Forkhead box F2 as a novel prognostic biomarker and potential therapeutic target in human cancers prone to bone metastasis: a meta-analysis

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Abstract
Objective: To undertake a systematic review and meta-analysis to evaluate the prognostic value of Forkhead box F2 (FOXF2) levels in different types of cancers prone to bone metastasis.
Methods: A systematic search of publications listed in electronic databases (The Web of Science, EMBASE®, PubMed®, PMC, Science Direct and CNKI) from inception to 5 November 2020 was conducted. The hazard ratios (HRs) and 95% confidence intervals (95% CIs) were used to assess the relationship between FOXF2 levels and patient prognosis including overall survival (OS) and disease-free survival (DFS).
Results: Sixteen studies enrolling 8461 participants were included in the meta-analysis. High levels of FOXF2 were a predictor of OS (HR: 0.66; 95% CI 0.51, 0.86) and DFS (HR: 0.60; 95% CI 0.48, 0.76). The trim-and-fill analysis, sensitivity analysis and subgroup analyses stratified by the study characteristics confirmed the robustness of the results.
Conclusion: These current findings indicate that high FOXF2 levels could be an indicator of a good prognosis in cancer patients with tumours that are prone to bone metastasis. FOXF2 levels might be a clinically important prognostic biomarker.

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Introduction

Distant organ metastasis is the main cause of death in many cancer patients.[1] The bone is the most common distant metastatic site of multiple cancer types and it is affected by specific mechanisms that disrupt bone homeostasis.[2] Osteolytic metastases, characterized by destruction of the bone structure and loss of bone mass, are detected mostly in breast cancer, lung cancer, multiple myeloma, melanoma and renal cell carcinoma.[3–7] In contrast, osteoblastic metastases, characterized by excessive bone formation, are found predominantly in prostate cancer.[8] Despite advances in surgical treatment and adjuvant techniques, the prognosis for tumours that are prone to form bone metastases remains poor.[9]

The Forkhead box (FOX) transcription factor family represents a group of genetically conserved transcriptional regulators that play important roles in both healthy biological functions and tumour progression, such as invasion, differentiation and development.[10] Forkhead box F2 (FOXF2; also known as FKHL6, FREAC-2 and FREAC2) is a member of the FOX transcription factor family, which locates at human chromosome 6p25.3 (Figure 1).[11] It consists of 6028 base pairs and produces a functional protein comprising of 444 amino acids.[11] During embryonic development and tissue differentiation, FOXF2 plays a key role in maintaining tissue homeostasis by promoting mesenchymal cell differentiation and inhibiting mesenchymal transformation of adjacent epithelial cells.[12]

Recent studies have shown that FOXF2 plays a critical role in the development and poor prognosis of several types of cancer prone to bone metastasis, such as breast cancer, oesophageal squamous cell cancer, gastric cancer, hepatocellular cancer, colorectal cancer, nonsmall-cell lung cancer, prostate cancer and renal cell carcinoma.[13] For example, a previous study demonstrated that FOXF2 was a new independent predictive factor for nonsmall-cell lung cancer.[14] Decreased levels were correlated with a poor prognosis, especially for patients with stage I nonsmall-cell lung cancer.[14] Decreased FOXF2 levels were also associated with early-onset metastasis and poor prognosis in patients with histological grade II and triple-negative breast cancer; and reduced FOXF2 in intestinal fibroblasts increased colon adenoma formation, suggesting a tumour-suppressive role for FOXF2.[15,16]

A previous observational study reported that FOXF2 levels were positively associated with bone metastasis and shorter bone metastasis-free survival in patients with breast cancer.[17] Moreover, targeting FOXF2 might be a promising therapeutic strategy to manage cancer bone metastasis.[17] The role of FOXF2 in transactivating bone-related genes implies a biological function for FOXF2 in regulating bone development and remodeling.[18] A number of observational studies have separately reported the relationship between FOXF2 protein levels and survival in cancer patients.[14,15] These studies have shown uncertain and conflicting results.[14,15] There has been no meta-analysis assessing the usefulness of FOXF2 levels for the prognosis of tumours prone to metastasizing to the bone. Therefore, the current study undertook a systematic review and meta-analysis to assess the prognostic value of FOXF2 in various cancer types prone to bone metastasis in order to determine if FOXF2 levels might be an effective biomarker for tumour therapy.

Materials and methods

Search strategy

This meta-analysis strictly followed the checklist of items established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A systematic search of publications listed in
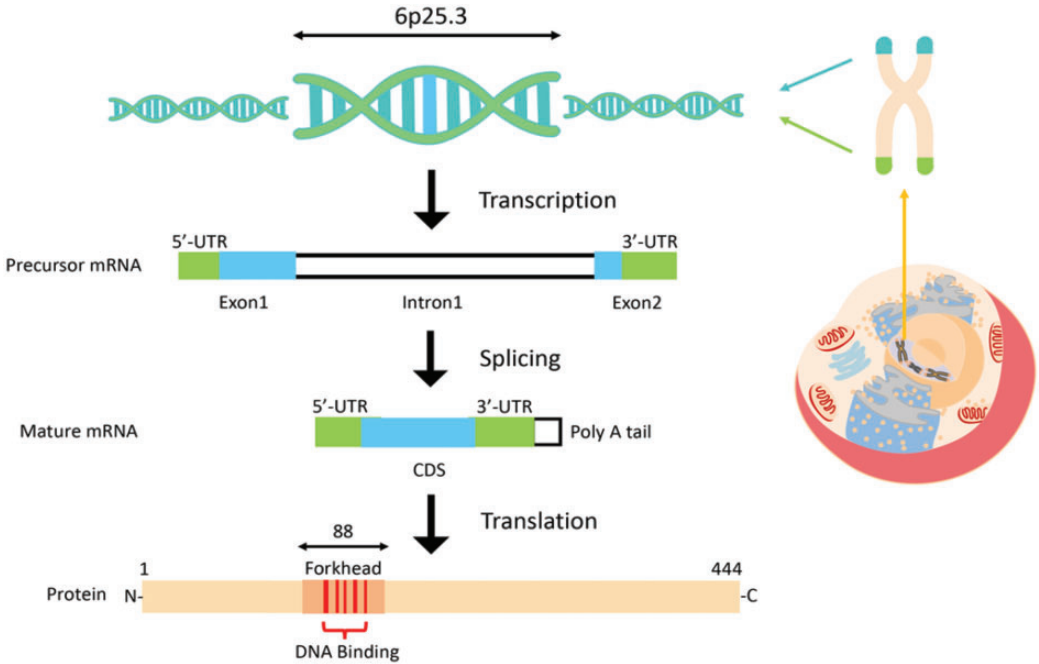
Figure 1. The structure of the transcription factor Forkhead box F2. The colour version of this figure is available at: http://imr.sagepub.com.

electronic databases (The Web of Science, EMBASE®, PubMed®, PMC, Science Direct, CNKI and Google) from inception to 5 November 2020 was conducted using the following MeSH terms: "FOXF2* or Forkhead box F2* or FOXF2 expression*", "metastasis* or bone metastasis", and "meta-analysis* or systematic review*", "cancer* or tumor* or tumour* or carcinoma*" and "prognosis* or survival outcome* or overall survival* or disease-free survival*".[19] Two reviewers (Q.C. & L.Z.) conducted an initial screening of the retrieved articles and reviews to carefully read the titles and abstracts. A manual review of references from primary or review articles was performed to identify any additional relevant studies. If there were multiple published studies from the same patient population, only the publication that included the most patients with complete information was selected. Disagreement was resolved by consensus.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they met the following criteria: (i) according to current clinical knowledge, the tumour type has a relatively high incidence of bone metastasis; (ii) studies described the levels of FOXF2 mRNA or protein in patient samples; (iii) the association between FOXF2 levels and survival status of patients with any type of tumours prone to bone metastasis was assessed; (iv) the subjects of the study were patients with cancer confirmed by pathological diagnosis, so studies of patients with precancerous lesions and benign tumours were excluded; (v) studies reported the correlation between FOXF2 levels and overall survival, disease-free survival or other survival outcomes; (vi) studies provided the risk-effect hazard ratio (HR) and its 95% confidence interval (CI) or the corresponding data could be extracted from the Kaplan–Meier survival curve.

