Clinicopathological features and prediction values of HDAC1, HDAC2, HDAC3, and HDAC11 in classical Hodgkin lymphoma

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Histone deacetylases (HDACs) are involved in multiple physical and pathological processes in classical Hodgkin lymphoma (cHL). The prognostic value of HDACs in cHL patients has not been discussed. The aim of the current study is to investigate the HDAC1, HDAC2, HDAC3, and HDAC11 expressions, and to evaluate the correlation of HDAC1, HDAC2, HDAC3, and HDAC11 expressions with the survival rate in cHL patients. We retrospectively analyzed clinicopathological data of 28 patients who were diagnosed with cHL between August 2002 and March 2010. Immunohistochemistry was used to detect the expression of HDAC1, HDAC2, HDAC3, and HDAC11 in these patients. The results showed that HDAC1, HDAC3, and HDAC11 were expressed at a higher level in Hodgkin Reed-Sternberg cells, whereas HDAC2 was expressed at a lower level in Hodgkin Reed-Sternberg cells. The expression of HDAC2 had a relationship with pathological type ($P = 0.012$). There was also a correlation between the expression of HDAC11 and the erythrocyte sedimentation rate ($P = 0.054$). Other clinicopathological parameters had no significant correlation with the expression of HDAC1, HDAC2, HDAC3, and HDAC11 in terms of survival ($P > 0.05$). The 10-year total survival rate by Cox multivariate analysis, after taking into account all clinical and pathological factors, showed that bulky disease retained significance ($P = 0.028$). Higher expression of HDAC1 predicted shorter progression-free survival and overall survival (OS) in cHL patients ($P < 0.05$, in both cases), and higher expression of HDAC11 might be correlated with lower OS ($P = 0.05$). The study showed that the expressions of HDAC2 and HDAC11 have a particular relationship with the pathologic subtype. Increased expression of HDAC1 was correlated negatively with progression-free survival and OS, and increased expression of HDAC11 had a borderline relationship with the OS rate in patients with cHL. Anti-Cancer Drugs 29:364–370 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: classical Hodgkin lymphoma, clinicopathological features, histone deacetylases, prognosis

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Introduction

Classical Hodgkin lymphoma (cHL), characterized by the emergence of Hodgkin Reed-Sternberg (HRS) cells in affected lymph nodes, is a particular kind of malignant tumor that originates from the B cells [1,2]. There are four types of cHL: nodular sclerosing HL (NSHL), mixed-cellularity HL (MCHL), lymphocyte-depleted HL (LDHL), and lymphocyte-rich HL (LRHL). Chemotherapy and radiation therapy, together with stem-cell transplantation, are the principal methods of treatment [3]. cHL is curable in the majority of cases by conventional methods of treatment. Although there has been good progress in targeted therapy and immunotherapy in recent years, the outcome for relapsed and/or refractory cHL needs to be further improved. However, the risks of lung and heart disease, or even other secondary cancers, are increased by these treatment methods [4]. Accordingly, further novel therapeutic options need to be explored.

Histone deacetylases (HDACs) are capable of regulating the structure of chromatin and controlling the transcriptional activity of particular genes [5–7]. HDACs consist of HDAC1 to HDAC11, of which HDAC1, HDAC2, HDAC3, and HDAC8 can be detected in the nucleus, HDAC6 is mostly expressed in the cytoplasm, whereas HDAC4, HDAC5, HDAC7, HDAC9, and HDAC10 are shuttled between the cytoplasm and the nucleus [8]. Previous studies have indicated that HDACs are generally expressed in almost all the tissues. The balance of HDACs and histone acetylases has been reported to be aberrantly regulated in multiple malignant tumors, leading to the inhibition of relevant tumor-suppressor genes [9].

HDAC inhibitors (HDACIs) are attracting considerable attention and have recently been the focus of intensive investigation [10]. HDACIs have been shown to induce a series of changes, including chromatin remodeling, regulation of transcription factor, cycle arrest, and induction
of apoptosis [11–13]. Despite the proven anticancer effects of HDACIs, the mechanisms of HDACs and the roles of HDACIs against cancer remain to be explored.

