

Analysis of independent prognostic factors for the occurrence and severity of heart failure after chemotherapy in patients with small cell lung cancer

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Abstract. Patients with small cell lung cancer (SCLC) may develop heart failure after chemotherapy; therefore, it is crucial to explore the factors that affect the occurrence of heart failure. The present study retrospectively collected data from 550 patients with SCLC who received chemotherapy. Analysis of differences between groups (patients with and without heart failure, as well as patients with different severities of heart failure) was performed on demographic characteristics and cardiac biomarkers, followed by multivariate and multinomial logistic regression analyses on factors that were found to be significantly different in the intergroup analysis, to screen for factors that significantly influence heart failure. Finally, receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of combined indicators for the occurrence and severity of heart failure.

Multivariate logistic regression analysis initially identified the cumulative dose of chemotherapy drugs, cardiac troponin I (cTnI), N-terminal pro-B-type natriuretic peptide, left ventricular ejection fraction (LVEF) and creatine kinase-myocardial band as independent prognostic factors of heart failure. Multinomial logistic regression analysis showed that both cTnI and LVEF had significant effects in predicting the severity of heart failure. ROC curve analysis demonstrated that a cTnI level ≥ 0.044 ng/ml and LVEF $\leq 39.083\%$ could predict the occurrence of heart failure, whereas a cTnI level ≥ 0.059 ng/ml and LVEF $\leq 37.216\%$ were associated with moderate-to-severe heart failure. The standardized combination indicators (cTnI and LVEF) also showed strong predictive ability (AUC > 0.75). In conclusion, the present study demonstrated that cTnI, LVEF and their combination may serve as independent prognostic factors for predicting the occurrence and severity of heart failure in patients with SCLC after chemotherapy. These findings suggest that cTnI and LVEF should be routinely monitored during the early stages of chemotherapy for identifying patients at high risk for heart failure and early intervention, ultimately improving patient prognosis.

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Abbreviations: SCLC, small cell lung cancer; cTnI, cardiac troponin I; cTnT, cardiac troponin T; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase-myocardial band; ROC, receiver operating characteristic; AUC, area under the curve; BMI, body mass index; OR, odds ratio; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; CRS, cardiotoxicity risk score

Key words: SCLC, chemotherapy, heart failure, prognostic factors, combined indicators

Introduction

Small cell lung cancer (SCLC) is an aggressive subtype of lung cancer, accounting for 10-15% of all lung cancer cases (1). Compared with non-SCLC, SCLC exhibits a more malignant biological behavior, characterized by rapid proliferation and a high propensity for widespread distant metastasis (2), and as a result, patients are often diagnosed at an advanced stage. Although targeted therapies and immunotherapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors and programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors have shown promising efficacy in certain patients with lung cancer in previous years, chemotherapy remains the mainstay of treatment for SCLC, especially in advanced-stage SCLC (3). However, the side effects of chemotherapy are

notable, with cardiotoxicity being a crucial factor affecting long-term survival (4,5).

Chemotherapeutic agents, particularly anthracyclines (such as doxorubicin) and platinum-based drugs (such as cisplatin), can induce marked cardiotoxicity while treating tumors (6). This toxicity primarily manifests as myocardial injury and left ventricular dysfunction, ultimately leading to heart failure. Heart failure not only markedly impacts the quality of life of patients but also increases the rates of rehospitalization and mortality (7,8). One study showed that SCLC patients with heart failure have an ~75% higher risk of death compared with those without heart failure (8). Therefore, early identification of high-risk patients and predicting the occurrence and severity of heart failure is of clinical importance (9).

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT) are currently the most commonly used cardiac biomarkers, released into the bloodstream during myocardial cell injury (10,11), with elevated levels of cTnI and cTnT being widely used for the early diagnosis of myocardial infarction and monitoring of cardiotoxicity. B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) are another class of biomarkers commonly used in the diagnosis of heart failure, with elevated levels typically associated with increased ventricular pressure load and wall stress (12). Additionally, left ventricular ejection fraction (LVEF) is a crucial indicator of left ventricular function that is commonly used to assess the severity of heart failure, and a decrease in LVEF is a marker of impaired cardiac systolic function and often indicates a poor prognosis (13).

However, the predictive ability of a single biomarker may be insufficient to address the complex cardiotoxicity that may arise after chemotherapy. Therefore, a comprehensive assessment combining multiple cardiac biomarkers and functional indicators may improve the accuracy of early detection and prediction of the severity of heart failure (14,15). Moreover, different tumor biological characteristics, treatment regimens and individual patient differences may also influence the risk of heart failure. Thus, a systematic analysis of these potential influencing factors is necessary to identify independent prognostic factors and develop an effective comprehensive predictive model.

The present study aimed to evaluate various clinical and laboratory indicators in patients with SCLC during the early phase of chemotherapy, in order to predict the occurrence and severity of heart failure. The goal was to provide a reliable risk assessment tool for clinical practice, guide intervention strategies and ultimately improve the long-term prognosis of patients with SCLC.

Materials and methods

Study subjects and data collection. The present study retrospectively included patients diagnosed with SCLC receiving chemotherapy at Hebei Provincial Hospital of Traditional Chinese Medicine (Shijiazhuang, China) from January 2016 to January 2018. The inclusion criteria were as follows: i) Patients diagnosed with SCLC through pathology; ii) patients receiving standard chemotherapy of etoposide combined with carboplatin, with the standard chemotherapy regimen dose and treatment cycle recommended by the

current National Comprehensive Cancer Network guidelines for SCLC (16); and iii) patients with complete follow-up data, including the occurrence and severity of heart failure during the chemotherapy course and follow-up period. Exclusion criteria included: i) Patients with a history of heart failure or other serious cardiovascular diseases (such as congenital heart disease and pulmonary hypertension); ii) patients who were lost to follow-up during the follow-up process; and iii) patients with severe mental illness or poor compliance (poor treatment adherence), including those with schizophrenia, major depression or bipolar disorder. It is noteworthy that the use of specific medications was not employed as an exclusion criterion in the present study. The patient screening process is shown in Fig. S1. All data in the present study were collected at the end of the first cycle of chemotherapy and follow-up period.

