Effect of Comorbidity on Outcomes of Patients with Advanced Non-Small Cell Lung Cancer Undergoing Anti-PD1 Immunotherapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDEG 1,2,3   **Xianghua Zeng***
BCD 1,2   **Shicong Zhu***
CF 4   **Cheng Xu**
CD 1,2   **Zhongyu Wang**
CD 1,2   **Xingxing Su**
CD 1,2   **Dong Zeng**
AF 1,2   **Haixia Long**
AG 1,2   **Bo Zhu**

1 Institute of Cancer, Xinqiao Hospital of The Third Military Medical University, Chongqing, P.R. China
2 Chongqing Key Laboratory of Immunotherapy, Xinqiao Hospital of Third Military Medical University, Chongqing, P.R. China
3 Division of Infectious Diseases, Chongqing Public Health Medical Center, Chongqing, P.R. China
4 Department of Oncology, General Hospital of The Central Theater Command of The People's Liberation Army, Wuhan, Hubei, P.R. China

* Xianghua Zeng and Shicong Zhu contributed equally
Corresponding Authors: Bo Zhu, e-mail: bo.zhu@tmmu.edu.cn, Haixia Long, e-mail: longhaixialhx@163.com
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Background: Comorbidities are reportedly related to the survival of patients with non-small cell lung cancer (NSCLC). The purpose of this study was to explore the impact of comorbidity, assessed by the Charlson comorbidity index (CCI) and the simplified comorbidity scores (SCS) on clinical outcomes of patients with NSCLC treated with immune checkpoint inhibitors.

Material/Methods: Sixty-six patients with NSCLC who received programmed cell death protein 1 (PD1) inhibitors in our institution in the past 2 years were enrolled in this retrospective study. Data on comorbidity (CCI and SCS) and clinical outcomes, including progression-free survival (PFS), immunotherapy responses, and immunotherapy-related adverse events, were analyzed.

Results: The disease control rate was obviously higher among patients in the CCI <1 group than the CCI ≥1 group ($P<0.001$), but were similar between the SCS <8 group and SCS ≥8 group ($P=0.585$). The median PFS in the CCI <1 group was 271.0 days (95% CI: 214.3–327.7 days) compared with 232.0 days (95% CI: 66.2–397.8 days) for the CCI ≥1 group ($P=0.0084$). However, the median PFS showed no difference between the groups with SCS <8 at 271.0 days (95% CI: 138.7–403.3 days) versus SCS ≥8 at 222.0 days (95% CI: 196.2–247.8 days), $P=0.2106$). The incidence of adverse events was similar among patients with high versus low comorbidity indexes (CCI: 35.8% versus 23.6%, $P=0.286$, respectively; and SCS: 28.0% versus 29.3%, respectively, $P=0.912$).

Conclusions: The comorbidity burden might be a predictor for survival in patients with NSCLC undergoing PD1 inhibitor immunotherapy.

MeSH Keywords: Comorbidity • Non-Small Cell Lung Cancer • Programmed Cell Death 1 • Progression Free Survival

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Background

Lung cancer is a top cause of cancer deaths worldwide, with about 781 000 new diagnoses each year in China [1]. Approximately 85% of all lung cancer patients have histological diagnosis of non-small cell lung cancer (NSCLC) [2]. In contrast with chemotherapy, immunotherapy targeting the pathway of programmed cell death receptor/ligand 1 (PD1/PD-L1) has been found to have clear and sustained effects on survival of patients with NSCLC and has accordingly been a recommended form of therapy in the past decade [3–5]. Inhibiting the interaction of PD-L1 constitutively expressed on tumor cells and PD1 expressed on activated T cells markedly enhances T cell function, resulting in anti-tumor activity [6]. The promising efficacy of PD1/PD-L1 inhibitors, including pembrolizumab, nivolumab and atezolizumab, in clinic trials has prompted their approval for the treatment of NSCLC by the US Food and Drug Administration [7–9].

The presence of comorbidities has been reported to exert great influence on anticancer effects in various malignancies, including NSCLC [10–12]. Nevertheless, the impact of comorbidity on the outcomes of NSCLC is still controversial [13,14]. Moreover, to the best of our knowledge, no studies have so far investigated the influence of comorbidities on outcomes during immunotherapy in patients with NSCLC. The simplified comorbidity score (SCS) and Charlson comorbidity index (CCI) are the 2 most extensively validated scoring systems for assessing comorbidities and predicting prognosis [15,16]. These 2 comorbidity indices have previously been used as prognostic factors in patients with various carcinomas [17–19]. Of interest, the SCS was designed specifically for lung cancer [20,21].

