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ORIGINAL RESEARCH

Elevated nuclear YBX1 expression and the clinicopathological characteristics of patients with solid tumors: a meta-analysis

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Purpose: Y-box binding protein 1 (YBX1) is a multifunctional protein linked to tumor progression and its elevated expression is an indicator of poor prognosis in various cancers. This meta-analysis aimed to investigate the prognostic value and clinical significance of YBX1 in malignant cancer.

Methods: Relevant articles published through September 12, 2018 were identified from a comprehensive electronic and manual search in PubMed, Web of Science and Embase databases. The combined odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (95% CIs) were used to estimate the relationship among clinicopathological characteristics, overall survival and disease-free-survival of patients with solid tumor and YBX1 expression.

Results: The study included 27 studies and 5,996 patients. Our analysis revealed significant association between increased YBX1 expression and tumor differentiation status, tumor size and lymph node metastasis; moreover, the pooled HR values demonstrated that high nuclear YBX1 expression was significantly associated with worse overall survival (HR=2.14; 95% CI: 1.72–2.67, $P<0.001$).

Conclusion: The evidence supports YBX1 as a tumor biomarker to guide clinical management and indicate prognosis.

Keywords: solid tumors, YBX1, prognosis, meta-analysis

Introduction

Y-box binding protein 1 (YBX1) is a multifunctional protein of the cold-shock superfamily which plays different roles in both nucleus and cytoplasm. As a transcription regulator within the nucleus, YBX1 regulates the expression of several genes by binding to the Y-box sequence located in the promoter which contributes to transcription regulation. In the cytoplasm, it binds to mRNA to regulate the translation process.[1] Hence, YBX1 plays prominent prooncogenic roles in DNA repair,[2] RNA splicing,[3,4] cell proliferation,[5,6] drug resistance,[6,7] tumor invasion[1,6,8] and metastasis,[8] and is an indicator of poor prognosis[1] in various cancers, including nasopharyngeal carcinoma,[1]bladder cancer,[7] breast cancer,[8] urothelial cancer,[6] and melanoma.[5] Recently, increasing researches has shown that nuclear expression of YBX1 correlates with poor prognosis in synovial sarcoma and colorectal cancer.[4,9,10] Simultaneously, it has been suggested that the value of cytoplasmic YBX1 can act as a prognostic marker for breast cancer.[11] This

meta-analysis aimed to investigate the prognostic value and clinical significance of YBX1 in malignant solid cancer.

Materials and methods

Literature search strategy and study selection

The literature related to YBX1 prior to September 12, 2018, was retrieved from PubMed, Web of Science and Embase databases. Web searches were performed using the terms: (YBX1 OR YB-1 OR Y-box binding protein 1) AND (cancer OR tumor OR carcinoma OR neoplasm) AND (survival OR prognosis OR prognostic OR outcome). The language was limited to English. The Cochrane Library was also reviewed for related papers.

Criteria for inclusion

The following inclusion criteria were used: (1) randomized controlled trial; (2) patients with pathological diagnosis of malignant solid tumor; (3) connections of YBX1 expression with overall survival (OS) and/or disease-free survival (DFS) were described; (4) the full text of YBX1 expression of original research was published in the aforementioned three databases; (5) the expression of YBX1 was assessed by immunohistochemistry (IHC); (6) hazard ratios (HRs) and confidence intervals (CIs) were available; (7) studies were related to the full protein of YBX1; and (8) the studies of reviews or insufficient data were not included.

Data extraction and quality assessment

Two investigators (Tingting Yin, Bo Xiao and Jing Chen) executed the data extraction and the quality assessment. The following data of the eligible studies included the name of first author; publication year; study region; pathological type of tumors; and number of patients,detection methods, cut-off values, and prognostic outcomes (overall survival [OS], disease-free survival [DFS]). We will use the Engauge Digitizer V4.1 (downloaded from the website at: https://engauge-digitizer.updatestar.com/en) to extract the data of survival when the studies did not have HRs but presented Kaplan-Meier curves.

The authors (Xueyuan Miao) assessed the qualities of the records by using the Newcastle-Ottawa Scale (NOS) independently.[12] Moreover, we assessed the score of each selected study based on the patient selection, comparability of the studied group and outcome according to the NOS. The final score of each selected research was scored when there were no conflicts.

Statistical analysis

Stata12.0 (Stata Corporation, College Station, TX, USA) software was used for meta-analysis and publication bias testing. The dichotomous data of hazard ratios (HRs) with 95% confidence intervals (CIs) were used to assess the relevance between YBX1 expression and OS and DFS, whereas pooled estimates of ORs with 95% CIs were used to assess the relevance between YBX1 expression and clinical characteristics. The I^2 statistical test was used for revealing heterogeneity among these studies, and the fixed-effects model and random-effects model were used for meta-analyses with low heterogeneity (I^2<30%) and high heterogeneity (I^2>30%) conditions. HRs>1 suggestedpoor prognosis of cancer patients with decreased YBX1 expression. Finally, we conducted a simple assessment by sensitivity analysis and evaluation of publication bias ($P\leq0.05$ was considered statistically significant), and the credibility of our research was confirmed.

