Prognostic role of dickkopf-1 in patients with cancer

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Abstract

As an antagonist for the WNT signal passway, dickkopf-1(DKK1) have a great important role in the occurence and development of various type cancer. The present paper performed a meta-analysis to evaluate the predictive significance of DKK1 in cancer.

To assess the relationship between the expression of DKK1 and prognostic role in human cancers, a total of 16 articals were screened from the multiple online databases (Pubmed, EMBASE, CNKI, Web of Science and Google Scholar) in our study. By using the STATA soft,pooled hazard ratio and 95% confidence intervals of overall survival (OS), progression-free survival, disease-free survival and time to recurrence were used to evaluate the strength of this relationship.

The meta-analysis showed that higher expression of DKK1 was significantly associated with shorter OS in cancer patients. In stratified analyzes, the higher expression of DKK1 could reduced the OS in patients with breast cancer,digestive system cancer and urogenital system cancer, but not patients with the lung cancer. It also showed that higher expression of DKK1 was significantly associated with shorter progression-free survival, disease-free survival and time to recurrence in cancer patients.

The present study indicate that higher expression of DKK1 predict an unfavorable clinical outcome in patients with breast cancer, digestive system cancer and urogenital system cancer.

Abbreviations: CI = confidence intervals, DFS = disease-free survival, DKK1 = dickkopf-1, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, TTR = time to recurrence.

Keywords: cancer, dickkopf-1, meta-analysis

1. Introduction

With the change of people's living habits and the deterioration of the environment, the incidence of cancer is increasing year by year. Although the detection methods have been improved a lot, most of the tumors are diagnosed at an advanced stage, resulting in a high mortality rates. Prognostic assessment can help doctors understand their patient's condition and follow-up development. In order to improve the survival time of patients, we can select appropriate targets and treatment methods through the study of prognostic diagnostic indicators and treatment methods. Research on markers related to prognosis of tumors is in full swing.

Dickkopf-1 (DKK1) is a secretory protein, which is a member of DKK family.[1] WNT /β-catenin pathway is a group of signal transduction pathway which plays a fundamental role in cell growth and development. When the WNT pathway is activated abnormally, the nuclear regulator β-catenin is increased, which is involved in the transcription of genetic information and induces many kinds of tumors.DKK1 can prevent Wnt signaling pathway from transmitting to Intracellular through combining with low density lipoprotein receptor-related protein LRP5/LRP6.[2,3] However,dkk1 was found to be highly or poorly expressed in various tumors, showing a variety of characteristics, such as high expression[4–6] in non-small cell lung cancer, liver cancer and esophageal cancer, while low expression[7–9] in colon cancer, renal cell cancer and leukemia. The main reason is that DKK1 plays different roles in different tumors and stages.

DKK1 is expressed differently in different tumors in the current published articles, and it is on this basis that we would like to find out whether its prognostic effects are consistent for tumors. This paper intends to explore the role of DKK1 in the prognosis of cancer by enlarging the research number and sample size, then making a meta-analysis on it.

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2. Methods

2.1. Search strategy

In order to evaluate the relationship between the expression of DKK1 and survival time in the patients with cancer,relative articles were searched from these online databases (Pubmed, EMBASE, CNKI, Web of Science and Google Scholar). The keywords for the search were: (DKK1 [Title/Abstract] OR DKK-1 [Title/Abstract] OR dickkopf-1 [Title/Abstract]) AND (neoplasms [Title/Abstract] OR tumor [Title/Abstract] OR cancer [Title/Abstract] OR carcinoma [Title/Abstract]) AND (prognosis [Title/ Abstract] OR survival [Title/Abstract]).

2.2. Inclusion and exclusion criteria

The selected study should meet the following Inclusion criteria:

(1) must be the original articles;
(2) Patients in the study were definitely diagnosed as cancer;
(3) Patients were divided into 2 groups according to the level of DKK1 expression;
(4) associations of DKK1 expression levels with overall survival (OS), progression-free survival (PFS), DFS, and time to recurrence (TTR) were described;
(5) hazard ratios (HRs) with 95% confidence of the OS, PFS, DFS, and TTR must be displayed directly or calculated indirectly by the author; and
(6) study should be published in English and must have the full text.

