Using the serum lactate dehydrogenase level to predict prognosis in the patients with soft tissue sarcoma: a retrospective case-control study

Taketsugu Fujibuchi (✉ buchi@m.ehime-u.ac.jp)

Ehime University Graduate School of Medicine <https://orcid.org/0000-0002-7543-4642>

Joji Miyawaki

Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Teruki Kidani

Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Hiroshi Imai

Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu

Hiromasa Miura

Ehime Daigaku Daigakuin Igakukei Kenkyuka Igakubu

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Abstract

Background Several studies have reported the prognostic factors for soft tissue sarcoma. Although serum lactate dehydrogenase (LDH) levels are reportedly associated with poor prognosis in several cancers, its role in sarcomas, especially in non-small-round cell sarcomas, remains unclear. This study aimed to evaluate the correlation between the clinical features, prognosis, and serum LDH level in soft tissue sarcoma. **Methods** A total of 67 patients with primary soft tissue sarcoma diagnosed between 2003 and 2014 were retrospectively reviewed. The serum LDH level at the first visit was stratified as >253 IU/L vs. ≤ 253 IU/L according to the standard values at our institution. The correlation between the stratified serum LDH level and clinical characteristics and the survival according to clinical characteristics including the serum LDH level were analyzed. **Results** A total of 15 patients showed high serum LDH level at the first visit. The presence of metastasis was significantly correlated with high serum LDH level ($p = 0.010$). In patients of all histologic types and even in those with non-small-round cell sarcoma without distant metastasis, the disease-specific survival was significantly worse in patients with high serum LDH level than those with normal serum LDH level ($p < 0.001$ and $p = 0.018$, respectively). **Conclusion** Elevated serum LDH level was found to be correlated with the presence of metastatic lesion. Moreover, in all soft tissue sarcomas and even in non-small-round cell sarcoma, high LDH level was one of the predictive factors for poor prognosis. Serum LDH level appeared to be associated with tumor cell activity and metastatic potential.

Background

The method for predicting the prognosis of soft tissue sarcoma has been one of the major concerns for orthopedic oncologists. Several reports on the prognostic factors of soft tissue sarcoma, such as age, tumor size, tumor depth, location, and histological grade, have already been published [1].

Lactate dehydrogenase (LDH) is a ubiquitous enzyme which is widely distributed in the body. It catalyzes the reversible transformation of lactate to pyruvate under anaerobic conditions, coupled with oxidation of NADH to NAD^+ [2]. In normal cells, the upregulation of LDH activity and increased production of pyruvate are confined to a certain stress condition, that is, tissue injury, necrosis, hypoxia, hemolysis, and myocardial infarction. However, LDH activity in cancer cells is upregulated even though it is not associated with stress condition and oxygen dependence of cancer cells is reduced. This is known as the Warburg effect [3, 4].

The serum LDH is clinically used for the late detection of myocardial infarction and the diagnosis of hemolytic anemia [5]. Its clinical importance in cancer has already reported. Several studies have reported that high LDH levels are associated with poor prognosis in several cancers, such as renal cell carcinoma, nasopharyngeal carcinoma, melanoma, prostate cancer, colorectal cancer, and lung cancer [6]. However, reports on sarcomas are limited, and high LDH levels have reportedly predicted poor overall survival rate in osteosarcoma [7–9] and Ewing sarcoma [10–12]. Furthermore, the correlation between LDH level and prognosis in all soft tissue sarcomas including non-small-round cell sarcoma has not yet been reported

and remains unknown. This study aimed to evaluate the correlation between clinical features and serum LDH levels and prognostic impact of serum LDH levels in all histologic types of soft tissue sarcoma and non-small-round cell sarcoma.

