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High expression of HOXB7 is an unfavorable prognostic factor for solid malignancies

A meta-analysis

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Abstract

Background: HOXB7 is abnormally expressed in a variety of tumors, but its prognostic value remains unclear due to sample size limitation and outcome inconsistency in previous studies. This meta-analysis was performed to explore the effect of HOXB7 expression on prognoses and clinicopathological factors in range of the whole solid tumors.

Methods: PubMed, EMBASE, and Web of Science databases were searched to identify included studies. Hazard ratios (HR) with its 95% confidence interval (CI) and clinicopathological factors were extracted. Subgroup analyses were performed according to histopathological type, tumor occurrence systems, and HOXB7 detection methods.

Results: A total of 3430 solid tumors patients from 20 studies (21 cohorts) were included in the meta-analysis. The results showed that high HOXB7 expression was significantly associated with worse survival (overall survival: HR = 1.98, 95%CI: 1.74–2.26, $P < .001$ and disease-free survival: HR = 1.59, 95%CI: 1.21–2.09, $P = .001$), more advanced tumor-node-metastasis (TNM) stage (odds ratio [OR] = 2.14, 95%CI: 1.68–2.73, $P < .001$), positive lymph node metastasis (OR = 2.16, 95%CI: 1.74–2.70, $P < .001$), more distant metastasis (OR = 1.63, 95%CI: 1.01–2.63, $P = .048$), poorer differentiation (OR = 1.48, 95%CI: 1.14–1.91, $P = .003$), and higher Ki-67 expression (OR = 2.53, 95%CI: 1.68–3.84, $P < .001$). Subgroup analysis showed that survival of patients with HOXB7 high expression was worse in either squamous cell carcinomas or non-squamous cell carcinomas, digestive tumors or non-digestive tumors, and protein level or mRNA level.

Conclusion: High HOXB7 expression might be a valuable biomarker of poor prognosis for solid tumors. HOXB7 promotes tumor proliferation and metastasis, and is associated with poorer differentiation, more advanced stage, even the chemotherapy resistance, suggesting that HOXB7 is a potential therapeutic target for solid tumors.

Abbreviations: CI = confidence interval, DFS = disease-free survival, EMT = epithelial-mesenchymal transition, HOX = homeobox, HR = hazard ratios, OR = odds ratio, OS = overall survival, OSCC = oral squamous cell carcinoma, TAM = tamoxifen.

Keywords: biomarker, HOXB7, meta-analysis, prognosis, solid tumors

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TZ and ZF contributed equally to this work.

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Keypoints

- HOXB7 high expression was correlated with worse OS and DFS in solid tumors. This OS differences existed whether in squamous or non-squamous cell carcinomas, digestive or non-digestive tumors, protein or mRNA level in subgroup analysis.
- HOXB7 high expression was correlated with poorer pathological differentiation, positive lymph-node or distant metastasis, more advanced TNM stage, and higher expression of Ki-67.

1. Introduction

As one of the leading causes of death worldwide, cancer has become the major public health problem with increasing morbidity and mortality. Statistics showed that there were 4,292,000 new cases and 2,814,000 cancer deaths in China in 2015.[1] In recent years, certain progression in early cancer screening and surgery-based comprehensive treatment have improved the 5-year overall survival (OS) of malignant tumors from 30.9% in 2003–05 to 40.5% in 2012–15.[2] However, the

curative efficacy and long-term survival of solid malignant tumor patients treated according to standard TNM staging are still largely heterogeneous. With the advent of precision treatment, it is urgent to identify novel molecular markers to monitor prognosis and guide treatment.

The homeobox (HOX) genes belong to a family of transcription factors that are evolutionarily highly conserved and functionally embryonic-development promoted. The 39 HOX gene family members are arranged separately on 4 chromosomes 7p14, 17q21, 12q13, and 2q31 and correspondingly named as HOXA, HOXB, HOXC, and HOXD clusters.[3] HOX genes are key factors in determining cell and tissue characteristics and play important roles in embryonic development. Under physical conditions, most members of this family are silenced or low-level expressed, except for structural expression in a few organs or tissues such as hematopoietic tissue, uterus in the menstrual cycle, and breast in pregnancy.[4–6] Ever since the identification of the first abnormal expression of HOX gene in leukemia in 1988, the relationship between HOX genes and tumorigenesis has been successively confirmed in leukemia, kidney cancer, colorectal cancer, lung cancer, cervical cancer, breast cancer, skin cancer, ovarian cancer, and thyroid cancer.[7,8] And most of the studies suggested that abnormal expression of the HOX genes contribute to tumor progression.

