Systematic Review and Meta-Analysis

Medicine

OPEN

# The clinicopathological and prognostic significance of mTOR and p-mTOR expression in patients with non-small cell lung cancer

## A meta-analysis

Weiwei Qiu, MA[a,b], Meiying Ren, MA[a,*], Cuifeng Wang, MA[a], Yuhua Fu, MA[a], Yan Liu, MA[a]

**Abstract**

**Background:** The mammalian target of rapamycin (mTOR) has a crucial role in carcinogenesis, angiogenesis, cellular proliferation, and metastasis; however, its significance in non-small cell lung cancer (NSCLC) remains contentious. Consequently, this study aims to assess the clinicopathological and prognostic importance of mTOR/p-mTOR expression in NSCLC.

**Methods:** Literature retrieval was undertaken by searching English databases PubMed, EMBASE, Web of Science, and Cochrane Library as well as Chinese databases CNKI, Wan Fang, and VIP for full-text publications that satisfied our eligibility criteria up to November 2021. STATA 12.0 was used to conduct statistical analysis (STATA Corporation, College Station, TX).

**Results:** This meta-analysis includes a total of 4683 patients from 28 primary publications. mTOR/p-mTOR expression was associated with sex (OR = 0.608, 95% CI: 0.442–0.836), lymph node metastasis (OR = 2.084, 95% CI: 1.437–3.182), and CEA (OR = 1.584, 95% CI: 1.135–2.209), but not with age, histological type, depth of tumor invasion, distant metastasis, TNM stage, differentiation degree, tumor size, or smoking. In addition, the expression of mTOR/p-mTOR is related to shorter overall survival in NSCLC patients (HR = 1.415, 95% CI: 1.051–1.905).

**Conclusion:** Positive mTOR/p-mTOR expression was substantially correlated with unfavorable conditions on the sex, lymph node metastases, and CEA levels. mTOR/p-mTOR may indicate a bad prognosis for NSCLC. The current findings must be confirmed and changed by other high-quality research employing a multivariate analysis on bigger sample size.

**Abbreviations:** ADC = adenocarcinoma, Akt = v-akt murine thymoma viral oncogene homolog 1, CI = confidence interval, HR = hazard ratio, IHC = immunohistochemistry, M = distant metastases, mTOR = mammalian target of rapamycin, mTORC2 = mTOR complex 2, N = lymph node metastasis, NOS = Newcastle–Ottawa scale, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, PI3K = phosphoinositide 3-kinase, p-mTOR = phosphorylated mammalian target of rapamycin, SCC = squamous cell carcinoma, T = depth of tumor invasion, TOR = target of rapamycin, U = univariate analysis.

**Keywords:** mammalian target of rapamycin, meta-analysis, non-small cell lung cancer, prognosis

## 1. Introduction

Non-small cell lung cancer (NSCLC) represents the most frequent type of respiratory tumor in clinical practice, with a percentage of 85% of all primary lung carcinomas.[1] Epidemiological data show[2] that by 2022, lung cancer will remain the leading cause of cancer-related death in China and emerge as the malignancy with the highest morbidity and mortality. In the past decade, low-dose CT-based lung cancer screening has significantly reduced the mortality of patients,[3] and the introduction of molecularly targeted drugs and immune checkpoint inhibitors has improved the prognosis of patients with advanced lung cancer,[4] but drug resistance and immune-related adverse effects have limited their clinical application.[5,6] So it is crucial to identify novel targets to enhance the prognosis of patients with non-small cell lung cancer.

The mammalian target of rapamycin (mTOR) is a highly conserved serine/threonine (Ser/Thr) kinase that serves as a critical

*This study was funded by the Natural Science Foundation of Inner Mongolia (no: 2021MS08004). The sponsor was not involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection, and analyses. The funder will have no input on the interpretation or publication of the study results.*

*The authors have no conflicts of interest to disclose.*

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

*[a] Department of Laboratory Medicine, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China, [b] Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China.*

** Correspondence: Meiying Ren, Department of Laboratory Medicine, the First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, 41 Linyin Road, Kundulun District, Baotou City, Inner Mongolia 014010, China (e-mail: 2418428858@qq.com).*



*How to cite this article: Qiu W, Ren M, Wang C, Fu Y, Liu Y. The clinicopathological and prognostic significance of mTOR and p-mTOR expression in patients with non-small cell lung cancer: A meta-analysis. Medicine 2022;101:51(e32340).*

*Received: 24 October 2022 / Received in final form: 30 November 2022 / Accepted: 30 November 2022*

*http://dx.doi.org/10.1097/MD.0000000000032340*

regulatory protein in proper cell growth, survival, metabolism, development, and angiogenesis.[7] mTOR regulates protein production via regulating transcription, translation, and ribosome biosynthesis, a process that affects cell growth and size and is essential for cell division.[8] Therefore, excessive activation of mTOR will result in elevated levels of cellular metabolism, sustained cell growth and proliferation, and prolonged cellular longevity, hence promoting the development of cancer and metabolic disorders.[9] Inhibition of mTOR can arrest the cell cycle in the G1 phase, as well as block mTOR-related signaling pathways, resulting in anti-proliferation, anti-inflammatory, autophagy-inducing, and apoptosis-inducing effects.[10] This provides a crucial direction for the development of anti-cancer and immunosuppressive drugs. In recent years, mTOR-targeted medicines have been widely developed and employed in preclinical and clinical trials for cancer.[11–14] As the first allosteric inhibitor of mTOR, Sirolimus, for instance, has been employed as an anti-tumor, anti-cardiovascular reconstruction, and anti-coronary restenosis therapy.[15,16] The discovery of mTOR inhibitors for use in cancer treatment has also demonstrated remarkable effectiveness. Tesirolimus is now licensed to treat advanced renal cell carcinoma, mantle cell lymphoma, platinum-refractory/drug-resistant ovarian cancer, and advanced/recurrent endometrial cancer.[17] Everolimus has shown partial effectiveness in the treatment of subependymal giant cell astrocytoma,[18] renal angiomyolipoma,[19] advanced nonfunctional pulmonary/gastrointestinal neuroendocrine tumor,[20] and advanced NSCLC.[21] In addition, the use of mTOR inhibitors in neuroblastoma, pediatric solid tumors, and sarcomas is still in the clinical trials phase.[22,23] In conclusion, mTOR, as the master switch of cellular metabolism, is an efficient anticancer therapeutic target. In cancers, blocking overactive mTOR signaling and associated pathways can cause potent antitumor effects. Currently, the therapeutic advantages of targeted cancer therapy are restricted to a minority of patients whose tumors are often caused by particular genetic abnormalities inside tumor cells.[24] Therefore, targeting the mTOR signaling pathway to block translation start is emerging as a possible treatment strategy. Results indicate the possible applicability of mTOR-targeted medicines as additional new chemotherapy components for a certain subgroup of lung cancer patients. Therefore, this meta-analysis is based on the theoretical basis that the role of mTOR in autophagy has an important impact on tumor occurrence and development, and further explores the correlation between mTOR expression and cancer progression and prognosis in clinical studies, which provides a practical basis for the development and research of mTOR targeted inhibitors.

Among the intracellular pathways that are abnormally elevated in cancer is the phosphoinositide 3-kinase (PI3K)-Akt-mTOR pathway. Oncogene-activating mutations, oncogene amplification, or tumor suppressor gene inactivation have been found in many malignancies, resulting in dysregulation of the PI3K-Akt-mTOR signaling pathway.[25] Data from current studies show that this pathway is activated in approximately 70% of ovarian or breast cancer[26]; abnormally activated this pathway is seen in 90% of lung adenocarcinomas (ADC) and 40% of lung squamous cell carcinomas[27]; 63.5% of hepatocellular carcinoma reported immunoreactivity of phosphorylated mTOR on tissue sections, and a significant association was found between p-mTOR expression and tumor size, metastasis and prognosis.[28] In addition, phosphorylation of PDK1 (phosphoinositide-dependent kinase-1) at Thr308 and mTORC2 (mTOR complex 2) at Ser473 was observed to be associated with worse overall survival in patients with AML (acute myeloid leukemia).[29,30] Numerous clinical studies have investigated the role and potential prognostic value of mTOR and p-mTOR in a variety of cancers. In a meta-analysis that pooled data from 915 patients with esophageal squamous cell carcinoma, mTOR/p-mTOR expression was found to be significantly associated with worse overall survival, disease-free survival, and cancer-specific survival.[31] In addition, breast cancer patients with mTOR overexpression had a threefold increased risk of recurrence compared to those without mTOR overexpression.[32] Meanwhile, studies on the relationship between mTOR/p-mTOR expression and gastric cancer, breast cancer, colorectal cancer, nasopharyngeal carcinoma, and urinary system tumors have shown that mTOR or p-mTOR may be considered promising markers for predicting aggressiveness and prognosis of cancer.[33–37] In NSCLC, dysregulation of Akt/mTOR signaling pathway activity is one of the primary factors of carcinogenesis. mTOR promotes tumorigenesis and progression through activation of the downstream eIF4 complexes.[38] As confirmed by immunohistochemical (IHC) staining, p-mTOR activation was observed in 50% to 60% of lung cancer patients, including 66% of NSCLC.[39] Among them, up to 90% of ADC, 60% of large cell carcinoma, and 40% of squamous cell carcinoma (SCC) were positive for p-mTOR, suggesting that mTOR may have a role in the morphogenesis or differentiation of glandular structure.[40] In addition, many studies have demonstrated that mTOR may be a factor in lymph node metastasis in SCC.[39] Collectively, these findings indicate that the stimulation of mTOR-mediated signaling may be clinically aggressive in specific populations. Therefore, clarifying the association between the clinicopathological features of various malignancies and mTOR, evaluating the sensitivity of each clinical lung cancer case to mTOR-targeted pharmacological therapy, and adopting specialized therapy for distinct subtypes of tumors may be a more valuable strategy.

Numerous research has been conducted on the association between the activation of mTOR and the clinicopathological characteristics and prognosis of NSCLC, but no clear result has been reached. In lung squamous cell carcinoma, mTOR/p-mTOR phosphorylation was positively connected with lymph node metastasis and distant metastasis, according to one research.[39,40] But it is unclear why lymph node metastasis is related to mTOR activation. S6K and 4E-BP1 are downstream signaling molecules of mTOR, and mTOR/S6K activation is associated with the differentiation, maintenance, and potential morphogenesis of some fractions of lung cancer (especially ADC).[41] An increase in eIF4F formation can boost translation initiation and cell proliferation.[38] The activation of S6K and 4E-BP1 has been found to determine cisplatin resistance in NSCLC. Nonetheless, 4E-BP1 or S6K activity has little prognostic value for lymph node metastasis or overall survival in NSCLC, whereas the influence of mTOR on the prognosis of NSCLC is still under investigation.[39] Numerous clinical papers have studied the involvement of mTOR and p-mTOR in NSCLC; however, due to the variability of IHC standards, the conclusions are inconsistent, and several contentious findings have not been adequately addressed. The predictive usefulness of the mTOR/p-mTOR expression and its association with certain common clinicopathological characteristics of NSCLC are still debatable. To assess the potential of mTOR/p-mTOR as a biomarker relevant for NSCLC progression and prognosis, to describe the differences in clinicopathological features and prognosis of mTOR/p-mTOR overexpression based on country, race, and specific populations, and to investigate its clinical role, we conducted the current meta-analysis, synthesizing appropriate evidence from homogenous studies to draw general conclusions.

