Clinical Trial/Experimental Study

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Association between microRNA-451a expression in serum and survival and prognosis in patients with Hodgkin's lymphoma

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Abstract

Background: MicroRNA-451a (miR-451a) is associated with the treatment response and outcomes in patients with Hodgkin lymphoma. The present study aimed to investigate the expression of miR-451a in patients with Hodgkin's lymphoma, and to analyze its association with survival and prognosis in clinical patients.

Methods: A total of 164 patients with Hodgkin's lymphoma and 164 healthy controls (control group) were enrolled in this study. Blood samples were collected from participants and expression levels of miR-451a were detected using reverse transcription quantitative polymerase chain reaction. Multivariate Cox-regression analysis was used to analyze the association between serum level of miR-451a and overall survival, as well as prognosis of Hodgkin's lymphoma patients. Kaplan–Meier curve was used to analyze the five-year recurrence.

Results: Outcomes demonstrated that Hodgkin's lymphoma patients had lower miR-451a serum level than healthy controls. The present results showed that expression of miR-451a was higher in the group where chemotherapy was effective than that patient where chemotherapy was ineffective. High serum levels of miR-451a were associated with longer overall survival and better prognosis of Hodgkin's lymphoma patients than patients who had lower serum miR-451a levels. Multivariate Cox-regression analysis identified miR-451a serum level was positively correlated with overall survival and prognosis in patients with Hodgkin's lymphoma.

Conclusion: The results of the present study demonstrate that serum levels of miR-451a is decreased in patients with Hodgkin's lymphoma. Data indicate that serum levels of miR-451a can be used as one of the potential biomarkers and prognosis for patients with Hodgkin's lymphoma.

Abbreviations: DLBCL = diffuse large B-cell lymphoma, miR-451a = microRNA-451a, miRNAs = microRNAs.

Keywords: Hodgkin's lymphoma, miR-451a, overall survival, prognosis

1. Introduction

Lymphoma is one of the most common human cancers and the most frequent cause of cancer-related mortality worldwide.[1] Lymphoma includes Hodgkin lymphoma and non-Hodgkin lymphoma. The incidence of lymphoma is expected to increase annually and survival of lymphoma patients is still poor due to local migration and long distance neoplasm metastasis.[2] Diffuse large B-cell lymphoma accounting for 30% to 40% of non-Hodgkin lymphoma cases is the most common type of malignant lymphoma, which displays difference heterogeneity with regard to genetic, pathological, and clinical features.[3–5] Despite various treatments have been developed in the diagnosis and treatment of diffuse large B-cell lymphoma (DLBCL), the survival is still poor due to therapeutic resistance and recurrence of this disease.[6] Hence, it is crucial to understand the potential mechanism of DLBCL.

MicroRNAs (miRNAs), 20 to 22 long small noncoding RNA molecules, are associated with posttranscriptionally regulate gene expression in cells.[7] The role of miRNAs in controlling signaling pathways implicate in tumorigenesis makes their application in diagnostics a powerful novel tool for the early detection, prognosis, and the development of innovative anti-cancer therapies.[8] MiRNAs exhibit high frequency genomic alterations in human cancer the changes of miRNAs expression have been proven to be linked with cancer progress.[9] Expression of miRNAs are associated with Hodgkin's lymphoma cell proliferation, migration and invasion by targeting

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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various genes.[10] In the case of classical Hodgkin lymphoma, microRNAs in plasma can serve as biomarkers and prediction factors.[11] MicroRNA signatures also are also associated with the treatment response and outcomes in patients with advanced classical Hodgkin lymphoma.[12] In addition, serum exosome microRNA-451a (miR-451a) has moderate diagnostic efficiency for DLBCL.[13] Furthermore, miR-451a also may be an potential indicator for therapy response monitoring in DLBCL.[14] Therefore, it is important to investigate the role of miR-451a in tumorigenesis, therapeutic strategies in lymphoma.

In the present study, we aimed to investigate the serum levels of miR-451a in patients with Hodgkin's lymphoma. This study also analyzed the corrections between miR-451a and survival in patients with Hodgkin's lymphoma.

