Association of cardiovascular disease and CIRS-G and ACE-27 comorbidity indices with pathological complete response of non-small cell lung cancer to neoadjuvant chemoimmunotherapy

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Abstract. Neoadjuvant chemoimmunotherapy (NCIO) is a new and effective treatment for cancer, but its efficacy in treating certain patients is unclear. We previously found that comorbidity was an independent factor associated with the pathological complete response (pCR) of non-small cell lung cancer (NSCLC) to NCIO. However, we did not address which comorbidities or comorbidity indices were associated with pCR. The present study retrospectively collected the data for NSCLC patients who underwent NCIO after surgery at The Second Xiangya Hospital of Central South University (Hunan, China) between January 2019 and July 2022. The associations between comorbidities/comorbidity indices and pCR rates/clinicopathological factors were analyzed. In total, 101 eligible patients with stage IIB-IIIC NSCLC were enrolled. Comorbid hypertension [odds ratio (OR)=0.321(0.110-0.937)], vascular disease [OR=0.275 (0.111-0.677)] and cardiovascular disease [OR=0.272 (0.114-0.646)] were all significantly associated with pCR (all P<0.05). The comorbidity indices Cumulative Illness Rating Scale-Geriatric (CIRS-G) ≥2 [OR=0.360 (0.154-0.840)], CIRS-G ≥3 [OR=0.404 (0.179-0.912)], CIRS-G ≥4 [OR=0.293 (0.105-0.817)] and Adult Comorbidity Evaluation-27 (ACE-27) ≥2 [OR=0.427 (0.192-0.950)] were all significantly associated with pCR (all P<0.05). Cardiovascular disease was the only independent risk factor for pCR [adjusted OR=0.272 (0.114-0.646); P=0.003] according to multivariate logistic analysis. In conclusion, cardiovascular comorbidities and the CIRS-G and ACE-27 indices were associated with the effectiveness of NCIO and clinicopathological factors. These results could help to screen for the most suitable NSCLC patients for NCIO.

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Introduction

According to Cancer Statistics 2022 (1), lung cancer is the second most common cancer and the leading cause of cancer death worldwide. The prognosis of lung cancer is poor and the mean 5-year overall survival (OS) rate of patients with lung cancer is only 4-17% (2). Non-small cell lung cancer (NSCLC) accounts for ~85% of lung cancers. The loss of surgical opportunity is one of the main reasons for poor prognosis. Neoadjuvant chemotherapy may benefit these patients and promoting the possibility of surgery. However, the absolute benefit of neoadjuvant chemotherapy to the 5-year OS rate is only 5-6% greater than that of surgery alone (3). Therefore, identifying new and more effective neoadjuvant treatment regimens is urgently needed.

The advent of immunotherapy has changed the landscape of advanced NSCLC treatment in the last decade, with improved responses and prognoses (4). In nearly 5 years, neoadjuvant immunotherapy has achieved encouraging results for early and locally advanced NSCLC. A 2018 trial (Checkmate-159 trial) showed that after two cycles of neoadjuvant nivolumab treatment, 15% (3/20) of patients exhibited pathological complete response (pCR) and 45% (9/20) major pathological response (MPR) (5). Neoadjuvant chemoimmunotherapy (NCIO) produced an improved pathological response (PR) compared with neoadjuvant immunotherapy. In the NADIM trial of stage IIIA NSCLC, three cycles of NCIO was associated with a pCR of 63% (26/41) and an MPR of 83% (34/41) (6). In the CheckMate 816 trial, compared with chemotherapy alone, NCIO achieved a greater pCR rate (24.0 vs. 2.2%; P<0.001) and longer median event-free survival (31.6 vs. 20. 8 months; P=0.005) as well as OS [both did not reach median survival time; hazard ratio (HR)=0.57; P=0.008] (7). A PR benefit was shown to result in a survival benefit in some studies (6,8,9). In the NADIM trial of NCIO, compared with the non-pCR group, the pCR group achieved

a superior 2-year progression-free survival (PFS) rate (96.2 vs. 57.1%; P=0.0023) and 2-year OS rate (100% vs. 85.7%; P=0.002) (6).

However, why only some patients benefit from NCIO is still unclear, as are biomarkers, such as histological type, cancer stage, programmed death ligand (PD-L)1 expression and treatment regimens, for identifying the most suitable patients. Our previous study (10) found that comorbidities, histological type, PD-L1 expression, tumor regression rate and therapeutic regimens were all significantly and independently associated with pCR/MPR and that comorbidity was associated with pCR [adjusted odds ratio (OR)=0.16; P=0.007] but not MPR. However, that study did not address the question of which comorbidities or comorbidity indices influenced the incidence of pCR. Comorbidities or comorbidity indices have frequently been reported to increase mortality risk in patients with NSCLC (11), but it has not been reported whether they influence the effectiveness of NCIO. The present study investigated which comorbidities or comorbidity indices influence pCR of NCIO in patients with NSCLC and which clinicopathological factors are associated with these comorbidities or comorbidity indices. These results could help to screen the most suitable NSCLC patients for NCIO and provide insights into further study on the biological role of comorbidities in the NCIO response of NSCLC patients.

Materials and methods

Study design and patients. The present study was a retrospective cohort study and its aims were to identify the detailed comorbidities or comorbidity indices associated with pCR and clinicopathological factors. The medical data for NSCLC patients who received NCIO after surgery between January 2019 and July 2022 at The Second Xiangya Hospital of Central South University (Hunan, China) were retrospectively collected. The inclusion criteria were: i) ≥18 years of age, ii) pathologically confirmed NSCLC, iii) clear clinical stage prior to surgery according to the American Joint Committee on Cancer Tumor Staging (8th edition) (12), iv) NCIO used, v) PR assessed after surgery and vi) Eastern Cooperative Oncology Group score 0 or 1 (13). The exclusion criteria were: i) Clinical M1 stage disease, ii) coexisting autoimmune disease or current use of immunosuppressive agents, iii) other types of cancer in the last 5 years and iv) known actionable driver oncogene mutations [seven patients were excluded because they benefited less from immunotherapy and target treatment should be recommended, according to NCCN guideline (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450)]. The present study followed the Declaration of Helsinki guidelines and was approved by the Ethics Commission of The Second Xiangya Hospital of Central South University (approval no. 2022-K060), the requirement for written informed consent was waived as the study involved retrospective research.

NCIO. NCIO was utilized in patients with clinical III stage (due to a larger tumor size or invasion of surrounding tissue), or II stage (due to a special anatomical position or invasion of surrounding tissue), according to NCCN guidelines (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450) and assessed by a multidisciplinary discussion, as these patients did not have direct surgical indication. The following immunotherapeutic drugs were used: Pembrolizumab, tislelizumab, sintilimab, camrelizumab, nivolumab and toripalimab. The following chemotherapeutic drugs were used: Paclitaxel, paclitaxel liposomes, nab-paclitaxel, pemetrexed, gemcitabine, carboplatin and cisplatin. The detailed treatment regimens used were described in our previous study (10). All of patients used the full dose of drugs and patients with complications did not prolong the interval of administration.

