

Prognostic value of spleen tyrosine kinase in human solid tumors

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Background: Spleen tyrosine kinase (SYK) was reported to be dysregulated in solid tumors and played an important role in cancer progression. However, the clinical and prognostic values of SYK in solid tumors remain unclear. This meta-analysis investigated the association between SYK expression and clinical outcomes in the patients with solid tumors.

Methods: A comprehensive literature search was conducted by screening the online electronic databases of PubMed, Embase, and the China National Knowledge Infrastructure. The hazard ratio (HR) with its corresponding 95% CI was used to explore the prognostic value of SYK.

Results: We analyzed a total of 1,075 patients from 10 studies, which met the criteria for this meta-analysis. Our pooled results demonstrated that a low expression of SYK did not correlate significantly with shorter overall survival (OS; HR=0.64, 95% CI: 0.34–1.21, $P=0.169$) or poorer disease-free survival (HR=0.51, 95% CI: 0.13–2.02, $P=0.338$). However, in a subgroup analysis based on tumor type and test method, under-expression of SYK was positively associated with worse OS in the groups of breast cancer (BC; HR=0.51, 95% CI: 0.32–0.80, $P=0.003$), hepatocellular carcinoma (HCC; HR=0.44, 95% CI: 0.29–0.69, $P<0.001$), methylation (HR=0.39, 95% CI: 0.30–0.51, $P<0.001$), and quantitative reverse transcription polymerase chain reaction (HR=0.24, 95% CI: 0.09–0.65, $P=0.005$).

Conclusion: This meta-analysis demonstrated that under-expression of SYK may serve as a predictive biomarker for poor prognosis in BC and HCC patients. In other solid tumors, the clinical usefulness should be confirmed by large-scale studies.

Keywords: spleen tyrosine kinase, solid tumor, prognosis, meta-analysis

Introduction

Cancer is one of the leading causes of morbidity and mortality worldwide.¹ With the recent advances in precision medicine, the subclassification of cancer according to genotype, mutations, or biomarkers became the guidance in the selection of cancer treatments and the factor in prognosis.² It is of great importance to investigate the potential biomarkers in cancers for both diagnostic and prognostic purposes.

The spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase that is expressed in most hematopoietic cells and functions as a hematopoietic cell-specific signaling molecule.^{3,4} SYK was first found to be a potential tumor suppressor in breast carcinoma in 2000.⁵ Since then, a growing amount of researches on SYK has been performed in non-hematopoietic tumors.^{6–8} Several clinical observations have indicated that patients with a low SYK expression have a significantly poorer prognosis than those with a high SYK expression.^{9–12} Functional studies have shown that overexpression of SYK is associated with cancer proliferation and metastasis.^{13–15} Epigenetic silencing through hypermethylation of promoter CpG islands has been proposed to be involved in the loss

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of SYK expression in various cancers.^{16–19} Yang et al¹² have reported that the expression level of SYK in tumor samples with unmethylated SYK gene was significantly higher than that in samples with methylated SYK gene. What is more, SYK methylation is correlated with poor overall survival (OS) in colorectal cancer (CRC). These data implicate SYK as a putative tumor suppressor in cancer. Contradictorily, recent studies have shown that SYK is upregulated in multiple types of tumors, including nasopharyngeal carcinoma (NPC),²⁰ small-cell lung cancer,²¹ and squamous cell carcinoma of the head and neck cancer (SCCHN),²² suggesting that SYK may serve as a proto-oncogene. Taken together, we suspect that SYK played complicated roles in multiple cancer types.

Nevertheless, the prognostic value of SYK in cancer has not yet been fully elucidated. No meta-analysis has been conducted to assess the association between SYK and the survival of patients with cancers so far. Therefore, we performed a meta-analysis to assess the prognostic value of SYK in patients with various solid tumors. OS and disease-free survival (DFS) were the primary end points.

Methods

Search strategies

The present study performed a thorough search for available literatures in databases of PubMed, Embase, and the China National Knowledge Infrastructure (CNKI) from inception up to August 2017. Search terms included “spleen tyrosine kinase”, “SYK”, or “P72-Syk”; “cancer”, “tumor”, “carcinoma”, or “neoplasms”; or “prognostic”, “prognosis”, “survival”, “mortality”, “recurrence”, or “outcome”. In addition, the references of eligible studies, relevant systematic reviews, and meta-analyses in this field were manually retrieved. Two of the authors carried out this procedure independently, and any discrepancy was resolved by discussion.

