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Prognostic value of octamer binding transcription factor 4 for patients with solid tumors

A meta-analysis

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Abstract

Background: Octamer binding transcription factor 4 (Oct4) is critically important in the development and progression of cancer, and is considered a potential biomarker for tumor prognosis. However, the prognostic value of Oct4 in patients with solid tumors remains elusive. Herein, we conducted a meta-analysis to assess the prognostic value of Oct4 in patients with solid tumors.

Methods: We conducted a literature search on PubMed, Embase, and Web of Science databases to retrieve comprehensive and eligible studies published until December 2019. The study was conducted per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. The pooled hazard ratios (HRs) with 95% confidence intervals (CIs) of overall survival (OS) and disease-free survival (DFS)/recurrence-free survival (RFS)/progress-free survival (PFS) were used to evaluate the prognostic value of Oct4 in patients with solid tumors via either random or fixed-effects models.

Results: In total, 36 studies with 5198 patients were included in the meta-analysis. Notably, elevated Oct4 expression was associated with worse OS (pooled HR: 2.02, 95% CI: 1.55–2.62, $P < .001$) and DFS/RFS/PFS (pooled HR: 2.34, 95% CI: 1.88–2.92, $P < .001$).

Conclusion: This work demonstrated that patients with solid tumors show high expression of Oct4 which is linked to worse prognosis in patients with solid tumors including hepatocellular carcinoma (OS, DFS/RFS/PFS), esophageal squamous cell carcinoma (OS), gastric cancer (OS), cervical cancer (OS, DFS/RFS/PFS), and colorectal cancer (OS, DFS/RFS/PFS), this implicated Oct4 as a potential biomarker to predict the prognosis of tumors.

Abbreviations: AFP = alpha fetal protein, Akt = protein kinase B, ATP = adenosine-triphosphate, CIs = confidence intervals, CSCs = cancer stem cells, DFS = disease-free survival, ESCC = esophageal squamous cell carcinoma, ESCs = embryonic stem cells, FOXC1 = forkhead box protein C1, GC = gastric cancer, HCC = hepatocellular carcinoma, HIF2-α = hypoxia-inducible factor-alpha, HRs = hazard ratios, KM = Kaplan–Meier, NF-κB = nuclear factor kappa-light-chain-en-hancer of activated B, NOS = Newcastle-Ottawa scale, Oct4 = octamer binding transcription factor 4, OR = odds ratio, OS = overall survival, OSCC = oral squamous cell carcinoma, PFS = progress-free survival, PI3K = phosphatidylinositol 3-kinase, *POU5F1* = Pit-Oct-Unc domain, class 5, transcription factor 1, RFS = recurrence free survival, RR = relative risk, STAT3 = signal transducing activator of transcription 3, TCF = transcription factor 3, TSCC = tongue squamous cell carcinoma, VEGF-C = vascular endothelial growth factor, VEGFR-3 = vascular endothelial growth factor receptor-3, vs = versus, WNT = wingless/integrated.

Keywords: meta-analysis, octamer transcription factor 4, prognosis, solid tumor

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XZ and HL contributed equally to this work.

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The authors follow field-specific standards for data deposition in publicly available resource. The data analyzed during this study are available from the corresponding author on reasonable request.

The authors report no conflicts of interest.

The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Among the several deadly diseases, neoplasm is highly associated with frequent death cases. The GLOBOCAN report released on September 12, 2018 showed that 18.1 million people were diagnosed with cancers, and 9.6 million deaths occurred, this was based on studies conducted from 185 countries.[1] Although researchers have focused on exploring the diagnosis and treatment of cancers, information on the clinical outcome and prognosis of cancer patients remains scanty. Cancer-associated biomolecules participate in proliferation, invasion, and metastasis of tumors and can be utilized as biomarkers, however, only a few have been used clinically. Thus, there is an urgent need to uncover additional valuable biomolecules that can accurately predict the prognosis and biological behavior of tumors at an early stage. The relationship between stem cells and cancers has been elucidated through an in-depth exploration of stem cells. Many researchers previously hold the opinion that cancer is related to stem cells, initially referred to as cancer stem cells (CSCs). Notably, CSCs are rare in cancer tissues,[2] though they have differentiation potential and self-renewal capacity, thus play a role in recurrence, metastasis, heterogeneity, multidrug resistance, and radiation resistance of tumors.[3,4]

Octamer binding transcription factor 4 (Oct4) is encoded by the Pit-Oct-Unc domain, class 5, transcription factor (*POU5F1*) gene, which is located on chromosome 6p21 and 17B1 in human and mouse genome, respectively.[5] Oct4 has previously been expressed in the embryonic stem cells (ESCs), germline stem cells, and CSCs.[6–8] During embryo development, the expression of Oct4 impacts the differentiation and dedifferentiation of ESCs, thereby maintaining the self-renewal ability of ESCs. Besides, Oct4 is highly expressed in germ cell tumors and embryonic cell tumors thus is considered a potential molecular marker of tumor germ cells.[5] In the recent past, some studies reported that Oct4 was highly expressed in CSCs.[9,10] CSCs could evade the lethality of radiation and chemotherapeutic agents more easily compared to other tumor cells, this was attributed to self-renewal ability, metastasis to distant sites, and infinite proliferation.[11,12] Further, the study inferred Oct4-positive cancer cells likely represent CSCs.[11,12] Other investigations have revealed that Oct4 is expressed abnormally in solid cancers, such as cervical carcinoma,[13] gastric carcinoma,[14] bladder carcinoma[15] among others.

Oct4 drives stemness in CSCs and has a potential role in chemoresistance and clinical prognostic value of cancer patients.[16] Of note, Oct4 expression has been revealed to be significantly correlated with tumor size, histological differentiation, and primary tumor classification.[17,18] However, the prognostic value of Oct4 is unclear. Several literature findings reveal that low overall survival (OS) and disease-free survival (DFS)/recurrence-free survival (RFS)/progress-free survival (PFS) is related to Oct4 overexpression in many types of tumors.[19–21] For instance, reports from 2 studies indicated that Oct4 overexpression was not significantly associated with OS in advanced small cell lung cancer and tongue squamous cell carcinoma (TSCC).[22,23] In hypopharyngeal squamous cell carcinoma and oral squamous cell carcinoma (OSCC), higher expression of Oct4 indicated a better prognosis.[24,25] This prompted us to conduct a meta-analysis aimed at evaluating the prognostic value of Oct4 in solid tumors.

2. Material and methods

2.1. Search strategy and ethical approval

Here, 2 authors (XY Zhao and Y Sun) independently retrieved articles published until December 1, 2019 from electronic databases (Pubmed, Embase, and Web of Science) by conducting a systematic search. The following strategies based on keywords and Mesh terms were used to identify eligible studies: "Pou5f1 OR Oct3 OR Oct4" AND "Neoplasia OR Neoplasias OR Tumor OR Cancer OR Cancers OR Malignant Neoplasms OR Malignant Neoplasm OR Neoplasm OR Neoplasms OR Malignant OR Malignancy OR Malignancies" AND "Prognoses OR Prognostic Factors OR Factor, Prognostic OR Factors, Prognostic OR Prognostic Factor OR outcome OR survival". Furthermore, the reference lists in eligible researches were carefully scrutinized not to miss out on pertinent studies. In this study, all the materials are based on published articles, and no patients or animals involved, thus, ethics approval is not necessary.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows:

1. the research published in English
2. studies involving cohorts;
3. the value of Oct4 expression in solid tumors was shown;
4. the full text of the article can be found;
5. sufficient and effective data, such as Kaplan–Meier (KM) plot, hazard risk (HR) or relative risk (RR), or odds ratio (OR) with 95% confidence interval (CI).

