

Relationship between high-mobility group box 1 overexpression in ovarian cancer tissue and serum: a meta-analysis

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Objective: To implement a meta-analysis to investigate the relationship between high-mobility group box 1 (HMGB1) overexpression in the tissue and serum of ovarian cancer patients, and to evaluate its prognostic significance.

Methods: Searches were made of China National Knowledge Infrastructure, EMBASE, WanFang, PubMed, MEDLINE, and Web of Science databases up to August 2015, with no language or style restrictions. Reference lists of related studies were also carefully reviewed to identify additional articles.

Results: The literature search identified a total of 12 relevant studies on HMGB1 expression for inclusion in the meta-analysis: seven in ovarian tumor tissue, four in ovarian tumor patient serum, and one in both tissue and serum. HMGB1 protein levels in ovarian cancer tissues were notably higher than those in normal ovarian tissues with no evidence of heterogeneity between studies (RD=0.64, 95% confidence interval (CI): 0.57–0.70, $Z=18.70$, $P<0.00001$, $I^2=15\%$), and also higher than those in benign tumor tissues with no evidence of heterogeneity between studies (RD=0.52, 95% CI: 0.43–0.61, $Z=11.14$, $P<0.00001$, $I^2=0$). Serum HMGB1 levels were similarly significantly higher in ovarian cancer patients than those with benign tumors or normal ovaries. Pooled mean differences of HMGB1 in ovarian cancer patients compared with patients with benign tumors or normal ovaries were 99.32 with 95% CI: 67.82–130.81, $Z=6.18$, $P<0.00001$, and 95.34 with 95% CI: 62.11–128.57, $Z=5.62$, $P<0.0001$. The pooled relative risk of ovarian cancer with high vs low HMGB1 expression levels was 1.40 with 95% CI: 1.09–1.79, $Z=2.66$, $P=0.008$, heterogeneity $I^2=50\%$.

Conclusion: This meta-analysis suggested that HMGB1 levels in both tissue and serum of ovarian cancer patients were significantly higher than those of benign tumor and normal ovarian samples. High serum or tissue HMGB1 expression may therefore be an effective molecular marker for ovarian benign or malignant tumor diagnosis and patient prognosis.

Keywords: high-mobility group box 1, HMGB1, ovarian cancer, meta-analysis, prognosis, tissue, serum

Introduction

Ovarian cancer has the highest mortality rate of six lethal gynecologic malignancies, and demonstrates rapid disease progression.^{1–3} Although progress has been made in ovarian cancer research,⁴ survival and cure rates remain low.⁵ Because its occurrence may go unnoticed through a lack of typical symptoms and limited early diagnostic methods, women are often diagnosed with advanced disease when they seek medical advice. Indeed, 75% of patients present with advanced (stage III or IV) cancer, and although more than 80% of these benefit from first-line therapy, tumor recurrences occur in almost all patients in a median time of 15 months from diagnosis.²

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Basic treatment for ovarian cancer involves traditional radical surgery with adjuvant chemotherapy, although new choices offered for middle–late ovarian cancer treatment include neoadjuvant chemotherapy, radiation therapy, biological therapy, immune therapy, and molecular target therapy. Ovarian cancer is heterogeneous, with each subtype associated with different genetic mutations, which can be used to predict the effect of targeted therapy. However, because tumor recurrence and metastasis are considered the main reasons for poor clinical outcome and morbidity,⁶ the identification of a protein that can be used to distinguish benign and malignant tumors would be beneficial in predicting patient prognosis. Moreover, studying the mechanism of tumor invasion and metastasis will provide further insights into the development and progression of ovarian cancer.