A study meeting any of the following exclusion criteria was excluded: (i) letter to the editor, guidance, comment, review, or systematic study; (ii) studied FOXF2 levels in animal models or cell lines; (iii) duplicate studies were excluded by verifying the names of the authors and the study details; (iv) the research data were incomplete and the risk effect indicator value could not be calculated because of lack of data; (v) the conclusion of the study was not related to the levels of FOXF2.

Quality assessment

According to the Cochrane Collaboration, the Newcastle-Ottawa Scale (NOS) was used to perform a quality assessment of the included studies.[20] The score assesses eight methods in three dimensions, including selection, comparability and outcome.[20] The reviewers judged the quality of each study within the scope of the eight items included in each tool.

Data extraction and data items

The data extraction was carried out independently by two researchers (Q.C. & L. Z.) and a third researcher (F.C.) was consulted in cases of disagreement. In order to standardize the data extraction process, a predefined Microsoft Excel® 2010 (Microsoft Corp., Redmond, WA, USA) spreadsheet was prepared based on previous studies focusing on similar topics and the PRISMA guidelines.[21] The following data were extracted from all included studies: (i) first author, year of publication and country; (ii) age, sex, population, cancer type, source of sample, methods of detection and follow-up period; (iii) clinicopathological parameters such as country, cancer type, tumour size, TNM stage and HRs with 95% CIs for overall survival (OS), recurrence-free survival (RFS), disease-free survival (DFS), cancer-specific survival (CSS) and distant metastasis-free survival (DMFS). The HRs and 95% CIs were extracted from the multivariate analysis. If only Kaplan–Meier survival curves were available, the Engauge Digitizer software (version 4.1) was used to extract the survival information from the plots; and Tierney's method was used to indirectly calculate HRs and 95% CIs.

Statistical analyses

Statistical analyses were performed using RevMan software version 5.3 (The Cochrane Collaboration, Oxford, UK) and STATA 15.0 (Stata Corporation, College Station, TX, USA). The prognostic value of FOXF2 levels was assessed across all included studies using pooled HR (95% CI) values. For the FOXF2 upregulated group, an $HR > 1$ indicated worse survival. If there was no overlap between the 95% CI and an HR of 1, the impact of FOXF2 on survival was considered statistically significant. χ^2-test-based Cochran's Q and I^2 statistics were used to calculate the heterogeneity of the individual HRs. For Q statistics, a $P < 0.05$ was considered statistically significant. For I^2 statistics, $I^2 < 25\%$ indicated no heterogeneity, $25\% < I^2 < 50\%$ indicated moderate heterogeneity, and $I^2 > 50\%$ indicated strong heterogeneity. If no obvious heterogeneity was found among the studies, a fixed effects model was used to combine the individual HR estimates; otherwise, a random effects model was applied. The Z test was used and then the significance of the pooled HRs were determined where $P < 0.05$ was considered statistically significant. Subgroup analysis was conducted as an additional parameter based on the heterogeneity of the relative contributions of one or more key variables, including the time period, tumour stage and other demographic factors.[22] Finally, funnel plot, Egger's linear regression asymmetry test and sensitivity analysis were performed to estimate the

publication bias.[23] Duval's non-parametric trim-and-fill procedure was applied to further assess the possible effect of publication bias.[24]

Results

A total of 825 relevant studies were retrieved from the electronic databases and Google (Figure 2). After 750 duplicates were removed, 75 records remained for further evaluation. Of these, 47 studies were excluded after screening the titles, abstracts and data because they did not include data on survival and FOXF2 levels or they did not discuss the prognostic significance of FOXF2 in cancer patients. After removing duplicates and abstract screening, 28 studies remained. Double verification of the reference lists of the remaining narrative reviews and meta-analyses revealed no further relevant missed studies.[25] After full-text screening, a further 12 articles were removed because of insufficient data, inability to calculate HR and 95% CI values, improper patient data, absence of Kaplan–Meier survival curves/HR values or no accurate investigation of the association between FOXF2 levels and survival outcomes. A total of 16 articles met the inclusion criteria and were included in this systematic review
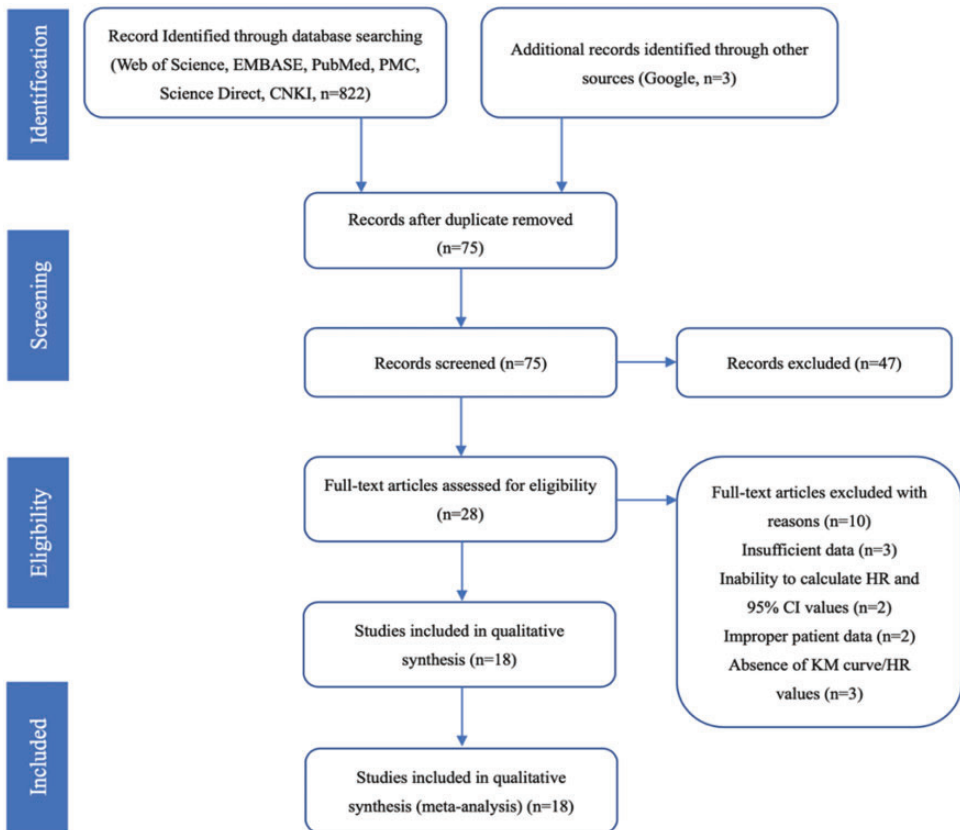

Figure 2. Flow diagram of eligible studies showing the number of citations identified, retrieved and included in the final meta-analysis of the role of the levels of the transcription factor Forkhead box F2 as a prognostic biomarker for bone metastases.

and meta-analysis.[14,16–18,26–37] Figure 2 presents an overview of the selection procedure.

The analysis included 16 studies with a total of 8461 participants (Table 1).[14,16–18,26–37] All 16 included studies were published from 2009 to 2019. Most of the studies were performed in China ($n = 12$); although other studies performed in Hong Kong, Slovenia, South Korea, USA and Switzerland were included. The studies examined populations with multiple types of cancer prone to bone metastasis, including breast cancer (BC) ($n = 9$), gastric cancer (GC) ($n = 2$), nonsmall-cell lung cancer (NSCLC) ($n = 2$), oesophageal squamous cell cancer (ESCC) ($n = 2$), renal cell carcinoma (RCC) ($n = 1$), hepatocellular cancer (HC) ($n = 1$) and colorectal cancer (CC) ($n = 1$). All of the studies provided information about sample size, sample source and HRs. All of the studies included in this meta-analysis were considered to be of good quality based on the NOS score. Reverse transcription–polymerase chain reaction was used to detect FOXF2 levels in all of the studies, although some studies also assessed FOXF2 levels using Western blotting and immunohistochemistry. Six studies mentioned age and seven included information on sex and tumour size. Almost all of the studies included information on the TNM stage and follow-up period. All 18 articles focused on the association between FOXF2 and survival outcomes, including OS, DFS, RFS, DMFS or CSS; two articles investigated both OS and DFS.

