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# Prognostic role of chromodomain helicase DNA binding protein 1-like protein in human solid cancers

## A meta-analysis

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## Abstract

**Background:** Chromodomain helicase DNA binding protein 1-like (CHD1L) played vital roles in tumorigenesis and development. Its aberrant expression was reported to be related to progression and prognosis in various tumors. However, no consensus on the prognostic value of CHD1L protein has been made. This meta-analysis was aimed to assess the clinical significance of CHD1L protein in human solid tumors.

**Methods:** Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases were extensively searched to retrieve publications that reported the association between CHD1L expression and cancer prognosis. Hazard ratios (HRs) or odds ratios (ORs) with their 95% confidence intervals (95% CIs) were applied to assess the strength of the associations through Stata statistical software version 12.0 or Revman software 5.3, respectively.

**Result:** A total of 14 studies were screened according to the inclusion criteria. The pooled results revealed patients with higher CHD1L expression manifested with decreased overall survival (OS) (HR: 1.59, 95% CI: 1.29–1.89, $P < .001$) and poorer disease-free survival (DFS) (HR: 1.66, 95% CI: 1.17–2.15, $P < .001$). The prognostic value of CHD1L protein for OS was further confirmed by performing subgroup meta-analysis. Furthermore, the pooled results revealed a positive correlation of CHD1L protein expression with tumor depth (OR: 1.87, 95% CI: 1.48–2.37), lymph node metastasis (OR: 1.46, 95% CI: 1.01–2.11), and distant metastasis (OR: 1.86, 95% CI: 1.45–2.38).

**Conclusion:** CHD1L overexpression was associated with poor prognosis and advanced clinicopathological features, CHD1L may be a valuable biomarker for prognostication of cancer patients.

**Abbreviations:** 95% CIs = 95% confidence intervals, ALC1 = amplified in liver cancer 1, BC = breast cancer, CHD1L = chromodomain helicase DNA binding protein 1-like, CNKI = China National Knowledge Infrastructure, CRC = colorectal carcinoma, DFS = disease-free survival, EC = esophageal carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HRs = hazard ratios, NOS = Newcastle-Ottawa Scale, NPC = nasopharyngeal carcinoma, NSCLC = nonsmall-cell lung cancer, OC = Ovarian carcinomas, ORs = odds ratios, OS = overall survival, PC = pancreatic cancer, TNM = tumor-node-metastasis.

**Keywords:** CHD1L, prognosis, protein expression, solid tumor

## 1. Introduction

Cancer has been the major disease which threatened the human life and lead to huge economic burden on society. In 2012, there were approximately 14.1 million new cancer cases and 8.2 million cancer deaths.[1] Despite of some advances in cancer treatment and diagnosis in recent years,[2–4] the prognosis for most cancer patients has still been unfavorable. No sufficient sensitive and specific prognostic indicators were available for clinical practice. Thus, it was significant to explore novel and promising prognostic biomarkers. Recently, CHD1L protein has been considered as a new candidate marker for predicting the prognosis of cancers.

Chromodomain helicase/ATPase DNA binding protein 1-like (CHD1L) gene was a recently identified oncogene localized at 1q21.[5] It was also known as ALC1 that belonged to SNF2-like subfamily of the sucrose nonfermenting 2 family. Most of those proteins participated in various nuclear activities, such as DNA repair, recombination and transcriptional activation or repression.[6–8] Evidences have demonstrated that CHD1L played an important role in the tumorigenesis and development.[9,10] It was reported to be frequently amplified and abnormally expressed in tumor tissues, and was closely related to tumor progression and prognosis in various cancers.[10–12] However, there was no consensus on the prognostic value of CHD1L protein in human cancers. And no systematic study was conducted to investigate

the prognostic value of CHD1L so far. Therefore, this meta-analysis was performed to synthetically evaluate the prediction value of CHD1L protein expression in solid tumors.