So far, the previous meta-analyses regarding effects of HOX gene family members on the prognoses of the patients were involved with HOXA10 and HOXA13, which showed that the expression of HOXA13 was an unfavorable prognostic factors in solid tumors and HOXA10 could serve as a tumor suppressor in prostate cancer.[9,10] Moreover, there were also 2 meta-analyses on relationship between HOXB7 and cancer, one of which explored the effects of HOXB7 on tumor metastasis, and the results showed that patients with HOXB7 high expression suffered from higher rates of both lymph node metastasis and distant metastasis.[11] Another study explored the effects of HOXB7 on the prognoses of patients with digestive system tumors. The results showed that high expression of HOXB7 was associated with poor prognosis, as well as advanced clinicopathologic characteristics such as tumor invasion, lymph node metastasis, distant metastasis, and higher TNM stage. In addition, expression of HOXB7 was also associated with lymph node metastasis and distant metastasis in variate tumors, indicating that the relationship between abnormal expression of HOX family and prognosis of cancer patients worth investigating.[12] The 2 meta-analyses mentioned above only dealt with the relationship between HOXB7 and digestive tumors or cancer metastasis. Considering that more relevant studies with a wider perspective have come out in recent years, we conducted this meta-analysis on the relationship between HOXB7 and clinicopathological characteristics/prognosis of solid cancer patients, aiming to supplement data regarding this issue and provide some clues for clinical practice.

2. Materials and methods

The study was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Ethics approval was not required for this research.

2.1. Literature search

A thorough literature retrieval was conducted in PubMed, EMBASE, and Web of Science database from inception to September 30, 2020 with keywords "HOXB7 OR HOX B7 OR HOXB 7 OR Homeobox B7" AND "tumor OR cancer OR carcinoma OR neoplasm".

2.2. Study end-point

The end-points of this meta-analysis were OS and disease-free survival (DFS) of solid tumor patients.

2.3. Inclusion and exclusion criteria

Inclusion criteria: studies about the association between HOXB7 expression and prognostic parameters; the objective of the studies are solid tumor patients; the value of hazard ratios (HR) and 95% confidence interval (CI) could be extracted from the data provided; full texts are available. Exclusion criteria: duplicate publications; reviews, letters, conference reports, case reports, meta-analysis; data are incomplete or unable to be extracted.

2.4. Study screening and data extraction

According to the inclusion and exclusion criteria, 2 independent investigators separately screened and reviewed the eligible articles, and the divergent literature was consulted with a third investigator. Through a standard information collection form, the data were extracted as follows: first author, year of publication, country of origin, cancer type, pathological type, sample size, cut-off value of HOXB7 expression, patient number of HOXB7 high or low expression, HOXB7 detection method, HR, 95%CI, gender, degree of tumor differentiation, lymph node status, distant metastasis status, TNM stage, Ki67 expression level. For literature that did not directly provide HR and 95%CI, extractions were performed from Kaplan-Meier curves using Engauge Digitizer 4.1 software and the Jayne F Tierney worksheet.

2.5. Quality assessment

Quality of all included studies was systematically assessed using the Newcastle-Ottawa Scale, which consisted of 3 parts as choice of the cohort, the comparability between exposed cohort and non-exposed cohort, and the results, with a total of 8 items and 9 points. The study with a Newcastle-Ottawa Scale score ≥6 was defined as high quality.

2.6. Statistical methods

All data analyses were computed with the STATA 14 software (STATA Corporation, College Station, TX). The effect size of survival data and categorical variables was based on HR and odds ratio (OR) respectively with their 95%CI. Heterogeneity analysis was performed on all included studies using chi-square test and quantitatively assessed by I^2 value. If heterogeneity exists, sensitivity analysis is used to evaluate the impact on the main results. When studies were considered as mild heterogeneity ($I^2 < 50\%$, $P > .1$), the M-H fixed effect model was applied. Conversely, for studies with significant heterogeneity ($I^2 \geq 50\%$, $P \leq .1$), random effects model was applied. The effect size was measured by Z test with the level at $\alpha = 0.05$. The Begg funnel plots and Egger test were applied to assess the potential publication bias, and the test level was $\alpha = 0.05$. The effect of publication bias on the results was evaluated by the cut and fill method.

