Clinical Significance of Preoperative Serum High Density Lipoprotein Cholesterol Levels in Soft Tissue Sarcoma

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Abstract: The prognostic value of lipid profile remains unclear in soft tissue sarcoma. The aim of the present study was to validate the prognostic value of preoperative plasma lipid profile (high density lipoprotein-cholesterol [HDL-C], low density lipoprotein-cholesterol [LDL-C], cholesterol, and triglycerides) levels on disease-free survival (DFS) and overall survival (OS) in soft tissue sarcoma (STS) patients undergoing extensive and radical surgical resection.

The preoperative plasma lipid profile levels of 234 STS patients, who were operated on between 2000 with 2010, were retrospectively evaluated. Kaplan-Meier curves and multivariate Cox proportional models were calculated for DFS and OS.

In univariate analysis, a decreased HDL-C level was significantly associated with decreased OS (hazard ratio [HR], 3.405; 95% confidence interval [CI], 1.271–3.422, P = 0.005) and remained significant in the multivariate analysis (HR, 5.615; 95% CI, 1.243–25.378, P = 0.025). Patients with HDL-C < 1.475 mmol/L showed a median OS of 71 months. In contrast, patients with HDL-C ≥ 1.475 mmol/L had a median OS of 101 months. In univariate analysis, a decreased LDL-C level was significantly associated with decreased DFS (HR, 2.085; 95% CI, 1.271–3.422, P = 0.004) and remained significant in the multivariate analysis (HR, 1.808; 95% CI, 1.118–2.924, P = 0.016). Patients with LDL-C < 1.475 mmol/L presented with a median DFS of 47 months, whereas patients with LDL-C ≥ 1.475 mmol/L had a median DFS of 78 months. In univariate analysis and multivariate analyses regarding OS and DFS, there was no significant association between the groups in terms of LDL-C, CHO, and TG.

Our study investigated the potential prognostic utility of preoperative plasma HDL-C levels as an independent factor in STS patients who had undergone radical surgical resection.

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value of HDL-C is still unknown in cancers. Recently, some studies have been examined the plasma lipid profile in sarcoma patients, and the results show that sarcoma patients have a highly significant reduction in serum levels of triglycerides and cholesterol and a moderate decrease in LDL-cholesterol and HDL-cholesterol when compared with normal control subjects.20 However, there is little information on the influence of lipid profile on clinical outcome in STS patients. Thus, predicting the survival of STS patients by measuring their lipid profile (HDL-cholesterol, LDL-cholesterol, cholesterol and triglycerides) may be helpful for prognostic assessment.

The aim of the current study was to assess the predictive value of the lipid profile for disease-free-survival (DFS) and overall survival (OS) in a cohort of STS patients who had undergone extensive and radical surgical resection.

**PATIENTS AND METHODS**

**Patient Selection**

A total of 234 STS patients who had undergone extensive and radical resection at Sun-Yat-sen University Cancer Center, Guangzhou, China from 2000 to 2010 were enrolled in this study. Written informed consent was obtained from each patient. Ethical approval was given by the medical ethics committee of Sun Yat-sen University Cancer Center IRB. All patients met the following eligibility criteria: all patients had confirmed STS, with no previous cancer; none had received treatment before serum collection; sera were obtained from all patients before therapy, and the levels of HDL-C, LDL-C, CHO, and TG were measured using a Hitachi 7600–020 automatic biochemical analyzer. Follow-up examinations were conducted at regular intervals (3-month intervals during years 1 to 3, 6-month intervals during years 4 to 5, and 12-month intervals during years 6 to 15 after diagnosis).

