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Review Article

Prognostic significance of FOXM1 in digestive system cancers: a systematic review and meta-analysis

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Abstract: Forkhead box M1 (FOXM1) has been revealed to play a regulatory role in tumor progression. The overexpression of FOXM1 is associated with the poor prognosis of patients with various types of neoplasms. A meta-analysis was conducted to assess the relationship between FOXM1 and several critical parameters in patients with digestive system cancer (DSC). Observational studies (up to January 2016) from PubMed, Embase and the Cochrane Library were searched. The hazard ratios (HRs) and relative risks (RRs) with 95% confidence intervals (CIs) measured the correlation between FOXM1 and the clinical parameters of the patients. Random or fixed effects models were applied for the analysis according to the value of the I^2 statistic. Cross-trial heterogeneity was quantified by the Q and I^2 statistics, while Begg's and Egger's tests were utilized to evaluate the publication bias. Eleven studies with 1512 cases of DSC were found using the search strategy and the inclusion criteria. When the high expression of FOXM1 was compared with the low expression of FOXM1 in tumors, the pooled HR of the overall survival was 2.01 (95% CI = 1.70-2.36, P < 0.001). Our analysis also revealed that the overexpression of FOXM1 tended to be associated with more lymph node metastasis (RR = 1.26, 95% CI = 1.09-1.45, P = 0.006), more vascular invasion (RR = 1.64, 95% CI = 1.09-2.47, P = 0.017) and higher clinical stage (RR = 1.70, 95% CI = 1.20-2.40, P = 0.003). Our analysis was determined to be stable after a sensitivity analysis and publication bias tests. In conclusion, the upregulated expression of FOXM1 in patients with DSC is significantly related to poorer survival, earlier lymph node metastasis, more severe vascular invasion and higher clinical stage.

Keywords: FOXM1, digestive system cancer, tumor prognosis, meta-analysis

Introduction

Digestive system cancers (DSCs) are the most common malignant tumors, and they account for nearly 30% of all cancers [1]. Approximately 300,000 new cases of DSC are expected with 150,000 estimated deaths for both sexes in the United States every year [2]. Colorectal cancer (CRC), gastric cancer (GC), esophageal cancer (EC), pancreatic cancer (PC), hepatocellular carcinoma (HCC) and gallbladder cancer, which are all considered to be DSCs, have high morbidity and mortality rates [2]. Therefore, to discover effective treatments and to improve the prognosis of DSC, a deep understanding of the mechanisms of cancer progression are needed, and efforts to develop new prognostic markers are indispensable.

Forkhead box M1 (FOXM1) is a member of the forkhead transcription factor family that has a winged-helix DNA-binding domain termed the forkhead box [3]. FOXM1 has been reported to be a critical regulator of both G1 to S and G2 to M phase transitions in the cell-cycle and mitotic-spindle integrity [4, 5]. Teh et al. and Gemenetzidis et al. found that aberrant FOXM1 expression was associated with oncogenesis and genomic instability and that this protein acted as a cancer-initiating factor [6, 7]. FOXM1 has been described as a major oncogenic transcription factor that participates in tumor initiation, promotion and progression [5, 8]. The high expression of FOXM1 is involved in resistance to chemotherapy, including resistance to platinum drugs [9, 10]. Accumulating evidence has revealed that FOXM1 is a valuable predictor of

overall survival, tumor differentiation, staging and other clinical parameters in patients with DSC [10-12].

Although numerous studies have indicated that FOXM1 overexpression is related to poor clinical condition and poor prognosis in patients with DSC, no systematic evidence has identified the prognostic and clinical significance of FOXM1 in DSC. In this study, we conducted a meta-analysis to evaluate the correlation of FOXM1 and clinical parameters of DSC, with the aim to decrease deficiencies in this research area and to reveal the potential predictive value of FOXM1.

Materials and methods

Literature retrieval

We collected studies that were published in PubMed, Embase, and the Cochrane Library as well as relevant trials from the references of selected studies (up to January 2016). The following search terms were used: "digestive system cancer", "digestive system tumor", "digestive system neoplasm", "gastroenterological cancer", "gastroenterological tumor", "gastroenterological neoplasm", "gastrointestinal cancer", "gastrointestinal tumor", "gastrointestinal neoplasm", "esophageal cancer", "gastric cancer", "hepatocellular carcinoma", "gallbladder cancer", "pancreatic cancer", "colon cancer", "rectal cancer" or "colorectal cancer" combined with "Forkhead box M1", "FOXM1", "FOXM1a", "FOXM1b" or "FOXM1c". The language of the publications was restricted to English. We carefully browsed and retrieved potentially eligible studies and references that met the inclusion criteria.

Literature inclusion and exclusion criteria

Studies that fulfilled the following criteria were considered: (1) observational studies that investigated the correlation between digestive system tumors and FOXM1; (2) FOXM1 expression was divided into two distinguishing grades: "positive" and "negative" or "high" and "low" in the original data regardless of the detection methods of FOXM1; (3) the hazard ratio (HR) and relative risk (RR) with a 95% confidence interval (CI) were provided or could be calculated. Exclusion criteria were accordingly established: (1) case reports, reviews or meta-analyses; (2) duplicate or overlapping publications.