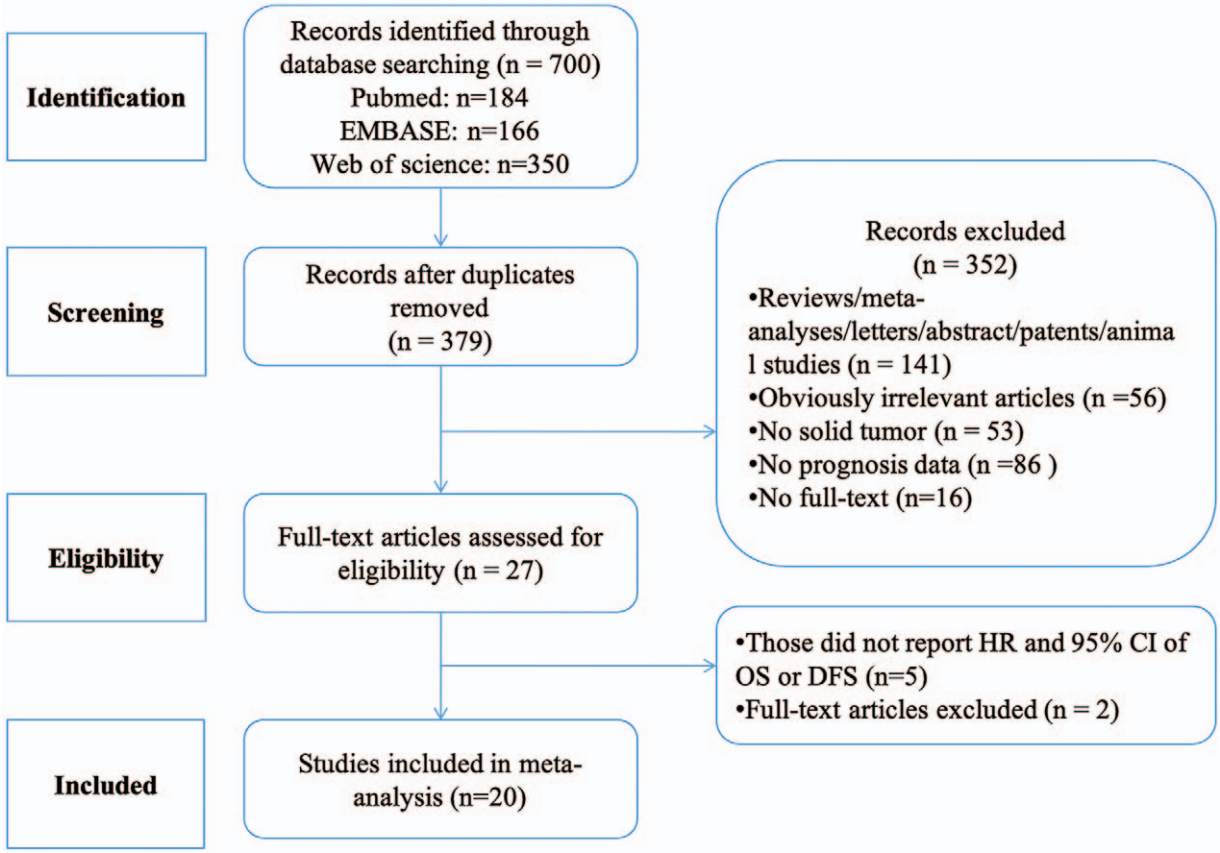

Figure 1. Flow diagram of the literature retrieval process. CI = confidence interval, DFS = disease-free survival, HR = hazard ratios, OS = overall survival.

3. Results

3.1. Literature search

Initially, 700 articles were found according to the search strategy. After the screening that was carried out in strict accordance with the inclusion and exclusion criteria, 20 studies with a total of 21 cohorts (including 2 cohorts in the study of Hui et al) that published from 2010 to 2020 were finally included. A flow diagram of the literature retrieval process was shown in Figure 1. A total of 3430 solid tumor patients, including 1629 patients with high expression and 1801 patients with low expression of HOXB7. A summary of the main characteristics of the included studies was shown in Table 1.

3.2. Clinical value of HOXB7 in solid tumors

Heterogeneity test was performed for the 20 studies, $I^2 = 35.3\%$, $P = .057$, suggesting that the heterogeneity between studies was small. Sensitivity analysis was performed, and the results were consistent with the main results, indicating that the results were robust. Therefore, fixed-effects model was applied. The results showed that patients with high HOXB7 expression had worse OS and DFS than those with low HOXB7 expression, HR = 1.98, 95%CI: 1.74–2.26, $P < .001$ and HR = 1.59, 95%CI: 1.21–2.09, $P = .001$, respectively (Figs. 2 and 3). The results of subgroup analysis showed that the survival of patients with HOXB7 high expression was worse compared to those with low expression in either squamous cell carcinomas or non-squamous cell carcinomas (HR = 2.15, 95%CI: 1.76–2.63, $P < .001$ and HR = 1.92, 95%CI: 1.63–2.27, $P < .001$) (Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A834), digestive system tumors or non-digestive system tumors (HR = 2.03, 95%CI: 1.74–2.37, $P < .001$ and HR = 1.78, 95%CI: 1.41–2.25, $P < .001$) (Figure S2, Supplemental Digital Content, http://links.lww.com/MD2/A835), and protein level or mRNA level (HR = 2.03, 95%CI: 1.79–2.31, $P < .001$ and HR = 1.87, 95%CI: 1.23–2.82, $P = .003$) (Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A836) (Table 2).

