

# World Journal of *Clinical Oncology*

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**META-ANALYSIS**

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# Metastatic potential and prognostic significance of SOX2: A meta-analysis

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## Abstract

### BACKGROUND

SOX2 is a regulator of pluripotent cellular transcription, yet it has been recently integrated in cancer biology. The present study provides an analytic insight into the correlation of SOX2 overexpression with cancer metastasis and patient survival.

### AIM

To investigate the association of SOX2 overexpression with metastasis and its implication in the prognosis of cancer patients.

### METHODS

A meta-analysis was conducted including studies that compared the association of low or high SOX2 expression with lymph node metastasis (LNM) and/or distant metastasis (DM). The following data were additionally extracted: survival, including the overall survival (OS) and disease-free survival (DFS), and prevalence of high and low SOX2 expression. Odds ratios (commonly known as ORs) and their respective 95% confidence intervals (CIs) were used to investigate the association between SOX2 expression and LNM and DM, while hazard ratios (commonly known as HRs) and 95% CIs were applied to evaluate the prognostic markers.

### RESULTS

In a total of 2643 patients (60.88% males), the pooled prevalence of SOX2 overexpression was 46.22% (95%CI: 39.07%-53.38%) in different types of cancer. SOX2 overexpression significantly correlated with DM (OR = 1.79, 95%CI: 1.20-3.25,  $P < 0.008$ ) compared to low SOX2 expression. In subgroups analyses, a high SOX2 expression was associated with LNM in cancers of the lung, breast, and colon and associated with DM in hepatic, head and neck, and colon cancers. SOX2 overexpression was also associated with a shorter OS (HR = 1.65, 95%CI:

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1.34-2.04,  $P < 0.001$ ) and DFS (HR = 1.54, 95% CI: 1.14-2.08,  $P = 0.005$ ).

## CONCLUSION

A remarkable role of SOX2 overexpression was observed in cancer biology and metastasis. However, many questions in the regulatory pathways need to be addressed to reveal as many functional aspects as possible to tailor new targeted therapeutic strategies.

**Key words:** Tumor progression; SOX2; Cancer; Cancer stem cell markers; Lymphatic metastasis

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**Core tip:** SOX2 overexpression is associated with both lymph node and distant metastasis predominantly in cancers of the colon and head and neck. Targeting the biological pathways of SOX2 seems to provide a promising rationale for developing relevant therapeutic interventions.

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## INTRODUCTION

The mechanisms by which the metastatic cascade is instigated and developed have merited the attention of the researchers worldwide. Tumor metastasis involves a sequential process, comprising cell invasion through the basement membrane and extracellular matrix followed by intravasation to access the vascular or lymphatic circulation, extravasation out of the circulatory system, and eventually distant localization and proliferation<sup>[1]</sup>. Failure to manage distant dissemination of cancer cells causes a significant mortality burden, with approximately 1500 cancer spread-related deaths reported daily<sup>[2]</sup>. A plethora of studies has been conducted on animal models to outline the metastatic phenotype. These studies usually employ intravenous injections for metastatic initiation. However, such an approach lacks the appropriate characterization of the origin of metastasis and, thus, multiple triggering factors are either still hypothesized or their contribution in metastasis is not fully delineated.

Of these factors, the transcription factor sex determining region Y-box 2 (SOX2) has been recently integrated in cancer biology<sup>[3]</sup>. SOX2 is one of the SOX proteins that has  $\geq 50\%$  similarity in the amino acid structure to a specific domain (HMG domain) of the sex-determining region located on the Y chromosome (*Sry*)<sup>[4]</sup>. The encoding gene was initially discovered in 1994 in human, being located on chromosome 3q26.3-q27<sup>[5]</sup>. Heterozygous mutations of the *SOX2* gene result in the development of anophthalmia syndrome, which includes an aberrant development of endodermal and ectodermal tissues<sup>[6]</sup>. SOX2 is an important regulator of pluripotent cellular transcription and is a crucial factor implicated in the development and maintenance of undifferentiated embryonic stem cells. Besides, it contributes to somatic cell reprogramming back towards pluripotent features and this process was shown to be co-induced by ectopic expression of *cMyc*, *Klf4*, and *Oct4*<sup>[3]</sup>.

Intriguingly, this discovery highlighted the role of SOX2 expression in different types of cancers. *SOX2* gene amplification or increased expression has been demonstrated in malignancy, yet its involvement in the most important aspects of patient survival and metastasis remains relatively unclear. Herein, we provide analytic insight into the association between metastasis and SOX2 expression in cancer patients, along with its relation to the prognostic profile.

## MATERIALS AND METHODS

A meta-analysis was conducted on studies that investigated the relationship between



development of a metastatic phenotype as well as the prognostic significance of such expression. The general outline of the study was based on the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (commonly known as PRISMA)<sup>[7]</sup>.

