

Prognostic value of programmed cell death ligand-1 expression in the tumor-infiltrating immune cells of patients with lung cancer: A meta-analysis

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Abstract. Several studies have investigated the prognostic significance of programmed cell death ligand 1 (PD-L1)-positive expression in the tumor cells (TC) of patients with lung cancer. However, tumor-infiltrating immune cell (TIIC)-based PD-L1 expression and its prognostic value remain controversial. The present meta-analysis was performed on 11 studies comprising 2,685 patients, which were identified by a systematic search on the PubMed, PMC, Web of Science and Embase databases. The databases were searched for published articles up to October 30, 2020. The studies that evaluated overall survival (OS) or disease-free survival (DFS) expressed as hazard ratios (HRs) in the PD-L1 TIIC of patients with lung cancer were analyzed. All statistical analyses were conducted using Stata software, version 16.0. The results demonstrated that PD-L1 expression in TIICs was not associated with OS [HR=0.98; confidence interval (CI)=0.73-1.33; P=0.53] and DFS (HR=1.05; CI=0.63-1.77; P=0.42) for all the cohort included in the study. However, subgroup analysis revealed that PD-L1 TIICs were associated with improved OS in lung squamous cell carcinoma (HR=0.76; CI=0.58-0.99; P=0.04), while poorer DFS was observed in lung adenocarcinoma (HR=1.30; CI=1.19-1.43; P=0.008) and at the >1% staining cutoff value (HR=1.56; CI=1.12-2.16; P=0.03). However, poor OS (P=0.21) and DFS (P=0.14) were observed in Asian populations, while DFS (P=0.07) for only-membrane staining was not statistically significant. The results of the present study suggested that adding PD-L1 TIICs to the existing diagnostic algorithm may

help to guide patient selection for anti-PD-1/PD-L1 therapy. Future large-scale studies are warranted for confirmation of the present findings.

Introduction

As the malignant tumor with highest morbidity and mortality, lung cancer remains a global major public health problem (1). In contrast to a steady increase in the survival of the majority of tumors, advances in lung cancer have been slow, and its 5-year relative survival rate is still ~19% (1). This may be attributed to the unsatisfactory efficacy of traditional treatments such as chemotherapy, radiotherapy and tumorectomy, particularly at advanced stages of the disease (2). Therefore, the introduction of immunotherapy targeting immune checkpoint molecules, such as programmed cell death ligand 1 (PD-L1), into clinical practice has recently gained increasing attention (3). Since PD-L1 expression on tumor cells (TC) is the mechanism by which TC could escape immune system surveillance, its expression is not only linked to the response of immune checkpoint therapy, but is also correlated with the prognosis of non-small cell lung cancer (NSCLC) (4,5). PD-L1, the predominant ligand for PD-1, can be expressed in multiple tissues, including tumor-infiltrating T and B lymphocytes, dendritic cells and other immune cells (5,6). To date, all previous meta-analyses have identified PD-L1 expression on TC as a putative prognostic biomarker in NSCLC (7-9). However, meta-analyses of the prognostic significance of PD-L1 in tumor-infiltrating immune cells (TIICs) have not yet been conducted. Recent clinical trials have revealed that higher response rate to PD-1/PD-L1 targeted therapy was associated with positive expression of PDL-1 in TIICs (10,11). This suggests that, in addition to using tumor cell-based PD-L1 expression, immune cell-based PD-L1 expression may be clinically relevant. Although a number of studies have reported the prognostic significance of PD-L1 expression on TIICs in lung cancer, the findings remain controversial.

The aim of the present study was to conduct a meta-analysis and to evaluate the prognostic value of PD-L1-positive expression in TIICs, which was expressed as the hazard ratio (HR) for overall survival (OS) and disease-free survival (DFS) in patients with lung cancer.

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Abbreviations: PD-L1, programmed cell death ligand-1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; IHC, immunohistochemistry

Key words: programmed cell death ligand 1, tumor-infiltrating immune cell, prognosis, meta-analysis, lung cancer

Materials and methods

Search strategy. For study search and selection, the recommendation (12) of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Relevant articles were retrieved from the electronic databases of PubMed, PMC, Embase and Web of Science. Studies published before October 30, 2020 were screened by their title and abstract. The key words used in the search strategy were ‘PD-L1 OR PD-L1 OR B7-H1 OR C274’ AND ‘tumor-infiltrating lymphocytes OR TIL OR tumor infiltrating immune cells OR TIIC’ AND ‘lung’ AND ‘cancer OR carcinoma OR neoplasm OR tumor’ AND ‘survival OR prognosis’. A manual search for references cited in the retrieved articles on the topic was also conducted.

Inclusion and exclusion criteria. Studies were considered eligible if they met the following criteria: i) Studies on patients with lung cancer in whom PD-L1 expression on TIICs was determined by immunohistochemistry (IHC); ii) studies reporting the prognostic value of PD-L1 on TIICs alongside OS and/or DFS, and HR with 95% confidence interval (CI); iii) and studies reporting sufficient data to calculate or extract HR values, such as Kaplan-Meier (KM) survival curves, were included in the meta-analysis.

Articles were excluded from the meta-analysis if they met the following criteria: i) The articles were conference abstracts, reviews or case studies; or ii) contained insufficient data to calculate or extract HR, or if KM information was not available; or) were not written in English.

Data extraction and quality assessment. Data extraction was performed by two authors using a predesigned data extraction form. The following data were extracted from eligible studies: Name of first author, publication year, country, subtype of lung cancer, number of patients, format of pathological section, tumor stage, IHC evaluation methods, antibody clones used for PD-L1 detection and positive cutoff value for expression of PD-L1 on TIICs.

Quality assessment of the included studies was performed by Newcastle-Ottawa scale. Studies that scored ≥ 6 points were considered to have a high quality.

Statistical analysis. Survival data were primarily extracted as HR and 95% CI. When studies reported HR of Cox univariate and multivariate analyses, the HR of Cox multivariate analysis was used, since it is good for situation with missing outcomes and usually leads to more precise conclusion. If HR was not directly available in the article, it was calculated from available data or extracted from the KM survival curve using WebPlotDigitizer (13). Statistical heterogeneity was assessed by χ^2 (I^2) and visual inspection of the forest plot. $I^2 > 50\%$ was considered to indicate the presence of heterogeneity. The random-effects model was used due to the presence of heterogeneous studies. To identify the source of heterogeneity and evaluate the influence of different adjustment factors or confounders, subgroup analysis was performed. Funnel plots were used to estimate publication bias and small-study effects. $HR > 1$ and $HR < 1$ indicated poor and improved prognosis, respectively, while

$HR = 1$ considered no effect. For all analyses, Stata software, version 16.0 was used. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Search results and study characteristics. The search was completed in October 2020. The detailed flow diagram for screening studies that identified a total of 8,311 search records is shown in Fig. 1. EndNote software, version X7 was used to identify duplicates and to manage citations. According to the established inclusion and exclusion criteria, and by thoroughly reviewing articles, 11 studies (2,685 patients) were included in the final analysis using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (12) for identified articles. The characteristics of the included studies are summarized in Tables I and II.