Qualitative assessment

The methodological quality of each included study was evaluated according to the nine-star Newcastle-Ottawa Scale (NOS) for non-RCT studies [13]. The selection of the study groups (0-4 points), the adjustment for known confounding factors (0-2 points) and the ascertainment of the outcome of interest (0-3 points) were three major aspects used in the calculation of the quality score of the included studies. We classified the studies into three quality grades as follows: low-(0-3 points), moderate-(4-6 points) or high-(7-9 points) quality by calculating the total scores.

Data extraction

Two reviewers independently assessed all eligible publications. Disagreements were resolved by discussion with a third reviewer. Extracted data included the first author, year of publication, country of study, cancer type, duration of the study, number of patients, detection method of FOXM1, and study design as well as the survival, tumor size, histological differentiation, lymph node metastasis, vascular invasion and clinical stage. For each study, we extracted HRs (95% CIs) of the overall survival time of the cancer patients. The RRs (95% CIs) of other clinical parameters were calculated with the data from the included articles.

Statistical analysis

We used the pooled RR with 95% CI to quantitatively assess the association between FOXM1 expression and some of the important clinical parameters in patients with DSC, whereas the pooled HR with 95% CI was utilized to evaluate the survival time of the patients. If no significant heterogeneity ($I^2 < 50\%$) was found among studies, a fixed effects model was used to combine the individual HR estimates; otherwise, a random effects model was chosen. The Q and I^2 statistics were applied to quantify the between-trial heterogeneity [14]. For the Q statistic, a P value of < 0.05 was considered to represent statistically significant heterogeneity. An I^2 value < 25% indicates a low level of heterogeneity, while values of 25%-50% and ≥ 50% represent moderate and high levels of heterogeneity, respectively [15]. We removed each study, in turn, to perform the sensitivity analysis and then tested the reliability of the overall pooled

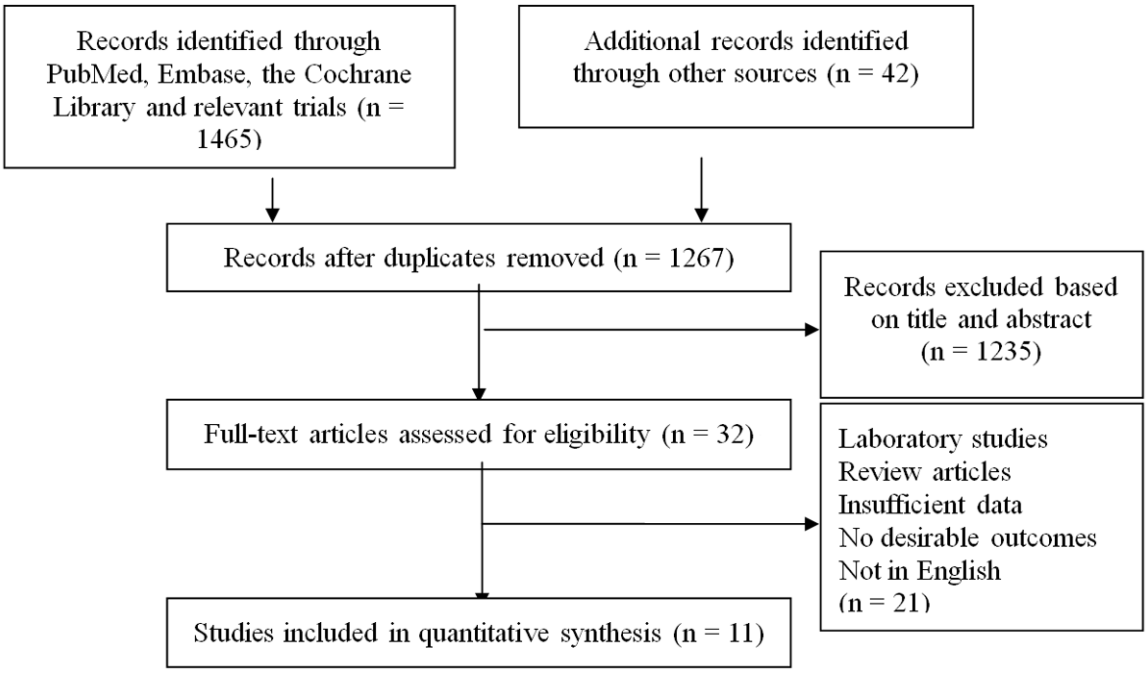

Figure 1. Flow chart of the literature and study selection process.

results. Publication bias was assessed using Begg's and Egger's tests. A *P* value of < 0.05 was considered statistically significant. All statistical analyses were performed using STATA software (version 13.0, College Station, TX, USA).

Results

Identification of relevant studies

According to the search strategy, the primary search identified 1507 articles from PubMed, Embase, and the Cochrane Library, as well as relevant trials from other sources. We removed duplicates and admitted 32 eligible articles by scanning the titles and abstracts. After the exclusion of laboratory studies, review articles, incomplete studies and studies not written in English, ultimately, 11 studies with 1512 cases were included in our quantitative synthesis. A flowchart that shows the inclusion of the studies is shown in **Figure 1**.

Study characteristics and quality assessment

Nine studies were conducted in China while the other two studies were performed in Japan. The cancer types in our study included HCC, GC, esophageal cancer, colon cancer, colorectal cancer and gallbladder cancer. Immunohistochemistry (IHC) was used in all studies to detect the expression of FOXM1. All 11 included studies [10-12, 16-23] provided the survival data of patients with DSC. Three studies [12, 16, 17] referred to tumor size and 9 studies [10-12, 16-22] contained information on histological differentiation. Six [10, 16-18, 22, 23] and 7 [10, 12, 16, 17, 19-21] studies assessed lymph node metastasis and vascular invasion, respectively. Clinical staging was performed and evaluated in 8 studies [12, 17-23]. According to the NOS, all studies were assigned a score of at least 7 stars. The characteristics of each included study are summarized in **Table 1**.

