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

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Research article

Keywords: YKL-40, solid tumor, cancer, prognosis, meta-analysis

DOI: https://doi.org/10.21203/rs.3.rs-26219/v1

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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 investigate the relationship between YKL-40 and prognosis in patients 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 strength of 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 on survival 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 cells(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
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 ratios (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 $\geq 0.05$ 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 (21, 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 (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 | Cut off value | Percentage of positive or high expression | Survival | HR | NO S |
|----------|------|---------|-------|--------|-----|--------|--------|----------------------------------------|---------------|----------------------------------------|-----------|----|------|
| Arbix et al. (21) | 2008 | France | GBM | 42 | 62.5y | Frozen tissue | RT-PCR | NR | Mean | 50% | OS | R | 9 |
| Pell oski et al. (18) | 2007 | USA | GBM | 509 | 55y | Tissue | IHC | NR | ≥ 10% stained cells | 60% | OS | R | 7 |
| Salvati et al. (22) | 2012 | Italy | GBM | 105 | 58y | Tissue | IHC | IRS | ≥ 2 | 32% | OS | SC | 8 |
| Bati sta1 et al. (23) | 2015 | Spain | GBM | 204 | 63y | Tissue | IHC | Subventricular | Median | 46% | OS | R | 6 |
| Bati sta et al. (24) | 2016 | Spain | GBM | 152 | 65y | Tissue | IHC | Age and Karnofsky | Median | 41% | OS | R | 6 |
| Ste ponaitis et al. (25) | 2016 | Lithuania | GBM | 98 | 50y | Frozen tissue | RT-PCR | Age and Pathological | Median | 25% | OS | R | 7 |
| Cas tell ano et al. (26) | 2009 | Italy | Anal cancer | 34 | NR | Tissue | IHC | Histological subtype | Median | OS, DFS | SC | 8 |
|------------------------|-------|-------|-------------|----|----|--------|-----|----------------------|--------|--------|----|-----|
| Mis tran gel o et al. (27) | 2013 | Italy | Anal cancer | 50 | 58.5y | Tissue | IHC | Sentinel lymph node and metastatic status | > 20% staining cell | 52% | OS, DFS | SC | 7 |
| Yang et al. (39) | 2009 | China | EO C | 74 | 50.5y | Tissue | IHC | Clinical stage | IRS ≥ 4 | 58.3% | OS | SC | 8 |
| Hø gda ll et al. (28) | 2009 | Denmark | EO C | 473 | 59y | Tissue | IHC | FIGO stage, histological type of cancer | ≥ 5% stained cells | 76% | OS | R | 8 |
| Law re nso n et al. (36) | 2014 | USA | EO C | 105 | NR | Tissue | IHC | High tum or grade | Mean | 70% | OS | SC | 9 |
| Chi ang et al. (40) | 2015 | Taiwan | EO C | 180 | 53.8y | Frozen tissue | RT-PCR | Histological type and che | Mean | 24% | OS | R | 6 |
| Study ID | Year | Country | Tumor Type | Tissue Type | IHC | Cut-off Value | Percentage of Positive | Survival | HR | NO |
|----------|------|---------|------------|-------------|-----|---------------|------------------------|----------|----|----|
| Kim et al. (37) | 2007 | USA | BC | Tissue | IHC | Tu | Median | 34% | DFS | SC | 6 |
| Roslind et al. (29) | 2008 | Denmark | Primary BC | Tissue | IHC | Higtumor differnetiation | IRS ≥ 2 | 63% | OS, DFS | R | 8 |
| Sha et al. (38) | 2010 | USA | BC | Tissue | IHC | Tu | Grade | IRS ≥ 5 | 29% | OS | SC | 8 |
| Kang et al. (41) | 2014 | Korea | BC | Tissue | IHC | Subtype, hormone receptor and molecular subtype | IRS ≥ 3 | 5% | OS, DFS | SC | 6 |
| vom Dorp et al. (30) | 2015 | Austria | Renal Cell Cancer | Tissue | RT-PCR | Tu | Stage | Median | 50% | OS | SC | 9 |

