

# Prognostic significance of macrophage migration inhibitory factor expression in cancer patients

## A systematic review and meta-analysis

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### Abstract

**Background:** Recent studies showed that Macrophage migration inhibitory factor (MIF) is overexpressed and closely associated with prognosis in cancer patients. The present study was systematically evaluated the prognostic significance of MIF expression in cancer patients.

**Methods:** PubMed, Cochrane library and Scopus were searched for eligible studies up to January 2020. Pooled hazard ratio with confidence interval (CI) was determined to assess the relationship between MIF expression and survival in cancer patients.

**Results:** A total of 8 studies comprising 847 cancer patients were included in this meta-analysis. For overall survival, the pooled hazard ratio was 2.23 (95% CI 1.67–2.99,  $P < .001$ ). For disease-free survival, the pooled hazard ratio was 2.24 (95% CI 1.69–2.96,  $P < .001$ ). The results suggested that high expression of MIF was significantly related to poor overall survival and disease-free survival in cancer patients.

**Conclusion:** MIF expression could be a valuable prognostic factor in cancer patients.

**Abbreviations:** CI = confidence interval, DFS = disease-free survival, HR = hazard ratio, MIF = macrophage migration inhibitory factor, NOS = Newcastle-Ottawa Scale, OS = overall survival, RFS = recurrence-free survival.

**Keywords:** cancer, macrophage migration inhibitory factor, meta-analysis, prognosis

## 1. Introduction

Cancer is a common cause of morbidity and mortality worldwide.<sup>[1]</sup> Due to the increasing prevalence of cancer risk factors, including overweight, physical inactivity, smoking, and changing reproductive patterns, the burden of cancer is still growing.<sup>[2]</sup> Despite intensive research efforts in genomics and drug development for cancer, the prognosis for patients with cancer remains poor. Therefore, a great deal of research is being

carried out to discover clinical outcome and efficacy of treatment for cancer patients using biomarkers.

Macrophage migration inhibitory factor (MIF) was identified in the 1960s as a soluble, protein factor secreted by T cells with the ability to inhibit the random migration of macrophages.<sup>[3]</sup> MIF is a unique cytokine and critical mediator of host defenses with a role in chronic inflammatory and autoimmune disease.<sup>[4]</sup> Recent studies showed that MIF is overexpressed in many solid cancers and is closely related in the tumor cell proliferation, angiogenesis and tumorigenesis.<sup>[3,5,6]</sup> Moreover, the overexpression of MIF has been associated to tumor progression, metastasis and unfavorable prognosis in gastric, hepatocellular, pancreatic, and lung cancers, and oral squamous cell carcinoma and metastatic melanoma.<sup>[3,7,8]</sup>

However, the association between MIF expression and survival in patients with cancer is not systematically understood. In this study, we performed meta-analysis to comprehensively assess the prognostic significance of MIF expression in cancer patients.

## 2. Materials and methods

### 2.1. Search strategy

Eligible studies were identified by searching PubMed, Cochrane library and Scopus up to January 2020 using the following terms: (MIF or macrophage migration inhibitory factor) and (cancer or tumor or carcinoma or neoplasm or malignancy) and (prognostic or predict or prognosis or survival or outcome). All significant publications in the references of the reviewed articles were also manually searched to find qualified articles. This study was based on previously published studies, so ethical approval and informed consent were not required.

