CHI3L1 Expression is a Prognostic Marker for Patients with Diagnosed Solid Tumors: Evidence from a Systematic Review and Meta-Analysis

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Abstract

Background: Accumulating studies have demonstrated YKL-40 associated with the prognosis of several cancers and contributed to the tumor progression through promoting tumor angiogenesis, migration, invasion and metastasis. The objective of this meta-analysis was to investigatethe relationship between YKL-40 and prognosis inpatients with solid tumors and seek for a new prognostic biomarker.

Method: Relevant studies were searched in the Medline (PubMed), Web of science, and Embase. Pooled HR of overall survival and disease-free survival (DFS) were calculated to evaluate the strengthof the association between YKL-40 and cancer prognosis by using Stata software 14.0.

Results: In total, 30 studies comprising 5160 patients were considered eligible and enrolled into the final meta-analysis. According to the meta-analysis results, higher expression of YKL-40 predicted poorer OS (pooled HR=1.85 CI%=1.58-2.18，P<0.001) and DFS (pooled HR =3.63 95% CI =2.63-5.01; P<0.001).

Conclusion: The current evidence suggests that YKL-40 has a predictive effect onsurvival of cancer patients as indexed by DFS and OS. YKL-40 tissue expression is a valuable prognostic biomarker and may be a promising therapeutic target for solid tumors.

Background

Cancer, a worldwide medical problem, is expected to rank as the leading cause of mortality in the 21st century(1). Although we have made a rapid progression in early diagnosis and treatment, cancer progression and development still cannot be effectively controlled by traditional diagnostic and therapeutic methods[2]. Therefore, a reliable biomarker to predict survival is needed, which will be beneficial to improve cancer patients' clinical outcome.

Human CHI3L1 is one of the members of the glycol-hydrolase family 18(3). Human CHI3L1 is a 40-kDa mammalian glycoprotein, and an essential glutamic acid was substituted by leucine in its domain[4]. It lacks chitinase/hydrolase activity and is also known as chitinase-3-like-1(CHI3L1), YKL-40 or Chondrex[5]. YKL-40 was first detected by Johansen in human articular chondrocytes and synovial cell[6]. YKL-40, an extracellular protein, presents in the Golgi apparatus and endoplasmic reticulum(ER)[7]. Past research showed that YKL-40 was secreted from different type of normal cells (activated neutrophils[8], monocytes[9], macrophages[10]) and cancer cell lines (osteosarcoma (MG-63) [11], ovarian cancer lines (SW626,SW480) [12], human adenocarcinoma cell lines [13] and brain tumor cell lines (U87, SNB-75) [14]. Past studies have demonstrated that YKL-40 contributed to tumor progression and development through promoting tumor angiogenesis, migration, invasion and metastasis[15–17].

Pelloski was the first reporter and found high YKL-40 tissue expression associated with aggressive behavior in Glioblastoma(GBM)(18). Several follow-up studies have proved that elevated serum level of YKL-40 or overexpression of YKL-40 was associated with poor prognosis in different type of tumors, such as lung cancer, anal cancer, glioblastoma, breast cancer, urologic neoplasms, Thyroid carcinoma and so on. A systemic review which investigated the prognostic value of serum/plasma YKL-40 in cancer patients has been finished by Bian et al[19]. His review revealed that elevated YKL-40 level in serum/plasma was a useful prognostic biomarker and associated with poor survival in cancer patients. However, till now, no systemic review is to analyze the prognostic value of CHI3L1 expression in patients with solid tumor. The present systematic review and meta-analysis was conducted to investigate the prognostic value of YKL-40 expression and explore that protein maybe a promising therapeutic target.

Methods

This systematic review was conducted and followed PRISMA guidelines(20).

Search Strategy

A comprehensive literature search of Medline (PubMed), Web of science, and Embase, for studies in the English language (last updated on November 30, 2019). MESH terms were "chitinase 3-like 1", "human cartilage glycoprotein-39", "chitinase 3-like 1 (cartilage glycoprotein-39) protein", "YKL40 protein", "YKL-40 protein, human", "human cartilage gp39", "HCGP39 protein", "HC-gp39 protein", "38-kDa heparin-binding glycoprotein", "GP39 protein", "cartilage gp-39", "Chondrex", "tumor", "neoplasm", "cancer" "survival", "outcome"and "prognosis".

Study Eligibility

Studies was enrolled into the final meta-analysis according the following inclusion criteria: (1) Studies must have been published in English and as original articles; (2) YKL-40 tissue expression was detected by IHC or RT-PCR; (3) Hazard ratios (HRs) with 95% confidence intervals (CIs) which investigated the relationship between YKL-40 levels and patients' survival outcomes were reported or enable to extrapolate these data from the data presented. Studies was excluded according the following exclusion criteria: (1) Lack of key information or could not be accessed in its entirely; (2) Letters to the editor, case report, conference abstracts, comments, review, and systemic review articles.

Quality Assessment

Two reviewers extracted data independently from the eligible studies and based on a standardized form, and any disagreement was resolved by the third author. To assess the quality of each study, we use Newcastle–Ottawa Scale (NOS) on the guidelines of the Newcastle–Ottawa Quality Assessment Scale. The main standards were: selection (0–4 points), outcome assessment (0–3points), and comparability (0–2 points). Finally, we calculated the NOS score of each study and assess the methodological quality.

