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Prognostic value of MSI2 expression in human malignancies

A PRISMA-compliant meta-analysis

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Abstract

Background: The prognostic value of Musashi-2 (MSI2) in human malignancies remains controversial. We thus conducted this meta-analysis to evaluate the association between MSI2 expression and prognosis of patients with malignancies.

Materials and Methods: We searched EMBASE, PubMed and Web of Science up to June 2021 for eligible studies. Hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated to assess the prognostic value of MSI2 expression. Odds ratios (ORs) with 95% CIs were calculated to evaluate the association between MSI2 expression and clinicopathological traits.

Results: Sixteen studies involving 2203 patients were finally included in this meta-analysis. We found that high MSI2 expression might predict unfavorable OS (HR = 1.85, 95% CI: 1.62–2.10, $P < .0001$) and DFS/RFS (HR = 2.19, 95% CI: 1.87–2.57, $P < .0001$). Besides, the pooled results indicated that increased MSI2 expression correlated with large tumor size, poor tumor differentiation, positive lymph node metastasis and advanced tumor stage.

Conclusions: Taken together, our data implies that MSI2 overexpression is related to poor survival outcomes in patients with malignancy. Therefore, MSI2 may serve as a novel prognostic biomarker and therapeutic target of malignancies. However, large-scale prospective and homogeneous investigations should be conducted in the future to further validate our findings.

Abbreviations: CI = confidence interval, DFS = disease free survival, HR = hazard ratio, MSI2 = musashi-2, NOS = Newcastle-Ottawa scale, OR = odds ratio, OS = overall survival, RFS = recurrence free survival.

Keywords: cancer, malignancy, meta-analysis, MSI2, prognosis

1. Introduction

Malignancy is a predominant cause of morbidity and mortality worldwide and brings serious economic burden to individual and society.[1,2] In 2018, approximately 1735,350 cancer cases were newly diagnosed and 609,640 patients died from cancer in the United States.[2] Notwithstanding a great progress in cancer treatment has been made during past decades, patients with most types of cancers still have rather unsatisfactory long-term prognosis.[3,4] Therefore, it is necessary and urgent to identify new prognostic biomarkers not only for predicting survival outcomes but also for developing novel therapeutic targets for cancer patients.

Musashi-2 (MSI2) belongs to the conserved gene family of RNA-binding protein, which was firstly discovered in Drosophila melanogaster.[5] MSI2 has been revealed to function as a translational repressor and play an essential role in maintaining self-renewal and pluripotency in hematopoietic stem cells during embryogenesis.[5] Over the past decade, numerous studies have explored the role of MSI2 in various malignancies, such as leukemia,[6,7] hepatocellular carcinoma,[8,9] bladder cancer,[10] gastric cancer,[11] lung cancer,[12] colorectal cancer[13] and so on. Evidence shows that MSI2 is deregulated in a multiple of cancers and it closely correlates with prognosis and clinicopathological characteristics of patients with cancer. However, the clinicopathological and prognostic significance remains controversial currently. Most of published studies suggested that MSI2 overexpression was closely related to unfavorable survival outcomes of patients with malignancies.[6,9,11,13–16] On contrast, a few studies indicated that there

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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was no significant correlation between MSI2 expression and prognosis in cancers.[17] Also, the clinicopathological significance of MSI2 expression in malignancies is conflicting in terms of tumor size, tumor stage, differentiation, metastasis and so on.[9,11,12,15] The majority of studies exploring the prognostic value of MSI2 were limited by small sample size, which may account for those controversial results. Therefore, herein we conducted a meta-analysis of literatures to comprehensively analyze the clinicopathological and prognostic value of MSI2 expression in patients in pan-cancers.

2. Materials and Methods

The PubMed, EMBASE and Web of Science databases (up to June 2021) were comprehensively screened for articles on both MSI2 and human malignancies. The literature search was conducted with the following terms: "Musashi-2" OR "MSI2" AND "cancer" OR "tumor" OR "adenocarcinoma" OR "carcinoma" OR "leukemia" OR "lymphoma" OR "malignancy." Besides, we also manually searched the eligible studies in the identified articles. The study is a meta-analysis, so the ethical approval was not necessary.