## 2. Materials and methods

### *2.1. Protocol*

This work was registered with PROSPERO (registration number: CRD42021292457) and followed the latest PRISMA 2020

statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis).[42]

### 2.2. Inclusion criteria

Articles were considered eligible if they met all the following standards: Patients were pathologically diagnosed with primary non-small cell lung cancer, without other malignant tumors, without any preoperative treatment such as chemotherapy/radiation, and with no age or gender restrictions; The expression of mTOR/p-mTOR should be analyzed independently rather than in collaboration with other biomarkers. IHC was the only experimental method used to stain NSCLC specimens; The study has sufficient data or adequate information to assess the odd ratios (ORs) to estimate the correlation between mTOR/p-mTOR expression and clinicopathological characteristics of NSCLC, or to assess the hazard ratios (HRs) and 95% confidence intervals (CIs) of overall survival (OS); The included studies are cohort study or case-control study.

### 2.3. Exclusion criteria

The following articles should be excluded: Animal experiments, case reports, reviews, conference abstracts, letters, and repeated data; Positive expression of mTOR/p-mTOR was not stained by IHC; Insufficient information to estimate the prognostic and clinicopathological correlation; Not written in English or Chinese.

### 2.4. Literature search strategy

We conducted a thorough literature search for relevant papers published through November 2021 in the following databases: PubMed, Web of Science, Cochrane Library, Embase, CNKI (China National Knowledge Infrastructure), WanFang, and VIP. No language or publication date restrictions were imposed on the search. In reference to a comparable meta-analysis examining the clinicopathological features and prognostic usefulness of biomarkers,[43,44] the following search phrases were employed: lung cancer or lung tumor or bronchogenic carcinoma or non-small cell lung cancer; mammalian target of rapamycin or mTOR or p-mTOR or phosphorylated mammalian target of rapamycin; prognosis or prognostic or survival. In addition, the references of relevant literature were manually examined to verify that the literature search was exhaustive.

### 2.5. Literature retrieval and quality assessment

Two researchers evaluated the listed studies independently using the Newcastle–Ottawa Scale (NOS).[45] The scale had eight items divided into three sections, with a total of nine points. Included were studies with or exceeding a score of 6. Discrepancies in appeal results were discussed or consulted with a third investigator.

### 2.6. Data extraction

All data were extracted and cross-checked independently by two reviewers from eligible studies with a predefined table. If there were inconsistencies that affected the quality of pooled results, a third investigator assessed and determined the data independently. These following variables have been retrieved: Publication information including first author, publication year, country, and language; Clinical information including total sample size, the number of patients with positive and negative expression of mTOR/p-mTOR, genders, ages, pathological type, clinical stage, pathological grade, lymph node metastasis, tumor size, differentiation, smoking status, CEA level; prognostic indicators including Endpoint events, follow-up periods, HRs and 95% CI (including univariate and multivariate analysis); Experimental data including experimental materials, detecting methods, IHC techniques (antibodies types, companies, and dilution), cutoff values.

### 2.7. Statistical analysis

Based on the level of mTOR/p-mTOR detection, the patients were divided into high-expression and low-expression groups. Pooled OR and 95% CI were adopted to evaluate the correlation between mTOR/p-mTOR expression and clinicopathological characteristics. Pooled HR and 95% CI were calculated as the effective index to estimate the impact of mTOR/p-mTOR expression on the OS/PFS of the patients.[46] If HR > 1 and its 95% CI did not overlap with 1, this indicated that positive mTOR/p-mTOR expression was a risk factor for the prognosis of NSCLC, namely, the higher the mTOR/p-mTOR expression, the worse the prognosis of patients; if HR < 1 and 95% CI did not overlap with 1, the opposite was true. The heterogeneity was measured by the Q test and the inconsistency index $I^2$. If the $P$ value was less than 0.1 or $I^2$ was greater than 50%, the heterogeneity was considered significant, and the random-effect model was adopted; otherwise, if the heterogeneity was not significant, the fixed-effect model was adopted.[47] To analyze the reliability of the pooled result, sensitivity analysis was performed by omitting every single study.[48] Additionally, subgroup analysis was also conducted; Begg's funnel plot and Egger's s bias indicator test were used to assessing the publication bias.[49] All $P$ values were two-tailed in this meta-analysis, and $P < .05$ was considered statistically significant. Data were processed using Stata version 12.0 (Stata Corporation, College Station, TX).

## 3. Results

### 3.1. Literature search

1263 pieces of relevant literature were retrieved; 178 duplicate articles were removed; 119 articles were checked automatically using Endnote software and 59 articles were checked manually; By reading the title and abstract, 1036 articles, including reviews, case reports, animal experiments, and unrelated articles, were removed; By carefully reading the full text, 21 articles were eliminated, including 1 article not written in English or Chinese, 3 reviews and conference abstracts, 7 repeated data studies, 8 studies that did not provide mTOR/p-mTOR positive expression rate or prognosis-related data, and 2 studies that did not directly report HR value and its 95% CI but only gave *K-M* survival curve,[50,51] and a total of 28 studies were determined to be included.[52–79] Figure 1 shows the flowchart of the literature search.

### 3.2. Study characteristics

This meta-analysis includes a total of 28 papers, 13 of which were authored in English and 15 in Chinese. The 28 included studies were published between 2008 and 2021, contained a total of 4683 patients, and had sample sizes ranging from 35 to 574. 23 of the 28 papers examined the association between mTOR/p-mTOR expression and clinicopathological characteristics of NSCLC,[52–57,61–77] whereas 10 examined the relationship between mTOR/p-mTOR expression and prognosis.[53,54,58–60,63,76–79] The positive expression rate of mTOR/p-mTOR was measured by immunohistochemical staining of paraffin-embedded tissues (IHC). Tables 1–3 outlines the general features and experimental materials of the included research.

### 3.3. Quality assessment

Two researchers evaluated the quality of the 28 included studies according to the NOS scale. The quality scores varied from 6 to

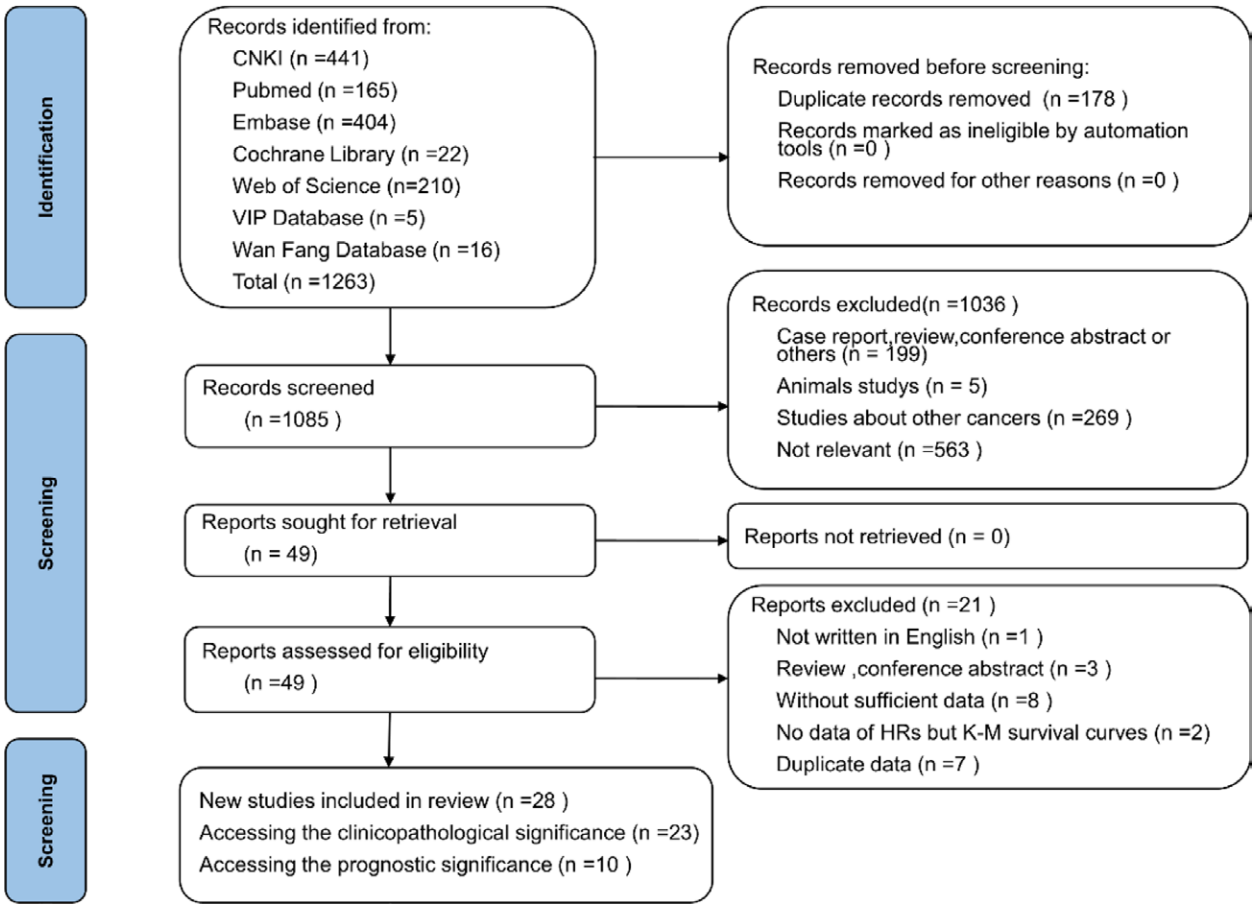


**Figure 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for literature retrieval.

8, and when the NOS score was equal to or more than 6, the articles were deemed to be of moderate to high quality. Table 4 displays the results.

### *3.4. Correlation between mTOR/p-mTOR expression and clinicopathological characteristics in NSCLC*

In our meta-analysis, as shown in Table 5; Figures 2 and 3, we investigated the following common clinicopathological parameters: genders, ages, histological type, tumor size, depth of tumor invasion (T), lymph node metastasis (N), distant metastasis (M), differentiation, and smoking. Our analysis showed that high expression of mTOR/p-mTOR was significantly correlated with gender (OR = 0.608, 95% CI: 0.442–0.836), lymph node metastasis (OR = 2.084, 95% CI:1.437–3.022) and CEA level (OR = 1.584, 95% CI: 1.135–2.209). In contrast, the correlations were not statistically significant between mTOR/p-mTOR level and ages (OR = 0.940, 95% CI: 0.794–1.113), histological type (OR = 1.519, 95% CI: 0.896–2.576), depth of tumor invasion (OR = 1.693, 95% CI: 0.543–5.283), distant metastasis (OR = 1.425, 95% CI: 0.634–3.203), TNM stage (OR = 1.318, 95% CI: 0.906–1.918), differentiation (OR = 1.256, 95% CI: 0.692–2.278, tumor size (OR = 0.908, 95% CI: 0.753–1.096), and smoking (OR = 0.719, 95% CI: 0.417–1.240). The results indicate that high expression of mTOR/p-mTOR was associated with female gender, more lymph node metastases, and higher CEA level. In addition, we analyzed the relationship between mTOR/p-mTOR and the above clinicopathological characteristics, respectively, and the results showed that the high expression of mTOR was significantly associated with more lymph node metastasis (OR = 2.074, 95% CI: 1.20–3.585); the high expression of p-mTOR was significantly associated with female gender (OR = 0.529, 95% CI: 0.313–0.896), more lymph node metastasis (OR = 2.123, 95% CI: 1.301–3.464) and more advanced TNM stage (OR = 2.049, 95% CI: 1.516–2.771) (Table 6); it coincided with the results of the above-combined analysis. All of these findings show that a high mTOR/p-mTOR expression ratio is particularly aggressive.