Study selection

The inclusion criteria for the studies were as follows: 1) studies exploring any of the solid tumors; 2) assessing the association of SYK with OS and/or DFS; and 3) reporting sufficient information to estimate the hazard ratio (HR) and 95% CI. The exclusion criteria were as follows: 1) studies on myelomas, lymphomas, or leukemia; 2) reviews, letters, case reports, and conference abstracts; 3) lacking essential information for calculating an HR and 95% CI; 4) overlapping or duplicate data; 5) laboratory studies on cell lines or animals level; and 6) studies with a sample size of <20 participants.

Data extraction

All eligible publications were reviewed by Ni and Li. The following information was collected: the first author’s name, country, year of publication, cancer type, number of patients, tumor stage, SYK test method, and outcome measures (OS and DFS). When HRs and their 95% CIs were given in the articles, these data were extracted directly. If the prognosis was plotted as Kaplan–Meier (K–M) curve, the data were digitized by the software Engauge Digitizer version 4.1 and calculated as described.²⁶

Quality assessment

The Newcastle–Ottawa Scale (NOS) was adopted to evaluate the quality of each eligible article.²⁴ The NOS criterion was scored based on three aspects: 1) subject selection; 2) comparability of subject; and 3) clinical outcome of three categories. A total of nine items were extracted, and each item scored 1. The total scores ranged from 0 to 9. Scores of 1–3, 4–6, and 7–9 were defined as low-, intermediate-, and high-quality studies, respectively.

Statistical analyses

The meta-analysis was conducted using Stata 12.0 software (StataCorp LP, College Station, TX, USA). For the quantitative aggregation of the survival results, HRs and their 95% CIs were used. In studies where HRs and corresponding 95% CIs were not directly reported, we estimated these values on the basis of available data, such as survival curves, using the methods developed by Parmar et al,²³ Williamson et al,²⁵ and Tierney et al.²⁶

Heterogeneity of the HR of each study was quantified using the chi-square-based Q -statistic test. The assumption of homogeneity was considered as invalid for $I^2 > 50\%$ and $P < 0.10$. When there was no statistically significant heterogeneity, we used the fixed-effects model for pooling the results; otherwise, the random-effects model was applied. The logHR and standard error were used for aggregation of the survival results. Publication bias was evaluated using funnel plots and Begg’s and Egger’s tests.^{27,28} All P -values were two sided, being statistically significant when P -value was < 0.05 .

Results

Search results

Our initial search retrieved 1,533 potentially relevant papers from PubMed, Embase and CNKI. A total of 1,070 relevant studies were identified after removing duplicated records.

After the screening of titles and abstracts, 1,037 studies were excluded. In all, 33 relevant studies were selected for further evaluation. A total of 23 studies were excluded after reviewing the full article. Thus, 10 studies, comprising a total of 1,075 patients, were included in the quantitative synthesis.^{10,12,14,20,22,29–33} The flow diagram of the study selection process is shown in Figure 1.

Characteristics of the included studies

The included studies were carried out in China (n=4), Japan (n=2), Korea (n=1), Canada (n=1), Sweden (n=1), and the UK (n=1). The number of patients in each study varied from 32 to 226. Quantitative reverse transcription polymerase chain reaction (qRT-PCR) (n=1), methylation (n=3), and immunohistochemistry (IHC) (n=6) were used to assess the SYK expression. The cutoff values varied across studies. The types of cancers involved in our study include SCCHN, NPC, CRC, hepatocellular carcinoma (HCC), gastric cancer (GC), oral squamous cell carcinoma (OSCC), non-small-cell lung cancer (NSCLC), and breast cancer (BC). There were

nine studies for OS and three for DFS. HRs and 95% CIs in five studies were extracted directly. HR values in five studies were extracted from K–M survival curves. The features of the 10 studies that qualified for the present meta-analysis are summarized in Table 1.