Results

The characteristics of the included studies

The detailed selection process is described in Figure 1. A total of 27 studies[9,11,13-37] published from 2001 to 2016, with 5,996 patients were selected to evaluate the relationship of YBX1 expression and tumor prognosis. All studies shown in Table 1 were published prior to September 12, 2018. The participants in the studies covered a wide variety of countries and cancer types including: gastric cancer, colorectal cancer, lung cancer, breast cancer, hepatocellular carcinoma, prostate cancer, sarcoma, renal cell carcinomas, lymphoma, uterine cervical cancer, pleural mesothelioma, non-Hodgkin's lymphomas, nasopharyngeal cancer, synovial sarcoma and bladder cancer. The NOS scores of the included 27 studies ranged from 5 to 8 and; therefore, they wewe high-quality.

Correlation of YBX1 expression with overall survival (OS)

OS was investigated in 25 studies including 5,768 patients. Two articles explored both nuclear YBX1 and cytoplasmic YBX1, so we regarded them as separate data. The pooled HR values revealed that high YBX1 expression was significantly associated with worse OS (HR=1.90; 95% CI:

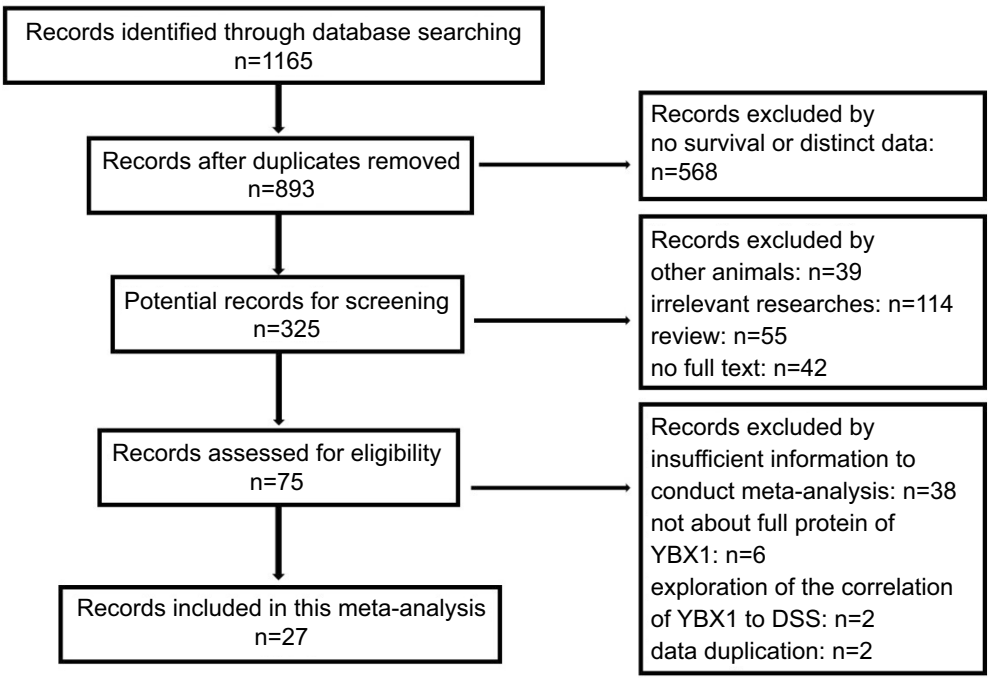

Figure 1 Flow diagram of the selection of eligible studies.

1.69–2.14, P=0.005, Figure 2). In addition, because of heterogeneity (I^2=46.0%), a random-effects model was used to pool HRs and 95% CIs. A subgroup analysis was conducted to detect the origin of heterogeneity depending on the type of YBX1(Figure 3). Increased nuclear expression of YBX1 (HR=2.14; 95% CI: 1.72–2.67, P<0.001) was significantly associated with worse OS in solid tumors but not with cytoplasmic expression of YBX1 (HR=1.79; 95% CI: 0.88–3.65, P=0.063) or elevated not reported YBX1 expression (HR=1.83; 95% CI: 1.61–2.09, P=0.734). These results indicate that increased nuclear expression of YBX1 is a prognostic factor for various solid tumors.

