Research Square

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Clinicopathological and Prognostic Significance of Maspin Expression in Resected Non-Small Cell Lung Cancer: A Meta-Analysis

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Abstract

Objective To explore the association of maspin expression with clinical pathological parameters and prognosis in non-small cell lung cancer (NSCLC) who received the surgical therapy.

Methods The EMBASE, Web of Science and PubMed were searched to identify eligible studies to 3 December, 2019. The correlation of maspin expression with clinicopathological characteristics and survival of resected NSCLC patients was assessed by the combined relative risk (RR) and hazard ratio (HR) with corresponding 95% confidence interval (CI), respectively. All statistical analyses were performed via the Stata 12.0 software.

Results A total of 12 articles involving 1771 patients were included. The results manifested that maspin was more prevalent in lung squamous cell carcinoma (SCC) (RR=0.36, 95% CI: 0.22-0.60, *P*<0.001) and significantly associated with P53 expression (RR=1.50, 95% CI: 1.00-2.24, *P*=0.048), while no significant correlation of maspin with other clinicopathological parameters such as the gender, age, tumor size, lymph node metastasis, tumor node metastasis (TNM) stage or differentiation status was observed. As for the prognosis representing as overall survival (OS), disease-free survival (DFS) and cancer-specific survival (CSS), only significant association between maspin and CSS (HR=1.58, 95% CI: 1.16-2.15, *P*=0.003) was revealed. However, the subgroup analysis for OS based on the histology demonstrated that maspin expression was an unfavourable and favourable prognostic indicator in lung adenocarcinoma (HR=3.36, 95% CI: 1.44-7.87, *P*=0.005) and SCC (HR=0.44, 95% CI: 0.27-0.71, *P*=0.001), respectively.

Conclusion Maspin expression was correlated with histology type and P53 expression, but no certain association of maspin with other clinicopathological characteristics or prognosis was observed in resected NSCLC. More well-designed prospective researches with big samples are still needed to further assess the clinicopathological and prognostic significance of maspin in NSCLC patients undergoing surgical resection.

Introduction

Despite the great advances in diagnosis and therapy strategies the prognosis of non-small cell lung cancer (NSCLC) remains poor, ever after the radical resection at an early stage [1, 2]. Therefore, in recent years, lots of investigation about the molecular pathogenesis of NSCLC has been done and an increasing number of cancer-specific biomarkers which are correlated with progression and prognosis of NSCLC patients have been reported, such as the melanoma associated antigen-A (MAGE-A) and EGFR [3, 4].

Maspin, a member of the serine protease inhibitor (serpin) family, is a 42-kDa protein and shows strong structural homology with other members of this serpin super-family, such as the α1-antitrypsin, plasminogen activator inhibitors1 and 2 [5]. It was first discovered in normal mammary epithelial cells and later in breast carcinoma [6]. In breast cancer, maspin was reported as a tumor suppressor and down-regulation of maspin indicated worse clinical outcomes [7]. Furthermore, a few studies have explored its clinicopathological and prognostic significance in several malignancies such as the ovary carcinoma [8], pancreatic carcinoma [9] and also NSCLC [10]. Some articles demonstrated that the expression of maspin was a predictor for the limited development, metastasis and improved survival in resected NSCLC [10–12]. However, other studies reported a significant correlation between upregulation of maspin and malignant development and poor prognosis of NSCLC patients who received the surgical therapy [13–15].

Therefore, the current meta-analysis was performed to further determine the clinical significance of maspin expression in resected NSCLC and then contribute to the risk evaluation and therapy strategy formulation of NSCLC patients.

Materials And Methods

Literature search

A publication search was performed through EMBASE, Web of Science and PubMed databases updated on 3 December, 2019. The following terms were used: maspin, lung, pulmonary, cancer, tumor, carcinoma and neoplasm and the specific search

strategy was: (lung OR pulmonary) AND (cancer OR tumor OR carcinoma OR neoplasm) AND maspin. Furthermore, the references cited in included articles were also reviewed for eligibility.

Inclusion and exclusion criteria

The following inclusion criteria were applied: 1) articles assessed the correlation of maspin expression with clinicopathological parameters and survival, especially with survival; 2) patients were diagnosed as NSCLC pathologically and received surgical resection; 3) articles directly reported the HRs with 95% CIs or provided enough information like the Kaplan-Meier curve to calculate them; 4) full texts were available; 5) if data were overlapped or duplicated, only the latest publication was included.

The exclusion criteria were as follows: 1) conference abstracts, letters, reviews, opinions, case reports and animal trials; 2) articles did not provide enough data to calculate HRs with 95% CIs when they were not directly reported.

The literature retrieval and selection were performed by two individual researchers (Yan Wang and Yi Wang) and all disagreements were resolved by team discussion.

Data extraction and assessment of literature quality

Necessary information was extracted from eligible articles by two authors (Yan Wang and Yi Wang) independently, including the name of first author, publication year, country, number of enrolled patients, gender, age, tumor size, lymph node metastasis status, tumor node metastasis (TNM stage), differentiation status, histology, P53 expression, number of patients with “positive maspin expression”, definition of “positive maspin expression”, detection method, endpoint events, HRs with corresponding 95% CIs.

