The high expression of CHD1L and its clinical significance in human solid tumors

A meta-analysis

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Abstract

Background: Chromodomain helicase DNA-binding protein 1-like (CHD1L) is an oncogene. It was cloned from 1q21 chromosome region of hepatocellular carcinoma in 1991. CHD1L is up-regulated in many kinds of cancers and is involved in the carcinogenesis and development of tumors. More and more studies have shown that over-expression of CHD1L is associated with poor prognosis of tumors. The purpose of this study was to evaluate the prognostic value of CHD1L in human solid tumors.

Methods: The key words in the database of PubMed, Web of Science, Embase, Cochrane library, and TCGA were searched for systematic literature retrieval. We collected relevant articles and data about CHD1L and prognosis of cancer and screened them according to the eligible criteria to evaluate the prognostic value of CHD1L in cancer patients. Then Stata SE12.0 software is used to analyze the data.

Results: In our meta-analysis, 2720 patients with a total of 15 articles involving multiple types of tumors showed that high expression levels of CHD1L were associated with shorter overall survival (OS) (hazard ratio = 2.21, 95% confidence interval [CI]: (1.49–3.30)] and (hazard ratio = 1.16, 95% CI: (1.01–1.32)] in the TCGA database, in addition, the pooled odds ratios (ORs) indicated high expression levels of CHD1L in tumors significantly are associated with TNM stage (OR=1.61, 95% CI: 1.01–2.55, P < .05), tumor size (OR=1.38, 95% CI: 1.07–1.78, P < .05), tumor differentiation (OR=2.13, 95% CI: 1.43–3.16, P < .05), and distant metastasis (OR=1.86, 95% CI: 1.46–2.39 P < .05). However, we did not observe a significant correlation between the high expression of CHD1L and age, gender.

Conclusion: The high expression of CHD1L is associated with poor OS as well as related to tumor differentiation, tumor size, and distant metastasis, which can be served as a prognostic marker and a potential predictor of clinical pathology in human solid tumors.

Abbreviations: BC = breast cancer, BLC = bladder cancer, C = chemotherapy, CCA = cholangiocarcinoma, CRC = colorectal cancer, DFS = disease-free survival, E = endocrine therapy, EC = esophageal cancer, GC = gastric cancer, HCC = hepatocellular cancers, IHC = immunohistochemistry, NPC = nasopharyngeal carcinoma, NR = not reported, NSCLS = non-small-cell lung cancer, OC = ovarian cancer, OS = overall survival, PC = pancreatic cancer, qPCR = quantitative real-time polymerase chain reaction, R = radiotherapy, S = surgery.

Keywords: CHD1L, clinical significance, tumor
1. Introduction

In recent years, cancer has become the major cause of death and leads to a serious burden of disease in the world. It is estimated there will be 18.1 million new cancer cases and 9.6 million cancer deaths worldwide by 2018. In addition, 48.4% of new cancer cases and 57.3% of cancer deaths occurred in Asia. Although some progress has been made in the diagnosis and treatment of cancer, the survival rate of many cancers is still unsatisfactory. Early diagnosis, early treatment are the keys to the treatment of cancers; therefore, finding new tumor markers is of great significance for the diagnosis and prognosis of cancers.

Regional chromosomal amplification is the primary mechanism of proto-oncogene activation during hepatocellular carcinoma (HCC) progression. The 1q21 amplification is thought to be an early genomic change during the progression of HCC because it is one of the most commonly detected changes in HCC. Chromodomain helicase DNA-binding protein 1-like (CHD1L), also known as amplified in liver cancer 1 gene (ALC1), has been identified as a novel target gene of 1q21, which was originally found to be significantly up-regulated in HCC. The molecular mechanism of CHD1L in tumorigenesis of liver cancer is related to its role in promoting cell proliferation and invasion and metastasis.

