Research Paper

Prognostic value of MET copy number gain in non-small-cell lung cancer: an updated meta-analysis

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Abstract

The alterations of MET have been detected in non-small-cell lung cancer (NSCLC). However, the prognostic impact of MET gene copy number gain (CNG) has not been consistent among studies. We performed this meta-analysis to evaluate the prognostic value of high MET CNG in patients with NSCLC. A systematic computerized search of the electronic databases including PubMed, EMBASE, Google scholar, and Cochrane Library (up to November 2017) was carried out. From twenty-one studies, 7,647 patients were included in the pooled analysis of hazard ratios (HRs) with 95% confidence intervals (CIs) for disease-free survival or overall survival. Compared with patients with NSCLC showing low MET CNG, those with tumors harboring high MET CNG showed significantly worse survival (HR = 1.45, 95% CI: 1.16-1.80, p = 0.001). Subgroup analyses showed that high MET CNG significantly correlated with a poor prognosis especially in patients with adenocarcinoma (HR = 1.41, 95% CI: 1.11-1.79, p = 0.005) and Asian populations (HR = 1.58, 95% CI: 1.32-1.88, p < 0.00001).

In conclusion, this meta-analysis indicates that high MET CNG is an adverse prognostic factor in patients with NSCLC. Subgroup analyses suggest that high MET CNG is associated with a worse prognosis, especially in patients with adenocarcinoma and Asian populations. However, large prospective studies using standardized methods based on the homogeneous populations are warranted to validate the prognostic value of MET amplification in patients with NSCLC.

Key words: MET copy number; MET amplification; non-small-cell lung cancer; meta-analysis

Introduction

Lung cancer is the leading cause of cancer-related death worldwide [1]. Despite recent advances in molecular targeted therapies, non-small-cell lung cancer (NSCLC) remains a lethal disease [1,2]. Therefore, there is a critical need to identify novel therapeutic targets promoting NSCLC pathogenesis and develop more efficacious targeted agents. The mesenchymal-epidermal transition (MET)/ hepatocyte growth factor (HGF) pathway has recently emerged as a potential therapeutic target in several types of human cancers including NSCLC [3,4].

MET, located at 7q21-q31, is a proto-oncogene that encodes the tyrosine kinase receptor for HGF.[5] The MET/HGF signaling pathway regulates multiple cellular functions, including differentiation, cell cycle progression, proliferation, and angiogenesis [3,6]. Therefore, dysregulation of the MET signaling pathway has been implicated in the pathogenesis of cancer, such as tumor cell proliferation and survival, invasion, and metastasis [7,8]. The MET/HGF pathway has also cross-talks with the epidermal growth factor receptor (EGFR) network at both

PI3K/Akt and MAPK nodes, suggesting mutual compensation [9]. Different molecular alterations in the MET gene have been found to determine the MET/HGF pathway activation: point mutations, amplifications, genetic polymorphisms, enhanced transcription, and autocrine activation [10-12].

Alterations in the MET gene, including overexpression, amplification, and mutations, have been also observed in NSCLC [13-17]. MET protein overexpression is variable in NSCLC, ranging from 5% to 74.6% [13,14]. Some studies have reported that high MET expression is associated with a worse prognosis in patients with NSCLC [14,15]. The rate of MET amplification (true amplification or copy gain) in NSCLC has been reported to range from 1% to 39% [18-39], depending on the histology and detection methods. Recently, *MET* amplification has been proposed as a potential mode of resistance to EGFR tyrosine kinase inhibitors in NSCLC [40-42]. In addition, several studies reported a negative prognostic impact of high MET gene copy number gain (CNG) in patients with NSCLC [20, 21,29,30,32,37,39,43,44]. However, the data are limited and other studies have failed to confirm this finding [17,19,22-28,31,33-36,38].

Because the prognostic impact of MET amplification has been inconsistent among studies, we performed this meta-analysis to gain a better insight into the prognostic role of high MET CNG in patients with NSCLC.

Materials and Methods

Publication searching strategy

The current study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [45]. A systematic computerized search of the electronic databases including PubMed, EMBASE, Google scholar, and Cochrane Library (up to November 2017) was performed. The search used the following keywords variably combined: "MET", "MET copy number", "MET amplification", "non-small-cell lung cancer or NSCLC", and "lung cancer". The related articles function in PubMed was used to identify all relevant articles.

Inclusion criteria

Eligible studies should meet the following inclusion criteria: (i) clinical trials and prospective or retrospective cohort studies investigating the correlation of MET amplification or CNG with disease-free survival (DFS) or overall survival (OS) in patients with NSCLC; (ii) the use of adequate detection methods including fluorescence *in situ* hybridization (FISH), silver *in situ* hybridization (SISH), bright-field *in situ* hybridization (BISH), or quantitative, real-time polymerase chain reaction (qPCR); (iii) results providing sufficient data for hazard ratios (HRs) with 95% confidence intervals (CIs) for DFS or OS; (iv) Studies published in peer-reviewed journals; and (v) articles written in English.

Data extraction

Two investigators (BJK and HSK) independently screened relevant studies and extracted the data from each eligible study. If these two authors did not agree, the principle investigator (JHK) was consulted to settle the dispute through discussion.

The following data were extracted from the included studies: the first author, year of publication, country, inclusion period, number of patients, stage, histology, detection method of MET amplification, cut-off criteria of high MET CNG, and HRs with their 95% CIs for DFS or OS. When there were both univariate and multivariate analysis for survival, the data were extracted preferentially from multivariate analysis.