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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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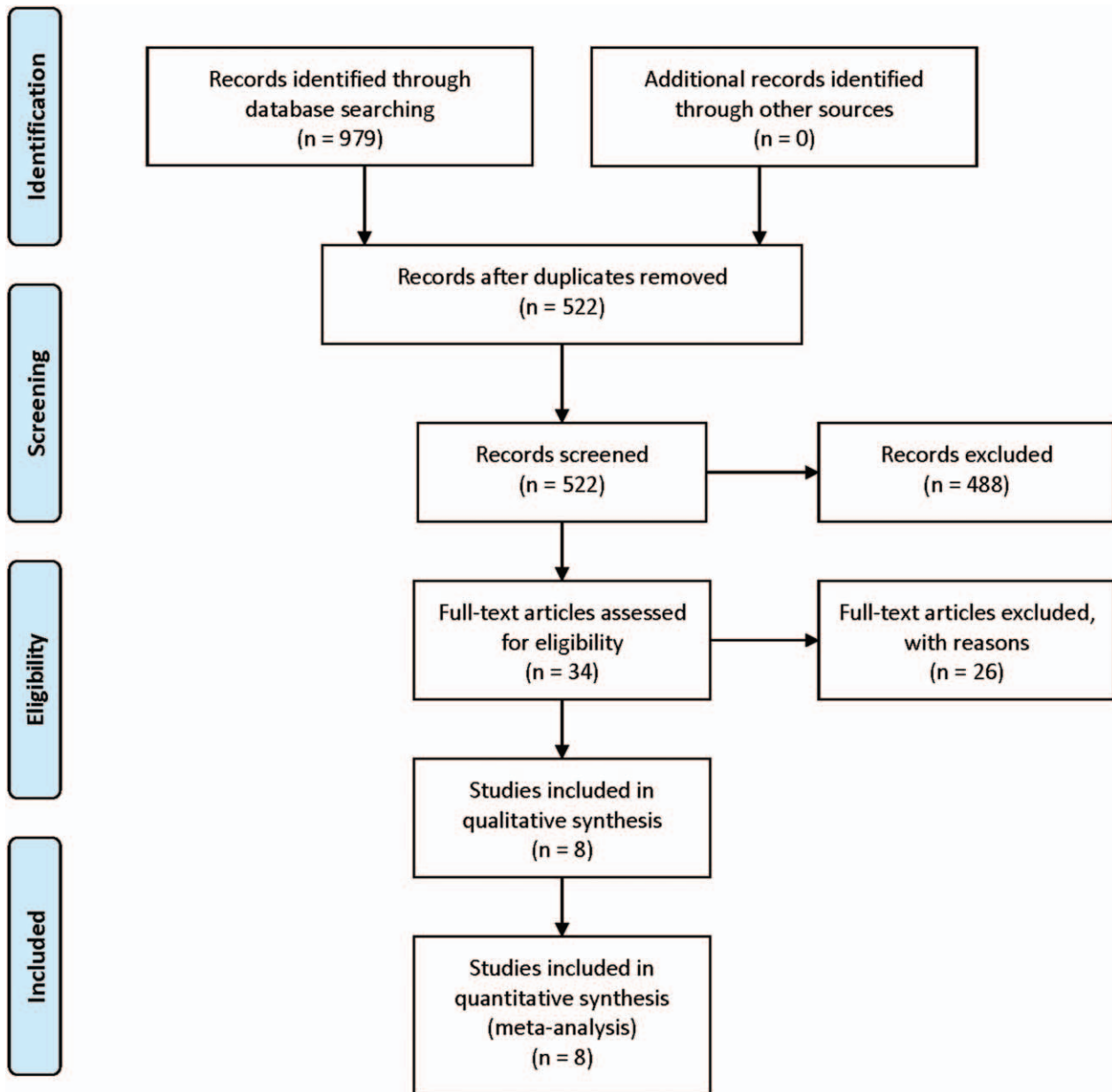


Figure 1. Flow diagram of study selection.

## 2.2. Inclusion and exclusion criteria

Eligible studies should be the following criteria:

- (1) the expression of MIF was detected in the tumor cells of human cancer tissue using immunohistochemistry;
- (2) the association between MIF expression and survival outcome was evaluated;
- (3) the hazard ratio (HR) and 95% confidence interval (CI) assessing multivariate Cox-regression for survival outcome were provided.

Studies were excluded if they met any of the following criteria:

- (1) duplicate studies;
- (2) conference abstracts, case reports, reviews, letters, and non-English articles;

- (3) studies of hematologic malignancy patients and children.