Next-generation sequencing (NGS). NGS was performed before selection of treatment regimens. NGS is a routine test for lung adenocarcinoma or other non-squamous NSCLC (as they may have a relatively high likelihood of driver mutations) and it is a recommended test for lung squamous cell carcinoma (as it may have a relatively low likelihood of driver mutations), according to NCCN guidelines (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450). The genomic mutation tests were performed at the Department of Pathology of The Second Xiangya Hospital of Central South University (Hunan, China). The DNA libraries were performed using human genomic mutation test kits, eight genes panel (Langke; cat. no. LK101; Burning Rock) and 520 genes panel (OncoScreen; cat. no. LK291; Burning Rock). The libraries were quantified with a Qubit 3.0 fluorometer (Thermo Fisher Scientific, Inc.). The loading concentration of the final library was 1.3 pmol/l. The nucleotide length of sequencing was 150 bp, except 100 bp for Gene$^+$ kits and the direction of sequencing was paired end. The libraries were run on IIIumina (cat. no. 1057939; IIIumina Inc.).

Outcome and comorbidity index assessment. The primary endpoint was the pCR rate. The definition of pCR was the absence of viable tumor cells in primary and metastatic lymph nodes (14). The Charlson Comorbidity Index (CCI) consists of 19 items from different organ systems with weights ranging from 0-6 points and the overall score is the sum of each index score (15). The age-adjusted CCI (ACCI) was calculated as the score on the basis of the CCI. The additional score was added to the age group; 40 years was considered the zero rank of age. For each 10-year increase, the age score correspondingly increased by 1 point (15). The simplified comorbidity score (SCS) consists of seven items from different organ systems with weights ranging from 1-7; tobacco consumption (weight 7); diabetes mellitus (weight 5); renal insufficiency (weight 4); and respiratory, neoplastic and cardiovascular comorbidities and alcoholism (weight 1 for each item); and the overall score was the sum of each index score (16). The Cumulative Illness Rating Scale-Geriatric (CIRS-G) consists of 14 items from different organ systems with weights ranging from 0-4 (0, none; 1, mild; 2, moderate; 3, severe; and 4, extremely severe) and the overall score is the sum of each index score (17). The Adult Comorbidity Evaluation-27 (ACE-27) consists of 27 items from different organ systems with weights ranging from 0-3 (0, none; 1, mild; 2, moderate; and 3, severe) and the overall score is defined by the highest score for a single comorbidity, except for two or more Grade 2 comorbidities occurring in different organ systems, in this situation, the overall score was recorded as Grade 3 (18).

Statistical analysis. The two groups of continuous variables with a normal distribution and homogeneity of variance were represented by the mean ± standard deviation and were compared with an independent sample unpaired t test; otherwise, they were represented by the median (interquartile range; IQR) and were compared with the Mann-Whitney U test. Classification variables are represented as a number (%) and were analyzed using the chi-square test or Fisher's exact test. The OR and adjusted OR were calculated by univariate and multivariate logistic regression analyses, respectively. SPSS version 25.0 (IBM Corp.) was used and P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. The present study enrolled 101 eligible NSCLC patients. There was no significant difference in clinicopathological characteristics at baseline between the comorbidity and noncomorbidity groups (Table I).

Comorbidities or comorbidity indices associated with pCR. The associations between comorbidities or comorbidity indices and pCR rates were compared (Table II). In terms of comorbidities in several main organ systems, hypertension, vascular disease and cardiovascular disease were all significantly associated with a reduction in the pCR rate (all P<0.05). Cardiac disease alone (23.08 vs. 50.0%; P=0.069) and peripheral vascular disease alone (26.32% vs. 51.22%; P=0.050) displayed marginally significant associations with the pCR rate.

In terms of comorbidity indices, CIRS-G ≥2, CIRS-G ≥3, CIRS-G ≥4 and ACE-27 ≥1 were all significantly associated with a reduction in the pCR rate (all P<0.05). However, neither the CCI/ACCI nor the SCS was significantly associated with the pCR rate.

Clinicopathological factors associated with comorbidities or comorbidity indices. The relationships between clinicopathological factors and the aforementioned significant comorbidities or comorbidity indices were analyzed (Tables III and IV). Hypertension was significantly associated with higher serum alanine aminotransferase (ALT) levels, peripheral blood total T-cell counts, $CD4^+$ T-cell counts and $CD4^+$ T-cell rates (all P<0.05). Vascular disease was significantly associated with older age and a higher white blood cell (WBC) count (all P<0.05). Cardiovascular disease was significantly associated with a higher incidence index of smoking (P=0.042), a trend toward a higher WBC count ($7.83x10^9$/l vs. $6.75x10^9$/l; P=0.079) and a trend toward lower PD-L1 expression levels (75.76 vs. 91.38%; P=0.083).

In terms of comorbidity indices, a higher smoking index was significantly associated with CIRS-G ≥2/3/4 as well as ACE-27 ≥1 (all P<0.05). A CIRS-G score ≥2 was significantly associated with a history of smoking and serum ALT and aspartate aminotransferase (AST) levels (all P<0.05). A CIRS-G score ≥3 was significantly associated with lower PD-L1 expression levels (P=0.047). A CIRS-G score ≥4 was significantly associated with older age and a history of smoking, the peripheral blood $CD4^+$ T-cell count and a high serum creatinine level (all P<0.05). An ACE-27 score ≥1 was significantly associated with a history of smoking and a higher ALT level (P<0.05).

Univariate and multivariate logistic regression analyses. For the above significant comorbidities or comorbidity indices associated with pCR, the present study further tested the significance of their OR values via univariate logistic regression analysis. It also chose peripheral vascular disease for univariate logistic analysis as it had marginal significance (P=0.050). Peripheral vascular disease did not significantly differ (P=0.057), but hypertension [OR=0.321 (95% CI 0.110-0.937); P=0.038], vascular disease [OR=0.275 (95% CI 0.111-0.677); P=0.005], cardiovascular disease [OR=0.272 (95% CI 0.114-0.646); P=0.003], CIRS-G ≥2 [OR=0.360 (95% CI 0.154-0.840); P=0.018], CIRS-G ≥3 [OR=0.404 (95% CI 0.179-0.912); P=0.029], CIRS-G ≥4 [OR=0.293 (95% CI 0.105-0.817); P=0.019] and ACE-27 ≥2 [OR=0.427 (95% CI 0.192-0.950); P=0.037] were significantly associated with pCR (Table V). CIRS-G ≥2, CIRS-G ≥3, CIRS-G ≥4, ACE-27 ≥2, hypertension, vascular disease and cardiovascular disease were chosen for the multivariate logistic regression analysis model, as they were significant according to univariate logistic analysis. Finally, only cardiovascular disease was an independent risk factor for pCR according to multivariate logistic regression analysis [adjusted OR=0.272 (95% CI 0.114-0.646); P=0.003; Table V].

