Neoplasma 2026; 73(1): 68–73

doi:10.4149/neo_2026_251018N437

Prognostic value and clinical significance of tumoral PD-L1 and stromal α-SMA expression in diffuse pleural mesothelioma

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Received October 18, 2025 / Accepted January 19, 2026

Diffuse pleural mesothelioma (PM) is a rare malignant neoplasm with an extremely poor prognosis. Prognostic assessment remains challenging, highlighting the urgent need for reliable biomarkers to guide precise and effective therapy. Programmed death ligand 1 (PD-L1) has been suggested as a predictive biomarker for PM, but existing data are limited and controversial. Although advances have been made in understanding cancer-associated fibroblasts (CAFs) within the PM tumor microenvironment, their clinical and prognostic significance remains poorly elucidated. A retrospective analysis of 51 pathologically diagnosed PM was performed. We evaluated clinicopathological factors (including tumoral PD-L1, stromal α-SMA, and Ki-67 percentage by immunohistochemistry) and analyzed their correlation with overall survival (OS) using Kaplan-Meier and multivariate Cox regression. A total of 12 potential prognostic factors were evaluated in the univariate analysis, and 6 factors were found to be significantly associated with a poor prognosis in PM patients. Multivariate analysis identified histological classification, TNM stage, and PD-L1 expression as independent prognostic factors in PM patients. Stromal α-SMA positivity, a marker of poor prognosis, was significantly correlated with male, non-epithelioid subtype, and a high Ki-67 index. Moreover, α-SMA positivity tended to show an increased likelihood of PD-L1 expression (p=0.065). The expression of tumor PD-L1 could serve as an adverse prognostic factor for PM patients. Its potential association with tumor stromal α-SMA expression warrants further investigation, particularly in the context of unmet needs in tumor immunotherapy.

Key words: diffuse pleural mesothelioma; cancer associated fibroblasts; α-SMA; PD-L1; prognosis

Diffuse mesothelioma is a kind of rare and poorly recognized mesothelial cell-derived, very aggressive neoplasm, with characteristics of diffuse serosal spread and a dismal prognosis [1]. It typically originates from the pleura but can occasionally develop from the peritoneum, pericardium, tunica vaginalis, and other organs [1]. Due to its highly mimicking to secondary pleural carcinoma, it is a great challenge to initially diagnose by non-specific clinical manifestations and usual imaging signs [1]. The final diagnosis of diffuse pleural mesothelioma (PM) should be made based on histological pattern and immunohistochemistry (IHC) findings from a deep histologic sample [2, 3]. Once confirmed, PM can be further categorized into three subtypes with roughly estimated prognostic stratification: epithelioid (best), biphasic (intermediate), and sarcomatoid (worst) [2].

While the lack of relatively reliable predictive biomarkers has hampered timely intervention for PM, which often presents at an advanced stage with extensive disease involvement, resulting in a median overall survival of 10–12 months in untreated patients [4]. Even with treatment, the 5-year overall survival (OS) estimate is at best between 5% and 12% [5]. Thus, despite advances in multimodal therapeutic approaches such as surgery, chemotherapy, and radiotherapy, its five-year mortality rate remains high [5]. Molecular features of PM exhibit prominent inter- and intratumor heterogeneity, primarily involving impairment in tumor suppressor genes (e.g., BAP1, CDKN2A, MTAP, and NF2),

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yet remain poorly understood [2]. Targeted therapy is not yet available for this deadly disease, even though several molecular pathways have been identified and biomarker-driven clinical trials have been conducted in PM to date [4, 6]. The recent approval of nivolumab plus ipilimumab as frontline treatment in treatment-naïve adult patients with non-epithelioid unresectable PM marks a significant milestone for the treatment of this disease [7].

