Original Article

A systematic and genome-wide correlation meta-analysis of PD-L1 expression and targetable NSCLC driver genes

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Background: Studies have shown that the ligand of programmed cell death protein 1 (B7-H1, CD274 or PD-L1) is related to lung cancer driver genes. Although studies have examined the association between lung cancer driver gene mutations or expression and PD-L1 expression, the present studies have not been mined the correlation systematically and genome-widely.

Methods: All relevant published PD-L1 articles with driver genes data and the RNA-seq dataset from The Cancer Genome Atlas (TCGA) were analyzed. We performed meta-analysis for data included in the selected literature, and then independently explored the correlation between genes by co-expression analysis of RNA-seq data in the TCGA database.

Results: A sum of 9,934 lung cancer cases were collected from 34 published studies. Higher PD-L1 expression was associated with wild-type epidermal growth factor receptor (EGFR) [odds ratio (OR): 0.68, 95% confidence interval (CI): 0.48–0.96, P=0.03], Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation (OR: 1.27, 95% CI: 1.02–1.58, P=0.03) or non-adenocarcinoma histology (OR: 0.68, 95% CI: 0.47–0.98, P=0.04). In addition, our analysis from TCGA data indicated that, compared with lung adenocarcinoma, the expression of PD-L1 was significantly higher than that of squamous cell carcinoma patients (P=0.023). The expression of targetable driver genes showed no correlations with PD-L1 expression in non-small cell lung cancer (NSCLC).

Conclusions: Our results suggest the presence of EGFR wild-type, KRAS gene mutations or squamous cell carcinoma were associated with high PD-L1expression, which provides potential benefited population for the administration of PD-1/PD-L1 blockade in human lung cancer.

Keywords: Programmed death-ligand 1 (PD-L1); driver genes; non-small cell lung cancer (NSCLC); The Cancer Genome Atlas (TCGA); immunotherapy

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Introduction

Targeted therapy and immunotherapy are innovative therapies for non-small cell lung cancer (NSCLC) after traditional chemotherapy and radiotherapy.

Though the later were considered as standard treatment for patients with advanced untargetable NSCLC (1), no more than one third of patients with metastatic NSCLC respond to platinum-based doublet chemotherapy (2). NSCLC is a disease sub-classified by molecular subsets with important driver oncogenes, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). In NSCLC patients with ALK translocation or EGFR mutation, molecular-targeted therapy is proved to be superior to chemotherapy (3,4), but acquired resistance after treatment initiation develops within 1 to 2 years in the majority of patients (5).

The binding of programmed death 1 (CD279, PD-1) molecules and its ligands PD-L1 and PD-L2 induces inhibitory immune signals, assisting the evasion of host immune response (6), which is immunotarget with therapeutic potential (7). Recently, blocking of the interaction has been reported as a promising strategy for NSCLC treatment (8-10). However, the appropriate combination of PD-1/PD-L1 blockade and the existing anti-cancer therapies are not clear.

High tumor mutational rate appears to contribute to enhanced tumor immunogenicity, indicating that there may be an increased sensitivity to immune checkpoint blockade in these tumors (11). Several studies have reported that the immune checkpoint inhibitor may be more effective in tumors bearing high levels of somatic mutations (10,12). Moreover, in terms of somatic mutation and tumor immunology, whether the gene mutation status related to tumor immune function is still unconfirmed.

Recently, the association between ALK, EGFR, and Kirsten rat sarcoma viral oncogene homolog (KRAS) status and PD-L1 expression are reported (13,14). However, the correlations between druggable NSCLC driver mutations and tumor PD-L1 expression remain inconclusive. Based on these results, a meta-analysis covering the current reported data from correlated studies in combination with a bioinformatic analysis of publicly available RNA sequencing data [from The Cancer Genome Atlas (TCGA)] was conducted to examine a creditable association between PD-L1 and targetable driver genes.

Methods

Search strategy for meta-analysis

All the potential articles in English were searched in the PubMed, Web of science and Embase databases. We use the keywords as: "B7-H1" or "CD274" or "PDL1" or "Programmed cell death 1 ligand 1" and "Programmed death-ligand 1" in combination with "lung cancer". Then we performed second round of searching by adding driver gene names such as ALK, EGFR, ROS1, MET, KRAS, BRAF, ERBB2, NRAS, PIK3CA or RET. The search was performed for records prior to September 1, 2016. The latest published studies will be used to analyze when the repeated population were included in different publications

Meta-analysis data collection

Included studies were based on the inclusion criteria as: (I) human lung cancer studies; (II) studies which reported the relationship between druggable genes alteration and tumor PD-L1 expression with defined level; (III) published in English. Exclusion criteria were: (I) case reports, conference abstract, editorials, expert opinions, letters, ongoing studies and reviews; (II) studies failed to extract or without usable data; (III) small cell lung cancer type; (IV) duplicate publications.