High-mobility group box 1 (HMGB1) was first identified in calf thymus as a highly conserved, nonchromosomal DNA-binding chromatin protein involved in DNA organization and the regulation of transcription.^{7,8} HMGB1 supports the transcription of many genes in its interaction with nucleosomes, transcription factors, and histones⁹ by inducing changes in nucleosome structure.¹⁰ Current research shows that HMGB1 plays a crucial role in Alzheimer's disease,¹¹ arthritis,¹² cardiovascular disease,¹³ inflammation,¹⁴ and sepsis.¹⁵ Moreover, it is significantly overexpressed in some cancers, including those of the bowel,^{16–18} pancreas,¹⁹ papillary thyroid,²⁰ lung,²¹ liver,^{22,23} cervix,²⁴ stomach,²⁵ and osteosarcoma.²⁶ Some studies also reported higher HMGB1 expression in ovarian cancer compared with normal ovarian tissues or those with benign cysts.^{27–35} Similarly, higher HMGB1 expression has been observed in the serum of ovarian cancer patients compared with control individuals or those with benign tumors. Such high HMGB1 expression was found to be associated with poor prognosis,^{36–39} so HMGB1 has been proposed as a potential biomarker for ovarian cancer. In the present meta-analysis, we identified studies that described HMGB1 expression in ovarian cancer, benign ovarian tumors, and normal ovaries and evaluated the association between tissue and serum HMGB1 overexpression with ovarian cancer.

Methods

Search strategy

We performed a literature search of the following databases for articles published up to August 2015: China National Knowledge Infrastructure, WanFang, Web of Science, PubMed, MEDLINE, and EMBASE. No language restrictions were placed on the search, and the following search terms were used: “HMGB1 Protein” or “HMGB1” or “HMGB1

Protein” or “HMGB1” or “high-mobility group box 1” or “high-mobility group box protein 1” and “ovarian cancer” or “ovarian carcinoma” or “ovarian tumor”. Additional relevant studies were identified from the reference lists of all selected original and review articles. The medical subject heading, methods, patient population, design, and outcome of these articles were used to identify relevant studies.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: 1) evaluated the association between HMGB1 overexpression in tissue and serum with ovarian cancer; 2) evaluated the association between HMGB1 overexpression and ovarian cancer prognosis; 3) used enzyme-linked immunosorbent assay to measure serum HMGB1 and immunohistochemistry for tissue HMGB1 expression; and 4) reported or acquired relative risk estimates with 95% confidence intervals (CIs) (or provided the data to calculate these). If the same data were published in studies of different languages, we only included the study with the largest number of cases. Exclusion criteria included: 1) use of the same population or an overlapping database; 2) the same study in a different language; and 3) use of cell culture or animal models (Figure 1).

Data extraction

Two authors (Wang and Qin) conducted independent data extraction, with disagreements resolved through discussion. The following data were extracted from each study: the first author's name, publication year, country where the study was implemented, sample size (cases and controls), and method of detection. Hazard ratio (HR) estimates with corresponding 95% CIs for high vs low expression of HMGB1 was also extracted from relative articles. The study quality was assessed using the nine-star Newcastle–Ottawa Scale.⁴⁰

Statistical analysis

Statistical heterogeneity among studies was evaluated using I^2 statistics.⁴¹ Mean differences with 95% CIs were calculated using a fixed or random effects model depending on heterogeneity. The random effects model was used when heterogeneity existed among studies ($I^2 > 25\%$), while the fixed effects model was used in the absence of statistical heterogeneity ($I^2 < 25\%$).

A meta-analysis was performed to compare HMGB1 protein expression levels between tissue and serum from ovarian cancer patients, those with benign tumors, and normal individuals. The multivariate HR was collected and the log

