75-2.26) | 0.344 | NA | NA |
| Marital status | | | | |
| Married | 1.00 (Reference) | | | |
| Unmarried | 1.24 (0.90-1.72) | 0.195 | NA | NA |
| Primary site | | | | |
| Extremities | 1.00 (Reference) | | 1.00 (Reference) | |
| Trunk | 1.49 (0.98-2.26) | 0.062 | 1.10 (0.66-1.86) | 0.708 |
| RIA | 1.93 (1.23-3.04) | 0.005 | 1.31 (0.77-2.22) | 0.319 |
| Thorax | 2.02 (0.62-6.61) | 0.243 | 0.76 (0.17-3.49) | 0.728 |
| Others | 2.16 (1.09-4.28) | 0.027 | 4.96 (1.03-23.88) | 0.046 |
| Histology | | | | |
| Well-Differentiated | 1.00 (Reference) | | | |
| Dedifferentiated | 1.16 (0.65-2.07) | 0.618 | NA | NA |
| Myxoid | 0.68 (0.36-1.28) | 0.233 | NA | NA |
| Pleomorphic | 1.37 (0.67-2.79) | 0.389 | NA | NA |
| Others | 0.36 (0.10-1.26) | 0.111 | NA | NA |
| Grade | | | | |
| Grade I | 1.00 (Reference) | | | |
| Grade II | 0.91 (0.45-1.84) | 0.799 | NA | NA |
| Grade III | 1.17 (0.65-2.09) | 0.603 | NA | NA |
| Grade IV | 1.50 (0.87-2.58) | 0.149 | NA | NA |
| T stage | | | | |
| T1 | 1.00 (Reference) | | 1.00 (Reference) | |
| T2 | 1.06 (0.49-2.28) | 0.880 | 1.16 (0.48-2.76) | 0.744 |
| N stage | | | | |
| N0 | 1.00 (Reference) | | 1.00 (Reference) | |
| N1 | 1.51 (0.90-2.51) | 0.117 | 0.98 (0.50-1.92) | 0.963 |
| Number of Met | | | | |
| ≤1 | 1.00 (Reference) | | 1.00 (Reference) | |
| >1 | 2.10 (1.43-3.09) | <0.001 | 1.46 (0.79-2.71) | 0.225 |
| Surg (prim) | | | | |
| None | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 0.35 (0.25-0.48) | <0.001 | 0.26 (0.17-0.41) | <0.001 |

Abbreviations: SEER: Surveillance, Epidemiology, and End Result; Met = Metastases. RIA: Retroperitoneal/intra-abdominal; IA: Indian/Alaska Native; API: Asian or Pacific Islander; Surg (prim): Surgery for primary site.

retroperitoneal/intra-abdominal area, thorax, or "other" site (compared with the extremities); dedifferentiated, myxoid, pleomorphic, and "other" histologic subtypes (compared with well-differentiated); tumor grade II, III, or IV; stage T2; and stage N1. In multivariate regression analysis, these factors were associated with distant metastasis: primary site in the trunk (versus extremities; OR, 1.69; 95% CI, 1.02-2.79; P=0.040); myxoid subtype (versus well-differentiated; OR, 2.65; 95% CI, 1.16-6.05; P=0.005); grade III (OR, 2.62; 95% CI, 1.17-5.88; P=0.019); grade IV (OR, 4.07; 95% CI, 1.84-9.00; P=0.001); stage T2 (OR, 2.71; 95% CI, 1.15-6.40; P=0.023); and stage N1 (OR, 9.44; 95% CI, 4.63-19.26; P<0.001) (**Table 3**).

**Table 3** also shows the risk factors associated with distant metastasis in specific organs. In multivariate logistic regression, stage N1 was a risk factor for metastasis to the lungs, liver, or bones. Dedifferentiated, pleomorphic, and "other" histologic subtypes were other risk factors for patients with lung metastasis. Uninsured status, primary tumor in the retroperitoneal or intra-abdominal area, and myxoid liposarcoma were risk factors for liver metastasis, whereas uninsured status and primary tumor in the thorax were risk factors for bone metastasis.