The Newcastle Ottawa Scale (NOS) score was applied to assess the quality of included studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) and articles which earned a score of 6 or higher were regarded as high-quality studies. Two reviewers (Yan Wang and Yi Wang) did this work independently and any disagreement was resolved through team discussion until a consensus reached.

Statistical analysis

We used the STATA 12.0 software to perform statistical analyses. The association of maspin expression with clinicopathological characteristics and prognosis in resected NSCLC were assessed by the pooled relative risks (RRs) and HRs with corresponding 95% CIs, respectively. HRs with 95 % CIs in multivariate models were used whenever available; and if the articles did not directly report them, they would be estimated from the Kaplan-Meier curves by the method described by Tierney et al. [16]. The Chi-square based Q-test and I^2 statistic were applied to assess the heterogeneity among included publications [17]. If significant heterogeneity representing as P 0.10 or/and I^2 50% was observed, the random-effect modes was applied; otherwise the fixed-effect model was used [18]. The sensitivity analysis was performed to assess the stability of our results. The potential publication bias was detected with the Begg’s funnel plot and Egger’s test [19]. A P value 0.05 was regarded as statistical significance.

Results

Literature selection process

According to the established retrieval strategy, 223 records, after removing 136 duplicates, were evaluated for eligibility and 18 publications were reviewed with full texts (Fig. 1). Eventually, a total of 12 articles [10–15, 20–25] were included into our analysis.

Basic characteristics of included studies

Most of included studies (10/12) were from Asian countries, China and Japan, and used the immunohistochemistry method to detect maspin expression. The sample size and proportion of patients with positive maspin expression ranged from 55 to 352 and from 25–68%. All publications were high-quality studies with a NOS score of 6 or higher. Detailed information was shown in Table 1.

Table 1
Basic characteristics of included studies.

Author	Year	Country	Sample size	Positive, n (%)	TNM stage	Definition of positive "maspin expression"	Detection method	Endpoint	Source of HR	NOS score
Hirai [21]	2005	Japan	132	73(55)	Ⅰ-Ⅲ	Maspin presence in ≥40% cancer cells	IHC	OS	R	8
Katakura [11]	2006	Japan	55	26(68)	Ⅰ-Ⅲ	Median maspin mRNA value (2.57)	RT-PCR	OS	R	7
Woenckhaus [22]	2006	Germany	352	133(38)	NR	Maspin presence in ≥10% cancer cells	IHC	CSS	E	7
Nakagawa [23]	2006	Japan	210	73(35)	Ⅰ-ⅢA	+/++	IHC	OS	R	7
Takanami [12]	2008	Japan	181	74(41)	Ⅰ-Ⅲ	Maspin presence in ≥5% cancer cells	IHC	OS/PFS	R	7
Wu [13]	2012	China	160	77(48)	Ⅰ-Ⅲ	Intensity score with percentage score ≥1	IHC	OS	R	6
Takagi [14]	2014	Japan	110	27(25)	Ⅰ-ⅢA	Maspin presence in ≥10% cancer cells	IHC	OS/DFS	R	7
Wang [24]	2014	China	98	26(27)	NR	++	IHC	OS/DFS	E	8
Matsuoka [15]	2015	Japan	101	25(25)	Ⅰ-ⅢA	Maspin presence in ≥10% cancer cells	IHC	DFS/CSS	R	7
Yaman [25]	2015	Turkey	80	26(32)	Ⅰ-Ⅲ	Maspin presence in ≥5% cancer cells	IHC	OS	E	7
Lu [16]	2016	China	111	59(53)	Ⅰ-Ⅲ	NR	QT-PCR	DFS	R	8
Ohno [26]	2018	Japan	181	45(25)	ⅠA	Maspin presence in ≥10% cancer cells	IHC	DFS/CSS	R	8

TNM: tumor-node-metastasis; IHC: immunohistochemistry; RT-PCR: reverse transcription polymerase chain reaction; OS: overall survival; DFS: disease-free survival; CSS: cancer-specific survival; HR: hazard ratio; R: reported; E: estimated; NOS: Newcastle–Ottawa scale.

Association between maspin expression and clinicopathological characteristics in resected NSCLC

We assessed the correlation of maspin with gender, age, tumor size, lymph node metastasis status, TNM stage, differentiation status, histology type and P53 expression based on available data. Our results manifested that maspin expression was more frequently observed in squamous cell carcinoma (SCC) than in adenocarcinoma (AC) (RR = 0.36, 95% CI: 0.22–0.60, P 0.001) and significantly associated with P53 expression (RR = 1.50, 95% CI: 1.00-2.24, P = 0.048). No significant relation of maspin with gender, age, tumor size, lymph node metastasis status, TNM stage or differentiation status was manifested in out meta-analysis. (Table 2)

Table 2
Association between maspin expression and clinicopathological characteristics in non-small cell lung cancer.