The expression and the prognostic role of HDACs have not been elucidated in cHL to date. Therefore, the expression of HDACs in patients with cHL and the prognostic roles of HDACs were analyzed in this study. Our data correlating HDAC expression with patient outcomes may illustrate the predictive role of HDACIs in the treatment of the patients with cHL.

**Patients and methods**

**Clinical specimens and patient data**

Tissue samples of 28 patients with a clear diagnosis of cHL between August 2002 and March 2010 were obtained from Shanghai Cancer Center, Fudan University (Shanghai, People’s Republic of China). All procedures were performed according to the Ethical Committee of Shanghai Cancer Center affiliated to Fudan University. Complete clinical, pathological, and follow-up data were well preserved. All enrolled patients signed the informed consent form and all procedures complied with the study protocol that had been approved by the Ethical Committee of Shanghai Cancer Center affiliated to Fudan University. Enrolled patients were followed up by telephone or at outpatient clinics annually until death or 17 February 2017.

**Immunohistochemistry and scoring**

For analysis of the expression of HDACs, the EnVision methodology was adopted. Briefly, tissues were embedded in paraffin and cut into 4-μm thick slices. The sections were heated at 73°C for 20 min and 62°C for 2 h. Subsequently, after dewaxing and rehydration, the sections were repaired with EDTA antigen retrieval solution under boiling conditions for 15 min. In addition, endogenous peroxidase activity was blocked by incubation with 3% hydrogen peroxide at room temperature for 5 min and then the sections were rinsed with PBS three times, each time for 5 min. The sections were incubated with rabbit polyclonal antibodies against human HDAC1 (H-51, sc-7872; Santa Cruz Biotechnology, Santa Cruz, California, USA), HDAC2 (H-54, sc-7899; Santa Cruz Biotechnology), HDAC3 (H-99, sc-11417; Santa Cruz Biotechnology), and HDAC11 (Y-25, sc-130776; Santa Cruz Biotechnology), which were diluted to 1/50, 1/200, 1/200, and 1/100, respectively, in the best working concentration of Tris-buffered saline (0.01 mol/l Tris–HCl, 0.15 mol/l NaCl, pH 7.6) at 4°C overnight, followed by incubation of Envision HRP-conjugated goat monoclonal against rabbit antibody (Envision-AP; Dako, Glostrup, Denmark) at 25°C for 1 h. After washing with PBS three times, each for 5 min, the sections were treated with the Metal Enhanced DAB Substrate Kit (Dako), stained by hematoxylin, dehydrated, dried, and sealed into neutral resins. Reactive proliferative lymph nodes were used as a control. Reactive proliferative lymph nodes were used as a control. As a negative control, PBS was substituted for the primary antibody.

All stained sections were read by Huang and Wang, and scoring was performed by Huang and Zhang independently. Any discrepancies were resolved by consensus with Sophia and Liu. Classification of pathologic type was performed by reference to the 2008 WHO classification of lymphoid neoplasms. Staining of positive cells was confirmed by the nuclei appearing as diffuse brown or brown yellow particles. Ten images of higher magnification (Scaled pixels: ×400) were selected in a randomized, double-blind manner, and 10 tumor cells were counted and scored in each image. The intensity of staining was scored in each specimen on a scale of 0 to 3 as 0 (negative staining), 1 (weakly positive staining), 2 (moderately positive staining), or 3 (strongly positive staining). The number of stained cells was counted and scored as 0 (<5%), 1 (5–25%), 2 (26–50%), 3 (51–70%), or 4 (>70%). Each patient was evaluated for the sum of the two parameters. Then, within a range of 0–7, the staining intensity was evaluated and graded as 0–2 (no staining), 3–4 (weak staining), and 5–7 (staining). Total scores of 0–4 were defined as low expression and scores of 5–7 were defined as high expression.

**Statistical analysis**

Data were analyzed using Social Science software 22.0 (SPSS Inc., Chicago, Illinois, USA). Pearson’s correlation coefficient analysis was carried out to analyze the correlation between HDACs expression and clinicopathological parameters. The Kaplan–Meier method was used to evaluate the correlation of the expression of HDACs with the 10-year overall survival (OS) and progression-free survival (PFS). A log-rank test was used to compare differences in the 10-year OS and PFS, and a multivariate Cox proportional hazards regression was performed to analyze predictive factors for 10-year OS and PFS. P less than 0.05 was considered statistically significant.