### **Eligibility criteria**

The included studies investigated at least the association of SOX2 expression, reported as “low” or “high” expression levels, and either lymph node metastasis (LNM) or distant metastasis (DM). When appropriate, patients’ prognosis should have been evaluated using survival analysis, where the overall survival (OS) and/or disease-free survival (DFS) were reported. Only peer-reviewed studies conducted on male or female human patients were considered. The cancer patients should have been diagnosed using pathological examinations. Studies were excluded if they provided insufficient data to be extracted or had employed animal subjects solely. Furthermore, non-English articles, case reports, reviews and cell experiments were omitted.

### **Information sources**

The following scientific databases were used for the search process: MEDLINE, Embase, Cochrane Library, and Google Scholar. Additionally, the bibliographies of the screened articles were thoroughly searched for eligible studies.

### **Search strategy**

Two authors performed the search process using the following key words: (“transcription factor sex determining region Y-box 2” OR “SOX2”) AND (“cancer” OR “metastasis”) AND (“prognosis” OR “survival” OR “hazard”). The publication dates of the included studies were limited to those articles published between 2010 and 2018, to attain the most recent evidence. Screening of the titles and abstracts was performed and the relevant articles were obtained for subsequent assessment of the full-texts. Any disagreement was resolved by discussion.

### **Data collection**

A specifically-designed form was used in Microsoft Excel spreadsheet software (version 2016) to extract data. The extracted data for each study were categorized into four main categories: (1) Study and patients’ characteristics, including the name of the first author, publication date, methods of detection of SOX2 expression, method of survival analysis, reported outcomes, number of samples, type of primary cancer, sex of patients, frequency of SOX2 expression (low or high), and clinical stage (I and II or III and IV); (2) Primary outcomes, including the frequency of reported samples with low or high SOX2 expression in the regional lymph nodes (*i.e.* LNM) or distant organs (*i.e.* DM); (3) Clinicopathological parameters, including SOX2 expression levels according to patients’ age, sex, clinical stage, and tumor size and differentiation; (4) Prognostic data, including direct extraction of the hazard ratios (HRs) and their respective 95% confidence intervals (CIs) of the OS and/or DFS. When both univariate and multivariate analyses were used for survival analysis, multivariate tests were preferentially used.

### **Quality assessment**

A specialized scale for quality assessment was used [*i.e.*, Newcastle-Ottawa scale (commonly known as NOS)]<sup>[8]</sup>, which employs a scoring system comprising nine items and yielding a total score of 0 to 9 for low-quality to high-quality articles, respectively. The assignment of such scores is based on the selection, comparability, and outcomes of the groups under investigation. A score of  $\geq 6$  indicated a high-quality study.

### **Statistical analysis**

The following formula was used for calculation of the prevalence rate of high SOX2 expression: (number of samples with high SOX2 expression/total number of samples)  $\times 100$ ; the standard error and 95% CIs were calculated as described previously<sup>[9]</sup>. The RevMan 5.3 software was used for statistical analysis (Review Manager, the Cochrane Collaboration, Oxford, United Kingdom). For dichotomous data (*e.g.*, LNM, DM and clinicopathological data), odds ratios (ORs) and their respective 95% CIs were applied. Regarding prognostic markers (OS and DFS), HRs and their respective 95% CIs were integrated in the meta-analysis. Statistical heterogeneity was assessed using the  $I^2$  statistical test, which was interpreted as a significant heterogeneity at  $I^2 > 50\%$ . In such instance, a random effects model was applied. On the other hand, a fixed effects model was used when the heterogeneity was insignificant. Subgroup analyses were performed according to sample size, the type of primary cancer, and quality score.

## RESULTS

### Results of the search process

**Figure 1** shows the outcomes of the employed search process. The initial search yielded a total of 1120 records, from which 45 records were considered duplicates, while an additional 5 records were identified from the bibliographies of the resultant records. Therefore, 1080 records were screened for eligibility through their titles and abstracts. Subsequently, the full-text versions of 23 articles were examined for inclusion. Ultimately, 20 studies were included in the meta-analysis.