Association of FOXM1 expression with overall survival in DSC

The association of FOXM1 with overall survival of patients with DSC was discussed in all included studies. As shown in **Figure 2**, the outcome measure showed significantly better overall survival in patients with lower expression of FOXM1, with a pooled HR of 2.01 (fixed effects model, 95% CI = 1.70-2.36, P < 0.001, **Figure 2**). The heterogeneity among these studies was moderate (I^2 = 29.5%, $P_{heterogeneity}$ = 0.165).

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

First author	Year	Country	Cancer type	Case number	Duration	Method	Study design	Survival assessment HR (95% CI)	Size assessment HR (95% CI)	Histological differentiation assessment RR (95% CI)	Lymph node metastatis assessment RR (95% CI)	Vascular invasion assessment RR (95% CI)	Clinical staging assessment RR (95% CI)	NOS score
Sun (a)	2011	China	HCC	99	2001-2009	IHC	Retrospective	3.97 (1.47-10.7)	N/A	2.71 (0.52-14.06)	N/A	5.43 (0.41-72.33)	3.62 (0.91-14.31)	8
Sun (b)	2011	China	HCC	150	2001-2008	IHC	Retrospective	3.75 (2.06-6.83)	N/A	2.06 (1.03-4.12)	N/A	3.23 (1.67-6.25)	3.15 (1.89-5.26)	8
Chu	2012	China	Colorectal cancer	112	2002-2004	IHC	Retrospective	2.03 (1.18-2.66)	0.96 (0.75-1.24)	0.72 (0.33-1.57)	1.69 (1.15-2.49)	0.9 (0.48-1.69)	N/A	7
Xia	2012	China	HCC	306	1999-2001	IHC	Retrospective	1.53 (1.10-2.12)	1.85 (1.35-2.53)	2.47 (1.58-3.84)	N/A	1.33 (1.05-1.69)	1.89 (1.22-2.92)	7
Li (a)	2013	China	Colon cancer	203	2001-2003	IHC	Retrospective	3.62 (1.91-6.88)	N/A	N/A	N/A	N/A	N/A	7
Li (b)	2013	China	GC	103	2007	IHC	Retrospective	1.98 (0.84-4.66)	0.89 (0.44-1.82)	0.93 (0.70-1.23)	0.95 (0.66-1.38)	1.15 (0.64-2.09)	0.78 (0.53-1.15)	7
Okada	2013	Japan	GC	77	2001-2008	IHC	Retrospective	3.9 (1.10-24.7)	N/A	1.11 (0.68-1.83)	1.23 (0.77-1.98)	1.29 (0.65-2.58)	N/A	8
Wang	2013	China	Gallbladder cancer	76	2002-2007	IHC	Retrospective	1.56 (0.97-2.51)	N/A	1.3 (0.82-2.05)	1.74 (0.68-4.47)	N/A	2.18 (1.12-4.23)	8
Takata	2014	Japan	Esophageal cancer	174	2001-2007	IHC	Retrospective	1.69 (1.06-2.75)	N/A	N/A	1.19 (0.97-1.46)	N/A	1.18 (0.91-1.52)	8
Hu	2015	China	GC	40	Not report	IHC	Retrospective	2.04 (0.34-12.16)	N/A	0.84 (0.49-1.44)	1.55 (0.98-2.45)	N/A	1.44 (0.97-2.13)	7
Meng	2015	China	HCC	172	2006-2010	IHC	Retrospective	2.07 (1.33-3.23)	N/A	1.34 (1.06-1.70)	N/A	6.38 (1.97-20.65)	2.6 (1.29-5.25)	8

HR = hazard ratio, RR = risk ratio, CI = confidential interval, NOS = Newcastle-Ottawa Scale, N/A = not available.