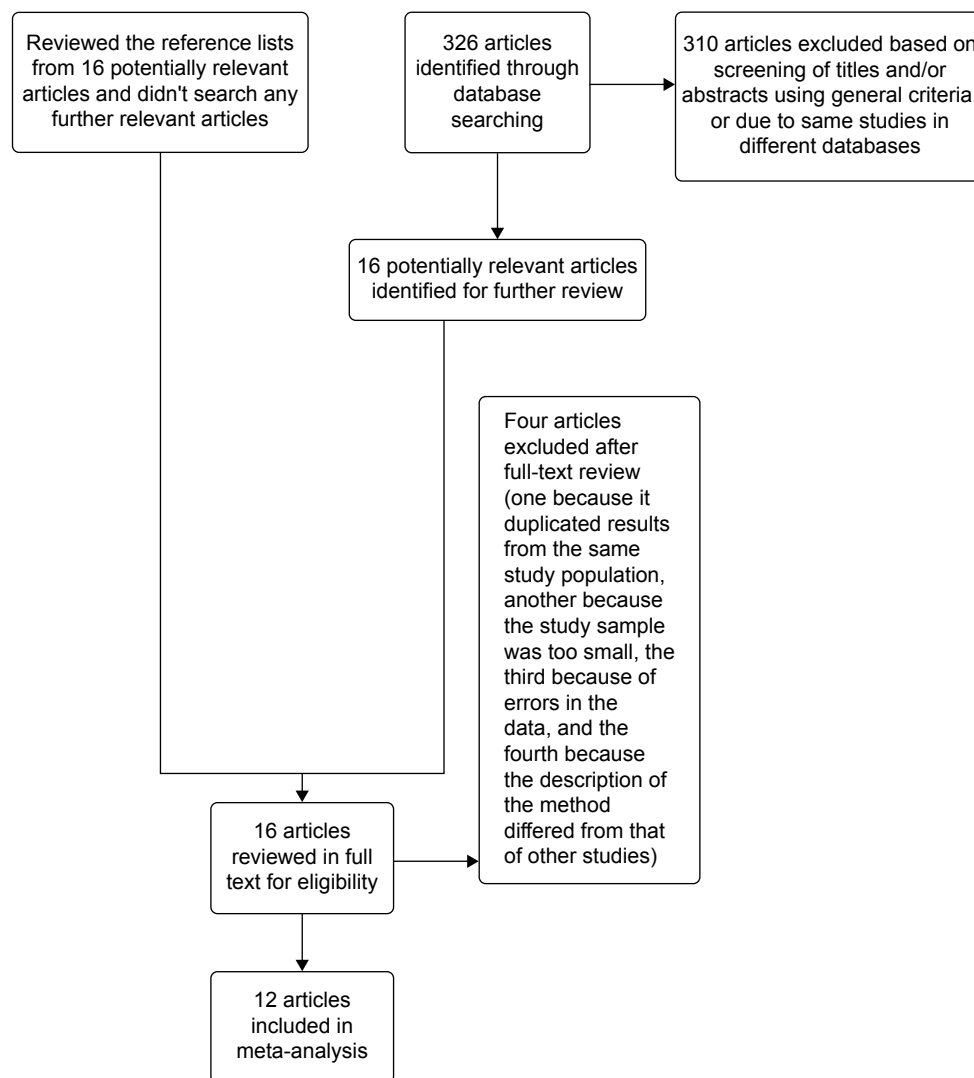


Figure 1 Flow diagram of the search and selection process of the studies.

HR and its standard errors were calculated for individual studies. The pooled HR with a 95% CI was calculated for the association between HMGB1 expression and prognosis. Beggar's funnel plots and Egger's linear regression asymmetry test were used to detect publication bias. Sensitivity analysis was performed in which one study at a time was removed and the rest analyzed to evaluate whether the results were remarkably affected by a single study. $P < 0.05$ was considered statistically significant. All analysis was performed using Review manager 5.3 and STATA 12.0 software.

Results

Literature search

Following the literature search and selection, a total of 12 studies^{28–39} were included in the meta-analysis examining the association between HMGB1 tissue or serum overexpression

with ovarian cancer. We identified seven potentially relevant articles concerning HMGB1 expression in tissue, four on HMGB1 expression in serum and one on HMGB1 expression in both serum and tissue. Four of 16 articles on HMGB1 expression in tissue were excluded: one because it duplicated results from the same study population, another because the study sample was too small, the third because of errors in the data,²⁷ and the fourth because the description of the method differed from that of other studies. The characteristics of included studies are listed in Table 1.

Study characteristics

HMGB1 expression in ovarian cancer tissue was shown to be significantly higher than in normal ovarian tissue and benign tumor tissue. There was no evidence of heterogeneity among studies of HMGB1 positive expression in tissue ($P = 0.32$,