Table 1 (continued)
| Study | Year | Country | Tissue Type | Age | Tumor Feature | IRS | OS | SC | 6 |
|-------|------|---------|-------------|-----|---------------|-----|----|----|----|
| Zhang et al. (42) | 2014 | China | Renal Cell Cancer | 73 | 53.9y | Tissue IHC | Tu mor size, TNM stage and metastasis | IRS > 3 | 13% | OS, SC | 6 |
| Peng et al. (43) | 2010 | China | Endometrial Cancer | 68 | 52y | Tissue IHC | NR | IRS > 3 | 38.2% | OS, DFS | SC | 7 |
| Bi et al. (44) | 2009 | China | PG C | 172 | 58y | Tissue IHC | Tu mor invasion and tumor or metastasis | IRS > 3 | 28.4% | OS | R | 9 |
| Pellosk i et al. (35) | 2005 | USA | GB M | 265 | 58y | Tissue IHC | Resistance to radiation therapy | IRS ≥ 2 | 58% (Total section) 26% (subsection) | OS, SC | 7 |
| Pan et al. (45) | 2013 | China | HC | 70 | NR | Tissue IHC | Tu mor size, invasion | IRS ≥ 3 | 61% | OS, DFS | R | 7 |
| Study          | Year | Country | Tissue Type | Age | Histological Grade | YKL-40 Concentration in Serum | Recurrence | OS Rate | DFS Rate | Tumor Size, IRS ≥ | Other Parameters |
|---------------|------|---------|-------------|-----|-------------------|-------------------------------|-------------|---------|----------|-----------------|-----------------|
| Harving et al. (31) | 2014 | Denmark | LT ST and S | 49  | 58y               | Tissue IHC Histological grade | > 20% staining cells | 43%       | OS       | SC       | 7               | Harving’s tissue IHC Histological grade |
| Tschirrneh et al. (32) | 2014 | Germany | UC B | 91  | NR                | Frozen tissue RT-PCR | YKL-40 concentration in serum | Median     | 50%      | OS, DFS  | R       | 7               | Tschirnneh's tissue RT-PCR YKL-40 concentration in serum |
| Wang et al. (46) | 2014 | China | NS CLC | 95  | 60y               | Tissue IHC Recurrence | IRS ≥ 4 | 56%      | OS, DFS  | SC       | 6               | Wang’s tissue IHC Recurrence IRS ≥ 4 |
| Krogh et al. (33) | 2015 | Denmark | Melanoma | 204 | 51y               | Tissue IHC Low Breslow thickness and Clark’s level | Mean       | NR       | OS       | R       | 7               | Krogh’s tissue IHC Low Breslow thickness and Clark’s level |
| Thom et al. (34) | 2016 | Denmark | Osteosarcoma | 48  | 26y               | Tissue IHC NR > 50% staining cells | 17%        | OS       | SC       | 6               | Thom’s tissue IHC NR > 50% staining cells |
| Luo et al. | 2016 | China | Thyroid carcinoma | 322 | 45y               | Frozen tissue RT-PCR Tumor size, IRS ≥ 4 | 51.86%      | DFS      | R        | 8               | Luo’s tissue RT-PCR Tumor size, IRS ≥ 4 |
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. 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 \((\text{pooled HR} = 1.85; \text{CI} = 1.58–2.18; P < 0.001)\). Obvious heterogeneity was existed among these studies \((p = 0.000; \text{I}^2 = 74.8\%)\).

Due to the high \(\text{I}^2\) 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 \([1.5(1.11–2.01); \text{I}^2 = 0\%; P = 0.39]\) and anal cancer \([3.69(1.62–8.44); \text{I}^2 = 0\%; P = 0.985]\).

### Table 2: Summary of the Subset Analysis

| Study          | Year | Country | Tumor Type | Tumor Source | Follow-up | Detection Method | HR   | OS  | PFS | SC  | NOS |
|----------------|------|---------|------------|--------------|-----------|----------------|------|-----|-----|-----|-----|
| Chen et al. (48) | 2017 | China   | Pancreatic Cancer | Tissue | 59y | IHC | 1.85 | 63.7% | R   | 7   |
| Cardona et al. (49) | 2019 | Colombia | Recurrent GBM | Frozen tissue | 43y | RT-PCR | 1.11 | 11.9% | SC  | 7   |

