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Original Article

Prognostic significance of interleukin 17 in cancer: a meta-analysis

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Abstract: The prognostic value of Interleukin 17 (IL-17) in cancer patients is currently under debate and remains inconclusive. We performed a systematic review and meta-analysis to evaluate the role of IL-17 as a prognostic marker in cancer. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were combined to measure the effective value of IL-17 expression on prognosis. Nineteen eligible studies enrolling 2390 patients were identified. We found expression of IL-17 was not significantly correlated with overall survival (OS) in cancer (HR=1.29, 95% CI: 0.94-1.76; P=0.12). Furthermore, compared to the data from our analysis that high expression of IL-17 predicted poor OS in both non-small cell lung carcinoma (NSCLC) (HR=2.30; 95% CI: 1.45-3.64; P<0.001; I^2=0%) and hepatocellular carcinoma (HCC) (HR=2.02; 95% CI: 1.44-2.83; P<0.001; I^2=0%), high expression of IL-17 was associated with favorable OS in esophageal squamous cell carcinoma (ESCC) (HR=0.63; 95% CI: 0.51-0.79; P<0.001; I^2=0%). This meta-analysis showed that IL-17 has the potential to become a novel prognostic marker in HCC, NSCLC and ESCC. It could potentially help to monitor patients' prognosis and assess therapeutic efficacy in clinical treatment.

Keywords: IL-17, prognosis, survival, meta-analysis

Introduction

Cancer is a class of diseases characterized by out-of-control cell growth. A total of 1,660,290 new cancer cases and 580,350 cancer deaths are projected to occur in the United States in 2013 [1]. Although, cancer death rates have decreased by 20% from their maximum in 1991 (215.1 per 100,000 population) to 2009 (173.1 per 100,000 population) [2], newer diagnostic methods with improved sensitivity and specificity are essential for the proper detection and prognosis of this fatal disease [3]. Recently, lots of biomarkers with potential prognostic value have been estimated in different types of cancers, such as osteopontin in hepatocellular carcinoma (HCC) [4], MET in gastric cancer [5] and CD44 in head and neck cancer [6]. There is still a great need for reliable and simple biomarkers to evaluate the prognostic significance of cancer.

IL-17 is a pro-inflammatory cytokine which is mainly produced by activated CD4+ T-helper cells (also known as Th17 cells), macrophages and CD8+ T cells [7]. As an essential pro-inflammatory cytokine, IL-17 induces a mass of cytokines and chemokines secretion, such as mesenchymal cells and myeloid cells, which recruit neutrophils and monocytes into the site of inflammation [8]. Furthermore, IL-17 correlates well with the graft-versus-host disease (GVHD), development of inflammation and autoimmune diseases [9-11].

In the recent time, accumulating evidence has shown that IL-17 has an influence on different kinds of cancer models [12], including prostate cancer [13], colorectal cancer [14], breast cancer [15], NSCLC [16], HCC [17], and ovarian cancer [18]. IL-17 promotes angiogenesis in tumor models [12, 19, 21] and granulopoiesis [20]. Moreover, some studies have shown that high

expression of IL-17 correlates with tumor development and patient prognosis. A combined analysis on recent studies will provide a precise estimate on the prognostic relevance of IL-17 expression in cancer patients which has not yet been performed.

Previous studies have suggested that expression of IL-17 in cancer might serve as a prognostic factor but the direct association of IL-17 expression with survival of patient remains to be under debate. In this study, we performed the first meta-analysis to evaluate the role of IL-17 as a prognostic marker in cancer.

Materials and methods

Literature search

A comprehensive search of PubMed, EMBASE, OVID, Cochrane Library, Web of Science databases and China National Knowledge Infrastructure (CNKI) was done from database inception to July 12 2014 without language restriction. The search strategy was "interleukin-17 OR IL-17 OR IL17" AND "tumor OR neoplasm OR cancer OR carcinoma". Furthermore, review articles and reference lists of retrieved articles were reviewed manually to complete our search. The database search was performed independently by X. Zhang and W. Weng. And disagreements were resolved through consensus by the review team.

Eligibility criteria

The studies included in this meta-analysis if the following conditions were met: (a) proven diagnosis of the IL-17 expression; (b) analyzed the correlation of IL-17 with survival outcome; (c) enrolled more than 30 patients (d) provided sufficient data to estimate the hazard ratio (HR) and 95% confidence intervals (CI) according to IL-17 expression; (e) when study patients overlapped with patients in other included studies, we selected the first study published. The two researchers (J. Wang and X. Zhang) independently read the titles and abstracts, and excluded the uncorrelated studies; then the full-texts were scrutinized by the review team. And we selected the studies for our meta-analysis according to the inclusion criteria.

Data abstraction

Two independent reviewers (X. Zhang and W. Weng) extracted the following information: authors, year of publication, country, tumor type, number of patients analyzed, distribution of age and gender, first-line therapies, tumor stage, method of IL-17 detection, cut-off level to consider IL-17 as highly expressed and HRs and their 95% CIs for OS, progression-free survival (PFS) in patients on palliative treatment or surgery and disease-free survival (DFS) for patients undergoing potentially curative resection. And we pooled the PFS of outcomes for patients on palliative treatment with DFS for patients undergoing surgery. We selected the multivariate analysis if univariate and multivariate analysis were both reported. Because the multivariate analysis has taken into consideration the confounding factor and is more accurate. If there were no HRs reported in the article, we used Engauge Digitizer version 4.1 (free software down-loaded from http://sourceforge.net) to read the Kaplane-Meier survival curves to get the HRs and their 95% CIs. If articles reported insufficient data (missing data, inconsistencies, or any other uncertainties), we asked corresponding authors for additional information.

