Clinical and Prognostic Significance of CD117 in Non-Small Cell Lung Cancer: A Systemic Meta-Analysis

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Keywords

Cancer stem cell · Cluster of differentiation 117 · Non-small cell lung cancer · Prognosis · Biomarker

Abstract

The aim of this study was to assess the relationship of cluster of differentiation 117 (CD117) expression with the clinicopathological characteristics and the prognosis in patients with non-small cell lung cancer (NSCLC). No meta-analysis concerning the correlation of CD117 expression with clinical and prognostic values of the patients with NSCLC is reported. A systematic literature search was conducted to achieve eligible studies. The combined odds ratios (ORs) or hazard ratios (HRs: multivariate Cox analysis) with their 95% confidence intervals (CIs) were calculated in this analysis. Final 17 eligible studies with 4,893 NSCLC patients using immunohistochemical detection were included in this meta-analysis. CD117 expression was not correlated with gender (male vs. female), clinical stage (stages 3–4 vs. stages 1–2), tumor grade (grade 3 vs. grades 1–2), T-stage (T-stages 3–4 vs. T-stages 0–2), distal metastasis, and disease-free survival (DFS) of NSCLC (all p values >0.05). CD117 expression was associated with lymph node metastasis (positive vs. negative: OR = 0.74, 95% CI = 0.56–0.97, $p = 0.03$), histological type (adenocarcinoma (AC) versus squamous cell carcinoma

(SCC): OR = 1.74, 95% CI = 1.26–2.39, $p = 0.001$), and a worse overall survival (OS) (HR = 1.89, 95% CI = 1.22–2.92, $p = 0.004$). The expression of CD117 was significantly higher in AC than in SCC. CD117 may be an independent prognostic indicator for worse OS in NSCLC.

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Introduction

Lung cancer is the most lethal human malignant tumor due to its high incidence and mortality in the world [1]. According to the GLOBOCAN estimates, approximately 2,093,876 new cases are clinically diagnosed with lung cancer, and an estimated 1,761,007 lung cancer deaths occur worldwide in 2018 [1]. Non-small cell lung cancer (NSCLC) is the most common subtype of lung cancer, accounting for approximately 85% of cases [2]. The prognosis of patients with NSCLC remains unsatisfactory, with a 5-year survival rate of about 16% and a high incidence of recurrence [3]. Histologically, NSCLC mainly includes 2 subtypes: adenocarcinoma (AC) and squamous cell carcinoma (SCC) [2, 4].

Cancer stem cells (CSCs) are a special subpopulation of cancer cells, which are responsible for the major capabilities of self-renewal and uncontrolled proliferation and dif-

ferentiation, and increasing evidence suggests that CSCs contribute to cancer metastasis, a worse prognosis, and resistance to chemotherapy or radiation therapy [5–7]. Cluster of differentiation 117 (CD117), termed c-kit proto-oncogene, encoded by the c-kit gene, and located on human chromosome 4q11-12, belongs to a type-III transmembrane receptor tyrosine kinase [8, 9]. CD117 could act as a receptor for stem cell factor and plays an important role in maintaining cellular and biological functions such as cell survival, metabolism, cell growth and progression, proliferation, apoptosis, cell migration, cell differentiation, cell adhesion, and chemotaxis [10, 11]. Studies have been reported that CD117 expression was observed in many cancers, including NSCLC [11, 12]. CD117 serves a key oncogenic role in gastrointestinal stromal tumor (GIST) [13, 14]. The drug that blocks the phosphorylation of CD117 tyrosine kinase provides effective treatment for patients with GIST [13, 15]. CD117 expression has been reported to be correlated with worse prognosis in many cancers, including thick vulvar melanoma [16], ovarian cancer [17], esophageal SCC [18], and breast phyllodes tumors [19]. However, the clinical significance of CD117 expression in patients with NSCLC remains controversial. For example, Micke et al. [20] showed that CD117 expression was correlated with poor overall survival (OS) in NSCLC. But Herpel et al. [21] reported no association between CD117 expression and the prognosis of NSCLC.