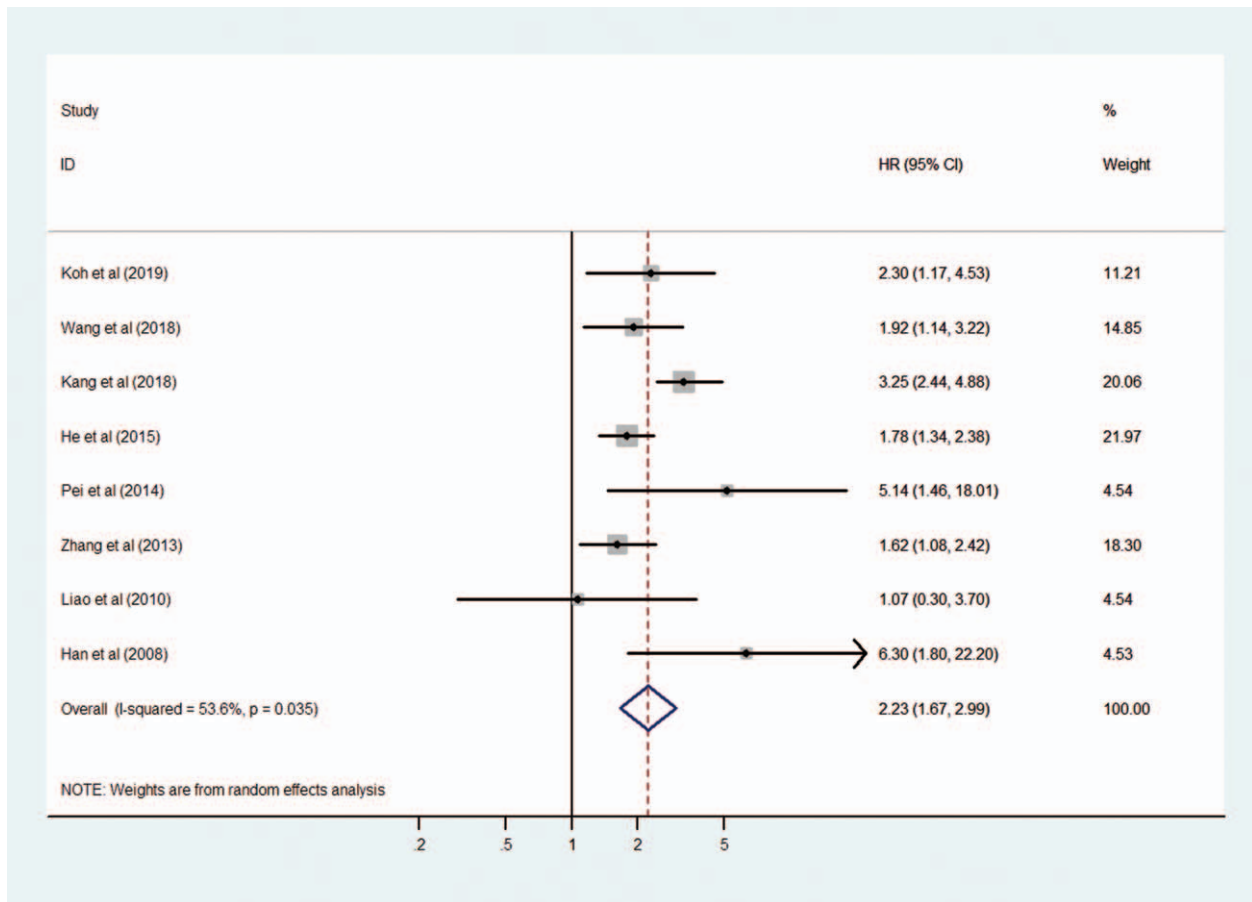
## 2.3. Data extraction and quality assessment

Two authors extracted necessary data independently and reached a consensus by discussion. The extracted data were as follows: first author, publication year, country, cancer type, sample size, sex, median age, tumor stage, study period, follow-up period, endpoints, MIF expression associated with poor prognosis, cut-off value of MIF expression, and adjusted HR with 95% CI for survival. The quality of eligible studies was assessed according to the Newcastle-Ottawa Scale (NOS). The scale included selection of the study group, comparability of groups and ascertainment of outcomes, and the NOS scores ranged from 0 to 9. The articles scored greater than 6 were considered as a high quality.

**Table 1**  
**Basic characteristics of the included studies.**

Study	Country	Cancer type	Sample size	Sex (M/F)	Median age (yr)	Tumor stage	Study period	Follow-up (mo)	Endpoints	MIF expression		NOS
										with poor prognosis	associated	
Koh et al (2019)	South Korea	lung squamous cell carcinoma	96	92/4	66.5	I-IV	2002-2009	NA	DSS, DFS	high proportion of positive tumor cells	> 80%	7
Wang et al (2018)	China	pancreatic ductal adenocarcinoma	85	51/34	NA	I-IV	2003-2007	NA	OS	high expression in tumor cells	H-score > 1.08	7
Kang et al (2018)	China	oral squamous cell carcinoma	90	50/40	NA	I-IV	2012-2013	NA	OS, RFS	high expression in tumor cells	double scoring system > 2	7
He et al (2015)	China	gastric cancer	116	74/43	61	I-IV	2001-2003	median 23 (range 5-80)	OS	high expression in tumor cells	Remmele score > 2	8
Pei et al (2014)	China	nasopharyngeal carcinoma	125	85/40	51 (23-77)	I-IV	2004-2010	median 32.5	OS	high expression in tumor cells	double scoring system > 3	8
Zhang et al (2013)	China	esophageal squamous cell carcinoma	136	111/62	62 (35-90)	I-IV	2000-2002	up to DEC 2011	OS, DFS	high expression in tumor cells	double scoring system	8
Liao et al (2010)	China	nasopharyngeal carcinoma	141	92/49	51 (5-76)	I-IV	1999-2007	mean 29.1 (range 2-59)	OS	high expression in tumor cells	double scoring system > 3	8
Han et al (2008)	South Korea	high-grade osteosarcoma	58	37/21	average 22.4 (4-81)	NA	1996-2002	mean 42 (range 12-110)	OS, MFS	high proportion of positive tumor cells	> 50%	8

DFS = disease-free survival, DSS = disease-specific survival, MIF = macrophage migration inhibitory factor, MFS = metastasis-free survival, NA = not available, NOS = Newcastle-Ottawa Scale, OS = overall survival, RFS = recurrence-free survival.



**Figure 2.** Forest plot reflecting the relationship between MIF expression and overall survival in cancer patients. MIF=macrophage migration inhibitory factor.