## 2. Materials and methods

### 2.1. Publication retrieval

Since this is a meta-analysis, ethical approval is not needed. To obtain relevant studies, a comprehensive retrieval was performed against several electronic databases, including Web of Science, PubMed, Embase, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The latest search was updated on November 1, 2017. The keyword combinations for the preliminary search were as follows: "CHD1L," "Chd1l," "amplified in liver cancer 1," "chromodomain helicase DNA binding protein 1-like," "chromodomain helicase/ATPase DNA binding protein 1-like protein" or "ALC1," AND "neoplasm," "cancer," "carcinoma," "tumor," or "malignancies." Manual retrievals were also performed on the reference lists of the retrieved articles. The full-text articles written in English or Chinese were included in this meta-analysis.

### 2.2. Inclusion and exclusion criteria

Eligible articles were identified based on the following inclusion criteria: studies that detected the expression of CHD1L protein in tissue samples from primary solid cancers; the association between CHD1L expression and overall survival (OS) or disease-free survival (DFS) was described; sufficient data were provided for calculating the hazard ratio (HR) with 95% confidence interval (CI) for survival rates. Patients were divided into 2 groups according to the CHD1L expression level in cancer tissues.

The following studies were excluded: those on hematologic tumors, or animal experiments; duplicate publications; reviews, case reports, and conference abstracts.

### 2.3. Data extraction

Data were extracted from identified studies by 2 investigators (Jiwei Xu and Caiyun Zhang) according to unified form, independently. And any disagreements were resolved by discussion with a third investigator (Wanwei Liu). Accordingly, the following data were collected: first author, publication year, country of origin, cancer type, sample size, expression pattern, tumor stage, criterion of overexpression, detection method, follow-up time, outcome measures, analysis type. In addition, the relevant information of clinicopathological features were also extracted, such as gender, histological grade, tumor depth, lymph node metastasis, distant metastasis, and tumor-node-metastasis (TNM) stage.

For the extraction of survival data, if a study reported the data in multivariate analysis or/and univariate analysis, the former was directly applied. If a study only provided Kaplan–Meier curves, the HRs and 95% CIs was retrieved with Engauge Digitizer version 4.1. The data for some clinicopathological factors (mentioned above) were directly extracted from identified studies.

For the quality assessment, the Newcastle-Ottawa Scale (NOS) was applied to assess the study qualities, this scale system consisted of 3 parts: selection of participants, comparability of study groups, and the ascertainment of outcomes of interest. The total score ranged from 0 to 9 points in this method. A high-quality study was identified with a score of $\geq 6$.

### 2.4. Statistical analysis

The Stata statistical software version 12.0 was applied to analyze the relationship between CHD1L expression and OS/DFS, the RevMan5.3 software was applied to calculate the association between CHD1L expression and clinicopathological features. For the association between CHD1L expression and OS, we also conducted the subgroup meta-analysis stratified by the cancer type, sample size, follow-up time, and analysis type.

The heterogeneity among studies was identified via $I^2$ statistics and Chi-square $Q$ test. The $I^2 \geq 50\%$ for $I^2$ statistics or the $P$-value $< .05$ for Chi-square $Q$ test was deemed to be significant heterogeneity, then the random effects model was adopted, by contrary, the fixed effects model was applied. Sensitivity analysis was applied to evaluate the stability of the overall results by excluding a single study one by one. The publication bias was assessed with the funnel plot and the Begg/Egger test. A $P$-value of less than .05 was considered as statistically significant.