Therefore, it was needed to make a comprehensive analysis of the clinical value of CD117 expression in NSCLC. To achieve this purpose, the present meta-analysis was conducted to assess the relationship of CD117 expression with the clinicopathological characteristics and the prognosis in patients with NSCLC.

Materials and Methods

Search Strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [22]. A comprehensive literature search from PubMed, EMBASE, Web of Science, and Cochrane Library databases was performed before June 20, 2019. The following key words and search terms were applied: “cluster of differentiation 117 OR CD117 OR c-KIT OR KIT,” “pulmonary OR lung,” “cancer OR tumor OR carcinoma OR neoplasm,” and “expression.” Additionally, the reference lists of the eligible studies were screened to identify other potential studies.

Study Selection

Eligible publications for this meta-analysis had to meet the following selection criteria: 1) patients were diagnosed with NSCLC; 2) studies investigated the expression of CD117 using immunohis-

tochemical (IHC) methods; 3) CD117 expression was defined as “positive” or “negative” based on the original articles; 4) studies examined CD117 expression with the clinicopathological features; and 5) studies investigated the prognostic role of CD117 expression using multivariable Cox analysis for OS and DFS. In the case of insufficient data, sufficient data were obtained by requesting the corresponding author. If authors published multiple articles using overlapping sample data from the same research institution, only the recent study or the study with the most complete information was selected. The main exclusion criteria were as follows: case reports, reviews, comments, letters, and animal or human cell lines. And articles lacking information on CD117 expression and NSCLC were excluded.

Data Extraction

Data were extracted independently by 2 authors using a standard form. Any disagreements were resolved by consensus with a third author. The following data were sought from the eligible studies: first author’s surname, publication year, country of origin, ethnicity, number of participants, mean or median age, antibody, cut-off values of CD117 expression, expression frequency, clinicopathological features such as gender (male vs. female), histological type (AC vs. SCC), clinical stage (stages 3–4 vs. stages 1–2), tumor grade (grade 3 vs. grades 1–2), T-stage (3–4 vs. 0–2), lymph node metastasis (positive vs. negative), distal metastasis (positive vs. negative), and survival data using multivariable Cox analysis with hazard ratio (HR) with 95% confidence interval (CI).

Statistical Analysis

This meta-analysis was conducted by using Stata software, version 12.0 (Stata Corp., College Station, TX, USA). The pooled odds ratio (OR) and 95% CI were applied to assess the relationship between the expression of CD117 and clinicopathological parameters, including gender, histological type, clinical stage, tumor grade, T-stage, lymph node metastasis, and distal metastasis. Pooled HR and 95% CI were used to evaluate the prognostic role of the expression of CD117 on patients with NSCLC, including OS and DFS, using multivariable Cox survival analysis. The random-effects model was used to estimate the results of OR and HR in this meta-analysis. Heterogeneity between studies was measured using Cochran’s Q statistic [23]; a Q test *p* value <0.1 indicated substantial heterogeneity. When significant heterogeneity was detected, sensitivity analyses were performed by omitting an individual study to confirm the influence of the pooled results. Publication bias was performed by using the Egger test for the results with more than or equal to 5 studies [24].

Results

Characteristics of the Included Studies

A flowchart of the literature selection process is shown in Fig. 1. According to the inclusion criteria, the final 17 eligible studies using the IHC method were included in this meta-analysis [12, 20, 21, 25–38]. A total of 4,893 patients with NSCLC from Germany, USA, Switzerland, Finland, Turkey, Sweden, Korea, China, Ja-

Fig. 1. Flow diagram of literature search and study selection. NSCLC, non-small cell lung cancer; CD117, cluster of differentiation 117.

pan, and India were enrolled. The included studies were published between 1998 and 2017. Sixteen studies with 4,813 NSCLC patients evaluated the association of CD117 expression with the clinicopathological features. Four articles reported the prognostic effect of CD117 expression using multivariable Cox analysis. The baseline characteristics of the eligible study are summarized in Tables 1 and 2.

Association of CD117 Expression with the Clinicopathological Characteristics

Data from 7 studies with 3,837 patients showed no association was found between CD117 expression and gender (male vs. female: OR = 1.00, 95% CI = 0.71–1.40, $p = 0.994$) (Fig. 2). Data from 15 studies with 4,249 patients demonstrated that CD117 expression was significantly associated with histological type (AC vs. SCC: OR = 1.74, 95% CI = 1.26–2.39, $p = 0.001$) (Fig. 3).

