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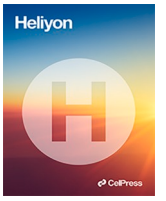

Research article

Prognostic value of body mass index for first-line chemoimmunotherapy combinations in advanced non-small cell lung cancer in Chinese population

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ABSTRACT

Background: Few studies have examined the correlation between body mass index (BMI) and effectiveness of first-line chemoimmunotherapy in patients with advanced non-small cell lung cancer (NSCLC); moreover, the conclusion remains elusive and no such studies have been conducted in the Chinese population. Our study aimed to validate the predictive significance of BMI in Chinese patients with advanced NSCLC receiving first-line chemoimmunotherapy combinations.

Methods: Data of patients with advanced NSCLC treated with first-line chemoimmunotherapy between June 2018 and February 2022 at three centers were retrieved retrospectively. The association between baseline BMI with progression-free survival (PFS) and overall survival (OS) was evaluated using the Kaplan–Meier method and Cox regression models. BMI was categorized according to the World Health Organization criteria.

Results: Of the included 805 patients, 5.3 % were underweight, 63.4 % had normal weight, 27.8 % were overweight, and 3.5 % were obese. Survival analysis showed that patients in the high BMI group had significantly better PFS ($p = 0.012$) and OS ($p = 0.014$) than those in the low BMI group. Further, patients in the overweight subgroup had better PFS ($p = 0.036$) and OS ($p = 0.043$) compared to the normal weight population. The results of Cox regression analysis confirmed the correlations between BMI and prognosis of advanced NSCLC patients receiving first-line chemoimmunotherapy combinations.

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Conclusions: Baseline BMI affected the clinical outcomes of first-line chemoimmunotherapy combinations in patients with advanced NSCLC, and was especially favorable for the overweight subgroup.

1. Introduction

Globally, lung cancer remains the leading cause of cancer-associated deaths, with a 5-year survival rate of approximately 19 %. Especially for patients with advanced lung cancer, whose 5-year survival rate is only 7 %, the current modalities for the treatment are still far from satisfactory [1,2]. Histologically, non-small cell lung cancer (NSCLC) represents approximately 85 % of lung cancer [3]. Immune checkpoint inhibitors (ICIs), which have the potential to produce long-lasting benefits for driver-negative metastatic NSCLC patients, have profoundly changed the treatment landscape of advanced NSCLC [4]. However, only approximately 20 % of patients show clinical response to ICIs monotherapy or chemoimmunotherapy combinations. There is still no obvious clinical response in 25 %–55 %. Hence, it is imperative to identify factors affecting the outcome of ICIs to pinpoint the patient populations that are more likely to benefit from them [5].

Presently, expression of programmed cell death protein 1 ligand (PD-L1) is the most commonly used predictive biomarker for ICIs therapy in patients with NSCLC. Although it canonically guides the treatment decision-making, there are still many limitations to its use owing to the variability of PD-L1 detection assays, differing PD-L1 expression cutoffs, inconclusive cell types tested for PD-L1 expression, and spatial and temporal heterogeneity of PD-L1 expression [6,7]. In addition, although, tumor mutation burden (TMB), tumor neoantigens, inflammation-related genes, driver gene mutations, and tumor microenvironment are usually focused on as tumor determinants, their prediction performance is unsatisfactory [8–15]. Furthermore, heterogeneous host factors, such as biomarkers in the peripheral blood, gut microbiota, and patient clinical characteristics, have also been known to be correlated with the prediction probability of ICIs response [8,16]. Obesity is one such host characteristic, which is visually represented by body mass index (BMI).

The association between obesity and NSCLC is complicated. Obesity is related to increased tumor incidence, rapid disease progression, and high recurrence after treatment; however, it seems to be an effective protective factor in patients with NSCLC treated with immunotherapy [17]. In a pooled post-hoc analysis of prospective trials, obesity was unexpectedly found to be associated with a survival benefit in patients who received atezolizumab, but not in those who were treated with chemotherapy, suggesting a special predictive role of high BMI for NSCLC immunotherapy [18]. In a Japanese cohort, however, no significant differences were observed in the clinical efficacy of PD-1 inhibitors as the first-line treatment between overweight and non-overweight patients with NSCLC [19,20]; however, BMI was significantly associated with the efficacy of ICIs in patients with NSCLC treated with second- or later-line PD-1/PD-L1 inhibitors [20]. In addition, among the European population, there is a remarkably favorable association between high baseline BMI and survival benefit in patients with NSCLC treated with first-line single-agent ICIs [21]; however, no significant association was noted in patients with metastatic NSCLC, who received first-line chemoimmunotherapy combinations [22].

These reports demonstrate that the association between enhanced ICIs efficacy and high BMI remains controversial. Moreover, the vast majority of studies have included only Caucasian populations, and to the best of our knowledge, there are no reports regarding the relationship between BMI and the efficacy of chemoimmunotherapy combinations in a large Chinese NSCLC cohort. Therefore, in this study, we analyzed the association between BMI and the clinical outcomes of first-line chemoimmunotherapy combinations in a cohort of Chinese patients with advanced NSCLC.