2.1. Inclusion and exclusion criteria

The eligible studies must be up to the following criteria: they were published in English; the prognostic significance of MSI2 expression in human malignancies was explored; and the patients were divided into 2 groups based on high or positive MSI2 expression and low or negative MSI2 expression. The exclusion criteria included: the hazard ratios (HRs) with their 95% confidence intervals (95% CIs) of the association between MSI2 expression and survival outcomes could not be obtained; comments, letters, conference abstracts, reviews or animal studies; studies based on The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO); or overlapped population.

2.2. Data extraction and quality assessment

The following information were collected from eligible studies by 2 independent authors: patient source, case number, the first name of author, study period, age gender, detection method, cut-off value of high MSI2 expression, malignancy type, HRs with CIs for the association of MSI2 expression with overall survival (OS), disease-free survival (DFS) or recurrence-free survival (RFS), method of assessing the prognostic value of MSI2 expression, clinicopathological features and follow-up. Multivariate analysis for HRs was selected, when both multivariate analysis and univariate analysis were available. The Newcastle-Ottawa scale score was calculated to evaluate the quality of the articles.[1,18] In this score system, the total scores varied from 0 to 9, and the study with no less than 6 scores was deemed to be a moderate or high quality.

2.3. Statistical methods

The relationship between MSI2 expression and survival outcomes in patients with malignant tumor was assessed by using HR and 95% CI, while the odds ratio (OR) and 95% CI was used to assess the association between MSI2 expression and clinicopathological features. When HRs with 95% CIs were not reported directly, we calculated them from the Kaplan–Meier curve using the Engauge Digitizer 10.8 software.[19] Heterogeneity among the included studies was estimated using chi-squared Q test and I-squared statistical test.[20] When the results ($I^2 > 50\%$ or $P < .05$) suggested the existence of heterogeneity, the random effects model was utilized for the pooled analysis.[20] otherwise, the fixed effects model was applied.[20] Subgroup analysis and sensitivity analysis were performed to assess the stability and robustness of the pooled results. Publication bias was statistically assessed using Egger's test and visually evaluated with a funnel plot. If there was significant publication bias, the trim-and-fill method was adopted to examine the robustness of the pooled results. The Stata 12.0 (STATA Corp., College Station, TX) software and the RevMan version 5.3 software were used for the statistical analysis in this meta-analysis.

3. Results

3.1. Literature selection and study characteristics

The study selection process is recapitulated in Figure 1. A total of 509 records were retrieved from Web of Science, PubMed and EMBASE databases according to the search strategy mentioned above. Of them, 310 articles were omitted for duplicate records. Then, 183 records were further excluded for the irrelevance to topic, unavailability of data, animal studies, meeting abstracts or letters. Finally, 16 studies with 2203 patients with malignancy were included in our meta-analysis.[6–17,21–24] All the articles were cohort studies published between 2013 and 2021, which referred to leukemia, hepatocellular carcinoma (HCC), colorectal cancer (CRC), non-small cell lung cancer (NSCLC), oral squamous cell carcinoma (OSCC), bladder cancer (BC), gastric cancer (GC) and pancreatic cancer (PC). Eleven studies detected MSI2 expression by immunohistochemistry (IHC), while 5 studies examined MSI2 expression using polymerase chain reaction (PCR). All the included studies reported data on OS, and 4 articles provided data on DFS. Besides, RFS and PFS were reported in 1 study. A total of 13 studies estimated HRs and their 95% CIs by Cox multivariate analysis, and directly presented them. Nevertheless, the remained 3 studies only provided Kaplan–Meier curves depicting the prognostic value of MSI2 expression. Each study was given no less than 6 scores based on NOS, suggesting that all the enrolled studies had a high methodological quality. The main characteristics of each eligible study are generalized in Table 1.