### *3.5. Correlation between mTOR/p-mTOR expression and OS of NSCLC*

***3.5.1. Relationship of mTOR expression with survival.*** Three articles were included in the meta-analysis of univariate analysis and four were included in the meta-analysis of multivariate analysis of the relationship between mTOR expression and prognosis. The three publications included in the meta-analysis for univariate analysis, with a total of 447 individuals, showed a pooled HR of 1.28 (95% CI: 0.65–2.51), demonstrating that there is no statistically significant association between mTOR expression and overall survival. A random effect model was adopted due to the considerable heterogeneity ($P = .008$, $I^2 = 79.5\%$). The multivariate study comprised four publications including a total of 580 patients in the meta-analysis. Using a random effect model ($P = .000$, $I^2 = 82.5\%$), the pooled HR was 1.62 (95% CI: 0.74–3.53). The connection between mTOR expression and prognosis remained negligible from a statistical standpoint. Table 7 and Figure 4 detail the HR and pooled HR for each research. In addition, we integrated the data from univariate and multivariate analyses to determine the pooled HR for a total of 7 data sets; the pooled HR is 1.47 (95% CI: 0.90–2.39). The results are compatible with the aforementioned conclusions.

**Table 1**

**The general characteristics of studies on mTOR expression.**

| First author (year) | Country | CP features/ Prognosis | No. of patients (mTOR PE/NE) | Genders (male/ female) | Age | Histological type (SCC/ ADC/Other) | Stage (I+II/III+IV) |
|---|---|---|---|---|---|---|---|
| Dan Liu 2011 | China | Y/Y | 134 (106/28) | 138/34 | <60 (81)/≥60 (91) | 77/75/20 | 85/87 |
| Oh Mee-Hye 2012 | Koreans | Y/N | 574 (376/198) | 398/176 | <65 (282)/≥65 (292) | 297/227/50 | 417/157 |
| Wang L 2012 | China | Y/N | 78 (51/27) | 66/12 | ≤60 (37)/> 60 (41) | 34/44 | NA |
| Kim HS 2012 | NA | Y/N | 245 (161/84) | 194/51 | <64 (130)/≥64 (115) | 91/154 | 167/78 |
| Valsamo K 2009 | USA | N/Y | 167 (94/73) | NA | 64 | 97/0 | NA |
| Dhillon T 2010 | Italy | N/Y | 134 (73/61) | 117/17 | <65 (77)/≥65 (57) | 41/56/37 | NA |
| Gately K 2012 | UK | N/Y | 141 (101/40) | 85/56 | <65 (67)/≥65 (74) | 60/67/14 | 141/0 |
| Guo K 2014 | China | Y/N | 82 (44/38) | 46/36 | <60 (58)/≥60 (24) | 43/39 | NA |
| Xu YY 2021 | China | Y/N | 35 (27/8) | 12/23 | <65 (23)/≥65 (12) | 33/2 | NA |
| Chen ZH 2013 | China | Y/N | 42 (21/21) | 22/20 | ≤60 (15)/ >60 (27) | 23/19 | 34/8 |
| Guo ZQ 2018 | China | Y/N | 105 (79/26) | 65/40 | ≤60 (32)/ >60 (73) | 35/70 | 63/42 |
| Hu ST 2010 | China | Y/N | 80 (42/38) | 64/16 | <60 (35)/≥60 (45) | 0/80 | 67/13 |
| Huang W 2019 | China | Y/N | 246 (136/110) | 150/96 | ≤60 (123)/>60 (123) | 154/92 | NA |
| Wang XC 2020 | China | Y/N | 93 (43/50) | 89/4 | ≤65 (63)/>65 (30) | 0/93 | NA |
| Yuan C 2017 | China | Y/N | 80 (46/34) | 59/21 | <60 (33)/≥60 (47) | 32/31/17 | 36/44 |
| Zhang JY 2020 | China | Y/N | 80 (49/31) | 56/24 | NA | NA | NA |
| Cai WK 2014 | China | N/Y | 138 (101/37) | 83/55 | <65 (63)/≥65 (75) | 68/59/11 | NA |
| **First author (year)** | **Node metastasis (Y/N)** | **Differentiation (G1 + G2/G3)** | **Estimates** | **Antibody** | **Company** | **Dilution** | **Cut off value** |
| Dan Liu 2011 | NA | 100/72 | OR, HR | RMA | CST, Beverly, MA | 01:50 | ≥2 |
| Oh Mee-Hye 2012 | 240/334 | NA | OR | RMA | Danvers, MA | NA | ≥3 |
| Wang L 2012 | 23/55 | 57/21 | OR | RMA | Beverly, MA | 01:50 | >2 |
| Kim HS 2012 | 106/139 | 206/39 | OR | RMA | Burlingame, Calif. | 1:100 | >2 |
| Valsamo K 2009 | NA | NA | HR | RMA | CST | 1:50 | >28 |
| Dhillon T 2010 | 34/100 | NA | HR | RMA | CST, Danvers, MA | 01:50 | >30 |
| Gately K 2012 | NA | NA | HR | RMA | CST, Danvers, MA | 01:50 | >30 |
| Guo K 2014 | 38/44 | 56/26 | OR | MMA | Abcam | NA | >2 |
| Xu YY 2021 | NA | NA | OR | RMA | Bioss, Beijing | 1:100 | ≥1 |
| Chen ZH 2013 | 20/22 | NA | OR | RMA | Bioss, Beijing | NA | ≥3 |
| Guo ZQ 2018 | 62/43 | 85/20 | OR | RMA | Boster, Wuhan | 01:50 | >3 |
| Hu ST 2010 | 65/15 | 68/12 | OR | RMA | CST | 1:100 | >1 |
| Huang W 2019 | 67/179 | NA | OR | RMA | NA | NA | ≥2 |
| Wang XC 2020 | 33/60 | NA | OR | NA | America SC | NA | >2 |
| Yuan C 2017 | 33/47 | 56/24 | OR | RMA | Abcam | NA | ≥1 |
| Zhang JY 2020 | NA | NA | OR | RMA | Shanghai YSRIBIO | NA | NA |
| Cai WK 2014 | 91/47 | 89/49 | HR | NA | NA | NA | NA |

ADC = adenocarcinoma, CP = clinicopathological, HR = hazard ratio, MMA = mouse monoclonal antibody, NA = not available, NE = negative expression, OR = odd ratio, PE = positive expression, RMA = rabbit monoclonal antibody, SCC = squamous cell carcinoma.

*3.5.2. Relationship of p-mTOR expression with survival.* Three of the 6 papers on p-mTOR reported HR via univariate analysis, whereas 4 reported HR using multivariate analysis. Initially, a meta-analysis was conducted using data from univariate analysis, which included 756 patients with a pooled HR of 1.33 (95% CI: 0.94–1.94) The combined HR for multivariate analysis of p-mTOR was 1.42 (95% CI: 0.50–3.00), whereas the combined HR for univariate and multivariate analysis was 1.37 (95% CI: 0.92–2.03). The random effect model was adopted due to the heterogeneity. There was no statistically significant correlation between p-mTOR expression and overall survival, according to any of these studies. (Table 7; Fig. 4)

*3.5.3. Relationship of mTOR and p-mTOR expression with survival.* Finally, we integrated all univariate and multivariate analyses of mTOR and p-mTOR into the meta-analysis to estimate the pooled HR to determine the association between mTOR and p-mTOR expression with OS in NSCLC patients. There were a total of 15 data sets, comprising 7 univariate analyses and 8 multivariate analyses, with a pooled HR of 1.415 (95% CI: 1.051–1.915). A random effect model was adopted due to the considerable heterogeneity between studies ($I^2$ = 80.6%, $P$ = .001). In addition, two sets of data demonstrated a correlation between mTOR/p-mTOR expression and PFS (Progression-Free Survival) with a combined HR of 1.631 (95% CI: 0.929–2.864) using a fixed effect model ($I^2$ = 46.8%, $P$ = .171). The statistical analysis revealed a correlation between the expression of mTOR/p-mTOR and shorter OS in patients with NSCLC, but not PFS. (Table 8; Fig. 5)

In terms of the link between mTOR/p-mTOR and OS, the independent and combined studies produced contradictory results. No statistically significant link was found between mTOR or p-mTOR and OS, regardless of whether univariate or multivariate analysis was included. We investigated the causes of this discrepancy. First, although the included studies satisfied the inclusion and exclusion criteria, the quality of individual research varied, resulting in heterogeneity within studies and disparities between the results of grouped and combined analyses. Secondly, the meta-analysis of mTOR or p-mTOR alone comprised a small number of studies, a small sample size of the study population, and high heterogeneity, which rendered the pooled conclusions unstable. Upon synthesis

**Table 2**

**The general characteristics of studies on p-mTOR expression.**

| First author (year) | Country | CP features/ prognosis | No. of patients (p-mTOR PE/NE) | Genders (male/female) | Age | Histological type (SCC/ADC/Other) |
|---|---|---|---|---|---|---|
| Dan Liu 2011 | China | Y/Y | 172 (89/83) | 138/34 | <60 (81)/≥60 (91) | 77/75/20 |
| Zhang Y 2013 | China | Y/Y | 120 (46/74) | 81/39 | <60 (54)/≥60 (66) | 57/63 |
| Lu J 2020 | China | Y/N | 341 (194/147) | 256/85 | <55 (137)/≥55 (204) | 182/159 |
| Shin E 2015 | USA | Y/N | 408 (180/228) | 289/119 | NA | 250/158 |
| Liu HB 2008 | China | Y/Y | 59 (24/35) | 43/16 | <60 (31)/≥60 (28) | 28/27/4 |
| Xu HR 2018 | China | Y/N | 82 (54/28) | 62/20 | ≤60 (36)/>60 (46) | 34/48 |
| A Wang DZ 2016 | China | Y/N | 49 (37/12) | 36/13 | <60 (30)/≥60 (19) | 20/29 |
| Huang W 2019 | China | Y/N | 246 (111/135) | 150/96 | ≤60 (123)/>60 (123) | 154/92 |
| Wang XC 2020 | China | Y/N | 93 (47/46) | 89/4 | ≤65 (63)/>65 (30) | 0/93 |
| Xu HR 2018 | China | Y/N | 82 (56/26) | 64/18 | ≤60 (44)/>60 (38) | 40/42 |
| Zhang XY 2019 | China | Y/N | 96 (64/32) | 62/34 | ≤60 (50)/>60 (46) | 46/50 |
| Yoshizawa A 2010 | USA | Y/Y | 276 (129/147) | NA | NA | 138/138 |
| Shimizu K 2014 | Japan | Y/Y | 104 (41/63) | 64/40 | ≤65 (31)/>65 (73) | 66/38 |
| Shimizu K 2014 | Japan | N/Y | 204 (56/148) | 119/85 | ≤65 (67)/>65 (137) | 142/62 |
| Gold KA 2014 | USA | N/Y | 370 | 186/184 | NA | 227/126/17 |

| First author (year) | TNM Stage (I+II/III+IV) | Node metastasis (Y/N) | Estimates | Antibody | Company | Dilution | Cut off value |
|---|---|---|---|---|---|---|---|
| Dan Liu 2011 | 85/87 | NA | OR, HR | ser2448, RMA | CST, Beverly, MA | 1:100 | ≥2 |
| Zhang Y 2013 | 72/48 | 69/51 | OR, HR | NA | CST | 01:50 | ≥2 |
| Lu J 2020 | 168/173 | 202/139 | OR | IgG isotype-matched antibody | NA | 1:100 | ≥2 |
| Shin E 2015 | NA | 25/383 | OR | NA | NA | NA | ≥4 |
| Liu HB 2008 | 41/18 | 38/21 | OR, HR | ser2448, RMA | CST | 1:100 | ≥2 |
| Xu HR 2018 | NA | 26/56 | OR | RMA | Santa Cruz | NA | >3 |
| A Wang DZ 2016 | 36/13 | 22/27 | OR | RMA | Shanghai Yuanmu | NA | ≥2 |
| Huang W 2019 | NA | 67/179 | OR | RMA | NA | NA | ≥2 |
| Wang XC 2020 | NA | 33/60 | OR | NA | America SC | NA | >2 |
| Xu HR 2018 | NA | 30/52 | OR | RMA | Santa Cruz | NA | >3 |
| Zhang XY 2019 | NA | 40/56 | OR | RMA | CST | NA | >3 |
| Yoshizawa A 2010 | NA | NA | OR, HR | ser2448, RMA | CST | 1:100 | TS3, TS4, TS5 |
| Shimizu K 2014 | 80/24 | 33/71 | OR, HR | RMA | CST, Danvers, MA | 1:80 | ≥2 |
| Shimizu K 2014 | 159/41 | 61/143 | HR | RMA | CST, Danvers, MA | 1:80 | ≥2 |
| Gold KA 2014 | 309/61 | NA | HR | NA | CST | 1:100 | ≥2 |

ADC = adenocarcinoma, CP = clinicopathological, HR = hazard ratio, NA = not available, NE = negative expression, OR = odd ratio, PE = positive expression, RMA = rabbit monoclonal antibody, SCC = squamous cell carcinoma.