### 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. 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 \((\text{pooled HR} = 1.85; \text{CI} = 1.58–2.18; P < 0.001)\). Obvious heterogeneity was existed among these studies \((p = 0.000; \text{I}^2 = 74.8\%)\).
In the two articles about renal cancer, the combined HR 1.67 (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), I² = 57.9%; P = 0.004; Asia group: 2.61(1.94–3.51), I² = 41.2%; P = 0.093; America group: 2.15(1.74–2.66), I² = 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); I² = 48.5%; P = 0.1] compared to immunohistochemistry (IHC) [1.85(1.58–2.18); I² = 74.8%; P = 0.000]. Another interesting finding was lower heterogeneity in the higher NOS score group [1.53(1.31–1.79); I² = 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 analyses 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   |
| **Geographic location** |             |                |                      |          |        |         |
| Subgroup analysis | No. of patients | No. of studies | Random-effects model | Heterogeneity |
|-------------------|----------------|---------------|----------------------|---------------|
|                   |                |               | HR (95% CI)          | P-value   | I2 (%) | P-value |
| 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 $3.63 \pm 95\% CI = 2.63–5.01; P < 0.001$ 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 cancer group [$3.31 (1.49–7.35); I^2 = 0\%; P = 0.905$] and digestive system group [$3.82 \pm 2.55–5.71; I^2 = 0\%; P = 0.904$] 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**

| 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 to 2 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 SW480 cell 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 cancer\(^{44}\), hepatocellular carcinoma\(^{45}\), NSCLC\(^{46}\), Melanoma\(^{33}\), Osteosarcoma\(^{34}\), Thyroid carcinoma\(^{47}\), and Pancreatic Cancer\(^{48}\). 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 cancer or digestive system cancer. That result was consistent with Allin's follow-up study in healthy population\(^{60}\). However, Roslind et al\(^{29}\) did not find any association between YKL-40 expression and DFS 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**
Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from Ethical Review Committee for Biomedical Research, Anhui Medical University. The study was performed in accordance with the Declaration of Helsinki. The study 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 extracted from published research. The data is available by contacting corresponding author or extracting from original published research.

Competing interests

The authors declare that they have no competing interests.

Funding

This research was founded by Hefei Municipal Health and Family Planning Commission (No. hwk2017yb012). We would like to thank all participants for their technical assistance and advice regarding statistical analysis.

Author’s contribution

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.
Acknowledgements

Not applicable.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

2. Siegel RL, Miller KD, Jemal A. Cancer statistics. 2016. CA Cancer J Clin. 2016;66(1):7–30.

3. Kzhyshkowska J, Yin S, Liu T, Riabov V, Mitrofanova I. Role of chitinase-like proteins. in cancer Biol Chem. 2016;397(3):231–47.

4. Renkema GH, Boot RG, Au FL, Donker-Koopman WE, Strijland A, Muijsers AO, et al. Chitotriosidase, a chitinase, and the 39-kDa human cartilage glycoprotein, a chitin-binding lectin, are homologues of family 18 glycosyl hydrolases secreted by human macrophages. Eur J Biochem. 1998;251(1–2):504–9.

5. Libreros S, Iragavarapu-Charyulu V. YKL-40/CHI3L1 drives inflammation on the road of tumor progression. J Leukoc Biol. 2015;98(6):931–6.

6. Johansen JS, Williamson MK, Rice JS, Price PA. Identification of proteins secreted by human osteoblastic cells in culture. J Bone Miner Res. 1992;7(5):501–12.

7. Johansen JS, Olee T, Price PA, Hashimoto S, Ochs RL, Lotz M. Regulation of YKL-40 production by human articular chondrocytes. Arthritis Rheum. 2001;44(4):826–37.

8. Coriati A, Masse C, Menard A, Bouvet GF, Berthiaume Y. Neutrophils as a Potential Source of Chitinase-3-like Protein 1 in Cystic Fibrosis. Inflammation. (2018). 41(5):1631–1639.

9. Di Rosa M, Tibullo D, Saccone S, Distefano G, Basile MS, Di Raimondo F, et al. CHI3L1 nuclear localization in monocyte derived dendritic cells. Immunobiology. 2016;221(2):347–56.

10. Chen Y, Zhang S, Cao J, Zhang X. Shrimp Antiviral mja-miR-35 Targets CHI3L1 in Human M2 Macrophages and Suppresses Breast Cancer Metastasis. Front Immunol. (2018). 9:2071.