Discussion

Comorbidities increase the mortality risk of NSCLC patients. A study of 10,378 NSCLC patients showed that cardiovascular disease independently increased mortality risk by 30%; diabetes, cerebrovascular disorders and chronic obstructive pulmonary disease (COPD) each independently increased mortality risk by 20%; and patients with one or more comorbidities independently increased mortality risks by 12 and 27%, respectively (11). Other studies have shown that tuberculosis increases the mortality risk of NSCLC patients by 30-136% (19,20). Comorbidities are commonly involved in immune checkpoint inhibitor (ICI) therapy and have a negative impact on treatment efficacy. In a study of 3,326 cancer patients treated with ICIs, the incidence of hypertension, diabetes mellitus, history of acute coronary syndrome and history of stroke were 37, 28, 17 and 7%, respectively (21). Hypertension, history of stroke and history of heart failure independently increase the mortality risk of cancer patients receiving ICI treatment and beta-blocker use increases the mortality risk of lung cancer patients by 39% (21).

However, ~60% of patients with comorbidities or poor performance status are excluded from clinical trials (22), which has led to a poor understanding of the impact of these conditions on immunotherapy efficacy. To the best of our knowledge, the present study is the first to report which comorbidities or comorbidity indices influence the PR of NCIO in patients with NSCLC. It showed that hypertension, vascular disease, cardiovascular disease, CIRS-G ≥2/3/4 and ACE-27 ≥1 were all significantly associated with pCR and each of them reduced the incidence of pCR by 60-70%. Cardiovascular disease was the strongest and only independent factor and the pCR rate was reduced by 73.8% (adjusted OR=0.272). However, the present study did not find a significant correlation between respiratory

Table I. Clinicopathological factors between comorbidity and non-comorbidity.

Variable	Comorbidity n=63 (%)	Non-comorbidity n=38 (%)	P-value
Sex			
Male, n (%)	57 (61.29)	36 (38.71)	
Female, n (%)	6 (75.00)	2 (25.00)	0.698
Age, years	58.52±7.80	60.87±6.21	0.118
Smoking history			
No, n (%)	19 (52.78)	17 (47.22)	
Yes, n (%)	44 (67.69)	21 (32.31)	0.138
Differentiation[a]			
Well, n (%)	5 (55.56)	4 (44.44)	
Moderate, n (%)	14 (56.00)	11 (44.00)	
Moderate-poor/poor/undifferentiated, n (%)	39 (63.93)	22 (36.07)	0.742
Histology[b]			
Squamous carcinoma, n (%)	42 (60.00)	28 (40.00)	
Non-squamous carcinoma, n (%)	17 (62.96)	10 (37.04)	0.789
Clinical T stage			
T1, n (%)	7 (58.33)	5 (41.67)	
T2, n (%)	26 (66.67)	13 (33.33)	
T3, n (%)	13 (61.90)	8 (38.10)	
T4, n (%)	17 (58.62)	12 (41.38)	0.904
Clinical N stage			
N0, n (%)	8 (61.54)	5 (38.46)	
N1-3, n (%)	55 (62.50)	33 (37.50)	1.000
Clinical TNM stage			
IIB-IIIA, n (%)	40 (62.50)	24 (37.50)	
IIIB-IIIC, n (%)	23 (62.16)	14 (37.84)	0.973
PD-L1 expression median (IQR)[c]			
<1%	9 (69.23)	4 (30.77)	
1-49%	29 (60.42)	19 (39.58)	
≥50%	20 (66.67)	10 (33.33)	0.775
Treatment cycles			
<3 cycles, n (%)	24 (63.16)	14 (36.84)	
≥3 cycles, n (%)	39 (61.90)	24 (38.10)	0.900
Immunotherapy regimens[d]			
Pembrolizumab, n (%)	22 (59.46)	15 (40.54)	
Terezumab, n (%)	20 (66.67)	10 (33.33)	
Schindelimab, n (%)	11 (61.11)	7 (38.89)	
Others, n (%)	10 (66.67)	5 (33.33)	0.922
Chemotherapy regimens			
Albumin-bound paclitaxel/platinum, n (%)	41 (62.12)	25 (37.88)	
Pemetrexed/platinum, n (%)	15 (62.50)	9 (37.50)	
Others, n (%)	7 (63.64)	4 (36.36)	0.995

[a]Six cases were excluded due to no exact differentiation grade; [b]two uncategorized and two adenosquamous cases were not entered into the calculation; [c]PD-L1 data were not available in 10 cases; [d]exact name of PD1 inhibitor was not known in one case. PD-L1, programmed death receptor-1 ligand; IQR, interquartile range.

comorbidities and pCR. Notably, the results of the present study showed a greater pCR in patients with COPD than in those without COPD (58.33 vs. 48.78%). Previous studies have shown that COPD increases the treatment efficacy of palliative ICI therapy in patients with NSCLC (23,24), which is consistent with the present study.

Table II. Comparisons of comorbidities and comorbidity indices between pCR and non-pCR groups.

A, Comorbidities distribution

Variable	pCR n=47 (%)	non-pCR n=54 (%)	P-value
Cardiac disease[a]			
No, n (%)	44 (50.00)	44 (50.00)	
Yes, n (%)	3 (23.08)	10 (76.92)	0.069
Hypertension			
No, n (%)	42 (51.85)	39 (48.15)	
Yes, n (%)	5 (25.00)	15 (75.00)	0.031
Peripheral vascular disease			
No, n (%)	42 (51.22)	40 (48.78)	
Yes, n (%)	5 (26.32)	14 (73.68)	0.050
Sum of vascular disease[b]			
No, n (%)	38 (56.72)	29 (43.28)	
Yes, n (%)	9 (26.47)	25 (73.53)	0.004
Sum of cardiovascular disease[c]			
No, n (%)	37 (57.81)	27 (42.19)	
Yes, n (%)	10 (27.03)	27 (62.97)	0.003
Diabetes			
No, n (%)	42 (46.15)	49 (53.85)	
Yes, n (%)	5 (50.00)	5 (50.00)	1.000
COPD			
No, n (%)	40 (48.78)	42 (51.22)	
Yes, n (%)	7 (58.33)	12 (41.67)	0.347
Respiratory system[d]			
No, n (%)	38 (48.72)	40 (51.28)	
Yes, n (%)	9 (39.13)	14 (60.87)	0.418
Digestive system[e]			
No, n (%)	32 (45.71)	38 (54.29)	
Yes, n (%)	15 (48.39)	16 (51.61)	0.804
Genitourinary system[f]			
No, n (%)	36 (46.75)	41 (53.25)	
Yes, n (%)	11 (45.83)	13 (54.17)	0.937
BMI[g]			
18.5-23.9, n (%)	24 (48.98)	25 (51.02)	
24-27.9, n (%)	16 (43.24)	21 (56.76)	
≥28, n (%)	6 (46.15)	7 (53.85)	0.870