2. Materials and methods

2.1. Patients and data source

This was a retrospective study of patients with stage IV NSCLC without known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements who received first-line chemoimmunotherapy combinations at four locations between June 2018 and February 2022, with follow up until April 2024. First-line chemoimmunotherapy combinations were administered to patients every 3 weeks (q3w), and the participating institutions performed radiographic evaluations every 6–8 weeks at baseline and during treatment. Patients who had received local radiation therapy for a primary chest lesion during this period were excluded. Baseline clinical (such as height, weight, etc.), pathological, and laboratory data prior to each patient's first chemoimmunotherapy combinations were collected from medical records. If data were not available within 30 days prior to the initiation of chemoimmunotheraphy combinations, they were considered unavailable.

2.2. Outcome indicators

Progression-free survival (PFS) and overall survival (OS) were the main clinical outcomes, and tumor response was evaluated separately in accordance with the Response Assessment Criteria in Solid Tumors (RECIST) V.1.1. PFS was defined as the period from the start of treatment to the relapse of the disease or death, whichever occurred first. OS was defined as the time between the start of treatment and death. The original investigator identified the causes of death, which were independently reviewed by the investigators of this study. If necessary, another investigator was consulted. All endpoints were assessed from the date of diagnosis to the date of the

initial recorded event. Patients who did not experience an event during the follow-up period were censored at the date of their last follow-up visit.

2.3. Baseline BMI assessment

BMI was calculated with the formula, weight (kg)/height (m)^2 and classified according to the World Health Organization (WHO) classification criteria. Underweight, normal weight, overweight, and obese individuals were defined as having a BMI <18.50 kg/m^2, 18.50–24.99 kg/m^2, 25.00–29.99 kg/m^2, and ≥30.00 kg/m^2, respectively. For the study purpose, the binomial cut-off for BMI < or ≥25 was used, and patients were categorized into low BMI group (<25) and high BMI group (≥25) for the primary analysis. Subsequently, patients were categorized in more detail into underweight, normal weight, overweight, and obese individuals for the final analysis according to the WHO classification criteria, where normal weight was used as a control group.

Covariates were chosen on a clinical prioritization basis, in view of their known prognostic role, including sex, age, smoking status, Eastern Cooperative Oncology Group performance status (ECOG-PS), primary tumor histology, PD-L1 Tumor Proportion Score (TPS;

Table 1
Patient baseline characteristics.

Characteristic		N (%)	Under weight	Normal weight	Overweight	Obese	p
Total number of patients		805	43 (5.3 %)	510 (63.4 %)	224 (27.8 %)	28 (3.5 %)	
BMI	Mean ± SD	23.52 ± 3.34					
Sex, n (%)	Female	181 (22.5)	9 (20.9)	100 (19.6)	58 (25.9)	14 (50)	0.001
	Male	624 (77.5)	34 (79.1)	410 (80.4)	166 (74.1)	14 (50)	
Age, n (%)	Mean ± SD	62.5 ± 8.9	63.9 ± 9.9	63.0 ± 8.3	61.5 ± 9.1	58.1 ± 13.8	0.006
	<70	624 (77.5)	29 (67.4)	395 (77.5)	179 (79.9)	21 (75)	0.342
	≥70	181 (22.5)	14 (32.6)	115 (22.5)	45 (20.1)	7 (25)	
Smoking history, n (%)	Never	310 (38.5)	13 (30.2)	181 (35.5)	99 (44.2)	17 (60.7)	0.007
	Former/current	495 (61.5)	30 (69.8)	329 (64.5)	125 (55.8)	11 (39.3)	
ECOG, n (%)	0 or 1	765 (95.0)	36 (83.7)	483 (94.7)	219 (97.8)	27 (96.4)	0.005
	≥2	40 (5.0)	7 (16.3)	27 (5.3)	5 (2.2)	1 (3.6)	
Histology, n (%)	SCC	179 (22.2)	14 (32.6)	108 (21.2)	52 (23.2)	5 (17.9)	0.181
	Adenocarcinoma	595 (73.9)	29 (67.4)	380 (74.5)	166 (74.1)	20 (71.4)	
	Others	31 (3.9)	0 (0)	22 (4.3)	6 (2.7)	3 (10.7)	
M*, n (%)	Mean ± SD	2.1 ± 1.4	2.4 ± 1.6	2.1 ± 1.4	2.0 ± 1.4	2.4 ± 1.9	0.227
	<3	583 (72.4)	28 (65.1)	367 (72)	168 (75)	20 (71.4)	0.580
	≥3	222 (27.6)	15 (34.9)	143 (28)	56 (25)	8 (28.6)	
Liver metastasis	No	692 (86.0)	31 (72.1)	445 (87.3)	191 (85.3)	25 (89.3)	0.064
	Yes	113 (14.0)	12 (27.9)	65 (12.7)	33 (14.7)	3 (10.7)	
Bone metastasis	No	451 (56.0)	23 (53.5)	288 (56.5)	122 (54.5)	18 (64.3)	0.765
	Yes	354 (44.0)	20 (46.5)	222 (43.5)	102 (45.5)	10 (35.7)	
Brain metastasis	No	579 (71.9)	34 (79.1)	361 (70.8)	164 (73.2)	20 (71.4)	0.659
	Yes	226 (28.1)	9 (20.9)	149 (29.2)	60 (26.8)	8 (28.6)	
PD-L1 TPS, n (%)	<50 %	146 (18.1)	6 (14)	104 (20.4)	27 (12.1)	9 (32.1)	0.051
	≥50 %	188 (23.4)	13 (30.2)	113 (22.2)	56 (25)	6 (21.4)	
	Not available	471 (58.5)	24 (55.8)	293 (57.5)	141 (62.9)	13 (46.4)	
ALB, n (%)	Normal	462 (66.0)	11 (28.9)	284 (64.4)	145 (74.4)	22 (84.6)	<0.001
(40–55 g/L)	Low	238 (34.0)	27 (71.1)	157 (35.6)	50 (25.6)	4 (15.4)	
	High	0					
Cr, n (%)	Normal	419 (60.6)	20 (52.6)	262 (59.8)	122 (64.2)	15 (60)	0.539
(59-104umol/L)	Low	272 (39.4)	18 (47.4)	176 (40.2)	68 (35.8)	10 (40)	
	High	0					
LDH, n (%)	Normal	406 (60.2)	22 (61.1)	259 (60.9)	110 (58.5)	15 (60)	0.954
(109–245U/L)	Low	0					
	High	268 (39.8)	14 (38.9)	166 (39.1)	78 (41.5)	10 (40)	
HDL, n (%)	Normal	208 (32.5)	13 (38.2)	133 (33.2)	53 (29.3)	9 (36)	0.630
(1.16–1.42 mmol/L)	Low	282 (44.1)	15 (44.1)	167 (41.8)	90 (49.7)	10 (40)	
	High	150 (23.4)	6 (17.6)	100 (25)	38 (21)	6 (24)	
LDL, n (%)	Normal	296 (46.2)	22 (64.7)	184 (46)	77 (42.5)	13 (52)	0.113
(2–3.12 mmol/L)	Low	57 (8.9)	4 (11.8)	35 (8.8)	18 (9.9)	0 (0)	
	High	287 (44.8)	8 (23.5)	181 (45.2)	86 (47.5)	12 (48)	
TG, n (%)	Normal	531 (83.0)	31 (91.2)	345 (86.2)	137 (75.7)	18 (72)	0.002
(0.3–1.7 mmol/L)	Low	0					
	High	109 (17.0)	3 (8.8)	55 (13.8)	44 (24.3)	7 (28)	
Hypertension, n (%)	No	611 (75.9)	38 (88.4)	394 (77.3)	161 (71.9)	18 (64.3)	0.042
	Yes	194 (24.1)	5 (11.6)	116 (22.7)	63 (28.1)	10 (35.7)	
Diabetes mellitus, n (%)	No	736 (91.4)	40 (93)	475 (93.1)	199 (88.8)	22 (78.6)	0.023
	Yes	69 (8.6)	3 (7)	35 (6.9)	25 (11.2)	6 (21.4)	