11. Junker N, Johansen JS, Hansen LT, Lund EL, Kristjansen PE. Regulation of YKL-40 expression during genotoxic or microenvironmental stress in human glioblastoma cells. Cancer Sci. 2005;96(3):183–
12. Kawada M, Seno H, Kanda K, Nakanishi Y, Akitake R, Komekado H, et al. Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer. Oncogene. (2012). 31(26): 3111–3123.

13. Jefri M, Huang YN, Huang WC, Tai CS, Chen WL. YKL-40 regulated epithelial-mesenchymal transition and migration/invasion enhancement in non-small cell lung cancer. BMC Cancer. (2015). 15(1): 590.

14. Francescone RA, Scully S, Faibish M, Taylor SL, Oh D, Moral L, et al. Role of YKL-40 in the angiogenesis, radioresistance, and progression of glioblastoma. J Biol Chem. 2011; 286(17): 15332–43.

15. Bakirci EM, Unver E, Degirmenci H, Kivanc T, Gunay M, Hamur H, et al. Serum YKL-40/chitinase 3-like protein 1 level is an independent predictor of atherosclerosis development in patients with obstructive sleep apnea syndrome. Turk Kardiyol Dern Ars. (2015). 43(4): 333–339.

16. Pedersen SJ, Sorensen IJ, Lambert RG, Hermann KG, Gamero P, Johansen JS, et al. Radiographic progression is associated with resolution of systemic inflammation in patients with axial spondylarthritis treated with tumor necrosis factor alpha inhibitors: a study of radiographic progression, inflammation on magnetic resonance imaging, and circulating biomarkers of inflammation, angiogenesis, and cartilage and bone turnover. Arthritis Rheum. 2011; 63(12): 3789–800.

17. El-Galaly TC, Bilgrau AE, Gaarsdal E, Klausen TW, Pedersen LM, Nielsen KR, et al. Circulating tumor necrosis factor-alpha and YKL-40 level is associated with remission status following salvage therapy in relapsed non-Hodgkin lymphoma. Leuk Lymphoma. (2015). 56(8): 2476–2478.

18. Pelloski CE, Ballman KV, Furth AF, Zhang L, Lin E, Sulman EP, et al. Epidermal growth factor receptor variant III status defines clinically distinct subtypes of glioblastoma. J Clin Oncol. 2007; 25(16): 2288–94.

19. Bian B, Li L, Yang J, Liu Y, Xie G, Zheng Y, et al. Prognostic value of YKL-40 in solid tumors: a meta-analysis of 41 cohort studies. Cancer Cell Int. 2019; 19(1): 259.

20. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. (2015). 4(1): 1.

21. Arboix A, Miguel M, Ciscar E, Garcia-Eroles L, Massons J, Balcells M. Cardiovascular risk factors in patients aged 85 or older with ischemic stroke. Clin Neurol Neurosurg. (2006). 108(7): 638–643.

22. Salvat M, Pichieri A, Piccirilli M, Floriana Brunetto GM, D'Elia A, Artizzu S, et al. Extent of tumor removal and molecular markers in cerebral glioblastoma: a combined prognostic factors study in a surgical series of 105 patients. J Neurosurg. 2012; 117(2): 204–11.

23. Pina Batista KM, Vega IF, de Eulate-Beramendi SA, Morales J, Kurbanov A, Asnel D, et al. Prognostic significance of the markers IDH1 and YKL40 related to the subventricular zone. Folia Neuropathol. (2015). 53(1): 52–59.