Statistical analysis

The cutoff value of YKL-40 tissue expression was defined and provided in each article. The pooled hazard rations (HRs) and 95% CI for two endpoints (OS and DFS) were used to evaluate the relationship between YKL-40 and cancer prognosis. Statistical heterogeneity among studies was assessed by using Cochran's *Q* test and the I^2 statistic. If a P value of ≥ 0.05 or $I^2 \leq 50\%$, indicating the statistically significant, a fixed-effects model was used. A random-effects model was applied to merge the HR when a P value of < 0.05 or $I^2 > 50\%$. The potential factors contributed to the heterogeneities were analyzed via sensitivity, subgroup analysis, and meta-regression analysis. Funnel plots, Begg's and Egger's tests were employed to estimate the publication bias. All statistical analyses were conducted using Stata SE 14.0.

Results

Study selection

A total of 1449 articles were collected from databases. After screening the full the articles, reasons for exclusion included manuscripts that focus on YKL-40 in the serum or plasma(n = 41), the study was systemic review(n = 1), insufficient data(n = 4), no survival data(n = 3). Finally, 30 articles that included 5160 participants were considered eligible in final meta-analysis. The flow chart of the study selection is shown in Fig. 1.

Characteristics And Quality Assessment Of The Included Studies

All cases of cancer were diagnosed via histopathology and included GBM, breast cancer, anal cancer, pancreatic cancer, renal cancer, epithelial ovarian carcinoma (EOC), etc. 28 studies included 4689 patients with OS data, and 11 studies included 2092 patients with DFS data. The study was carried out in Europe(21–34), America [18, 25, 35–38] and Asian[39] [40–48] and its number was 14, 6 and 10, respectively. YKL-40 tissue expression was measured by immunohistochemistry in 23 studies [18, 22–24, 26–29, 31, 33–39, 41–46, 48]and RT-PCR in 7 studies[21, 25, 30, 32, 36, 47, 49], although the difference of cutoff values exist among these studies. 4 studies had a score of 9, 7 studies had a score of 8, 11 studies had a score of 7, and 7 studies had a score of 6. The details of assessment results and the relationship between YKL-40 and other clinical features were presented in the **Table 1**.

Table 1
Main characteristics of the eligible studies.

Study ID	Year	Country	Tumor	Number	Age	Sample	Method	YKL-40 associated with clinical features	Cutoff value	Percentage of positive or high expression	Survival
Arboix et al. (21)	2008	France	GBM	42	62.5y	Frozen tissue	RT-PCR	NR	Mean	50%	OS
Pelloski et al. (18)	2007	USA	GBM	509	55y	Tissue	IHC	NR	≥ 10% stained cells	60%	OS
Salvati et al. (22)	2012	Italy	GBM	105	58y	Tissue	IHC	NR	IRS ≥ 2	32%	OS
Batista1 et al. (23)	2015	Spain	GBM	204	63y	Tissue	IHC	Subventricular	Median	46%	OS
Batista et al. (24)	2016	Spain	GBM	152	65y	Tissue	IHC	Age and Karnofsky	Median	41%	OS
Steponaitis et al. (25)	2016	Lithuania	GBM	98	50y	Frozen tissue	RT-PCR	Age and Pathological grade	Median	25%	OS
Castellano et al. (26)	2009	Italy	Anal cancer	34	NR	Tissue	IHC	Histological subtype	Median	44%	OS, DFS
Mistrangelo et al. (27)	2013	Italy.	Anal cancer	50	58.5y	Tissue	IHC	Sentinel lymph node and metastatic status	> 20% staining cell	52%	OS, DFS
Yang et al. (39)	2009	China	EOC	74	50.5y	Tissue	IHC	Clinical stage	IRS ≥ 4	58.3%	OS
Høgdall et al. (28)	2009	Denmark	EOC	473	59y	Tissue	IHC	FIGO stage, histological type of cancer	≥ 5% stained cells	76%	OS
Lawrenson et al. (36)	2014	USA	EOC	105	NR	Tissue	IHC	High tumor grade	Mean	70%	OS
Chiang et al. (40)	2015	Taiwan	EOC	180	53.8y	Frozen tissue	RT-PCR	Histological type and chemoresistance	Mean	24%	OS
Kim et al. (37)	2007	USA	BC	109	52y	Tissue	IHC	Tumor size and differentiation	Median	34%	DFS
Roslind et al. (29)	2008	Denmark	Primary BC	630	47y	Tissue	IHC	High tumor differentiation	IRS ≥ 2	63%	OS, DFS
Shao et al. (38)	2010	USA	BC	79	56.5y	Tissue	IHC	Tumor grade	IRS ≥ 5	29%	OS
Kang et al. (41)	2014	Korea	BC	425	45y	Tissue	IHC	Subtype, hormone receptor and molecular subtype	IRS ≥ 3	5%	OS,DFS
Vom Dorp et al. (30)	2015	Austria	Renal Cell Cancer	101	65y	Frozen tissue	RT-PCR	Tumor stage	Median	50%	OS

Table 1 (continued)