### Characteristics of the included studies

**Table 1** demonstrates the main characteristics of the included studies. A total of 2643 patients (60.88% males) were investigated for eight types of cancer, including cancers of the breast<sup>[10,11]</sup>, cervix<sup>[12]</sup>, colon<sup>[13]</sup>, esophagus<sup>[14-16]</sup>, head and neck<sup>[17-23]</sup>, liver<sup>[24]</sup>, lung<sup>[25]</sup>, and stomach<sup>[26-29]</sup>. The sample sizes ranged between 20 and 307 patients. Excluding three studies in which the clinical stage was not reported<sup>[10,13,24]</sup>, 1265 patients (54.98%) were at stage III or IV. Immunohistochemical staining was utilized in all studies to detect SOX2 expression. With respect to outcomes, only two studies did not report LNM<sup>[12,17]</sup>, while DM was reported in 11 studies<sup>[12-14,17,19,20,22-24,26,27]</sup>, OS in 11 studies<sup>[12,15-23,26]</sup>, and DFS in 3 studies<sup>[17-19]</sup>. Two studies were performed in European countries<sup>[13,19]</sup>, one in Africa<sup>[10]</sup>, and the remaining studies in Asia. All of the included studies scored a NOS equal to or greater than 6, indicating the inclusion of high-quality studies.

### Prevalence of high SOX2 expression and its relationship to the clinicopathological parameters

The pooled prevalence of high SOX2 expression in different types of cancer was 46.22% (95%CI: 39.07%-53.38%) with a significant heterogeneity among the included studies ( $I^2 = 94\%$ ). Subgroup analysis was performed to detect the sources of heterogeneity, yet it remained significant for most of the subgroups. As for the clinicopathological parameters, SOX2 expression was not significantly correlated to patient's age, sex and clinical stage as well as the size and differentiation of tumors (**Table 2**).

### Relationship between SOX2 expression and metastasis

Although applying a random effects model yielded no remarkable association between high SOX2 expression and LNM (**Figure 2A**), the relationship was significant in the subgroup analyses for specific types of tumors, including cancers of the colon (OR = 4.15, 95%CI: 1.43-12.09,  $P = 0.009$ ), breast (OR = 2.78, 95%CI: 1.50-5.50,  $P = 0.002$ ,  $I^2 = 0\%$ ), and lung (OR = 1.74, 95%CI: 1.02-2.89,  $P = 0.04$ ) (**Table 3**).

Interestingly, SOX2 was highly expressed in distant metastatic tumors (OR = 1.79, 95%CI: 1.20-3.25,  $P < 0.008$ ; **Figure 2B**) despite the existence of a significant heterogeneity between studies ( $I^2 = 57\%$ ). Such relationship was also consistent for hepatic (OR = 4.80, 95%CI: 1.56-14.76,  $P = 0.006$ ), colon (OR = 3.04, 95%CI: 1.15-8.04,  $P = 0.03$ ), and head and neck tumors (OR = 2.46, 95%CI: 1.63-3.72,  $P < 0.001$ ) (**Table 3**).

### Relationship between SOX2 expression and patient prognosis

As compared to low SOX2 expression, high SOX2 expression was significantly associated with shorter OS and the studies showed no heterogeneity (HR = 1.65, 95%CI: 1.34-2.04,  $P < 0.001$ ,  $I^2 = 44\%$ ; **Figure 3A**). Similarly, the included studies showed a significantly shorter DFS when SOX2 was highly expressed without heterogeneity (HR = 1.54, 95%CI: 1.14-2.08,  $P = 0.005$ ,  $I^2 = 15\%$ ; **Figure 3B**).

## DISCUSSION

Cancer biology involves a number of hallmarks that enable cellular division and spread, including continued proliferative signaling, initiation and maintenance of metastasis, and evasion of cell death<sup>[30]</sup>. SOX2 has exhibited various roles in these hallmarks *via* promoting cellular proliferation through the induction of cyclin D3 transcription and enabling S-phase entry<sup>[31]</sup> as well as evading apoptotic signals by precluding *ORAI1* expression and subsequently reducing store-operated  $Ca^{2+}$  entry<sup>[32]</sup>. The present meta-analysis showed that SOX2 contributed to the development of a metastatic phenotype to distant organs and its high expression was associated with shorter OS and DFS in patients with cancer.

SOX2 is one of the embryonic cell fate determinants which have been linked to increasing tumor aggressiveness, metastasis, and poor prognosis. In addition to SOX2,