Meta-analysis: SYK expression, OS, and DFS in cancers

Nine studies were included in the meta-analysis of OS. High heterogeneity among studies ($I^2=90.3%$, $P<0.001$) was detected when nine studies were pooled. To make a conservative estimate, a random-effects model rather than a fixed-effects model was used to account for the highly significant inter-study heterogeneity. The results showed that a lower expression level of SYK did not correlate significantly with OS (HR=0.64, 95% CI: 0.34–1.21, $P=0.169$; Figure 2). A meta-analysis of HRs for DFS was performed on three studies. With obvious statistical heterogeneity ($I^2=90.7%$, $P<0.001$), a random-effects model was used to pool HRs. Based on these limited data, no significant difference was

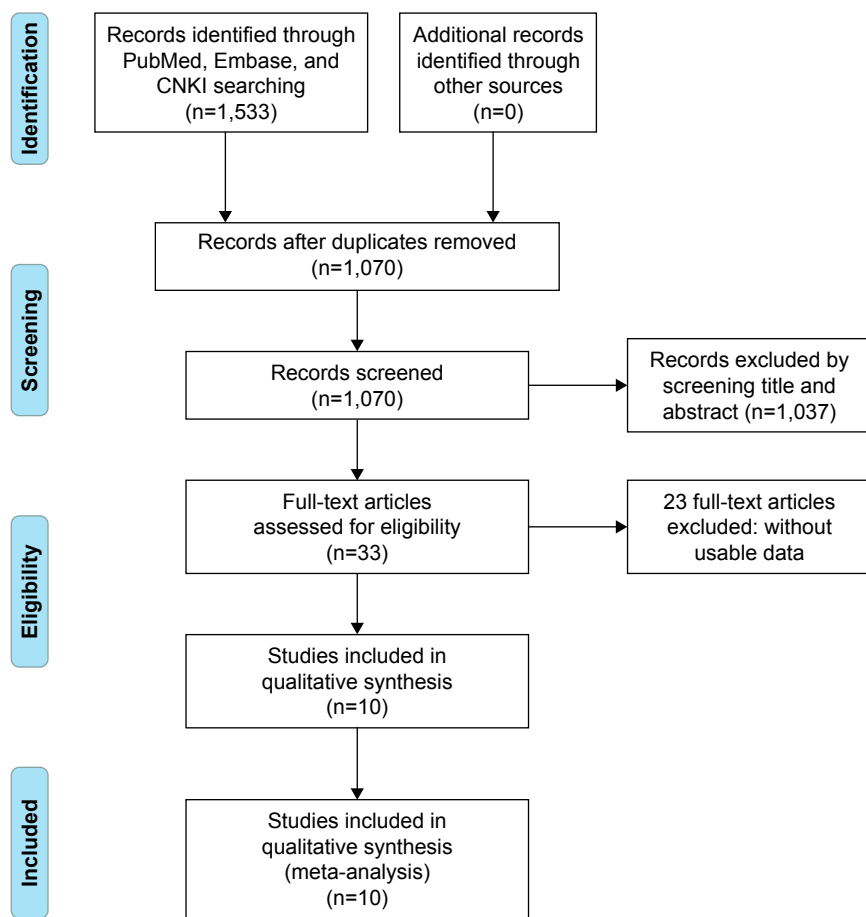


Figure 1 Flow diagram of study selection in present meta-analysis.

Abbreviation: CNKI, China National Knowledge Infrastructure.

Table 1 Characteristics of the studies included in the present meta-analysis

Author	Region	Year	Cancer	Cases	Tumor stage	Test methods	Outcome indexes	HR (95% CI)	NOS score
Toyama et al ²⁹	Japan	2003	BC	90	Mixed	qRT-PCR	OS, DFS	OS: 0.24 (0.09–0.65) DFS: 0.24 (0.09–0.62)	9
Dejmek et al ³⁰	Sweden	2005	BC	75	Mixed	IHC	OS	0.62 (0.37–1.03)	6
Nakashima et al ¹⁰	Japan	2006	GC	110	Mixed	IHC	OS	0.72 (0.26–1.96)	8
Yuan et al ¹⁴	China	2006	HCC	124	Mixed	MSP	OS	0.25 (0.12–0.55)	9
Luangdilok et al ²²	UK	2007	SCCHN	38	Mixed	IHC	OS	3.10 (1.84–5.21)	8
Du et al ²⁰	China	2012	NPC	226	Mixed	IHC	OS, DFS	OS: 1.91 (1.27–2.88) DFS: 1.55 (1.13–2.13)	8
Yang et al ¹²	China	2013	CRC	210	Mixed	MSP	OS	0.36 (0.26–0.51)	7
Shin et al ³¹	Korea	2014	HCC	95	Mixed	MethyLight	OS	0.58 (0.34–0.98)	8
Fu et al ³²	Canada	2016	OSCC	32	Mixed	IHC	DFS	0.30 (0.12–0.76)	7
Gao ³³	China	2016	NSCLC	75	Mixed	IHC	OS	0.34 (0.07–1.56)	5