However, only a minority of patients respond to this immunotherapy, and current clinical stratification relies largely on histological subtype [8]. Given these limitations, prognosis prediction is a key step in the management and treatment stratification of PM. Identification of reliable prognostic biomarkers for this disease is therefore urgently needed. For the time being, PD-L1 expression has failed to be a powerful predictive biomarker for ICIs treatment in PM; however, some studies have reported prognostic value [9–11]. Considering its central role in antitumoral immune response evasion, this study aims to validate the relationship between PD-L1 expression and survival outcomes in PM tissues. Additionally, the tumor microenvironment (TME) has emerged as a promising alternative predictive biomarker for immunotherapy [12]. Cancer-associated fibroblasts (CAFs) are an abundant cell type in TME and have been shown to drive the progression of several malignancies [13]. Notably, marked desmoplastic reactions, an indicator of CAFs activation and accumulation, are frequently observed in PM [14]. This strongly implies that CAFs may contribute to PM progression and immune escape, while their specific roles in mesothelioma remain largely unknown.

Therefore, to identify reliable prognostic and therapeutically relevant biomarkers for PM, this study examined the correlations between PM patient prognosis and the expression of CAFs marker α-SMA in fibrotic stroma, alongside PD-L1 and cell proliferation marker (Ki-67) in tumor cells.

Materials and methods

This study was approved by the Institutional Review Boards at the Xiangya Second Hospital Affiliated to Central South University School and conducted in accordance with the Declaration of Helsinki. Fifty-one cases of PM in our departmental archives with available clinical data, hematoxylin and eosin-stained slides, and formalin-fixed paraffin-embedded (FFPE) blocks were enrolled in this study. These patients were treated with core needle biopsy, local excision, and surgical resection of primary pleura-occupied lesions between April 2007 and August 2021. The definitive diagnosis was established by routine pathological examination and confirmed by IHC. None of the patients received any oncologic treatment before the diagnosis. Pathologic parameters of all PM cases were reassessed according to the 8th edition American Joint Commission on Cancer (AJCC) tumor staging system. The time of follow-up was from initial diagnosis to August 2021 (range from 3–58 months).

IHC for α-SMA (Clone 1A4, dilution 1:100; Yongnian Tech), VENTANA PD-L1 (Clone SP263), and Ki-67 (Clone 1A1–D3, dilution 1:100; Wondfo) was performed on FFPE tumor slides. Immunostaining of all markers was conducted on Ventana Automated Immunostainer (Ventana Medical Systems), following the manufacturer's protocols. IHC analysis was performed according to descriptions in prior studies. Intratumoral fibroblast α-SMA expression (≥1%) was interpreted as positive. Positive PD-L1 expression was defined as ≥1% membranous staining in tumor cells. Ki-67 proliferation index was calculated as the percentage of positive cells in the total number of tumor cells and further classified as low (≤25%) or high (>25%) positivity, as previously reported [15].

Parameters were collected as potential prognostic factors including age (≤61 or >61 years), gender (male or female), smoking history (absence or presence), Eastern Cooperative Oncology Group performance status (ECOG PS) scores (<2 or ≥2 points), effusion (absence or presence), weight loss (absence or presence), histopathological subtype (epithelioid or non-epithelioid), TNM (early [I/II] or late [III/IV]), treatment (best supportive care [BSC] or adjuvant therapies). Adjuvant therapies included chemotherapy, radiotherapy, immunotherapy, surgery, or a combination of any of the above treatment strategies.

Univariate survival analysis utilized the Kaplan-Meier method and log-rank test. OS was measured from the date of a definitive diagnosis of PM to the date of death from any cause or the last follow-up time. Variables with p-value <0.05 (two-sided) were considered statistically significant. Variables with significant univariate associations, together with those deemed clinically relevant or of research interest, were selected for further multivariate survival analysis. Chi-squared test was performed to assess the relationships between α-SMA expression and clinicopathological characteristics (including PD-L1 and Ki-67 expression). Above all, statistical analyses were performed using Stata 18.0 (StataCorp, College Station, TX, USA).