Among the included studies, 8 (11,14-20) were focused on non-small cell lung cancer (NSCLC), of which, 1 study was on pulmonary squamous cell carcinoma (14) and 1 on lung adenocarcinoma (16). The remaining studies were on pulmonary neuroendocrine carcinoma (21,22) and SCLC (23). All studies assessed PD-L1 expression on TIICs using IHC. In total, 7 different types of monoclonal antibody were used, among which, SP142 clone was used in 4 studies (11,15,17,21) while the other antibodies were used once. A total of 4 studies (17,19,21,22) defined membranous and/or cytoplasmic staining of PDL-1 in TIICs as positive, whereas 5 studies (14,15,20,23,24) considered positive expression only the cases with membranous staining of PD-L1 in TIICs. The cutoff values for evaluating the positive expression of PD-L1 in TIICs were divided into two types: i) Proportion of stained cells $\geq 5\%$ and ii) proportion of stained cells $\geq 1\%$. While 9 studies (11,15,16,19-23) used 1% cutoff value for evaluation, only 2 studies (14,17) used 5% cutoff value for evaluation. In 10 of 11 studies, whole slides (11,14-17,20-23) were used for evaluating cancer samples, while only 1 study used tissue microarray assay (19). Among the included studies, 3 were prospective cohort studies, 7 were retrospective cohort studies and 1 was a randomized control trial study (RCT).

PD-L1 expression and OS. The pooled result of 9 studies did not reveal a statistically significant association between PD-L1 expression in TIICs and OS ($HR = 0.98$, $CI = 0.73-1.33$, $P = 0.53$; Fig. 2A). This may be attributed to the presence of heterogeneity among all the included studies.

Subgroup analysis between PD-L1 TIIC expression and OS. To identify the source of heterogeneity, subgroup analysis in subtypes of lung cancer, cutoff values, ethnicity, study design and staining localization was conducted. Lung squamous cell carcinoma was associated with improved prognosis ($HR = 0.76$, $CI = 0.58-0.99$, $P = 0.04$; Fig. 3A). However, PD-L1 expression in TIICs assessed by $\geq 1\%$ cutoff value ($P = 0.48$) and $\geq 5\%$ cutoff value ($P = 0.38$) was not significantly associated with OS ($P = 0.53$) (Fig. 4A). Although Asian ethnicity ($P = 0.21$) and membrane-only staining ($P = 0.21$) tended to be associated with worse OS, the association was not statistically significant

Table I. Characteristics of the studies included in the present meta-analysis.

Author (year)	Country	Subtype of lung cancer	Stage	Number of patients	Age, median years (range)	(Refs.)
Fehrenbacher <i>et al</i> (2016)	USA	NSCLC	NR	86	NR	(11)
Yang <i>et al</i> (2016)	China	NSCLC (Squamous cell carcinoma)	I	105	40-85	(14)
Theelen <i>et al</i> (2019)	Netherlands	NSCLC	I-IV	286	NR	(15)
Mignon <i>et al</i> (2020)	Belgium	Adenocarcinoma	I-III	237	NR	(16)
Vallonthaiel <i>et al</i> (2017)	India	NSCLC	I-IV	62	58 (29-78)	(17)
Chen <i>et al</i> (2109)	China	NSCLC	I-IV	234	NR	(18)
Paulsen <i>et al</i> (2017)	Norway	NSCLC	I-III	505	67 (28-85)	(19)
Sumitomo <i>et al</i> (2019)	Japan	NSCLC	I-III	160	NR	(20)
Wang <i>et al</i> (2018)	China	Pulmonary neuroendocrine tumors	I-III	159	59.5 (30-83)	(21)
Kim <i>et al</i> (2018)	Korea	High-grade neuroendocrine carcinoma	I-IV	192	66 (36-89)	(22)
Bonanno <i>et al</i> (2018)	Italy	Small cell lung cancer	I-IV	104	69 (47-86)	(23)

NSCLC, non-small cell lung cancer; NR, not reported.

Table II. Assessment methods of the included studies.

Study	Tissue slides	Antibody	Staining location	Median follow up (months)	Outcome	PD-L1 TIIC cutoff value (%)	NOS quality assessment	(Refs.)
Fehrenbacher <i>et al</i> (2016)	Whole slide	SP142	NR	15	OS	1	7	(11)
Yang <i>et al</i> (2016)	Whole slide	NR	Membrane	79	OS and DFS	5	6	(14)
Theelen <i>et al</i> (2019)	Whole slide	SP142	Membrane	96	OS	1	6	(15)
Mignon <i>et al</i> (2020)	Whole slide	NR	NR	NR	OS	1	6	(16)
Vallonthaiel <i>et al</i> (2017)	Whole slide	SP142	Membrane/cytoplasm	16	DFS	5	7	(17)
Chen <i>et al</i> (2109)	Whole slide	E1L3N	Membrane	NR	DFS	1	6	(18)
Paulsen <i>et al</i> (2017)	Tissue microarray	E1L3N	Membrane/cytoplasm	NR	OS and DFS	1	7	(19)
Sumitomo <i>et al</i> (2019)	Whole slide	SP263	Membrane	42.8	OS and DFS	1	6	(20)
Wang <i>et al</i> (2018)	Whole slide	SP142	Membrane/cytoplasm	NR	OS	1	6	(21)
Kim <i>et al</i> (2018)	Whole slide	NR	Membrane/cytoplasm	80.7	OS	1	7	(22)
Bonanno <i>et al</i> (2018)	Whole slide	22C3	Membrane	13.4	OS	1	6	(23)

PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; NR, not reported; OS, overall survival; DFS, disease free survival; NOS, Newcastle-Ottawa scale.