Data collection included the following aspects: i) Baseline demographic information: Age, sex, body mass index (BMI), smoking history and alcohol consumption history; ii) tumor characteristics: Clinical staging of the tumor, primary tumor staging (according to the TNM classification) (17) and gene mutation status; iii) chemotherapy-related information, such as the cumulative dose of chemotherapy drugs received by the patients; iv) cardiac function and biomarkers: LVEF measured by echocardiography (Philips iE33; Philips Medical Systems B.V.), diastolic function assessed for normalcy using echocardiography (Philips iE33), cTnI and cTnT measured by immunoassay (ARCHITECT i2000SR; Abbott), BNP and NT-proBNP measured by immunoassay (Roche Cobas e411; Roche Diagnostics GmbH) and creatine kinase-myocardial band (CK-MB) measured by enzymatic assay (AU5800; Beckman Coulter, Inc.). The specific procedures for BNP and NT-proBNP were as follows: First, peripheral venous blood was collected using ethylenediaminetetraacetic acid (EDTA)-anticoagulated tubes, and after centrifugation (2,000 x g, 10 min, 4°C), plasma was separated, labeled, registered and loaded onto the analyzer (Roche Cobas e411; Roche Diagnostics GmbH). The samples were then loaded onto an automated immunoassay analyzer (Roche Cobas e411; Roche Diagnostics GmbH) for analysis, and the instrument automatically completed the immunoreaction, signal detection and quantitative determination. The collection method for CK-MB involved peripheral venous blood sampling followed by centrifugation (2,000 x g, 10 min, room temperature) to obtain serum; the samples were subsequently labeled, registered, and loaded onto the analyzer, and CK-MB was measured on an automated biochemical analyzer (AU5800; Beckman Coulter, Inc.), with the instrument automatically completing the detection and calculating CK-MB levels. Heart failure was monitored in all patients, who were followed up for 5 years. Throughout the follow-up period, heart failure occurrence was recorded and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) classification (18) into three levels: Mild heart failure (asymptomatic or mild), moderate-to-severe heart failure and life-threatening heart failure or death. Mild heart failure (asymptomatic or mild) includes CTCAE grade 1 (asymptomatic, with only detected cardiac dysfunction) and grade 2 (symptomatic but with minimal impact on daily activities, possibly requiring medication). Moderate-to-severe heart failure includes CTCAE grade 3 (notable symptoms, impacting daily activities, requiring hospitalization). Life-threatening

heart failure or death includes CTCAE grade 4 (life-threatening heart failure, usually requiring emergency treatment or life support) and grade 5 (death related to heart failure).

Treatment regimen. All patients received antiemetic therapy, gastric protection and nutritional support during chemotherapy. The standard triple antiemetic regimen was used to adequately prevent both acute and delayed nausea and vomiting. Approximately 30 min before the start of chemotherapy, ondansetron (8-16 mg, IV) was administered once, together with dexamethasone 12 mg orally; aprepitant 125 mg orally was given 1 h before chemotherapy. To cover the risk of delayed nausea and vomiting, aprepitant 80 mg and dexamethasone 8 mg were continued orally each morning on days 2-4 after chemotherapy. The same regimen was applied in each chemotherapy cycle. Oral high-protein supplements providing ~15-25 g of protein per day were administered throughout the entire chemotherapy cycle. On the first day of each treatment cycle, carboplatin (Furen Pharmaceutical Group Co., Ltd.) was administered at 200-400 mg/m² via intravenous infusion once; simultaneously, etoposide injection (Jiangsu Hengrui Pharmaceuticals Co., Ltd.) at 120 mg/m² was administered via intravenous infusion on days 1-3, once daily. Each cycle lasted 21 days, the remaining days of the cycle served as a rest period, with a total of 4-6 cycles followed.

Statistical analysis. All statistical analyses in this study were performed using R software version 4.4.0 (19). Continuous variables are presented as median (minimum-maximum), and categorical variables are presented as frequency (percentage). Fisher's exact test or χ^2 test was used to analyze the association between categorical variables (such as smoking history, alcohol consumption history and tumor staging) and the occurrence and severity of heart failure. For continuous variables (such as LVEF, cTnI and NT-proBNP), Unpaired Student's t-test or Mann-Whitney U test was used to compare differences between the heart failure group and the non-heart failure group. One-way ANOVA or Kruskal-Wallis test was used to analyze the expression differences of continuous variables among the three heart failure groups (mild, moderate-to-severe and life-threatening or death). No post-hoc tests were performed, and the reported P-values represent the overall comparison among the three groups. P<0.05 was considered to indicate a statistically significant difference.

Multivariate logistic regression analysis. Variables with P<0.05 from the aforementioned statistical analysis were included in a multivariate logistic regression model to identify independent prognostic factors associated with heart failure. Logistic regression analysis was used to calculate the odds ratio (OR) and 95% confidence interval for each variable.

Multinomial logistic regression analysis. A multinomial logistic regression analysis was used to assess the factors influencing the severity of heart failure. 'No symptoms or mild heart failure' and 'moderate-to-severe heart failure' were set as the reference categories. The regression coefficients, OR and P-values for each independent variable were calculated.

Combined indicator construction and receiver operating characteristic (ROC) curve analysis. Because these two variables differ in their units and numerical ranges, Z-score standardization was applied to transform them into distributions

with a mean of 0 and a standard deviation of 1, allowing for direct comparison within the same model. After standardizing cTnI and LVEF, a combined predictive index was constructed using the formula Combined indicator = -LVEF_std + cTnI_std (where 'std' indicates the Z-score standardized value of the variable). The performance of cTnI and LVEF individually and their combination in predicting the occurrence and severity of heart failure was analyzed using ROC curves (AUC value, 95% confidence interval, threshold, youden index, sensitivity and specificity). In the analysis of heart failure severity, 'no symptoms or mild heart failure' was compared with other heart failure categories and 'life-threatening heart failure or death' was compared with the other two categories.