Statistical analysis

The survival outcomes were stratified according to MET CNG (low vs. high). Statistical values were obtained directly from the original articles. When papers had no HR and/or its 95% CI, the Engauge Digitizer (version 9.1) was used to estimate them from Kaplan-Meier curves. The effect size of DFS and OS was pooled through HR and its 95% CI. Subgroup analyses were performed according to the histological subtypes (adenocarcinoma or squamous cell carcinoma) and ethnic source (Asian or non-Asian). The heterogeneity across studies was estimated by the Q statistics and I^2 inconsistency test. The fixed-effect model (Mantel–Haenszel method) was used for pooling homogeneous outcomes ($p \geq 0.1$ and $I^2 \leq 50\%$), and the random-effects model (DerSimonian–Laird method) was selected when significant heterogeneity was observed ($p < 0.01$ and $I^2 > 50\%$).

The RevMan version 5.2 was used to combine the data. The plots show a summary estimate of the results from all the studies combined. The size of the squares represents the estimate from each study, reflecting the statistical 'weight' of the study. Outcomes are provided as forest plots with diamonds representing the estimate of the pooled effect and the width of diamond implying its precision. The line of no effect is number one for binary outcomes, which depicts statistical significance if not crossed by the diamond [46]. HR > 1.0 implies worse survival for patients with high MET CNG.
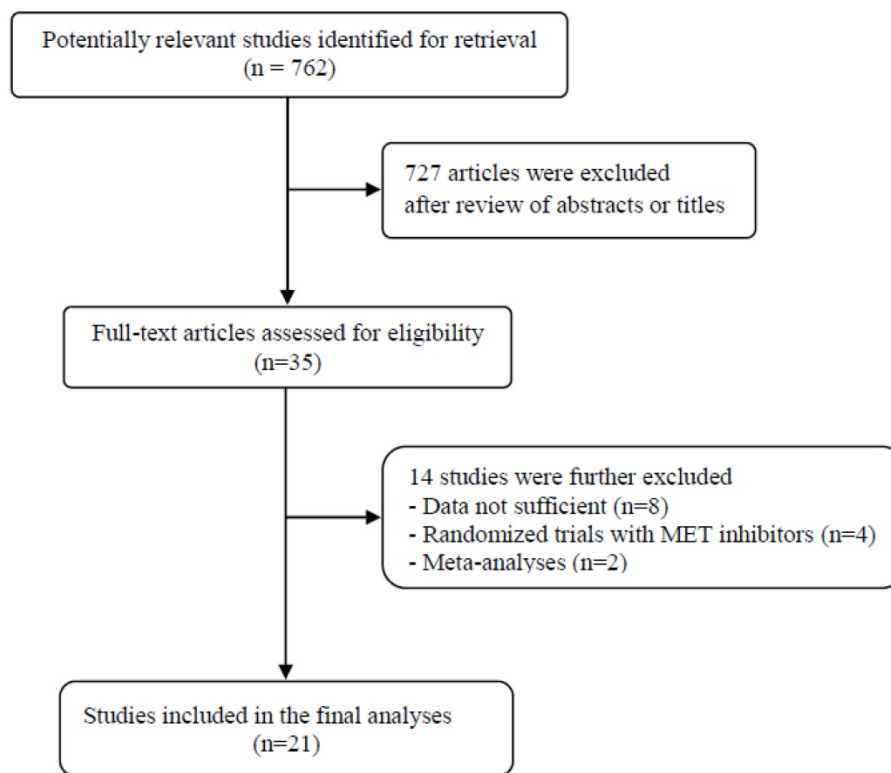
Figure 1. Flow diagram of search process

The possibility of publication bias was assessed with the Egger's test and visual inspection of the funnel plot [47,48]. Statistical significance was considered for a p-value of less than 0.05 for summary HR and publication biases.

Results

Results of search

A total of 762 potentially relevant articles were initially found, but 727 of them were excluded after careful screening of the titles and abstracts. Of the remaining 35 potentially eligible studies, 14 were further excluded by the inclusion criteria. Finally, 21 studies were included in the meta-analysis [19-39]. Figure 1 shows the search flow diagram of this meta-analysis.

Characteristics of the included studies

Table 1 summarizes the main characteristics and clinical outcomes of the eighteen studies. Except for two with a prospective cohort [26,32], most were retrospective studies. The detection method and cut-off criteria for high MET CNG were variable across studies: FISH were most commonly used [20,21,23,24,26,27,32-37], but various cut-off criteria were adopted [19-39]. Frequencies of high MET CNG in the included studies ranged from 1% to 38.9% depending on the technique used and the cut-point for positivity. Twelve studies were conducted in Asian populations and six were performed in non-Asian countries. Thirteen studies contained NSCLC of all histological subtypes, while 7 studies involved either adenocarcinoma (ADC) [22,24,26,30, 32,33] or squamous cell carcinoma (SQCC) [21]. One study involved patients with stage I ADC [30], and another one involved patients with advanced (stage III-IV) ADC harboring EGFR mutations [32]. While patients with MET CNG had a better OS in one study [34], seven studies reported high MET CNG as an adverse prognostic factor [20,21,29,30,32,37,39]. The remaining 13 studies failed to observe statistically significant impact of high MET CNG on survival, irrespective of whether these studies used univariate or multivariate analyses.

Prognostic impacts of MET CNG

Impact of high MET CNG on DFS

From five studies [26,28,30,31,38], a total of 2,141 patients were included in the meta-analysis of HRs for DFS. The random-effects model was selected because there was significant heterogeneity among studies (X^2 = 20.46, p = 0.0004, I^2 = 80%). There was no significant correlation between high MET CNG and DFS (HR = 1.37, 95% CI: 0.88-2.12, p = 0.16) (Data not shown).