Correlations of YBX1 expression with disease-free survival (DFS)

DFS was investigated in 15 studies including 4,788 patients. One of the studies was treated as the two data in both nucleus and cytoplasm. The pooled HR values revealed that there was a clear correlation between a high expression of YBX1 and a worse DFS (HR=1.84; 95% CI: 1.60–2.12, P<0.001, Figure 4) with obvious heterogeneity ((I^2=70.0%), so we adopted a random-effect model for the analysis. The effects of YBX1 expression on DFS in different types of YBX1 protein are shown in Figure 5. Increased nuclear YBX1 expression (HR=3.44; 95% CI: 2.42–4.89, P<0.001) was significantly associated with worse DFS, whereas elevated cytoplasmic expression of YBX1 (HR=1.49; 95% CI: 0.97–2.27, P=0.520) and high expression of YBX1 not reported (HR=1.64; 95% CI: 1.40–1.93, P=0.120) with poor DFS were not significantly associated.

Correlations of YBX1 expression with clinicopathological parameters

Seventeen eligible articles were used to collect the clinical and pathological parameters. The clinical features of the selected studies are listed in Table S1. Meanwhile, the association of YBX1 expression with clinicopathological parameters is illustrated in Table 2. Elevated expression of YBX1 was related to tumor differentiation status (OR=2.85, 95% CI: 2.10–3.88), tumor size (OR=2.16, 95% CI: 1.61–2.73) and lymph node metastasis (OR=1.74, 95% CI: 1.38–2.19) which were independent of gender (OR=1.06, 95% CI: 0.85–1.33), distant metastasis (OR=1.27, 95% CI: 0.88–1.84) and clinical stages (OR=1.41, 95% CI: 0.94–2.11).

Assessment of heterogeneity and sensitivity analysis

Publications about OS, DFS and clinical pathological parameter analyses adopted the random-effect models because there was significant heterogeneity (I^2>30%). Moreover,

Table 1 Main characteristics of studies exploring the relationship between YBX1 expression and tumor prognosis

Author	Cancer type	Year	Region	Brand of antibody	Stage/ grade	No. of patients	Follow-up time (months)	Cut-off value	Outcomes	Subtype of YBX1	NOS score
Liu Q et al[25]	Hepatocellular carcinoma	2016	China	Santa Cruz Biotechnology	I–IV	109	NR	Scores >4	OS	NR	7
Shiraiwa S et al[29]	Colorectal cancer	2016	Japan	NR	III	124	NR	NR	OS, DFS	Nuclear	7
Yan XB et al[35]	Colorectal cancer	2014	China	Epitomics	A–D	170	NR	Scores ≥3	OS	NR	7
Jürchott K et al[23]	Colorectal cancer	2010	Germany	NR	NR	118	NR	Scores ≥2	OS	Nuclear, Cytoplasmic	7
Wu Y et al[34]	Gastric cancer	2012	Japan	NR	IB, II–IV	98	66 (2–200)	>25%	OS, DFS	NR	6
Tay WL et al[32]	Nasopharyngeal cancer	2009	Singapore	NR	I–IV	135	750 d	IPS≥200	OS	NR	8
Wang Y et al[33]	Renal cell carcinoma	2015	China	Abcam	I–IV	80	13	Scores >3	OS	Nuclear	7
Zhao S et al[36]	Lung adenocarcinoma	2016	China	Abcam	IA, IB, IIA	75	32	Scores >3.5	OS, DFS	NR	6
Hyogotani A et al[20]	Lung cancer	2012	Japan	Nichirei	I–IV	105	NR	>10%	OS	Nuclear	7
Shibahara K et al[28]	Non-small cell lung cancer	2001	Japan	NR	NR	196	75.6 (25–110)	NR	OS	Nuclear	8
Kashihara M et al[24]	Non-small cell lung cancer	2009	Japan	NR	NR	104	1511.5 (159–3801 d)	Scores ≥2	OS	Nuclear	7
Gessner C et al[17]	Non-small cell lung cancer	2004	Germany	NR	I–IV	77	5	>10%	OS	Nuclear	7
Abd El-Maqsoud NM et al[14]	Prostate cancer	2016	Egypt	Abcam	I–IV	106	21 (4–60)	Scores >4	OS	Nuclear, cytoplasm	7
Imada K et al[21]	Prostate cancer	2013	Japan	Epitomics	NR	165	5.01 y	N≥10%, C≥7	DFS	Nuclear, cytoplasm	8
Lee A et al[11]	Breast cancer	2016	Korea	Novus Biologicals	I–V	233	59.0±25.1	Scores >4	OS, DFS	Cytoplasm	7
Maciejczyk A et al[37]	Breast cancer	2012	Poland	NR	II	101	14.2 (9.1 –16.5 y)	Scores ≥4	OS, DFS	Nuclear	8
Dahl E et al[15]	Breast cancer	2009	Germany	NR	I–IV	159	90 (72–109)	Scores >3	OS, DFS	Nuclear	7
Gluz O et al[18]	Breast cancer	2009	Germany	NR	I–III	211	61.7	Scores >1	OS, DFS	NR	8
Habibi G et al[19]	Breast cancer	2008	Canada	Gift	I–III	3097	20 y	Scores ≥1	OS	NR	7

(*Continued*)

Table 1 (Continued).