Quality assessment

To identify high-quality studies, two independent investigators (X. Zhang and J. Wang) underlined with descriptive information and scored each publication based on the Newcastle-Ottawa Quality Assessment Scale [22] for cohort studies with moderate modifications (www.ncbi.nlm.nih.gov/pubmedhealth/PMH0015974). Scores were added up to compare study quality in a quantitative manner. Study with a score of 6 or higher was considered as a high quality study. We also searched for the impact factor of each study and calculated the mean value.

Statistical analysis

Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were combined to measure the effective value of IL-17 expression on prognosis. An HR >1 suggested poor prognosis in patients with high expression of IL-17. And P values <0.05 denoted statistical significance. If the study didn't report the HRs, the Engauge Digitizer version 4.1 was used to read the kaplane-Meier curves to estimate the HRs and the 95% CIs. Three independent investigators (J. Wang, W. Weng and X. Zhang) read the curves in order to reduce reading variability. The heterogeneity among the studies was mea-

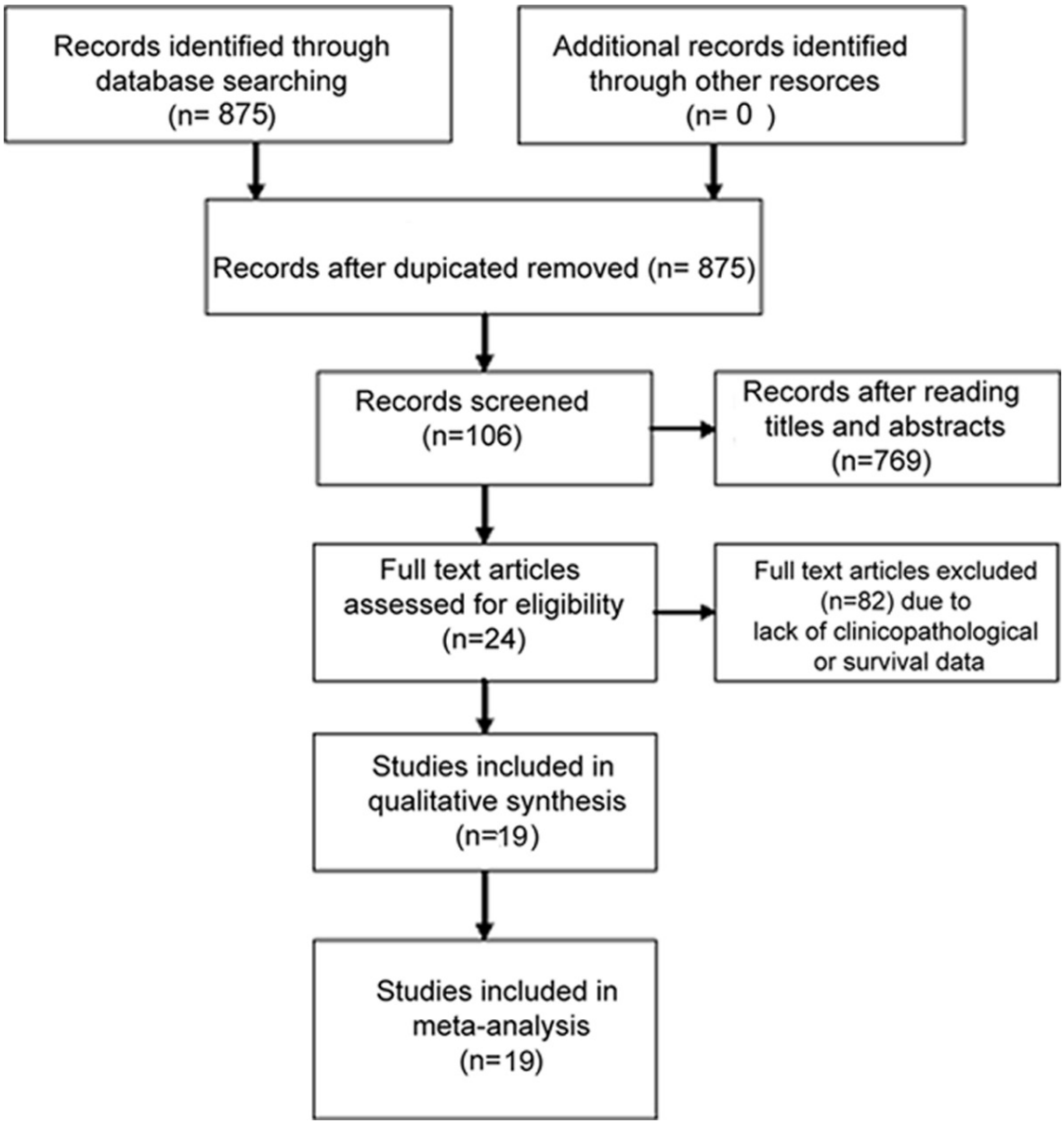

Figure 1. Flow diagram summarizing the selection of eligible studies.

sured using the Q test and I^2 test. The pooled HR for survival was calculated by random-effects models when heterogeneity among the studies was observed. Sensitivity analyses were carried out to test the robustness of the results of meta-analysis. Subgroup analyses were performed to investigate the value of IL-17 expression as a prognostic indicator for cancer patients in studies of tumor type, duration of follow-up, IL-17 expression detection methods and type of method used to obtain the HR. We also conducted tests of interaction to test for differences between subgroups. These analyses were performed by Review Manager Version 5.1 software (http://ims.cochrane.org/revman). The Begg's and Egger's test was performed by R (http://cran.r-project.org/bin/windows/base).