Author	Gender (M vs F)	Age (≥ 60 vs <60)	Tumor size (T3,4 vs T1,2)	Lymph node metastasis (N + vs -)	TNM (Ⅲ,Ⅳ vsⅠ,Ⅱ)	Differentiation (poor vs moderate or well)	Histology (AC vs SCC)	P53 expression (+ vs -)
Hirai [21]	1.156 (0.814–1.640)	-	-	1.206 (0.883–1.647)	1.957 (1.438–2.663)	0.765 (0.487–1.202)	0.879 (0.639–1.209)	1.986 (1.329–2.968)
Katakura [11]	-	-	-	-	-	-	-	-
Woenckhaus [22]	-	-	1.311 (0.946–1.817)	0.993 (0.772–1.278)	-	-	0.244 (0.131–0.458)	1.060 (0.811–1.384)
Nakagawa [23]	2.202 (1.250–3.880)	-	-	-	0.867 (0.571–1.315)	0.933 (0.600-1.452)	0.152 (0.090–0.258)	1.708 (1.177–2.480)
Takanami [12]	2.207 (1.197–3.432)	-	1.172 (0.807–1.703)	0.988 (0.688–1.418)	1.100 (0.760–1.591)	-	0.348 (0.235–0.514)	-
Wu [13]	0.954 (0.639–1.424)	0.8883 (0.641–1.217)	-	0.632 (0.447–0.892)	0.390 (0.269–0.563)	0.765 (0.491–1.194)	0.586 (0.369–0.931)	-
Takagi [14]	1.455 (0.744–2.844)	-	-	2.858 (1.541–5.301)	3.206 (1.762–5.834)	-	-	-
Wang [24]	1.196 (0.595–2.405)	0.951 (0.491–1.840)		0.182 (0.068–0.489)		1.492 (0.771–2.887)	0.421 (0.214–0.829)	-
Matsuoka [15]	0.717 (0.266–1.937)	-	-	2.521 (1.325–4.796)	2.045 (0.962–4.347)	1.433 (0.636–3.229)	-	-
Yaman [25]	-	-	-	-	-	-	0.261 (0.131–0.520)	-
Lu [16]	1.029 (0.725–1.461)	1.026 (0.710–1.481)	0.735 (0.337–1.602)	0.784 (0.549–1.121)	0.744 (0.491–1.129)	-	-	-
Ohno [26]	1.351 (0.811–2.250)	-	-	2.211 (1.358–3.599)	-	2.628 (1.614–4.280)	-	-
Overall	1.25 (1.06–1.46)	0.95 (0.75–1.19)	1.19 (0.94–1.50)	1.11 (0.78–1.56)	1.17 (0.69–1.96)	1.18 (0.78–1.79)	**0.36 (0.22–0.60)**	**1.50 (1.00-2.24)**

M: male; F: female; TNM: tumor-node-metastasis; AC: adenocarcinoma; SCC: squamous cell carcinoma

Association between maspin expression and prognosis in resected NSCLC

The results demonstrated that maspin expression was not significantly associated with overall survival (OS) (HR = 0.86, 95% CI: 0.42–1.76, $P = 0.671$) (Fig. 2) or disease-free survival (DFS) (HR = 1.51, 95% CI: 0.96–2.38, $P = 0.077$) (Fig. 3), but the significant correlation between maspin and cancer-specific survival (CSS) (HR = 1.58, 95% CI: 1.16–2.15, $P = 0.003$) was observed (Fig. 4).

We also conducted the subgroup analysis based on the histology type, which demonstrated that maspin expression was an unfavourable and favourable prognostic indicator in lung adenocarcinoma (HR = 3.36, 95% CI: 1.44–7.87, *P* = 0.005) and SCC (HR = 0.44, 95% CI: 0.27–0.71, *P* = 0.001), respectively. (Table 3)

Table 3
Meta-analyses for the association of maspin expression with survival of resected non-small cell lung cancer patients.

	No. of studies	HR	95% CI	*P* value	Heterogeneity (P, I^2 (%))
Overall survival	8	0.86	0.42–1.76	0.671	0.001, 80.8
Histology	4	0.70	0.23–2.16	0.539	0.001, 82.6
Non-small cell lung cancer	2	0.44	0.27–0.71	0.001	0.717, 0.0
Squamous cell carcinoma	2	3.36	1.44–7.87	0.005	0.582, 0.0
Adenocarcinoma					
Disease-free survival	6	1.51	0.96–2.38	0.077	0.006, 69.5
Cancer-specific survival	3	1.58	1.16–2.15	0.003	0.473, 0.0
HR: hazard ratio; CI: confidence interval.					

Sensitivity analysis

To evaluate the stability of our pooled results, we conducted the sensitivity analysis by excluding single study each time and it indicated that our results were stable. (Fig. 5)

Publication bias

The Begg's funnel plot was not asymmetrical (*P* = 0.108) and the *P* value of Egger's test was 0.057, which indicated that no significant publication bias existed (Fig. 6).

Discussion

After combining relevant studies explored the association of maspin expression with clinical pathological characteristics and survival in resected NSCLC. The results indicated that maspin was more prevalent in lung SCC and significantly correlated with P53 expression. Unfortunately, no certain relation between maspin and prognosis was observed based on the current meta-analysis.