Exclusion criteria for the articles included:

(1) Study have no complete data, unable to extract relevant data for us;
(2) duplicated publications;
(3) were not published as research articles including summaries, commentary, case reports, letters or non-case-control studies.

2.3. Endpoints

In this article, we defined OS as the primary endpoint; PFS, DFS, and TTR as the secondary endpoint. OS refers to the period from the beginning of curative operation to the end of the last follow-up or death of any cause. While the PFS was the time from the beginning of curative operation to the progression of tumors or the death of any cause, DFS to the recurrence of cancer or death, TTR was The time from CR or PR to PD (Progressive Disease) or any cause of death.

2.4. Data extraction and quality assessment

The following information were extracted from all included eligible studies independently by 2 authors (WB K and JF H):the name of first author, year of publication, cancer type, clinical Stage,total number of patients, outcome measures, the patient numbers of high/low DKK1 expression, year of survival and HR and its corresponding 95% confidence intervals (CI). Enguage Digitizer (Version 4.1) software were used to extract the data from the papers only have Kaplan-Meier curves. We would rather choose multivariate analysis than univariate ones because multivariate analysis have more accurate statistical significance. When inconsistencies arise, a third person (T L) will evaluate again.

The Quality of the studies were assessed by the Newcastle-Ottawa Scale (NOS), The score of NOS scoring system ranged from 0 to 9, more than 6 points are of high quality.
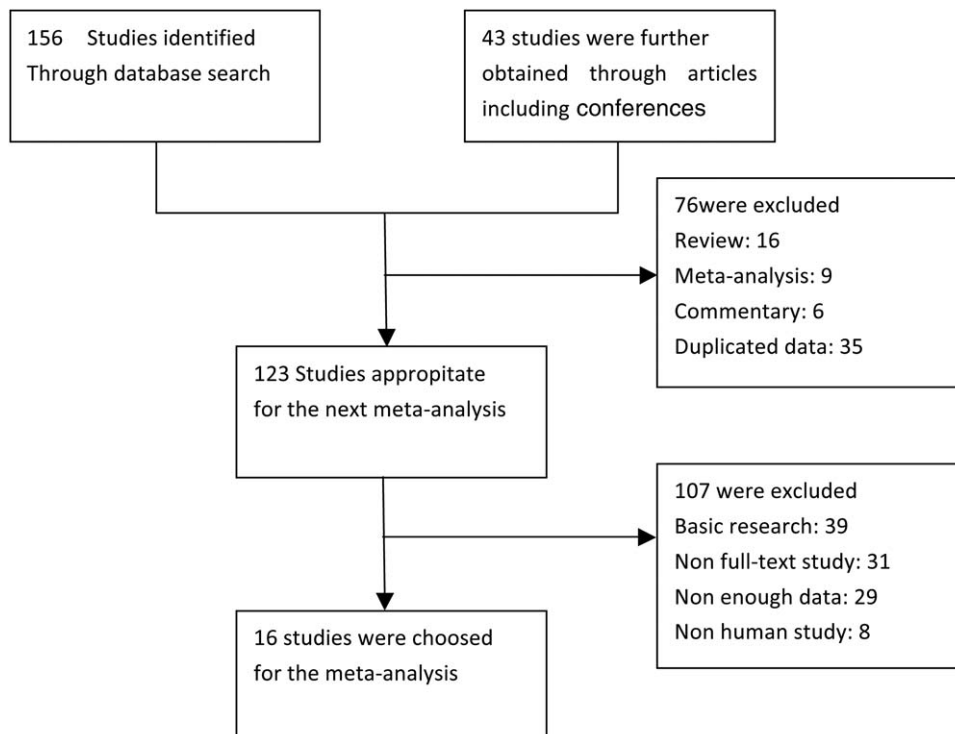

Figure 1. Flow chart diagram of selecting eligible studies for meta-analysis.

Table 1

Main characteristics of included eligible studies.