2. Materials and method

2.1. Participants

The cohort included 186 Hodgkin's lymphoma patients and age-matched healthy controls (n = 164) were recruited in the Second Affiliated Hospital of Mudanjiang Medical College between July 2014 and October 2016. Hospitalized patients with only Hodgkin's lymphoma were diagnosed by 3 oncologists and healthy controls were confirmed by routine physical examinations in our hospital. There were 91 males and 73 females with median age of 56.5 (range, 42–74) years. A total of 22 Hodgkin's lymphoma patients were excluded. All Hodgkin's lymphoma patients included in the study receive the standard radiotherapy or ABVD chemotherapy.[15] The efficacy of chemotherapy and radiotherapy was assessed using Response Evaluation Criteria in Solid Tumors version 1.1. Exclusion criteria were as follows: (1) age < 18 years; (2) patients with metastatic Hodgkin's lymphoma; (3) patients with cancer history; (4) the estimated survival time <12 months; (5) patients will not receive radiotherapy or chemotherapy. Post-treatment surveillance evaluation was recorded through outpatient follow-up or telephone interviews every 3 months in the follow-up period. The cutoff date for follow-up was October 31, 2021. This study was approved by the ethical committee of the Second Affiliated Hospital of Mudanjiang Medical College (Ethical approval number: 20140701CAX10). All patients gave the written informed consent.

2.2. Patient tissue and serum samples

Lymphatic tumor tissues and adjacent normal tissues were collected after surgery and immediately stored in -80 °C for qRT-PCR analysis. Blood samples were obtained from all participants and stored in -35 °C.

2.3. Reverse transcription quantitative polymerase chain reaction

Total RNA was extracted from cells and tissues with RNeasy Mini kit (Invitrogen Life Technologies, Carlsbad, CA). RNA (500 ng) was reverse transcribed into cDNA using cDNA Synthesis Kit (Product code: 11117831001, Roche, Shanghai, China). The expression level of miR-451a was measured using a SYBR-Green qRT-PCR assay (Takara Bio, Inc., Kusatsu). Expression levels of miR-451a were analyzed using mirVana™ qRT-PCR miRNA measurement kit (Ambion, Austin, TX) according to the manufacture's instrument. The assays were performed in triplicate for all samples. $2^{-\Delta Ct}$ represents the normalized miRNAs expression level.

2.4. Statistical analysis

Data are expressed as mean ± standard deviation or n (%). Comparison of miR-451a level between cancer patients and healthy controls was conducted by Wilcoxon rank sum test. Multi-variate analyses were performed on these patients to assess for radiotherapy or chemotherapy therapy efficacy. Multivariate Cox-regression analysis was used to evaluate the correction between level of miR-451a and metastasis, survival, and prognosis. Kaplan–Meier method was used to determine the overall survival of patients with Hodgkin's lymphoma. The difference in OS probability was determined by log-rank test. Data were analyzed using GraphPad Prism 6.0 (GraphPad Software Inc., San Diego, CA). The significance level was set at $P < .05$.

3. Results

3.1. Characteristic of patients

A total of 186 patients with Hodgkin's lymphoma were recruited and 22 were excluded according to the inclusion criteria. The flow diagram of the Hodgkin's lymphoma patients was shown in Fig. 1. There were 91 males and 73 females with median age of 56.5 (range, 42–74) years. A total of 68 (41.5%) patients had B-symptoms. 98 (59.8%) and 66 (40.2%) patients had supradiaphragmatic and infradiaphragmatic presentation, respectively. All patients featured Hodgkin's lymphoma with I–II tumor stage. The number of patients in clinical Stage IA, IB, IIA, IIB, was seen in 46 (28.0%), 43 (26.2%), 38 (23.2%), and 37 (22.6%), respectively. All patients received radiotherapy or chemotherapy. The follow-up was 60 months. Characteristics of patients with Hodgkin's lymphoma were listed in Table 1.

3.2. Expression of miR-451a in lymphoma tissues

The expression levels of miR-451a in lymphoma tissues and adjacent normal tissues were investigated in this study. The results in Fig. 2 showed that miR-451a expression was significantly downregulated in lymphoma tissues compared to adjacent normal tissues (1.25 vs 8.86, $P < .01$).

3.3. Serum level of miR-451a in patients with Hodgkin's lymphoma

The serum levels of miR-451a were analyzed in patients with Hodgkin's lymphoma and healthy controls. All illustrated in Fig. 3, patients with Hodgkin's lymphoma had lower serum level of miR-451a than healthy controls (1.22 vs 5.56, $P < .01$).