3.2. Correlation between MSI2 expression and clinicopathological features

It has been well established that many clinicopathological features, such as tumor size, differentiation, metastasis and stage, may affect the prognosis of cancer patients. Thus, the relationship between MSI2 expression and these parameters was first

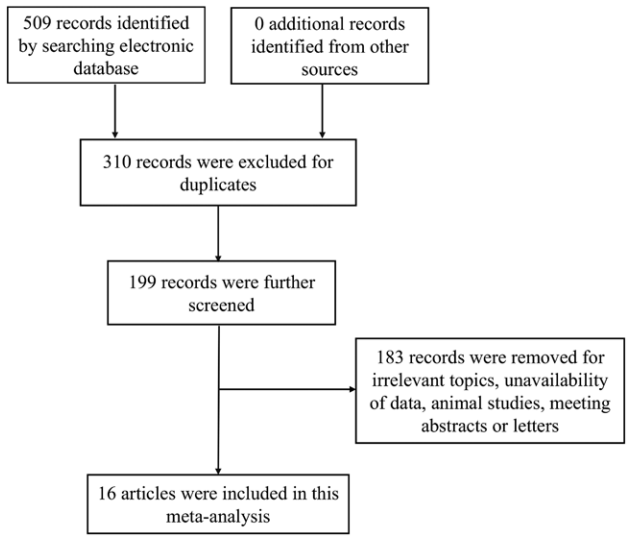

Figure 1. Flow diagram of study search and selection process.

Table 1

Characteristics of studies included in this meta-analysis.

Study SIRT6	Country	Study period	Sample size	Tumor type	Age (mean/ median)	Gender (F/M)	Detection method	Cutoff value	Survival outcome	Method of assessing the prognostic value of MSI2 expression	Follow-up (Months)	NOS score
ALY RM 2015	Egypt	2011–2014	140	ALL	H: 45 (19–52) L: 40 (19–53)	64/76	PCR	Median value of MSI2 levels	OS, DFS	Multivariate analysis	NR	7
Byers RJ 2011	United Kingdom	1994–2005	120	AML	H: 61.5 (17–82) L: 52.5 (17–83)	62/58	IHC	IHC score ≥ 3	OS	Multivariate analysis	NR	7
Fang T 2016	China	NR	122	HCC	<50 yr, 49/34 ≥50 yr, 23/16	17/105	IHC	NR	OS	Kaplan–Meier analysis	NR	6
He L 2014	China	2005–2010	149	HCC	≤50 yr, 43/36 >50 yr, 30/40	NR	IHC	IHC score > 1.5	OS	Multivariate analysis	NR	7
Hu FH 2018	China	NR	78	CCA	≤60 yr, 13/14 >60 yr, 30/21	35/43	IHC	IHC score > 3	OS, DFS	Multivariate analysis	19.5	7
Liu YQ 2018	China	2003–2007	162	CC	≤50 yr, 59/50 >50 yr, 32/21	162/0	IHC	IHC score > 4	OS	Multivariate analysis	NR	7
Mu QT 2013	China	2000–2010	116	ALL	H: 35 (15–65) L: 34 (15–68)	53/63	PCR	Upper quartile (Q4) of MSI2 levels	OS, RFS	Multivariate analysis	NR	7
Thol F 2013	Germany	NR	454	AML	H: 47 (25–60) L: 46 (17–60)	210/244	PCR	Upper quartile (Q4) of MSI2 levels	OS	Multivariate analysis	NR	7
Topchu I 2021	Russia	NR	40	NSCLC	NR	28/12	IHC	H-score > 170	OS	Kaplan–Meier analysis	NR	6
Troiano G 2019	Italy	1997–2012	108	OSCC	NR	29/79	IHC	IHC score > 0	OS	Multivariate analysis	47.34	7
Wang MH 2015	China	2005–2007	106	HCC	≤50 yr, 22/16 >50 yr, 42/26	12/94	IHC	IHC score > 1	OS, DFS	Multivariate analysis	NR	7
Yang CL 2016	China	2006–2009	167	BC	≤60 yr, 24/52 >60 yr, 33/58	61/106	IHC	IHC score > 3	OS, DFS	Multivariate analysis	NR	7
Yang ZG 2019	China	2012	67	GC	<60 yr, 24/9 ≥60 yr, 18/16	16/51	PCR	Ratio of MSI2 levels in tumor versus normal tissue > 2	OS	Kaplan–Meier analysis	NR	6
Zhao HZ 2016	China	2007–2010	119	ALM	H: 7.5 (1–14) L: 6 (1–14)	43/76	PCR	Upper quartile (Q4) of MSI2 levels	OS	Multivariate analysis	NR	7
Zhou L 2020	China	2006–2017	91	PC	≤65 yr, 28/47 >60 yr, 8/8	36/55	IHC	IHC score > 3	OS	Multivariate analysis	NR	7
Zong Z 2016	China	2007–2012	164 CRC		≤60 yr, 27/49 >60 yr, 27/61	57/107	IHC	IHC score > 1.5	OS	Multivariate analysis	NR	7