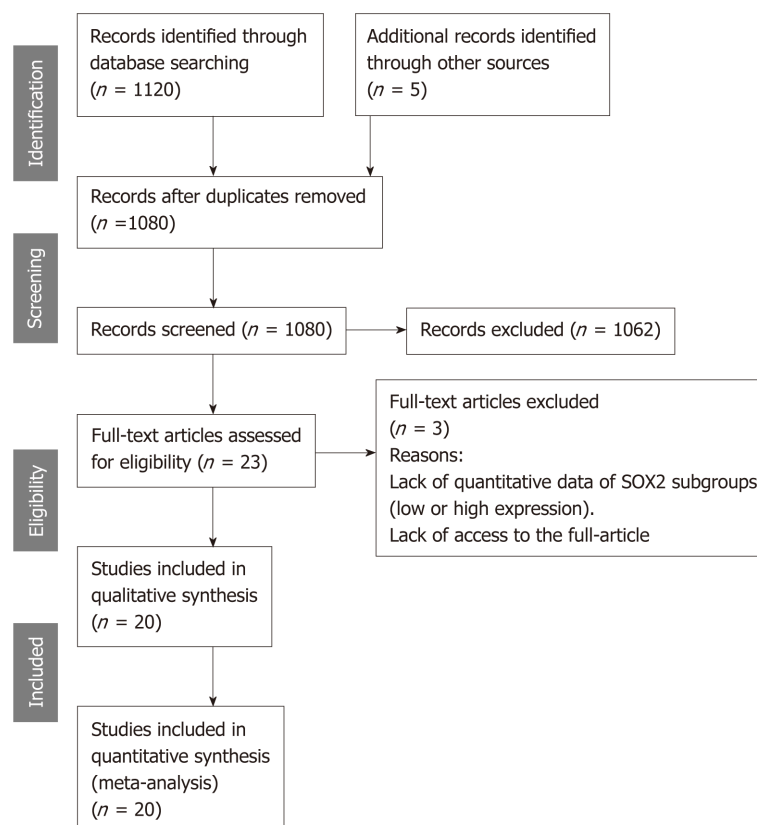


Figure 1 Flow diagram showing the search process used in the present study.

these factors, namely the Yamanaka factors<sup>[3]</sup>, include *Oct4*, *Klf4*, and *Myc*, among others. SOX2 determines distinct cell fate decisions during embryonic development *via* antagonization of CDX2, NKX2-1, MITF, and other tissue-specific factors<sup>[33]</sup>. In cancer, evidence from experimental studies has revealed different mechanisms of SOX2-mediated metastasis. Girouard *et al.*<sup>[34]</sup> showed that the transduction of G361 cells, which normally express low SOX2 levels, to enhance SOX2 overexpression led to a 3.8-fold increase in invasiveness ( $P = 0.0004$ ) and, on the other hand, SOX2 knockdown in melanoma cells resulted in a significant reduction of invasiveness and diminished matrix metalloproteinase (MMP)-3 expression by 87.8%. Furthermore, invasion and migration of cancer cells in colorectal cancer (CRC), malignant glioma, and laryngeal squamous cell carcinoma were attributed to MMP-2-mediated effects and this was associated with SOX2 overexpression<sup>[35-37]</sup>. Therefore, in the current study, it was not surprising that SOX2 overexpression was associated with LNM and DM in colon cancer and DM in head and neck cancer. MMP-2 is a type of IV collagenase that has been implicated previously in carcinogenesis and metastasis<sup>[38]</sup>. In general, MMPs comprise a family of zinc-dependent endopeptidases that degrade extracellular matrix proteins and they are involved in metastasis *via* several aspects, including tumor invasion, angiogenesis, and establishing metastatic foci<sup>[39]</sup>.

In hepatocellular carcinoma, SOX2 induced cell invasion and hence was associated with DM. SOX2 expression was low in non-carcinogenic liver cells, moderate in non-invasive cells, and highest in the invasive cells<sup>[24]</sup>. Such an effect is mediated by enhancing cancer stemness properties through activation of the epithelial-to-mesenchymal transition (EMT) process, which is characterized by remarkable activation of distinct transcriptional factors, including Snail, Twist, and Slug. The SOX2-Slug axis has been consistently reported not only in hepatocellular carcinoma but also in esophageal squamous cell carcinoma and muscle-invasive bladder cancer<sup>[24,40,41]</sup>. SOX2-mediated Slug expression was suppressed by inhibition of STAT3/HIF-1 $\alpha$  signaling using siRNA, indicating a role of such pathway in the co-expression of SOX2 and Slug<sup>[40]</sup>. Nonetheless, the exact regulatory mechanisms between EMT and SOX2 and other stemness-related transcriptional factors, considering their contribution to cancer metastasis, have yet to be clearly revealed. Through its common activating effect on EMT, SOX2 exerts its metastatic potential in CRC *via* a different mechanism. Activation of the WNT pathway, which is thought to