## Discussion

In the present study evaluating a large cohort of patients with liposarcoma, survival was poor in patients with distant metastasis. The 5-year survival rate was only 12.1% (95% CI, 5.0-19.0) for patients with metastasis, in contrast to 75.4% (95% CI, 73.6-77.2) for patients without metastasis. This negative effect of distant metastasis on survival in patients with liposarcoma has been reported in previous studies [9, 11].

Lungs were the most frequent organ of distant metastasis in our study, which is consistent with the results reported in the literature. We found worse OS in patients with lung metastasis than that in those with liver or bone metastasis. In a prior study, lungs were the metastatic site in 75% (33) of 44 patients with dedifferentiated liposarcoma who had distant metastasis [9]. Another previous study reported lung metastasis in 27% (14) of 52 patients with myxoid/round-cell liposarcoma who had metastasis [7]. In another study, which included multiple histologic subtypes, lungs were the site of metastasis in 45% of all metastases [12]. In the present study, lung metastasis represented 38.3% of all distant metastases. The varying incidences for lung metastasis between studies may be at least partly attributed to differences in histologic subtypes. Dedifferentiated and pleomorphic subtypes were identified as independent risk factors for the development of lung metastasis in the current study. Therefore, accurate pathologic diagnosis is essential for predicting the odds of lung metastasis.

Extrapulmonary metastases were previously reported in 73% of patients with myxoid/round cell liposarcoma [13]. In the present study, extrapulmonary metastases comprised 68.7% of all metastases. Heterogeneous risk factors were revealed for metastasis to the liver and bones. Brain metastasis is rare in patients with liposarcoma and has been primarily described in case reports [14, 15]. In a study of 148 patients with 44 metastases, only one incidence of brain metastasis was observed [9]. In our study, we identified 7 patients with brain metastasis and noted that OS was worse in these patients than in patients with metastasis to the lungs, liver, or bones. Therefore, early identification of brain metastasis is important, especially in patients with a primary tumor in the thorax.

We also explored risk factors for distant metastasis to improve early screening for metastasis. A previous study revealed no significant factors predictive of the development of distant metastasis in patients with liposarcoma [7]. Other studies have reported associations between the development of distant metastasis and tumor size >10 cm [16], high tumor grade for dedifferentiated liposarcoma [9], or male sex [17]. In the current study, primary tumor site in the trunk, myxoid subtype, grade III or IV, stage T2, and stage N1 were associated with the development of metastasis. Patients with these risk factors should be closely monitored during follow-up.

Prognostic factors for survival in patients with liposarcoma have been previously investigated [3, 18]. Age >60 years [11] and >65 years [18] were previously reported prognostic factors for poor survival. In the present study, we also observed worse survival in older patients with

**Table 3.** The risk factors for survival in liposarcoma patients with distant metastasis diagnosed between 2010 and 2016 by logistic regression analysis

