Prognostic value of tumor mutation burden in non-small cell lung cancer: A Meta-Analysis and system review

kun zou(Former Corresponding Author)
central hospital of wuhan, Tongji Medical College of Huazhong University of Science and Technology
https://orcid.org/0000-0002-0320-3976
Li Li
central hospital of wuhan, Tongji Medical College of Huazhong University of Science and Technology
Shuailong Yang
central hospital of wuhan, Tongji Medical College of Huazhong University of Science and Technology
Zhang Lei(New Corresponding Author) (leizhangwhzx@163.com)

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Abstract

Background: We performed this meta-analysis to assess the prognostic value of tumor mutation burden (TMB) for patients with non-small cell lung cancer (NSCLC).

Methods: Tow authors independently searched the studies in PubMed, web of science, Google Scholar, Cochrane library (from inception to November 2019), according to the key words “non-small cell lung cancer”, “tumor mutation burden”, “prognosis”. The studies were set up according to the inclusion/exclusion criteria. The estimate hazard ratio (HR), odds ratio (OR), risk ratio (RR) and their 95% confidence intervals (95% CIs) were set as effect measures. All analyses were performed by STATA 12.0.

Results:28 studies were involved in this meta-analysis, high TMB was associated with good overall survival (OS) (HR=0.53; 95% CI: 0.42-0.67, p<0.001), progression-free survival (PFS) (HR = 0.53; 95% CI: 0.46-0.62, p<0.001), durable clinical benefits (RR = 2.27; 95% CI: 1.79-2.89, P<0.001), and object response rate (RR = 2.27; 95% CI: 1.80-2.85; p<0.001) in patients treated with immune checkpoint inhibits (ICIs). For treated with non-ICIs, poor PFS (HR = 1.62; 95% CI: 1.27-2.07, p<0.001) and OS (HR = 1.56; 95% CI: 1.30-1.87, p=0.001) was found in high TMB. Compared with chemotherapy, ICIs treatment alone had better OS (HR = 0.68; 95% CI: 0.56 to 0.82, p<0.001) and PFS (HR = 0.64; 95% CI: 0.55 to 0.76, p<0.001) for patients with high TMB, however, for low TMB patients, no benefit was found in ICIs treatment. TMB was correlated with EGFR status (OR = 0.28; 95% CI: 0.08- 0.95; p= 0.040), ECOG score (OR = 1.79; 95% CI: 1.09-2.92; p=0.021) and smoking history (OR = 6.01; 95% CI: 1.28 - 28.13; p=0.023).

Conclusions: TMB was associated with better survival in cancer patients receiving immunotherapy, and worse survival in cancer patients receiving non-ICIs. Compared with chemotherapy, ICIs was more effective in high TMB patients, but not in low TMB patients.

Background

Lung cancer is the most common histologic malignant tumor in the world. Most of them are non-small cell lung cancer, and the prognosis of NSCLC is relatively poor[1]. Over the past decades, the 5-year survive rate is around 15%-30% in patients with unresectable lung cancer or distant stage [2].In recent years, the treatment strategy of NSCLC has changed dramatically. Immunotherapy has greatly improved the long-term survival of patients. In view of the significant clinical research results, Immunotherapy is approved for second-line treatment or combination chemotherapy for first-line treatment in NSCLC[3].Although immunotherapy has revolutionary improved the treatment in advanced NSCLC, the objective response rate is relatively low (about 50% for first-line treatment[4] and 30% for second-line treatment[5]), and most patients cannot benefit from immunotherapy, patient selection is still a challenge.

Cancer is a genetic disease,and its occurrence and development is a process of somatic mutation accumulation in cell DNA. Genomic sequencing studies have demonstrated that tumors, such as NSCLC, with particularly high number of somatic mutations, are more likely to respond to immunotherapy[6].TMB is usually defined as the total somatic mutations or mutations per analyzed genomic region in tumor

tissues, and it has emerged as an indirect measure of genomic instability and neoantigens in tumor. Tumor-specific mutations may lead to the production of neoantigens and increase of immunogenicity in tumor. And thus, a large number of cytotoxic T lymphocytes target tumor cells to cause T cell immune response and increase the sensitivity to immune checkpoint inhibits (ICIs)[7]. In recent years, more and more studies show that TMB may serve as a promising prognostic biomarker in NSCLC.

Recently, the meta-analysis has shown that TMB is a reliable biomarker in predicting treatment outcomes of cancer patients, especially for patients receiving ICIs[8]. As the limited studies, the prognostic value of TMB in NSCLC is not clear. Based on the phase 2 TMB data from CheckMate 026 trail[9], high TMB was demonstrated with better immune efficacy. Contrary to low/medium TMB, patients with high TMB had longer PFS and higher ORR in nivolumab group, however, patients with high TMB trended to have worse PFS and ORR in chemotherapy group. Among the patients with a high TMB, the response rate was higher (47% vs. 28%), and progression-free survival was longer (median, 9.7 vs. 5.8 months) in the nivolumab group than chemotherapy group, but no difference was found for OS between nivolumab group and chemotherapy group. The similar result was also found in patients treated with atezolizumab[10] and pembrolizumab[11].Besides, some new research was published with new sight of the value of TMB in NSCLC patients treated with non-ICIs (such as surgery, chemotherapy, molecular target therapy), and controversial results were found[12–14].

With the controversies existed in the prognostic role of TMB for non-small cell lung cancer, here, we conducted the meta-analysis of published studies to evaluate the prognostic value of TMB in NSCLC patients treated with ICIs or non-ICIs and explore the value of TMB for monitoring treatment efficacy, determining treatment strategies, and predicting survival of NSCLC patients.

Methods

Search Strategy

Two authors (ZK and LL) systematically searched the studies independently with key words “non-small cell lung cancer”, “NSCLC”, “tumor mutation burden”, “TMB”, “prognosis” in PubMed, web of science, Google Scholar, Cochrane library (from inception to November 2019) without language limitation. The clinical trial registration website was also searched to gain information of other potentially relevant studies. The difference of the retrieves between the two authors was confirmed by the third author (YSL).