Table 1. Summary of the 21 included studies

First author (year) [ref]	Country	No. of pts	Inclusion period	Stage	Histology	Method	Cut-off	No. of pts with high MET CNG (%)	HR for DFS (95% CI)	HR for OS (95% CI)	Adjusted variables
Okuda (2008) [19]	Japan	213	2003-2007	I-IV	NSCLC	qPCR	> 3 copies	12 (5.6%)	NA	1.88 (0.93-3.81) p = 0.081	Age, sex, smoking, histology, stage, differentiation, EGFR mutations
Cappuzzo (2009) [20]	Italy	447	2000-2004	I-IV	NSCLC	FISH	Cappuzzo system	48 (11.1%)	NA	1.52 (1.01-2.28) p = 0.04	Sex, smoking, histology, stage, grade, EGFR-FISH
Go (2010) [21]	Korea	97	1995-2000	I-IV	SQCC	FISH	Cappuzzo system or UCCC criteria	8 (8.2%) or 30 (30.9%)	NA	3.37 (1.38-8.23) P = 0.008	Age, sex, smoking, stage, EGFR-FISH
Onitsuka (2010) [22]	Japan	183	2003-2007	IA-IIIB	ADC	qPCR	≥1.31 copies	8 (4.4%)	NA	2.0 (0.85-4.72) p = 0.112	Age, sex, stage (T, N), EGFR or KRAS mutations, p-Met or HGF expression
Chen (2011) [23]	Taiwan	208	1996-2004	I-IV	NSCLC	FISH	≥3 copies	22 (10.9%)	NA	1.84 (0.81-4.19) p = 0.147	Age, sex, smoking, histology, stage, EGFR copy, EGFR or KRAS mutations
Tachibana (2012) [24]	Japan	106	2001-2008	I-III	ADC	FISH	> 3 copies	11 (10.4%)	NA	1.79 (0.35-9.0) p = 0.483	Vascular or pleural invasion, lymphatic permeation, nuclear grade, LN status, MET or HGF expression
Tsuta (2012) [25]	Japan	844	1997-2007	I-IV	NSCLC	BISH	UCCC criteria	92 (10.9%)	NA	1.295 (0.92-1.82) p = 0.135	Univariate
Tanaka (2012) [26]	Japan	138	2004-2009	I-IV	ADC	FISH	Cappuzzo system or MET/CEP7≥2.0	21 (15.2%) or 6 (4.3%)		3.28 (1.02-10.53) p = 0.05	1.60 (0.21-12.16) Univariate
Park (2012) [27]	Korea	380	1994-2001	I-IV	NSCLC	FISH	Cappuzzo system or UCCC criteria	27 (7.1%) or 42 (11.1%)	NA	1.11 (0.7-1.76) p = 0.675 * ADC: 1.56 (0.66-3.69) * SQCC: 1.0 (0.45-2.24)	Age, sex, smoking, histology, stage, MET or EGFR IHC, EGFR- FISH
Dziadziuszko (2012) [28]	USA	140	NA	I-IV	NSCLC	SISH	Cappuzzo system	14 (10%)	0.88 (0.72-1.07) p = 0.19	0.90 (0.73-1.10) p = 0.29	Demographic and clinical features (not specified)
Sun (2013) [29]	China	61	2004-2008	I-IV	NSCLC	qPCR	> 3 copies	11 (18%)	NA	9.49 (2.5-35.85) p = 0.001	Stage, MET expression
Jin (2014) [30]	Korea	141	2003-2009	I	ADC	SISH	≥3.4 copies	34 (24.1%)	5.474 (2.16-13.85) p < 0.001	NA	NA
Kowalczuk (2014) [31]	Poland	151	2003-1020	I-IIIA	NSCLC	qPCR	> 3 copies	28 (18.5%)	1.21 (0.92-1.59) p = 0.175	1.03 (0.76-1.40) p = 0.849 * ADC: 1.17 (0.79-1.74) * SQCC: 0.65 (0.35-1.20)	Age, sex, smoking, stage, LN status, MET mRNA in tumor, Log2 (MET mRNA RQ), MET mRNA RQ
Noro (2015) [32]	Japan	35	2008-2010	III-IV	ADC with EGFR mutations	FISH	Colorado criteria	11 (31.4%)	NA	2.25 (1.07-4.74) p = 0.03	Univariate
Park (2015) [33]	Korea	316	2004-2011	I-IV	ADC	FISH	UCCC criteria	123 (38.9%)	NA	1.32 (0.88-1.98) p = 0.183	Age, differentiation, LN status, stage, EGFR-TKI, MET IHC, MET amplification
Inoue (2015) [34]	Japan	240	1990-2011	I-III	NSCLC	FISH	MET/CEP7 >2.0	28 (15.8%)	NA	1.32 (0.55-3.17)	Univariate
Tran (2016) [35]	Australia	300	1994-2002 2010-2012	I-III	NSCLC	FISH	UCCC criteria	22 (8.1%)	NA	0.35 (0.15-0.8) p < 0.05	Stage, vessel or lymphatic invasion, perineural invasion, histology, grade, MET IHC
Song (2016) [36]	China	791	2011-2014	I-IV	NSCLC without EGFR mutations	FISH	MET/CEP7 >2.2	8 (1%)	NA	1.97 (0.62-6.3) p = 0.251	Age, sex, stage, smoking, histology, MET expression
Tong (2016) [37]	China (Hong Kong)	687	1995-2011	I-IV	NSCLC	FISH	MET/CEP7 ≥5	8 (1.2%)	NA	3.44 (1.4-8.48) p = 0.007	Age,sex, smoking, stage, LN status, tumor size, MET mutation, MET IHC, EGFR mutations
Bubendorf (2017) [38]	Europe	1572	NA	I-III	NSCLC	SISH	Cappuzzo system	65 (4.1%)	0.86 (0.53-1.40)	0.84 (0.47-1.49)	Univariate
Al-Saad (2017) [39]	Norway	298	1990-2004	I-III	NSCLC	SISH	> 3 copies	18 (6%)	NA	2.29 (1.21-4.35) p = 0.011	Differentiation, performance status, stage,