24. Batista K, Costa B, Pablo I, Vega IF, Morales J, Alvarez AV, et al. Analysis of Olig2 and YKL-40 expression: a clinicopathological/immunohistochemical study for the distinction between subventricular zone II and III glioblastomas. Folia Neuropathol. (2016). 54(1): 31–39.
25. Steponaitis G, Skiriute D, Kazlauskas A, Golubickaite I, Stakaitis R, Tamasauskas A, et al. High CHI3L1 expression is associated with glioma patient survival. Diagn Pathol. (2016). 11(1):42.
26. Castellano I, Mistrangelo M, Crudo V, Chiusa L, Lupo R, Ricardi U, et al. YKL-40 expression in anal carcinoma predicts shorter overall and disease-free survival. Histopathology. (2009). 55(2):238–240.
27. Mistrangelo M, Senetta R, Racca P, Castellano I, Chiusa L, Bello M, et al. A novel biomarker-based analysis reliably predicts nodal metastases in anal carcinoma: preliminary evidence of therapeutic impact. Colorectal Dis. (2013). 15(11):1382–1391.
28. Hogdall EV, Ringsholt M, Hogdall CK, Christensen IJ, Johansen JS, Kjaer SK, et al. YKL-40 tissue expression and plasma levels in patients with ovarian cancer. BMC Cancer. (2009). 9(1):8.
29. Roslind A, Knoop AS, Jensen MB, Johansen JS, Nielsen DL, Price PA, et al. YKL-40 protein expression is not a prognostic marker in patients with primary breast cancer. Breast Cancer Res Treat. 2008;112(2):275–85.
30. Vom Dorp F, Tschirdewahn S, Niedworok C, Reis H, Krause H, Kempkensteffen C, et al. Circulating and Tissue Expression Levels of YKL-40 in Renal Cell Cancer. J Urol. (2016). 195(4 Pt 1):1120–1125.
31. Harving ML, Christensen LH, Ringsholt M, Lausten GS, Petersen MM. YKL-40 expression in soft-tissue sarcomas and atypical lipomatous tumors. An immunohistochemical study of 49 tumors. Acta Orthop. (2014). 85(2):195–200.
32. Tschirdewahn S, Reis H, Niedworok C, Nyirady P, Szendröi A, Schmid KW et al, editors. Prognostic effect of serum and tissue YKL-40 levels in bladder cancer. Urologic Oncology: Seminars and Original Investigations; 2014. Elsevier.
33. Krogh M, Christensen I, Bouwhuis M, Johansen JS, Norgaard P, Schmidt H, et al. Prognostic and predictive value of YKL-40 in stage IIB-III melanoma. Melanoma Res. 2016;26(4):367–76.
34. Thorn AP, Daugaard S, Christensen LH, Christensen IJ. Petersen MM. YKL-40 protein in osteosarcoma tumor tissue. APMIS. (2016). 124(6):453–461.
35. Pelloski CE, Mahajan A, Maor M, Chang EL, Woo S, Gilbert M, et al. YKL-40 expression is associated with poorer response to radiation and shorter overall survival in glioblastoma. Clin Cancer Res. 2005;11(9):3326–34.
36. Lawrenson K, Mhawech-Fauceglia P, Worthington J, Spindler TJ, O’Brien D, Lee JM, et al. Identification of novel candidate biomarkers of epithelial ovarian cancer by profiling the secretomes of three-dimensional genetic models of ovarian carcinogenesis. Int J Cancer. 2015;137(8):1806–17.
37. Kim SH, Das K, Noreen S, Coffman F, Hameed M. Prognostic implications of immunohistochemically detected YKL-40 expression in breast cancer. World J Surg Oncol. 2007;5(1):17.
38. Shao R, Cao QJ, Arenas RB, Bigelow C, Bentley B, Yan W. Breast cancer expression of YKL-40 correlates with tumour grade, poor differentiation, and other cancer markers. Br J Cancer. 2011;105(8):1203–9.
39. Yang GF, Cai PY, Li XM, Deng HX, He WP, Xie D. Expression and clinical significance of YKL-40 protein in epithelial ovarian cancer tissues. Ai Zheng. 2009;28(2):142–5.
40. Chiang YC, Lin HW, Chang CF, Chang MC, Fu CF, Chen TC, et al. Overexpression of CHI3L1 is associated with chemoresistance and poor outcome of epithelial ovarian carcinoma. Oncotarget. (2015). 6(37):39740–39755.

41. Kang EJ, Jung H, Woo OH, Park KH, Woo SU, Yang DS, et al. YKL-40 expression could be a poor prognostic marker in the breast cancer tissue. Tumour Biol. 2014;35(1):277–86.

42. Zhang JP, Yuan HX, Kong WT, Liu Y, Lin ZM, Wangs WP, et al. Increased expression of Chitinase 3-like 1 and microvessel density predicts metastasis and poor prognosis in clear cell renal cell carcinoma. Tumour Biol. 2014;35(12):12131–7.

43. Peng C, Peng J, Jiang L, You Q, Zheng J. Ning X. YKL-40 protein levels and clinical outcome of human endometrial cancer. J Int Med Res. 2010;38(4):1448–57.