In addition, correlations between HOXB7 expression and clinicopathologic factors of solid tumor patients were analyzed, including the following items: gender (male vs female), degree of tumor pathological differentiation (G3 vs G1/2) (Figure S4, Supplemental Digital Content, http://links.lww.com/MD2/A837), lymph-node status (N+ vs N–) (Figure S5, Supplemental Digital Content, http://links.lww.com/MD2/A838), distant metastasis (M1 vs M0) (Figure S6, Supplemental Digital Content, http://links.lww.com/MD2/A839), TNM staging (III–IV vs I–II) (Figure S7, Supplemental Digital Content, http://links.lww.com/MD2/A840), and Ki-67 expression (high vs low) (Figure S8, Supplemental Digital Content, http://links.lww.com/MD2/A841). The results showed that patients with high HOXB7 expression commonly had poorer tumor differentiation (OR = 1.48, 95%CI: 1.14–1.91, $P = .003$) and more advanced tumor stage (OR = 2.14, 95%CI: 1.68–2.73 $P < .001$), were prone to have lymph-node metastasis (OR = 2.16, 95%CI: 1.74–2.70, $P < .001$) and distant metastasis (OR = 1.63, 95%CI: 1.01–2.63,

Table 1

Main characteristics of the included studies.

Author	Year	Country	Cancer type	Pathological type	Samples	Cut-off (high HOXB7 expression)	HOXB7 expression		Detection method	OS		DFS	
							High	Low		Pooled HR (95%CI)	*P* value	Pooled HR (95%CI)	*P* value
De Souza Setubal Destro MF	2010	Brazil	OSCC	Squamous	35	>38.2% positive cells	19	16	IHC	1.74 (0.81–3.73)	.08	2.48 (0.92–6.65)	.1
Liao WT	2011	China	CRC	Non-squamous	224	≥2 intensity score with ≥50% positive cells	121	103	IHC	2.28 (1.06–2.69)	.027	NA	NA
Bitu CC	2012	Brazil	OSCC	Squamous	115	>31% positive cells	55	60	IHC	2.74 (1.96–6.32)	.009	1.65 (0.78–2.41)	.083
Nguyen Kovochich A	2013	America	PDAC	Non-squamous	145	Semi-quantitative histoscores >110	55	90	IHC	1.50 (1.01–2.22)	.04	NA	NA
Xie X	2013	China	ESCC	Squamous	179	>0.52 with 76.9% sensitivity and 42.5% specificity	115	64	qRT-PCR	1.86 (1.17–2.95)	.008	NA	NA
Long QY	2014	China	ESCC	Squamous	76	≥2 intensity score	41	35	IHC	3.41 (1.81–6.41)	<.001	NA	NA
Zhang R	2014	China	PDAC	Non-squamous	44	NA	29	15	IHC	2.69 (1.25–5.78)	.012	NA	NA
Yuan	2014	China	LAC	Non-squamous	75	≥3 extent score	57	18	IHC	2.15 (0.93–4.97)	<.01	NA	NA
Li H	2015	China	ESCC	Squamous	177	>25% positive cells	124	53	IHC	1.75 (1.04–2.93)	.036	NA	NA
					103	>25% positive cells	61	42	IHC	1.84 (1.18–2.86)	.024	NA	NA
Tu W	2015	China	GC	Non-squamous	96	(intensity score + extent score) ≥2	66	30	IHC	4.74 (1.10–20.45)	.037	3.74 (1.08–13.00)	.038
Komatsu H	2016	Japan	HCC	Non-squamous	103	NA	52	51	IHC	2.04 (1.08–3.10)	.027	NA	NA
Cai JQ	2016	China	GC	Non-squamous	70	NA	35	35	qRT-PCR	1.89 (0.75–4.8)	.245	NA	NA
Huan	2017	China	HCC	Non-squamous	77	≥2 intensity score with ≥0% positive cells	37	40	IHC	2.51 (1.52–4.13)	<.001	NA	NA
Wang WM	2017	China	HCC	Non-squamous	394	NA	181	213	IHC	1.72 (1.33–2.23)	<.001	1.41 (1.10–1.81)	.006
Zhou T	2019	China	ESCC	Squamous	143	(intensity score + extent score) ≥2	72	71	IHC	2.59 (1.59–4.2)	<.002	NA	NA
Fang HY	2019	China	GC	Non-squamous	593	NA	285	308	Database	1.38 (1.14–1.68)		NA	NA
Guo Y	2019	China	HCC	Non-squamous	80	Staining score ≥2 with at least 50% of malignant cells	28	52	IHC	2.00 (1.10–3.40)	.014	NA	NA
Song Z	2019	China	PCa	Non-squamous	281	NA	141	140	Database	1.58 (1.19–2.10)	.001	NA	NA
Dai L	2019	China	ICC	Non-squamous	49	NA	32	17	IHC	2.50 (1.01–6.25)	.012	NA	NA
Cai L	2019	China	HCC	Non-squamous	371	NA	23	348	Database	3.70 (2.22–6.25)	<.05	NA	NA