NSCLC, non-small-cell lung cancer; ADC, adenocarcinoma; SQCC, quamous cell carcinoma; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; SISH, silver in situ hybridization; BISH, bright-field in situ hybridization; qPCR, real-time, quantitative polymerase chain reaction; pts, patients; HR, hazard ratio; CI, confidence interval; DFS, disease-free survival; OS, overall survival; IHC, immunohistochemistry; LN, lymph node; NA, not available; Cappuzzo system: MET FISH-positive group was defined by mean MET gene copy number ≥5 copies per cell; UCCC(University of Colorado Cancer Center) criteria: MET status classified into two groups according to the frequency of tumor cells with specific copy numbers of the MET gene and chromosome 7 centromere (FISH-positive: MET/CEP ratio ≥ 2; > 15 copies of MET signals in > 10% of tumor cells; small gene cluster [4-10 copies]; or innumerable tight gene clusters in > 10% of tumor cells); Colorado criteria: MET/CEP ratio ≥ 2 and mean MET per cell ≥ 5 copies.

Impact of high MET GCN on OS

From 20 studies [19-29, 31-39], a total of 7,506 patients were included in the meta-analysis of HRs for OS. Compared with patients with NSCLC showing low MET CNG, patients with tumors harboring high MET CNG showed significantly worse survival (HR = 1.45, 95% CI: 1.16-1.80, p = 0.001) (Figure 2A). There was a significant heterogeneity among studies (X^2 = 51.75, p < 0.0001, I^2 = 63%). Further analyses indicated that the observed heterogeneity was associated with the inclusion of the three studies by Dziadziuszko *et al.* [28], Sun *et al.* [29], and Tran *et al.* [35]. When excluding these studies from the meta-analysis for OS, less heterogeneity was observed (X^2 = 21.93, p = 0.15, I^2 = 27%) and the pooled results remained significant (HR = 1.39, 95% CI: 1.21-1.59, p < 0.0001) (Figure 2B)

Subgroup-analyses according to the histology and ethnicity

When we pooled HRs for OS according to histological subtypes (ADC or SQCC), the combined HRs were 1.41 (95% CI: 1.11-1.79, p = 0.005, fixed-effect model) for ADC and 1.25 (95% CI: 0.49-3.16, p = 0.64, random-effects model) for SQCC (Figure 3A and 3B).

For Asian populations, high MET CNG was significantly associated with a worse prognosis (HR = 1.58, 95% CI: 1.32-1.88, p < 0.00001, fixed-effect model), but this significant correlation was not observed for non-Asian populations (HR = 1.04, 95% CI: 0.75-1.44, p = 0.81, random-effects model) (Figure 4A and 4B).

Publication bias

We did not perform publication bias test for DFS because there was a small number of studies included. Begg's funnel plot and Egger's test indicated no evidence of substantial publication bias for OS (Begg's p = 0.113, Egger's p = 0.148) (Figure 5).

Discussion

The MET signaling pathway has recently emerged as a potential molecular target for the treatment of NSCLC. However, the survival impact of MET amplification is still controversial. In the current meta-analysis, we evaluated the prognostic value of MET CNG in patients with NSCLC.

Out of the included 21 studies, only five reported the data regarding DFS. The pooled analysis failed to show a significant correlation between high MET CNG and DFS (HR = 1.37, p = 0.16). Because a limited number of studies were included in the meta-analysis

and there was a significant heterogeneity among them (I^2 = 80%), our finding seemed not sufficient to determine the correlation between high MET CNG and DFS in patients with resected NSCLC. In terms of OS, however, the meta-analysis revealed that high MET CNG was associated with a worse prognosis (HR = 1.45, p = 0.001).

Subgroup analysis in the current study showed that high MET CNG significantly correlated with shorter survival especially in patients with ADC (HR = 1.41, p = 0.005). Because the subgroup analysis included a limited number of studies (only 3) in the SQCC group and there was a significant heterogeneity across them (I^2 = 78%), however, the prognostic significance of MET CNG in NSCLC according to the histology is still unclear. Go *et al.* reported that tumors with high MET CNG showed a significantly worse prognosis than those without MET amplification (HR = 3.37, p = 0.008) in NSCLC patients with SQCC [21]. These results suggest that MET amplification may be involved in the carcinogenesis of both ADC and SQCC in NSCLC. Subgroup analysis also showed a different prognostic impact of MET CNG between Asian (HR = 1.58, p < 0.00001) and non-Asian populations (HR = 1.04, p = 0.81). The effect of dual positivity for MET amplification and EGFR mutations might account for the different impacts of high MET CNG on the prognosis between Asian and non-Asian populations. However, the subgroup analysis included only 6 studies in non-Asian subset and there was a significant heterogeneity (I^2 = 72%) among them. Therefore, these data seemed not sufficient to determine the prognostic value of high MET CNG in non-Asian populations. Further studies are still needed to verify the prognostic role of MET amplification according to the histology or ethnicity in patients with NSCLC.

