Prognostic significance of pretreatment lymphocyte/monocyte ratio in retroperitoneal liposarcoma patients after radical resection

Background: The aim of this study was to evaluate the prognostic value of pretreatment inflammatory biomarkers in retroperitoneal liposarcoma (RPLS) patients after radical resection.

Patients and methods: One hundred patients with RPLS who underwent radical resection between September 2004 and October 2010 at Fudan University Shanghai Cancer Center were included in this study. Laboratory tests of peripheral blood were sampled before surgery. The optimal cutoff values of systemic inflammatory markers were defined by receiver-operating curve analyses. Curves of disease-free survival (DFS) and overall survival (OS) were obtained by the Kaplan–Meier method. Cox proportional hazards regression modeling was used to perform univariate and multivariate analyses.

Results: The median follow-up time was 53 months. The median DFS and OS were 27 and 86 months, respectively. On the basis of the optimal cutoff value of 3, 24 patients were classified into low lymphocyte/monocyte ratio (LMR) group and 76 patients into high LMR group. In univariate analysis, low LMR group had significantly shorter DFS (HR=1.681, 95% CI 1.392–5.851, P=0.002) and OS (HR=3.897, 95% CI 1.681–9.033, P=0.004) compared to high LMR group. In multivariate analysis, low LMR was demonstrated as an independent negative prognostic factor for both DFS (HR=2.854, 95% CI=1.392–5.851, P=0.004) and OS (HR=3.897, 95% CI=1.681–9.033, P=0.002).

Conclusion: Pretreatment LMR is a useful prognostic marker in RPLS patients after radical resection.

Keywords: retroperitoneal liposarcoma, inflammatory biomarkers, prognosis, lymphocyte, monocyte ratio.

Background

Liposarcoma (LS), a rare disease derived from adipocyte progenitor, is the second most common soft tissue sarcoma (STS) affecting adulthood, accounting for approximately 20% of new diagnoses. Extremities (24%) and retroperitoneum (45%) are two predilection sites for LS.1

With surgical resection maintaining the cornerstone of curative treatment, the 5-year disease-free survival (DFS) and 5-year overall survival (OS) of retroperitoneal liposarcoma (RPLS) were 41%–50% and 54%–70%, respectively.2,3 A number of existing literatures reported the prognostic factors of RPLS.4–8 However, the inaccuracy and inadequacy of those established parameters for predicting prognosis including multifocality, tumor integrity, histological subtype, margin status, and the Union for International Cancer Control (UICC) TNM stage have gradually been demonstrated in clinical practice. Therefore, a more reliable and more convenient predictor for RPLS patients after radical resection is in urgent need.
Recent studies proved the important role of inflammatory response in tumorigenesis and tumor progression.\(^6\) Besides, an increasing number of researches revealed that systemic inflammatory markers such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), platelet/monocyte ratio (PMR), and albumin/globulin ratio (AGR) could be utilized to evaluate the prognosis of various malignancies, including colorectal cancer, adrenocortical carcinoma, pancreatic cancer, ovarian cancer, and STS.\(^9\)-\(^19\) However, there was no literature focusing on the correlation between inflammatory markers and the prognosis of RPLS. As a result, we conducted this study to explore the prognostic value of NLR, PLR, LMR, PMR, and AGR in RPLS patients after radical resection.

**Patients and methods**

**Patient selection**

This study was approved by the ethics committee of Fudan University Shanghai Cancer Center, and written informed consent was obtained from all patients. The criteria for inclusion were as follows: 1) 18 years of age or older; 2) histologically confirmed diagnosis of LS by two experienced pathologists; 3) radically resected (R0/R1 resection) localized disease (without distant metastasis) at the time of surgery; 4) no metabolic, infectious, chronic inflammatory, or autoimmune diseases; 5) no treatment of antibiotics, steroid, chemotherapy, or radiotherapy before surgery; and 6) laboratory tests of peripheral blood sample before surgery.\(^19\) Ultimate, 100 patients with RPLS who underwent radical resection between September 2004 and October 2017 at Fudan University Shanghai Cancer Center were included in this study.

