**Review paper**

**CD117 expression is correlated with poor survival of patients and progression of lung carcinoma: a meta-analysis with a panel of 2645 patients**

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The aim of this research was to investigate the clinical role and prognostic value of CD117 expression assessed immunohistochemically in lung carcinoma through a comprehensive meta-analysis in which 27 publications were acquired and 2645 patients were ultimately analysed. Statistical analysis and corresponding plots were performed using STATA version 12.0. Publication bias was assessed by Begg’s funnel plots and Egger’s test. Pooled HR and its 95% CI (HR = 1.53, 95% CI: 1.13-2.07, p = 0.007) for overall survival of patients indicated a poor prognostic value for CD117 expression in lung carcinoma, which was accompanied by heterogeneity and publication bias. In the subgroup analysis, there was strong evidence that could support an association between CD117 expression and poor prognosis in NSCLC patients (HR = 2.03, 95% CI: 1.41-2.90, p < 0.001; heterogeneity: I² = 41.9%, χ² = 15.49, p = 0.078). Multivariate analysis also revealed consistent results in high-quality studies with reported HRs (HR = 2.16, 95% CI: 1.67-2.79, p < 0.001), and Asian patients (HR = 2.12, 95% CI: 1.45-3.10, p < 0.001). The correlations between CD117 expression and age, clinical stage, TNM stage, lymph node metastasis, or histology were not statistically significant. In conclusion, CD117 expression might be a potential marker for predicting poor prognosis, faster tumour growth, and early lymph node metastasis in NSCLC.

Key words: CD117; lung carcinoma; prognosis; clinicopathological parameter; overall survival.

**Introduction**

Lung carcinoma is the leading cause of cancer-related death in modern times [1, 2]. Recent research suggests that the high morbidity of lung cancer results from air pollution, tobacco consumption, and hereditary factors [3, 4, 5, 6, 7]. According to morphological and immunological characteristics, lung carcinoma is divided clinicopathologically into two types: small cell lung carcinoma (SCLC) and non-small cell lung carcinoma (NSCLC). The most common histological subtypes of NSCLC include adenocarcinoma, squamous cell carcinoma, and large cell neuroendocrine carcinoma [8, 9, 10, 11, 12, 13].

Distinguishing the subtypes of lung carcinoma is crucial for determining the best choice of therapeutic strategies [14]. Although a lot of research has been done for the diagnosis and treatment of lung cancer over the last decade, the death rate of patients with lung cancer remains high. Patients with advanced stage disease are prone to higher morbidity when compared with those at early stages. Unfortunately,
most patients have already progressed to an advanced stage when their diagnosis is made, having missed the optimal treatment timing [15, 16, 17, 18, 19]. This situation emphasises the importance and value of searching for biomarkers that are conducive to predict the prognosis of lung carcinoma.

One of potential markers is CD117, a transmembrane protein that receives the message from a stem-cell factor (SCF). CD117 protein is encoded by the proto-oncogene c-kit and belongs to the tyrosine kinase receptor family [20, 21]. Recent studies have suggested that CD117 protein is aberrantly regulated in malignancies of the salivary gland [22], retinoblastoma [23], endometrium [24], papillary thyroid [25], and breast [26]. CD117 is also an authoritative protein in the diagnosis of gastrointestinal stromal tumours (GIST), where it generally shows positive expression [27]. Several studies that concentrated on CD117 protein in lung cancer showed that CD117 protein expression had no effect on progression and prognosis of lung carcinoma [20, 28], whereas other studies have suggested that CD117 protein could be used as a biomarker for lung carcinoma [29, 30, 31]. The purpose of the present comprehensive meta-analysis was to clarify the relationship between CD117 protein and lung carcinoma.

### Material and methods

#### Search strategy

A systematic search was conducted in PubMed, Cochrane Central Register of Controlled Trials, EMBASE, Science Direct, ISI Web of Science, and Wiley Online Library databases. Literature published in Chinese was searched in CNKI, Chongqing VIP, China Biology Medicine disc, and Wanfang databases. The search string consisted of: (tumor or tumour or cancer or carcinoma or neoplasia or neoplasm or malignant*) and (lung or pulmonary or pneumocyte or alveoli or respiration or respiratory or bronchi or bronchioles) and (CD117 or c-kit or kit). The last retrieval was made on Jun 1, 2018.

#### Selection of studies

Studies included the reported detection of CD117 expression in lung carcinoma tissue and analysis of the relationship between CD117 expression and clinicopathological parameters or survival time of the patients. No restriction was placed on the CD117 expression testing method. Studies were excluded if they failed to offer available data or full text or if they were published as reviews or case reports. Language was restricted to English and Chinese. If repeated cohorts were found, studies with more detailed information would be selected.

#### Extraction of data

The data extracted from each article were as follows: name of first author, publication year, regions of patients, sample size, cancer type, testing method, cut-off value, and clinicopathological parameters (i.e. gender, age, and TNM stage). Hazard ratios (HRs) and 95% confidence intervals (CIs) were extracted directly if available in the studies; otherwise, the available numerical data or Kaplan-Meier curves were used to calculate HRs and 95% CIs according to Parmar [32] and Tierney [33].

#### Quality assessment

The Newcastle-Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp) was used to evaluate the quality of the included studies. Selection, comparability of cohorts, and assessment of outcome were assessed in cohort studies. Selection of cases and controls, comparability of cases and controls, and ascertainment of exposure were assessed in case-control studies. The score ranged from zero to nine. This process was performed by four researchers independently (Yi-nan Guo, Mei Wu, Shuang Ren, and Lu Liang), and conflicting opinions were resolved through further discussion with other researchers (Wei-jia Mo and Gang Chen).