## 3. Results

### 3.1. Study characteristics

According to the inclusion and exclusion criteria mentioned above, finally, a total of 14 publications that up to the inclusion norm were selected for this meta-analysis.[11–24] All those eligible articles included 2597 patients with a median sample-size of 185.5 (ranged from 53 to 616). Among the 14 publications, there were totally eleven different kinds of solid tumors, including pancreatic cancer (PC), hepatocellular carcinoma (HCC), breast cancer (BC), nonsmall-cell lung cancer (NSCLC), esophageal carcinoma (EC), nasopharyngeal carcinoma (NPC), gastric cancer (GC), colorectal carcinoma (CRC), ovarian carcinomas (OC), glioma, and bladder cancer. All these articles were written in English and came from Asian countries (China and Korea). The publication period was ranged from 2011 to 2017. All those papers investigated the relevance between CHD1L protein expression and solid tumor prognosis. And the quality scores of all included studies were varied from 7 to 9, with a mean value of 7.8 (Supplementary Information, http://links.lww.com/MD/C347). The detailed process of study search and selection was presented (Fig. 1). The main characteristics of all included studies were summarized (Table 1).

### 3.2. Results of the meta-analysis

#### 3.2.1. CHD1L protein and OS in human solid cancers. The relationship between CHD1L protein and OS in human solid cancers was reported in 12 studies including 2263 cases. From the results (Fig. 2), there was no significant heterogeneity across-studies ($I^2 = 30.9\%$; $P = .144$), and the pooled results revealed that increased expression of CHD1L in cancer tissues was significantly correlated with poor OS (HR: 1.59, 95% CI: 1.29–1.89, $P < .001$) (Fig. 2). Therefore, CHD1L may serve as a valuable prognostic biomarker for human solid cancers.

To further assess the prognostic value of CHD1L protein in human solid cancers, subgroup meta-analysis was performed based on the cancer type, sample size, follow-up time and analysis type (Table 2). The results showed that CHD1L protein could act as prognostic indicator of OS for patients with digestive system cancers (HR: 2.05, 95% CI: 1.43–2.66, $P < .001$). After
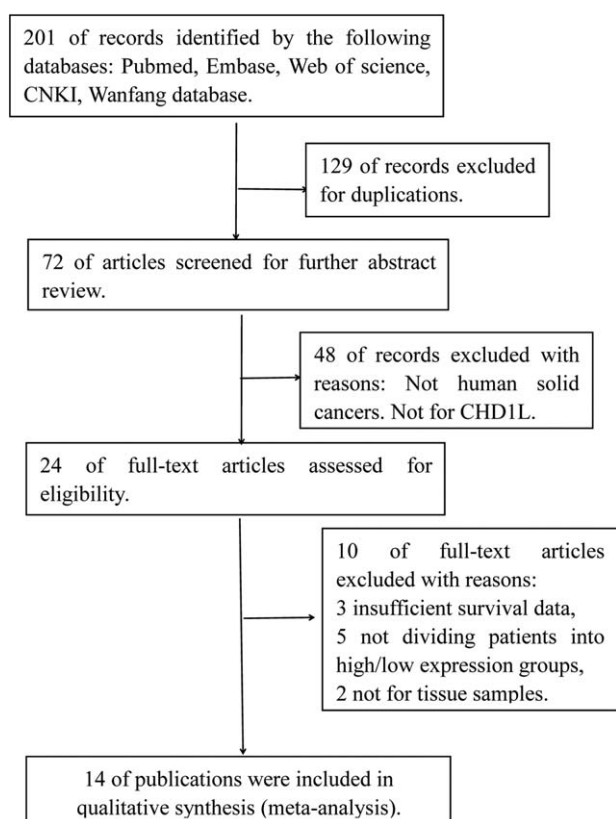
Figure 1. The steps for screening eligible articles.

stratification by sample size, the pooled HRs were 1.66 (95% CI: 1.25–2.09) for studies with equal or greater than 200 cases and 1.53 (95% CI: 1.12–1.95) for studies with less than 200 cases. In the subgroup analyses stratified by follow-up time, we found that CHD1L protein could act as a prognostic factor in group with follow-up time of ≥5 years (HR: 1.59, 95% CI: 1.17–2.01, $P < .001$) or group with follow-up time of <5 years (HR: 1.59, 95% CI: 1.16–2.02, $P < .001$). In addition, the pooled HRs was significantly and consistently greater than 1 in subgroup meta-analysis stratified by the analysis type, suggesting that CHD1L was an independent prognostic marker for OS (HR: 1.52, 95% CI: 1.19–1.85, $P < .001$).