The results of previous studies about the clinical significance of maspin were highly controversial. A few studies demonstrated that maspin could serve as an inhibitor of angiogenesis and contributed to improved prognosis [26, 27]. It can act directly on endothelial cells by suppressing their migration to vascular endothelial growth factor (VEGFs) and basic fibroblast growth factors and then inhibit tumor angiogenesis [26]. Besides, Wu et al [12] demonstrated that vasculogenic mimicry (VM), an angiogenesis-independent pathway, was an independent prognostic factor and maspin expression was negatively associated with VM. However, some studies reported that maspin displayed an adverse influence on the tumor development and was a predictor for unfavourable prognosis in NSCLC [13–15]. TP53 was proven to be significantly associated with maspin expression [20, 22] and Zou et al [28] manifested that TP53 could activate maspin by directly binding to TP53 consensus-binding site of maspin promoter. In other words, maspin may be one of the TP53-targeted genes which involved in the process of cancer invasion and metastasis [28]. Thus, maspin might play a complex role in the process of tumorigenesis and progression in NSCLC patients.

There are several possible reasons for this phenomenon. Goulet et al [29] reported that nuclear maspin expression in tumor cells contributed to its tumor suppressor activity. However, Takagi et al [13] manifested that cytoplasmic accumulation was an unfavourable prognostic factor of NSCLC patients, although the exact molecular mechanisms are unclear, and Takanami et al [10] found that cytoplasmic plus nuclear maspin expression was an independent favourable prognostic indicator in lung SCC. Therefore, cytoplasmic and nuclear expression of maspin may exhibit very different biological characteristics. Besides, the subgroup analysis for OS based on the histology proved that maspin expression was an unfavourable and favourable prognostic indicator in lung adenocarcinoma (HR = 3.36, 95% CI: 1.44–7.87, P = 0.005) and SCC (HR = 0.44, 95% CI: 0.27–0.71, P = 0.001), respectively, which indicated that maspin might also play a totally different role in different histological subtypes. Our meta-analysis demonstrated that maspin expression was much more prevalent in lung SCC than in AC, which may lead to the inaccuracy of the results of studies that did not perform subgroup analyses based on histology type.

In addition to what was mentioned above, there are still many fields about maspin expression in NSCLC that deserve further investigation. A few publications reported the significant correlation between maspin expression and TNM stage in NSCLC [12, 13, 20], although we did not get a positive result. Thus, we still need to further investigated the influence caused by maspin on tumor development. It is well known that P53 mutation was significantly related with smoking [30] and maspin was shown as significant association with P53 expression; however, few included studies explored the influence of smoking on maspin expression. Besides, few studies conducted subgroup analyses stratified by the TNM stage which was an important prognostic factor and we suspected that maspin may show very different prognostic significance in patients with different TNM stage.

Although we were not able to draw a very certain conclusion about the prognostic value of maspin in resected NSCLC, we revealed the current advance and provided some valuable research directions about maspin expression in NSCLC. We expect that the current meta-analysis could help with the formulation of study program and interpretation of results in future investigation.

There are some limitations that should be addressed. First of all, all included studies are retrospective with relatively small samples. Second, due to lack of original data, we were unable to conduct subgroup analyses stratified by age, TNM stage, smoking status and et al. Third, significant heterogeneity among included studies was observed in our meta-analysis; unfortunately, we failed to determine the source of heterogeneity. Four, the cut-off thresholds for the definition of positive maspin expression were different among included studies and we could not confirm the optimal one based on current information.

Conclusions

In conclusion, we demonstrated that maspin expression was correlated with histology type and P53 expression, but no certain correlation of maspin with other clinicopathological characteristics or prognosis was observed in resected NSCLC. More well-designed prospective researches with big samples are urgently needed to further assess the clinicopathological and prognostic significance of maspin in NSCLC patients undergoing surgical resection.

Abbreviations

NSCLC: Non-small cell lung cancer; HR: Hazard ratio; CI: Confidence interval; RR: Relative risk; SCC: Squamous cell carcinoma; TNM: Tumor-node-metastasis; OS: Overall survival; DFS: Disease-free survival; CSS: Cancer-specific survival; MAGE-A: melanoma associated antigen-A; AC: adenocarcinoma; IHC: Immunohistochemistry; RT-PCR: Reverse transcription polymerase chain reaction; NOS: Newcastle–Ottawa scale; VEGFs: vascular endothelial growth factor; VM: vasculogenic mimicry.

Declarations

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Not applicable

Authors’ contributions

GWC conceived and designed the analyses. YW and YW performed the literature search and selection, collected data and wrote the paper. YXD and JLL performed statistical analyses. All authors contributed substantially to its revision.

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Availability of data and materials

All data are fully available without restriction.

Ethics approval and consent to participate

This paper did not use the experimental data from human subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