| Subject characteristics | Total Met (Univariate) | | Total Met (Multivariate) | | Lung Met (Multivariate) | | Liver Met (Multivariate) | | Bone Met (Multivariate) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | OR (95% CI) | *P-value* | OR (95% CI) | *P-value* | OR (95% CI) | *P-value* | OR (95% CI) | *P-value* | OR (95% CI) | *P-value* |
| Sex | | | | | | | | | | |
| Male | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Female | 0.84 (0.64-1.11) | 0.225 | 0.87 (0.58-1.29) | 0.487 | 0.71 (0.36-1.40) | 0.327 | 1.37 (0.56-3.34) | 0.488 | 0.80 (0.33-1.93) | 0.623 |
| Age (year) | | | | | | | | | | |
| <60 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| ≥60 | 1.34 (1.02-1.75) | 0.035 | 1.37 (0.92-2.06) | 0.123 | 1.12 (0.58-2.13) | 0.739 | 2.71 (0.99-7.43) | 0.053 | 1.16 (0.47-2.83) | 0.750 |
| Race | | | | | | | | | | |
| White | 1.00 (Reference) | | | | | | 1.00 (Reference) | | | |
| Black | 1.00 (0.63-1.59) | 1.000 | NA | NA | NA | NA | 0.59 (0.07-4.81) | 0.626 | NA | NA |
| AI | 0.49 (0.07-3.59) | 0.483 | NA | NA | NA | NA | NA | NA | NA | NA |
| API | 1.03 (0.66-1.63) | 0.888 | NA | NA | NA | NA | 2.16 (0.69-6.72) | 0.184 | NA | NA |
| Insurance recode | | | | | | | | | | |
| Insured | 1.00 (Reference) | | 1.00 (Reference) | | | | 1.00 (Reference) | | 1.00 (Reference) | |
| Uninsured | 2.07 (1.17-3.66) | 0.013 | 2.06 (0.83-5.10) | 0.120 | NA | NA | 10.36 (2.27-47.30) | 0.003 | 4.28 (1.05-17.48) | 0.043 |
| Marital status | | | | | | | | | | |
| Married | 1.00 (Reference) | | | | | | 1.00 (Reference) | | | |
| Unmarried | 1.26 (0.95-1.66) | 0.107 | NA | NA | NA | NA | 1.18 (0.48-2.93) | 0.719 | NA | NA |
| Primary site | | | | | | | | | | |
| Extremities | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Trunk | 2.22 (1.59-3.10) | <0.001 | 1.69 (1.02-2.79) | 0.040 | 1.56 (0.70-3.48) | 0.281 | 1.85 (0.46-7.42) | 0.385 | 1.03 (0.38-2.78) | 0.950 |
| RIA | 2.19 (1.52-3.14) | <0.001 | 1.53 (0.86-2.73) | 0.150 | 0.80 (0.30-2.14) | 0.657 | 6.16 (1.59-23.81) | 0.008 | 0.17 (0.02-1.47) | 0.107 |
| Thorax | 3.44 (1.01-11.66) | 0.048 | 2.65 (0.54-13.09) | 0.232 | 2.64 (0.31-22.84) | 0.377 | NA | NA | 7.24 (1.23-42.68) | 0.029 |
| Others | 6.06 (3.10-11.84) | <0.001 | 1.09 (0.20-5.84) | 0.917 | 1.47 (0.15-14.07) | 0.736 | 1.96 (0.07-58.35) | 0.697 | 1.28 (0.09-18.29) | 0.856 |
| Histology | | | | | | | | | | |
| Well-Differentiated | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Dedifferentiated | 7.92 (4.89-12.83) | <0.001 | 1.97 (0.82-4.71) | 0.127 | 5.62 (1.41-22.37) | 0.014 | 2.66 (0.44-16.01) | 0.285 | 1.24 (0.16-9.69) | 0.836 |
| Myxoid | 4.26 (2.55-7.13) | <0.001 | 2.65 (1.16-6.05) | 0.020 | 1.54 (0.35-6.85) | 0.567 | 7.60 (1.51-38.20) | 0.014 | 2.25 (0.35-14.33) | 0.392 |
| Pleomorphic | 5.92 (3.21-10.93) | <0.001 | 1.95 (0.70-5.43) | 0.204 | 5.93 (1.26-27.91) | 0.024 | 3.35 (0.24-46.59) | 0.367 | 2.95 (0.35-24.84) | 0.321 |
| Others | 4.90 (2.12-11.31) | <0.001 | 2.13 (0.65-7.04) | 0.214 | 8.03 (1.56-41.43) | 0.013 | 6.39 (0.53-77.04) | 0.144 | 2.81 (0.28-28.22) | 0.381 |
| Grade | | | | | | | | | | |
| Grade I | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Grade II | 3.40 (1.97-5.84) | <0.001 | 1.74 (0.79-3.84) | 0.170 | 0.11 (0.01-1.02) | 0.052 | 0.88 (0.19-4.07) | 0.869 | 2.41 (0.44-13.08) | 0.309 |
| Grade III | 5.35 (3.30-8.68) | <0.001 | 2.62 (1.17-5.88) | 0.019 | 0.56 (0.16-2.01) | 0.377 | 2.35 (0.53-10.36) | 0.258 | 3.93 (0.66-23.42) | 0.133 |
| Grade IV | 9.14 (5.81-14.36) | <0.001 | 4.07 (1.84-9.00) | 0.001 | 1.46 (0.45-4.73) | 0.529 | 0.87 (0.16-4.81) | 0.873 | 3.09 (0.50-19.26) | 0.227 |
| T stage | | | | | | | | | | |
| T1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| T2 | 2.06 (1.11-3.82) | 0.022 | 2.71 (1.15-6.40) | 0.023 | 6.34 (0.85-47.49) | 0.072 | 1.17 (0.24-5.74) | 0.842 | 4.35 (0.57-33.47) | 0.158 |
| N stage | | | | | | | | | | |
| N0 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| N1 | 13.45 (7.99-22.63) | <0.001 | 9.44 (4.63-19.26) | <0.001 | 7.55 (2.72-20.95) | <0.001 | 24.17 (7.86-74.30) | <0.001 | 13.67 (3.72-50.29) | <0.001 |