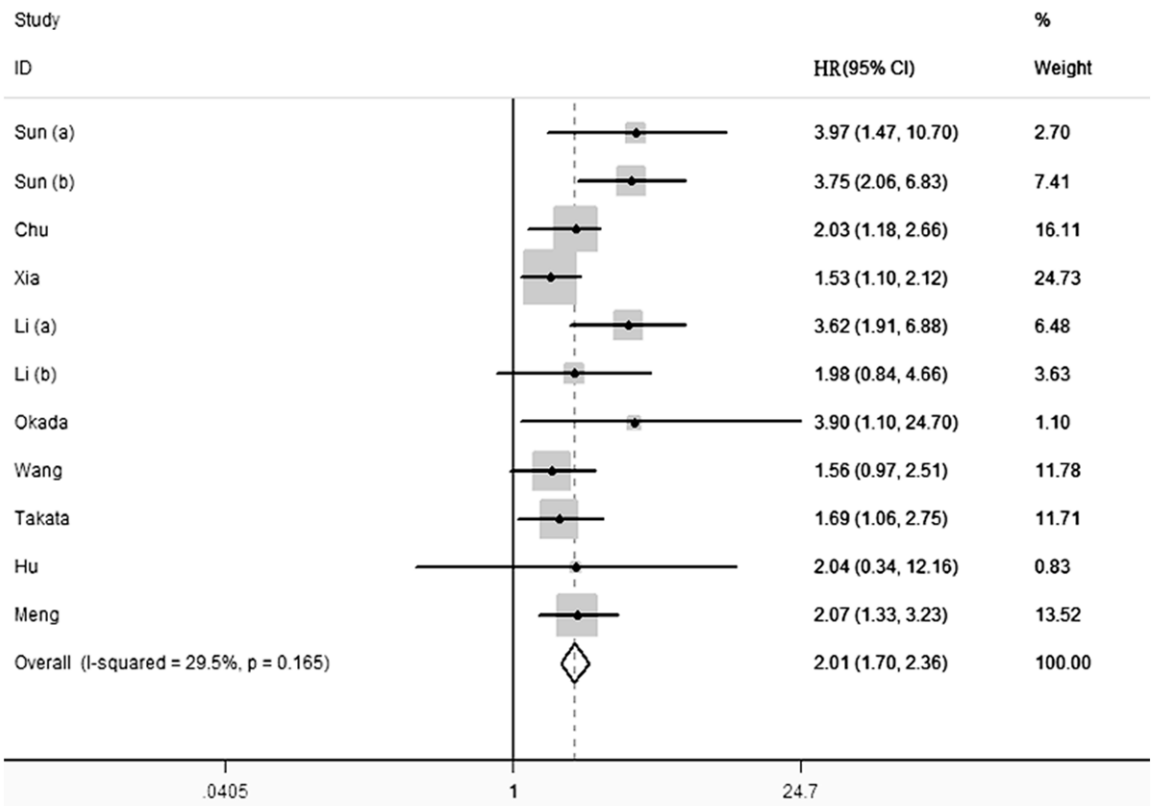

Figure 2. Forest plot for high versus low FOXM1 and overall survival time.

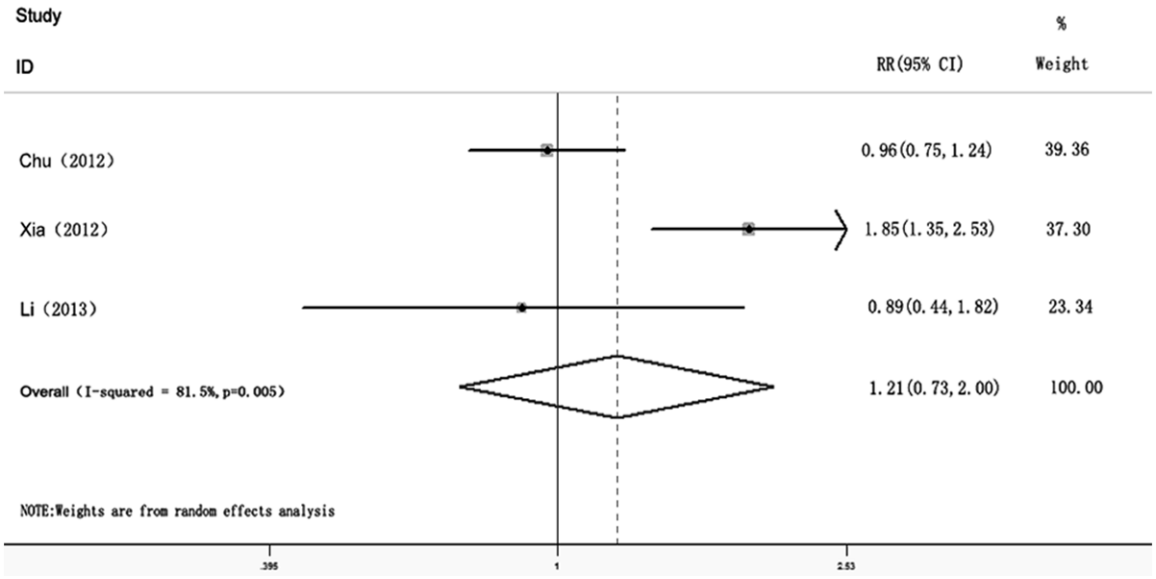

Figure 3. Forest plot for high versus low FOXM1 and tumor size.

Association of FOXM1 expression with clinical parameters in DSC

No obvious differentiation was observed in tumor size between DSC patients with higher and lower FOXM1 levels (random effects model, RR = 1.21, 95% CI = 0.73-2.00, P = 0.463, **Figure 3**). However, the heterogeneity among these studies was significant (I^2 = 81.5%, $P_{heterogeneity}$ = 0.005). FOXM1 expression was not