**Table 3**

**Prognostic characteristics of studies on mTOR/p-mTOR expression.**

| First author (year) | Analysis | Univariate HR (95% CI) | Multivariate HR (95% CI) | Endpoints |
|---|---|---|---|---|
| mTOR | | | | |
| Dan Liu 2011 | U | 0.645 (0.377–1.103) | NA | OS |
| Valsamo K 2009 | M | NA | 0.48 (0.24–0.98) | OS |
| Dhillon T 2010 | U&M | 1.77 (1.17–2.73) | 1.66 (1.01–2.74) | OS |
| Gately K 2012 | U&M | 1.85 (0.98–3.49) | 2.18 (1.12–4.23) | OS |
| Cai WK 2014 | M | NA | 3.697 (1.687–5.195) | OS |
| p-mTOR | | | | |
| Dan Liu 2011 | U&M | 1.917 (1.349–2.724) | 3.299 (1.928–5.645) | OS |
| Zhang Y 2013 | M | NA | 2.642 (1.157–4.904) | OS |
| Liu HB 2008 | M | NA | 0.686 (0.274–1.721) | OS |
| Yoshizawa A 2010 | U | 1.01 (0.75–1.36) | NA | OS |
| Shimizu K | U | 1.079 (0.597–1.948) | NA | OS, PFS |
| Shimizu K | U | 1.475 (0.868–2.505) | NA | OS, PFS |
| Gold KA | M | NA | 0.662 (0.460–0.952) | OS |

CI = confidence interval, HR = hazard ratio, M = multivariate analysis, NA = not available, OS = overall survival, PFS = progression-free survival, U = univariate analysis.

of all investigations, the sample size increased, resulting in statistically significant findings. In addition, the grouping analysis was not based on randomized comparisons, and the probability of false negative/false positive significance tests rose without modifying the significance test level; hence, the results' dependability is questionable. Lastly, p-mTOR is the phosphorylated version of mTOR and the downstream protein of mTOR; both serve the same role in the control of autophagy, therefore we feel that combining the two studies is compatible with its mechanism, hence increasing the sample size and the reliability of the results.

**Table 4**

**NOS scores of included studies.**

| Study (year) | Selection | Comparability | Exposure/outcome | Quality scores | Grade |
|---|---|---|---|---|---|
| Dan Liu 2011 | 4 | 1 | 2 | 7 | high |
| Zhang Y 2013 | 4 | 1 | 3 | 8 | high |
| Oh Mee-Hye 2012 | 3 | 1 | 3 | 7 | high |
| Lu J 2020 | 3 | 2 | 3 | 8 | high |
| Wang L 2012 | 3 | 1 | 2 | 6 | high |
| Kim HS 2012 | 3 | 2 | 2 | 7 | high |
| Anagnostou 2009 | 4 | 1 | 2 | 7 | high |
| Dhillon T 2010 | 4 | 1 | 3 | 8 | high |
| Gately K 2012 | 4 | 1 | 2 | 7 | high |
| Shin E 2015 | 3 | 1 | 3 | 7 | high |
| Guo K 2014 | 3 | 2 | 2 | 7 | high |
| Liu HB 2008 | 4 | 1 | 3 | 8 | high |
| Xu YY 2021 | 3 | 2 | 2 | 7 | high |
| Xu HR 2018 | 3 | 2 | 2 | 7 | high |
| A Wang DZ 2016 | 3 | 2 | 2 | 7 | high |
| Chen ZH 2013 | 3 | 2 | 2 | 7 | high |
| Guo ZQ 2018 | 3 | 1 | 2 | 6 | high |
| Hu ST 2010 | 3 | 2 | 2 | 7 | high |
| Huang W 2019 | 3 | 1 | 2 | 6 | high |
| Wang XC 2020 | 3 | 2 | 2 | 7 | high |
| Xu HR 2018 | 3 | 2 | 2 | 7 | high |
| Yuan C 2017 | 3 | 2 | 2 | 7 | high |
| Zhang XY 2019 | 3 | 2 | 2 | 7 | high |
| Zhang JY 2020 | 3 | 1 | 2 | 6 | high |
| Yoshizawa A 2010 | 4 | 1 | 2 | 7 | high |
| Shimizu K 2014 | 4 | 1 | 2 | 7 | high |
| Gold KA 2014 | 4 | 1 | 3 | 8 | high |
| Cai WK 2014 | 4 | 1 | 2 | 7 | high |

NOS = Newcastle–Ottawa scale.

**Table 5**

**Meta-analysis of relationships between mTOR and p-mTOR expression and clinicopathological characteristics of NSCLC.**

| | | No. samples | | | | | | | Publication bias | |
|---|---|---|---|---|---|---|---|---|---|---|
| Clinicopathological characteristics | No. | Total | PE | NE | OR (95% CI) | *P* value | Model | Heterogeneity ($I^2$, *P*) | Begg (*P*) | Egger (*P*) |
| Gender (Male vs Female) | 20 | 3158 | 1803 | 1355 | 0.608 (0.442–0.836) | .002* | Random | $I^2$ = 63.4%, *P* = .000 | 0.538 | 0.615 |
| Age (old vs young) | 18 | 2409 | 1428 | 981 | 0.940 (0.794–1.113) | .475 | Fixed | $I^2$ = 0.0%, *P* = .525 | 0.449 | 0.66 |
| HT (ADC vs non-ADC) | 20 | 3502 | 1982 | 1520 | 1.519 (0.896–2.576) | .121 | Random | $I^2$ = 91.1%, *P* = .000 | 0.922 | 0.261 |
| N (N1-3 vs N0) | 19 | 2793 | 1646 | 1147 | 2.084 (1.437–3.022) | .000* | Random | $I^2$ = 75.8%, *P* = .000 | 0.08 | 0.01 |
| TNM(III-IV vs I-II | 11 | 1921 | 1175 | 746 | 1.318 (0.906–1.918) | .149 | Random | $I^2$ = 62.3%, *P* = .003 | 0.876 | 0.652 |
| Differentiation (G3 vs G1/G2) | 8 | 1279 | 761 | 518 | 1.256 (0.692–2.278) | .454 | Random | $I^2$ = 78.6%, *P* = .000 | 0.536 | 0.789 |
| Tumor size (>3 vs ≤ 3) | 15 | 2186 | 1310 | 876 | 0.908 (0.753–1.096) | .314 | Fixed | $I^2$ = 41.0%, *P* = .049 | 0.692 | 0.318 |
| Smoking (Y vs N) | 8 | 2050 | 1124 | 926 | 0.719 (0.417–1.240) | .235 | Random | $I^2$ = 84.6%, *P* = .000 | 0.536 | 0.305 |
| CEA (high vs low) | 4 | 678 | 337 | 341 | 1.584 (1.135–2.209) | .007* | Fixed | $I^2$ = 45.5%, *P* = .138 | 1.000 | 0.690 |
| T (3-4 vs 1-2) | 3 | 897 | 588 | 309 | 1.693 (0.543–5.283) | .364 | Random | $I^2$ = 89.2%, *P* = .000 | 0.296 | 0.104 |
| M (M1 vs M0) | 3 | 786 | 533 | 253 | 1.425 (0.634–3.203) | .392 | Fixed | $I^2$ = 0.0%, *P* = .372 | 1.000 | 0.987 |

ADC = adenocarcinoma, CI = confidence interval, Fixed = fixed-effects model, HT = histological type, M = distant metastases, mTOR = mammalian target of rapamycin, N = lymph node metastasis, NE = negative expression, NO = reference count, OR = odds ratio, PE = positive expression, p-mTOR = phosphorylated mammalian target of rapamycin, Random = random effects model, T = depth of tumor invasion.

*p-value <0.05.

### *3.6. Subgroup analyses on the prognostic value of mTOR/p-mTOR expression for OS*

To further assess the predictive importance of mTOR/p-mTOR, we conducted a stratified analysis; the findings are presented in Table 9. All of the included studies were divided into subgroups based on area, sample size, statistical analysis, cutoff values, gender, and histological type. Stratifying by geographic region, the pooled HR for studies done in China was 1.787 (95% CI: 1.013–3.15), indicating that mTOR/p-mTOR expression was substantially related to poor prognosis; however, the outcome was different in the non-China subgroup (HR = 1.212, 95% CI: 0.886–1.646). The association between mTOR/p-mTOR expression and poor prognosis remained statistically significant in subgroups with fewer ADC patients (HR = 1.825, 95% CI: 1.322–2.521) and subgroups with fewer males (HR = 1.563, 95% CI: 1.098–2.224). mTOR/p-mTOR expression was not statistically related to prognosis in any category when categorized by statistical analysis method and cutoff value. In conclusion, the findings of the subgroup analysis revealed that the positive expression of mTOR/p-mTOR increased the probability of mortality in Chinese female squamous carcinoma patients, giving a rationale for the use of mTOR inhibitors in certain groups.