The exclusion criteria were as follows:

1. repeated researches;
2. basic and animal articles;
3. conference abstracts, reviews, case reports;
4. HR/RR/OR and 95% CI could not be obtained via evaluation.

The retrieved articles were screened carefully by 2 authors (XY Zhao and H Lu). A third author (HF Wang) was consulted to solve any conflicting searches.

2.3. Data extraction

Data on the first authors name, the year of publication, region of the population enrolled, cancer type, sample size, tumor stage, the maximum month of follow-up, detection method, Oct4 (−/+), the cut-off value of Oct4 overexpression, multivariate analysis (yes/no), the source of HR/RR/OR, HR/RR/OR and corresponding 95% CIs for OS/DFS/RFS/PFS were collected independently by 3 investigators (XY Zhao, H Lu, and L Liu). When a study provided data on univariate and multivariate analysis, then, the latter would be selected considering the influence of confounding factors which potentially gave inaccurate results. Besides, if a study did not provide survival data, KM curves would be used to obtain consequences of interest in line with methods suggested by Tierney et al.[26]

2.4. Quality assessment

The Newcastle-Ottawa scale (NOS) adopted to evaluate the quality of each included study, 2 investigators (XY Zhao, Y Sun)

completed this part. A third author (HF Wang) was consulted to settle any conflicting findings. The NOS scores ranged from 0 to 9 including 3 categories for cohort researches (the selection of study groups, comparability of groups, and ascertainment of outcomes),.[27] Studies with scores ≥6 were treated to be high-quality.

2.5. Statistical analysis

The STATA version 12.0 (Stata Corporation, College Station, TX, USA) was used to analyze all statistical data. We used HRs with 95% CIs extracted from selected studies to evaluate the prognosis value. Since the outcome of the tumor is rare in all populations, differences between the OR, RR, and HR could generally be ignored, the pooled ORs or RRs with 95% CIs were suitable for the assessment thus were treated as HRs for data analysis.[28] The Chi-Squared (evaluating the P value) and I^2 tests among studies were used to evaluate heterogeneity results, this indicated significant heterogeneity if the $I^2 \geq 50\%$ and $P \leq .05$. Then, the random-effects model (the DerSimonian-Laird method) was used to analyze the pooled HRs. Otherwise, the fixed-effects model (Mante-Haenszel method) was selected ($I^2 < 50\%$ and $P > .05$). Subgroup analysis and meta-regression analysis were conducted to ascertain the source of heterogeneity. Moreover, we conducted a sensitivity analysis by independently eliminating each study. Publication bias was evaluated using Funnel plots, Eggers and Begg tests. $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics

A total of 3222 articles were retrieved from the database via the search strategy. Following the above inclusion and exclusion criteria, 36 articles[14,15,17,18,22–25,29–55]were enrolled in this

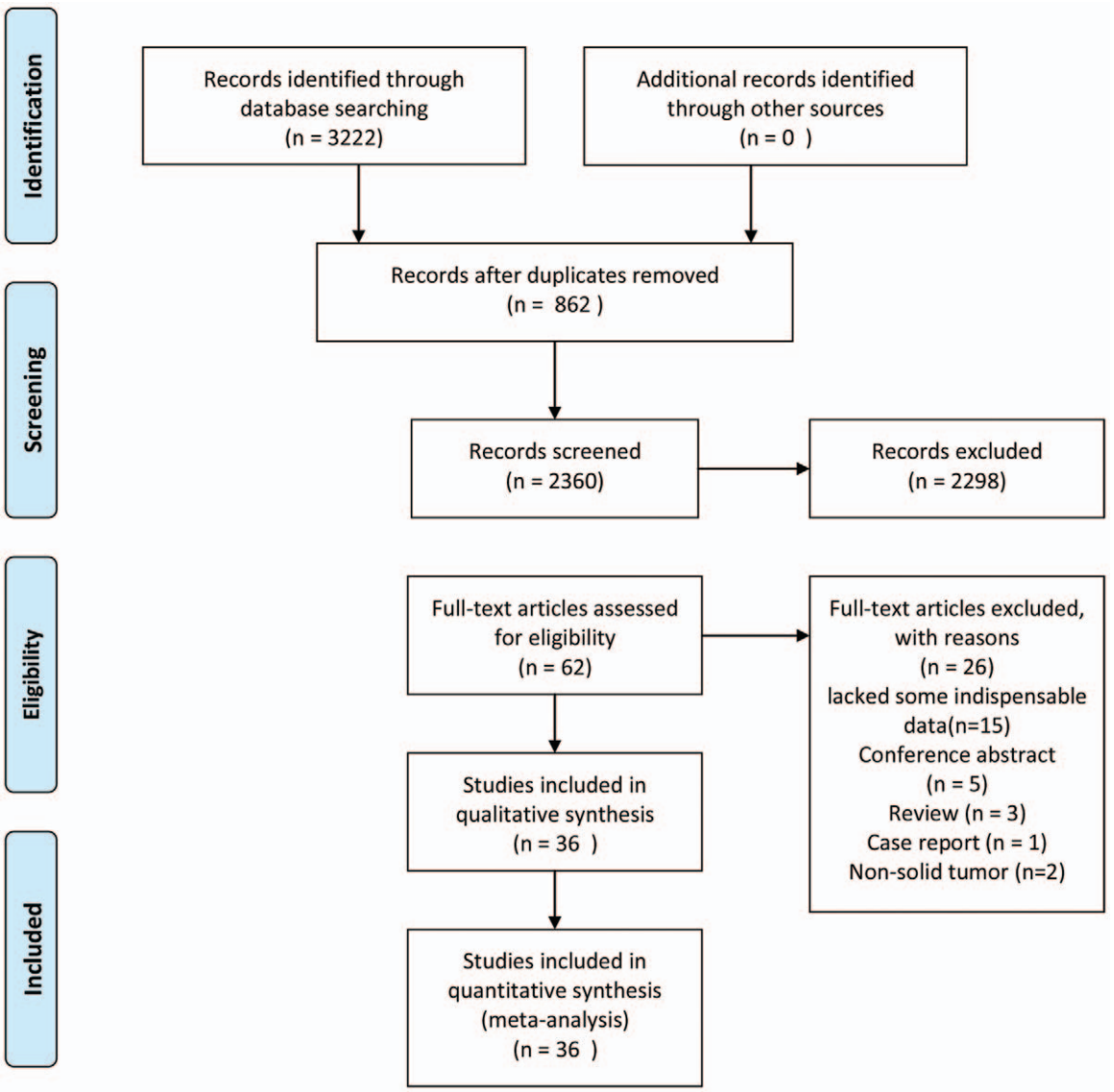

Figure 1. Flow diagram for the selection of studies in the meta-analysis.

Table 1

Characteristics of the included studies.