Data extraction

To find all appropriate researches, two researchers, based on the inclusion criteria, independently searched the available data for meta-analysis. We resolved our disagreements through discussion and consultation. The extraction data included the leading author, publication year, the lung cancer subtype, the patient ethnicity, the PD-L1 expression data, gene mutation state and the clinical variables. We assessed the quality of included studies by the Newcastle-Ottawa scale.

Summary effect analysis

All the analyses were conducted using the Review Manager 5.2. The results were presented in the form of pooled odds ratios (ORs) with 95% confidence interval (CI) and P value (less than 0.05 was considered as statistical

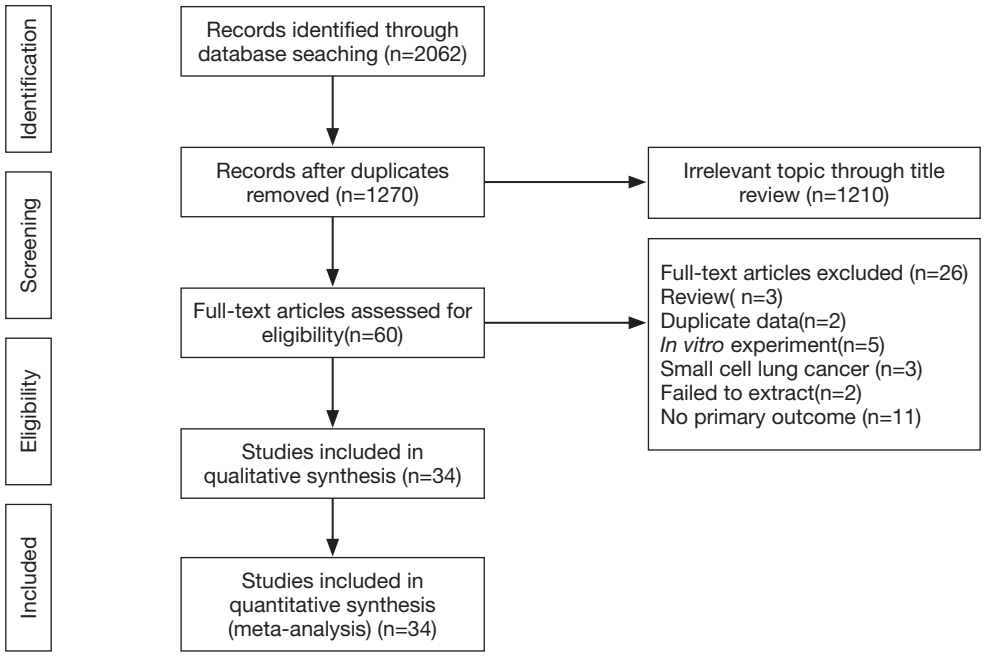

Figure 1 A flowchart illustrated the study selection process.

significance). The fixed effect mode (I^2 values <50%) and the random-effects model (I^2 values ≥50%) were used according to the outcome of heterogeneity. Subgroup and sensitivity analysis were stratified for predisposed factors when available.

Publication bias

The potential publication bias was minimized by extensive search strategy. The publication bias was visually assessed by graphical funnel plot. Begg's test was employed to detect funnel plot asymmetry.

TCGA lung cancer RNA-seq analysis

RNA expression information and the corresponding clinical data of 1,089 lung cancer cases were collected from TCGA level 3 RNA-seq database (http://cancergenome.nih.gov/). These datasets represent the normalized gene expression values of lung adenocarcinoma and lung squamous cancers and include 60,483 discrete genes. The associations of tumor PD-L1 expression and targetable lung cancer driver genes were calculated by Pearson correlation analysis and Z-test. We further used the Wilcoxon signed-rank test to examine whether there is a PD-L1 expression difference between lung adenocarcinoma and lung squamous cancers. Two genes were correlated if the correlation coefficient is more than 0.5.