(Figs. 5A and 6A, respectively). Subgroup analysis by research design revealed that prospective cohort studies tended to be associated with better prognosis (HR=0.79,

CI=0.21-2.96, P=0.24), while retrospective cohort studies had a borderline effect (HR=1.07, CI=0.79-1.45, P=0.36), although neither design exhibited a statistically significant

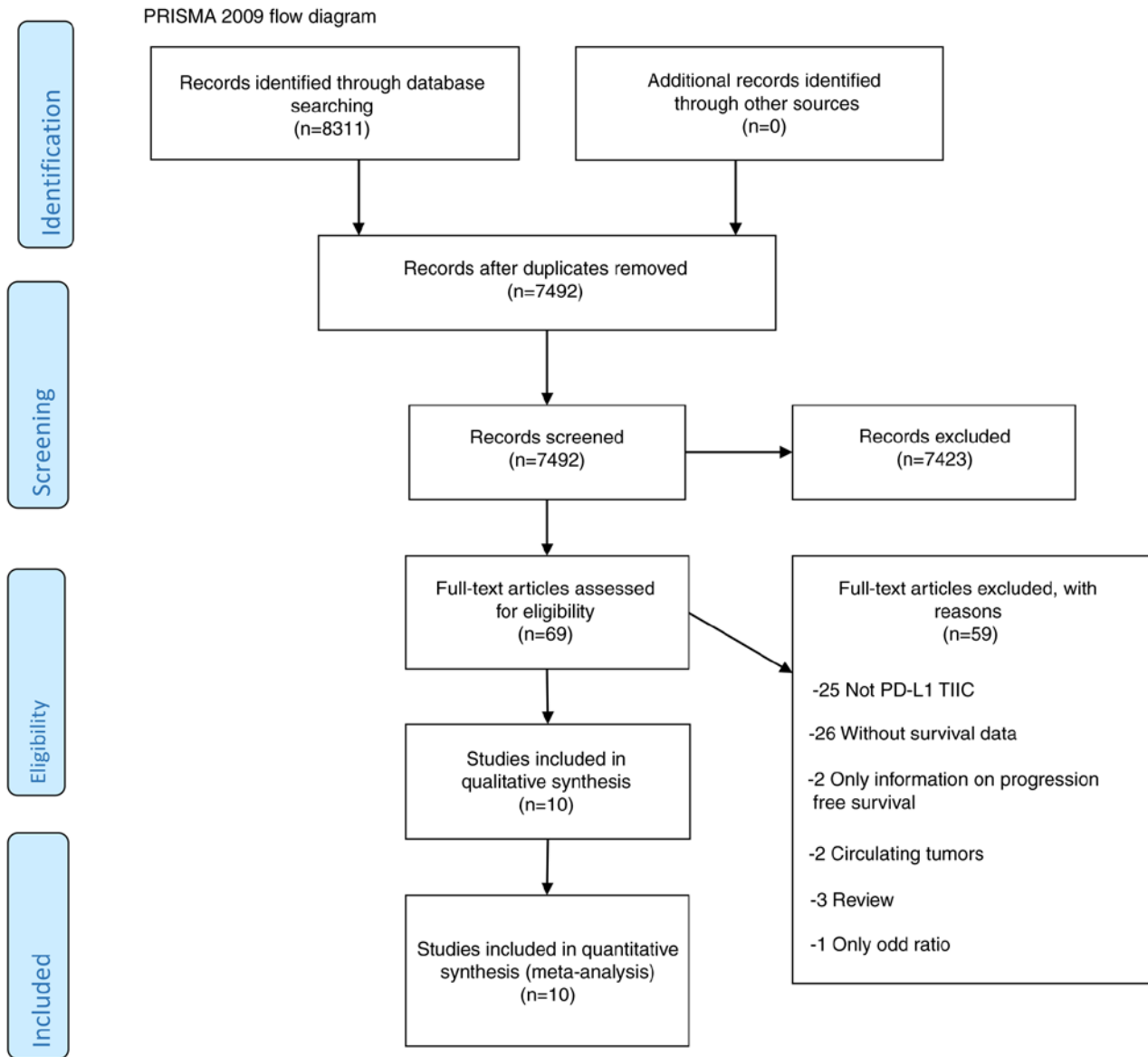


Figure 1. PRISMA flow diagram presenting the retrieved articles for the current review (n=11). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells.

difference (Fig. 7). Only a randomized control study that demonstrated improved survival was reported. Excluding this RCT study design from all other study designs did not alter the meta-analysis pooled result. Furthermore, funnel plot testing for publication bias showed that there were no small-study effects for OS (Fig. 8).

PD-L1 expression in TIICs and DFS. Only 5 studies were investigated the pooled results of which did not show a statistically significant association between PD-L1 TIIC and DFS (HR=1.05, CI=0.63-1.77, P=0.42; Fig. 2B). This result may be due to the presence of heterogeneity.

Subgroup analysis between PD-L1 TIIC expression and DFS. Subgroup analysis showed that PD-L1 TIIC expression in pulmonary adenocarcinoma (HR=1.30, CI=1.19-1.43, P=0.008) and assessment by $\geq 1\%$ staining cutoff value (HR=1.56, CI=1.12-2.16, P=0.03) exhibited an opposite

survival trend (Figs. 3B and 4B, respectively). Although Asian ethnicity (P=0.14) and membrane-only staining appeared to be poor predictors of prognosis (P=0.07), the correlation was not statistically significant (Figs. 5B and 6B, respectively).

Discussion

A number of meta-analyses (25-29) demonstrated that PD-L1 expression on TC is becoming a powerful prognostic tool in guiding patient selection for PD-1/PD-L1 inhibitor therapy in various cancer types, including lung cancer. To the best of our knowledge, the present study is the first meta-analysis to assess the prognostic value of PD-L1 expression in TIICs in patients with lung cancer. Here, 10 of 11 included studies in the meta-analysis were observational studies. As univariate analysis data are difficult for clinical interpretation in observational studies, multivariate model was used as this model usually