ALL = acute lymphoid leukemia, AML = acute myeloid leukemia, BC = bladder cancer, CC = cervical cancer, CCA = cholangiocarcinoma, CRC = colorectal cancer, DFS = disease-free survival, F = female, GC = gastric cancer, H = high MSI2 expression, HCC = hepatocellular carcinoma, IHC = immunohistochemistry, L = low MSI2 expression, OSCC = oral squamous cell carcinoma, M = male, NR = not reported, PC = pancreatic cancer, PCR = polymerase chain reaction, NOS = Newcastle-Ottawa scale, NSCLC = non-small cell lung cancer, OS = overall survival, RFS = recurrence-free survival.

evaluated, before we assessed the role of MSI2 as a prognostic indicator for malignancies. Eight studies comprising 939 patients reported the link of MSI2 expression with tumor size.[8,9,11,13,15,16,21,22] The pooled result implied that higher MSI2 was marginally correlated with larger tumor size (OR = 1.58, 95% CI: 0.97–2.59, $P = .07$, random effects model, Fig. 2A). Association between MSI2 expression and tumor differentiation was reported in 9 articles involving 1106 patients.[8–11,13,15,16,21,22] As shown in Figure 2B, high expression of MSI2 was tightly related to poor tumor differentiation (OR = 1.42, 95% CI: 1.10–1.84, $P = .008$, fixed effects model). A total of 567 patients from 5 studies were included to analyze the relationship between MSI2 expression and lymph node metastasis,[10,11,13,15,16] and the pooled result indicated a positive correlation in this regard (OR = 2.20, 95% CI: 1.45–3.36, $P = .0002$, fixed effects model, Fig. 2C). Tumor size and metastasis are 2 key parameters for grading tumor stage. As expected, our meta-analysis of 6 studies enrolling 668 patients[8,11,13,15,16,22] suggested that increased MSI2 expression closely correlated advanced tumor stage (OR = 2.32, 95% CI: 1.60–3.38, $P < .0001$, fixed effects model, Fig. 2D). Collectively, these data implied that MSI2 overexpression may reflect the aggressive property of human malignancy.

3.3. Relationship between MSI2 expression and prognosis

Sixteen studies involving 2203 patients were included to evaluate the association between MSI2 expression and OS.[6–17,21–24] In consideration of subtle heterogeneity ($I^2 = 37\%$, $P = .07$), the fixed effects model was adopted to merge the HRs and 95% CIs. As illustrated in Figure 3, MSI2 overexpression was prominently correlated with poor OS (HR = 1.85, 95% CI: 1.62–2.10, $P < .0001$, fixed effects model). Consistently, a positive association between MSI2 expression and OS was found in all subgroups by country, malignancy type, sample size, detection

method of MSI2 level and method of assessing the prognostic value of MSI2 expression (Table 2). For DFS/RFS, only 5 studies were eligible for meta-analysis.[6–8,10,15] Considering the statistical similarity of DFS and RFS, we merged them together for meta-analysis. Because no substantial heterogeneity existed (I^2 = 0%, P = .85), the fixed effects model was adopted. The pooled analysis implied an inverse relationship between MSI2 expression and DFS/RFS (HR = 2.19, 95% CI: 1.87–2.57, P < .0001, fixed effects model) (Fig. 4).

3.4. Sensitivity analysis and publication bias

To evaluate the stability and robustness of the meta-analysis, sensitivity analysis was performed by omitting single study step by step. It was found that deletion of any individual study had no apparent effects on the pooled HRs for prognosis (Fig. 5A and supplement 1A, http://links.lww.com/MD/I15) and ORs for clinicopathological features (supplement 1B–E, http://links.lww.com/MD/I15). Begg's test and Egger's test were adopted to evaluate the publication bias for OS. No significant publication bias was found by Begg's test (P = .418) and Egger's test (P = .168). Meanwhile, the Begg's funnel plot visually displayed an apparent asymmetry, which further indicated no substantial publication bias for OS (Fig. 5B). Because the number of studies included for DFS/RFS and clinicopathological features was less than 10, publication bias assessment was not conducted in this regard. Taken together, these data indicated that our meta-analysis are stable and reliable.