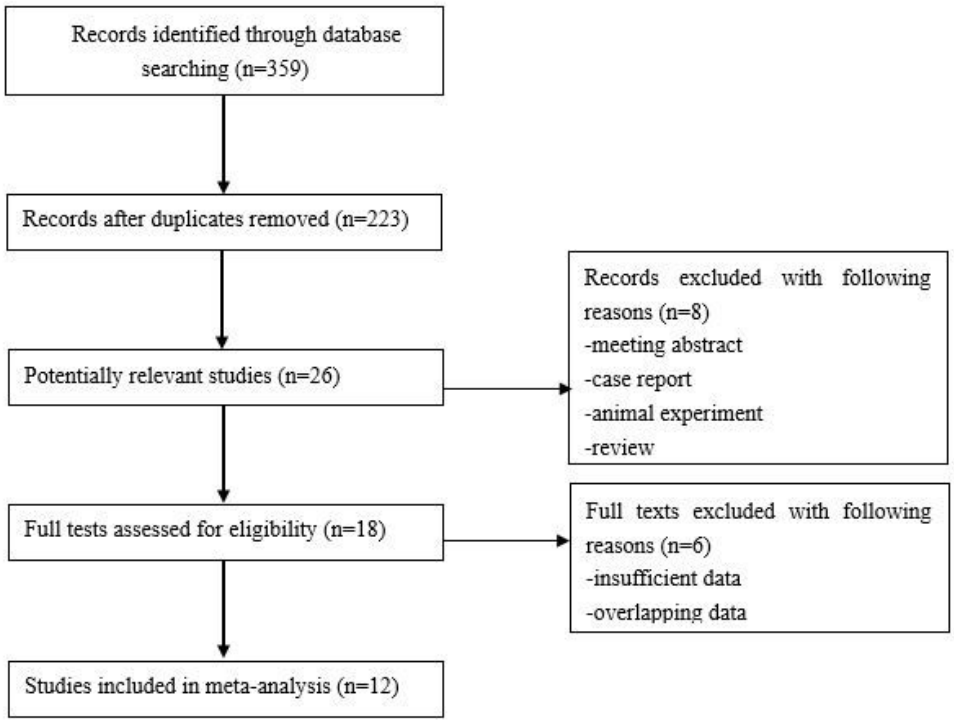

Figure 1

The flow diagram of this meta-analysis.

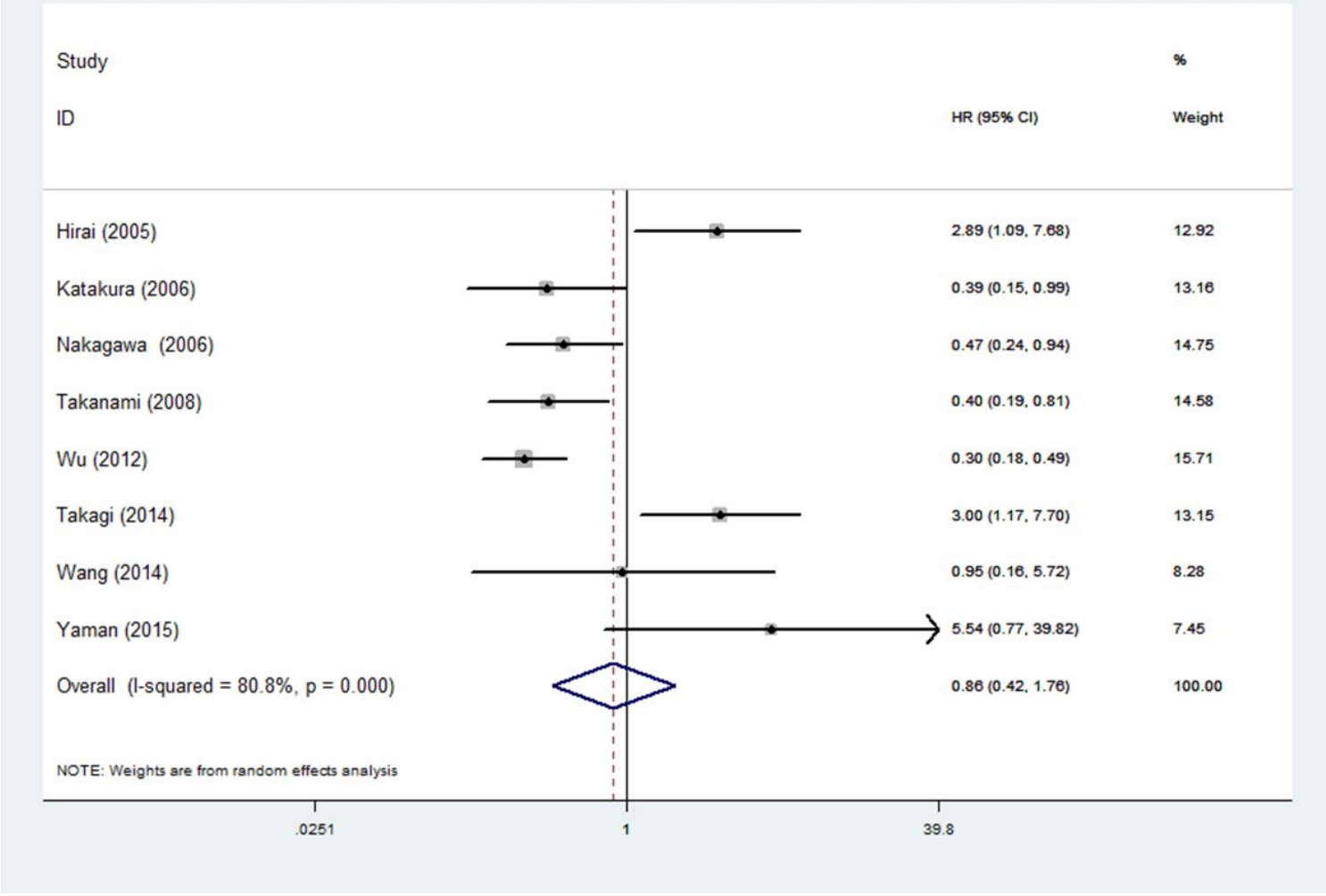

Figure 2

Forest plot of the association between maspin and overall survival.