Clinical information, including treatment scheme and histopathological diagnosis, were obtained from the patients’ history. For the present study all histologic specimens were centrally re-reviewed by an independent experienced pathologist specialized in diagnosing STS at the Sun-Yat-sen University Cancer Center. The stage was classified according to the American Joint Committee on Cancer (AJCC) 7th Edition21 and tumors were graded according to the French Federation of Cancer Centers Sarcoma group (FNCLCC) grading system.22

**Statistical Analysis**

Overall survival (OS), the primary end point of our study, was estimated in days from the time of radical operation until the time of death. The secondary end point was disease-free survival (DFS), which was determined from the date of curative resection to the date of the tumor recurrence or distant metastasis. We performed a receiver operating curve (ROC) analysis to determine the optimal cutoff values for the lipid profile. Chi-square test was used for analyzing the relationship between HDL-C level and clinic-pathological parameters. Kaplan-Meier method was used to calculate the survival probabilities and log-rank test was used to compare survival curves. The significance of the variables for survival was analyzed using the Cox proportional hazards model (univariate and multivariate analysis). A P < .05 was considered statistically significant. All statistical analyses were performed using the SPSS software package (SPSS Statistics 17.0).

**TABLE 1. Baseline Patient Characteristics**

| Age at operation (years) | N     | %    |
|--------------------------|-------|------|
| <65                      | 216   | 92.3 |
| ≥65                      | 18    | 7.7  |

| Gender                  |       |      |
|-------------------------|-------|------|
| Female                  | 101   | 43.2 |
| Male                    | 133   | 56.8 |

| BMI                      |       |      |
|--------------------------|-------|------|
| <25                      | 184   | 78.6 |
| ≥25                      | 50    | 21.4 |

| Tumor grade              |       |      |
|--------------------------|-------|------|
| G1                       | 66    | 28.2 |
| G2                       | 107   | 45.7 |
| G3                       | 37    | 15.8 |
| Unknown                  | 24    | 10.3 |

| Tumor site               |       |      |
|--------------------------|-------|------|
| Upper extremity          | 23    | 9.8  |
| Lower extremity          | 63    | 26.9 |
| Thoracic/trunk           | 81    | 34.6 |
| Intra-abdominal          | 38    | 16.2 |
| Head/neck                | 29    | 12.4 |

| AJCC stage               |       |      |
|--------------------------|-------|------|
| IA+IB                    | 69    | 29.5 |
| IIA+IIIB                 | 115   | 49.1 |
| III+IV                   | 35    | 15.0 |
| Unknown                  | 15    | 6.4  |

N = number, AJCC = American Joint Committee on Cancer.

**TABLE 2. Histologic Type**

|                | N     | %    |
|----------------|-------|------|
| Undifferentiated pleomorphic sarcoma/MFH | 63    | 26.9 |
| Fibrosarcoma  | 20    | 8.5  |
| Dermatofibrosarcoma proberans             | 28    | 12.0 |
| Well-differentiated liposarcoma           | 14    | 6.0  |
| Myxoid liposarcoma                        | 12    | 5.1  |
| Pleomorphic liposarcoma                    | 5     | 2.1  |
| Leiomyosarcoma                            | 13    | 5.6  |
| Rhabdomyosarcoma                          | 10    | 4.3  |
| Synovial sarcoma                          | 30    | 12.8 |
| Epithelioid sarcoma                       | 1     | 0.4  |
| Angiosarcoma                              | 8     | 3.4  |
| Alveolar soft part sarcoma                 | 5     | 2.1  |
| MPNST                                     | 12    | 5.1  |
| PNET                                      | 8     | 3.4  |
| Malignant Triton tumor                     | 1     | 0.4  |
| Mesenchymal chondrosarcoma                 | 4     | 1.7  |

MFH = malignant fibrous histiocytoma, MPNST = malignant peripheral nerve sheath tumor, N = number, PNET = primitive neuroectodermal tumor.
RESULTS

Patient Characteristics and Histologic Subtype

In our study, 234 patients underwent extensive and radical surgical resection for soft tissue sarcoma and their general characteristics are presented in Table 1. The pathological subtype of soft tissue sarcoma was summarized and shown in Table 2. The median age at time of surgery was 41 years (range from 5 to 78 years) and the median follow-up period was 79 months (range from 1 to 176 months). After performing receiver operating curve (ROC) analysis, the optimal cutoff value for HDL was 1.475 mmol/L (AUC: 0.545, 95% CI = 0.434–0.631). For LDL, the cutoff value was 2.895 mmol/L (AUC: 0.545, 95% CI = 0.479–0.677). The optimal cutoff value for TG was 0.815 mmol/L (AUC: 0.532, 95% CI = 0.434–0.631).