Data from 3 studies involving 337 patients showed no association between CD117 expression and tumor grade (grade 3 vs. grades 1–2: OR = 1.00, 95% CI = 0.62–1.60, $p = 0.997$) (Fig. 2). Moreover, no correlation was observed between CD117 expression and clinical stage (stages 3–4 vs. stages 1–2: OR = 0.78, 95% CI = 0.56–1.06, $p = 0.116$) (Fig. 2), including 3 studies with 1,758 patients.

Data from 5 studies involving 1,938 cases demonstrated no relationship between CD117 expression and T-

stage (T-stages 3–4 vs. T-stages 0–2: OR = 1.11, 95% CI = 0.49–2.51, $p = 0.801$) (Fig. 4). Data from 5 studies with 1,943 cases showed CD117 expression was negatively correlated with lymph node metastasis (positive vs. negative: OR = 0.74, 95% CI = 0.56–0.97, $p = 0.03$) (Fig. 4). No association was found between CD117 expression and distal metastasis (positive vs. negative: OR = 0.91, 95% CI = 0.43–1.90, $p = 0.794$) (Fig. 4), including 2 studies with 1,560 patients.

Prognostic Effect of CD117 Expression Using Multivariable Cox Analysis

CD117 expression was not correlated with DFS among 4 studies with 265 patients (HR = 1.41, 95% CI = 0.62–3.22, $p = 0.414$) but was significantly associated with poor OS among 4 studies with 261 patients (HR = 1.89, 95% CI = 1.22–2.92, $p = 0.004$) (Fig. 5).

Heterogeneity Analysis

Obvious heterogeneity was detected in relation to gender and T-stage ($p < 0.1$); sensitivity analyses were conducted to assess the stability of the pooled results based on the omission of an individual study. When the study of Kriegsmann et al. [27] was removed, the re-calculated OR was still not significant between CD117 expression and gender (OR = 1.12, 95% CI = 0.79–1.59, $p = 0.513$), with no heterogeneity ($p = 0.234$), suggesting the stability