There has been a strong rationale for the development of MET inhibitors in NSCLC [49]. Increased MET signaling is linked to a worse prognosis for NSCLC [14-17]. Moreover, MET amplification has been described as a mechanism of acquired resistance to EGFR-TKIs in EGFR-mutant NSCLC [40-42]. The survival efficacy of MET inhibitors (onartuzumab and tivantinib) has been controversial, even in patients with NSCLC showing MET overexpression [50-57]. A couple of randomized trials reported that the addition of a MET inhibitor to erlotinib, an EGFR-TKI, was associated with improved survival in NSCLC patients with MET overexpression [50,56].
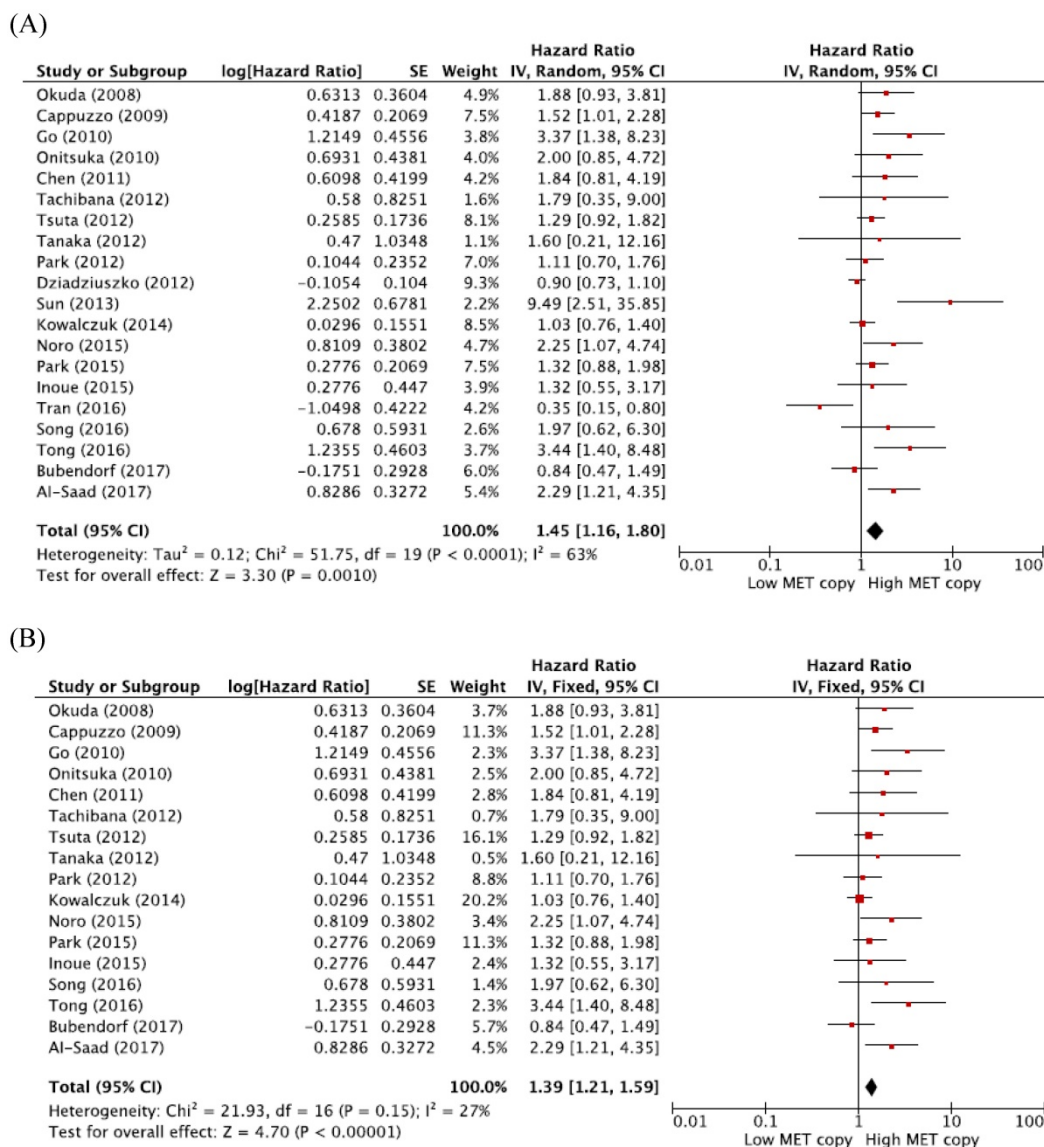
(A)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Okuda (2008)	0.6313	0.3604	4.9%	1.88 [0.93, 3.81]	
Cappuzzo (2009)	0.4187	0.2069	7.5%	1.52 [1.01, 2.28]	
Go (2010)	1.2149	0.4556	3.8%	3.37 [1.38, 8.23]	
Onitsuka (2010)	0.6931	0.4381	4.0%	2.00 [0.85, 4.72]	
Chen (2011)	0.6098	0.4199	4.2%	1.84 [0.81, 4.19]	
Tachibana (2012)	0.58	0.8251	1.6%	1.79 [0.35, 9.00]	
Tsuta (2012)	0.2585	0.1736	8.1%	1.29 [0.92, 1.82]	
Tanaka (2012)	0.47	1.0348	1.1%	1.60 [0.21, 12.16]	
Park (2012)	0.1044	0.2352	7.0%	1.11 [0.70, 1.76]	
Dziadziuszko (2012)	-0.1054	0.104	9.3%	0.90 [0.73, 1.10]	
Sun (2013)	2.2502	0.6781	2.2%	9.49 [2.51, 35.85]	
Kowalczuk (2014)	0.0296	0.1551	8.5%	1.03 [0.76, 1.40]	
Noro (2015)	0.8109	0.3802	4.7%	2.25 [1.07, 4.74]	
Park (2015)	0.2776	0.2069	7.5%	1.32 [0.88, 1.98]	
Inoue (2015)	0.2776	0.447	3.9%	1.32 [0.55, 3.17]	
Tran (2016)	-1.0498	0.4222	4.2%	0.35 [0.15, 0.80]	
Song (2016)	0.678	0.5931	2.6%	1.97 [0.62, 6.30]	
Tong (2016)	1.2355	0.4603	3.7%	3.44 [1.40, 8.48]	
Bubendorf (2017)	-0.1751	0.2928	6.0%	0.84 [0.47, 1.49]	
Al-Saad (2017)	0.8286	0.3272	5.4%	2.29 [1.21, 4.35]	
Total (95% CI)			**100.0%**	**1.45 [1.16, 1.80]**	

