Original Article

Prognostic value of plasma D-dimer levels in advanced non-small cell lung cancer patients treated with immune checkpoint inhibitors: a retrospective study

Xiaoyan Li[1,2], Di Lu[1,2], Zhibo Zhang[3], Yuning Zhang[1,2], Jinliang Wang[1], Yi Hu[1]

[1]Department of Medical Oncology, Senior Department of Oncology, The Fifth Medical Center of PLA General Hospital, Beijing, China; [2]Medical School of Chinese PLA, Beijing, China; [3]Department of Cardiothoracic Surgery, The 78th Group Army Hospital of Chinese PLA, Mudanjiang, China

Contributions: (I) Conception and design: X Li; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: D Lu, Z Zhang; (V) Data analysis and interpretation: X Li, Z Zhang, Y Zhang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yi Hu. Department of Medical Oncology, Senior Department of Oncology, The Fifth Medical Center of PLA General Hospital, Beijing, China. Email: huyi301zlxb@sina.com.

Background: Plasma D-dimer is of great significance for the clinical exclusion of tumor-related thrombosis. Previous studies have shown its predictive role in non-small cell lung cancer (NSCLC) treated with chemotherapy. However, whether pretreatment D-dimer could predict the efficacy and prognosis in NSCLC patients treated with immune checkpoint inhibitors (ICIs) remains unclear.

Methods: Advanced NSCLC patients treated with ICIs at the Chinese PLA General Hospital between January 2015 and March 2019 were enrolled. Patients were divided into a pretreatment normal D-dimer group (≤0.5 μg/mL) and high D-dimer group (>0.5 μg/mL). Optimization-based approach was applied to balance baseline covariates between the 2 groups, including age, sex, histological type, smoking history, stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), lines of treatment, ICI drugs, brain metastasis, treatment type, and D-dimer levels. Kaplan-Meier analysis and Cox proportional hazards model were used for analyzing survival data, including progression-free survival (PFS, the time from initial ICI treatment to PD or death), overall survival (OS, the time between initial ICI treatment and death), and hazard ratio (HR). Follow-up of all patients was performed by searching electronic medical records and counseling telephone. The follow-up cut-off date was July 6, 2020.

Results: This study included 277 advanced NSCLC patients. Among the enrolled patients, 23.1% were female, 64.6% had non-squamous cell lung cancer, and 79.4% were stage IV. Univariate and multivariate analysis showed that pretreatment high D-dimer levels were independently associated with shortened PFS and OS (P<0.01). Subgroup analysis confirmed that pretreatment high D-dimer levels were associated with poor prognosis in most subsets. After balancing baseline covariates between the high D-dimer group and normal D-dimer group, the results indicated that patients with pretreatment high D-dimer levels had significantly shorter PFS [median: 6.4 *vs.* 11.5 months; HR, 1.70; 95% confidence ratio (CI): 1.25–2.37; P<0.001] and OS (median: 12.7 *vs.* 30.4 months; HR, 2.29; 95% CI: 1.54–3.41; P<0.001) than those with pretreatment normal D-dimer levels.

Conclusions: Pretreatment plasma D-dimer could serve as a convenient prognostic biomarker for advanced NSCLC patients receiving ICI treatment. Patients with pretreatment high D-dimer levels may have poor PFS and OS.

Keywords: D-dimer; immune checkpoint inhibitor (ICI); non-small cell lung cancer (NSCLC); biomarker