Table 1. Main characteristics of the included studies

First author	Country	Ethnicity	Age	Stage	Histology	Antibody	Sources of antibody	Staining	Cut-off values (IHC) (%)	Cancer, N (E+ %)	Clinical features	MA-survival
Pietsch et al. [38]	Germany	Caucasian	na	na	NSCLC	Anti-c-kit	MAb ID29.3 D6, Dianova, Hamburg, Germany	Cytoplasm	>30	106 (24.5)	Yes	na
Arber et al. [37]	USA	Caucasian	na	na	NSCLC	Anti-c-kit	Medical and Biological Laboratories Co., Ltd., Nagoya, Japan	Cytoplasm	Moderate-strong	55 (7.3)	Yes	na
Lonardo et al. [36]	USA	Caucasian	na	na	NSCLC	Anti-c-kit	Recognizing epitope 963–973, Dako	Membrane/cytoplasm	>20	57 (1.8%)	Yes	na
Butnor et al. [35]	USA	Caucasian	na	na	NSCLC	Anti-c-kit	Rabbit IgG polyclonal; Dako Corporation, Carpinteria, California	Cytoplasm	>10	60 (11.7)	Yes	na
Went et al. [33]	Switzerland	Caucasian	na	na	NSCLC	Anti-c-kit	A4502 (Dako)	Membrane/cytoplasm	>30	144 (12.5)	Yes	na
Micke et al. [20]	Germany	Caucasian	62.8	1–4	AC	Anti-c-kit	Dako	Cytoplasm	>10	95 (64.2)	Yes	OS
Yoo et al. [34]	Korea	Asian	58	1–3	NSCLC	Anti-c-kit	Santa Cruz Biotechnology, Inc., Santa Cruz, CA	Membrane/cytoplasm	≥30	147 (72.8)	Yes	na
Sihto et al. [32]	Finland	Caucasian	na	na	NSCLC	Anti-c-kit	A4502; Dako, Glostrup, Denmark	na	>0	41 (12.2)	Yes	na
Yaren et al. [31]	Turkey	Caucasian	58.2	1–4	NSCLC	Anti-c-kit	Dako, Glostrup, Denmark	Cytoplasm	≥4 scores	69 (7.2)	Yes	na
Herpel et al. [21]	Germany	Caucasian	64	1–2	NSCLC	Anti-c-kit	Dako	Membrane/cytoplasm	>0	86 (50)	Yes	OS, DFS
Gottschling et al. [12]	Germany	Caucasian	62.7	1–2	NSCLC	Anti-c-kit	Dako	na	≥10	80 (51.3)	na	OS, DFS
Salomonsson et al. [30]	Sweden	Caucasian	na	1–3	NSCLC	Anti-c-kit	Dako, Glostrup, Denmark	Membrane	>10	68 (33.8)	Yes	na
Xiao et al. [29]	China	Asian	63.3	1–4	NSCLC	Anti-c-kit	Phospho Y703; DakoCytomation, Glostrup, Denmark	na	≥5	146 (46.6)	Yes	na
Matsumura et al. [28]	Japan	Asian	na	na	NSCLC	Anti-c-kit	DakoCytomation	na	>20 score	375 (9.6)	Yes	na
Kriegsmann et al. [27]	Germany	Caucasian	63	1–4	NSCLC	Anti-c-kit	A4502 (Dako)	Membrane/cytoplasm	≥1	1,465 (9.9)	Yes	na
Sakabe et al. [26]	Japan	Asian	69	1–3	NSCLC	Anti-c-kit	Cat. no. ab32363; clone YR145; Abcam, Cambridge, MA, USA	Membrane	>0	99 (17.2)	Yes	DFS
Jha et al. [25]	India	Caucasian	55	na	NSCLC	Anti-c-kit	Biocare Medical, clone: EP10	Membrane/cytoplasm	≥1	1,800 (9.5)	Yes	na

NSCLC, non-small cell lung cancer; AC, adenocarcinoma; IHC, immunohistochemical; OS, overall survival; DFS, disease-free survival; na, not applicable; N, number of the study population; E+, CD117 positivity; MA, multivariable Cox analysis; CD117, cluster of differentiation 117.

Table 2. Detailed characteristics of the eligible studies with the clinicopathological characteristics

First author	Country	Age	Stage	Staining	Cut-off val- ues (IHC) (%)	Cancer N (E+ %)	Male E+/ total	Female E+/ total	Stages 3-4 E+/ total	Stages 1-2 E+/ total	Grade 3 E+/ total	AC E+/ total	SCC E+/ total	pT- stages 3-4 E+/ total	pT- stages 0-2 E+/ total	Lymph node metastasis (yes) E+/ total	Lymph node metastasis (no) E+/ total	Distal metastasis (yes) E+/ total	Distal metastasis (no) E+/ total
Pietsch et al. [38]	Germany	na	na	Cytoplasm	>30	106 (24.5)					14/60	12/46	15/50	7/46					
Arber et al. [37]	USA	na	na	Cytoplasm	Moderate- strong	55 (7.3)						4/34	0/21						
Lonardo et al. [36]	USA	na	na	Membrane/ cytoplasm	>20	57 (1.8)						1/30	0/24						
Butnor et al. [35]	USA	na	na	Cytoplasm	>10	60 (11.7)						4/23	2/22						
Went et al. [33]	Switzerland	na	na	Membrane/ cytoplasm	>30	144 (12.5)						9/48	1/49						
Micke et al. [20]	Germany	63	1-4	Cytoplasm	>10	95 (64.2)	18/27	43/68						34/53	25/40			27/41	34/54
Yoo et al. [34]	Korea	58	1-3	Membrane/ cytoplasm	≥30	147 (72.8)	74/106	33/41	91/126	16/21		46/60	45/63	59/87	48/60	90/126	17/21		
Siihto et al. [32]	Finland	na	na	na	>0	41 (12.2)						2/10	1/10						
Yaren et al. [31]	Turkey	58	1-4	Cytoplasm	≥4 scores	69 (7.2)						2/28	2/36						
Herpel et al. [21]	Germany	64	1-2	Membrane/ cytoplasm	>0	86 (50)	33/61	10/25			30/56	13/29	21/36	19/34	1/2	42/85	11/25	32/61	
Salomonsson et al. [30]	Sweden	na	1-3	Membrane	>10	68 (33.8)						14/46	0/13						
Xiao et al. [29]	China	63	1-4	na	≥5	146 (46.6)	39/84	29/62	19/47	49/99	20/45	48/101	37/78	31/68	18/22	50/124	28/66	40/80	
Matsumura et al. [28]	Japan	na	na	na	>20 score	375 (9.6)						6/202	5/122						
Kriegsmann et al. [27]	Germany	63	1-4	Membrane/ cytoplasm	≥1	1,465 (9.9)	89/1,016	56/448	42/489	103/976		97/711	34/586	21/296	134/1,169	62/710	83/755	2/39	143/1,426
Sakabe et al. [26]	Japan	69	1-3	Membrane	>0	99 (17.2)	14/59	3/40				11/73	6/26			2/22	15/77		
Jha et al. [25]	India	55	na	Membrane/ cytoplasm	≥1	1,800 (9.5)	121/1,250	50/550				120/980	40/720						
IHC, immunohistochemical; na, not applicable; N, number of the study population; E+, CD117 positivity; AC, adenocarcinoma; SCC, squamous cell carcinoma; CD117, cluster of differentiation 117.																			