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SCC = Squamous cell carcinoma; M* = number of distantly metastasized organs; PD-L1 TPS = programmed death ligand-1 Tumor Proportion Score; ALB = Albumin; Cr = Creatinine; LDH = lactate dehydrogenase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

PD-L1 TPS), number of distantly metastasized organs (M), liver/bone/brain metastasis, albumin (ALB) levels, lactate dehydrogenase (LDH) levels, creatinine (Cr) levels, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), hypertension, and diabetes mellitus. Of these, according to the 8th edition of the tumor node metastasis (TNM) staging system of the International Association for the Study of Lung Cancer, only 5.6 % of the patients were in stage IV A, therefore we selected the median number of distant metastasized organs "2" as the cutoff value, divided into <3 and ≥ 3 distant metastasized organs.

2.4. Statistical analysis

To investigate the potential correlations between baseline characteristics and BMI subgroups, we first evaluated the distribution of patient characteristics. Baseline characteristics of NSCLC patients were reported using descriptive statistics, and chi-squared tests were used to compare categorical variables. The inverse Kaplan–Meier approach was used to determine the duration of the follow-up period. OS and PFS were compared and evaluated using the Kaplan–Meier method and the log-rank test. Using Cox proportional risk regression, successive univariate and multivariate analyses of PFS and OS were performed, and 95 % confidence intervals (CIs) of hazard ratio (HR) were computed. Forest plots were selected for subgroup analysis. Missing values for the clinicopathological characteristics were excluded from the descriptive analysis and multivariate regression models. All p-values were two-sided, the 95 % level was used to create confidence intervals, and the threshold for significance was set at 0.05. All analyses were conducted with IBM SPSS statistical software (Version 26, IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Patient and baseline characteristics

A total of 805 patients with advanced NSCLC who received first-line chemoimmunotherapy combinations between June 2018 and February 2022 were identified. The characteristics of the study population stratified by WHO BMI subgroups are summarized in Table 1. Patients were followed up with a median follow-up period of 29.93 months (range, 0.2–61.6 months). The median BMI was 23.52 kg/m^2 (range, 14.19–36.73 kg/m^2). In total, 43 patients (5.3 %) were underweight, 510 (63.4 %) normal weight, 224 (27.8 %) overweight, and 28 (3.5 %) obese. PD-L1 tumor expression was evaluable in 334 (41.5 %) patients, showing a TPS of ≥50 % in 188 (23.4 %) and <50 % in 146 (18.1 %) patients, respectively. Several baseline clinicopathological characteristics were notably different across the BMI classifications. Overweight and obese patients with NSCLC were more likely to be women ($p = 0.001$), never smokers ($p = 0.007$), with a better baseline ECOG-PS ($p = 0.005$), normal albumin levels ($p < 0.001$), and have a high TG level ($p = 0.002$) and hypertension ($p = 0.042$).