Methods

Patients and Methods

A total of 98 patients with soft tissue sarcoma patients treated in our hospital between April 2003 and March 2014 were retrospectively reviewed. Among them, 31 were treated after an unplanned resection or referred for additional treatment and excluded from this study. The remaining 67 patients with soft tissue sarcoma were included. A blood test including LDH was performed for all patients during their first visit to our hospital. Histological diagnosis was made using core needle, incisional, or excisional biopsies, and computed tomography was performed to screen for distant metastasis. Treatment was performed in 60 cases with surgical resection, 23 cases with chemotherapy, and 15 cases with radiation therapy. Age, sex, tumor depth, tumor size, presence or absence of metastasis, histology, and serum LDH levels were extracted from clinical data. Serum LDH levels were stratified as >253 IU/L and ≤ 253 IU/L according to the standard values at our institution, age was stratified as ≥ 50 years and < 50 years [13], and tumor size as ≥ 5 cm and < 5 cm [14], in accordance with previous reports. The histological type was divided into small-round cell and non-small-round cell sarcomas. The correlation between stratified serum LDH level and age, sex, tumor depth, tumor size, presence or absence of distant metastases, and histological type was analyzed. Patient's disease-specific survival (DSS) and event-free survival (EFS) were analyzed on the basis of clinical characteristics including the serum LDH levels. DSS was defined as the interval between the date of first visit to our institute and date of death. EFS was defined as the interval between the date after the primary treatment and date of local recurrence or distant metastasis. Patients who achieve tumor-free status at the initial treatment were excluded from the EFS analysis. DSS and EFS were examined both in patients of all histologic types and in those with non-small-round cell sarcoma.

Statistical analysis

Categorical data were evaluated using Fisher's exact test. Survival curves were constructed using Kaplan–Meier method and the generalized Wilcoxon test was used to compare the survival of patients with clinical characteristics. Statistical analyses were performed using JMP® 11 (SAS Institute Inc., Cary, NC, USA). A p -value of < 0.05 was considered statistically significant.

Results

Patient demographics

The mean age of patients was 57.5 (standard deviation [SD], 22.4) years. The patients comprised 42 men and 25 women, and 15 tumors were superficial, whereas 52 were deep. The mean tumor size was 94.2 (SD, 53.4) mm; 53 patients showed no metastasis and 14 patients showed distant metastases at first visit. The mean serum LDH level was 279 (SD, 369) IU/L, and 15 patients had high serum LDH levels and 48 had normal serum LDH levels on the basis of the above-mentioned stratification. The most frequently diagnosed tumors were malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma (17 patients), followed by liposarcoma (16 patients), leiomyosarcoma (8 patients), malignant peripheral nerve sheath tumor (6 patients), rhabdomyosarcoma (5 patients), synovial sarcoma (4 patients), Ewing sarcoma (3 patients), and other histologic types (8 patients). The tumors were located in the thigh (37 patients), trunk (7 patients), lower leg (5 patients), buttocks (4 patients), retroperitoneum (4 patients), forearm (4 patients), upper arm (3 patients), and others (3 patients).

Serum LDH level and clinical characteristics

The presence or absence of distant metastasis at the first visit showed significant correlation with serum LDH level ($p = 0.01$). The histologic type was also significantly correlated with serum LDH level ($p = 0.011$). The difference in age, sex, tumor depth, and tumor size was not significant in patients with high and normal LDH levels (Table 1).

DSS and clinical characteristics of patients in all histologic types

The correlation between DSS and clinical characteristics are shown in Table 2. Patients with high LDH levels exhibited significantly worse DSS than those with normal LDH levels ($p < 0.001$) (Figure 1). Patients with distant metastases at the first visit also exhibited worse DSS than those without distant metastases ($p < 0.001$). Age, sex, tumor depth, tumor size, and histology were not associated with DSS.

EFS and clinical characteristics of patients in all histologic types

EFS was evaluated in 52 patients who achieved a tumor-free status at the initial treatment. Patients with small tumor sizes showed a significantly better EFS rate than those with large tumor sizes ($p = 0.015$). Age, sex, tumor depth, histology, and LDH level were not associated with EFS (Table 3).