Results

Characteristics of identified studies

Following an initial search, 875 published studies were identified. However, after screening of

Table 1. Impact factors of studies included in the meta-analysis

Study	Year	Impact factor
Chen [33]	2013	2.857
Chen [16]	2010	3.392
Chen [23]	2011	3.168
Cui [34]	2013	3.168
Gu [27]	2012	4.12
He [24]	2011	2.464
Jain [28]	2012	5.935
Lan [35]	2013	3.677
Liao [36]	2013	3.066
Liu [25]	2011	2.406
Liu [29]	2012	3.382
Lv [26]	2011	3.73
Wang [37]	2013	3.637
Wu [30]	2012	3.73
Zhang [31]	2012	1.271
Zhang [17]	2009	9.858
Zhuang [32]	2012	12.821
Xu [51]	2014	1.879
Lu [52]	2013	3.463
Mean value		4.107

the titles and abstracts and further reviewing in detail, nineteen studies were included in our meta-analysis [16, 17, 23-37, 51, 52]. The process of article identification, inclusion, and exclusion was summarized in **Figure 1**.

The baseline characteristics of the included studies were presented in Table S1. These studies concerned different cohorts of patients published between 2009 and 2014. The median sample size was 125 patients (range, 32-300 patients). Fourteen studies used immunohistochemistry (IHC) to detect the IL-17 positive cells [16, 17, 23-27, 31, 33-37, 52]; three studies applied flow cytometry [28, 29, 32]; one study applied ELISA [51] and one study quantified the serum concentration of IL-17 [30]. Three studies assessed hepatocellular carcinoma (HCC) [17, 30, 36], three studies assessed gastric cancer [23, 29, 32], three studies assessed non-small cell lung cancer (NSCLC) [16, 31, 51], three studies assessed esophageal squamous cell carcinoma (ESCC) [26, 37, 52] and one each for pancreatic cancer [24], ovarian cancer [35], intrahepatic cholangiocarcinoma (ICC) [27], glioblastoma [34], colorectal cancer [25], chronic lymphocytic leukemia [28] and breast cancer [33]. Seventeen studies [16, 17, 23-27, 51, 52] were in China and the remaining two were in the United States [28] and Taiwan [33] respectively. Eighteen studies provided UICC stage [16, 17, 23-27, 29-37, 51, 52] and the other one did not mention it. OS was obtained in 18 studies [16, 17, 23-33, 35-37, 51, 52], and PFS/DFS was obtained in 6 studies [16, 17, 32-35].

Qualitative assessment

To evaluate the quality of studies included in our meta-analysis, we assessed representativeness of the exposed cohort, ascertainment of exposure, outcome of interest, comparability of cohorts, assessment of outcome and adequacy of follow up for each study [22]. All of the 16 inclusions were of high quality with scores ranging from 7 to 9 (Table S2). And the mean impact factor was 4.107 (**Table 1**).

Meta-analysis

Overall, eighteen studies including 2390 tumor patients reported data on IL-17 expression and OS in solid tumors. The combined analysis of the 17 studies showed that expression of IL-17 was not significantly correlated with OS in cancer (HR=1.29, 95% CI: 0.94-1.76; P=0.12). Furthermore, there was heterogeneity between studies (I^2=80%, P<0.001) (**Figure 2A**), and a publication bias became obvious when visually inspecting the funnel plot (**Figure 2B**). The *P*-value of begg's test was 0.302 and the *P*-value of egger's test was 0.018 (Table S3). As for PFS, the HR was 1.78 (95% CI 0.83-3.81; P=0.14; I^2=84%) (**Figure 3A**) and a publication bias was not obvious (**Figure 3B**). No publication bias was tested in the Begg's (P=1.000) and Egger's test (P=0.213) (Table S3).

Tumor type

The results of the subgroup analyses were summarized in Table S3. Firstly, a subgroup analysis by tumor type was performed (**Figure 4**). We found high expression of IL-17 was significantly associated with poor OS in HCC (HR=2.02, 95% CI: 1.44-2.83; P <0.001), and slight heterogeneity was observed in the data (I^2=0%; P=0.48). High expression of IL-17 in NSCLC also suggested a similar result (HR=2.30, 95% CI: 1.45-3.64; P<0.001) without heterogeneity (I^2=0.0%; P=0.89). But high expression of IL-17 predicted improved OS in ESCC (HR=0.63, 95% CI: 0.51-0.79; P<0.001) and no heterogeneity was observed (I^2=0.0%; P=0.92). In gastric cancer,

