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Systematic review and meta-analysis of PD-L1 expression discordance between primary tumor and lung cancer brain metastasis

Raees Tonse, Muni Rubens, Haley Appel, Martin C. Tom, Matthew D. Hall, Yazmin Odia, Michael W. McDermott, Manmeet S. Ahluwalia, Minesh P. Mehta, and Rupesh Kotecha

Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (R.T., H.A., M.C.T., M.D.H., M.P.M., R.K.); Office of Clinical Research, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (M.R.); Herbert Wertheim College of Medicine, Florida International University, Miami, Florida, USA (M.C.T., M.D.H., Y.O., M.W.M., M.S.A., M.P.M., R.K.); Division of Neuro-Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (Y.O.); Department of Neurosurgery, Miami Neuroscience Institute, Baptist Health South Florida, Miami, Florida, USA (M.W.M.); Department of Medical Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, Florida, USA (M.S.A.)

Corresponding Author: Rupesh Kotecha, MD, Office 1R203, Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida. Miami, FL 33176, USA (rupeshk@baptisthealth.net).

Abstract

Background. Novel immunotherapeutic strategies targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis are often administered when metastatic tumors show PD-L1 positivity, even in the setting of lung cancer brain metastasis (LCBM). However, biological differences exist between primary tumors and metastatic sites. The objective of this study was to analyze rates of PD-L1 receptor discordance between primary tumors and LCBM.

Methods. A systematic review of studies of biopsied or resected LCBM evaluating PD-L1 discordance published in the Medline database was performed using PRISMA guidelines. Weighted random effects models were used to calculate pooled estimates.

Results. Six full-text articles (n = 230 patients) with a median of 32 patients in each study (range: 24–73) reported PD-L1 receptor expression analyses of both primary lung tumors and brain metastases and met inclusion criteria. The pooled estimate for tumor cell (TC) PD-L1 receptor discordance between primary tumors and LCBM was 19% (95% confidence interval [CI]: 10–27%). For PD-L1 receptor expression in tumor-infiltrating lymphocytes (TIL), the weighted pooled estimate for discordance was 21% (95% CI: 8–44%). For primary versus LCBM, the positive rates by expression levels of <1%, 1–50%, and >50% were 52% (95% CI: 30–73%) versus 56% (95% CI: 34–76%), 30% (95% CI: 22–40%) versus 20% (95% CI: 10–35%), and 15% (95% CI: 6–36%) versus 22% (95% CI: 15–31%) (P = .425), respectively.

Conclusions. PD-L1 discordance occurs in ~20% of LCBM, with the greatest discordance in the 1–50% expression category. Although controversial, confirming discordance might be important for selection of immune checkpoint inhibitor therapy and in the analysis of patterns of failure after treatment.

Key Points

- The pooled estimate for TC PD-L1 receptor discordance between primary tumors and LCBM was 19% (95% CI: 10–27%).
- For PD-L1 receptor expression in TIL, the weighted pooled estimate for discordance was 21% (95% CI: 8–44%).
- PD-L1 discordance occurs in ~20% of LCBM, with the greatest discordance in the 1–50% expression category

Importance of the Study

Novel immunotherapeutic strategies targeting the PD-1/PD-L1 axis are often administered when metastatic tumors show PD-L1 positivity, even in the setting of LCBM. However, brain metastases from NSCLC demonstrate variable response rates to anti-PD-L1 therapy, and potentially discordant from patients derived clinical benefit from the therapy. Understanding the potential reasons may help in improving patient selection for these therapies and evaluating response to treatment. Growing evidence suggests that PD-L1 expression varies in response to the tumor microenvironment. A thorough examination of PD-L1 expression is necessary in order to determine the best treatment options. The objective of this study was to analyze rates of PD-L1 receptor discordance in both TC and TIL between primary tumors and LCBM.