Results

Baseline characteristics. A total of 550 eligible patients with SCLC were included in the present study, with a mean age of 47 years (ranging from 19-75±14.2 years), and 51.09% of the patients were male (n=281). The average BMI of the patients was 21.4 kg/m², with 36.73% having a history of smoking and 43.09% having a history of alcohol consumption. Regarding tumor staging, 49.64% of the patients were in stage I, 25.27% were in stage II, 16.91% in stage III and 8.18% in stage IV. Analysis of the genetic mutation status showed that 18.36% of the patients had TP53 mutations and 29.64% had RB1 mutations. All patients received standard chemotherapy regimens, with a mean cumulative chemotherapy dose of 354 (range, 114-595) mg/m². Tumor staging (P<0.001) and primary tumor staging (P<0.001) were significantly associated with the occurrence of heart failure (Table I). During the follow-up period, a total of 93 patients (16.91%) developed heart failure; according to the CTCAE classification, 68 patients (73.12%) experienced asymptomatic or mild heart failure, 19 patients (20.43%) developed moderate-to-severe heart failure and 6 patients (6.45%) experienced life-threatening heart failure or death. The mean age of patients who developed heart failure was 48±11.8 years, with 54.84% being male, 27.96% having a history of smoking and 48.39% having a history of alcohol consumption. The differences in tumor staging (P<0.001) and primary tumor staging (P=0.008) among the groups were statistically significant, suggesting that these factors may be related to the severity of heart failure. Other variables such as age, sex, BMI, smoking, alcohol consumption and genetic mutation status did not show statistically significant differences among the groups (Table II).

Cardiac function and biomarkers. Among the 550 patients with SCLC, the cumulative chemotherapy dose was significantly higher in the heart failure group compared with the dose in the non-heart failure group (398 vs. 346 mg/m²; P=0.007), and the levels of cTnI and cTnT were also significantly elevated in the heart failure group compared with those in the non-heart failure group (0.06 vs. 0.05 ng/ml, P=0.038; 0.013 vs. 0.014 ng/ml, P=0.036, respectively). Additionally, the LVEF was significantly reduced (38.0 vs. 43.6%; P=0.004), the proportion of patients with abnormal diastolic dysfunction was higher (39.78 vs. 28.01%; P=0.026) and CK-MB levels were significantly elevated (7.63 vs. 6.96 ng/ml; P=0.017) in the heart failure group. Conversely, BNP and NT-proBNP levels were higher in the heart failure group but the differences did

Table I. Baseline data analysis of patients with and without heart failure after chemotherapy.

Characteristic	All patients (n=550)	Heart failure		P-value
		Yes (n=93)	No (n=457)	
Age, years	47 (19-75)	48 (27-74)	47 (19-75)	0.138
Sex, n (%)				0.495
Male	281 (51.09)	51 (54.84)	230 (50.33)	
Female	269 (48.91)	42 (45.16)	227 (49.67)	
BMI, kg/m ²	21.4 (18.3-24.9)	22 (18.4-24.9)	21.4 (18.3-24.9)	0.195
Smoking, n (%)				0.059
Yes	202 (36.73)	26 (27.96)	176 (38.51)	
No	348 (63.27)	67 (72.04)	281 (61.49)	
Alcohol consumption, n (%)				0.301
Yes	237 (43.09)	45 (48.39)	192 (42.01)	
No	313 (56.91)	48 (51.61)	265 (57.99)	
Tumor stage, n (%)				<0.001
I	273 (49.64)	39 (41.94)	234 (51.2)	
II	139 (25.27)	21 (22.58)	118 (25.82)	
III	93 (16.91)	12 (12.9)	81 (17.72)	
IV	45 (8.18)	21 (22.58)	24 (5.25)	
Gene mutation status, n (%)				0.169
TP53	101 (18.36)	11 (11.83)	90 (19.69)	
RB1	163 (29.64)	30 (32.26)	133 (29.1)	
WYC	120 (21.82)	26 (27.96)	94 (20.57)	
Others	166 (30.18)	26 (27.96)	140 (30.63)	
Primary tumor stage, n (%)				<0.001
T1	217 (39.45)	34 (36.56)	183 (40.04)	
T2	150 (27.27)	32 (34.41)	118 (25.82)	
T3	117 (21.27)	7 (7.53)	110 (24.07)	
T4	66 (12)	20 (21.51)	46 (10.07)	

BMI, body mass index.

not reach statistical significance. These results suggested that cumulative chemotherapy dose, cTnI, cTnT, LVEF, diastolic function and CK-MB potentially play important roles in predicting the risk of heart failure after chemotherapy in patients with SCLC (Table III). Among the 93 patients with heart failure, as the severity of heart failure increased, the cumulative chemotherapy dose (P=0.040) and cTnI levels (P=0.023) significantly increased, whereas LVEF significantly decreased (P=0.027). Although cTnT levels were slightly higher in the most severe heart failure group, the difference was not statistically significant (P=0.254). Additionally, BNP and CK-MB levels were significantly elevated in patients with more severe heart failure (P=0.031 and P=0.020, respectively), and the proportion of patients with abnormal diastolic dysfunction increased with the severity of heart failure (P=0.013). However, this did not occur between the moderate/severe and life-threatening groups. These results indicated that cumulative chemotherapy dose, cTnI, BNP, LVEF, diastolic function and CK-MB may be closely related to and are potential indicators for predicting the severity of heart failure (Table IV).

Multivariate logistic regression analysis. Based on the aforementioned factors that were significantly associated with heart failure, further logistic regression analysis showed that cumulative chemotherapy dose, cTnI, BNP, LVEF and CK-MB were independent prognostic factors for heart failure. Cumulative chemotherapy dose (OR=1.002; P=0.016), cTnI (OR=12.953; P=0.032), BNP (OR=1.002; P=0.020) and CK-MB (OR=1.150; P=0.041) were significantly associated with an increased risk of heart failure, whereas low levels of LVEF (OR=0.929; P=0.012) were significantly associated with a risk of heart failure (Table V).

Multinomial logistic regression analysis. Based on the aforementioned factors influencing significantly the severity of heart failure, further multinomial logistic regression analysis was conducted. The results showed that cumulative chemotherapy dose exhibited significant differences between asymptomatic vs. moderate and life-threatening heart failure (both P<0.010) but not between moderate and life-threatening heart failure (P>0.050). cTnI exhibited significant differences

Table II. Baseline data analysis of patients with cardiac toxicity after chemotherapy.