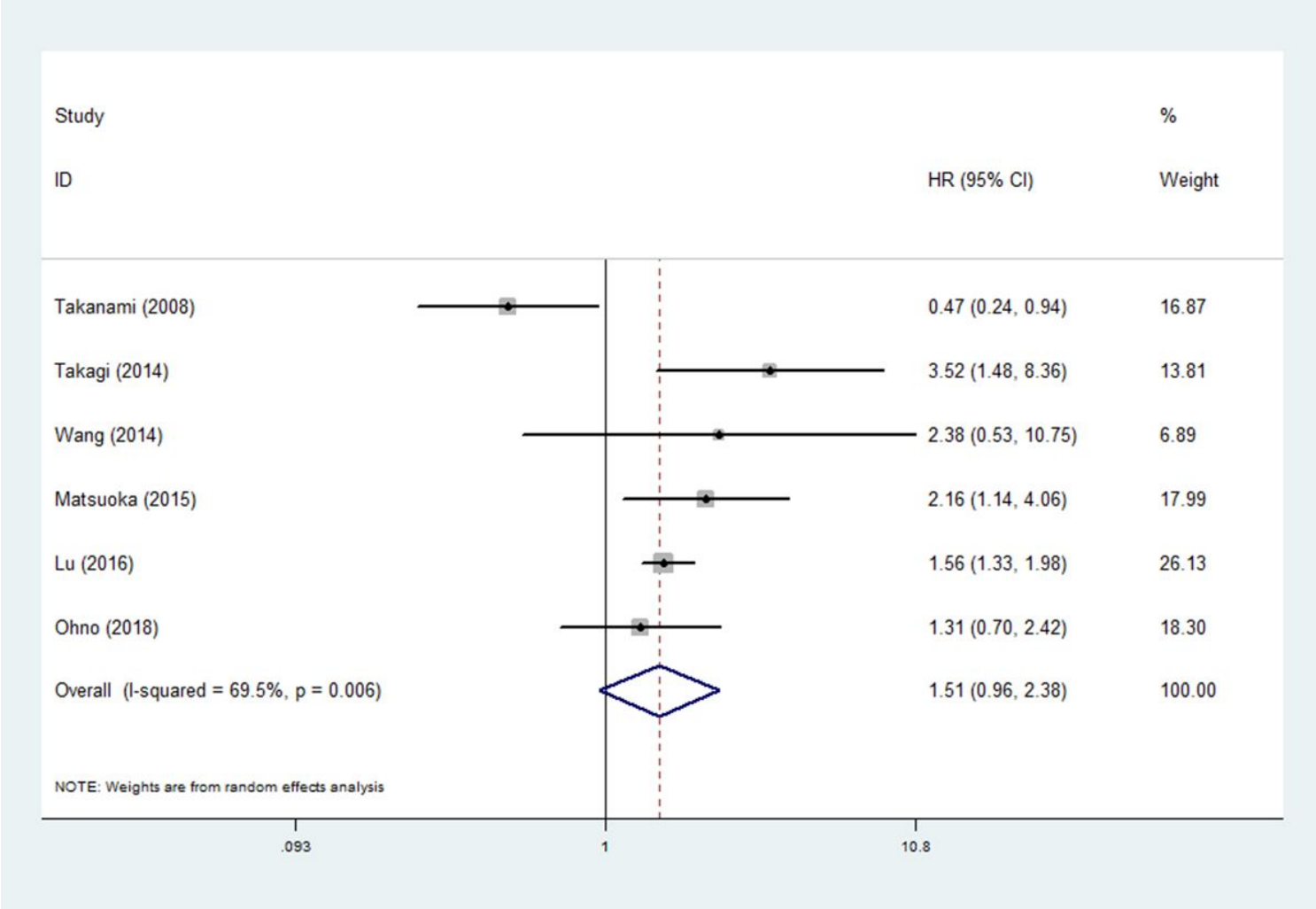

Figure 3

Forest plot of the association between maspin and disease-free survival.