Lung cancer accounts for nearly half of patients diagnosed with brain metastasis (BM) in adults. Resection, whole brain radiotherapy, and stereotactic radiosurgery remain the standard-of-care options.[1] Increasingly, blood–brain barrier penetrating second- and third-generation receptor tyrosine kinase inhibitors targeting specific signaling pathways are being considered for up-front use, especially for small, asymptomatic brain metastases.[2]

Novel immunotherapeutic strategies, such as those targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis, have shown promising results in patients with metastatic lung cancer and are often administered when tumors show PD-L1 positivity.[3] These agents have been demonstrated to be effective in non-small cell lung cancer (NSCLC) in multiple studies; consequently, recent guidelines reflect the importance of selecting an immunotherapy treatment regimen based on the PD-L1 receptor status.[4] However, brain metastases from NSCLC demonstrate variable response rates to anti-PD-L1 therapy, and potentially discordant from patients derived clinical benefit from the therapy.[5] Understanding the potential reasons may help in improving patient selection for these therapies and evaluating response to treatment.

Growing evidence suggests that PD-L1 expression varies in response to the tumor microenvironment.[6] In one recent study, PD-L1 expression varied depending on metastatic locations and histological transformation.[7] A thorough examination of PD-L1 expression is necessary in order to determine the best treatment options. The differential PD-L1 expression in primary lung tumors and corresponding BM has only been addressed in a few studies. While the optimum criteria for selecting immune checkpoint inhibitors are still being debated, the tumor cell (TC) PD-L1 expression in general predicts a higher likelihood of response.[8] In addition, although most legacy studies have focused on the expression of PD-L1 in TC alone, emerging reports indicate the significance of PD-L1 expression in tumor-infiltrating lymphocytes (TIL) for predicting the response to anti-PD-1/PD-L1 inhibitors in breast cancer.[9] Few studies have looked into the discordance of PD-L1 expression in TC and TIL between primary lung cancers and BM.[10] Therefore, the objective of this meta-analysis was to analyze PD-L1 receptor discordance in both TC and TIL between the primary tumor and lung cancer brain metastasis (LCBM). To the best of our knowledge, this is the first meta-analysis assessing PD-L1 expression for both TC and TIL in primary lung cancer and associated BM.

Methods

Selection of Articles

All studies of biopsied or resected LCBM evaluating PD-L1 discordance that were published prior to June 2021 in the Medline database were systematically reviewed using PRISMA guidelines.[11] MEDLINE (PubMed) and Cochrane electronic bibliographic databases were queried to identify appropriate published studies. Additional studies were included after review of the bibliographies of the selected articles. To achieve a thorough initial search, key words included "lung cancer" and "brain metastasis" combined with "programmed death ligand 1/PD-L1," "receptor discordance," and "receptor concordance." Only full-text publications written in English were considered for further evaluation.

The initial inquiry yielded 269 publications which were screened by careful review of all pertinent details. All original articles of 15 adult patients and above directly reporting PD-L1 expression status in primary lung tumors compared to LCBM and receptor conversion/discordance were included in this analysis. Nonclinical papers, expert opinions, commentaries, studies without data on <15 patients, and reports that only compared receptor discordance between extracranial metastases and the primary tumor were excluded. Publications in other languages or available only in abstract form were not included. A thorough review of the references of the retrieved articles was also conducted. Duplicate studies were reviewed for new information, with the most recent report with the most patients being included in the final analysis. Supplementary Figure 1 depicts the search approach for this report as well as the study inclusion technique.

The year of publication, single center or multi-institutional study, duration of the study period, number of patients included, median age, sex (male/female), smoking status (smoker/never smoker), and histology (NSCLC/small cell lung cancer [SCLC]) were all abstracted for this analysis. The timing of BM (synchronous/metachronous) was documented, and chemotherapy, radiotherapy, and corticosteroid usage prior to BM surgery was noted.

These studies included the assay used for assessing the PD-L1 expression and the criteria for PD-L1 expression scoring. Various cutoff levels for PD-L1 expression in TC and TIL between primary tumors and LCBM, such as <1%, 1–50%, and >50%, were extracted. The PD-L1 expression concordance and discordance between primary tumors and LCBM in both TC and TIL was documented.

Outcome Measures and Statistical Analysis

PD-L1 expression status at diagnosis of the primary tumor and of LCBM was extracted for both TC and TIL. A trichotomized approach of scoring, using <1%, 1–50%, and >50% expression, was utilized. We defined PD-L1 concordance (c) as "concordance = [{number of patients expressing PD-L1 both in the primary tumor and also in the BM (sometimes also known as 'positive concordance', p) + number of patients not expressing PD-L1 both in the primary tumor and the BM (sometimes also known as negative concordance", *n*)}/total number of patients evaluated for receptor expression in the primary and BM, t] × 100 (c = [(p+n)/t] × 100). Discordance (d) was defined as = 100- concordance (d = 100-c). Discordance would include the following scenarios: A. Primary expresses receptor, but the BM does not. B. Primary does not express the receptor, but the BM does.