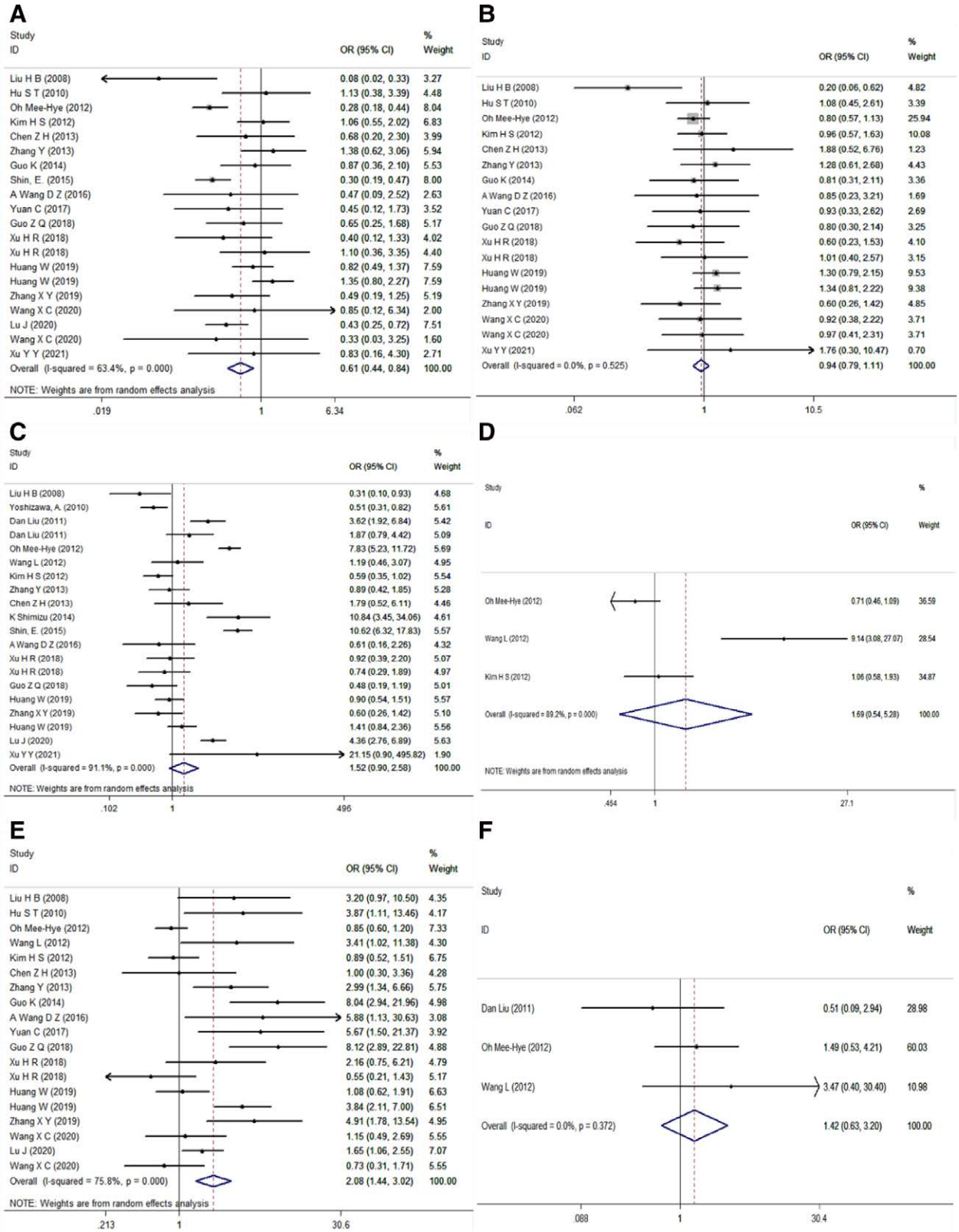


**Figure 2.** Meta-analysis on the relationship between mTOR/p-mTOR expression and clinicopathological characteristics of NSCLC, including (A) genders, (B) ages, (C) histological type, (D) tumor invasion, (E) lymph node metastasis, (F) distant metastasis. CI = confidence interval, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OR = odds ratio, p-mTOR = phosphorylated mammalian target of rapamycin.

### *3.7. Sensitivity analysis*

A sensitivity analysis was conducted to determine the dependability of the aggregated results. We assessed the reliability and consistency of the pooled data by analyzing the impact of excluding each study on the overall results. Among the clinicopathological parameters, seven studies with substantial variability were analyzed for sensitivity, including gender, histological type, tumor invasion (T), lymph node metastasis

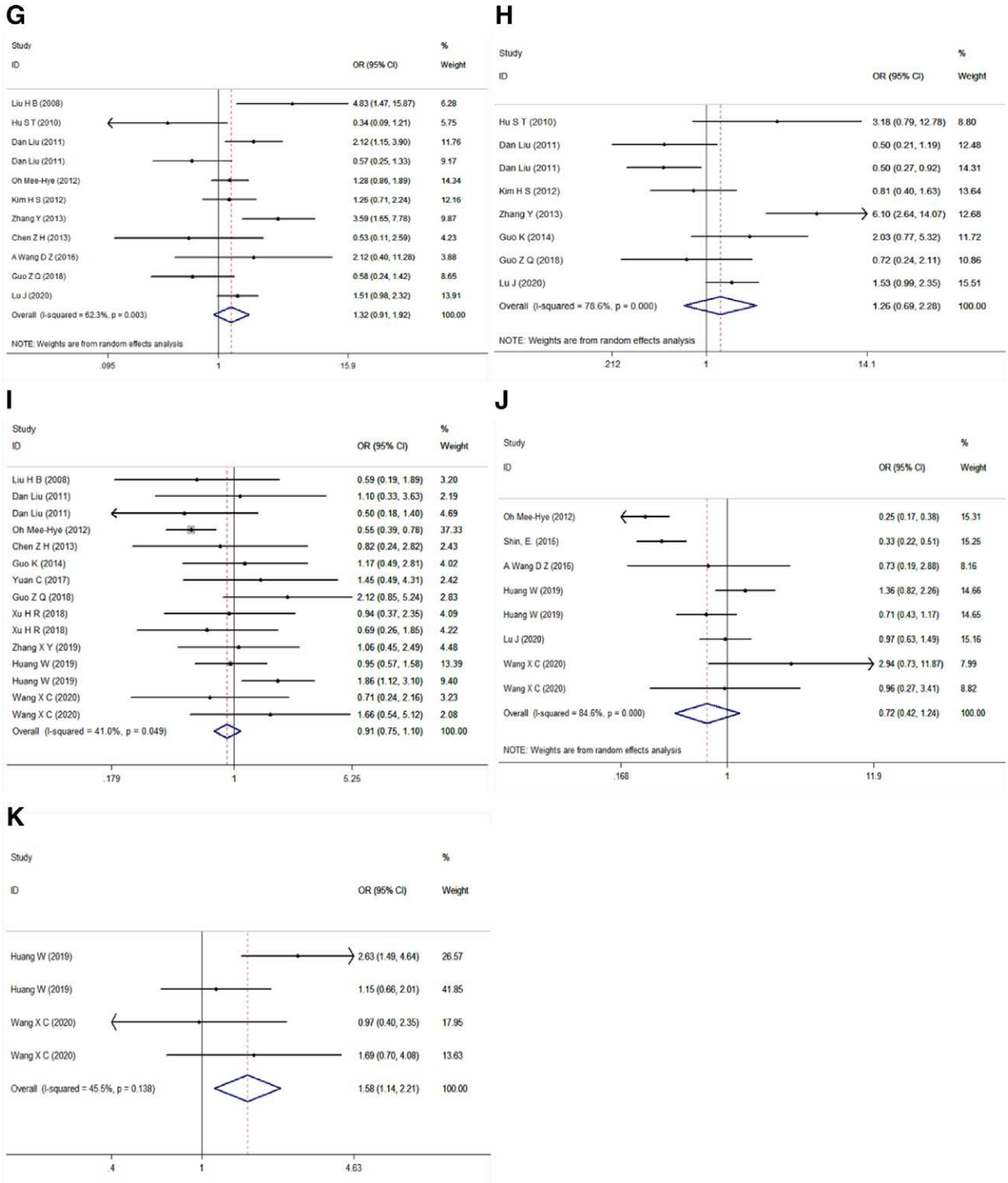


**Figure 3.** Meta-analysis on the relationship between mTOR/p-mTOR expression and clinicopathological characteristics of NSCLC, including (A) TNM stage, (B) differentiation degree, (C) tumor size, (D) smoking, (E) CEA. CI = confidence interval, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OR = odds ratio, p-mTOR = phosphorylated mammalian target of rapamycin.

(N), TNM stage, differentiation, and smoking status. In the examination of each clinicopathological feature, excluding any one research did not affect the pooled OR. As shown in Figure 6, the pooled results of OS did not change after excluding studies with substantial heterogeneity, such as Yoshizawa, A. et al and K Shimizu (HR = 1.489, 95% CI: 1.052–2.108), showing that the results were consistent.

### *3.8. Publication bias*

Begg's funnel plot and Egger's s bias indicator test were used to investigating publication bias. In none of the included research was a substantial publication bias identified (Tables 5 and 7).

## 4. Discussion

From yeast to humans, autophagy is a highly conserved mechanism dependent on the activity of a core group of autophagy-related proteins.[80] mTOR was identified as the homologous gene of rapamycin protein target (TOR) in yeast mutants in 1991.[8] mTOR binds to multiple proteins to form two distinct

**Table 6**

**Relationships between mTOR/p-mTOR expression and clinicopathological characteristics of NSCLC.**

| Clinicopathological characteristics | mTOR | | | | | p-mTOR | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | OR (95% CI) | *P* value | Model | Heterogeneity ($I^2$, *p*) | No. | OR (95% CI) | *p* value | Model | Heterogeneity ($I^2$, *p*) |
| Gender (Male vs Female) | 10 | 0.675 (0.452–1.007) | .054 | Random | $I^2$ = 50.8%, *P* = .032 | 10 | 0.529 (0.313–0.896) | .018* | Random | $I^2$ = 73.1%, *P* = .000 |
| Age (old vs young) | 10 | 0.959 (0.777–1.183) | .693 | Fixed | $I^2$ = 0.0%, *P* = .889 | 8 | 0.908(0.684–1.206) | .506 | Fixed | $I^2$ = 39.7%, *P* = .114 |
| HT (ADC vs non-ADC) | 8 | 1.672 (0.692–4.043) | .253 | Random | $I^2$ = 91.0%, *P* = .000 | 12 | 1.432 (0.710–2.890) | .316 | Random | $I^2$ = 91.9%, *P* = .000 |
| N (N1-3 vs N0) | 10 | 2.074 (1.200–3.585) | .009* | Random | $I^2$ = 79.3%, *P* = .000 | 9 | 2.123 (1.301–3.464) | .003* | Random | $I^2$ = 66.6%, *P* = .002 |
| TNM (III-IV vs I-II | 6 | 0.989 (0.754–1.297) | .937 | Fixed | $I^2$ = 41.6%, *P* = .128 | 5 | 2.049 (1.516–2.771) | .000* | Fixed | $I^2$ = 32.8%, *P* = .202 |
| Differentiation (G3 vs G1/G2) | 5 | 0.984 (0.654–1.481) | .94 | Fixed | $I^2$ = 49.2%, *P* = .096 | 3 | 1.613 (0.489–5.318) | .432 | Random | $I^2$ = 91.3%, *P* = .000 |
| Tumor size (>3 vs ≤ 3) | 8 | 0.798 (0.630–1.009) | .06 | Fixed | $I^2$ = 39.6%, *P* = .115 | 7 | 1.141 (0.835–1.559) | .407 | Fixed | $I^2$ = 32.2%, *P* = .182 |
| Smoking (Y vs N) | 3 | 0.505 (0.213–1.197) | .121 | Random | $I^2$ = 82.8%, *P* = .003 | 5 | 0.900 (0.443–1.830) | .771 | Random | $I^2$ = 83.9%, *P* = .000 |
| CEA (high vs low) | 2 | 1.283 (0.801–2.054) | .3 | Fixed | $I^2$ = 0.0%, *P* = .473 | 2 | 1.695 (0.643–4.47) | .286 | Random | $I^2$ = 71%, *P* = .063 |

ADC = adenocarcinoma, CI = confidence interval, Fixed = fixed-effects model, HT = histological type, M = distant metastases, mTOR = mammalian target of rapamycin, N = lymph node metastasis, NE = negative expression, NO = reference count, OR = odds ratio, PE = positive expression, random = random effects model, T = depth of tumor invasion.
*p-value <0.05.

**Table 7**

**Relationships between mTOR/p-mTOR expression and OS of NSCLC.**

| | Endpoint event | No. | HR (95% CI) | *P* value | Heterogeneity ($I^2$, *P*) | Model |
|---|---|---|---|---|---|---|
| mTOR | OS | 7 | 1.47(0.9, 2.39) | .124 | 81.1%, .000 | Random |
| p-mTOR | OS | 8 | 1.37(0.92, 2.03) | .119 | 81.7%, .000 | Random |

CI = confidence interval, HR = hazard ratio, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, p-mTOR = phosphorylated mammalian target of rapamycin.