3.2. BMI dichotomy and outcomes for first-line chemoimmunotherapy combinations in patients with advanced NSCLC

For analysis and comparison, we first divided the patients into the following two groups: a high (BMI ≥25 kg/m^2: overweight group + obese group) and low BMI groups (BMI <25 kg/m^2: underweight group + normal-weight group). Compared with the patients in the low BMI group, the high BMI group had a significantly prolonged PFS (high BMI, 12.97 months vs. low BMI, 10.13 months, $p = 0.012$) and OS (high BMI, 42.30 months vs. low BMI, 21.80 months, $p = 0.014$; Fig. 1 A and B).

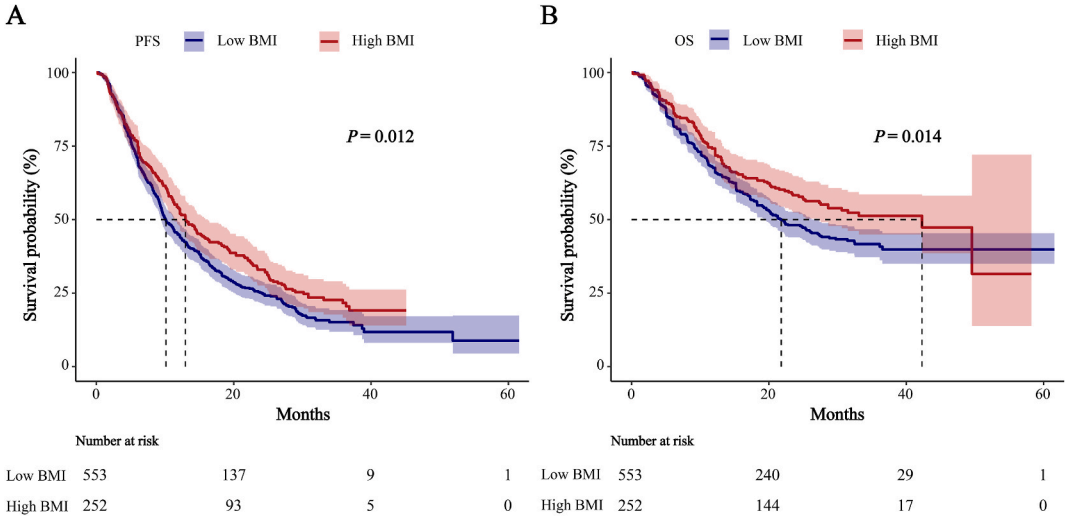

Fig. 1. Kaplan-Meier analysis of PFS and OS according to BMI status (Low BMI: BMI <25Kg/m2 vs. High BMI: BMI ≥25Kg/m2). (A) PFS. (B) OS. Abbreviations: BMI = body mass index; PFS = progression-free survival; OS = overall survival.

In the Cox regression analysis, univariate analysis demonstrated that high BMI was a significant favorable factor for PFS (HR = 0.81 [95 % CI: 0.68–0.96], p = 0.013) and OS (HR = 0.77 [95 % CI: 0.62–0.95], p = 0.015). This difference remains after adjusting for confounding factors (PFS: adjusted HR [aHR] = 0.80 [95 % CI: 0.66–0.97], p = 0.024; OS: aHR = 0.79 [95 % CI: 0.62–0.99], p = 0.048; Tables 2 and 3).

3.3. Obesity level and outcomes for first-line chemoimmunotherapy combinations in patients with advanced NSCLC

As patients in the high BMI group had significantly better PFS and OS than those in the low BMI group, we further segmented the patients into underweight, normal weight, overweight, and obese groups. We then compared the overweight and obese groups with the normal weight group respectively, with the results revealing that the overweight group's PFS (overweight, 13.17 months vs. normal weight, 10.13 months, $p = 0.036$) and OS (overweight, 49.57 months vs. normal weight, 22.17 months, $p = 0.043$) were significantly longer than that of the normal weight group (Fig. 2 A and B), while no significant difference in the PFS (obese, 10.90 months vs. normal weight, 10.13 months, $p = 0.727$) and OS (obese, 25.33 months vs. normal weight, 22.17 months, $p = 0.211$) was observed between obese and normal weight group (Fig. 2 A and B).

In the COX univariate regression analysis of the four subgroups, overweight but not obese could be regarded as a protective factor for PFS (HR = 0.80 [95 % CI: 0.67–0.96], p = 0.016) and OS (HR = 0.78 [95 % CI: 0.62–0.98], p = 0.031). After adjustment for potential confounders, this association between PFS (aHR = 0.81 [95 % CI: 0.66–0.99], p = 0.037) and overweight remained independent, and OS (aHR = 0.79 [95 % CI: 0.62–1.01], p = 0.061) approached statistical significance (Table 4).

Table 2
Univariate and multivariate analysis of progression free survival in BMI dichotomy.

