Original Article

Risk factors for brain metastases in patients with non-small cell lung cancer: a meta-analysis of 43 studies

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Background: Lung cancer is a leading cause of cancer-related mortality worldwide. The purpose of our meta-analysis was to assess the risk factors for brain metastases (BM) in patients with non-small cell lung cancer (NSCLC).

Methods: Multiple databases, including PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang, were systematically searched to recruit relevant studies investigating the risk factors for BM in NSCLC patients. The Newcastle-Ottawa Scale was used to evaluate literature quality, and the meta-analysis was performed using the Review Manager 5.3. Evidence quality evaluation was carried out according to the Grading of Recommendation Assessment, Development and Evaluation (GRADE) standard. The estimated odds ratio (OR) and 95% confidence intervals (CIs) were set as effect measures. Funnel plots and sensitivity analyses were used to assess publication bias and the robustness and reliability of the combined results, respectively.

Results: A total of 43 studies with 11,415 participants were included in this meta-analysis. The results indicated that the following factors were significantly associated with an increased risk of BM in NSCLC patients (P<0.05): (I) gender (female) (OR =1.32, 95% CI: 1.17–1.49, P<0.00001); (II) adenocarcinoma (OR =2.34, 95% CI: 1.76–3.11, P<0.00001) or non-squamous cell carcinoma (OR =0.63, 95% CI: 0.42–0.94, P=0.02); (III) advanced tumor stage (OR =1.48, 95% CI: 1.01–2.17, P=0.04); (IV) node stage (OR =2.19, 95% CI: 1.39–3.45, P=0.0007); (V) lymphatic metastasis (OR =2.43, 95% CI: 1.76–3.36, P<0.00001); (VI) epidermal growth factor receptor (EGFR) gene mutation (OR =1.88, 95% CI: 1.26–2.80, P=0.002); (VII) kirsten rat sarcoma viral oncogene (KRAS) gene mutation (OR =2.99, 95% CI: 1.82–4.91, P<0.00001); (VIII) higher levels of carcinoembryonic antigen (P<0.00001), carbohydrate antigen 199 (P<0.0001), cytokeratin-19 fragment (P=0.04), neuron-specific enolase (P<0.00001), and carbohydrate antigen 125 (P=0.0005).

Conclusions: This meta-analysis demonstrated that NSCLC patients with BM have more aggressive clinical features.

Keywords: Non-small cell lung cancer (NSCLC); brain metastases (BM); risk factors; meta-analysis; prognosis

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Introduction

Lung cancer is one of the most common malignant tumors worldwide (1). Non-small cell cancer (NSCLC) is the prevailing histological subtype of lung cancer, accounting for approximately 80–85% (2). Given that its early clinical symptoms are not typical, NSCLC diagnosis is usually based on tumor markers, imaging, and histopathological characteristics. It is estimated that approximately 40% of NSCLC patients present with concomitant metastatic disease at initial diagnosis (3,4), most commonly of the brain, bone, liver, etc. Despite advancements in therapy (1), the prognosis for patients with advanced lung cancer is not good, especially for patients combined with brain metastases (BM) (5).

Previous studies have shown that BM is a key cause of morbidity and mortality in cancer and that approximately 20–40% of NSCLC patients will develop BM (6). The median survival period of NSCLC patients with BM is only about 3–6 months (7). Although some targeted methods can play a role in controlling the intracranial metastasis of tumors, few drugs can effectively cross the blood-brain barrier (8). At present, radiation therapy and surgical intervention are the most effective therapeutic options for BM; however, these two treatments may significantly impact the quality of life of patients (9). A meta-analysis of the risk factors for the occurrence of BM in NSCLC has not yet been performed. Therefore, there is a pressing need for greater assessment of the risk factors associated with BM in NSCLC patients, which may allow for prevention and earlier treatment of BM and help patients achieve prolonged survival. The purpose of our meta-analysis was to summarize the risk factors and clinical characteristics of NSCLC patients with BM.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1722).

Methods

Search strategy

Various databases, including PubMed, EMBASE, Cochrane Library, China National Knowledge Infrastructure (CNKI), and WanFang, were systematically searched from the date of inception of the database to February 2020, without language, publication, or time restrictions. The search terms included “brain metastases”, “nervous metastases” or “cerebral metastases” and “non-small cell cancer”, “lung cancer” or “malignant lung disease”. Finally, we reviewed the references of the relevant studies to identify potentially related articles.

Eligibility/exclusion criteria

Inclusion criteria

(I) Cross-sectional, case-control, and cohort studies assessing the risk factors for NSCLC patients with BM.
(II) Studies with clear and unified diagnostic criteria for NSCLC and BM, including histologically or cytologically confirmed NSCLC, and imaging findings, including computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) confirmed BM.
(III) Odds ratio (OR), the hazard ratio (HR), relative risk (RR), or weighted mean difference (WMD) and 95% confidence intervals (95% CIs) for BM development and clinicopathological factors could be obtained from multivariate analysis or could be calculated based on relevant data.
(IV) The number of cancers with BM in the article was more than 20.

Exclusion criteria

(I) Studies based on overlapping patients.
(II) Meta-analyses, reviews, case reports, or reports based on expert experience.
(III) No effective data like ominous, poor quality, and repeated documents could be extracted.

Data extraction and assessment of study quality

Two reviewers (Chen and Hua) independently extracted the data from all included studies, and any disagreements were resolved by discussion with the third reviewer (Zhang). The following data were retrieved from the studies: (I) basic characteristics including the first author’s name, year of publication, country, characteristics of the study population (e.g., gender, age, number), and study design; (II) clinical characteristics, including age, gender, smoking history, treatment history, pathological type, tumor (T) stage, node (N) stage, lymphatic metastasis, distant metastasis (except outside the brain), epidermal growth factor receptor (EGFR) gene mutation, Kirsten rat sarcoma viral oncogene (KRAS) gene mutation, and ECOG scale; (III) clinical laboratory parameters, including the levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), cytokeratin-19 fragment (CYFRA21-1), neuron-specific

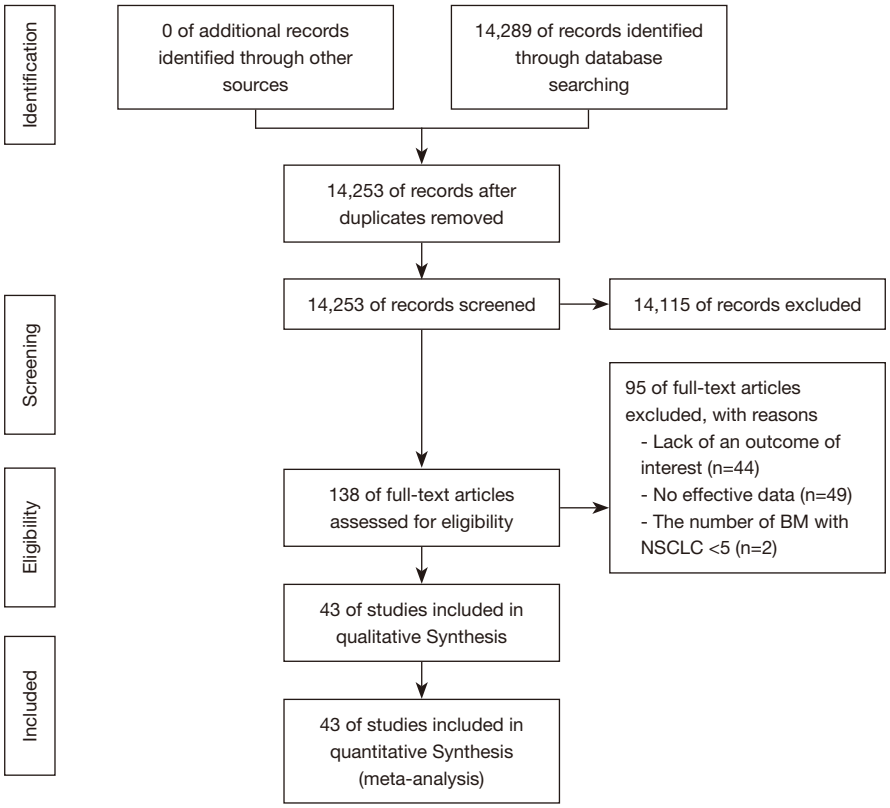

Figure 1 Selection of the included studies.

enolase (NSE), and carbohydrate antigen 125 (CA125).