The comprehensive information of age, gender, tumor size, admission status, and treatment records were obtained from medical history. Histological subtype was categorized into well-differentiated LS (WDLS), dedifferentiated LS (DDLS), myxoid LS (MLS), round cell LS (RLS), and pleomorphic LS (PLS) on the basis of the Evans classification.\(^20\) WDLS and MLS are low-grade tumors, which featured a low frequency of metastasis, whereas DDLS, RLS, and PLS are high-grade tumors with more aggressive biological behavior leading to worse prognosis.\(^21\) Multifocal disease was defined as having more than one distinct tumor nodules. Tumor integrity was classified into fragmentary group (piecemeal resection or tumor rupture during resection) and intact group on the basis of operative report and/or pathology report. The results of laboratory tests including pretreatment hematologic cell counts and albumin and globulin level were obtained from medical records.

The NLR was derived by dividing the neutrophil count by the lymphocyte count; the PLR was derived by dividing the platelet count by the lymphocyte count; the LMR was derived by dividing the lymphocyte count by the monocyte count; the PMR was derived by dividing the platelet count by the monocyte count; and the AGR was obtained by dividing the albumin level by the globulin level.

**Follow-up data**

After radical resection, all patients were arranged for surveillance imaging such as ultrasound, computed tomography, or magnetic resonance every 3–4 months for the first year, then every 6 months for the next 2 years, and then yearly.

OS was counted as the interval from the date of surgery to the date of death (event) related to the disease (or complications). DFS was calculated from the date of surgery to the date of disease relapse (local recurrence or distant metastases) or death without evidence of disease relapse. For patients alive and without records of disease relapse, follow-up was censored at the time of last follow-up. Follow-up data were collected by phone call and/or outpatient records. All 100 patients were continuously followed up to March 2018, the time of final follow-up, or the date of death.

**Statistical analysis**

SPSS 21.0 (IBM Corporation, Armonk, NY, USA) was applied for statistical analysis. Differences between groups were compared by the chi-squared test. Receiver operating characteristic (ROC) analyses were conducted with OS as endpoint. The optimal cutoff values of LMR, NLR, PMR, PLR, and AGR were determined at the point of the maximal Youden’s index.\(^18\),\(^23\) The median OS and DFS were calculated using the Kaplan–Meier method. Curves of DFS and OS were also obtained by the Kaplan–Meier method. Log-rank test was applied to compare the survival between groups. Cox proportional hazards regression modeling was used to perform univariate and multivariate analyses. The factors that identified statistical significance in the univariate analysis were then put into multivariate analysis. All tests were two sided with a significance level set at \(P<0.05\).

**Results**

**Patient characteristics and optimal cutoff values**

The clinicopathological characteristics of the 100 RPLS patients were listed at length in Table 1. There were 48 males and 52 females. The median age was 50 years (range, 27–78 years). Fifty-eight patients presented with primary
tumor, while 42 with recurrent disease. The median tumor size was 18 cm (range, 2–50 cm), <20 cm in 56 patients and ≥20 cm in 44 patients. Eighty-eight patients underwent surgery with intact tumor, while 12 received piecemeal resection. Concomitant organ resection was performed on 52 patients. Twenty-five patients presented with multifocal disease. In case of histological subtypes, 39 patients were of WDLS, 51 DDLS, 3 MLS, 2 RLS, and 5 PLS. As a result, there were 42 patients with low-grade tumors, while 58 with high-grade tumors. Of 100 patients, 10 patients received adjuvant chemotherapy, seven gained adjuvant radiotherapy, and five obtained both therapies. The average cell count (×10⁹/L) of neutrophil, lymphocyte, platelet, and monocyte was 3.93±1.56, 1.58±0.48, 245.50±91.47, and 0.48±0.16, respectively. The average level (g/L) of albumin and globulin were 41.28±5.32 and 29.66±5.43, respectively.

