Quality of Life in patients with non-small cell lung cancer treated with PD-1/PD-L1 Inhibitors: A systematic review and meta-analysis

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Research Article

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Abstract

Background

Immune checkpoint inhibitors (ICIs) have dramatically prolonged survival in non-small cell lung cancer (NSCLC) patients, but little research had focused on its impact on quality of life. The purpose of our study was to compare the quality of life (QOL) in patients with NSCLC treated with programmed cell death protein-1/programmed cell death-ligand 1 (PD-1/PD-L1) inhibitors versus chemotherapy.

Methods

We searched for randomized controlled trials utilizing the Quality of Life Questionnaire Core 30 items (QLQ-C30) and the EuroQol Five Dimensions Questionnaire-3L (EQ-5D-3L) to assess the QOL of NSCLC treated with PD-1/PD-L1 inhibitors versus chemotherapy. We collected hazard ratios (HRs) for the time from baseline to the first clinically deterioration (TTD) and Effect Size as the difference in mean change between and within treatment groups in patients reported outcomes (PROs). (PROSPERO registration number CRD42022296680).

Results

In the five trials reported by QLQ-C30, TTD was longer in PD-1/PD-L1 inhibitors compared with control groups (HR = 0.86; 95% CI = 0.76, 0.97; *P* = 0.013), with similar results in terms of physical function, role function, and pain. The difference in mean change between the PD-1/PD-L1 inhibitors group and the chemotherapy group in QLQ-C30 and EQ-5D VAS was 3.64 (95% CI = 1.62, 5.66; *P* = 0.001) and 4.74 (95% CI = 2.65, 6.83; *P* = 0.001), which supported PD-1/PD-L1 inhibitors. However, there was no significant difference between the two groups in the EQ-5D Utility index (mean change = 0.03; 95% CI = -0.01, 0.07; *P* = 0.094). The mean change from baseline to follow-up in PD-1/PD-L1 inhibitors group was 2.57 (95% CI = 0.43, 4.71; *P* = 0.019) and chemotherapy group was − 1.31 (95% CI = -3.71, 1.09; *P* = 0.284), correspondingly. The subgroup analysis (≤ 15 w vs. > 15 w) for the mean difference between groups in QLQ-C30 favored PD-1/PD-L1 inhibitors.

Conclusion

In conclusion, PD-1/PD-L1 inhibitors could improve the QOL of patients with NSCLC compared to chemotherapy and reduce the unfavorable symptoms during treatment.

Background

ICIs treat cancer by regulating T cell cytotoxicity to tumors, mainly including cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), PD-1, and PD-L1 [1], NSCLC accounts for approximately 85% of lung cancers, and the current first-line treatment of NSCLC is PD-1/PD-L1 inhibitors combined with or without chemotherapy [2–3]. ICIs improve survival [4], and can also lead to immune-related adverse events by releasing autoreactive T cells, such as immune-related pneumonia, vomiting, rash, diarrhea [5].

QOL is a subjective scale to collect the severity of patients' symptoms at a specific time point. QOL is not only an independent prognostic factor for lung cancer patients, but also evaluates the benefit-risk ratio of immune checkpoint inhibitors [6–7]. One of the most common questionnaires used to evaluate patients with lung cancer is the QLQ-C30, which consists of five functional scales (physical, role, cognitive, emotional, and social) and nine symptom scales (fatigue, pain, nausea and vomiting, dyspnea, appetite loss, constipation, diarrhea, sleep disturbance), as well as a global health and quality-of-life scale [8]. The EQ-5D-3L primarily consists of the EQ-5D utility index and the EQ visual analogue scale (VAS). EQ-5D-3L describes five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and three levels in each dimension represent no problems, moderate problems, and extreme problems respectively [9–10]. Fewer studies have systematically assessed the QOL of ICIs in patients with NSCLC due to the heterogeneity in the quality assessment of phase II to III clinical trials in patients with various types of cancer. A series of 10 eligible trials were included in this meta-analysis, and the QLQ-C30 and EQ-5D-3L questionnaires were applied to assess the QOL of patients with NSCLC in terms of TTD and the differences in mean change between and within groups. The study was designed to systematically investigate whether PD-1/PD-L1 inhibitors (atezolizumab, avelumab, durvalumab, nivolumab, pembrolizumab) improved the QOL of patients with NSCLC compared to chemotherapy based on published randomized controlled trials.

Materials And Methods

Search strategy and study selection

Study selection corresponded with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [11]. This study was registered on Prospero (ID # CRD42022296680). We searched Pubmed, EMBASE and the Cochrane Library databases. Search deadline was on 15th January 2022. Search terms were as follows: ((atezolizumab OR (avelumab) OR (durvalumab) OR (nivolumab) OR (pembrolizumab)) AND ((non small cell lung cancer) OR (carcinoma, non small cell lung) OR (carcinomas, non-small-cell lung) OR (lung carcinoma, non-small-cell) OR (non-small-cell lung carcinomas) OR (non-small-cell lung carcinoma) OR (lung carcinomas, non-small-cell) OR (carcinoma, non-small cell lung) OR (non-small cell lung carcinoma) OR (non-small cell lung cancer)) AND ((life quality) OR (health-related quality of life) OR (health-related quality of life) OR (hrqol)) .