B, Comorbidity indices

Variable	pCR n=47 (%)	non-pCR n=54 (%)	P-value
CCI			
0	30 (50.00)	30 (50.00)	
≥1	17 (41.46)	24 (58.54)	0.398
0-1	41 (47.13)	46 (52.87)	
≥2	6 (42.86)	8 (57.14)	0.766
0-2	45 (46.39)	52 (53.61)	
≥3	2 (50.00)	2 (50.00)	1.000
ACCI			
0-1	13 (37.14)	22 (62.86)	
≥2	34 (51.52)	32 (48.48)	0.168
0-2	35 (49.30)	36 (50.70)	
≥3	10 (35.71)	18 (64.29)	0.222
0-3	43 (47.78)	47 (52.22)	
≥4	4 (36.36)	7 (63.64)	0.474
SCS			
0-6	15 (44.12)	19 (55.88)	
≥7	32 (47.76)	35 (52.24)	0.729
0-7	30 (52.63)	27 (47.37)	
≥8	17 (38.64)	27 (61.36)	0.162
0-8	37 (48.68)	39 (51.32)	
≥9	10 (40.00)	15 (60.00)	0.450
CIRS-G			
0-1	22 (62.86)	13 (37.14)	
≥2	25 (37.88)	41 (62.12)	0.017
0-2	32 (56.14)	25 (43.86)	
≥3	15 (34.09)	29 (65.91)	0.028
0-3	41 (53.25)	36 (46.75)	
≥4	6 (25.00)	18 (75.00)	0.015
ACE-27			
0	30 (58.82)	21 (41.18)	
≥1	17 (34.00)	33 (66.00)	0.012
0-1	40 (47.06)	45 (52.94)	
≥2	7 (43.75)	9 (56.25)	0.808

[a]Myocardial infarction, angina or coronary artery disease, congestive heart failure, arrhythmia and valvular disease; [b]hypertension, peripheral vascular disease and cerebrovascular disease; [c]cardiac disease and vascular disease; [d]chronic obstruction pulmonary disease, asthma, restrictive lung disease, history of active pulmonary tuberculosis and sleep apnea syndrome; [e]digestive ulcer, chronic hepatitis, cirrhosis, fatty liver and drug liver injury (aminotransferase/total bilirubin/conjugated bilirubin/alkaline phosphatase ≥2 times the upper limit of the normal value); [f]chronic renal insufficient with creatinine >177 mmol/l, nephrotic syndrome, renal calculus, uronephrosis, hyperplasia of prostate gland and genitourinary tract infection; [g]two patients with BMI<18.5 were not included. pCR, pathologic complete response; COPD, chronic obstructive pulmonary disease; BMI, body mass index (weight divided by height^2); CCI, Charlson comorbidity index; ACCI, age-adjusted Charlson comorbidity index; SCS, simplified comorbidity score; CIRS-G, cumulative illness rating scale; ACE-27, adult comorbidity evaluation-27.

Table III. Associations of comorbidities or comorbidity indices with clinicopathological factors.

A, Hypertension and vascular disease

Variable	Hypertension n=20 (%)	Non-hypertension n=81 (%)	P-value	Vascular disease n=34 (%)	Non-vascular disease n=67 (%)	P-value
Sex						
Male, n (%)	17 (85.00)	76 (93.83)		30 (88.24)	63 (94.03)	
Female, n (%)	3 (15.00)	5 (6.17)	0.397	4 (11.76)	4 (5.97)	0.529
Age, years (IQR)	61.00 (57.00-65.75)	58.00 (54.00-65.00)	0.150	61.00 (57.00-67.00)	58.00 (54.00-63.00)	0.038
Smoking history						
No, n (%)	7 (35.00)	29 (35.80)		9 (26.47)	27 (40.30)	
Yes, n (%)	13 (65.00)	52 (64.20)	0.947	25 (73.53)	40 (59.70)	0.170
Smoking index[a]	700 (0-1,150)	600 (0-800)	0.441	775 (225-1,000)	400 (0-800)	0.024
Histology type[b]						
Squamous cell carcinoma, n (%)	12 (63.16)	58 (74.36)		22 (66.67)	48 (75.00)	
Nonsquamous cell carcinoma, n (%)	7 (36.84)	20 (25.64)	0.329	11 (33.33)	16 (25.00)	0.386
cTNM stage						
IIB-IIIA, n (%)	16 (80.00)	47 (58.02)		22 (64.71)	41 (61.19)	
IIIB-IIIC, n (%)	4 (20.00)	34 (41.98)	0.069	12 (35.29)	26 (38.81)	0.731
PD-L1 expression, n (%)[c]						
-	2 (10.00)	11 (15.28)		6 (20.00)	7 (11.11)	
+	17 (90.00)	61 (84.72)	0.875	24 (80.00)	5 (88.89)	0.439
Median (IQR)	15.00 (2.00-70.00)	17.50 (1.00-60.00)	0.456	12.50 (1.00-70.00)	20.00 (2.00-60.00)	0.699
WBC count, $x10^9$/l (IQR)	7.46 (5.89-8.38)	6.85 (5.88-8.26)	0.443	7.84 (6.29-89.98)	6.74 (5.72-8.10)	0.044
Hemoglobin, g/l	144.40±16.54	139.68±15.08	0.250	144.44±16.89	138.99±14.49	0.094
Platelet count, $x10^9$/l (IQR)	245.00 (156.25-278.25)	244.00 (207.50-303.00)	0.221	250.50 (202.50-276.75)	243.00 (207.00-307.00)	0.433
Neutrophil count, $x10^9$/l	5.08±1.43	5.10±2.4	0.995	5.27±1.55	4.98±2.59	0.561
Neutrophil rate, %	66.95±7.08	66.95±7.47	0.980	67.56±7.22	66.69±7.42	0.576
Lymphocyte count, $x10^9$/l	1.84±0.55	1.66±0.46	0.129	1.78±0.52	1.64±0.46	0.172
Lymphocyte rate, %	24.54±6.05	23.53±6.76	0.535	23.67±6.44	23.74±6.69	0.958
Monocyte count, $x10^9$/l, median (IQR)	0.43 (0.29-0.51)	0.39 (0.32-0.50)	0.733	0.41 (0.31-0.50)	0.39 (0.32-0.51)	0.765
Monocyte rate, % (IQR)	5.50 (4.75-6.08)	5.50 (4.75-6.75)	0.915	5.25 (4.65-6.00)	5.70 (4.80-7.20)	0.296
Creatinine, μmol/l	73.2±14.5	73.6±14.6	0.897	71.11±14.22	74.77±1.55	0.230
ALT, U/l, median (IQR)	28.9 (21.23-36.43)	20.85 (14.40-28.70)	0.021	25.85 (19.98-34.03)	19.65 (14.60-29.13)	0.082
AST, U/l, median (IQR)	21.85 (17.88-23.43)	20 (17.1-24.00)	0.786	21.25 (17.70-23.28)	19.85 (17.03-24.00)	0.977
T cell count per μl	1,485.33±485.65	1,156.57±390.41	0.043	1403.50±568.88	1156.41±339.01	0.099
T cell rate, %, (IQR)	71.00 (67.50-76.50)	67.63 (62.50-75.25)	0.193	70 (66.25-76.00)	68 (64-75)	0.542
$CD4^+$ T cell count per μl	985.89±350.62	644.07±213.05	0.001	905.50 (539.25-1064.25)	669 (482.00-837.00)	0.094

Table III. Continued.