Study ID	Year	Country	Tumor	Number	Age	Sample	Method	YKL-40 associated with clinical features	Cutoff value	Percentage of positive or high expression	Survival
Zhang et al. (42)	2014	China	Renal Cell Cancer	73	53.9y	Tissue	IHC	Tumor size, TNM stage and metastasis	IRS > 3	13%	OS
Peng et al. (43)	2010	China	Endometrial Cancer	68	52y	Tissue	IHC	NR	IRS > 3	38.2%	OS, DFS
Bi et al. (44)	2009	China	PGC	172	58y	Tissue	IHC	Tumor invasion and tumor metastasis	IRS > 3	28.4%	OS
Pelloski et al. (35)	2005	USA	GBM	265	58y	Tissue	IHC	Resistance to radiation therapy	IRS ≥ 2	58% (Total section)	OS

										26% (subsection)	
Pan et al. (45)	2013	china	HC	70	NR	Tissue	IHC	Tumor size, invasion, stage and metastasis	IRS ≥ 3	61%	OS, DFS
Harving et al. (31)	2014	Denmark	STS and LT	49	58y	Tissue	IHC	Histological grade	> 20% staining cell	43%	OS
Tschirdewahn et al. (32)	2014	Germany	UCB	91	NR	Frozen tissue	RT-PCR	YKL-40 concentration in serum	Median	50%	OS, DFS
Wang et al. (46)	2014	China	NSCLC	95	60y	Tissue	IHC	Recurrence	IRS ≥ 4	56%	OS, DFS
Krogh et al. (33)	2015	Denmark	Melanoma	204	51y	Tissue	IHC	Low Breslow thickness and Clark's level	Mean	NR	OS
Thorn et al. (34)	2016	Denmark	Osteosarcoma	48	26y	Tissue	IHC	NR	> 50% staining cells	17%	OS
Luo et al. (47)	2016	China	Thyroid carcinoma	322	45y	Frozen tissue	RT-PCR	Tumor size, metastasis, invasion and stage	IRS ≥ 4	51.86%	DFS
Chen et al. (48)	2017	China	Pancreatic Cancer	234	59y	Tissue	IHC	Tumor size, stage, invasion, metastasis, and postoperative relapse	IRS > 3	63.7%	OS, PFS
Cardona et al. (49)	2019	Colombia	Recurrent GBM	59	43y	Frozen tissue	RT-PCR	CD133 mRNA	Mean	11.9%	OS, PFS

Ykl-40 And Os

Overall survival data were reported or extrapolated from 28 of the studies(18, 21–36, 38–46, 48, 49), and 2 HRs were extracted from 1 study because of 2 cohorts in this study[35]. HR was merged by using a random-effects model and the forest plot was shown in Fig. 2. The pooled HR showed a clear association between high expression of YKL-40 and poor OS (pooled HR = 1.85 CI%=1.58–2.18;P < 0.001). Obvious heterogeneity was existed among these studies (p = 0.000; I^2 = 74.8%).

Due to the high I^2 values in the analysis, we then conducted the subgroup analyses following tumor type, tumor source, geographical location, detected method, number of the cases, HR acquisition method, and NOS score, the detailed data are summarized in Table 2. Of note, the results showed an obvious decrease in heterogeneity in the subgroup analysis of tumor type. The heterogeneity reduced to zero in patients with breast cancer [1.5(1.11–2.01);I^2 = 0%; P = 0.39] and anal cancer [3.69(1.62–8.44)，I^2 = 0%; P = 0.985] (Fig. 3). In the two articles about renal cancer, the combined HR1.67 (95% CI: 0.62–4.48, P = 0.309) indicated that overexpression of YKL-40 would not precisely in predicting poor OS (Fig. 3). When coming to the tumor source subgroup analysis, the pooled HR 3.06(95%CI:2.10–4.44, P < 0.001)showed YKL-40 was a strong predictor of poor OS in patients with digestive system cancer. In the 3 articles about urogenital system cancer using OS to assess clinical outcome, the combined HR 1.31 (95% CI: 0.91–1.87, P = 0.144), implying the association between overexpression of YKL-40 and poor OS was not significant **(Figures S1)**. Interestingly, the heterogeneity showed a remarkable change in the research region [European group: 1.36(1.17–1.57), I^2 = 57.9%; P = 0.004; Asia group: 2.61(1.94–3.51), I^2 = 41.2%; P = 0.093; America group: 2.15(1.74–2.66), I^2 = 0%; P = 0.531] **(Figures S2)**. However, the heterogeneity was not changed in patients with glioblastoma and epithelial ovarian carcinoma, or tumor source is nervous system and reproductive system (Table 2). A lower heterogeneity and prediction function of YKL-40 using RT-PCR method[1.37(1.02–1.848); I^2 = 48.5%; P = 0.1] compare to immunohistochemistry (IHC) [1.85(1.58–2.18)，I^2 = 74.8%; P = 0.000]. Another interesting finding was lower heterogeneity in the higher NOS score group[1.53(1.31–1.79)，I^2 = 26.3%; P = 0.202] than the lower NOS score group (Table 2). The other subgroup analyses without statistically significant heterogeneity are according to HR acquisition method and number of cases.

Table 2
Subgroup analyzes for the associations between YKL-40 and overall survival of patients with solid tumors.