Inclusion criteria were as below: (a) Patients with NSCLC were studied. (b) The trial group received PD-1/PD-L1 inhibitors excluding single CTLA-4, while the control group received standard platinum-based chemotherapy. (c) PROs were reported. We excluded reviews, case reports, and retrospective studies (Fig. 1).

The study was approved by the ethics committees of Nanjing Brain Hospital. Due to the retrospective nature of the study, the requirement for informed patient consent was waived.

Data extraction

The extracted data includes trial name, first author, phase, masking, study type, NCT number, QOL Measure, ECOG PS, follow Up, intervention arm, comparison arm, TTD, and difference in mean change between and within groups from baseline to follow up (Table 1).

Table 1
Characteristics of the studies included in the meta-analysis.

trial name	First author, yr	Phase	Masking	Study Type	NCT Number	QOL Measure	ECOG PS	Treatment arms	FollowUp,wk
KEYNOTE-010	Barlesi F, 2019	II/III	open-label	RCT	NCT01905657	EQ-5D-3L, EORTC QLQ-C30, EORTCQLQ-LC13.	0–1	Pembrolizumab 2 mg/kg Q3W, Pembrolizumab 10 mg/kg Q3W; Docetaxel 75 mg/m2 Q3W	12
CheckMate 057	Reck M, 2018	III	open-label	RCT	NCT01673867	LCSS, EQ-5D 3L	0–1	nivolumab 3 mg/kg Q2W; Docetaxel75 mg/m2 Q3W	66
KEYNOTE-024	Brahme JR,2017	III	open-label	RCT	NCT02142738,	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-3L.	0–1	Pembrolizumab 200 mg Q3W; Five platinum-based chemotherapy regimens Q3W : carboplatin + pemetrexed (500 mg/m²), cisplatin (75 mg/m²) + pemetrexed (500 mg/m²), carboplatin + gemcitabine (1250 mg/m²), cisplatin (75 mg/m²) + gemcitabine (1250 mg/m²), or carboplatin + paclitaxel (200 mg/m²).	15
OAK	Bordoni R,2018	III	open-label	RCT	NCT02008227	EORTCQLQ-C30, EORTC QLQ-LC13.	0–1	Atezolizumab 1200 mg Q3W; Docetaxel 75 mg/m2 Q3W	15
CheckMate 017	Reck M,2017	III	open-label	RCT	NCT01642004	LCSS, EQ-5D	0–1	Nivolumab 3 mg/kg Q2W; Docetaxel 75 mg/m2 Q3W	60
KEYNOTE-407	Mazieres J,2018	III	double-blind	RCT	NCT02775435	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D-3L	0–1	Pembro 200 mg Q3W; Pbo Q3W + carboplatin AUC 6 and paclitaxel 200 mg/ m2 Q3W or nab-paclitaxel 100 mg/m2 QW	18
PACIFIC	Hui R, 2019	III	double-blind	RCT	NCT02125461	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D	0–1	Durvalumab 10 mg/kg Q2W; Matching placebo 1 – 42 days after chemoradiotherapy	48
EVIDENS	Pero IM,2019	N/A	double-blind	RCT	NCT03382496	EQ-5D-3L	0–1	Nivolumab; NA	36

trial name	First author, yr	Phase	Masking	Study Type	NCT Number	QOL Measure	ECOG PS	Treatment arms	FollowUp,wk
KEYNOTE-189	Garassino MC, 2020	III	double-blind	RCT	NCT02578680	EORTC QLQ-C30, EORTC QLQ-LC13	0–1	Pembrolizumab (200 mg) or saline placebo Q3W; Pemetrexed (500 mg/m²) with carboplatin (5 mg/mL per min) or cisplatin (75 mg/m²; investigator's choice) Q3W for four cycles, followed by pemetrexed maintenance therapy Q3W	21
MYSTIC(D/D + T)	Garon EB.,2021	III	open-label	RCT	NCT02453282	EORTC QLQ-C30, EORTC QLQ-LC13	0–1	Durvalumab 20 mg/kg Q4W, durvalumab 20 mg/kg Q4W plus tremelimumab 1 mg/kg Q4W; investigator's choice of platinum-based doublet chemotherapy (four to six cycles)	24