**Results**

**Expression of histone deacetylases in classical Hodgkin lymphoma tissues**

To analyze the expression of HDAC1, HDAC2, HDAC3, and HDAC11 in cHL tissues, a total of 28 cases of cHL were enrolled in the study. Staining positive cells of HDACs showed diffuse brown or brown yellow particles in the nucleus of HRS cells. Immunohistochemistry indicated that HDAC1 (Fig. 1a), HDAC3 (Fig. 1c), and HDAC11 (Fig. 1d) were expressed at a higher level in HRS cells, whereas HDAC2 (Fig. 1b) was expressed at a lower level in HRS cells. Expression of HDAC1, HDAC2, HDAC3, and HDAC11 in the 28 cHL cases was 78.6, 10.7, 89.3, and 32.1%, respectively.

Expression of HDAC1, HDAC2, HDAC3, and HDAC11 was 35.7, 0, 46.4, and 10.7%, respectively, in 14 cases of nodular sclerosis; 35.7, 7.1, 35.7, and 17.9%, respectively, in 11 cases of mixed cell type; 3.6, 3.6, 7.1, and 0%, respectively, in lymphocyte depletion type; and 7.1, 0, 7.1, and 0%, respectively, in the lymphocyte-rich type.
Correlation of histone deacetylases with multiple clinicopathological parameters

Correlations between the expression of HDACs with clinicopathological parameters including sex, age, histological type, American Joint Committee on Cancer stage (Ann Arbor staging system), bulky disease, B-symptoms, extranodal invasion, and erythrocyte sedimentation rate (ESR) were analyzed (Table 1). Fifteen patients were men and 13

HDAC1, HDAC2, HDAC3, and HDAC11 were stained by immunohistochemistry in the tissues of the enrolled classical Hodgkin lymphoma (cHL) patients and reactive proliferative lymph nodes (Scaled pixels: ×200). HDAC1 (a), HDAC3 (c), and HDAC11 (d) were expressed to a higher level in Hodgkin Reed-Stainberg (HRS) cells, whereas HDAC2 (b) was expressed to a lower level in HRS cells. (e, f) Reactive proliferative lymph nodes as a negative control.
patients were women, with a median age of 44 years, and 17 cases were patients aged over 45 years. In addition, eight patients were diagnosed with the bulky disease, 12 patients had B-symptoms, three patients presented with extranodal invasion, and four patients had a higher level of ESR. Stage I, II, III, and IV cases were found in 10, 10, six, and two patients, respectively. No statistical significance was found between HDACs expression and sex, age, American Joint Committee on Cancer stage, bulky disease, or B-symptoms. However, expression of HDAC2 was related to pathological type ($P = 0.012$). In addition, there was a potential correlation between the expression of HDAC11 and ESR ($P = 0.054$). Other clinicopathological parameters had no significant correlation with the expression of HDAC2, HDAC3, or HDAC11 in survival ($P > 0.05$) (Table 2 and Fig. 2). The 10-year survival rate as shown by multivariate Cox-regression analysis, after taking into account all clinical and pathologic factors, showed that bulky disease retained significance ($P = 0.028$) (Tables 3 and 4).

**Discussion**

ABVD remains the most used first-line therapy in patients with advanced-stage HL. High-dose chemotherapy with peripheral stem-cell transplantation can improve the outcome for relapsed patients after first-line chemotherapy [14,15]. Although there has been good progress in targeted therapy and immunotherapy in recent years, the outcome for relapsed and/or refractory cHL needs to be improved further. However, long-term complications such as secondary cancers, cardiopulmonary disorders, and infertility induced by intensive therapy require special attention. Tumor markers to predict the prognosis for patients with cHL and development of the novel targeted drugs merit further investigation.