A, Hypertension and vascular disease

Variable	Hypertension n=20 (%)	Non-hypertension n=81 (%)	P-value	Vascular disease n=34 (%)	Non-vascular disease n=67 (%)	P-value
$CD4^+$ T cell rate, (%)	46 (44-48)	37 (32-46)	0.030	42.92±7.17	39.12±9.45	0.222
$CD8^+$ T cell count per μl (IQR)	484.00 (367.00-632.50)	397.00 (295.00-560.25)	0.309	460.50 (325.75-652.75)	397 (298-558)	0.594
$CD8^+$ T cell rate, % (IQR)	25.00 (19.50-29.50)	26.00 (20.00-32.00)	0.733	23.00 (19.25-29.75)	26.50 (20.00-31.25)	0.701
$CD4^+/CD8^+$ T cell	1.98±0.52	1.64±0.74	0.206	1.86±0.61	1.65±0.74	0.398
B cell count, per μl (IQR)	201.00 (95.00-287.00)	147.50 (102.50-214.00)	0.351	186 (87.50-264.00)	148 (104.00-235.00)	0.784
B cell rate (%)	9.89±4.57	10.02±3.87	0.934	9.29±4.11	10.29±3.95	0.474
NK count, per μl	289.00 (221.00-462.00)	304.50 (223.50-386.00)	0.677	362.5 (248.5-428.00)	293 (207.00-375.00)	0.280
NK cell rate, % (IQR)	15.00 (13.00-21.00)	20.00 (14.00-24.00)	0.307	16.5 (13.25-24.25)	19 (14.00-23.50)	0.802

B, Cardiovascular disease and CIRS-G

Variable	Cardiovascular disease n=37 (%)	Non-cardiovascular disease n= 64 (%)	P-value	CIRS-G ≥2 n=66 (%)	CIRS-G 0-1 n=35 (%)	P-value
Sex						
Male, n (%)	33 (89.19)	60 (93.75)		61 (92.42)	32 (91.43)	
Female, n (%)	4 (10.81)	4 (6.25)	0.663	5 (7.58)	3 (8.57)	1.000
Age, years (IQR)	61.00 (56.00-67.00)	58.00 (54.25-63.00)	0.064	58.73±7.66	60.69±6.48	0.201
Smoking history						
No, n (%)	10 (27.03)	26 (40.63)		17 (25.78)	19 (54.29)	
Yes, n (%)	27 (72.97)	38 (59.37)	0.169	49 (74.22)	16 (45.71)	0.004
Smoking index[a]	600 (0-1000)	400 (0-800)	0.042	600 (0-900)	0 (0-600)	0.019
Histology type[b]						
Squamous cell carcinoma, n (%)	24 (68.57)	46 (74.19)		46 (73.02)	24 (70.59)	
Nonsquamous cell carcinoma, n (%)	11 (31.43)	16 (25.81)	0.553	17 (26.98)	10 (29.41)	0.799
cTNM stage						
IIB-IIIA, n (%)	22 (59.46)	41 (64.06)		41 (62.12)	22 (62.86)	
IIIB-IIIC, n (%)	15 (40.54)	23 (35.94)	0.645	25 (37.88)	13 (37.14)	0.942
PD-L1 expression, n (%)[c]						
-	8 (24.24)	5 (8.62)		10 (15.15)	3 (8.57)	
+	25 (75.76)	53 (91.38)	0.083	52 (84.85)	26 (91.43)	0.679
Median (IQR)	10.00 (0.50-65.00)	30.00 (2.00-61.25)	0.208	15.00 (1.00-60.00)	20.00 (2.00-67.50)	0.672
WBC count, $x10^9/l$	7.83 (6.06-8.95)	6.75 (5.76-8.05)	0.079	6.98 (6.06-8.49)	7.00 (5.53-8.10)	0.275

Table III. Continued.

B, Cardiovascular disease and CIRS-G

Variable	Cardiovascular disease n=37 (%)	Non-cardiovascular disease n= 64 (%)	P-value	CIRS-G ≥2 n=66 (%)	CIRS-G 0-1 n=35 (%)	P-value
Hemoglobin, g/l	144.46±16.68	138.72±14.45	0.072	142.11±16.81	138.40±12.44	0.254
Platelet count, x10^9/l	250.00 (197.00-278.50)	243.00 (207.00-305.00)	0.420	245.00 (205.50-283.00)	244.00 (212.00-320.00)	0.394
Neutrophil count, x10^9/l	5.19±1.54	5.03±2.65	0.738	4.71 (3.74-5.86)	4.58 (3.54-5.45)	0.454
Neutrophil rate (%)	67.40±7.24	66.69±7.47	0.641	67.04±6.89	66.87±8.19	0.908
Lymphocyte count, x10^9/l	1.77±0.51	1.65±0.46	0.220	1.74±0.47	1.59±0.48	0.122
Lymphocyte rate (%)	23.81±6.37	23.69±6.80	0.929	23.70 (20.30-28.38)	22.20 (16.60-28.30)	0.422
Monocyte count, x10^9/l	0.41 (0.31-0.50)	0.39 (0.32-0.52)	0.992	0.40 (0.30-0.49)	0.40 (0.34-0.52)	0.365
Monocyte rate (%)	5.2 (4.6-6.0)	5.75 (4.83-7.18)	0.220	5.25 (4.50-6.33)	5.80 (5.10-7.20)	0.113
Creatinine μmol/l	72.85±16.03	73.94±13.61	0.716	74.77±14.78	71.21±13.78	0.241
ALT, U/l (IQR)	24.90 (19.95-33.10)	19.65 (14.18 (30.45)	0.114	25.15 (18.33-33.33)	16.80 (13.50-24.90)	0.007
AST, U/l (IQR)	21.30 (17.95-23.35)	19.75 (17.03-24.00)	0.856	21.75 (18.10-24.58)	18.90 (15.98-22.13)	0.039
T cell count, per/μl (IQR)	1418.00 (866.00-1775.50)	1198.50 (999.75-1421.25)	0.503	1287.46±463.05	1144.40±371.76	0.320
T cell rate (%)	69.00 (63.31-7)	68.50 (64.00-75.25)	0.952	68.62±8.35	68.00±9.01	0.827
$CD4^+$ T cell count, per/μl (IQR)	890.50 (500.00-1060.50)	677.50 (509.00-840.25)	0.283	842.50 (520.75-958.50)	651.00 (445.00-744.00)	0.112
$CD4^+$ T cell rate (%)	41.31±8.98	39.76±9.00	0.386	44.00 (35.51-47.00)	36.00 (31.00-46.00)	0.131
$CD8^+$ T cell count, per/μl (IQR)	437.00 (307.00-632.50)	401.50 (329.50-560.25)	0.870	397.00 (324.75-576.50)	446.00 (298.00-567.00)	0.862
$CD8^+$ T cell rate (%)	25.00 (19.50-29.50)	27.00 (20.00-32.00)	0.675	23.11 (19.50-28.50)	28.00 (21.00-34.00)	0.170
$CD4^+$/$CD8^+$ T cell	1.79±10.37	1.68±0.74	0.673	1.85±0.73	1.50±0.63	0.136
B cell count, per/μl (IQR)	172 (86.5-263.00)	149.50 (122.75-237.50)	0.917	173.00 (99.50-267.25)	147.00 (129.00-162.00)	0.299
B cell rate, %	9.19±3.96	10.37±4.00	0.294	10.26±4.24	9.53±3.58	0.582
NK count, per/μl (IQR)	385 (259-451)	288.50 (200.75-372.00)	0.140	291.00 (187.50-409.50)	329.00 (237.00-375.00)	0.697
NK cell rate, per/μl (IQR)	18.00 (13.50-27.02)	18 (14-22)	0.795	16.00 (13.00-24.50)	20.00 (16.00-22.00)	0.370

C, CIRS-G

Variable	CIRS-G ≥3 n=44 (%)	CIRS-G 0-2 n=57 (%)	P-value	CIRS-G ≥4 n=24 (%)	CIRS-G 0-3 n=77 (%)	P-value
Sex						
Male, n (%)	40 (90.91)	53 (92.98)		24 (100.00)	69 (89.61)	
Female, n (%)	4 (9.09)	4 (7.02)		0 (0.00)	8 (10.39)	0.225
Age, years (IQR)	61.00 (54.25-67.00)	58.00 (55.00-63.00)	0.096	62.29±7.70	58.51±6.98	0.026

Table III. Continued.