In the present study, we intended to explore the association of comorbidities evaluated by CCI and SCS with clinical outcomes, including survival and immune-related adverse events (irAEs), in a cohort of patients with advanced NSCLC undergoing immunotherapy with anti-PD1/PD-L1 agents in China.

Material and Methods

Participants

The cohort of this retrospective study comprises 66 consecutive patients with NSCLC who were treated with PD1 inhibitors (pembrolizumab, nivolumab, and toripalimab) in the Institute of Cancer, Xinqiao Hospital of the Third Military Medical University, Chongqing, China and between February 2017 and November 2019. Pre-immunotherapy data on the following variables were recorded for analysis: age, sex, height, weight, tumor stage (TNM), pathological tumor type, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), drinking status, and comorbid diseases.

This study was in compliance with the Declaration of Helsinki and also approved by the Ethics Committee of Xinqiao Hospital, Third Military Medical University (Chongqing, China). The recorded data were analyzed anonymously.

Comorbidity assessment

The CCI and SCS were used to assess the severity of comorbidities of all patients before commencement of PD1 inhibitors. As shown in Tables 1 and 2, the CCI and the SCS are individually weighted indexes of 19 and 7 different comorbid conditions, respectively, the maximum scores being 33 for the CCI and 20 for the SCS [19]. Three of the authors, all physicians in oncology, independently reviewed each patient's comorbidities and calculated the CCI and SCI scores.

Assessment of outcomes

Progression-free survival (PFS) is the primary endpoint to evaluate the efficacy of PD1 inhibitor immunotherapy according to iRECIST (immune responses Response Evaluation Criteria in Solid Tumors) [22]. In our study, PFS was referred to interval from the time of the most recent computed tomography (CT) or positron emission tomography (PET)-CT scan prior to the first cycle of immunotherapy to the time of tumor progression, death, or last follow-up. Secondary end points included but were not limited to a comparison of the overall response rate and disease control rate based on the comorbid status.

Organ specific immune-related adverse events (dermatological: rash and pruritus, gastrointestinal: diarrhea and colitis, hepatic: hepatitis, endocrine: hypophysitis and thyropathy, and respiratory: pneumonitis) throughout the study and until at least 1 month after the last cycle were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analyses

All data are expressed as the median (95% confidence interval [CI]), mean±standard deviation (SD), or number (percentage) as appropriate. Differences between groups were compared using by a χ^2 test or Student's t-test. PFS was plotted using the Kaplan-Meier method and compared by the Wilcoxon test. A P-value of less than 0.05 was referred to denote a significant difference.

GraphPad Prism version 7 (GraphPad Software, San Diego, CA, USA) and SPSS 20.0 software (IBM Corp., Armonk, NY, USA) were used for all data analyses.

Table 1. The Charlson comorbidity index weights.

Weight	Comorbidity conditions
1 point	History of myocardial infarction; Congestive heart failure; Peripheral disease (includes aortic aneurysm ≥6 cm); Cerebrovascular disease (with mild or no residua or transient ischemic attack); Dementia; Chronic pulmonary disease; Connective tissue disease; Peptic ulcer disease; Mild liver diseases (no portal hypertension, including chronic hepatitis); Diabetes without end-organ damage
2 points	Hemiplegia; Moderate or severe renal disease; Diabetes with end-organ damage; Other tumors without metastasis (exclude if >5 years from diagnosis of non-small cell lung cancer); Leukemia (acute or chronic); Lymphoma
3 points	Moderate or severe liver disease
6 points	Other metastatic solid tumors (exclude if >5 years from diagnosis of non-small cell lung cancer); Acquired immunodeficiency syndrome (not just human immunodeficiency virus positive)
33 points	Maximum comorbidity score

Table 2. The simplified comorbidity score weights.