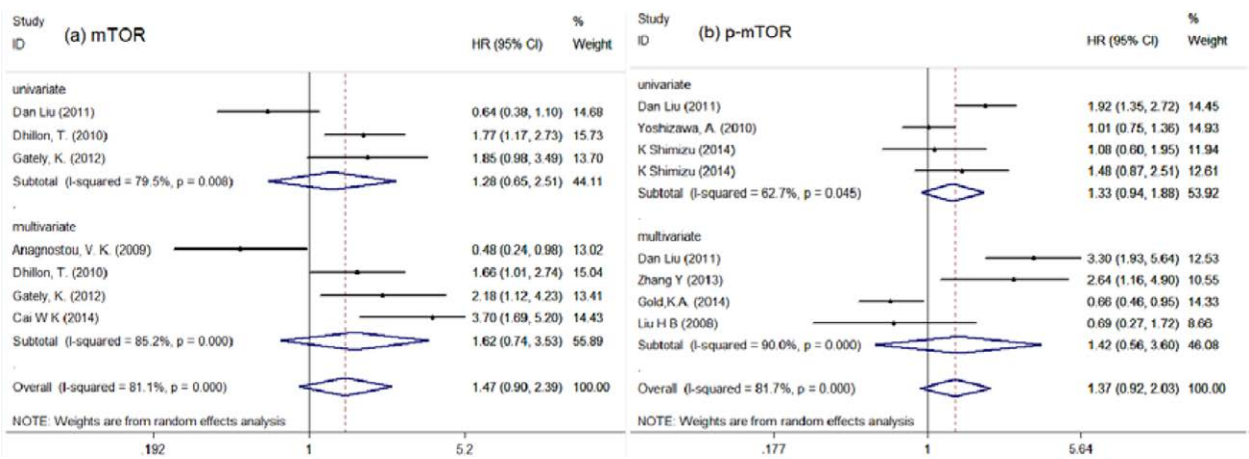


**Figure 4.** Forest plots on the prognostic significance of mTOR or p-mTOR expression for OS in NSCLC. CI = confidence interval, HR = hazard ratio, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, p-mTOR = phosphorylated mammalian target of rapamycin.

signaling complexes, mTORC1 (comprised of mTOR, Raptor, mLST8, PRAS40, and DEPTOR) and mTORC2 (comprised of mTOR, Rictor, mLST8, mSin1, Hsp70, and DEPTOR), which trigger different downstream signals to regulate cellular function by binding to specific substrates.[81] mTORC2 facilitates phosphorylation of AKT at Ser473, therefore activating mTORC1; active mTORC1 promotes ribosomal protein S6 kinase (S6K), which drives the mTORC2 complex. In addition, mTORC1 is sensitive to energy and pressure and strongly inhibited by rapamycin, whereas mTORC2 is insensitive to rapamycin and nutrition,[82,83] but its activity is inhibited by long-term long-lasting rapamycin treatment.[84] mTOR

**Table 8**

**Meta-analysis of prognostic roles of mTOR/p-mTOR expression in NSCLC.**

| Endpoint event | No. | HR (95% CI) | *P* value | Heterogeneity (*I*, *P*) | Model | Publication bias | |
|---|---|---|---|---|---|---|---|
| | | | | | | Begg (*P*) | Egger (*p*) |
| OS | 15 | 1.415 (1.051–1.905) | .022* | 80.6%, .000 | Random | 0.843 | 0.54 |
| PFS | 2 | 1.631 (0.929–2.864) | .089 | 46.8%, .171 | Fixed | 1.000 | / |

CI = confidence interval, HR = hazard ratio, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, p-mTOR = phosphorylated mammalian target of rapamycin.

*p-value <0.05.

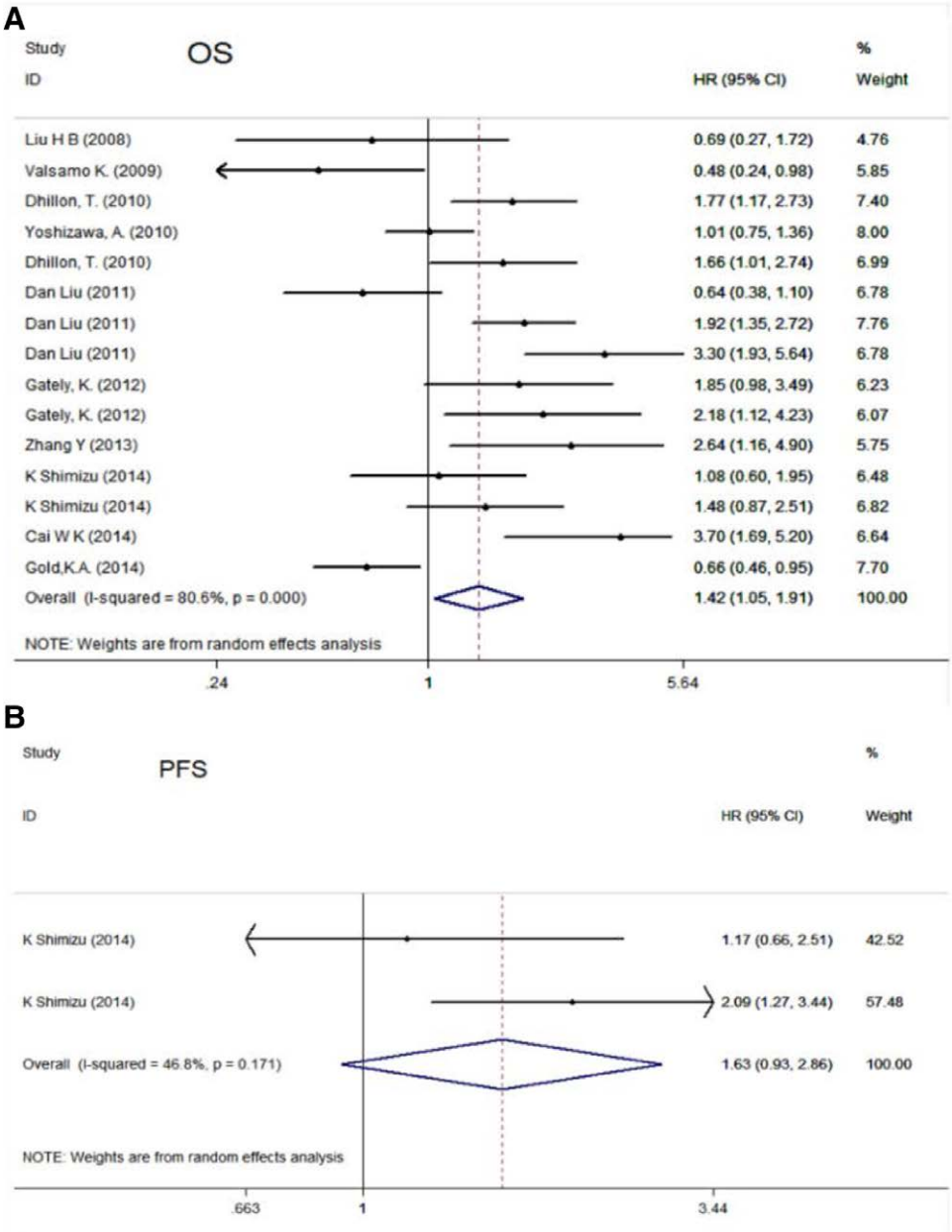


**Figure 5.** Meta-analysis on the prognostic significance of mTOR and p-mTOR expression for OS, PFS in patients with NSCLC. CI = confidence interval, HR = hazard ratio, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, PFS = progression-free survival, p-mTOR = phosphorylated mammalian target of rapamycin.

signaling plays a central role as a central controller in the energy supply for cell survival, growth, metabolism, proliferation, and death, such as the classical PI3K/AKT/mTOR signaling pathway being highly activated in several tumor types, regulating several cellular mechanisms, transmitting signals from upstream regulatory proteins such as PTEN, PI3K, and RTKs, as well as many downstream effectors, such as GSK-3, FOXO, and MDM2.[85] In addition, the Liver kinase B1/

**Table 9**

**Subgroup analyses for the relationship between mTOR/p-mTOR expression and OS in NSCLC.**

| Subgroups | No. | HR (95% CI) | *P* value | Heterogeneity ($I^2$, *P*) |
|---|---|---|---|---|
| By statistical analysis | | | | |
| Univariate analysis | 7 | 1.314 (0.976–1.767) | .071 | 66.3%, .007 |
| Multivariate analysis | 8 | 1.517 (0.859–2.682) | 0.151 | 87.0%, .000 |
| By region | | | | |
| China | 6 | 1.787 (1.013–3.15) | 0.045* | 83.6%, .000 |
| non-China | 9 | 1.212 (0.893–1.646) | 0.218 | 71.6%, .000 |
| By No. of patients | | | | |
| <200 | 12 | 1.575 (1.128–2.200) | 0.008* | 76.4%, .000 |
| ≥200 | 3 | 0.963 (0.643–1.443) | 0.857 | 69.5%, .038 |
| By male (%) | | | | |
| <70 | 9 | 1.563 (1.098–2.224) | .013* | 79.9%, .000 |
| ≥70 | 6 | 1.214 (0.709–2.080) | .479 | 79.9%, .000 |
| By cutoff values | | | | |
| ≥2 | 7 | 1.523 (0.849–2.735) | .159 | 88.9%, .000 |
| non-≥2 | 8 | 1.330 (0.998–1.774) | .052 | 60.1%, .014 |
| By ADC (%) | | | | |
| <50 | 10 | 1.825 (1.322–2.521) | .000* | 71.0%, .000 |
| ≥50 | 5 | 0.893 (0.642–1.241) | .499 | 60.3%, .039 |

ADC = adenocarcinoma, CI = confidence interval, HR = hazard ratio, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, p-mTOR = phosphorylated mammalian target of rapamycin.

*p-value <0.05.

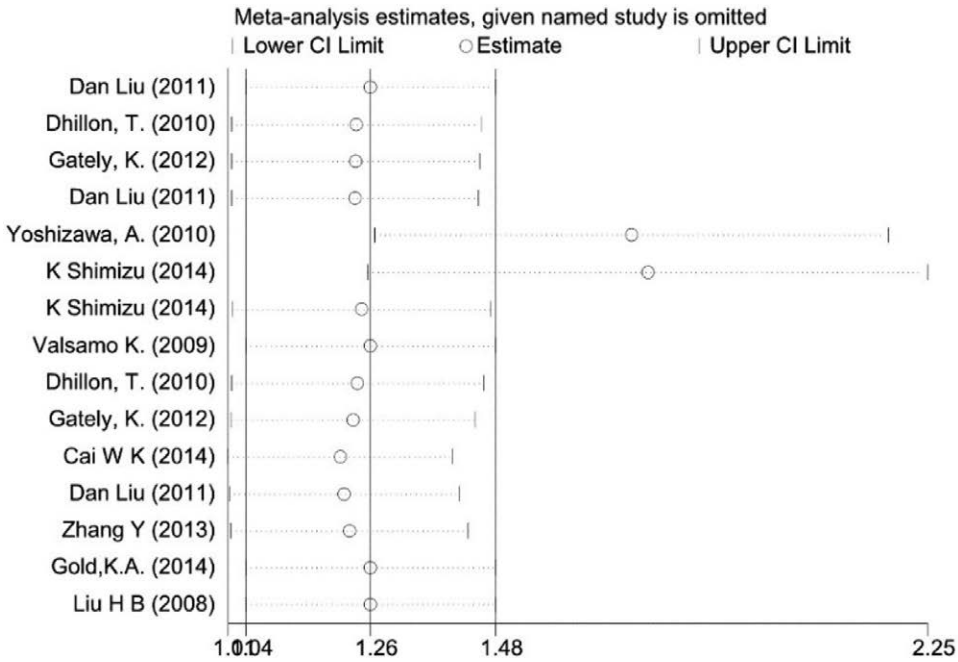


**Figure 6.** Sensitivity analysis on the prognostic value of mTOR/p-mTOR expression for OS in patients with NSCLC. CI = confidence interval, mTOR = mammalian target of rapamycin, NSCLC = non-small cell lung cancer, OS = overall survival, p-mTOR = phosphorylated mammalian target of rapamycin.

