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Original Article

Factors affecting chemotherapy-induced nausea and vomiting in patients with lung squamous cell carcinoma

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Abstract: Objective: To identify factors associated with the severity of chemotherapy-induced nausea and vomiting (CINV) in patients with lung squamous cell carcinoma. Methods: A retrospective analysis was conducted on 301 LSCC patients who received chemotherapy between January 2021 and December 2024. CINV severity was assessed using the Index of Nausea, Vomiting, and Retching. Post-chemotherapy assessments included blood measurements, inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and serum albumin levels. Multivariate logistic regression was performed to identify factors associated with CINV severity. Results: A history of coronary heart disease significantly increased the risk of moderate to severe CINV ($P = 0.010$). Higher forced expiratory volume in one second (FEV_1) was associated with a reduced risk of severe CINV ($P = 0.053$). Higher albumin levels were associated with more severe CINV ($P = 0.048$). Elevated IL-6 levels were found to have a protective effect against severe CINV ($P < 0.001$). Higher partial pressure of oxygen (PaO_2) significantly reduced the risk of severe CINV ($P = 0.002$), while increased partial pressure of carbon dioxide ($PaCO_2$) was associated with greater CINV severity ($P = 0.017$). Conclusion: CINV severity in LSCC patients is influenced by a combination of pulmonary function (FEV_1, PaO_2, $PaCO_2$), inflammatory markers (IL-6, CRP, TNF-α), serum albumin levels, and cardiovascular comorbidities. These findings provide a foundation for personalized supportive care to enhance the quality of life in patients receiving chemotherapy.

Keywords: Lung squamous cell carcinoma, chemotherapy-induced nausea and vomiting, pre-chemotherapy anxiety, pulmonary function, nutritional status, inflammatory markers

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with lung squamous cell carcinoma (LSCC) comprising a substantial proportion of cases [1]. Chemotherapy remains a cornerstone in LSCC treatment but is frequently associated with adverse effects, most notably chemotherapy-induced nausea and vomiting (CINV). These distressing symptoms not only diminish patients' quality of life but also hinder treatment adherence and therapeutic efficacy [2-4]. Given the profound impact of CINV on clinical outcomes, identifying the factors that influence its severity is critical for improving supportive care.

CINV is a multifactorial condition influenced by both patient-specific and treatment-related variables. Established factors such as age, sex, performance status, and comorbidities have been shown to affect CINV severity, although findings remain inconsistent across studies [5-7]. Increasing attention has been directed toward physiologic factors- particularly pulmonary and cardiovascular function - due to their role in mediating systemic responses to chemotherapy. In LSCC patients, compromised respiratory function may be especially relevant, as tumor localization within the lung may exacerbate treatment-related toxicity [8-10].

Psychologic conditions, especially anxiety, have also emerged as significant contributors to CINV severity [11-13]. Anxiety not only affects patients' psychological preparedness for chemotherapy but may also intensify physical symptoms through bidirectional communication between the central nervous system and the gastrointestinal tract - an interaction well-documented in disorders such as irritable bowel syndrome [14]. Several studies have dem-

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onstrated that elevated pre-treatment anxiety is associated with an increased incidence and severity of CINV [15], suggesting that managing anxiety could represent a novel target for intervention.

Additionally, emerging evidence implicates inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) in the pathophysiology of CINV [16]. These findings further underscore the complex interplay of biological, psychological, and treatment-related mechanisms in CINV development.

To explore systematically the predictive and modifiable factors associated with CINV severity, a comprehensive and integrative framework was warranted. This study aims to address this need by investigating the associations among physiological function, psychological state, and inflammatory profiles in LSCC patients undergoing chemotherapy. Through this approach, we aimed to identify key determinants of CINV severity and propose targeted strategies to enhance symptom control and improve patient outcomes.

Materials and methods

Ethics statement

This study was approved by the Institutional Review Board and Ethics Committee of West China Hospital of Sichuan University. As only de-identified patient data were used and there was no potential risk to patient care, the requirement for informed consent was waived. This waiver was granted in accordance with relevant regulatory and ethical guidelines for retrospective research.

Research design

Grouping criteria: This retrospective study analyzed the medical records of 301 patients diagnosed with squamous cell lung carcinoma who were hospitalized between January 2021 and December 2024 and received chemotherapy. Patient data were extracted from the hospital's electronic medical record system. To investigate the factors associated with CINV, patients were divided into two groups based on symptom severity: a mild group (n = 185) and a moderate-to-severe group (n = 116).