Heterogeneity: Tau² = 0.12; Chi² = 51.75, df = 19 (P < 0.0001); I² = 63%
Test for overall effect: Z = 3.30 (P = 0.0010)

Low MET copy High MET copy

(B)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Okuda (2008)	0.6313	0.3604	3.7%	1.88 [0.93, 3.81]	
Cappuzzo (2009)	0.4187	0.2069	11.3%	1.52 [1.01, 2.28]	
Go (2010)	1.2149	0.4556	2.3%	3.37 [1.38, 8.23]	
Onitsuka (2010)	0.6931	0.4381	2.5%	2.00 [0.85, 4.72]	
Chen (2011)	0.6098	0.4199	2.8%	1.84 [0.81, 4.19]	
Tachibana (2012)	0.58	0.8251	0.7%	1.79 [0.35, 9.00]	
Tsuta (2012)	0.2585	0.1736	16.1%	1.29 [0.92, 1.82]	
Tanaka (2012)	0.47	1.0348	0.5%	1.60 [0.21, 12.16]	
Park (2012)	0.1044	0.2352	8.8%	1.11 [0.70, 1.76]	
Kowalczuk (2014)	0.0296	0.1551	20.2%	1.03 [0.76, 1.40]	
Noro (2015)	0.8109	0.3802	3.4%	2.25 [1.07, 4.74]	
Park (2015)	0.2776	0.2069	11.3%	1.32 [0.88, 1.98]	
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Song (2016)	0.678	0.5931	1.4%	1.97 [0.62, 6.30]	
Tong (2016)	1.2355	0.4603	2.3%	3.44 [1.40, 8.48]	
Bubendorf (2017)	-0.1751	0.2928	5.7%	0.84 [0.47, 1.49]	
Al-Saad (2017)	0.8286	0.3272	4.5%	2.29 [1.21, 4.35]	
Total (95% CI)			**100.0%**	**1.39 [1.21, 1.59]**	

Heterogeneity: Chi² = 21.93, df = 16 (P = 0.15); I² = 27%
Test for overall effect: Z = 4.70 (P < 0.00001)

Low MET copy High MET copy

Figure 2. Meta-analysis of hazard ratios for overall survival. (A) Forest plot of 20 studies. (B) Forest plot of 17 studies excluding 3 with a significant heterogeneity.
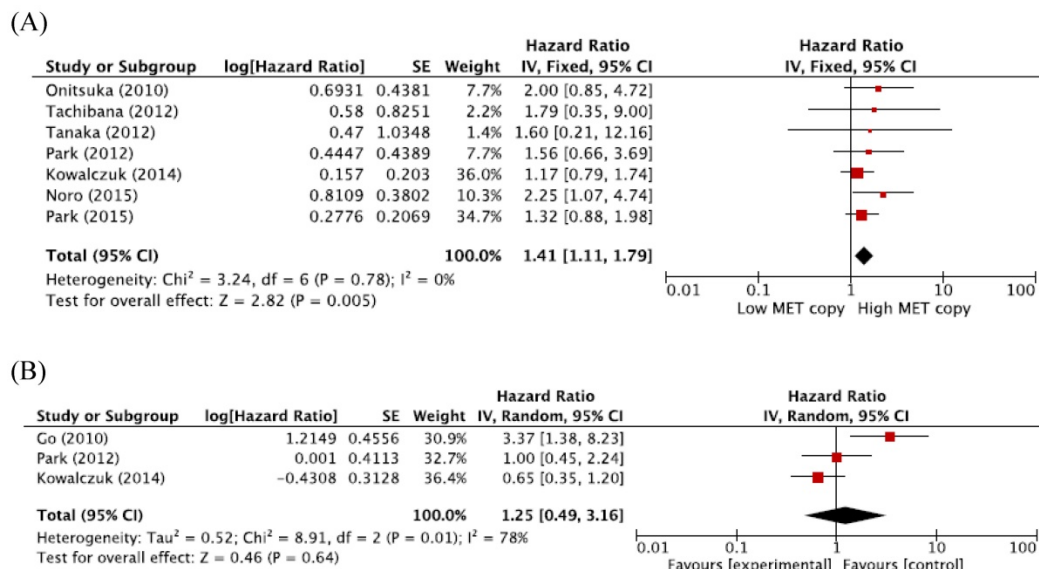
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Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
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Tachibana (2012)	0.58	0.8251	2.2%	1.79 [0.35, 9.00]	
Tanaka (2012)	0.47	1.0348	1.4%	1.60 [0.21, 12.16]	
Park (2012)	0.4447	0.4389	7.7%	1.56 [0.66, 3.69]	
Kowalczuk (2014)	0.157	0.203	36.0%	1.17 [0.79, 1.74]	
Noro (2015)	0.8109	0.3802	10.3%	2.25 [1.07, 4.74]	
Park (2015)	0.2776	0.2069	34.7%	1.32 [0.88, 1.98]	
Total (95% CI)			**100.0%**	**1.41 [1.11, 1.79]**	