In recent decades, the role of HDACs in cHL had been widely investigated. The correlation of prognosis with the expression of HDACs in prostate cancer, gastric cancer, colorectal cancer, and breast cancer has been reported previously. However, no consensus has been reached on

Table 1 Correlation of clinicopathological parameters with the HDAC1, HDAC2, HDAC3, and HDAC11 expression in enrolled classical Hodgkin lymphoma patients

| Parameters            | HDAC1 |          |          |          | HDAC2 |          |          |          | HDAC3 |          |          | HDAC11 |          |          |
|-----------------------|-------|----------|----------|----------|-------|----------|----------|----------|-------|----------|----------|-------|----------|----------|----------|
| N                     |       | Low      | High     | $P$      | Low   | High     | $P$      | Low      | High  | $P$      | Low      | High  | $P$      | Low      | High     |
| N                     | 28    | 6        | 22       | 1.000    | 25    | 3        | 0.000    | 3        | 25    | 0.538    | 19       | 9     | 0.435    |          |          |
| Sex                   |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| Man                   | 15    | 3        | 12       |         | 13    | 2        | 1        | 14       | 1     | 0.543    | 1        | 16    | 0.543    | 9        | 6        |
| Woman                 | 13    | 3        | 10       |         | 2     | 1        | 1        | 2        | 11    |          | 10       | 13    |          | 10       | 3        |
| Age (years)           |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| < 45                  | 17    | 2        | 15       | 0.174    | 16    | 1        | 0.543    | 1        | 16    | 0.543    | 13        | 4     | 0.409    |          |          |
| ≥ 45                  | 11    | 4        | 7        |         | 9     | 2        |          | 2        | 9     |          | 6        | 5     |          |          |          |
| Histological type     |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| NSHL                  | 14    | 4        | 10       | 0.130    | 14    | 0        | 0.012    | 1        | 13    | 0.032    | 11        | 3     | 0.196    |          |          |
| MCHL                  | 11    | 1        | 10       |         | 9     | 2        |          | 1        | 10    |          | 6        | 5     |          |          |          |
| LDHL                  | 1     | 1        | 0        |         | 0     | 1        |          | 1        | 0     |          | 0        | 1     |          |          |          |
| LRCHL                 | 2     | 0        | 2        |         | 2     | 0        |          | 0        | 2     |          | 2        | 0     |          |          |          |
| AJCC                  |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| I                     | 10    | 4        | 6        | 0.120    | 10    | 0        | 0.199    | 0.464    | 0.061 |          |          |          |          |          |          |
| II                    | 10    | 0        | 10       |         | 9     | 1        |          | 2        | 8     |          | 7        | 3     |          |          |          |
| III                   | 6     | 2        | 4        |         | 4     | 2        |          | 1        | 5     |          | 3        | 3     |          |          |          |
| IV                    | 2     | 0        | 2        |         | 2     | 0        |          | 0        | 2     |          | 1        | 1     |          |          |          |
| Bulky                 |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| Yes                   | 8     | 2        | 6        | 0.568    | –     | –        |          | –        | –     |          | 0        | 8     |          | 5        | 3        |
| No                    | 20    | 4        | 16       |         | –     | –        |          | 3        | 17    |          | 14       | 6     |          |          |          |
| B-symptom             |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| Yes                   | 12    | 2        | 6        | 0.479    | 8     | 0        | 0.171    | 0.171    | 0.612 |          |          |          |          |          |          |
| No                    | 16    | 4        | 10       |         | 17    | 3        |          | 3        | 17    |          | 11       | 5     |          |          |          |
| Extranodal invasion   |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| Yes                   | 3     | 1        | 2        | 0.530    | 12    | 0        | 0.298    | 0.702    | 0.704 |          |          |          |          |          |          |
| No                    | 25    | 5        | 20       |         | 13    | 3        |          | 3        | 22    |          | 17       | 8     |          |          |          |
| ESR                   |       |          |          |         |       |          |          |          |       |          |          |       |          |          |          |
| < 50                  | 24    | 5        | 19       | 1.000    | 22    | 0        | 0.382    | 0.382    | 0.054 |          |          |          |          |          |          |
| ≥ 50                  | 4     | 1        | 3        |         | 23    | 2        | 1        | 3        | 1     |          |          |          |          |          |          |