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Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading cause of cancer-related deaths worldwide (1). Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancers. The majority of NSCLC patients are diagnosed with advanced disease and are treated with chemotherapy (2). However, the overall response rate to chemotherapy in NSCLC patients is only 30–40%, and the median survival time is below 12 months (3). The promising anti-tumor activity of immune checkpoint inhibitors (ICIs), such as programmed cell death-1/programmed cell death-ligand 1 (PD-1/PD-L1) antibodies, has led to regulatory approvals of these agents for the treatment of a variety of malignancies (4). Numerous clinical trials (5-9) have proved that ICIs treatment has brought about a new dawn for NSCLC patients' treatment, with very durable responses and long-term benefits. However, the benefit brings by ICIs is only limited to a subset of NSCLC patients, of which the overall response rate was about 20% (10), while some even experiencing serious adverse reactions. Therefore, biomarkers that can predict response to NSCLC patients treated with ICIs are being extensively investigated for further advance precision immunotherapy. PD-L1 expression and tumor mutational burden (TMB) have so far been the most widely studied predictors of clinical benefit in advanced NSCLC patients treated with ICIs (11,12), although these biomarkers require pathological tissue specimens and biomarkers cannot accurately predict the response to ICI treatment (13-16). Thus, identification of convenient and noninvasive biomarkers is urgently needed for advanced NSCLC patients receiving ICI therapy.

Inappropriate activation of both coagulation and fibrinolysis is usually discovered in carcinoma patients, especially in those with metastatic disease (17-20). Plasma D-dimer, the smallest cross-linked protein produced in the proteolytic process, is a marker for detecting malignancy and is of great significance for the clinical exclusion of tumor-related thrombosis (21). Previous studies have shown the predictive role of plasma D-dimer in many malignancies treated with chemotherapy, including lung cancer (22-26), colorectal cancer (27), gallbladder carcinoma (20), and breast cancer (28). However, whether pretreatment D-dimer can predict therapeutic efficacy and prognosis in advanced NSCLC patients receiving ICI treatment remains unclear. Hence, we aimed to determine whether pretreatment D-dimer levels could predict clinical benefits from ICIs in advanced NSCLC patients. We present the following article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1363/rc).

Methods

Patients and data collection

We retrospectively collected advanced NSCLC patients from the Chinese People's Liberation Army General Hospital (Beijing, China) between January 2015 and March 2019. Patients were selected by the following inclusion criteria: (I) NSCLC diagnosed by histology evidence; (II) clinical stage IIIB–IV classified according to the 8th edition of the TNM classification for NSCLC; (III) patients received ICIs treatment for at least 6 weeks, and treatment response were evaluated at least once time; (IV) pretreatment D-dimer levels were measured within 5 days before the first ICI treatment.

Radiographic evidences were used to evaluate the treatment responses. Responses were classified into complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (29). Research indicators including: Progression-free survival (PFS), which was defined as the time from the first ICI treatment to PD or death (whichever occurred first); Overall survival (OS), which was the time between the first ICI treatment and death; Objective response rate (ORR), which was defined as the ratio of patients who reached CR and PR; As well as disease control rate (DCR), which was defined as the ratio of patients who reached CR, PR, and SD. Follow-up of all patients was performed by searching electronic medical records and counseling telephone. The follow-up cut-off date was July 6, 2020.

Patient's clinical characteristics and blood test results were collected, including age, sex, smoking history, stage, histological type, Eastern Cooperative Oncology Group Performance Status (ECOG PS), lines of treatment, ICI drugs, treatment type (monotherapy, combination therapy), brain metastasis, pretreatment D-dimer levels, and venous thromboembolism (VTE).

D-dimer was a routine clinical examination in our center, for the patients who were newly diagnosed as cancer patients, and the cancer patients who routinely accept anti-tumor treatment, at least 1 day before their anti-cancer therapy. D-dimer was measured by nephelometry immunoassay with the STA-Liatest D-Di kit as instruction. The reference for normal D-dimer level was 0–0.5 μg/mL.