Abbreviations: SEER: Surveillance, Epidemiology, and End Result; Met = Metastases. RIA: Retroperitoneal/intra-abdominal; IA: Indian/Alaska Native; API: Asian or Pacific Islander; Surg (prim): Surgery for primary site.

**Table 4.** Summary of studies on risk factors and prognostic factors for liposarcoma patients with distant metastases

| Author | Publication Year | Type of Tumor | Numbers of Patients | Risk Factors | Survival Times | Prognostic Factors |
|---|---|---|---|---|---|---|
| Tirumani [9] | 2015 | DDLPS | 44/148 (metastases/total) | tumor grade<br>local recurrence | 28 months (median, with metastases)<br>38 months (median, without metastases) | - |
| Muratori [19] | 2018 | MLPS<br>PLPS<br>DDLPS | 36/307 (metastases/total) | surgical margins<br>tumor size<br>local recurrence | - | - |
| Muratori [12] | 2018 | MLPS | 20/148 (metastases/total) | type of presentation<br>tumor grade<br>surgical margins<br>local recurrence | - | - |
| Vos [10] | 2018 | All types | 57/441 (metastases/total) | tumor subtypes | - | - |
| Langmans [20] | 2019 | DDLPS MLPS<br>PLPS | 100 (inoperable or metastatic) | - | 13 months (median OS) | metastasectomy response<br>to first-line chemotherapy |

Abbreviations: DDLPS, dedifferentiated liposarcoma; MLPS, myxoid/round cell liposarcoma; PLPS, pleomorphic liposarcoma.

liposarcoma who had distant metastasis, compared with younger patients. Therefore, more extensive follow-up should be considered for older individuals. As summarized in **Table 4**, a series of risk factors and prognostic factors for liposarcoma patients with distant metastases were previously reported [9, 10, 12, 19, 20]. Treatment has an important impact on the survival of patients with soft tissue sarcomas, and surgery is a widely accepted treatment approach. Complete surgical resection was previously reported to significantly improve survival in patients with dedifferentiated liposarcoma [21]. Similarly, our results revealed an association between surgery of the primary tumor and improved OS in patients with distant metastasis. Chemotherapy is also an important treatment for liposarcoma, as discussed in a recent review article describing current and potential future strategies for patients with metastatic or unresectable liposarcoma [22]. New drugs, such as trabectedin [23] and eribulin [24], have been approved for the treatment of unresectable metastatic liposarcoma. Unfortunately, the SEER database contains no clear information regarding chemotherapy, so we were unable to examine its effects on survival.

Several limitations of the present study deserve consideration. Only metastasis to the lungs, liver, bones, and brain was recorded in the SEER database, preventing us from investigating factors associated with metastasis to other sites, such as lymph nodes, glands, and subcutaneous soft tissues. We also did not investigate the incidence and patient survival rates for distant metastasis in the decades preceding 2010. Similarly, we were also unable to collect detailed information from the SEER database regarding the surgical procedures; the benefits of surgery in patients with advanced disease should be thoroughly evaluated in relation to specific types of procedures. All predictive factors identified in this study should be validated both internally and externally in the future.