The included studies' quality was assessed using the Newcastle-Ottawa Scale (NOS) (10); scores of 5–9 were considered fair, while scores of 1–4 indicated a high risk of bias. The results of this meta-analysis were evaluated using the GRADE profiler, and degradation was assessed in terms of evidence quality, including the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Simultaneously, upgradation was expressed by large effect, plausible confounding, and dose-response gradient (11).

Statistical analysis

Data in our meta-analysis were analyzed using Review Manager (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. The estimated OR and WMD were used to evaluate the affiliation between the incidence of BM and the clinicopathological features of NSCLC patients. All statistic values were reported with 95% CIs, and the two-sided P value threshold for statistical significance was set at 0.05. The Chi-square test and the I^2 statistic were used to evaluate heterogeneity among studies. Specifically, I^2 >50% and P<0.05 for the Chi-square test suggested significant heterogeneity among the included studies. When the homogeneity hypothesis was not rejected, a fixed-effects model was used; otherwise, a random-effects model was used to estimate the OR and 95% CI (12).

To investigate the effects of individual studies on the overall results, we also performed a sensitivity analysis by successively excluding each study. Finally, a funnel plot was used to assess potential publication bias. Considering that a small number of included studies may result in publication bias, Egger's and Begg's Tests and funnel plots were generated for indexes with more than 10 relevant studies (13).

Results

Baseline study characteristics and quality assessment

We identified 14,289 studies in our initial literature search, as shown in *Figure 1*. Thirty-six studies were excluded due to duplication. After reviewing the titles and abstracts,

we identified 138 potentially eligible studies for full-text assessment. A further 95 studies were excluded because they either lacked an outcome of interest or had no compelling information and control groups. Ultimately, 43 studies met our selection criteria and were included in the final analysis. All studies' characteristics and demographic data are presented in *Table 1*. The retrieved studies were published between 2004 and February 2020, and a total of 11,415 patients were involved. Of the 43 included studies, 26 were cohort studies, and the remaining 17 were case-control studies. Since all of the included studies were either cohort or case-control studies, the NOS was used for quality assessment, and the results showed that all included studies were of fair quality (*Table 1*).

A meta-analysis of clinical characteristics of patients

Our meta-analysis (*Figure 2*) suggested that the prevalence of BM was significantly higher among female patients (OR =1.32, 95% CI: 1.17–1.49, P<0.00001) (*Figure 2B*). However, patients that were younger than 60 years old (OR =1.12, 95% CI: 0.97–1.29, P=0.13) (*Figure 2A*), had a history of smoking (OR =1.53, 95% CI: 1.00–2.34, P=0.05) (*Figure 2C*), and treatment history (OR =0.77, 95% CI: 0.54–1.11, P=0.16) (*Figure 2D*) did not show significant differences between the NSCLC with BM group and the sample NSCLC group. Obvious heterogeneity was observed in age (I^2=90%, P<0.00001) and smoking history (I^2=59%, P=0.02), and thus, a random-effects model was utilized. A fixed-effects model was also used for the other indexes, as there was no obvious heterogeneity in the above studies.

A meta-analysis of tumor-related indexes

Our meta-analysis (*Figure 3*) indicated that adenocarcinoma (OR =2.34, 95% CI: 1.76–3.11, P<0.00001) (*Figure 3A*) was a risk factor for BM in NSCLC patients. Conversely, squamous carcinoma was found to be a protective factor (OR =0.63, 95% CI: 0.42–0.94, P=0.02) (*Figure 3B*). Meanwhile, the prevalence of BM was significantly higher among patients with higher T stage (OR =1.48, 95% CI: 1.01–2.17, P=0.04) (*Figure 3C*), higher N stage (OR =2.19, 95% CI: 1.39–3.45, P=0.0007) (*Figure 3D*), the number of lymphatic metastasis larger than six (OR =2.43, 95% CI: 1.76–3.36, P<0.00001) (*Figure 3E*), EGFR gene mutation (OR =1.88, 95% CI: 1.26–2.80, P=0.002) (*Figure 3G*), and KRAS gene mutation (OR =2.99, 95% CI: 1.82–4.91, P<0.00001) (*Figure 3H*). In contrast, patients with other distant metastases (OR =0.81, 95% CI: 0.29–2.33, P=0.7) (*Figure 3F*) and ECOG scale (OR =1.15, 95% CI: 0.78-1.70, P=0.47) (*Figure 3I*) did not show significant differences between the two groups. Since there was no obvious sample heterogeneity in the above studies, a fixed-effects model was utilized, while a random-effects model was used for studies with obvious heterogeneity.

A meta-analysis of clinical laboratory parameters

The results of our meta-analysis showed that NSCLC patients with BM had higher levels of CEA (WMD =10.94, 95% CI: 7.47–14.40, P<0.00001) (*Figure 4A*), CA199 (WMD =20.23, 95% CI: 12.20–28.26, P<0.0001) (*Figure 4B*), CYFRA211 (WMD =1.78, 95% CI: 0.04–3.51, P=0.04) (*Figure 4C*), NSE (WMD =9.66, 95% CI: 6.18–13.14, P<0.00001) (*Figure 4D*), and CA125 (WMD =22.39, 95% CI: 9.79–34.98, P=0.0005) (*Figure 4E*). Obvious heterogeneity was observed among these five indexes (I^2 >50%; P<0.05), and thus, a random-effects model was utilized.

Sensitivity analysis and risk of bias

The NOS Quality Assessment (*Table 1*) and GRADE evaluation (*Figures 5*,*6*) indicated that the included studies were of acceptable quality. A sensitivity analysis was conducted to evaluate each included study's influence; the results showed that heterogeneity and the pooled ORs or WMDs of BM were not significantly altered by any single study, indicating that our conclusions were relatively reliable. Funnel plots were generated for the indexes and are shown in Figures S1-S3. Egger's and Begg's tests are shown in Figures S4,S5.

Discussion

Our meta-analysis of 43 studies involving 11,415 participants assessed the risk factors and prognosis of BM in NSCLC patients. Our findings may be important in the prevention and evaluation of NSCLC patients with BM. The results were divided into four categories: clinical characteristics, tumor-related indexes, clinical laboratory parameters, and survival rates of patients.

By examining all relevant studies, we found that gender (female), adenocarcinoma or non-squamous cell carcinoma, advanced tumor stage, node stage, lymphatic metastasis, EGFR gene mutation, KRAS gene mutation, as well as

Table 1 Basic characteristics of the retrieved studies.