R version 4.1.0 and R package *metafor* were used for statistical analyses.[12] We used method proposed by DerSimonian and Laird to estimate variances and weighted random effects models to calculate pooled estimates.[13] Due to the heterogeneity of studies included in the analysis, we used the random effects model, instead of the fixed effects model, when calculating pooled estimates.[14] For identifying heterogeneity, we used I^2 statistic; values of 0%, 25%, 50%, and 75% were inferred as absent, low, moderate, and high heterogeneity, respectively.[15] For identification of publication bias, Funnel plots and the Egger test were used; a *P* value of <.05 indicated presence of publication bias. Finally, meta-regression analysis was used to detect associations between selected covariates and PD-L1 expression status.

Results

We identified 6 full-text articles (*n* = 230 patients) that met inclusion criteria with a median of 32 (range: 24–73) patients in each study (Table 1). All patients had at least one intracranial lesion biopsy or excision, which was compared to the primary tumor. There was no evidence of publication bias (*P* > .05) across the included reports (Supplementary Figure 2). All of the studies included were retrospective and should be considered hypothesis-generating evidence. Four of 6 studies were single-institution reports and 2 were multi-institutional.

The included literature did not report key patient features, demographics, or treatment information in a uniform or consistent manner for all patients. Across all studies, 60% of patients were male with a median age of 60 years (range: 57–64). The majority of patients (81%)

Table 1. Primary Lung Cancer and Brain Metastases PD-L1 Study Details and Patient Characteristics

Author	Year	Institution	Years	Evidence Quality	N	Sex		Smoking status		Histology		BM Timing		CT prior Lung Sx		RT prior Lung Sx		Steroid prior BM Sx		CT prior BM Sx		RT prior BM Sx	
						Male		Smoker	Never smoker	NSCLC	SCLC	Synchronous	Metachronous	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Mansfield et al.[16]	2016	Single-center	1994-2015	Low	73	40	33	58	15	56	17	8	5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bherghoff et al.[17]	2016	Single-center	1990-2010	Low	32	NA	NA	NA	NA	0	32	NA	NA	NA	NA	NA	NA	NA	NA	15	17	3	29
Takamori et al.[18]	2018	Multi-center	2005-2016	Low	15	64	21	11	23	9	30	2	NA	NA	3	12	NA	NA	NA	NA	NA	13	2
Zhou et al.[19]	2018	Single-center	2006-2014	Low	25	57	18	7	7	5	NA	NA	11	14	NA	NA	NA	NA	NA	NA	NA	NA	NA
Teglasi et al.[20]	2019	Single-center	NA	Low	61	60	30	31	56	5	NA	NA	NA	NA	4	57	2	59	37	15	32	29	5	56
Batur et al.[10]	2019	Multi-center	NA	Low	24	NA	20	4	NA	NA	22	2	24	0	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

BM, brain metastasis; CT, chemotherapy; N, number; NA, not available; NSCLC, non-small cell lung cancer; RT, radiotherapy; SCLC, small cell lung cancer; Sx, surgery.

were smokers, with 67% NSCLC and 33% SCLC. The BM interval across studies was recorded as synchronous in 43 patients, metachronous in 19 patients, and unknown/not reported in 168 patients. Only one study reported steroid usage (37 patients) prior to BM surgery. The most commonly used assay across studies was the Dako assay for PD-L1 expression in primary tumor and LCBM (Table 2).

The pooled estimate for overall PD-L1 receptor concordance in TC between primary and LCBM was 81% (95% CI: 70–88%) (Figure 1A). The PD-L1 receptor positivity rate varied when analyzed by various expression levels. For <1%, 1–50%, and >50% PD-L1 expression, the positivity rates for primary tumors versus BM were 52% (95% confidence interval [CI]: 30–73%) versus 56% (95% CI: 34–76%), 30% (95% CI: 22–40%) versus 20% (95% CI: 10–35%), and 15% (95% CI: 6–36%) versus 22% (95% CI: 15–31%) (P = .425), respectively (Figure 2). The overall pooled estimate for PD-L1 positivity in the primary lung tumor was 59% (95% CI: 42–74%), with a negative rate of 41% (95% CI: 26–58%). In LCBM, the PD-L1 positivity rate was 64% (95% CI: 24–91%) and negative in 36% (95% CI: 9–76%). The overall pooled estimate for overall PD-L1 discordance between primary and LCBM was 19% (95% CI: 10–27%) (Figure 1B).