Results

Literature retrieval results

The initial search obtained 1,270 potential datasets from publicly available literature. Of these, 1,210 were excluded since they lacked detailed data regarding PD-L1 and driver genes (expression or mutation). In the remaining 60 literature sources for full-text assessment, 34 were finally included for this meta-analysis. *Figure 1* summarizes the selection process.

Studies features

The total number of NSCLC patients was 9,934 cases, of which 6,202 were Asian origin. The expression rate of PD-L1 was 43.4% (95% CI: 37.4–49.6%). In the subgroup analysis, we found the overall PD-L1 expression rate was 45.3% (95% CI: 34.3–56.9%) in squamous cell lung cancer and 41.4% (95% CI: 34.1–49.2%) in adenocarcinoma. In addition, compared with the PD-L1 expression rate by studies from different ethnicities, the Asian population had

a higher expression rate of 47.5% (95% CI: 41.8–53.2%) than non-Asians population 34.5% (95% CI: 22.5–48.9%). *Table 1* shows the clinical and demographic features of the included studies.

PD-L1 expression is associated with EGFR expression

To explore the potential correlation between EGFR mutation and PD-L1 expression, we further subgroup-analyzed data obtained from twenty-one studies with 4,857 patients. Among 1,435 tumors with EGFR mutations, 608 (36.7%) had PD-L1 expression positive status, while 1,456 (44.1%) of 3,422 EGFR wild type tumors showed positive PD-L1 expression. A significant correlation (OR: 0.68, 95% CI: 0.48–0.96; P=0.03) between EGFR wild type and PD-L1 expression was found (*Figure 2A*).

KRAS mutation is associated with PD-L1 expression

Data extracted from sixteen studies, including a total of 3,295 cases, was analyzed the association between KRAS mutation and PD-L1 expression. In 528 patients with KRAS mutations, 215 (44.6%) patients were positive PD-L1 expressed, while 1,189 (42.2%) of 2,767 wild-type KRAS cases showed positive PD-L1 expression. In this analysis, we reported a significant association (OR: 1.27, 95% CI: 1.02–1.58; P=0.03) between KRAS mutation and PD-L1 expression in clinical dataset (*Figure 2B*).

The ALK status and PD-L1 expression

In 13 studies, including 3,576 patients, were previously reported the association between ALK translocation and PD-L1 expression. In tumors with ALK translocation, 89 (50.0%) of the 149 tumors specimen had positive PD-L1 expression, while 1,532 (42.8%) of 3,427 ALK wild type tumors stained as PD-L1 positive. In this analysis with large population, the correlation between ALK translocation and PD-L1 expression was unable to detect (OR: 1.23, 95% CI: 0.71–2.12; P=0.45) (*Figure 2C*).

Correlation between clinical features and PD-L1 expression

At the end of our literature review, fifteen studies, included 4,829 cases, had reported the association of histological types of lung cancer and PD-L1 expression. The positive expression rate of PD-L1 in adenocarcinoma tumors and non-adenocarcinoma tumors were 902 (33.3%) of 2,873 and 723 (42.5%) of 1,956, respectively. A significant correlation (OR: 0.68, 95% CI: 0.47–0.98; P=0.04) between the expression of PD-L1 and non-adenocarcinoma exists (*Figure 3A*). Moreover, we interrogated the lung adenocarcinoma and squamous lung cancer genome-wide RNA sequencing dataset of TCGA, consisting of 1,089 cases in total, and found significantly lower PD-L1 expression in lung adenocarcinoma than in lung squamous cancer (P=0.023) (*Figure 3A*). Similar to the mentioned meta-analysis process, we included thirty-two studies with 8,013 patients for studying the association between gender and PD-L1 expression, no significant association was found (OR: 0.87, 95% CI: 0.73–1.04; P=0.12) (*Table 2*). Likewise, clinical data including thirty studies with a total of 7,362 cases were used for the assessment of the association between smoking history and PD-L1 expression. However, our results showed that no significant association was indicated (OR: 1.20, 95% CI: 0.95–1.52; P=0.12) (*Table 2*).

Subgroup analysis

We conducted further subgroup analysis based on two major lung cancer histology (adenocarcinoma against squamous carcinoma). In the former, ALK translocation and KRAS mutation status is associated with PD-L1 expression (*Figure 3B-D*, *Table 2*). However, in lung squamous carcinoma, our results showed that the genetic status of EGFR, KRAS, gender or smoking status had no association with PD-L1 expression (*Figure 4A,B*, *Table 2*).