Study	Year	Country	Gender (M/F)	Age	BM/total	Ad/other	BM diagnosis	Study design	NOS
Bajard *et al*. (14)	2004	France	279/26	62 [33–88]	77/305	87/218	CT	Cohort	8
Carolan *et al*. (15)	2005	Canada	47/36	NM	29/83	NM	NM	Cohort	6
Arrieta *et al*. (16)	2009	Mexico	164/129	60.7±0.7	170/293	190/103	CT	Cohort	8
Liang *et al*. (17)	2010	China	132/61	58 [31–77]	67/193	NM	MRI/CT	Cohort	6
Huang *et al*. (18)	2010	China	74/50	59.81 [40–75]	35/124	73/51	MRI/CT/PET	Case control	6
Dimitropoulos *et al*. (19)	2011	Greece	143/18	65.1±8.9	39/161	59/102	CT	Cohort	5
Jie *et al*. (20)	2012	China	63/47	63 [38–86]	22/110	51/59	MRI/CT/PET	Case control	6
Xiao *et al*. (21)	2012	China	156/61	60 [27–79]	53/217	112/105	MRI/CT	Cohort	5
Liu *et al*. (22)	2012	China	62/41	58.6±14.9	41/103	NM	MRI	Cohort	7
Cao *et al*. (23)	2012	China	94/20	NM	36/114	35/79	NM	Cohort	5
Cui *et al*. (24)	2013	China	95/55	60.42±11.33	100/150	61/89	NM	Case control	6
Hsiao *et al*. (25)	2013	China	271/211	67.5±13.4	173/482	369/113	MRI/CT	Cohort	7
Ji *et al*. (26)	2014	China	286/60	NM	74/346	NM	MRI/CT	Cohort	8
Iuchi *et al*. (27)	2014	Japan	735/392	67 [30–93]	154/1127	895/232	MRI	Cohort	6
Zhang *et al*. (28)	2014	China	132/61	59.5±4.5	77/193	NM	CT	Cohort	7
Li *et al*. (29)	2014	China	116/68	58.43±12.68	96/184	86/98	MRI/CT/PET	Case control	7
Zhao *et al*. (30)	2015	China	86/72	55 [28–80]	62/158	112/46	CT	Cohort	5
Hui *et al*. (31)	2015	China	175/97	57 [31–82]	78/272	93/179	MRI	Case control	8
Zhou *et al*. (32)	2015	China	146/68	63 [25–77]	121/214	NM	MRI/CT	Case control	6
Liu *et al*. (33)	2015	China	72/80	55 [28–80]	62/158	112/46	MRI/CT	Case control	6
Xing *et al*. (34)	2015	China	78/46	63 [55–80]	51/124	65/59	NM	Case control	6
Zheng *et al*. (35)	2015	China	147/66	56.7±18.3	51/213	96/117	MRI/CT	Cohort	5
Zeng *et al*. (36)	2015	China	129/46	55 [29–76]	36/175	NM	MRI/CT	Cohort	7
Hsu *et al*. (37)	2016	Canada	216/327	66 [58–74]	143/543	NM	MRI/CT	Cohort	6
Hendriks *et al*. (38)	2016	Holland	535/303	63±10	153/838	324/514	MRI/PET	Cohort	5
Zhang *et al*. (39)	2016	China	486/151	60 [30–82]	NM/637	305/332	NM	Cohort	5
Koh *et al*. (40)	2016	Korea	166/94	59.5 [30–84]	94/260	194/66	MRI/CT	Cohort	8
Chen *et al*. (41)	2016	China	51/16	NM	27/67	NM	MRI/CT	Case control	5
Duan *et al*. (42)	2016	China	55/27	31–81	41/82	NM	NM	Case control	5
Tomasini *et al*. (43)	2016	France	94/48	62 [31–88]	81/142	NM	NM	Cohort	6
Wei (44)	2017	China	95/53	61.2±5.8	35/148	103/45	NM	Cohort	7
Fang (45)	2017	China	84/64	NM	47/148	108/40	MRI/CT/PET	Case control	5
Gong *et al*. (46)	2017	China	86/42	56.86±9.88	62/128	92/36	MRI/CT	Case control	7
Dai *et al*. (47)	2017	China	40/32	49.26±10.36	15/72	NM	MRI/CT	Cohort	6
Chang *et al*. (48)	2018	China	250/241	NM	78/491	444/47	MRI/CT	Cohort	8

Table 1 (*continued*)

Table 1 (*continued*)

Study	Year	Country	Gender (M/F)	Age	BM/total	Ad/other	BM diagnosis	Study design	NOS
Zhao *et al*. (49)	2018	China	66/66	38–82	65/132	91/41	MRI/CT	Case control	6
Li *et al*. (50)	2018	China	88/65	NM	41/153	123/30	MRI/CT	Case control	6
Hu *et al*. (51)	2018	China	57/103	58.21±11.73	41/160	96/41	MRI/CT	Cohort	7
Zhou *et al*. (52)	2019	China	80/55	62.8±2.8	57/135	79/191	MRI/CT	Case control	6
Liu *et al*. (53)	2019	China	NM	51.85±13.73	51/125	NM	MRI/CT	Case control	6
Liu *et al*. (54)	2019	China	74/46	NM	40/80	NM	MRI/CT	Case control	5
Xin *et al*. (55)	2019	China	897/568	25–84	319/1,465	972/493	MRI/CT	Cohort	8
Hu *et al*. (56)	2019	China	84/26	61±17	27/110	38/72	MRI/CT	Cohort	6

M/F, male/female; BM, brain metastasis; TNM, tumor node metastasis stage; Ad, adenocarcinoma; NOS, Newcastle Ottawa Quality Assessment Scale; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; NM, not mentioned.

higher levels of CEA, CA199, CYFRA211, NSE, and CA125 were clinical risk factors that can predict BM.

Some multivariate analyses have already shown that the risk of BM is reduced with age; however, our meta-analysis found that age ≤60 years old was associated with BM's incidence. The reason why an increased risk exists in the younger age cohort remains unclear; although, a possible mechanism for this may be due to the differential expression of some biological markers associated with BM, such as E-cadherin and Caspase-3, between younger and older patients (57). Also, it is well established that adenocarcinoma is common in females and often metastasizes to the brain, explaining why females have a higher incidence of BM (24). Moreover, a recent study (58) has demonstrated that the proportion of lung cancers diagnosed among smokers is increasing and that the risk of developing lung cancer is 20–40 times higher in smokers compared to never-smokers, which may explain the high proportion of smoking history in NSCLC patients with BM.

BM is closely associated with tumor-related indicators. In 2015, Won *et al*. (59) established a nomogram for predicting BM in NSCLC patients and found that histological type, T stage, and N stage were closely linked to BM. Similarly, Wang *et al*. (60) reported that non-squamous cell carcinoma and multiple lymphatic metastases were both risk factors for BM, consistent with the results of our study. We found that non-squamous cell carcinoma, especially adenocarcinoma, was an independent risk factor for BM, which may be attributed to adenocarcinoma's invasive growth. Previous research (61) speculated that if a tumor spreads to the chest's lymphatic system, it will also involve distant metastasis to other organs (including bone, liver, and kidney), and if distant metastasis occurs, the probability of BM will increase. Our study is consistent with these studies in identifying lymphatic metastasis as a significant prognostic factor. A previous meta-analysis involving 22 studies reported that patients with EGFR mutation were more susceptible to BM than those with wild type EGFR (OR =1.99, 95% CI: 1.59–2.48, P=0.000) (62). A possible mechanism for this may involve EGFR activating MET via protein kinases and activating STAT3 via interleukin-6 to promote BM in NSCLC (63,64).

Our study also found that the levels of relevant serum tumor markers were related to BM in NSCLC patients. We identified five prognostic factors: higher CEA levels, CA199, CYFRA211, NSE, and CA125. It has been previously reported that CEA-positive tumor cells can cross the blood-brain barrier more easily and adhere to the cerebral vasculature, which promotes the occurrence of BM (65). Our study also found that a higher level of CEA was a risk factor for BM. Meanwhile, previous studies (45,49) demonstrated that serum CEA, CA199, CA125, and CYFRA211 were higher in the BM group than the control group, providing an important reference for the early detection of BM in NSCLC patients.