Assessment of CINV: CINV was assessed using the Index of Nausea, Vomiting, and Retching (INVR) scale [17]. This instrument includes 8 items scored on a Likert scale from 0 ("not at all") to 4 ("very severe"), yielding a total score ranging from 0 to 32. Items 1, 6, and 7 are reverse-scored, while the remaining items are scored positively. In this study, patients with INVR scores < 16 were categorized as experiencing mild nausea and vomiting, while those with scores ≥ 16 were classified as having moderate to severe symptoms.

Inclusion and exclusion criteria

Inclusion criteria: (1) Pathologically confirmed diagnosis of squamous cell lung carcinoma; (2) Age > 45 years; (3) Body mass index (BMI) between 18 and 30 kg/m^2; (4) American Society of Anesthesiologists (ASA) physical status classification I-II; (5) Expected survival of at least 10 months; (6) Undergoing the combination of Etoposide and Cisplatin (EP) chemotherapy regimen; (7) Availability of complete and accessible medical records.

Exclusion criteria: (1) Allergy to any study drugs; (2) History of alcohol consumption or use of sedatives, analgesics, or psychotropic drugs; (3) Drug abuse or addiction; (4) Inability to complete the Mini-Mental State Examination (MMSE); (5) History of stroke, transient ischemic attack, or traumatic brain injury; (6) Severe respiratory dysfunction (forced expiratory volume in 1 second or forced vital capacity [FVC] < 50% of predicted values); (7) New York Heart Association class III-IV heart failure; (8) Severe hepatic or renal impairment (creatinine > 176 μmol/L, blood urea nitrogen > 7.1 mmol/L, or albumin < 30 g/L); (9) Cognitive impairment, schizophrenia, autoimmune diseases, active infections, incomplete medical records, or current use of broad-spectrum antibiotics at chemotherapy initiation.

EP chemotherapy regimen

During the first cycle, patients received concurrent chemoradiotherapy, followed by three additional cycles of consolidation chemotherapy using the EP regimen. All patients were treated with a standardized protocol. On Day 1, cisplatin (Lot No. X20010743, Jiangsu Hengrui Pharmaceuticals Co., Ltd., China) was administered at a dose of 40-80 mg/m^2, adjusted

according to the patient's respiratory function. Etoposide (Lot No. H32025583, Jiangsu Hengrui Pharmaceuticals Co., Ltd., China) was administered at 80-100 mg/m^2 from Day 1 to Day 3. Thoracic radiotherapy was initiated concurrently with the first chemotherapy cycle, starting on Day 1, and delivered by an anterior-posterior/posterior-anterior (AP/PA) field technique. Radiation was given at 2.0 Gy/day for 22 sessions (excluding weekends and holidays), reaching a cumulative dose of 44 Gy.

Blood tests

Laboratory data: Blood samples were collected from patients after fasting and analyzed using the automated hematology analyzer (Sysmex XN-1000, Sysmex Corporation, Japan) for neutrophils, red blood cell count, white blood cell count, platelet count, and lymphocyte count. Hemoglobin concentration was determined by colorimetric assay using the Stanbio HiCN Lyophilized Reagent Set (Stanbio Laboratory, USA) to form a stable cyanmethemoglobin complex, which was then quantified by measuring absorbance at 540 nm using the spectrophotometer (Hitachi U-1900, Hitachi High-Tech Corporation, Japan). Albumin levels, creatinine levels, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), total cholesterol (TC), and total bilirubin (T-Bil) were measured using the automated biochemical analyzer (Roche Cobas c702, Roche Diagnostics, Switzerland).

Tumor markers: Serum samples were collected from patients and analyzed using the electrochemiluminescence analyzer (Roche Cobas e601, Roche Diagnostics, Switzerland) to detect tumor markers, including neuron-specific enolase (NSE), pro-gastrin-releasing peptide (Pro-GRP), carcinoembryonic antigen (CEA), and cytokeratin 19 fragment (CYFRA 21-1).