Relationship Between the HDL-C Level and Other Clinical Characteristics

The HDL-C level was significantly associated with tumor grade (P = 0.001) and tumor site (P = 0.034). Females tended to have a higher level of HDL-C than males. None of the other clinicopathological parameters was associated with an HDL-C <1.475 mmol/L, including age at operation, tumor grade, BMI, tumor size, tumor histology and AJCC stage (Table 3).

Prognostic Significance of the Clinical Characteristics in STS

In univariate analyses, we found significant associations of tumor grade, tumor size, tumor site, AJCC stage and HDL-C level with DFS and OS. In the multivariate analysis we observed significant associations of tumor grade, tumor site and HDL-C level with OS and DFS (Tables 4 and 5). The multivariate analysis was carried out based on age at operation, gender, BMI, tumor grade, tumor size, tumor site, AJCC stage, adjuvant radiotherapy, HDL-C level, LDL-C level, CHO level and TG level.

In both univariate and multivariate analysis, we found no significant associations of BMI with DFS and OS (Tables 4 and 5). So it is indicated that BMI was not an independent prognostic factor predicting the survival of soft-tissue-sarcoma. In addition, BMI was not significantly associated with the HDL-C concentration in our manuscript (Table 3).

Prognostic Significance of the Serum Lipid Profile in STS

Among the 234 patients, local recurrence or metastatic disease after curative surgical resection was diagnosed in 87 of 179 (48.6%) patients with an HDL-C level <1.475 mmol/L and in 17 of 55 (32.1%) patients with an HDL-C level ≥1.475 mmol/L (P = 0.021). Regarding OS, death occurred in 49 of 179 (26.8%) patients with an HDL-C level <1.475 mmol/L and in 7 of 55 (13.2%) patients with HDL-C level ≥1.475 mmol/L (P = 0.002).

In univariate analysis, a decreased HDL-C level was significantly associated with decreased OS (HR, 3.405; 95% CI, 1.243–8.021, P = 0.005) (Table 4; Figure 1) and remained significant in the multivariate analysis that included tumor site, tumor grade (HR, 5.615; 95% CI, 1.243–25.378, P = 0.025) (Table 4). Patients with HDL-C <1.475 mmol/L showed a median OS of 71 months. In contrast, patients with HDL-C ≥1.475 mmol/L had a median OS of 101 months. In univariate analysis, a decreased HDL-C level was significantly associated with decreased DFS (HR, 2.085; 95% CI, 1.271–3.422, P = 0.004) (Table 5; Figure 2) and remained significant in the multivariate analysis that included tumor grade, tumor size and tumor site and tumor (HR, 1.808; 95% CI, 1.118–2.924, P = 0.016) (Table 5). Patients with HDL-C <1.475 mmol/L presented with a median DFS of 47 months, whereas patients with HDL-C ≥1.475 mmol/L had a median DFS of 78 months.

In individual subgroup analyses, we found a significant association between decreased HDL-C levels and decreased OS in >5 cm tumors in univariate analysis (HR, 6.402; 95% CI, 1.963–20.880, P = 0.002) and in multivariate analysis (HR, 9.667; 95% CI, 1.155–80.918, P = 0.036). Patients with decreased HDL-C levels showed increased OS also in I+II stage in univariate analysis (HR, 8.624; 95% CI, 2.049–36.301, P = 0.003) and in multivariate analysis (HR, 6.355; 95% CI, 1.395–28.957, P = 0.017) (see Supplementary Table 1, http://links.lww.com/MD/A270, Supplemental digital content, http://links.lww.com/MD/A270, which showed the association between HDL-C levels and OS in individual subgroup).