A growing number of studies have shown that CHD1L is also significantly up-regulated in other cancers, such as breast cancer, gastric cancer, esophageal carcinoma, and so on, which can be used as a cancer-promoting factor and have an impact on diagnosis and treatment. Many researchers reported that CHD1L is associated with tumor initiation and progression, suggesting that it is associated with cancer prognosis. So far, however, there is no specific meta-analysis to systematically elucidate the prognostic value of CHD1L in cancer. Therefore, we conducted a current meta-analysis to assess the potential value of CHD1L as a prognostic biomarker.

2. Materials and methods

2.1. Literature search

To determine potentially eligible studies, a comprehensive literature retrieval was conducted in Web of Science, PubMed, Embase, and Cochrane library databases, with a deadline of June 15, 2019. The keywords for the search were (“Chromodomain helicase DNA-binding protein 1-like” OR “CHD1L” OR “ALC1” OR “amplified in liver cancer 1 gene”) AND (“cancer” OR “carcinoma” OR “neoplasm” OR “tumor”) AND (“prognosis” OR “survival”). In addition, other relevant articles were also manually reviewed from the reference lists.

2.2. Inclusion and exclusion criteria

Inclusion criteria for the articles were as follows: the roles of CHD1L in the development of human solid tumors were investigated; associations of CHD1L expression with prognosis were depicted; the expression level of CHD1L in human solid tumors was determined by immunohistochemistry, quantitative real-time polymerase chain reaction; patients were separated into high and low expression groups according to the expression level of CHD1L.

Exclusion criteria were as follows: duplicate publications; studies without valuable data or data obtained from animal experiments; case reports, reviews, letters, and expert opinions; the expression level of CHD1L was detected in serum.

2.3. Date extraction and quality assessment

Two investigators (LZ and YFJ) extracted the data and information independently from all eligible studies by crossing check. The first author’s name, publication year, total number of patients, study country, cancer type, the criteria for high CHD1L expression, determination method, follow-up period, outcome measures, hazard ratios (HRs), and corresponding 95% CIs were collected from each study.

If a study provided the results of both univariate and multivariate analysis, then only the latter was applied directly because it could improve the accuracy of interpreting confounding factors. Any studies that only reported Kaplan–Meier curves but did not provide multivariate data were excluded. If there was a disagreement, an agreement was reached by a third investigator (PPJ). The quality of all included studies was evaluated using the Newcastle-Ottawa Scale (NOS). The NOS scores ranged from 0 to 9, with ≥ 6 considered to indicate high study quality. The quality of all studies included in this meta-analysis varied from 5 to 9, with a mean value of 6.5.

2.4. Statistical methods

This meta-analysis was performed with Stata SE12.0. We evaluated the heterogeneity across included studies with the $\chi^2$-based Q test and F statistic. A P value less than .05 for the Q test and an I² value more than 50% were considered to indicate significant heterogeneity. For studies with no obvious heterogeneity (P $\chi$ >.05, I² < 50%), the fixed-effects model was adopted, and the random-effects model was applied for others (P $\chi$ ≤ .05, I² ≥ 50%). Begg test and Egger tests were used to assess potential publication bias. The sensitivity analysis was performed to examine the stability of the results. Differences with P values of less than .05 were considered statistically significant.

2.4.1. Data extraction and analysis method in the TCGA database

The TCGA-pancancer data of the CHD1L expression levels and their matched survival were collected from the cBio Cancer Genomics Portal (www.cbioportal.org). Median expression was used as the cut-off value in Cox regression model, HRsand corresponding 95% CIs of the 2 groups were calculated through the cox regression model.