Subgroup analysis	No. of patients	No. of studies	Random-effects model		Heterogeneity	
			HR (95% CI)	P-value	I2 (%)	P-value
OS	4689	28	1.85(1.58–2.18)	< 0.001	74.8	0.000
PFS	2092	11	3.63(2.63–5.01)	< 0.0001	18.6	0.267
Tumor type						
GBM	1434	9	1.58(1.27–1.97)	< 0.001	80.7	0.000
EOC	832	4	2(1.13–3.56)	0.008	84.5	0.000
BC	1134	3	1.5(1.11–2.01)	0.007	0	0.39
Anal cancer	84	2	3.69(1.62–8.44)	0.002	0	0.985
Renal cancer	174	2	1.67(0.62–4.48)	0.309	39	0.2
Other	1031	9	2.24(1.62–3.11)	< 0.001	47.8	0.053
Tumor source						
Digestive system	560	5	3.06(2.10–4.44)	< 0.001	32.6	0.204
Urogenital system	265	3	1.31(0.91–1.87)	0.144	0	0.42
Nervous system	1434	8	1.58(1.27–1.97)	< 0.001	80.7	0.000
Reproductive system	900	5	2.02(1.2–3.41)	0.008	79.5	0.001
Other	1530	7	1.64(1.29–2.08)	< 0.001	0	0.591
Geographical location						
Europe	2281	13	1.36(1.17–1.57)	< 0.001	57.9	0.004
Asia	1391	9	2.61(1.94–3.51)	< 0.001	41.2	0.093
America	1017	6	2.15(1.74–2.66)	< 0.001	0	0.531
YKL-40 detected method						
RT-PCR	391	5	1.37(1.02–1.84)	0.037	48.5	0.1
IHC	4298	23	1.98(1.64–2.40)	< 0.0001	72.7	0.000
HR acquisition method						
Reported	3133	16	1.72(1.39–2.12)	< 0.0001	82.8	0.000
Extrapolated	1556	12	1.85(1.58–2.18)	< 0.0001	74.8	0.000
Number of cases						
≥ 100	3959	14	1.82(1.47–2.24)	< 0.0001	79.80%	0.000
< 100	930	14	2.02(1.48–2.75)	< 0.0001	62.70%	0.001
NOS score						
≥ 8	1710	10	1.53(1.31–1.79)	< 0.0001	26.3%	0.202
< 7	3179	18	2.09(1.64–2.66)	< 0.0001	81.5%	0.000

Ykl-40 And Dfs

DFS data were reported or extrapolated from 11 studies, representing a total of 2092 patients(26, 27, 29, 32, 37, 41, 43, 45–49). The pooled HR and 95%CI was calculated by using a fixed-effects model, heterogeneities between HR estimates was no significantly in this meta-analysis (I^2 = 18.6; P = 0.267). The pooled HR was 3.63（95%CI = 2.63–5.01; P < 0.001）and the forest plot was shown in Fig. 4. The result showed that YKL-40 has a stronger relationship with poorer DFS and better predictive effector in solid tumor. Interestingly, we come to subgroup analysis by tumor type and tumor source, the heterogeneity reduced to zero in anal caner group [3.31(1.49–7.35);I^2 = 0%; P = 0.905] and digestive system group[3.82（2.55–5.71），I^2 = 0%; P = 0.904]（data not shown）.

Heterogeneity Analysis

Meta-regression analyses were conducted to explore the potential reasons of heterogeneity, and we use follow covariates: geographical location, tumor type, tumor source, YKL-40 detected method, HR acquisition method and number of cases. The results show in Table 3 and indicate that Geographical location(P = 0.108), tumor source(P = 0.282), tumor type(P = 0.454), YKL-40 detected method(P = 0.541), HR acquisition method(P = 0.349) and number of cases(P = 0.603) did not contribute to the reasons of heterogeneity of the OS analysis.

Table 3
Results of meta-regression analyses exploring causes of heterogeneity with overall survival

Covariates	OS Multivariate analysis P Value
Geographical location	0.108
Tumor type	0.454
Tumor source	0.282
YKL-40 detected method	0.541
HR acquisition method	0.349
Number of cases	0.603

Publication Bias And Sensitivity Analysis

To evaluate the confidence of this study, Begg's rank correlation and Egger's linear regression were used to assess publication bias. The shapes of the funnel plot for the OS is asymmetric **(Figure S4)**, and the p value of Egger's test was < 0.01, but the p value of Begg's tests was 0.159. However, the funnel plot for the DFS did not show obvious evidence of asymmetry **(Figure S5)**; the p value of Begg's and Egger's test were 0.533 and 0.571, respectively. Sensitivity analysis were further conducted to assess the stability and credibility of the heterogeneity through omitting individual studies in the OS analysis. The results were shown in **Figure S3** and no individual study obviously dominated the combined HR.

Discussion

YKL-40, an extracellular protein, its gene located on chromosome 1q32.1 and could be secreted by several types of normal and abnormal cells. Due to multi-functional of YKL-40 in the microenvironment of tumor, researchers found it could promote tumor progression through different regulatory mechanisms.