#### 2.4. Statistical analysis

StataSE 12 (Stata, College Station, TX) was used for meta-analysis. The prognostic significance of MIF expression was evaluated using pooled HR and 95% CI. The heterogeneity among the enrolled studies was assessed by the Higgins'  $I^2$  statistics and the chi-square  $Q$  test and an  $I^2$  statistic  $> 50\%$  or a  $P$  value  $< .1$  was considered as significant in a random effects model. Subgroup analysis was also performed to reveal the cause of heterogeneity. The publication bias was assessed by Funnel plot and Egger regression test. And the sensitivity analysis was conducted to estimate the consistency of the pooled results.  $P$  values  $< .05$  were regarded as statistically significant.

### 3. Results

#### 3.1. Search results

Figure 1 shows the process flow diagram of study selection. After removing due to duplication and screening the titles and abstracts, 34 full-text articles are assessed for eligibility. Finally, 8 studies comprising 847 cancer patients were included for our meta-analysis.

#### 3.2. Study characteristics

The basic characteristics of included studies are summarized in Table 1. Two studies were performed in South Korea, while the

others were performed in China, published between 2008 and 2019. A total of 847 patients were included, and the enrolled studies were consisted of seven types of cancers, including lung squamous cell carcinoma ( $n=1$ ), pancreatic ductal adenocarcinoma ( $n=1$ ), oral squamous cell carcinoma ( $n=1$ ), gastric cancer ( $n=1$ ), nasopharyngeal carcinoma ( $n=2$ ), esophageal squamous cell carcinoma ( $n=1$ ), and high-grade osteosarcoma ( $n=1$ ). HR and 95% CI were obtained directly multivariate analysis from all of original articles. All the studies conducted immunohistochemistry to evaluate MIF expression in the tumor cells of human cancer tissue. NOS scores of all include studies ranges from 7 to 8.

#### 3.3. Relationship between MIF expression and overall survival (OS)

We assessed 8 studies to reveal the relationship between MIF expression and OS including disease-specific survival. A random-effect model was used due to significant heterogeneity ( $I^2=53.6\%$ ,  $P=.035$ ). The pooled HR for OS in cancer patients with high expression of MIF compared with low expression was 2.23 (95% CI 1.67–2.99,  $P<.001$ ), indicating that high expression of MIF was significantly associated with poor OS in cancer patients (Fig. 2). Moreover, subgroup analyses according to cancer type (digestive system cancer or non-digestive system cancer) and sample size (fewer than 100 or more than 100) were conducted to reveal sources of heterogeneity (Fig. 3A, B). The results showed