#### Statistical analysis

Odds ratios (ORs) and their 95% CIs were calculated to analyse the prognostic value and the relationship between CD117 expression and clinicopathological parameters. Heterogeneity among studies was assessed by inconsistency ($I^2$) and $\chi^2$ tests [34, 35]. Heterogeneity was considered not statistically significant when $p \geq 0.05$ and $I^2 \leq 50\%$. Data were pooled using a fixed-effects model when heterogeneity was not significant; otherwise, a random-effects model was used. Sensitivity and subgroup analyses were conducted for ascertaining the possible source of heterogeneity. Publication bias was tested using Begg’s funnel plots [36] and Egger’s test [37]. The trim and fill method [38] was applied as a remedy measure when publication bias was found. Stata 12.0 was used to calculate the necessary data and pooled estimate values, as well as to draw forest plots. All tests were conducted as two-tailed, and a $p$ value less than 0.05 was considered statistically significant.

#### Results

#### Description of studies

Using the keywords mentioned above, 3476 papers (3074 in English, 402 in Chinese) were retrieved (Fig. 1). After scrutinising the titles and abstracts...
and then excluding duplications, we chose 46 papers (40 in English, 6 in Chinese) that preliminarily reported the expression of CD117 protein in lung cancer specimens. Five studies with unavailable full texts, 13 studies with insufficient data, and one study with a dual cohort were excluded at the full-text reviewing step. Ultimately, 27 papers were involved in the meta-analysis. The publication period of the included literature fell between 2002 and 2017. Among these papers, 22 were published in English and five in Chinese. Twelve out of 27 studies were from Europe (five from Germany, four from Italy, two from Spain, and one from Turkey), 11 studies were published in Asia (seven, three, and one were from China, Japan, and Korea, respectively), and four studies were from North America (three from the USA and one from Canada).

Lung cancer patients (n = 2645), ranging in number from 13 to 204 patients for each study, were included in this meta-analysis, with 969 NSCLC patients (ranging from 33 to 147) from 10 studies and 1506 SCLC patients (ranging from 13 to 204) from 17 studies; two studies researched both NSCLC and SCLC [39, 40]. In addition, 170 neuroendocrine carcinoma (NEC) patients from two studies were also included. Immunohistochemistry (IHC) was the only method used to detect the expression of CD117 protein in all the included studies, with different cut-off values. A GIST was used as a positive control in eight studies [39, 4, 41, 42, 43, 44, 45, 46]. The effect of CD117 expression on the prognosis of patients was analysed in 27 studies, and the overall survival (OS) was analysed in all 27 studies, whereas disease-free survival was also analysed in three articles. The HRs and their 95% CIs were extracted directly from seven studies [28, 30, 31, 47, 48, 49], and all data were reported with multivariate analysis. In the remaining studies without reported HRs, the available data and reported Kaplan-Meier curves were used to estimate HRs.

Seven studies showed an association between CD117 expression and poor survival of lung cancer patients [28, 30, 44, 46, 49, 50], whereas three studies [29, 42, 51] reported a relationship between CD117 expression and longer survival time of lung cancer patients. The other studies indicated no relationship between CD117 expression and the survival time of patients. The score of quality assessment ranged from six to eight points in 27 included studies, while the other three papers scored five points. The basic information of the included literature is shown in Table I.

![Flow chart of literature search and study selection](image)
| First Author | Year | Country | Cancer Type | Cases | Pathology Stage | Adjuvant Therapy Ratio | Method | Cut-off Value | Survival Data Type | Follow-up Time (Month) | HR ESTIMATION | HR 95% CI | Antibody | Quality Score |
|--------------|------|---------|-------------|-------|-----------------|------------------------|--------|---------------|-------------------|----------------------|---------------|-----------|----------|---------------|
| Sakabe       | 2017 | Japan   | NSCLC       | 99    | I-III           | I-IV                   | IHC    | 0%            | OS                | 2-104                | 4.672         | 2.26-9.638 | ab32363; clone YR145, Abcam, USA | 7            |
| Xiao         | 2014 | China   | NSCLC       | 146   | I-IV            | I-IV                   | IHC    | 5%            | OS                | 4-32                 | 1.49          | 0.88-2.50 | Y703, Dako, Cytomation, Glostrup, Denmark | 7            |
| Gottschling  | 2013 | Germany | NSCLC       | 100   | I-III           | I-IV                   | IHC    | 10%           | OS                | 53.3 (median)       | 5.2           | 1.1-23.9  | Dako      | 7             |
| Lu           | 2012 | China   | SCLC        | 34&   | I-IV            | NR                     | IHC    | 5%            | OS                | 22-125               | 1.16          | 0.37-3.85 | Dako, Glostrup, Denmark | 6             |
| Terada       | 2012 | Japan   | SCLC        | 54    | I-IV            | NR                     | IHC    | 10%           | OS                | 3-27                 | 0.90          | 0.47-1.71 | Dako, Glostrup, Denmark | 8             |
| Erler        | 2011 | USA     | SCLC        | 68    | NR              | NR                     | IHC    | 0%            | OS                | 1-105                | 1.50          | 0.93-2.40 | Cell Marque Corporation, Rocklin, CA | 5             |
| Lopez-Martín| 2007 | Spain   | SCLC        | 204   | I-IV            | 100%                   | IHC    | 0%            | OS                | 0.4-108              | 0.88          | 0.71-1.09 | Dako, Glostrup, Denmark | 8             |
| Yaren        | 2006 | Turkey  | NSCLC       | 69    | I-IV            | 100%                   | IHC    | 4 points*     | OS                | 3-103                | 3.43          | 0.50-23.67 | Dako, Glostrup, Denmark | 5             |
| Camps        | 2005 | Spain   | SCLC        | 70    | I-IV            | 0%                     | IHC    | 0%            | OS                | 0.3-37               | 1.45          | 0.77-2.73 | Dako, Cytomation, Denmark | 7             |
| Micke (1)    | 2004 | Germany | LUAD        | 95    | I-IV            | 24%                    | IHC    | 10%           | OS                | 2-4                  | 1.78          | 1.00-3.16 | Dako, Hamburg, Germany | 7             |
Table I. Characteristics of the studies included in the meta-analysis (cont.)