3.4. Association between miR-451a expression and efficacy of radiotherapy or chemotherapy in Hodgkin's lymphoma patients

The serum levels of miR-451a were recorded in patients before and after chemotherapy. Data demonstrated that patients with high serum level of miR-451a had good response to radiotherapy or chemotherapy compared to patients who had low serum level of miR-451a (Table 2). There was a positive correlation between serum level of miR-451a and therapeutic efficacy of radiotherapy or chemotherapy in patients with Hodgkin's lymphoma (Table 3).

3.5. Analysis of the association between miR-451a and survival in Hodgkin's lymphoma patients

The association between miR-451a and recurrence was investigated in Hodgkin's lymphoma patients. Data observed that Hodgkin's lymphoma patients with high serum levels of miR-451a had longer overall survival than patients who had low serum levels of miR-451a ($P < .01$, Fig. 4). Multivariate Cox-regression analysis revealed that high serum level of miR-451a was positively correlated with overall survival of patients with Hodgkin's lymphoma patients ($R = 0.828$, $P < .01$, Table 4). The

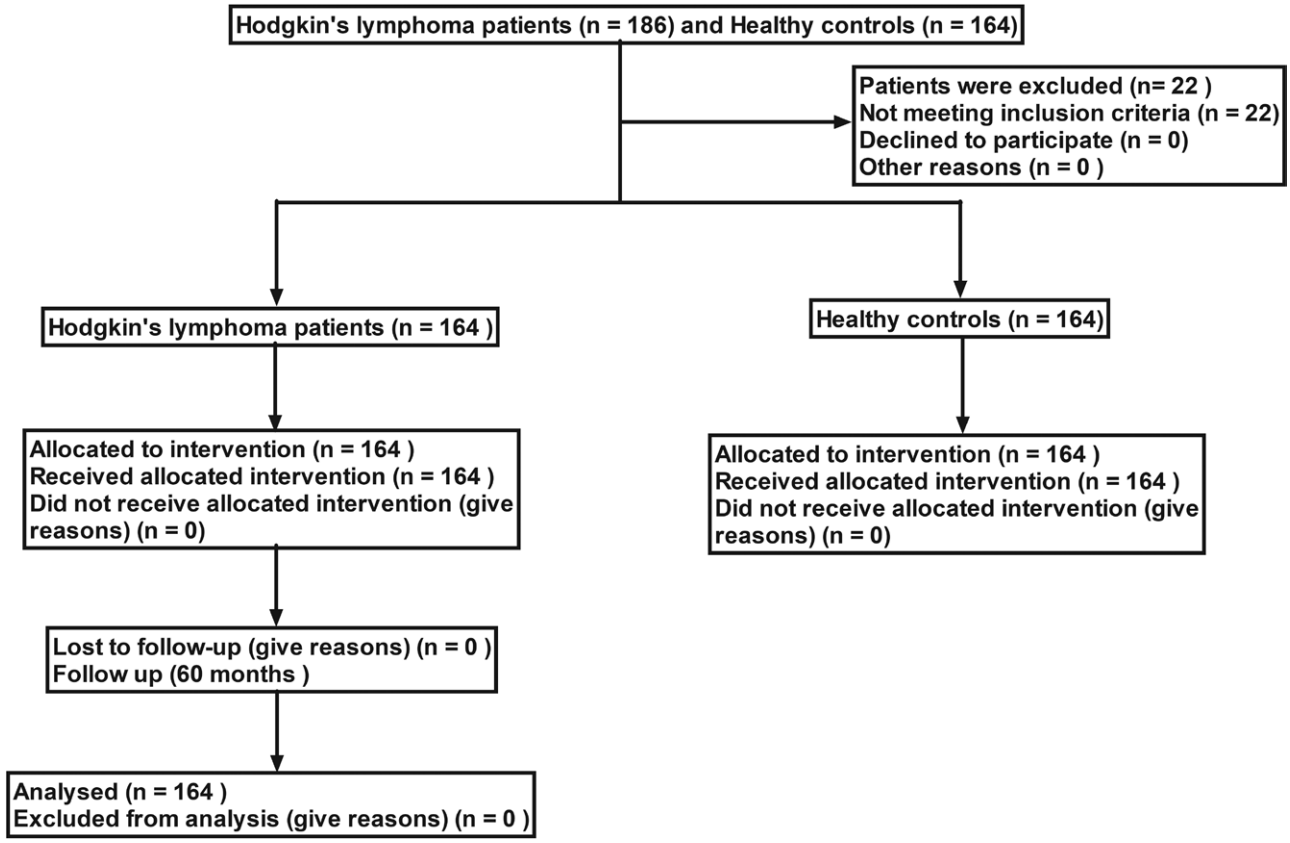

Figure 1. The flow diagram of patients with Hodgkin's lymphoma in this study.