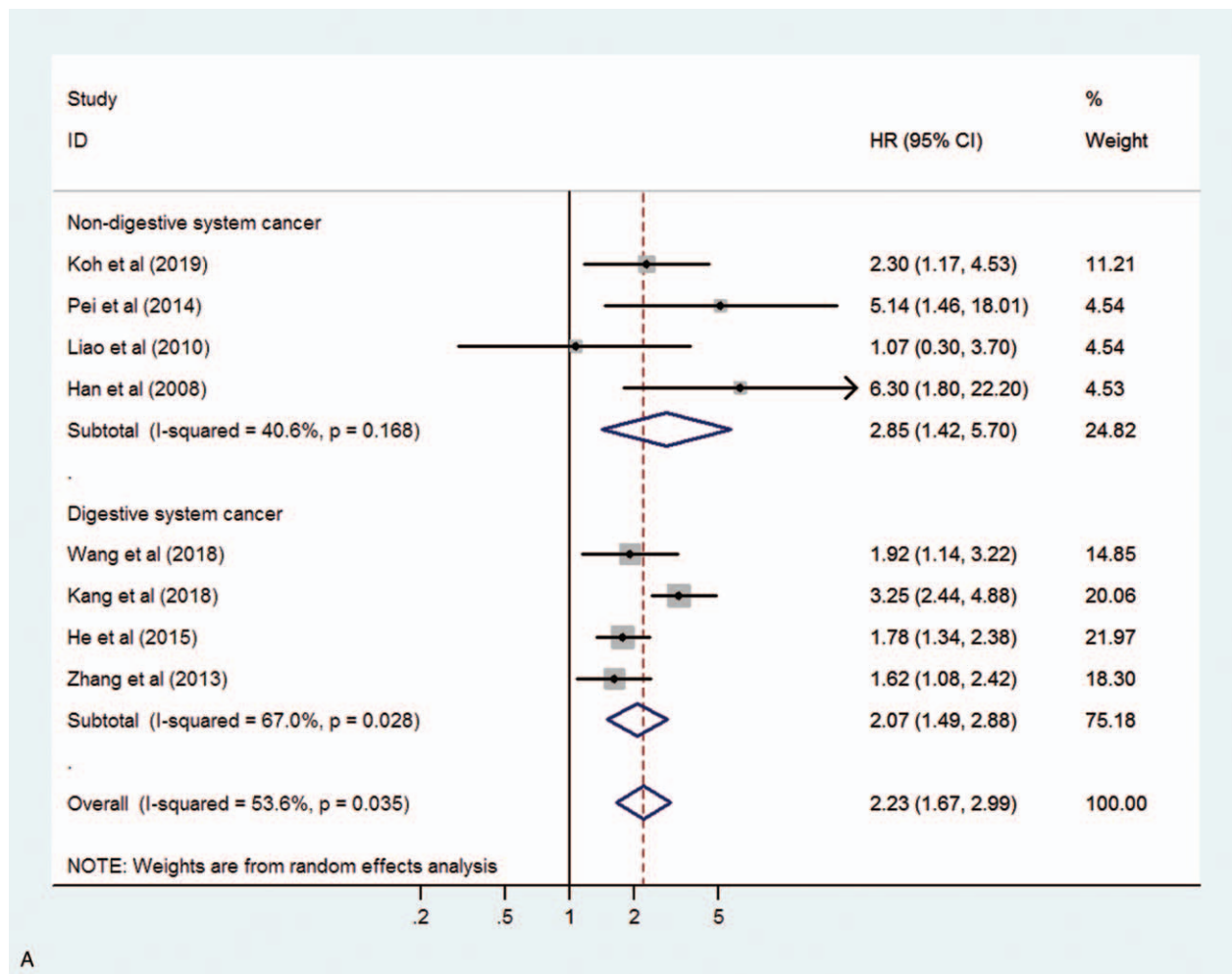


Figure 3. Forest plot showing the subgroup analysis stratified by cancer type (A) and sample size (B).

that the cancer type may be the source of heterogeneity, however this did not affect the overall results.

### 3.4. Relationship between MIF expression and disease-free survival (DFS)

We evaluated 4 studies to reveal the relationship between MIF expression and DFS including recurrence-free survival and metastasis-free survival. A fixed-effect model was used because of no obvious heterogeneity ( $I^2 = 12.6\%$ ,  $P = .330$ ). The pooled HR for DFS in cancer patients with high expression of MIF compared with low expression was 2.24 (95% CI 1.69–2.96,  $P < .001$ ), indicating that high expression of MIF was significantly related with worse DFS in cancer patients (Fig. 4). Subgroup analysis was not conducted for DFS due to the limited number of studies and the uniformity among studies.

### 3.5. Publication bias

We performed Funnel plot and Egger regression test to assess the publication bias. For OS, the Funnel plot seemed

asymmetrical (Fig. 5A). However, Egger regression test did not demonstrate the publication bias ( $P = .503$ ). We also performed the trim and fill analysis. The result revealed that there is no basis for questioning the validity of the overall results in this study ( $P < .001$ ) (Fig. 5B). For DFS, the Funnel plot also seemed asymmetrical (Fig. 5C). But, Egger test did not show the publication bias ( $P = .140$ ). In addition, trim and fill analysis showed a similar finding ( $P < .001$ ) as shown in the analysis for OS (Fig. 5D).

### 3.6. Sensitivity analysis

We conducted sensitivity analysis to detect the influences of individual studies and the consistency of our results by omitting single study consecutively. For OS, the sensitivity analysis revealed that omitting the study of Kang et al, the pooled HR appears to be 1.88 (95% CI 1.55–2.29), indicating a significant change compared to the result including all studies (the pooled HR, 2.23; 95% CI, 1.67–2.99). On the other hand, other studies showed that each does not differ much from the overall HR (Fig. 6A). For DFS, no individual study influenced the overall results (Fig. 6B).