Weight	Comorbidity conditions
1 point	Respiratory diseases; cardiovascular diseases; alcoholism; neoplastic comorbidity
4 points	Renal insufficiency
5 points	Diabetes mellitus
7 points	Tobacco consumption
17 points	Maximum comorbidity score

Results

A total of 66 patients with NSCLC who received immunotherapy with PD1 inhibitors (pembrolizumab, nivolumab, and toripalimab) from February 2017 to November 2019, were enrolled in our study. Baseline characteristics of the whole cohort and of subgroups formed according to CCI and SCS scores are exhibited in Table 3. Mean age of all patients was 58.5±10.8 years, the mean body mass index was 22.8±3.6 kg/m^2, and 78.8% of the cohort were males. The mean CCI and SCC scores for all participants were 0.74 (range: 0–3) and 5.56 (range: 0–18), respectively. The distribution of comorbidities on the basis of CCI and SCS systems is presented in Figure 1. According to the CCI system, 38 patients (57.6%) had no comorbidities and the most common comorbid condition was chronic pulmonary disease (13.6%), whereas according to SCS scores, 17 patients (25.8%) had no comorbidities and the most common comorbidities were smoking (54.5%), followed by respiratory diseases (36.4%), and alcohol consumption (15.2%). There was a weak correlation between these 2 scoring systems (r=0.334; P=0.006). Patients with SCS ≥8 were significantly older than those with SCS <8 group (62.5±9.1 years versus 56.1±11.1 years, P=0.019). Additionally, compared with the SCS <8 group, the SCS ≥8 group had a significantly higher percentage of smokers

(88.0% versus 31.7%), alcohol intake (40.0% versus 8.3%) and males (100% versus 65.9%). However, no differences were found in other variables (body mass index, tumor stage, pathological type, and ECOG PS) between these 2 groups. When the CCI <1 and CCI ≥1 groups were compared, the only factor that differed significantly was mean age (P=0.018).

Efficacy

The immunotherapy response rates are shown in Table 4. The disease control rate achieved by PD1 inhibitors was 81.8% in the entire cohort (36.4% partial response and 45.4% stable disease); however, no patients achieved complete responses. Progressive disease occurred in 12 patients (18.2%). Further subgroup analysis revealed that the disease control rate was much higher in the CCI <1 group than the CCI ≥1 group (P<0.001); but showed no significant difference between the SCS <8 group and the SCS ≥8 group (P=0.585). Overall response rates did not differ significantly between the CCI <1 group and the CCI ≥1 group (P=0.883) or between the SCS <8 group and the SCS ≥8 group (P=0.301). The median PFS of all patients was 264.0 days (95% CI: 211.8–316.2 days). As shown in Figure 2, the median PFS in the CCI <1 group was 271.0 days (95% CI: 214.3–327.7 days) compared with 232.0 days (95% CI: 66.2–397.8 days) in the CCI ≥1 group (P=0.0084). However, the median PFS did not differ between the SCS <8 group and the SCS ≥8 group (271.0 days; 95% CI: 138.7–403.3 days versus 222.0 days; 95% CI: 196.2–247.8 days, respectively; P=0.2106).

Toxicity

Data regarding irAEs in all patients are summarized in Table 5. In all, 20 patients (30.3%) developed irAEs, the most common being skin rash (n=6, 9.1%) and pneumonitis (n=6, 9.1%), followed by hypothyroidism (n=4, 6.1%), hepatitis (n=3, 4.5%), and colitis (n=1, 1.5%). Only 2 patients (3%) had severe

Table 3. Baseline and comparison of characteristics in patients with NSCLC based on the Charlson comorbidity index and simplified comorbidity score.