For PD-L1 TIL receptor positivity, the weighted pooled concordance estimate was 79% (95% CI: 56–92%) (Figure 1C). The PD-L1 receptor positivity rate varied when analyzed by various expression levels. For <1%, 1–50%, and >50% PD-L1 expression in TILs, the positivity rates for primary tumors versus BM were 42% (95% CI: 22–65%) versus 44% (95% CI: 21–71%), 40% (95% CI: 27–56%) versus 47% (95% CI: 24–72%), and 13% (95% CI: 7–22%) versus 7% (95% CI: 3–15%) (P = .042) (Figure 3). The weighted pooled estimate for overall PD-L1 discordance between primary and LCBM TILs was 21% (95% CI: 8–44%) (Figure 1D). Figure 4 illustrates a chordial representation of the PD-L1 expression between primary tumors and LCBM in TCs and TILs. Meta-regression analysis showed that patient factors such as age, sex, smoking status, and histology were not associated with PD-L1 receptor discordance.

Discussion

BM occur frequently in NSCLC patients; approximately 10% of NSCLC patients have BM at the time of diagnosis, and 30% develop intracranial relapse through the course of their disease.[21] The FDA recently approved pembrolizumab, nivolumab, atezolizumab, and nivolumab plus ipilimumab as first-line treatment for metastatic NSCLC, and these treatments have shown to be efficacious and tolerable. Various immune checkpoint inhibitors and their approved indications are summarized in Supplementary Table 1. In a recent autopsy study, Suda et al. reported that PD-L1 expression heterogeneity was dependent on the site of the metastatic lesion.[7]

Although immune checkpoint inhibitors are now widely used in the treatment of lung cancer,[22] several clinical trials still exclude patients with BM.[23] PD-L1 is a predictive biomarker for immune checkpoint treatment response.[24] However, the selection criteria for anti PD-1/PD-L1 therapy are still contentious, their predictive value in the context of LCBM is mostly unknown. PD-L1 expression in TCs and TILs could potentially affect the response to anti PD-1/PD-L1 therapy. We note that PD-L1 expression frequently changed between primary and LCBM, with discordance in TC and TIL reported in 19% and 21% of patients, for a total pooled discordance rate of approximately 20%. If a strong relationship between PD-L1 expression in BM and treatment response is established, this biomarker could become crucial.

Differences in antibodies and IHC platforms for PD-L1 have generated concerns regarding the comparability and diagnostic utility of these assays.[25] SP142, SP263, 28-8, and 22C3 are the 4 FDA-approved antibodies for PD-L1 immunohistochemistry (IHC).[26] The SP142 assay was found to be an outlier in most PD-L1 IHC comparative studies, as it stained less TCs than the other 3 assays. However, TIL staining for PD-L1 varied between all the 4 assays.[26] The biomarker evaluation positivity thresholds also varied between studies and could be a cause of variation in the subgroup analysis. Different IHC scoring methods, such as combined positive score, tumor proportion score, and immune cell proportion score, which are widely used for IHC assessment of immunological checkpoints, could also potentially explain the variability between studies.[27] The PD-L1 discordance was more common in studies using immune cell proportion score, which could be related to changes in micro-environmental immune infiltration between primary and metastatic tumors.[28]