Table 1 Characteristics of the included studies

Study	YOP	Patients, M/F/T	SOX2 expression, high/low	Clinical stage, I+II/ III +IV	Cancer type	Outcomes	Survival analysis	NOS
Abd El-Maqsoud <i>et al</i> <sup>[10]</sup>	2014	0/126/126	42/84	NA	IBC	LNM	NA	7
Chen <i>et al</i> <sup>[26]</sup>	2016	59/18/77	28/49	26/51	GC	DM, LNM, OS	Mu	8
Chen <i>et al</i> <sup>[27]</sup>	2016	233/74/307	96/211	95/212	GC	DM, LNM	NA	8
Chuang <i>et al</i> <sup>[14]</sup>	2015	72/3/75	40/35	21/27	ESCC	DM, LNM	NA	6
Dai <i>et al</i> <sup>[17]</sup>	2014	75/56/131	82/49	77/54	ACC	DM, OS, DFS	Mu	7
Ge <i>et al</i> <sup>[18]</sup>	2010	84/1/85	67/18	21/64	HSCC	LNM, OS, DFS	Mu	7
González-Márquez <i>et al</i> <sup>[19]</sup>	2014	203/17/220	74/146	24/196	SCC	DM, LNM, OS, DFS	Mu	6
Liu <i>et al</i> <sup>[23]</sup>	2018	35/26/61	39/22	46/15	TSCC	DM, LNM, OS	Mu	7
Liu <i>et al</i> <sup>[11]</sup>	2018	0/237/237	122/115	167/70	BC	LNM	NA	7
Luo <i>et al</i> <sup>[20]</sup>	2013	92/30/122	68/54	33/89	NPC	DM, LNM, OS	Mu	6
Neumann <i>et al</i> <sup>[13]</sup>	2011	58/56/114	24/90	NA	CC	DM, LNM	NA	7
Saigusa <i>et al</i> <sup>[15]</sup>	2011	18/2/20	8/12	10/10	ESCC	LNM, OS	U	7
Shen <i>et al</i> <sup>[12]</sup>	2014	0/132/132	83/49	70/62	CSCC	DM, OS	Mu	8
Sun <i>et al</i> <sup>[24]</sup>	2013	65/10/75	46/29	NA	HCC	DM, LNM	NA	6
Tang <i>et al</i> <sup>[21]</sup>	2013	152/9/161	88/73	65/96	LSCC	LNM, OS	Mu	8
Wang <i>et al</i> <sup>[16]</sup>	2018	87/30/117	54/63	48/69	ESCC	LNM, OS	Mu	7
Wang <i>et al</i> <sup>[28]</sup>	2015	132/71/203	48/155	65/138	GC	LNM	NA	6
Yang <i>et al</i> <sup>[25]</sup>	2013	140/82/222	124/98	173/49	SCLC	LNM	NA	7
Yoshihama <i>et al</i> <sup>[22]</sup>	2016	69/39/108	63/45	64/44	OSCC	DM, LNM, OS	Mu	7
Zhang <i>et al</i> <sup>[29]</sup>	2010	35/15/50	16/34	31/19	GC	LNM	NA	6

ACC: Adenoid cystic carcinoma of the salivary gland; CC: Colon cancer; CSCC: Cervical squamous cell carcinoma; DFS: Disease-free survival; DM: Distant metastasis; ESCC: Esophageal squamous cell carcinoma; F: Female; GC: Gastric cancer; HCC: Hepatocellular carcinoma; HSCC: Hypopharyngeal squamous cell carcinoma; IBC: Invasive breast cancer; LNM: Lymph node metastasis; LSCC: Laryngeal squamous cell carcinoma; M: Male; Mu: Multivariate; NOS: Newcastle-Ottawa scale; NPC: Nasopharyngeal carcinoma; OS: Overall survival; OSCC: Oral squamous cell carcinoma; SCLC: Small cell lung cancer; T: Total; TSCC: Tongue squamous cell carcinoma; U: Univariate; YOP: Year of publication.

be critical for CRC tumorigenesis, was demonstrated in CRC and cisplatin-resistant lung adenocarcinoma cells<sup>[35,42]</sup>.

In contrast to our results, in ovarian cancer cells, SOX2 overexpression increased phosphorylation of Src and FAK proteins<sup>[43]</sup>, both of which are well-established as prometastatic proteins through their abilities to mediate EMT<sup>[44]</sup>. Additionally, SOX2 functionality was linked to the Hedgehog signaling pathway in controlling different hallmarks of prostate cancer, such as reduction of apoptotic death, increasing cellular proliferation, and augmenting the metastatic ability<sup>[45]</sup>. This was also confirmed by the effects of SOX2 silencing, where it lowered the migration capabilities of different prostate cancer cell lines by 11%-31%<sup>[45]</sup>. Similarly, SOX2 gene knockout or silencing led to loss of tumorigenic properties and reduced cellular proliferation in lung cancer<sup>[46]</sup>, glioblastoma<sup>[47]</sup>, and pancreatic cancer<sup>[31]</sup>. Paradoxically, SOX2 overexpression was found in gastric cancer and could contribute to cellular invasion<sup>[48]</sup>, while it was found to be significantly downregulated in the same type of cancer in other studies<sup>[28,49,50]</sup>.