Results

Patient's clinicopathological characteristics. Fifty-one PM patients were enrolled in this study, with detailed clinical and pathological information summarized in Table 1. PD-L1 protein was expressed on the membrane of tumor cells in 19 cases. Positive α-SMA expression was observed in 32 cases. High Ki-67 expression was detected in 27 cases.

Univariate analysis. All 12 variables were enrolled in the Kaplan-Meier method and univariate analysis. Six factors were significantly associated with PM prognosis ($p<0.05$, Table 2). Favorable prognostic factors associated with prolonged survival included epithelioid subtype, early TNM stage, treatment received, and minimal or low IHC expression of PD-L1, α-SMA, and Ki-67. The survival curves of α-SMA and PD-L1 are presented in Figure 1.

Multivariate analysis. A total of 4 potential prognostic factors in PM were chosen for further multivariate analysis (Table 2). The results of multivariate analysis showed that histopathological subtype (HR=4.103; 95% CI=1.600–10.518; p=0.003), stage (HR=2.526; 95% CI=1.182–5.399; p=0.017), and PD-L1 expression (HR=2.159; 95% CI=1.019–4.573; p=0.044) were independent prognostic factors for PM.

Relationship between stromal α-SMA expression and clinicopathological characteristics. Statistically significant correlations were identified between stromal α-SMA expression and gender (p=0.046), histopathological subtype (p=0.013), and Ki-67 index (p=0.003) (Table 3). Specifically, α-SMA positivity was more frequently detected in male patients, non-epithelioid PM subtype, and cases with high Ki-67 index. Moreover, stromal α-SMA-positive PM patients exhibited a trend toward increased PD-L1 expression, though this association did not reach statistical significance (p=0.065). Representative tissue sections having concurrent stromal α-SMA and tumoral PD-L1 expression in PM cases are provided in Figure 2.

Discussion

Existing models like the CALGB, despite effectiveness, are not commonly adopted due to their time-consuming nature and requirement of expensive equipment [11]. Hence, more accurate prognostic information is needed in PM research. Currently, the established uniform prognostic factors still mainly involve tumor stage and histology, as reaffirmed in this study. Furthermore, our survival analysis demonstrated the OS significance of α-SMA, PD-L1, and Ki-67 in PM patients.

Over the past decades, no significant progress has been made in the treatment of PM aside from the approval of the first chemotherapy-free regimen based on the dual ICI nivolumab plus ipilimumab in non-epithelioid PM. Many investigated drugs, either alone or in combination regimens, have failed to demonstrate efficacy. In this study, PD-L1

Table 1. Demographic features of diffuse pleural mesothelioma patients.

Features	Pleural N (%)
Number of patients	51 (100)
Median age	61
Gender	
male	33 (64.71)
female	18 (35.29)
Smoking	
absence	23 (45.10)
presence	28 (54.90)
ECOG PS Score	
<2	36 (70.59)
≥2	15 (29.41)
Effusion	
absence	10 (19.61)
presence	41 (80.39)
Weight loss	
absence	29 (56.86)
presence	22 (43.14)
Subtype	
epithelioid	35 (68.63)
biphasic	11 (21.57)
sarcomotoid	6 (11.76)
TNM	
early (I/II)	24 (47.06)
late (III/IV)	27 (52.94)
Treatment	
adjuvant therapies	13 (25.49)
BSC	38 (74.51)
Stromal α-SMA expression	
absence	19 (37.25)
presence	32 (62.75)
PD-L1	
TPS=0	32 (62.75)
TPS≥1	19 (37.25)
Ki-67	
≤25%	24 (47.06)
>25%	27 (52.94)