| Table 2. Relationship Between HDL Concentration and Clinical Characteristics in 234 Patients With Soft-Tissue-Sarcoma |
|---|
| Characteristics | HDL-C <1.475 (mmol/L) | HDL-C ≥1.475 (mmol/L) | P |
| Age at operation(years) | | | |
| <65 | 165 | 51 | 1.000 |
| ≥65 | 14 | 4 | |
| Gender | | | |
| Female | 67 | 34 | 0.001 |
| Male | 112 | 21 | |
| BMI | | | |
| <25 | 141 | 43 | 0.926 |
| ≥25 | 38 | 12 | |
| Tumor grade | | | |
| G1þG2 | 130 | 43 | 0.522 |
| G3 | 31 | 6 | |
| Unknown | 18 | 6 | |
| Tumor size | | | |
| <5 cm | 78 | 29 | 0.233 |
| ≥5 cm | 101 | 26 | |
| Tumor site | | | |
| Upper extremity | 17 | 6 | 0.034 |
| Lower extremity | 44 | 19 | |
| Thoracic/trunk | 58 | 23 | |
| Intra-abdominal | 36 | 2 | |
| Head/neck | 24 | 5 | |
| Tumor histology | | | |
| Fibrosarcoma | 35 | 13 | 0.824 |
| Liposarcoma | 23 | 8 | |
| UPS | 51 | 12 | |
| Synovial sarcoma | 24 | 6 | |
| Others | 46 | 16 | |
| AJCC stage | | | |
| IA+IB | 49 | 20 | 0.638 |
| IIA+IIB | 90 | 25 | |
| IIB+IV | 28 | 7 | |
| Unknown | 12 | 3 | |

AJCC = American Joint Committee on Cancer, UPS = undifferentiated high-grade pleomorphic sarcoma.
In addition, patients with decreased HDL-C levels showed decreased DFS in \(> 5\) cm tumors in univariate analysis (HR, 2.485; 95% CI, 1.307–4.723, \(P = 0.005\)) and multivariate analysis (HR, 1.773; 95% CI, 1.016–3.096, \(P = 0.044\)). While patients with decreased HDL-C levels shown decreased DFS in I+II stage only in univariate analysis (HR, 2.229; 95% CI, 1.226–4.053, \(P = 0.009\)) (see Supplementary Table 2, http://links.lww.com/MD/A270, Supplemental digital content, http://links.lww.com/MD/A270, which shown the association between HDL-C levels and DFS in individual subgroup).

**DISCUSSION**

Previous studies proposed that abnormal lipid profiles may be associated with the occurrence and progression of cancers.\(^{23–25}\) In recent years, there has been increasing evidence that HDL-C correlates with clinical outcome in patients with some cancers.\(^{26–28}\) In gastrointestinal cancer patients, a low preoperative serum HDL-C concentration is a potential biomarker of advanced Pn2–3 stages.\(^{29}\) Van Duijnhoven FJ reported that high concentrations of serum HDL are associated with a decreased risk of colon cancer based on cohort studies.\(^{9}\) In lung cancer, a higher HDL-C concentration has been proven to be associated with a decreased risk of cancer overall.\(^{12,30}\) In prostate cancer, high HDL-C is regarded as a prognostic factor indicating a poor clinical outcome.\(^{19}\) However, in STS, there have not been any studies that have indicated an association between lipid profile and disease outcome. In this present study, we established the association between HDL-C and soft tissue sarcoma and showed that decreased pre-operative HDL-C in the peripheral blood was associated with decreased DFS and OS in STS patients following radical surgery.