Outcomes and inclusion, exclusion criteria

Primary outcomes were the prognostic effect of TMB on overall survival (OS), progression-free survival (PFS), durable clinical benefit (DCB) and objective response rate (ORR) in NSCLC patients treated with ICIs and/or non-ICIs. The prognostic effect on efficacy between ICIs and chemotherapy and the correlation on clinical characteristics of TMB was set as the secondary outcomes. The inclusion criteria: (1) studies evaluate the association between the tumor mutation burden and either OS or PFS; (2) sufficient data to calculate a hazard ratio (HR)，risk ratio (RR) or odds ratio (OR) and 95% confidence

interval (95%CI); The exclusion criteria: (1) outcome is not clear or the apparent paradox exists; (2) no sufficient data can be used to calculate the outcome; (3) the publication of the lack of reliability.

Data Extraction

Data retrieved from the studies included: first author's name, year of publication, number of patients, cut-off of TMB, detection method, country, treatment, research design, programmed cell death protein ligand 1(PDL-1) status, end point (PFS, OS) and hazard ratio (HR) etc. For studies with multiple arms (i.e. discovery and validation cohort), multiple treatment (i.e. monopoly immunotherapy, combination immunotherapy and chemotherapy), different sex (i.e. male and female) or multiple detection method (i.e. WES and NGS), each of the subgroups was considered an independent data set. If the original study did not show the HR and its 95%CI for survival outcome directly, we calculated these values from available reported data by using the software designed by Tierney et al.[15]In order to assess the quality of retrieved studies, we used the Newcastle– Ottawa scale (NOS) with the definition of a high-quality study of at least six stars[16]. All data extraction and quality assessment was performed independently by two investigators (LL and LZ), and any disagreement between the reviewers was resolved by consensus. This meta-analysis follows the QUORUM and the Cochrane Collaboration guidelines (http://www.cochrane.de) for reporting meta-analysis PRISMA statement).

Statistical Analysis

STATA 12.0 package (StataCorp, College Station, TX, USA) was used to analyze the data in our meta-analysis. The estimated HR was used to evaluate the prognostic effect (PFS and OS) and HR>1 reflects more deaths or progression in the high TMB arm or ICIs treated arm, and the estimated risk ratio (RR) was used to evaluate the efficacy of ICIs (DCB and ORR) and odds ratio (OR) summarized the association between TMB and clinical characteristics in NSCLC. All statistical values (pooled HR, RR and OR) were combined with a 95% CI and the p-value threshold was set at 0.05. Heterogeneity was assessed by I^2inconsistency test andX^2-based Cocran's Q statistic test and I^2>50%, or p<0.1 indicated significant heterogeneity[17]. The random effect model was used with significant heterogeneity between studies, or the fixed effects model conversely[18]. Publication bias was detected by Begg's test and Egger's test. P<0.05 was considered of significant publication bias[19]. Furthermore, subgroup analyses of PFS and OS in patients treated with ICIs were made according to PDL-1 status, detection method, research design, treatment, TMB cutoff and score of the quality assessment. Sensitivity analysis was also performed to evaluate the reliability of pooled results if studies were with significant heterogeneity and involved studies less than five.

Result

According to the above retrieval method, 377 potentially relevant studies were assessed. Detailed steps were shown in Fig 1. After the selection procedure, 28 studies were finally included[6,9-14,20-40], 18 studies with a total of 3830 NSCLC patients were treated with ICIs, and 9 studies with 2038 NSCLC

patients were treated with non-ICIs. 5 studies with 1146 NSCLC patients investigated the different efficacy between ICIs and chemotherapy. 5 studies provided the association between TMB and clinical characteristics. The basic characteristics and the quality assessment of these studies were showed in Table 1. These studies were published between 2015 and 2019.

For the involved studies with patients treated with ICIs, 2 studies targeted the PDL-1 positive patients, and the others targeted the unselected patients. 11 studies were treated with anti- PD-(L)1 monotherapy, seven were anti- PD-(L)1 and anti-CTLA-4 combination therapy. The cutoff of TMB ranged from 5.73 Mut/Mb to 20 Mut/Mb with a media cutoff of 10 Mut/Mb between the retrieved studies detected by NGS, which ranged from 157 Mut to 248 Mut with a media cutoff of 200 Mut for studies detected by WES, and four studies used the media value as the cutoff and those studies were categorized as relatively low-TMB cutoff groups.

Prognostic value of TMB in patients treated with ICIs

19 data from 15 studies were available for PFS in patients treated with ICIs, the pooled HR was 0.53 (95% CI: 0.46-0.62, p<0.001) (Fig 2a), as the significant heterogeneity (I^2=31.8% and p=0.091), a random effect model was used. The notable heterogeneity was also found on OS (I^2=61.8%, P=0.004), and the pooled HR for OS was 0.53 (95% CI: 0.42-0.67, p<0.001) (Fig 2b) and a significant difference was found. The results indicated that high TMB was with significant prognostic value for NSCLC patients treated with ICIs. Compared with low TMB, high TMB can reduce the risk of deaths or progression by 47%.

ORR and DCB of TMB in patients treated with ICIs

10 data from 8 studies was available for ORR. No significant heterogeneity was found (I^2=0.0%, p=0.746), the pooled RR was 2.27(95% CI: 1.80-2.85, p<0.001) (Fig 2c) with a fixed effects model. Compared with the low TMB population, the high TMB population has a higher therapeutic efficiency when treated with ICIs.

Durable clinical benefit (DCB) was defined as the percentage of patients who achieved complete response or partial response or stable disease lasted > 6 months. For DCB, 9 data from 6 studies was available with no significant heterogeneity, and the fixed effects model was used. The pooled RR was 2.27 (95% CI: 1.79-2.89, p<0.001) (Fig 2d). This suggested high TMB was associated with long duration of treatment response for NSCLC patients treated with ICIs. The rate of DCB in high TMB patients was 2.27 times higher than low TMB patients.