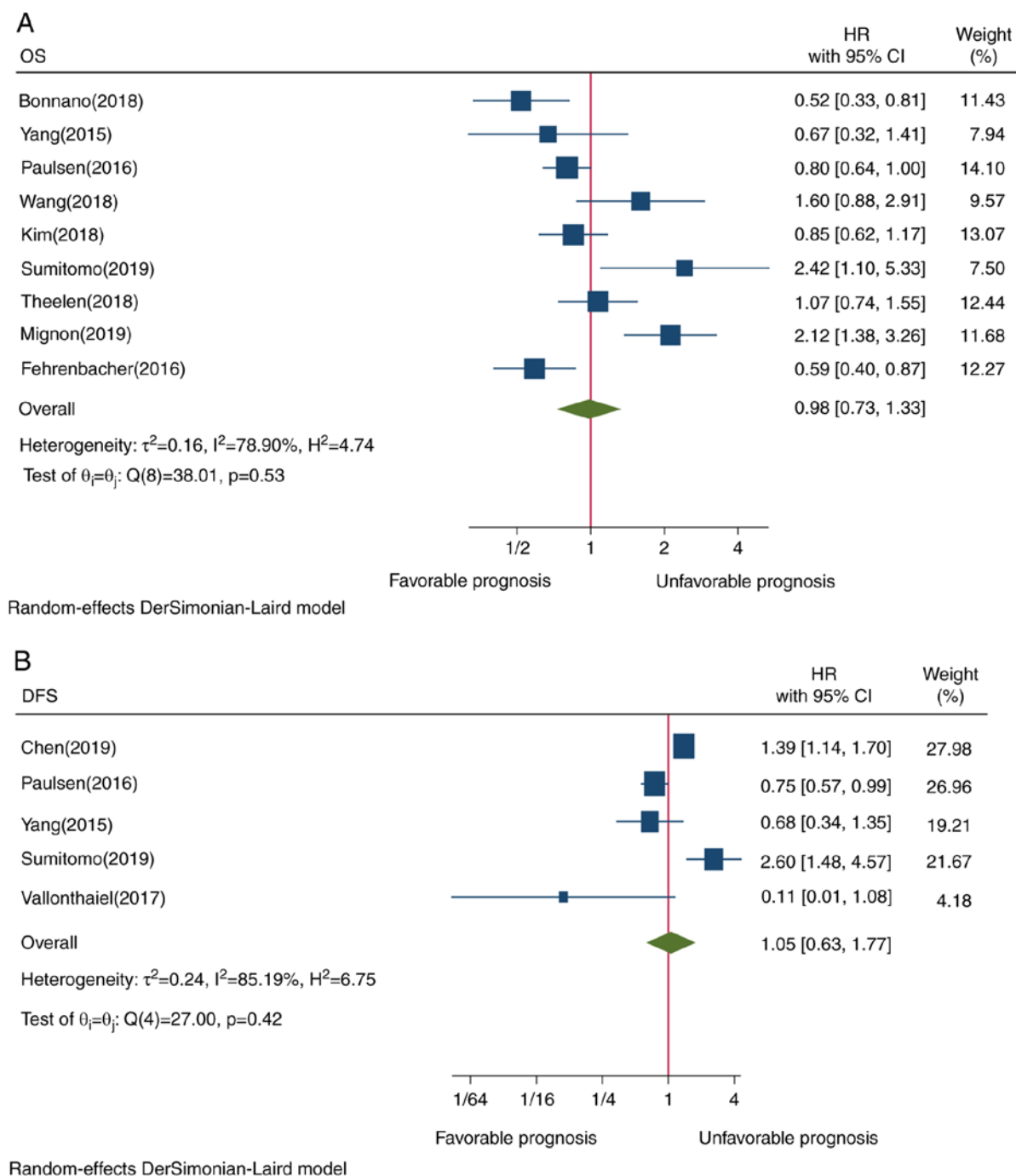


Figure 2. Forest plot presenting the relationship between PD-L1 TIIC and lung cancer prognosis for all included studies. (A) OS and (B) DFS in PD-L1 TIIC. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

leads to more precise conclusion. There were three studies that reported both univariate and multivariate results. Interestingly, in these studies, the difference between univariate and multivariate result was small and statistical/clinical conclusions didn't change.

The overall pooled result showed that PD-L1 expression in TIICs was not associated with OS or DFS in any of the included populations with lung cancer. This finding is consistent with a meta-analysis of the included cancer types (30), and with the results reported in tumors of the digestive system (6), as well as cohort studies (31,32). However, the present result

contradicts previous studies that revealed that PD-L1 TIIC in primary breast cancer (26) was associated with improved OS, while in SCLC (33) and in head and neck cancer (34) it was associated with longer DFS. The differences in the definition of PD-L1 positivity, cancer type, IHC methods used, therapeutic regimen and other clinicopathological variables may account for the contradictory results. Additionally, the differences in primary endpoint outcome may also be another source of variation: While the present study used OS and DFS, other studies (33,34) reported relapse-free survival as the primary endpoint outcome.