Abbreviations: HR, hazard ratio; NOS, Newcastle–Ottawa Quality Assessment Scale; BC, breast cancer; qRT-PCR, quantitative reverse transcription polymerase chain reaction; OS, overall survival; DFS, disease-free survival; IHC, immunohistochemistry; GC, gastric cancer; HCC, hepatocellular carcinoma; MSP, methylation-specific polymerase chain reaction; SCCHN, squamous cell carcinoma of the head and neck; NPC, nasopharyngeal carcinoma; CRC, colorectal cancer; OSCC, oral squamous cell carcinoma; NSCLC, non-small-cell lung cancer.

observed in survival between SYK expression and DFS (HR=0.51, 95% CI: 0.13–2.02, *P*=0.338; Figure 3).

Given that the substantial heterogeneity exhibited in the trials aggregated with respect to the OS, subgroup analyses were carried out to explore the heterogeneity of covariates including country, tumor type, test method, and extracting method. As indicated in Table 2, according to subgroups of different countries, both China group and non-China group showed no significant HR (China HR=0.52, 95% CI: 0.17–1.56,

P=0.243; non-China HR=0.75, 95% CI: 0.32–1.74, *P*=0.503, random-effects model). For the tumor type, the subgroups (HCC and BC) were explored, from which the lower SYK expression was identified as a worse prognostic marker (HCC HR=0.44, 95% CI: 0.29–0.69, *I*²=67.3%, *P*<0.001; BC HR=0.51, 95% CI: 0.32–0.80, *I*²=64.2%, *P*=0.003, fixed-effects model). Other cancers group showed no significant HR (HR=0.94, 95% CI: 0.34–2.6, *I*²=93.8%, *P*=0.903, random-effects model). In the subgroup analysis based on