Inflammatory markers: Blood samples were collected from patients, and C-reactive protein (CRP) was measured using the automated biochemical analyzer (Beckman Coulter AU5800, Beckman Coulter, USA). Interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and procalcitonin were measured using the electrochemiluminescence analyzer (Roche Cobas e601, Roche Diagnostics, Switzerland). Fibrinogen was measured using the automated coagulation analyzer (Sysmex CA-7000, Sysmex Corporation, Japan).

Respiratory function indicators

Arterial blood samples were collected to measure the partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$), using a blood gas analyzer (Beijing Pulang New Technology Co., Ltd.). Pulmonary function was assessed by spirometry, recording forced expiratory volume in one second (FEV_1) and FVC.

Cognitive function

Cognitive function was evaluated using the MMSE and the Rey Cognitive Screening Questionnaire (RCSQ). The MMSE has a maximum score of 30, with higher scores indicating better cognitive function. Its reliability, measured by Cronbach's alpha, was 0.756 [18]. The RCSQ has a maximum score of 55, with higher scores reflecting better cognitive status, and demonstrated excellent reliability (Cronbach's alpha = 0.964) [19].

Eastern Cooperative Oncology Group (ECOG) performance status and TNM staging system

The ECOG performance status scale was used to assess patients' functional status and tolerance to treatment. It includes six grades: 0: Fully active. 1: Restricted in physically strenuous activity but ambulatory. 2: Ambulatory and capable of self-care, but unable to carry out work activities more than half of their waking hours; 3 for those with limited self-care abilities who spend more than half of their time in bed or a chair; 4 for completely incapable individuals who are bedridden or confined to a chair; and 5 for deceased individuals. Cohen's kappa for inter-rater reliability was 0.486 [20]. The TNM (Tumor Node Metastasis) staging system was used to assess tumor progression, with higher stages indicating more advanced disease [21].

Assessment of anxiety levels before chemotherapy

Anxiety levels prior to chemotherapy were assessed using the Visual Analog Scale (VAS), which demonstrated good internal consistency (Cronbach's alpha = 0.796) [22]. The VAS consists of a horizontal line marked from 0 ("no anxiety at all") to 10 ("extreme anxiety"). Patients indicated their level of anxiety by marking a point along the line. Scores were categorized as follows: 0-3.00 indicated mild anxiety; 3.01-

Table 1. General characteristics of patients grouped by severity of nausea and vomiting

Characteristic	Mild nausea and vomiting (n = 185)	Moderate to severe nausea and vomiting (n = 116)	t/χ^2	P
Gender (Male/Female)	119 (64.32%)/66 (35.68%)	74 (63.79%)/42 (36.21%)	0.009	0.925
Age (years)	63.43 ± 3.10	63.83 ± 3.27	1.050	0.294
BMI (kg/m)	20.22 ± 2.49	20.48 ± 2.55	0.870	0.385
Marital status (Married/Others)	163 (88.11%)/22 (11.89%)	102 (87.93%)/14 (12.07%)	0.002	0.963
Educational Level			1.678	0.432
Junior High School and Below	117 (63.24%)	80 (68.97%)		
High school	47 (25.41%)	22 (18.97%)		
College and Above	21 (11.35%)	14 (12.07%)		
Hypertension	120 (64.86%)	63 (54.31%)	3.332	0.068
Diabetes mellitus	44 (23.78%)	26 (22.41%)	0.075	0.784
Cardiovascular disease	43 (23.24%)	25 (21.55%)	0.117	0.733
History of depression	16 (8.65%)	13 (11.21%)	0.536	0.464
History of coronary heart disease	17 (9.19%)	20 (17.24%)	4.288	0.038
History of brain disease	20 (10.81%)	17 (14.66%)	0.977	0.323
ASA classification			1.188	0.276
I	147 (79.46%)	98 (84.48%)		
II	38 (20.54%)	18 (15.52%)		
MMSE score	26.90 ± 2.22	27.09 ± 2.18	0.706	0.481
RCSQ score	17.70 ± 4.28	18.03 ± 4.22	0.656	0.512
TNM stage (≤ II/> II)	54 (29.19%)/131 (70.81%)	39 (33.62%)/77 (66.38%)	0.656	0.418
ECOG performance status (0/≥ 1)	109 (58.92%)/76 (41.08%)	68 (58.62%)/48 (41.38%)	0.003	0.959
INVR score	15.79 ± 0.95	17.18 ± 1.19	10.603	< 0.001
Before chemotherapy	6.04 ± 0.49	6.08 ± 0.42	9801.500	0.207
VAS Scores Before chemotherapy	5.96 ± 0.51	6.12 ± 0.47	2.838	0.005
Previous chemotherapy			1.902	0.168
≤ 2	138 (74.59%)	78 (67.24%)		
> 2	47 (25.41%)	38 (32.76%)		