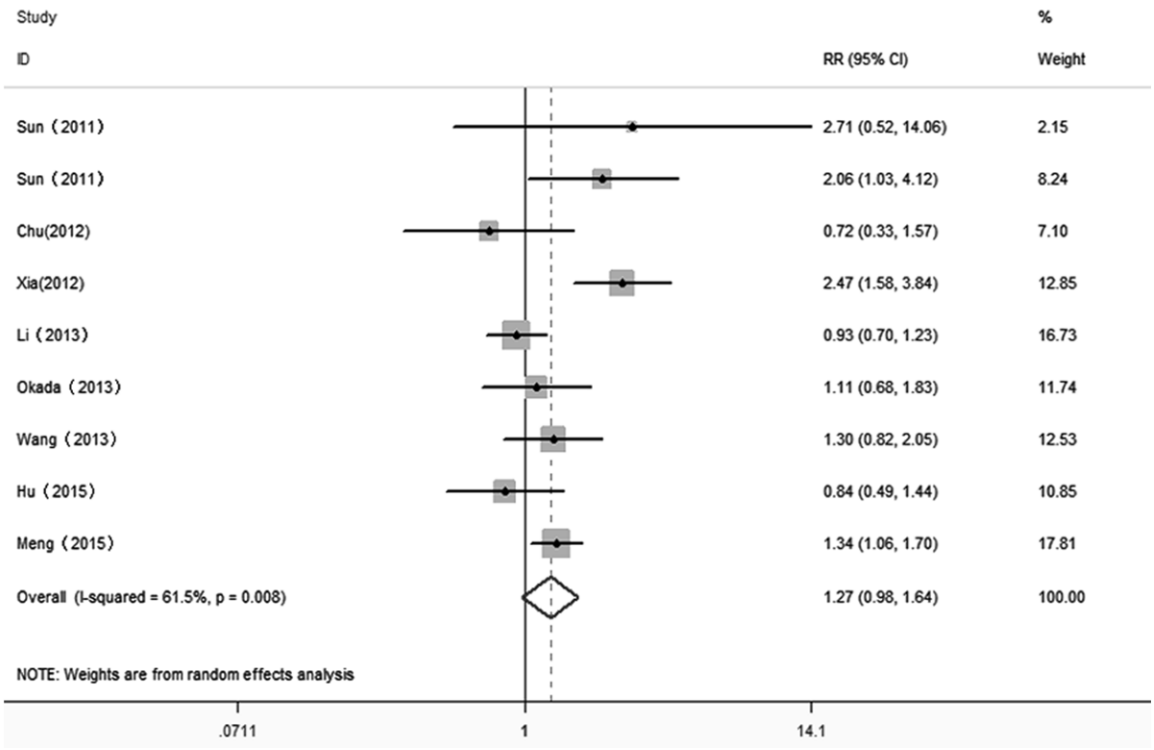

Figure 4. Forest plot for high versus low FOXM1 and histological differentiation.

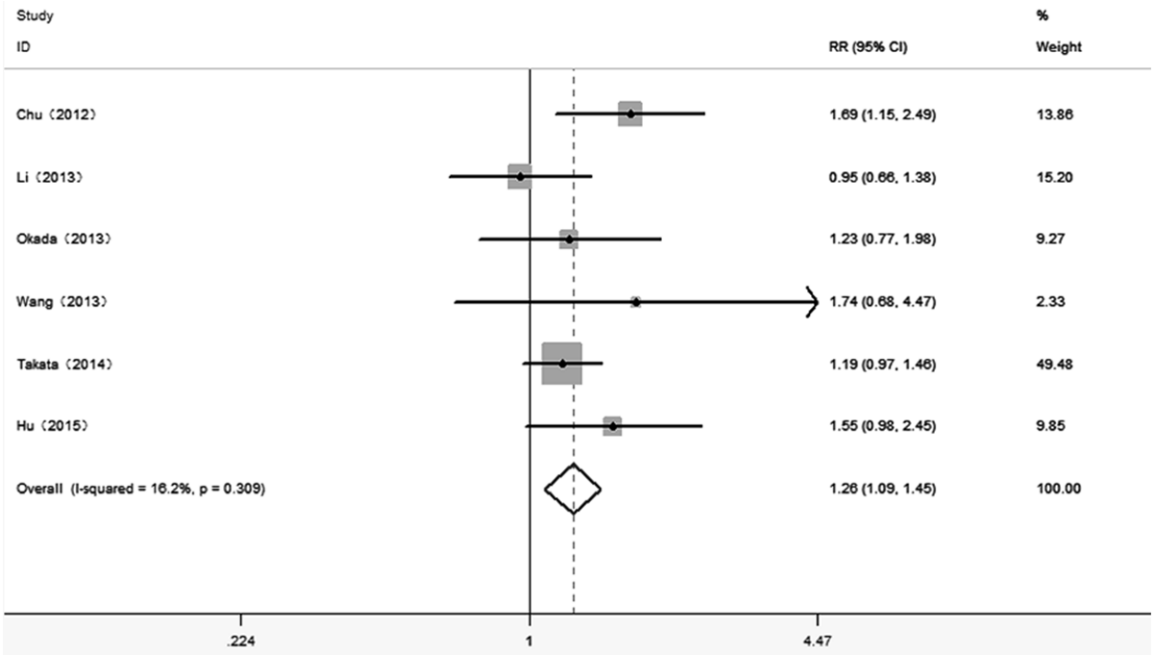

Figure 5. Forest plot for high versus low FOXM1 and lymph node metastasis.

significantly different between patients with well- and poorly-differentiated tumor histology (random effects model, RR = 1.27, 95% CI = 0.98-1.64, P = 0.066, I^2 = 61.5%, $P_{heterogeneity}$ = 0.008, **Figure 4**). DSC patients with high FOXM1 expression exhibited a higher rate of lymph node metastasis compared with patients with low FOXM1 expression (fixed effects model, RR = 1.26, 95% CI = 1.09-1.45, P = 0.006, I^2 = 16.2%, $P_{heterogeneity}$ = 0.309, **Figure 5**). Vascular