Pembrolizumab, an anti-PD-1 drug, was approved as first-line treatment for NSCLC patients with ≥50% TC PD-L1 expression.[29] The 5% cutoff threshold was used in a number of CheckMate studies,[30] with more recent studies adopting a PD-L1 expression of 1% or greater and less than 1% cutoff level.[31] We observed that the greatest discordance in PD-L1 expression between primary and LCBM was noted in the 1–50% PD-L1 expression category for TC (30% vs 20%) and in the >50% PD-L1expression category for TIL (13% vs 7%). It is worthwhile to be mindful of this discrepancy, particularly when selecting an immune checkpoint inhibitor therapy, as it may aid to analyze potential failure trends in LCBM patients. Although the outcomes of concordant or discordant brain metastasis cases were not uniformly described, the clinical significance and relevance of PDL-1 expression discordance remains of key interest. In select studies, outcomes were compared among patient subgroups. For example, Takamori et al. reported that the PD-L1-positive BM group had a substantially shorter brain-specific disease-free survival than the PD-L1-negative BM group (P < .05).[18] However, the OS did not differ significantly between the PD-L1 positive and negative BM groups (P = .33). According to Berghoff et al., patients with PD-L1 expression on TILs for BM had a better survival prognosis (29 vs 6 months; P = .002).[17] Furthermore, the presence of PD-L1 in more than 5% of viable tumor cells showed no correlation with survival. None of the studies included in the meta-analysis reported response and outcomes between discordant and nondiscordant cases, which could be taken into account in future studies.

Lung cancer is frequently treated with various systemic therapy and radiation therapy; therefore, it is crucial to examine if the BM TC PD-L1 positivity changes are

Table 2. Primary Lung Cancer and Brain Metastasis PD-L1 Expression and Discordance Status

Author	Year	N	Assay name	Criteria for PD-L1 expression measurement	PDL1 expression in TC (Lung)			PDL1 expression in TIL (Lung)			PDL1 in lung		PDL1 expression in TC (BM)			PDL1 expression in TIL (BM)			PDL1 in BM		Concordance in Lung/BM PDL1 TC (*n* [%])	Discordance in Lung/BM PDL1 TC (*n* [%])	Concordance in Lung/BM PDL1 TIL (*n* [%])	Discordance in Lung/BM PDL1 TIL (*n* [%])
					<1	1 to 50	>50	<1	1 to 50	>50	Positive	Negative	<1	1 to 50	>50	<1	1 to 50	>50	Positive	Negative				
Mansfield et al.[16]	2016	73	Leica Bond RX stainer	PDLI in >5%	NA	NA	NA	NA	NA	NA	32	41	NA	NA	NA	NA	NA	NA	24	49	63 (86%)	10 (14%)	54 (74%)	19 (26%)
Bherghoff et al. [17]	2016	32	Dako assay/ IHC	PDLI in >5%	NA	NA	NA	NA	NA	NA	24	8	NA	NA	NA	NA	NA	NA	11	21	22 (70%)	10 (30%)	NA	NA
Takamori et al. [18]	2018	15	Dako assay/ IHC	PDLI in >5%	10	3	2	NA	NA	NA	4	11	11	1	3	NA	NA	NA	3	12	11 (75%)	4 (25%)	NA	NA
Zhou et al. [19]	2018	25	Shuwen Biotech Co	PDLI in >5%	NA	NA	NA	NA	NA	NA	17	8	NA	NA	NA	NA	NA	NA	16	9	18 (72%)	7 (28%)	15 (60%)	10 (40%)
Teglasi et al. [20]	2019	61	Ventana	PDL1 for Tumor Cell 1%, 5%, and 50%	39	18	4	34	20	6	61	0	40	10	11	38	19	4	61	0	NA	NA	NA	NA
Batur et al. [10]	2019	24	Dako assay/ IHC	PDL1 for Tumor Cell 1%, 5%, and 50%	6	9	9	6	13	5	18	6	7	9	8	6	16	2	17	7	23 (98%)	1 (2%)	23 (98%)	1 (2%)

BM, brain metastasis; IHC, immunohistochemistry; N, number; NA, not available; PD-L1, programmed death-ligand 1; TC, tumor cell; TIL, tumor-infiltrating lymphocytes.