Subgroup analyses on PFS and OS in patients treated with ICIs

With the significant heterogeneity on PFS and OS for patients treated with ICIs, we did the subgroup analyses to evaluate the reliability of the pooled results and clarify the intra-study inconsistencies according to the variables mentioned above (such as PDL-1 status, detection method, research design,

treatment, TMB cutoff and score of the quality assessment). The results were shown in table 2. High TMB was with significant prognostic value for OS and PFS, and demonstrated a decrease of risk for deaths or progression in patients treated with ICIs among all subgroups. The pooled HR on PFS and OS in monotherapy, high TMB-cutoff and quality score subgroup was more conspicuous compared with that of its paired subgroup. The prognosis value of high TMB in patients treated with anti-PDL-1 monotherapy or with higher TMB boundary value may be more remarkable. When the subgroup analyses were made by PDL-1 status, no matter in unselected population or PDL-1 positive population, high TMB had better OS and PFS than low TMB. The HR on PFS and OS in PDL-1 positive population was 0.60 (95% CI: 0.50-0.73, p<0.001) and 0.66 (95% CI: 0.47-0.93, p=0.016), respectively. For the significant heterogeneity between these studies, we found it dropped to insignificant level in both subgroups when studies were stratified by study design. The study design may be the main resource of the heterogeneity in our meta-analysis.

Prognostic value of TMB in patients treated with non-ICIs

9 studies were retrieved in our meta-analysis to explore the prognostic value of TMB in patients treated with non-ICIs, and the results were shown in figure 3. 7 studies mentioned the difference on PFS between high TMB and low TMB population for patients treated with non-ICIs. With relatively consistency between these studies (I^2=37.9%, p=0.140), a fixed model was used and the pooled HR on PFS was 1.62 (95% CI: 1.27-2.07, p<0.001) (Fig 3a). 6 studies were used to explore OS. Significant heterogeneity was found, and the pooled HR was 1.56(95% CI: 1.30-1.87, p=0.001) (Fig 3b). These results indicated that high TMB was a poor prognostic value in NSCLC patients treated with non-ICIs. There were more deaths, tumor progression or recurrence in high TMB patients than low TMB patients, when treated with non-ICIs.

Efficacy between ICIs and chemotherapy according to the level of TMB

5 retrieved studies in our meta-analysis investigated the efficacy comparison for ICIs versus chemotherapy according to the level of TMB. As the result of the multiple arms and treatment, multiple independent data were collected. For the patients with high TMB, 7 data were available for PFS, 5 for OS. The fixed effect model was used with no obvious heterogeneity. The pooled HR for PFS was 0.64 (95% CI: 0.55 to 0.76, p<0.001) (Fig 4a), while the pooled HR for OS was 0.68 (95%CI: 0.56 to 0.82, p<0.001) (Fig 4b). For the patients with low TMB, the pooled HR for PFS and OS was 1.13 (95% CI 0.86 to 1.49, p=0.371) (Fig 4c) and 0.76 (95% CI 0.61 to 0.94, p=0.013) (Fig 4d), respectively. Since the significant heterogeneity and limited data for efficacy in patients with low TMB, the sensitivity analysis was performed to evaluate the reliability of pooled results. The result for PFS was stable after eliminate any of the involved data (Fig 4e), however the result for OS changed obviously (Fig 4f). The pooled HR became with no statistical difference. Thus, we thought the pooled result for OS in patients with low TMB was not reliable, and the efficacy of ICIs may not better than chemotherapy in low TMB NSCLC patients.

Correlation between TMB and clinical characteristics

5 studies provided the data to evaluate the correlation between TMB and clinical characteristics, and the results were shown in table 3. We found that TMB was associated with EGFR status, ECOG score and

smoking history. The pooled OR for smoking history was 6.01 (95% CI: 1.28-28.13) by random effect model (I^2=66.3%, P=0.031). The high TMB patients tend to more common in current or before smoking history than the low TMB patients. With no significant heterogeneity, the pooled OR for EGFR status and ECOG score was 0.28 (0.08- 0.95) and 1.79 (1.09- 2.92) respectively. High TMB is more frequency in EGFR wild type and high ECOG score patients than the paired group. The TMB was no associated with gender, stage of disease and line of therapy (the OR was 1.00, 1.20 and 0.74 with no statistical difference, respectively).

Publication Bias

Publication bias was made for prognostic values of patients treated with ICIs, and detected by Begg's test and Egger's test. $p<0.05$ confirmed the existence of publication bias. No publication bias was shown in PFS (Begg's p=0.276, Egger's p=0.144) and OS (Begg's p=0.213, Egger's p=0.209).

Discussion

Immune Checkpoint inhibits is by now an accepted treatment progression in cancer especially in NSCLC. Because of the widely immune resistance, most patients do not benefit from the treatment. To seek approaches to circumvent immune resistance, more understanding about the genetic and biologic factors that affect anticancer immune response is needed and finally to find promising prognostic biomarkers of ICIs treatment, thus patients can receive appropriately personalized treatment and gain better efficacy. In recently, TMB as the total somatic mutation of tumor represented indirectly biomarker of neoantigens in tumor and showed a promising prognostic value in NSCLC[41, 42]. For the moment, this is the firstly meta-analysis to assess the value of TMB for prognosis, efficacy evaluation and treatment options in NSCLC patients. In this meta-analysis, we demonstrated that TMB was a reliable predictive biomarker for NSCLC patients. Our results indicated that high TMB was associated with good prognosis and efficacy in patients with ICIs treatment. High TMB patients could gain longer prognosis and duration of response than low TMB patients by treated with ICIs. The efficacy (ORR and DCB) of ICIs in high TMB patients was also superior to low TMB patients. However, high TMB was demonstrated with poor prognosis in patients receiving non-ICIs treatment, and high TMB was associated with more deaths, tumor progression or recurrence than low TMB in patients treated with non-ICIs (such as, surgery, molecular targeted therapy or chemotherapy). We further found that TMB could be used in the selection of appropriately treatment for NSCLC patients. Compared to chemotherapy, the immunotherapy was more effective in high TMB patients, but not in low TMB patients.