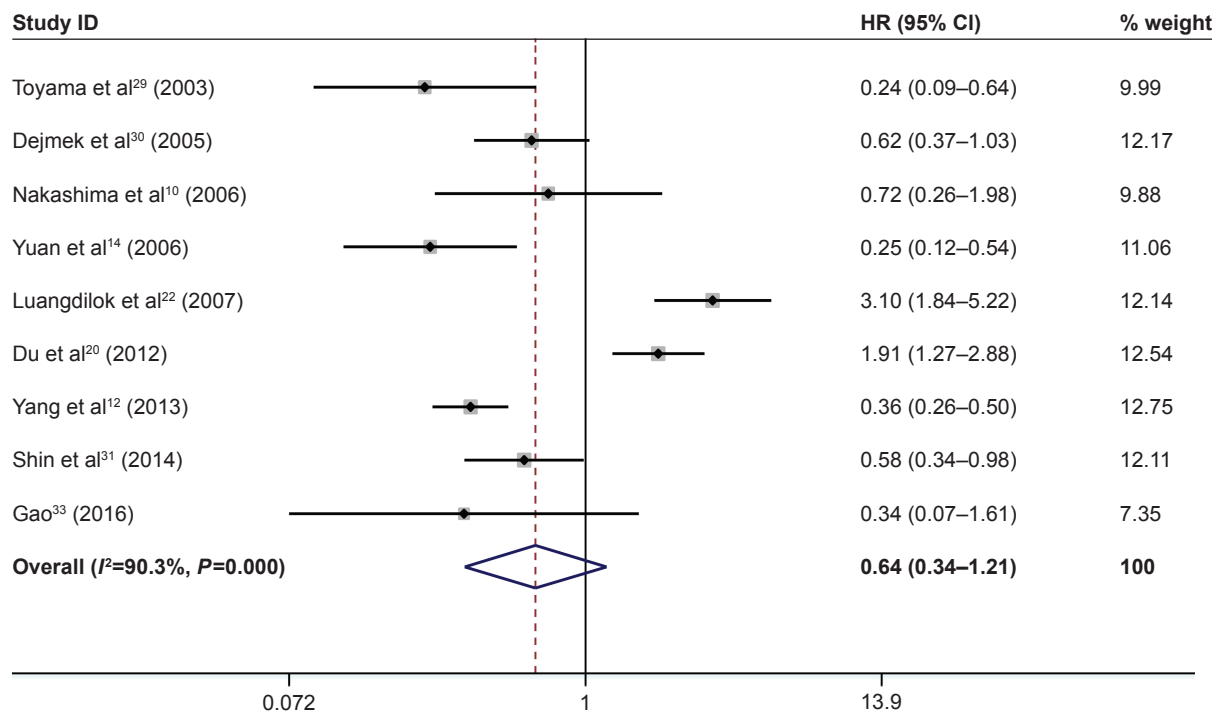


Figure 2 Forest plot of the relationship between SYK expression and OS in patients with solid tumors.

Note: Weights are from random-effects analysis.

Abbreviations: SYK, spleen tyrosine kinase; OS, overall survival; HR, hazard ratio.

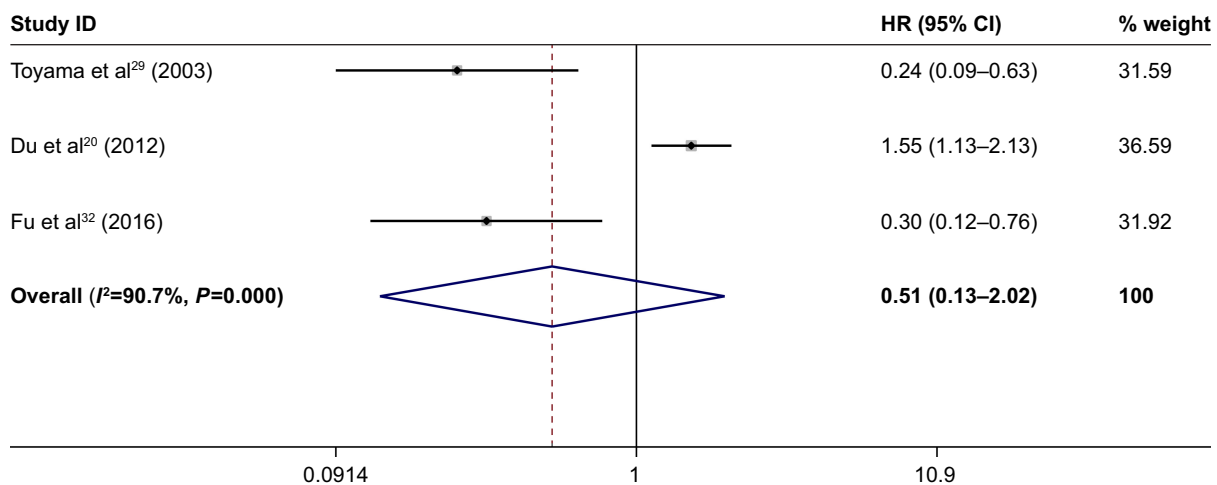


Figure 3 Forest plot of the relationship between SYK expression and DFS in solid tumors.

Note: Weights are from random-effects analysis.

Abbreviations: SYK, spleen tyrosine kinase; DFS, disease-free survival; HR, hazard ratio.

test methods, the IHC group (HR=1.18, 95% CI: 0.54–2.35, $I^2=84.5%$, $P=0.75$, random-effects model) showed no significant HR, while the methylation group (HR=0.39, 95% CI: 0.30–0.51, $I^2=44.7%$, $P<0.001$, random-effects model) and the qRT-PCR group (HR=0.24, 95% CI: 0.09–0.65, $P=0.005$) showed significant HR. Similar to country-based subgroups analysis, both groups showed no significant HR in the subgroup analysis of extracting method.