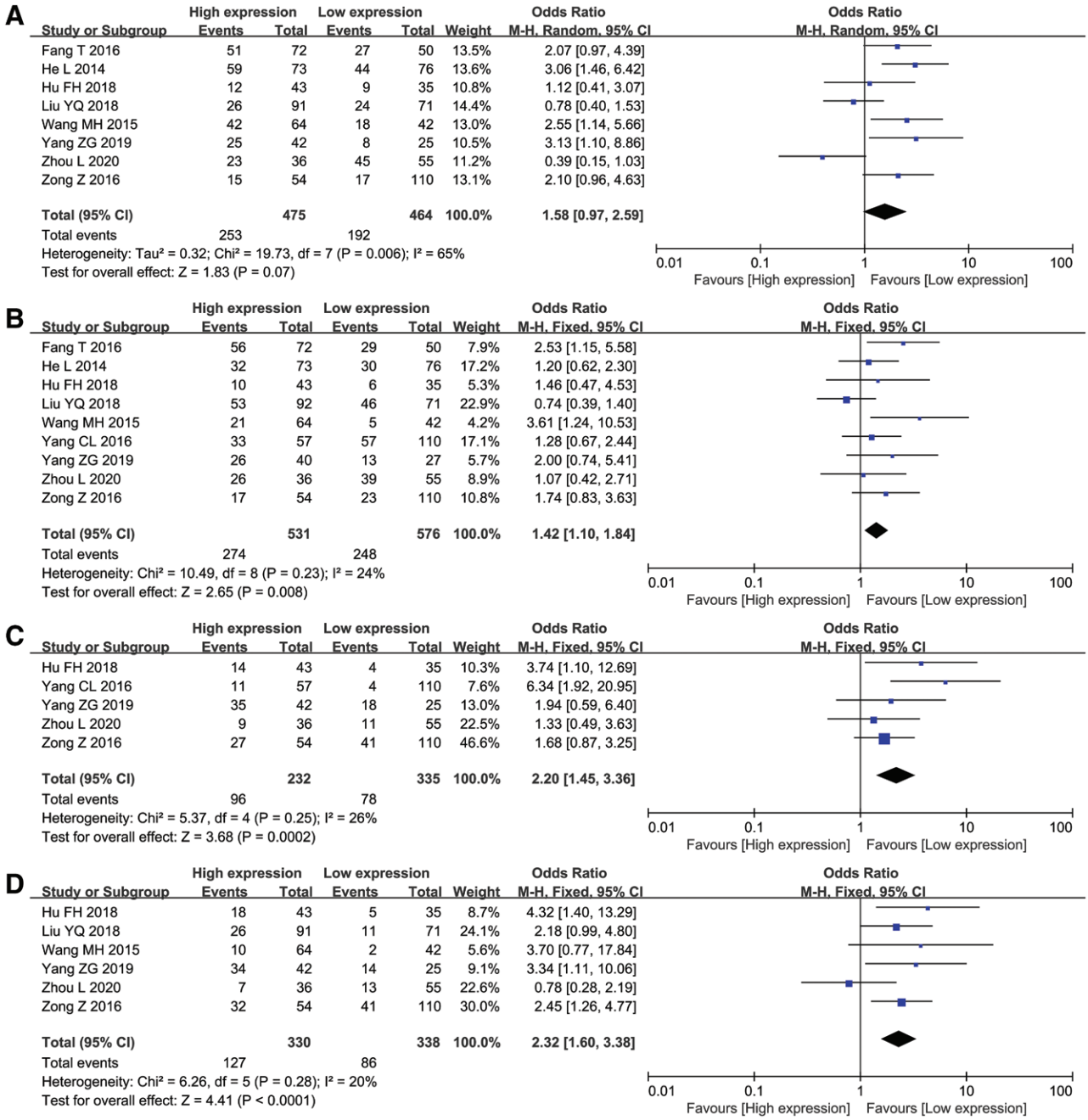

Figure 2. Forest plot for the link between MSI2 expression and clinicopathological features in malignancies. (A) tumor size. (B) tumor differentiation. (C) lymph node metastasis. (D) tumor stage. MSI2 = musashi-2.