Characteristic	Degree of heart failure				P-value
	All patients n=93	Asymptomatic or mild symptomatic (n=68)	Moderate-to-severe symptomatic (n=19)	Life-threatening or death (n=6)	
Age, years	48 (27-74)	45.5 (41-64)	52 (38-71)	52.5 (27-74)	0.708
Sex, n (%)					0.676
Male	51 (54.84)	36 (48.53)	12 (52.63)	3 (50)	
Female	42 (45.16)	33 (51.47)	7 (47.37)	2 (50)	
BMI, kg/m ²	22 (18.4-24.9)	21.7 (18.5-24.8)	21.6 (19.5-24.6)	24 (18.4-24.9)	0.304
Smoking, n (%)					0.068
Yes	26 (27.96)	15 (22.06)	9 (47.37)	2 (33.33)	
No	67 (72.04)	53 (77.94)	10 (52.63)	4 (66.67)	
Alcohol consumption, n (%)					0.051
Yes	45 (48.39)	35 (51.47)	10 (52.63)	0 (0)	
No	48 (51.61)	33 (48.53)	9 (47.37)	6 (100)	
Tumor stage, n (%)					<0.001
I	39 (41.94)	37 (54.41)	2 (10.53)	0 (0.00)	
II	21 (22.58)	17 (25.00)	4 (21.05)	0 (0.00)	
III	12 (12.9)	4 (5.88)	6 (31.58)	2 (33.33)	
IV	21 (22.58)	10 (14.71)	7 (36.84)	4 (66.67)	
Gene mutation status, n (%)					0.512
TP53	11 (11.83)	7 (10.29)	3 (15.79)	1 (16.67)	
RB1	30 (32.26)	20 (29.41)	8 (42.11)	2 (33.33)	
WYC	26 (27.96)	20 (29.41)	3 (15.79)	3 (50.00)	
Others	26 (27.96)	21 (30.88)	5 (26.32)	0 (0.00)	
Primary tumor stage, n (%)					0.008
T1	34 (36.56)	30 (44.12)	2 (10.53)	2 (33.33)	
T2	32 (34.41)	18 (26.47)	12 (63.16)	2 (33.33)	
T3	7 (7.53)	4 (5.88)	1 (5.26)	2 (33.33)	
T4	20 (21.51)	16 (23.53)	4 (21.05)	0 (0)	

BMI, body mass index.

across all comparisons made between different levels of heart failure severity (all $P < 0.001$). BNP also showed significant differences between asymptomatic and life-threatening heart failure ($P = 0.014$), while LVEF exhibited significant differences between asymptomatic and life-threatening and between moderate and life-threatening heart failure ($P = 0.012$ and $P = 0.015$, respectively). However, the difference in diastolic function did not show statistical significance ($P > 0.050$). CK-MB showed a significant difference between asymptomatic and moderate heart failure ($P = 0.031$). These results indicated that cTnI and LVEF may be key factors influencing the severity of heart failure (Table VI).

ROC curve analysis of independent prognostic factors and combined indicators. In summary, cTnI and LVEF were identified as independent prognostic factors for the occurrence and severity of heart failure. ROC curves were plotted, and the area under the curve (AUC) values for cTnI were 0.651, 0.753 and

0.711 for predicting mild, moderate and life-threatening heart failure respectively, with optimal thresholds of 0.044, 0.059 and 0.063 ng/ml, respectively. These findings indicated that when cTnI is < 0.044 ng/ml, heart failure is not expected to occur; however, when cTnI is ≥ 0.044 ng/ml and < 0.059 ng/ml, asymptomatic or mild heart failure is likely; when cTnI is ≥ 0.059 ng/ml and < 0.063 ng/ml, moderate-to-severe heart failure is likely; and when cTnI is ≥ 0.063 ng/ml, life-threatening heart failure or death is expected (Fig. 1). For LVEF, the AUC values were 0.671, 0.724 and 0.749 for predicting mild, moderate and life-threatening heart failure respectively, with optimal thresholds of 39.083, 37.216 and 35.532%, respectively. These findings indicated that when LVEF is $> 39.083\%$, heart failure is not expected to occur; when LVEF is $\leq 39.083\%$ and $> 37.216\%$, asymptomatic or mild heart failure is likely; when LVEF is $\leq 37.216\%$ and $> 35.532\%$, moderate-to-severe heart failure is likely; and when LVEF is $\leq 35.532\%$, life-threatening heart failure or death is expected (Fig. 2).

Table III. Comparison of clinical indicators between patients with and without heart failure.

Clinical indicator	Reference range	All patients (n=550)	Heart failure		P-value
			Yes (n=93)	No (n=457)	
Cumulative dose, mg/m ²	-	354 (114-595)	398 (120-588)	346 (114-595)	0.007
cTnI, ng/ml	<0.0400	0.0548 (0.0303-0.0799)	0.0557 (0.0306-0.0788)	0.05 (0.0303-0.0799)	0.038
cTnT, ng/ml	<0.0140	0.0135 (0.00801-0.0200)	0.013 (0.00801-0.0200)	0.014 (0.00826-0.0198)	0.036
BNP, pg/ml	<100	304 (81.1-546)	319 (81.1-546)	267 (81.8-546)	0.242
NT-proBNP, pg/ml	<125	311 (101-499)	296 (115-499)	276 (101-493)	0.098
LVEF, %	50.0-70.0	41.8 (25.1-52.6)	38.0 (25.1-49.5)	43.6 (37.3-52.6)	0.004
Diastolic function, n (%)	-				0.026
Normal		385 (70.00)	56 (60.22)	329 (71.99)	
Abnormal		165 (30.00)	37 (39.78)	128 (28.01)	
CK-MB, ng/ml	0.00-5.00	7.04 (4.00-9.99)	7.63 (4.01-9.9)	6.96 (4.00-9.99)	0.017

cTnI, cardiac troponin I; cTnT, cardiac troponin T; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase-myocardial band.

Table IV. Comparison of clinical indicators among patients with different degrees of heart failure.