Table 1 Main characteristics of included studies

Study	Year	Country	Sample size			Method	Tissue or serum
			Ovarian tumor	Benign ovarian tumor	Normal control		
He et al ³²	2011	People's Republic of China	26	40	30	Immunohistochemistry and ELISA	Tissue and serum
Zhou et al ²⁹	2011	People's Republic of China	56	18	20	Immunohistochemistry	Tissue
Liu et al ³³	2011	People's Republic of China	56	24	20	Immunohistochemistry	Tissue
Wei ³¹	2012	People's Republic of China	46	24	20	Immunohistochemistry	Tissue
Chen and Yuan ³⁰	2012	People's Republic of China	75	Not mentioned	40	Immunohistochemistry	Tissue
Xiao et al ³⁵	2014	People's Republic of China	55	Not mentioned	18	Immunohistochemistry	Tissue
Kong ³⁷	2014	People's Republic of China	32	79	45	ELISA	Serum
Zhi et al ²⁸	2014	People's Republic of China	40	60	30	Immunohistochemistry	Tissue
Li et al ³⁸	2014	People's Republic of China	105	46	33	ELISA	Serum
Li et al ³⁹	2014	People's Republic of China	47	30	30	ELISA	Serum
Zhi et al ³⁶	2014	People's Republic of China	40	60	30	ELISA	Serum
Paek et al ³⁴	2015	Republic of Korea	74	Not mentioned	Not mentioned	Immunohistochemistry	Tissue

Abbreviation: ELISA, enzyme-linked immunosorbent assay.

$I^2=15\%$ [ovarian cancer tissue vs normal tissue]; $P=0.62$, $I^2=0$ [ovarian cancer tissue vs benign tumor tissue]), but it was observed among studies of HMGB1 expression in serum ($P<0.00001$, $I^2=97\%$ [ovarian cancer patients vs normal patients]; $P<0.00001$, $I^2=97\%$ [ovarian cancer patients

vs benign tumor patients]). The pooled risk difference for ovarian cancer vs normal ovarian tissue was 0.64 with 95% CI: 0.57–0.70, $Z=18.70$, $P<0.00001$, heterogeneity $P=15\%$ (Figure 2A), and for ovarian cancer vs benign tumor tissue was 0.52 with 95% CI: 0.43–0.61, $Z=11.14$, $P<0.00001$,

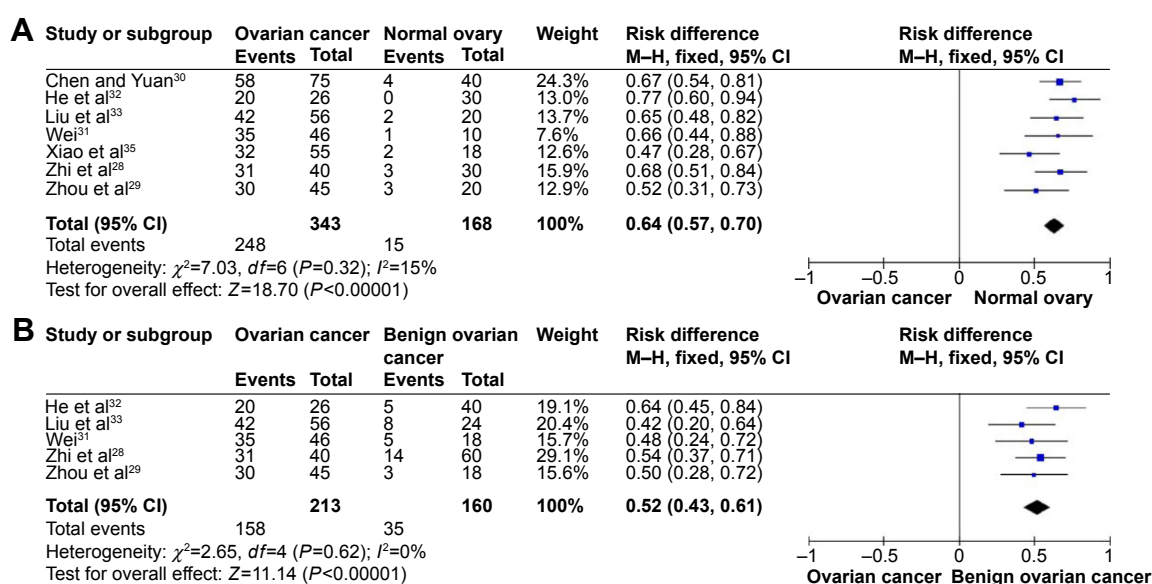


Figure 2 Forest plots for HMGB1 in tissue with ovarian cancer and normal ovary (A) and for HMGB1 in tissue with ovarian cancer and benign ovarian cancer (B).