Author	Cancer type	Year	Region	Brand of antibody	Stage/ grade	No. of patients	Follow-up time (months)	Cut-off value	Outcomes	Subtype of YBX1	NOS score
Saji H et al[27]	Breast cancer	2003	Japan	Gift	NR	31	NR	>10%	DFS	Nuclear	6
El-Naggar AM et al[16]	Sarcoma	2015	Canada	Santa Cruz Biotech/ Cell Signaling Technology	NR	34	NR	NR	OS, DFS	NR	6
Oda Y et al[9]	Synovial sarcoma	2003	Japan	NR	III, IV	54	46.9 (1–233)	>10%	OS	Nuclear	6
Iwanami T et al[22]	Pleural mesothelioma	2014	Japan	NR	I–IV	33	357 d	>60%	OS	NR	6
Zhao Z et al[13]	Natural Killer/ T-cell lymphoma	2014	China	Cell Signaling Technology	I–II	36	59.6 (4–132)	Hscore ≥200	OS, DFS	NR	5
Szczuraszek K et al[31]	Non-Hodgkin's lymphoma	2011	Poland	NR	I–IV	56	32 (1–102)	Scores ≥6	OS, DFS	NR	5
Nishio S et al[26]	Uterine cervical cancer	2014	Japan	NR	I–II	204	25.1	Scores ≥2	OS, DFS	Nuclear	7
Song YH et al[30]	Bladder cancer	2014	Japan	Epitomics	NR	53	25	Scores >4	OS	NR	6

Abbreviations: NR, not reported; y, years; d, days; OS, overall survival; DFS, disease-free survival; IPS, intensity–percentage score; N, Nuclear; C, Cytoplasm.

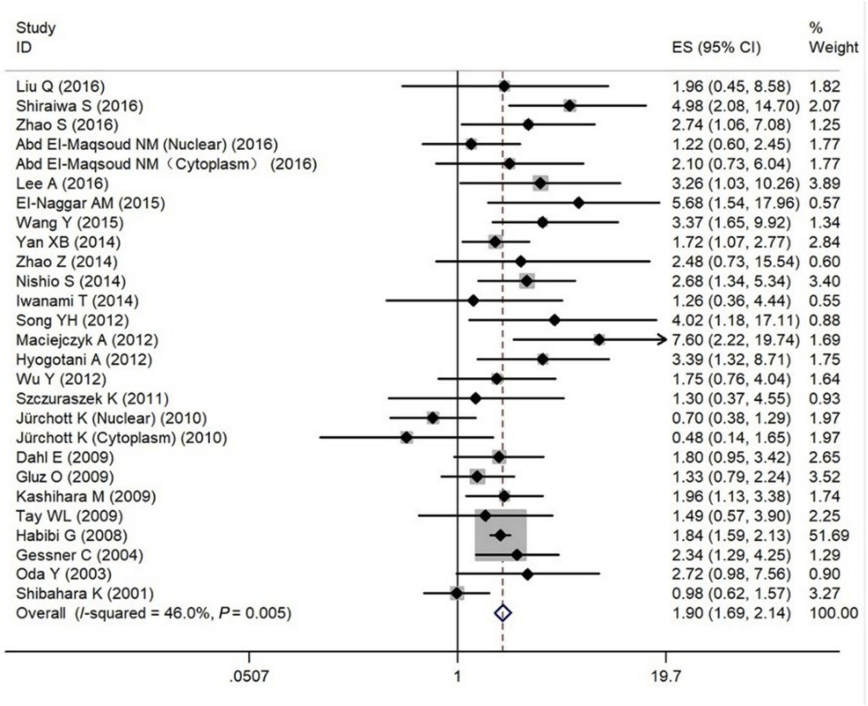

Figure 2 Forest plot describing the association between YBX1 expression and overall survival (random-effects analysis).
Abbreviation: ES, effect size.