DSS and clinical characteristics in patients with non-small-round cell sarcoma patients without distant metastasis

In this study, patients with non-small-round cell sarcomas and metastatic disease were showed significantly high LDH levels. Patients with distant metastasis at first visit have been known to have poor prognosis [15][16], and some reports showed high serum LDH levels indicated poor prognosis especially in Ewing sarcoma [12]. Therefore, survival in 49 patients with non-small-round cell tumor without distant metastasis was analyzed to eliminate their effects (Table 4). Patients with high LDH levels showed significantly worse DSS than those with normal LDH level, even in the cohort of patients with non-small-round cell sarcoma without distant metastasis ($p = 0.018$) (Figure 2). Age, sex, tumor depth, and tumor size were not associated with DSS.

EFS and clinical characteristics in patients with non-small-round cell sarcoma

In patients with non-small-round cell sarcoma, tumor size was significantly correlated with EFS ($p = 0.021$) (Table 5). Age, sex, tumor depth, and LDH level were not associated with EFS.

Discussion

The patients of this study demonstrated that patients with small-round-cell sarcomas and patients with metastases at the first visit showed high LDH levels. LDH is a ubiquitous enzyme among vertebrate organisms and catalyzes the interconversion of pyruvate and lactate concurrently with the interconversion of NAD^+ and NADH.[2] LDH has five major isoenzymes, numbered LDH-1 through LDH-5, formed by the association between two different types of subunits, M and H, and encoded by two different genes: *ldh-a* and *ldh-b*. LDH-1 and LDH-5 are commonly known as LDHB and LDHA, respectively. The profile ratio of LDH isozyme is tissue-specific. Tumor tissues showing an anaerobic condition express LDH-4 and LDH-5 [17].

The Warburg effect has been shown as the role of LDH in cancer metabolism [3]. In most cells, glucose is metabolized to pyruvate via glycolysis, and then most pyruvate are completely oxidized into CO_2 in the mitochondria under the condition of abundant oxygen, a process known as oxidative phosphorylation. When oxygen shortage occurs, the pyruvate is redirected from the mitochondrial oxidative phosphorylation by generating lactate, a process known as anaerobic glycolysis. In normal cells, lactate generation by anaerobic glycolysis is limited to the condition of oxygen shortage; however, in cancer cells, most glucose is converted to lactate regardless of whether oxygen is present. This aerobic glycolysis is known as the Warburg effect [18].

According to the Warburg effect theory, the serum LDH level is increased in patients with metastatic tumor, comprising several active tumor cells. In this study, the serum LDH level was not associated with the tumor size. The serum LDH level may be more strongly associated with tumor activity and metastatic potential than mere tumor size.

Several studies have investigated the prognostic factors associated with soft tissue sarcoma. Distant metastasis at the first visit is evidently a poor prognostic factor [15, 16]. According to recent review papers on the prognostic factors in soft tissue sarcoma, age as a continuous nonlinear variable has an important effect on disease-specific mortality. Tumor size, grade, and margin were prognostic factors for both local recurrence and disease-specific mortality, and compartmentalization and anatomical location of tumors are only associated with disease-specific mortality [1]. Regarding the biomarkers, the pretreatment serum C-reactive protein level was correlated with prognosis [19–21], high neutrophil-lymphocyte ratio was also associated with poor prognosis in soft tissue sarcoma [20, 21], although available reports were limited. Furthermore, serum albumin [22] and hemoglobin [23] levels were also reported as prognostic biomarkers of soft tissue sarcomas. Among them, this study showed that the presence of distant metastases at the first visit was a poor prognostic factor for DSS in patients of all histologic types, and tumor size was a poor prognostic factor for EFS in both patients of all histologic types and those with non-small-round cell sarcomas. Several studies have reported the relationship between distant metastasis and poor DSS [11, 12], and relationship between large tumor size and local relapse risk [24] or distant recurrence [25]. Although some reports showed inconsistent results, our results are generally consistent with those of previous reports.