In conclusion, OS of patients with liposarcoma who had distant metastasis (21.4 months) was significantly worse than OS of patients without metastasis (68.0 months). Risk factors for distant metastasis included a primary site in the trunk, myxoid subtype, grade III or IV, stage T2, and stage N1. Age ≤60 years and surgery were factors independently associated with improved OS. Patients with liposarcoma in the thorax require close follow-up, particularly focusing on early detection of brain metastasis. Homogeneous and heterogeneous risk and prognostic factors were identified for patients with metastasis to different organs. The factors identified in this study may aid in the creation of individualized screening and treatment plans for patients with liposarcoma.

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## Disclosure of conflict of interest

None.

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**Supplementary Materials.** The results of Cox regression analysis for survival of patients with metastasis to the lungs, liver, bones, or brain are shown in the Supplementary Materials

| | Lung metastasis | | | | Liver metastasis | | | | Bone metastasis | | | | Brain metastasis | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariable | | Multivariable | | Univariable | | Multivariable | | Univariable | | Multivariable | | Univariable | |
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Sex | | | | | | | | | | | | | | |
| Male | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Female | 0.92 (0.56-1.52) | 0.755 | 0.85 (0.42-1.74) | 0.664 | 0.90 (0.46-1.78) | 0.769 | 1.07 (0.41-2.75) | 0.894 | 1.64 (0.88-3.09) | 0.122 | 1.84 (0.52-6.57) | 0.347 | 3.16 (0.44-22.76) | 0.253 |
| Age | | | | | | | | | | | | | | |
| < 60 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | | |
| ≥60 | 1.37 (0.84-2.24) | 0.207 | 1.59 (0.84-3.00) | 0.155 | 1.11 (0.54-2.26) | 0.779 | 2.49 (0.97-6.39) | 0.059 | 1.17 (0.62-2.22) | 0.620 | 0.79 (0.15-4.24) | 0.788 | NA | NA |
| Race | | | | | | | | | | | | | | |
| White | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | |
| Black | 1.52 (0.74-3.09) | 0.252 | NA | NA | 0.82 (0.28-2.42) | 0.720 | NA | NA | 1.89 (0.44-8.09) | 0.392 | NA | NA | 0.87 (0.14-5.32) | 0.879 |
| AI | 1.43 (0.65-3.18) | 0.375 | NA | NA | 3.39 (0.44-26.29) | 0.243 | NA | NA | NA | NA | NA | NA | NA | NA |
| API | NA | NA | NA | NA | 0.65 (0.23-1.88) | 0.431 | NA | NA | 1.22 (0.37-4.03) | 0.740 | NA | NA | NA | NA |
| Insurance recode | | | | | | | | | | | | | | |
| Insured | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | |
| Uninsured | 1.06 (0.46-2.47) | 0.889 | NA | NA | 1.17 (0.44-3.11) | 0.755 | NA | NA | 0.91 (0.35-2.39) | 0.847 | NA | NA | 0.34 (0.04-2.93) | 0.324 |
| Marital status | | | | | | | | | | | | | | |
| Married | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | |
| Unmarried | 1.14 (0.70-1.88) | 0.597 | NA | NA | 0.87 (0.43-1.75) | 0.696 | NA | NA | 0.87 (0.46-1.66) | 0.677 | NA | NA | 0.32 (0.04-2.28) | 0.253 |
| Primary site | | | | | | | | | | | | | | |
| Extremities | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | | | NA | |