Statistical analysis

The primary outcomes of our study:(a) TTD was defined as the time from baseline to first clinically deterioration in PROs. (b)The pooled difference mean change between and within groups from baseline to follow up, which all assessed by QLQ-C30 and EQ-5D-3L. We collected hazard ratios (HRs) for TTD and performed Effect Size as the difference in mean change in PROs between and within treatment groups. We performed a methodological quality assessment of the enrolled trials using the Cochrane Risk of Bias tool, which consists of six items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each risk of bias item was classified as high risk, low risk, and unclear risk [12]. We use the Consolidated Standards of Reporting Trials (CONSORT) PRO checklist to assess the quality of PRO [13]. Two authors (WL and QZ) independently extracted data and performed quality assessment in this process and discrepancies were resolved by consensus (CH X). We use each pooled Effect Size to estimate means of the random effects model according to the DerSimonian and Laird method [14]. Heterogeneity was assessed using Cochrane's Q statistic and I^2 statistic. I^2 values of 25%, 50%, and 75% represented low, moderate, and high heterogeneity, respectively. Begg's and Egger's tests were used to assess publication bias for meta-analyses for QOL. Sensitivity analyses were also conducted. Two-sided $P < 0.05$ was considered statistically significant. All analyses were performed by using the Stata 16.0 software except for quality assessment which was performed using Review Manager 5.3.

Results

Literature search and characteristics of the studies

We searched the Pubmed, EMBASE, and Cochrane library databases for a total of 1973 publications according to the PICOS principles, of which 577 duplicates were removed, and a total of 10 publications met the inclusion criteria after screening (Fig. 1). There were eight phase III trials in this study, one was phase II/III, and the other was not explained in the original study, among those, clinical trials were performed with Pembrolizumab (n = 4), Nivolumab (n = 3), Durvalumab (n = 2), Atezolizumab (n = 1). Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0–1. The follow-up period ranged from 12 to 66 weeks. PRO tools involved in these trials included EQ-5D-3L, EORTC QLQ-C30, EORTC QLQ-LC13, and LCSS, the most common of which are EORTC QLQ-C30 and EQ-5D-3L (n = 7, 70%) (Table 1). Quality assessment was reported in Fig. 4.

Time from baseline to first deterioration

A total of 5 articles report TTD results in PROs using QLQ-C30 [15–19]. The TTD was significantly longer with PD-1/PD-L1 inhibitors than with platinum-based chemotherapy in QOL, with an HR of 0.86 (95% CI = 0.76, 0.97; $P = 0.013$; Fig. 2A). There was no heterogeneity (Q = 3.28; I^2 =

0.0%; $P = 0.512$), Egger's Test ($P = 0.057$) and Begg's Test ($P = 0.027$) indicating no publication bias. Moreover, PD-1/PD-L1 inhibitors also demonstrated to delay TTD in physical function, pain and role function on the QLQ-C30, with an HR of 0.79 (95% CI = 0.69, 0.90; $P = 0.000$; $I^2 = 67.0\%$; Fig. 2B), with an HR of 0.78 (95% CI = 0.69, 0.89; $P = 0.000$; $I^2 = 0.0\%$; Fig. 2C), with an HR of 0.84 (95% CI = 0.73, 0.96; $P = 0.012$; $I^2 = 74.3\%$; Fig. 2D), respectively. Sensitivity analysis of TTD was shown in Fig. 5A-D.

The difference of mean changes between groups

The mean changes from baseline to follow-up in QOL between groups were reported with the QLQ-C30 in six trials [15–18, 20–21], the EQ-5D Utility index in three trials [22–24], and the EQ-5D VAS in four trials [15, 20, 23, 24]. The difference in mean change between the PD-1/PD-L1 inhibitors group and the chemotherapy group in QLQ-C30 was 3.64 (95%CI = 1.62, 5.66; $P = 0.00$; Fig. 3A) favoring PD-1/PD-L1 inhibitors, with no heterogeneity (Q = 9.30; $I^2 = 46.24\%$; $P = 0.10$) and no publication bias (Begg's test $P = 1.000$, Egger's test $P = 0.431$). In addition, the same trend was also found for the EQ-5D VAS with a mean difference of 4.74 (95%CI = 2.65, 6.83; $P = 0.00$; Fig. 3B) and with no heterogeneity (Q = 3.06; $I^2 = 1.83\%$; $P = 0.383$). However, the pooled difference in mean change between PD-1/PD-L1 inhibitors and control groups in the EQ-5D Utility index was 0.03 (95%CI= -0.01, 0.07; $P = 0.094$; $I^2 = 0.00\%$; Fig. 3C) with no statistically significant. Sensitivity analysis of the difference of mean changes between groups was shown in Fig. 5E-G.

The difference of mean changes within groups

There were eight trials accessible for the within-group analysis [16–19, 20–21]. The pooled mean change from baseline to follow-up in PD-1/PD-L1 inhibitors in the QLQ-C30 was 2.57 (95%CI = 0.43, 4.71; $P = 0.019$, $I^2 = 75.79\%$) and in chemotherapy was − 1.31 (95%CI = -3.71, 1.09; $P = 0.284$; $I^2 = 69.76\%$, Fig. 3D-E), suggesting a change within the PD-1/PD-L1 inhibitors group. Statistically significant heterogeneity was observed in both studies (Q = 16.52, $I^2 = 75.79\%$, $P = 0.002$; Q = 13.23, $I^2 = 69.76\%$, $P = 0.010$). Sensitivity analysis of the difference of mean changes within groups was shown in Fig. 5H-I.