Characteristics	Value	CCI			SCS		
		<1 (n=38)	≥1 (n=28)	P	<8 (n=41)	≥8 (n=25)	P
Age (years)	58.5±10.8	55.9±10.0	62.1±10.9	0.018	56.1±11.1	62.5±9.1	0.019
Sex				0.971			0.001
Male	52 (78.8%)	30 (78.9%)	22 (78.6%)		27 (65.9%)	25 (100%)	
Female	14 (21.2%)	8 (21.1%)	6 (21.4%)		14 (34.1%)	0	
BMI (kg/m²)	22.8±3.6	23.0±3.1	22.6±4.2	0.736	22.8±3.2	22.8±4.2	0.991
TNM stages				0.241			0.878
III	23 (34.8%)	11 (28.9%)	12 (42.9%)		14 (34.1%)	9 (36.0%)	
IV	43 (65.2%)	27 (71.1%)	16 (57.1%)		27 (65.9%)	16 (64.0%)	
Pathological type				0.684			0.888
Adenocarcinoma	39 (59.1%)	23 (60.5%)	16 (57.1%)		25 (61.0%)	14 (56%)	
Squamous cell carcinoma	24 (36.4%)	14 (36.8%)	10 (35.7%)		14 (34.1%)	10 (40.0%)	
Other types	3 (4.5%)	1 (2.6%)	2 (7.2%)		2 (4.9%)	1 (4.0%)	
ECOG PS				0.826			0.262
0–1	64 (97.0%)	37 (97.4%)	27 (96.4%)		39 (95.1%)	25 (100%)	
≥2, n (%)	2 (3.0%)	1 (3.6%)	1 (3.6%)		2 (4.9%)	0	
PD1 inhibitors				0.049			0.900
Nivolumab	17 (25.8%)	6 (15.8%)	11 (39.3%)		10 (24.4%)	7 (28.0%)	
Pembrolizumab	23 (34.8%)	13 (34.2%)	10 (35.7%)		14 (34.1%)	9 (36.0%)	
Toripalimab	26 (39.4%)	19 (50.0%)	7 (25.0%)		17 (41.5%)	69(36.0%)	
Smoking history				0.840			<0.001
Never	31 (47.0%)	17 (44.7%)	14 (50.0%)		28 (68.3%)	3 (12.0%)	
Ever	16 (24.2%)	12 (31.6%)	7 (25.0%)		6 (14.6%)	13 (52.0%)	
Current	19 (28.8%)	9 (23.7%)	7 (25.0%)		7 (17.1%)	9 (36.0%)	
Drinking status				0.180			0.003
Never	53 (80.3%)	28 (73.7%)	25 (89.3%)		38 (92.7%)	15 (60.0%)	
Ever	5 (7.6%)	7 (18.4%)	1 (3.6%)		1 (2.4%)	7 (28.0%)	
Current	8 (12.1%)	3 (7.9%)	2 (7.1%)		2 (4.9%)	3 (12.0%)	

Data are presented as mean±standard deviation or n (%).NSCLC – non-small cell lung cancer; BMI – body mass index; CCI – Charlson comorbidity index; ECOG PS – Eastern Cooperative Oncology Group performance status; PD1 – programmed cell death protein 1; SCS – simplified comorbidity score.

pneumonitis (CTCAE: III), and none died from irAEs. irAEs occurred in 10 patients (26.3%) with CCI <1 and in 10 patients (35.7%) with CCI ≥1 (*P*=0.286). Similarly, the incidence of irAEs was comparable in the SCS <8 group (31.7%) and the SCS ≥8 group (28.0%) (*P*=0.912).

Discussion

Immunotherapy with anti-PD1/PD-L1 agents has progressed dramatically since it was found that these agents can achieve long-lasting responses in NSCLC. However, few studies have
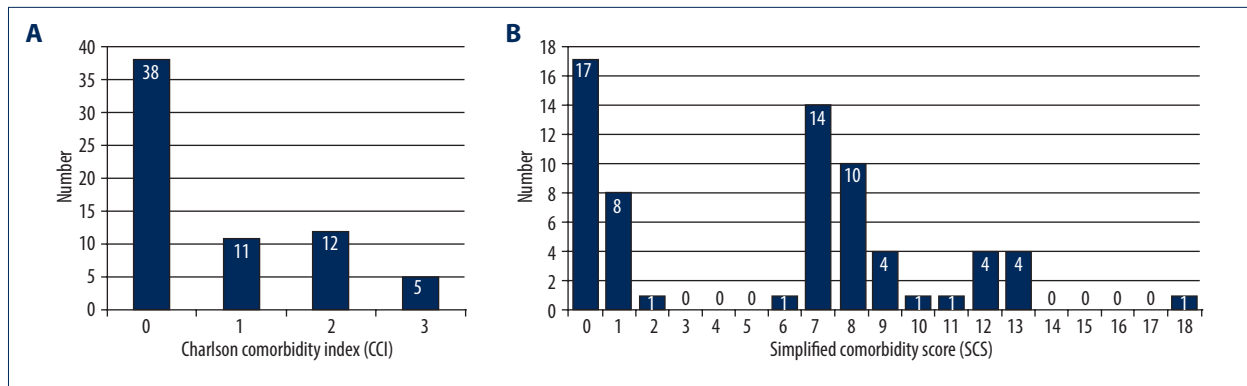
Figure 1. Distribution of comorbidity assessed by Charlson comorbidity index (**A**) and simplified comorbidity score (**B**) in patients with non-small cell lung cancer. Horizontal axis means the absolute points of each scoring system and vertical axis represents the number of patients.