Table 1 Characteristics of 277 patients with advanced NSCLC

Characteristics	No. of patients	Percentage (%)
Age (year), median (range)	61 (33–91)	–
<70	224	80.9
≥70	53	19.1
Sex		
Male	213	76.9
Female	64	23.1
Stage		
IIIB/C	57	20.6
IV	220	79.4
Histological type		
Non-squamous	179	64.6
Squamous	98	35.4
Smoking history		
No	103	37.2
Yes	174	62.8
ICIs		
PD-1 inhibitor	265	95.7
PD-L1 inhibitor	12	4.3
ECOG PS		
0–1	247	89.2
≥2	30	10.8
Brain metastasis		
Yes	46	16.6
No	231	83.4
Treatment lines		
1 line	87	31.4
2 lines	97	35.0
≥3 lines	93	33.6
Treatment type		
Monotherapy	126	45.5
Combination therapy	151	54.5
Anticoagulant therapy		
Yes	35	12.6
No	242	87.4
D-dimer level (μg/mL)		
Median (range)	0.92 (0.09–21.0)	–
Normal (≤0.5)	70	25.3
High (>0.5)	207	74.7

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of the Chinese PLA General Hospital (No. S2018-092-01). The individual consent for this retrospective analysis was waived.

Statistical analysis

Patients were divided into a normal D-dimer group (≤0.5 μg/mL) and high D-dimer group (>0.5 μg/mL) based on the upper limit of the reference for normal pretreatment D-dimer levels. The optimization-based approach was applied to balance baseline covariates between the two groups (30). Each patient was weighted according to the following criteria: (I) absolute value of standardized mean difference less than 0.15, and (II) variance ratio of 0.67 (1/1.5) to 1.5. The PASS software (version 11.0) was used to validate the effective sample size in the weighted sample (α=0.05, 1-β=0.8, proportion in control group =0.3, accrual time =5 years). Chi-square test was used to calculate intergroup differences in ORR. Survival data was analyzed by the Kaplan-Meier method and log-rank test. Cox proportional hazards models calculated hazard ratio (HR) with its 95% confidence interval (CI). All statistical tests were bilateral with a significance level of 0.05. All statistical analyses were performed with R software, using the packages of WeightIt version 0.5.1 (https://cran.r-project.org/web/ packages/WeightIt/index.html) for optimization-based methods and survey version 3.36 (https://cran.r-project.org/web/packages/survey/index.html) in the weighted samples.

Results

Patient characteristics

A total of 277 advanced NSCLC patients treated with ICIs at the Chinese PLA General Hospital between January 2015 and March 2019 were included. The last follow-up date was July 6, 2020. The median follow-up time was 15.0 months with a 95% CI of 12.2 months to 17.6 months. Detailed characteristics of patients are shown in *Table 1*. The median age of this cohort was 61 years (range, 33–91 years). Among the patients, 76.9% were male, 79.4% were stage IV according to the 8th edition of TNM staging by the International Association for the Study of Lung Cancer (31), 64.6% were non-squamous NSCLC patients, 35.4% were squamous cell

Table 2 Comparing responses between normal and high D-dimer groups

Responses	Normal D-dimer group	High D-dimer group	P value
CR, n (%)	0 (0)	0 (0)	–
PR, n (%)	21 (30.0)	31 (15.0)	–
SD, n (%)	41 (58.6)	103 (49.8)	–
PD, n (%)	8 (11.4)	73 (35.3)	–
ORR, n (%)	21 (30.0)	31 (15.0)	0.005
DCR, n (%)	62 (88.6)	134 (64.8)	<0.001

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

lung cancer patients, 62.8% had a history of smoking, and about 90% had an ECOG PS of 0–1. Treatment lines 1, 2, and ≥3 accounted for 31.4%, 35.0%, and 33.6% of patients, respectively. Patients receiving ICI monotherapy accounted for 45.5% of the sample, and 54.5% of patients received ICIs in combination with chemotherapy or antiangiogenic agents. A total of 265 (95.7%) patients received PD-1 inhibitor treatment and 12 patients (4.3%) received PD-L1 inhibitor treatment. A total of 207 patients (74.7%) had pretreatment high D-dimer levels. At the start of ICI treatment, 35 patients (12.6%) who had VTE or high risk of thromboembolism (myocardial infarction, cerebral infarction, and surgery) were receiving anticoagulant therapy (Aspirin, Clopidogrel, Rivaroxaban, Ticagrelor, or Nadroparin calcium). The patient size-277 was validated appropriate by PASS software (version 11.0) which showed the sample size should not be less than 260.