Subgroup analysis

For the mean difference between groups, the two groups (≤ 15w vs. > 15w) was divided according to the follow-up duration with the QLQ-C30 [15–18, 20–21], and the results of subgroup analysis suggested that the change from baseline to follow-up favored PD-1/PD-L1 inhibitors in ≤ 15w groups with 4.16 (95%CI = 1.26, 7.06; $I^2 = 31.88\%$), and the same trend was in > 15w groups with 3.34 (95%CI = 0.19, 6.49; $I^2 = 63.99\%$) (Fig. 3F). The outcomes of TTD and within-group were not available for subgroup analysis due to small group size.

Discussion

This study compared the TTD and the difference of mean changes in PROs in NSCLC receiving PD-1/PD-L1 inhibitors and chemotherapy. Regardless of QLQ-C30 or EQ-5D-3L, the results of the meta-analysis suggested that NSCLC patients with PD-1/PDL-1 inhibitor had a more favorable difference in mean change from baseline to follow-up compared to those with chemotherapy and had a significantly delayed clinical deterioration. The changes of QOL between groups showed that PD-1/PDL-1 inhibitors were more beneficial versus chemotherapy, furthermore, there was a statistically significant favourable change for the within-group in NSCLC treated with PD-1/PD-L1 inhibitors during the follow-up duration. Recently, a meta-analysis demonstrated that ICIs were positively associated with higher levels of QOL and longer time to deterioration in cancer patients, which was consistent with our results, but the study incorporated a variety of cancer types and was not specific to PD-1/PD-L1 inhibitors, thus was not as homogenous as our study [25]. Nishijima TF et al. similarly found that patients treated with PD-1/PD-L1 inhibitors had higher QOL and fewer adverse effect than chemotherapy, yet there was no significant change in the mean difference in patients with PD-1/PD-L1 inhibitors, which contradicted our findings [26]. Gonzalez BD et al. also found no change in overall QOL in ICIs, which may be associated with the different subject, small sample size, and the failure to include specific symptom toxicities associated with ICIs in lung cancer [27–28].

Notably, we are the first study to perform a systematic meta-analysis of the relationship between PD-1/PD-L1 inhibitors and standard chemotherapy in NSCLC on QOL. However, there are some limitations of our study. Firstly, these data were extracted from published articles and were not original. Secondly, fewer articles were eligible for inclusion, and subgroup analysis of heterogeneous studies was difficult to conduct with some publication bias. Thirdly, as QOL questionnaires require patients to complete at a point time, the patients are vulnerable to losing follow-up. Fourthly, it is difficult to directly compare different trials at different time points, and other functions and symptoms of PROs can't be studied due to lack of data and heterogeneity. Lastly, despite questionnaires reporting quality of life are currently considered to be of high quality, there are currently no international guidelines for statistical analysis of QOL in cancer patients using ICIs, and there is still lack of confirmation of research hypotheses and questionnaires in cancer patients treated with ICIs in methodological aspects [29]. ECOG PS ≥ 2 was almost excluded from clinical trials, and future studies should be focused on older and weak patients [30–31].

Conclusion

Our meta-analysis reported that patients treated with PD-1/PD-L1 inhibitors had higher QOL and fewer adverse symptoms than those with standard chemotherapy, indicating that early social, psychological, and spiritual support can improve the quality of life. The shift from traditional therapy to immunotherapy in cancer treatment will take the consideration of the patient-centered quality of life assessment into account, which can have a positive impact on the development of oncological care in the future. It has reference value for clinicians in the real world and more studies will be needed to validate.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Wei Liu and Qian Zhang searched the database, judged study eligibility, and extracted data. Wei Liu, Tiantian Zhang, and Li Li analyzed data and wrote the paper. Chunhua Xu and Jue Zou designed the study and revised this paper. All authors have read and approved this version of the article.

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Availability of data and materials

Not applicable.

Ethics approval and consent to participate

The study was approved by the ethics committees of Nanjing Brain Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