### TABLE 4. Univariate and Multivariate Cox Proportional Analysis Regarding Overall Survival

| Parameter                        | Univariate Analysis | Multivariate Analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | HR (95% CI)         | \(P\)                 | HR (95% CI)     | \(P\)                 |
| Age at operation (years)         |                     |                       |                 |                       |
| \(< 65\)                         | 1 (referent)        | 0.442                 | 1 (referent)    | 0.946                 |
| \(\geq 65\)                      | 1.397 (0.596–3.275) | 0.044                 | 1.039 (0.342–3.163) | 0.044                 |
| Gender                           |                     |                       |                 |                       |
| Female                           | 1 (referent)        | 0.714                 | 1 (referent)    | 0.549                 |
| Male                             | 1.110 (0.636–1.937) | 0.176                 | 1.238 (0.616–2.489) | 0.376                 |
| BMI                              |                     |                       |                 |                       |
| \(< 25\)                         | 1 (referent)        | 0.382                 | 1 (referent)    | 0.576                 |
| \(\geq 25\)                      | 1.505 (0.648–3.225) | 0.032                 | 1.639 (0.575–4.882) | 0.043                 |
| Tumor grade                      |                     |                       |                 |                       |
| G1                               | 1 (referent)        | <0.001                | 1 (referent)    | 0.026                 |
| G2                               | 4.492 (1.688–11.618) | 0.003                 | 5.882 (1.236–27.997) | 0.043                 |
| G3                               | 7.137 (2.437–20.897) | 0.002                 | 10.697 (1.075–106.416) | 0.043                 |
| Tumor size                        |                     |                       |                 |                       |
| \(< 5\) cm                       | 1 (referent)        | 0.022                 | 1 (referent)    | 0.265                 |
| \(\geq 5\) cm                    | 2.629 (1.420–4.867) | 0.002                 | 1.560 (0.714–3.405) | 0.001                 |
| Tumor site                        |                     |                       |                 |                       |
| Trunk & extremity                | 1 (referent)        | <0.001                | 1 (referent)    | <0.001                |
| Head/neck & intra-abdominal       | 4.736 (2.715–8.260) | 0.001                 | 3.759 (1.878–7.523) | 0.001                 |
| AJCC stage                       |                     |                       |                 |                       |
| Localised at diagnosis           | 1 (referent)        | <0.001                | 1 (referent)    | 0.676                 |
| Metastasised at diagnosis         | 2.584 (1.684–3.966) | 0.002                 | 0.783 (0.249–2.466) | 0.362                 |
| Adjuvant radiotherapy             |                     |                       |                 |                       |
| Yes                              | 1 (referent)        | 0.647                 | 1 (referent)    | 0.918                 |
| No                               | 1.148 (0.635–2.076) | 0.044                 | 1.043 (0.468–2.325) | 0.844                 |
| HDL-C (mmol/L)                   |                     |                       |                 |                       |
| \(< 1.475\)                      | 3.405 (1.445–8.021) | 0.005                 | 5.615 (1.243–25.378) | 0.025                 |
| \(\geq 1.475\)                   | 1 (referent)        | 0.005                 | 1 (referent)    | 0.362                 |
| LDL-C (mmol/L)                   |                     |                       |                 |                       |
| \(< 2.895\)                      | 1.392 (0.803–2.412) | 0.238                 | 1.453 (0.650–3.248) | 0.362                 |
| \(\geq 2.895\)                   | 1.190 (0.526–2.285) | 0.060                 | 0.982 (0.415–2.321) | 0.966                 |
| CHO (mmol/L)                     |                     |                       |                 |                       |
| \(< 4.120\)                      | 1.105 (0.562–1.835) | 0.043                 | 1 (referent)    | 0.528                 |
| \(\geq 4.120\)                   | 1.361 (0.662–2.799) | 0.403                 | 1 (referent)    | 0.528                 |

CHO = total cholesterol, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.
There are several possible reasons, which could account for the association between HDL-C levels and tumorigenesis. First, it has been established that a major function of HDL is to maintain normal cell cholesterol homeostasis by removing excess cholesterol from an intracellular pool. Cancer cells need excess cholesterol and intermediates of the cholesterol biosynthesis pathway to maintain a high level of proliferation. The up-regulation of cholesterol biosynthesis and uptake are considered to be consistent with carcinogenesis. The possible factor that promote the upregulation of cellular cholesterol synthesis are the abundant availability of precursors (acetyl-CoA), via glycolysis that potentiates de novo fatty acid synthesis. Based on these data, the explanation of the reduction of HDL-C levels in plasma is that the activity of HDL-C receptor pathway was enhanced to prevent the accumulation of intracellular cholesterol during tumor development and lymphatic spread.

Another mechanism includes the involvement of HDL in the regulation of levels of proinflammatory cytokines and modulation of oxidative stress. Decreased levels of HDL have been associated with increased circulating levels of proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α receptors, whereas increased levels of HDL-C are related to raised levels of anti-inflammatory cytokines such as IL-10. These proinflammatory cytokines are considered to stimulate cellular proliferation and inhibit apoptosis. In contrast, anti-inflammatory cytokines inhibit the production of these proinflammatory cytokines. In addition, HDL protects LDL from oxidative damage, which has been described as a cause of tumorigenesis.