A developing tumor needs tumor angiogenesis to provide enough oxygen or nutrients, which is essential for tumor progression. 1) Colon cancer cell lines (HCT-116) and breast cancer cell lines (MDA-MB-231), which express ectopic YKL-40 in vitro, co-cultured with human microvascular endothelial cells (HMVECs). YKL-40 could enhance HMVECs proliferation and migration(50). The researchers injected MDA-MB-231 or HCT-116 cell lines into mice, by week six, the volume of tumor was about 4-8-fold bigger than control mice. Histologically, the vessels density of the tumor with MDA-MB-231 or HCT-116 were approximately 1.8 to2 fold higher compared to control tumors. Consistent results were also found in two another studies [12] [51]. 2) In physiological angiogenesis, VEGF (vascular endothelial growth factor) and bFGF (basic fibroblast growth factor) are the important factors in stimulating vessel formation through enhancing the proliferation and survival of ECs[52]. It was suggested that YKL-40 had a positive effect in stimulating VEGF expression in brain tumor cell lines (U87) [14]. 3) Endothelial cells (ECs), pericytes or vascular smooth muscle cells (VSMC) were recruited and form new vessels. VSMC migration, adhesion and spreading could be promoted by YKL-40 protein in vitro[53]. YKL-40 also promoted the adhesion of ECs and restricted the permeability of HMVEC by inducing the VE-cadherin/β-catenin/actin pathway[54]. In human tumor specimens, researchers also found that a positive relationship between YKL-40 over expression and microvascular density in breast cancer[50], cervical cancer[51]and non-small lung cancer [46].

MMP-9 and MMP-2, belong to matrix metalloproteinases (MMPs), promoted extracellular matrix remodeling and enhanced tumor growth in a variety of cancers (55). Researchers found that YKL-40 also had the effect in inducing secretion of MMP-9 in macrophages[55]. In a human glioma cell line(shRNA-U87MG), secretion of MMP-2 was significantly inhibited via knockdown YKL-40[56]. It is reported that YKL-40 up-regulated epithelial mesenchymal transition (EMT) in lung cancer and prostate cancer through AKT signaling pathway [13, 57]. Two type of chemokines (CXCL8 and MCP-1) could be induced by YKL-40 through the MAPK signaling pathway in colorectal cancer SW480cell line [58]. Those studies suggested that YKL-40 protein play a vital role in tumor metastasis and invasion through promoting cancer cell migration and EMT. Therefore, overexpression of YKL-40 protein could promote cancer progression in the tumor microenvironment and associated with poor prognosis in patients with solid tumor.

Recently, a 10-years follow-up study revealed that serum level of YKL-40 keep stable if participants remained healthy during follow-up period(59). Another follow-up study suggested the morbidity of gastrointestinal cancer was upregulated with the increasing serum of YKL-40 level[60]. Clinical studies have proved that YKL-40 expression or serum of YKL-40 level was a promising biomarker in predicting the prognosis of cancer patients, such as glioblastoma, breast cancer, bladder cancer, pancreatic cancer. To our knowledge, Qin et al[61]and Wan et al[62] finished the meta-analysis on the prognosis of glioblastoma and breast cancer and YKL-40 expression, respectively. The meta-analysis based on the level of serum/plasma of YKL-40 and prognosis of patients with solid tumor was finished by Bian et al[19]. However, our research is the first systematic analysis of 30 studies comprising 5160 patients and investigated on the YKL-40 tissue expression and prognosis of 15 different types of solid tumor. The pooled results provide the evidence and strongly supported the viewpoint that an overexpression of YKL-40 was associated with the poorer OS and DFS. Additionally, we include fourteen different cancer types, including GBM[35], Anal cancer[26], epithelial ovarian carcinoma[39], breast cancer [29], Renal Cell Cancer[30], carcinoma of the bladder[32

,Primary gastric cancer44, hepatocellular carcinoma45, NSCLC46, Melanoma33, Osteosarcoma34, Thyroid carcinoma47, and Pancreatic Cancer48. To further evaluate the prognostic value of YKL-40 in different cancers, subgroup analyses were conducted for OS and DFS. A stronger relationship was found between YKL-40 overexpression and patients with anal caner or digestive system cancer. That result was consistent with Allin's follow-up study in healthy population60. However, Roslind et al29 did not find any association between YKL-40 expression and DSF or OS in primary breast cancer. For this study result, we cannot exclude the impact of limitations of study design.

Although the prognostic value of YKL-40 was confirmed in our study, some limitations still need to be acknowledged. First, the total sample size was relatively small and only 30 studies were included in this meta-analysis, so failed to detect the association between overexpression of YKL-40 and some clinicopathological parameters. Second, the method of detected YKL-40 and the cutoff value of YKL-40 expression were not uniform in all the studies. Third, of the 30 studies, 14 directly provided HRs, and individual HRs of the remaining studies were extracted from survival curve using the methods reported by Tierney et al(63), which inevitably produced small statistical errors. Finally, a subgroup analysis of study types found that there was a big difference among different subgroup analysis and overall results. Still, we cannot explain the high heterogeneity for the investigated outcomes through sensitivity and meta-regression analyses.