The results of the cohort and case-control studies were also analyzed separately (*Table 2*). The statistical results reported in the cohort studies were consistent with the results of the case-control studies, except for smoking history, adenocarcinoma, squamous cell carcinoma, and higher tumor stage. Considering that cohort studies had

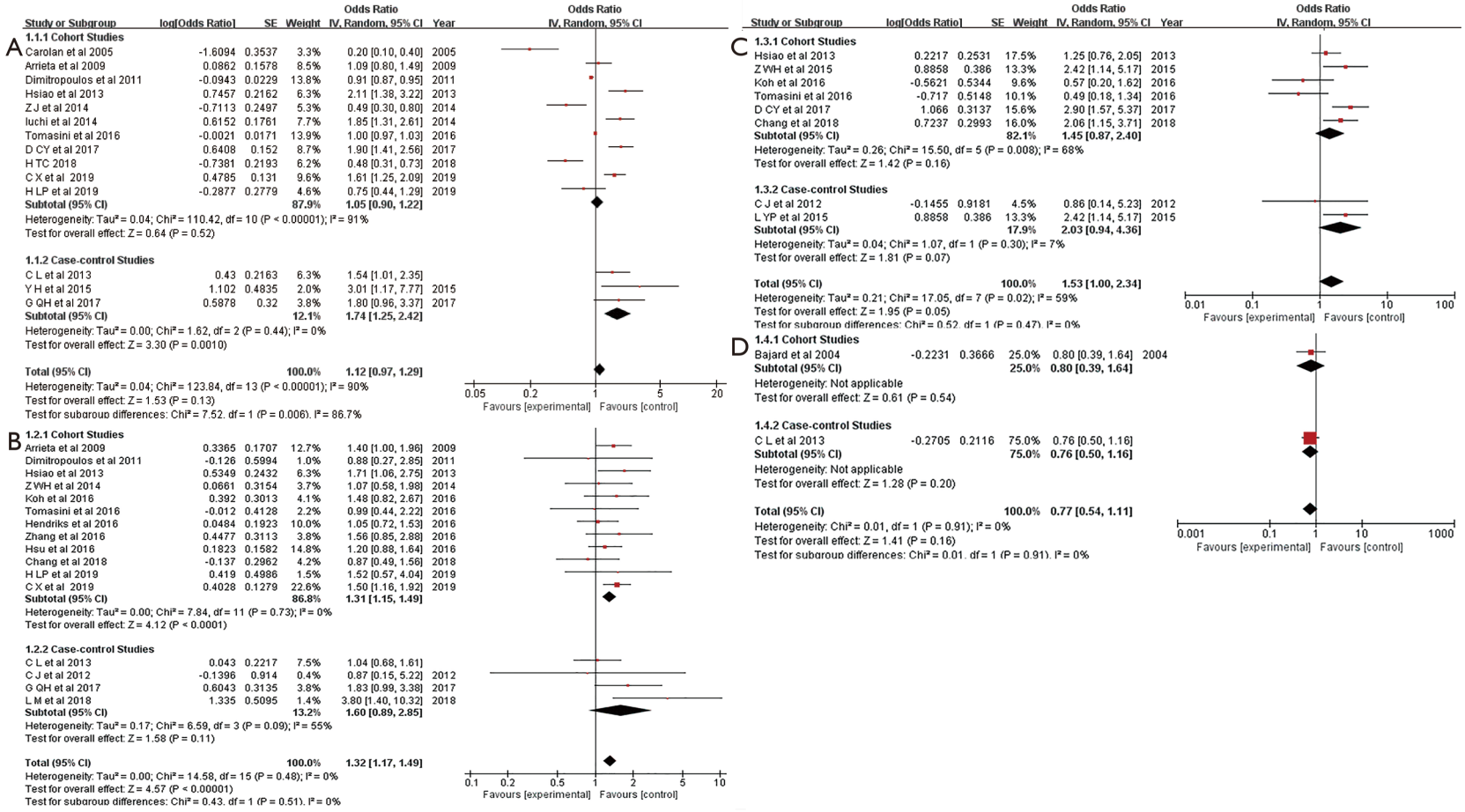

Figure 2 Meta-analysis of clinical characteristics. (A) Age younger than 60 years old, (B) gender is female, (C) a smoking history, (D) a treatment history.

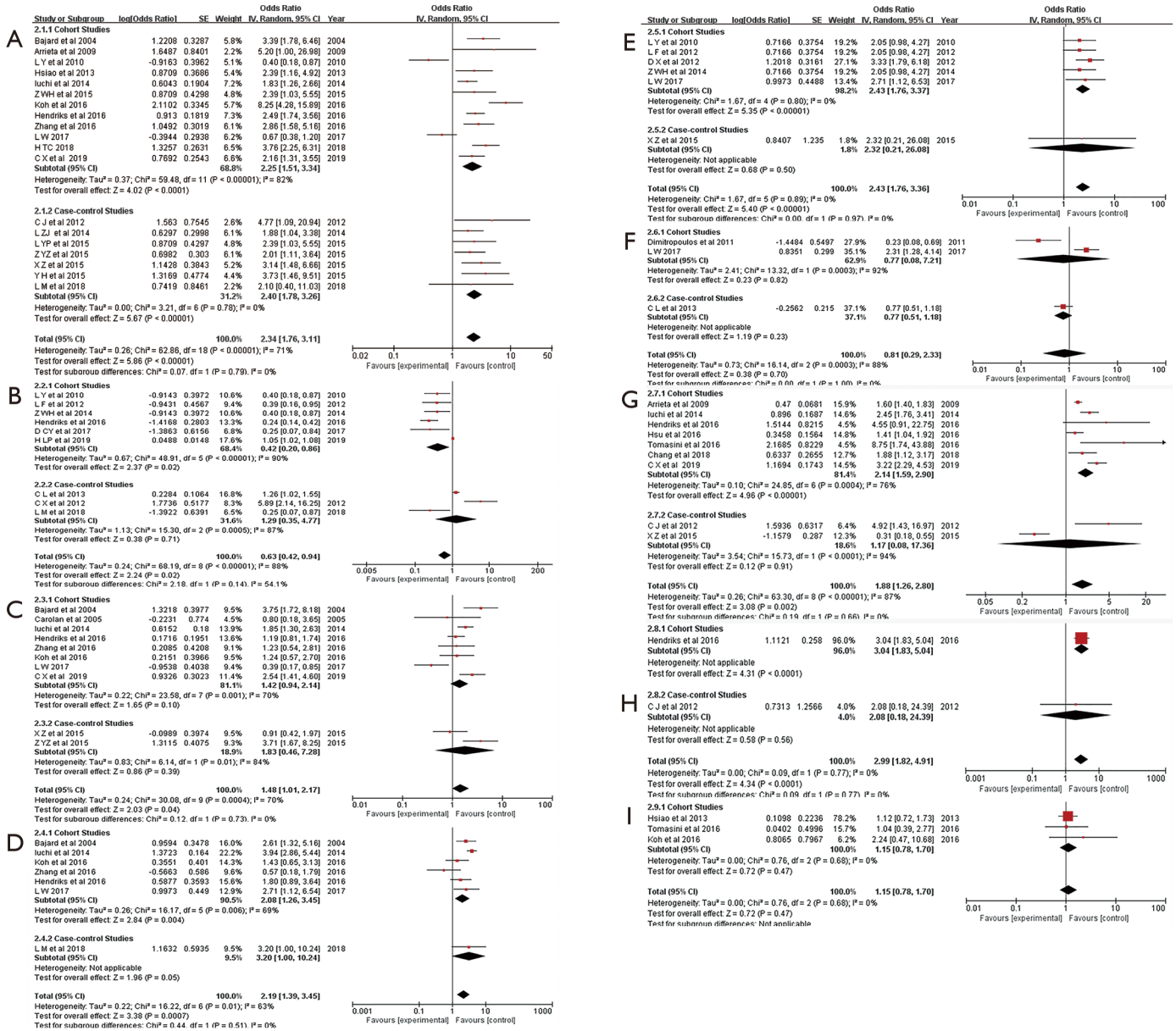

Figure 3 Meta-analysis of tumor-related indexes. (A) Adenocarcinoma, (B) squamous cell carcinoma, (C) advanced tumor stage, (D) advanced node stage, (E) the number of lymphatic metastasis more than 6, (F) distant metastasis, (G) EGFR gene mutuation, (H) KRAS gene mutation, (I) ECOG scale more than 2. EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene.