Baseline covariates balanced between the 2 groups

An optimization-based approach was used to balance baseline covariates between the normal D-dimer group and the high D-dimer group. We matched a total of 61 patients in the normal D-dimer subset and 204 patients in the high D-dimer subset. The aim was to eliminate some of the differences between the 2 groups during the matching process.

Pretreatment D-dimer associated with clinical outcomes

After comparing treatment responses, the results showed that pretreatment normal D-dimer levels were associated with higher ORR (30.0% *vs.* 15.0%, P=0.005) and DCR (88.6% *vs.* 64.8%, P<0.001) compared with pretreatment high D-dimer levels (*Table 2*). Univariate analysis demonstrated that pretreatment high D-dimer levels increased the risk of disease progression (HR, 1.80; 95% CI: 1.30–2.49) and death (HR, 2.29; 95% CI: 1.52–3.46) compared with normal D-dimer levels, and subgroup analysis confirmed that pretreatment high D-dimer levels were associated with worse PFS and OS in most subsets (*Figures 1*,*2*). After balancing baseline covariates between the high D-dimer group and normal D-dimer group, the results showed that patients with pretreatment high D-dimer levels had obviously shorter PFS (median: 6.4 *vs.* 11.5 months; P<0.001) and OS (median: 12.7 *vs.* 30.4 months; P<0.001) than patients with pretreatment normal D-dimer levels (*Figure 3*).

As shown in *Table 3*, univariate analysis found that age, smoking history, stage, ECOG PS, treatment type, treatment lines, brain metastasis, and pretreatment D-dimer levels were associated with PFS (P<0.05), and multivariate analysis demonstrated that age, ECOG PS, treatment lines, and pretreatment D-dimer levels were independently related to PFS (P<0.05). Baseline variates of age <70, ECOG PS ≥2, ICI monotherapy, later treatment lines, and pretreatment high D-dimer levels were independently associated with shortened PFS (P<0.05). As shown in *Table 4*, univariate analysis revealed that stage, ECOG PS, treatment type, brain metastasis, treatment lines, and pretreatment D-dimer levels were associated with OS (P<0.05), and multivariate analysis demonstrated that ECOG PS, treatment lines, and pretreatment D-dimer levels were independently related to OS (P<0.05). Baseline variates of ECOG PS ≥2, ICI monotherapy, later treatment lines, and pretreatment high D-dimer levels were independently associated with shortened OS (P<0.05).

Discussion

Although progress has been made in cancer immunotherapy, and the use of ICIs has had considerable positive effects on some NSCLC patients, most do not benefit from ICI immunotherapy (7). The predictive ability of some molecules, such as PD-L1 and TMB in advanced NSCLC patients treated with ICIs remains unsatisfactory due to a lack of sensitivity and specificity (32), and thus additional predictive biomarkers are urgently needed in clinical practice to avoid the use of ineffective treatment (10).