3. Results

3.1. Study characteristics

The literature retrieval process (Fig. 1) yielded a total of 15 eligible articles, which were all from Asia. The mean patient sample size was 181 (from 53 to 616) and there were a total of 2720 cancer patients. In our study, 11 different solid tumor types were evaluated, including 3 hepatocellular cancers, 2 breast cancers, and 1 each of bladder cancer, pancreatic cancer, ovarian carcinoma, glioma, esophageal carcinoma, cholangiocarcinoma, gastric cancer, colorectal cancer, non-small-cell lung cancer, and nasopharyngeal carcinoma. All cancerous specimens were well preserved and relied on pathology to make a diagnosis. The main characteristics are summarized (Table 1).
3.2. The association between increased CHD1L and overall survival (OS)

The overall survival (OS) according to CHD1L expression was reported in 9 articles. We adopted the random-effects model to estimate the pooled HRs and corresponding 95% CIs. The results showed an obviously heterogeneity across studies ($I^2 = 71.7\%$, $P_h = .000$). The HRs for the high CHD1L expression group versus the low CHD1L expression group were 2.21 (95% CI: 1.49–

### Table 1

Main characteristics of all included studies.

| First author | Publication year | Cancer type | Total number | Tumor stage | Follow up (years) | Detection method | Outcome measure | Multivariate analysis | Treatment received | Study type |
|--------------|------------------|-------------|--------------|-------------|------------------|-----------------|------------------|---------------------|-------------------|------------|
| Heyon        | 2012             | HCC         | 281          | 232/49 (I-II/III-IV) | >10 yr           | IHC             | DFS              | Yes                  | S                 | Retrospective study |
| Tian         | 2013             | BLC         | 153          | 96/57 (I-II/III-IV) | >5 yr            | IHC             | OS               | Yes                  | S                 | Retrospective study |
| Su           | 2014             | GC          | 616          | 264/252 (I-II/III-IV) | >6 yr            | IHC             | OS               | Yes                  | S                 | Retrospective study |
| Wu           | 2014             | BC          | 179          | 172/7 (I-II/III-IV) | >8 yr            | IHC             | OS+DFS           | Yes                  | S                | Retrospective study |
| Liu C        | 2017             | PC          | 112          | 34/78 (I-II/III-IV) | >4yr             | IHC             | OS               | Yes                  | S                 | Prospective study   |
| Chen         | 2010             | HCC         | 109          | 87/22 (I-II/III-IV) | >6yr             | IHC             | NR               | NR                  | S                 | Prospective study   |
| He           | 2012             | OC          | 102          | 29/73 (I-II/III-IV) | >10 yr           | IHC             | OS               | Yes                  | S                 | Retrospective study |
| Sun          | 2015             | Glioma      | 81           | 22/59 (I-II/III-IV) | >6 yr            | IHC             | OS               | Yes                  | S                 | Prospective study   |
| Liu ZH       | 2017             | EC          | 191          | 94/97 (I-II/III-IV) | >6 yr            | IHC             | OS               | Yes                  | S                 | Prospective study   |
| Hua          | 2018             | CCA         | 108          | 60/48 (I-II/III-IV) | >3 yr            | IHC             | NR               | NR                  | S                 | Prospective study   |
| Chen         | 2010             | HCC         | 53           | 38/14 (I-II/III-IV) | >8 yr            | IHC             | NR               | NR                  | S                 | Prospective study   |
| Ji           | 2015             | CRC         | 86           | 44/42 (I-II/III-IV) | >6 yr            | IHC             | NR               | NR                  | S                 | Prospective study   |
| He           | 2015             | NSCLC       | 248          | 141/107 (I-II/III-IV) | >3 yr            | IHC             | OS               | Yes                  | S                 | Retrospective study |
| Su FR        | 2014             | NPC         | 133          | 45/88 (I-II/III-IV) | >7 yr            | IHC             | OS               | Yes                  | S                 | Prospective study   |
| Mu           | 2015             | BC          | 268          | NR           | >8 yr            | IHC             | NR               | NR                  | S                 | Prospective study   |
3.30) (Fig. 2A). After stratification by prognosis, the HRs for the high CHD1L expression group versus the low CHD1L expression group were 2.65 (95% CI: 1.71–4.11) in harm and 1.10 (95% CI: 0.63–1.93) in no impact (Fig. 2B). After stratification by study type showed a significant association between enhanced expression of CHD1L was 1.50 in retrospective studies (95% CI: 0.97–2.31), 2.77 in prospective studies (95% CI: 1.63–4.70), and poor OS (Fig. 2C). Moreover, a significant association was found between higher expression of the CHD1L and poorer OS in surgery (HR = 2.42, 95% CI: 1.62–3.60), compared with the surgery plus chemotherapy plus radiotherapy plus endocrine therapy (S+C+R+E) (HR = 0.66, 95% CI: 0.21–2.07, Fig. 2D), A significantly shorter OS was observed in patients with high CHD1L expression versus those with low CHD1L expression. Thus, we concluded that high expression of CHD1L was associated with poor OS.