**3.2.2. CHD1L protein and DFS in human solid cancers.** Only 4 studies with 599 cases reported the relationship between CHD1L protein and DFS. According to the results (Fig. 3), it showed that the patients with high CHD1L protein expression had a worse DFS than those with low protein expression (HR: 1.66, 95% CI: 1.17–2.15, $P < .001$) (Fig. 3). CHD1L might be a significant prognostic factor for DFS in cancer patients.

**3.2.3. Association between CHD1L overexpression and clinicopathological parameters of patients with solid cancers.** Pooled ORs for CHD1L expression showed that CHD1L overexpression level was correlated with tumor depth (OR: 1.87, 95% CI: 1.48–2.37), lymph node metastasis (OR: 1.46, 95% CI: 1.01–2.11) and distant metastasis (OR: 1.86, 95% CI: 1.45–2.38) (Table 3). However, no clear correlation was found between CHD1L expression and gender (OR: 1.01, 95% CI: 0.71–1.44), histological grade (OR: 1.45, 95% CI: 0.83–2.56) and TNM stage (OR: 1.37, 95% CI: 0.87–2.15) (Table 3).

**3.2.4. Publication bias.** The funnel graph is presented in Fig. 4, no significant publication bias was found among studies. The test

### Table 1

**Main characteristics of all studies included in the meta-analysis.**

| Refs. | Cancer type | Country | Sample size | OE (N, %) | Tumor stage | Follow-up, y | Criterion of OE | Detection method | Outcome measures | Multivariate analysis |
|---|---|---|---|---|---|---|---|---|---|---|
| Liu et al[11] | PC | China | 112 | 70, 63.5% | I–IV | <5 | Staining intensities (2–3) | IHC | OS | Yes |
| Chen et al[12] | HCC | China | 53 | 29, 54.7% | I–III | ≥5 | Staining intensities (2–3) | IHC | DFS | K-M |
| Sun et al[13] | Glioma | China | 81 | 43, 53.1% | II–IV | ≥5 | The extent × intensity of staining (5–9) | IHC | OS | Yes |
| Mu et al[14] | BC | China | 268 | 112, 41.8% | NR | ≥5 | Staining intensity × positive cells percentage (2–9) | IHC | OS | K-M |
| He et al[15] | NSCLC | China | 233 | 98, 42.1% | I–III | <5 | Staining intensity × positive cells percentage (3–12) | IHC | OS | Yes |
| Su et al[16] | NPC | China | 133 | 88, 66.2% | I–IV | ≥5 | Staining intensities (2–3) | IHC | OS | Yes |
| Wu et al[17] | BC | China | 179 | 87, 48.6% | NR | ≥5 | Staining intensity × positive cells percentage (4–12) | IHC | OS, DFS | Yes |
| Su et al[18] | GC | China | 616 | 361, 58.7% | I–IV | ≥5 | Staining intensity + proportion of stained cells (2–7) | IHC | OS | Yes |
| Tian et al[19] | Bladder cancer | China | 153 | 81, 52.9% | NR | ≥5 | The extent × intensity of staining (4–9) | IHC | OS | Yes |
| Ji et al[20] | CRC | China | 86 | 53, 61.6% | I–III | ≥5 | Positive staining (+) | IHC | OS, DFS | K-M |
| Hyeon et al[21] | HCC | Korea | 281 | 48, 17.1% | 0–A–B–C | ≥5 | staining intensity + proportion of stained cells (2–7) | IHC | DFS | Yes |
| He et al[22] | OC | China | 102 | 52, 51.0% | I–IV | ≥5 | Staining intensity × positive cells percentage (4–12) | IHC | OS | Yes |
| Chen et al[23] | HCC | China | 109 | 55, 50.5% | I–III | ≥5 | Staining intensities (2–3) | IHC | OS | K-M |
| Liu et al[24] | EC | China | 191 | 86, 45.0% | I–IV | ≥5 | Staining intensity × positive cells percentage (4–12) | IHC | OS | Yes |