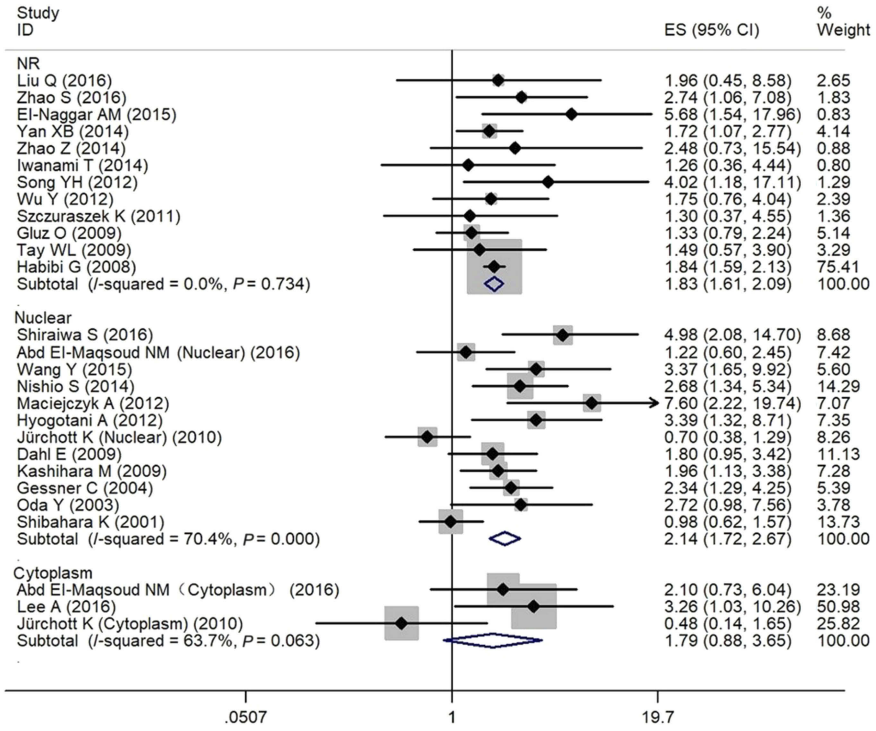

Figure 3 Subgroup analysis of overall survival and YBX1 protein type (random-effects analysis).
Abbreviation: ES, effect size.

a sensitivity analysis was used to determine whether modifications of the included criteria affected the results (Figure 6). The results indicated that the pooled estimates of the effect of high-expressed YBX1 on OS and DFS in solid tumors did not vary significantly with the exclusion of any individual studies.

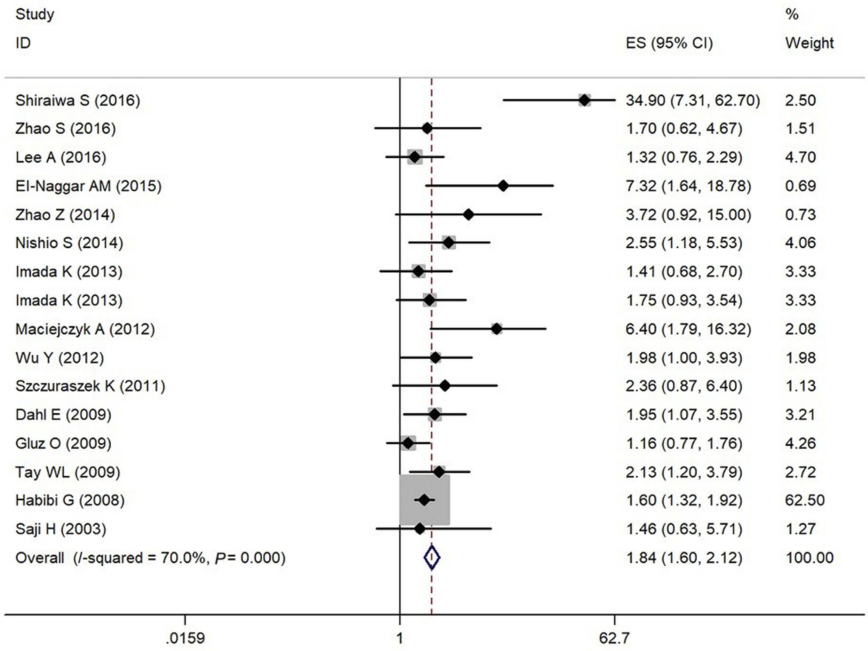

Figure 4 Forest plot describing the association between YBX1 expression anddisease-free survival (random-effects analysis).
Abbreviation: ES, effect size.