Coagulation disorders, which are frequently observed

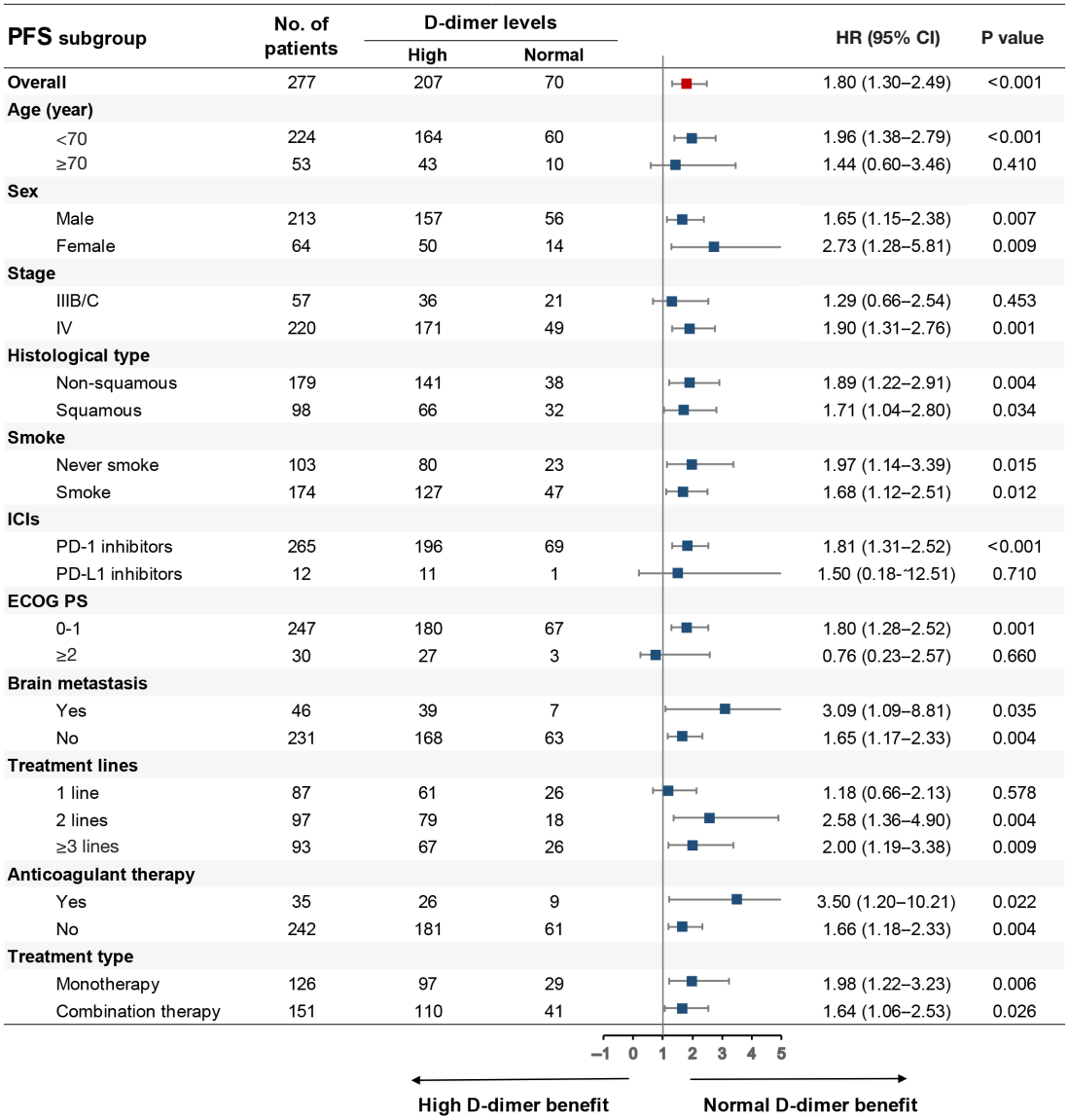

Figure 1 Forest plot of PFS. PFS, progression-free survival; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; CI, confidence interval.

in cancer patients (33), promote tumor angiogenesis, invasion, and metastasis, and ultimately lead to a poor prognosis for tumor patients (34,35). Plasma D-dimer is a stable end product degraded by plasmin-induced fibrinolytic activity and increased by enhanced fibrin formation and fibrinolysis (36). Plasma D-dimer is a useful biomarker for diagnosing VTE, cardiovascular disease, disseminated intravascular coagulation, infectious disease, and cancer (37-39). Previous studies reported that increased plasma D-dimer levels were associated with poor survival in cancer patients through VTE (40,41), which could increase the risk of bleeding during antitumor therapy (42-44). The research of Wang *et al.* showed that a baseline signature of low D-dimer values was associated with a better survival outcome for early lung cancer (stage I–II) patients treated with surgery (45). Gao *et al.* found that D-dimer was strongly associated with lymph node metastasis in NSCLC (46-48). Louneva *et al.* reported