Publication bias

The Begg's funnel plot and Egger's test were performed to evaluate the publication bias. As shown in Figure 4A,

Table 2 Subgroup analyses for associations between SYK expression and OS

Subgroup	No of studies	Heterogeneity		P-value	HR (95% CI)
		I^2 (%)	P-value		
Country					
China	4	93.3	0.000	0.243	0.52 (0.17–1.56)
Non-China	5	88.0	0.000	0.503	0.75 (0.32–1.74)
Tumor type					
HCC	2	67.3	0.080	0.000	0.44 (0.29–0.69)
BC	2	64.2	0.095	0.003	0.51 (0.32–0.8)
Other	5	93.8	0.000	0.903	0.94 (0.34–2.6)
Test method					
IHC	5	84.5	0.000	0.750	1.18 (0.54–2.35)
Methylation	3	44.7	0.164	0.000	0.39 (0.30–0.51)
qRT-PCR	1	NA	NA	0.005	0.24 (0.09–0.65)
Extracting method					
K–M curve	4	90.4	0.000	0.540	0.68 (0.20–2.29)
Report	5	91.0	0.000	0.200	0.60 (0.27–1.32)

Abbreviations: SYK, spleen tyrosine kinase; OS, overall survival; HR, hazard ratio; HCC, hepatocellular carcinoma; BC, breast cancer; IHC, immunohistochemistry; qRT-PCR, quantitative reverse transcription polymerase chain reaction; NA, not available; K–M, Kaplan–Meier.

the shape of the funnel plot was relatively symmetrical and no publication bias was found in the OS meta-analysis (Begg's test, $P=0.917$; Egger's test, $P=0.698$). In the DFS meta-analysis, the Egger's test was significant ($P=0.024$) for publication bias but the Begg's test was not ($P=0.296$; Figure 4B). Considering the abnormal distribution of the included patient numbers and the discrepancies of these three tests, the Egger test was not trusted. Therefore, there is no significant publication bias in the abovementioned analysis.

Discussion

To the best of our knowledge, no meta-analysis has been conducted to assess the possible prognostic role of SYK downregulation in solid malignancies before. To provide comprehensive and reliable conclusions, we conducted the present meta-analysis to assess the prognostic value of SYK in tumors.

The potential role of SYK in cancer prognosis has been extensively explored in various cancers.^{29–36} However, inconsistent results were found in different studies.^{10,12,20,22} More and more evidence has demonstrated that SYK acts as a tumor suppressor and is frequently downregulated in multiple types of cancer. In BC patient samples, Moroni et al³⁷ found that the loss of SYK expression was progressive during tumor development and the low SYK levels were correlated with an increased risk of metastasis. In GC, loss of SYK expression was closely related to the malignant property of GC in the context of tumor depth and lymph node metastasis, especially in early GC.¹⁰ Similarly, Ogane et al⁸ found that SYK was downregulated in OSCC and correlated significantly with tumor metastasis to cervical lymph nodes. Bailet et al³⁸ also demonstrated that SYK exerted its