Seven articles comprising 2572 cases were included in the meta-analysis for OS (Figure 3).[26,28–33] Pooled HRs and 95% CIs were used to evaluate the correlation between FOXF2 levels and OS. FOXF2 levels were associated with increased OS in patients with various cancers prone to bone metastasis (HR = 0.66; 95% CI 0.51, 0.86; $P = 0.002$; $Z = 3.04$). Higher levels of FOXF2 decreased the likelihood of death by 34%, which suggests that FOXF2 might be an excellent predictor of survival in patients with cancers prone to bone metastasis.

Strong heterogeneity ($I^2 = 63\%$, $P = 0.008$) was observed when the pooled HR for OS was analysed using a random effects model. Sensitivity analysis indicated that the pooled HR was not significantly affected by the exclusion of any of the studies. As shown in Table 2 (Figure 4), subgroup analyses were performed to identify the source of the heterogeneity, including subgroups based on location (China and other countries), cancer type (BC, GC, NSCLC, ESCC, HC, CC and RCC), follow-up period (≥ 120 months and < 120 months), sample size (≥ 200 and < 200), sample source (tissue and datasets), detection methods (tissue microarray and immunohistochemistry) and HR extraction (reported and Kaplan–Meier survival curve). These analyses found that higher levels of FOXF2 were significantly correlated with better OS regardless of the study location, follow-up period, sample size, detection method and HR extraction. However, increased levels of FOXF2 had different prognostic values in different cancer types prone to bone metastasis. Higher levels of FOXF2 were associated with better OS in patients with GC (HR = 0.42; 95% CI 0.25, 0.71; $P = 0.001$), NSCLC (HR = 0.78; 95% CI 0.63, 0.97; $P = 0.020$) and HC (HR = 0.65; 95% CI 0.42, 0.99; $P = 0.050$), whereas higher FOXF2 levels were associated with poorer OS in patients with ESCC (HR = 2.39; 95% CI 1.36, 4.18; $P = 0.002$). There was no correlation between OS and FOXF2 levels in patients with BC (HR = 1.09; 95% CI 0.50, 2.40), CC (HR = 0.27; 95% CI 0.03, 2.10) or RCC (HR = 0.94; 95% CI 0.79, 1.12). Additionally, in the subgroup analysis by sample source, there was a strong association between OS and FOXF2 levels when

Table 1. Major characteristics of the 16 studies included in a meta-analysis of the role of the levels of the transcription factor Forkhead box F2 as a prognostic biomarker for bone metastases.[14,16–18,26–37]

Author	Country	Type of cancer	Sample size (F/M)	Methods of detection	Follow-up period, months	Age, years	Tumour size	TNM stage	HR	End point	Quality rating NOS
Tian et al., 2015	China	BC	427	RT-PCR	60	NA	NA	NA	KM	DFS	Satisfactory
Higashimori et al., 2018	China	CC	103	RT-PCR, WB, IHC	60	NA	NA	I–IV	KM	OS	Good
Kong et al., 2016[4]	China	GC	243	RT-PCR	60	NA	NA	I–IV	KM	OS	Good
	China/Hongkong	NSCLC	84 (62/22)	RT-PCR	120	>60 (34) ≥60 (50)	Provided	I–IV	HR/KM	OS/DFS	Satisfactory
Kong et al., 2013	China	BC	305	RT-PCR	120	≤45 (78) >45 (227)	Provided	I–III	KM	OS/DFS	Good
Wang et al., 2018	China	BC	914	RT-PCR, WB, IHC	120	NA	NA	NA	KM	OS/DFS	Good
	China	BC	34		60	NA	NA	NA	KM	DFS	Good
Chen et al., 2017	China	ESCC	135 (126/9)	RT-PCR	125	<60 (58) ≥60 (77)	NA	I–IV	HR/KM	OS	Good
Cai et al., 2015	China	BC	156	RT-PCR, WB, IHC	120	NA	NA	NA	KM	DFS	Satisfactory
Yang et al., 2009	China	BC	233	RT-PCR	60	≤50 (122) >50 (111)	Provided	I–III	KM	DFS	Satisfactory
Hauptman et al., 2019	Slovenia	CC	115 (61/54)	RT-PCR	NA	NA	Provided	I–IV	HR	OS	Good
Shi et al., 2016	China	HC	295 (261/34)	RT-PCR, WB, IHC	40.3	<52 (156) ≥52 (139)	Provided	I–IV	HR/KM	OS/DFS	Good
Seok et al., 2017	Korea	NSCLC	804 (588/216)	RT-PCR	120	<64 (393) ≥64 (411)	NA	I–IIIA	HR/KM	OS/DFS	Satisfactory
Lo, 2018	USA	BC	3554	RT-PCR	250	NA	NA	NA	HR/KM	RFS	Satisfactory
Zheng et al., 2015	China	ESCC	188 (51/137)	RT-PCR	129	NA	Provided	I–III	HR/KM	CSS	Good
Wang et al., 2019	China	BC	368	RT-PCR	150	NA	NA	NA	HR/KM	DMFS	Good
Meyer-Schaller et al. 2018	Switzerland	BC	352	RT-PCR	240	NA	NA	NA	KM	OS	Good
Jia et al., 2018	China	RCC	525 (184/341)	RT-PCR	150	NA	Provided	I–IV	HR	OS	Good

F, female; M, male; HR, hazard ratio; NOS, Newcastle-Ottawa Scale; BC, breast cancer; RT–PCR, reverse transcription–polymerase chain reaction; NA, not available; KM, Kaplan-Meier; DFS, disease-free survival; CC, colorectal cancer; WB, Western blot; IHC, immunohistochemistry; OS, overall survival; GC, gastric cancer; NSCLC, Nonsmall-cell lung cancer; ESCC, oesophageal squamous-cell carcinoma; HC, hepatocellular carcinoma; RFS, recurrence-free survival; CSS, cancer-specific survival; DMFS, distant metastasis-free survival; RCC, renal cell carcinoma.
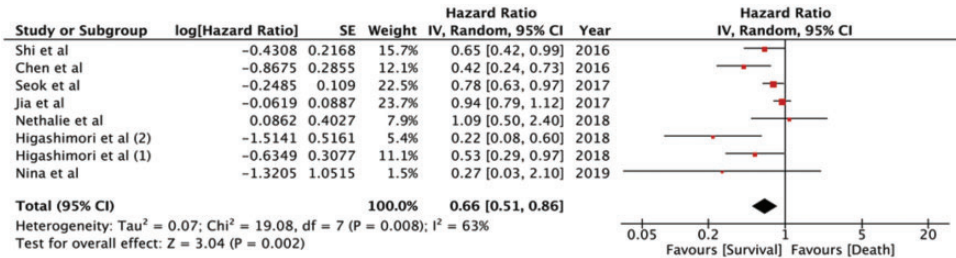
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Shi et al	−0.4308	0.2168	15.7%	0.65 [0.42, 0.99]	2016
Chen et al	−0.8675	0.2855	12.1%	0.42 [0.24, 0.73]	2016
Seok et al	−0.2485	0.109	22.5%	0.78 [0.63, 0.97]	2017
Jia et al	−0.0619	0.0887	23.7%	0.94 [0.79, 1.12]	2017
Nethalie et al	0.0862	0.4027	7.9%	1.09 [0.50, 2.40]	2018
Higashimori et al (2)	−1.5141	0.5161	5.4%	0.22 [0.08, 0.60]	2018
Higashimori et al (1)	−0.6349	0.3077	11.1%	0.53 [0.29, 0.97]	2018
Nina et al	−1.3205	1.0515	1.5%	0.27 [0.03, 2.10]	2019
Total (95% CI)			**100.0%**	**0.66 [0.51, 0.86]**	

Heterogeneity: Tau² = 0.07; Chi² = 19.08, df = 7 (P = 0.008); I² = 63%
Test for overall effect: Z = 3.04 (P = 0.002)

Figure 3. Forest plot of the meta-analysis to evaluate the association between the levels of the transcription factor Forkhead box F2 and overall survival in patients with tumours that usually metastasise to bone. [26,28–33]

Table 2. Results of subgroup analyses of the association between the levels of the transcription factor Forkhead box F2 and overall survival or disease-free survival.