BMI: body mass index; ASA: The American Society of Anesthesiologists; MMSE: Mini-Mental State Examination; RCSQ: Rey Cognitive Screening Questionnaire; TNM stage: Tumor Node Metastasis stage; ECOG: Eastern Cooperative Oncology Group; INVR: Index of nausea, vomiting, and retching; VAS: Visual Analogue Scale.

6.99 indicated moderate anxiety; > 7.00 indicated severe anxiety.

Statistical methods

Statistical analysis was performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were presented as frequencies and percentages [n (%)] and compared using the chi-square test or Fisher's exact test when appropriate. The Shapiro-Wilk test was used to assess normality of continuous variables. Normally distributed data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) and compared using the independent samples t-test, while non-normally distributed data were expressed as median (interquartile range) and compared using the Wilcoxon rank-sum test. A *p*-value < 0.05 was considered significant. To identify factors influencing CINV severity in LSCC patients, univariate and multivariate logistic regression analyses were conducted.

Results

Comparison of general characteristics by CINV severity

Among the 301 patients evaluated, 185 experienced mild nausea and vomiting, while 116 reported moderate to severe symptoms (**Table 1**). No significant differences were found between the two groups regarding gender, age, BMI, marital status, education level, hypertension, diabetes, or general cardiovascular disease (all P > 0.050). However, a history of coronary heart disease was significantly more prevalent in the moderate to severe group (P = 0.038).

Table 2. Comparison of laboratory data before chemoradiotherapy between two groups

Characteristic	Mild nausea and vomiting (n = 185)	Moderate to severe nausea and vomiting (n = 116)	t	P
Neutrophils (×10³/μL)	3.29 ± 1.17	3.58 ± 1.08	2.140	0.033
Red blood cells (×10³/mL)	6.34 ± 1.03	6.11 ± 1.04	1.826	0.069
White blood cells (×10³/mL)	6.41 ± 1.22	6.53 ± 1.13	0.840	0.402
Hemoglobin, g/dL	11.79 ± 2.35	12.14 ± 2.16	1.316	0.189
Platelet (×10³/mL)	225.96 ± 56.78	238.66 ± 55.97	1.905	0.058
Lymphocyte (/μL)	6.34 ± 2.11	5.92 ± 1.92	1.768	0.078
Albumin (g/dl)	3.76 ± 0.38	3.88 ± 0.43	2.377	0.018
Creatinine (mg/dL)	7.01 ± 1.64	7.13 ± 1.29	0.694	0.489
AST (U/L)	20.13 ± 5.59	19.58 ± 5.23	0.869	0.386
ALT (U/L)	17.65 ± 3.48	16.82 ± 3.89	1.883	0.061
LDH (U/L)	179.85 ± 33.16	182.23 ± 32.56	0.612	0.541
BUN (mg/dl)	17.49 ± 3.49	16.84 ± 3.41	1.596	0.112
TC (mg/dl)	1.66 ± 0.47	1.59 ± 0.54	1.241	0.216
T-Bil (mg/dL)	0.64 ± 0.15	0.63 ± 0.13	1.152	0.250

AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; BUN: Blood Urea Nitrogen; TC: total cholesterol; T-Bil: total bilirubin.

Table 3. Comparison of tumor markers before chemoradiotherapy between two groups

Characteristic	Mild nausea and vomiting (n = 185)	Moderate to severe nausea and vomiting (n = 116)	t	P
NSE (ng/mL)	10.89 ± 3.04	10.62 ± 2.89	0.789	0.431
Pro GRP (pg/mL)	21.22 ± 7.21	22.47 ± 6.67	1.540	0.125
CEA (ng/mL)	2.57 ± 1.01	2.39 ± 1.04	1.464	0.145
CYFRA 21-1 (ng/mL)	1.75 ± 0.46	1.86 ± 0.56	1.820	0.070

NSE: Neuron-Specific Enolase; Pro GRP: Pro-Gastrin-Releasing Peptide; CEA: Carcinoembryonic Antigen; CYFRA 21-1: Cytokeratin 19 Fragment.