	Univariate analysis			Multivariate analysis		
	HR	95 % CI	p	aHR	95 % CI	p
BMI (kg/m^2)						
≥25 vs. <25	0.81	0.68–0.96	0.013	0.80	0.66–0.97	0.024
Sex						
Male vs. Female	0.94	0.79–1.13	0.534			
Age						
≥70 vs. <70	1.13	0.94–1.36	0.204			
Smoking history						
Former/current vs. Never	0.87	0.74–1.02	0.078	0.77	0.64–0.93	0.007
ECOG						
≥2 vs. 0 or 1	1.55	1.10–2.16	0.011	1.16	0.81–1.66	0.415
Histology						
Adenocarcinoma vs. SCC	0.83	0.69–1.00	0.052	0.90	0.72–1.11	0.314
Others vs. SCC	1.05	0.68–1.60	0.838	0.90	0.57–1.41	0.636
Metastasis						
Liver (Yes vs. No)	1.62	1.31–2.01	<0.001	1.43	1.11–1.85	0.007
Bone (Yes vs. No)	1.51	1.29–1.77	<0.001	1.31	1.09–1.58	0.004
Brain (Yes vs. No)	0.91	0.76–1.08	0.228			
M*						
≥3 vs. <3	1.49	1.25–1.76	0.000	1.28	1.04–1.58	0.022
PD-L1 TPS						
≥50 % vs. <50 %	0.57	0.44–0.74	0.000	0.53	0.39–0.72	0.000
Not available vs. <50 %	1.04	0.85–1.28	0.684	1.01	0.81–1.26	0.914
ALB						
Low vs. Normal	1.43	1.20–1.70	0.000	1.28	1.06–1.56	0.013
Cr						
Low vs. Normal	1.15	0.97–1.36	0.113			
LDH						
High vs. Normal	1.41	1.19–1.67	0.000	1.28	1.07–1.53	0.008
HDL						
Low vs. Normal	1.25	1.03–1.53	0.027	1.27	1.03–1.56	0.024
High vs. Normal	0.98	0.78–1.25	0.880	1.02	0.80–1.31	0.857
LDL						
Low vs. Normal	0.99	0.73–1.35	0.955			
High vs. Normal	0.87	0.73–1.05	0.144			
TG						
High vs. Normal	0.88	0.70–1.11	0.296			
Hypertension						
Yes vs. No	0.93	0.78–1.12	0.463			
Diabetes mellitus						
Yes vs. No	1.01	0.77–1.33	0.944			

Abbreviations: aHR = adjusted HR; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SCC = Squamous cell carcinoma; M* = number of distantly metastasized organs; PD-L1 TPS = programmed death ligand-1 Tumor Proportion Score; ALB = Albumin; Cr = Creatinine; LDH = lactate dehydrogenase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

Table 3
Univariate and multivariate analysis of overall survival in BMI dichotomy.

	Univariate analysis			Multivariate analysis		
	HR	95 % CI	p	aHR	95 % CI	p
BMI (kg/m^2)						
≥25 vs. <25	0.77	0.62–0.95	0.015	0.79	0.62–0.99	0.048
Sex						
Male vs. Female	1.35	1.06–1.72	0.017	1.08	0.82–1.40	0.595
Age						
≥70 vs. <70	1.60	1.29–1.98	0.000	1.61	1.26–2.06	0.000
Smoking history						
Former/current vs. Never	1.13	0.93–1.38	0.231			
ECOG						
≥2 vs. 0 or 1	1.99	1.37–2.88	0.000	1.34	0.90–1.98	0.146
Histology						
Adenocarcinoma vs. SCC	0.66	0.53–0.82	0.000	0.85	0.66–1.09	0.198
Others vs. SCC	1.02	0.63–1.64	0.932	0.98	0.58–1.65	0.933
Metastasis						
Liver (Yes vs. No)	1.83	1.43–2.34	<0.001	1.34	1.00–1.80	0.047
Bone (Yes vs. No)	1.63	1.34–1.98	<0.001	1.47	1.17–1.84	0.001
Brain (Yes vs. No)	0.85	0.68–1.06	0.152			
M*						
≥3 vs. <3	1.54	1.25–1.89	0.000	1.72	1.38–2.14	0.000
PD-L1 TPS						
≥50 % vs. <50 %	0.51	0.37–0.72	0.000	0.61	0.42–0.89	0.011
Not available vs. <50 %	1.14	0.89–1.47	0.299	1.17	0.89–1.52	0.262
ALB						
Low vs. Normal	1.68	1.37–2.06	0.000	1.37	1.09–1.73	0.008
Cr						
Low vs. Normal	1.05	0.86–1.29	0.633			
LDH						
High vs. Normal	1.64	1.34–2.01	0.000	1.59	1.28–1.97	0.000
HDL						
Low vs. Normal	1.34	1.06–1.70	0.016	1.34	1.05–1.72	0.021
High vs. Normal	0.88	0.65–1.18	0.393	0.91	0.67–1.24	0.554
LDL						
Low vs. Normal	0.71	0.48–1.07	0.103	0.58	0.38–0.88	0.009
High vs. Normal	0.84	0.68–1.05	0.122	0.97	0.77–1.21	0.764
TG						
High vs. Normal	0.87	0.66–1.15	0.323			
Hypertension						
Yes vs. No	1.20	0.97–1.50	0.095	1.06	0.83–1.35	0.664
Diabetes mellitus						
Yes vs. No	1.02	0.73–1.43	0.895			

Abbreviations: aHR = adjusted HR; BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; SCC = Squamous cell carcinoma; M* = number of distantly metastasized organs; PD-L1 TPS = programmed death ligand-1 Tumor Proportion Score; ALB = Albumin; Cr = Creatinine; LDH = lactate dehydrogenase; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