According to the ROC analysis (Figure 1), the area under the curve (AUC) for NLR, PLR, LMR, PMR, and AGR were 0.548 (95% CI, 0.434–0.658, \( P=0.4615 \)), 0.537 (95% CI, 0.423–0.648, \( P=0.5772 \)), 0.651 (95% CI, 0.538–0.753, \( P=0.0164 \)), 0.647 (95% CI, 0.533–0.749, \( P=0.0189 \)), and 0.686 (95% CI, 0.574–0.784, \( P=0.0020 \)), respectively.

### Table 1: Patients’ characteristics

| Variable                  | Total (N=100) | LMR≤3 (n=24) | LMR>3 (n=76) | \( P \)-value |
|---------------------------|---------------|--------------|--------------|--------------|
| Gender                    |               |              |              |              |
| Male                      | 48            | 13           | 35           | 0.488        |
| Female                    | 52            | 11           | 41           |              |
| Age (years)               |               |              |              |              |
| ≥50                       | 53            | 12           | 41           | 0.736        |
| <50                       | 47            | 12           | 35           |              |
| Presentation              |               |              |              |              |
| Recurrent                 | 42            | 9            | 33           | 0.608        |
| Primary                   | 58            | 15           | 43           |              |
| Tumor size (cm)           |               |              |              |              |
| ≥20                       | 44            | 11           | 33           | 0.836        |
| <20                       | 56            | 13           | 43           |              |
| Tumor integrity           |               |              |              |              |
| Fragmentary               | 12            | 4            | 8            | 0.420        |
| Intact                    | 88            | 20           | 60           |              |
| Organ resection           |               |              |              |              |
| Yes                       | 52            | 15           | 37           | 0.238        |
| No                        | 48            | 9            | 39           |              |
| Multifocality             |               |              |              |              |
| Yes                       | 25            | 5            | 20           | 0.589        |
| No                        | 75            | 19           | 56           |              |
| Tumor grade               |               |              |              |              |
| High grade                | 58            | 20           | 38           |              |
| Low grade                 | 42            | 4            | 38           | 0.004        |
| Adjuvant therapy          |               |              |              |              |
| Yes                       | 22            | 6            | 16           | 0.684        |
| No                        | 78            | 18           | 60           |              |
| NLR                       |               |              |              |              |
| >2.74                     | 32            | 19           | 13           | <0.001       |
| ≤2.74                     | 68            | 5            | 63           |              |
| PLR                       |               |              |              |              |
| >212                      | 21            | 17           | 4            | <0.001       |
| ≤212                      | 79            | 7            | 72           |              |
| PMR                       |               |              |              |              |
| ≤610                      | 54            | 7            | 47           | 0.058        |
| >610                      | 46            | 17           | 29           |              |
| AGR                       |               |              |              |              |
| ≤1.55                     | 62            | 21           | 41           | 0.003        |
| >1.55                     | 38            | 3            | 35           |              |

**Abbreviations:** AGR, albumin/globulin ratio; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PMR, platelet/monocyte ratio.
respectively. The maximal Youden’s index for NLR, PLR, LMR, PMR, and AGR were 0.132, 0.140, 0.329, 0.299, and 0.377, respectively. The optimal cutoff value for NLR, PLR, LMR, PMR, and AGR were 2.74, 212, 3, 610, and 1.55, respectively. Details of ROC analysis were summarized in Table 2.

### Data analysis

At the end of the study follow-up, 67 patients remained alive, and 66 patients suffered disease recurrence. The 5-year DFS and 5-year OS rates were 20.6% and 64.7%, respectively. The median follow-up duration, median DFS, and median OS were 53, 27, and 86 months, respectively.