BC = breast cancer, CRC = colorectal carcinoma, DFS = disease-free survival, EC = esophageal carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, IHC = immunohistochemistry, K-M = Kaplan–Meier analysis, NPC = nasopharyngeal carcinoma, NR = not report, NSCLC = nonsmall-cell lung cancer, OC = ovarian carcinomas, OE = overexpression, OS = overall survival, PC = pancreatic cancer.
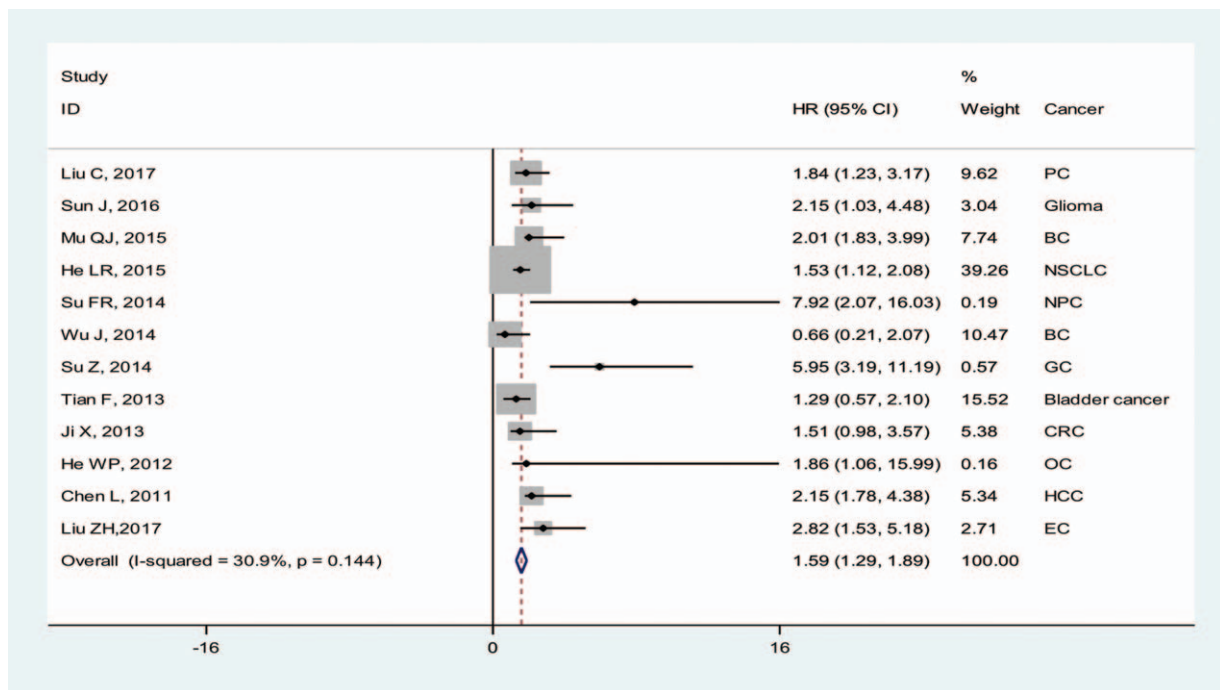
**Figure 2.** Meta-analysis of the pooled HRs of OS of patients with high CHD1L expression.

results also demonstrated the for publication bias was negative ($P_{Begg test} = 0.891$; $P_{Egger test} = 0.450$).

***3.2.5. Sensitivity analysis.*** Sensitivity analysis was conducted to assess the potential impact of any individual study on the pooled results. As shown in Fig. 5, it suggested the robustness of our data.