Conclusion

In summary, our comprehensive analysis clearly demonstrated the relationship between high YKL-40 expression in solid tumor tissues and cancer patient's survival. Thus, we can conclude that YKL-40 is a reliable prognostic biomarker and may be a promising therapeutic target for solid tumors. Given the limitations of the current study, prospective clinical trials, multicenter, and higher-quality studies with a unified criterion for determining YKL-40 expression are necessary to confirm the results of this study.

Abbreviations

DFS, disease-free survival; OS, overall survival; GBM,glioblastoma□EOC, epithelial ovarian carcinoma; STS and LT, Soft-tissue sarcomas and lipomatous tumors; BC, breast cancer; IHC, immunohistochemistry; IRS, immunoreactivity score; NSCLC, non-small-cell lung cancer; OSSC, oral squamous cell carcinoma; R, reported; NR;, no reported; SC, survival curve; UCB, carcinoma of the bladder;PGC□Primary gastric cancer□HC□Hepatocellular carcinoma; NOS, Newcastle-Ottawa Scale.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Ethical Review Committeefor Biomedical Research, Anhuimedical University. Thestudy was performed in accordance with the Declaration of Helsinki. Thestudy is a systematic review and meta-analysis and no patients involved.

Consent for publication

This study did not contain any individual person's data.

Availability of data and material

This study is a systematic review and meta-analysis, the data was extractedfrom published research. The data is available by contacting correspondingauthor or extracting from original published research.

Competing interests

The authors declare that they have no competing interests.

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Author'scontribution

JY P conceived and designed the study. LP W, SW Y, J F, J Z, ZF C, and YQ T acquisition of data. LP W and SW Y analysis and interpretation of data. JY P and M M drafting of the manuscript. All authors critical revision of the manuscript for important intellectual content.

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Figures

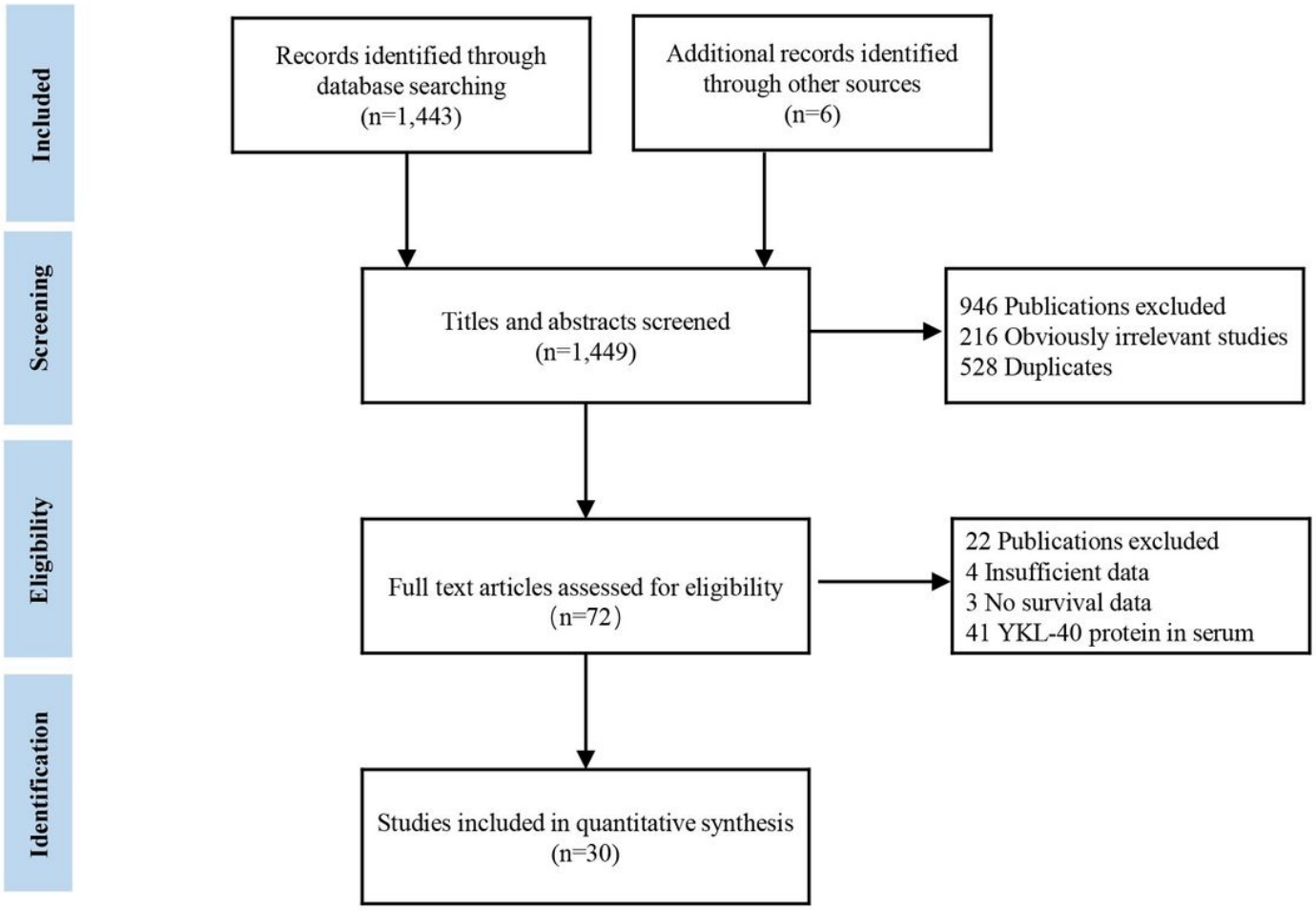

Figure 1

Flow diagram of the studies retrieved for the review.