Up to now, a growing number of studies showed the ICIs could provide a substantial clinical benefit and gradually change the treatment strategy in part of NSCLC patients. But it is still a challenge to identify appropriate population who are more effective to ICIs. In this meta-analysis, we firstly evaluated the prognostic value of TMB in NSCLC patients treated with ICIs, and our findings suggested that high TMB was associated with clinical benefits of ICIs compared to low TMB group, both in survival time and response rates. Additionally, high TMB patients could gain longer duration of clinical benefit than low

TMB. The DCB rate was 2.27 times higher in high TMB than low TMB. As significant heterogeneity in pooled prognostic effect of ICIs, we made the sub-analysis according to the variables involved in studies. The prognostic value of TMB was not affected by any of the variables. When studies were stratified by study design, the heterogeneity of PFS and OS dropped to insignificant level in both subgroups. This indicated study design was the main sources of heterogeneity of the meta-analysis. Interestingly we found the prognostic value in high TMB-cutoff sub-group was more conspicuous than its paired group. The result indicated that the level of TMB was positively correlated with the prognosis of patients and higher TMB could achieve better prognosis, this result was also confirmed in Kowanetz et al.[10]

TMB is an independent prognostic biomarker for NSCLC patients. The previous study found TMB was not associated with PDL-1 expression[43]. The same result was also found in our meta-analysis, when the sub-analysis was made according to the PDL-1 status, no matter in unselected population or PDL-1 positive population, high TMB was associated with better OS and PFS than low TMB. At present, the common sample for TMB detection is tumor tissue. Recent studies showed that TMB could also be detected from blood sample. Wang et al[30] found blood TMB correlated well with the matched tissue TMB, high blood TMB was associated with superior progression-free survival and objective response rates, when patients were treated with ICIs. Gandara et al[34] also reported that compared with docetaxel, high blood TMB was associated with better PFS and OS for atezolizumab in NSCLC. The detection of most biomarkers for immunotherapy needs the tumor tissues (such as, PDL-1and microsatellite instability)[44]. There are some potential problems for these biomarkers. For example, the acquisition of tumor tissue is invasive and causes extra pain, the level of PDL-1 expression may change over time and anatomical site, detection of PDL-1 expression from small biopsy specimens may be inadequate or inaccurate[45–48]. The detection of TMB from blood sample can overcome these obstacles with real-time, non-invasive and convenient. Blood TMB can be used to real time monitor treatment effect and timely replacement of treatment plan.

For patients treated with ICIs alone versus chemotherapy, we secondly found high TMB patients gained better benefit from ICIs alone than chemotherapy. Compared to chemotherapy, high TMB patients had longer PFS and OS in ICIs alone group. ICIs alone reduced 36% rate of tumor progression and about 32% rate of death in high TMB patients. For low TMB patients, we found that the PFS between ICIs alone and chemotherapy was of no obvious difference while the pooled OS showed significant. With the limited data and heterogeneity for prognostic value in low TMB patients, we did sensitivity analysis for PFS and OS. As showed in Fig. 4e.f, after omitted any one of the involved data, the pooled PFS was not changed obviously, however, the pooled OS became of no significant difference between ICIs alone and chemotherapy. So we thought only high TMB patients could benefit from ICIs alone compared with chemotherapy, the low TMB patients may need intensive treatment, such as ICIs and chemotherapy combination therapy. In addition, in checkmate 227, regardless of TMB status or PDL-1 expression, the overall survival rate of immunotherapy was better than that of chemotherapy, but it was of no different in low TMB PDL-1 negative patients[32]. This suggested that TMB combined with PDL-1 may be better in predicting the efficacy of patients.

Though high TMB is a biomarker of good prognosis for NSCLC patients treated with immunotherapy, it is contrary for patients treated with non-ICIs. Our meta-analysis next indicated that high TMB for non-ICIs was associated with more deaths, tumor progression or recurrence than low TMB. In order to expect a better outcome, the detection of TMB may help to choose what kind of treatments should be administrated. Owada-Ozaki et alfound that for completely resected NSCLC patients, even in stage I patients, high TMB patients were with high recurrence and poor OS and DFS. 3-year survival rate in high TMB patients was 58.9%, which was 90.3% in low TMB patients. These results indicated that earlier or stronger chemotherapy maybe needed for high TMB early stage NSCLC. Moreover, Offin et al[13]found for patients treated with molecular targeted therapy, there was significantly shorter OS for patients with higher TMB, higher TMB was found in EGFR 21-exons L858r mutation patients than 19-exons deletion patients, this may explain why patients with 19-exons deletion had better prognosis[49]. Saito et al[50]demonstrated that bevacizumab plus erlotinib combination therapy improved progression-free survival compared with erlotinib alone. Thus, EGFR tyrosine kinase inhibitor plus anti-vascular endothelial growth factor receptor combination treatment may be more appropriate for the high TMB EGFR mutation NSCLC patients. So we thought detection TMB could identify patients with poor prognosis as early as possible, so as to give patients earlier or stronger treatment and gain better outcomes.

At last, we evaluated the correlation between detection of TMB and clinical characteristics, and found TMB was associated with EGFR status, ECOG score and smoking history of NSCLC patients. For smoking history, the pooled OR was 6.01(1.28–28.13), the TMB in current or before smoking patients was six times high than never smoking patients. Carcinogens in tobacco smoking can cause the mutagenesis and contribute to the accumulation of somatic mutations in lung cancers[51]. Although smoking was demonstrated to be associated with good prognosis for patients treated with ICIs in previous studies[66], in light of results in our meta-analysis, we suspected it was TMB, not smoking history, related to prognosis of NSCLC patients. This was also stated in other study. Rizvi et al. showed that in NSCLCs treated with pembrolizumab, it was the elevated nonsynonymous mutation burden, not smoking status that strongly associated with clinical efficacy[11].