3.4. Subgroup analysis

The estimated PFS benefit of overweight individuals compared with normal-weight individuals differed numerically between different subgroups. Age, sex, smoking history, histology, M, LDH, ALB and PD-L1 TPS were chosen for subgroup analysis to accurately determine the beneficiary population and analyze the source of heterogeneity. In this investigation, we discovered that overweight patients had significantly longer OS (aHR = 0.60 [95 % CI: 0.39–0.91], $p = 0.017$), and PFS approaching statistical significance (aHR = 0.69 [95 % CI: 0.48–1.00], $p = 0.050$) in low ALB levels subgroup, but BMI had no bearing on PFS and OS when ALB levels were normal (Fig. 3 A and B). Besides, for patients with the pathologic type of squamous cell carcinoma (SCC), being overweight was notably correlated with better prognosis (PFS: HR = 0.41 [95 % CI:0.27–0.62], p = 0.000; OS: HR = 0.41 [95 % CI: 0.25–0.67], p = 0.000). Meanwhile, the only benefit for PFS was from those who were never smokers (aHR = 0.66 [95 % CI:0.49–0.90], $p = 0.008$), women (aHR = 0.63 [95 % CI:0.41–0.96], $p = 0.031$), or those who were <70 years (aHR = 0.77, 95 % CI:0.61–0.97, $p = 0.026$), as shown in Fig. 3 A and B.

4. Discussion

Currently for patients with advanced NSCLC without oncogenic driver mutations, the mainstream first-line treatment is chemo-immunotherapy combinations. In this study, our findings suggest that high baseline BMI is significantly positively associated with prolonged PFS and OS in patients with advanced NSCLC receiving first-line chemoimmunotherapy combinations. Additionally, further analysis revealed that the association was present only in the overweight subgroup, but not in the obese subgroup. Furthermore,

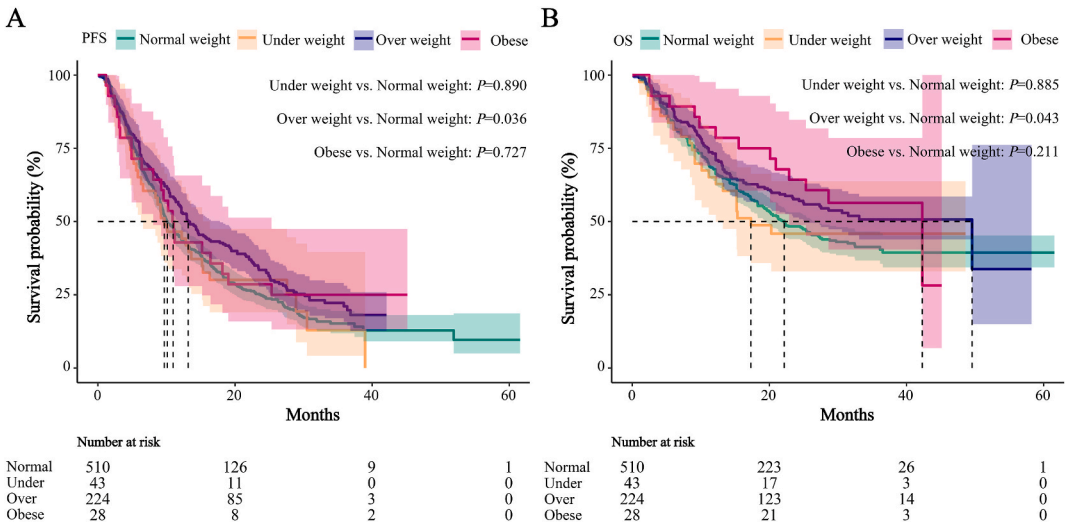

Fig. 2. Kaplan-Meier survival estimates of patients with the overweight and obese group versus the normal weight group. (A) PFS and (B) OS of overweight compared to normal weight. (C) PFS and (D) OS of obese compared to normal weight. Abbreviations: BMI = body mass index; PFS = progression-free survival; OS = overall survival.

Table 4
Univariate and multivariate analysis of progression free survival and overall survival in BMI quartet.

	PFS			OS		
	HR	95 % CI	p	aHR	95 % CI	p
Univariate analysis						
Underweight vs. Normal weight	1.02	0.72–1.44	0.921	1.03	0.68–1.58	0.881
Overweight vs. Normal weight	0.80	0.67–0.96	0.016	0.78	0.62–0.98	0.031
Obese vs. Normal weight	0.84	0.54–1.31	0.440	0.68	0.39–1.19	0.180
Multivariate analysis						
Underweight vs. Normal weight	0.88	0.58–1.32	0.528	0.74	0.45–1.23	0.251
Overweight vs. Normal weight	0.81	0.66–0.99	0.037	0.79	0.62–1.01	0.061
Obese vs. Normal weight	0.77	0.48–1.24	0.284	0.67	0.37–1.22	0.189

Abbreviations: aHR = adjusted HR; PFS = progression-free survival; OS = overall survival.

subgroup analysis demonstrated that the benefit of first-line chemoimmunotherapy combinations from being overweight tended to be limited to patients with low serum ALB levels or those with SCC.