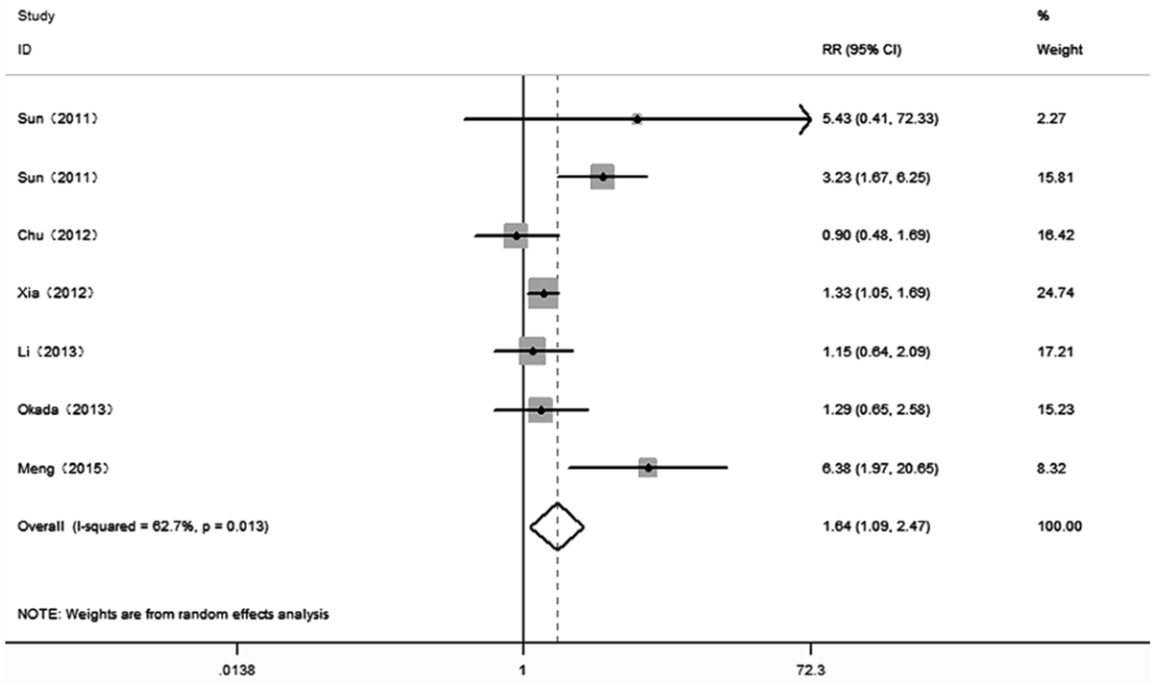

Figure 6. Forest plot for high versus low FOXM1 and vascular invasion.

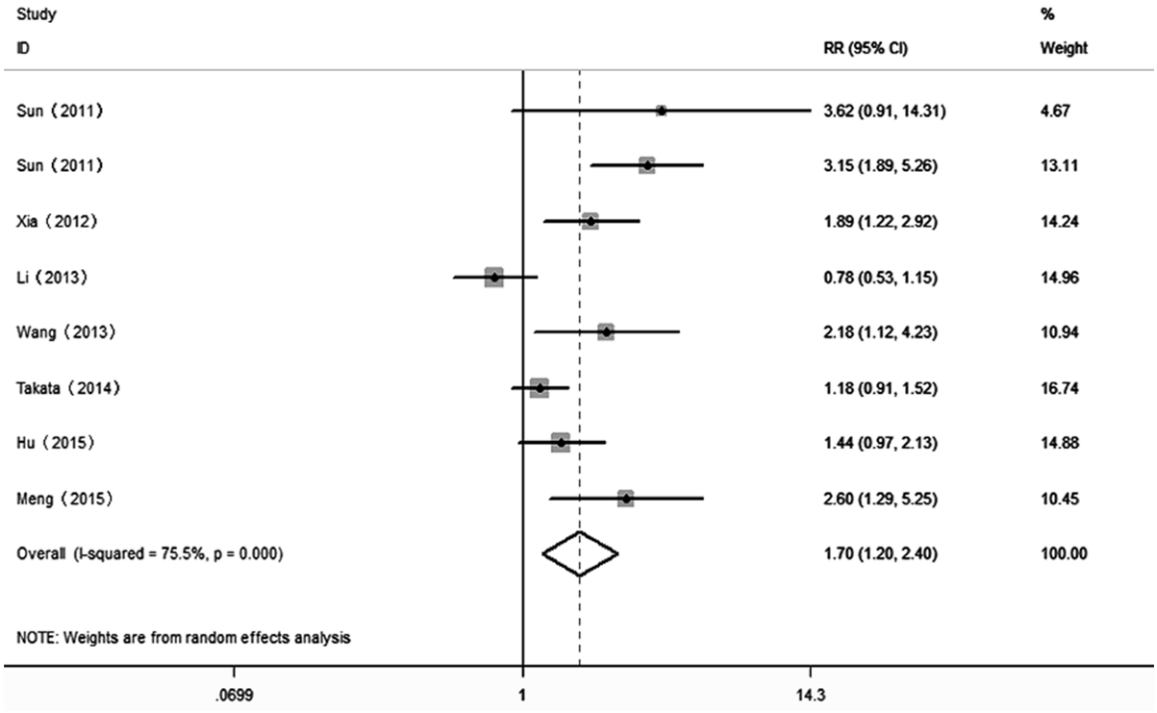

Figure 7. Forest plot for high versus low FOXM1 and clinical staging.

invasion tended to occur in the DSC patients with high levels of FOXM1 expression (random effects model, RR = 1.64, 95% CI = 1.09-2.47, P = 0.017, **Figure 6**), but the heterogeneity across those studies was high (I^2 = 62.7%, $P_{heterogeneity}$ = 0.013). FOXM1 expression was obviously higher in advanced- stage tumors (TNM stages 3 and 4) compared with early-