C, CIRS-G

Variable	CIRS-G ≥3 n=44 (%)	CIRS-G 0-2 n=57 (%)	P-value	CIRS-G ≥4 n=24 (%)	CIRS-G 0-3 n=77 (%)	P-value
Smoking history						
No, n (%)	10 (22.73)	26 (45.61)		3 (12.50)	33 (42.86)	
Yes, n (%)	34 (77.27)	31 (54.39)	0.017	21 (87.50)	44 (57.14)	0.007
Smoking index[a]	675 (70-1000)	300 (0-750)	0.010	700 (450-1150)	400 (0-800)	0.013
Histology type[b]						
Squamous cell carcinoma, n (%)	30 (71.43)	40 (72.73)		19 (79.17)	51 (69.86)	
Nonsquamous cell carcinoma, n (%)	12 (28.57)	15 (27.27)	0.888	5 (20.83)	22 (30.14)	0.378
cTNM stage						
IIB-IIIA, n (%)	28 (63.64)	35 (61.40)		15 (62.50)	48 (62.34)	
IIIB-IIIC, n (%)	16 (36.36)	22 (38.60)	0.818	9 (37.50)	29 (37.66)	0.989
PD-L1 expression (%)[c]						
-, n (%)	9 (22.50)	4 (7.84)		3 (14.29)	10 (14.29)	
+, n (%)	31 (77.50)	47 (92.16)	0.047	18 (85.71)	60 (85.71)	1.000
Median (IQR)	12.50 (1.00-60.00)	30.00 (2.00-65.00)	0.275	15.00 (1.00-60.00)	22.50 (1.75-66.25)	0.567
WBC count x10^9/l	7.46 (6.14-8.74)	6.61 (5.64-8.12)	0.128	7.72 (6.12-9.01)	6.97 (5.72-8.10)	0.164
Hemoglobin (g/l)	143.73±16.34	138.58±14.51	0.097	146.00 (134.50-161.25)	142.00 (130.00-149.00)	0.094
Platelet count x10^9/l, median (IQR)	246.50 (207.25-274.75)	243.00 (207.00-320.50)	0.288	258.00 (209.75-273.75)	243.00 (207.00-314.00)	0.678
Neutrophil count, x10^9/l	5.06±1.40	5.09±2.81	0.950	5.34 (3.83-6.12)	4.57 (3.68-5.53)	0.154
Neutrophil rate, %	67.20±7.09	66.81±7.57	0.792	67.95±6.64	66.69±7.55	0.473
Lymphocyte count, x10^9/l	1.75±0.48	1.64±0.48	0.238	1.75±0.44	1.67±0.49	0.465
Lymphocyte rate, %	23.97±6.08	23.52±6.99	0.735	23.67±5.77	23.73±6.84	0.966
Monocyte count, x10^9/l, median (IQR)	0.41 (0.29-0.49)	0.39 (0.33-0.53)	0.556	0.42 (0.35-0.49)	0.39 (0.31-0.52)	0.658
Monocyte rate, % (IQR)	5.15 (4.50-6.08)	5.80 (4.90-7.15)	0.099	5.25 (4.50-6.25)	5.60 (4.85-6.75)	0.555
Creatinine μmol/l	74.36±15.74	72.91±13.52	0.620	78.98±15.13	71.84±13.93	0.034
ALT, U/l (IQR)	24.65 (18.58-32.65)	20.35 (13.93-27.80)	0.135	24.65 (15.80-32.65)	22.30 (14.85-31.28)	0.594
AST, U/l (IQR)	21.45 (18.13-23.43)	19.40 (16.58-24.00)	0.460	21.05 (18.13-23.15)	20.30 (16.80-24.00)	0.891
T cell count per μl, median (IQR)	1,418.00 (868.00-1,527.00)	1,152.50 (921.25-1344.25)	0.214	1,466.20±413.97	1,198.06±428.40	0.198
T cell rate, % (IQR)	68.50 (59.45-75.75)	69.00 (65.00-76.00)	0.577	66.45±6.05	68.74±8.90	0.551
$CD4^+$ T cell count per μl median (IQR)	889 (471-1068)	677.50 (525.25-836.50)	0.299	996.80±307.83	682.68±263.97	0.020
$CD4^+$ T cell rate, (%)	39.76±10.01	40.59±8.31	0.777	43.53±7.66	39.68±9.09	0.336
$CD8^+$ T cell count per μl, median (IQR)	437 (317-673)	401.50 (308.50-552.25)	0.564	437.00 (343.00-632.50)	401.50 (312.25-560.25)	0.659
$CD8^+$ T cell rate, %	22.06 (20.00-29.75)	27 (19.25-31.25)	0.599	20.06 (19.75-25.58)	27 (19.75-30.50)	0.297

Table III. Continued.

C, CIRS-G

Variable	CIRS-G ≥3 n=44 (%)	CIRS-G 0-2 n=57 (%)	P-value	CIRS-G ≥4 n=24 (%)	CIRS-G 0-3 n=77 (%)	P-value
$CD4^+/CD8^+$ T cell	1.74±0.73	1.70±0.71	0.856	2.03±0.57	1.68±0.72	0.246
B cell count per μl, median (IQR)	172 (93-265)	149.50 (114.75-228.00)	0.829	216.00±102.91	165.82±75.27	0.191
B cell rate (%)	9.49±4.14	10.32±3.91	0.528	10.49±3.65	9.90±4.07	0.744
NK count per μl median (IQR)	385 (207-468)	288.50 (230.50-36.25)	0.166	434.00 (292.00-583.00)	291.00 (223.50-377.50)	0.081
NK cell rate, % (IQR)	19 (13.00-28.18)	17.50 (14.13-22.00)	0.709	23.50 (17.00-26.46)	17.00 (13.75-22.00)	0.184

[a]Smoking index=(number of cigarettes/day) *years; [b]Two uncategorized and two adenosquamous cases were not entered into the calculation; [c]PD-L1 data were not available in 10 cases; PD-L1, programmed death receptor-1 ligand; IQR, interquartile range; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIRS-G, Cumulative Illness Rating Scale-Geriatric.