Study	year	Cancer type	Number	DKK1 expression High/Low number	survival	HR(95%CI)	NOS
Weikai S[10]	2019	breast cancer	85	52/33	OS/PFS	3.812 (0.689–17.698)	7
You F[11]	2018	multiple myeloma	58	34/24	OS	2.045 (0.34–3.13)	7
Hong S[12]	2018	gastric cancer	158	85/73	OS/PFS	2.13 (1.37–3.312)	8
S. Han[13]	2015	pancreatic cancer	60	45/15	OS	1.667 (1.543–1.801)	8
Liu DJ[14]	2017	pancreatic cancer	311	205/106	OS	1.623 (1.189–2.215)	6
Sun DK[15]	2015	bladder cancer	94	48/46	OS	2.365 (1.873–8.881)	8
Shen Q[16]	2015	hepatocellularcarcinoma	266	135/131	OS/TTR	1.69 (1.1–2.6)	7
Aguilera[17]	2015	colorectal cancer	699	592/107	OS/PFS	1.654 (1.22–2.24)	6
Rachner[18]	2014	prostate cancer	80	40/40	OS	3.73 (1.44–9.66)	6
Chen C[19]	2014	chondrosarcoma	63	37/26	OS	15.479 (2.535–94.51)	8
Zhou SJ[20]	2014	breast cancer	125	63/62	OS/PFS	2.19 (1.28–9.24)	8
Dong LL[21]	2014	lung cancer	150	75/75	OS	3.98 (2.19–4.83)	7
Shi RY[22]	2013	cholangiocarcinoma	138	85/53	OS/TTR	1.568 (1.025–2.399)	6
Xu W[23]	2012	breast cancer	85	52/33	OS/PFS	3.756 (0.78–18.077)	8
Shen C[24]	2010	urothelial carcinoma	75	39/36	OS/DFS	2.7 (0.74–9.9)	8
Shen S[25]	2009	lung cancer	212	148/164	OS	1.18 (1.08–1.28)	6

CI=confidence intervals, DFS=disease-free survival, HR=hazard ratio, NOS = Newcastle-Ottawa scale, OS=overall survival, PFS = progression-free survival, TTR = time to recurrence.

2.5. Statistical analysis

The meta-analysis was performed by the software STATA 15.0. The heterogeneity between studies were assessed by the chi-squared based Q-test or I^2 test. $P < .05$ for the Q test (Ph) and $I^2 > 50\%$ were considered to be significantly heterogeneous. When heterogeneity occurs, the random effect model is used, otherwise the fixed effect models is used. Begg funnel plot and Egger test were applied to checkout the potential publication bias. The sensitivity analysis was used to judge the stability of the results. $P < .05$ was considered to be statistically significant.