Comparison variable	Overall Survival			Disease-free survival		
	Included studies	HR (95% CI)	P-value	Included studies	HR (95% CI)	P-value
Total	8	0.79 (0.70, 0.89)	$P < 0.001$	8	0.70 (0.59, 0.83)	$P < 0.001$
Country						
China	5	0.80 (0.69, 0.92)	$P = 0.002$	7	0.69 (0.60, 0.78)	$P < 0.001$
Others	3	0.79 (0.64, 0.97)	$P = 0.020$	1	0.89 (0.76, 1.04)	NS
Cancer type						
BC	1	1.09 (0.50, 2.40)	0.830	5	0.71 (0.61, 0.82)	$P < 0.001$
GC	2	0.42 (0.25, 0.71)	$P = 0.001$	–	–	–
NSCLC	1	0.78 (0.63, 0.97)	$P = 0.020$	2	0.85 (0.73, 0.99)	$P = 0.040$
ESCC	1	2.39 (1.36, 4.18)	$P = 0.002$	–	–	–
HC	1	0.65 (0.42, 0.99)	NS	1	0.67 (0.50, 0.91)	$P = 0.010$
CC	1	0.27 (0.03, 2.10)	0.210	–	–	–
RCC	1	0.94 (0.79, 1.12)	0.490	–	–	–
Follow-up period						
≥ 120 months	4	0.84 (0.74, 0.96)	$P = 0.010$	5	0.80 (0.70, 0.91)	$P < 0.001$
< 120 months	3	0.55 (0.39, 0.76)	$P = 0.003$	3	0.70 (0.60, 0.83)	$P < 0.001$
Sample size						
≥ 200	5	0.84 (0.74, 0.95)	$P = 0.006$	5	0.78 (0.69, 0.88)	$P < 0.001$
< 200	3	0.48 (0.31, 0.68)	$P < 0.001$	3	0.71 (0.59, 0.87)	$P < 0.001$
Sample source						
Tissue	5	0.69 (0.58, 0.82)	$P < 0.001$	6	0.66 (0.52, 0.84)	$P < 0.001$
Datasets	3	0.91 (0.77, 1.08)	NS	2	0.76 (0.67, 0.87)	$P < 0.001$
Detection methods						
TMA	6	0.82 (0.72, 0.93)	$P = 0.003$	5	0.78 (0.69, 0.88)	$P < 0.001$
IHC	2	0.61 (0.43, 0.86)	$P = 0.005$	3	0.74 (0.62, 0.88)	$P < 0.001$
HR extraction						
Reported	4	0.82 (0.72, 0.93)	$P = 0.002$	3	0.81 (0.71, 0.93)	$P = 0.003$
Survival curve	4	0.54 (0.36, 0.83)	$P = 0.005$	5	0.71 (0.61, 0.82)	$P < 0.001$

HR, hazard ratio; CI, confidence interval; BC, breast cancer; GC, gastric cancer; NSCLC, Nonsmall-cell lung cancer; ESCC, oesophageal squamous-cell carcinoma; HC, hepatocellular carcinoma; CC, colorectal cancer; RCC, renal cell carcinoma; TMA, tissue microarray; IHC, immunohistochemistry; NS, no significant association ($P \geq 0.05$).
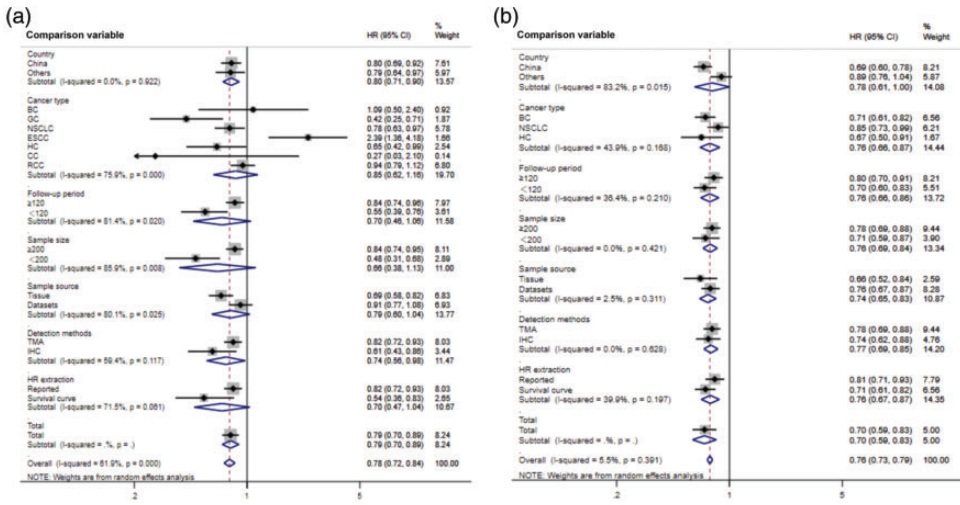
(a)

(b)

Figure 4. Forest plots of the subgroup meta-analysis to evaluate the association between the levels of the transcription factor Forkhead box F2 and overall survival (a) and disease-free survival (b) in patients with tumours that usually metastasise to bone.[14,16–18,26–37]
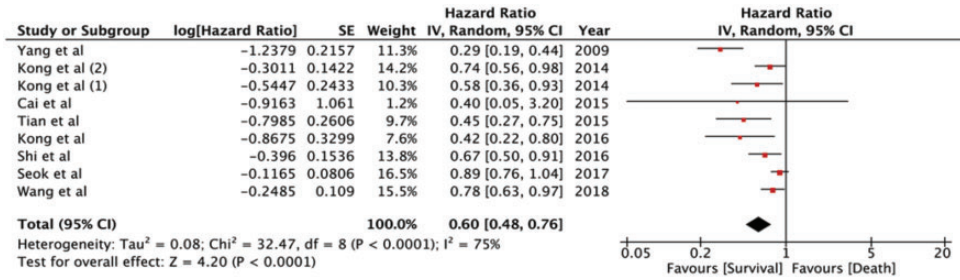

Figure 5. Forest plot of the meta-analysis to evaluate the association between the levels of the transcription factor Forkhead box F2 and disease-free survival in patients with tumours that usually metastasis to bone.[16,26,27,33–36]

tissue was used to measure the levels of FOXF2 (HR = 0.69; 95% CI 0.58, 0.82; $P < 0.001$). However, no significant correlation was observed between OS and FOXF2 levels in studies in which the sample source was a dataset (HR = 0.91; 95% CI 0.77, 1.08).

Eight studies examined the association between FOXF2 expression and DFS.[14,16,26,27,33–36] As shown in Figure 5, FOXF2 levels had a significant positive effect on DFS (HR = 0.60; 95% CI 0.48, 0.76; $P < 0.0001$). A random effects model

was used because there was high heterogeneity among the studies ($I^2 = 75\%$, $P < 0.001$). Due to the heterogeneity, a sensitivity analysis was performed by excluding each study. After excluding one study,[36] the pooled HR shifted to 0.70 (95% CI 0.59, 0.83), the heterogeneity decreased ($I^2 = 48\%$, $P = 0.06$) and the robustness of the result was confirmed. In order to avoid heterogeneity, further subgroup analysis was conducted.[38] Table 2 shows the results of the subgroup analysis for DFS based on the clinical

characteristics described above (Figure 4). The results showed that increased FOXF2 levels were predictive of better DFS regardless of cancer type, follow-up period, sample size, sample source, detection method and HR extraction. When stratified by location, increased levels of FOXF2 predicted a significantly improved DFS among Chinese patients (HR = 0.69; 95% CI 0.60, 0.78; $P < 0.001$). However, no association was observed in patients from other countries (HR = 0.89; 95% CI 0.76, 1.04).