The first author's name	Year	Country	Cancer type	Sample size	Maximum month of follow-up	Detection method	Oct4 (−/+)	Cut-off value	NOS score	Reference number
Dong Z	2012	China	Hepatocellular carcinoma	152	60	IHC	49/103	IRS≥4	8	[16]
Matsuoka J	2012	Japan	Gastric carcinoma	290	120	IHC	161/129	IRS ≥5	8	[13]
Fu TY	2016	China	Oral squamous cell carcinoma	436	236.3	IHC	72/364	IRS ≥2	7	[24]
Ge N	2010	China	Hypopharyngeal squamous cell carcinoma	85	69.5	IHC	71/14	4≤IRS≤7	6	[23]
Gwak JM	2017	Korea	Breast cancer	319	127.68	IHC	270/49	Nuclear staining ≥10%	7	[28]
He W	2012	China	Esophageal squamous cell carcinoma	153	155	IHC	105/48	IRS≥2	7	[17]
Huang P	2011	China	Hepatocellular carcinoma	136	83	QT-PCR	44/92	NR	7	[29]
Kim BW	2015	Korea	Cervical cancer	161	179	IHC	69/92	NR	7	[12]
Kong D	2014	China	Gastric cancer	158	60	IHC	99/59	IRS=1–3	8	[30]
Huang CF	2014	China	Tongue squamous cell carcinoma	66	104	IHC	31/35	IRS≥1	8	[22]
Krogh Petersen J	2016	Denmark	Anaplastic astrocytoma	18	108	IHC	NR	NR	8	[31]
Li C	2012	China	Esophageal squamous cell carcinoma	50	80	IHC	31/19	IRS≥3	7	[32]
Li N	2014	China	Gastric cancer	69	50	IHC	32/37	IRS≥5	7	[33]
Liu CG	2011	China	Breast cancer	126	90	IHC	74/52	IRS≥1	8	[18]
Miyoshi N	2018	Japan	Colorectal cancer	95	84	QT-PCR	79/16	NR	8	[19]
Sodja E	2016	Slovenia	Small-cell lung cancer	50	32.5	QT-PCR	25/25	Threshold cycle < 38.0	6	[21]
Wang QH	2018	China	Colon cancer	70	60	IHC	44/26	IRS≥10	8	[20]
Yang Y	2014	China	Cervical cancer	630	117	IHC	341/289	IRS≥1	8	[34]
You L	2017	China	Rectal Cancer	153	62.4	IHC	85/68	HSCORE≥0.7	7	[35]
Yu B	2016	China	Renal cell carcinoma	86	43.2	IHC	57/29	Scores≥6	7	[36]
Zhang JM	2018	China	Breast cancer	127	105	IHC	95/32	HSCORE≥0.7	8	[37]
Zhang X	2013	China	Lung adenocarcinoma	126	60	IHC	35/91	Cytoplasm staining is blue, nuclear staining is green	8	[38]
Zhang XY	2010	China	Lung adenocarcinoma	134	108	IHC	35/99	Nuclear staining is green	7	[39]
Zhao RC	2016	China	Hepatocellular carcinoma	86	72	IHC	34/52	IRS≥4	8	[40]
Zou Q	2013	China	Gallbladder adenocarcinoma	108	18	IHC	48/68	IRS≥3	7	[41]
Jiang XD	2017	China	Tongue squamous cell carcinoma	51	118	IHC	24/27	IRS≥4	8	[42]
Yin X	2013	China	Hepatocellular carcinoma	57	58	QT-PCR	38/19	NR	7	[43]
Zhou J	2016	China	Bladder cancer	195	84	IHC	79/116	IRS=2–3	7	[14]
Kosaka T	2016	Japan	Prostate cancer	205	72	IHC	NR	Median score=1	7	[44]
Shen L	2014	China	Cervical Squamous Cell Carcinoma	132	85.5	IHC	56/76	NR	7	[45]
Huang P	2011	China	Bladder tumor	78	60	IHC	25/53	NR	7	[46]
Lai SC	2019	China	Hepatocellular carcinoma	144	120	QT-PCR	29/115	Tumor tissue / adjacent peritumor tissue ≥ 2	7	[47]
Roy S	2019	Indian	Oral squamous cell carcinoma	102	50	IHC	44/58	Nuclear staining	7	[48]
Zhang MX	2019	China	Intrahepatic cholangiocarcinoma	116	100	IHC	67/49	IRS≥ 8	7	[49]
Bsati G	2019	Ilam	Gastric cancer	100	50	QT-PCR	50/50	NR	7	[50]
Yang F	2018	China	HER2+ breast cancer	134	150	IHC	98/36	HSCORE≥0.7	8	[51]

HSCORE = histological score, IHC = immunohistochemistry, IRS = immunoreactive score, NOS = Newcastle-Ottawa Scale, NR = no report, Oct4 = octamer binding transcription factor 4, QT-PCR quantitative time polymerase chain reaction.

meta-analysis (Fig. 1) and had 5198 cancer patients from China, Korea, Slovenia, Iran, Denmark, and Japan, who had been diagnosed with all types of solid tumors involving hepatocellular carcinoma (HCC), gastric cancer (GC), OSCC, esophageal squamous cell carcinoma (ESCC), cervical cancer, TSCC, breast carcinoma, colorectal carcinoma, gallbladder carcinoma, lung carcinoma, bladder carcinoma, anaplastic astrocytoma, prostate cancer, renal cell carcinoma, and so on. The key characteristics of the 36 articles are summarized in Table 1. Notably, 31 articles reported that Oct4 expression was associated with OS, whereas 12 articles revealed that Oct4 expression was correlated with DFS/RFS/PFS. The majority of studies reported HRs directly, however, in 2 studies, HRs were indirectly estimated by the KM survival curves. The NOS scores of 36 studies ranged from 6 to 9, an indication that each study adopted a reliable methodology thus was suited for further analyses.

3.2. High expression of Oct4 for OS and DFS/RFS/PFS

Upon analysis of data retrieved from 31 articles with a total of 4395 patients, we revealed that Oct4 overexpression was

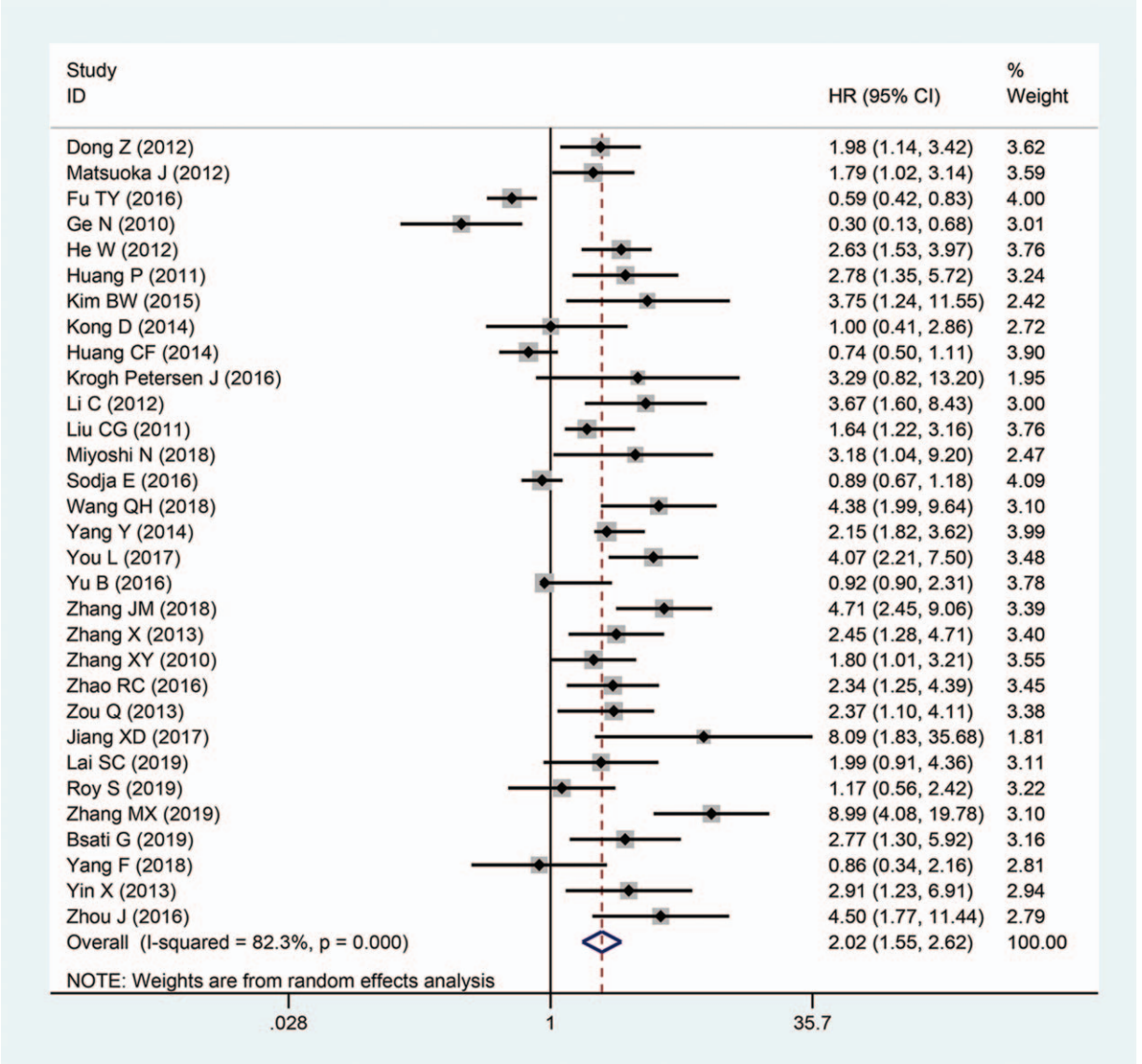

Figure 2. Forest plots showing the relationship between Oct4 and OS.