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

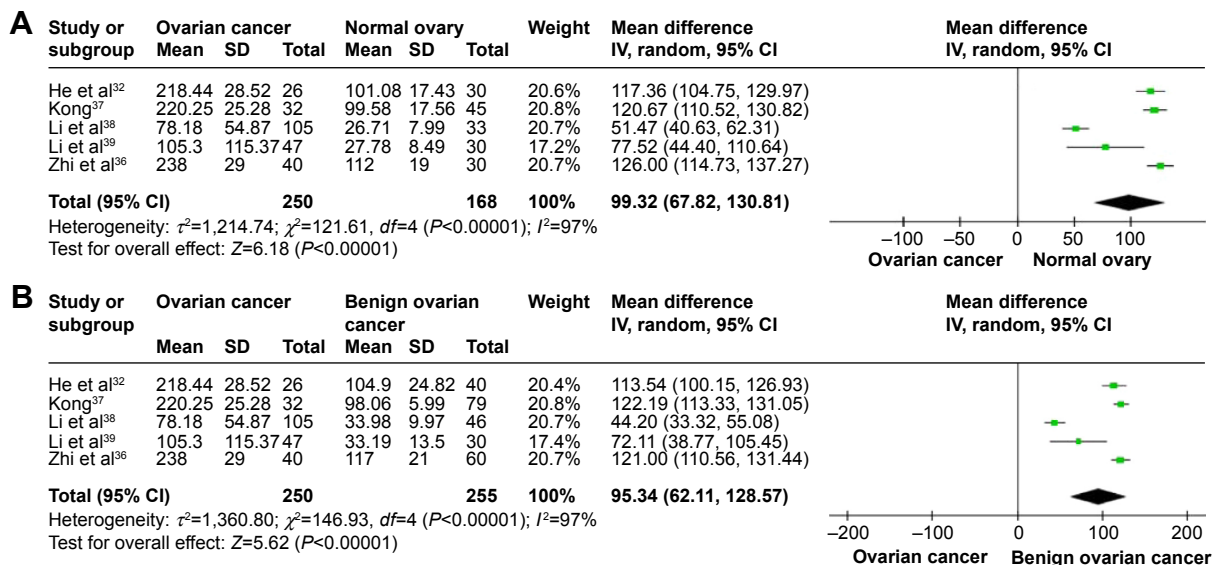


Figure 3 Forest plots for HMGB1 in serum with ovarian cancer and normal ovary (A) and for HMGB1 in serum with ovarian cancer and benign ovarian cancer (B).
Abbreviations: CI, confidence interval; IV, inverse variance.

heterogeneity $P=0$ (Figure 2B). Similarly, HMGB1 protein levels in ovarian cancer patient serum were significantly higher than in serum from control individuals or those with benign tumors. The pooled mean difference was 99.32 with 95% CI: 67.82–130.81, $Z=6.18$, $P<0.00001$, heterogeneity $P=97\%$; 95.34 with 95% CI: 62.11–128.57, $Z=5.62$, $P<0.0001$, heterogeneity $P=97\%$ (Figure 3).

HRs showed that overall survival was significantly shorter in ovarian cancer patients with high HMGB1 expression compared with those with low HMGB1 expression. The pooled HR was 1.40 with 95% CI: 1.09–1.79, $Z=2.66$, $P=0.008$, heterogeneity $P=50\%$ (Figure 4).

Sensitivity analysis and publication bias

To explore heterogeneity among studies, we performed sensitivity analyses. The overall statistical significance was not found to change when any single study was omitted, indicating the stability of our analyses (Figure 5). There was also no publication bias in the positive association of HMGB1 levels with progression of ovarian cancer both in tissue ($P=0.881$) and serum ($P=0.05$) in this meta-analysis.

Discussion

The findings from this meta-analysis indicate that HMGB1 expression in both tissue and serum from ovarian cancer patients is higher than in those with benign tumors or normal controls. Moreover, the pooled HR of patients with high HMGB1 expression is increased by 1.40-fold compared with those with low HMGB1 expression, suggesting that HMGB1 plays a crucial role in the pathogenesis of ovarian cancer. HMGB1 is a potential tissue and serum biomarker for ovarian cancer diagnosis, so the determination of HMGB1 levels in affected patients will help distinguish benign and malignant tumors and assess prognosis.