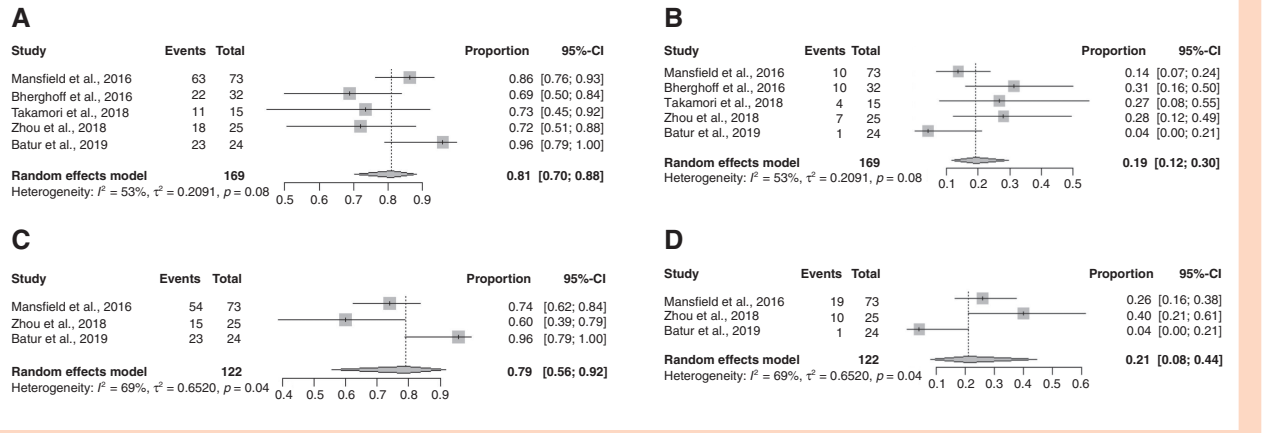

Figure 1. Forest plots of concordance and discordance rates of PD-L1 expression in tumor cell (TC) and tumor-infiltrating lymphocytes (TIL) for primary lung tumor and brain metastasis (BM); (A) Concordance between PD-L1 expression in TC for primary lung tumor and BM; (B) Discordance between PD-L1 expression in TC for primary lung tumor and BM; (C) Concordance between PD-L1 expression in TIL for primary lung tumor and BM; (D) Discordance between PD-L1 expression in TIL for primary lung tumor and BM. The square boxes correspond to proportions from each study and the size of the box corresponds to the weight of each study, and horizontal line represents 95% confidence interval (CI). The diamonds are pooled estimates of the outcomes with 95% CI.