In univariate analysis, shorter OS was significantly associated with fragmentary resection (median OS, 33 vs 115 months, *P* = 0.004), multifocality (median OS, 48 vs 97 months, *P* = 0.001), high-grade tumor (median OS, 58 vs 158 months, *P* = 0.001), low LMR (median OS, 48 vs 86 months, *P* < 0.001), low PMR (median OS, 72 vs 158 months, *P* = 0.030; Figure 2A), and low AGR (median OS, 66 vs 81 months, *P* = 0.026). Shorter DFS was significantly associated with recurrent disease (median DFS, 21 vs 30 months, *P* = 0.031), fragmentary resection (median DFS, 11 vs 28 months, *P* = 0.011), multifocality (median DFS, 12 vs 31 months, *P* < 0.001), high-grade tumor (median DFS, 21 vs 46 months, *P* < 0.001), high PLR (median DFS, 20 vs 30 months, *P* = 0.050), and low LMR (median DFS, 13 vs 31 months, *P* < 0.001; Figure 2B). Details of univariate analysis were presented in Table 3.

In multivariate analysis, fragmentary resection (OS: HR, 4.602, 95% CI, 1.851–11.438, *P* = 0.001; DFS: HR, 2.697, 95% CI, 1.350–5.385, *P* = 0.005), multifocality (OS: HR, 4.265, 95% CI, 1.836–9.906, *P* = 0.001; DFS: HR, 3.415, 95% CI, 1.737–6.716, *P* < 0.001), high-grade tumor (OS: HR, 6.515, 95% CI, 1.059–3.463, *P* = 0.031), and low LMR (OS: HR, 3.897, 95% CI, 1.681–9.033, *P* = 0.002; DFS: HR, 2.854, 95% CI, 1.392–5.851, *P* = 0.004) remained statistically significant for both OS and DFS. Details of multivariate analysis were listed in Table 4.

### Discussion

Increasing evidences revealed the correlation between inflammatory biomarkers and the prognosis of diversified malignancies, including STS.9–19 However, almost all of the existing literatures about STS were histology non-specific, which mingled various histologic subtypes of STS.9,14–17 As known earlier, STS represented a complex group of neoplasms of mesenchymal origin, and the prognosis might vary markedly based on different histologic subtypes and different tumor locations. Therefore, we argued that it would be more helpful in clinical practice if we could conduct histology- and location-specific researches.

This is the first study, to the best of our knowledge, that focuses specifically on the prognostic values of the inflammatory biomarkers in radically resected RPLS patients. In addition, our findings prove preoperative LMR to be an independent prognostic factor of both OS and DFS for radically resected RPLS patients.

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**Table 2** Results of ROC curve analyses

| Variable | AUC   | 95% CI     | P-value | Maximal Youden’s index | Optimal cutoff |
|----------|-------|------------|---------|------------------------|---------------|
| NLR      | 0.548 | 0.434–0.658| 0.4615  | 0.132                  | 2.74          |
| PLR      | 0.537 | 0.423–0.648| 0.5772  | 0.140                  | 212           |
| LMR      | 0.651 | 0.538–0.753| 0.0164  | 0.329                  | 3             |
| PMR      | 0.647 | 0.533–0.749| 0.0189  | 0.299                  | 610           |
| AGR      | 0.686 | 0.574–0.784| 0.0020  | 0.377                  | 1.55          |

Abbreviations: AGR, albumin/globulin ratio; AUC, area under the curve; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; PMR, platelet/monocyte ratio; ROC, receiver operating characteristic.
Figure 2 Kaplan–Meier survival curves for OS (A) and DFS (B) according to pretreatment LMR. 
Abbreviations: DFS, disease-free survival; LMR, lymphocyte/monocyte ratio; OS, overall survival.