## 4. Discussion

CHD1L was frequently overexpressed in many types of solid tumor, which was considered as treatment target in specific subtypes of tumors. Studies have found that CHD1L expression was significantly upregulated in cancerous tissues or cancer cells, compared with that of in normal samples, and there was a correlation between CHD1L positive status and aggressive tumor

biology.[20–22] These findings revealed that CHD1L might be a new target for future cancer immunotherapy. Although CHD1L have been discovered for almost 10 years, its functional role in carcinogenesis has not been fully elucidated. Based on the review of relevant publications, CHD1L has participated in cancer development and progression through multiple pathways.

Amplification and overexpression of CHD1L have be deemed as one of the most frequent genetic alterations in HCC, and CHD1L was a critical biological cellular process in hepatocarcinogenesis.[12,23] CHD1L showed strong tumorigenic abilities both in vivo and in vitro, overexpression of CHD1L could promote cell proliferation, invasiveness and metastasis.[25–27] Kazal-like domains proteoglycan 1 and N-terminal kinase like, as 2 of CHD1L targets, upregulated or activated by CHD1L, participated in tumorigenicity of HCC.[28,29] Additionally, a novel molecular pathway, CHD1L/TCTP/Cdc25C/Cdk1, was

**Table 2**

Results of subgroup analysis of pooled HRs of OS of cancer patients with CHD1L overexpression.

| Stratified analysis | No. of studies | No. of patients | Pooled HR (95% CI) | P | Heterogeneity | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | | | $I^2$ (%) | $P_{het}$ |
| (1) Cancer type | | | | | | |
| Digestive system cancers | 5 | 1114 | 2.05 (1.43–2.66) | <.001 | 23.3 | .266 |
| Others | 7 | 1149 | 1.45 (1.11–1.79) | <.001 | 24.9 | .239 |
| (2) Sample size | | | | | | |
| ≥200 | 3 | 1117 | 1.66 (1.25–2.09) | <.001 | 61.0 | .077 |
| <200 | 9 | 1146 | 1.53 (1.12–1.95) | <.001 | 24.6 | .224 |
| (3) Follow-up time, y | | | | | | |
| ≥5 | 10 | 1918 | 1.59 (1.17–2.01) | <.001 | 42.3 | .076 |
| <5 | 2 | 345 | 1.59 (1.16–2.02) | <.001 | 0.0 | .570 |
| (4) Analysis type | | | | | | |
| Multivariate analysis | 9 | 1800 | 1.52 (1.19–1.85) | <.001 | 44.6 | .071 |
| Kaplan–Meier analysis | 3 | 463 | 1.90 (1.21–2.60) | <.001 | 0.0 | .767 |