OS subgroup	No. of patients	D-dimer levels		HR (95% CI)	P value
		High	Normal		
Overall	277	207	70	2.29 (1.52–3.46)	<0.001
Age (year)					
<70	224	164	60	2.61 (1.65–4.11)	<0.001
≥70	53	43	10	1.32 (0.50–3.45)	0.577
Sex					
Male	213	157	56	2.29 (1.43–3.65)	0.001
Female	64	50	14	2.57 (1.08–6.11)	0.034
Stage					
IIIB/C	57	36	21	1.20 (0.54–2.68)	0.656
IV	220	171	49	2.73 (1.66–4.47)	<0.001
Histological type					
Non-squamous	179	141	38	2.52 (1.41–4.51)	0.002
Squamous	98	66	32	2.20 (1.22–3.99)	0.009
Smoke					
Never smoke	103	80	23	2.40 (1.23–4.68)	0.011
Smoke	174	127	47	2.29 (1.36–3.86)	0.002
ICIs					
PD-1 inhibitors	265	196	69	2.28 (1.51–3.45)	<0.001
PD-L1 inhibitors	12	11	1	25 (0–1434137)	0.567
ECOG PS					
0-1	247	180	67	2.33 (1.50–3.61)	<0.001
≥2	30	27	3	0.79 (0.23–2.69)	0.708
Brain metastasis					
Yes	46	39	7	3.65 (0.88–15.27)	0.076
No	231	168	63	2.05 (1.33–3.17)	0.001
Treatment lines					
1 line	87	61	26	2.35 (0.97–5.69)	0.058
2 lines	97	79	18	2.52 (1.20–5.27)	0.014
≥3 lines	93	67	26	1.99 (1.08–3.68)	0.027
Anticoagulant therapy					
Yes	35	26	9	3.24 (0.95–11.00)	0.060
No	242	181	61	2.19 (1.41–3.39)	<0.001
Treatment type					
Monotherapy	126	97	29	2.23 (1.30–3.82)	0.004
Combination therapy	151	110	41	2.45 (1.29–4.65)	0.006

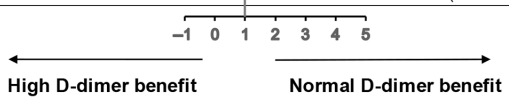

Figure 2 Forest plot of OS. OS, overall survival; ICIs, immune checkpoint inhibitors; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; CI, confidence interval.

that the level of plasma D-dimer was closely related to the prognosis of solid tumors (49). Some clinical studies have also shown that plasma D-dimer level was significantly associated with poor prognosis in lung cancer treated with chemotherapy (50,51). Similarly, a meta-analysis found that for postoperative NSCLC patients, high pretreatment D-dimer level was an independent predictor of poor prognosis (52). Another meta-analysis, which included 7 studies involving 964 patients from China, showed that elevated pretreatment D-dimer level was significantly correlated with worse OS and PFS in patients with small cell lung cancer (53). However, the predictive role of D-dimer in advanced NSCLC patients treated with ICIs remains unclear.

The present study demonstrated the relationship between pretreatment high D-dimer levels and poor clinical outcomes in advanced NSCLC patients treated with ICIs. To our knowledge, this is the first study that addressed the prognostic value of pretreatment D-dimer levels in advanced NSCLC patients treated with ICIs.