remarkably associated with worse OS in patients with solid tumors. The pooled HR was 2.02 (95% CI: 1.55–2.62, $P < .001$) (Fig. 2). We adopted a random-effects model to pool HRs because of existing apparent statistical heterogeneity ($I^2 = 82.3\%$, $P < .001$) in these studies. However, due to the small number of studies on the relationship between Oct4 and DFS/RFS/PFS, DFS was combined with RFS/PFS and defined as the "DFS/RFS/PFS" group. Of note, 12 studies with 1569 patients reported on the association of Oct4 overexpression with DFS/RFS/PFS. In these studies, there was no apparent heterogeneity ($I^2 = 15.60\%$, $P = .291$), thus we applied the fixed-effects model, which revealed that high expression of Oct4 was remarkably associated with to poor DFS/RFS/PFS in patients with solid tumors. The pooled HR was 2.34 (95% CI: 1.88–2.92, $P < .001$), (Fig. 3).

3.3. Subgroup and meta-regression analyses

On account of the conspicuous heterogeneity in these studies, we conducted subgroup analysis via the random-effects model for OS considering the following parameters: tumor types, digestive system tumor, sample size, the maximum month of follow-up, and the source of HR. In accordance with tumor type, the elevated Oct4 levels demonstrated a worse prognosis in patients with HCC (pooled HR: 2.30; 95% CI: 1.69–3.12; $P < .001$), GC (pooled HR: 1.81; 95% CI: 1.12–2.95; $P = .016$), ESCC (pooled HR: 2.85; 95% CI: 1.89–4.32; $P < .001$), cervical cancer (pooled HR: 2.26; 95% CI: 1.63–3.15; $P < .001$) and colorectal cancer (pooled HR: 4.00; 95% CI: 2.57–6.22; $P < .001$) (Fig. 4). Nevertheless, no significant relationship was found between the overexpression of Oct4 and OS in breast cancer, TSCC, OSCC, and lung carcinoma. Other outcomes of subgroup analysis are highlighted in Table 2. All frost plots of different subgroups on the association of Oct4 overexpression with OS are displayed in Fig. 5. Considering the significant heterogeneity, we performed a meta-regression analysis for OS. In general, the differences were not statistically significant in OS as shown in Table 2.

Despite not observing obvious statistical heterogeneity, we conducted subgroup analysis to assess each subgroup of pooled

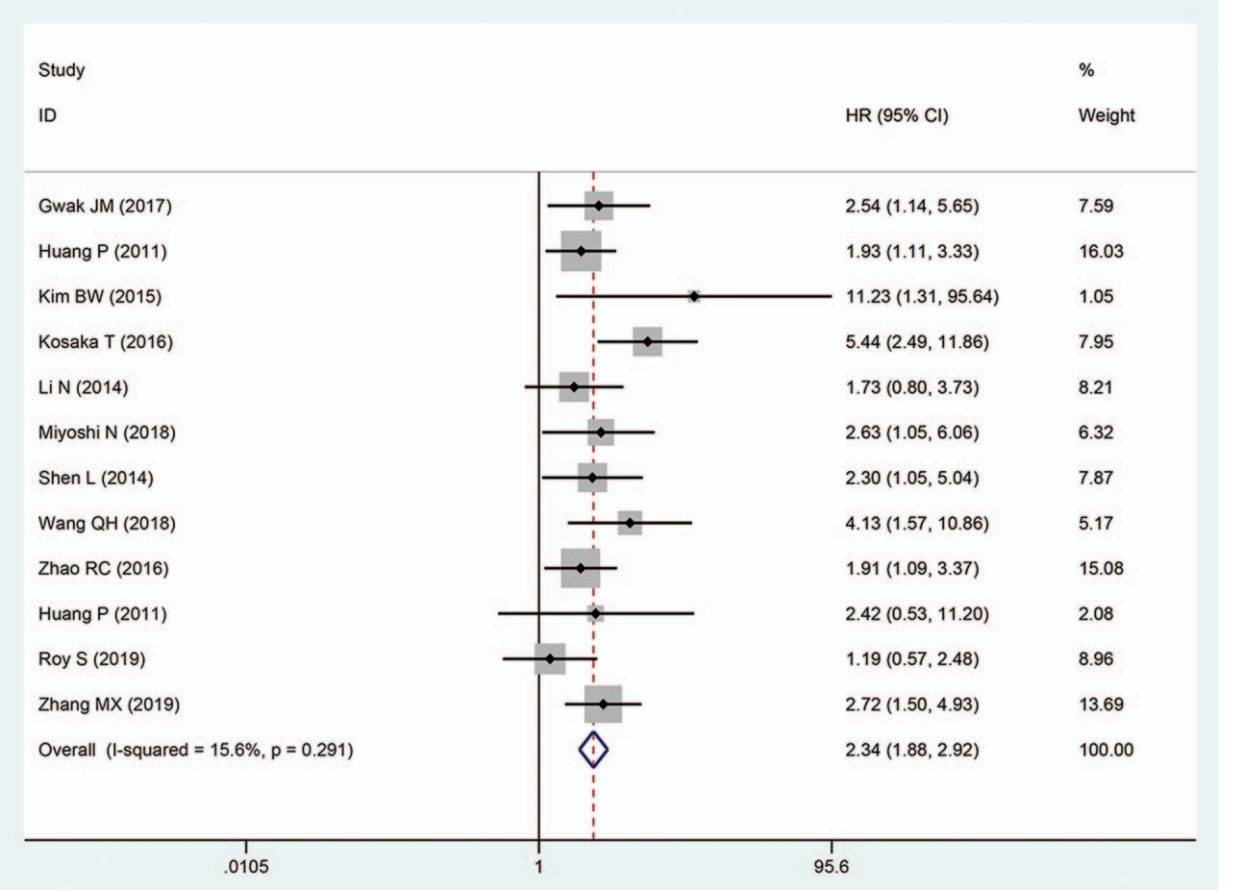

Figure 3. Forest plots showing the relationship between Oct4 and DFS/RFS/PFS.

HRs using the fixed-effects model considering the parameters including tumor type, digestive system tumor, sample size, and maximum follow-up period (months). Results indicated that patients overexpressing Oct4 had poorer DFS/RFS/PFS, including HCC (pooled HR: 1.92; 95% CI: 1.30–2.85; $P = .001$), cervical cancer (pooled HR: 2.77; 95% CI: 1.33–5.79; $P = .007$), colorectal cancer (pooled HR: 3.22; 95% CI: 1.68–6.16; $P < .001$), others (pooled HR: 2.39; 95% CI: 1.74–3.27; $P < .001$). Detailed results are displayed in Table 3, whereas all frost plots of subgroup analysis for DFS/RFS/PFS are shown in Fig. 6. Moreover, the relationships between Oct4 expression and clinicopathological features were assessed in HCC and GC. The results were shown in Table 4. The level of Oct4 expression was significantly related to the lymph node metastasis and vascular invasion in GC.