CI = confidence interval, HR = hazard ratio.
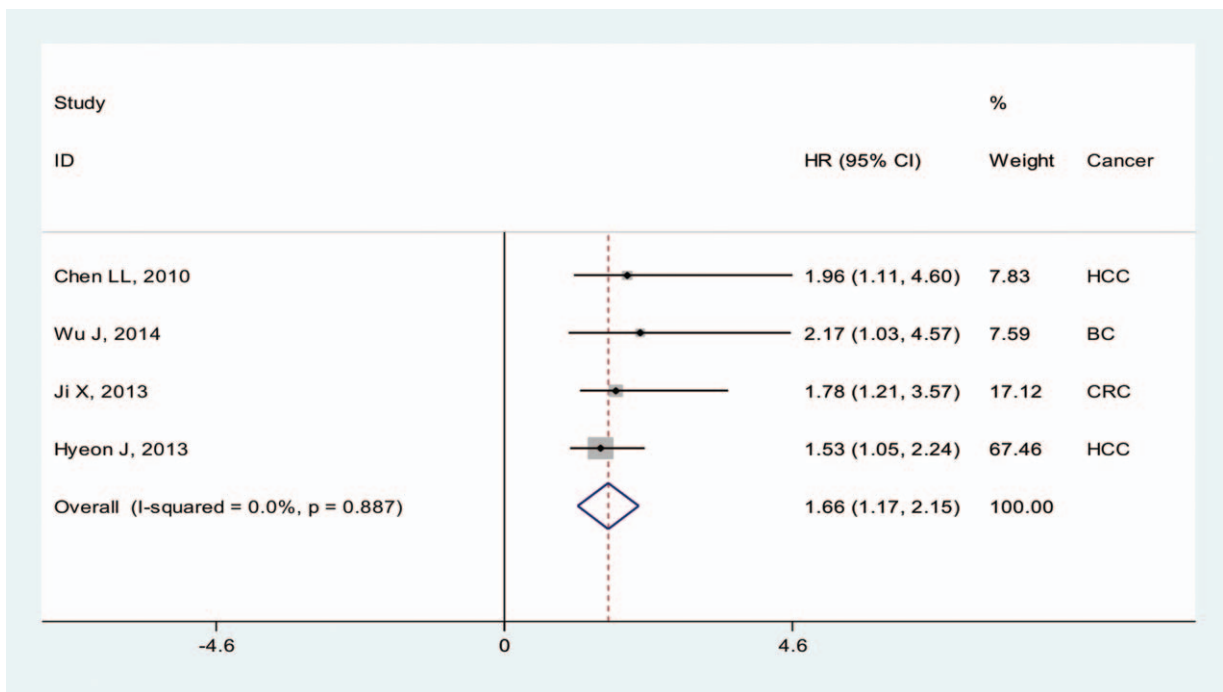
**Figure 3.** Meta-analysis of the pooled HRs of DFS of patients with high CHD1L expression.

### Table 3

**Results of meta-analysis of CHD1L overexpression and clinicopathological features in solid cancers.**

| Clinicopathological parameter | Studies (n) | Number of patients | OR (95% CI) | P | $I^2$ (%) | $P_{het}$ | Model |
|---|---|---|---|---|---|---|---|
| Gender (male vs female) | 11 | 2048 | 1.01 (0.71–1.44) | .95 | 60 | .006 | Random |
| Histological grade (G3/G2 vs G1) | 7 | 1056 | 1.45 (0.83–2.56) | .19 | 59 | .02 | Random |
| Tumor depth (T3–4 vs T1–2) | 6 | 1528 | 1.87 (1.48–2.37) | <.001 | 0 | .57 | Fixed |
| Lymph node metastasis (yes vs no) | 7 | 1627 | 1.46 (1.01–2.11) | .05 | 65 | .010 | Random |
| Distant metastasis (yes vs no) | 4 | 1127 | 1.86 (1.45–2.38) | <.001 | 0 | .75 | Fixed |
| TNM stage (III–IV vs I–II) | 11 | 1983 | 1.37 (0.87–2.15) | .17 | 78 | <.00001 | Random |

CI = confidence interval, OR = odds ratio, TNM = tumor-node-metastasis.

demonstrated to induce mitotic defects and chromosome missegregation in HCC development.[30] Researcher also found that CHD1L showed a strong oncogenic ability in CRC, the overexpression of which could promote tumor progression by promoting G1/S-phase cells and inhibiting apoptosis in CRC.[20]

And in PC, CHD1L-Wnt/β-catenin was showed to be a novel pathway involved in PC progression.[11] Another study by Mu et al[14] showed that CHD1L could promote the invasion and metastasis of BC cells via the PI3K/Akt/ARK5/mTOR/MMP signaling pathway in BC. Furthermore, CHD1L was also
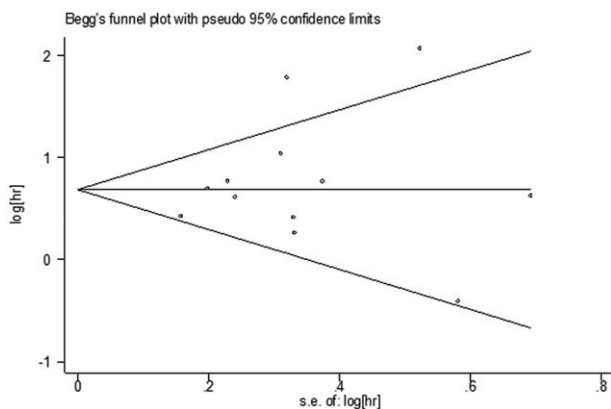