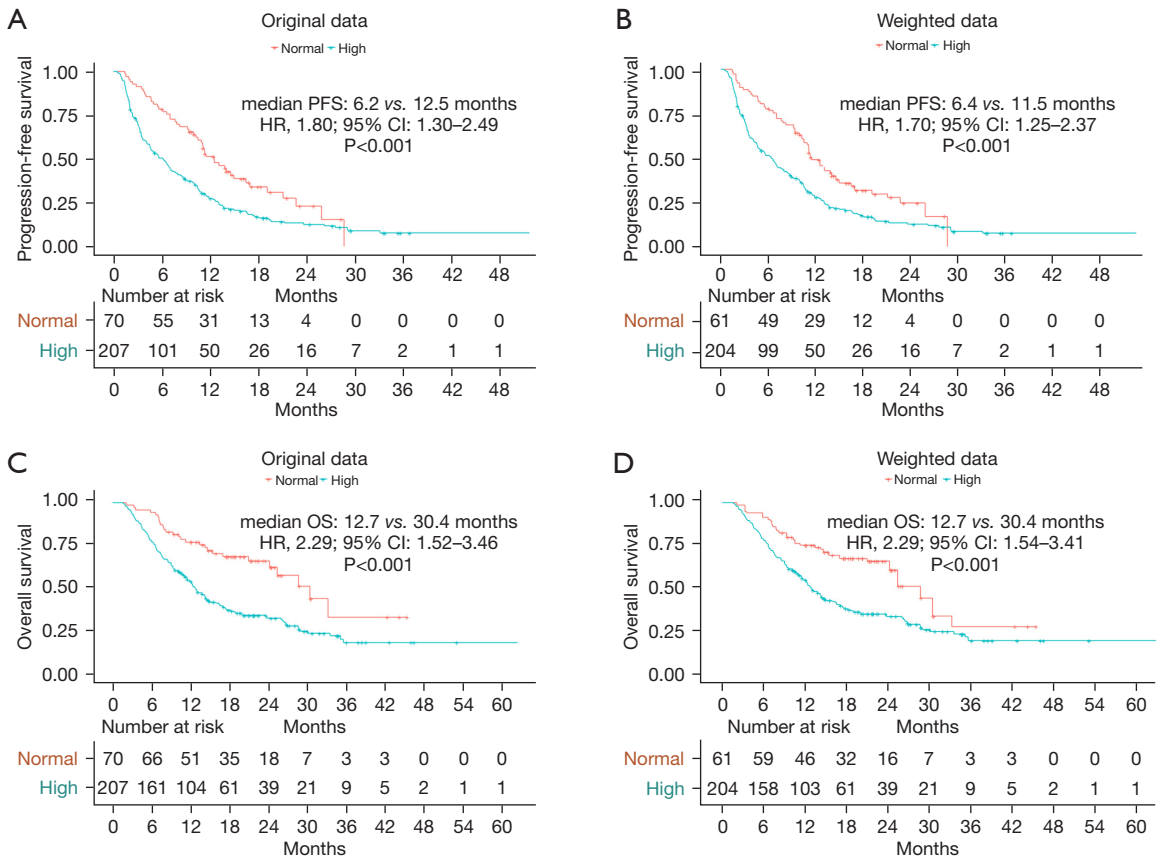

Figure 3 Kaplan-Meier curves of PFS and OS. (A) PFS curve drawn using original data; (B) PFS curve drawn using weighted data; (C) OS curve drawn using original data; (D) OS curve drawn using weighted data. PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

In this study, although 12.6% of all included patients were receiving different types of anticoagulant therapy at the start of ICI treatment, both univariate analysis and multivariate analysis showed that pretreatment D-dimer levels were independently associated with PFS and OS. Subgroup analysis also confirmed that pretreatment high D-dimer levels were associated with poor prognosis in patients with or without anticoagulant therapy. In patients with advanced NSCLC treated with ICIs, high pretreatment D-dimer levels had a statistically significant association with shortened PFS and OS. Our data provided strong evidence that pretreatment high D-dimer levels were independently associated with poor clinical outcomes in advanced NSCLC patients receiving PD-1/PD-L1 inhibitors.

Chen *et al.* found that increasing the threshold value of D-dimer from 0.5 to 0.981 μg/mL was statistically significant across different age groups (54). They concluded that the cut-off value of 0.5 μg/mL could not reflect the correlation between age and D-dimer. We did not consider the influence of age factors on D-dimer level and used the critical cut-off value of 0.5 μg/mL. There were other limitations in the present study. First, we only analyzed the prognostic value of pretreatment D-dimer level and not the relationship between changes in D-dimer with efficacy and prognosis of ICI treatment. Second, although we used the optimization-based method to eliminate the bias of baseline covariates between the high D-dimer group and normal D-dimer group, other covariates we did not consider may have also been potential confounders. Third, the retrospective nature of this study may have resulted in unknown selection bias. In addition, how D-dimer affects the efficacy and prognosis of advanced NSCLC patients treated with ICIs remains unclear and needs further investigation.