There are some limitations in our meta-analysis. Firstly, part of the involved data for prognostic value in the meta-analysis was calculated from survival curve of the studies, not directly supplied by the author. Secondly, significant heterogeneity was existed in OS and PFS for patients treated with ICIs. Although the heterogeneity of the two subgroups decreased to an insignificant level when the study was stratified according to the study design, we could not exclude all possible confounding factors that may cause heterogeneity because it was impossible to obtain all variables of the patients. Thirdly, variety of detection methods and tumor related genes panel for NGS were used to detect TMB, and the definition standard of high TMB was also different. Besides, as lack of sufficient data, the value of combined detection of TMB and PD-L1 expression was not assessed in this study. Similarly, the study did not explore the value of TMB in molecular targeted therapy. At last, most studies were retrospectively, so large scale prospective study on these topics is still needed.

Conclusion

In conclusion, our meta-analysis has evidenced the significant prognostic value of TMB for non-small cell lung cancer patients, and TMB was associated with smoking and EGFR status. For the patients treated with ICIs, we proved that high TMB was associated with good prognosis and efficacy. TMB was a poor prognostic biomarker for non-ICIs. Compared to chemotherapy, the immunotherapy was more effective in high TMB patients, but not in low TMB patients. Moreover, large prospective studies are needed to validate the prognostic values of TMB.

Declarations

Ehics approval and consent to participate: Not applicable;

Consent for publication: All authors agree to publish.

Availability of data and materials: The datasets of this article are included within the article.

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Abbreviations

TMB: tumor mutation burden; NSCLC: non-small cell lung caner; NGS: next-generation sequencing; WES: whole exome sequencing; ICIs: immune checkpoint inhibits; PD-1: programmed cell death protein 1; PDL-1: programmed cell death protein ligand 1; CTLA-4: cytotoxic T-lymphocyte–associated antigen 4; Mut: mutations; OS: overall survival; PFS: progression-free survival; DCB: durable cnilical benefit; ORR: object response rate; HR: Hazard ratio, RR: Risk ratio; OR: odds ratio; 95% CI: 95% confidence intervals.

Tables

Table 1.Baseline characteristics and Quality assessment by the Newcastle–Ottawa scale of eligible studies.

study	Number	Cutoff of TMB	Detection method	country	treatment	Research design	PDL-1 status	End point	score
Chae Y K 2019[20]	34	15 Mut/Mb	NGS	USA	anti–PD-(L)1 monotherapy	retrospectively	unselected	PFS/OS	7
Fang W 2019[21]	78	157 Mut 10 Mut /Mb	NGS/WES	CHINA	anti–PD-(L)1 monotherapy	Prospectively	unselected	PFS	8
Heeke S 2019[22]	36	9.39 Mut /Mb	NGS	France	anti–PD-1 monotherapy	Prospectively	unselected	PFS	6
Jiang T 2019[12]	189	9.43 Mut /Mb	WES	CHINA	Surgery	retrospectively	unselected	OS/DFS	7
Liu L 2019[23]	240	media	WES	CHINA	anti-PD-(L)1 OR combine with anti-CTLA-4	retrospectively	unselected	PFS	5
Offin M 2019[13]	153	4.85 Mut /Mb	NGS	USA	molecularly targeted therapy	retrospectively	unselected	PFS/OS	6
Ready N 2019[24]	98	10 Mut/Mb	NGS	USA Canada	anti-PD-1 combine with anti-CTLA-4	prospectively	unselected	PFS	8
Richard C 2019[25]	77	5.73 Mut/Mb	NGS	France	anti–PD-1 monotherapy	retrospectively	unselected	PFS/OS	6
Samstein R M 2019[26]	350	13.8 Mut/Mb	NGS	World-wide	anti-PD-(L)1 OR Combine anti-CTLA-4	retrospectively	unselected	OS	6
Singal G 2019[27]	1290	20 Mut/Mb	NGS	World-wide	anti–PD-(L)1 monotherapy	prospectively	unselected	OS	6
Wang S 2019[28]	349	media	WES	World-wide	anti-PD-(L)1 OR combine anti-CTLA-4	retrospectively	unselected	OS	5
Wang C 2019[29]	101	media	WES	CHINA	Non-ICIs	retrospectively	unselected	DFS	5
Wang Z 2019[30]	50	6 Mut/Mb	NGS	CHINA	anti–PD-(L)1 monotherapy	prospectively	unselected	PFS	7
Yu H 2019[31]	155	31 Mut/Mb	NGS	USA	Non-ICIs	prospectively	unselected	OS	5
Hellmann M D 2019[32]	299	10 Mut/Mb	NGS	World-wide	anti-PD-1 combine with anti-CTLA-4	retrospectively	unselected	OS	7
DevarakondaS 2018[14]	908	8 Mut/Mb	NGS	USA	chemotherapy	retrospectively	unselected	OS/DFS	6
Owada-Ozaki Y 2018[33]	90	62 Mut	WES	JAPAN	Surgery	retrospectively	unselected	OS/DFS	6
Dudnik E 2018[34]	82	20 Mut/Mb	NGS	Israel	anti–PD-(L)1 monotherapy	retrospectively	unselected	PFS/OS	6
Hellmann M D 2018-I[35]	75	158Mut	WES	USA	anti-PD-1 combine with anti-CTLA-4	retrospectively	unselected	PFS	7
Hellmann M D 2018-II[36]	1021	10 Mut/Mb	NGS	worldwide	anti-PD-1 combine with anti-CTLA-4	retrospectively	unselected	PFS	7
Rizvi H 2018[37]	240	media	WES	USA	anti-PD-(L)1 OR combine anti-CTLA-4	retrospectively	unselected	PFS/OS	6
Gandara D R 2018[38]	794	16 Mut/Mb	NGS	World-wide	ICI s VS chemotherapy	prospectively	unselected	PFS/OS	6
Goodman A M 2017[6]	36	20 Mut/Mb	NGS	USA	anti-PD-(L)1 OR combine anti-CTLA-4	retrospectively	unselected	PFS/OS	6
Carbone D P 2017[9]	158	248 Mut	WES	World-wide	anti–PD-1 monotherapy	prospectively	PDL-1 >5%	PFS	7
Kowanetz M 2017[10]	565	media	NGS	World-wide	anti–PDL-1 monotherapy	retrospectively	PDL-1 >5%	PFS/OS	5
Jiang T 2017[39]	48	media	NGS	USA	chemotherapy	prospectively	unselected	PFS	7
Rizvi N A 2015[11]	34	209 Mut/ 200 Mut	WES	USA	anti–PD-1 monotherapy	prospectively	unselected	PFS	6
Campesato L F 2015[40]	31	7Mut/Mb 13Mut/Mb	NGS	USA	anti–PD-1 monotherapy	retrospectively	unselected	PFS	5

NGS, next-generation sequencing; WES, whole exome sequencing; ICIs, immune checkpoint inhibits; PD-1, programmed cell death protein 1;PDL-1,programmed cell death protein ligand 1; CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; Mut, mutations; OS, overall survival; PFS,

progression-free survival; DFS, disease-free survival; Stars : 0-5 means low quality; 6-9 means high quality.