Clinical indicator	Reference range	All patients (n=93)	Degree of heart failure			P-value
			Asymptomatic or mild symptomatic (n=68)	Moderate-to-severe symptomatic (n=19)	Life-threatening or death (n=6)	
Cumulative dose, mg/m ²	-	398 (120-588)	282 (134-450)	298 (200-426)	362 (120-588)	0.040
cTnI, ng/ml	<0.0400	0.0557 (0.0306-0.0788)	0.0469 (0.0323-0.0624)	0.0502 (0.0311-0.0773)	0.0608 (0.0306-0.0788)	0.023
cTnT, ng/ml	<0.0140	0.013 (0.00801-0.0199)	0.013 (0.00894-0.0143)	0.0132 (0.00821-0.0197)	0.0144 (0.00801-0.0199)	0.254
BNP, pg/ml	<100	319 (81.1-546)	178 (117-333)	262 (81.1-546)	354 (129-537)	0.031
NT-proBNP, pg/ml	<125	296 (115-498)	276 (138-408)	341 (115-458)	347 (81.1-546)	0.413
LVEF, %	50.0-70.0	38.0 (25.1-49.5)	39.9 (34.1-48.7)	37.3 (30.4-49.5)	34.4 (25.1-41.3)	0.027
Diastolic function, n (%)	-					0.013
Normal		56 (60.22)	46 (68.66)	7 (35.00)	3 (50.00)	
Abnormal		37 (39.78)	21 (31.34)	13 (65.00)	3 (50.00)	
CK-MB, ng/ml	0.00-5.00	7.63 (4.01-9.90)	4.65 (4.01-6.14)	7.05 (4.10-9.47)	7.16 (4.04-9.90)	0.020

cTnI, cardiac troponin I; cTnT, cardiac troponin T; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-BNP; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase-myocardial band.

For the combined cTnI and LVEF indicator, the AUC values were 0.763, 0.775 and 0.777 for predicting mild, moderate and life-threatening heart failure, respectively, with optimal thresholds of -0.035, 1.317 and 1.682, respectively. These findings indicated that when the combined indicator is <-0.035, heart failure is not expected to occur; when the combined indicator is \geq -0.035 and <1.317, asymptomatic or mild heart failure is likely; when the combined

indicator is \geq 1.317 and <1.682, moderate-to-severe heart failure is likely; and when the combined indicator is \geq 1.682, life-threatening heart failure or death is expected (Fig. 3). The AUC values of the combined indicator showed higher diagnostic efficacy, especially in predicting life-threatening heart failure, with a sensitivity of 0.831 and a specificity of 0.645. These results suggested that the combination of cTnI and LVEF may have higher diagnostic value in

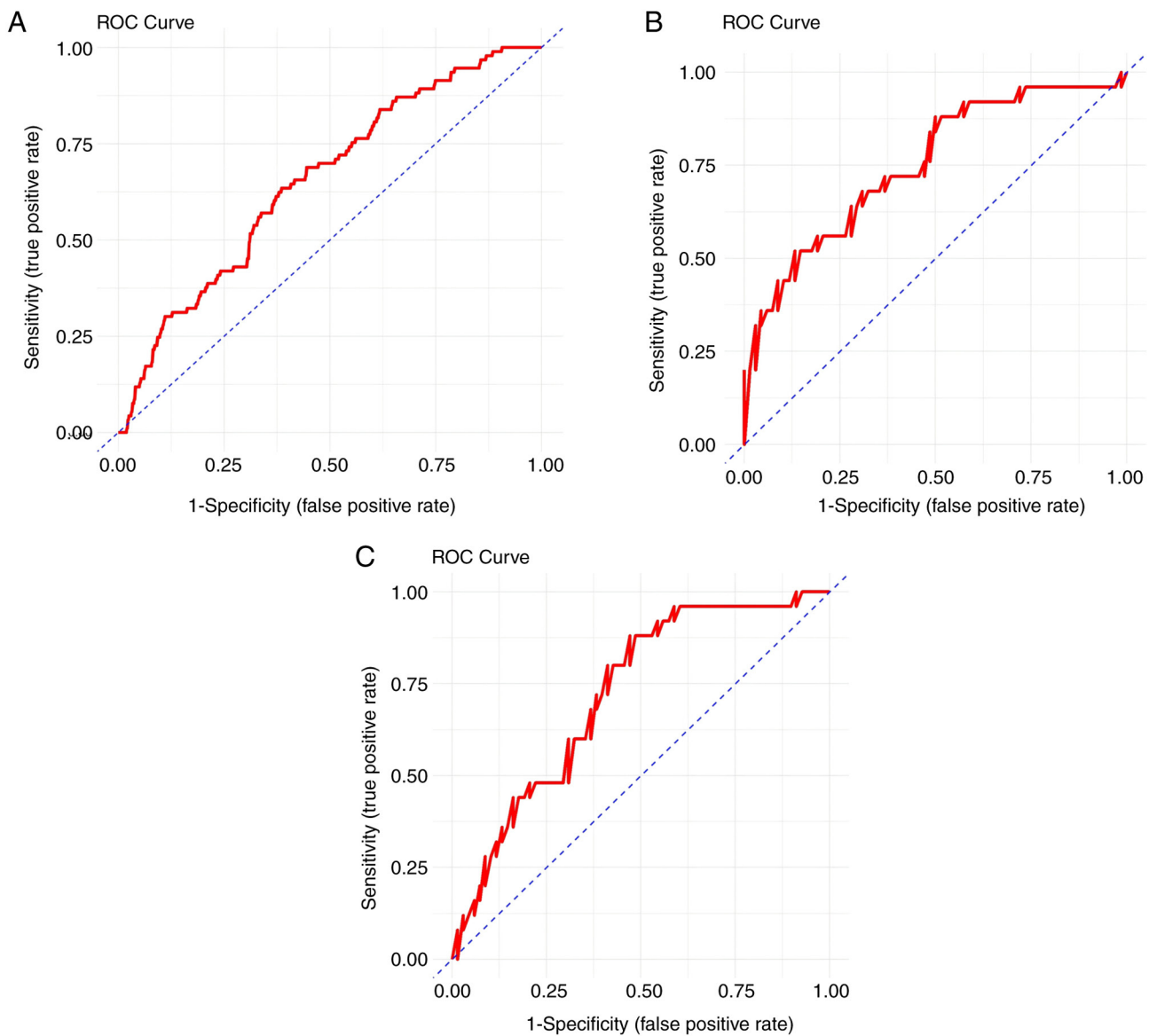


Figure 1. ROC curve evaluation of the ability of cTnI to predict heart failure. The ability of cTnI to predict the occurrence of (A) mild heart failure, (B) moderate-to-severe heart failure and (C) life-threatening heart failure or death. ROC, receiver operating characteristic.

predicting heart failure compared with individual indicators (Table VII).

Discussion

The present study systematically collected demographic characteristics and cardiac function biomarkers of patients with SCLC in the early stage of chemotherapy. Through intergroup comparisons, multivariate logistic regression and multinomial logistic regression analyses, risk factors related to heart failure were identified, and the predictive performance of risk factors was evaluated through ROC curve analysis.