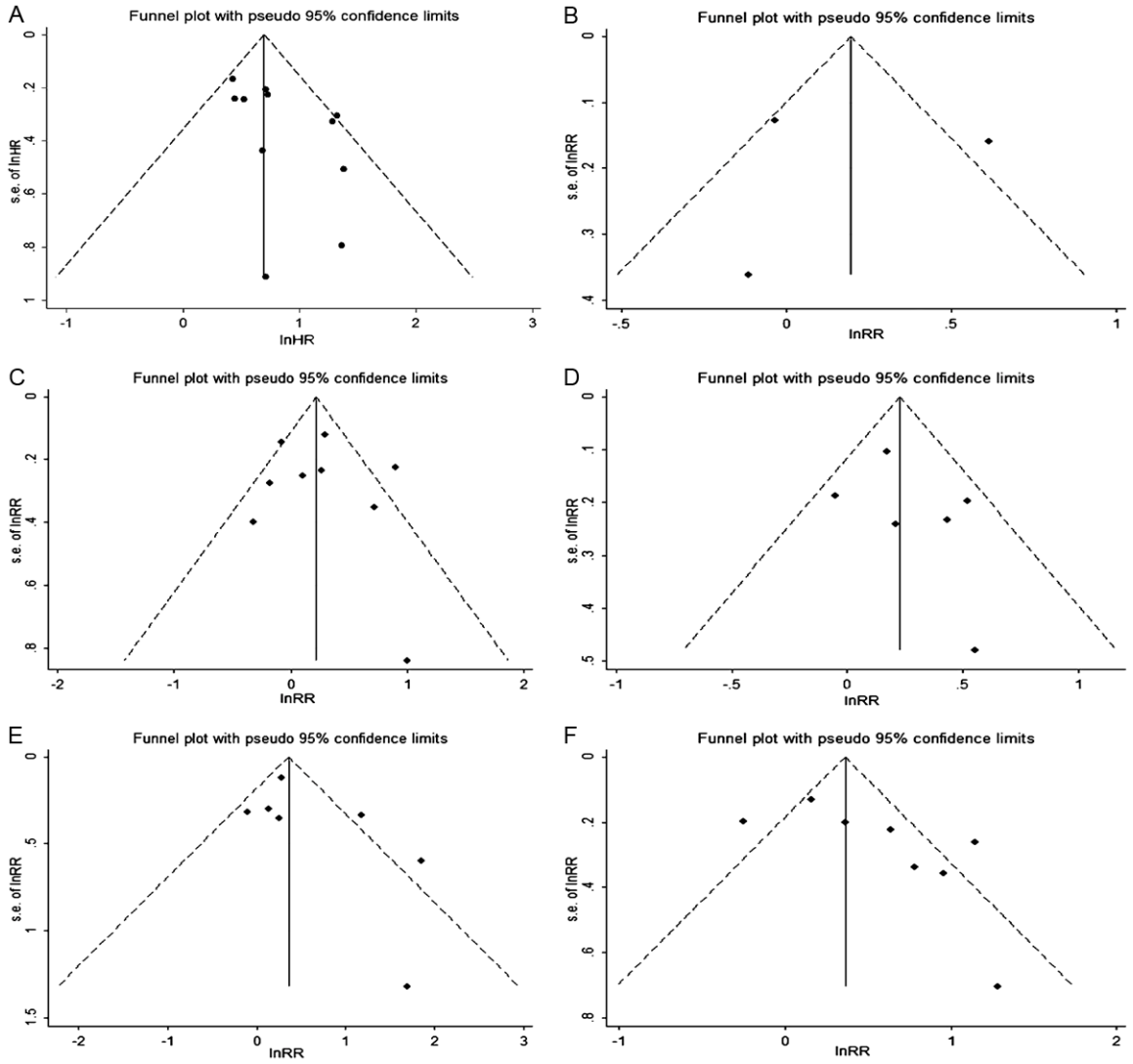

Figure 8. Funnel plot assessing publication bias: (A) overall survival (B) tumor size (C) histological differentiation (D) lymph node metastasis (E) vascular invasion (F) clinical staging.

stage tumors (TNM stages 1 and 2) (random effects model, RR = 1.70, 95% CI = 1.20-2.40, P = 0.003, I^2 = 75.5%, $P_{heterogeneity}$ < 0.001, **Figure 7**).

Sensitivity analysis and publication bias

Sensitivity analysis was performed by removing each study in sequence in all comparisons. Our analysis was stable because the pooled HRs and RRs were not significantly changed in the sensitivity analysis. The publication bias was detected using Begg's and Egger's tests. As shown in **Figure 8**, the shape of all funnel plots was largely symmetrical, which indicates a lack of obvious publication bias in our analysis.