CI = confidence interval, CRC = colorectal cancer, DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratios, ICC = intrahepatic cholangiocarcinoma, IHC = immunohistochemistry, LAC = lung adenocarcinoma, NA = not available, OS = overall survival, OSCC = oral squamous cell carcinoma, PCa = prostate cancer, PDAC = pancreatic ductal adenocarcinoma, qRT-PCR = quantitative real-time polymerase chain reaction.

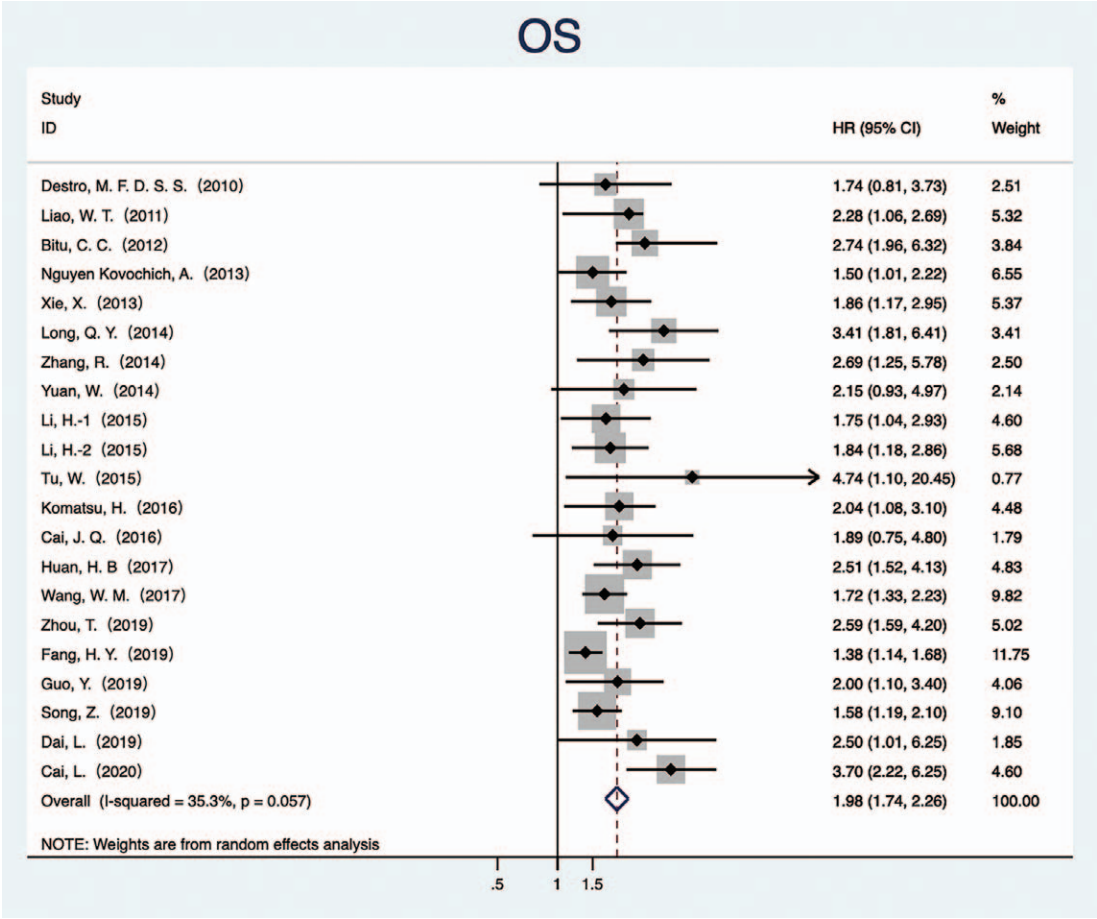

Figure 2. Forest plot for the relationship between HOXB7 expression and OS. OS = overall survival.