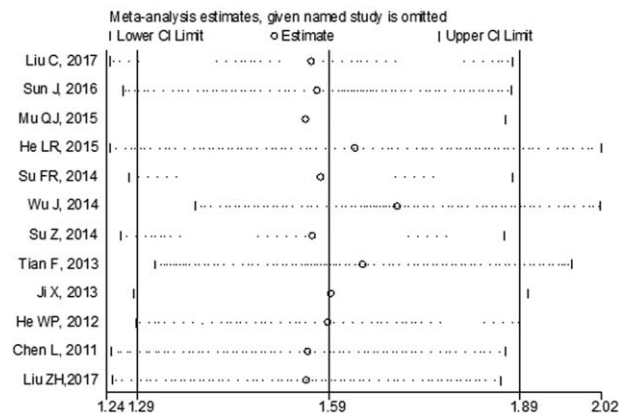**Figure 4.** Funnel plots for publication bias test for OS.



**Figure 5.** Sensitivity analysis for OS.

involved in the progression of glioma, Sun et al[13] reported that suppression of CHD1L could induce cell cycle arrest and increase apoptosis in glioma cells, and the knockdown of CHD1L could significantly accelerate migration and invasion ability. These findings suggested that CHD1L would be a key target in integrative tumor development and may be a novel target for further therapy.

This present meta-analysis revealed strong evidence that expression level of CHD1L protein was significantly associated with patient survival and clinical progression in human solid cancers; the patients with increased CHD1L showed a poor prognosis, with shorter OS and wore DFS. The subgroup analyses also further demonstrated the prognostic value for OS in human solid cancers. Furthermore, our pooled results showed that high expression of CHD1L was significantly associated with higher tumor depth, and CHD1L was involved in tumor metastasis, including lymph node metastasis and distant metastasis. However, the association between CHD1L expression and gender, histological grade or clinical stage was not statistically different. Those results indicated an important role of CHD1L in the development and progression of cancer, indicating the clinical value of CHD1L as a promising prognostic marker in human solid cancers.

To the best of our knowledge, this has been the first meta-analysis providing clear evidences that CHD1L protein could serve as a promising prognostic marker in human solid cancers. However, some limitations in our meta-analysis should be treated seriously. First, the sample size and number of articles included were relatively small, only 12 studies were included in this study for OS, and only 4 studies were included for exploring the relationship between CHD1L and DFS. The credibility of results would be reduced. Second, there were some heterogeneity among studies, which may derive from different tumor types and patient characteristics as well as the reported HR adjusted different factors. Third, studies collected in this meta-analysis all came from Asian countries, researches from other countries and races were relatively less, which might limit the application of the conclusions. Fourth, the cut-off values of CHD1L expression were different in those studies. However, if the CHD1L would like to be a prognostic predicting factor, the determination approach of CHD1L should be established and standardized, including the sampling, reagents, procedures and threshold. At last, other factors could also influence the patient survival, such as the difference in chemotherapies or surgeries for these various cancer or the different clinical stages when diagnosed.

In conclusion, this study showed that CHD1L could be applied for improving prognosis estimation of human solid cancers. Considering the limitations in the analysis, the conclusion should be regarded cautiously. Certainly, well-designed prospective multicenter studies with larger sample size would be warranted to further confirm the prognosis value of CHD1L in cancer patients.

## Author contributions

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Supervision: Wanwei Liu.
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Visualization: Wanwei Liu.
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Writing – review & editing: Wanwei Liu.

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