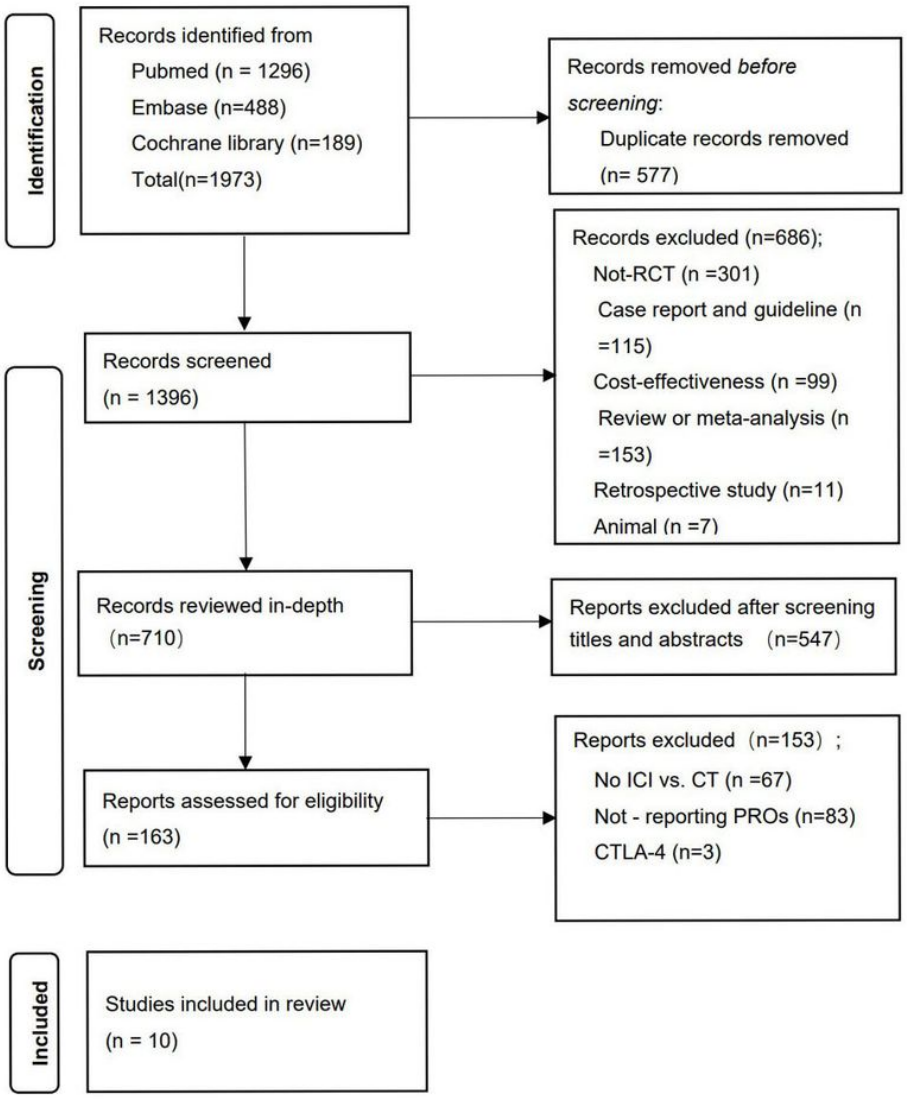

Figure 1

The PRISMA flowchart: the selection process for the eligible studies.