In addition, this study newly showed that high LDH level is associated with poor DSS rate in patients of all histologic types. Moreover, even in the cohort of patients with non-small-round cell sarcoma without distant metastasis, high LDH level is associated with poor DSS rate. LDH levels are reportedly diagnostic, prognostic, and a predictive markers of therapeutic response in many cancers [4, 6, 17], including renal cell carcinoma [26], nasopharyngeal carcinoma [27], melanoma [28], prostate cancer [29], colorectal cancer [30], and lung cancer [31]. In terms of bone and soft tissue sarcoma, high LDH level was shown to be a significant predictive factor for disease-free survival or overall survival in patients with osteosarcoma [7–9] and Ewing sarcoma [10–12]; however, the relationship between LDH level and prognosis in other sarcomas including non-small-round cell sarcoma, a major component of soft tissue sarcomas, has not been reported. The serum LDH level is a prognostic factor in both patients of all histologic types and those with non-small-round cell sarcomas.

As mentioned above, if the serum LDH level is associated with tumor cell activity and metastatic potential, these results can be reported in the same mechanism. Patients with soft tissue sarcoma showing high serum LDH levels are highly at risk of metastasis, which has a major impact on the patient's prognosis; therefore, patients with soft tissue sarcoma with high serum LDH level show poor prognosis.

This study has some limitations. First, the number of patients was relatively less compared with the article that examined other prognostic factors. Accordingly, multivariate analysis was considered to be somewhat inappropriate and has not been performed in this study. When multivariate analysis was performed using the LDH level and metastasis at the first visit as variables, high LDH level was an independent risk factor for DSS (hazard ratio, 3.89; 95% confidence interval, 1.15–13.6; $p = 0.029$, Cox regression proportional hazard model). Second, high- and low-grade histologic tumors were analyzed

together. Although analyzing the prognostic factors for high-grade sarcomas only may be interesting, it was not performed due to the small number of patients. Moreover, this analysis method was reasonable to investigate the prognostic factor for all histologic types of soft tissue sarcomas. Third, LDH isozyme was not distinguished. Not only LDH-4 and LDH-5 were expressed in tumor tissues, but also other LDH isoenzymes should have been evaluated together in this study. Therefore, the possibility that other isoenzyme levels were elevated due to other mechanisms cannot be entirely negated. However, in routine blood tests, LDH isozyme was not usually tested, and special examination is required to identify only LDH-4 and LDH-5. This problem should be addressed in a future research.

Conclusions

High serum LDH level was correlated with and a predictive factor of the presence of metastatic lesions. Patients with high LDH levels exhibited significantly worse DSS than those with normal LDH level in all histologic types and non-small-round cell sarcomas. High serum LDH level was one of the predictive factors of poor DSS in the patients with soft tissue sarcoma. Therefore, the serum LDH level appeared to be associated with tumor cell activity and metastatic potential.

Abbreviations

LDH: Lactate dehydrogenase; DSS: Disease-specific survival; EFS: Event-free survival; SD: Standard deviation

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Review Board of the Ehime University Hospital (1510010). The requirement for informed consents was waived due to the retrospective nature without identifiable patient information.

Consent for Publication

Not applicable

Availability of data and materials

The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

TF participated in the design of the work and drafted the manuscript. TF, JM and KT participated in collection, analysis, and interpretation of data. HI and HM gave advice on the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1 Correlation between serum LDH levels and clinical characteristics

	No. of patients	LDH normal (≤ 253 IU/L)	LDH high (> 253 IU/L)	<i>P</i>
Age				
<50 years	18	12	6	0.205
≥ 50 years	49	40	9	
Sex				
Male	42	35	7	0.225
Female	25	17	8	
Tumor depth				
Superficial	15	12	3	1.000
Deep	52	40	12	
Tumor size				
<5 cm	11	9	2	0.714
≥ 5 cm	56	43	13	
Metastasis				
M0	53	45	8	0.01
M1	14	7	7	
Histology				
Non-small-round cell sarcoma	59	49	10	0.011
Small-round cell sarcoma	8	3	5	