Heterogeneity: Chi² = 3.24, df = 6 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.82 (P = 0.005)

Low MET copy High MET copy

(B)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Go (2010)	1.2149	0.4556	30.9%	3.37 [1.38, 8.23]	
Park (2012)	0.001	0.4113	32.7%	1.00 [0.45, 2.24]	
Kowalczuk (2014)	-0.4308	0.3128	36.4%	0.65 [0.35, 1.20]	
Total (95% CI)			**100.0%**	**1.25 [0.49, 3.16]**	

Heterogeneity: Tau² = 0.52; Chi² = 8.91, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 0.46 (P = 0.64)

Favours [experimental] Favours [control]

Figure 3. Subgroup meta-analysis of hazard ratios for overall survival according to the histology. (A) Forest plot of patients with adenocarcinoma. (B) Forest plot of patients with squamous cell carcinoma.
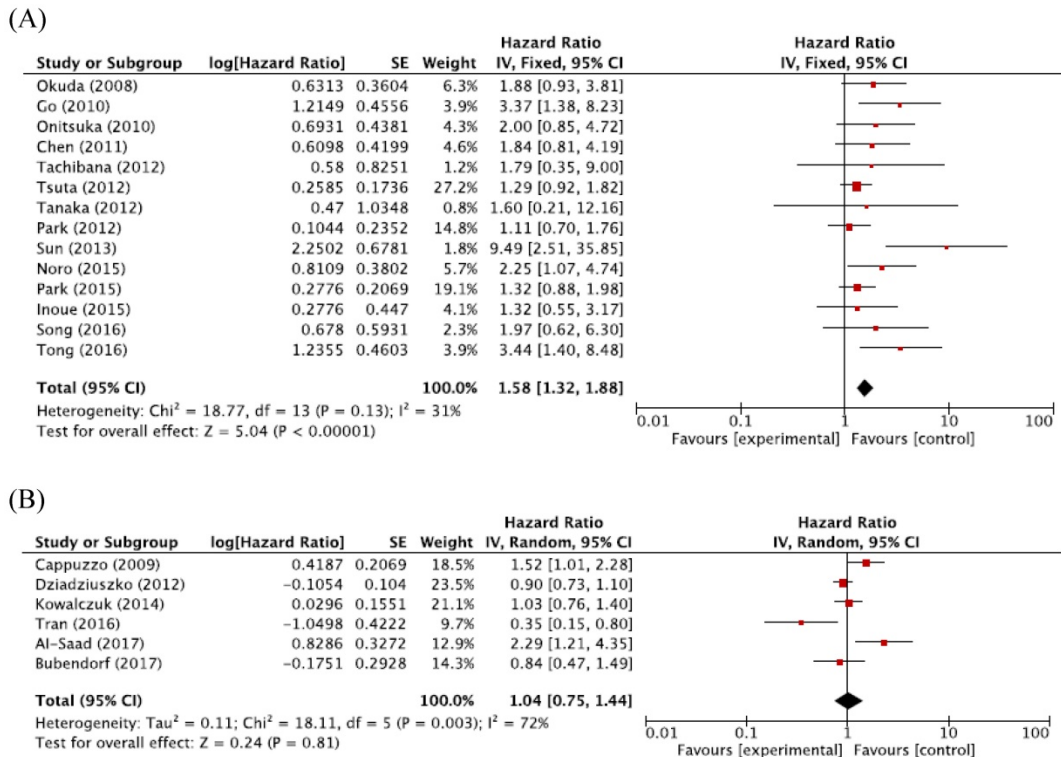
(A)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Okuda (2008)	0.6313	0.3604	6.3%	1.88 [0.93, 3.81]
Go (2010)	1.2149	0.4556	3.9%	3.37 [1.38, 8.23]
Onitsuka (2010)	0.6931	0.4381	4.3%	2.00 [0.85, 4.72]
Chen (2011)	0.6098	0.4199	4.6%	1.84 [0.81, 4.19]
Tachibana (2012)	0.58	0.8251	1.2%	1.79 [0.35, 9.00]
Tsuta (2012)	0.2585	0.1736	27.2%	1.29 [0.92, 1.82]
Tanaka (2012)	0.47	1.0348	0.8%	1.60 [0.21, 12.16]
Park (2012)	0.1044	0.2352	14.8%	1.11 [0.70, 1.76]
Sun (2013)	2.2502	0.6781	1.8%	9.49 [2.51, 35.85]
Noro (2015)	0.8109	0.3802	5.7%	2.25 [1.07, 4.74]
Park (2015)	0.2776	0.2069	19.1%	1.32 [0.88, 1.98]
Inoue (2015)	0.2776	0.447	4.1%	1.32 [0.55, 3.17]
Song (2016)	0.678	0.5931	2.3%	1.97 [0.62, 6.30]
Tong (2016)	1.2355	0.4603	3.9%	3.44 [1.40, 8.48]
Total (95% CI)			**100.0%**	**1.58 [1.32, 1.88]**

Heterogeneity: Chi^2 = 18.77, df = 13 (P = 0.13); I^2 = 31%
Test for overall effect: Z = 5.04 (P < 0.00001)