Table 1

Characteristics of patients with Hodgkin's lymphoma.

Characteristic	Hodgkin's lymphoma patients	Healthy control	*P*-value
Age (Years)	56.5 (range, 42–74)	56.2 (range, 42–72)	.88
Gender (n, %)			
Male	91 (55.5%)	88 (53.7%)	.82
Female	73 (44.5%)	76 (46.3%)	.86
B-symptoms			
Yes	68 (41.5%)	–	–
No	96 (58.5%)	–	–
Clinical stage			
IA	46 (28.0%)	–	–
IB	43 (26.2%)	–	–
IIA	38 (23.2%)	–	–
IIB	37 (22.6%)	–	–

overall survival of patients with high serum level of miR-451a was 46.2 months (range, 32.5–75.8 months), while the overall survival of patients with low serum level of miR-451a was 40.2 months (95% CI: 26.8–58.2 months) (Table 5).

3.6. Serum level of miR-451a is associated with prognosis in Hodgkin's lymphoma patients

The association between serum level of miR-451a and prognosis was investigated in patients with Hodgkin's lymphoma. Patients with high serum level of miR-451a showed lower metastasis than patients who had low serum level of miR-451a (Fig. 5). This study analyzed the association between miR-451a and prognosis of patients with Hodgkin's lymphoma during the follow-up period. Multivariate Cox-regression analysis demonstrated that serum level of miR-451a was positively correlated with prognosis in Hodgkin's lymphoma patients (Table 6, $R = 0.648$, $P < .01$).

4. Discussion

Serum exosome miR-451a has moderate diagnostic efficiency for DLBCL.[16] However, the association between miR-451a and overall survival of Hodgkin's lymphoma patients has not investigated, yet. In this study, we reported the decreasing expression of miR-451a in lymphoma tissues and in serum level in patients with Hodgkin's lymphoma. Findings in the current study found that miR-451a was associated with the responses to radiotherapy or chemotherapy, survival, and prognosis in patients with Hodgkin's lymphoma.

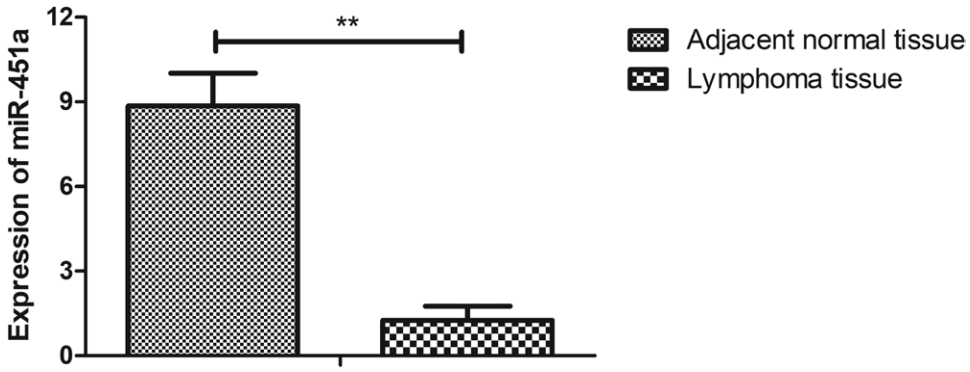

Figure 2. Expression of miR-451a in lymphoma tissues in patients with Hodgkin's lymphoma. Expression level of miR-451a between lymphoma tissues normal lymphatic tissues were measured using qRT-PCR. $^{**}P < .01$.