3.4. Sensitivity analysis and publication bias

Here, we conducted a sensitivity analysis by sequentially eliminating studies independently. Any study could not influence the outcomes of the relationship between OS and DFS/RFS/PFS (Fig. 7). The funnel plots for OS and DFS/RFS/PFS (Fig. 8) seemed asymmetric, although the Begg test (OS: $P = .139$; DFS/RFS/PFS: $P = 1.000$) and Egger's tests (OS: $P = .116$; DFS/RFS/PFS: $P = .142$) were not statistically significant. Consequently, the trim-and-filled model was introduced to neutralize potential bias, notably the correlation of Oct4 with survival was statistically significant (OS, HR: 1.59, 95% CI: 1.24–2.06, $P < .0001$; DFS/PFS/RFS, HR: 2.301, 95% CI: 1.849–2.864, $P < .0001$). According to the Cochran manual, the potential cause of funnel plot asymmetry in this study was selection bias, which includes publication bias and selective result reports, the low methodological quality which results in a false exaggeration of efficacy in small sample studies, true heterogeneity, human factors, and opportunities.

4. Discussion

Cancer is lethal and poses a threat to mankind. Exploring more cancer markers is highly crucial for the diagnosis and prognosis of cancer. Notably, CSCs account for only a small fraction of cells in tumors and have self-renewal ability, producing multiple cell progeny thus have been revealed to play a role in metastasis, invasion, therapy resistance, and recurrence.[3,9,56] Additionally, CSCs release a variety of stemness molecules, among them, Oct4, SRY-related HMG-box gene 2, Nanog, among others. Of note, Oct4, in particular, has been reported to induce a variety of CSCs thus exerts potential regulatory roles.[57,58] Therefore, we speculated that CSC surface markers could serve as a biomarker for predicting the prognosis of cancer, this provides molecular targeted therapy for a variety of cancers using the therapeutic antibodies specific to CSC surface markers.

Oct4, as a CSCs marker, exhibits "stemness" characteristic, which is linked to a variety of biological behaviors and can cause cell immortality or account for the self-renewal ability, making

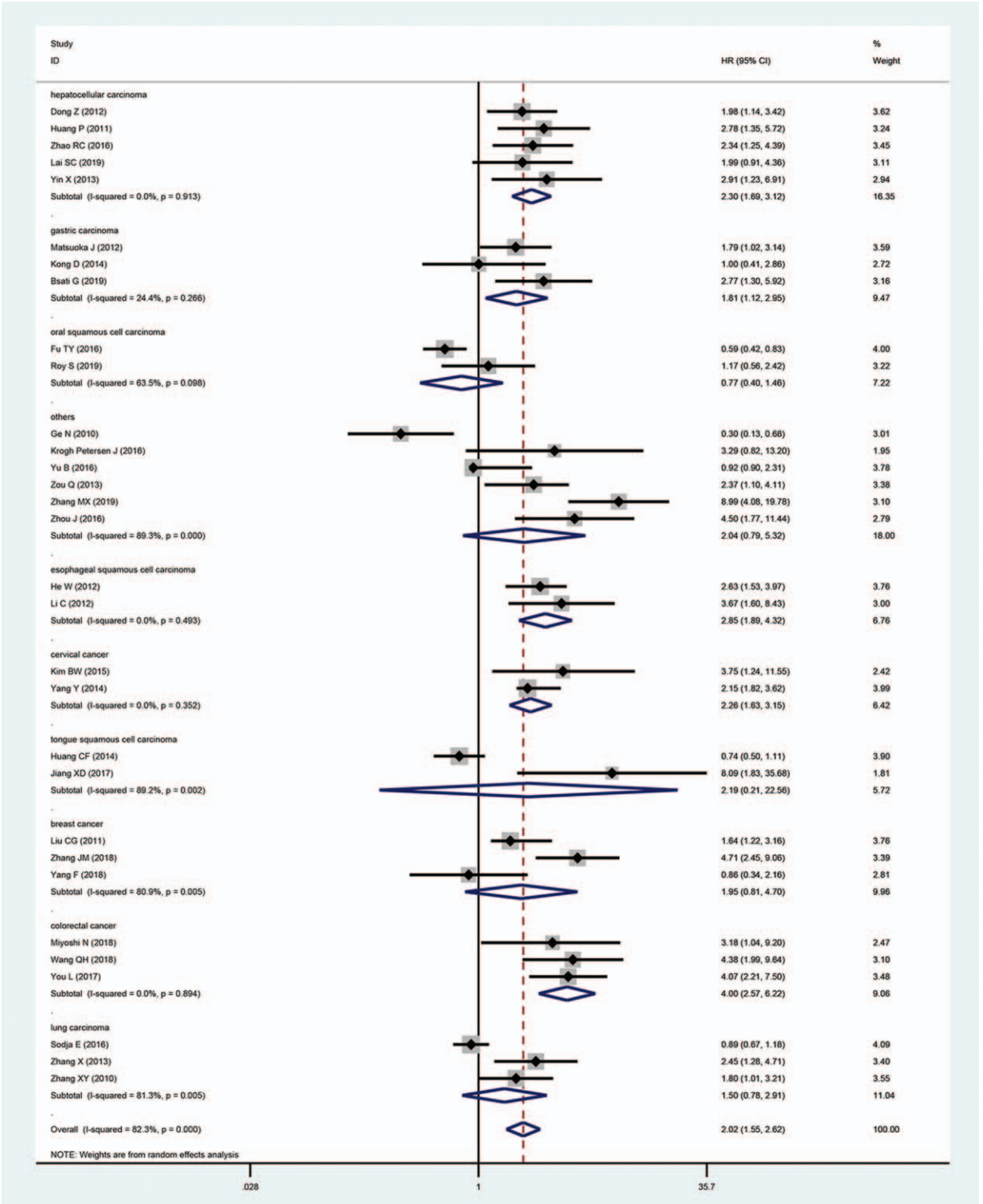

Figure 4. Forest plots to assess the relationship between Oct4 and OS based on the subgroup of tumor type.

cancer cells invasive.[23] Some studies indicated that high expression of Oct4 was observed in multiple human solid tumors. Based on these reports, we speculated that Oct4 could be utilized as a putative prognostic marker for predicting the prognosis of solid tumors. Furthermore, Oct4 had been confirmed to participate in initiation, chemoresistance, radiation resistance, metastasis, and invasion of solid tumors via cancer cell proliferation, migration, epithelial-mesenchymal transition, anti-apoptosis, and dedifferentiation,[59–62] this led to poor prognosis of tumor patients.

In addition, Oct4 function either directly or indirectly in the biological behavior of tumors. For instance, Oct4 can play a role

Table 2

Pooled HR for OS based on subgroup analysis.