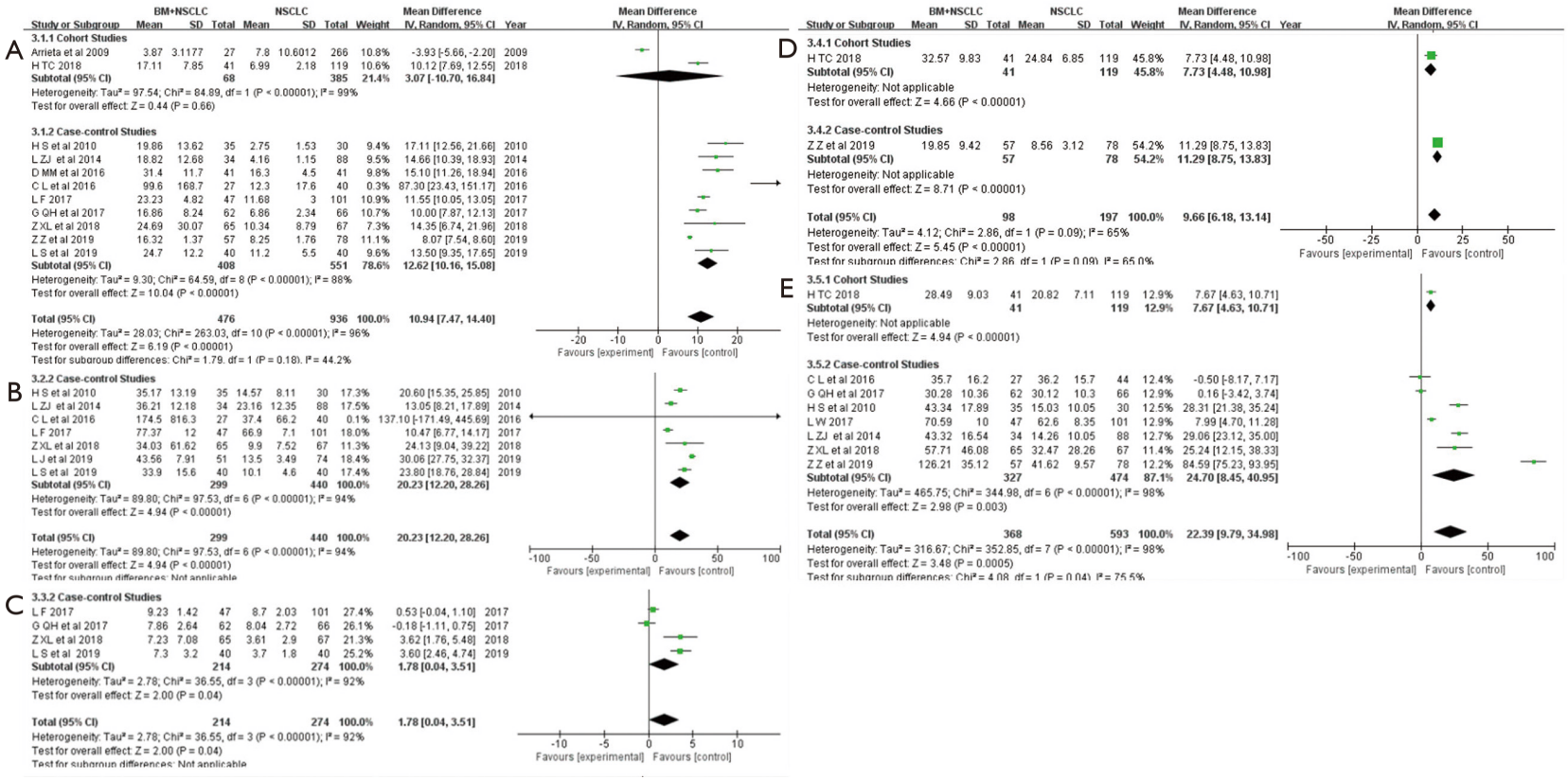

Figure 4 Meta-analysis of clinical laboratory parameters. (A) CEA , (B) CA199, (C) CA125, (D) CYFRA211, (E) NSE. CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase.

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Settings:
Bibliography: . Risk factors for brain metastases in patients with non-small cell lung cancer. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+NSCLC versus NSCLC	Control	Relative (95% CI)	Absolute		
Age - Cohort Studies												
11	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.05 (0.90 to 1.22)	- -	⊕⊕OO LOW	IMPORTANT
Age - Case-control Studies												
3	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.74 (1.25 to 2.42)	- -	⊕⊕OO LOW	IMPORTANT
Female - Cohort Studies												
12	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.31 (1.15 to 1.49)	- -	⊕⊕OO LOW	IMPORTANT
Female - Case-control Studies												
4	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.40 (1.01 to 1.95)	- -	⊕⊕OO LOW	IMPORTANT
A smoking history - Cohort Studies												
6	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.45 (0.87 to 2.40)	- -	⊕⊕OO LOW	IMPORTANT
A smoking history - Case-control Studies												
2	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 2.03 (0.94 to 4.36)	- -	⊕⊕OO LOW	IMPORTANT
A treatment history - Cohort Studies												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 0.80 (039 to 1.64)	- -	⊕⊕OO LOW	IMPORTANT
A treatment history - Case-control Studies												
1	observational studies[1]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	not pooled	- not pooled	⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+NSCLC versus NSCLC	Control	Relative (95% CI)	Absolute		
Adenocarcinoma - Cohort Studies												
12	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[3]	-	- 0%	OR 2.25 (1.51 to 3.34)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Adenocarcinoma - Case-control Studies												
7	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	0%	OR 2.40 (1.78 to 3.26)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Squamous cell carcinoma - Cohort Studies												
6	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[3]	-	- 0%	OR 0.42 (0.20 to 0.86)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Squamous cell carcinoma - Case-control Studies												
3	observational studies[2,4]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	0%	OR 1.29 (0.35 to 4.77)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Advanced tumor stage - Cohort Studies												
8	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 1.42 (0.94 to 2.14)	- -	⊕⊕OO LOW	IMPORTANT
Advanced tumor stage - Case-control Studies												
2	observational studies[2,5]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 1.83 (0.46 to 7.28)	- -	⊕⊕OO LOW	IMPORTANT
Node Stage - Cohort Studies												
6	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	-	- 0%	OR 2.08 (1.26 to 3.45)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Node Stage - Case-control Studies												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[6]	-	0%	OR 3.20 (1.00 to 10.24)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Lymphatic metastasis - Cohort Studies												
5	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[7]	-	- 0%	OR 2.43 (1.76 to 3.37)	- -	⊕⊕⊕O MODERATE	CRITICAL
Lymphatic metastasis - Case-control Studies												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[8]	-	0%	OR 2.32 (0.21 to 26.08)	- -	⊕⊕⊕O MODERATE	CRITICAL
Distant metastasis - Cohort Studies												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 0.77 (0.08 to 7.21)	- -	⊕⊕OO LOW	CRITICAL
Distant metastasis - Case-control Studies												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[9]	-	0%	OR 2.01 (0.51 to 1.18)	- -	⊕⊕⊕O MODERATE	CRITICAL
EGFR gene mutuation - Cohort Studies												
7	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	OR 2.14 (1.59 to 2.90)	- -	⊕⊕OO LOW	CRITICAL
EGFR gene mutuation - Case-control Studies												
2	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association[10]	-	0%	OR 1.17 (0.08 to 17.36)	- -	⊕⊕⊕⊕ HIGH	CRITICAL
Kras gene mutuation - Cohort Studies												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association[11]	-	- 0%	OR 3.04 (1.83 to 5.04)	- -	⊕⊕⊕O MODERATE	IMPORTANT
Kras gene mutuation - Case-control Studies												
1	observational studies[2]	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	0%	OR 2.08 (0.18 to 24.39)	- -	⊕⊕OO LOW	IMPORTANT
ECOG - Cohort Studies												
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	-	- 0%	RR 1.30 (0.89 to 1.91)	- -	⊕⊕OO LOW	NOT IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	BM+NSCLC versus NSCLC		Relative (95% CI)	Absolute		
CEA												
11	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	0 cases 0 controls and 476/0 exposed 936/0 unexposed	0%	OR 10.94 (7.47 to 14.4)	- -	⊕⊕⊕⊕ HIGH	
CEA - Cohort Studies (range of scores: 0-100; Better indicated by lower values)												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	68	385	-	MD 3.07 higher (10.7 lower to 16.84 higher)	⊕⊕⊕O MODERATE	
CEA - Case-control Studies												
9	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	408 cases 551 controls	0%	OR 12.62 (10.16 to 15.08)	- -	⊕⊕⊕⊕ HIGH	
CA199												
7	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	299 cases 440 controls	0%	OR 20.23 (12.2 to 28.26)	- -	⊕⊕⊕⊕ HIGH	
CA199 - Case-control Studies												
7	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	299 cases 440 controls	0%	OR 20.23 (12.2 to 28.26)	- -	⊕⊕⊕⊕ HIGH	
CYFRA211												
5	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	271 cases 352 controls	0%	OR 2.9 (-0.44 to 6.24)	- -	⊕⊕⊕O MODERATE	
CYFRA211 - Case-control Studies (Better indicated by lower values)												
5	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	strong association	271	352	-	- MD 2.9 higher (0.44 lower to 6.24 higher)	⊕⊕⊕O MODERATE	
NSE (Better indicated by lower values)												
3	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	160	263	-	- MD 6.18 higher (1.03 lower to 13.39 higher)	⊕⊕⊕⊕ HIGH	
NSE - Cohort Studies (range of scores: 0-100; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	41	119	-	MD 7.73 higher (4.48 to 10.98 higher)	⊕⊕⊕⊕ HIGH	
NSE - Case-control Studies												
2	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	119 cases 144 controls	0%	OR 5.42 (-6.12 to 16.95)	- -	⊕⊕⊕⊕ HIGH	
CA125												
8	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	0 cases 0 controls and 368/0 exposed 593/0 unexposed	0%	OR 22.39 (9.79 to 34.98)	- -	⊕⊕⊕⊕ HIGH	
CA125 - Cohort Studies (range of scores: 0-100; Better indicated by lower values)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	41	119	-	MD 7.67 higher (4.63 to 10.71 higher)	⊕⊕⊕⊕ HIGH	
CA125 - Case-control Studies (Better indicated by lower values)												
7	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	very strong association	327	474	-	- MD 24.7 higher (8.45 to 40.95 higher)	⊕⊕⊕⊕ HIGH	