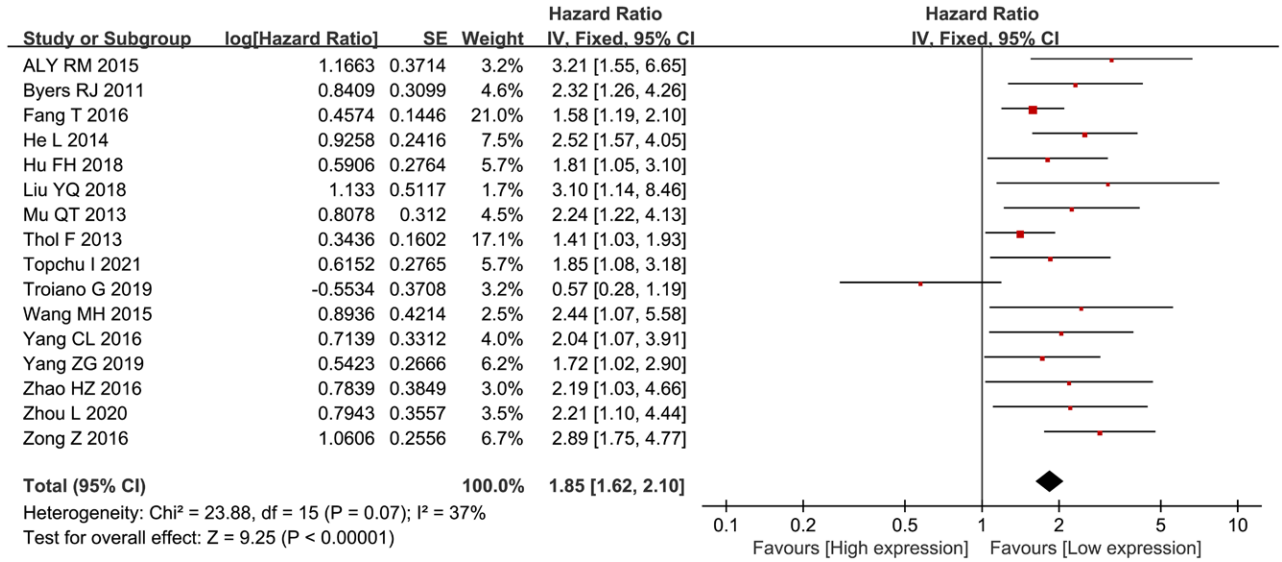

Figure 3. Forest plot for the association between MSI2 expression and OS in malignancies. OS = overall survival.

Table 2

Subgroup analysis for overall survival.

Variables	No. of studies	Pooled HR (95%CI)	*P* value	Heterogeneity I^2	Heterogeneity *P* value
1. Country					
China	11	2.01(1.71–2.35)	<.01	0	.69
Other	5	1.62(1.03–2.55)	.04	70	<.01
2. Sample size					
n > 149	4	2.07(1.36–3.17)	<.01	57	.07
n ≤ 149	12	1.85(1.59–2.16)	<.01	35	.11
3. Malignancy type					
ALL	2	2.6(1.63–4.16)	<.01	0	.46
AML	3	1.72(1.22–2.42)	<.01	26	.26
HCC	3	1.96(1.39–2.77)	<.01	39.2	.19
Others	8	1.85(1.35–2.53)	<.01	51	.04
4. Method of detecting MSI2 level					
PCR	5	1.75(1.4–2.18)	<.01	27	.24
IHC	11	1.9(1.62–2.23)	<.01	45	.05
5. Method of assessing the prognostic value					
Kaplan–Meier	3	1.65(1.32–2.07)	<.01	0	.87
Multivariate	13	2.03(1.62–2.55)	<.01	46	.04

ALL = acute lymphoid leukemia, AML = acute myeloid leukemia, CI = confidence interval, HCC = hepatocellular carcinoma, HR = hazard ratio, IHC = immunohistochemistry, OS = overall survival, PCR = polymerase chain reaction.