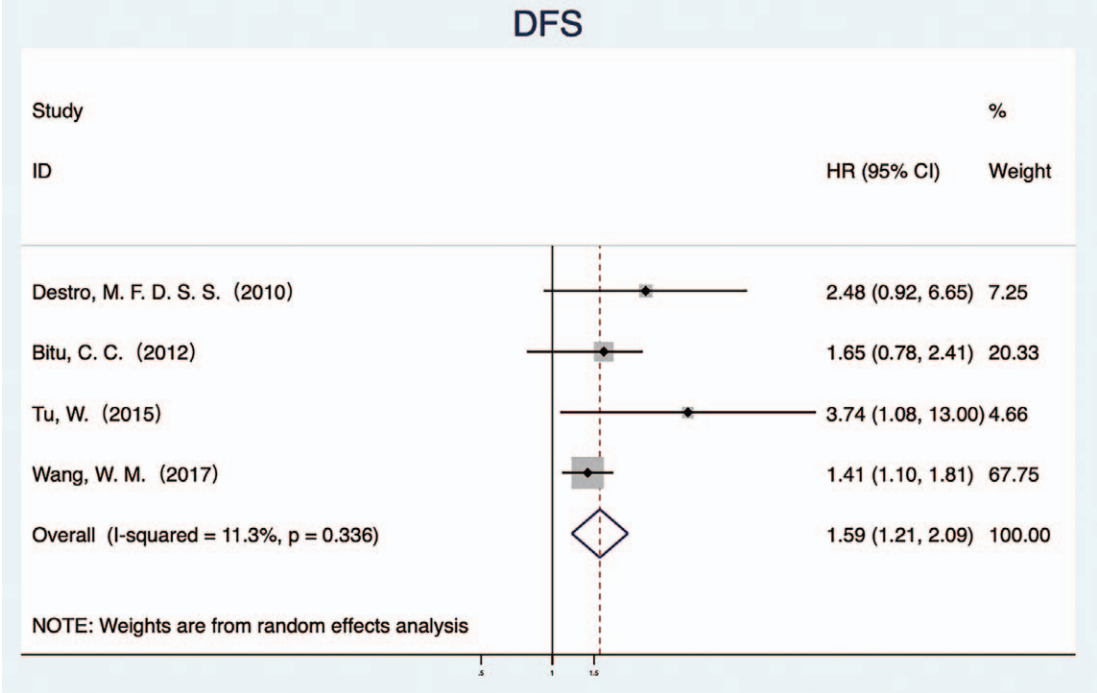

Figure 3. Forest plot for the relationship between HOXB7 expression and DFS. DFS = disease-free survival.

Table 2

Results of subgroup analysis for pooled patients with different expression of HOXB7.

Item	No. of studies	No. of samples	HOXB7 Expression		OS		Heterogeneity*	
			High	Low	Pooled HR (95%CI)	*P* value	I^2 (%)	*P* value
Pathological type								
Squamous	6 (7 cohorts)	828	487	341	2.15 (1.76–2.63)	<.001	0	.541
Non-squamous	14	2602	1142	1460	1.92 (1.63–2.27)	<.001	42.3	.048
System of occurrence								
Digestive	16 (17 cohorts)	2924	1357	1567	2.03 (1.74–2.37)	<.001	42.6	.033
Non-digestive	4	506	272	234	1.78 (1.41–2.25)	<.001	0	.398
Detection method								
IHC	15 (16 cohorts)	1936	1030	906	2.03 (1.79–2.31)	<.001	0	.676
qRT-PCR	2	249	150	99	1.87 (1.23–2.82)	.003	0	.976

CI = confidence interval, HR = hazard ratios, IHC = immunohistochemistry, OS = overall survival, qRT-PCR = quantitative real-time polymerase chain reaction.
* The fixed-effects model was applied in all subgroup analysis.

P = .048), and higher Ki-67 which is related to tumor proliferation (OR = 2.45, 95%CI: 1.67–3.72, *P* < .001) (Table 3).

3.3. Publication bias analysis

The Begger funnel plots and Egger test were used to quantitatively analyze the publication bias of included studies. The results showed z = 2.26, Pr > |z| = 0.024 (Fig. 4) which indicated publication bias. The influence of publication bias on the main results was analyzed by cut and fill method. The results were consistent with the main results that patient of high HOXB7 expression had worse OS (HR = 1.65, 95%CI: 1.42–1.91, *P* < .001), suggested the original results were robust.