In the present meta-analysis, SOX2 correlated with poor prognosis in different types of cancers. Other investigations have also indicated higher rates of recurrence and that its expression was associated with the parameters of worse outcome in primary cancers of the head and neck<sup>[51]</sup>. Furthermore, SOX2 was associated with advanced tumor stages in head and neck adenoid cystic carcinoma<sup>[52]</sup>. However, we failed to prove such a relationship, possibly because the included studies had to report at least one parameter of metastasis (LNM and/or DM) in addition to the prognostic data. Thus, several prognosis-relevant studies might have escaped inclusion.

**Table 2 Pooled effect of the relationship between SOX2 expression (high vs low) and the clinicopathological parameters of cancer patients in the included studies**

Variable	Studies	Model ( $I^2$ %)	OR (95%CI)	P-value
Age	17	F (0)	1.07 (0.90-1.28)	0.43
Sex	16	F (0)	1.13 (0.90-1.41)	0.29
Clinical stage	18	R (79)	1.51 (0.97-2.37)	0.07
Tumor size	9	F (27)	1.06 (0.84-1.33)	0.64
Tumor differentiation	14	R (54)	1.19 (0.80-1.75)	0.39

CI: Confidence interval; F: Fixed effects model; OR: Odds ratio; R: Random effects model.

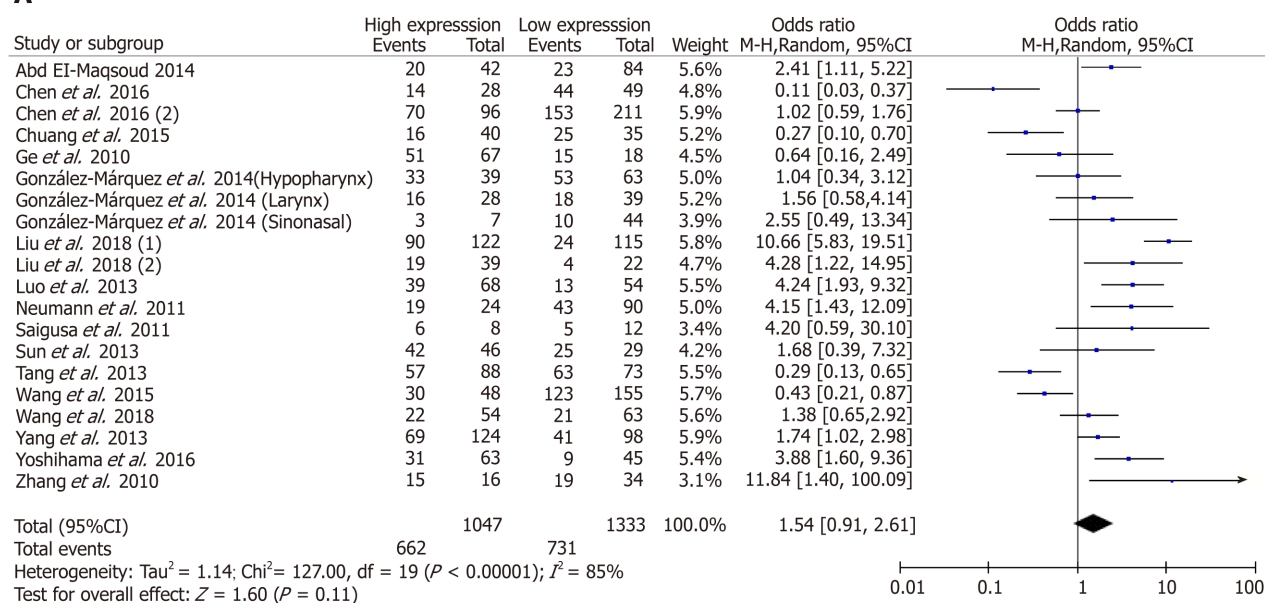
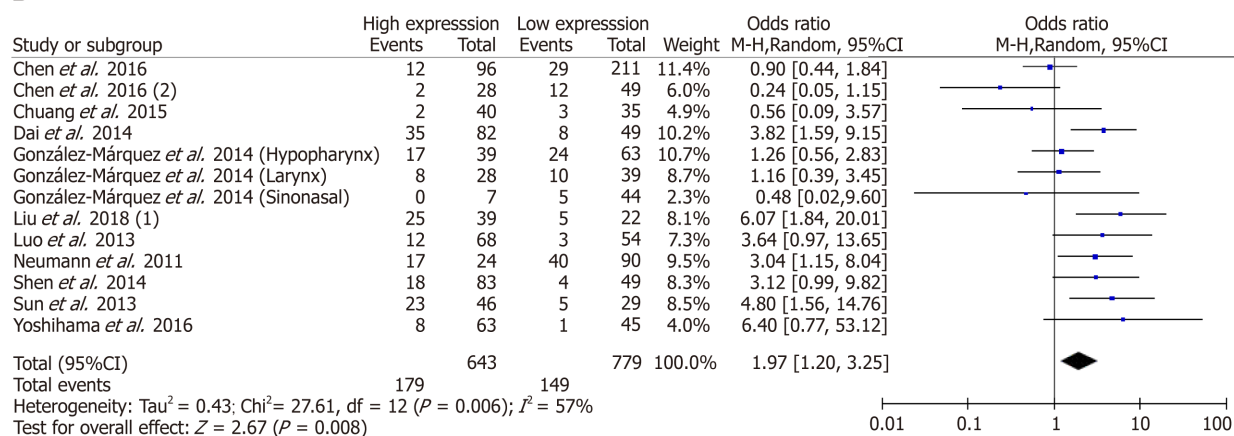
Given that SOX2 expression was detected not only in the nuclei of cancer cells but also in the their cytosols in hepatic cancer, pancreatic cancer and CRC<sup>[24,32,35]</sup>, it is plausible that the intranuclear existence might explain its transcriptional role; yet, its functional role in the cytosol remains only fairly understood. In light of the confirmed transcriptional roles, functional-depletion of SOX2, *via* knockdown approaches using siRNA, is possible experimentally; although, its clinical application is challenging. Alternatively, researchers should strive to identify the possible regulatory mechanisms of SOX2 to tailor distinct targeted therapies accordingly.