Genome-wide correlation analysis of PD-L1 and druggable genes

To further investigate whether the common NSCLC driver genes (*EGFR*, *KRAS*, ALK, *MET*, *ROS1*, *PIK3CA*, *RET*) were correlated with PD-L1 expression, we analyzed 1,089 patient data sets from TCGA level 3 RNA-seq using Pearson's correlation coefficient. There were weak or no correlation between PD-L1 expression level and druggable genes expression, ALK (r_a=0.149, r_s=0.033), BRAF (r_a=0.113, r_s=−0.05), EGFR (r_a=0.251, r_s=−0.044), ERBB2 (r_a=−0.195, r_s=−0.148), KRAS (r_a=0.006, r_s=0.006), MET (r_a=0.361, r_s=0.135), NRAS (r_a=0.225, r_s=−0.093), PIK3CA (r_a=0.308, r_s=0.115), RET (r_a=−0.17, r_s=−0.043) or ROS1 (r_a=0.295, r_s=0.074), in either lung adenocarcinoma (*Figure 4C*) or squamous cancer (not show).

Table 1 Demographic baseline and PD-L1 expression assessment of the studies

First author and year of publication	Classification of lung cancer	Ethnicity	Assessment of IHC staining	Cut off for PD-L1 positive	Reference
Kim 2015	SQCC	Asia	Percentage	10%	(15)
D'Incecco 2015	NSCLC	Non-Asia	H-score	10	(14)
Cooper 2015	NSCLC	Non-Asia	Percentage	50%	(16)
Chang 2015	LLC	Asia	Percentage	5%	(17)
Yang 2014	AD	Asia	Percentage	5%	(18)
Yang 2016	SQCC	Asia	Percentage	5%	(19)
Zhang 2014	AD	Asia	Quickscore	8	(20)
Tang 2015	NSCLC	Asia	H-score	5	(13)
Rizvi 2015	NSCLC	Non-Asia	Percentage	1%	(10)
Ji 2016	AD	Asia	H-score	10	(21)
Scheel 2016	NSCLC	Asia	Percentage	1%	(22)
Chang 2016	pleomorphic carcinoma	Asia	Percentage	5%	(23)
Fang 2015	LLC	Asia	Percentage	5%	(24)
Inoue 2016	NSCLC	Asia	H-score	5	(25)
Koh 2015	AD	Asia	Percentage	5%	(26)
Tao 2016	SCLC	Asia	Percentage	5%	(27)
Ameratunga 2016	NSCLC	Non-Asia	H-score	100	(28)
Velcheti 2014	NSCLC	Non-Asia	NA	NA	(29)
Mu 2011	NSCLC	Asia	H-score	Median value	(30)
Chen 2013	NSCLC	Asia	H-score	9	(31)
Chen 2012	NSCLC	Asia	H-score	3	(32)
Takada 2016	AD	Asia	Percentage	1%	(33)
Song 2016	AD	Asia	Percentage	5%	(34)
Song 2016	SQCC	Asia	H-score	5	(35)
Calles 2015	NSCLC	Non-Asia	Percentage	5%	(36)
Shimoji 2016	NSCLC	Asia	NA	NA	(37)
Schmidt 2015	NSCLC	Non-Asia	Percentage	5%	(38)
Sorensen 2016	NSCLC	Non-Asia	Percentage	1%	(39)
Chen 2016	NSCLC	Asia	Allred score	1	(40)
Jiang 2015	LLC	Asia	Percentage	5%	(41)
Sun 2016	NSCLC	Asia	Percentage	1%	(42)
Lin 2015	AD	Asia	H score	Mean H-score	(43)
Jia 2016	NSCLC	Asia	Percentage	10%	(44)
Huynh 2016	AD	Non-Asia	Percentage	5%	(45)

Quickscore = SI (staining intensity) × PPC (percentage of positive cells score). SI was determined as: 0, negative; 1, weak; 2, moderate; and 3, strong. PPC was defined as: 1, 0–4%; 2, 5–19%; 3, 20–39%; 4, 40–59%; 5, 60–79%; 6, 80–100%. H-score = summation (1+i)pi. PD-L1, programmed death-ligand 1; AD, adenocarcinoma; LLC, lymphoepithelioma-like carcinoma; NSCLC, non-small cell lung cancer; SQCC, squamous cell lung carcinoma.