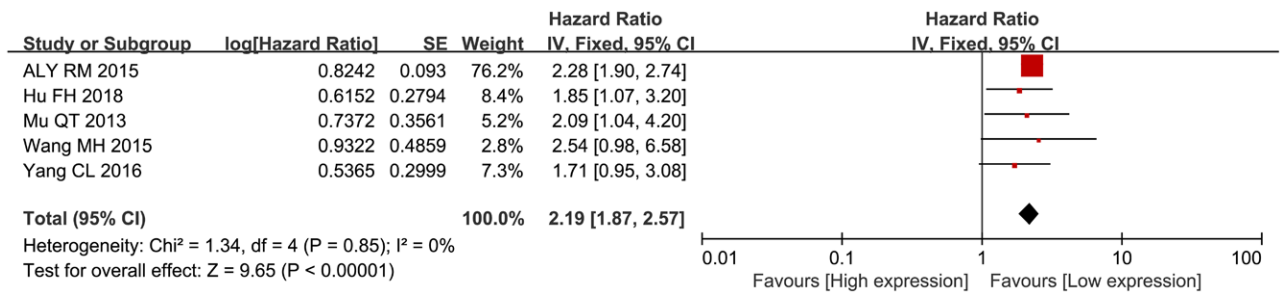

Figure 4. Forest plot for the association between MSI2 expression and DFS/RFS in malignancies. DFS = disease-free survival, MSI2 = musashi-2, RFS = recurrence-free survival.

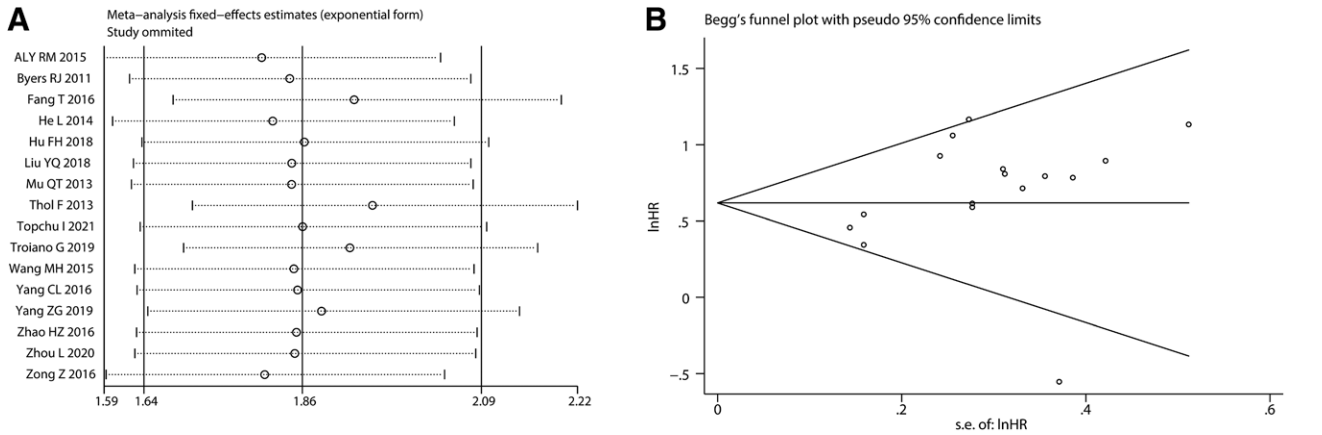

Figure 5. Sensitivity analysis and publication bias assessment for OS. (A) sensitivity analysis. (B) publication bias. OS = overall survival.