Figure 5 Summary of Findings table. BM, brain metastases; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase.

BM+NSCLC versus NSCLC for brain metastases in patients with non-small cell lung cancer

Patient or population: patients with brain metastases in patients with non-small cell lung cancer
Settings:
Intervention: BM+NSCLC versus NSCLC

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk BM+NSCLC versus NSCLC	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Age - Cohort Studies	**Study population**		**OR 1.05** (0.90 to 1.22)	0 (11 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Age - Case-control Studies	See comment	See comment	**OR 1.74** (1.25 to 2.42)	0 (3 studies[1])	See comment	0 cases and 0 controls in case-control studies
Female - Cohort Studies	**Study population**		**OR 1.31** (1.15 to 1.49)	0 (12 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Female - Case-control Studies	See comment	See comment	**OR 1.40** (1.01 to 1.95)	0 (4 studies[1])	See comment	0 cases and 0 controls in case-control studies
A smoking history - Cohort Studies	**Study population**		**OR 1.45** (0.87 to 2.40)	0 (6 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
A smoking history - Case-control Studies	See comment	See comment	**OR 2.03** (0.94 to 4.36)	0 (2 studies[1])	See comment	0 cases and 0 controls in case-control studies
A treatment history - Cohort Studies	**Study population**		**OR 0.80** (039 to 1.64)	0 (1 study)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
A treatment history - Case-control Studies	See comment	See comment	Not estimable	0 (1 study[1])	⊕⊕⊕⊕ **low**	0 cases and 0 controls in case-control studies

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk BM+NSCLC versus NSCLC	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Adenocarcinoma - Cohort Studies	**Study population**		**OR 2.25** (1.51 to 3.34)	0 (12 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Adenocarcinoma - Case-control Studies	See comment	See comment	**OR 2.40** (1.78 to 3.26)	0 (7 studies[1])	See comment	0 cases and 0 controls in case-control studies
Squamous cell carcinoma - Cohort Studies	**Study population**		**OR 0.42** (0.20 to 0.86)	0 (6 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Squamous cell carcinoma - Case-control Studies	See comment	See comment	**OR 1.29** (0.35 to 4.77)	0 (3 studies[1,2])	See comment	0 cases and 0 controls in case-control studies
Advanced tumor stage - Cohort Studies	**Study population**		**OR 1.42** (0.94 to 2.14)	0 (8 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Advanced tumor stage - Case-control Studies	See comment	See comment	**OR 1.83** (0.46 to 7.28)	0 (2 studies[1,3])	See comment	0 cases and 0 controls in case-control studies
Node Stage - Cohort Studies	**Study population**		**OR 2.08** (1.26 to 3.45)	0 (6 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Node Stage - Case-control Studies	See comment	See comment	**OR 3.20** (1.00 to 10.24)	0 (1 study[1])	See comment	0 cases and 0 controls in case-control studies
Lymphatic metastasis - Cohort Studies	**Study population**		**OR 2.43** (1.76 to 3.37)	0 (5 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Lymphatic metastasis - Case-control Studies	See comment	See comment	**OR 2.32** (0.21 to 26.08)	0 (1 study[1])	⊕⊕⊕⊕ **moderate**[4]	0 cases and 0 controls in case-control studies
Distant metastasis - Cohort Studies	**Study population**		**OR 0.77** (0.08 to 7.21)	0 (2 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Distant metastasis - Case-control Studies	See comment	See comment	**OR 2.01** (0.51 to 1.18)	0 (1 study[1])	See comment	0 cases and 0 controls in case-control studies
EGFR gene mutuation - Cohort Studies	**Study population**		**OR 2.14** (1.59 to 2.90)	0 (7 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
EGFR gene mutuation - Case-control Studies	See comment	See comment	**OR 1.17** (0.08 to 17.36)	0 (2 studies[1])	See comment	0 cases and 0 controls in case-control studies
Kras gene mutuation - Cohort Studies	**Study population**		**OR 3.04** (1.83 to 5.04)	0 (1 study)	⊕⊕⊕⊕ **moderate**[5]	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
Kras gene mutuation - Case-control Studies	See comment	See comment	**OR 2.08** (0.18 to 24.39)	0 (1 study[1])	⊕⊕⊕⊕ **low**	0 cases and 0 controls in case-control studies
ECOG - Cohort Studies	**Study population**		**RR 1.30** (0.89 to 1.91)	0 (3 studies)	See comment	
	See comment	See comment				
	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk	Corresponding risk BM+NSCLC versus NSCLC	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
CEA	See comment	See comment	**OR 10.94** (7.47 to 14.4)	0 (11 studies)	⊕⊕⊕⊕ **high**	0 cases and 0 controls in case-control studies; 476 events in 0 exposed and 936 events in 0 unexposed in other studies
CEA - Cohort Studies Scale from: 0 to 100.	The mean cea - cohort studies in the control groups was **ng/ml**	The mean cea - cohort studies in the intervention groups was **3.07 higher** (10.7 lower to 16.84 higher)		453 (2 studies)	⊕⊕⊕⊕ **moderate**	
CEA - Case-control Studies	See comment	See comment	**OR 12.62** (10.16 to 15.68)	0 (9 studies)	⊕⊕⊕⊕ **high**	408 cases and 551 controls in case-control studies
CA199	See comment	See comment	**OR 20.23** (12.2 to 28.26)	0 (7 studies)	⊕⊕⊕⊕ **high**	299 cases and 440 controls in case-control studies
CA199 - Case-control Studies	See comment	See comment	**OR 20.23** (12.2 to 28.26)	0 (7 studies)	⊕⊕⊕⊕ **high**	299 cases and 440 controls in case-control studies
CYFRA211	See comment	See comment	**OR 2.9** (-0.44 to 6.24)	0 (5 studies)	⊕⊕⊕⊕ **moderate**	271 cases and 352 controls in case-control studies
CYFRA211 - Case-control Studies	See comment	See comment		623 (5 studies)	⊕⊕⊕⊕ **moderate**	271 cases and 352 controls in case-control studies
NSE	See comment	See comment		423 (3 studies)	⊕⊕⊕⊕ **high**	0 cases and 0 controls in case-control studies; 160 events in 0 exposed and 263 events in 0 unexposed in other studies
NSE - Cohort Studies Scale from: 0 to 100.	The mean nse - cohort studies in the control groups was **ng/ml**	The mean nse - cohort studies in the intervention groups was **7.73 higher** (4.48 to 10.98 higher)		160 (1 study)	⊕⊕⊕⊕ **high**	
NSE - Case-control Studies	See comment	See comment	**OR 5.42** (-6.12 to 16.95)	0 (2 studies)	⊕⊕⊕⊕ **high**	119 cases and 144 controls in case-control studies
CA125	See comment	See comment	**OR 22.39** (9.79 to 34.98)	0 (8 studies)	⊕⊕⊕⊕ **high**	0 cases and 0 controls in case-control studies; 368 events in 0 exposed and 593 events in 0 unexposed in other studies
CA125 - Cohort Studies Scale from: 0 to 100.	The mean ca125 - cohort studies in the control groups was **ng/ml**	The mean ca125 - cohort studies in the intervention groups was **7.67 higher** (4.63 to 10.71 higher)		160 (1 study)	⊕⊕⊕⊕ **high**	
CA125 - Case-control Studies	See comment	See comment		801 (7 studies)	⊕⊕⊕⊕ **high**	327 cases and 474 controls in case-control studies