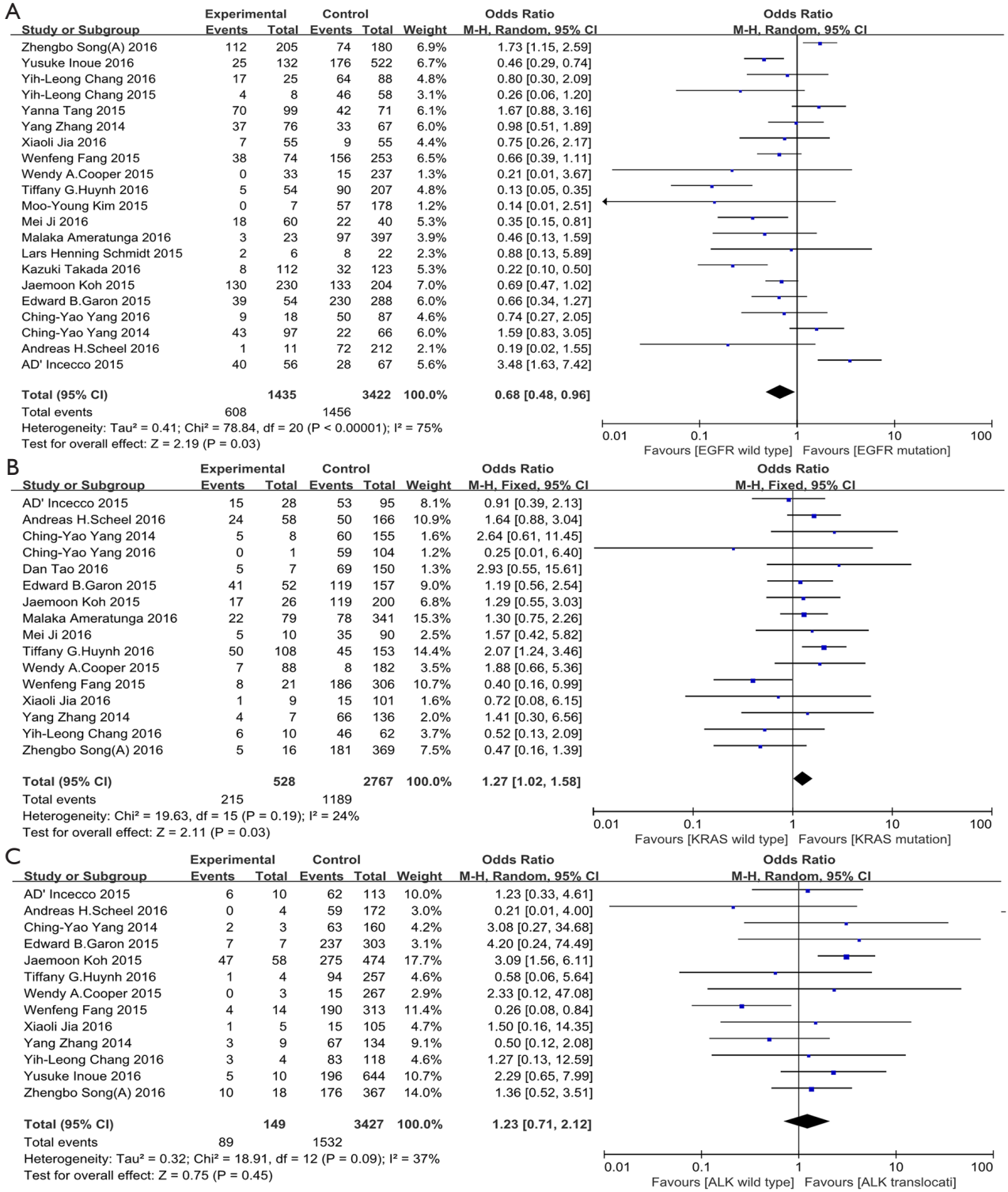

Figure 2 Forest plot represented the correlation between gene mutation and PD-L1 expression; (A) EGFR, (B) KRAS; (C) ALK. The event defined as positive PD-L1 expression. PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase.