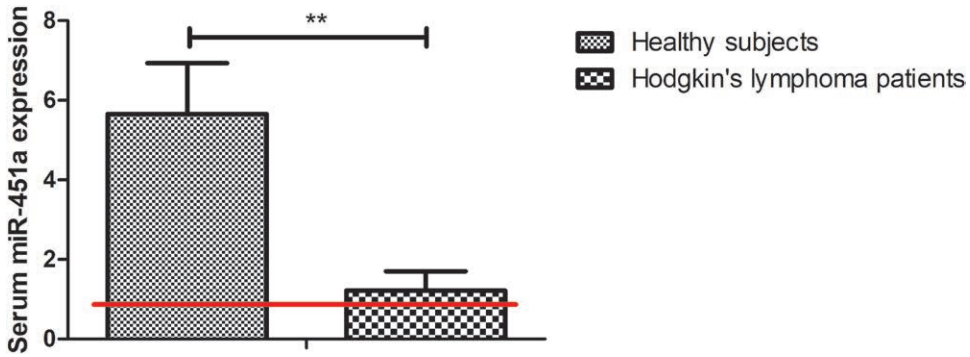

Figure 3. Serum level of miR-451a in patients with Hodgkin's lymphoma. Expression level of miR-451a was measured using qRT-PCR. $^{**}P < .01$.

Table 2

Association between serum level of miR-451a and efficacy of radiotherapy or chemotherapy in Hodgkin's lymphoma patients.

	Low miR-451a		High miR-451a	
	Good	Poor	Good	Poor
Radiotherapy	8 (4.9%)	61 (37.2%)	20 (12.2%)	3 (1.8%)
Chemotherapy	6 (3.7%)	40 (24.4%)	22 (13.4%)	4 (2.4%)

Table 3

Correlation between serum level of miR-451a and therapeutic efficacy of radiotherapy or chemotherapy in patients with Hodgkin's lymphoma.

	r	*P* value
Radiotherapy	0.812	.0022
Chemotherapy	0.764	.0035

Table 4

Correlation between serum level of miR-451a and overall survival in patients with Hodgkin's lymphoma.

	r	*P* value
Overall survival	0.828	.0016

MiR-451a serves as a tumor suppressor in various cancers.[17,18] Down-regulation of miR-451a is observed in cancer patients.[19,20] Analytic strategies based on antitumor miR-451a are effective tools for inhibiting cancer cell growth and aggressiveness features.[21,22] Data in this study demonstrated that miR-451a was downregulated in lymphoma in patients with Hodgkin's lymphoma. Consistent with tissue expression, we found serum levels of miR-451a were also decreased in patients with Hodgkin's lymphoma. We assumed that miR-451a could serve as an indicator for diagnosis of patients with Hodgkin's lymphoma. These data suggest that the serum level of miR-451a could serve as feedback the severity of Hodgkin's lymphoma patients' condition.

MiR-451a is associated uniquely with resistance to radiation treatment in the cell lines, and with the response to neoadjuvant chemoradiotherapy in patient serums.[23] Circulating miR-451a levels can be as a potential biomarker for triple negative breast cancer patients undergoing TAC chemotherapy.[24] Circulating miR-451a may be an potential indicator for therapy response monitoring in diffuse large B cell lymphoma.[14] Data in this study observed increased serum level of miR-451a was correlated with the therapeutic efficacy of radiotherapy or chemotherapy in patients with Hodgkin's lymphoma, suggesting miR-451a may be a potential of biomarker to monitor responses to treatment and predict relapse. Plasma miR-451a levels may be a useful minimally invasive biomarker for the prediction of recurrence and prognosis in patients with pancreatic ductal adenocarcinoma.[25] In addition to its primary role