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Figure 6 GRADE evidence profile. BM, brain metastases; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase.

Table 2 The results stratified by study design for risk factors included in the meta-analysis

Study factors	Study type	No. of studies	OR (95% CI) or WMD (95% CI)	P	Heterogeneity		Model used
					I^2 (%)	P_h	
Age	Cohort studies	11	1.05 (0.90–1.22)	0.52	91%	<0.00001	Random
	Case-control studies	3	1.74 (1.25–2.42)	0.83	90%	<0.00001	
Gender (female)	Cohort studies	12	1.31 (1.15–1.49)	<0.00001	0	0.73	Fixed
	Case-control studies	4	1.40 (1.01–1.95)	0.11	55%	0.09	
A smoking history	Cohort studies	6	1.45 (0.87–2.40)	0.16	68%	0.008	Random
	Case-control studies	2	2.03 (0.94–4.36)	0.07	7%	0.30	
A treatment history	Cohort studies	1	0.80 (0.39–1.64)	0.54	–	–	Fixed
	Case-control studies	1	0.76 (0.5–1.16)	0.20	–	–	
Adenocarcinoma	Cohort studies	12	2.25 (1.51–3.34)	<0.00001	82%	<0.00001	Random
	Case-control studies	7	2.40 (1.78–3.26)	<0.00001	0	0.78	
Squamous cell carcinoma	Cohort studies	6	0.42 (0.20–0.86)	0.02	90%	<0.00001	Random
	Case-control studies	3	1.29 (0.35–4.77)	0.71	87%	0.0005	
Tumor stage	Cohort studies	8	1.42 (0.94–2.14)	0.10	70%	0.001	Random
	Case-control studies	2	1.83 (0.46–7.28)	0.39	84%	0.01	
Node stage	Cohort studies	6	2.08 (1.26–3.45)	0.004	73%	0.006	Random
	Case-control studies	1	3.20 (1.00–10.24)	0.05	92%	–	
1ymphatic metastasis	Cohort studies	5	2.43 (1.76–3.37)	<0.00001	0%	0.89	Fixed
	Case-control studies	1	2.32 (0.21–26.08)	0.5	–	–	
Distant metastasis	Cohort studies	2	0.77 (0.08–7.21)	0.82	92%	0.0003	Random
	Case-control studies	1	2.01 (0.51–1.18)	0.23	88%	0.0003	
EGFR gene mutation	Cohort studies	7	2.14 (1.59–2.90)	<0.00001	76%	0.0004	Random
	Case-control studies	2	1.17 (0.08–17.36)	0.91	94%	<0.00001	
KRAS gene mutation	Cohort studies	1	3.04 (1.83–5.04)	<0.00001	–	–	Fixed
	Case-control studies	1	2.08 (0.18–24.39)	0.56	–	–	
ECOG scale >2	Cohort studies	3	1.30 (0.89–1.91)	0.47	0	0.68	Fixed
CEA level	Cohort studies	2	3.07 (–10.70–16.84)	0.66	99%	<0.00001	Random
	Case-control studies	9	1.68 (1.04–2.31)	<0.00001	88%	<0.00001	
CA199 level	Case-control studies	7	20.23 (12.20–28.26)	<0.0001	94%	<0.00001	Random
CYFRA211 level	Case-control studies	4	1.78 (0.04–3.51)	0.04	92%	<0.00001	Random
NSE level	Cohort studies	1	7.73 (4.48–10.98)	<0.0001	–	–	Random
	Case-control studies	2	5.42 (–6.12–16.95)	0.36	97%	<0.00001	
CA125 level	Cohort studies	1	7.67 (4.63–10.71)	<0.0001	–	–	Random
	Case-control studies	7	24.7 (8.45–40.95)	0.003	98%	<0.00001	

OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase; CA125, carbohydrate antigen 125.

a higher proportion and were more likely to be authentic, we believe that random-effects models were suitable for these four indexes. Moreover, the heterogeneity of all five serum tumor markers was significant (P<0.05), which may be attributable to a failure to publish studies with negative results or different means of measurement. After stratifying by study design, we found that there were only case-control studies for some indexes, and thus, further investigation is required to confirm the conclusion.

Also, we assessed the differences in 1-, 2-, 3-, and 5-year survival rates between NSCLC patients with BM and sampled NSCLC patients, respectively. The results indicated that the NSCLC + BM group had a significantly lower survival rate (P<0.05, Figure S6). A possible explanation for this is that patients with BM are more likely to present with distant metastasis of other sites, thus increasing these patients' mortality rates. Furthermore, the results also indicated that NSCLC patients with an advanced tumor stage were more likely to have BM, which can also decrease the survival time of NSCLC patients.

Our study had some shortcomings and omissions that should be noted. Firstly, the studies included in our meta-analysis were all either cohort or case-control studies, and the NOS quality assessment showed that the 43 included studies had relatively low scores (5-8), indicating that the results may have been subject to selection bias. Secondly, potential risk factors, such as cancer history, treatment approach, or other biological markers, could also promote BM's occurrence and affect the prognosis of cancers. However, these factors were not explored in this meta-analysis because the included studies may not have provided the required information. Thirdly, funnel plots showed no obvious publication bias for indexes with more than 10 relevant studies; however, potential bias could not be completely excluded for indexes with fewer than 10 studies.