Generally, obesity is a well-established risk factor for the development of multiple malignant tumors and an unfavorable prognostic factor [23–25]. While in the era of immunotherapy, incremental analyses of clinical data have tended to show better responses and survival benefit of immunotherapy in overweight patients [26], giving rise to a so-called “obesity paradox” [17]. Except for the confirmation of clinical research data, obesity is also associated with enhanced efficacy of PD-1/PD-L1 blockade in a tumor-bearing mice model [27]. Mechanistically, obesity could result in increased immune aging and PD-1-mediated T-cell dysfunction via leptin, which in turn enhances the efficacy of PD-1/PD-L1 blockade [27]. In addition, adipose tissue could contribute to immune homeostasis. White adipose tissue, being a source of cytokines and chemokines such as leptin and lipocalin is involved in the induction and/or coordination of host defenses [28]. Furthermore, in a preclinical study, white adipose tissue of mice accumulated pathogen-specific memory T-cells following a microbial infection, including tissue-resident cells expressing a distinct metabolic profile [29]. This supports the idea that adipose tissue may act as a repository for memory T cells with potent proliferative effects and protective potential and may be a special immune compartment that permits long-term maintenance of memory T cells and quick reactivation [29].

A previous study showed that baseline obesity was significantly associated with improved objective response rate, PFS, and OS in patients with advanced NSCLC with high PD-L1 expression receiving first-line pembrolizumab but not in patients treated with chemotherapy, supporting the hypothesis that obesity may have immunomodulatory rather than prognostic effects [21]. It is well established that adding chemotherapy to ICI can increase tumor antigenicity and enhance treatment results. However, the current results showed that BMI seems to be of higher value in predicting the efficacy of mono-immunotherapy. In the Caucasian population, Cortellini et al. observed a notable correlation between high BMI and clinical prognosis of patients with advanced NSCLC treated with first-line immune monotherapy [21], but the correlation between BMI and prognosis was not significant in patients with advanced NSCLC treated with first-line chemoimmunotherapy combinations [22]. One possible explanation is that the addition of the chemotherapy backbone could potentially mitigate the suppression of T cells responsivity mediated by obesity enhanced immunogenicity, which in turn minimizes the role of BMI and obesity in magnifying the effect of immunotherapy [27]. However, in this study, it was

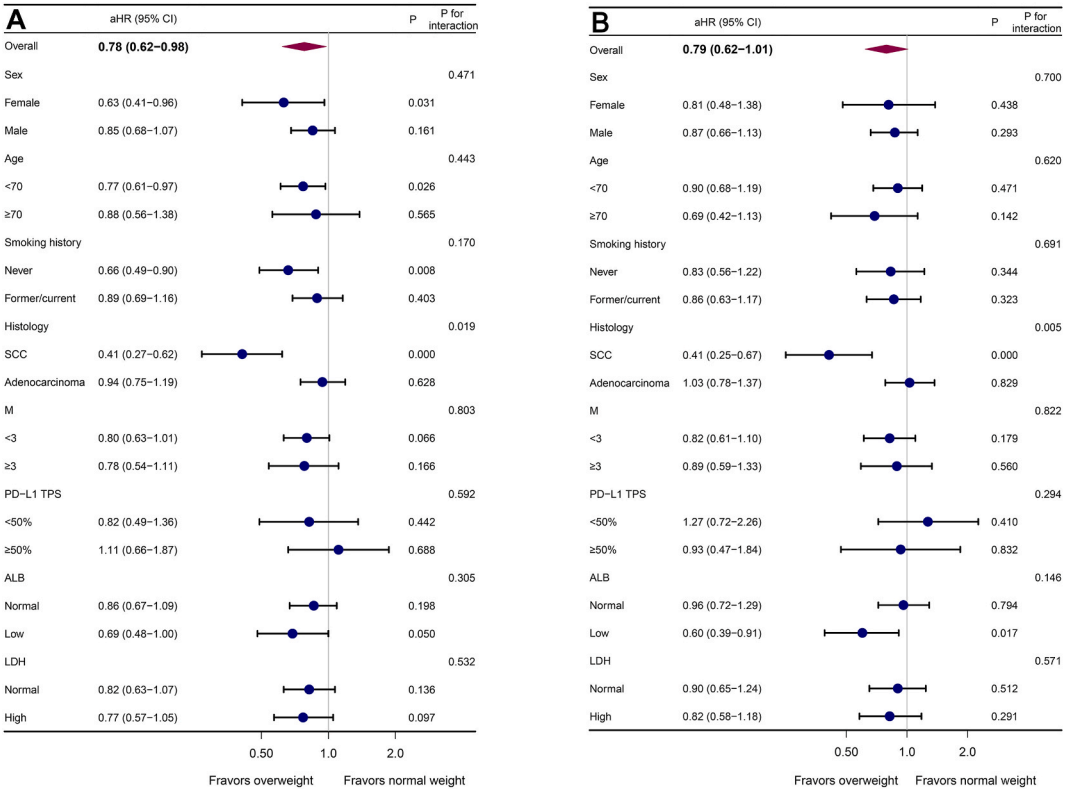

Fig. 3. Forest plot graph of patients with the overweight group versus the normal weight group. (A) PFS and (B) OS. Abbreviations: aHR = adjusted HR; SCC = Squamous cell carcinoma; M* = number of distantly metastasized organs; PD-L1 TPS = programmed death ligand-1 Tumor Proportion Score; ALB = Albumin; LDH = lactate dehydrogenase.

observed that high BMI is significantly associated with prolonged PFS and OS in Chinese patients with metastatic NSCLC receiving chemoimmunotherapy combinations, especially overweight patients. The trend observed in this study was similar but more significant compared with the findings of Cortellini et al. The disagreement between the two studies implemented in different races can be attributed to ethnic differences. Moreover, the inclusion criteria of the two studies were slightly different; in the study by Cortellini et al. patients with oncogene-addicted disease after treatment with targeted agents were included, who were excluded in this study. Growing prospective clinical trials of ICIs consider EGFR-mutant lung cancers refractory to ICIs compared with EGFR wild-type lung cancers [30–34]. Moreover, the proportion of high PD-L1 expression in patients with known PD-L1 levels was 23.4 % in this study, which was remarkably higher than that of 17.4 % in Cortellini et al. research.