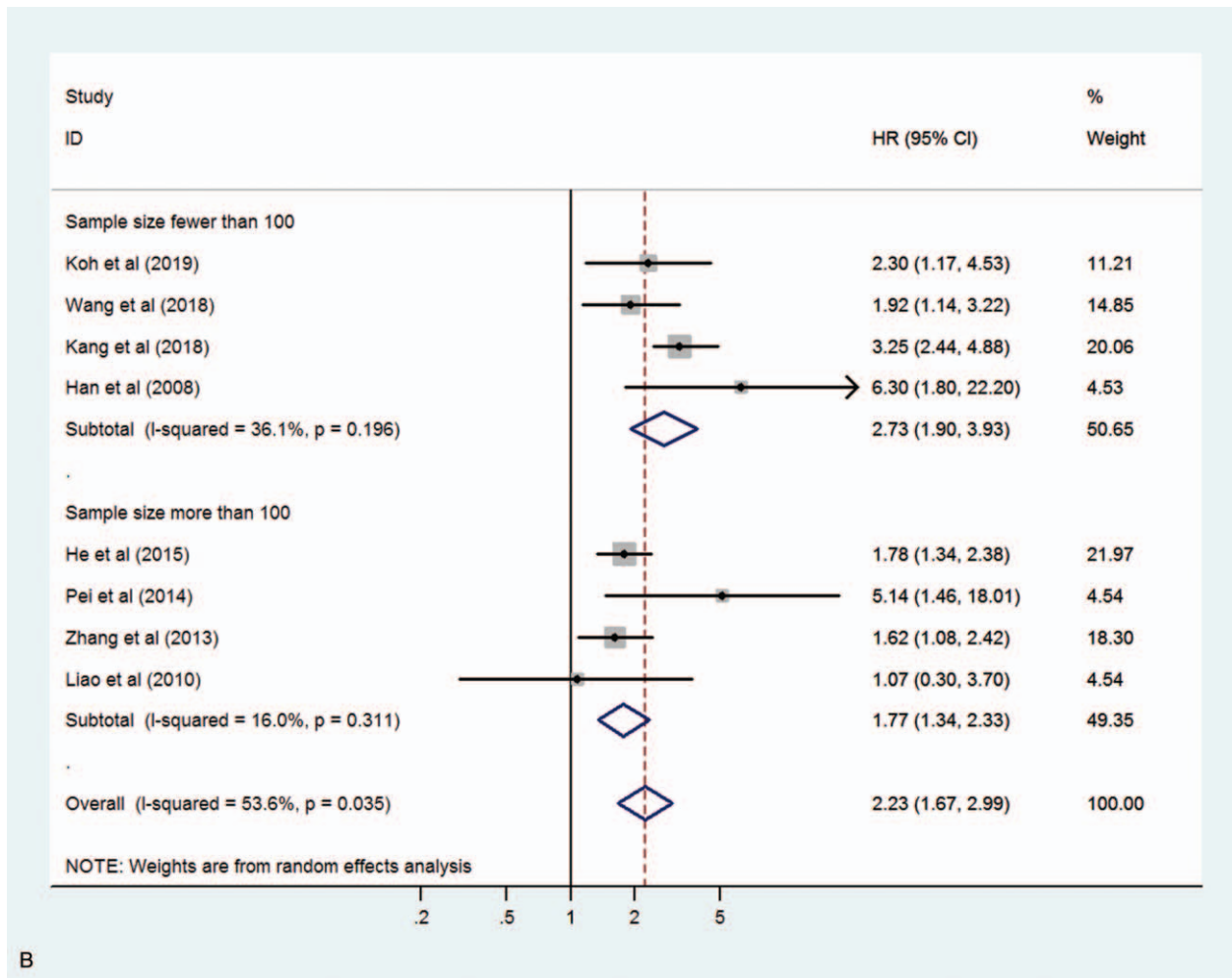


Figure 3. (Continued).

#### 4. Discussion

MIF is a pleiotropic inflammatory mediator that is considered the first cytokine activity to be reported.<sup>[9]</sup> MIF plays a central role in acute and chronic inflammatory diseases as well as autoimmune diseases. Recently, it is known not only to play a role in inflammatory diseases, but also to involve in tumorigenesis and tumor progression. MIF contributes to tumor development, progression and tumor cell survival through inhibition of p53-mediated apoptosis.<sup>[5]</sup> MIF also functions as a pro-survival and anti-apoptotic factor for cancer cells through the activation of PI3K/Akt cascade.<sup>[5]</sup> Moreover, MIF enables cancer cell growth and metastasis by activating HIF-1 $\alpha$  under hypoxic condition.<sup>[10]</sup> Furthermore, MIF has been suggested as a potential prognostic factor for various cancers including gastric, hepatocellular, pancreatic, and lung cancers, and oral squamous cell carcinoma and metastatic melanoma.<sup>[3,7,8]</sup> Therefore, we conducted this meta-analysis to calculate the prognostic significance of MIF expression in cancer patients.

We found 8 eligible studies. Han et al<sup>[11]</sup> showed that high expression of MIF was related with poor OS and metastasis-free survival in patients with high-grade osteosarcoma. Zhang et al<sup>[12]</sup>

and Koh et al<sup>[8]</sup> demonstrated significantly poorer OS or disease-specific survival and DFS with high expression of MIF compared with low expression in patient with esophageal squamous cell carcinoma and lung squamous cell carcinoma, respectively. Kang et al<sup>[13]</sup> revealed the relationship between MIF expression and OS and recurrence-free survival in patients with oral squamous cell carcinoma. Liao et al<sup>[14]</sup> and Pei et al<sup>[15]</sup> showed that high expression of MIF was associated with poor OS in patients with nasopharyngeal carcinoma. He et al<sup>[6]</sup> and Wang et al<sup>[16]</sup> revealed that high expression of MIF was related with unfavorable OS in patients with gastric cancer and pancreatic ductal adenocarcinoma, respectively.