3.3. Associations between CHD1L expression and clinicopathological parameters

The pooled results (Table 2) indicated that increased CHD1L was significantly associated with TNM stage (OR = 1.61, 95% CI: 1.01–2.55) (Fig. 3A), tumor size (OR = 1.38, 95% CI: 1.07–1.78) (Fig. 3B), tumor differentiation (OR = 2.13, 95% CI: 1.43–3.16) (Fig. 3C), and distant metastasis (OR = 1.86, 95% CI: 1.45–2.39) (Fig. 3D). However, no significant correlation was observed between increased CHD1L expression and age, sex (data not shown). We failed to detect a relationship between over-expression of CHD1L and other clinicopathological parameters due to insufficient data.

3.4. Sensitivity analysis

For the meta-analysis of the association between the CHD1L expression level and OS, sensitivity analysis was performed by sequentially removing each study from the pooled analysis. The purpose of this process aimed to assess the impact of the deleted data set on the overall HRs. The results were robust and were not significantly affected by the exclusion of any study (Fig. 4).

3.5. Publication bias

To meta-analyze the correlation between CHD1L expression levels and OS, publication bias was tested by Begg test and Egger
test. The results indicated that there was no publication bias among the included studies (Fig. 5).

3.6. The association between CHD1L increase and overall survival (OS) in the TCGA database

To study the expression of CHD1L and the prognosis of tumors in the TCGA database, we searched the TCGA database and found that there were 23 tumor types reporting the relationship between CHD1L expression and OS. The random-effects model was adopted to estimate the pooled HRs and corresponding 95% CIs. The results showed an obvious heterogeneity across studies ($I^2 = 57.9\%$, $P_h = .000$). The HRs for the high CHD1L expression group versus the low CHD1L expression group were $1.16$ (95% CI: $1.01$–$1.32$) (Fig. 6).

The TCGA-pancancer data of the CHD1L expression levels and their matched survival were also collected from the cBio Cancer Genomics Portal. The pooled results (Supplementary Table 2) are shown in the figure.

### Table 2

| Clinopathological parameter | Studies (n) | No. of patients | OR (95% CI) | $P$ value (95% CI) | $I^2$ (%) | $P_h$ | Model       |
|----------------------------|-------------|-----------------|-------------|-------------------|----------|-------|------------|
| Age (small vs. big)        | 14          | 2089            | 1.21 (0.91–1.61) | .182 48.2 .022 | Random-effects |
| Sex (male vs. female)      | 12          | 2156            | 0.99 (0.70–1.41) | .956 56.9 .008 | Random-effects |
| Lymph node metastasis (yes vs. no) | 8          | 1818            | 1.02 (0.53–1.98) | .942 90.3 .000 | Random-effects |
| TNM stage (III-IV vs. I-II) | 12          | 2027            | 1.61 (1.01–2.55) | .043 74.1 .000 | Random-effects |
| Tumor differentiation (poor vs. well/moderate) | 10          | 1820            | 2.13 (1.43–3.16) | .000 40.5 .008 | Random-effects |
| Tumor size (big vs. small) | 10          | 1440            | 1.38 (1.07–1.78) | .012 0.0 .506 | Fixed-effects |
| Distant metastasis (yes vs. no) | 4          | 1116            | 1.86 (1.45–2.39) | .000 0.0 .685 | Fixed-effects |