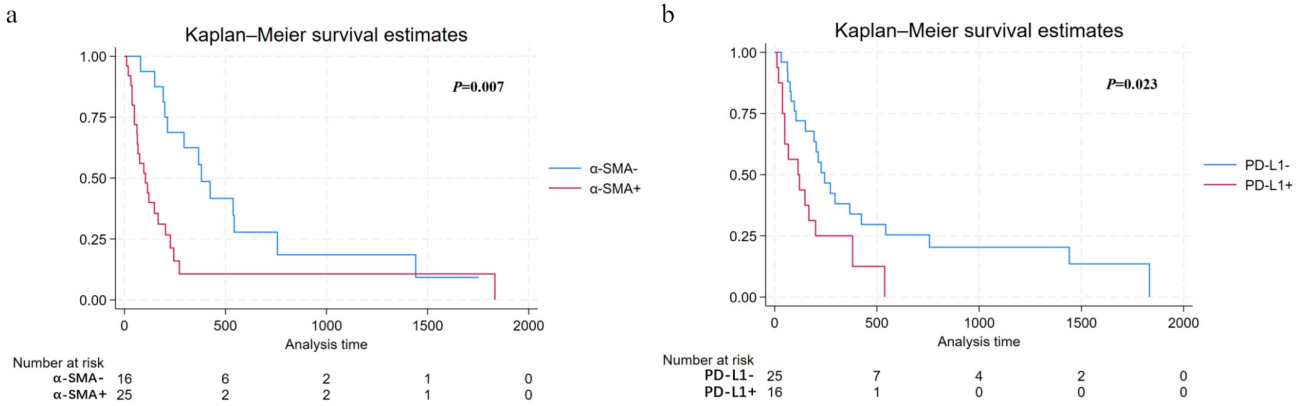

Figure 1. Kaplan-Meier survival curves of α-SMA (a) and PD-L1 (b) in PM patients.

Table 2. Univariate and multivariate analysis of parameters in diffuse pleural mesothelioma patients.

Variables (N=41)	Univariate analysis			Multivariate analysis		
	O/N*	Survival[a] (months)	p-value	HR	95% CI	p-value
Age (≤61 vs. >61)	20/22 vs. 15/19	13.28 vs. 9.02	0.468			
Gender (Male vs. Female)	23/27 vs. 12/14	8.41 vs. 16.89	0.289			
Smoking (Yes vs. No)	19/22 vs. 16/19	8.76 vs. 14.25	0.451			
ECOG PS score (<2 vs. ≥2)	22/28 vs. 13/13	13.67 vs. 6.22	0.061			
Effusion (Yes vs. No)	29/34 vs. 6/7	11.03 vs. 12.67	0.899			
Weight loss (Yes vs. No)	16/18 vs. 19/23	9.58 vs. 12.66	0.450			
Subtype (Epithelioid vs. Others)	22/28 vs.13/13	15.03 vs. 3.28	**0.000**	**4.103**	**1.600–10.518**	**0.003**
TNM (Early vs. Late)	14/18 vs. 21/23	16.96 vs. 6.88	**0.010**	**2.526**	**1.182–5.399**	**0.017**
Treatment (Yes vs. No)	8/12 vs. 27/29	19.14 vs. 8.07	**0.012**			
α-SMA (Yes vs. No)	22/25 vs. 13/16	7.48 vs. 17.29	**0.007**	2.086	0.853–5.101	0.107
PD-L1 (TPS: 0 vs. ≥1)	21/25 vs. 14/16	15.24 vs. 5.15	**0.023**	**2.159**	**1.019–4.574**	**0.044**
Ki-67(≤25% vs. >25%)	14/18 vs. 21/23	15.80 vs. 7.79	**0.042**			

Notes: *O-observed death number; *N-total patient number; [a]survival (months)