HMGB1 is a multifunctional factor that is functionally influenced by its subcellular location. It mainly exists in eukaryotic chromosomes in the cell nucleus, where it acts as a DNA chaperone to bind to minor grooves of DNA, stabilize nucleosides, and facilitate the assembly of site-specific DNA-binding proteins such as the nuclear hormone/nuclear hormone receptor complex. HMGB1 establishes protein–protein interactions and enhances the activities of a number of transcription factors implicated in cancer development, including all class I steroid receptors,⁴² HOX,⁴³ P53, P73,

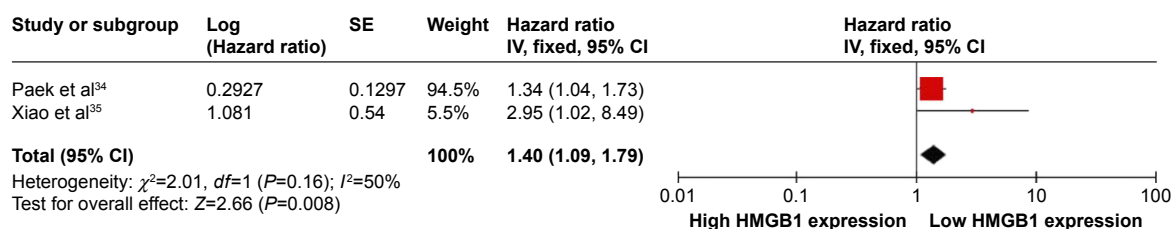


Figure 4 Forest plot for the association of HMGB1 expression level and the risk of ovarian cancer.

Abbreviations: CI, confidence interval; IV, inverse variance; SE, standard error.