Meng et al. found that more $CD8^+$ tumor-infiltrating lymphocytes were detected in the cancer nests from patients with NSCLC with SCC than those without SCC [35]. In accordance with this, our study validated that being overweight is a remarkably favorable prognostic marker for lung SCC patients. Pretreatment serum ALB, a known prognostic and predictive factor in ICI-treated patients, has also been proposed as a potential pharmacokinetic surrogate marker for anti-PD1/PD-L1 antibodies. Study shows that elevated clearance of monoclonal antibodies is correlated with low pretreatment ALB across many antibody drugs and diseases [36,37]. Meanwhile, there is a significant negative correlation between ALB and C-reactive protein, suggesting that hypoalbuminemia in patients with cancer occurs in the context of chronic inflammation [38], and this may be synergistic with BMI. Furthermore, serum ALB reflects patients' nutritional status [39], which along with BMI is one of the markers of cancer cachexia. Cachexia, which is associated with a worse prognosis regardless of PD-L1 expression, occurs in nearly 38.7%–48.1 % of patients with advanced or recurrent advanced NSCLC [40,41]. Consequently, only patients with advanced NSCLC receiving first-line immune combination therapy were included in this study to exclude, to the greatest extent possible, the effects of advanced tumor cachexia on clinical outcomes. Due to the aggressive nature of lung cancer, patients with metastatic NSCLC frequently have a poor clinical status, and lose serum ALB and weight while receiving first-line therapy [42]. Higher baseline BMI may be a sign of functional reserve and a protective factor in patients with advanced NSCLC, which may improve tolerance to anti-cancer therapies, improve the quality of life, and, perhaps, survival [43,44].

Based on our findings, we believe that BMI could serve as a cost-effective, easy-to-measure, and implementable predictive biomarker in NSCLC chemoimmunotherapy combinations. The conclusions of the current analysis on the relationship between high BMI and better survival in patients with advanced NSCLC treated with chemoimmunotherapy combinations may be useful as a stratification factor in prospective interventional trials. The findings of this investigation also suggest that dietary therapy to maintain

a patient's BMI is beneficial for oncological treatment. In addition, for patients with advanced NSCLC with low BMI, the advantages and disadvantages of chemoimmunotherapy combinations versus other therapeutic options, such as anti-vascular combination chemotherapy, deserve further investigation as a way of clarifying the optimal treatment options for this population.

4.1. Limitations

Our study has some limitations, primarily related to its retrospective design, absence of a matched control cohort receiving first-line immunotherapy and chemotherapy, absence of a centralized data/imaging review, incomplete molecular profiles of all patients, and uncertain PD-L1 status of the majority of patients. Second, BMI does not sufficiently reflect complex body compositions, and thus there are still some restrictions on using BMI to define overweight and obesity [17]. The lipid indicators, which are closely related to obesity, are easily available and will be analyzed in a separate study. Additionally, anthropometric measurements such as waist circumference and waist-hip ratio, as well as image-based measures such as computed tomography or magnetic resonance imaging can be used to characterize obesity as well; however, they could not be obtained from medical records in this study and may be collected prospectively in the follow-up [17,45,46]. Finally, it has been shown that BMI is positively correlated with the incidence of immune-related adverse events (irAE) [47]; however, since this study focused on the relationship between BMI and prognosis of chemoimmunotherapy combinations, the analysis regarding irAE was not performed, but we plan to do so in a follow-up study.

5. Conclusions

To the best of our knowledge, this study is the first to investigate the relationship between BMI and the effectiveness of first-line chemoimmunotherapy combinations in advanced NSCLC in a Chinese population. The findings suggest that high BMI is a favorable prognostic factor for first-line chemoimmunotherapy combinations in patients with advanced non-small cell lung cancer. In further analysis, it was shown that moderately overweight individuals may benefit from immunotherapy; however, extremely obese individuals lose this protective impact.

Ethical approval

This study was approved by the Institutional Review Board of the Affiliated Cancer Hospital of Shandong First Medical University (ethics approval number: SDTHEC2023006034). The protocol was conformed to *Good Clinical Practice guidelines* and *Declaration of Helsinki principles*. Individual patient consent was not required due to the retrospective nature of the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon request.

Conflict of interest disclosure statement

The authors have no conflicts of interests to declare.

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CRediT authorship contribution statement

Yanxin Sun: Writing – original draft, Supervision, Investigation, Formal analysis, Data curation. **Qi Dang:** Writing – original draft, Validation. **Yihui Ge:** Investigation, Formal analysis, Data curation. **Jian Zhang:** Methodology, Formal analysis, Data curation. **Qinglei Cheng:** Methodology, Investigation. **Haifeng Sun:** Software, Investigation. **Leirong Wang:** Methodology, Formal analysis, Data curation. **Aiqin Gao:** Writing – review & editing, Project administration, Funding acquisition. **Yuping Sun:** Supervision, Conceptualization. **Juan Li:** Writing – review & editing, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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No additional information is available for this study.

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