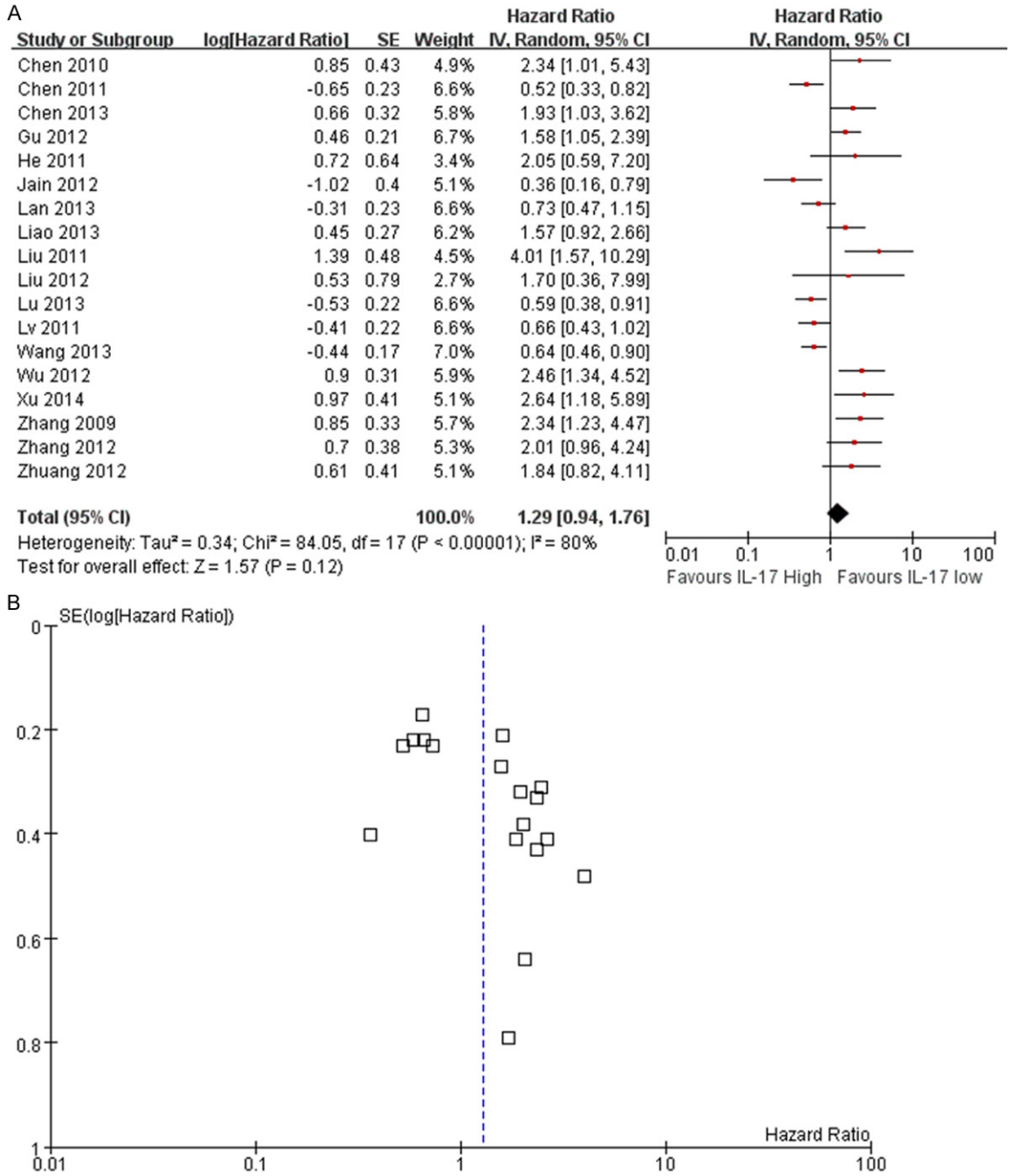

Figure 2. Meta-analysis comparing IL-17 expression and overall survival (OS) in cancer patients. A. The individual and pooled HR with 95% CIs was shown by forest blot. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). B. Funnel blot was used to reflect a potential publication bias.

high expression of IL-17 was not an obvious prognostic factor (HR=1.06, 95% CI: 0.39-2.86; P=0.91). Moreover, there was only one study each evaluating the association between high expression of IL-17 and OS in pancreatic cancer, ovarian cancer, ICC, colorectal cancer, chronic lymphocytic leukemia and breast cancer. The pooled HR was 1.30 (95% CI: 0.72-2.36; P=0.38; I^2=80; P≤0.001). In chronic lymphocytic leukemia and ovarian cancer, higher expression of IL-17 was correlated with better OS and in other four types of cancer, higher expression of IL-17 was associated with worse OS (**Figure 4**).