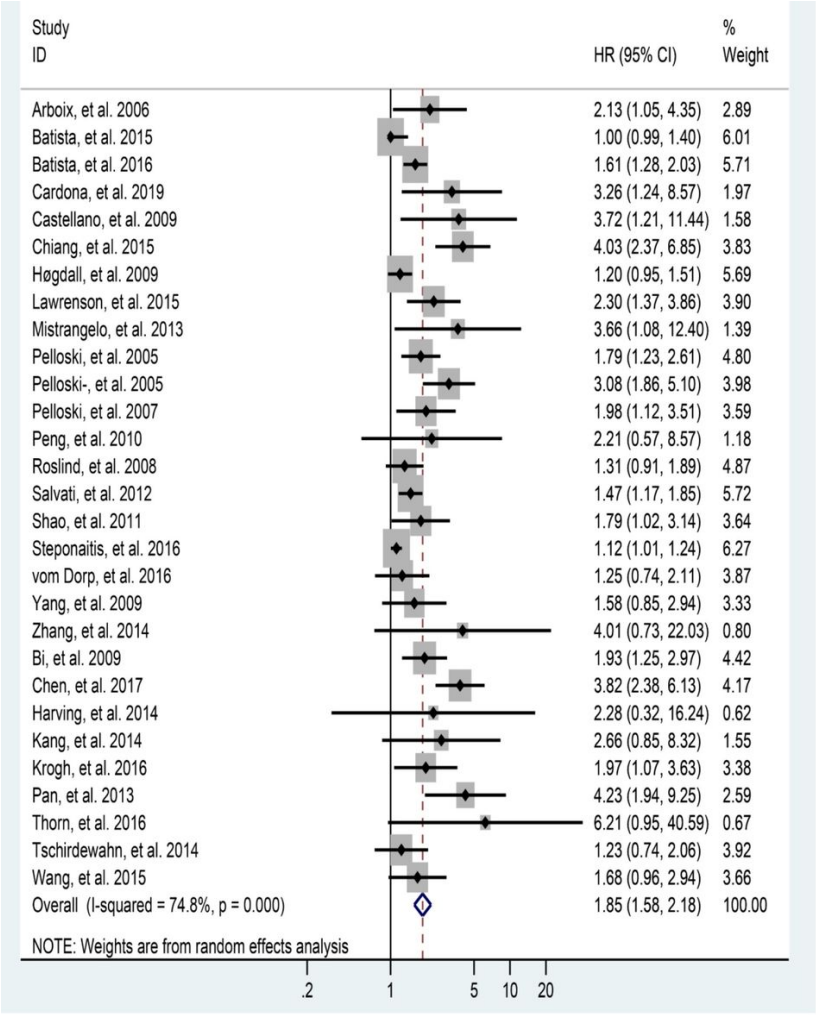

Figure 2

Summary estimates and 95% CIs for overall survival, for associations between YKL-40 and survival of patients with solid tumors. Weights are from random effects analysis. CI, confidence interval; HR, hazard ratio; W (random), Weights (random effects model).