Limited data were available to assess the prognostic value of FOXF2 levels for RFS, DMFS and CSS. One dataset each evaluated the association between FOXF2 levels and RFS and DMFS for BC and one dataset examined the association between FOXF2 levels and CSS in ESCC.[18,28,35] The results from two studies indicated that elevated FOXF2 levels were associated with shorter RFS and DMFS among BC patients (HR = 1.25; 95% CI 1.11, 1.39; HR = 2.23; 95% CI 1.16, 3.12; respectively). However, in patients with ESCC, decreased FOXF2 levels were significantly correlated with an unfavourable CSS (HR = 1.71; 95% CI 1.08, 2.71).

Figures 6 and 7 show the results of the Egger's linear regression and Begg's funnel plot tests, respectively, which were used to
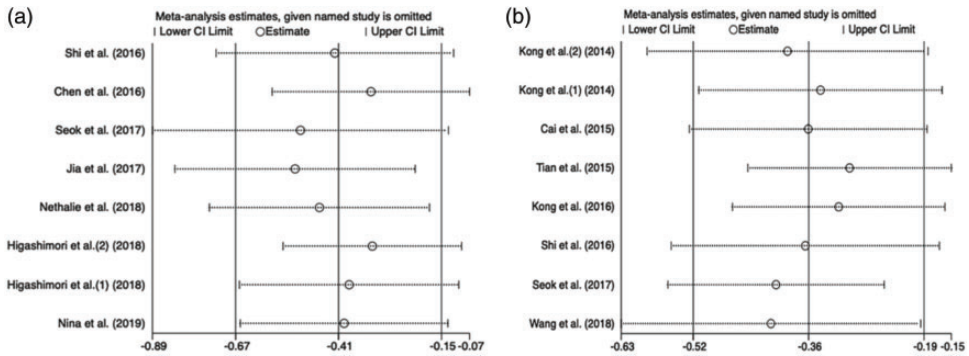

Figure 6. Egger's linear regression tests of the pooled hazard ratios for the meta-analysis of the association between the levels of the transcription factor Forkhead box F2 and overall survival (a) and disease-free survival (b) in patients with tumours that usually metastasise to bone.[14,16–18,26–37]
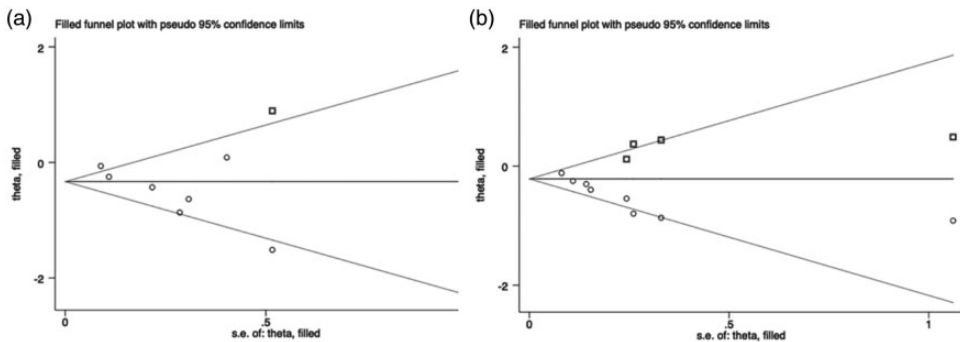

Figure 7. Begg's funnel plots for the meta-analysis of the association between the levels of the transcription factor Forkhead box F2 and overall survival (a) and disease-free survival (b) in patients with tumours that usually metastasise to bone.[14,16–18,26–37]

assess the publication bias in the current meta-analysis. For OS, the shape of the funnel plots appeared slightly asymmetrical, which might indicate the presence of publication bias ($P = 0.035$ for Begg's test; $P = 0.174$ for Egger's test). After adding two studies by the trim-and-fill method to adjust for publication bias, the corrected pooled HR of OS was 0.83 (95% CI 0.74, 0.94; $P = 0.003$). For DFS, there was also evidence of asymmetry, suggesting that the asymmetry could be attributed mainly to publication bias, which was further confirmed with Begg's and Egger's tests ($P = 0.035$ and $P = 0.006$, respectively). An adjusted random effects summary HR of 0.78 (95% CI 0.65, 0.94; $P = 0.007$) was obtained using the trim-and-fill method when including the four missing studies.

Discussion

As transcription factors, the members of the FOX family play important roles in cell cycle regulation, embryonic development, aging, immune regulation and other biological processes.[39–41] Increasing evidence has demonstrated that the regulation of FOXF2 is related to the aggressive phenotype in cancer cells and promotes cell invasion, proliferation and metastasis.[42] To the best of our knowledge, no systematic review and meta-analysis has investigated the relationship between FOXF2 levels and oncological outcomes. The results of this current meta-analysis demonstrated that the prognostic role of FOXF2 in cancer was consistent with previous studies in which FOXF2 levels were found to be positively correlated with bone metastasis in breast cancer.[17,42–44] This current study extends the role of FOXF2 as a prognostic marker for bone metastasis-prone cancers. The combined results of all published studies in the field indicate that increased FOXF2 levels results in positive clinical outcomes and prognosis for patients in cancer types prone to bone

metastasis. The limitations of this current study were generally attributed to the absence of high-quality clinical studies published in this area of research. The aim of this study was to help the clinical decision-making process by developing a prognostic factor, not only to help healthcare professionals predict clinical outcomes, but also to prevent cancer metastasis, particularly bone metastasis in patients with cancer. The results obtained will contribute to the ability of physicians and patients to make informed decisions and may lead to a better quality of life for cancer patients.

The present meta-analysis systematically aggregated the data from 16 studies including 8461 cancer patients that assessed the relationship between FOXF2 levels and OS, DFS, RFS, CSS and DMFS.[14,16–18,26–37] These current results demonstrated that FOXF2 might be a potentially promising prognostic biomarker. The upregulation of FOXF2 levels was independently associated with better OS (HR = 0.66; 95% CI 0.51, 0.86; $P = 0.002$) and DFS (HR = 0.60; 95% CI 0.48, 0.76; $P < 0.0001$). Further subgroup analysis indicated that FOXF2 had a substantial prognostic role in most of the subgroups examined, including subgroups based on study location, cancer type, follow-up period, sample size, sample source, detection methods and HR extraction. This current meta-analysis was supported by the evaluation of different modules of publication bias, including the use of Begg's and Egger's tests, funnel plots and the trim-and-fill method. Overall, these current findings indicate that high FOXF2 levels could be an indicator of a good prognosis in cancer patients with tumours that are prone to bone metastasis.

The FOX transcription factors are highly conserved, although they serve different functions in cancer and other diseases.[45,46] Three previous systematic reviews have outlined the relationship between levels of the FOX family members and outcomes in multiple cancer

types.[19,47,48] The first meta-analysis included eight studies involving 529 patients with gastric cancer.[47] The meta-analysis demonstrated that the levels of FOXM1 were associated with TNM stage (odds ratio [OR] = 0.482; 95% CI 0.275, 0.845; $P = 0.011$), depth of invasion (OR = 0.617; 95% CI 0.382, 0.998; $P = 0.049$), lymph node metastasis (OR = 2.084; 95% CI 1.305, 3.328; $P = 0.002$) and 5-year overall survival (OR = 0.180; 95% CI 0.095, 0.341; $P < 0.001$).[47] Another meta-analysis studied the prognostic value of FOXC1 in various cancers from 16 studies and demonstrated a statistically significant association between FOXC1 protein levels and survival (HR = 1.186; 95% CI 1.122, 1.255; $P < 0.001$).[19] A total of 1520 patients from six studies (seven cohorts) with multiple malignant tumours were included in a third meta-analysis.[48] The meta-analysis found that high FOXQ1 expression could significantly predict worse OS, with a pooled HR of 1.38 (95% CI 1.17, 1.59; $P < 0.001$).[48] The subgroup analysis suggested that elevated levels of FOXQ1 were associated with worse OS in patients with hepatocellular carcinoma (HR = 1.34; 95% CI 1.11, 1.57; $P < 0.001$) and other cancers (HR = 1.62; 95% CI 1.09, 2.14; $P < 0.001$).[48]

Previous research has examined the mechanism underlying the association between the levels of FOXF2 and poor prognosis in patients with multiple types of cancer (Table 3).[16,18,26,27,30,34,35,49–57] Other studies suggested that the regulation of FOXF2 levels is involved in tumorigenesis, development and metastasis in breast cancer and other cancer types.[28,32] Studies suggest that FOXF2 may be dependent on different breast cancer subtypes, thereby affecting treatment response and prognosis of breast cancer patients.[16,18] FOXF2 is known to be highly expressed in triple-negative/basal-like breast cancers and lowly expressed in luminal subtype breast

cancers, while independently predicting poor prognosis in triple-negative breast cancer patients.[16] Bone metastasis is a process attributed to the loss of intercellular cohesion of s welling cells, cell migration, angiogenesis, entry into the humoral circulation, evasion of local immune responses and colonization of bone.[58] Further research revealed the role and specific mechanism of FOXF2 in breast cancer bone metastasis, in which FOXF2 initiates the epithelial-to-bone fusion transition through multiple counteracting activation of the BMP4/SMAD1 signalling pathway.[17] Since the exact role of FOXF2 in other tumours prone to bone metastases remains unknown, further studies in larger populations are needed to gain a deeper understanding of the mechanisms underlying the development of bone metastasis in different types of cancer.