In conclusion, SOX2 has exhibited a significant metastatic potential in various types of cancer, including colorectal, head and neck, liver and breast. It can also be regarded as a poor prognostic indicator, and recurrence may be expected in patients with SOX2 overexpression. Different transcriptional regulation mechanisms of SOX2 are involved, yet promotion of the EMT was apparently of paramount importance. Implementing targeted therapies aimed to counteract high SOX2 expression might be beneficial to treat this deadly disease.

**Table 3** Subgroup analysis of the association between SOX2 expression (high vs low) and LMN and DM

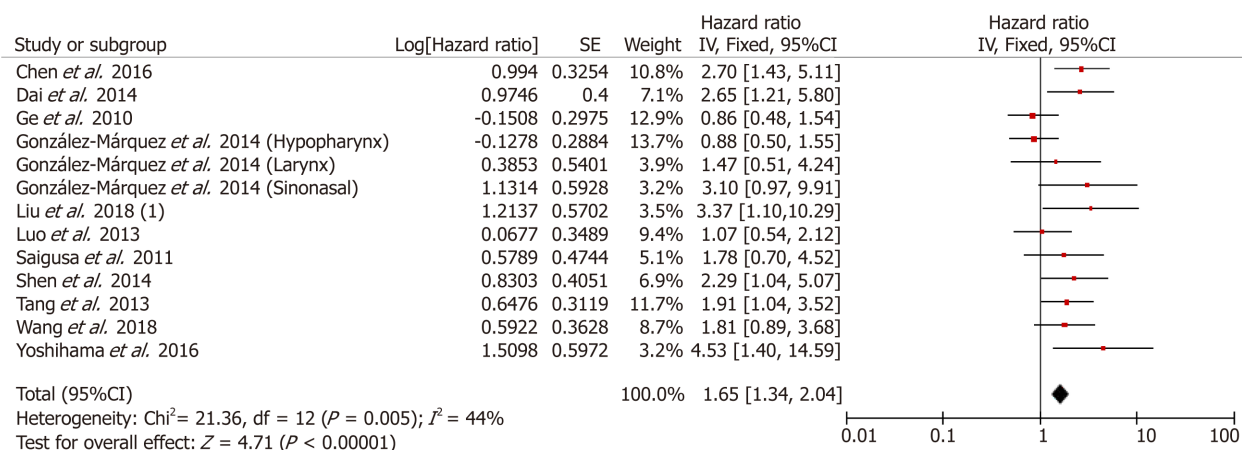
Variable	LMN				DM			
	Studies	Model ( $I^2$ )	OR (95%CI)	P-value	Studies	Model ( $I^2$ )	OR (95%CI)	P-value
Sample size								
< 150	13	R (83)	1.85 (0.96-3.56)	0.06	12	F (47)	2.16 (1.61-2.91)	< 0.0001
≥ 150	5	R (85)	0.93 (0.43-2.01)	0.11	1	N/A	0.24 (0.05-1.15)	0.007
Cancer type								
Head and neck	6	R (88)	1.89 (0.72-4.96)	0.19	7	F (39)	2.46 (1.63-3.72)	< 0.0001
Esophagus	3	R (79)	0.98 (0.24-4.04)	0.98	1	N/A	0.56 (0.09-3.57)	0.54
Cervix	-	-	-	-	1	N/A	3.12 (0.99-9.82)	0.05
Stomach	4	R (85)	0.68 (0.21-2.24)	0.53	2	R (56)	0.56 (0.16-1.96)	0.36
Breast	2	F (0)	2.87 (1.50-5.50)	0.002	-	-	-	-
Liver	1	N/A	1.68 (0.39-7.32)	0.49	1	N/A	4.80 (1.56-14.76)	0.006
Lung	1	N/A	1.74 (1.02-2.89)	0.04	-	-	-	-
Colon	1	N/A	4.15 (1.43-12.09)	0.009	1	N/A	3.04 (1.15-8.04)	0.03
Quality score								
≥ 7	12	R (88)	1.64 (0.82-3.27)	0.16	7	R (69)	2.23 (1.04-4.77)	0.04
< 7	6	R (79)	1.38 (0.60-3.18)	0.45	6	F (35)	1.71 (0.89-3.27)	0.11