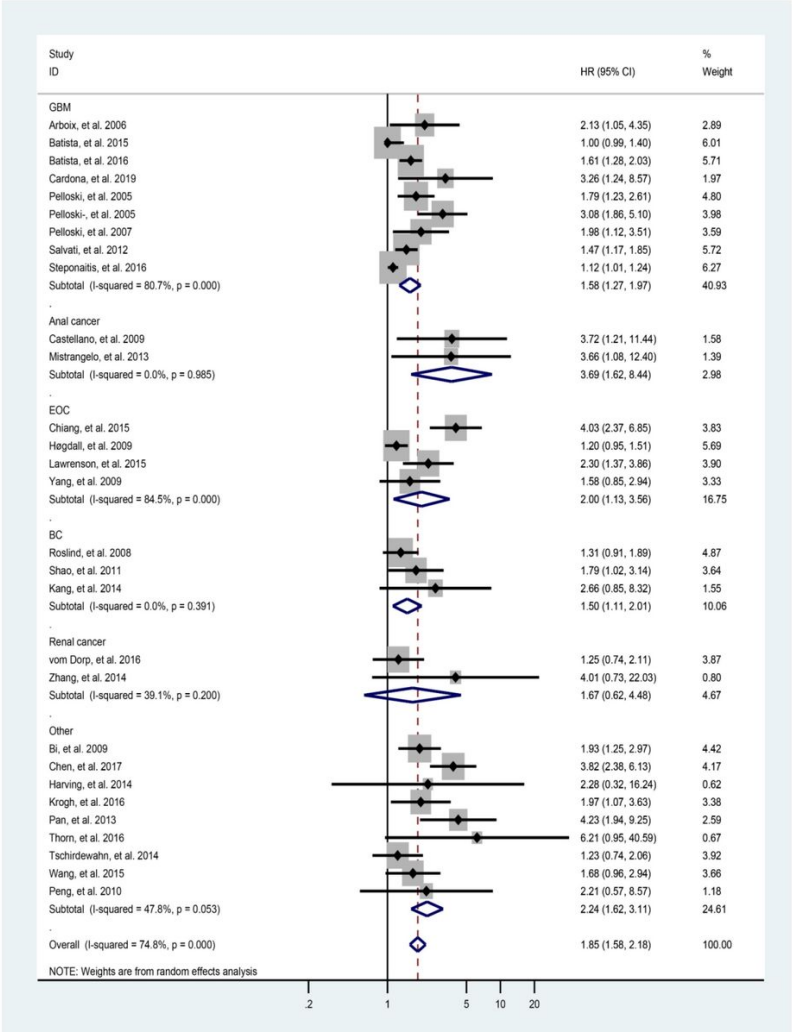

Figure 3

Forest plot of studies evaluating the relationship between high YKL-40 expression and OS in patients with different cancers. GBM, glioblastoma; EOC, epithelial ovarian carcinoma; BC, breast cancer; OS, overall survival; CI, confidence interval; HR, hazard ratio.

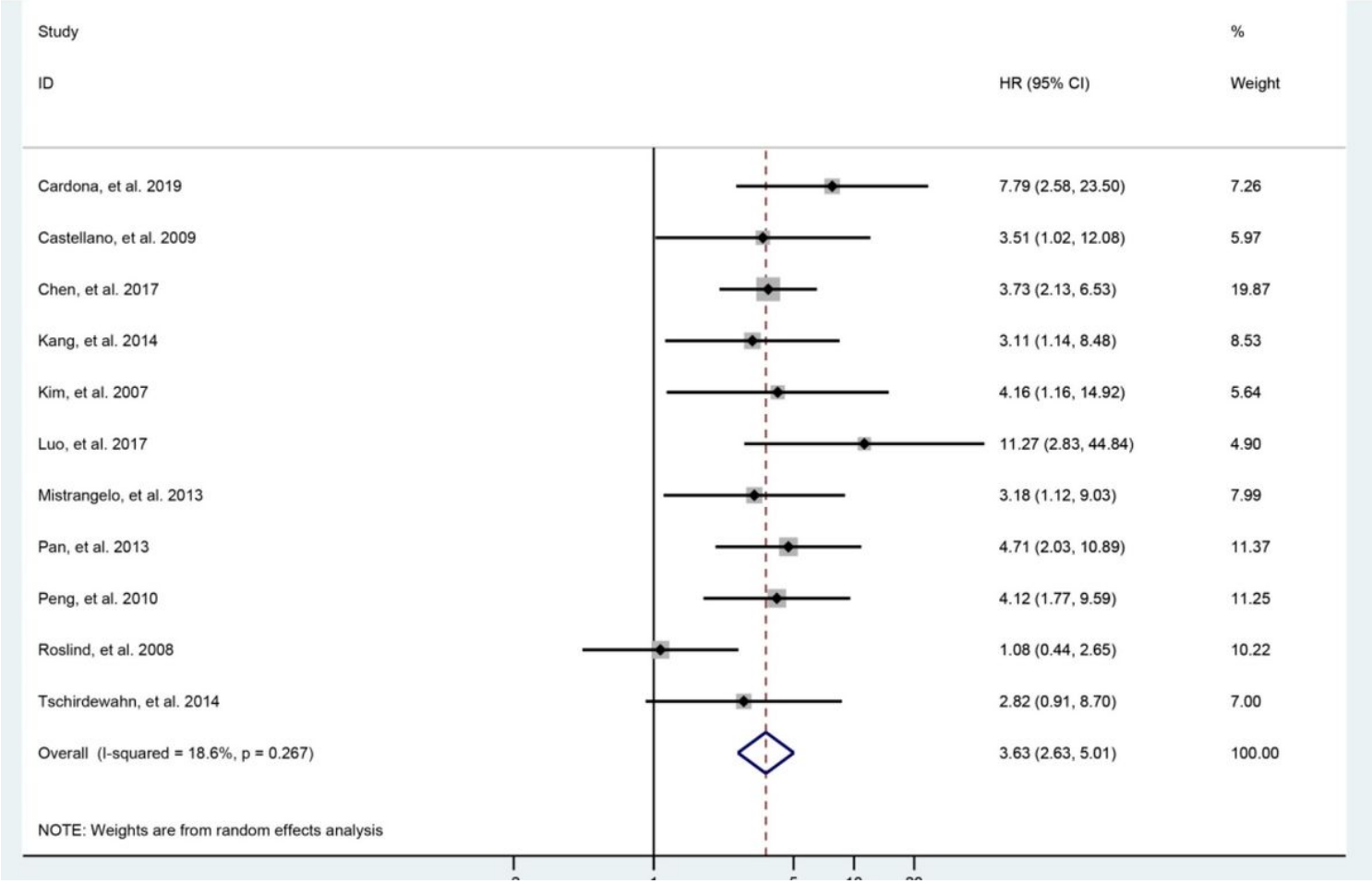

Figure 4

Forest plot of studies evaluating the relationship between high YKL-40 expression and DFS in patients with solid tumor. CI, confidence interval; HR, hazard ratio.

Supplementary Files

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