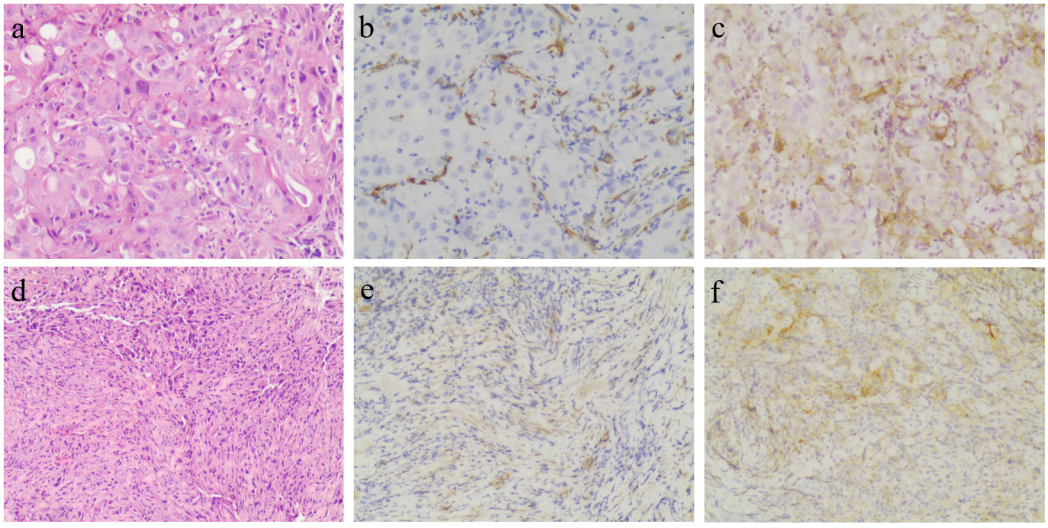

Figure 2. Immunohistochemical co-expression of α-SMA and PD-L1 in PM subtypes. Epithelioid subtype (magnification a–c 200×): a representative case (a) exhibiting concurrent expression of cytoplasmic α-SMA in stromal fibroblast-like cells (b) and membranous PD-L1 in tumor cells (c). Sarcomatoid subtype (magnification d–f 100×): a representative case (d) with expression of cytoplasmic α-SMA in stromal cells (e) and membranous PD-L1 in tumor cells (f).

was detected by IHC in tumor cells in 37.25% of total cases, consistent with the reported high range of PD-L1 expression in PM [11]. Even if different antibodies and cut-offs were adopted, this study confirmed PD-L1 positivity signifies a poor prognosis in PM and serves as an independent prognostic factor [9–11]. Compared to the great progress of immunotherapy in other solid tumors, the restricted therapeutic effect also reminds us that much attention needs to be paid to overcoming the immune resistance in most PM patients.

TME, particularly CAFs, represents a promising focus for understanding this resistance. Chrisochoidou et al. have used co-cultures of patient-derived mesothelioma cell lines and lung fibroblasts to observe that fibroblast activation is a self-propagated process, leading to the generation of a fibrotic extracellular matrix in tumor stroma and triggering drug resistance in mesothelioma cells [16]. However, the characteristics and roles of CAFs in PM progression remain poorly understood. Recently, Mathilakathu et al. found that using conditional media from CAFs could activate the MAPK signaling cascade in PM cell lines, which was accompanied by changes in biological behavior and contributed to tumor progression [17]. Ries et al. demonstrated that mesothelioma-associated CAFs with high expression levels of α-SMA promote proliferation and migration of PM cells via c-Met/PI3K and WNT signaling, but do not confer cisplatin resistance [18]. In a cohort of 37 epithelioid PM cases, α-SMA-positive CAFs were also identified as a marker of shortened OS but not associated with clinicopathological features [14]. Therefore, α-SMA was used

as the CAFs marker in this expanded cohort to evaluate its prognostic value across all PM subtypes, including non-epithelioid. Our results showed that α-SMA-positive PM patients had a dismal prognosis, although it did not have an independent prognostic role. Moreover, it was revealed that stromal α-SMA positivity was associated with male gender, non-epithelioid subtype, high Ki-67 index, and even a higher tendency for PD-L1 expression. These findings align with previous reports linking PD-L1 expression to the sarcomatous and biphasic PM [19].