Fig. 2. Forest plot for the relationship of CD117 expression with gender (male vs. female: OR = 1.00, 95% CI = 0.71–1.40, $p = 0.994$), tumor grade (grade 3 vs. grades 1–2: OR = 1.00, 95% CI = 0.62–1.60, $p = 0.997$), and clinical stage (stages 3–4 vs. stages 1–2: OR = 0.78, 95% CI = 0.56–1.06, $p = 0.116$). OR, odds ratio; CI, confidence interval; CD117, cluster of differentiation 117.

Fig. 3. Forest plot for the relationship of CD117 expression with histological type (AC versus SCC: OR = 1.74, 95% CI = 1.26–2.39, $p = 0.001$). SCC, squamous cell carcinoma; AC, adenocarcinoma; OR, odds ratio; CI, confidence interval; CD117, cluster of differentiation 117.

of this result. When the study of Xiao et al. [29] was deleted, the re-calculated OR was changed and was slightly associated with T-stage (OR = 0.68, 95% CI = 0.47–0.98, $p = 0.04$), with no heterogeneity ($p = 0.647$), which suggested that this result was not stable.

Publication Bias

No publication bias was measured among CD117 expression and histological type, gender, T-stage, and lymph node metastasis (all p values >0.05) (Fig. 6).

Fig. 4. Forest plot for the relationship of CD117 expression with T-stage (T-stages 3–4 vs. T-stages 0–2: OR = 1.11, 95% CI = 0.49–2.51, $p = 0.801$), lymph node metastasis (positive vs. negative: OR = 0.74, 95% CI = 0.56–0.97, $p = 0.03$), and distal metastasis (positive vs. negative: OR = 0.91, 95% CI = 0.43–1.90, $p = 0.794$). OR, odds ratio; CI, confidence interval; CD117, cluster of differentiation 117.

Fig. 5. Forest plot for the relationship of CD117 expression with the prognosis. CD117, cluster of differentiation 117; OS, overall survival; DFS, disease-free survival; HR, hazard ratio.

Discussion

CSCs have been identified to be responsible for tumor progression and metastasis, and resistance to conventional therapy [39, 40]. Targeting CSCs could become the most promising therapeutic strategy [41]. CD117 is a transmembrane receptor tyrosine kinase that involves in

cell differentiation, proliferation, survival, and migration, cell adhesion, chemotaxis, and apoptosis [11, 42]. CD117 is expressed in many human tumors such as ovarian cancer, renal cell carcinoma, thymic carcinoma, and NSCLC [11, 12]. The expression of CD117 is associated with an unfavorable prognosis in some cancers, such as ovarian cancer and esophageal SCC [17, 18]. Recently, CD117 ex-

Fig. 6. Publication bias using Egger's test.

pression in NSCLC has been frequently reported. However, some studies have showed controversial correlations of CD117 IHC expression with the clinicopathological characteristics and prognostic outcomes in NSCLC [20, 21, 25–28]. To our knowledge, no systematic evidence-based meta-analysis is currently performed to assess the clinical significance of CD117 in NSCLC patients. Therefore, we conducted a meta-analysis enrolling 17 studies with 4,893 patients to identify whether CD117 may serve as a potential useful biomarker and as a promising therapeutic target for the management of patients with NSCLC.