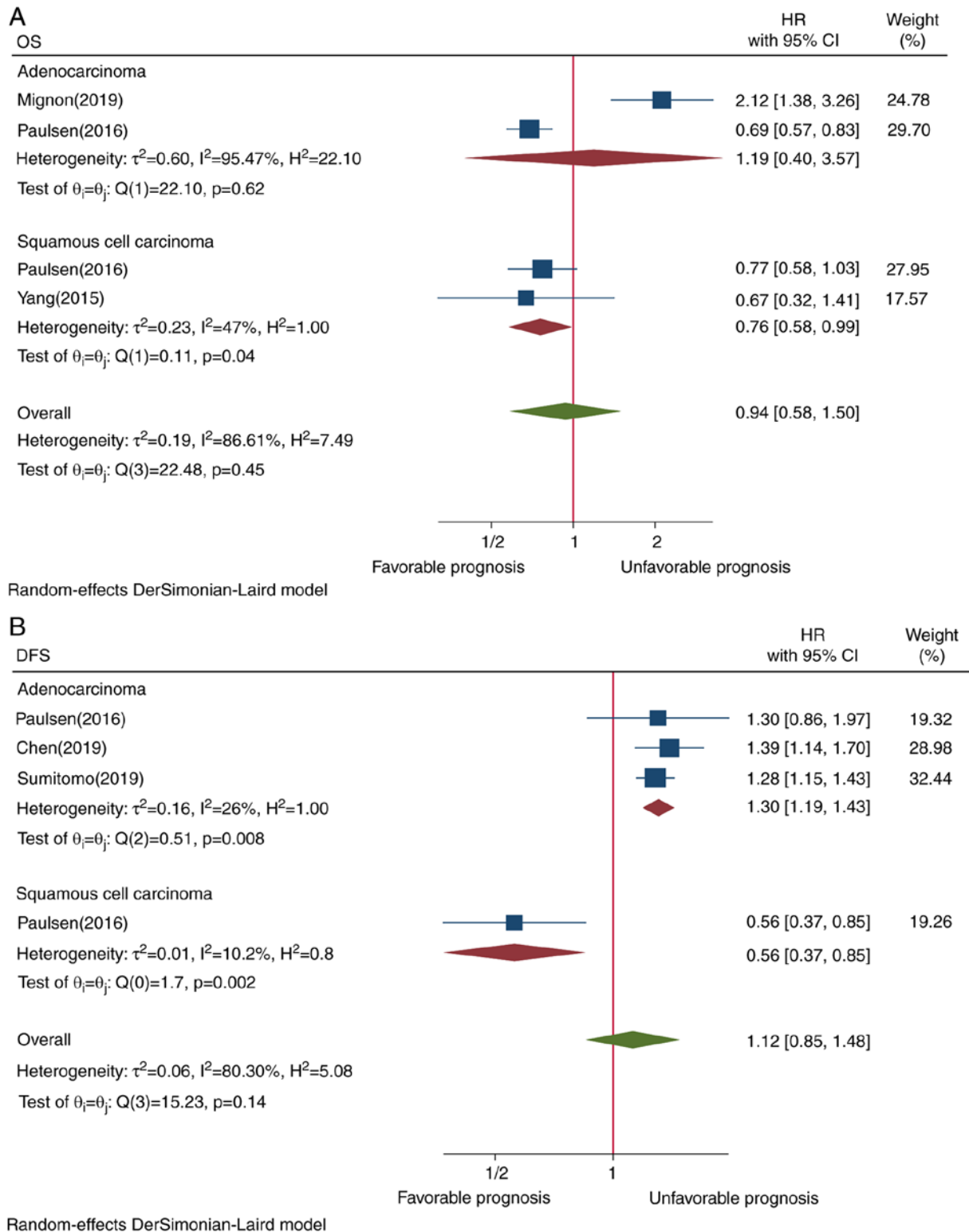


Figure 3. Forest plot showing the relationship between PD-L1 TIIC and prognosis by subtype of lung cancer. (A) OS and (B) DFS for patients with lung adenocarcinoma and squamous cell carcinoma. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

In the present meta-analysis, due to the presence of heterogeneity, subgroup analysis was performed by subtype of lung cancer, cutoff value, ethnicity and staining localization in order to identify the source of heterogeneity.

As regards tumor subtype, the present results showed that PD-L1 TIIC overexpression in adenocarcinoma was

associated with poor DFS. This finding is consistent with a meta-analysis (35) and a cohort study (36) on PD-L1 in TC in pulmonary adenocarcinoma. However, the present study demonstrated that PD-L1 TIIC expression was associated with improved OS for patients with pulmonary squamous cell carcinoma. This indicates that the presence of a heterogeneous

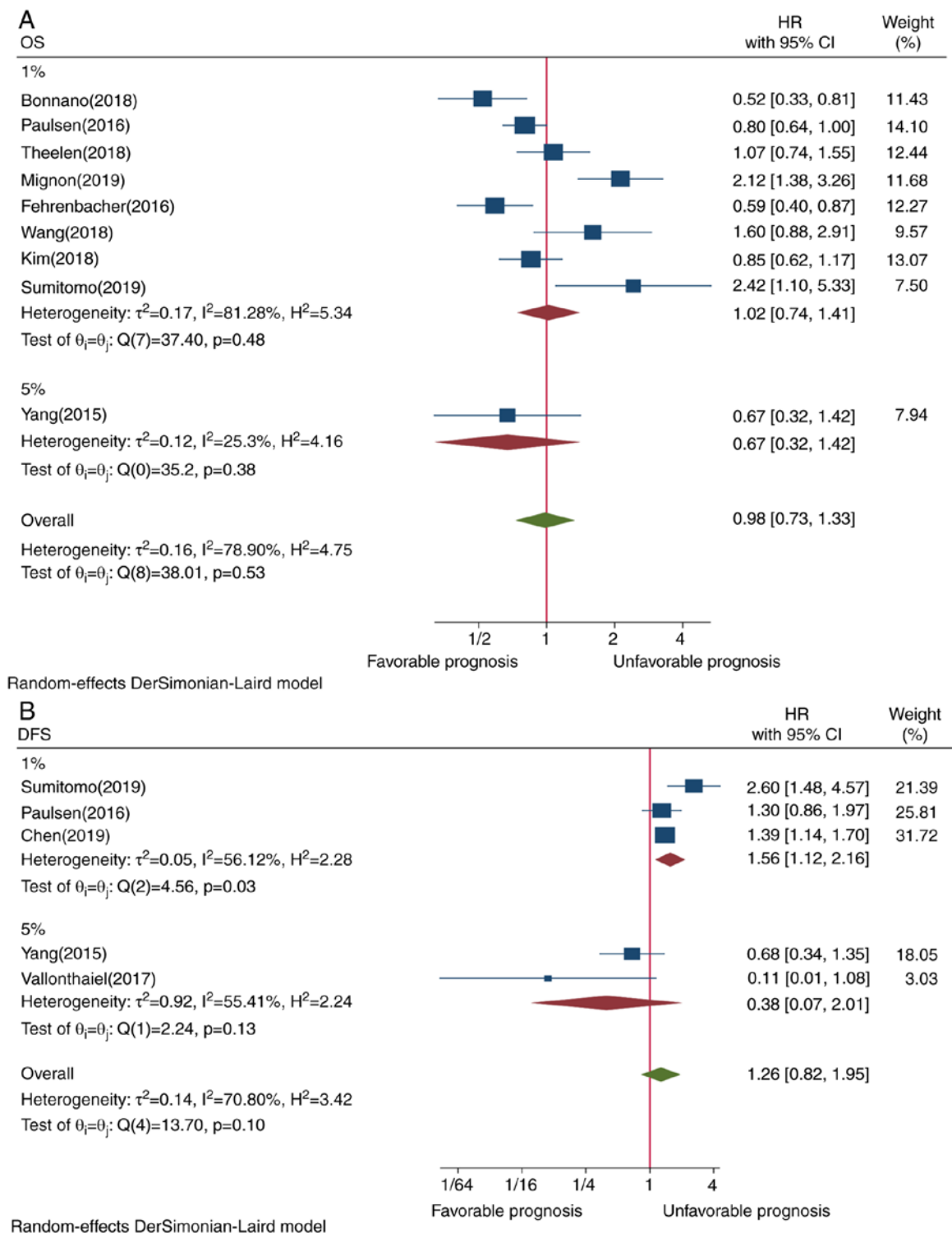


Figure 4. Forest plot presenting the relationship between PD-L1 TIIC and prognosis using the staining cutoff value. (A) OS and (B) DFS for 1 and 5% cutoff values. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

tumor microenvironment in the subset of cells along with their unique molecular mechanism may greatly affect PD-L1 induction (37) and, in turn, the clinical outcome of the patients. Thus, PD-L1 expression generate differently could respond to therapeutic strategies distinctly (38). On this basis, classifying patients with lung cancer is important for the safety and efficacy of treatment, as well as for improving prognosis.