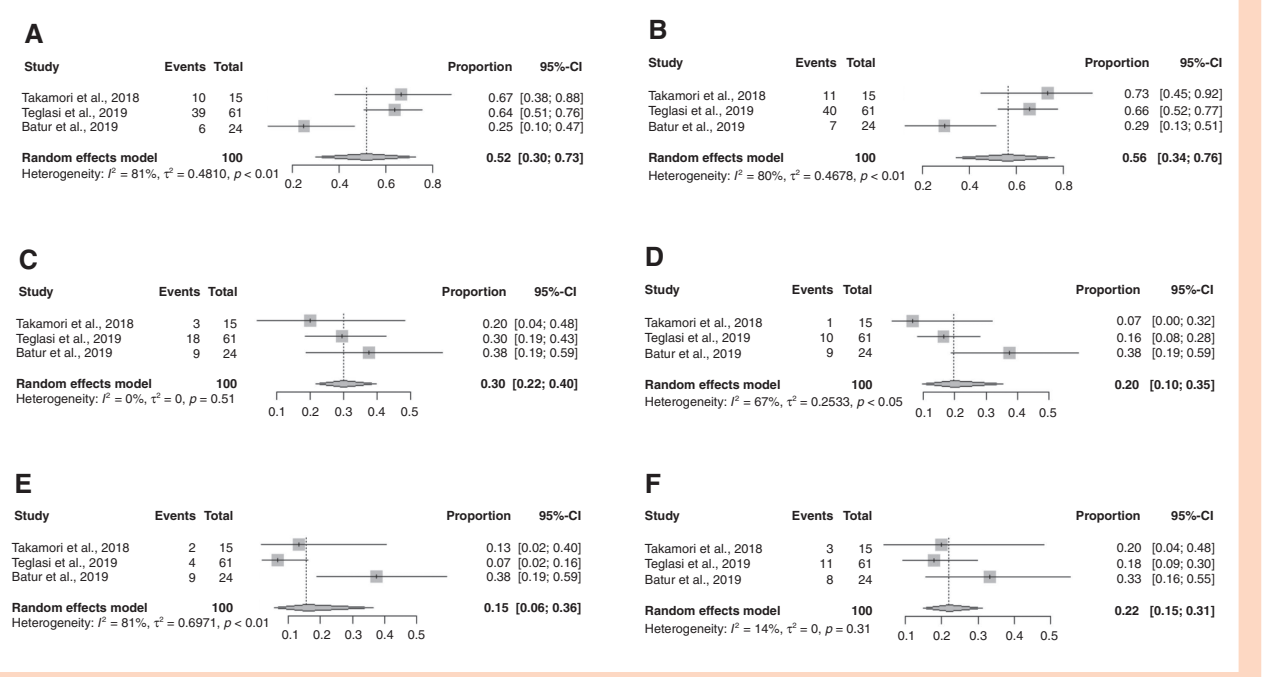

Figure 2. Forest plots of various cutoff levels of PD-L1 expression in tumor cells (TC) for primary lung tumor and brain metastasis (BM): (A) Lung PD-L1 <1%; (B) BM PD-L1 <1%; (C) Lung PD-L1 1–50%; (D) BM PD-L1 1–50%; (E) Lung PD-L1 >50%; (F) BM PD-L1 >50%. The square boxes correspond to proportions from each study and the size of the box corresponds to the weight of each study, and horizontal line represents 95% confidence interval (CI). The diamonds are pooled estimates of the outcomes with 95% CI.

consequential to exposure to various therapies. Studies have shown that the PD-L1 conversion rate is higher in metachronous compared to synchronous metastases, which could possibly be related to therapeutic selection pressure.[20] Takamori et al. reported that smoking status and BM irradiation were both linked with PD-L1 positivity rates in the BM.[18] Several in vivo and in vitro preclinical studies have shown that radiation up-regulates PD-L1 expression in BM.[32] Furthermore, experimental studies have revealed that irradiation facilitates CD8+ T-cell recruitment, which is associated with intratumoral PD-L1 expression.[33,34] In this analysis, we did not find an

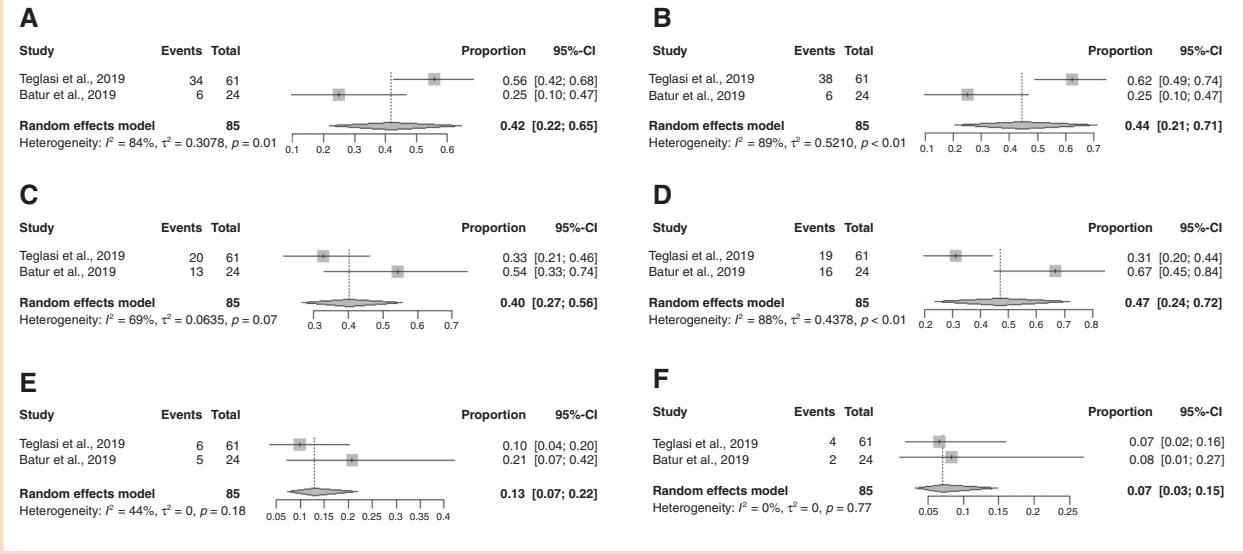

Figure 3. Forest plots of various cutoff levels of PD-L1 expression in tumor-infiltrating lymphocytes for primary lung tumor and brain metastasis (BM): (A) Lung PD-L1 <1%; (B) BM PD-L1 <1%; (C) Lung PD-L1 1–50%; (D) BM PD-L1 1–50%; (E) Lung PD-L1 >50%; (F) BM PD-L1 >50%. The square boxes correspond to proportions from each study and the size of the box corresponds to the weight of each study, and horizontal line represents 95% confidence interval (CI). The diamonds are pooled estimates of the outcomes with 95% CI.