These findings prompt a consideration of mechanisms. First, PM comprises epithelioid, biphasic, and sarcomatoid subtypes with distinct epithelial-mesenchymal transition (EMT) phenotypes. Data mining reveals that EMT-related genes are associated with survival in PM and are significantly more expressed in non-epithelioid subtypes [20]. And non-epithelioid PM shows higher stromal scores, which correlate with poorer survival [20]. Our study of the close correlation between α-SMA-positivity CAFs and both Ki-67 index and the non-epithelioid PM further supports that CAFs are prognostically more critical in the non-epithelioid subtype. Thus, a CAFs-dominated fibrotic microenvironment may be the principal driver of progression in non-epithelioid PM, whereas tumor-cell-intrinsic alterations might play a more dominant role in epithelioid PM. Additionally, given the relatively low mutation load and fewer neoantigens in PM, the initial anti-tumor immune response is inherently limited [2]. This weak immunosurveillance may allow CAFs to play a more dominant role in shaping the tumor immune microenvironment (TIME). Through direct cytokine secretion as well as indirect signaling crosstalk with immune cells, activated CAFs foster an immunosuppressive niche (e.g., upregulation of PD-L1 on tumor cells), thereby driving tumor progression and immunotherapy resistance [21]. The observed trend between α-SMA positivity and PD-L1 expression aligns with this mechanism and may help explain the particularly poor prognosis associated with non-epithelioid PM subtype, in which CAF-driven fibrosis and TIME are especially prominent. To summarize, CAFs may play a more crucial role in the TME of non-epithelioid than epithelioid PM, aiding in immune evasion and potentially influencing therapy outcomes. Therefore, it is reasonable to incorporate the estimation of stromal CAFs in prognosis prediction and a comprehensive investigation into the role of CAFs and immune status in PM.

In conclusion, although some studies have questioned the reliability of PD-L1 for guiding therapy selection, our findings confirm its role as an independent prognostic factor in PM. This emphasizes the importance of further investigation into its prognostic utility to improve prognostic models and optimize treatment strategies. Meanwhile, our findings also highlighted α-SMA-positive stromal CAFs as a clinically significant marker of poor prognosis and associated with non-epithelioid PM, supporting their incorporation into future prognostic prediction. Therefore, a deeper exploration of CAFs-immune interactions and the underlying mechanisms is essential to overcome therapeutic resistance and uncover novel therapeutic targets.

Table 3. Relationship between stromal α-SMA expression and clinical pathological characteristics in diffuse pleural mesothelioma patients.

Variables N=51	α-SMA presence N (%)	α-SMA absence N (%)	p-value
Age (years)			0.539
≤58	14 (43.75)	10 (52.63)	
>58	18 (56.25)	9 (47.37)	
Gender			**0.046**
male	24 (75.00)	9 (47.37)	
female	8 (25.00)	10 (52.63)	
Smoking			0.405
absence	13 (40.62)	10 (52.63)	
presence	19 (59.38)	9 (47.37)	
ECOG PS Score			0.794
<2	23 (71.88)	13 (68.42)	
≥2	9 (28.12)	6 (31.58)	
Effusion			0.869
absence	7 (21.87)	3 (15.79)	
presence	25 (78.13)	16 (84.21)	
Weight loss			0.909
absence	18 (56.25)	11 (57.89)	
presence	14 (43.75)	8 (42.11)	
Subtype			**0.013**
epithelioid	18 (56.25)	17 (89.47)	
non-epithelioid	14 (43.75)	2 (10.53)	
TNM			0.513
early (I/II)	14 (43.75)	10 (52.63)	
late (III/IV)	18 (56.25)	9 (47.37)	
PD-L1			0.065
TPS=0	17 (53.13)	15 (78.95)	
TPS≥1	15 (46.87)	4 (21.05)	
Ki-67			**0.003**
≤25%	10 (31.25)	14 (73.68)	
>25%	22 (68.75)	5 (26.32)	

Acknowledgments: This research was funded by the National Natural Science Foundation Incubation Project of Xinhua Hospital of Shanghai Jiao Tong University (FH2024G001), the Natural Science Foundation of Hunan Province (No.2022JJ40693), and Ningbo Top Medical and Health Research Program (No.2022030208).

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