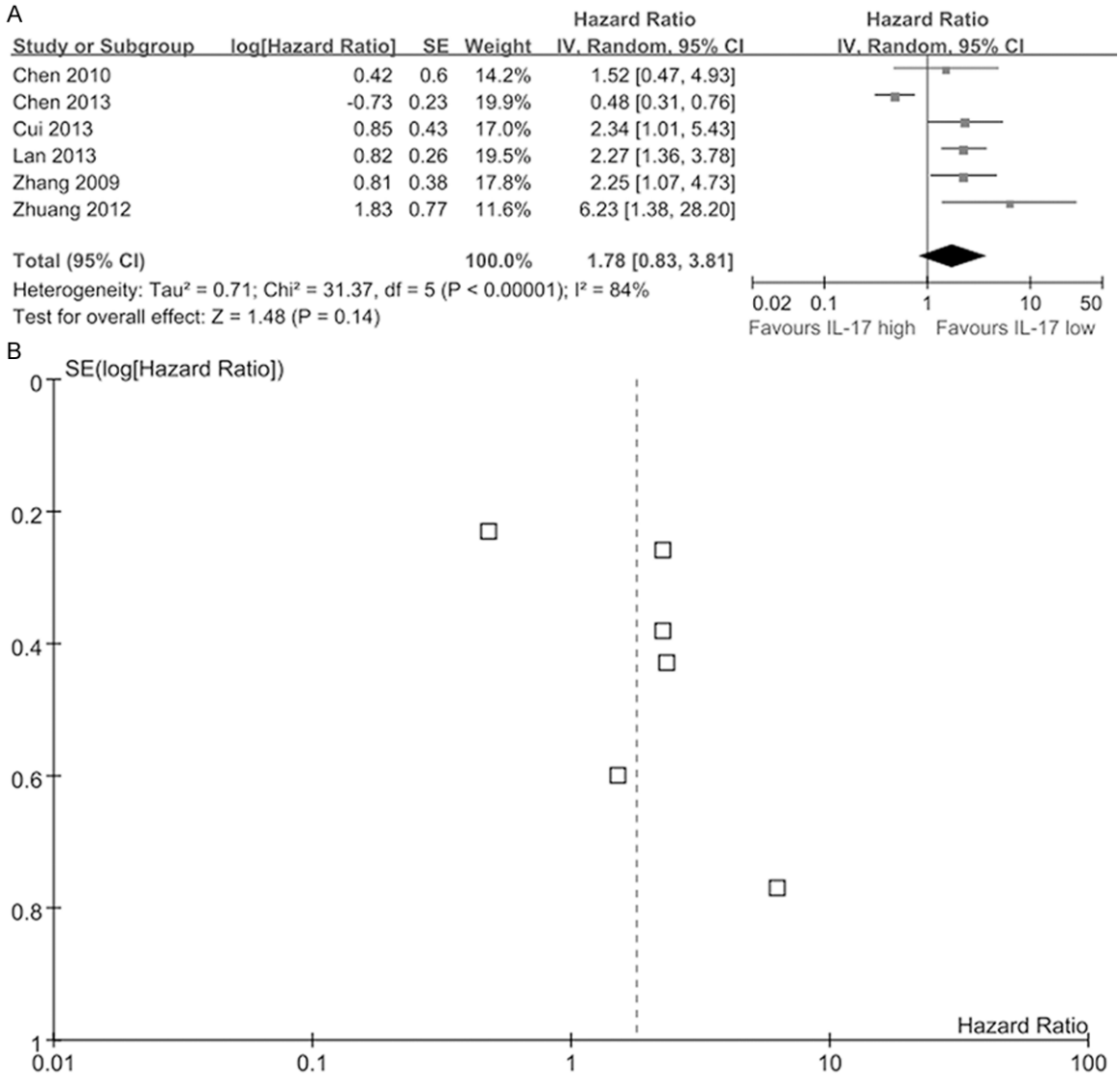

Figure 3. Meta-analysis comparing IL-17 expression and progression-free survival (PFS) in cancer patients. A. The individual and pooled HR with 95% CIs was shown by forest blot. Heterogeneity was calculated by measuring the inconsistency (I^2) and by the Cochrane Q test (Chi-squared test; Chi^2). B. Funnel blot was used to reflect a potential publication bias.

Other subgroup analysis

As shown in Table S3, we performed other subgroup analysis including duration of follow-up, detection method and method to obtain HR. Studies with a median follow-up of more than 60 months showed favorable OS for high expression of IL-17 (HR=0.83, 95% CI: 0.43-1.58; I^2=83, P=0.003) and studies with a median follow-up of less than 60 months was associated with poor OS for high expression of IL-17 (HR=1.82, 95% CI: 1.33-2.51; I^2=0, P=0.71). Studies that applied IHC found higher expression of IL-17 suggested worse OS (HR=1.31, 95% CI: 0.91-1.87; I^2=80, P<0.001) and PFS (HR=1.84, 95% CI: 0.77-4.39; I^2=87, P<0.001). No significant associations between CD4+IL17+ T cells and prognostic effect were determined. There was only one study each using flow cytometry to detect CD8+IL17+ T cells and quantifying the serum concentration of IL-17, therefore the results were related entirely to the individual studies. Furthermore, both reported in text (OS: HR=1.44 95% CI: 0.90-2.31; PFS: HR=1.78 95% CI: 0.61-5.17) and estimated by us (OS: HR=1.28 95% CI: 0.81-2.00; PFS: HR=2.01 95% CI 1.07-3.77) did not show a significant association with OS, because some contradictory results were in presence (Table S3).