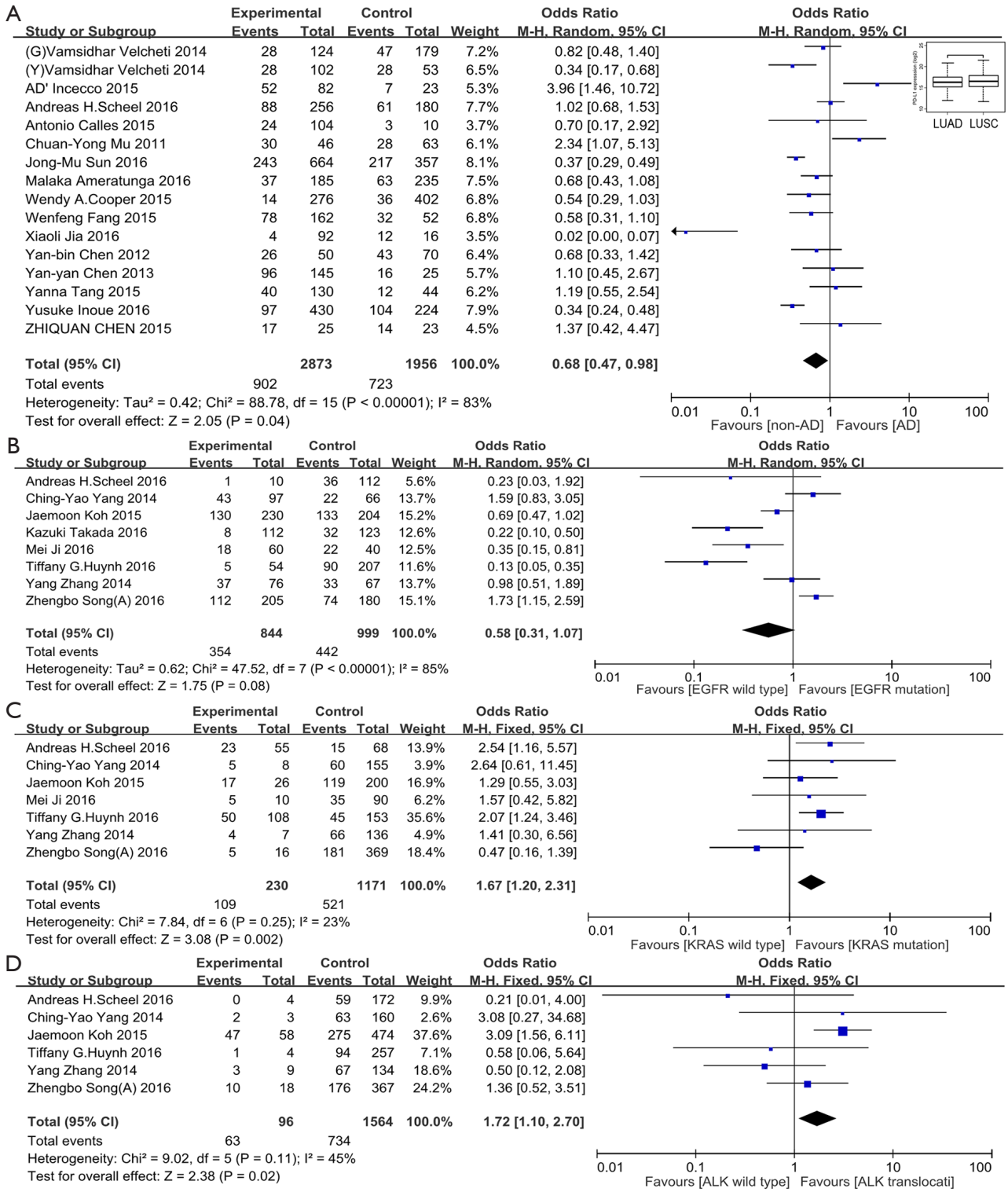

Figure 3 The relationship between clinicopathological characteristics and the expression of PD-L1. (A) PD-L1 expression difference between LUAD and non-AD or LUSC. The subgroup analysis (adenocarcinoma) for the association of (B) PD-L1 expression and EGFR alteration; (C) PD-L1 expression and KRAS alteration; (D) PD-L1 expression and ALK alteration. PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog; ALK, anaplastic lymphoma kinase.

Table 2 Summary of the association of lung cancer patients' gender and smoking with PD-L1

Types of lung cancer	Clinical features	No. of studies	OR	95% CI	P	Heterogeneity	I^2
Overall	Male *vs.* female	32	0.87	0.73–1.04	0.12	0.0001	56%
	Non-smoking *vs.* smoking	30	1.20	0.95–1.52	0.12	0.00001	70%
Adenocarcinoma	Male *vs.* female	10	0.82	0.61–1.10	0.18	0.01	57%
	Non-smoking *vs.* smoking	10	1.48	0.92–2.38	0.11	<0.0001	77%
Squamous carcinoma	Male *vs.* female	6	1.32	0.87–2.00	0.19	0.19	32%
	Non-smoking *vs.* smoking	6	1.19	0.79–1.78	0.41	0.36	9%

PD-L1, programmed death-ligand 1; OR, odds ratio; CI, confidence interval.