The results of the present meta-analysis suggest that patients with lung adenocarcinoma with PD-L1-positive expression in TIICs may benefit from anti-PD-L1 treatment. This hypothesis was supported by previous cohort studies demonstrating that PD-L1 overexpression in TIICs predicted response to anti-PD-1/PD-L1 therapy with atezolizumuab (11,36,39). This, in turn, suggests that adding PD-L1 TIIC to the existing

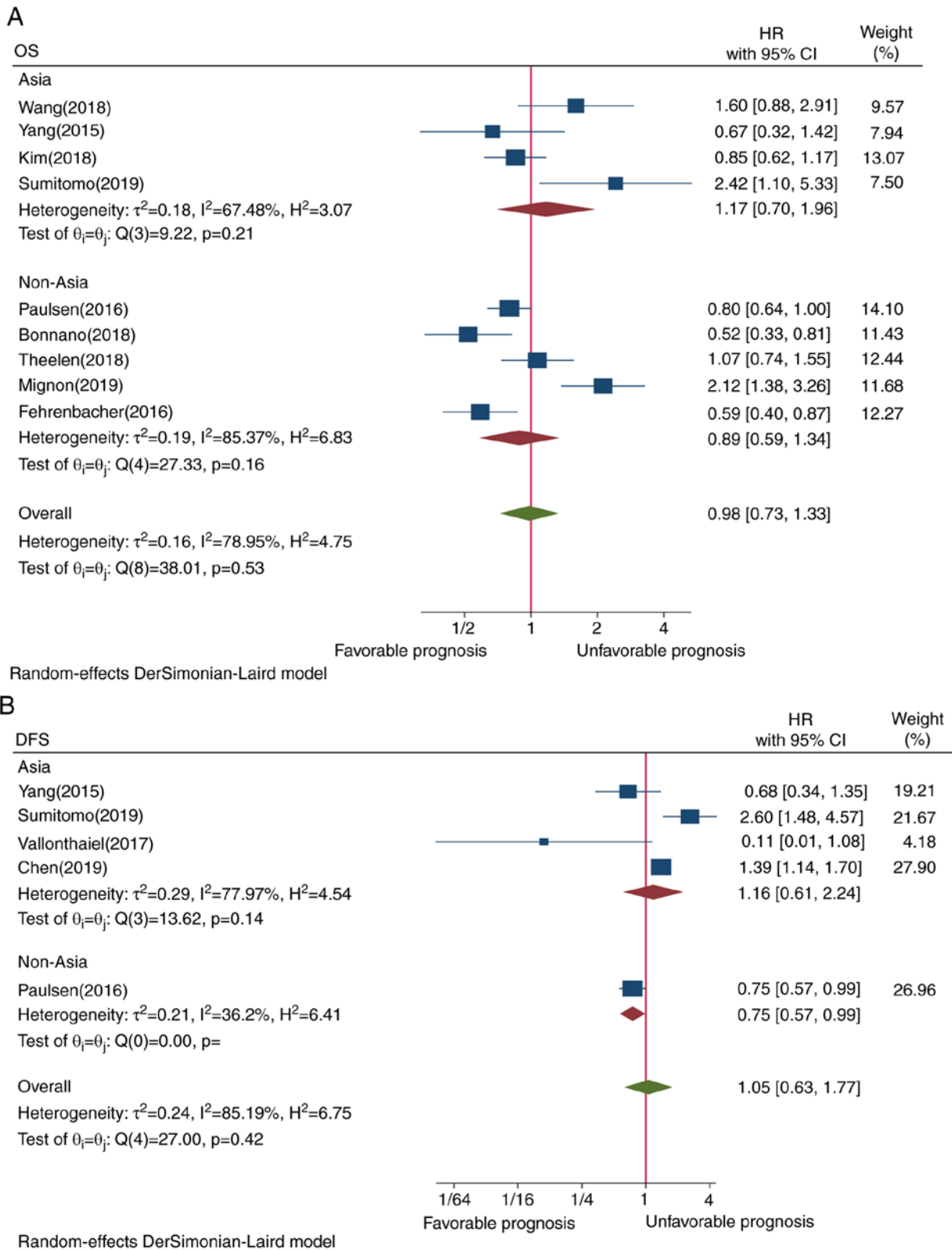


Figure 5. Forest plot presenting the relationship between PD-L1 TIIC and prognosis by ethnicity. (A) OS and (B) DFS. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

PD-L1 tumor cell (TC) in the diagnostic algorithm could help to select patients.

As regards staining localization, there are certain concerns with regard to the challenges in distinguishing membranous from cytoplasmic staining (19,40) and controversies

regarding the need to classify the localization to predict prognosis. The results of the present meta-analysis revealed that membrane-only staining tended to predict worse DFS, although the association was not significant. This may be partly due to the fact that, although there may exist variations