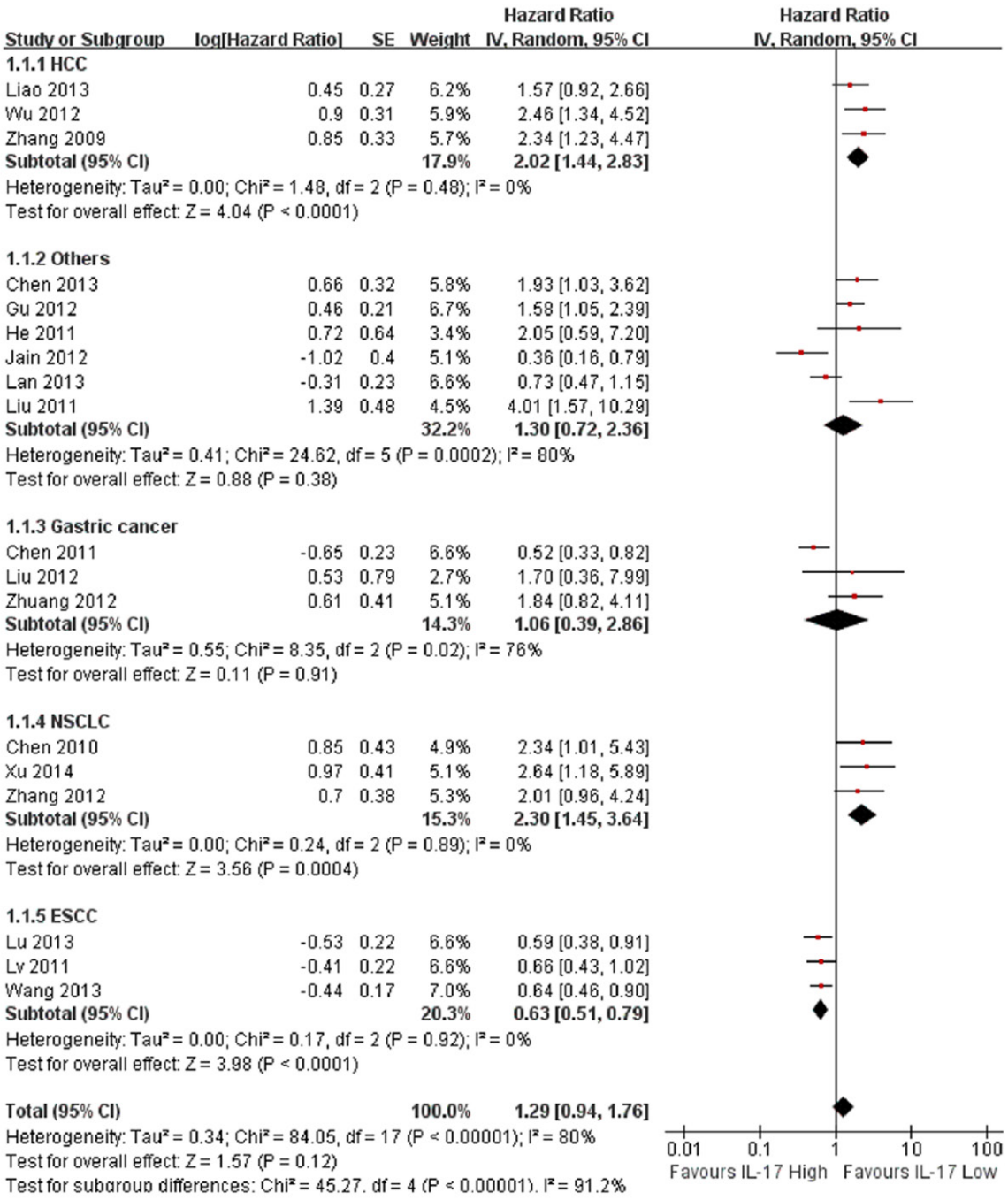

Figure 4. Meta-analysis of the association between high expression of IL-17 and overall survival (OS) in different tumor types.

Sensitivity analyses

We performed sensitivity analyses to explore the heterogeneity among studies. However, with omitting 1 study at a time, there was still obvious heterogeneity among these studies (**Table 2**). So the heterogeneity was not generated by one individual study.

Discussion

Chronic inflammation plays an active role in cancer, IL-17 can promote cancer-elicited inflammation and prevent cancer cells from immune surveillance [38]. It can enhance T cell mediated anti-tumor responses by induction of MDSCs [39] and inhibit cytotoxic lymphocytes

Table 2. The influence of individual study on the pooled estimate (HR)

Study omitted	Year	HR	95% CI	Heterogeneity	
				I^2	*P* value
None		1.29	0.94-1.76	80	<0.001
Chen [33]	2013	1.25	0.91-1.73	80	<0.001
Chen [16]	2010	1.25	0.90-1.71	80	<0.001
Chen [23]	2011	1.37	0.99-1.88	78	<0.001
Gu [27]	2012	1.27	0.91-1.77	80	<0.001
He [24]	2011	1.26	0.92-1.74	80	<0.001
Jain [28]	2012	1.37	1.00-1.88	78	<0.001
Lan [35]	2013	1.34	0.96-1.87	80	<0.001
Liao [36]	2013	1.27	0.91-1.77	80	<0.001
Liu [25]	2011	1.21	0.89-1.65	78	<0.001
Liu [29]	2012	1.28	0.93-1.76	80	<0.001
Lv [26]	2011	1.35	0.97-1.88	80	<0.001
Wang [37]	2013	1.36	0.98-1.88	77	<0.001
Wu [30]	2012	1.23	0.90-1.69	78	<0.001
Zhang [31]	2012	1.25	0.91-1.73	79	<0.001
Zhang [17]	2009	1.24	0.90-1.70	80	<0.001
Zhuang [32]	2012	1.26	0.91-1.74	80	<0.001
Xu [51]	2014	1.23	0.90-1.70	79	<0.001
Lu [52]	2013	1.36	0.98-1.88	79	<0.001

activities [40, 41]. IL-17 can also enhance migration and recruitment of tumor cell [42, 43]. However, IL-17 is associated with some anti-tumor mechanisms. It can reduce tumor growth and metastasis by promoting protective tumor immunity [44, 45]. So we combined and investigated these data and performed a meta-analysis to obtain a further understanding of a potential association between IL-17 and prognosis in cancer patients. Moreover, it is the first meta-analysis regarding IL-17 in cancer prognosis features.