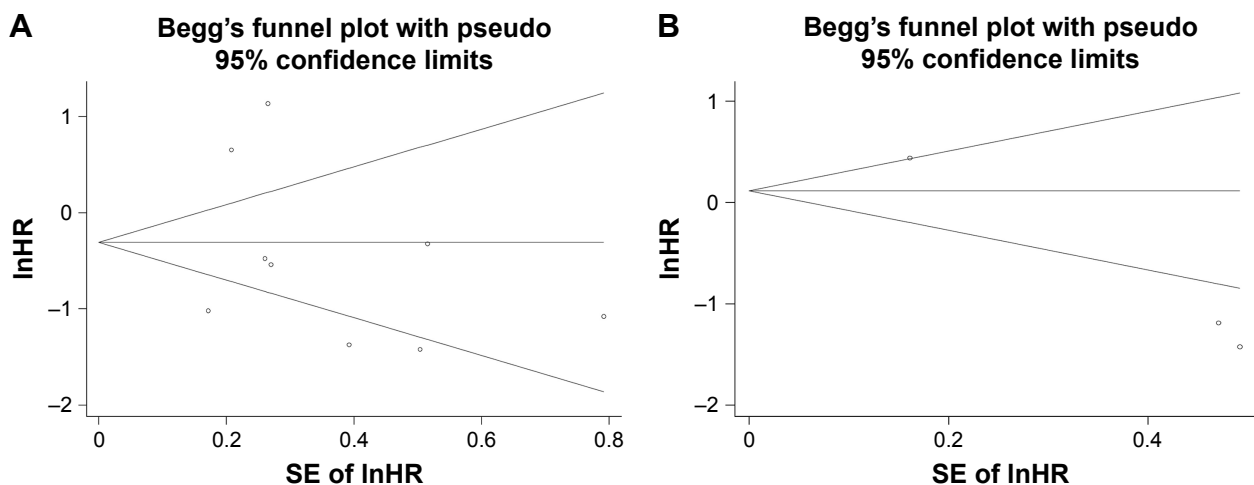


Figure 4 Funnel plot to evaluate potential publication bias of the included studies.

Notes: (A) Funnel plot for nine studies reporting OS. (B) Funnel plot for three studies reporting DFS.

Abbreviations: OS, overall survival; DFS, disease-free survival; SE, standard error; HR, hazard ratio.

antitumor activity through induction of a senescence-like growth arrest and activation of a p53-dependent pathway, suggesting that loss of SYK may contribute to the senescence bypass generally observed in malignant melanoma. Moreover, Yu et al³⁹ observed that inhibition of SYK potentiated paclitaxel-induced cytotoxicity in ovarian cancer cells by stabilizing microtubules. In CRC, SYK(L) and SYK(S) could increase the cellular sensitivity to 5-fluorouracil.⁴⁰ On the other hand, in NPC, a high expression of SYK is associated with tumor recurrence and poor prognosis of patients.²⁰ Udyavar et al²¹ reported that SYK was highly overexpressed in small-cell lung cancer tissues compared to normal tissues and SYK knockdown caused a significant decrease in proliferation rates compared to scrambled control in both H69 and H146. Further experiments need to be conducted to elucidate the role of SYK in carcinogenesis. However, among all the studies referring to the relationship between SYK and OS/DFS, there are still some contradictory results requiring adequate attention; a comprehensive study is therefore in urgent need.

Pooled analysis of 10 studies with 1,075 patients demonstrated no significant difference in survival between OS/DFS and SYK expression, which may partly be because of the small eligible number of studies and high heterogeneity. Subgroup analysis in OS was performed to explore the source of heterogeneity based on country, tumor type, test method, and extracting method. Based on the analysis and summary of existing literature, we found that under-expression of SYK is related to poorer OS in the qRT-PCR group and the methylation group, whereas there was no significant association between under-expression of SYK and OS in

the IHC group. By analyzing the subgroup stratified by cancer type, we found that the magnitude effect of SYK on OS appeared to perform its best predicted effect on cancer patient's prognosis in BC and HCC. We suspected that the differences in SYK behavior in different cancer types may be due in part to unique pathogenic mechanisms in each cancer type and differences in the contribution of SYK to tumor biology.

Some limitations should be noted for this meta-analysis. First of all, despite the usage of random-effects model and subgroup analysis, the heterogeneity across studies failed to be eliminated completely, which could result in bias of the outcome to a certain extent. Second, some HRs and their corresponding 95% CIs were estimated from K–M survival curves, which may bring a slight error in HR and 95% CI; hence, the prognostic value of SYK expression may be overestimated. Third, although we performed a comprehensive analysis and got significant conclusions, the general problems with meta-analysis, ie, limited number of studies, the heterogeneity among the studies, and so on, should be considered and verified in the future applications. Fourth, this study included different types of solid tumors to gain a general insight into the association between SYK expression and the clinical outcomes. However, different cancer types are likely to have different pathogenic mechanisms; therefore, SYK may play complicated roles in various cancers. Despite the limitations mentioned earlier, there are still numerous valuable implications in the current study. High-quality, large-sample, and multi-center prospective studies are preferable to confirm the findings of this study before the application of SYK for the prognosis of cancers.

Conclusion

This systematic review and comprehensive meta-analysis demonstrates that a low expression of SYK plays an important role in human solid tumors.

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Disclosure

The authors report no conflicts of interest in this work.

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