| FIRST AUTHOR | YEAR | COUNTRY | CANCER TYPE | CASES | PATHOLOGY STAGE | ADJUVANT THERAPY RATIO | METHOD | CUT-OFF VALUE | SURVIVAL DATA TYPE | FOLLOW-UP TIME (MONTH) | HR | 95% CI | ANTIBODY | QUALITY SCORE |
|--------------|------|---------|-------------|-------|-----------------|------------------------|--------|---------------|---------------------|-----------------------|----|--------|-----------|---------------|
| Pelosi (1)   | 2004 | Italy   | LCNEC       | 39    | I-III           | 100%                   | IHC    | 5%            | OS                  | 2-136                 | 2.76| 0.91-8.44| Dako, Cyromation, Glostrup, Denmark | 8  |
| Boldrini     | 2004 | Italy   | SCLC        | 55    | I-III           | 0%                     | IHC    | 30%           | NR                  | NR                   | NR | NR     | Dako, NCL-CD117 clone | 7  |
| Rohr         | 2004 | Germany | SCLC        | 203   | I-IV            | 0%                     | IHC    | 0%            | OS                  | 1-83                  | 0.48| 0.37-0.64| A4502, Dako, Hamburg, Germany | 7  |
| Yoo          | 2004 | Korea   | NSCLC       | 147   | I-III           | 0%                     | IHC    | 30%           | OS                  | 0.3-37                | 1.30| 0.88-1.93| Santa Cruz Biotechnology | 8  |
| Casali       | 2004 | Italy   | LCNEC       | 33    | I-IIIA          | Some*                   | IHC    | 50%           | OS                  | 2-118                 | 5.04| 0.93-27.3| clone DAK-A3; Dako, Glostrup, Denmark | 6  |
| Blackhall    | 2003 | Canada  | SCLC        | 41    | NR              | NR                     | IHC    | 35%           | OS                  | Reported (MV)         | 1.1 | 0.5-2.3| Dako Laboratories | 7  |
| Potti        | 2002 | USA     | SCLC        | 193   | III-IV          | 100%                   | IHC    | 10%           | OS                  | 3-71                  | 0.66| 0.48-0.90| A4502, IMPATH, CA, USA | 8  |
| Araki        | 2003 | Japan   | LCNEC       | 40    | I-IV            | 29.9%                  | IHC    | 10%           | OS                  | 8-75                  | 0.62| 0.11-3.63| Dako, Glostrup, Denmark | 7  |
| Naeem        | 2002 | USA     | SCLC        | 30    | I-IV            | 13.3%                  | IHC    | 50%           | OS                  | 1-81                  | 2.43| 0.65-9.26| A4502; Dako, Carpenteria, CA | 6  |
| Micke (2)    | 2003 | Germany | SCLC        | 102   | I-IV            | 88%                    | IHC    | 10%           | OS                  | Reported (MV)         | 2  | 1.17-3.41| Dako, Hamburg, Germany | 8  |
Table I. Characteristics of the studies included in the meta-analysis (cont.)

| First Author | Year | Country | Cancer Type | Cases | Pathology Stage | Adjuvant Therapy Ratio | Method | Cut-off Value | Survival Data Type | Follow-up Time (Month) | HR (95% CI) | Antibody | Quality Score |
|--------------|------|---------|-------------|-------|----------------|------------------------|--------|---------------|---------------------|------------------------|-------------|----------|---------------|
| Pelosi (2)   | 2004 | Italy   | LUAD        | 88    | I              | 0%                     | IHC    | 5%            | OS                  | 2-159                  | Reported (MV) | 1.7       | 0.6-4.6       | 8            |
|              |      |         | LUSC        | 113   | I              | 0%                     | IHC    | 5%            | DFS                 |                        | 1.5         | 0.6-3.6   |               |
| Dong         | 2010 | China   | LCNEC       | 80    | I-III          | NR                     | IHC    | 5%            | OS                  |                         | NR          | NR        | NR            | NR           |
| Han          | 2006 | China   | SCLC        | 65    | NR             | 0%                     | IHC    | 5%            | OS                  | 1.4-176                 | 4.13        | 2.62-6.51 | Santa Cruz Biotechnology |
| Zhao         | 2005 | China   | LCNEC       | 90    | I-IV           | NR                     | IHC    | 10%           | OS                  | 0-111                  | 2.80        | 1.52-5.16 | Zymed, USA    |
| Sun          | 2006 | China   | SCLC        | 100   | I-III          | NR                     | IHC    | 0%            | OS                  | 1-77                   | 2.95        | 1.55-5.63 | Gentech GA450202 |
| Jiang        | 2004 | China   | SCLC        | 52    | I-IV           | NR                     | IHC    | 10%           | OS                  |                         |             |           | Dako          | 6            |

NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer; LCNEC – large cell neuroendocrine of the lung; NEC – neuroendocrine carcinoma; AD – adenocarcinoma; SCC – squamous cell carcinoma; NR – not reported; IHC – immunohistochemistry; OS – overall survival; DFS – disease-free survival; HR – hazard ratio; SC – survival curve; UV – univariate; MV – multivariate; CI – confidence interval.