2.6. Medical ethics

The ethical approval in this paper was not necessary because it is a Meta analysis, so there is no need to deal with ethical issues.
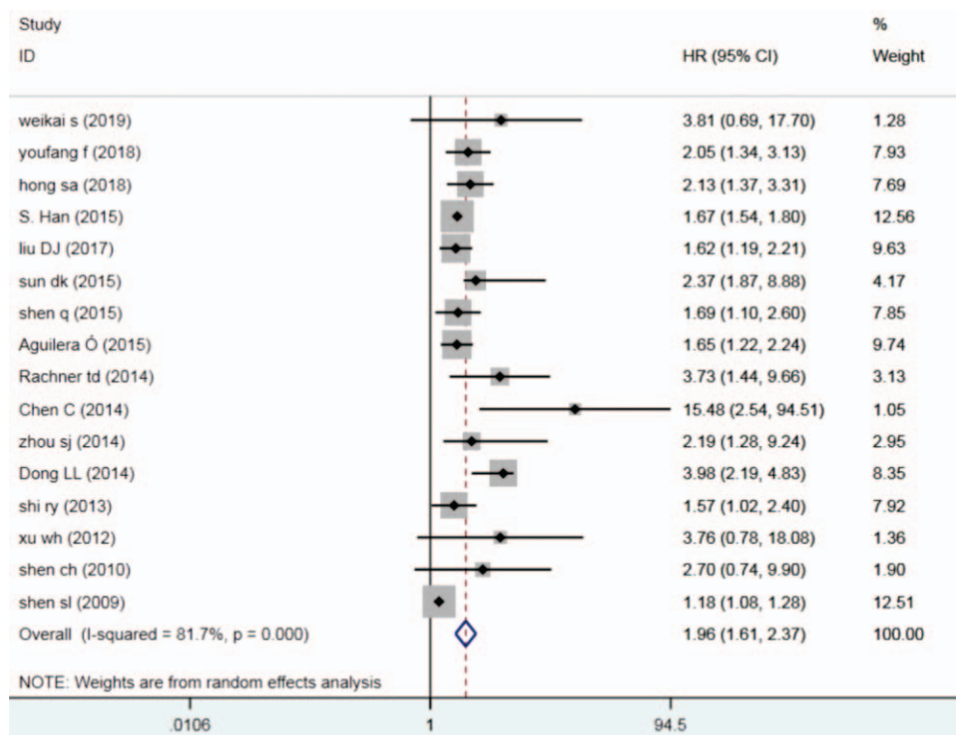
Figure 2. Forest plots describing HR of the association between DKK1 expression and OS in human tumors from 16 papers, DKK1=dickkopf-1, HR=hazard ratio, OS=overall survival.
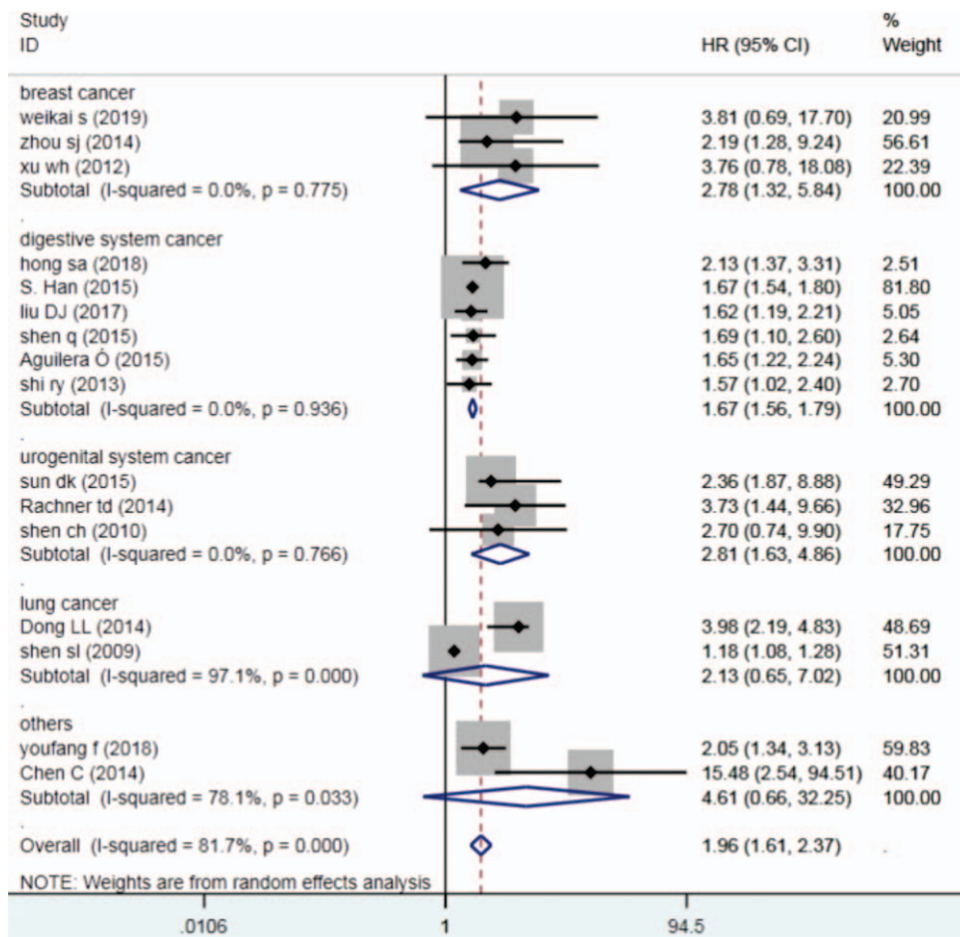
Figure 3. Forest plots of subgroup analysis (cancer type) describing HR of the association between DKK1 expression and OS in human tumors, DKK1 = dickkopf-1, HR = hazard ratio, OS = overall survival.