The key indicators identified in the present study as independent prognostic factors for heart failure include the cumulative dose of chemotherapy drugs, cTnI, NT-proBNP, LVEF and CK-MB. Previous research has found that the platinum-based chemotherapy may be associated with cardiotoxicity. Carboplatin has been shown to promote the generation of reactive oxygen species, leading to mitochondrial dysfunction

in cardiomyocytes, which in turn induces cell apoptosis and impairs myocardial contractile function, thereby increasing the risk of heart failure (20). The elevation of cTnI and BNP are considered a reliable biomarker for myocardial stress and injury (21), and a decrease in LVEF typically indicates a weakened pumping function of the heart, thus increasing the likelihood of developing heart failure in the future (22,23). In addition, CK-MB serves as a specific marker of myocardial injury, and its elevation indicates damage to myocardial cells, thus increasing the risk of future heart failure (24).

ROC curve analysis showed that combining cTnI and LVEF provides a more accurate prediction of heart failure occurrence and severity in patients with SCLC following chemotherapy when compared against using only one of the two biomarkers. The present study identified several key thresholds that can help clinicians monitor and manage the cardiac health of patients more effectively in daily practice. For example, when the level of cTnI is ≥ 0.044 ng/ml or LVEF is $\leq 39.083\%$, this indicates that the patient may develop heart

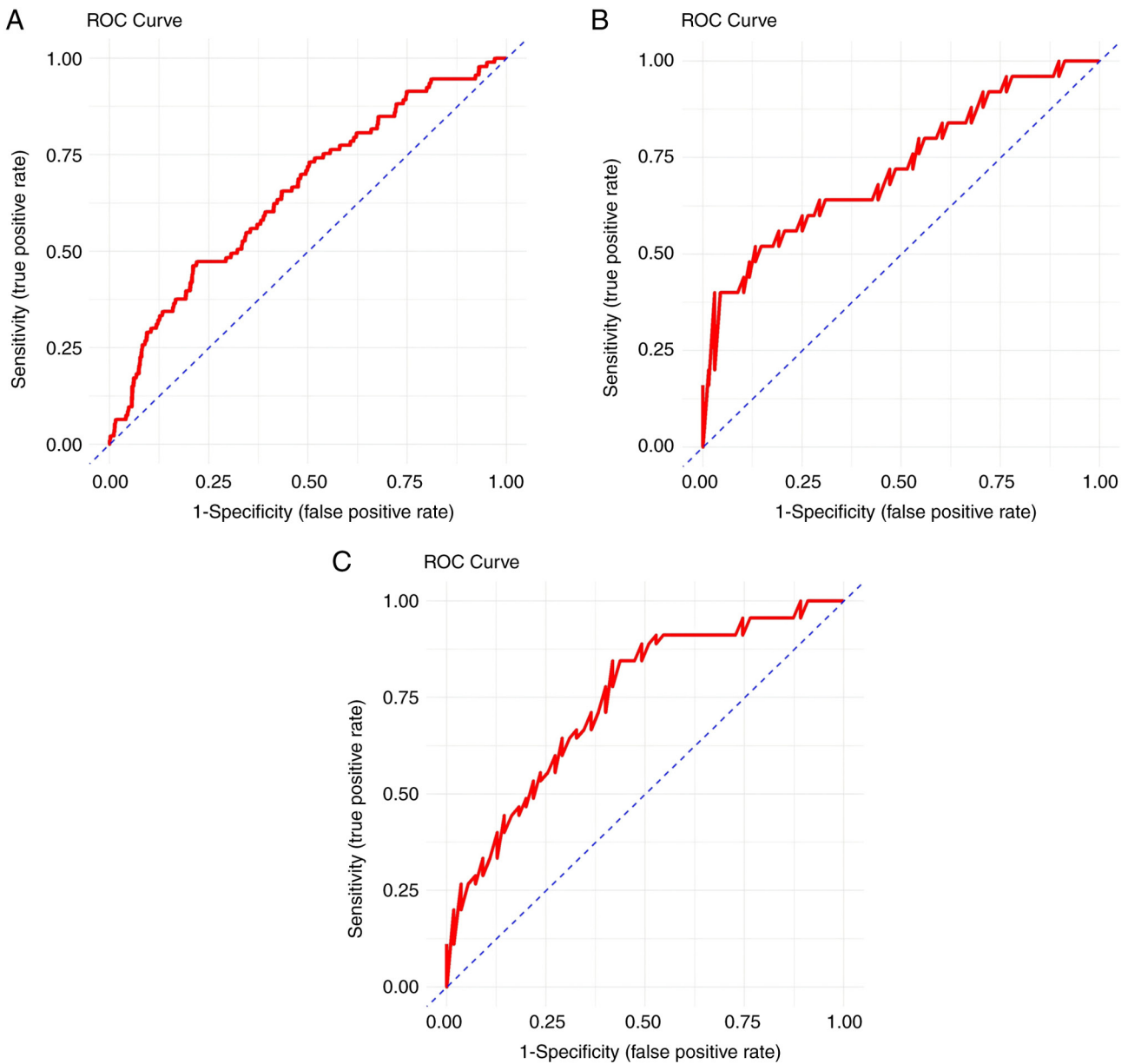


Figure 2. ROC curve evaluation of the ability of LVEF to predict heart failure. The ability of LVEF to predict the occurrence of (A) mild heart failure, (B) moderate-to-severe heart failure and (C) life-threatening heart failure or death. ROC, receiver operating characteristic.

failure in the future, and this information is crucial for the timely adjustment of treatment plans. When cTnI levels rise to 0.063 ng/ml or LVEF drops $\leq 35.532\%$, this indicates a risk of life-threatening heart failure, necessitating more aggressive treatment measures to prevent further deterioration of the cardiac function, such as early initiation of angiotensin-converting enzyme inhibitors (25). Additionally, the present study established a standardized combined indicator, optimizing the combined use of cTnI and LVEF to enhance the predictive ability for heart failure occurrence. Specifically, the results demonstrated that when the value of this combined indicator is ≥ -0.035 , it can predict the occurrence of heart failure; when it is ≥ 1.682 , it strongly suggests that the patient may be at risk of life-threatening heart failure. This standardized indicator may provide clinicians with a more intuitive and easy-to-apply tool that can serve as a reference in the routine monitoring of patients.