* 23 patients were followed up and included in survival analysis.
* Reported by neither specific number nor percentage.
* Score was comprehensively evaluated by distribution of cytoplasmic stain and intensity of staining.
Prognostic role of CD117 expression in lung carcinoma

The relationship between CD117 expression and the overall survival (OS) of patients of lung cancer was analysed. In a panel of 2332 patients from 24 studies, the HRs obtained from multivariate analysis in seven studies and univariate analysis in 17 studies were included to pool the estimate value with the random effects model. A statistically significant poor effect of CD117 expression was observed on the OS (HR = 1.53, 95% CI: 1.13-2.07, p = 0.007), as shown in Fig. 2. Heterogeneity among the studies was revealed by the Cochrane Q test ($\chi^2 = 144.58$, p = 0.015), and the inconsistency was quantified ($I^2 = 83.4\%$). Publication bias was detected by Begg’s funnel plot (Fig. 3A) and Egger’s test (p = 0.003). The results were corrected by a trim and fill method [38], and Begg’s funnel plot became symmetrical after correction (Fig. 3B). The adjusted HR was changed to 0.424, and the corresponding 95% CI was 0.118 to 0.730.

Subgroup analysis

Sensitivity analysis was performed to elucidate whether any single study was responsible for the observed heterogeneity. No individual study contributed predominantly to heterogeneity according to the sensitivity analysis. Considering that multiple factors might lead to heterogeneity, subgroup analysis was conducted based on lung carcinoma pathology type, the region of patients, language, variable type, and cut-off value. The results of this subgroup analysis are shown in Table II.

As shown in Fig. 4, 969 NSCLC patients from 10 studies and 1506 SCLC patients from 17 studies were analysed. In the NSCLC subgroup, CD117 expression had a negative effect on the OS of patients (HR = 2.03, 95% CI: 1.41-2.90, p < 0.001), whereas CD117 expression had no prognostic value in patients in the SCLC group (HR = 1.15, 95% CI: 0.82-1.61, p = 0.406). Heterogeneity was statistically significant in the SCLC group (heterogeneity: $I^2 = 61.1\%$, p < 0.001) but not in the NSCLC group.

![Fig. 2. Forest plot of the hazard ratio reflecting the relationship between CD117 expression and overall survival of patients with lung carcinoma. HR > 1 and corresponding 95% confidence interval was not covered; 1 implied poor prognosis in the CD117 positive group](image-url)
Table II. Subgroup analyses for CD117 impact on overall survival of patients with lung cancer

| Subgroup                  | Number of studies | Pooled Value | Model | Heterogeneity |
|---------------------------|-------------------|--------------|-------|---------------|
|                           |                   | HR (95% CI)  | p     | \(\chi^2\) I^2 p |
| NSCLC                     | 10                | 2.03 (1.41-2.90) | < 0.001 | Fixed | 15.49 41.9 0.078 |
| Region                    |                   |              |       |               |
| Europe                    | 12                | 1.30 (0.87-1.93) | 0.200 | Random | 76.62 83.0 < 0.001 |
| Asia                      | 11                | 2.12 (1.45-3.10) | < 0.001 | Random | 33.52 70.2 0.001 |
| North America             | 4                 | 1.12 (0.64-1.96) | 0.702 | Random | 10.62 71.7 0.014 |
| Survival analysis         |                   |              |       |               |
| Multivariate              | 7                 | 2.16 (1.67-2.79) | < 0.001 | Fixed | 12.82 29.8 0.171 |
| Univariate                | 19                | 1.32 (0.93-1.86) | 0.116 | Random | 143.92 87.5 < 0.001 |
| Cut-off                   |                   |              |       |               |
| > 5%                      | 13                | 1.76 (1.15-2.68) | 0.009 | Random | 60.69 80.2 < 0.001 |
| \(\leq 5\%\)              | 11                | 1.40 (0.93-2.09) | 0.104 | Random | 108.81 88.1 < 0.001 |
| > 10%                     | 4                 | 1.38 (0.99-1.92) | 0.057 | Random | 3.38 11.3 0.336 |
| \(\leq 10\%\)             | 24                | 1.53 (1.10-2.12) | 0.011 | Random | 185.06 87.6 < 0.001 |

The results obtained using the random effects model showed a satisfactory effect of CD117 expression on prognosis in Asian patients (HR = 2.12, 95% CI: 1.45-3.10, p < 0.001; heterogeneity: \(c^2 = 33.52, p = 0.001, I^2 = 70.2\%\)), but no relationship was found for Europeans (HR = 1.30, 95% CI: 0.87-1.93, p = 0.200; heterogeneity: \(c^2 = 76.62, p < 0.001, I^2 = 83.0\%\)) or North Americans (HR = 1.12, 95% CI: 0.64-1.96, p = 0.702; heterogeneity: \(c^2 = 10.62, p = 0.014, I^2 = 71.7\%\)), and heterogeneity was evident in all three subgroups.

In subgroups based on analysis type (univariate or multivariate), the studies published in Chinese (HR = 3.43, 95% CI: 2.49-4.71, p < 0.001; heterogeneity: \(c^2 = 1.27, p = 0.529, I^2 = 0\%\)) and the HR determined by multivariate analysis (HR = 2.16, 95% CI: 1.67-2.79, p < 0.000; heterogeneity: \(c^2 = 12.82, p = 0.171, I^2 = 29.8\%\)) gave results that agreed with the general conclusion without significant heterogeneity. Literature evaluated by univariate analysis (HR = 1.32, 95% CI: 0.93-1.86, p = 0.116; heterogeneity: \(c^2 = 143.92, p = 0.000, I^2 = 87.5\%\)) showed that CD117 protein had no obvious effect on patient survival time.
CD117 and prognosis in lung carcinoma patients

Fig. 4. Forest plot of the hazard ratio reflecting the relationship between CD117 expression and overall survival of patients with non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). HR > 1 and the corresponding 95% confidence interval were not covered; 1 implied poor prognosis in the CD117 positive group.