3. Results

3.1. Studies searching results and characteristics of eligible studies

We finally chose 16 studies about the relationship between the expression of DKK1 and survival time in the patients with cancer which all meet the inclusion criteria. The whole screening process was shown in the Figure 1. All the acquired papers were calculated by the NOS. Characteristics of included studies were shown in the Table 1.

3.2. Meta-analysis of the association between the expression of DKK1 and OS

The random-effects model was used in this Meta-analysis because of the heterogeneity test ($I^2 = 81.7\%$, $P < .001$).It showed that higher expression of DKK1 was significantly associated with shorter OS in cancer patients (HR = 1.96, 95% CI 1.61-2.37, $P < .001$). (Fig. 2).

In stratified analyses according to cancer types,the higher expression of DKK1 could reduce the OS in patients with breast cancer (HR = 1.96, 95% CI 1.61-2.37, $P = .007$),digestive system cancer (HR = 1.67,95% CI 1.56-1.79, $P < .001$)and urogenital system cancer (HR = 2.81,95%CI 1.63-7.486, $P < .001$),but not patients with the lung cancer (Fig. 3).

### 3.3. Meta-analysis of the association between the expression of DKK1 and PFS

Meta-analysis also showed that higher expression of DKK1 was significantly associated with shorter PFS in patients with breast cancer, gastric cancer and colorectal cancer (HR = 1.89,95% CI 1.56-2.30, $P < .001$) (Fig. 4).

3.4. Meta-analysis of the association between the expression of DKK1 and disease-free survival (DFS) and TTR

The results indicated that the higher DKK1 expression level group can reduce the TTR in cancer patients(HR = 2.02,95% CI 1.51-2.71, $P < .001$) and the time to DFS (HR = 2.36,95% CI 1.06-5.25, $P = .035$) (Fig. 5).