AMP-activated protein kinase/mTOR pathway works as a molecular characterization of the tumor suppressor axis, suggesting a connection between cancer and metabolism.[86] The aforementioned molecular mechanisms reveal that mTOR may activate and phosphorylate diverse stimuli and signals via several signaling pathways to govern the pathophysiology of cancer. The expression of mTOR/p-mTOR is increasingly recognized as being associated with a variety of malignancies. Aberrant activation of mTOR signal caused by genetic or metabolic disorders can significantly promote tumor growth, angiogenesis, and metastasis.[87] Additional signal components of the upstream and downstream mTOR pathways are also altered during proliferation disorders, which is associated with the poor prognosis of cancers.[88]

In recent years, several clinical studies have investigated the relationship between the positive expression of mTOR/p-mTOR and numerous prevalent malignancies, such as NSCLC. This meta-analysis collected a wide number of clinicopathological parameters, examined both mTOR and p-mTOR expression, and employed univariate and multivariate analyses. Secondly, no publication bias was identified in the study, and sensitivity analysis revealed no statistically significant differences when omitting any articles. Positive expression of mTOR/p-mTOR was related to females, more lymph node metastases, and higher CEA levels, which was partly consistent with the findings of Xin-Chen Wang et al[89] We hypothesize that the clinicopathological relevance of mTOR/p-mTOR expression may partially explain its prognostic role in NSCLC. However, more clinical studies

with larger samples are required to determine if mTOR is an observable indicator for the development of NSCLC. Moreover, while utilizing mTOR inhibitors, the combination of personalized medications can be considered after stratification according to the clinicopathological features of patients, therefore minimizing drug resistance, enhancing effectiveness, and enhancing prognosis. Further research is required to determine the precise molecular mechanism behind the relationship between mTOR and other clinicopathological parameters.

Notably, the meta-analysis revealed that the expression of mTOR/p-mTOR was related to a shorter OS in NSCLC patients. The strong connection remained statistically significant in subgroups stratified by geographic region, sample size, gender, and histological type. All of these pooled analyses indicate that mTOR/p-mTOR may be an indicator of a poor prognosis in NSCLC. If the HR is larger than 2, prognostic indicators are deemed to have a significant predictive value for a poor prognosis; however, the HR in this study is less than 2. As evidence remains limited, the validity of these findings may be compromised by very short follow-up periods and small sample sizes. In addition, the accuracy of the overall pooled results of OS based on univariate analysis may be marginally diminished by unremoved confounding variables that may influence the prognosis of NSCLC, including TNM stage, tumor invasion, differentiation, and LNM. The determination of the real involvement of mTOR and p-mTOR in NSCLC may be hindered by these potential factors. Therefore, based only on the findings of 13 retrospective observational studies, the current findings are insufficient for drawing definitive conclusions. The influence of mTOR/p-mTOR activation on the prognosis of NSCLC should be explored further in long-term studies with bigger sample numbers and more extensive follow-ups.

In addition, the pooled HR for overall survival revealed a correlation between the expression of mTOR and p-mTOR with the prognosis of NSCLC. However, when the association between mTOR/p-mTOR and survival was evaluated independently, the results indicated that the expression of mTOR/p-mTOR was not statistically significant with NSCLC patients' prognosis. This contradiction may be a result of the small number of original studies included in this meta-analysis. In addition, when stratified by geographical region, gender, and histological type, the link between mTOR/p-mTOR expression and poor prognosis was maintained in the Chinese subgroup, which included a greater number of female patients and fewer individuals with ADC. The prognostic significance of mTOR/p-mTOR expression in various malignancies has been extensively researched in the past. Xian-Fei Ding et al[90] revealed that the overexpression of p-mTOR in breast cancer was not substantially connected with the prognosis of OS and disease recurrence. In head and neck cancers, it has been suggested that mTOR pathway proteins can be employed as survival predictors for patients with head and neck cancer, given that their expression was substantially connected with poor OS and short DFS.[91] In research on gastric cancer, Hua Wang et al found that mTOR overexpression significantly predicts a bad prognosis. In contrast, the cumulative survival rate of patients with mTOR expression was considerably greater in Xiao et al[92] research than that of patients lacking mTOR expression. In addition, a study on nasopharyngeal cancer revealed that the overexpression of mTOR predicted poor overall survival and disease-free survival in patients with nasopharyngeal carcinoma.[93] Therefore, no conclusion has been made about the predictive importance of mTOR/p-mTOR in cancer.

There are several limitations in our meta-analysis. First, despite a comprehensive literature search, the number of studies on the relationship between mTOR/p-mTOR expression and prognosis was too small, and this portion of the data was also excluded because extraction of survival data from the K-M curves may produce inaccurate results,[94] so the pooled HRs may be overestimated or underestimated due to the small and incomplete raw data. Only one of the included articles examined the association between mTOR/p-mTOR expression and PFS, only two data sets were studied, and the findings of the meta-analysis were inconclusive. In addition, unknown confounding factors in the original studies may have influenced the outcomes of the pooled HRs. Secondly, in the pooled analysis of clinicopathological features, the grouping criteria of some studies were contradictory with those of other research, making their inclusion difficult. The heterogeneity of the studies included in some statistical indicators was high, but the stratified analysis was impossible to undertake due to insufficient information in the original articles. Thirdly, although all studies used IHC to detect mTOR/p-mTOR expression, the proportion of positive samples varied widely, ranging from 38.3% to 77.1%, suggesting that the level of homogeneity of included studies may be affected by the assessment criteria of staining, cutoff values, antibodies and dilutions of experimental reagents, and the level of laboratory personnel, which may be an important source of deviation. Even while no significant publishing bias was discovered, it is still possible that bias exists, given there is a general inclination to report significant positive outcomes.

## 5. Conclusions

In conclusion, our meta-analysis revealed a correlation between the positive expression of mTOR/p-mTOR and gender, lymph node metastasis, and CEA level. mTOR/p-mTOR may also be predictive of a poor outcome in NSCLC. However, numerous difficulties and limitations have not been sufficiently addressed in this meta-analysis. More high-quality research based on multivariate analysis with large sample size is required to validate and modify our existing findings.

## Author contributions

**Conceptualization:** Weiwei Qiu, Meiying Ren.
**Data curation:** Yuhua Fu, Yan Liu.
**Formal analysis:** Weiwei Qiu, Meiying Ren.
**Investigation:** Cuifeng Wang, Yuhua Fu, Yan Liu.
**Methodology:** Weiwei Qiu, Meiying Ren, Cuifeng Wang.
**Software:** Weiwei Qiu, Meiying Ren.
**Writing – original draft:** Weiwei Qiu, Yan Liu.
**Writing – review & editing:** Meiying Ren, Weiwei Qiu.

## References

[1] Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin. 2022;72:7–33.
[2] Xia C, Dong X, Li H, et al. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. Chin Med J (Engl). 2022;135:584–90.
[3] Oudkerk M, Liu S, Heuvelmans MA, et al. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. Nat Rev Clin Oncol. 2021;18:135–51.
[4] Memmott RM, Wolfe AR, Carbone DP, et al. Predictors of response, progression-free survival, and overall survival in patients with lung cancer treated with immune checkpoint inhibitors. J Thorac Oncol. 2021;16:1086–98.
[5] Passaro A, Brahmer J, Antonia S, et al. Managing resistance to immune checkpoint inhibitors in lung cancer: treatment and novel strategies. J Clin Oncol. 2022;40:598–610.
[6] Shankar B, Zhang J, Naqash AR, et al. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol. 2020;6:1952–6.
[7] Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. Mol Cancer. 2020;19:12.
[8] Heitman J, Movva NR, Hall MN. Targets for cell cycle arrest by the immunosuppressant rapamycin in yeast. Science. 1991;253:905–9.
[9] Boutouja F, Stiehm CM, Platta HW. mTOR: a cellular regulator interface in health and disease. Cells. 2019;8:18.
[10] Schmelzle T, Hall MN. TOR, a central controller of cell growth. Cell. 2000;103:253–62.