For the subgroup analysis based on different cut-off values, the studies were grouped twice with a cut-off of 5% or 10%. The group with a cut-off point > 5% (HR = 1.76, 95% CI: 1.15-2.68) predicted similar results to the general population, whereas other groups with other cut-off values showed negative results. Nevertheless, heterogeneity still existed except for the group with a cut-off value > 10%.

The clinical value of CD117 expression in lung carcinoma was also investigated in the current meta-analysis. As shown in Table III, CD117 expression was associated with a larger size of tumour (OR = 2.01, 95% CI: 1.07-3.79, p = 0.030), gender (OR = 0.76, 95% CI: 0.59-0.98, p = 0.037), and lymph node metastasis (OR = 0.55, 95% CI: 0.31-0.96, p = 0.037). The association between CD117 expression and other features was found to be insignificant, such as: age (OR = 0.88, 95% CI: 0.67-1.16, p = 0.371), clinical stage (OR = 0.93, 95% CI: 0.68-1.27, p = 0.638), T stage (OR = 1.04, 95% CI: 0.52-2.10, p = 0.902), N stage (OR = 0.76, 95% CI: 0.49-1.19, p = 0.229), M stage (OR = 1.05, 95% CI: 0.66-1.68, p = 0.836), and histology (OR = 1.05, 95% CI: 0.67-1.66, p = 0.819; Figs. 7, 8).

Fig. 5. Begg’s funnel plot for visual detection of potential publication bias of studies included in the NSCLC group.
Fig. 6. Begg’s funnel plot for visual detection of potential publication bias of studies included in the small cell lung cancer (SCLC) group. A) Before trim and fill method used. B) After correction by a trim and fill method.

Table III. The relationship between CD117 expression and clinicopathological parameters

| Clinopathological features | Number of studies | Number of cases | Pooled value OR (95%CI) | Model | Heterogeneity | χ² | I² | p |
|----------------------------|------------------|----------------|-------------------------|-------|---------------|----|----|---|
| Gender                     | 16               | 1525           | 0.76 (0.59-0.98)        | 0.037 | Fixed         | 16.80 | 0.0% | 0.537 |
| Age                        | 11               | 1031           | 0.88 (0.67-1.16)        | 0.371 | Fixed         | 7.03  | 0.0% | 0.723 |
| Stage                      | 9                | 836            | 0.99 (0.71-1.38)        | 0.942 | Fixed         | 13.91 | 28.1% | 0.177 |
| T stage                    | 8                | 750            | 1.04 (0.50-2.16)        | 0.902 | Random        | 24.36 | 71.3% | 0.001 |
| N stage                    | 6                | 651            | 0.76 (0.49-1.19)        | 0.229 | Fixed         | 2.18  | 0.0% | 0.904 |
| M stage                    | 3                | 296            | 1.05 (0.66-1.68)        | 0.836 | Fixed         | 1.25  | 0%   | 0.535 |
| Lymphatic Metastasis       | 4                | 318            | 0.55 (0.31-0.96)        | 0.037 | Fixed         | 6.65  | 38.0% | 0.168 |
| Tumour size                | 6                | 532            | 2.01 (1.07-3.79)        | 0.030 | Random        | 13.81 | 63.8% | 0.017 |
| Histology                  | 4                | 461            | 1.05 (0.67-1.66)        | 0.819 | Fixed         | 1.36  | 0.0% | 0.714 |

Fig. 7. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) Gender; B) Age; C) Stage; D) T stage.
Fig. 7. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) Gender; B) Age; C) Stage; D) T stage (cont.)
Fig. 8. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) N stage; B) M stage; C) Lymph node metastasis; D) Tumour size; E) Histology
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Fig. 8. Forest plot of the odds ratio reflecting the relationship between CD117 expression and the clinicopathological parameters of patients. A) N stage; B) M stage; C) Lymph node metastasis; D) Tumour size; E) Histology (cont.)

Discussion

The value of CD117 expression in lung carcinoma is a matter of debate because some studies have identified CD117 expression as a prognostic marker for undesirable outcome while others have suggested that CD117 expression is a prognostic marker for good patient outcome. Therefore, a pooled analysis of data from these studies was of great importance.

A previous meta-analysis of CD117 expression in lung carcinoma was published as a part of the analysis conducted by Zhao et al. [52]. When compared to their eight included studies on lung carcinoma, our meta-analysis had a larger sample size. In addition, the relationship between CD117 expression and clinicopathological features was also analysed in the current meta-analysis. The results from Zhao et al. implied that CD117 expression had no relationship with the OS or disease-free survival (DFS) of patients with lung carcinoma. However, the subgroup analysis based on cancer type showed a significant correlation between CD117 expression and the OS of NSCLC patients [52]. The same conclusion was made in a multivariate analysis of eight Asian groups in a paper published in Chinese. Our meta-analysis also showed that a larger tumour size was accompanied by a high CD117 expression, and this finding was supported by the meta-analysis by Yan et al. [53], who found that mutation of CD117 protein was more frequently-seen in larger tumours than in smaller ones in GISTs. They suggested that CD117 might be a promoter of tumour growth in lung carcinoma and GISTs.