However, compared with cTnI and LVEF, the predictive value of other traditional myocardial markers (such as CK-MB) is relatively limited. This may be because CK-MB has a short half-life and is typically used to reflect acute and short-term myocardial injury (26). Therefore, its ability to predict long-term heart failure is inferior to that of LVEF and cTnI. This may also be one of the reasons why CK-MB demonstrated lower significance compared with cTnI and LVEF in the present study.

In the baseline data analysis performed in the present study, there was no significant association between the occurrence of gene mutations and heart failure after chemotherapy. Overall, the relationship between gene mutations and chemotherapy-induced HF remains uncertain, the evidence is mixed, and further studies are needed. However, specific gene mutations, such as TP53 and RB1, have been found to be closely associated with the efficacy and prognosis of patients

Table V. Multivariate logistic regression analysis of factors affecting heart failure in patients with small cell lung cancer undergoing chemotherapy.

Indicator	B	SE	P-value	OR	CI lower	CI upper
Cumulative dose, mg/m ²	0.002	0.001	0.016	1.002	1.000	1.004
cTnI, ng/ml	2.561	0.291	0.032	12.953	7.314	22.954
BNP, pg/ml	0.002	0.001	0.020	1.002	1.000	1.005
LVEF, %	-0.073	0.029	0.012	0.929	0.878	0.984
CK-MB, ng/ml	0.140	0.068	0.041	1.150	1.006	1.315

SE, standard error; OR, odds ratio; CI, confidence interval; cTnI, cardiac troponin I; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase-myocardial band.

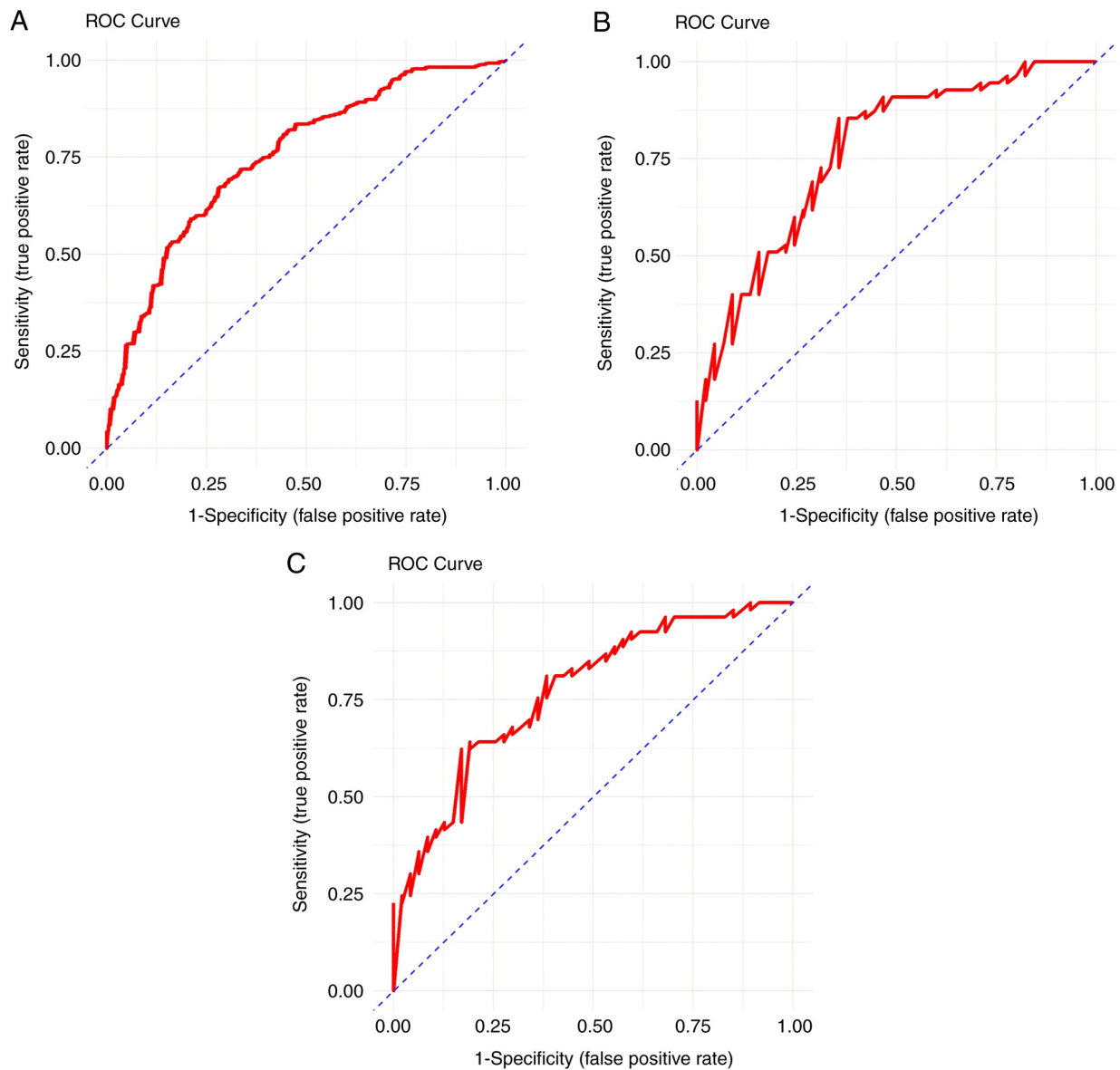


Figure 3. ROC curve evaluation of the ability of the combined indicator to predict heart failure. The ability of cTnI and LVEF combined to predict the occurrence of (A) mild heart failure, (B) moderate-to-severe heart failure and (C) life-threatening heart failure or death. ROC, receiver operating characteristic.

with SCLC after chemotherapy (27). Patients carrying these mutations may have different reactions to chemotherapy and exhibit a higher risk of disease recurrence. It has been

suggested that specific gene mutations, such as those related to cardiac function, such as TTN truncating variants (28), may affect the structure and function of the heart and be associated

Table VI. Factors affecting the degree of heart failure in patients with small cell lung cancer undergoing chemotherapy.