AJCC, American Joint Committee on Cancer; ESR, erythrocyte sedimentation rate; HDACs, histone deacetylases; LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-poor Hodgkin lymphoma; MCHL, mixed-cellularity Hodgkin lymphoma; NSHL, nodular sclerosing Hodgkin lymphoma.
Table 2 Univariate analysis of clinicopathological parameters and the expression of HDAC1, HDAC2, HDAC3, and HDAC11 with 10-year overall survival and progression-free survival in classical Hodgkin lymphoma patients by cox proportional hazards regression

| Clinicopathological parameters | 10-year OS (%) | P | 10-year PFS (%) | P |
|-------------------------------|---------------|---|----------------|---|
| Sex                           |               |   |                |    |
| Man                           | 38.2          | 0.451 | 23.1          | 0.065 |
| Woman                        | 43.7          | 0.223 | 34.8          | 0.007 |
| Age (years) < 45              | 41.3          | 0.223 | 32.7          | 0.057 |
| ≥ 45                         | 44.2          | 0.223 | 51.1          | 0.057 |
| AJCC                          |               |   |                |    |
| I                            | 50.0          | 0.447 | 66.7          | 0.265 |
| II                           | 46.7          | 0.567 | 23.3          | 0.638 |
| III                          | 40.0          | 0.567 | 33.3          | 0.638 |
| IV                           | 40.0          | 0.567 | 50.0          | 0.567 |
| Bulky                         |               |   |                |    |
| Yes                          | 37.5          | 0.186 | 50.0          | 0.387 |
| No                           | 53.5          | 0.186 | 40.4          | 0.847 |
| B-symptom                    |               |   |                |    |
| Yes                          | 35.4          | 0.386 | 50.0          | 0.943 |
| No                           | 31.7          | 0.386 | 35.7          | 0.943 |
| Extranodal invasion          |               |   |                |    |
| Yes                          | 0.00          | 0.567 | 33.3          | 0.638 |
| No                           | 52.5          | 0.567 | 47.6          | 0.638 |
| ESR                          |               |   |                |    |
| < 50                         | 81.8          | 0.231 | 83.3          | 0.176 |
| > 50                         | 75.0          | 0.231 | 75            | 0.176 |
| Treatment period with ABVD   |               |   |                |    |
| < 6                          | 57.1          | 0.329 | 25            | 0.865 |
| 6                            | 43.4          | 0.329 | 30.8          | 0.865 |
| Radiotherapy                 |               |   |                |    |
| Yes                          | 47.6          | 0.436 | 67.7          | 0.665 |
| No                           | 43.0          | 0.436 | 77.1          | 0.665 |
| HDAC1                        |               |   |                |    |
| Low                          | 25.0          | 0.111 | 20.6          | 0.012 |
| High                         | 66.7          | 0.111 | 80.0          | 0.012 |
| HDAC2                        |               |   |                |    |
| Low                          | 50.0          | 0.273 | 33.3          | 0.492 |
| High                         | 40.0          | 0.273 | 41.4          | 0.492 |
| HDAC3                        |               |   |                |    |
| Low                          | 39.9          | 0.349 | 42.0          | 0.442 |
| High                         | 50.0          | 0.349 | 33.3          | 0.442 |
| HDAC4                        |               |   |                |    |
| Low                          | 75.6          | 0.056 | 37.0          | 0.170 |
| High                         | 62.3          | 0.056 | 36.8          | 0.170 |

ABVD, doxorubicin, bleomycin, vincristine, and dacarbazine; HDAC, histone deacetylase; LDHL, lymphocyte-depleted Hodgkin lymphoma; LRHL, lymphocyte-rich Hodgkin lymphoma; MCHL, mixed-cellularity Hodgkin lymphoma; NSHL, nodular sclerosing Hodgkin lymphoma; OS, overall survival; PFS, progression-free survival.

the association between the expression of HDACs and clinicopathological parameters or the prognosis in patients with cHL. In contrast, HDAC1, HDAC2, HDAC3, and HDAC11 were specifically important in cHL. Class I HDACs were consistently expressed at a high level across different types of cancers. Class I and IV (HDAC111) enzymes were consistently expressed at a high level in all cell lines and primary tumors studied; however, most of the class II HDACs were not [16]. We speculated that the HDACs (class I) were specifically important in cHL as they regulate the expression of tumor suppressors or oncogenes by modifications of the constituent histones in the nucleus.