44. Bi J, Lau SH, Lv ZL, Xie D, Li W, Lai YR, et al. Overexpression of YKL-40 is an independent prognostic marker in gastric cancer. Hum Pathol. (2009). 40(12):1790–1797.

45. Pan JJ, Ge YS, Xu GL, Jia WD, Liu WF, Li JS, et al. The expression of chitinase 3-like 1: a novel prognostic predictor for hepatocellular carcinoma. J Cancer Res Clin Oncol. 2013;139(6):1043–54.

46. Wang XW, Cai CL, Xu JM, Jin H, Xu ZY. Increased expression of chitinase 3-like 1 is a prognosis marker for non-small cell lung cancer correlated with tumor angiogenesis. Tumour Biol. (2015). 36(2):901–907.

47. Luo D, Chen H, Lu P, Li X, Long M, Peng X, et al. CHI3L1 overexpression is associated with metastasis and is an indicator of poor prognosis in papillary thyroid carcinoma. Cancer Biomark. (2017). 18(3):273–284.

48. Chen HT, Zheng JM, Zhang YZ, Yang M, Wang YL, Man XH, et al. Overexpression of YKL-40 Predicts Poor Prognosis in Patients Undergoing Curative Resection of Pancreatic Cancer. Pancreas. (2017). 46(3):323–334.

49. Cardona AF, Rojas L, Wills B, Ruiz-Patino A, Abril L, Hakim F, et al. A comprehensive analysis of factors related to carmustine/bevacizumab response in recurrent glioblastoma. Clin Transl Oncol. (2019). 21(10):1364–1373.

50. Shao R, Hamel K, Petersen L, Cao QJ, Arenas RB, Bigelow C, et al. YKL-40, a secreted glycoprotein, promotes tumor angiogenesis. Oncogene. 2009;28(50):4456–68.

51. Ngernyuang N, Francescone RA, Jearanaikoon P, Daduang J, Supoken A, Yan W, et al. Chitinase 3 like 1 is associated with tumor angiogenesis in cervical cancer. The International Journal of Biochemistry Cell Biology. 2014;51:45–52.

52. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer. 2002;2(10):795–803.

53. Nishikawa KC. Millis AJ. gp38k (CHI3L1) is a novel adhesion and migration factor for vascular cells. Experimental cell research. (2003). 287(1):79–87.

54. Francescone R, Ngernyuang N, Yan W, Bentley B, Shao R. Tumor-derived mural-like cells coordinate with endothelial cells: role of YKL-40 in mural cell-mediated angiogenesis. Oncogene. (2014). 33(16):2110–2122.
55. Libreros S, Garcia-Areas R, Shibata Y, Carrio R, Torroella-Kouri M, Iragavarapu-Charyulu V. Induction of proinflammatory mediators by CHI3L1 is reduced by chitin treatment: decreased tumor metastasis in a breast cancer model. Int J Cancer. 2012;131(2):377–86.

56. Ku BM, Lee YK, Ryu J, Jeong JY, Choi J, Eun KM, et al. CHI3L1 (YKL-40) is expressed in human gliomas and regulates the invasion, growth and survival of glioma cells. Int J Cancer. 2011;128(6):1316–26.

57. Hao H, Wang L, Chen H, Xie L, Bai T, Liu H, et al. YKL-40 promotes the migration and invasion of prostate cancer cells by regulating epithelial mesenchymal transition. American journal of translational research. 2017;9(8):3749.

58. Kawada M, Seno H, Kanda K, Nakanishi Y, Akitake R, Komekado H, et al. Chitinase 3-like 1 promotes macrophage recruitment and angiogenesis in colorectal cancer. Oncogene. (2012).31(26):3111.

59. Schultz NA, Johansen. JS. YKL-40—a protein in the field of translational medicine: a role as a biomarker in cancer patients?Cancers. (2010).2(3):1453–1491.

60. Allin KH, Bojesen SE, Johansen JS, Nordestgaard BG. Cancer risk by combined levels of YKL-40 and C-reactive protein in the general population. Br J Cancer. 2012;106(1):199–205.

61. Qin G, Li X, Chen Z, Liao G, Su Y, Chen Y, et al. Prognostic Value of YKL-40 in Patients with Glioblastoma: a Systematic Review and Meta-analysis. Mol Neurobiol. (2017).54(5):3264–3270.