Table 4. Tumor response in patients with NSCLC treated with PD1 inhibitors.

Response evaluation	All (n=66)		CCI			SCS		
			<1 (n=38)		≥1 (n=28)		<8 (n=41)		≥8 (n=25)
Disease control rate	54	(81.8%)	36	(94.7%)	18	(64.3%)	34	(82.9%)	20	(80.0%)
Overall response rate	24	(36.4%)	14	(36.8%)	10	(35.7%)	16	(39.0%)	8	(32.0%)
Complete response	0		0		0		0		0	
Partial response	24	(36.4%)	14	(36.8%)	10	(35.7%)	16	(39.0%)	8	(32.0%)
Stable disease	30	(45.4%)	22	(57.9%)	8	(28.6%)	18	(43.9%)	12	(48.0%)
Progressive disease	12	(18.2%)	2	(5.3%)	10	(35.7%)	7	(17.1%)	5	(20%)

NSCLC – non-small cell lung cancer; PD1 – programmed cell death protein 1; CCI – Charlson comorbidity index; SCS – simplified comorbidity score.
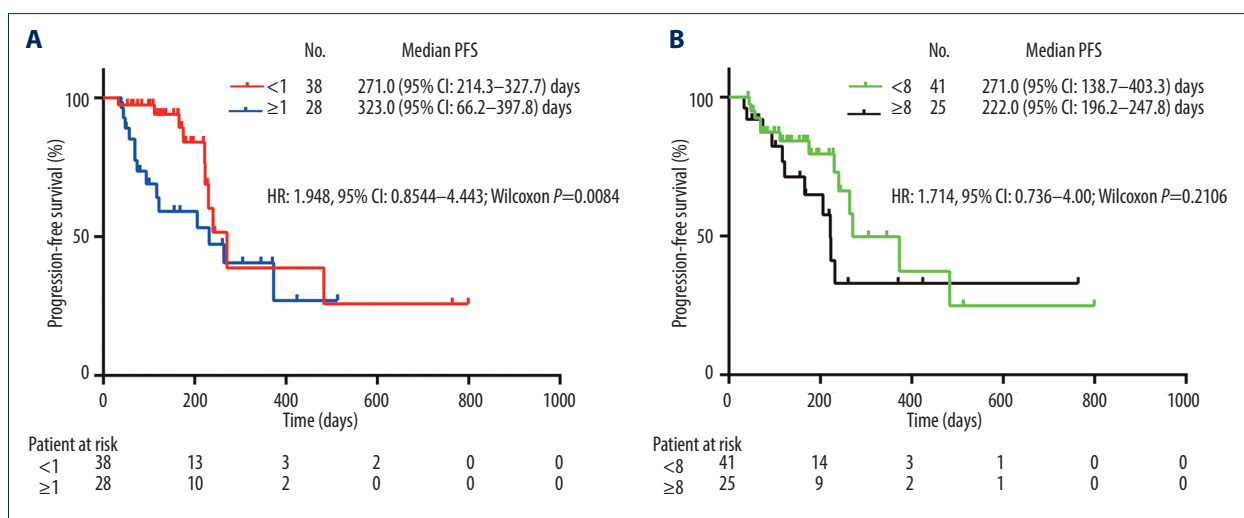

Figure 2. Kaplan-Meier plots of PFS in patients with non-small cell lung cancer undergoing PD1 inhibitors based on comorbidity conditions assessed by Charlson comorbidity index (**A**) and simplified comorbidity score (**B**). HR – hazard ratio; CI – confidence interval; PFS – progression-free survival.

Table 5. Incidence of immune-related adverse events in all recipients of PD1 inhibitors.