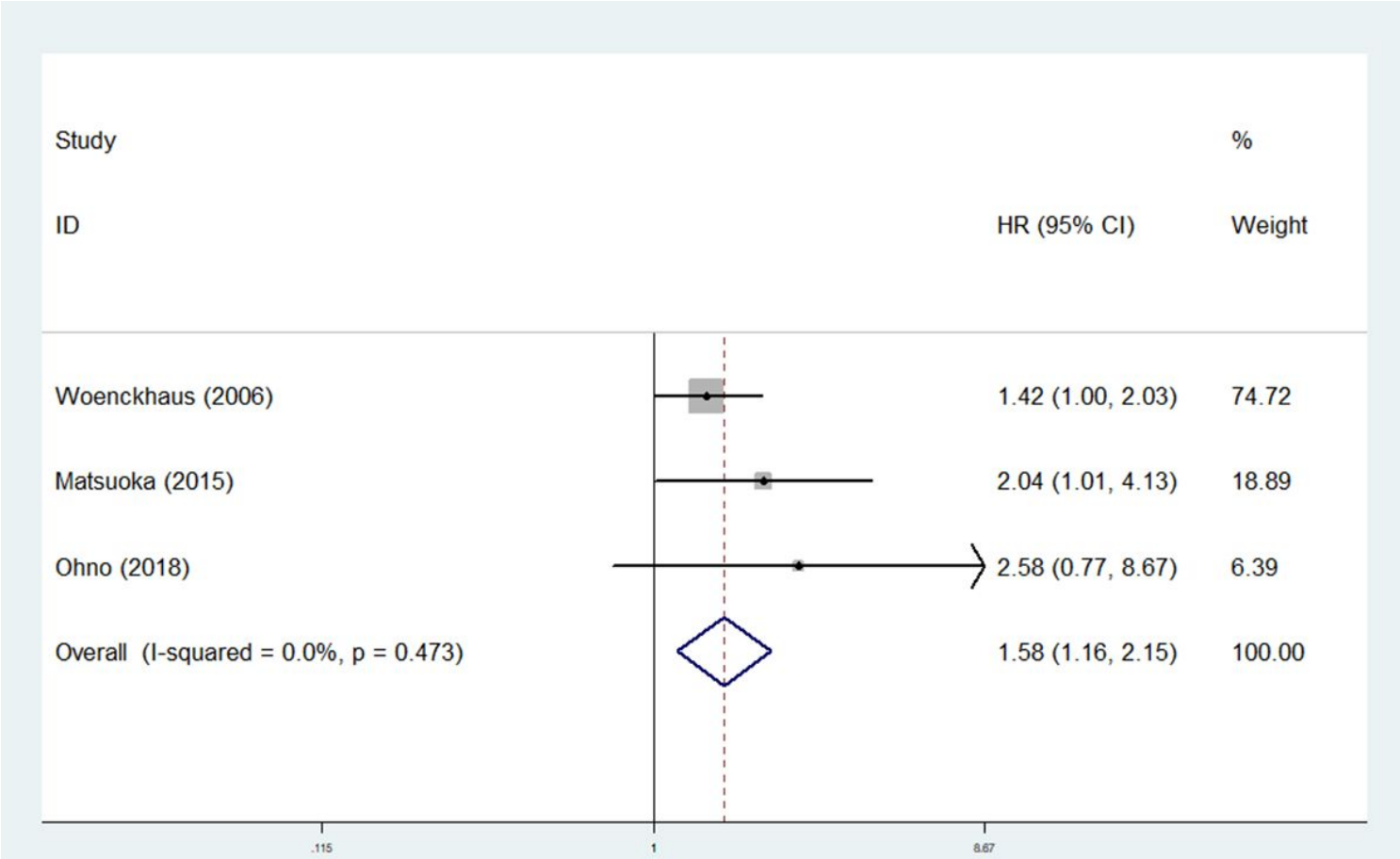

Figure 4

Forest plot of the association between maspin and cancer-specific survival.