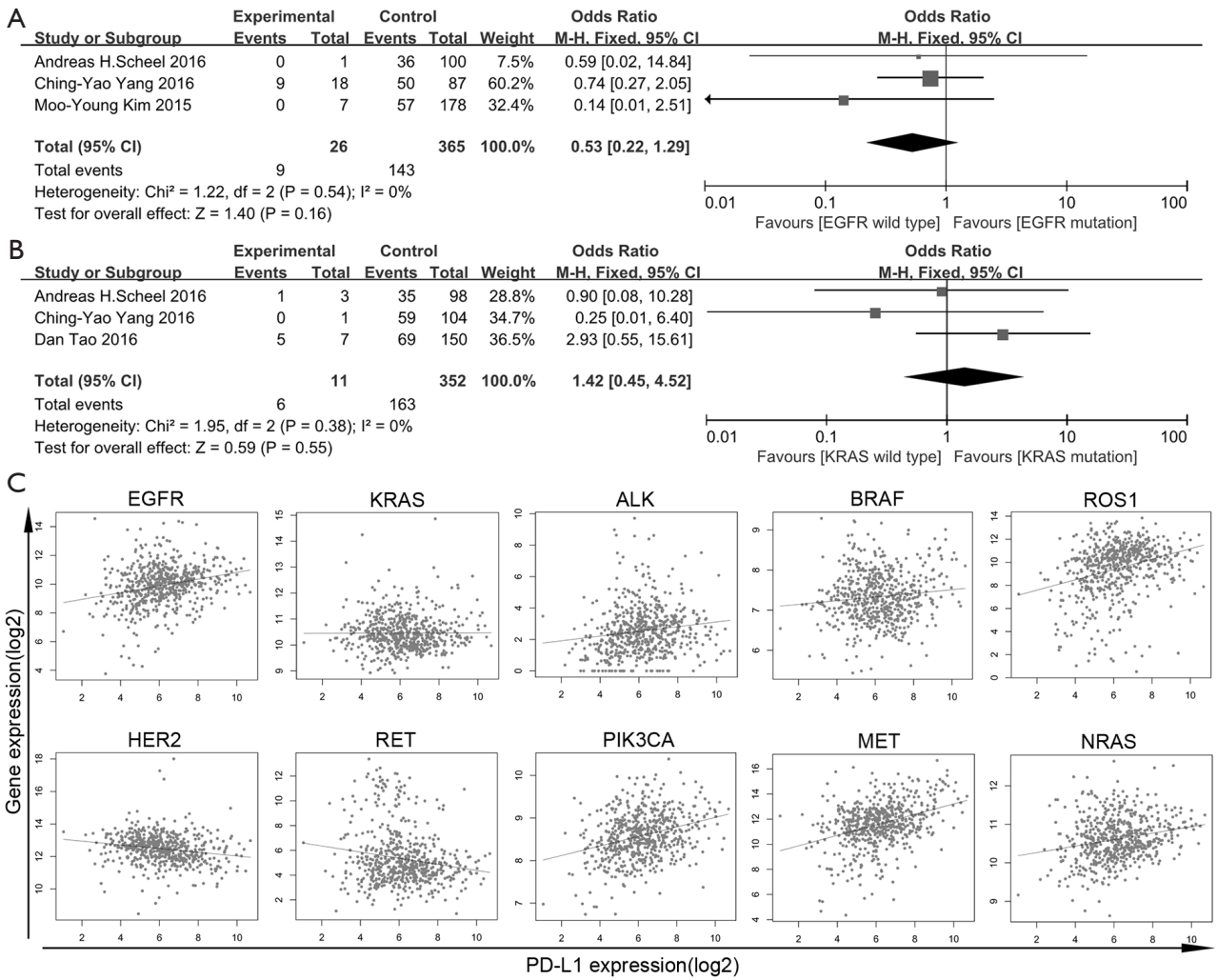

Figure 4 The correlation of gene alteration and PD-L1 expression. The subgroup analysis (squamous cell lung cancer) of the association between (A) EGFR alteration and PD-L1 expression; (B) KRAS mutation and PD-L1 expression; (C) the association between common lung cancer driver genes expression in lung adenocarcinoma and PD-L1 expression. PD-L1, programmed death-ligand 1; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma viral oncogene homolog.