In our meta-analysis, expression of IL-17 was not significantly correlated with OS in cancer (HR=1.28, 95% CI: 0.94-1.76, P=0.12) (**Figure 2A**). So we did not regard IL-17 as a good prognostic marker since 6 of these 18 studies reported the opposite results and significant heterogeneity was observed among the studies (I^2=80%, P<0.001). In our subgroup analysis for tumor type, higher expression of IL-17 predicted worse OS in HCC (HR=2.02, 95% CI: 1.44-2.83; P<0.001) with no heterogeneity in the data (I^2=0%; P=0.48) (**Figure 4**). Thus, IL-17 may serve as a prognostic marker and therapeutic target for HCC. Recently, some studies reported that IL17A promoted HCC metastasis via NF-kB induced matrix metalloproteinases 2 and 9 expression [46] and tumor progression with AKT-dependent IL-6/JAK2/STAT3 activation [47]. Tumor metastasis and progression are usually correlated with poor prognosis [48]. Interleukin-17-activated monocytes were reported to suppress cytotoxic T-cell function through B7-H1 in hepatocellular carcinoma patients and IL-17 plays a contributing role in the induction of immune escape in HCC [53]. Furthermore, higher expression of IL-17 was also significantly related with worse OS in NSCLC (HR=2.3, 95%: CI 1.45-3.64; P<0.001) with no heterogeneity (I^2=0%, P=0.89) (**Figure 4**). Studies also reported that IL-17 is related with the NSCLC invasion and increases lymph-angiogenesis in NSCLC by enhancing production of VEGF-C to promote tumor metastasis [49, 50]. Numasaki et al [54] demonstrated that IL-17 increases the net angiogenic activity and in vivo growth of NSCLC via promoting CXCR-2-dependent angiogenesis. Li et al [55] found that IL-17 could directly promote the invasion of NSCLC cells both in vitro and in vivo and IL-6-Stat3 pathway was crucial for IL-17 to enhance the invasive potential of NSCLC cells. These findings all demonstrate that IL-17 is a pivotal cytokine involved in tumor progression of NSCLC. However, we found in ESCC, high expression of IL-17 suggested improved OS (HR=0.63, 95% CI 0.51-0.79; P<0.001) without heterogeneity (I^2=0%; P=0.91) (**Figure 4**). Lv et al [26] considered that IL-17 producing cells in ESCC might exert anti-tumor effects by enhancing cytotoxic T lymphocytes and NK cell responses. More mechanisms regarding IL-17 in ESCC need to be investigated in the future to confirm the speculation.

However, this study has several limitations. Firstly, the detection methods were different among these studies. Fourteen studies used IHC to detect IL-17 positive cells. Three studies performed flow cytometry. Wu et al [30] quantified serum IL-17 level. Although these studies were all correlated with IL-17 expression, they might cause statistical and clinical heterogeneity and the sensitivity of those methods is varied. Secondly, in the studies, cut-off values were also different, which might therefore account for the inconsistencies observed. Thirdly, most reports included in this meta-analysis come from one country, the representation is low. The HRs we estimated may be the

source of heterogeneity because they are not the original clinical data. To account for heterogeneity, we used a random effects model, performing subgroup analyses to elucidate this heterogeneity. Finally, studies about each cancer type are not enough and in each subgroup, the sample size of patient case is low. We still need more studies in a certain cancer type to analyze the role of IL-17 in prognostic value features.

Despite these limitations, conclusive results are firstly provided in HCC, NSCLC, ESCC and patient survival by this meta-analysis. We still need more studies in different tumor types to assess the prognostic significance of IL-17. If the significance of IL-17 in cancer is better understood, we can generate a more efficient therapeutic strategy targeting IL-17 in cancer.

Conclusions

IL-17 was not significantly associated with overall survival in cancer patients. However, subgroup analysis showed that high expression of IL-17 predicted poor prognosis in both NSCLC and HCC, and high expression of IL-17 predicted favorable OS in ESCC. IL-17 may become a novel disease marker in different cancer and a more efficient therapeutic strategy targeting IL-17 can be generated with the further investigation of IL-17.

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Disclosure of conflict of interest

None.

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Table S1. Baseline characteristics of studies included in the meta-analysis