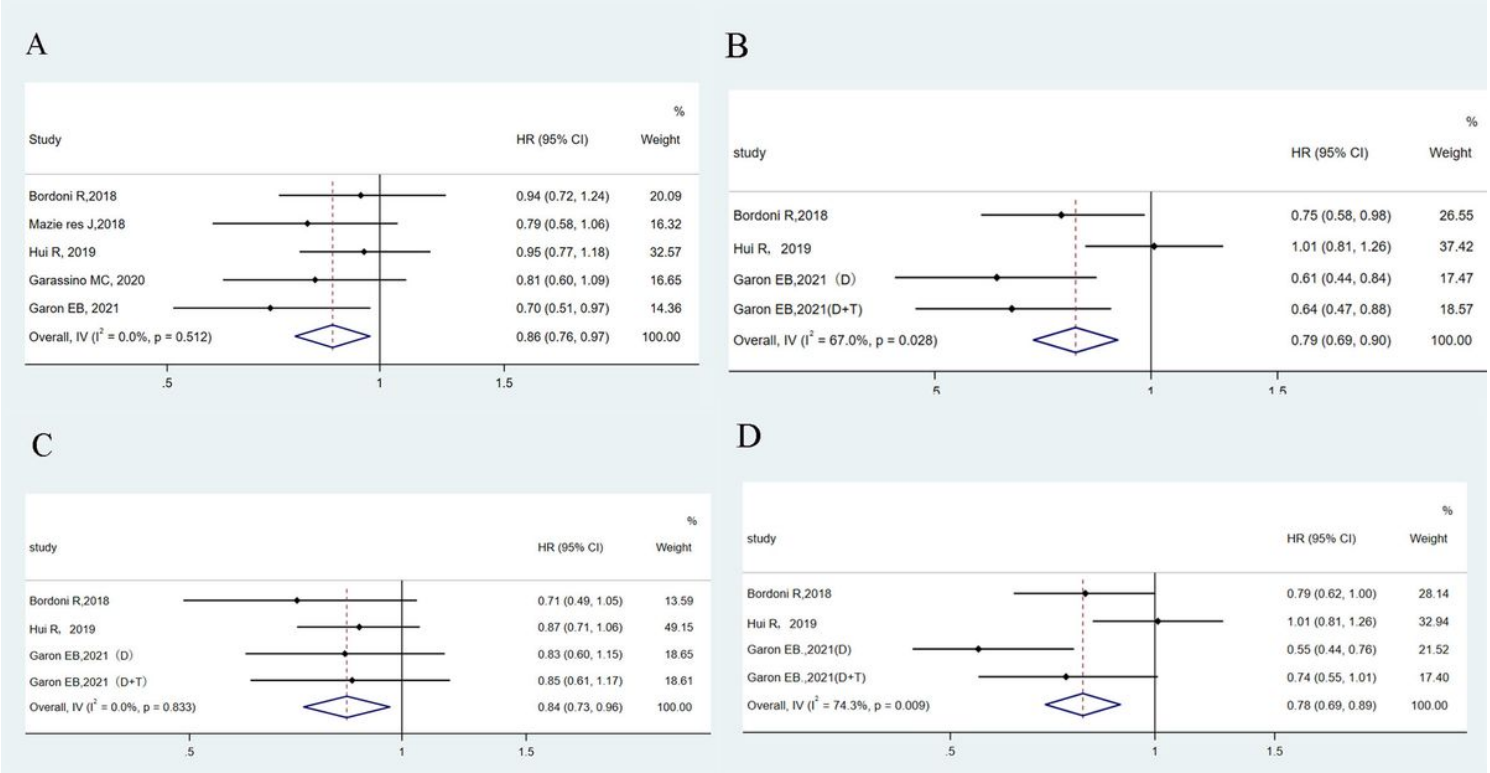

Figure 2

Forest plot of hazard ratios for the time from baseline to first deterioration in the Quality of Life Questionnaire Core 30 items on quality of life (A), physical function (B), pain (C), and role function (D). (A) Random effect: *P* = 0.013; Egger's test: *P* = 0.057; Begg's Test: *P* = 0.027. (B)Random effect: *P* = 0.000; Egger's test: *P* = 0.020; Begg's Test: *P* = 0.089. (C) Random effect: *P* = 0.000; Egger's test: *P* = 0.226; Begg's Test: *P* = 0.308. (D) Random effect: *P* = 0.012; Egger's test: *P* = 0.293; Begg's Test: *P* = 0.308.