Table2. Results of subgroup analyses on PFS and OS in patients treated with ICIs.

Variables	PFS				OS			
	HR[95%CI]	N	I^2 (%)	P^d	HR[95%CI]	N	I^2 (%)	P^d
Overall	0.53[0.46-0.62]	19	31.8%	0.091	0.53[0.42-0.67]	11	47.5%	0.040
PDL-1 status								
unselected	0.50[0.41-0.61]	16	40.1%	0.049	0.50[0.38-0.67]	9	52.6%	0.032
PDL-1 positive	0.60[0.50-0.73]	3	0.0%	0.599	0.66[0.47-0.93]	2	0.0%	0.398
method								
NGS	0.55[0.47-0.64]	12	2.3%	0.422	0.49[0.33-0.72]	8	53.8%	0.034
WES	0.52[0.38-0.69]	7	58.6%	0.025	0.55[0.41-0.73]	3	48.4%	0.144
design								
retrospectively	0.61[0.52-0.72]	11	23.3%	0.222	0.57[0.49-0.67]	10	5.7%	0.389
prospectively	0.43[0.35-0.54]	8	0.0%	0.632	-	-	-	-
treatment								
monotherapy	0.49[0.40-0.59]	14	26.9%	0.165	0.45[0.25-0.80]	6	66.1%	0.011
combination	0.63[0.51-0.77]	5	24.4%	0.259	0.54[0.45-0.64]	5	0.2%	0.405
TMB-cutoff								
High	0.48[0.37-0.62]	9	21.5%	0.252	0.35[0.19-0.67]	5	56.9%	0.055
Low	0.58[0.49-0.68]	10	30.8%	0.163	0.59[0.49-0.72]	6	22.8%	0.263
Score of quality assessment								
High	0.51[0.42-0.61]	14	24.3%	0.192	0.48[0.32-0.70]	7	54.9%	0.038
Low	0.59[0.45-0.76]	5	43.8%	0.130	0.57[0.42-0.78]	4	46.2%	0.134

Table 3. Correlation between TMB and clinical characteristics

Variables	OR[95%CI]	*P*	I^2 *(%)*	P^d
EGFR status （Mutant vs. wild type）	0.28（0.08- 0.95）	0.040	0.0	0.557
ECOG score（≥2vs. 0-1）	1.79（1.09- 2.92）	0.021	0.0	0.518
Smoking history（current or before vs. never）	6.01（1.28-28.13）	0.023	66.3	0.031
Stage of Disease (IV VS I-III)	1.20（0.73- 1.97）	0.480	13.1	0.327
Line of therapy (more vs. less)	0.74（0.13- 4.26）	0.735	70.2	0.067
Gender (male vs. female)	1.00（0.58- 1.71）	0.987	1.0	0.387