3.5. Sensitivity analysis and publication bias

The results showed that each result had no significant effect on overall HR for OS, PFS, TTR, and DFS. According to Funnel plot and Egger test,there was no publication bias in our papers between DKK1 expression and OS ($P = .392$) or PFS ($P = .07$).
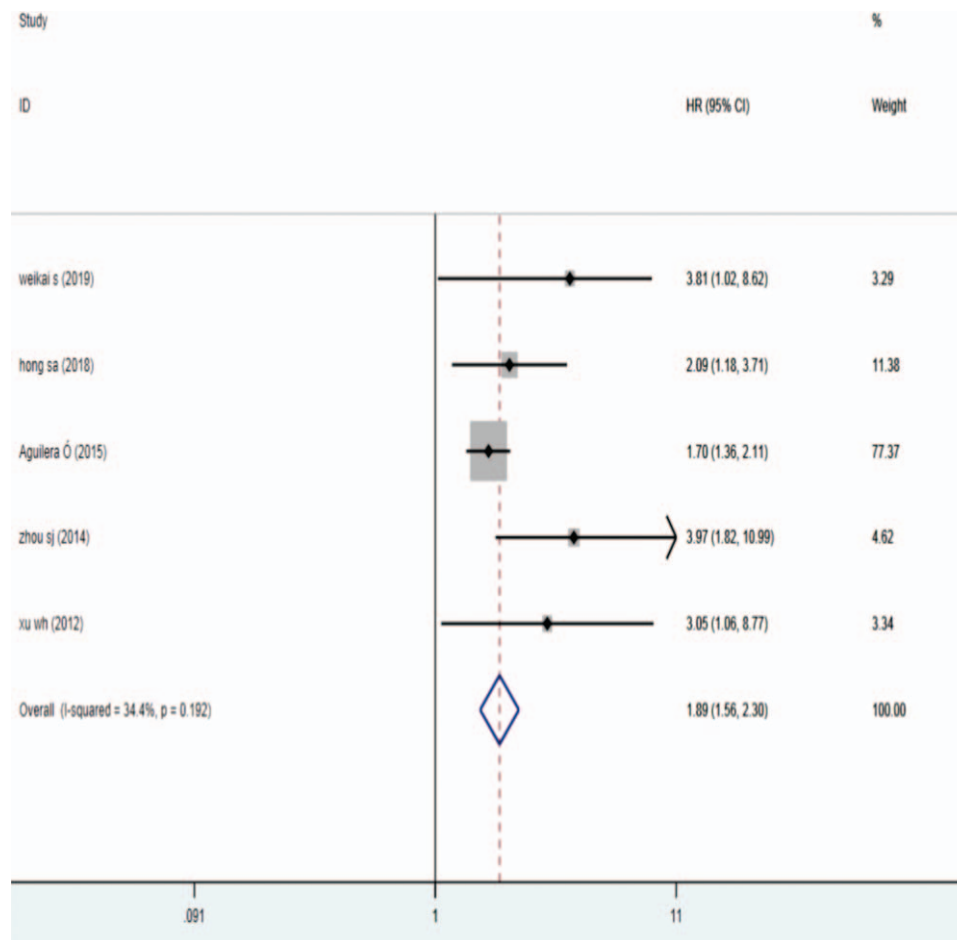
Figure 4. Forest plots describing HR of the association between DKK1 expression and PFS in human tumors from 5 papers, DKK1 = dickkopf-1, HR = hazard ratio, PFS = progression-free survival.

4. Discussion

The human cancer has the following characteristics: high morbidity, high mortality, low early detection rate and low survival rate. Despite the large amount of funds and money in recent years are used to support cancer research about diagnosis and treatment, the effect is not as good as expected. The Oncology research has a long way to go. We must go ahead bravely.

DKK1, 1 of the DKK family genes, inhibits WNT signaling pathway through 2 mechanisms: binding with low density lipoprotein receptor related proteins (LRP5/LRP6) and Kremen1, Kremen2, which are the co-receptor of WNT, then inducing rapid endocytosis, reducing the level of LRP5/LRP6 on the cell membrane, thus blocking Wnt signal transmission to the Intracellular;[26] Besides, DKK1 could block the formation of WNT-guided LRP6 complex by connecting with LRP6.[27] In many tumors, Wnt pathway is over-activated. DKK-1, as a classical Wnt Pathway inhibitors, have also attracted much attentions, and more and more studies have been carried out on them.

In previous studies, DKK1 was found to be highly or poorly expressed in various tumors, showing a variety of characteristics, such as high expression[4–6] in non-small cell lung cancer, liver cancer and esophageal cancer, while low expression[7–9] in colon cancer, renal cell cancer and leukemia. It is associated with the

invasion and metastasis of most tumors, but not with the proliferation of tumor cells. It is 1 of the new indicators for the diagnosis of potential malignant tumors and may be 1 of the potential therapeutic targets for malignant tumors. Most studies have shown that its expression level is correlated with survival.

In our meta-analysis, our main aim was to analyze the correlation between DKK1 expression and prognosis of tumors. As described in the above results, the higher the level of DKK-1, the shorter the OS, PFS, DFS, and TTR in cancer patients. This indicates that DKK1 predict poor prognosis in most human tumors.