We finally identified that cancer patients with high expression of MIF tended to have worse OS and DFS than those with low expression through meta-analysis. The pooled HR was 2.23 (95% CI 1.67–2.99,  $P < .001$ ) and 2.24 (95% CI 1.69–2.96,  $P < .001$ ) for OS and for DFS, respectively. Therefore, MIF expression could be used as a prognostic biomarker for OS and for DFS in cancer patients. To the best of our knowledge, this is the first meta-analysis to evaluate the prognostic significance of MIF expression in cancer patients.

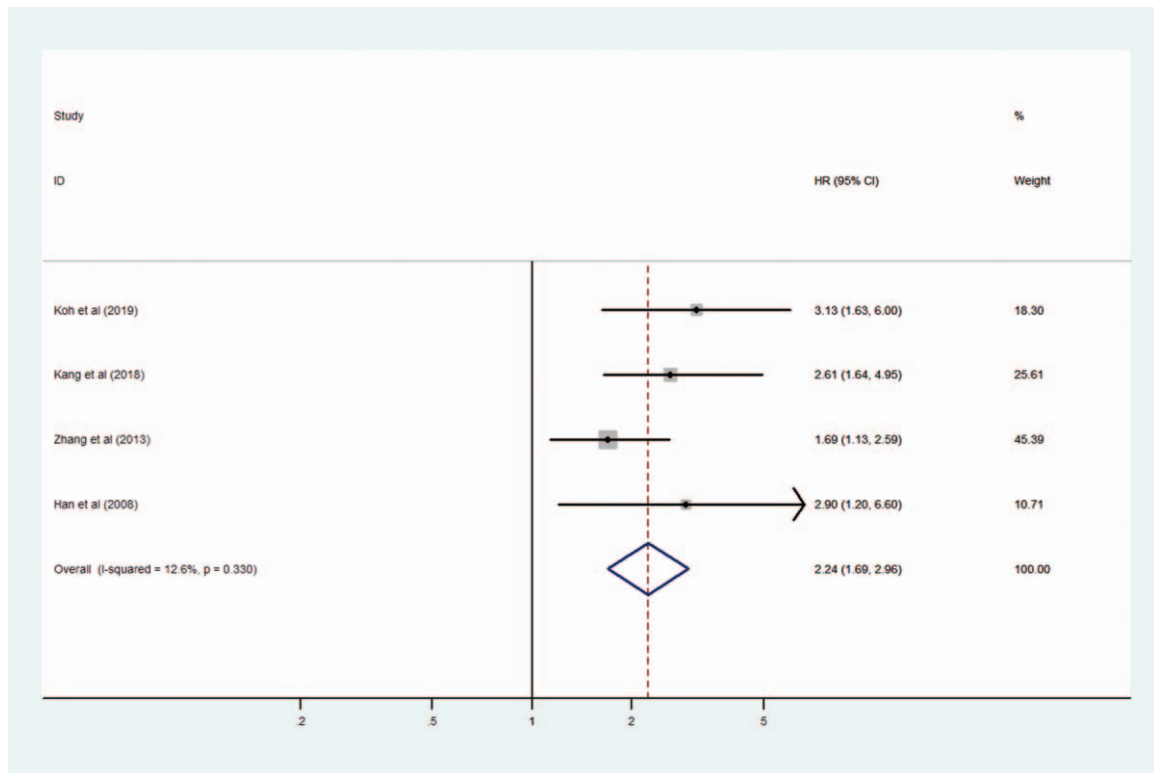


Figure 4. Forest plot reflecting the relationship between MIF expression and disease-free survival in cancer patients. MIF = macrophage migration inhibitory factor.