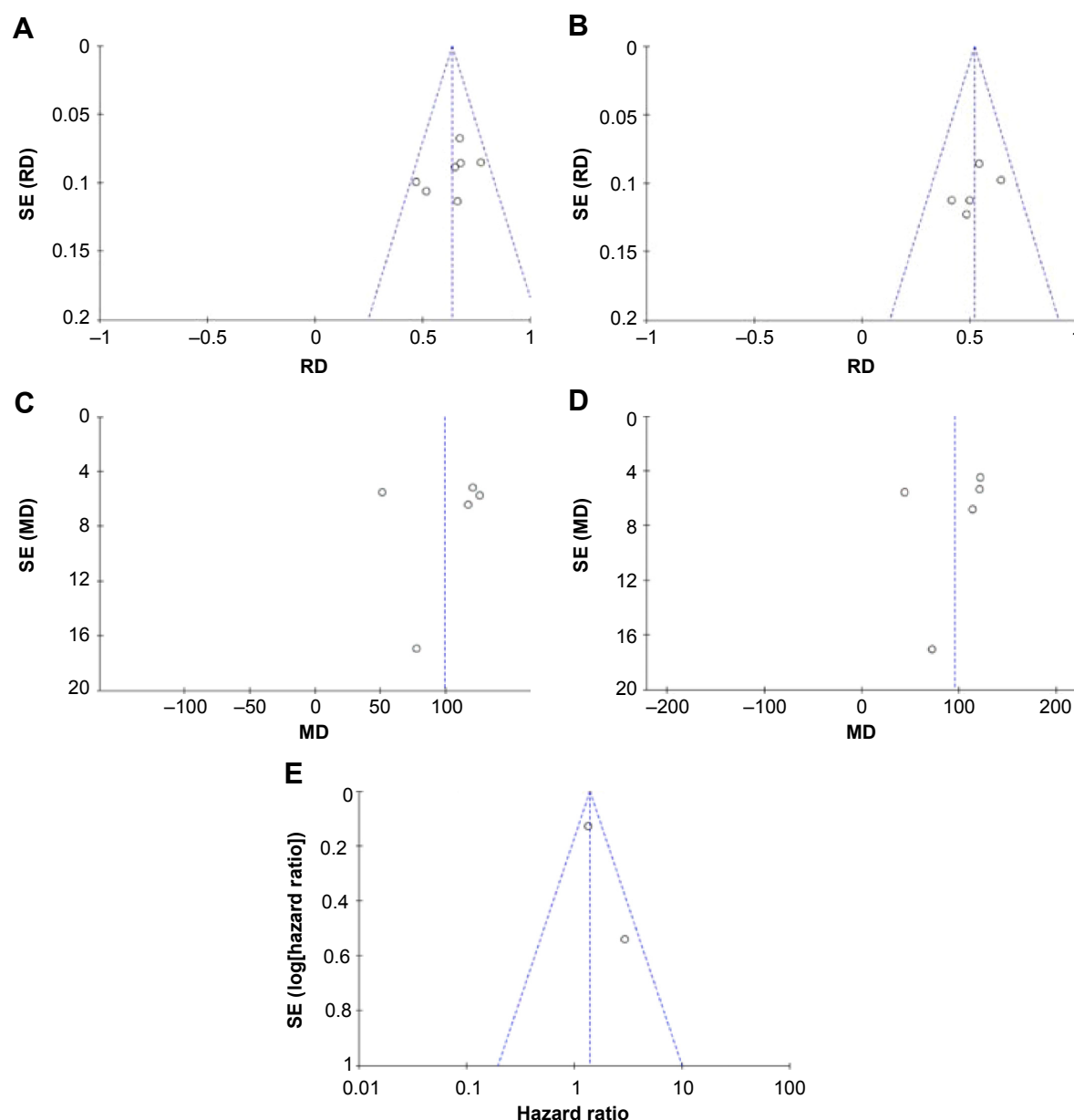


Figure 5 Funnel plots for publication bias.

Notes: HMGB1 in tissue with ovarian cancer and normal ovary (A). HMGB1 in tissue with ovarian cancer and benign ovarian cancer (B). HMGB1 in serum with ovarian cancer and normal ovary (C). HMGB1 in serum with ovarian cancer and benign ovarian cancer (D). The association of HMGB1 expression level and the risk of ovarian cancer (E).

Abbreviations: MD, mean difference; RD, risk difference; SE, standard error.

members of the Rel/nuclear factor (NF)- κ B family, nuclear hormone receptors including estrogen receptor,⁴⁴ and retinoblastoma protein transcription complexes.^{45,46} In doing so, it regulates DNA structure, DNA repair, transcription, V(D)J recombination, differentiation, development, and extracellular signaling.^{47,48} HMGB1 also regulates the transcription of many cancer genes, such as E-selectin, tumor necrosis factor- α , insulin receptor, and *BRCA1*.^{49–51} Moreover, its binding to cell membrane receptors, including receptor for advanced glycation end products (RAGE), Toll-like receptors (TLRs: TLR2, TLR4, and TLR9), mitogen-activated protein kinase, NF- κ B, syndecan, and a specific receptor-tyrosine

phosphatase,⁵² appears to be important in cancer progression⁴⁴ and the coordination of immune system activation, cell migration, cell growth, angiogenesis, tissue repair, and regeneration.⁵³ Krynetski et al⁵⁴ previously suggested that HMGB1 plays a critical role in DNA repair through its involvement in the cytotoxic response to DNA modified by the incorporation of anticancer nucleoside analogs. HMGB1 also maintains genomic stability during tumor growth,⁵⁵ and several malignancies, including gastric cancer,⁵⁶ breast cancer,⁵⁷ nasopharyngeal cancer,⁵⁸ and squamous cell cancer of the head and neck⁵⁹ are associated with HMGB1 overexpression. Indeed, a number of studies have reported

that HMGB1 overexpression is crucial for ovarian cancer tumorigenesis, expansion, and invasion.^{39,60}

New research has demonstrated that the function of HMGB1 extends beyond the nucleus, in an extracellular role in inflammation or cancer. Immune cells, including macrophages, mature dendritic cells, and natural killer cells release HMGB1 into the extracellular environment or serum by active and passive mechanisms in response to injury, infection, or other inflammatory stimuli.^{61,62} HMGB1 can also be passively released into the extracellular space or serum following the unscheduled apoptosis of tumor cells,⁶³ which is why it can be detected in the serum of cancer patients.^{64,65} Extracellular HMGB1 might contribute to cancer cell survival, proliferation, and the invasion of various cells.^{66,67} Thus, the evaluation of serum HMGB1 levels is essential for the diagnostic significance of HMGB1 in ovarian cancer and the inhibition of cancer progression by blocking serum HMGB1. Indeed, several studies have reported elevated serum HMGB1 levels in patients with various types of cancer.^{67,68}