[11] Popova NV, Jücker M. The role of mTOR signaling as a therapeutic target in cancer. Int J Mol Sci. 2021;22:1743.
[12] Wu J, Zhao X, Sun Q, et al. Synergic effect of PD-1 blockade and endostar on the PI3K/AKT/mTOR-mediated autophagy and angiogenesis in Lewis lung carcinoma mouse model. Biomed Pharmacother. 2020;125:109746.
[13] Xu F, Na L, Li Y, et al. Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. Cell Biosci. 2020;10:54.
[14] Tan AC. Targeting the PI3K/Akt/mTOR pathway in non-small cell lung cancer (NSCLC). Thor Cancer. 2020;11:511–8.
[15] Mukherjee S, Mukherjee U. A comprehensive review of immunosuppression used for liver transplantation. J Transplant. 2009;2009:701464.
[16] Park H, Garrido-Laguna I, Naing A, et al. Phase I dose-escalation study of the mTOR inhibitor sirolimus and the HDAC inhibitor vorinostat in patients with advanced malignancy. Oncotarget. 2016;7:67521–31.
[17] Emons G, Kurzeder C, Schmalfeldt B, et al. Temsirolimus in women with platinum-refractory/resistant ovarian cancer or advanced/recurrent endometrial carcinoma. A phase II study of the AGO-study group (AGO-GYN8). Gynecol Oncol. 2016;140:450–6.
[18] Franz DN, Belousova E, Sparagana S, et al. Long-term use of everolimus in patients with tuberous sclerosis complex: final results from the EXIST-1 study. PLoS One. 2016;11:e0158476.
[19] Bissler JJ, Kingswood JC, Radzikowska E, et al. Everolimus for angiomyolipoma associated with tuberous sclerosis complex or sporadic lymphangioleiomyomatosis (EXIST-2): a multicentre, andomized, double-blind, placebo-controlled trial. Lancet. 2013;381:817–24.
[20] Yao JC, Fazio N, Singh S, et al.; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387:968–77.
[21] Soria JC, Shepherd FA, Douillard JY, et al. Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors. Ann Oncol. 2009;20:1674–81.
[22] Mody R, Naranjo A, Van Ryn C, et al. Irinotecan-temozolomide with temsirolimus or dinutuximab in children with refractory or relapsed neuroblastoma (COG ANBL1221): an open-label, randomised, phase 2 trial. Lancet Oncol. 2017;18:946–57.
[23] Becher OJ, Gilheeney SW, Khakoo Y, et al. A phase I study of perifosine with temsirolimus for recurrent pediatric solid tumors. Pediatr Blood Cancer. 2017;64.
[24] Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005;5:341–54.
[25] Nepstad I, Hatfield KJ, Gronningsaeter IS, et al. Effects of insulin and pathway inhibitors on the PI3K-Akt-mTOR phosphorylation profile in acute myeloid leukemia cells. Signal Transduct Target Ther. 2019;4:20.
[26] du Rusquec P, Blonz C, Frenel JS, et al. Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive HER2 negative advanced breast cancer. Ther Adv Med Oncol. 2020;12:1758835920940939.
[27] Dobashi Y, Watanabe Y, Miwa C, et al. Mammalian target of rapamycin: a central node of complex signaling cascades. Int J Clin Exp Pathol. 2011;4:476–95.
[28] Feng Z, Fan X, Jiao Y, et al. Mammalian target of rapamycin regulates expression of beta-catenin in hepatocellular carcinoma. Hum Pathol. 2011;42:659–68.
[29] Gallay N, Dos Santos C, Cuzin L, et al. The level of AKT phosphorylation on threonine 308 but not on serine 473 is associated with high-risk cytogenetics and predicts poor overall survival in acute myeloid leukaemia. Leukemia. 2009;23:1029–38.
[30] Kornblau SM, Womble M, Qiu YH, et al. Simultaneous activation of multiple signal transduction pathways confers poor prognosis in acute myelogenous leukemia. Blood. 2006;108:2358–65.
[31] Li S, Wang Z, Huang J, et al. Clinicopathological and prognostic significance of mTOR and phosphorylated mTOR expression in patients with esophageal squamous cell carcinoma: a systematic review and meta-analysis. BMC Cancer. 2016;16:877.
[32] Bose S, Chandran S, Mirocha JM, et al. The Akt pathway in human breast cancer: a tissue-array-based analysis. Mod Pathol. 2006;19:238–45.
[33] Wang H, Li J. A systematic review and meta-analysis protocol of clinical characteristics and prognostic significance of mammalian target of rapamycin for gastric cancer patients. Medicine. 2020;99:e21138.
[34] Liu M, Li L, Huang S, et al. Prognostic and therapeutic values of autophagy-related genes in triple-negative breast cancer. Recent Patents Anticancer Drug Discov. 2021;17:380–6.
[35] Zouki DN, Giannopoulou I, Alexandrou PT, et al. MTOR/4EBP1 signaling and MMR status in colorectal cancer: new correlations and arising perspectives. Pathol Res Pract. 2021;228:153655.
[36] Wang Y, Sun J, Yao N. Correlation of the AKT/mTOR signaling pathway with the clinicopathological features and prognosis of nasopharyngeal carcinoma. Eur J Histochem. 2021;65:3304.
[37] Lu Q, Wang J, Yu G, et al. Expression and clinical significance of mammalian target of rapamycin/P70 ribosomal protein S6 kinase signaling pathway in human colorectal carcinoma tissue. Oncol Lett. 2015;10:277–82.
[38] Petroulakis E, Mamane Y, Le Bacquer O, et al. mTOR signaling: implications for cancer and anticancer therapy. Br J Cancer. 2006;94:195–9.
[39] Dobashi Y, Suzuki S, Kimura M, et al. Paradigm of kinase-driven pathway downstream of epidermal growth factor receptor/Akt in human lung carcinomas. Hum Pathol. 2011;42:214–26.
[40] Dobashi Y, Suzuki S, Matsubara H, et al. Critical and diverse involvement of Akt/mammalian target of rapamycin signaling in human lung carcinomas. Cancer. 2009;115:107–18.
[41] Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell. 2006;124:471–84.
[42] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
[43] Chen M, Li Q, Chen W, et al. Diagnostic and prognostic value of Beclin 1 expression in melanoma: a meta-analysis. Melanoma Res. 2021;31:541–9.
[44] Wang BJ, Tang YD, Yu BY, et al. Expression of autophagy-related factor p62 for lung cancer diagnosis and prognosis: a systematic review and meta-analysis. Math Biosci Eng. 2019;16:6805–21.
[45] Quigley JM, Thompson JC, Halfpenny NJ, et al. Critical appraisal of nonrandomized studies – a review of recommended and commonly used tools. J Eval Clin Pract. 2019;25:44–52.
[46] Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17:2815–34.
[47] Zhang C, Chen M, Wang X. Statistical methods for quantifying between-study heterogeneity in meta-analysis with focus on rare binary events. Stat Interface. 2020;13:449–64.
[48] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
[49] Shi L, Lin L. The trim-and-fill method for publication bias: practical guidelines and recommendations based on a large database of meta-analyses. Medicine. 2019;98:e15987e15987.
[50] Kitano H, Chung JY, Ylaya K, et al. Profiling of phospho-AKT, phospho-mTOR, phospho-MAPK and EGFR in non-small cell lung cancer. J Histochem Cytochem. 2014;62:335–46.
[51] Crees ZD, Shearrow C, Lin L, et al. EGFR/c-Met and mTOR signaling are predictors of survival in non-small cell lung cancer. Ther Adv Med Oncol. 2020;12:1758835920953731.
[52] Lu J, Zang H, Zheng H, et al. Overexpression of p-Akt, p-mTOR and p-eIF4E proteins associates with metastasis and unfavorable prognosis in non-small cell lung cancer. PLoS One. 2020;15:e0227768.
[53] Liu D, Huang Y, Chen B, et al. Activation of mammalian target of rapamycin pathway confers adverse outcome in nonsmall cell lung carcinoma. Cancer. 2011;117:3763–73.
[54] Zhang Y, Ni HJ, Cheng DY. Prognostic value of phosphorylated mTOR/RPS6KB1 in non-small cell lung cancer. Asian Pac J Cancer Prev. 2013;14:3725–8.
[55] Oh MH, Lee HJ, Yoo SB, et al. Clinicopathological correlations of mTOR and pAkt expression in non-small cell lung cancer. Virchows Arch. 2012;460:601–9.
[56] 蔡文科,石云,赵青.哺乳动物雷帕霉素靶蛋白表达与早期非小细胞肺癌预后的关系[J].中华肿瘤杂志. 2014;36:120–2.
[57] Wang L, Yue W, Zhang L, et al. mTOR and PTEN expression in non-small cell lung cancer: analysis by real-time fluorescence quantitative polymerase chain reaction and immunohistochemistry. Surg Today. 2012;42:419–25.
[58] Kim HS, Kim GY, Lim SJ, et al. Expression of the mammalian target of rapamycin pathway markers in lung adenocarcinoma and squamous cell carcinoma. Pathobiology. 2012;79:84–93.
[59] Anagnostou VK, Bepler G, Syrigos KN, et al. High expression of mammalian target of rapamycin is associated with better outcome for patients with early stage lung adenocarcinoma. Clin Cancer Res. 2009;15:4157–64.
[60] Dhillon T, Mauri FA, Bellezza G, et al. Overexpression of the mammalian target of rapamycin: a novel biomarker for poor survival in resected early stage non-small cell lung cancer. J Thor Oncol. 2010;5:314–9.

[61] Gately K, Al-Alao B, Dhillon T, et al. Overexpression of the mammalian target of rapamycin (mTOR) and angioinvasion are poor prognostic factors in early stage NSCLC: a verification study. Lung Cancer. 2012;75:217–22.
[62] Shin E, Choi CM, Kim HR, et al. Immunohistochemical characterization of the mTOR pathway in stage-I non-small-cell lung carcinoma. Lung Cancer. 2015;89:13–8.
[63] 郭凯, 黄波, 王晓东. 自噬相关蛋白在肺鳞癌和腺癌组织中的表达及相关性研究. [J]. 天津医药 2014;42:536–9+626.
[64] 刘红兵, 宋勇, 吴颖. p-mTOR在I～III期非小细胞肺癌组织中的表达及其与预后的关系. 中国呼吸与危重监护杂志 2008;5:354–7+401–402.
[65] 徐云云. 自噬标记蛋白 (Beclin1、LC3、p62、mTOR)在恶性肺结节中的表达及临床意义 [40]. 西北民族大学 2021.
[66] 许浩然, 何世杰, 孙亚东, 张秀娟, 孙秀娟. 非小细胞肺癌组织PTEN、p-Akt及p-mTOR的表达及意义. [J]. 广东医学 2018;39:710–6.
[67] 阿旺旦增, 吕广超, 赵慧, 王凯忠, 王凯. STAT3, mTOR, ERK1/2磷酸化在非小细胞肺癌中的表达. [J]. 中国老年学杂志 2016;36:354–6.
[68] 陈朝晖, 徐滨, 李媛媛, 刘雨清, 李前仁, 丁洪基. 非小细胞肺癌组织中CCR7、mTOR表达变化及意义. [J]. 山东医药 2013;53:41–3.
[69] 郭志强, 钱正宇, 米小芳, 郑绘霞. PTEN和mTOR在非小细胞肺癌中的表达及意义. [J]. 山西医科大学学报 2018;49:602–5.
[70] 胡述提. mTOR及eIF4E在Ia期～IIIa期肺鳞癌组织中的表达及临床意义 [45]. [D]. 郑州大学 2010.
[71] 黄伟. mTOR信号通路在非小细胞肺癌组织的表达与预后的关系 [46]. [D]. 温州医科大学 2019.
[72] 王昕晨, 黄燕燕, 陆畅畅, et al. mTOR信号通路相关分子在肺鳞癌组织中表达的意义. [J]. 浙江医学 2020;42:1689–93+1791.
[73] 许浩然, 何世杰, 张秀义, 景卫革, 孙亚东, 王嘉. 非小细胞肺癌组织p-mTOR、p70s6k、PTEN蛋白的表达变化及其意义. [J]. 山东医药 2018;58:46–9.
[74] 袁超. CHI3L1和PI3K/AKT/mTOR信号通路在非小细胞肺癌细胞的表达及其意义 [49]. [D]. 泰山医学院 2017.
[75] 张秀义, 许浩然, 景卫革, 孙亚东, 孙秀娟, 何士杰. 非小细胞肺癌中p-mTOR、Beclin1及LC3蛋白的表达及意义. [J]. 广东医学 2019;40:895–901.
[76] 张晋源. p62和mTOR在非小细胞肺癌中的表达及临床意义. [J]. 基层医学论坛 2020;24:155–7.
[77] Yoshizawa A, Fukuoka J, Shimizu S, et al. Overexpression of phospho-eIF4E is associated with survival through AKT pathway in non-small cell lung cancer. Clin Cancer Res. 2010;16:240–8.
[78] Shimizu K, Kaira K, Tomizawa Y, et al. ASC amino-acid transporter 2 (ASCT2) as a novel prognostic marker in non-small cell lung cancer. Br J Cancer. 2014;110:2030–9.
[79] Gold KA, Kim ES, Liu DD, et al. Prediction of survival in resected non-small cell lung cancer using a protein expression-based risk model: implications for personalized chemoprevention and therapy. Clin Cancer Res. 2014;20:1946–54.
[80] Han J, Hou W, Goldstein LA, et al. A Complex between Atg7 and Caspase-9: a novel mechanism of cross-regulation between autophagy and apoptosis. J Biol Chem. 2014;289:6485–97.
[81] Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. J Clin Invest. 2015;125:25–32.
[82] Loewith R, Jacinto E, Wullschleger S, et al. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol Cell. 2002;10:457–68.
[83] Liu G, Pei F, Yang F, et al. Role of autophagy and apoptosis in non-small-cell lung cancer. Int J Mol Sci. 2017;18:367.
[84] Sarbassov DD, Ali SM, Sengupta S, et al. Prolonged rapamycin treatment inhibits mTORC2 assembly and Akt/PKB. Mol Cell. 2006;22:159–68.
[85] Ersahin T, Tuncbag N, Cetin-Atalay R. The PI3K/AKT/mTOR interactive pathway. Mol Biosyst. 2015;11:1946–54.
[86] Green AS, Chapuis N, Lacombe C, et al. LKB1/AMPK/mTOR signaling pathway in hematological malignancies: from metabolism to cancer cell biology. Cell Cycle. 2011;10:2115–20.
[87] Ali ES, Mitra K, Akter S, et al. Recent advances and limitations of mTOR inhibitors in the treatment of cancer. Cancer Cell Int. 2022;22:284.
[88] Hay N, Sonenberg N. Upstream and downstream of mTOR. Genes Dev. 2004;18:1926–45.
[89] 王昕晨, 黄燕燕, 陆畅畅, et al. mTOR信号通路相关分子在肺鳞癌组织中表达的意义. 浙江医学 2020;42:1689–93+1791.
[90] Ding XF, Li LF, Zhou XL, et al. P-mTOR expression and implication in breast carcinoma: a systematic review and meta-analysis. PLoS One. 2017;12:e0170302.
[91] Marques AE, Elias ST, Porporatti AL, et al. mTOR pathway protein immunoexpression as a prognostic factor for survival in head and neck cancer patients: a systematic review and meta-analysis. J Oral Pathol Med. 2016;45:319–28.
[92] Xiao L, Wang YC, Li WS, et al. The role of mTOR and phospho-p70S6K in pathogenesis and progression of gastric carcinomas: an immunohistochemical study on tissue microarray. J Exp Clin Cancer Res. 2009;28:152.
[93] Ooft ML, Braunius WW, Heus P, et al. Prognostic significance of the EGFR pathway in nasopharyngeal carcinoma: a systematic review and meta-analysis. Biomark Med. 2015;9:997–1010.
[94] Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.