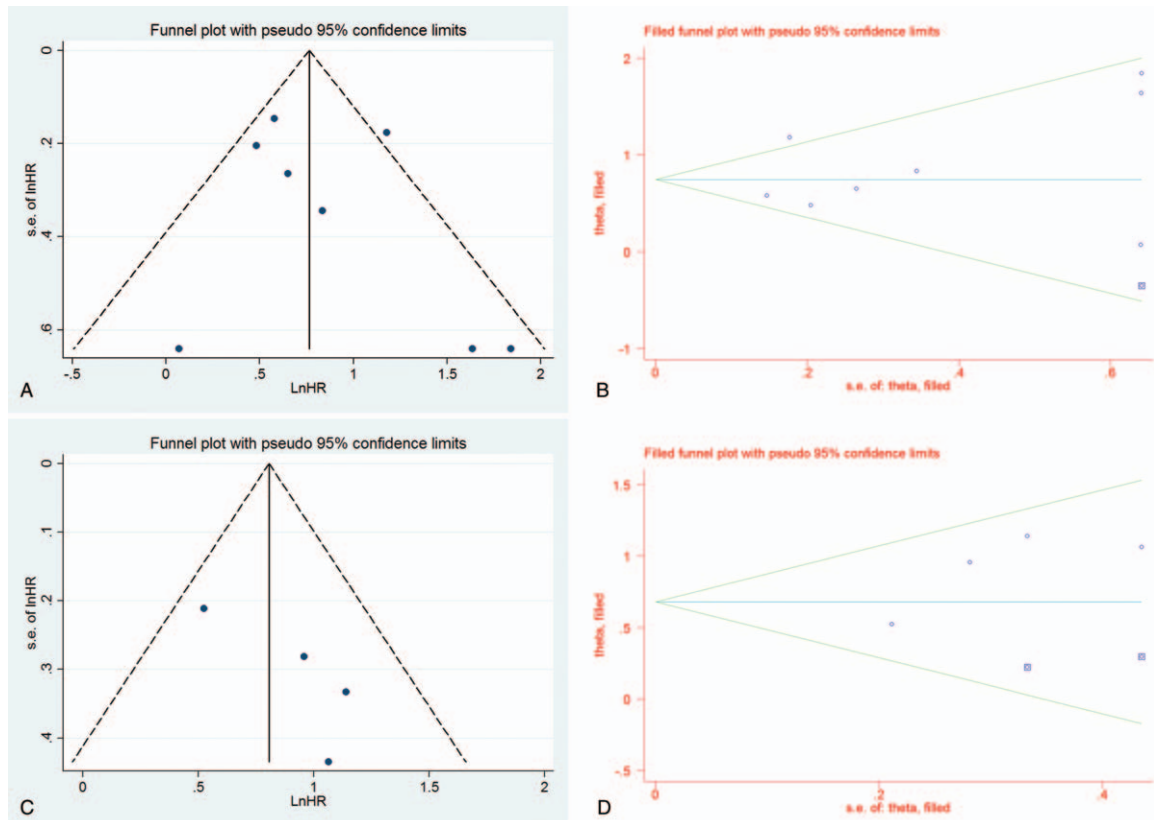


Figure 5. Funnel plot and trim and fill analysis for overall survival (A, B) and for disease-free survival (C, D).

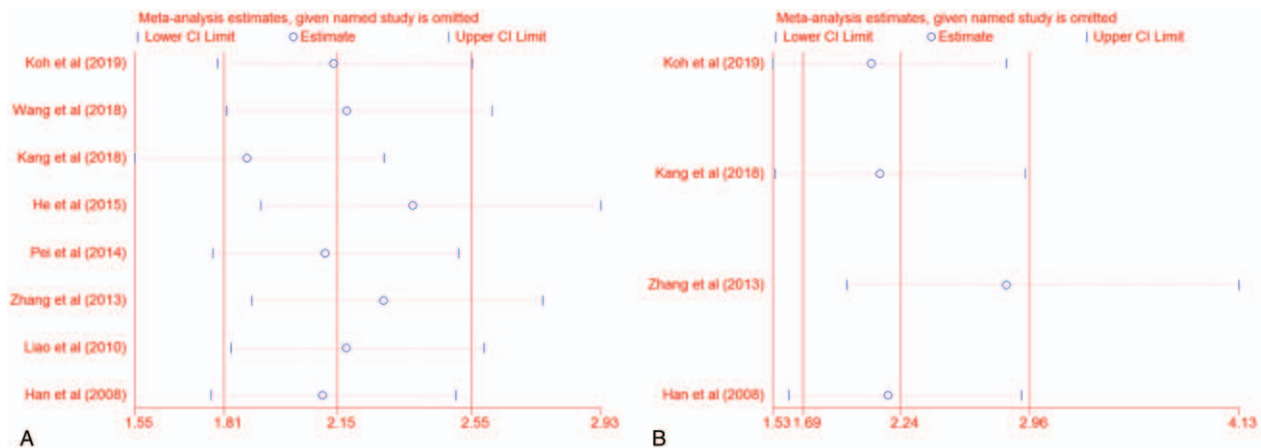


Figure 6. Sensitivity analysis for overall survival (A) and disease-free survival (B).

## 5. Limitations

There are several limitations to this study. First, all included studies were performed in Asia, which may affect the reliability of our results in western countries. Second, the diversity of included studies may have led to some heterogeneity although we selected eligible studies by uniform criteria. Third, the number and the sample size of eligible studies were limited with only 8 studies consisting 847 cancer patients. Thus, further studies should be designed on a large-scale and individual cancers.

## 6. Conclusion

This meta-analysis revealed that high expression of MIF was associated with poor survival in cancer patients and could be a useful prognostic factor.

## Author contributions

**Conceptualization:** Hyun Min Koh, Dong Chul Kim

**Data curation:** Hyun Min Koh, Dong Chul Kim

**Formal analysis:** Hyun Min Koh, Dong Chul Kim

**Investigation:** Hyun Min Koh, Dong Chul Kim

**Resources:** Hyun Min Koh, Dong Chul Kim

**Supervision:** Dong Chul Kim

**Validation:** Hyun Min Koh, Dong Chul Kim

**Writing – original draft:** Hyun Min Koh

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