Subgroup	Number of studies	Number of patients	Random effects model		*P* value of pooled HR	Heterogeneity		*P* value of meta-regression
			Pooled HR	95%CI		I2(%)	*P* value	
Overall	31	4395	2.02	1.55–2.62	<.001	82.3	<.001	
Tumor type								.401
HCC	5	575	2.30	1.69–3.12	<.001	0.0	.913	
GC	3	548	1.81	1.12–2.95	.016	24.4	.266	
OSCC	2	538	0.77	0.40–1.47	.420	63.5	.098	
Others	6	608	2.04	0.79–5.3	.143	89.3	<.001	
ESCC	2	203	2.85	1.89–4.32	<.001	0.0	.493	
Cervical cancer	2	791	2.26	1.63–3.15	<.001	0.0	.352	
TSCC	2	117	2.19	0.21–22.56	.511	89.2	.002	
Breast cancer	3	387	1.95	0.81–4.70	.136	80.9	.005	
Colorectal cancer	3	318	4.00	2.57–6.22	<.001	0.0	.894	
Lung carcinoma	3	310	1.50	0.78–2.91	.227	81.3	.005	
Digestive system tumor								.839
Yes	20	2608	2.08	1.43–3.02	.001	84.5	<.001	
No	11	1787	1.91	1.31–2.77	<.001	78.6	<.001	
Sample size								.871
≥120	16	3255	2.00	1.30–3.09	.002	84.6	<.001	
<120	15	1140	2.05	1.48–2.84	<.001	79.1	<.001	
Maximum months of follow-up								.323
≥60	25	3892	2.17	1.59–2.95	<.001	82.7	<.001	
<60	6	503	1.50	0.96–2.34	.077	72.7	.003	
Source of HR								.292
Report	29	4143	1.95	1.48–2.55	<.001	82.7	<.001	
Sc	2	252	3.56	1.89–6.70	<.001	0.0	.501	

CI = confidence interval, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, HR = hazard ratio, I^2 = Chi-Squared, OS = overall survive, OSCC = oral squamous cell carcinoma, Sc = survival curve, TSCC = tongue squamous cell carcinoma.

in chemoresistance via multiple signaling pathways such as WNT/Notch-β-catenin-TCF-Oct4, PI3K-AKt-FOXC1-β-catenin-TCF-Oct4, HIF2α-NF-κB-Oct4, among others.[16] Interestingly, in HCC, Oct4 has been revealed to confer chemoresistance on HCC cells through protein kinase B Akt-mediated upregulation of ATP-binding cassette transporter G2, while it promoted cancer cell proliferation and migration via the survivin/STAT3 pathway, leading to poor prognosis.[63,64] Moreover, a study reported that Oct4 played an important role in radiation resistance by promoting the epithelial-mesenchymal transformation process in rectal carcinoma.[65] Elsewhere, Li et al demonstrated that Oct4 was essential in an antiapoptotic behavior of chemo-resistant colorectal cancer cells enriched for CSCs, whose effects were associated with STAT3/Survivin.[66,67] Also, Oct4 promoted tumorigenesis by inhibiting apoptosis in cervical carcinoma, implicating it as a key molecule involved in the inhibition of tumor cell apoptosis.[66,67] Additional findings revealed that greatly induced the transition of epithelial-mesenchymal via VEGF-C/VEGFR-3 signal pathway, thus contributed to metastasis.[68] Conversely, the expression of programmed death-ligand 1 in tumor cells was induced by activating Oct4 signaling to play a role in immune evasion, this suggested that CSCs might participate in tumor metastasis through immune evasion.[69] Another investigation showed that Oct4 could regulate the stability of mitosis and inactivate retinoblastoma tumor suppressor pathway, thus enhancing the aggressiveness of ovarian cancer.[70] Besides, Kumar et al observed that Oct4-mediated tumor cell dedifferentiation and potentially played a key role in tumor progression.[57] On the other hand, Oct4 knockdown could significantly reduce migration and progression in pancreatic cancer and colorectal cancer and cause breast CSC-like cell apoptosis, this strongly suggested that targeting Oct4 might offer vital clinical applications in cancer therapy.[62,71,72] Conclusively, these findings demonstrated that Oct4 remarkably impacts the process of tumor initiation, development, and progression.

Moreover, findings from our study implicated Oct4 as a detrimental prognostic marker for malignant tumors. High expression of Oct4 was dramatically associated with worse OS and DFS/RFS/PFS in patients with solid tumors. Besides, elevated Oct4 levels indicated worse prognosis in patients with HCC, ESCC, GC, cervical cancer, and colorectal cancer. These observations suggested that Oct4 may be utilized as a potential prognostic marker and therapeutic target for most solid tumors. Notably, only 2 studies revealed that patients exhibiting high expression of Oct4 survived longer and had a lower recurrence rate in hypopharyngeal squamous cell carcinoma, and OSCC patients expressing high levels of Oct4 had better cumulative OS, the underlying mechanism is unclear, thus, additional in-depth researches are needed.[24,25] Nevertheless, when the 2 above-mentioned items were excluded from the analysis, the association between Oct4 and OS in solid tumor patients did not change (excluded: pooled HR: 2.23; 95% CI: 1.75–2.84; $P < .001$, included: pooled HR: 2.02, 95% CI: 1.55–2.62, $P < .001$).

There were a few limitations that should be addressed in our study. First, the number of published articles on each type of tumor was relatively small, such as for TSCC, bladder cancer, gastric cancer among others, therefore, the included studies were mixed and analyzed in order to assess the relationship between the Oct4 expression and solid tumors, which might be a

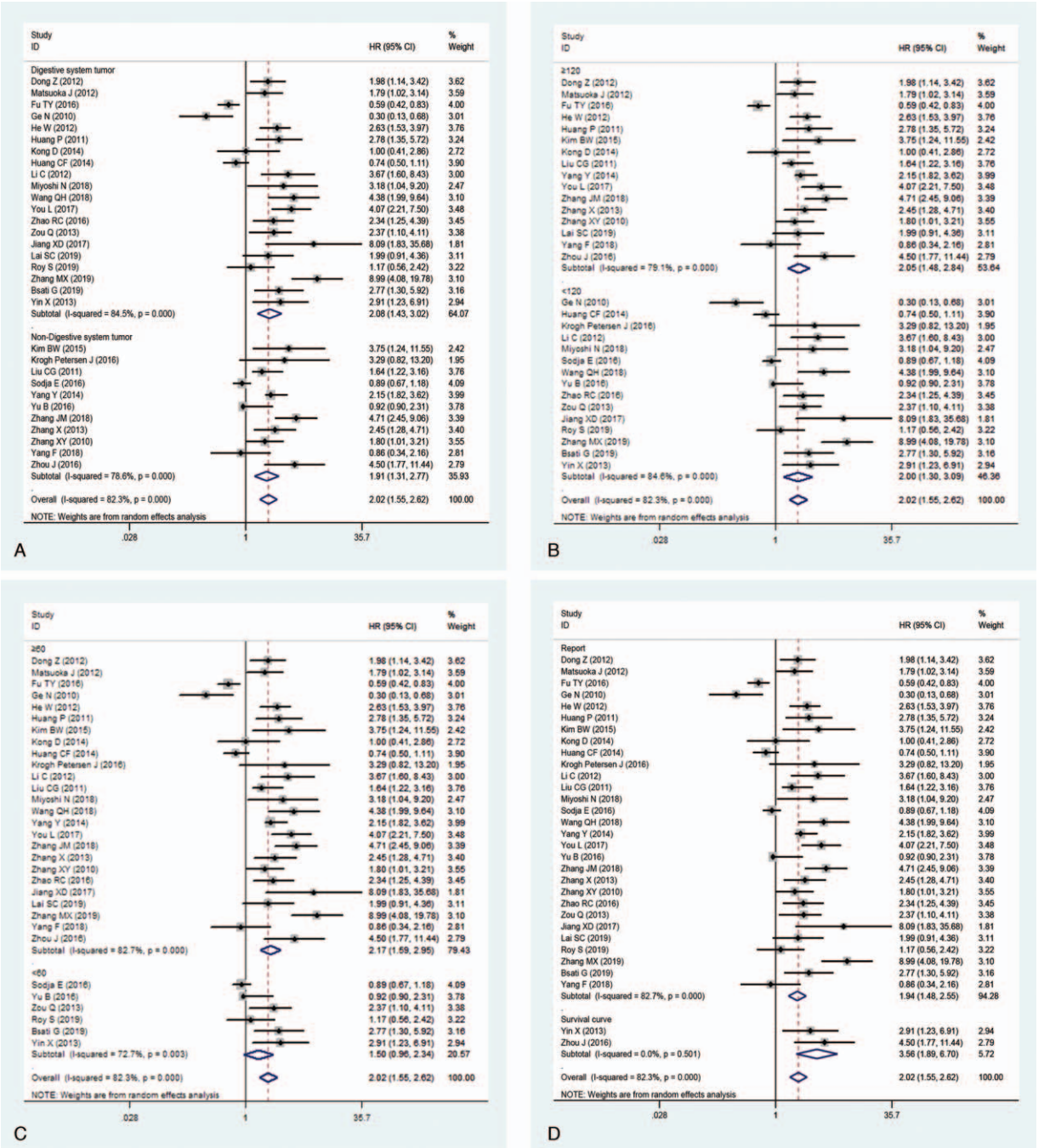

Figure 5. Subgroup analysis of OS. A, digestive system tumor; B, sample size; C, maximum month of follow-up; D, the source of HR.