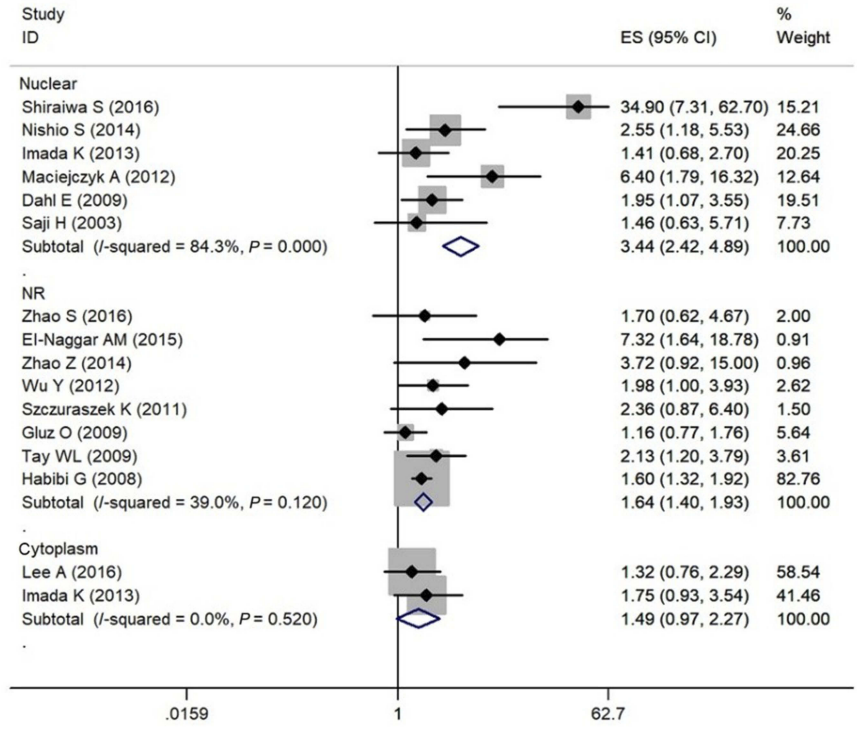

Figure 5 Subgroup analysis of disease-free survival and YBX1 protein type (random-effects analysis).
Abbreviation: ES, effect size.

Publication bias

The publication bias of these applicable studies was constructed using Begg's funnel plot with pseudo–95% confidence limits and Egger's test to assess. The shapes of the funnel plots for OS, DFS and clinicopathological parameters showed no evidence of obvious asymmetry, and

Table 2 Meta-analystic results of the associations of increased YBX1 expression with clinicopathological parameters

Clinicopathological parameter	Number of studies	Overall OR (95%CI)	Heterogeneity test (I^2, *P*-value)
Gender (male vs female)	14	1.06 (0.85, 1.33)	22.6% 0.208
Tumor differentiation status (poor vs well)	15	2.85 (2.10, 3.88)	54.3% 0.006
Tumor size (T3–4 vs T1–2)	13	2.16 (1.61, 2.73)	71.4% 0.000
Lymph node metastasis (yes vs no)	13	1.74 (1.38, 2.19)	59.0% 0.004
Distant metastasis (yes vs no)	12	1.27 (0.88, 1.84)	66.0% 0.001
Clinical stage (III–IV vs I–II)	7	1.41 (0.94, 2.11)	78.3% 0.000

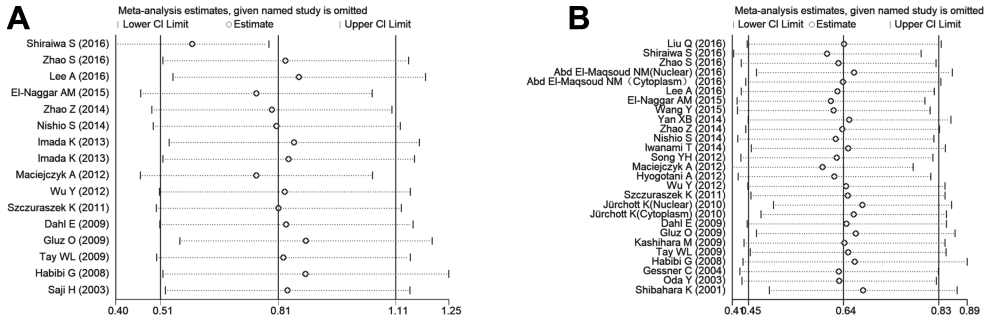

Figure 6 Sensitivity analysis of the overall survival (OS) and disease-free survival (DFS) in the meta-analysis. (**A**) DFS; (**B**) OS.