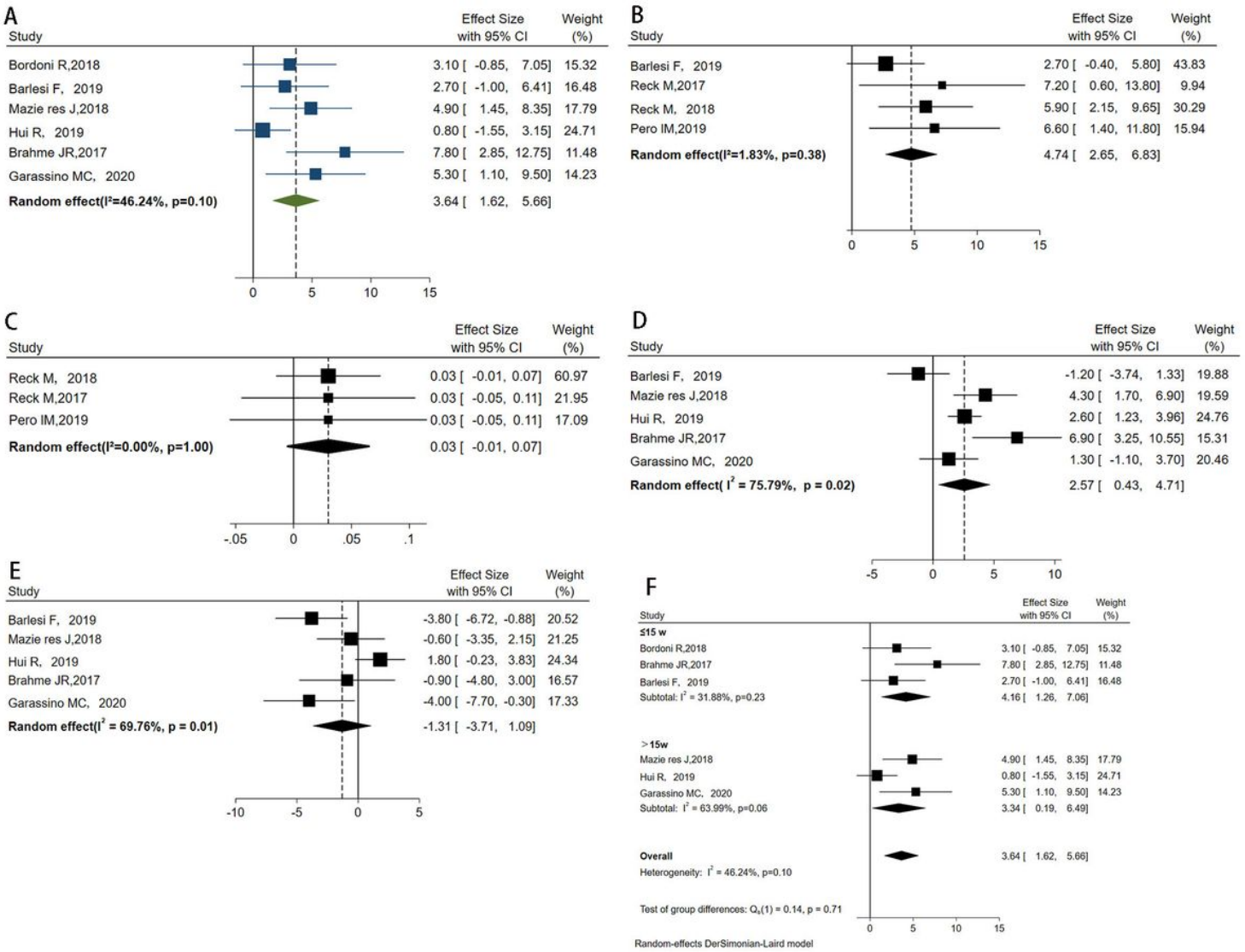

Figure 3

Forest plot of the difference in mean change from baseline to follow-up between groups for the Quality of Life Questionnaire Core 30 items (A), EQ-5D VAS (B), and EQ-5D Utility index (C). (A)Random effect: *P* = 0.00; Egger's test: *P* = 0.431; Begg's Test: *P* = 1.000. (B) Random effect: *P* = 0.00; Egger's test: *P* = 0.128; Begg's Test: *P* = 0.296. (C) Random effect: *P* = 0.094; Begg's Test: *P* = 0.296.

Forest plot of the difference in mean change from baseline to follow-up within groups: PD-1/PD-L1 inhibitors (D) and controls (E). (D) Random effect: *P* = 0.019; Egger's test: *P* = 0.969; Begg's Test: *P* = 1.000. (E) Random effect: *P* = 0.284; Egger's test: *P* = 0.141; Begg's Test: *P* = 0.462. (F)Subgroup analysis for the mean difference between the two groups (≤15w vs. >15w) according to the follow-up duration with the QLQ-C30.

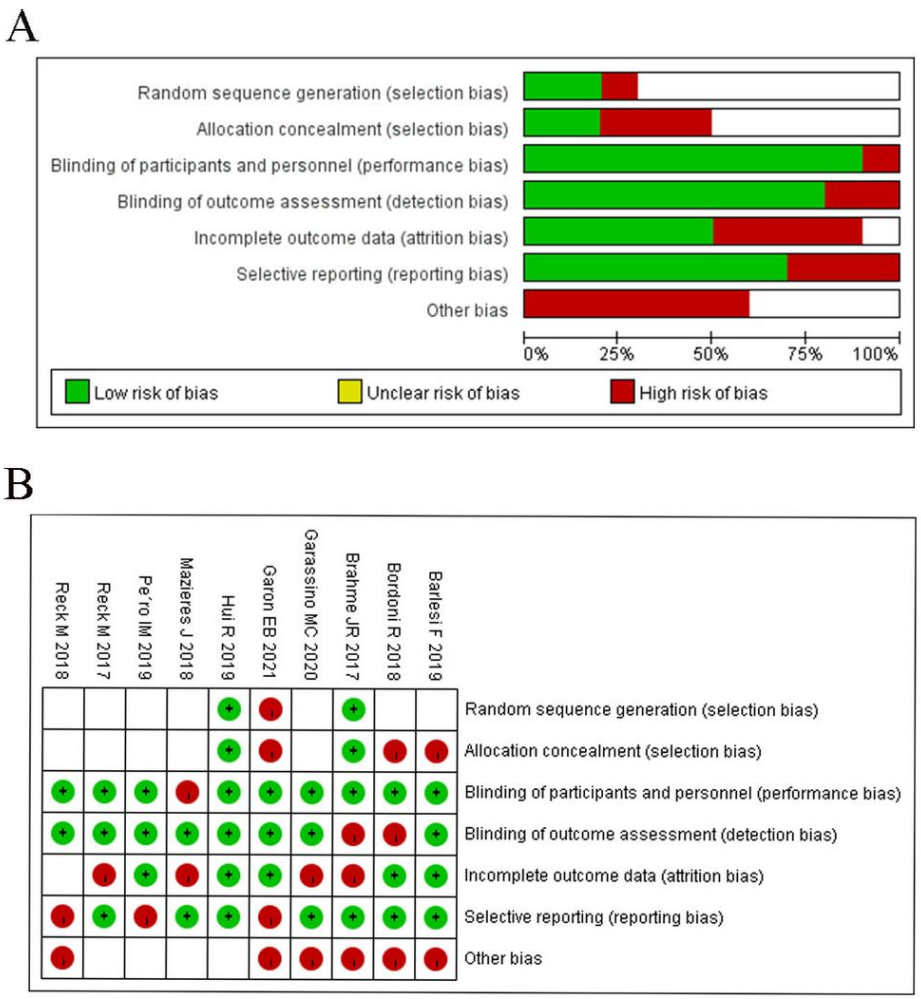

Figure 4

Quality assessment of the eligible studies in risk of bias graph (A) and risk of bias summary (B).