limitation in our study. In the future, we will also analyze and assess the role of Oct4 in a particular type of cancer as the number of studies increases. Second, survival curves were used to evaluate HRs in 2 of the included studies, this possibly affected the precision of results. Third, in this study, a large number of patients were Asian, thus, the results may not be applicable to other ethnic groups and might not be generalized and be valid globally. More assessments on the relationship between the expression level of Oct4 and prognosis in cancer patients of other ethnic groups are needed to further validate our findings. Fourth, various cut-off values of Oct4 were applied in each study. Fifth, different subtypes of Oct4 might lead to varying prognosis for cancer patients, however, in the included studies, no subtypes were distinguished. Therefore, these data could not be extracted. Finally, the articles included were all in English, which might result in potential language bias.

5. Conclusion

This study provides the first report that sheds light on the prognostic role of elevated Oct4 expression in multiple solid tumors. Oct4 was revealed as a potential novel biomarker and a

Table 3

Pooled HR for DFS/RFS/PFS based on subgroup analysis.

Subgroup	Number of studies	Number of patients	Fixed effects model		*P* value of pooled HR	Heterogeneity	
			Pooled HR	95%CI		I^2(%)	*P* value
DFS/RFS/PFS			2.34	1.88–2.92	<.001	15.6	0.291
Tumor type							
Others	6	889	2.39	1.74–3.27	<.001	42.0	.125
HCC	2	222	1.92	1.30–2.85	.001	0.0	.984
Cervical cancer	2	293	2.77	1.33–5.79	.007	46.0	.174
Colorectal cancer	2	165	3.22	1.68–6.16	<.001	0.0	.496
Digestive system tumor							
Yes	7	674	2.07	1.60–2.68	<.001	0.0	.47
No	5	895	3.27	2.14–5.04	<.001	4.9	.379
Sample size							
≥120	5	953	2.70	1.91–3.81	<.001	37.6	.171
<120	7	616	2.12	1.60–2.82	<.001	0.0	.477
Maximum months of follow-up							
≥60	10	1398	2.59	2.04–3.30	<.001	0.0	.486
<60	2	171	1.42	0.84–2.42	.193	0.0	.489

CI = confidence interval, DFS = disease-free survival, HCC = hepatocellular carcinoma, HR = hazard ratio, I^2 = Chi-Squared, PFS = progress-free survival, RFS = recurrence-free survival.

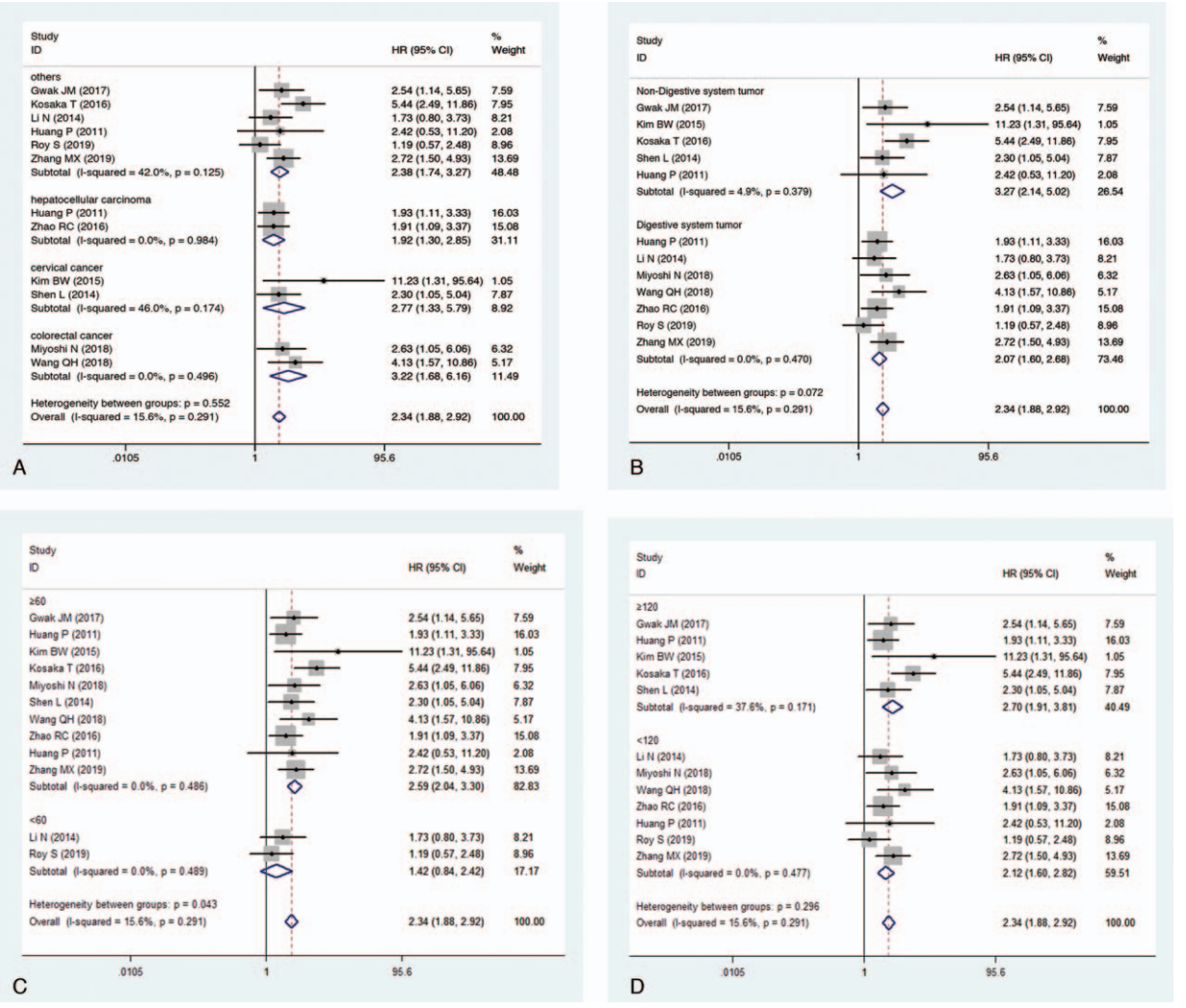

Figure 6. Subgroup analysis of DFS/RFS/PFS. A, type of tumor; B, digestive system tumor; C, maximum month of follow-up; D, sample size.

Table 4

Results of meta-analysis of increased Oct4 expression and clinicopathological features of HCC and GC.