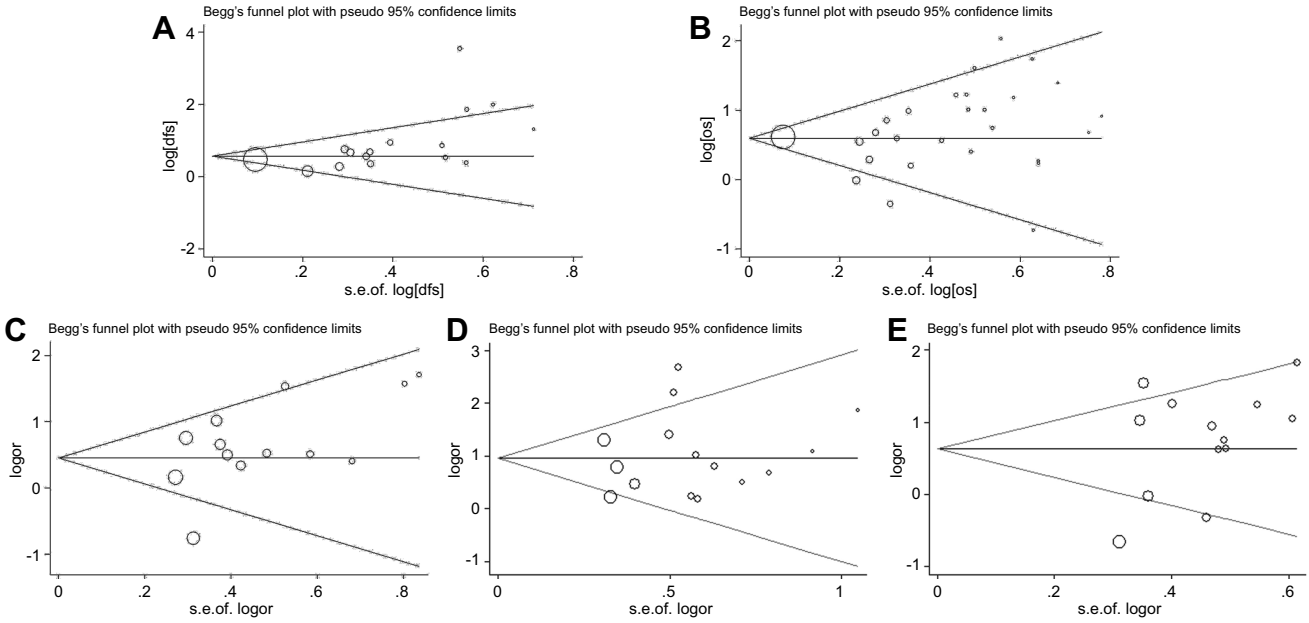

Figure 7 Funnel plot for the assessment of potential publication bias regarding overall survival (OS), disease-free survival (DFS) and clinicopathological parameters in the meta-analysis. (**A**) DFS; (**B**) OS; (**C**) lymph node metastasis; (**D**) tumor differentiation status; (**E**) tumor size.

Egger's test indicated the absence of publication bias (P>0.05). The preceding results revealed that this meta-analysis was statistically reliable. Furthermore, these findings provided other strong evidence to verify that high-level of YBX1 was a prognostic indicator for cancer patients (Figure 7).

Discussion

YBX1 (Y-box-binding protein 1) is encoded by the YBX1 gene expression in the nucleus and the cytoplasm and plays pleiotropic roles in DNA repair,[2] RNA splicing,[3,4] drug resistance, cancer progression, invasion, and metastasis.[6–8] Previous massive studies proved that high level expressions

of YBX1, whether in nucleus or cytoplasm were significantly correlated with the clinicopathological features as poor prognostic factors in various cancers.[7,9–11]

Here, we reviewed almost all available published articles and conducted the present meta-analysis to investigate the prognostic value and clinical significance of YBX1 in solid malignant cancers. The meta-analysis of 27 studies based on the random-effects model is to discuss all the reported research exploring the hypothesis that a high-level nuclear expression of YBX1 was a promising prognostic factor for worse DFS and OS in patients with various solid tumors. Moreover, phosphorylated YBX1 enters into the nuclear compartment and binds to the promoter region of targeted genes,[38] one of the 27 studies explored the relationship between phosphorylated YBX1 and overall survival in patients with high-grade serous ovarian cancer (HR=2.41, 95% CI: 1.34–4.33). This result coincides with our conclusion. However, in our study, although the high expression of YBX1 in cytoplasm was not statistically significant due to the number of cases or to the other reason, the HR value proved that YBX1 was associated with OS and DFS. Therefore, we could not deny directly that increased cytoplasmic YBX1 expression was not associated with OS or DFS. Elevated expression of YBX1 has degenerative feedback regulation with tumor differentiation status, tumor size and lymph node metastasis. Sensitivity analysis showed that no individual studies affected the overall results, indicating the stability of the aggregated results. Furthermore, no publication bias was observed. Thus, we conclude that the expression of YBX1 may be a biomarker of poor clinically pathologic prognostic factors in cancers.