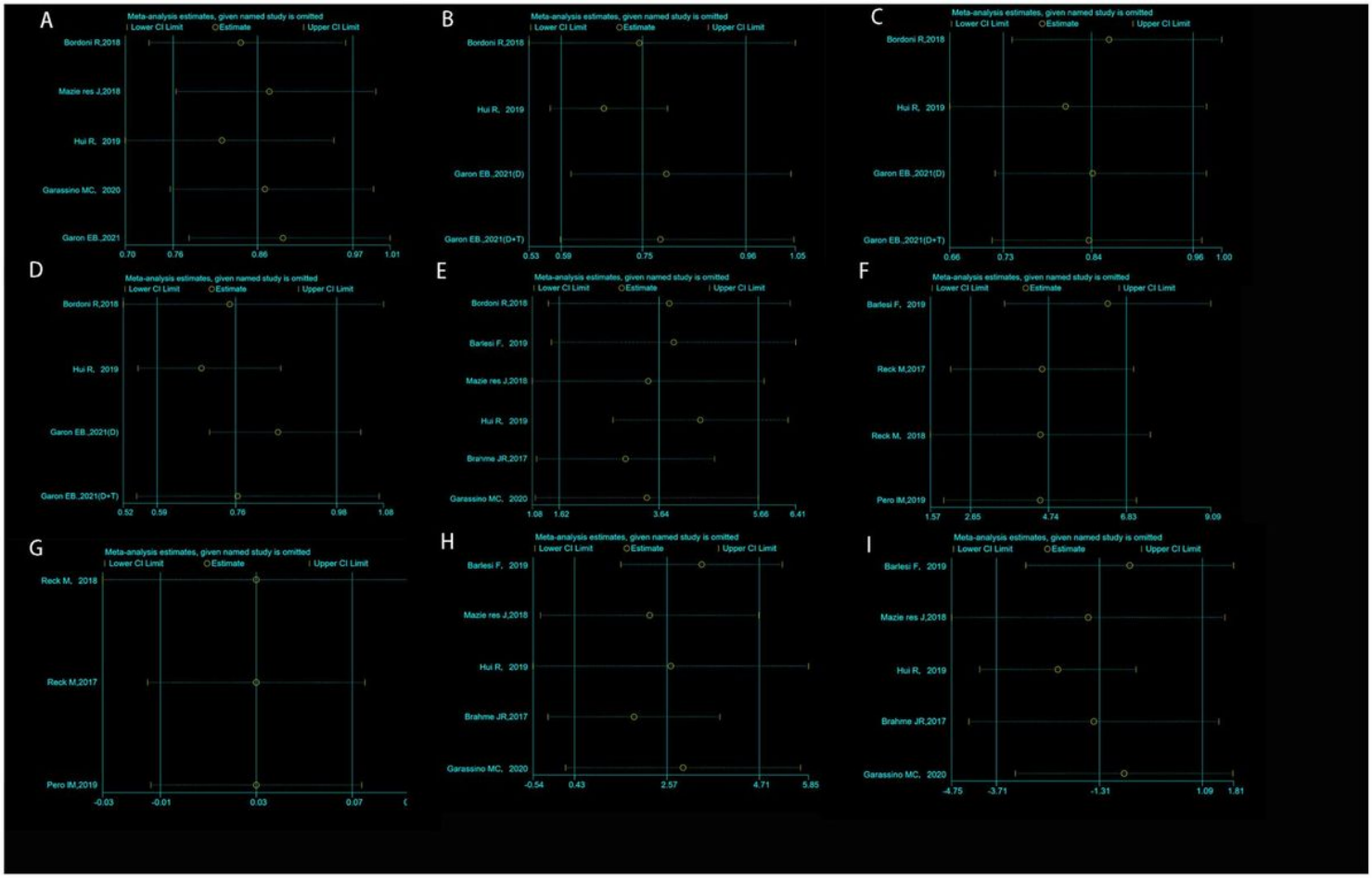

Figure 5

Sensitivity analyses of time from baseline to first deterioration in the Quality of Life Questionnaire Core 30 items on quality of life (A), physical function (B), pain (C), and role function (D). Sensitivity analyses of mean change from baseline to follow-up between groups for the Quality of Life Questionnaire Core 30 items (E), EQ-5D VAS (F), and EQ-5D Utility index (G). Sensitivity analyses of difference in mean change from baseline to follow-up within groups: PD-1/PD-L1 inhibitors (H) and controls (I).