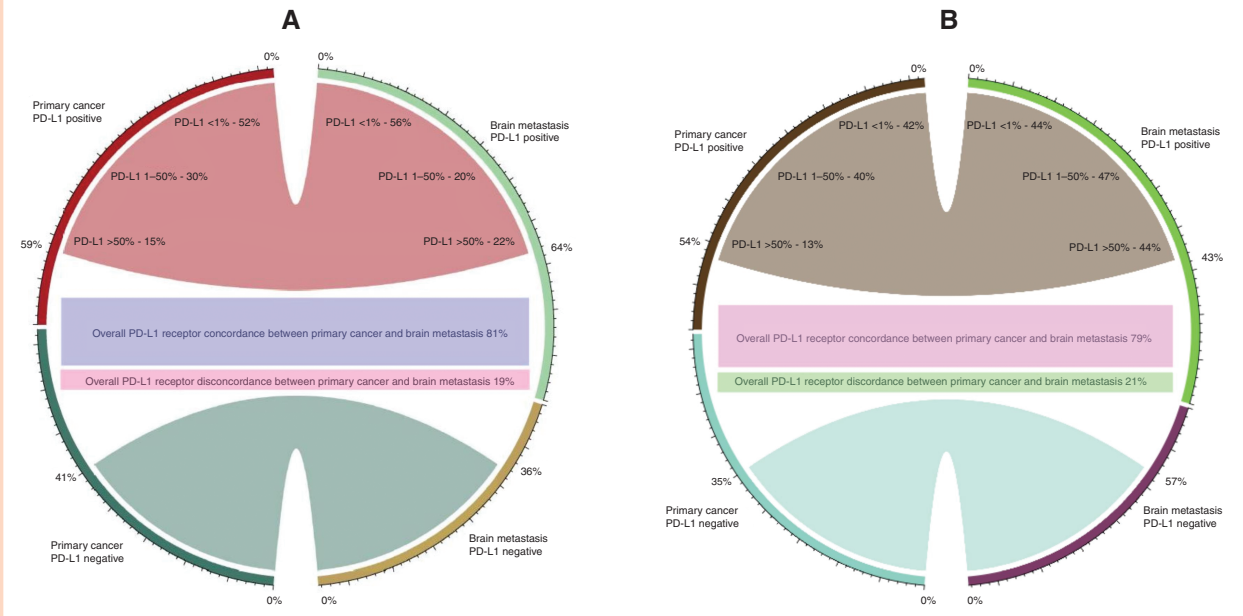

Figure 4. Chordial diagram illustrating the PD-L1 expression between primary tumor and brain metastasis; (A) tumor cells, (B) tumor-infiltrating lymphocytes.

association between patient factors such as age, sex, smoking status, histology, and prior treatment with chemotherapy, radiotherapy, and corticosteroid usage with PD-L1 discordance.

The current study has several limitations. Because the included studies were retrospective, some inherent methodologic bias was unavoidable. Second, due to the small number of patients involved in some of the reports, the pooled analysis of conversion rates demonstrates significant heterogeneity. Third, most studies did not adequately document systemic therapy and radiation therapy details for each individual, nor did they investigate the

effect of these treatments on PD-L1 conversion. Fourth, the reported studies contained few patients overall and therefore the overall sample size of this study appears low. Fifth, the response rates and outcomes between discordant and nondiscordant cases were not reported in the studies. For further validation, high-quality studies with prospective designs, large sample sizes, and detailed reporting of patient and tumor biology characteristics are required in the future.

Conclusion

PD-L1 status discordance in TCs and TILs occurs in approximately 20% of LCBM, with the greatest discordance in the 1–50% expression category in TC between primary and LCBM. Assessing PD-L1 expression in both the primary tumor and the LCBM is highly recommended for providing an informed clinical decision on immune checkpoint treatment.

Keywords

brain | discordance | lung cancer | metastasis | PD-L1 | receptor

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