When explaining the results of our meta-analysis, we should consider some restrictions. One of the major restrictions is a lack of stratified analysis for different tumor subtypes, different clinical stages or others. For instance, we previously mentioned that nuclear YBX1 expression predicts poor clinical outcome in stage III colorectal cancer,[10] but fewer studies were focused on the other clinical stages of colorectal cancer. Additional studies with larger samples and standard testing methods are required to reach a consensus. Next, different threshold values of high-level YBX1 expression in each study may have led to an increase in the heterogeneity. A common cutoff value should be defined. The third restriction is that all incorporated studies are retrospective studies with positive results, which was considered to be more easily published. Thus, our assessment of the relationship betweene elevated YBX1 expression and outcome carries the possibility of overestimation. Finally, the literature was restricted to English-written papers, which may have introduced language bias. Many included studies that did not report clinicopathological features, which may lead to bias. Given all theselimitations, our results should be considered cautiously.

Conclusion

The present meta-analysis, according to published articles, demonstrated that elevated nuclear YBX1 expression was closely correlated with poorer survival of patients with various solid cancers, such as prostate cancer, sarcoma, renal cell carcinomas, lymphoma, uterine cervical cancer, and pleural mesothelioma. In addition, there are remarkably negative relevant relationships between highly -expressed YBX1 and tumor differentiation status, tumor size and lymph node metastasis. Last, our results should be interpreted carefully for the aforementioned heterogeneity and limitations. The results of this meta-analysis warrant performance of additional clinical studies of YBX1 in human solid tumors.

Acknowledgments

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Disclosure

The authors declare no potential conflicts of interest in this work.

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Supplementary material

Table S1 Summarized data of clinical and pathological parameters from the eligible studies

First author	Subgroup type	Gender				Tumor differentiation status				Tumor size				Lymph node metastasis				Distant metastasis				Clinical stage			
		Male		Female		Poor /middle/ undifferentiated		Well-differentiated		T3-4		T1-2		Yes		No		Yes		No		III-IV		I-II	
		+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
Liu Q et al[1]		59	22	17	11	58	6	18	27	NR	NR	NR	NR	NR	NR	NR	NR	35	17	41	16	22	22	37	5
Shiraiwa S et al[2]		45	32	33	14	10	5	68	41	68	36	10	10	78	46	NR	NR	126	69	30	23	NR	NR	NR	NR
Zhao S et al[3]		16	21	15	23	21	15	10	29	NR	NR	NR	NR	5	5	26	39	5	3	26	41	NR	NR	31	44
Abd El-Maqsoud NM et al[4]	Nuclear	NR	NR	NR	NR	24	35	4	13	16	20	12	28	7	8	21	40	19	23	9	25	19	20	9	28
	Cytoplasm	NR	NR	NR	NR	38	21	10	7	26	10	22	18	13	2	35	26	25	13	19	15	30	9	18	19
Lee A et al[5]		NR	NR	NR	NR	91	65	20	52	10	4	102	117	44	43	68	78	NR	NR	NR	NR	NR	NR	NR	NR
Wang Y et al[6]		44	50	36	35	31	19	49	66	43	17	37	68	NR	NR	NR	NR	28	7	52	78	31	19	49	66
Yan XB et al[7]		53	38	35	44	NR	NR	NR	NR	36	47	52	35	36	49	52	33	NR	NR	NR	NR	NR	NR	NR	NR
Zhao Z et al[8]		9	14	5	8	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nishio S et al[9]		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	18	36	23	127	27	82	14	81	NR	NR	41	163
Song YH et al[10]		24	18	6	5	28	19	2	4	23	8	7	15	10	2	19	21	22	9	8	14	NR	NR	NR	NR
Hyogotani A et al[11]		28	33	12	32	34	25	6	40	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	15	12	25	53
Wu Y et al[12]		23	44	6	25	NR	NR	NR	NR	10	29	19	40	21	42	8	27	0	2	29	67	18	34	11	35
Szczuraszek K et al[13]		27	5	21	3	25	3	21	5	NR	NR	NR	NR	NR	NR	NR	NR	15	2	29	5	34	7	8	0
Dahl E et al[14]		NR	NR	NR	NR	41	101	1	16	17	19	25	98	26	54	15	60	NR	NR	NR	NR	NR	NR	NR	NR
Gluz O et al[15]		NR	NR	NR	NR	119	77	5	9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tay WL et al[16]		39	59	13	24	NR	NR	NR	NR	23	36	28	43	40	57	11	22	1	7	50	73	NR	NR	NR	NR
Shibahara K et al[17]	NSCLC	53	78	35	30	63	71	22	31	30	17	58	91	46	37	41	70	NR	NR	NR	NR	NR	NR	NR	NR
	Adenocarcinoma	33	29	30	23	42	29	19	21	20	8	43	44	28	17	34	34	NR	NR	NR	NR	NR	NR	NR	NR
	Squamous cell carcinoma	20	49	5	7	21	42	3	10	10	9	15	47	18	20	7	36	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: NSCLC, non-small cell lung cancer; NR, not reported.

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