62. Wan G, Xiang L, Sun X, Wang X, Li H, Ge W, et al. Elevated YKL-40 expression is associated with a poor prognosis in breast cancer patients. Oncotarget. (2017).8(3):5382–5391.

63. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. (2007).8(1):16.

Figures
Figure 1

Flow diagram of the studies retrieved for the review.
| Study ID | HR (95% CI)       | Weight |
|----------|-------------------|--------|
| Arboix, et al. 2006 | 2.13 (1.05, 4.35) | 2.89   |
| Batista, et al. 2015 | 1.00 (0.99, 1.40) | 6.01   |
| Batista, et al. 2016 | 1.61 (1.28, 2.03) | 5.71   |
| Cardona, et al. 2019 | 3.26 (1.24, 8.57) | 1.97   |
| Castellano, et al. 2009 | 3.72 (1.21, 11.44) | 1.58   |
| Chiang, et al. 2015 | 4.03 (2.37, 6.85) | 3.83   |
| Høgdall, et al. 2009 | 1.20 (0.95, 1.51) | 5.69   |
| Lawrenson, et al. 2015 | 2.30 (1.37, 3.86) | 3.90   |
| Mistrangelo, et al. 2013 | 3.66 (1.08, 12.40) | 1.39   |
| Pelloski, et al. 2005 | 1.79 (1.23, 2.61) | 4.80   |
| Pelloski-, et al. 2005 | 3.08 (1.86, 5.10) | 3.98   |
| Pelloski, et al. 2007 | 1.98 (1.12, 3.51) | 3.59   |
| Peng, et al. 2010 | 2.21 (0.57, 8.57) | 1.18   |
| Roslind, et al. 2008 | 1.31 (0.91, 1.89) | 4.87   |
| Salvati, et al. 2012 | 1.47 (1.17, 1.85) | 5.72   |
| Shao, et al. 2011 | 1.79 (1.02, 3.14) | 3.64   |
| Steponaitis, et al. 2016 | 1.12 (1.01, 1.24) | 6.27   |
| vom Dorp, et al. 2016 | 1.25 (0.74, 2.11) | 3.87   |
| Yang, et al. 2009 | 1.58 (0.85, 2.94) | 3.33   |
| Zhang, et al. 2014 | 4.01 (0.73, 22.03) | 0.80   |
| Bi, et al. 2009 | 1.93 (1.25, 2.97) | 4.42   |
| Chen, et al. 2017 | 3.82 (2.38, 6.13) | 4.17   |
| Harving, et al. 2014 | 2.28 (0.32, 16.24) | 0.62   |
| Kang, et al. 2014 | 2.66 (0.85, 8.32) | 1.55   |
| Krogh, et al. 2016 | 1.97 (1.07, 3.63) | 3.38   |
| Pan, et al. 2013 | 4.23 (1.94, 9.25) | 2.59   |
| Thorn, et al. 2016 | 6.21 (0.95, 40.59) | 0.67   |
| Tschiridewahn, et al. 2014 | 1.23 (0.74, 2.06) | 3.92   |
| Wang, et al. 2015 | 1.68 (0.96, 2.94) | 3.66   |
| **Overall (I-squared = 74.8%, p = 0.000)** | **1.85 (1.58, 2.18)** | **100.00** |

