Prognostic value of octamer binding transcription factor 4 for patients with solid tumors
A meta-analysis

Xiaoyan Zhao, MD\textsuperscript{a}, Hui Lu, MD\textsuperscript{a}, Yan Sun, MD\textsuperscript{b}, Li Liu, PhD\textsuperscript{c}, Huafang Wang, MD, PhD\textsuperscript{a,\textsuperscript{*}}

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, CSCCs = 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-\alpha = hypoxia-inducible factor-alpha, HRs = hazard ratios, KM = Kaplan–Meier, NF-\kappaB = 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, OSCI = 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
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.\[11\] 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 S, transcription factor (POUSF1) 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) are 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

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**Figure 1.** Flow diagram for the selection of studies in the meta-analysis.
Table 1
Characteristics of the included studies.

| Author          | 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]             |
| Gnai 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]             |
| Soda E          | 2016   | Slovenia  | Small-cell lung cancer                | 50          | 32.5                        | QT-PCR           | 25/25      | Threshold cycle < 38.0 | 6 | [21]             |
| Wang GH         | 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              | 57/20      | 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      | 152         | 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                          | 116         | 100                         | IHC              | 67/49      | IRS ≥ 8      | 7          | [49]             |
| Boati 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
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 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 forest 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
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 forest 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, \( P < .0001 \); DFS/PFS/RFS: \( P < .0001 \)). 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...
cancer cells invasive.\textsuperscript{[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.\textsuperscript{[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
in chemoresistance via multiple signaling pathways such as WNT/Notch-β-catenin-TCP-Oct4, PI3K-Akt-FOXC1-β-catenin-TCP-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.\[13,64\] 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 inactive 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.\[17\] 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/PPS 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
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 | Pooled HR 95%CI | P value of pooled HR | I² (%) | 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, I² = Chi-Squared, PFS = progress-free survival, RFS = recurrence-free survival.

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**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 | Heterogeneity |
|----------------------------------------------|-------------------|--------------------|---------------------|---------------|
|                                              |                   |                    | Pooled OR           | 95% CI        | P value of pooled OR | I² (%) | 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       | .988    |
| AFP (>400 vs ≤400)                            | 2                 | 222                | 1.087               | 0.635–2.783   | .572                     | 5.8     | .143    |
| HBsAg (positive vs negative)                  | 4                 | 431                | 1.364               | 0.629–2.791   | .069                     | 0       | .878    |
| Relapse (yes vs no)                           | 2                 | 238                | 3.245               | 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               | 1.597–5.824   | .001                     | 0       | .843    |
| Gender (female vs male)                       | 2                 | 227                | 0.783               | 0.216–2.895   | .782                     | 0       | .388    |

AFP = alpha fetal protein, GC = gastric cancer, HCC = hepatocellular carcinoma, I² = 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.
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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Figure 8. Funnel plot for publication bias assessment. A, OS; B, DFS/RFS/PFS.
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