4. Discussion

The association between MSI2 expression and prognosis of patients with malignancy has been researched[5,10,14,16]; Nevertheless, the prognostic significance of MSI2 remains controversial. Herein, we thus carried out this meta-analysis to systematically evaluate the prognostic value of MSI2 expression in human malignancies. In our meta-analysis, we merged 16 studies involving 2203 patients with malignancy. Our overall combined results indicated that high MSI2 expression might predict unfavorable OS (HR = 1.85, 95% CI: 1.62–2.10, $P < .0001$) and DFS/RFS (HR = 2.19, 95% CI: 1.87–2.57, $P < .0001$). Furthermore, the overall pooled results were verified to be robust and reliable by our subgroup analysis, sensitivity analysis and publication bias. In addition, we also conducted the meta-analysis of the relationship between MSI2 expression and clinicopathological features, which could influence survival outcomes, to further confirm the prognostic role of MSI2. As expected, the pooled results indicated that high MSI2 expression was correlated with large tumor size, poor tumor differentiation, positive lymph node metastasis and advanced tumor stage. Collectively, MSI2 overexpression may contribute to the aggressiveness of malignancy and predict poor prognosis.

MSI2, as an evolutionarily conserved translational modulator, plays a crucial part in the stemness maintenance and differentiation in hematopoietic stem cells under physiological condition.[25–27] In recent years, MSI2 was found to be dysregulated in various malignancies and act as an oncogene in multiple malignant tumors, which may explain the results in this meta-analysis. In 2010, Ito et al first demonstrated the oncogenic property of MSI2 in chronic myeloid leukemia (CML) mouse model.[28] A recent study revealed that MSI2 controls the myeloid leukemia stem cell program through indirectly interacting with SYNCRIP to maintain HOXA9 translation.[26] Hattori et al verified that MSI2 upregulates FLT3 expression in leukemia cells to negatively regulate clonogenic growth of leukemia.[29] Besides, MSI2 is also aberrantly upregulated in multiple solid malignancies and functions as an oncogene. For example, MSI2 can contribute to the stemness of liver cancer stem cells via LIN28A activation and notch1 signaling pathway.[9] Interestingly, a most recent study uncovered that MSI2 overexpression in myofibroblasts could also maintain the stemness of liver cancer stem cells by inducing ERK/1/2-dependent IL-6 and IL-11 secretion.[25] In lung cancer, MSI2 enhances TGF-β signaling transduction, but suppresses claudins to facilitate tumor metastasis.[30] Moreover, Makhov et al demonstrated that MSI2 could promote EGFR protein expression and its phosphorylation to sensitize EGFR-mut non-small cell lung cancer (NSCLC) cells to EGFR inhibitors.[31] As for bladder cancer, MSI2 can facilitate tumor progression through activating the JAK2/STAT3 pathway and upregulating KRAS expression.[10] In addition, MSI2 also positively regulates the malignant phenotypes of many other malignancies, such as glioma,[32] cervical cancer,[33] ovarian cancer,[34] thyroid cancer[35] and osteosarcoma,[36] though the molecular mechanisms have not been elucidated. Overall, these studies regarding the roles of MSI2 in malignancies strongly supported the findings of our meta-analysis.

To our best knowledge, this study was the first meta-analysis to comprehensively evaluate the prognostic value of MSI2 expression in human malignancies. However, there are some limitations in this meta-analysis. First, we could not sufficiently assess the association between MSI2 expression and each malignancy type. In particular, most of included studies focused on solid tumors. Hence, more studies should be performed to analyze the prognostic value of MSI2 expression in hematologic tumors. Second, several studies did not directly provided HRs with 95% CI for OS, and thereby we estimated HR by the Kaplan–Meier curve, which may cause a degree of error. Third, the majority of included studies enrolled populations from China, so the results of this meta-analysis may be cautiously generalized into other populations. Last but not least, although no statistically significant heterogeneity was found among the included studies, the pooled results may be still challenged by the potential heterogeneity. That is, all the included studies were retrospective studies, and the baselines of these studies may be inconsistent unavoidably.

5. Conclusion

Our data suggests that high MSI2 expression is significantly related to poor survival outcomes in patients with malignancy. Therefore, MSI2 may serve as a prognostic biomarker and therapeutic target of malignancies. However, large-scale prospective and homogeneous clinical studies should be conducted in the future to further confirm our findings.

Author contribution

Wei Wu, Jialin Li and Jun Xie designed this study, extracted and analyzed the data of included studies, as well as wrote the manuscript. Dejia Dong and Fafu Dou took part in data extraction; Jun Xie, Xiaoye Yang, Yong Lin and Yan Zhou participated in revising the manuscript. Each author has read and approved the final manuscript. All authors declare that they have no competing interests.

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