Comparison	P-value for cumulative dose	P-value for cTnI	P-value for BNP	P-value for LVEF	P-value for diastolic function	P-value for CK-MB
Asymptomatic or mild symptomatic vs. moderate-to-severe symptomatic heart failure	0.006	<0.001	0.223	0.091	0.131	0.031
Asymptomatic or mild symptomatic vs. life-threatening heart failure or death	0.008	<0.001	0.014	0.012	0.126	0.201
Moderate-to-severe symptomatic heart failure vs. life-threatening heart failure or death	0.072	<0.001	0.048	0.015	0.493	0.853

cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEF, left ventricular ejection fraction; CK-MB, creatine kinase-myocardial band.

Table VII. Receiver operating characteristic curve parameters for independent risk factors.

A, cTnI							
Prediction	AUC	AUC CI lower	AUC CI upper	Threshold	Youden index	Sensitivity	Specificity
Occurrence of mild heart failure	0.651	0.591	0.710	0.044	0.279	0.785	0.495
Occurrence of moderate-to-severe heart failure	0.753	0.647	0.859	0.059	0.428	0.840	0.588
Occurrence of life-threatening heart failure or death	0.711	0.467	0.954	0.063	0.408	0.833	0.575
B, LVEF							
Prediction	AUC	AUC CI lower	AUC CI upper	Threshold	Youden index	Sensitivity	Specificity
Occurrence of mild heart failure	0.671	0.611	0.731	39.083	0.302	0.634	0.667
Occurrence of moderate-to-severe heart failure	0.724	0.604	0.843	37.216	0.458	0.840	0.618
Occurrence of life-threatening heart failure or death	0.749	0.615	0.883	35.532	0.586	1.000	0.586
C, cTnI and LVEF							
Prediction	AUC	AUC CI lower	AUC CI upper	Threshold	Youden index	Sensitivity	Specificity
Occurrence of mild heart failure	0.763	0.661	0.861	-0.035	0.463	0.646	0.817
Occurrence of moderate-to-severe heart failure	0.775	0.704	0.835	1.317	0.352	0.742	0.610
Occurrence of life-threatening heart failure or death	0.777	0.697	0.835	1.682	0.476	0.831	0.645

AUC, area under the curve; CI, confidence interval; cTnI, cardiac troponin I; LVEF, left ventricular ejection fraction.

with changes in the levels of cardiac markers, such as BNP and cTnI (29). In the future, large-scale longitudinal cohort studies should be considered to determine which specific gene mutations are associated with changes in cardiac markers and explore whether these factors can predict the occurrence of heart failure alone or in combination.

As a retrospective study, the present research provided a foundation for future validation of the prediction model in different centers and populations. Through comprehensive analysis, the importance of the combined indicator of cTnI and LVEF was confirmed in predicting chemotherapy-related heart failure in patients with SCLC. Existing models, such

as the cardiotoxicity risk score (CRS) (30), primarily assess clinical risk factors such as age, history of cardiovascular disease, hypertension and chemotherapy dosage; however, these static variables mainly reflect the baseline condition of the patient and do not directly capture the extent of myocardial injury or the actual status of cardiac function, which creates certain limitations in predicting heart failure. By contrast, the present study identified cTnI and LVEF as core indicators that directly reflect the cardiac status, and their combined use may enable a more accurate prediction of the occurrence and severity of heart failure. Even when based solely on early data before chemotherapy, these indicators may potentially compensate for the limitations of the CRS model in assessing myocardial damage or changes in cardiac function; however, this is merely a hypothesis proposed in the present study and requires validation in future research,

cTnI and LVEF are important indicators for assessing myocardial injury and cardiac function, and numerous studies have applied them to the evaluation of heart failure and its prognosis (31). For example, in pediatric patients with heart failure, cTnI levels at admission have marked clinical value in assessing the severity and progression of heart failure (32), and continuous measurement of cTnI is closely associated with the prognosis of acute heart failure (33). However, to the best of our knowledge, studies focusing on chemotherapy-related heart failure in patients with SCLC remain relatively limited, and research on the combined use of these two indicators for predicting heart failure is even rarer. The present study demonstrated that cTnI and LVEF can predict the occurrence and severity of heart failure in patients with SCLC undergoing chemotherapy, providing a reference for clinical monitoring and intervention.

The present study also has certain limitations. As a retrospective analysis, the current study is subject to selection bias and information bias, and some important confounding factors, such as nutritional status, hypertension and diabetes, may not have been fully controlled. The lack of dynamic monitoring of cardiac biomarkers (such as cTnI, CK-MB and NT-proBNP) during chemotherapy and the reliance solely on baseline values for analysis, may underestimate the true risk of heart failure and the predictive capability of these biomarkers. Future prospective studies should incorporate dynamic monitoring to more comprehensively evaluate the predictive value of temporal changes in cardiac biomarkers for heart failure and provide a basis for early intervention. Although the present study explored the association between chemotherapy-related factors and heart failure, other potential risk factors (such as hypertension and diabetes) were not monitored. Furthermore, due to the retrospective nature of the present study, causal relationships cannot be established. Lastly, the data may be affected by time-related changes, as certain chemotherapy regimens and cardiac function evaluation methods may have evolved. Therefore, future multicenter, large-sample, prospective studies are needed to validate these findings.

In conclusion, the present study showed that cTnI and LVEF are independent prognostic factors for predicting heart failure and its severity in patients with SCLC following chemotherapy, and the combined indicator of cTnI with LVEF demonstrated higher accuracy. The key thresholds and standardized combined indicator identified in the present study provide clinicians with effective tools for the early identification of

high-risk patients. This offers important scientific evidence for improving treatment outcomes in patients with SCLC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JZ and XW were responsible for the conceptualization of the present study, data curation, creation of the study design and analysis plan, software tools used for data analysis and visualization, and writing the original draft. XLi, WZ, XLu and RL were involved in the statistical analysis of the collected data, project administration and creation of figures and charts. XS was responsible for the collection of data, performing experiments or assessments related to the study, checking the accuracy and reliability of the collected data and analyses, supervision, and reviewing and editing the manuscript. All authors read and approved the final manuscript. JZ and XS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted in accordance with The Declaration of Helsinki and was approved by the Ethics Committee of Hebei Provincial Hospital of Traditional Chinese Medicine (approval no. 20240910; Shijiazhuang, China). The requirement for informed consent was waived due to the retrospective nature of the study, which involved anonymized clinical data and posed no more than minimal risk to the participants.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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