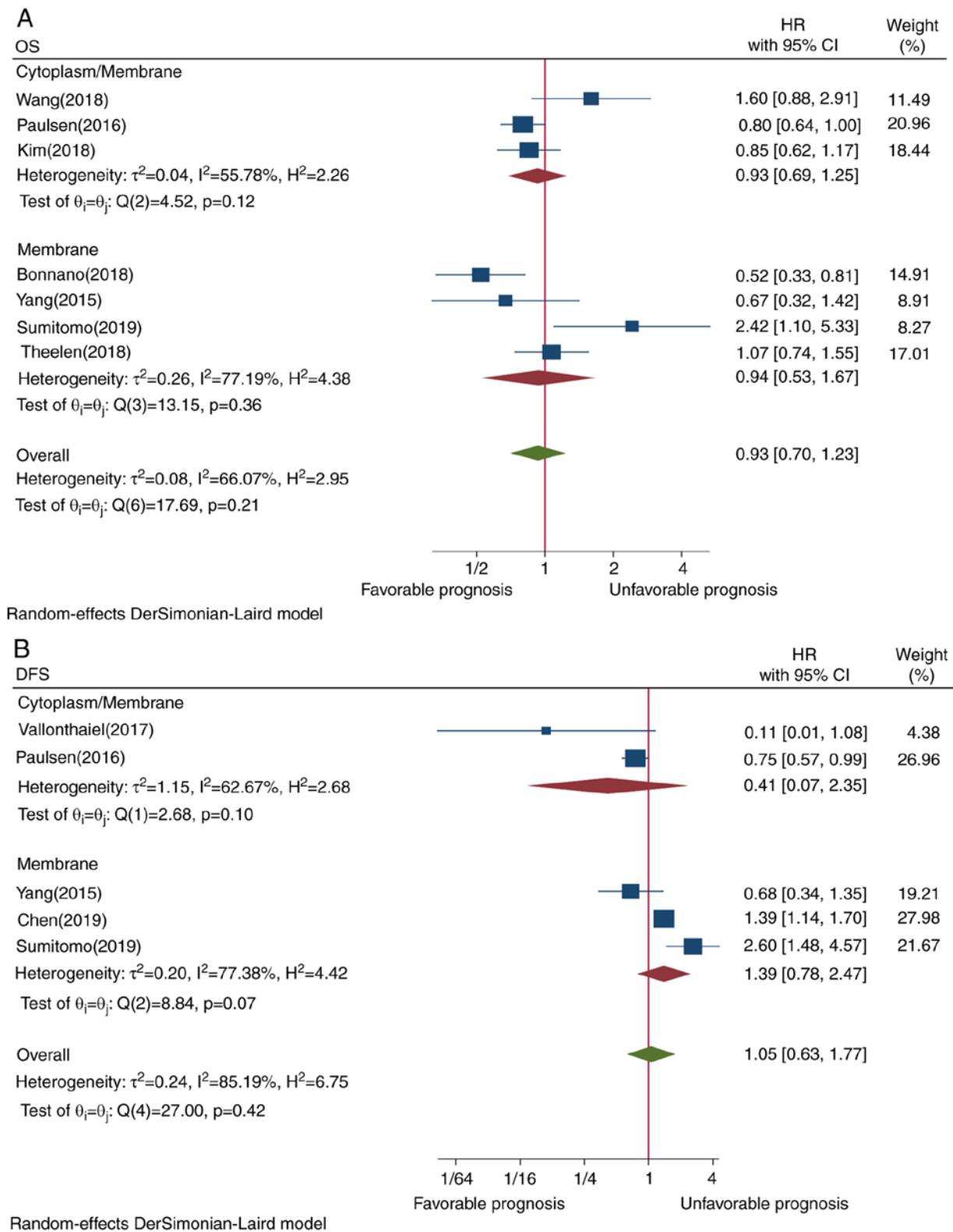


Figure 6. Forest plot presenting the relationship between PD-L1 TIIC and prognosis by staining location. (A) OS and (B) DFS for only-membrane and cytoplasm/membrane staining. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

in staining expression status, the characteristics of PD-L1 IHC assay and staining priority pattern of assays mainly determine prognosis. Previous studies indicate that both the SP142 and E1L3N clones are more specific against intracellular PD-L1 (40,41), while SP142 is less sensitive compared with

other assays (42). In other words, antibodies that are directed against the extracellular compartment could have limited influence on other intracellular PD-L1 forms (cytoplasmic and nuclear-PD-L1), which could, to certain extent, affect the efficacy of PD-L1-based immunotherapy (43). By contrast, it

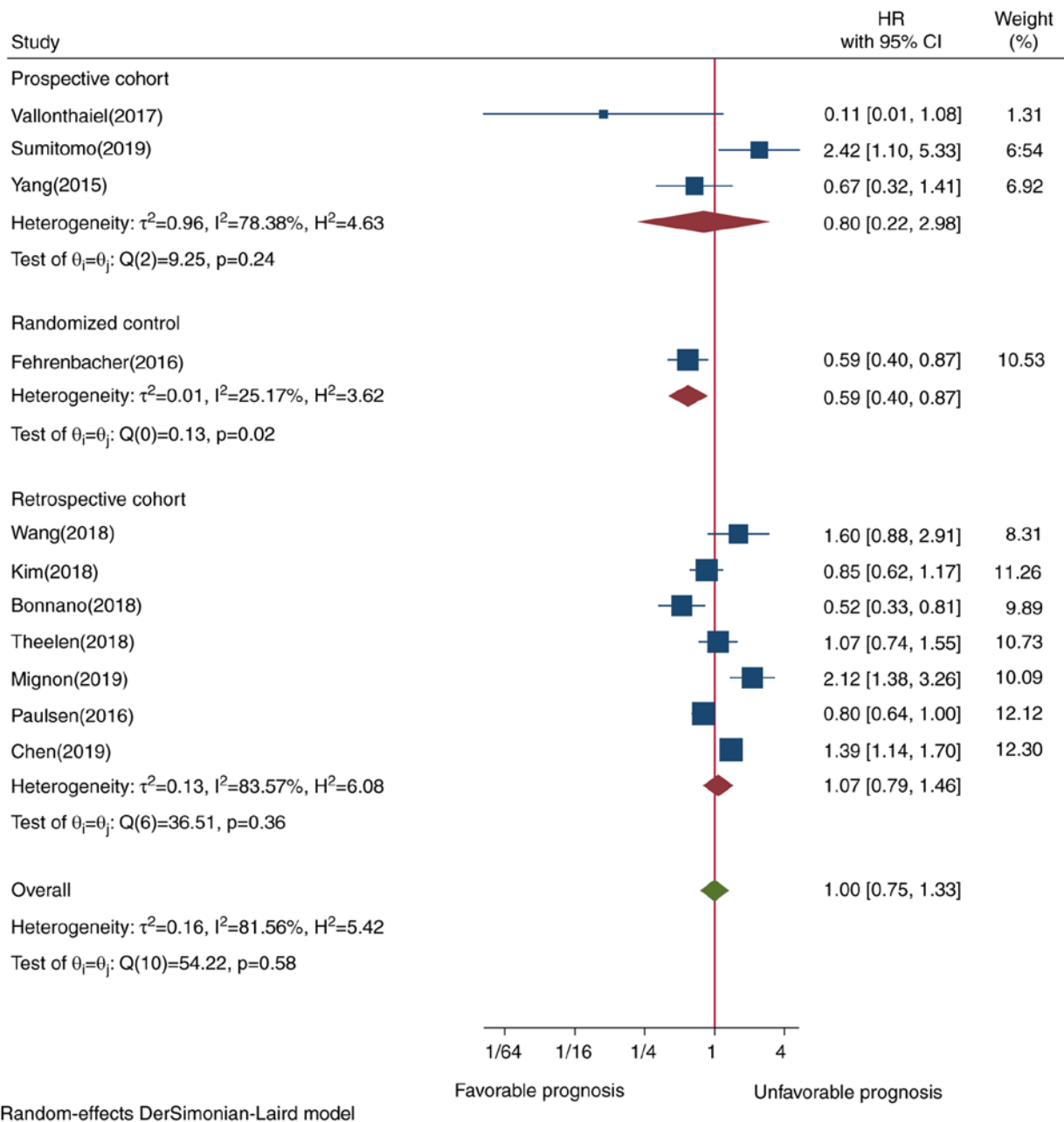


Figure 7. Forest plot presenting the relationship between PD-L1 TIIC and OS by study design. PD-L1, programmed cell death ligand 1; TIIC, tumor infiltrating immune cells; OS, overall survival; DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

was previously reported that specific monoclonal antibodies that recognize PD-L1 variants in the extracellular compartment could also detect PD-L1 determinants retained in the cytoplasm (40). Taken together, these findings suggest that having a detailed knowledge of the functional and structural integrity of membranous and cytoplasmic (mPD-L1/cPD-L1) is important for selecting patients who may benefit from this classification, and to reduce anti-PD-1/PD-L1 therapy-associated toxicity. Large, comprehensive and well-designed studies are required in this field, investigating cytoplasm-and/or membrane-infiltrating immune cells.