DM: Distant metastasis; F: Fixed effects model; LNM: Lymph node metastasis; OR: Odds ratio; R: Random effects model.

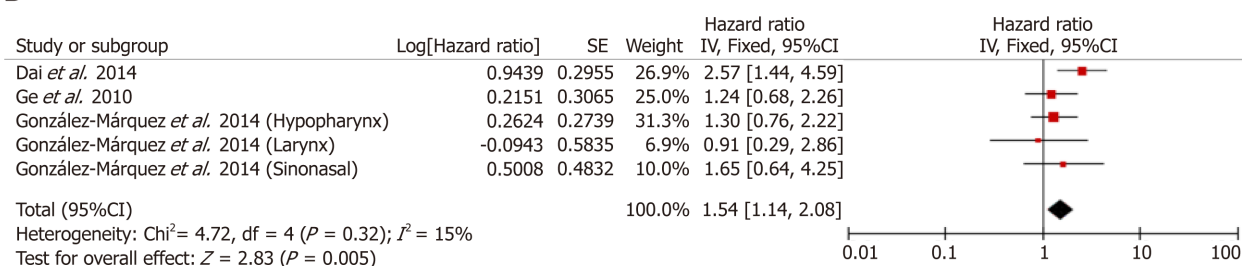
**A****B**

**Figure 2** Forest plot of the association between SOX2 expression and lymph node metastasis and distant metastasis. A: Lymph node metastasis; B: Distant metastasis.

## A



## B



**Figure 3** Forest plot of the association between high SOX2 expression and lymph node metastasis and distant metastasis. A: Lymph node metastasis; B: Distant metastasis.

## ARTICLE HIGHLIGHTS

### Research background

SOX2 is a significant regulator of pluripotent cellular transcription and it helps in the reprogramming of somatic cells to the pluripotent properties. The involvement of SOX2 in cancer biology has been recently demonstrated.

### Research motivation

Metastasis comprises the most important aspect of cancer-related mortality. Linking SOX2 expression to metastasis and subsequently to patient's survival may open novel horizons for the implementation of future therapeutic strategies that target SOX2 biological pathways.

### Research objectives

To investigate the association between SOX2 overexpression and the development of a metastatic phenotype as well as the survival patterns of patients with increased SOX2 expression.

### Research methods

A meta-analysis was conducted, including studies that recruited patients with different types of cancer and reporting SOX2 expression as either "low" or "high", and evaluating patient survival using the relevant analytical methods [overall survival (OS) and/or disease-free survival (DFS)]. A comprehensive search of articles published between 2010 and 2018 was performed in distinct scientific databases.

### Research results

A total of 20 studies involving 2643 patients (60.88% males) were included. SOX2 overexpression was significantly associated with distant metastasis (odds ratio = 1.79, 95%CI: 1.20-3.25,  $P < 0.008$ ), while it was associated with lymph node metastasis only in subgroup analyses of cancers of the colon, breast, and lung. Both OS and DFS were shorter in patients expressing high SOX2, as compared to those with low SOX2 expression (hazard ratio = 1.65, 95%CI: 1.34-2.04,  $P < 0.001$  and hazard ratio = 1.54, 95%CI: 1.14-2.08,  $P = 0.005$ , respectively).

### Research conclusions

The present study adds a comprehensive insight into the significant role of SOX2 in distant metastasis of different types of cancers and its correlation to poor prognosis rather than the



outcomes obtained by individual studies. In line with the increased research interest in SOX2, we showed that it can be used as a prognostic marker in cancer patients, while, on the other hand, new therapeutic strategies are urgently needed to target the biological pathways implicated in SOX2 overexpression for more effective cancer treatment.

### Research perspectives

Targeting SOX2 expression in cancer regimens is warranted. Future research studies should focus on developing novel drugs as well as the identification of the cut-off values of poor prognosis.

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