The finding that CD117/c-kit, a member of the type III tyrosine kinase receptor family [54], is aber-
rantly expressed in various malignancies [20, 55, 56], aroused tremendous interest in investigating its effect on the progression and prognosis of cancer. GISTs are the most authoritative cancer with known CD117 upregulation, and studies have suggested that the up-regulation or mutation of c-kit is correlated with the prognosis and progression of GISTs [57, 58, 59, 60, 61]. For example, Ma et al. [57] reported that CD117 played an oncogenic role in GISTs, based on the finding that CD117 protein was co-expressed with Ki-67 and negatively correlated with apoptotic protease-activating-1 (APAF-1) in GIST tissues. Based on results from an in vitro study, Nakahara et al. [62] suggested that c-kit mutation could promote self-activation and proliferation of GIST cells because c-kit was a membrane receptor that regulated the proliferation and survival of cells. It has been reported in the literature that more than 70% of cases of SCLC and LCNEC express the c-Kit receptor [20, 31, 63], while it is rare in NSCLC [28]. Simultaneously, CD117 overexpression in high-grade tumours was observed in SCLC and LCNEC [40]. In other words, CD117 expression is common in more aggressive and fast-growing tumours. However, the Information about histological grade of lung carcinoma included is too small, so we cannot perform statistical analysis. More research on CD117 expression in lung carcinoma is needed.

Some studies have suggested that c-kit mutation in GISTs could stimulate the resistance to chemotherapy [64, 65, 66, 67]. Lu et al. found that no mutation in c-kit exons 9 and 11 was detected in the 36 included cases [68]. In Boldrini’s study, 60 SCLC samples were tested, about 40% of which expressed c-kit, two patients had mutations in exon 9, and three patients had mutations in exon 11. The low mutation rate of c-kit gene may be one of the reasons that the expression of CD117 protein is not strongly correlated with the activation mutation in SCLC [69]. CD117 promoted the development of prostate cancer through the JAK2/STAT1 signal pathway [70] and the ERK pathway, and induced the proliferation and metastatic activity of colorectal cancer cells [71]. In a study of lung maintenance and repair, Liu et al. [72] found that CD117-positive cells participated in vascular endothelial repair rather than acting on lung epithelial cells.

Several studies have focused on the mechanism of CD117 expression in lung carcinoma. However, CD117 expression had a negative effect on the OS of lung carcinoma patients, possibly due to its contribution to chemo-resistance [73, 74]. In the subgroup analysis of lymph node metastasis, only one case of NSCLC and LCNEC, and three cases of SCLC were included. Moreover, the correlation between lymph node metastasis and CD117 expression is mainly reflected in SCLC [39, 75], which may be biologically relevant to the clinical behaviour of SCLC. The small sample size may be an important reason for publica-

tion bias. In the subgroup analysis of gender, we found that the positive rate of CD117 expression in male patients was higher than in female patients. Xiao et al. [20] proposed in their study that the expression of CD117 is related to smoking, and the global smoking rate in men is higher than in women, which may be one of the reasons why there are more men in CD117 protein-expressed patients. Unfortunately, due to too few data on smoking to be statistically analysed, more literature needs to be included in the future.

The pooled HR in the present meta-analysis, based on the data from all the included studies, was accompanied by conspicuous heterogeneity. The sensitivity analysis results indicate that the heterogeneity did not arise predominantly from any individual study. Stratified analysis shows that studies with a focus on NSCLC revealed consistent conclusions whereby a high level of CD117 expression was associated with a shorter patient survival time. Studies that used multivariate analysis also confirmed these results. Thus, the heterogeneity mainly came from the different types of lung carcinoma from all the included studies.

This meta-analysis had some limitations. Because of the language capabilities of the authors, only papers published in Chinese and English were included. The scale of included studies in our meta-analysis was not sufficiently large to illustrate the role of CD117 protein in lung carcinoma. Some of the included studies also had a small sample size, which could have led to bias. The use of estimated HRs and their 95% CIs from studies that provided available data or Kaplan-Meier survival curves reduced the reliability of the results. These limitations, together with other factors, like the standard of TNM stage, diagnosis guidelines from different periods, and positive result bias, caused publication bias in this analysis.

Conclusions

The current analysis shows that CD117 expression is significantly associated with poor prognosis in lung carcinoma and especially in NSCLC. In particular, evidence from studies that performed multivariate analysis confirmed the value of CD117 expression as a marker for the prognosis of lung carcinoma. The analysis of the relationship between CD117 expression and clinicopathological features revealed an association between CD117 expression and tumour growth, patient gender, and lymph node metastasis. Considering the limitations of the present meta-analysis, larger scale and high-quality studies of the influence of CD117 expression on lung carcinoma are needed to provide further confirmation of the role of CD117 expression in lung carci

The authors declare no conflicts of interest.
References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68:7-30.

2. Tan Q, Cui J, Huang J, et al. Genomic Alteration During Metastasis of Lung Adenocarcinoma. Cell Physiol Biochem 2016; 38: 469-486.

3. Grellier L, Cortot AB, Viguier J, et al. Perception of Lung Cancer Risk: Impact of Smoking Status and Nicotine Dependence. Curr Oncol Rep 2018; 20 (Suppl 1): 18.

4. Stone E, Jett J, Warren G, et al. Cannabis Use, Lung Cancer, and Related Issues. J Thorac Oncol 2018; 13: 480-487.

5. Li TT, Gao X, Gao L, et al. Role of upregulated miR-136-5p in lung adenocarcinoma: A study of 1242 samples utilizing bioinformatics analysis. Pathol Res Pract 2018; 214: 750-766.