Table 2 DSS and clinical characteristics in patients of all histologic types

	No. of patients	5-Years DSS (%)	<i>P</i>
Age			
<50 years	18	75.7	0.836
≥ 50 years	49	73.7	
Sex			
Male	42	77.0	0.939
Female	25	70.7	
Tumor depth			
Superficial	15	77.4	0.593
Deep	52	74.1	
Tumor size			
<5 cm	11	90.9	0.247
≥ 5 cm	56	70.1	
Metastasis			
M0	53	83.5	<0.001
M1	14	36.9	
Histology			
Non-small-round cell sarcoma	59	79.2	0.071
Small-round cell sarcoma	8	37.5	
Serum LDH level			
Normal (≤ 253 IU/L)	52	85.1	<0.001
High (> 253 IU/L)	15	38.1	

Abbreviation: DSS, disease-specific survival

Table 3 EFS and clinical characteristics in patients of all histologic types

	No. of patients	5-Years EFS (%)	<i>P</i>
Age			
<50 years	9	66.7	0.224
≥50 years	43	50.9	
Sex			
Male	31	51.1	0.805
Female	21	58.0	
Tumor depth			
Superficial	13	49.7	0.816
Deep	39	54.3	
Tumor size			
<5 cm	8	100	0.015
≥5 cm	44	44.1	
Histology			
Non-small-round cell sarcoma	49	57.7	0.233
Small-round cell sarcoma	3	0	
Serum LDH level			
Normal (≤253 IU/L)	44	58.4	0.088
High (>253 IU/L)	8	29.2	

Abbreviation: EFS, event-free survival

Table 4 DSS and clinical characteristics in patients with non-small-round cell sarcoma without distant metastasis at the first visit

	No. of patients	5-Years DSS (%)	<i>P</i>
Age			
<50 years	7	100	0.266
≥50 years	42	81.7	
Sex			
Male	31	88.2	0.514
Female	18	77.4	
Tumor depth			
Superficial	13	91.7	0.898
Deep	36	83.2	
Tumor size			
<5 cm	8	100	0.209
≥5 cm	41	80.8	
Serum LDH level			
Normal (≤253 IU/L)	43	88.4	0.018
High (>253 IU/L)	6	60.0	

Abbreviation: DSS, disease-specific survival

Table 5 EFS and clinical characteristics in patients with non-small-round cell sarcoma

	No. of patients	5-Years EFS (%)	<i>P</i>
Age			
<50 years	7	85.7	0.117
≥50 years	42	52.3	
Sex			
Male	31	51.2	0.490
Female	18	70.5	
Tumor depth			
Superficial	13	49.7	0.944
Deep	36	59.1	
Tumor size			
<5 cm	8	100	0.021
≥5 cm	41	48.0	
Serum LDH level			
Normal (≤253 IU/L)	43	59.9	0.238
High (>253 IU/L)	6	41.7	

Abbreviation: EFS, event-free survival

Figures

Figure 1

DSS in all patients by LDH level in patients of all histologic types The 5-year DSS was 85.1% in patients with low LDH levels, whereas that in patients with high LDH levels was 38.1%. Patients with high LDH levels exhibited significantly worse DSS than those with normal LDH levels ($p < 0.001$).

Figure 2

DSS in patients with non-small-round cell sarcoma without distant metastasis by LDH level The 5-year DSS was 88.4% in patients with non-small-round cell sarcoma without distant metastasis showing low LDH levels, whereas that in patients with high LDH levels was 60.0%. Patients with high LDH levels exhibited significantly worse DSS than in those with non-small-round cell sarcoma without distant metastasis showing normal LDH levels ($p = 0.018$).