Table 3 Univariate and multivariate analyses for PFS

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (year)	≥70 *vs.* <70	0.70 (0.49–0.99)	0.044	0.67 (0.46–0.98)	0.039
Sex	Female *vs.* Male	1.26 (0.93–1.71)	0.144	–	
Smoking history	Yes *vs.* No	0.76 (0.58–0.99)	0.043	0.95 (0.71–1.28)	0.754
Histology	Squamous *vs.* non-squamous	1.03 (0.79–1.36)	0.818	–	
Stage	IV *vs.* IIIB/C	1.60 (1.13–2.25)	0.008	1.17 (0.81–1.68)	0.403
ECOG PS	≥2 *vs.* 0–1	1.91 (1.29–2.82)	0.001	1.78 (1.17–2.70)	0.007
Treatment type	Combination therapy *vs.* Monotherapy	0.75 (0.58–0.97)	0.031	0.80 (0.61–1.05)	0.104
Treatment lines	2 lines *vs.* 1 line	2.11 (1.51–2.96)	<0.001	1.81 (1.27–2.57)	0.001
	≥3 lines *vs.* 1 line	2.44 (1.73–3.44)	<0.001	2.22 (1.54–3.20)	<0.001
Brain metastasis	Yes *vs.* No	1.57 (1.11–2.23)	0.011	1.09 (0.76–1.58)	0.643
Anticoagulant therapy	Yes *vs.* No	1.22 (0.82–1.82)	0.323	–	
D-dimer (μg/mL)	High *vs.* Normal	1.80 (1.30–2.49)	<0.001	1.84 (1.32–2.56)	<0.001

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 4 Univariate and multivariate analyses for OS

Variable	Category	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (year)	≥70 *vs.* <70	0.86 (0.58–1.26)	0.433	–	
Sex	Female *vs.* male	1.18 (0.83–1.67)	0.352	–	
Smoking history	Yes *vs.* No	0.77 (0.57–1.04)	0.092	–	
Histology	Squamous *vs.* Non-squamous	1.13 (0.83–1.54)	0.432	–	
Stage	IV *vs.* IIIB/C	1.62 (1.08–2.45)	0.021	1.20 (0.78–1.84)	0.405
ECOG PS	≥2 *vs.* 0–1	2.38 (1.58–3.57)	<0.001	1.94 (1.29–2.93)	0.002
Treatment type	Combination therapy *vs.* Monotherapy	0.54 (0.40–0.73)	<0.001	0.56 (0.41–0.76)	<0.001
Treatment lines	2 lines *vs.* 1 line	2.39 (1.60–3.59)	<0.001	1.85 (1.22–2.82)	0.004
	≥3 lines *vs.* 1 line	2.24 (1.49–3.39)	<0.001	2.09 (1.36–3.21)	0.001
Brain metastasis	Yes *vs.* No	1.71 (1.18–2.47)	0.004	1.20 (0.81–1.76)	0.365
Anticoagulant therapy	Yes *vs.* No	1.42 (0.91–2.23)	0.124	–	
D-dimer (μg/mL)	High *vs.* Normal	2.29 (1.52–3.46)	<0.001	2.13 (1.40–3.25)	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Conclusions

Pretreatment plasma D-dimer could serve as a predictive biomarker for the efficacy and prognosis of advanced NSCLC patients treated with ICIs. Patients with pretreatment high D-dimer levels may have poor PFS and OS. Further studies are warranted for validation.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1363/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1363/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-1363/coif). All authors report that this study was supported by the Military Health Special Research Project under grant 20BJZ37. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of the Chinese PLA General Hospital (No. S2018-092-01). The individual consent for this retrospective analysis was waived.

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