This current meta-analysis had several strengths. First, the studies chosen for the systematic review and meta-analysis were published in multiple online databases with no publication status limitation, ensuring all the relevant studies were selected.[59] Secondly, a comprehensive and clear search strategy was used to identify studies investigating the prognostic value of FOXF2 levels in cancers prone to bone metastasis. The search strategy followed a prespecified protocol to guide the collection of evidence, noting any deviations from protocol. Thirdly, the studies included in this meta-analysis provided a sample size of 8461, which should have enabled this meta-analysis to obtain accurate and reasonable results. Fourthly, appropriate subgroup analyses were used for key characteristics, including study location, cancer type, follow-up period, sample size, sample source, detection method and HR extraction, which confirmed that most of the studies' characteristics were consistent. Fifthly, the included studies reported various survival endpoints (OS, DFS, RFS,

Table 3. The expression, target gene and molecular mechanism of the transcription factor Forkhead box F2 (FOXF2) in various cancer types. [16,18,26,27,30,34,35,49–57]

Tumour type	FOXF2 levels	Key gene target	Key message	Citation
Breast cancer	FOXF2↓	miR-301	FOXF2 is targeted by miR-301 and miR-301 depletion reduced Wnt5a expression via the miR-301/FOXF2/Wnt5a axis.	Shi et al.[26]
	FOXF2↓	NR	FOXF2 expression indicates the early-onset metastasis and poor prognosis for patients with histological grade II and triple-negative breast cancer.	Kong et al.[16]
	FOXF2↓	TWIST1	FOXF2 deficiency enhances metastatic ability of BLBC cells by activating the EMT programme through upregulating the transcription of TWIST1.	Wang et al.[35]
	FOXF2↓	DNMT/SP1	Expression and function of FOXF2 in breast cancer cells are regulated through the combined effects of DNA methylation and SP1 transcriptional regulation.	Tian et al.[34]
	FOXF2↓	FOXC2	FOXF2 transcriptionally targets FOXC2 and suppresses EMT and multidrug resistance by negatively regulating the transcription of FOXC2 in BLBC cells.	Cai et al.[27]
	FOXF2	CDK2/ TGFβ	FOXF2 possesses a dual function to negatively regulates DNA replication or drives EMT and metastatic progression.	Lo[18]
	FOXF2↓	miR-182	miR-182 promote cell proliferation and migration in TNBC possible via downregulation of FOXF2.	Yu et al.[49]
	FOXF2↓	MAZ	The MAZ-FOXF2 axis reflect the pleiotropic nature of multifunctional transcription factors in regulating the different stages of cancer development and progression.	Yu et al.[50]
	FOXF2↓	miR-200c	miR-200c could inhibit the metastasis of breast cancer cells by downregulating FOXF2 expression.	Zhang et al.[51]
	FOXF2↓	VEGF-C	FOXF2 controls the activation of the VEGF-C/VEGFR3 signalling pathway in BLBC cells.	Wang et al.[35]
	FOXF2↓	NCoR1	FOXF2 functioned as a transrepressor by recruiting NCoR1-HDAC3 to the promoter of target genes in BLBC cells.	Kang et al.[52]
Hepatocellular cancer	FOXF2↓	NR	FOXF2 downregulation was observed in HCC tissues compared with peritumorous tissues, and its expression levels were correlated with overall survival and recurrence-free survival in patients with HCC. RNAi-mediated silencing of the FOXF2 gene in the cell line significantly promoted proliferation and anti-apoptosis.	Shi et al.[26]

Table 3. Continued.

Tumour type	FOXF2 levels	Key gene target	Key message	Citation
	FOXF2↓	miR-519a	miR-519a regulates FOXF2 abundance in HCC. miR-519a may potentiates proliferation and inhibits apoptosis of HCC cells by targeting FOXF2.	Shao et al.[53]
	FOXF2↓	MET	FOXF2 induced MET in cancer cells that might facilitate the colonization of circulating tumour cells and the formation of metastasis.	Dou et al.[54]
Cervical cancer	FOXF2↓	Wnt	FOXF2 inhibits Hela cell proliferation, migration and invasion through regulating the Wnt signalling pathway.	Zhang et al.[55]
Gastric cancer	FOXF2↓	IRF2BPL	FOXF2-mediated upregulation of the E3 ligase IRF2BPL drives ubiquitylation and degradation of β-catenin in gastric cancer, blunting Wnt signalling and suppressing carcinogenesis.	Higashimori et al.[30]
	FOXF2↓	SRF	FOXF2 regulation of SRF/myocardin transcriptional complexes and altered transcriptional activity of contractile protein genes in the stomach of patients suggest that SRF containing transcriptional complexes may play a central role in the pathological changes that lead to gastric cancer.	Herring et al.[56]
Prostate cancer	FOXF2↓	miR-185-p	The level of FOXF2 expression is downregulated by miR-185-p in prostate cancer.	Hirata et al.[57]

miR, micro RNA; Wnt, wingless; NR, no response; TWIST1, twist family bHLH transcription factor 1; BLBC, basal-like breast cancer; EMT, epithelial-mesenchymal transition; DNMT, DNA methyltransferase 1; SP1, sp1 transcription factor; FOXC2, forkhead box c2; CDK2, cyclin dependent kinase 2; TGFβ transforming growth factor beta 1; TNBC, triple negative breast cancer; MAZ, myc associated zinc finger protein; VEGF-C, vascular endothelial growth factor c; VEGFR3, vascular endothelial growth factor receptor 3; NCoR1, nuclear receptor corepressor 1; HDAC3, histone deacetylase 3; HCC, hepatocellular carcinoma; RNAi, RNA interference; MET, mesenchymal-epithelial transition; IRF2BPL, interferon regulatory factor 2 binding protein like; SRF, serum response factor.

CSS and DMFS) and this ensured analysis of all the included cancer survival data. Lastly, the standard PRISMA guidelines were used to assess the quality of the evidence. Additionally, many factors that could have influenced the pooled results were extracted to objectively assess the data so that reasonable methodological quality could be confirmed for the majority of the studies.

This current meta-analysis had several limitations. First, some of the information in the included studies was incomplete. For example, clinicopathological parameters will affect the results of the corresponding HR for survival curve processing. Secondly, different methods were used to determine the levels of FOXF2, which may cause statistical heterogeneity. Thirdly, the populations of the included studies were Chinese, Korean, American, Slovenian and Swiss, and many other ethnicities were not included, so the results might be more representative of Asians. Therefore, an ethnicity bias may exist. Fourthly, some of the HRs and corresponding 95% CIs were not directly available, so survival data were extracted from the Kaplan–Meier curves. These data were less reliable than those directly obtained from survival data, which might affect the overall group analysis. Finally, studies regarding various tumours did not have a consistent cut-off value for FOXF2, which may limit the general applicability of the findings. Therefore, a unified cut-off value for FOXF2 is warranted. Because of these limitations, the current outcomes should be interpreted with caution and the conclusions of this meta-analysis require detailed consideration.[60–62]

In conclusion. this current systematic review and meta-analysis demonstrated that FOXF2 may be a clinically important prognostic factor for patients with various types of cancer prone to bone metastasis. FOXF2 might be a potential biomarker for prognosis and response to therapy.