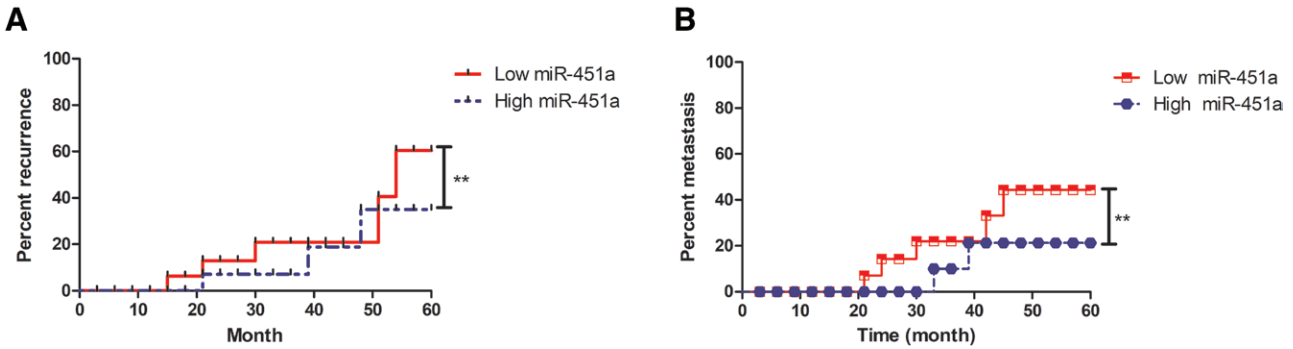

Figure 4. Overall survival analysis of Hodgkin's lymphoma patients with high or low serum level of miR-451a. Kaplan-Meier was used to analyze the survival. $^{**}P < .01$.

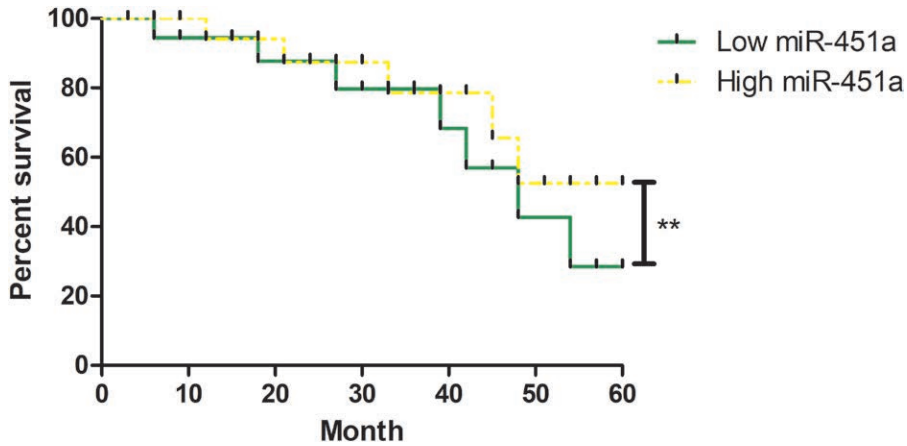

Figure 5. Metastasis of Hodgkin's lymphoma patients with high or low serum level of miR-451a. $^{**}P < .01$.

Table 5

Survival time in Hodgkin's lymphoma patients with low or high miR-451a expression during 60-month follow up.

Event	Low miR-451a	High miR-451a	*P* value
Overall survival (month)	40.2 (26.8–58.2)	46.2 (32.5–75.8)	.0086

Table 6

Correlation between serum level of miR-451a and prognosis in patients with Hodgkin's lymphoma.

Event	r	*P* value
Prognosis	0.648	.0054

in predicting the resistance of radiotherapy or chemotherapy, miR-451a had additional functions that was positively correlated with survival and prognosis of patients with Hodgkin's lymphoma. It is therefore possible that increased levels of miR-451a contributed to the increased sensitivity to radiotherapy or chemotherapy, which might contribute to longer survival of patients with Hodgkin's lymphoma. Unlike other studies reporting that miR-451a predicts the severity of cancer, we found that miR-451a might exert a predictor of survival in patients with Hodgkin's lymphoma.

Several limitations should address. First, this study only used one type of lymphoma patients. Second, a potential weakness of this study is that we only assessed serum levels of miR-451a in 164 patients with Hodgkin's lymphoma. Third, this study did not analyze the exact mechanism related to increased serum levels of miR-451a in patients with Hodgkin's lymphoma.

5. Conclusion

In conclusion, data in the current study suggest that serum level of miR-451a is closely related to responses to radiotherapy or chemotherapy, survival, and prognosis in patients with Hodgkin's lymphoma.

Author contributions

Conceptualization: Fuying Huo.
Data curation: Fuying Huo.
Formal analysis: Fuying Huo.
Funding acquisition: Fuying Huo, Chunhuan Hu.
Investigation: Fuying Huo, Chunhuan Hu.
Methodology: Chunhuan Hu.
Project administration: Chunhuan Hu, Qi Zhang.
Resources: Qi Zhang.
Software: Qi Zhang, Fangyuan Chai.

Supervision: Qi Zhang, Fangyuan Chai.
Validation: Qi Zhang, Fangyuan Chai.
Visualization: Fangyuan Chai.
Writing – original draft: Fangyuan Chai.
Writing – review & editing: Fangyuan Chai.

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