(B)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Cappuzzo (2009)	0.4187	0.2069	18.5%	1.52 [1.01, 2.28]
Dziadziuszko (2012)	-0.1054	0.104	23.5%	0.90 [0.73, 1.10]
Kowalczuk (2014)	0.0296	0.1551	21.1%	1.03 [0.76, 1.40]
Tran (2016)	-1.0498	0.4222	9.7%	0.35 [0.15, 0.80]
Al-Saad (2017)	0.8286	0.3272	12.9%	2.29 [1.21, 4.35]
Bubendorf (2017)	-0.1751	0.2928	14.3%	0.84 [0.47, 1.49]
Total (95% CI)			**100.0%**	**1.04 [0.75, 1.44]**

Heterogeneity: Tau^2 = 0.11; Chi^2 = 18.11, df = 5 (P = 0.003); I^2 = 72%
Test for overall effect: Z = 0.24 (P = 0.81)

Figure 4. Figure 5: Subgroup meta-analysis of hazard ratios for overall survival according to the ethnicity. (A) Forest plot of Asian patients. (B) Forest plot of non-Asian patients.

Figure 5. Funnel plot for publication bias regarding overall survival.

However, other randomized studies failed to show survival benefit of adding a MET inhibitor to first-line platinum-based chemotherapy or erlotinib in patients with high MET expression [51-53,55]. In the METLung study of 499 patients with NSCLC showing high MET expression (MET immunohistochemistry 2+ or 3+), especially, the addition of onartuzumab to erlotinib failed to prolong OS over placebo (HR = 1.27, p = 0.067) [51]. These results suggest that MET protein status may not be the optimal predictor for MET inhibitors in NSCLC. MET overexpression is a late

event consecutive to the transformed phenotype, deriving from transcriptional up-regulation of MET in absence of gene amplification or mutations or ligand-dependent autocrine or paracrine mechanism [10-12]. Thus, targeting MET pathway in the tumors with MET overexpression as a late event would probably not draw survival benefit. Therefore, there is a need to identify more specific biomarkers for defining the subset of patients benefiting from MET targeted agents. Emerging data have suggested that splice-site mutations (MET exon 14) or MET

amplification lead to significant responses to MET inhibitors [54,58-61]. In a randomized phase II study of erlotinib plus tivantinib or placebo in patients with previously treated NSCLC, the combination of erlotinib and tivantinib showed a consistent trend toward benefit in the small cohort with increased MET CNG [54]. In EGFR mutant NSCLC with showing acquired resistance to EGFR TKIs, the observed response rate of combining an EFGR inhibitor and a MET inhibitor (INC280) was 0% among patients with a mean MET/cell of < 5 and 40% among those with mean MET/cell ≥ 5 [60]. In addition, a recent phase I study of crizotinib (a MET/ALK/ROS1 inhibitor) in 14 patients with MET amplification reported a 0%, 17%, and 67% response rate in the low- (1.8 ≤ MET/CEP ratio ≤ 2.2), intermediate- (2.2 < MET/CEP ratio < 5), and high-MET amplification (MET/CEP ratio ≥ 5) groups, respectively [61]. Thus, MET amplification may represent a better predictive biomarker for MET targeted therapies, especially MET TKIs. However, determining the appropriate measure and threshold for MET amplification is one of the major challenges for clinical development of MET targeted therapies [62].

A variety of methods, such as qPCR, FISH, SISH, and BISH, are currently used for assessing MET amplification [43,44,62]. There are no standardized methods for detecting high MET CNG. In this meta-analysis, FISH was the most commonly used technique for determining MET CNG. FISH can be applied to formalin-fixed paraffin-embedded tumor tissues, thus facilitating the exclusive estimation of tumor cells [62]. However, the cut-off criteria for high MET CNG are various across studies [20,43,44,62,63]. The discrepancies in the prognostic value of MET CNG among studies might be attributable to the different cut-off points for defining MET amplification. Therefore, the definition of a reliable guideline for high MET CNG is an essential prerequisite for assessing the prognostic role of MET amplification and developing MET inhibitors in NSCLC.

Our study has several inherent limitations that needed to be discussed. First, the included studies showed considerable differences in the detection methods and cut-off criteria, types and numbers of target genes, tumor histology and stage, treatment, and other demographic or clinicopathological data. Second, there was a significant heterogeneity among the included studies (X^2 = 51.75, p < 0.0001, I^2 = 63%), which was primarily associated with the three studies by Dziadziuszko *et al.* [28], Sun *et al.* [29], and Tran *et al.* [35]. Sun *et al.* [29] employed RT-PCR that used the same primers and similar PCR conditions as others [19,22,31]. Tran *et al.* [36] employed FISH with the UCCC criteria [63], and Dziadziuszko *et al.* [28] used SISH that is a newly approved technology for gene copy assessment. Therefore, technical issue did not seem to address the heterogeneity. However, this variation might correlate with no standardized criteria for defining high MET CNG. Third, most studies were retrospectively performed and therefore might carry the biases of the retrospective design. Fourth, there already were two meta-analyses regarding the prognostic impact of MET CNG in NSCLC in the literature [43,44]. However, they included a relatively small number of articles reported before 2014. Our meta-analysis included additional 10 studies published between 2014 and 2017 [30-39], and most of them used more solid criteria for MET amplification. Finally, articles published only in English were included, which might bias the results.

In conclusion, our meta-analysis indicates that high MET CNG is an adverse prognostic factor in patients with NSCLC. Subgroup analysis suggests that high MET CNG is associated with a worse prognosis, especially in patients with ADC and Asian populations. However, large prospective studies using standardized methods based on the homogeneous populations are warranted to validate the prognostic value of MET amplification in patients with NSCLC.

Competing Interests

The authors have declared that no competing interest exists.

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