Previous cohorts demonstrated that the largest survival benefit was obtained for the highest level of PD-L1 (TC \geq 50% or IC \geq 10%) (11,39). However, \geq 50% PD-L1 was not included in the present meta-analysis, as the included primary

studies were assessed either by 1 or 5% cutoff value. For cutoff value subgroup analysis, it was reported that 1%, but not 5%, cutoff value for PD-L1 TIIC was associated with poor DFS. This is partially in agreement with previous meta-analyses (6,7,44). However, there was a contradictory trend when \geq 1 or \geq 5% staining cutoff value was used for assessing the association of PD-L1 TIIC with the prognosis of patients with cancer. Thus, multi-classification of cutoff values for evaluating PD-L1-positive expression in TIICs may be feasible and reasonable.

The present meta-analysis has certain limitations. First, different research designs, such as observational studies and randomized control studies, were combined. Second, there were differences in the antibody clone used and the scoring criteria. Third, the present study was limited to studies

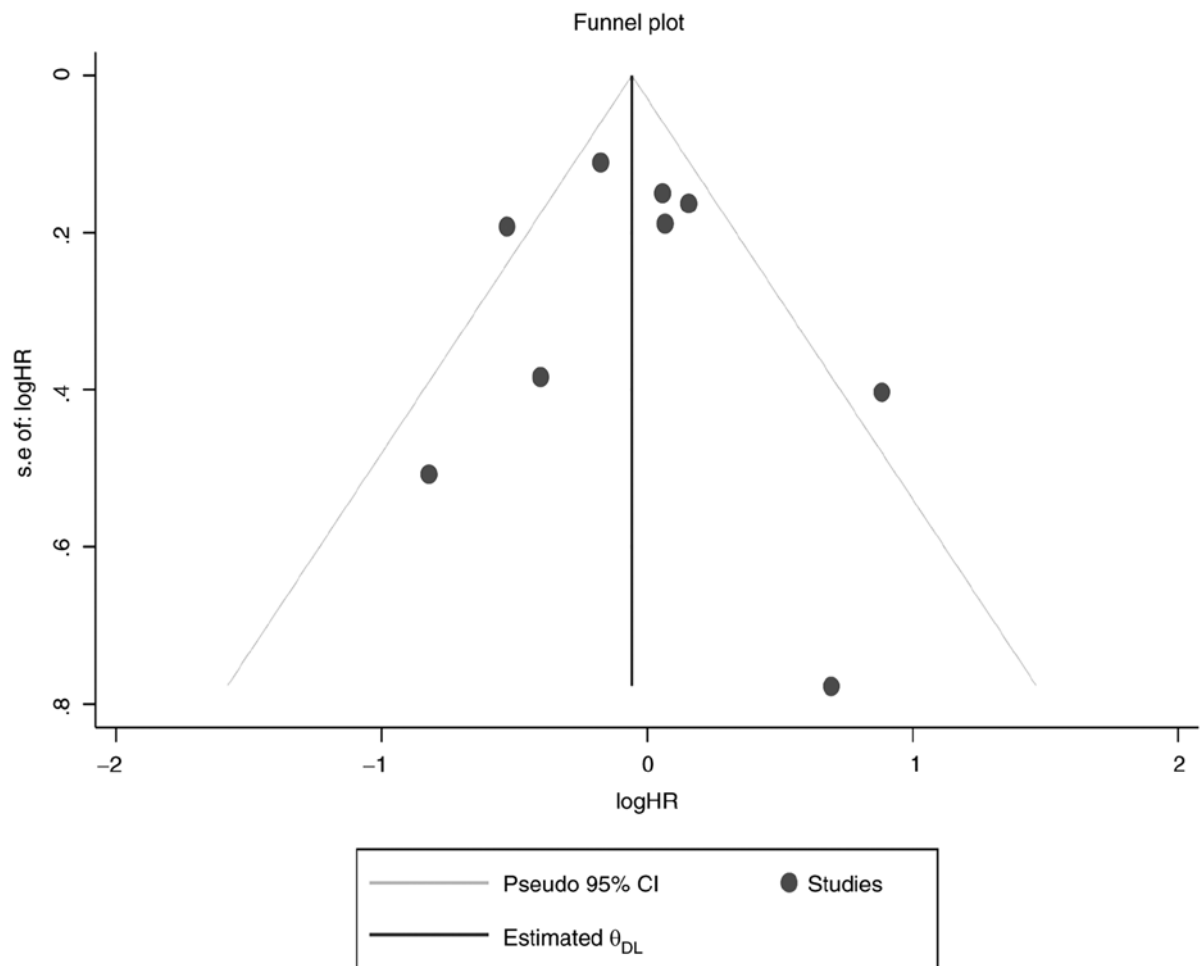


Figure 8. Funnel plot showing to estimate publication bias. HR, hazard ratio.

published in English. Fourth, due to insufficient data, clinicopathological factors on PD-L1 TIIC could not be analyzed. However, the present results may serve as a useful guide for future studies.

In conclusion, based on the present pooled meta-analysis results, positive PD-L1 expression in TIICs was not associated with OS or DFS in the total population of the included studies on patients with lung cancer. However, it was correlated with subtype of lung cancer, since PD-L1 expression in TIICs was associated with worse DFS in patients with lung adenocarcinoma, but with improved OS in patients with lung squamous cell carcinoma. This suggests that adding PD-L1 TIIC to existing PD-L1 TC in the diagnostic algorithm may help with the selection of patients who may benefit from this classification, particularly those with lung adenocarcinoma. However, future large-scale studies are required to verify these findings.

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Availability of data and materials

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

Authors' contributions

BAB and GY conceived and designed the current study, acquired and analyzed the data, and revised the manuscript. TW conceived and designed the current study, analyzed the data and revised the manuscript. BAB and GY confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interests.

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