In stratified analyses, the higher expression of DKK1 could reduced the OS in patients with breast cancer, digestive system cancer and urogenital system cancer,but not patients with the lung cancer. But in perious papers, DKK1 is highly expressed in the serum of lung cancer patients. Overexpression of DKK1 promotes migration and invasion of lung cancer cells.[28] On metastasis of tumors, complex and diverse research results have emerged in different tumors and microenvironments: Serum DKK1 concentration in patients with non-bone metastasis of non-small cell lung cancer was significantly higher than that in patients with bone metastasis.[29] However, a recent study[30] by the Chinese Academy of Sciences showed that breast cancer patients with higher DKK1 secretion tended to metastasize to bone, while those with lower DKK1 secretion tended to
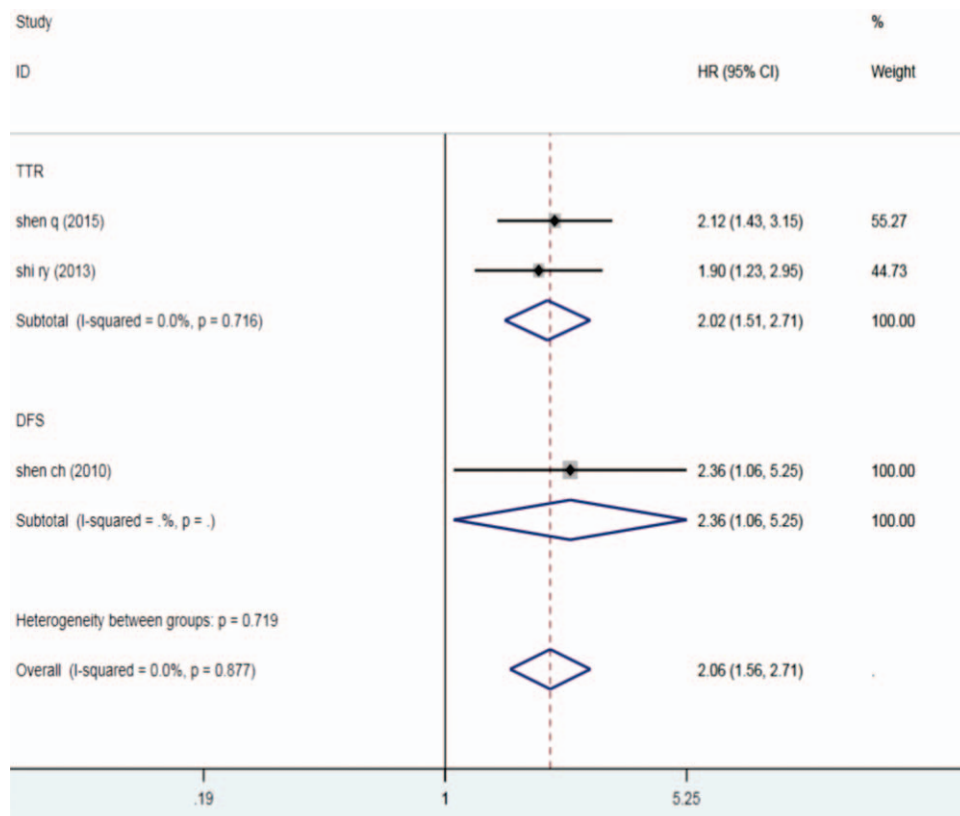
Figure 5. Forest plots describing HR of the association between DKK1 expression and TTR and DFS in human tumors from 3 papers, DKK1 = dickkopf-1, HR = hazard ratio, DFS = disease-free survival, TTR = time to recurrence.

metastasize to lung. These different findings suggest that there are many unknown areas of DKK1 expression in lung cancer, waiting for us to uncover.

There are still some limitations in this meta-analysis. First, the total number of studies included is still small. Second, there is no uniform standard for cut-off values from different research methods. Third, There are only 2 studies on the relationship between DKK1 and TTR in cancer patients, and only 1 study reporting the relationship between DKK1 and DFS, we couldn't get a better pooled result for them. Finally, unpublished studies with negative results may lead to potential publication bias.

In summary, our study showed that cancer patients with higher DKK1 expression may have a shorter survival time. DKK1 can be used as a new target for diagnosis and treatment of tumors. These conclusions need a lot of clinical and basic experiments to verify.

Author contributions

JF H and T L conceived and designed this study;

JF H and WB K searched databases and collected the data;

JF H performed the statistical analysis;

T L drafted the manuscript. All authors reviewed the final manuscript.

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