The present study explored the clinicopathological factors or mechanisms that were influenced by comorbidities or comorbidity indices. Hypertension was significantly associated with a higher peripheral blood total T-cell count, $CD4^+$ T-cell count/rate and ALT level. Our previous study found that patients with pCR had an clearly lower peripheral blood $CD4^+$ T-cell count/rate at baseline than non-pCR patients and a reduced peripheral blood $CD4^+$ T-cell count/rate increased the incidence of pCR by 5.20 and 5.87 times, respectively (10). Currently, the detailed underlying mechanism is unclear, but some studies have shown that this condition is indeed associated with improved clinical outcomes, which may be related to the recruitment of peripheral blood immune cells to the tumor microenvironment (TME) after immunotherapy. A study of ICI treatment for advanced melanoma showed that early loss of peripheral blood $CD4^+$ and $CD8^+$ T cells was associated with improved OS (2-year OS: 77.8 vs. 50.6%) and PFS (not reached vs. 3 months) (25). Patients with early loss of $CD4^+$ and $CD8^+$ cells in peripheral blood had more $CD4^+$ and $CD8^+$ cells in tumor tissue (25). Another study of ICI treatment for advanced NSCLC was consistent with these results, with fewer baseline circulating $CD8^+$ T cells associated with lasting clinical benefit (accuracy=70%) (26). The results of the present study were consistent with those of the aforementioned two studies (25,26). Elevated ALT levels may predict poor treatment response to chemotherapy or prognosis. A study of esophageal cancer patients treated with neoadjuvant chemotherapy showed that, compared with the non-ORR group, the ORR group had lower baseline levels of ALT (27). In a study of surgical colorectal cancer patients treated with or without adjuvant/neoadjuvant chemotherapy, a higher ALT level was significantly associated with poorer OS (28). Currently, there are no reports on the association between aminotransferase (ALT or AST or both) levels and the efficacy of ICIs in treating cancer. The present study hypothesized that increased aminotransferase (ALT or AST or both) levels may be a new biomarker for predicting PR to NCIO in patients with NSCLC.

The present study showed that vascular disease is associated with older age and a higher WBC count. Advanced age may be associated with immunosenescence, which is a result of a decrease in naive T cells and T-cell receptors and changes in regulatory T-cell populations (29). Most pooled analyses have shown that ICI treatment may be less effective in older patients (30,31), although a few pooled studies have shown no relationship between age and the efficacy of ICI treatment (32,33). An elevated WBC count has a negative impact on the outcome of ICI therapy. In a study of nivolumab treatment for NSCLC, a lower WBC or neutrophil count at baseline was associated with an improved disease control rate (56 vs. 18%; P=0.01) and OS (17.7 vs. 3 months; P=0.004) (34). In another study of advanced NSCLC patients treated with ICIs, higher baseline WBC and neutrophil counts were found to be independent factors for poor OS (35). Blood WBC or neutrophil counts are directly related to the neutrophil count in the TME and can inhibit the secretion of cytotoxic T cells or proinflammatory cytokines to promote tumor growth, invasion, metastasis and drug resistance (36).

The present study also showed that cardiovascular disease is associated with a higher smoking index and a trend toward a higher WBC count but lower PD-L1 expression level. Although

Table IV. ACE-7 associations of comorbidities or comorbidity indices with clinicopathological factors.

Variable	ACE-27≥1 n=50 (%)	ACE-27=0 n=51 (%)	P-value
Sex			
Male, n (%)	46 (92.00)	47 (92.16)	
Female, n (%)	4 (8.00)	4 (7.84)	
Age, years	59.74±7.59	59.08±7.06	0.651
Smoking history			
No, n (%)	12 (24.00)	24 (47.06)	
Yes, n (%)	38 (76.00)	27 (52.94)	0.016
Smoking index[a]	600 (45-1,000)	200 (0-650)	0.012
Histology type[b]			
Squamous cell carcinoma, n (%)	33 (68.75)	37 (75.51)	
Nonsquamous cell carcinoma, n (%)	15 (31.25)	12 (24.49)	0.458
cTNM stage			
IIB-IIIA, n (%)	34 (68.00)	29 (56.86)	
IIIB-IIIC, n (%)	16 (32.00)	22 (43.14)	0.248
PD-L1 expression, n (%)[c]			
-	8 (17.78)	5 (10.87)	
+	37 (82.22)	41 (89.13)	0.346
Median (IQR)	15.00 (1.00-70.00)	17.50 (1.75-60.00)	0.699
WBC count x10^9/l, median (IQR)	7.23 (6.06-8.94)	6.74 (5.70-7.90)	0.107
Hemoglobin, g/l	143.58±16.89	138.12±13.57	0.076
Platelet count x10^9/l, median (IQR)	248.50 (210.75-277.50)	241.00 (201.00-307.00)	0.729
Neutrophil count x10^9/l	5.33±2.43	4.83±2.15	0.284
Neutrophil rate, %	67.74±7.12	66.24±7.52	0.308
Lymphocyte count x10^9/l	1.77±0.56	1.61±0.38	0.106
Lymphocyte rate %	23.56±6.25	23.87±6.95	0.811
Monocyte count x10^9/l, median (IQR)	0.41 (0.30-0.50)	0.39 (0.32-0.50)	0.911
Monocyte rate, %	5.25 (4.50-6.15)	5.80 (4.90-7.20)	0.217
Creatinine μmol/l	76.19±14.45	72.90±14.61	0.655
ALT U/l, median (IQR)	25.15 (18.33-34.85)	19.55 (13.78-26.73)	0.028
AST U/l, median (IQR)	21.10 (17.80-24.58)	19.40 (16.80-23.78)	0.542
T cell count per μl	1221.94±518.94	1239.74±370.06	0.901
T cell rate, %	67.63 (61.47-71.00)	71.00 (65.00-76.00)	0.265
$CD4^+$ T cell count per μl, median (IQR)	870 (473.75-1031.25)	680.00 (547.00-835.00)	0.392
$CD4^+$ T cell rate, (%)	41.38±7.54	39.43±9.89	0.502
$CD8^+$ T cell count per μl, median (IQR)	382.00 (302.75-518.50)	451.00 (340.00-657.000	0.284
$CD8^+$ T cell rate, %	23.00 (19.50-27.49)	28.00 (20.00-34.00)	0.146
$CD4^+$/$CD8^+$ T cell	1.84±0.55	1.63±0.80	0.330
B cell count per μl, median (IQR)	186.50 (97.25-281.50)	148.00 (104.00-200.00)	0.384
B cell rate (%)	11.03±4.38	9.22±3.54	0.156
NK count per μl, median (IQR)	316.50 (237.25-428.00)	297.00 (207.00-375.00)	0.416
NK cell rate, %	20.00 (14.00-15.30)	17.00 (13.00-22.00)	0.502

[a]Smoking index, [b]two uncategorised and adenosquamous cases were not entered into the calculation, [c]PD-L1 data were not available in 10 cases. ACE-27, adult comorbidity evaluation-27; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

smoking has been reported to be associated with improved clinical outcomes during immunotherapy (29,30,37), the present study revealed a higher smoking index or smoking history in patients with cardiovascular disease, a CIRS-G ≥2/3/4 and an ACE-27 ≥1. It found that the benefit in smokers was mainly observed in those treated with ICIs alone (30,37); however, several meta-analyses have shown that both nonsmokers and smokers can benefit from ICIs + chemotherapy (29,30,37). It appears that nonsmokers may benefit more from ICIs + chemotherapy than smokers (29,37) and this is more evident

Table V. Logistic regression results were associated with pCR.