| Variable                  | DFS | OS |
|---------------------------|-----|----|
|                           | Median, months (95% CI) | HR (95% CI) | P-value | Median, months (95% CI) | HR (95% CI) | P-value |
| Gender                    |     |    |
| Male                      | 28 (21.9–34.1) | 0.88 (0.54–1.43) | 0.592 | 72 (51.1–92.9) | 1.29 (0.65–2.56) | 0.473 |
| Female                    | 23 (14.4–31.6) |   |   | 115 (55.8–174.2) |   |   |
| Age (years)               |     |    |
| ≥50                       | 28 (22.3–33.7) | 0.87 (0.54–1.42) | 0.570 | 86 (54.7–117.3) | 1.13 (0.57–2.25) | 0.730 |
| <50                       | 22 (19.6–24.4) |   |   | 81 (35.2–126.8) |   |   |
| Presentation              |     |    |
| Recurrent                 | 21 (15.1–26.9) | 1.68 (1.03–2.74) | 0.031 | 97 (49.5–144.5) | 1.09 (0.55–2.17) | 0.804 |
| Primary                   | 30 (25.2–34.8) |   |   | 81 (59.6–102.4) |   |   |
| Tumor size (cm)           |     |    |
| ≥20                       | 31 (24.7–37.3) | 0.86 (0.53–1.40) | 0.536 | 81 (55.3–106.7) | 1.10 (0.55–2.18) | 0.795 |
| <20                       | 24 (16.9–31.1) |   |   | 97 (53.1–104.9) |   |   |
| Tumor integrity           |     |    |
| Fragmentary               | 11 (5.9–16.1) | 2.26 (1.17–4.35) | 0.011 | 33 (27.4–38.6) | 3.03 (1.38–6.64) | 0.004 |
| Intact                    | 28 (23.2–32.8) |   |   | 115 (59.1–170.9) |   |   |
| Organ resection           |     |    |
| No                        | 24 (14.4–33.6) | 1.14 (0.69–1.85) | 0.612 | 81 (52.2–109.8) | 0.87 (0.44–1.73) | 0.689 |
| Yes                       | 31 (18.5–43.5) |   |   | 86 (50.7–121.3) |   |   |
| Multifocality             |     |    |
| Yes                       | 12 (9.3–14.7) | 2.91 (1.66–5.09) | <0.001 | 48 (35.2–60.8) | 3.11 (1.55–6.24) | 0.001 |
| No                        | 31 (26.1–35.9) |   |   | 97 (74.6–119.4) |   |   |
| Tumor grade               |     |    |
| High grade                | 21 (15.2–26.8) | 2.67 (1.55–4.63) | <0.001 | 58 (40.1–75.9) | 10.30 (3.13–33.88) | <0.001 |
| Low grade                 | 46 (18.8–73.2) |   |   | 158 |   |   |
| Adjuvant therapy          |     |    |
| Yes                       | 21 (16.7–25.3) | 1.60 (0.92–2.78) | 0.072 | 66 (48.3–83.7) | 1.82 (0.86–3.82) | 0.111 |
| No                        | 28 (21.1–34.9) |   |   | 97 (59.3–134.7) |   |   |
| NLR                       |     |    |
| >2.74                     | 22 (18.1–25.9) | 1.44 (0.85–2.42) | 0.166 | 72 (55.6–88.4) | 1.67 (0.82–3.38) | 0.151 |
| ≤2.74                     | 30 (24.4–35.6) |   |   | 97 (61.8–132.2) |   |   |
| PLR                       |     |    |
| >212                      | 20 (3.6–36.4) | 1.78 (0.98–3.24) | 0.050 | 48 (20.7–75.3) | 1.96 (0.89–4.29) | 0.088 |
| ≤212                      | 30 (24.5–35.5) |   |   | 81 (65.3–96.7) |   |   |
| LMR                       |     |    |
| ≤3                        | 13 (2.7–23.3) | 2.66 (1.55–4.58) | <0.001 | 48 (17.0–79.0) | 3.44 (1.70–6.94) | <0.001 |
| >3                        | 31 (24.4–37.6) |   |   | 86 (67.9–104.1) |   |   |
| PMR                       |     |    |
| ≤610                      | 24 (18.6–29.4) | 1.48 (0.89–2.44) | 0.122 | 72 (51.7–92.3) | 2.37 (1.06–5.28) | 0.030 |
| >610                      | 31 (10.9–51.1) |   |   | 158 |   |   |
| AGR                       |     |    |
| ≤1.55                     | 26 (17.6–34.4) | 1.26 (0.76–2.08) | 0.368 | 66 (50.7–81.3) | 2.52 (1.09–5.85) | 0.026 |
| >1.55                     | 27 (15.9–38.1) |   |   | 81 (48.7–113.3) |   |   |