Thus, we used immunohistochemistry to detect the expression of HDAC1, HDAC2, HDAC3, and HDAC11 in cHL tissues. The expression of HDAC2 and HDAC11 has a particular relationship with the pathologic subtype. Increased expression of HDAC1 was correlated negatively with PFS and OS, and increased expression of HDAC11 had a borderline relationship with the OS rate in patients with cHL.

Adams et al. [17] found that HDAC1, HDAC2, and HDAC3 were expressed more intensely on the basis of the analysis in multiple cases of cHL tissues. Younes et al. [16] carried out a comprehensive study of HDAC1 to HDAC11 in 22 cases of cHL tissues, and reported that the expression of HDAC1, HDAC2, HDAC3, and HDAC8 was 100%, and the expression of HDAC11 was 82%. However, the correlation of HDACs with prognosis has not been mentioned in the report.

The prognostic role of HDACs has been investigated in multiple studies. HDAC4 overexpression was reported to be correlated with chromosomal instability, which could be a chromosomal instability marker [18]. In a chronic hepatitis C study, the rs3778216, rs976552, and rs368328 of HDAC2, HDAC3, and HDAC5 were related to a sustained virological response, indicating that the polymorphisms of HDACs might play predictive roles [19]. In urothelial cancer, the mRNA of HDAC2 and HDAC8 were upregulated, whereas the mRNA of HDAC4, HDAC5, and HDAC7 were downregulated. However, none of these HDACs were predictive for treatment response [20].

Our study found that HDAC1, HDAC3, and HDAC11 were more intensely expressed, whereas HDAC2 was less expressed in HRS cells, and that increased expression of HDAC1 was correlated negatively with PFS and OS. Adams et al. [17] also reported that HDAC1, HDAC2, and HDAC3 were expressed at a higher level in cHL, and that a higher expression of HDAC1 predicts a poorer outcome. To date, few studies have reported on the role of HDAC2 and HDAC3 in cHL. One study found that Myc-induced miR-15a/16-1 of HDAC3 in aggressive B-cell malignancies played an important role in c-Myc-driven microRNA suppression and malignant transformation [21]. Giohghini et al. [16] analyzed the expression of class I and class II HDACs, and found that class I HDACs were expressed at a higher level. HDAC1 expression in the proliferating germinal center lymphocytes was more intense compared with nonproliferating germinal center lymphocytes, whereas class II HDACs showed various expressions in lymphocytes. It was interesting that HDAC11 was not expressed in any cases of cHL, which is consistent with our study that HDAC11 was expressed in cHL tissues (high expression in 9/22 cases and low expression in 13/22). Thus, more studies are needed to investigate the expression of HDAC11.

HDAC11 has been reported to be related to immunomodulatory function [22]. HDAC11 was capable of regulating OX40L expression and the inhibition of HDAC11 produces a favorable antitumor immune response in
Correlation of progression-free survival (PFS) and overall survival (OS) with the HDAC1, HDAC2, HDAC3, and HDAC11 expression in the enrolled classical Hodgkin lymphoma (cHL) patients. (a, b) Higher expression of HDAC1 had a statistically significantly lower PFS ($P < 0.05$) and OS ($P < 0.05$). (c–f) No statistical significance was found between the expression of HDAC2 or HDAC3 and the PFS or OS ($P > 0.05$). (g) No statistical significance was found between the expression of HDAC11 and PFS ($P = 0.05$). (h) There is a possibility that the higher expression of HDAC11 might be correlated with the lower OS ($P = 0.05$).