Figures

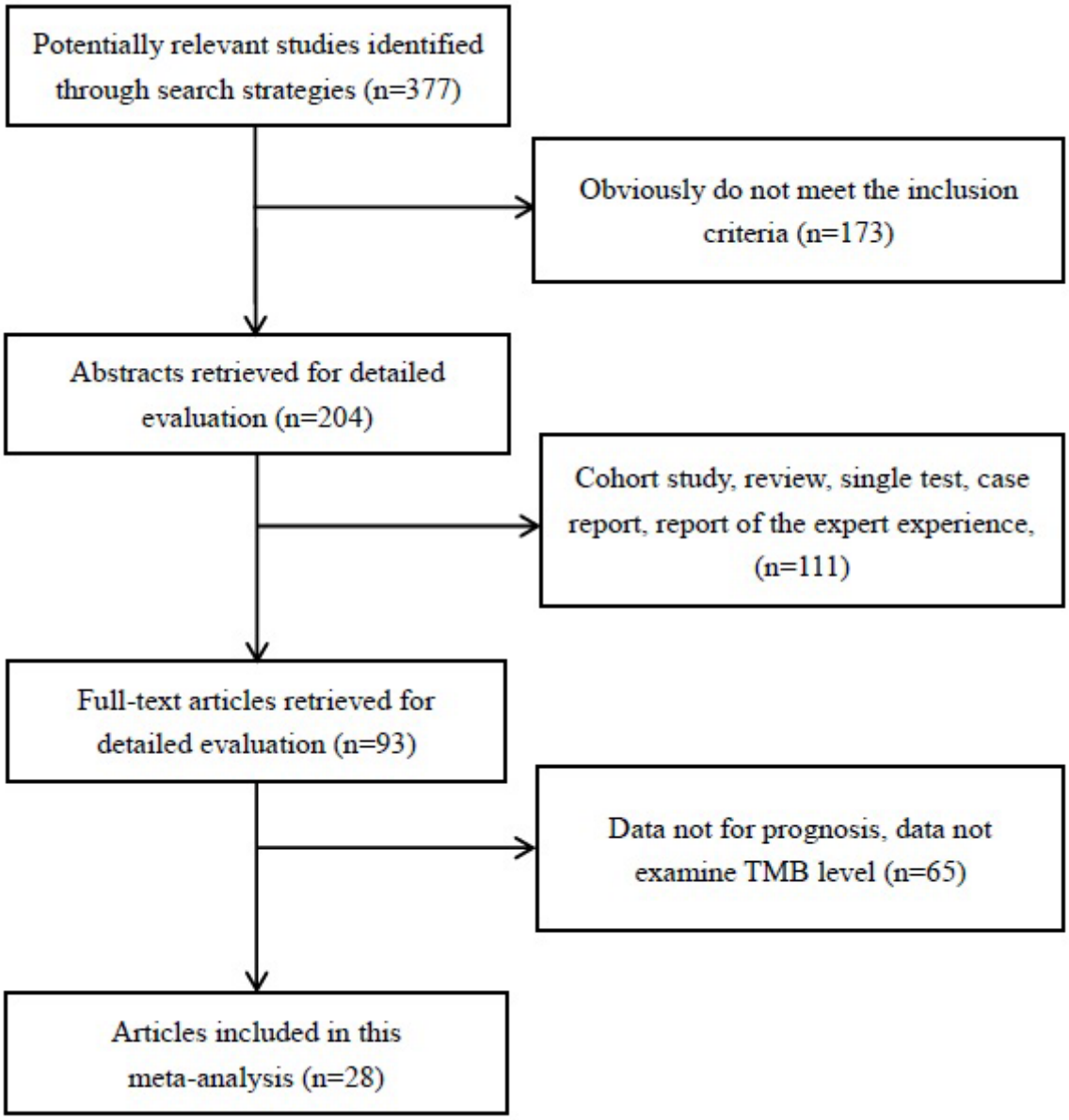

Figure 1

Selection of the included studies.

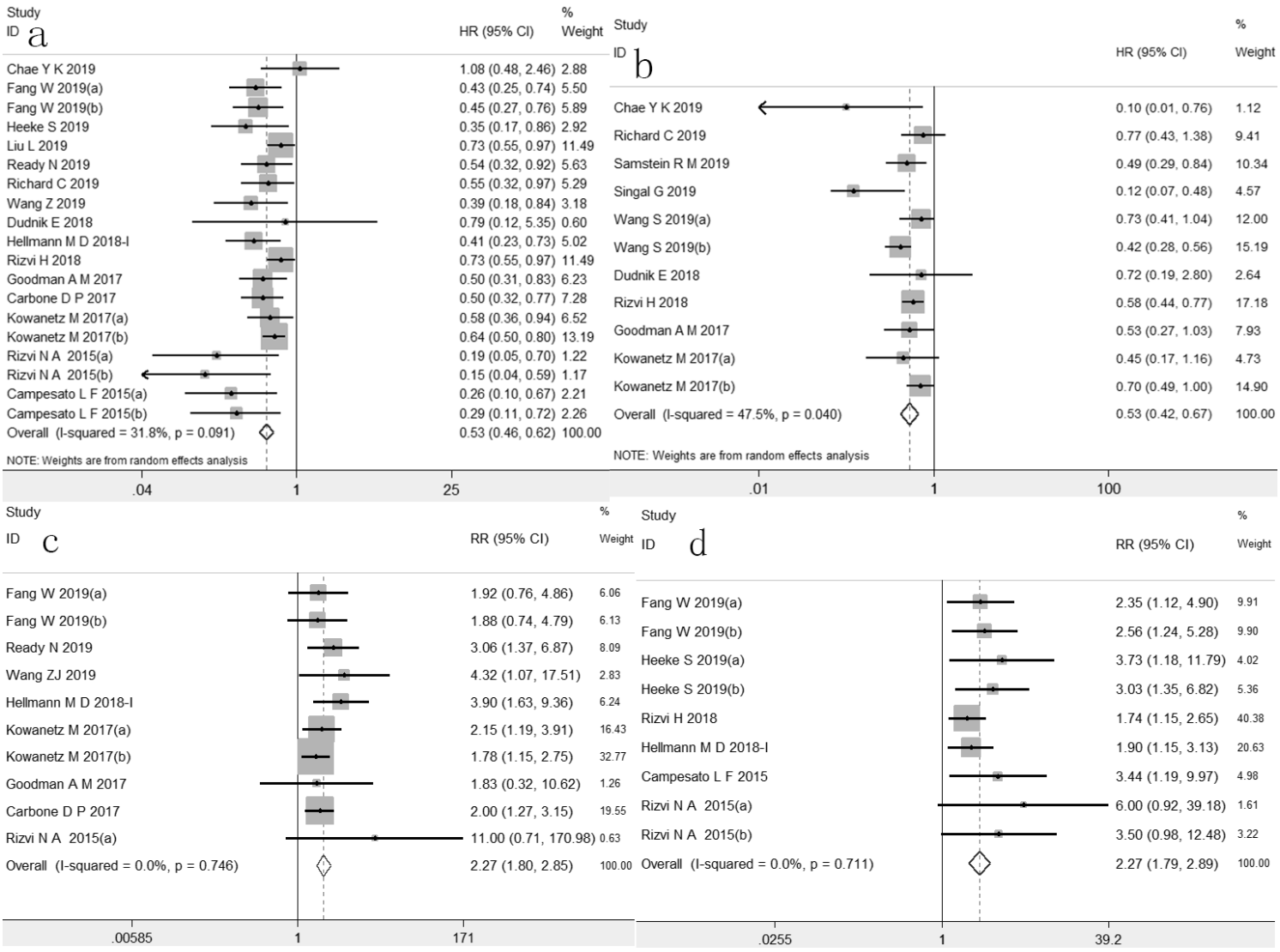

Figure 2

Prognostic value of TMB in patients treated with ICIs. PFS (a), OS (b), ORR (c), DCB (d).