Study	Year	Country	Tumor Type	Sample/ male	Age (year)	Treatment	Tumor stage	Detection method	Cut-off for high expression	High expression (%)	Survival condition	HR estimation	median follow-up date (months)
Chen [33]	2013	Taiwan	Breast cancer	207/0	Median 51 Range 23-78	Surgery	I-III	IHC	positive cells >90	37 (18)	OS DFS	E	67.2
Chen [16]	2010	China	Lung cancer	52/41	≥60 21 40%	Surgery	I-III	IHC	positive cells >5%	25 (48)	OS DFS	R	NR
Chen [23]	2011	China	Gastric cancer	192/129	Median 58 Range 17-85	Surgery	I-IV	IHC	density of positive cells	100 (52)	OS	R	61
Cui [34]	2013	China	Glioblastoma	41/18	Median 47 range 14-67	Untreated	IV	IHC	positive cells >15%	30 (73)	PFS	R	12.9
Gu [27]	2012	China	ICC	123/62	Median 55 Range 18-78	Surgery	I-III	IHC	positive cells >111	NR	OS	R	13
He [24]	2011	China	Pancreatic cancer	46/31	>60 29 63%	Surgery	I-IV	IHC	density of positive cells	NR	OS	E	48
Jain [28]	2012	USA	lymphocytic leukemia	66	NR	Untreated or Surgery	NR	Flow cytometry	positive cells ≥5.6	33 (50)	OS	E	NR
Lan [35]	2013	China	Ovarian cancer	104/0	Median 53 Range 27-81	Untreated or Surgery	III-IV	IHC	positive cells >35%	68 (65)	OS PFS	E	NR
Liao [36]	2013	China	HCC	300/253	≤53 157 52%	Surgery	I-IV	IHC	density of positive cells	161 (54)	OS	E	NR
Liu [25]	2011	China	Colorectal cancer	52/31	≥60 20 33%	Surgery	III	IHC	positive cells >5%	26 (50)	OS	R	NR
Liu [29]	2012	China	Gastric cancer	32/21	range 22-69	Untreated	I-IV	Flow Cytometry	positive cells ≥ median	16 (50)	OS	E	NR
Lv [26]	2011	China	ESCC	181/141	≥60 76 42%	Surgery	I-IV	IHC	density of positive cells	91 (50)	OS	R	NR
Wang [37]	2013	China	ESCC	215	NR	Surgery	I-IV	IHC	density of positive cells	NR	OS	R	>100
Wu [30]	2012	China	HCC	105/91	Median 53	Surgery	I-IV	Serum level	≥0.9 pg/ml	42 (40)	OS	R	NR
Zhang [31]	2012	China	Lung cancer	102/66	>45, <60: 31% ≥60: 61%	Surgery	I-III	IHC	density of positive cells	71 (70)	OS	E	30.2
Zhang [17]	2009	China	HCC	178/159	Median 49	Surgery	I-IV	IHC	density of positive cells	NR	OS DFS	R	NR
Zhuang [32]	2012	China	Gastric cancer	85/64	≥65: 38%	Surgery	I-IV	Flow cytometry	positive cells ≥2.75%	42 (49)	OS DFS	E	NR
Xu [51]	2014	China	Lung cancer	128/77	≥60: 65	Surgery	I-IV	ELISA	≥16 pg/ml	NR	OS	R	24
Lu [52]	2013	China	ESCC	181	NA	Surgery	NA	IHC	density of positive cells	91 (50)	OS	E	NR

Table S2. Study quality assessment based on the NEWCASTLE-OTTAWA QUALITY ASSESSMENT SCALE

Studies	Years	1	2	3	4	5A	5B	6	7	8	Scores
Chen [16]	2010	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Chen [23]	2011	Y	Y	N	Y	Y	N	Y	Y	Y	7
Chen [33]	2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	9
Cui [34]	2013	Y	Y	Y	N	Y	Y	Y	N	Y	7
Gu [27]	2012	Y	Y	Y	Y	Y	Y	Y	N	Y	7
He [24]	2011	Y	Y	N	Y	Y	Y	Y	N	Y	7
Jain [28]	2012	Y	Y	Y	Y	Y	N	Y	N	Y	7
Lan [35]	2013	Y	Y	Y	Y	Y	Y	Y	Y	N	8
Liao [36]	2013	Y	Y	Y	Y	Y	Y	Y	N	N	7
Liu [29]	2012	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Liu [25]	2011	Y	Y	Y	N	Y	Y	Y	N	Y	7
Lv [26]	2011	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Wang [37]	2013	Y	Y	N	Y	Y	N	Y	Y	Y	7
Wu [30]	2012	Y	Y	Y	Y	Y	N	Y	Y	N	7
Zhang [31]	2012	Y	Y	Y	N	Y	N	Y	Y	Y	7
Zhang [17]	2009	Y	Y	N	Y	Y	Y	Y	Y	N	7
Zhuang [32]	2012	Y	Y	Y	Y	Y	N	Y	N	Y	7
Xu [51]	2014	Y	Y	Y	Y	Y	Y	Y	N	Y	8
Lu [52]	2013	Y	Y	Y	Y	N	N	Y	Y	Y	7

Table S3. A summary of hazard ratios (HRs) for the overall and subgroup analyses of IL-17 expression and survival of cancer patients

						Heterogeneity		Publication Bias	
Subgroup	Patient cases	No. of studies	Pooled HR	95% CI	*P*-value	I^2 (%)	*P*-value	Begg's test	Egger's test
OS									
Overall	2390	18	1.29	0.94-1.76	0.12	80	<0.001	0.302	0.018
NSCLC	282	3	2.3	1.45-3.64	<0.001	0	0.89		
HCC	583	3	2.02	1.44-2.83	<0.001	0	0.48		
Gastric cancer	309	3	1.06	0.39-2.86	0.91	76	0.02		
ESCC	577	3	0.63	0.51-0.79	<0.001	0	0.92		
Others	639	6	1.3	0.72-2.36	0.38	80	<0.001		
Duration of follow-up									
<60 months	312	4	1.82	1.33-2.51	<0.001	0	0.71		
≥60 months	614	3	0.83	0.43-1.58	0.57	83	0.003		
Detection method									
IHC	1974	13	1.31	0.91-1.87	0.14	80	<0.001		
Serum concentration	105	1	2.46	1.34-4.52	0.004				
Flow cytometry	183	3	0.98	0.3-2.25	0.97	78	0.01		
ELISA	128	1	2.64	1.18-5.89	0.02				
Method to obtain HR									
Reported	1267	9	1.44	0.90-2.31	0.13	86	<0.001		
Estimated	1123	9	1.28	0.81-2.00	0.29	66	0.004		
PFS									
Overall	667	6	1.78	0.61-5.17	0.29	90	<0.001	1	0.213
Detection method									
IHC	582	5	1.84	0.77-4.39	0.17	87	<0.001		
Flow cytometry (CD8+)	85	1	1.52	0.47-4.85	0.48	-			
Method to obtain HR									
Reported	478	4	1.78	0.61-5.17	0.29	90	<0.001		
Estimated	189	2	2.01	1.07-3.77	0.03	0	0.48		