Events	All (n=66)		CCI			SCS		
			<1 (n=38)		≥1 (n=28)		<8 (n=41)		≥8 (n=25)
All	20	(30.3%)	10	(26.3%)	10	(35.7%)	13	(31.7%)	7	(28.0%)
Skin rash	6	(9.1%)	5	(13.2%)	1	(3.6%)	3	(7.3%)	3	(12.0%)
Pneumonitis	6	(9.1%)	3	(7.9%)	3	(10.7%)	5	(12.2%)	1	(4.0%)
Hypothyroidism	4	(6.1%)	1	(2.6%)	3	(10.7%)	2	(4.9%)	2	(8.0%)
Hepatitis	3	(4.5%)	1	(2.6%)	2	(7.1%)	2	(4.9%)	1	(4.0%)
Colitis	1	(1.5%)	0		1	(3.6%)	1	(2.4%)	0	

PD1 – programmed cell death protein 1; CCI – Charlson comorbidity index; SCS – simplified comorbidity score.

yet focused on assessing comorbidities and their influence on the prognosis of patients with NSCLC in developing countries. So far as we know, this study is the first study from China to use 2 different comorbidity scoring systems (i.e., CCI and SCS) to investigate whether comorbidities affected the outcomes of patients with NSCLC undergoing treatment with PD1 inhibitors. In our study, high CCI scores, not SCS scores, may have been associated with poor survival because of the shorter PFS, but there was no significant impact found on the incidence of irAEs in patients with NSCLC who received anti-PD1 treatment.

CCI, a comprehensive index of multi-morbidities, is a good indicator of a patient's global status and has been demonstrated to affect the prognosis of patients with lung cancer [17,23]. The variables in the CCI model are readily available and scores can easily be calculated by physicians. Recent studies have reached controversial conclusions on the prognostic significance of the CCI [17,23,24]. Additionally, no studies have investigated the predictive significance of CCI in patients with NSCLC receiving treatment with PD1 inhibitors; accordingly, so we used a cutoff point of 1 for further investigation, as used by Pylvalainen et al. [18]. Our findings indicated that the PFS of patients with higher CCI scores (CCI ≥1) were inferior to those of patients with lower CCI scores (CCI <1) (*P*=0.0048), which was consistent with previously published findings [18,25].

The SCS was first constructed by Pujol et al. in 2005 and was verified in a large population of patients with NSCLC. This scoring system is much more convenient in routine clinical practice because it incorporates only 6 factors. Smoking status has the largest weight in the index (7 points), followed by diabetes mellitus (5 points) and renal insufficiency (4 points). Using 8 points as the cutoff, we found that patients with higher SCS points had a shorter PFS than those with lower points, but the difference was not significant (*P*=0.2106) [26]. In other studies, SCS >9 was reported to be associated with poor prognosis in NSCLC patients undergoing chemotherapy [16,21]. In this study, only 11 patients had severe comorbidities (SCS >9), and further analysis revealed

that no significant difference was found between the patients with SCS ≤9 and the patients with SCS >9 in disease response rate (both 81.8%) or PFS (271.0 days; 95% CI: 139.0–403.0 days versus 206.0 days; 95% CI: 92.1–319.9 days; *P*=0.7601). Therefore, we did not find a correlation between this scoring system and survival. One possible explanation for this lack of correlation was the high proportion of smokers in the group with higher SCS values [27]. Most patients with SCS ≥8 had smoking history (88.0%). It has been reported that there is a positive association between cigarette smoking and the efficacy of anti-PD1 immunotherapy due to the higher tumor mutation burden, microsatellite instability-high, a higher rate of infiltrating CD4+ and CD8+ T cells in smokers [28–30]. Another important reason might be that males might have more benefit from anti-PD1 immunotherapy among NSCLC patients [27]. In our study, all 25 patients with SCS ≥8 were males. To sum up, although higher values of the SCS scoring system means serious comorbid status, males with smoking history might benefit from anti-PD1 immunotherapy. Considering the contradictory conclusion, the predictive value of the SCS in lung cancer patients remained nonsignificant.

This study had several limitations. Firstly, it was a single institution retrospective study. Secondly, the sample size was relatively small because immunotherapy has only been administered in China in the past 3 years. Thus, the findings are speculative rather than definitive. Prospective studies with larger cohorts would be more convincing. Thirdly, the median follow-up time in the current study was too short in that most participants had not reached the end point, resulting in information bias.

Conclusions

To the best of our knowledge, we have demonstrated for the first time, that comorbidities might correlate with the prognosis in NSCLC patients treated with PD1 inhibitors. However, large-scale prospective research is still needed to confirm

these findings considering the aforementioned study limitations. Additionally, an innovative comorbidity assessment model which incorporates immune diseases or other factors that affect the immunity of patients should be developed for predicting the efficacy of immunotherapy.

Conflict of interest

None.

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