Conclusions

In summary, our meta-analysis revealed that gender (female), adenocarcinoma or non-squamous cell carcinoma, advanced tumor stage, node stage, lymphatic metastasis, EGFR gene mutation, KRAS gene mutation, as well as higher levels of CEA, CA199, CYFRA211, NSE, and CA125 were risk factors for BM in NSCLC patients. We also determined that BM's presence could significantly decrease the survival time of NSCLC patients, indicating a poor survival prognosis. This meta-analysis demonstrated that NSCLC patients with BM have more aggressive clinical features and a poor survival prognosis.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-1722). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

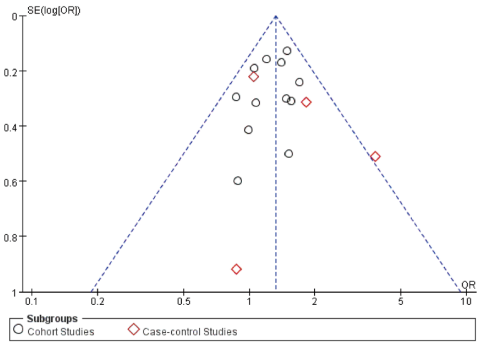

Figure S1 Funnel plots for the indexes (Female).

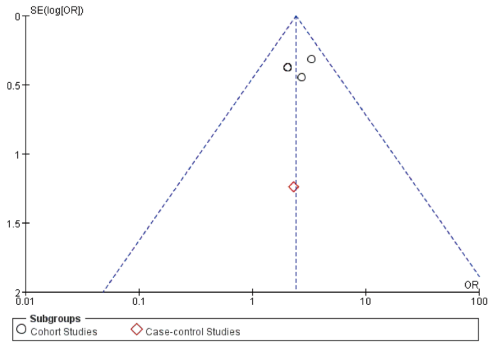

Figure S2 Funnel plots for the indexes (1ymphatic metastasis larger than 6).

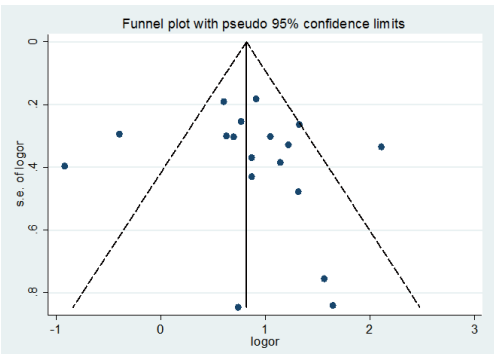

Figure S3 Funnel plots for the indexes (adenocarcinoma).

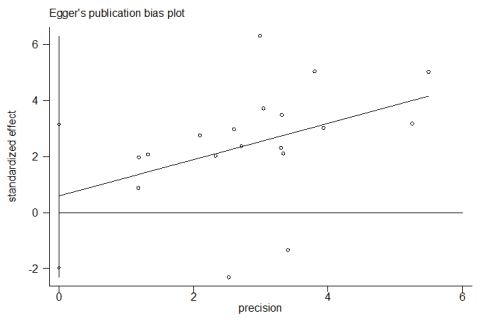

Figure S4 Egger's publication bias plot (adenocarcinoma).

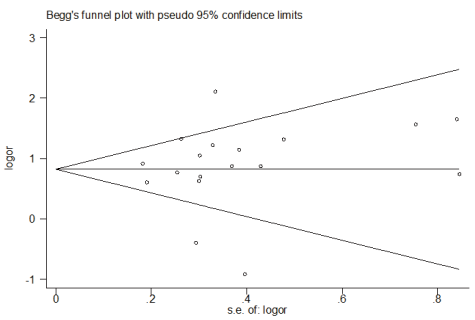

Figure S5 Begg's funnel plot (adenocarcinoma).

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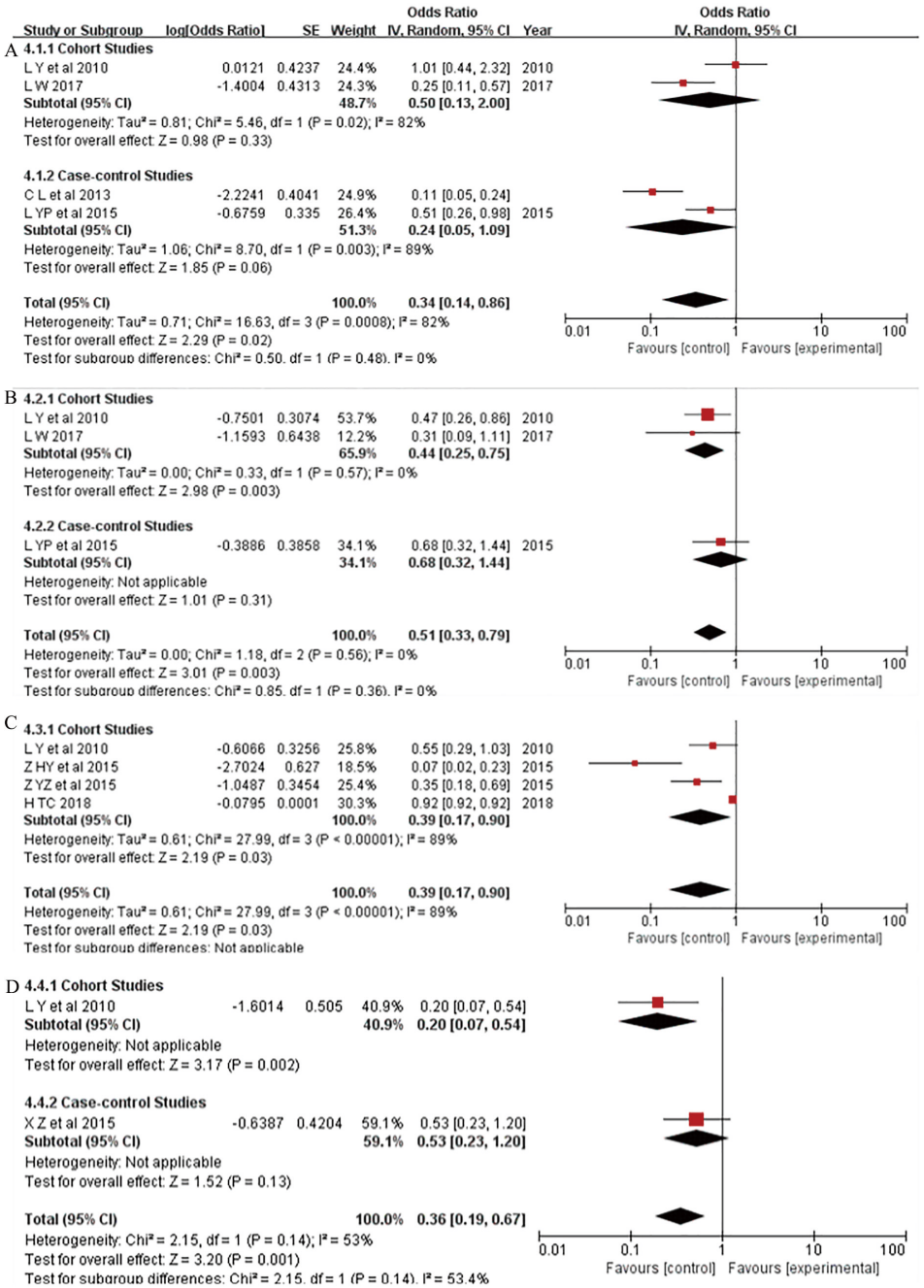

Figure S6 Meta-analysis of survival rates. (A) 1-year survival rate; (B) 2-year survival rate; (C) 3-year survival rate; (D) 5-year survival rate.

http://dx.doi.org/10.21037/apm-20-1722