Discussion

Blocking the binding between PD-L1 and its receptor is a promising therapeutic strategy for cancer immunotherapy, which is a new paradigm for the NSCLC treatment. But none of previous studies extensively explored the association of somatic gene mutation or expression and PD-L1in lung cancer. In our analysis, we found that wild-type EGFR lung cancer patients, KRAS mutation and non-adenocarcinoma histological type were associated with lung cancer PD-L1 expression. However, in mRNA level PD-L1 expression did not correlate with the expression of druggable driver genes.

In this meta-analysis, we found that PD-L1 expression inclined to be associated with wild-type EGFR, but not with EGFR mutation. In previous studies, investigators showed that PD-L1 expressed higher in EGFR-mutant NSCLC cells than in EGFR-wild-type cells (46-48), suggesting that PD-L1 is expressed differently and may function through independent mechanism by EGFR states. In notice, therapeutic effect of anti-PD-1/PD-L1 immunotherapy is associated with the PD-L1 expression level. For example, studies have demonstrated that first-line immunotherapy with pembrolizumab can significantly improve survival in EGFR- or ALK-wildtype and high PD-L1 expressed patients (49). On the contrary, in lung cancer patients with EGFR mutations, the response rate of PD-1 antibodies is low in comparison with wild-type EGFR patients (50-52). For our results revealed that PD-L1 expression is not correlated with EGFR mutation and previous clinical trial showed that PD-1/PD-L1 inhibitors are ineffective in patients with EGFR mutation, it gives us reason to believe that the therapeutic discrepancy is caused by altered immune state after EGFR mutation.

Some studies have reported ALK acts as a regulatory molecule in PD-L1 expression via *in vitro* experiments (53,54). EML4-ALK can positively regulate PD-L1 expression in NSCLC through activating MEK-ERK and PI3K-AKT signaling pathways (53,55). Koh *et al.* further proved that EML4-ALK mediated PD-L1 up-regulation in pulmonary adenocarcinoma (26). However, our results showed that no significant correlation in clinical samples between ALK translocation and PD-L1 exists. There may be several reasons for this seeming discrepancy. Firstly, compared to clinical samples with heterogenicity, in-vitro studies were limited to monoclonal cell lines culture. Secondly, the presented study was performed on a large-scale collection of clinical data with varied sample size, baseline clinical characteristics and the definition of positive PD-L1 expression. Even if PD-L1 expression can affect the function ALK expression and EML4-ALK, or vice versa, following our negative results obtained from large-scale comprehensive analysis, the heating prospect of PD-1/PD-L1 inhibitor combined with ALK multi-target protein kinase inhibitor is insecure.

To analyze the association between *KRAS* gene mutation and PD-L1 expression, we found that *KRAS* gene mutation is related to PD-L1 expression, suggesting that PD-L1 overexpression could be driven or activated by *KRAS* gene mutation. This indicates that patients with *KRAS* gene mutations may be beneficial from PD-1/PD-L1 blockade. Further clinical trials are warranted for this seemingly therapeutic alternative.

As shown by our meta-analysis, we observed a significant PD-L1 expression difference between lung adenocarcinoma and non-adenocarcinoma lung cancer. We also observed, via TCGA RNA-seq data, that PD-L1 expression was significantly lower in patients with adenocarcinoma than in those with lung squamous cell carcinoma (P=0.023). Clinical data indicate that patients with squamous tumors and who were administrated with immunotherapy had higher overall responses rates (ORR) than patients with non-squamous tumors (56). It provides evidence that a potential biomolecular mechanism exists for the explanation of different ORR and PD-L1 expression level in the two major types of lung cancer.

From the current literature, we reported that the presence of EGFR wild-type, KRAS mutations and pulmonary non-adenocarcinoma were associated with expression of PD-L1. While the correlations of PD-L1 and other druggable driver genes are limited. This suggests that for certain subset of lung cancer, PD-1/PD-L1 blockade may have the priority of use as a first line therapeutic strategy, which consisted to the up-to-date concept that higher PD-L1 expression, greater clinical benefit in lung cancer patients (57,58). Though we are the first to apply bioinformatic analysis and meta-analysis to answer whether the current targetable NSCLC driver genes associated with PD-L1 expression, further researches from bench to bed are warranted to verify the benefit of anti-PD-1/PD-L1 combined with modern anti-cancer strategies prior to its extensive clinical applications.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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