High-quality studies with large patient cohorts using modern sequencing technologies are needed to confirm the validity of the predictive role of FOXF2 for clinical guidance in cancer.

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References

1. Bergers G and Fendt SM. The metabolism of cancer cells during metastasis. *Nat Rev Cancer* 2021; 21: 162–180. DOI: 10.1038/s41568-020-00320-2.
2. Wang M, Xia F, Wei Y, et al. Molecular mechanisms and clinical management of cancer bone metastasis. *Bone Res* 2020; 8: 30. DOI: 10.1038/s41413-020-00105-1.
3. Mandal CC. Osteolytic metastasis in breast cancer: effective prevention strategies. *Expert Rev Anticancer Ther* 2020; 20: 797–811. DOI: 10.1080/14737140.2020.1807950.
4. Wang M, Chao CC, Chen PC, et al. Thrombospondin enhances RANKL-dependent osteoclastogenesis and facilitates lung cancer bone metastasis. *Biochem Pharmacol* 2019; 166: 23–32. DOI: 10.1016/j.bcp.2019.05.005.

5. Idowu BM. Prostate carcinoma presenting with diffuse osteolytic metastases and supra-clavicular lymphadenopathy mimicking multiple myeloma. *Clin Case Rep* 2017; 6: 253–257. DOI: 10.1002/ccr3.1336.

6. Wang J, Chen GL, Cao S, et al. Adipogenic niches for melanoma cell colonization and growth in bone marrow. *Lab Invest* 2017; 97: 737–745. DOI: 10.1038/labinvest.2017.14.

7. Umer M, Mohib Y, Atif M, et al. Skeletal metastasis in renal cell carcinoma: A review. *Ann Med Surg (Lond)* 2018; 27: 9–16. DOI: 10.1016/j.amsu.2018.01.002.

8. Elshafae SM, Dirksen WP, Alasonyalilar-Demirer A, et al. Canine prostatic cancer cell line (LuMa) with osteoblastic bone metastasis. *Prostate* 2020; 80: 698–714. DOI: 10.1002/pros.23983.

9. Kim R and Kin T. Clinical Perspectives in Addressing Unsolved Issues in (Neo) Adjuvant Therapy for Primary Breast Cancer. *Cancers (Basel)* 2021; 13: 926. DOI: 10.3390/cancers13040926.

10. Kalin TV, Ustiyan V and Kalinichenko VV. Multiple faces of FoxM1 transcription factor: lessons from transgenic mouse models. *Cell Cycle* 2011; 10: 396–405. DOI: 10.4161/cc.10.3.14709.

11. He W, Kang Y, Zhu W, et al. FOXF2 acts as a crucial molecule in tumours and embryonic development. *Cell Death Dis* 2020; 11: 424. DOI: 10.1038/s41419-020-2604-z.

12. Aitola M, Carlsson P, Mahlapuu M, et al. Forkhead transcription factor FoxF2 is expressed in mesodermal tissues involved in epithelio-mesenchymal interactions. *Dev Dyn* 2000; 218: 136–149. DOI: 10.1002/(SICI)1097-0177(200005)218:1<136::AID-DVDY12>3.0.CO;2-U.

13. Wu Q, Li W and You C. The regulatory roles and mechanisms of the transcription factor FOXF2 in human diseases. *PeerJ* 2021; 9: e10845. DOI: 10.7717/peerj.10845.

14. Kong PZ, Li GM, Tian Y, et al. Decreased expression of FOXF2 as new predictor of poor prognosis in stage I non-small cell lung cancer. *Oncotarget* 2016; 7: 55601–55610. DOI: 10.18632/oncotarget.10876.

15. Nik AM, Reyahi A, Ponten F, et al. Foxf2 in intestinal fibroblasts reduces numbers of Lgr5 (+) stem cells and adenoma formation by inhibiting Wnt signaling. *Gastroenterology* 2013; 144: 1001–1011. DOI: 10.1053/j.gastro.2013.01.045.

16. Kong PZ, Yang F, Li L, et al. Decreased FOXF2 mRNA expression indicates early-onset metastasis and poor prognosis for breast cancer patients with histological grade II tumor. *PLoS One* 2013; 8: e61591. DOI: 10.1371/journal.pone.0061591.

17. Wang S, Li GX, Tan CC, et al. FOXF2 reprograms breast cancer cells into bone metastasis seeds. *Nat Commun* 2019; 10: 2707. DOI: 10.3892/mco.2015.511.

18. Lo PK. FOXF2 differentially regulates expression of metabolic genes in noncancerous and cancerous breast epithelial cells. *Trends Diabetes Metab* 2018; 1. DOI: 10.15761/tdm.1000103.

19. Sabapathi N, Sabarimurugan S, Madurantakam Royam M, et al. Prognostic Significance of FOXC1 in Various Cancers: A Systematic Review and Meta-Analysis. *Mol Diagn Ther* 2019; 23: 695–706. DOI: 10.1007/s40291-019-00416-y.

20. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010; 25: 603–605. DOI: 10.1007/s10654-010-9491-z.

21. Tam WWS, Tang A, Woo B, et al. Perception of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement of authors publishing reviews in nursing journals: a cross-sectional online survey. *BMJ Open* 2019; 9: e026271. DOI: 10.1136/bmjopen-2018-026271.

22. Madhav MR, Nayagam SG, Biyani K, et al. Epidemiologic analysis of breast cancer incidence, prevalence, and mortality in India: Protocol for a systematic review and meta-analyses. *Medicine (Baltimore)* 2018; 97: e13680. DOI: 10.1097/md.0000000000013680.

23. Cheng Z, Guo Y and Ming L. Functional Foxp3 polymorphisms and the susceptibility to cancer: An update meta-analysis. *Medicine (Baltimore)* 2018; 97: e11927. DOI: 10.1097/md.0000000000011927.

24. Duval S and Tweedie R. Trim and fill: A simple funnel-plot-based method of testing

and adjusting for publication bias in meta-analysis. *Biometrics* 2000; 56: 455–463.

25. Li JY, Zheng LL, Wang TT, et al. Functional Annotation of Metastasis-associated MicroRNAs of Melanoma: A Meta-analysis of Expression Profiles. *Chin Med J (Engl)* 2016; 129: 2484–2490. DOI: 10.4103/0366-6999.191793.

26. Shi Z, Liu J, Yu X, et al. Loss of FOXF2 Expression Predicts Poor Prognosis in Hepatocellular Carcinoma Patients. *Ann Surg Oncol* 2016; 23: 211–217. DOI: 10.1245/s10434-017-6002-4.

27. Cai J, Tian AX, Wang QS, et al. FOXF2 suppresses the FOXC2-mediated epithelial-mesenchymal transition and multidrug resistance of basal-like breast cancer. *Cancer Lett* 2015; 367: 129–137. DOI: 10.1016/j.canlet.2015.07.001.

28. Chen X, Hu H, Liu J, et al. FOXF2 promoter methylation is associated with prognosis in esophageal squamous cell carcinoma. *Tumour Biol* 2017; 39: 1010428317692230.

29. Hauptman N, Jevsinek Skok D, Spasovska E, et al. Genes CEP55, FOXD3, FOXF2, GNAO1, GRIA4, and KCNA5 as potential diagnostic biomarkers in colorectal cancer. *BMC Med Genomics* 2019; 12: 54.

30. Higashimori A, Dong Y, Zhang Y, et al. Forkhead Box F2 Suppresses Gastric Cancer through a Novel FOXF2-IRF2BPL-β-Catenin Signaling Axis. *Cancer Res* 2018; 78: 1643–1656. DOI: 10.1158/0008-5472.Can-17-2403.

31. Jia Z, Wan F, Zhu Y, et al. Forkhead-box series expression network is associated with outcome of clear-cell renal cell carcinoma. *Oncol Lett* 2018; 15: 8669–8680. DOI: 10.1186/s13058-018-1043-6.