HMGB1 has a diverse range of functions in cancer, including anti-apoptosis, cell cycle progression, cell growth, invasion, migration, and metastasis.^{69,70} As it was described in previous study,⁷¹ malignant transformation and melanoma development were just caused by overexpression of HMGB1 in melanoma. Besides, HMGB1 played a crucial role in anti-apoptotic procession by leading to NF- κ B and c-IAP (inhibitor of apoptosis) that is a target gene product.⁷² These studies indicated that HMGB1 could promote tumor occurrence and development by functioning as an oncoprotein. Li et al³⁸ found that ovarian cancer patient serum HMGB1 levels decreased significantly after they went into remission, while those with recurrence had higher serum HMGB1 levels compared with nonrecurrent patients, indicating that serum HMGB1 plays a key role in tumor progression. Cellular origin of serum HMGB1 should be carefully identified when we diagnosed cancers, which is useful for improving the sensitivity of tumor diagnosis. However, the source of secreted HMGB1 was not easy to be discriminated from clinical patient's serum because it was hard to differentiate secreted HMGB1 between immune cells and cancer cells. As we know, HMGB1 can also secrete from immune cells, which might lead to elevation of serum HMGB1 in cancer of early stage.

According to Hanahan and Weinberg, tumors can be characterized by six properties: unlimited replicative potential, angiogenesis, evasion of apoptosis, self-sufficiency in growth signals, insensitivity to inhibitors of growth, and tissue invasion and metastasis. A seventh property is

suggested to be inflammation.⁷³ Most cancer deaths are caused by tumor invasion and metastasis rather than by the primary tumor itself. Previous studies found that tissue or serum HMGB1 expression is associated with poor prognosis in a variety of cancers, including laryngeal squamous cell carcinoma,⁷⁴ gastric cancer,⁷⁵ pancreatic cancer,⁷⁶ colorectal cancer,⁷⁷ and cervical cancer.⁷⁸ Huttunen⁷⁹ previously showed that the suppression of RAGE and HMGB1 by antisense S-oligodeoxynucleotide or HMGB1 150–183 peptide (RAGE-binding motif) inhibits the growth, migration, and invasion in cancer cells in vitro. This indicated that HMGB1-RAGE signaling plays a key role in tumor invasion and metastasis, leading to the observed poor prognosis.

Several studies also demonstrated a positive correlation between HMGB1 serological activity and the progression of ovarian cancer.^{34,35} Our meta-analysis was in agreement with this, finding that serum HMGB1 levels were connected with poor prognosis. Pooled HR was shown to be increased by 1.40-fold in ovarian cancer patients with high HMGB1 expression compared with those with low HMGB1 expression, suggesting that high HMGB1 expression is significantly associated with patient mortality. Additionally, serum HMGB1 levels in patients with stages III–IV cancer were significantly higher than in those with stages I–II cancer, as well as in those ovarian cancer tissues with lymph node metastasis compared with those without. Thus, serum HMGB1 levels were inversely correlated with overall survival in patients with far-advanced stage or lymph node metastasis, suggesting that they could be a potential prognostic factor for ovarian cancer patients. HMGB1 may also serve as a therapeutic target, because *HMGB1* knockdown was able to inhibit ovarian cancer growth and metastasis.

Conclusion

This meta-analysis demonstrated that HMGB1 is more highly expressed in the tissue and serum of ovarian cancer patients compared with controls and those with benign tumors, and that the increased serum levels may contribute to aggressive tumor progression. HMGB1 is also significantly associated with the prognosis of patients with ovarian cancer. Therefore, the early detection of elevated HMGB1 serum levels may help clinicians offer therapeutic strategies to improve the survival of ovarian cancer patients.

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Disclosure

The authors report no conflicts of interest in this work.

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