Table 3 Univariate analysis of clinicopathological parameters with 10-year progression-free survival in classical Hodgkin lymphoma patients by Cox proportional hazards regression

| Parameters                  | β    | SE   | Wald | d.f. | P   | RR  | 95% CI       |
|-----------------------------|------|------|------|------|-----|-----|--------------|
| Sex                         | 1.153| 1.029| 1.254| 1    | 0.263| 3.166| 0.421–23.808 |
| Age (years)                 | 1.169| 1.276| 0.838| 1    | 0.360| 3.218| 0.264–39.255 |
| Histological type           | 0.457| 1.263| 0.131| 1    | 0.717| 1.579| 0.133–18.782 |
| ESR                         | −0.874| 1.642| 0.284| 1    | 0.594| 0.417| 0.017–10.418 |
| AJCC                        | 1.568| 2.438| 0.838| 1    | 0.360| 3.218| 0.264–39.255 |
| Bulky                       | −2.820| 1.708| 2.727| 1    | 0.099| 0.060| 0.002–1.693  |
| B symptom                   | −0.389| 1.031| 0.142| 1    | 0.706| 0.678| 0.090–5.114  |
| Overall response after chemotherapy | −0.510| 1.580| 0.203| 1    | 0.767| 0.314| 0.004–0.770  |
| IR                          | 2.043| 2.304| 0.787| 1    | 0.375| 7.715| 0.084–70.299 |

AJCC, American Joint Committee on Cancer; CI, confidence interval; ESR, erythrocyte sedimentation rate; IR, irradiation; RR, relative risk.

Table 4 Univariate analysis of clinicopathological parameters with 10-year overall survival in classical Hodgkin lymphoma patients by Cox proportional hazards regression

| Parameters                  | β    | SE   | Wald | d.f. | P   | RR  | 95% CI       |
|-----------------------------|------|------|------|------|-----|-----|--------------|
| Sex                         | 0.181| 0.760| 0.057| 1    | 0.812| 1.199| 0.270–5.315  |
| Age                         | 0.873| 0.858| 1.034| 1    | 0.309| 2.394| 0.445–12.874 |
| Histological type           | 2.004| 1.276| 2.468| 1    | 0.116| 7.422| 0.690–90.493 |
| ESR                         | −1.566| 1.779| 0.775| 1    | 0.379| 0.209| 0.006–6.824  |
| AJCC                        | −0.722| 2.053| 0.124| 1    | 0.725| 0.486| 0.009–27.159 |
| Bulky                       | −3.704| 1.882| 4.848| 1    | 0.028| 0.025| 0.001–0.666  |
| B-symptom                   | −0.487| 0.813| 0.329| 1    | 0.566| 0.627| 0.157–3.086  |
| Overall response after chemotherapy | 2.314| 2.332| 0.984| 1    | 0.321| 10.112| 0.105–977.655 |
| IR                          | 1.087| 2.624| 0.165| 1    | 0.684| 2.906| 0.017–498.062 |

AJCC, American Joint Committee on Cancer; CI, confidence interval; ESR, erythrocyte sedimentation rate; IR, irradiation; RR, relative risk.
patients with HL [23]. However, the prognosis effect of HDAC11 for HL has not been discussed previously, and our study is the first to report that the higher expression of HDAC11 might be correlated with lower OS for patients with cHL. A recent report showed that the HDAC5 expression was associated inversely with ESR, but the association of HDAC11 with ESR had not been examined in the study [24]. Our study shows that HDAC11 had a borderline association with ESR.

ABVD is still the standard first-line induction therapeutic treatment of cHL, but side effects are often inevitable. Recently, considerable progress has been made in drug discovery and development of HDACIs [25]. HDACIs could promote an open chromatin structure, and thus result in the gene transcription of the relevant tumor-suppressor gene, and induce apoptosis [9]. Previous studies have indicated that HDACIs could not only induce the apoptosis of the HRS cells but could also assist in re-stimulating the cellular immune function in the cell microenvironment [26]. Advancement of modern molecular targeting HDACIs has led to improved treatments for patients with cHL. HDACs show promise as the prognostic factors to monitor the status of cHL and to evaluate its treatment effects. More clinical trials are essential to validate the roles of HDAC expression and to provide a basis for new therapeutic approaches to patients with cHL.

Conclusion
Our study investigated the expression of HDACs in patients with cHL and showed that higher expression of HDAC1 was associated with a poor prognosis. On the basis of our study and previous research, we can conclude that HDACs play an important role in patients with cHL. Currently, HDACIs are being developed as new target drugs, showing antitumor activity in relapsed cHL patients. Further studies are warranted to validate the practical value of HDACs and to reveal their underlying roles in the treatment of the patients with cHL.

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Conflicts of interest
There are no conflicts of interest.

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