Clinicopathological features	Number of studies	Number of patients	Fixed effects model		*P* value of pooled OR	Heterogeneity	
			Pooled OR	95%CI		I^2(%)	*P* value
HCC							
Age (>50 vs ≤50)	3	345	1.723	0.227–2.419	.359	0	.385
Gender (female vs male)	4	431	1.458	0.165–2.751	.565	0	.993
Tumor Size (>5cm vs ≤5cm)	4	431	1.236	0.469–3.734	.386	0	.528
Liver cirrhosis (yes / no)	4	431	1.099	0.447–1.751	.235	0	.986
AFP (>400 vs≤400)	2	222	1.087	0.635–2.783	.572	5.8	.143
HBsAg (positive vs negative)	4	431	1.364	0.569–2.791	.069	0	.876
Relapse (yes vs no)	2	238	3.248	1.163 -7.658	.149	0	.469
Vascular invasion (yes vs no)	2	193	1.506	0.751–3.764	.191	0	.479
Tumor encapsulation (incomplete vs complete)	3	279	0.895	0.247- 1.543	.685	0	.808
GC							
Lymph node metastasis (yes vs no)	2	448	2.785	1.238–4.765	<.001	0	.852
Vascular invasion (yes vs no)	2	448	3.002	1.597–2.824	.001	0	.843
Gender (female vs male)	2	227	0.783	0.216–3.895	.792	0	.368

AFP = alpha fetal protein, GC = gastric cancer, HCC = hepatocellular carcinoma, I^2 = Chi-Squared, Oct4 = octamer binding transcription factor 4, OR = odds ratio, vs = versus.

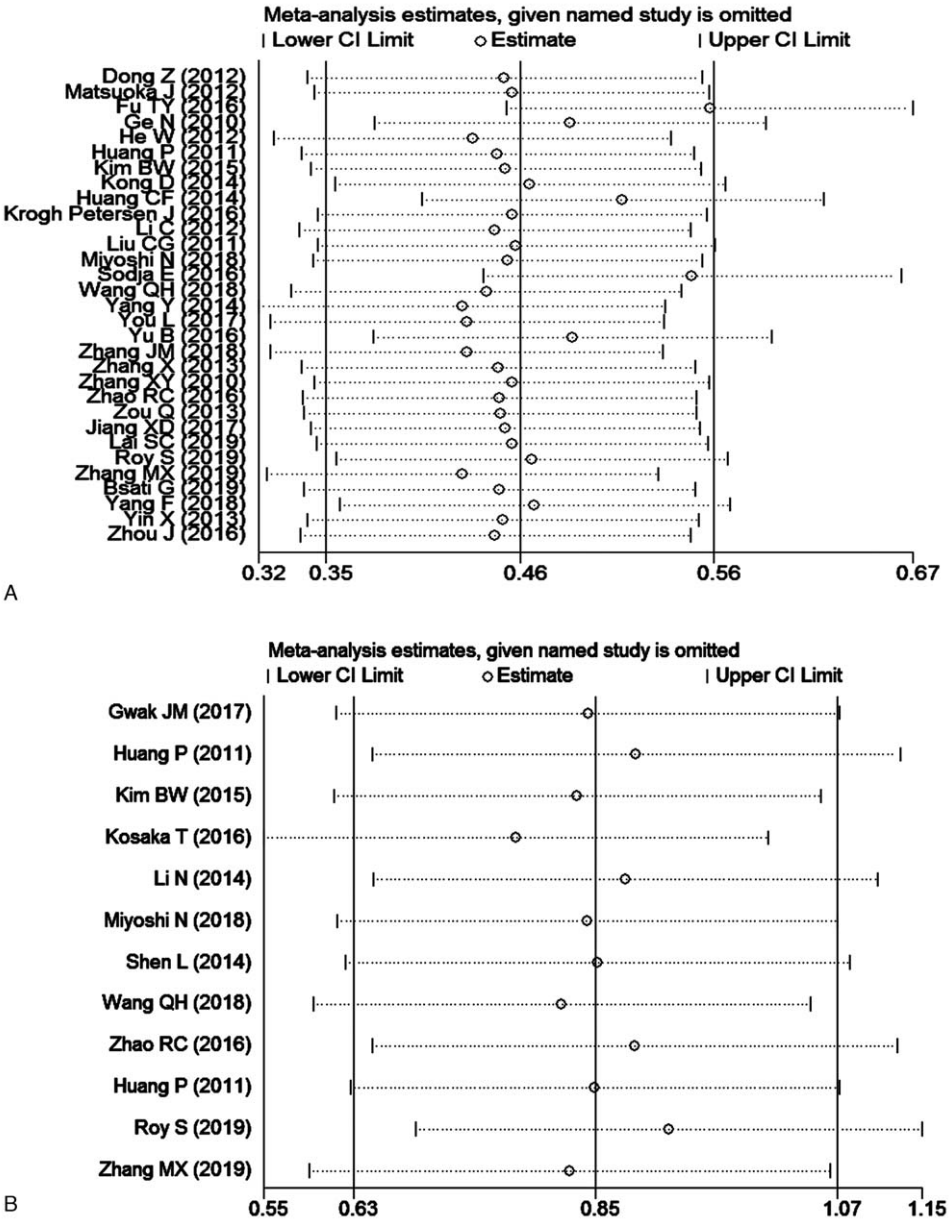

Figure 7. Sensitivity analysis of the meta-analysis. A, OS; B, DFS/RFS/PFS.

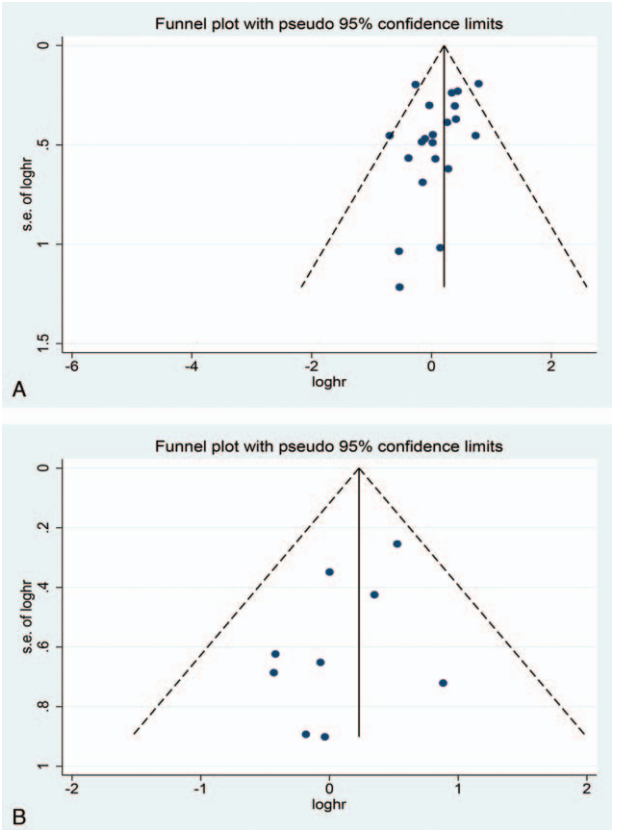

Figure 8. Funnel plot for publication bias assessment. A, OS; B, DFS/RFS/PFS.

potential therapeutic target for cancer patients. Notably, overexpression of Oct4 is linked to poor prognosis in patients with solid tumors, among them, HCC (OS, DFS/RFS/PFS), ESCC (OS), GC (OS), cervical cancer (OS, DFS/RFS/PFS), and colorectal cancer (OS, DFS/RFS/PFS). However, additional high-quality studies are needed to explore the relationship between Oct4 expression and prognosis in patients with each type of tumor.

Author contributions

Data curation: Xiaoyan Zhao, Hui Lu.
Funding acquisition: Huafang Wang.
Methodology: Li Liu, Huafang Wang.
Writing – original draft: Xiaoyan Zhao, Hui Lu.
Writing – review & editing: Xiaoyan Zhao, Yan Sun, Li Liu, Huafang Wang.

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