| Trunk (Head and neck) | 0.88 (0.47-1.63) | 0.679 | NA | NA | 1.21 (0.42-3.49) | 0.718 | NA | NA | 1.61 (0.74-3.49) | 0.226 | NA | NA | 1.00 (Reference) | |
| Retroperitoneal/intra-abdominal | 1.46 (0.72-2.97) | 0.297 | NA | NA | 1.11 (0.39-3.16) | 0.847 | NA | NA | 2.71 (0.94-7.82) | 0.066 | NA | NA | 4.47 (0.29-70.09) | 0.286 |
| Thorax | 1.05 (0.24-4.59) | 0.943 | NA | NA | NA | NA | NA | NA | 1.41 (0.31-6.33) | 0.657 | NA | NA | 2.15 (0.13-34.56) | 0.588 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Others | 1.56 (0.65-3.79) | 0.321 | NA | NA | 1.14 (0.30-4.26) | 0.850 | NA | NA | 1.66 (0.63-4.39) | 0.308 | NA | NA | 14.09 (0.47-426.83) | 0.128 |
| Histology | | | | | | | | | | | | | | |
| Well-Differentiated | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Dedifferentiated | 0.94 (0.38-2.27) | 0.883 | NA | NA | 1.17 (0.36-3.77) | 0.793 | NA | NA | 0.60 (0.18-1.99) | 0.405 | 3.56 (0.66-19.12) | 0.139 | NA | NA |
| Myxoid | 0.64 (0.23-1.75) | 0.380 | NA | NA | 0.33 (0.08-1.34) | 0.121 | NA | NA | 0.26 (0.08-0.87) | 0.029 | 0.75 (0.09-6.33) | 0.791 | 0.47 (0.03-8.53) | 0.607 |
| Pleomorphic | 0.75 (0.27-2.07) | 0.580 | NA | NA | 0.28 (0.03-2.51) | 0.254 | NA | NA | 0.63 (0.17-2.38) | 0.494 | 2.93 (0.46-18.67) | 0.255 | 0.16 (0.01-4.11) | 0.271 |
| Others | 0.56 (0.11-2.76) | 0.472 | NA | NA | 0.68 (0.15-3.08) | 0.615 | NA | NA | 0.16 (0.02-1.43) | 0.100 | 1.35 (0.08-22.08) | 0.831 | NA | NA |
| Grade | | | | | | | | | | | | | | |
| Grade I | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | | | | 1.00 (Reference) | |
| Grade II | 0.62 (0.13-2.88) | 0.541 | NA | NA | NA | NA | NA | NA | 0.52 (0.13-2.08) | 0.353 | NA | NA | NA | NA |
| Grade III | 0.72 (0.28-1.82) | 0.482 | NA | NA | 1.55 (0.49-4.90) | 0.458 | NA | NA | 1.48 (0.46-4.77) | 0.507 | NA | NA | NA | NA |
| Grade IV | 1.11 (0.53-2.32) | 0.787 | NA | NA | 1.82 (0.49-6.74) | 0.368 | NA | NA | 1.10 (0.34-3.60) | 0.878 | NA | NA | 0.02 (0.00-194.49) | 0.393 |
| T stage | | | | | | | | | | | | | | |
| T1 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | | |
| T2 | 0.90 (0.28-2.91) | 0.860 | 1.48 (0.32-6.86) | 0.614 | 1.18 (0.16-8.86) | 0.874 | 8.98 (0.88-91.23) | 0.063 | 0.91 (0.21-3.86) | 0.896 | 0.53 (0.09-3.03) | 0.473 | NA | NA |
| N stage | | | | | | | | | | | | | | |
| N0 | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | | |
| N1 | 0.89 (0.39-2.01) | 0.773 | 0.72 (0.27-1.91) | 0.511 | 1.07 (0.44-2.64) | 0.878 | 0.55 (0.17-1.81) | 0.323 | 2.61 (1.06-6.43) | 0.037 | 2.88 (0.66-12.54) | 0.159 | NA | NA |
| Number of mets | | | | | | | | | | | | | | |
| ≤1 | 1.00 (Reference) | | | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| >1 | 1.40 (0.86-2.27) | 0.182 | NA | NA | 2.26 (1.11-4.59) | 0.024 | 3.99 (1.26-12.64) | 0.019 | 3.00 (1.58-5.71) | 0.001 | 1.96 (0.45-8.66) | 0.373 | 0.93 (0.18-4.74) | 0.927 |
| Surg (prim) | | | | | | | | | | | | | | |
| None | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | | 1.00 (Reference) | |
| Yes | 0.42 (0.24-0.73) | 0.002 | 0.34 (0.17-0.69) | 0.003 | 0.33 (0.16-0.69) | 0.003 | 0.33 (0.12-0.90) | 0.031 | 0.41 (0.21-0.78) | 0.007 | 0.18 (0.04-0.76) | 0.020 | 3.16 (0.44-22.76) | 0.253 |