4. Discussion

4.1. HOXB7

HOXB7, a member of the HOX gene family, is located at 17q21 and promotes ureteral development and fetal lung development.[13–15] A number of studies have shown that HOXB7 is abnormally expressed in a variety of solid tumors including oral squamous cell carcinoma (OSCC), colon cancer, breast cancer, esophageal cancer, pancreatic cancer, lung cancer, gastric cancer, and liver cancer.[16] However, the development and outcome of the disease caused by this abnormal expression are not always consistent, which is manifested in: Although most studies have supported the conclusion that abnormally high expression of HOXB7 was related to worse survival of the patients, there are still several studies with different results showing a correlation trend but without statistical significance between high expression of HOXB7 and poorer survival of salivary gland tumor patients, OSCC patients, and gastric cancer patients.[17–19] However, there were some shortcomings in these 3 studies, such as the pathological types were mixed with benign and malignant tumors, which resulted in the different treatment options, most of the included patients were in stage III/IV and insufficient of sample size as well as follow-up time. Several studies showed that the correlation between high expression of HOXB7 and survival of the patients only existed in the subtypes of certain tumors. As found in studies on breast cancer, the prognosis of patients with HOXB7 high expression was only reflected in 72/286 patients that with HER-2 positive.[20] Xie et al[21] also found that the prognostic advantage of low expression of HOXB7 was only reflected in the tumor of small length, early pathological T stage and pathological No. The effects of HOXB7 on tumorigenesis and cancer progression are not consistent under different time and space backgrounds. For example, Chen et al[20] found that overexpression of HOXB7 played a dual role in tumors in HER-

Table 3

Results of the correlations of HOXB7 expression level with clinicopathological factors.

Item		No. of studies	No. of samples	HOXB7 Expression		OR (95%CI)	*P* value	Heterogeneity*	
				High	Low			I^2 (%)	*P* value
Gender (male vs female)	Male	16 (17 cohorts)	2072	833	629	1.18 (0.97–1.44)	.108	0	.58
	Female			329	281				
Differentiation (G3 vs G1/2)	G3	12 (13 cohorts)	1297	271	168	1.48 (1.14–1.91)	.003	13	.31
	G1/2			461	397				
Lympha-node status (N+ vs N–)	N+	12 (13 cohorts)	1492	464	246	2.16 (1.73–2.69)	<.001	0	.85
	N–			379	40				
Distant metastasis (M1 vs M0)	M1	6	649	62	34	1.63 (1.01–2.63)	.048	0	.68
	M0			314	239				
Stage (III/IV vs I/II)	III/IV	11 (12 cohorts)	1279	374	164	2.14 (1.68–2.73)	<.001	27.9	.17
	I/II			394	347				
Ki-67 expression (high vs low)	High	3	374	121	71	2.45 (1.67–3.72)	0	0.1	.37
	Low			74	108				

CI = confidence interval, OR = odds ratio.
* The fixed-effects model was applied in all subgroup analysis.

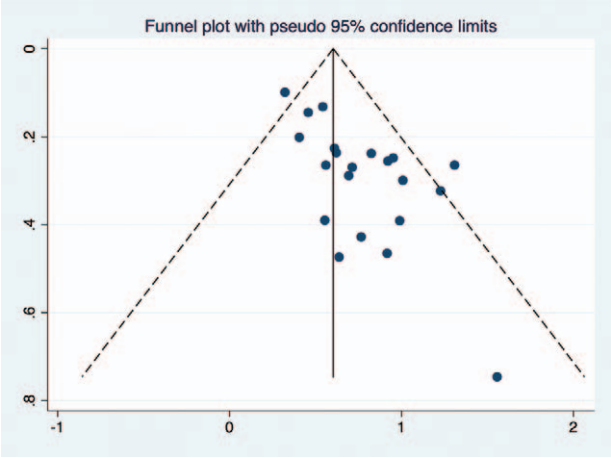

Figure 4. Begg funnel plot analysis of potential publication bias in the meta-analysis.

2/neu-induced breast cancer mouse models, which inhibited tumorigenesis initially, but promoted subsequent progression and metastasis of the tumor. On the other hand, the promotion function of HOXB7 in the double-strand break repair process suggested that HOXB7 promotes normal cell repair before tumorigenesis, however, once tumor occurs, it would in turn promote the damage repair of tumor cell, including the damage caused by chemotherapeutic drugs such as cisplatin, of which the main mechanism is DNA damage. Therefore, HOXB7 has a role in tumor progression or drug resistance. For the function itself, HOXB7 promotes tissue differentiation as an embryo-related gene, but it also promotes de-differentiation of mature tissues and acquisition of cell stemness. Therefore, a meta-analysis would facilitate a more comprehensive understanding of the prognostic significance of HOXB7 in solid tumors.

4.2. HOXB7 is a poor prognostic factor for solid malignant tumors

The solid tumor types in this meta-analysis included OSCC, esophageal squamous cell carcinoma, gastric cancer, colorectal cancer, liver cancer, pancreatic cancer, lung adenocarcinoma, and salivary gland cancer. It was found that the expression of HOXB7 was higher in cancer tissues as compared with that in normal tissues, either at mRNA or protein levels. The pooled analysis showed that the OS and DFS of HOXB7 high expressed patients were worse than those with low expression of HOXB7. Further subgroup analysis showed that the survival disadvantage of HOXB7 high expression was commonly found in squamous cell carcinomas and non-squamous cell carcinomas, digestive system tumors and non-digestive system tumors, protein level and mRNA level. Therefore, the results of this study suggested that HOXB7 high expression was one of the unfavorable prognostic factors for solid malignancies. HOXB7 affects the biological behavior of solid malignant tumors and the prognosis of patients in many aspects as follows.