Univariate logistic regression		
Variable	OR (95% CI)	P-value
CIRS-G (≥2 vs. 0-1)	0.360 (0.154-0.840)	0.018
CIRS-G (≥3 vs. 0-2)	0.404 (0.179-0.912)	0.029
CIRS-G (≥4 vs. 0-3)	0.293 (0.105-0.817)	0.019
ACE-27 (≥1 vs. 0)	0.427 (0.192-0.950)	0.037
Hypertension (Yes vs. No)	0.321 (0.110-0.937)	0.038
Peripheral vascular disease (Yes vs. No)	0.340 (0.112-1.031)	0.057
Sum of vascular disease (Yes vs. No)	0.275 (0.111-0.677)	0.005
Sum of cardiovascular disease (Yes vs. No)	0.272 (0.114-0.646)	0.003
Multivariate logistic regression		
Variable	OR (95% CI)	P-value
Sum of cardiovascular disease (Yes vs. No)	0.272 (0.114-0.646)	0.003

pCR, pathological complete response; OR, odds ratio; CI, confidence interval; CIRS-G, Cumulative Illness Rating Scale; ACE-27, Adult Comorbidity Evaluation-27.

for patients receiving pembrolizumab + chemotherapy (30). A high PD-L1 expression level was a positive and independent factor for pCR/MPR and increased the incidence of pCR and MPR by 9.66 and 5.35 times, respectively, in our previous study (10); moreover, this trend was also observed in the NADIM (6) and CheckMate 816 (7) trials of NCIO for NSCLC.

The CCI was first devised and verified to predict mortality risk in a cohort of 685 patients with breast cancer by Charlson *et al* (15) in 1987. This index has been widely used for various cancers (38). In lung cancer, it was shown to predict cancer-specific mortality and 3-year and 5-year survival in population-based cohort studies (38). According to a study of ICI treatment for advanced NSCLC, patients with a CCI <1 had a greater disease control rate (94.7 vs. 64.3%) and PFS (271.0 vs. 232.0 days) than patients with a CCI ≥1 (39). However, in the present study, a higher CCI or ACCI was not significantly associated with pCR. In another study of lung cancer chemotherapy, the CCI was also not associated with efficacy (40). The potential limitations of the CCI include that it does not take in hypertension, that some comorbidity ratings are insufficient (e.g., cardiovascular and pulmonary disease) and that some comorbidities (e.g., hematopoietic and psychiatric disorders) are ignored. The SCS was originally designed to predict the mortality risk of NSCLC patients (16). This was verified in several studies and a higher SCS was associated with shorter OS in patients with NSCLC (41,42). However, in a study of ICI treatment for advanced NSCLC, the presence of SCS did not predict treatment response or prognosis (39). In the present study, the SCS was not significantly associated with pCR, but patients with an SCS >8 had a trend toward a lower pCR rate than those with an SCS <8 (38.64 vs. 52.63%). The potential limitations of this index are that its items are not comprehensive (only seven organ systems are included) and that it ignores comorbidity ratings within each item.

The CIRS was first devised and verified by Linn *et al* (43) in 1968, with the aim of comprehensively recording physical impairment. The original CIRS included 13 organ systems with four different comorbidity ratings within each item. However, it did not precisely define the comorbidity rating in the original version. Later, the CIRS was modified for use in geriatric populations (CIRS-G) by increasing the score to 14 items and adding a definition for comorbidity ratings (17). The CIRS/CIRS-G scores are widely used for predicting mortality, admission rate, length of stay, readmission rate and functional disability (17). The ability of the CIRS-G to predict mortality risk has been verified in cancer patients, including those with NSCLC (44,45), laryngeal cancer (46) and breast cancer (47). In the present study, three different CIRS-G scores (2, 3 and 4) were associated with pCR to NCIO and smoking. A CIRS ≥2 was associated with higher ALT and AST levels, a CIRS ≥3 was associated with lower PD-L1 expression levels and a CIRS ≥4 was associated with older age, higher serum creatinine levels and a higher circulating $CD4^+$ T-cell count. As previously described, PD-L1 expression and the circulating $CD4^+$ T-cell count were found to be influential factors in the response to NCIO. As with the ALT concentration, the AST level may be a new indicator of immunotherapy efficacy. Metabolic reprogramming provides cancer cell growth with a high amount of energy and matter. AST is elevated by reducing reactive oxygen species and increasing NADPH synthesis to promote cancer cell growth and resistance (48) and glycolysis (49). ALT is synthesized mainly in the liver, whereas AST is synthesized in various tissues. Therefore, an elevated AST specifically reflects cancer severity. However, few studies have reported

the relationship between elevated serum creatinine levels and chemotherapeutic efficacy in cancer patients. An abnormal serum creatinine level predicted a worse objective response rate and poor PFS and OS (P=0.004) in a study of hepatocellular carcinoma chemoembolization (50).

The ACE-27 score was initially calculated from the Kaplan-Feinstein index and it was modified and tested to incorporate cancer-related items (51). It was initially mainly used in head and neck cancer for predicting patient prognosis (51), but subsequently, it was validated for lung cancer (52) and colorectal cancer (53). As its name suggests, the ACE-27 includes 27 items and precisely defines comorbidity ratings (18). The overall score relies on the highest score of one item, except for two or more Grade 2 fractures occurring in different organ systems; in this situation, the overall score is recorded as Grade 3. The present study showed that ACE-27 was associated with a greater smoking history, smoking index and ALT level. There are no related reports on its predictive value for ICI response.

The present study had several limitations. First, it did not establish a predictive model with these comorbidities or comorbidity indices because a predictive model for pCR with four comprehensive and independent factors was already established in our previous study and the area under the curve was 0.848 (10). Second, it did not detect the TME in surgical specimens after NCIO, so the correlations of comorbidities or comorbidity indices with the TME were not analyzed. Third, the associations of comorbidities or comorbidity indices with the TMB/phenotype of immune cells were not analyzed due to insufficient data. Fourth, the median follow-up is 2 years at present, which is insufficient to analyze the impact of complications on long-term survival.

In summary, the present study showed that cardiovascular disease, vascular disease, hypertension, CIRS-G ≥2/3/4 and ACE-27 ≥2 all had an effect on pCR of NCIO in NSCLC. Cardiovascular disease was the strongest independent factor. All of the above factors were associated with significant clinicopathological factors. These results could help to screen the most suitable patients with NSCLC for NCIO and provide insights into studies of the biological role of comorbidities in NCIO response. Considering that no similar studies have been reported, further studies with large sample sizes or involving multiple centers are needed.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author. The information of genetic mutations test is provided on figshare (https://doi.org/10.6084/m9.figshare.25375123.v1).

Authors' contributions

XSH contributed to the data collection, data analyses and article writing. PZ contributed to the data analyses. JPX contributed to the data collection and interpretation. CYL, XLL and CHH contributed to the conception and design of this study. XSH and JPX confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Commission of The Second Xiangya Hospital of Central South University and the requirement for written informed consent was waived for retrospective research (approval no. 2022-K060).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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