### TABLE 5. Univariate and Multivariate Cox Proportional Analysis Regarding Disease-Free-Survival

| Parameter                        | Univariate Analysis |          |          | Multivariate Analysis |          |          |
|----------------------------------|---------------------|----------|----------|-----------------------|----------|----------|
|                                  | HR (95% CI)         | P        | HR (95% CI) | P        |
| Age at operation (years)         |                     |          |          |                       |
| <65                              | 1 (referent)        | 0.005    | 1 (referent) | 0.083   |
| ≥65                              | 2.354 (1.291–4.293) |          | 1.849 (0.922–3.706) |          |
| Gender                           |                     |          |          |                       |
| Female                           | 1 (referent)        | 0.733    | 1 (referent) | 0.248   |
| Male                             | 1.068 (0.733–1.556) |          | 1.297 (0.834–2.017) |          |
| BMI                              |                     |          |          |                       |
| <25                              | 1 (referent)        | 0.790    | 1 (referent) | 0.960   |
| ≥25                              | 1.064 (0.673–1.685) |          | 1.014 (0.600–1.711) |          |
| Tumor grade                      |                     |          |          |                       |
| G1                               | 1 (referent)        | <0.001   | 1 (referent) | 0.022   |
| G2                               | 2.809 (1.602–4.927) | <0.001   | 3.068 (1.180–7.978) | 0.003   |
| G3                               | 6.201 (3.312–11.642)|          | 8.544 (2.121–34.419)|          |
| Tumor size                       |                     |          |          |                       |
| <5 cm                            | 1 (referent)        | <0.001   | 1 (referent) | 0.001   |
| ≥5 cm                            | 2.874 (1.902–4.345) |          | 2.364 (1.444–3.870) |          |
| Tumor site                       |                     |          |          |                       |
| Trunk & extremity                | 1 (referent)        | <0.001   | 1 (referent) | 0.050   |
| Head/neck & intra-abdominal      | 2.152 (1.471–3.148) |          | 1.557 (1.000–2.425) |          |
| AJCC stage                       |                     |          |          |                       |
| Localised at diagnosis           | 1 (referent)        | <0.001   | 1 (referent) | 0.739   |
| Metastasised at diagnosis        | 2.208 (1.644–2.965) |          | 0.882 (0.422–1.844) |          |
| Adjuvant radiotherapy            |                     |          |          |                       |
| Yes                              | 1 (referent)        | 0.802    | 1 (referent) | 0.710   |
| No                               | 0.949 (0.632–1.426) |          | 0.911 (0.559–1.487) |          |
| HDL-C (mmol/L)                   |                     |          |          |                       |
| <1.475                           | 2.085 (1.271–3.422) | 0.004    | 1.808 (1.118–2.924) | 0.016   |
| ≥1.475                           | 1 (referent)        |          | 1 (referent) |          |
| LDL-C (mmol/L)                   |                     |          |          |                       |
| <2.895                           | 1.457 (1.004–2.115) | 0.048    | 1.506 (0.810–2.800) | 0.196   |
| ≥2.895                           | 1 (referent)        |          | 1 (referent) |          |
| CHO (mmol/L)                     |                     |          |          |                       |
| <4.12                            | 1.097 (0.641–1.810) | 0.796    | 1 (referent) | 0.553   |
| ≥4.12                            | 1.382 (0.837–2.252) |          | 1.337 (0.752–2.377) |          |

CHO = total cholesterol, CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, LDL-C = low-density lipoprotein cholesterol, TG = triglycerides.
Furthermore, some other data supports the notion that cancer cells are able to uptake cholesterol from the plasma. For example, there is an increased expression of LDL-C receptor in breast cancer tissue compared to normal tissue. These findings suggest that during the process of carcinogenesis, tumor cells exploit the cholesterol from peripheral tissues to satisfy their increased cholesterol requirements.

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