4.2.1. Clinicopathological aspects. The results showed that patients with HOXB7 high expression often had more advanced TNM stages ($P < .001$), higher lymph-node metastasis rate ($P < .001$) and distant metastasis rate ($P = .048$), poorer pathological differentiation ($P = .003$), and higher Ki-67 expression ($P < .001$).

4.2.2. Cell biological properties. It has been found in previous studies that HOXB7 high expression promoted malignant biological behavior such as acceleration of cell proliferation, inhibition of apoptosis, acquisition of cell stemness, and enhancement of motility and angiogenesis.[8,22,23]

4.2.2.1. HOXB7 effects PI3K/AKT and MAPK pathways. He et al[24] found in gastric cancer that HOXB7 promoted cell proliferation, inhibited apoptosis, and induced epithelial-mesenchymal transition (EMT) and metastasis by activating PI3K/AKT and MAPK pathways. Further, Liao et al[25] demonstrated in colorectal cancer that by activating these pathways, HOXB7 modulated checkpoint proteins (up-regulated Cyclin D1 and down-regulated P27Kip1), which accelerated G1-S cell cycle transition and cell proliferation. Huan et al[26] found that HOXB7 promoted the stemness acquisition of hepatoma cells by regulating PI3K/AKT/c-Myc axis, and promoted EMT by regulating PI3K/AKT/Slug axis to accelerate the malignant progression of hepatocellular carcinoma.

4.2.2.2. HOXB7 promotes the expression of basic fibroblast growth factor in the downstream. In melanoma and ovarian cancer, HOXB7 was identified to activate basic fibroblast growth factor and promote cell proliferation. Further, in hepatocellular carcinoma and breast cancer, the activation of HOXB7 on basic fibroblast growth factor was found to be direct, and the MAPK pathway was thereby activated to promote proliferation and EMT, which further induced cancer cells toward a more aggressive phenotype.[27–30]

4.2.2.3. HOXB7 regulates the angiogenesis-related factors. Previous study has found that HOXB7 was involved in angiogenesis by up-regulating vascular endothelial growth factor A, fibroblast growth factor-2, matrix metalloproteinase-2, WNT5a and platelet derived growth factor A, and down-regulating thrombospoindin-2[32] in myeloma cancer. Meanwhile, in HOXB7-transfected breast cancer cells, except for VEGF, the expression of interleukin-8 and angiopoietin-2 was also upregulated.[31,32] In cervical cancer, VEGF was verified as a downstream transcriptor regulated by HOXB7, therefore, the miR-196b/HOXB7/VEGF axis played a critical role in the development and progression of cervical cancer.[33] Additionally, high expression of HOXB7 was also detected in the hemangiometastoma model.[34]

4.3. Treatment resistance

Related studies have found that treatment resistance caused by HOXB7 high expression is another important reason for poor prognosis of the patients. Jin et al[35] found that HOXB7 is an ERα response gene. In ERα breast cancer patients, after the treatment of tamoxifen (TAM), HOXB7 expression increased and binded with EGFR promoter, which resulted in the enhancement of the transcriptional activity and expression of EGFR, and ultimately lead to TAM resistance and poor prognosis. Interestingly, this TAM resistance would be reversed by HOXB7 siRNA. Therefore, HOXB7 expression in ERα breast cancer might be an indicator for anti-EGFR therapy. In addition,

Rubin et al[36] found that the human mammary epithelial cell line MCF10A transformed by exogenous HOXB7 was more resistant to ionizing radiation. They found 4 proteins, Ku70, Ku80, DNA-PKcs, and PARP, which could bind to HOXB7 directly by GST pull-down/affinity chromatography and immunoprecipitation. The 4 proteins were considered to be DNA repair related proteins, suggesting that HOXB7 is involved in the repair of non-homologous end joining of double-strand break, which was further confirmed in colon cancer.[37] In addition, in the studies of lung cancer, esophageal cancer and cervical cancer, it has been confirmed that the high expression of the above 4 non-homologous end joining-related molecules was associated with resistance to chemoradiotherapy.[37–41] Therefore, the expression of HOXB7 might be an indicator for the sensitivity of radiotherapy and/or chemotherapy.

5. Conclusion

High expression of HOXB7 promoted tumor proliferation and metastasis, and were associated with poor differentiation, more advanced stage, as well as chemotherapy resistance. Therefore, HOXB7 might be a valuable prognostic biomarker for human solid tumors. When HOXB7 expression was suppressed, its adverse effects could be alleviated, suggesting that HOXB7 is a potential therapeutic target in solid malignancies.

Author contributions

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