**NOTE:** Weights are from random effects analysis.
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).
| Study ID | HR (95% CI) | Weight |
|----------|-------------|---------|
| GBM      |             |         |
| Arboix, et al. 2006 | 2.13 (1.55, 3.35) | 2.69     |
| Batista, et al. 2015 | 1.00 (0.89, 1.10) | 6.01     |
| Batista, et al. 2016 | 1.61 (1.20, 2.13) | 5.71     |
| Cardone, et al. 2019 | 3.26 (1.24, 8.57) | 1.97     |
| Pelloski, et al. 2005 | 1.79 (1.23, 2.61) | 4.80     |
| Pelloski, et al. 2005 | 3.06 (1.56, 5.90) | 3.98     |
| Pelloski, et al. 2007 | 1.96 (1.12, 3.51) | 3.59     |
| Salves, et al. 2012 | 1.47 (1.17, 1.86) | 5.72     |
| Stoepstor, et al. 2016 | 1.12 (1.01, 1.24) | 6.27     |
| Subtotal (I-squared = 80.7%, p = 0.000) | 1.56 (1.27, 1.97) | 48.09    |
| Anal cancer |             |         |
| Castellano, et al. 2009 | 3.72 (1.21, 11.44) | 1.58     |
| Mistrajteo, et al. 2013 | 3.66 (1.08, 12.40) | 1.39     |
| Subtotal (I-squared = 0.0%, p = 0.985) | 3.69 (1.82, 8.44) | 2.98     |
| EOC      |             |         |
| Chis, et al. 2015 | 4.03 (2.37, 6.85) | 3.83     |
| Heggtell, et al. 2009 | 1.20 (0.55, 2.61) | 5.69     |
| Lannervson, et al. 2015 | 2.30 (1.37, 3.98) | 3.90     |
| Yang, et al. 2009 | 1.56 (0.85, 2.94) | 3.33     |
| Subtotal (I-squared = 84.5%, p = 0.000) | 2.00 (1.13, 3.56) | 16.78    |
| BC       |             |         |
| Roslin, et al. 2008 | 1.31 (0.91, 1.89) | 4.87     |
| Shao, et al. 2011 | 1.75 (1.02, 3.14) | 3.64     |
| Kang, et al. 2014 | 2.66 (0.85, 8.32) | 1.55     |
| Subtotal (I-squared = 0.0%, p = 0.391) | 1.50 (1.11, 2.01) | 10.80    |
| Renal cancer |             |         |
| Vom Dorp, et al. 2016 | 1.25 (0.74, 2.11) | 3.87     |
| Zhang, et al. 2014 | 4.01 (0.73, 22.03) | 0.80     |
| Subtotal (I-squared = 39.1%, p = 0.200) | 1.67 (0.62, 4.48) | 4.67     |
| Other    |             |         |
| Bi, et al. 2009 | 1.93 (1.25, 2.97) | 4.42     |
| Chen, et al. 2017 | 3.82 (2.38, 6.13) | 4.17     |
| Harving, et al. 2014 | 2.26 (0.32, 16.24) | 0.62     |
| Kroh, et al. 2016 | 1.97 (1.07, 3.63) | 3.38     |
| Pan, et al. 2013 | 4.23 (1.94, 9.25) | 2.59     |
| Thom, et al. 2016 | 6.21 (0.95, 40.59) | 0.67     |
| Tschirrewahm, et al. 2014 | 1.23 (0.74, 2.06) | 3.92     |
| Wang, et al. 2015 | 1.68 (0.96, 2.94) | 3.66     |
| Peng, et al. 2010 | 2.21 (0.57, 8.57) | 1.18     |
| Subtotal (I-squared = 47.8%, p = 0.053) | 2.24 (1.62, 3.11) | 24.81    |
| Overall (I-squared = 74.6%, p = 0.000) | 1.85 (1.58, 2.18) | 100.00   |

NOTE: Weights are from random effects analysis.
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.

| Study          | HR (95% CI)       | Weight |
|----------------|-------------------|--------|
| Cardona, et al. 2019 | 7.79 (2.58, 23.50) | 7.26   |
| Castellano, et al. 2009 | 3.51 (1.02, 12.08) | 5.97   |
| Chen, et al. 2017     | 3.73 (2.13, 6.53)  | 19.87  |
| Kang, et al. 2014     | 3.11 (1.14, 8.48)  | 8.53   |
| Kim, et al. 2007      | 4.16 (1.16, 14.92) | 5.64   |
| Luo, et al. 2017      | 11.27 (2.83, 44.84)| 4.90   |
| Mistrangelo, et al. 2013 | 3.18 (1.12, 9.03)  | 7.99   |
| Pan, et al. 2013      | 4.71 (2.03, 10.89) | 11.37  |
| Peng, et al. 2010     | 4.12 (1.77, 9.59)  | 11.25  |
| Roslin, et al. 2008   | 1.08 (0.44, 2.65)  | 10.22  |
| Tschirnewahn, et al. 2014 | 2.62 (0.91, 8.70)  | 7.00   |
| Overall (I-squared = 18.6%, p = 0.267) | 3.63 (2.63, 5.01) | 100.00 |

NOTE: Weights are from random effects analysis

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.

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• FigureS4.tif
• FigureS5.tif
• FigureS1.tif
• FigureS5.tif
• FigureS3.tif
• FigureS2.tif