6. Huang WT, Cen WL, He RQ, et al. Effect of miR-16a5p on tumor growth in NSCLC using chick chorioallantoic membrane assay and bioinformatics investigation. Mol Med Rep 2017; 16: 8781-8792.

7. He RQ, Li XJ, Liang L, et al. The suppressive role of miR-542-5p in NSCLC: the evidence from clinical data and in vivo validation using a chick chorioallantoic membrane model. BMC Cancer 2017; 17: 655.

8. Konopka KE. Diagnostic Pathology of Lung Cancer. Semin Respir Crit Care Med 2016; 37: 681-688.

9. Liang YY, Huang JC, Tang RX, et al. Clinical value of miR-198-5p in lung squamous cell carcinoma assessed using microarray and RT-qPCR. World J Surg Oncol 2018; 16: 22.

10. Song X, Wang Z. Clinical efficacy of tyrosine kinase inhibitors for non-adenocarcinoma lung cancer patients harboring EGFR-sensitizing mutations. Onco Targets Ther 2017; 10: 3119-3122.

11. Gao X, Tang RX, Xie QN, et al. The clinical value of miR-193a-3p in non-small cell lung cancer and its potential molecular mechanism explored in silico using RNA-sequencing and microarray data. FEBS Open Bio 2018; 8: 94-109.

12. Zhang Y, Chen WJ, Gan TQ, et al. Clinical Significance and Effect of IncRNA HOXA11-AS in NSCLC: A Study Based on Bioinformatics, In Vitro and In Vivo Verification. Sci Rep 2017; 7: 5567.

13. Mengoli MC, Longo FR, Fraggetta F, et al. The 2015 World Health Organization Classification of lung tumors: new entities since the 2004 Classification. Pathologica 2018; 110: 39-67.

14. Chen Y, Li C, Pan Y, et al. The Emerging Role and Promise of Long Noncoding RNAs in Lung Cancer Treatment. Cell Cancer Med 2018; 68: 7-30.

15. Zhao H, Chen KZ, Hui BG, et al. Role of circulating tumor DNA in the management of early-stage lung cancer. Thorac Cancer 2018; 9: 509-515.

16. Kazaz SN, Oztop I. Immune Checkpoint Inhibitors in Advanced-Stage Non-small Cell Lung Cancer. Turk Thorac J 2017; 18: 101-107.

17. Xu-Welliver M, Carbone DP. Blood-based biomarkers in lung cancer: prognosis and treatment decisions. Transl Lung Cancer Res 2017; 6: 708-712.

18. Tang Y, Qiao G, Xu E, et al. Biomarkers for early diagnosis, prognosis, prediction, and recurrence monitoring of non-small cell lung cancer. Onco Targets Ther 2017; 10: 4527-4534.

19. Wei K, Ye Z, Li Z, et al. An immunohistochemical study of cyclin-dependent kinase 5 (CDK5) expression in non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC): a possible prognostic biomarker. World J Surg Oncol 2016; 14: 34.

20. Xiao H, Wang J, Liu Y, et al. Relative influence of c-kit expression and epithelial growth factor receptor gene amplification on survival in patients with non-small cell lung cancer. Oncol Lett 2014; 8: 582-588.

21. Salomonsson A, Jonsson M, Isaksson S, et al. Histological specificity of alterations and expression of KIT and KITLG in non-small cell lung carcinoma. Genes Chromosomes Cancer 2013; 52: 1088-1096.

22. Salehinejad M, Mohtasham N, Bagherpour A, et al. Evaluation of c-kit protein (CD117) expression in common salivary gland neoplasms. J Oral Maxillofac Pathol 2014; 18: 177-182.

23. Youssif NS, Said AM. Immunohistochemical expression of CD117 and vascular endothelial growth factor in retinoblastoma: possible targets of new therapies. Int J Clin Exp Pathol 2014; 7: 5725-37.

24. Sehitoglu I, Bedir R, Ural UM, et al. Relationships between C-kit expression and mean platelet volume in benign, preneoplastic and neoplastic endometrium. Asian Pac J Cancer Prev 2015; 16: 1495-1499.

25. Punzatszeri MP, Sadow PM, Faquin WC. CD117: a novel ancillary marker for papillary thyroid carcinoma in fine-needle aspiration biopsies. Cancer Cytopathol 2014; 122: 596-605.

26. Jansson S, Bendahl PO, Grabau DA, et al. The three receptor tyrosine kinases c-KIT, VEGFR2 and PDGFRalpha, closely spaced at 4q12, show increased protein expression in triple-negative breast cancer. PLoS ONE 2014; 9: e102176.

27. Xu CW, Lin S, Wang WL, et al. Analysis of mutation of the c-Kit gene and PDGFRα in gastrointestinal stromal tumors. Exp Ther Med 2015; 10: 1045-1051.

28. Gottschling S, Jensen K, Herth FJ, et al. Lack of prognostic significance of neuroendocrine differentiation and stem cell antigen co-expression in resected early-stage non-small cell lung cancer. Anticancer Res 2013; 33: 981-990.

29. Rehfeld N, Geddert H, Atamna A, et al. Coexpression of fragile histidine triad and c-kit is relevant for prediction of survival in patients with small cell lung cancer. Cancer Epidemiol Biomarkers Prev 2006; 15: 2232-2238.

30. Micke P, Bassai M, Faldum A, et al. Characterization of c-kit expression in small cell lung cancer: prognostic and therapeutic implications. Clin Cancer Res 2003; 9: 188-194.

31. Pelosi G, Barsella M, Pasini F, et al. CD117 immunoreactivity in stage I adenocarcinoma and squamous cell carcinoma of the lung: relevance to prognosis in a subset of adenocarcinoma patients. Mod Pathol 2004; 17: 711-721.

32. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 1998; 17: 2815-2834.

33. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

34. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997; 127: 820-826.

35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

36. Peters JL, Sutton AJ, Jones DR, et al. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008; 61: 991-996.

37. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

38. Moreno SG, Sutton AJ, Ades AE, et al. Assessment of regression-based methods to adjust for publication bias through a comprehensive simulation study. BMC Med Res Methodol 2009; 9: 2.

39. Pelosi G, Masullo M, Pasini F, et al. CD117 immunoreactivity in high-grade neuroendocrine tumors of the lung: a comparative study of 39 large-cell neuroendocrine carcinomas and 27 surgically resected small-cell carcinomas. Virchows Arch 2004; 455: 449-455.

40. Araki K, Ishii G, Yokose T, et al. Frequent overexpression of the c-kit protein in large cell neuroendocrine carcinoma of the lung. Lung Cancer 2003; 40: 173-180.

41. Boldrini L, Ursino S, Gisfredi S, et al. Expression and mutational status of c-kit in small-cell lung cancer: prognostic relevance. Clin Cancer Res 2004; 10: 4101-4108.
42. Rohr UP, Rehfeld N, Pilgfield L, et al. Expression of the tyrosine kinase c-kit is an independent prognostic factor in patients with small cell lung cancer. Int J Cancer 2004; 111: 259-263.
43. Yoo J, Kim CH, Song SH, et al. Expression of c-kit and p53 in non-small cell lung cancer. Cancer Res Treat 2004; 36:167-172.
44. Leina S. Expression of c-Kit Protein in Small Cell Lung Cancer and Its Prognostic Implications. Tianjin Medical University; 2005.
45. Na D, Leina S, Zhongli Z, et al. Expression of c-KIT, PDGFR-β and PDGFR-α protein in neuroendocrine lung cancer tissues and its clinical significance. Shandong Med J 2010; 2010: 4-6.
46. Po Z, Ning H, Yun S, et al. Clinicopathological significance of expression of c-kit protein in neuroendocrine lung carcinoma. Nat Med J China 2003; 2005: 1526-1529.
47. Casali C, Stefani A, Rossi G, et al. The prognostic role of c-kit protein expression in resected large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg 2004; 77: 247-252.
48. Blackhall FH, Pintilie M, Michael M, et al. Expression and prognostic significance of kit, protein kinase B, and mitogen-activated protein kinase in patients with small cell lung cancer. Clin Cancer Res 2003; 9: 2241-2247.
49. Mické P, Hengstler JG, Albrecht H, et al. c-kit expression in adenoscarcinomas of the lung. Tumour Biol 2004; 25: 252-254.
50. Jiang X, Zhao P Expression of c-kit protein and its significance in human small cell lung cancer. Chin J Lung Cancer 2004; 7: 206-208.
51. Potti A, Moazam N, Ramar K, et al. CD117 (c-KIT) overexpression in patients with extensive-stage small-cell lung carcinoma. Ann Oncol 2003; 14: 894-897.
52. Zhao F, Chen Y, Wu Q, et al. Prognostic value of CD117 in cancer: a meta-analysis. Int J Clin Exp Pathol 2014; 7: 1012-1021.
53. Yan L, Zou L, Zhao W, et al. Clinicopathological significance of c-kit mutation in gastrointestinal stromal tumors: a systematic review and meta-analysis. Sci Rep 2015; 5: 13718.
54. Rossi G, Cavazza A, Marchioni A, et al. Kit expression in small cell carcinomas of the lung: effects of chemotherapy. Mod Pathol 2003; 16: 1041-1047.
55. Gillinov M, Moskowitz AJ, Argenziano M. Surgical Ablation for Atrial Fibrillation. N Engl J Med 2015; 373: 484.
56. Conic I, Stanojevic Z, Janjovic Velickovic L, et al. Epithelial ovarian cancer with CD117 phenotype is highly aggressive and resistant to chemotherapy. J Obstet Gynaecol Res 2015; 41: 1630-1637.
57. Ma YY, Yu S, He XJ, et al. Involvement of c-kit mutation in the development of gastrointestinal stromal tumors through proliferation promotion and apoptosis inhibition. Oncol Targets Ther 2014; 7: 637-643.
58. Xu C, Han H, Wang J, et al. Diagnosis value of CD117 and PDGFRA, alone or in combination DOG1, as biomarkers for gastrointestinal stromal tumors. Ann Transl Med 2015; 3: 308.
59. Xu CW, Lin S, Wang WL, et al. Analysis of mutation of the c-kit gene and in gastrointestinal stromal tumors. Exp Ther Med 2015; 10: 1045-1051.
60. Makami T, Nemoto Y, Numata Y, et al. Small gastrointestinal stromal tumor in the stomach: identification of precursor for clinical gastrointestinal stromal tumor using c-kit and alpha-smooth muscle actin expression. Hum Pathol 2013; 44: 2628-2635.
61. Novelli M, Rossi S, Rodriguez-Justo M, et al. DOG1 and CD117 are the antibodies of choice in the diagnosis of gastrointestinal stromal tumours. Histopathology 2010; 57: 259-270.
62. Nakahara M, Isozaki K, Hirota S, et al. A novel gain-of-function mutation of c-kit gene in gastrointestinal stromal tumors. Gastroenterology 1998; 115: 1090-1095.
63. Camps C, Sirera R, Bremnes RM, et al. Analysis of c-kit expression in small cell lung cancer: prevalence and prognostic implications. Lung Cancer 2006; 52: 343-347.