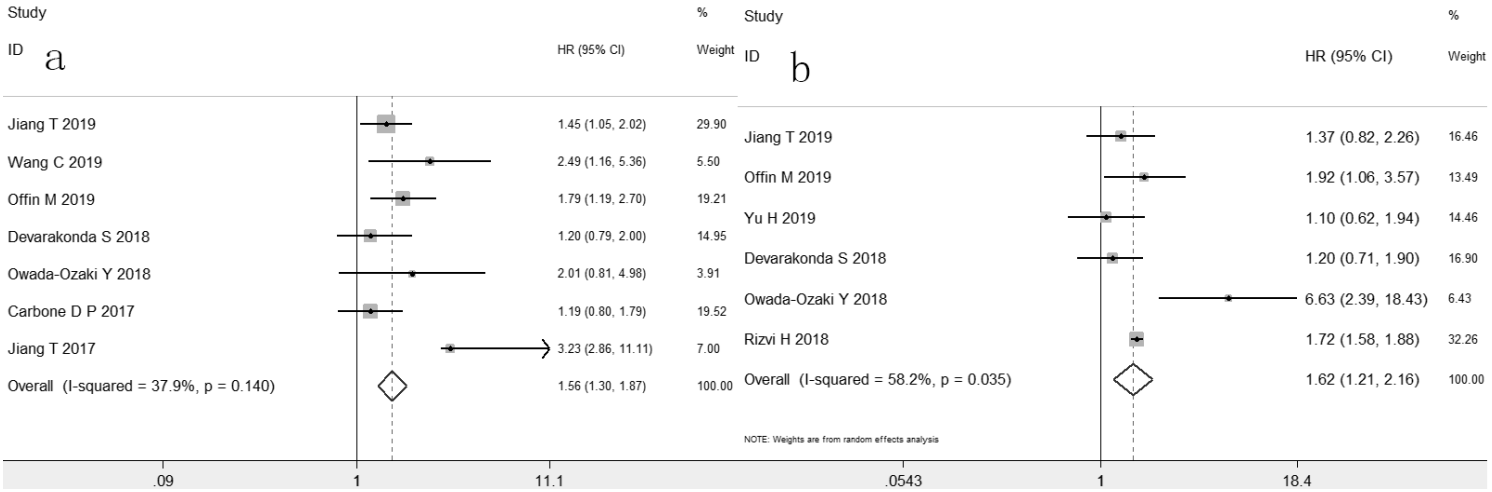

Figure 3

Prognostic value of TMB in patients treated with non-ICIs. PFS (a), OS(b).

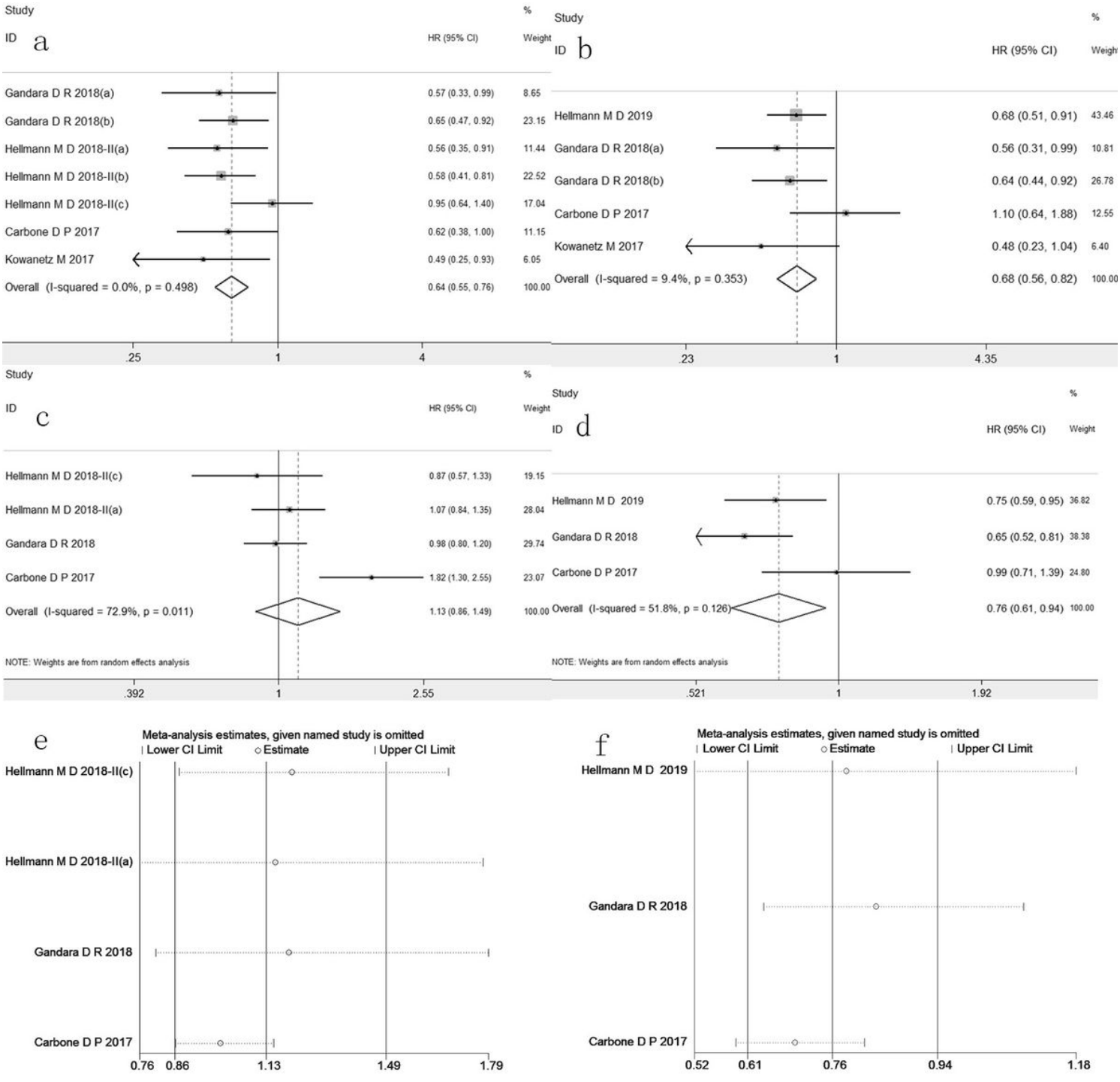

Figure 4

Efficacy between ICIs and chemotherapy according to the level of TMB, PFS (a) and OS (b) in high TMB, PFS (c) and OS (d) in low TMB, sensitive analysis for PFS (e)and OS (f) in low TMB.

Supplementary Files

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