Discussion

In the present meta-analysis, we identified the relationship between FOXM1 expression and the prognosis of patients with DSC. A high FOXM1 level was significantly associated with poorer survival, more lymph node metastasis, more vascular invasion and higher clinical stage. However, DSC patients with high FOXM1 levels failed to exhibit any obvious differences in terms of tumor size and histological differentiation compared with DSC patients with lower FOXM1 expression. Therefore, the overexpression of FOXM1 may indicate a worse prognosis of DSC and may be associated with an adverse effect on the patients. According to recent stud-

ies, the referred signaling pathways of FOXM1 include FOXM1-ras-ROS, FOXM1-Skp2-p27 and FOXM1-Raf/MEK/MAPK [24-27]. FOXM1 can activate the malignant proliferation of tumor cells, and at the same time, inhibit cellular aging [28-30]. Some studies have revealed that FOXM1 facilitates metastasis via the regulation of matrix metalloproteinases and epithelial-mesenchymal transition [31, 32]. In previous studies, FOXM1 expression was found to be related to the survival of patients with various tumors, including breast cancer, GC, HCC, lung cancer, ovarian cancer and renal cell carcinoma [10, 12, 33-36]. In a recent meta-analysis, Dai et al. demonstrated that FOXM1 overexpression may lead to a poor prognosis of patients with malignant solid tumors (HR = 1.99, 95% CI = 1.79-2.21, P < 0.001) [37]. To summarize, the overexpression of FOXM1 is associated with the tendency of tumors to exhibit a worse course, including earlier lymph node metastasis, more severe vascular invasion, more advanced clinical stage and shorter survival time. DSC is a major cause of high morbidity, mortality, and health-related costs throughout the world. Clinical staging of tumors is critical in terms of the choice of therapeutic regimens. In addition, the assessment of tumor prognosis largely relies on changes in clinical parameters. Our analysis focused on tumors of the digestive system and explored the effect of high FOXM1 expression on specific clinical parameters. During the treatment period of patients with DSC, FOXM1 detection can assist clinical staff in making refined decisions and in modifying the treatment strategy according to the level of FOXM1.

The relationship between FOXM1 expression and the prognosis of DSC had not been previously clarified before our meta-analysis. Our analysis also revealed that the FOXM1 level is relevant to some specific clinical parameters in patients with DSC. In addition to the overall survival time, clinical parameters such as lymph node metastasis, vascular invasion and tumor stage are essential to the assessment of the tumor status. We analyzed not only survival time but also other important parameters in DSC patients with different expression levels of FOXM1. Based on the included studies, we did not find a significant correlation between FOXM1 and tumor size or between FOXM1 expression and histological differentiation, which might help resolve disputes among different research groups.

We combined 11 studies on DSC and FOXM1 and included 1512 patients with DSC. The individual studies with a limited number of cases were collected to provide sufficient statistical power and a reliable estimation of the relationships examined. IHC is more commonly used in the detection of FOXM1 expression than other methods such as PCR, and thus we adopted IHC so that we could include more cases to obtain a more stable result. All included studies provided the percentage of FOXM1 overexpression, which ranged from 42% to 79%. The American Joint Committee on Cancer (AJCC) seventh edition TNM classification has been regarded as a gold standard for tumor staging. We combined both the TNM and Nevin staging systems into the AJCC TNM staging system. The effect magnitudes adopted in the assessment of survival time and other parameters were the HR and RR, respectively. The HR of survival was obtained directly from the included studies or was extracted from survival curves. Since original articles did not provide sufficient information for calculation of the HRs, we computed the RR of other parameters in each study. Xia et al. and Sun et al. reported that overexpression of FOXM1 was clearly connected with larger tumor size and worse histological differentiation [12, 20, 21]. However, our analysis failed to detect an exact relationship between FOXM1 and tumor size or histological differentiation in patients with DSC. The reasons for these contradictory results are unclear. In the assessment of some parameters, significant heterogeneity among studies could not be ignored, which indicates that the prognostic value of our results may be limited.

In terms of its role as an important regulator of the pathological processes of tumors, FOXM1 has been a hot research topic. The mechanism of FOXM1 signal transduction is still unclear, and therefore, it might become the next target in DSC research. In addition to DSC, more studies are required regarding the function of FOXM1 in other types of tumors. According to our analysis, some of the pooled results conflicted with the conclusions of the included studies. Small case number size, limited numbers of patients with certain cancer types and imperfect research design may have led to the-

se conflicting results. Moreover, further studies that aim to solve these contradictory points are needed.

Obviously, this study is restricted due to some limitations. Our study was restricted in terms of our language ability, as only studies in English were included, which may have led to some selection bias. Moreover, we did not search all databases due to limited manpower. Therefore, some relevant studies may not have been included, which may abolish the robustness of the results. All patients included in our study were of Asian ethnicity (Chinese and Japanese) because Asian researchers may be more interested in DSC. The types of DSCs in our analysis were limited, and thus the results may not be applicable to other cancers. The heterogeneity in some comparisons was significant, which may have influenced the stability of the conclusions. A random effects model and a sensitivity analysis were utilized to diminish the influence of heterogeneity in our analysis. Confounding factors could not be differentiated from the effect of FOXM1 in the prognosis of DSC patients, and these included age, gender, BMI, smoking status, nutrition status, and therapeutic regimen, among others. The effect magnitudes of survival in some studies were obtained from survival curves, which means that the HRs were less precise compared with those obtained from directly extracted data. Unstable results may have resulted from these limitations, and thus additional studies are needed to explore the exact relationship between FOXM1 expression and the prognosis of patients with DSC. In conclusion, our meta-analysis revealed that upregulated FOXM1 expression is significantly correlated with shorter survival time, earlier lymph node metastasis, more severe vascular invasion and higher clinical stage of DSC. However, FOXM1 overexpression is not clearly associated with tumor size and histological differentiation. In addition, these results can guide us to more precise recommendations for the prediction and observation of the prognosis of patients with DSC.

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Disclosure of conflict of interest

None.

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