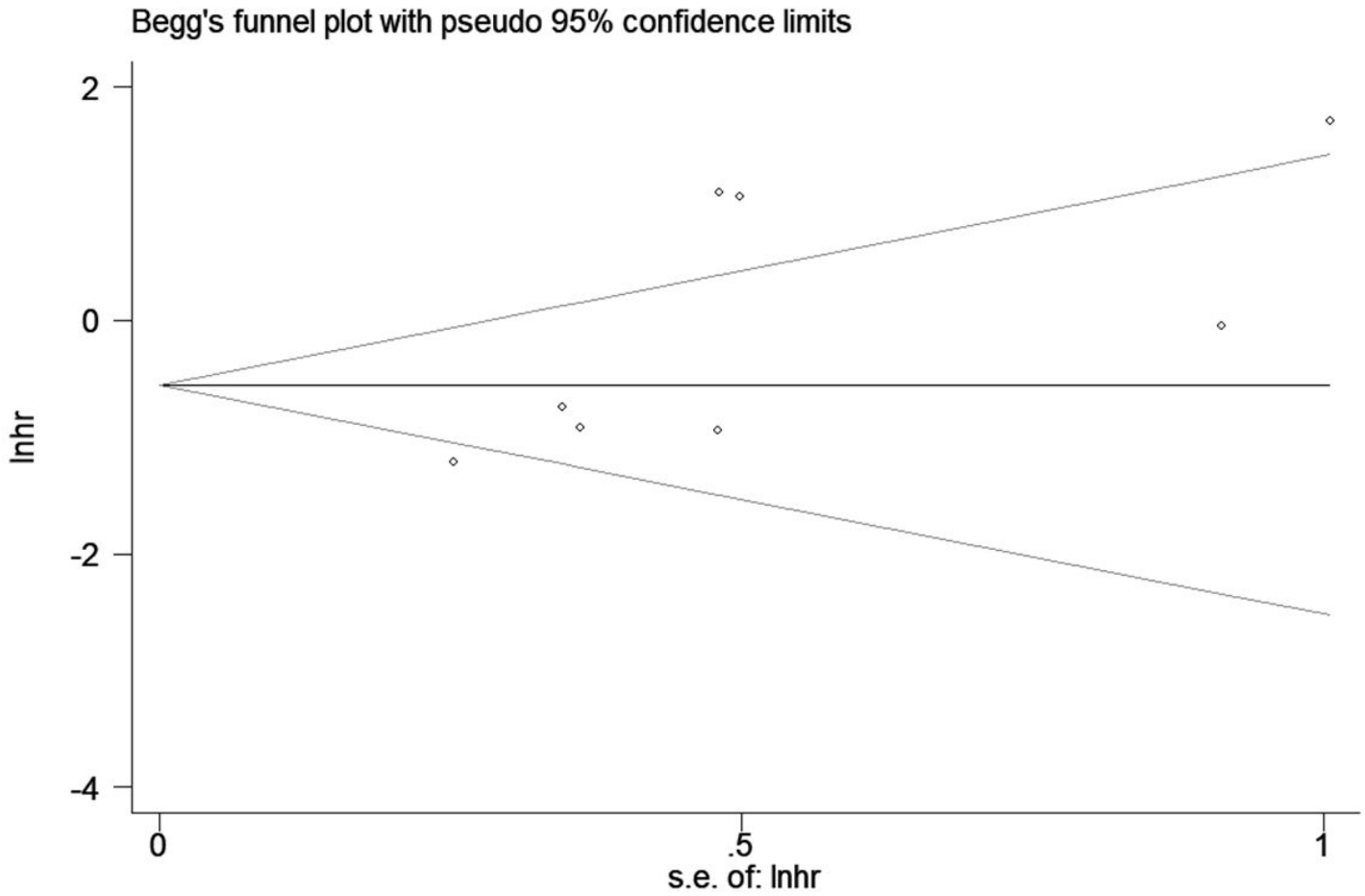

Figure 5

Sensitivity analysis of the association between maspin and overall survival

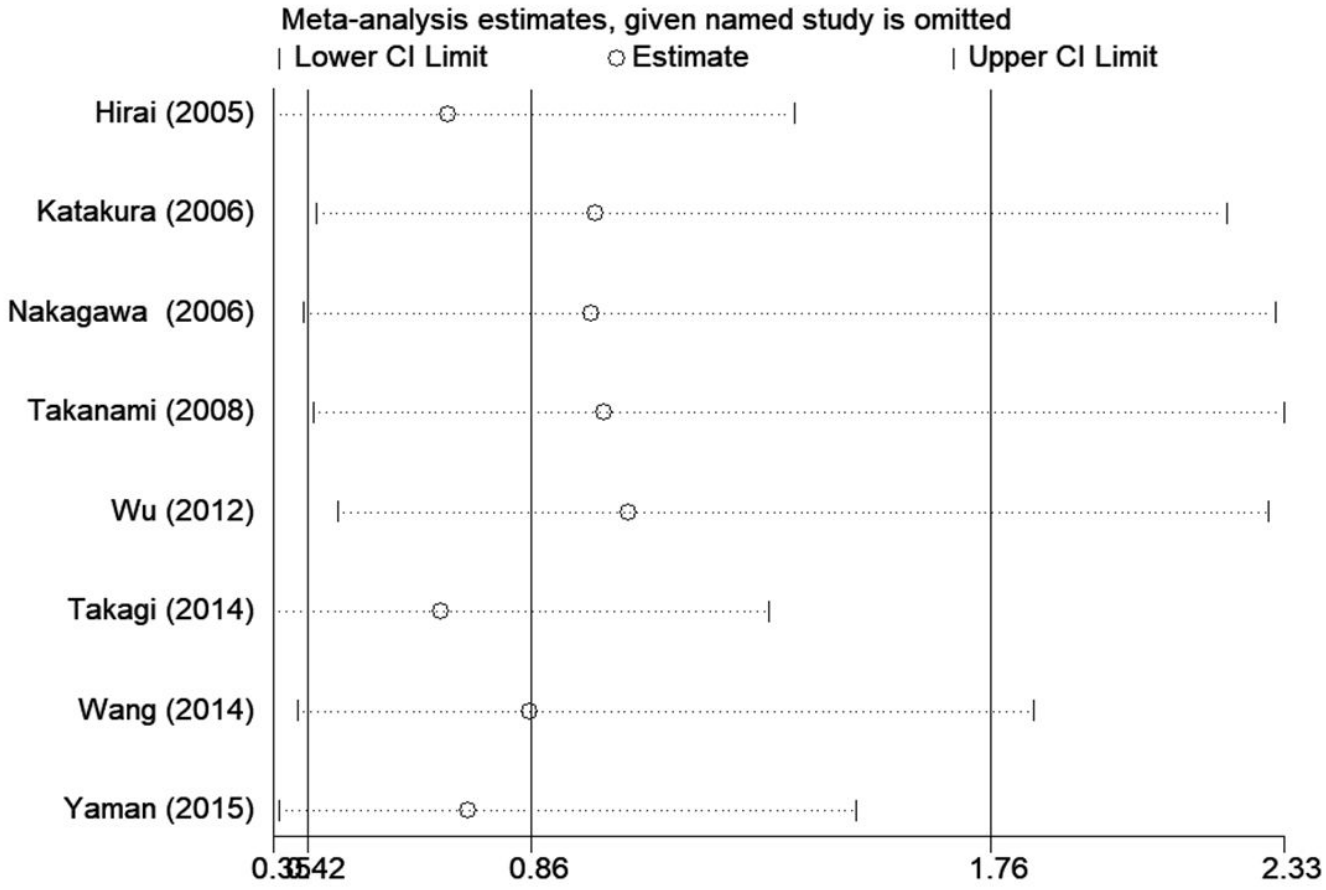

Figure 6

Begg's funnel plot of the association between maspin and overall survival.