Abbreviations: AGR, albumin/globulin ratio; DFS, disease-free survival; LMR, lymphocyte/monocyte ratio; NLR, neutrophil/lymphocyte ratio; OS, overall survival; PLR, platelet/lymphocyte ratio; PMR, platelet/monocyte ratio; ROC, receiver operating characteristic.
In this study, we retrospectively assessed the prognostic values of NLR, PLR, LMR, PMR, and AGR by using the clinicopathologic data of 100 patients. NLR was the most common reported inflammatory index for STS.\(^9,^{15,16}\) However, we did not observe any significant effect of NLR on patients’ outcome in this cohort. There was also a study showing that low PLR was associated with poor survival among STS patients, an effect that was not observed in this study.\(^7\) The absence of prognostic value of NLR and PLR in this cohort might be explained by the following two reasons. First, perhaps NLR and PLR possessed no prognostic value for RPLS instead. As previous researches contained various histologic subtypes of STS, the correlations between RPLS and NLR/PLR were probably obscured by the large number of the entire samples.\(^9,^{15,16}\) Second, our samples might be not large enough to discover their prognostic values. In case of PMR, there was no report showing the prognostic significance of PMR in patients with malignancy. In this study, low PMR was adversely associated with OS (\(P=0.030\)) in univariate analysis. However, it lost the significance in multivariate analysis (\(P=0.677\)). In the previous report that comprised 5,336 patients from our institution, low AGR was proven to be an independent predicator for colorectal cancer patients after curative resection.\(^{19}\) In this study, low AGR group showed worse OS in univariate analysis (\(P=0.026\)), but it was not statistically significant in multivariate analysis (\(P=0.677\)). In terms of LMR, pretreatment LMR was reported to be independently associated with patients’ outcomes among various malignancies, including colorectal cancer, malignant pleural mesothelioma, hepatocellular carcinoma, gastric cancers, and STS.\(^{14,19,24-26}\) Szkandera et al\(^{14}\) reported that LMR<2.85 was associated with worse prognosis in STS patients. In this research, low LMR was proven to be an independent adverse prognostic factor for both OS (\(P=0.002\)) and DFS (\(P=0.004\)).

| Variable                                      | DFS HR (95% CI) | P-value | OS HR (95% CI) | P-value |
|-----------------------------------------------|-----------------|---------|----------------|---------|
| Presentation (primary vs recurrent)           | 1.142 (0.651–2.003) | 0.643   |                |         |
| Tumor integrity (intact vs fragmented)       | 2.697 (1.350–5.385) | 0.005   | 4.602 (1.851–11.438) | 0.001   |
| Multifocality (no vs yes)                    | 3.415 (1.737–6.716) | <0.001  | 4.265 (1.836–9.906) | 0.001   |
| Tumor grade (low vs high)                    | 1.915 (1.059–3.463) | 0.031   | 6.515 (1.773–23.946) | 0.005   |
| PLR (<212 vs ≥212)                           | 1.191 (0.545–2.601) | 0.31    |                |         |
| LMR (>3 vs ≤3)                               | 2.854 (1.392–5.851) | 0.004   | 3.897 (1.681–9.033) | 0.002   |
| PMR (>610 vs ≤610)                           | 1.230 (0.519–2.913) | 0.639   |                |         |
| AGR (<1.55 vs >1.55)                         | 1.280 (0.458–3.579) | 0.638   |                |         |

Abbreviations: AGR, albumin/globulin ratio; DFS, disease-free survival; LMR, lymphocyte/monocyte ratio; OS, overall survival; PLR, platelet/lymphocyte ratio; PMR, platelet/monocyte ratio.
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Disclosure

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