We demonstrated that CD117 expression was predominantly found in AC. The expression of CD117 was relatively lower in SCC. Thus, CD117 as a marker may be helpful in the differential diagnosis of AC and SCC. We also found that CD117 was an independent biomarker for predicting worse prognosis. The previous meta-analysis evaluated the role of CD117 in lung cancer based on a panel of 2,645 patients [43]. This previous meta-analysis reported no asso-

ciation between CD117 expression and histology. However, we must realize that some limitations such as an insufficient study population could impair the reliability and robustness of pooled results. Our study involved larger sample sizes with 4,893 NSCLC patients and observed that CD117 expression was associated with the histological type.

In this work, the relationship of CD117 expression with the clinicopathological characteristics of NSCLC was analyzed. We demonstrated that CD117 expression was not associated with gender, which is consistent with the previous studies [20, 21, 25, 29, 34]. No association of CD117 expression with clinical stage and tumor grade was found in this study, which is consistent with the previous publications for the assessment between CD117 expression and clinical stage [27, 29, 34] and tumor grade [21, 29, 38]. CD117 expression was not found to be correlated with T-stage and distal metastasis of NSCLC; our results are consistent with the previous studies for the assessment between CD117 expression and T-stage [20, 21, 27, 34] and

distal metastasis [20, 27]. CD117 expression was observed to be negatively associated with lymph node metastasis. Additionally, our result demonstrated that CD117 expression was significantly associated with the histological type (AC vs. SCC: OR = 1.74, $p = 0.001$). And it was significantly higher in AC than in SCC. This finding was consistent with the previously published articles, which reported that CD117 expression correlated with histological type of NSCLC [25, 27, 33]. Especially in 2 clinical studies with a large study population (~3,000), they found that AC is the most common tumor to express CD117 [25, 27]. Based on these results, our work suggested that CD117 may play a more important role in the pathology of AC.

We further determined whether CD117 expression correlated with the prognosis of NSCLC based on multivariable Cox analysis. Data from this meta-analysis showed that CD117 expression was not linked to the DFS of NSCLC patients. However, CD117 expression was associated with worse OS (HR = 1.89, 95% CI = 1.22–2.92, $p = 0.004$), suggesting that CD117 could be an independent prognostic biomarker for predicting poor prognosis of NSCLC in OS.

Some limitations should be addressed in this meta-analysis. First, studies published in English were finally included. Other articles published in other languages, unpublished articles, and conference abstracts were lacking based on the insufficient information. Second, significant heterogeneity was measured between CD117 and gender and T-stage; we conducted sensitivity analyses to estimate the change in heterogeneity and stability of the pooled results. However, the reasons of heterogeneity were not very clear, perhaps because different cut-off values of IHC staining were used from the eligible studies, which might lead to the potential source of heterogeneity in the current meta-analysis. Third, sample sizes with regard to CD117 expression with the prognosis of NSCLC were small. More studies using larger patient samples with multivariable Cox survival analysis are needed to clarify this issue.

Conclusion

In conclusion, our results demonstrated that CD117 expression was not linked to gender, clinical stage, tumor grade, T-stage, distal metastasis, and DFS of NSCLC but was related to lymph node metastasis, histological type, and worse OS. And CD117 expression was significantly higher in AC than in SCC. Our data suggest that CD117 is not only a promising therapeutic target but also a useful prognostic factor for predicting OS in NSCLC. Additional prospective clinical studies are needed to validate our results in the future.

Conflict of Interest Statement

All the authors declare that they have no conflict of interest.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work.

Availability of Data and Material

The datasets used or/and analyzed during the current study are available from the corresponding author on reasonable request.

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