Figure 3. Forest plots of HR for the relationship between high CHD1L expression and clinicopathological parameters: (A) TNM stage; (B) tumor size; (C) tumor differentiation; (D) distant metastasis.
table 1, http://links.lww.com/MD/F856) indicated that increased CHD1L was significantly associated with pathologic T (OR = 1.16, 95% CI: 1.04–1.29) (Supplementary Fig 1A, http://links.lww.com/MD/F855), pathologic stage (OR = 1.16, 95% CI: 1.04–1.28 (Supplementary Fig 1B, http://links.lww.com/MD/F855). However, no significant correlation was observed between increased CHD1L expression and age, sex, residual tumor and primary lymph node presentation assessment (data not shown).

4. Discussion

Cancer is a kind of genomic disease. It is found that there are a lot of somatic mutations, gene recombination, and structural mutations by studying the human cancer genome in the carcinogenesis process.[25] Amplification of 1q21 gene in solid tumors is one of the most frequent epigenetic changes, chromodomain helicase/ATPase binding protein 1-like gene (CHD1L) is an oncogene isolated from 1q21 amplification,
which is often amplified and expressed in hepatocellular carcinoma.\textsuperscript{[4]}

It has been proved that CHD1L is highly expressed in many kinds of tumor tissues, such as liver cancer,\textsuperscript{[4]} colorectal cancer,\textsuperscript{[14]} gastric cancer,\textsuperscript{[9]} ovarian cancer,\textsuperscript{[13]} and glioma.\textsuperscript{[17]} Recent studies have shown that CHD1L is related to proliferation, migration, invasion, and metastasis of tumor cells.\textsuperscript{[18,23,24]} In addition, overexpression of CHD1L was closely related to clinical features and poor prognosis. The positive expression of CHD1L plays an important role in tumorigenesis, development, invasion and metastasis, and may become a new independent marker of tumor progression, prognosis, and survival time.

In this paper, we assessed the relationship between survival and CHD1L expression in patients with solid tumors. Analysis shows that high expression of CHD1L was associated with shorter OS in solid tumor patients, in additional, increased CHD1L was significantly associated with TNM stage, tumor size, tumor differentiation, and distant metastasis. We failed to detect a relationship between overexpression of CHD1L and other clinicopathological parameters because of the insufficient data. The number of studies included is small and its statistical capacity is still limited. Although the results of publication bias indicate that there is no publication bias, due to the limited number of studies that can be included, there may be publication bias. Fourth, different methods, platforms, and judging criteria for IHC testing are inconsistent, various sample sources and different types of disease may lead to deviations in the results of the meta-analysis. Fifth, all the studies of the meta-analysis were conducted in Asian, which may limit the application of our conclusions. Finally, the prognostic value of combination of CHD1L and other tumor markers was not

Figure 6. Forest plots of HR for the relationship between high CHD1L expression and OS in the TCGA database.
evaluated. Therefore, higher quality, larger, multicenter studies, as well as uniform criteria for determining CHD1L expression, are necessary for validating our findings.

5. Conclusions
In this study, meta-analysis was used to evaluate the prognostic role of CHD1L in solid tumors. Our results suggest that CHD1L may be a useful prognostic biomarker, and targeted CHD1L may be a promising therapy for solid tumors. However, CHD1L still requires further data on the potential impact of different solid tumors in future studies.

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Author contributions
LZ and YFJ participated in the collection and analysis of data. YFJ, LZ, and PJH performed the statistical analyses. LZ, XHD, and YCX conceived the study and designed the manuscript. All authors have read and approved the final manuscript.

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