32. Meyer-Schaller N, Heck C, Tiede S, et al. Foxf2 plays a dual role during transforming growth factor beta-induced epithelial to mesenchymal transition by promoting apoptosis yet enabling cell junction dissolution and migration. *Breast Cancer Res* 2018; 20: 118. DOI: 10.1038/s41467-019-10379-7.

33. Seok Y, Kang HG, Lee SY, et al. Polymorphisms in Epithelial-Mesenchymal Transition-Related Genes and the Prognosis of Surgically Treated Non-small Cell Lung Cancer. *Ann Surg Oncol* 2017; 24: 3386–3395. DOI: 10.1245/s10434-017-6002-4.

34. Tian HP, Lun SM, Huang HJ, et al. DNA Methylation Affects the SP1-regulated Transcription of FOXF2 in Breast Cancer Cells. *J Biol Chem* 2015; 290: 19173–19183.

35. Wang QS, He R, Yang F, et al. FOXF2 deficiency permits basal-like breast cancer cells to form lymphangiogenic mimicry by enhancing the response of VEGF-C/VEGFR3 signaling pathway. *Cancer Lett* 2018; 420: 116–126. DOI: 10.1016/j.canlet.2015.07.001.

36. Yang F, Li L, Li XQ, et al. Clinical Significance of Foxf2 lnRNA Expression in Primary Breast Cancer. *Chinese Journal of Clinical Oncology* 2009; 36: 752–754.

37. Zheng YZ, Wen J, Cao X, et al. Decreased mRNA expression of transcription factor forkhead box F2 is an indicator of poor prognosis in patients with resected esophageal squamous cell carcinoma. *Mol Clin Oncol* 2015; 3: 713–719. DOI: 10.1016/j.cellsig.2016.06.021.

38. Wu B, Sun C, Feng F, et al. Do relevant markers of cancer stem cells CD133 and Nestin indicate a poor prognosis in glioma patients? A systematic review and meta-analysis. *J Exp Clin Cancer Res* 2015; 34: 44. DOI: 10.1186/s13046-015-0163-4.

39. Eijkelenboom A and Burgering BM. FOXOs: signalling integrators for homeostasis maintenance. *Nat Rev Mol Cell Biol* 2013; 14: 83–97. DOI: 10.1038/nrm3507.

40. Oellerich MF and Potente M. FOXOs and sirtuins in vascular growth, maintenance, and aging. *Circ Res* 2012; 110: 1238–1251. DOI: 10.1161/circresaha.111.246488.

41. Kim DY, Hwang I, Muller FL, et al. Functional regulation of FoxO1 in neural stem cell differentiation. *Cell Death Differ* 2015; 22: 2034–2045. DOI: 10.1038/cdd.2015.123.

42. Westergren R, Nilsson D, Heglind M, et al. Overexpression of Foxf2 in adipose tissue is associated with lower levels of IRS1 and decreased glucose uptake in vivo. *Am J Physiol Endocrinol Metab* 2010; 298: E548–E554. DOI: 10.1152/ajpendo.00395.2009.

43. Sabarimurugan S, Madurantakam Royam M, Das A, et al. Systematic Review and Meta-analysis of the Prognostic Significance of miRNAs in Melanoma Patients. *Mol Diagn Ther* 2018; 22: 653–669. DOI: 10.1007/s40291-018-0357-5.

44. Tian T, Wang M, Lin S, et al. The Impact of lncRNA Dysregulation on Clinicopathology and Survival of Breast Cancer: A Systematic Review and Meta-analysis. *Mol Ther Nucleic Acids* 2018; 12: 359–369. DOI: 10.1016/j.omtn.2018.05.018.

45. Herman L, Todeschini AL and Veitia RA. Forkhead Transcription Factors in Health and Disease. *Trends Genet* 2020:S0168-9525(20)30308-5. DOI: 10.1016/j.tig.2020.11.003. Epub ahead of print.

46. Moparthi L and Koch S. A uniform expression library for the exploration of FOX transcription factor biology. *Differentiation* 2020; 115: 30–36. DOI: 10.1016/j.diff.2020.08.002.

47. Jiang D, Jiang L, Liu B, et al. Clinicopathological and prognostic significance of FoxM1 in gastric cancer: A meta-analysis. *Int J Surg* 2017; 48: 38–44. DOI: 10.1016/j.ijsu.2017.09.076.

48. Cui X, Zhang J, Lv J, et al. Prognostic value of FOXQ1 in patients with malignant solid tumors: a meta-analysis. *Onco Targets Ther* 2017; 10: 1777–1781. DOI: 10.2147/OTT.S130905.

49. Yu J, Shen W, Gao B, et al. MicroRNA-182 targets FOXF2 to promote the development of triple-negative breast cancer. *Neoplasma* 2017; 64: 209–215. DOI: 10.4149/neo_2017_206.

50. Yu ZH, Lun SM, He R, et al. Dual function of MAZ mediated by FOXF2 in basal-like breast cancer: Promotion of proliferation and suppression of progression. *Cancer Lett* 2017; 402: 142–152. DOI: 10.1016/j.canlet.2017.05.020.

51. Zhang T, Wan JG, Liu JB, et al. MiR-200c inhibits metastasis of breast tumor via the downregulation of Foxf2. *Genet Mol Res* 2017; 16. DOI: 10.4238/gmr16038971.

52. Kang LJ, Yu ZH, Cai J, et al. Reciprocal transrepression between FOXF2 and FOXQ1 controls basal-like breast cancer aggressiveness. *FASEB J* 2019; 33: 6564–6573. DOI: 10.1096/fj.201801916R.

53. Shao J, Cao J, Liu Y, et al. MicroRNA-519a promotes proliferation and inhibits apoptosis of hepatocellular carcinoma cells by targeting FOXF2. *FEBS Open Bio* 2015; 5: 893–899. DOI: 10.1016/j.fob.2015.10.009.

54. Dou C, Jin X, Sun L, et al. FOXF2 deficiency promotes hepatocellular carcinoma metastasis by inducing mesenchymal-epithelial transition. *Cancer Biomark* 2017; 19: 447–454. DOI: 10.3233/CBM-170139.

55. Zhang J, Zhang C, Sang L, et al. FOXF2 inhibits proliferation, migration, and invasion of Hela cells by regulating Wnt signaling pathway. *Biosci Rep* 2018; 38: BSR20180747. DOI: 10.1042/BSR20180747.

56. Herring BP, Hoggatt AM, Gupta A, et al. Gastroparesis is associated with decreased FOXF1 and FOXF2 in humans, and loss of FOXF1 and FOXF2 results in gastroparesis in mice. *Neurogastroenterol Motil* 2019; 31: e13528. DOI: 10.1111/nmo.13528.

57. Hirata H, Ueno K, Shahryari V, et al. MicroRNA-182-5p promotes cell invasion and proliferation by down regulating FOXF2, RECK and MTSS1 genes in human prostate cancer. *PLoS One* 2013; 8: e55502. DOI: 10.1371/journal.pone.0055502.

58. Macedo F, Ladeira K, Pinho F, et al. Bone Metastases: An Overview. *Oncol Rev* 2017; 11: 321. DOI: 10.4081/oncol.2017.321.

59. Mei ZB, Duan CY, Li CB, et al. Prognostic role of tumor PIK3CA mutation in colorectal cancer: a systematic review and meta-analysis. *Ann Oncol* 2016; 27: 1836–1848. DOI: 10.1093/annonc/mdw264.

60. Wu P, Wu D, Zhao L, et al. Prognostic role of STAT3 in solid tumors: a systematic review and meta-analysis. *Oncotarget* 2016; 7: 19863–19883. DOI: 10.18632/oncotarget.7887.

61. Chen Y, Qi X, Bian C, et al. The association of FOXP3 gene polymorphisms with cancer susceptibility: a comprehensive systemic review and meta-analysis. *Biosci Rep* 2019; 39: BSR20181809. DOI: 10.1042/bsr20181809.

62. Zhang Z, Chen Y, Jiang Y, et al. Prognostic and clinicopathological significance of CXCL1 in cancers: a systematic review and meta-analysis. *Cancer Biol Ther* 2019; 20: 1380–1388. DOI: 10.1080/15384047.2019.1647056.