Cognitive function and sleep quality, assessed by MMSE and RCSQ scores, respectively, showed no significant intergroup differences (both P > 0.05). Additionally, INVR scores were significantly higher in the moderate to severe group (P < 0.001). Pre-chemotherapy anxiety scores were also significantly higher in this group (P = 0.005).

TNM staging and ECOG performance status did not significantly differ between groups (both P > 0.05). Although patients with moderate to severe symptoms tended to have undergone more previous chemotherapy sessions, the difference was not statistically significant (P = 0.168).

Comparison of neutrophils, platelets, and albumin

Neutrophil counts were significantly higher in the moderate to severe group compared to the mild group (P = 0.033) (**Table 2**). Platelet counts were also higher in the moderate to severe group, approaching significance (P = 0.058). Serum albumin levels were significantly higher in the moderate to severe group (P = 0.018).

Comparison of tumor markers

There were no significant differences in tumor marker levels - NSE (P = 0.431), Pro-GRP (P = 0.125), CEA (P = 0.145), and CYFRA21-1 (P = 0.070) - between the two groups, suggesting these markers are not associated with CINV severity (**Table 3**).

Comparison of pulmonary function and blood gas analysis

FEV_1% was significantly higher in the mild group compared to the moderate to severe group (P = 0.028) (**Figure 1**). Although FVC% was also

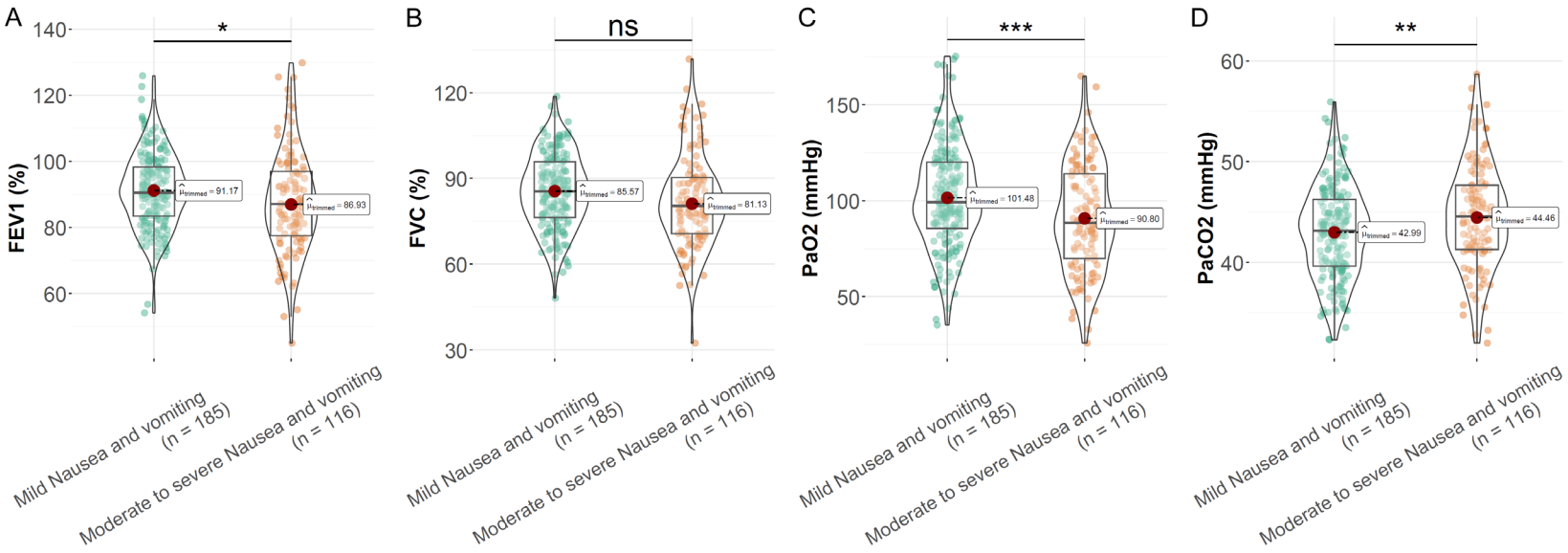

Figure 1. Comparison of respiratory function indicators before chemoradiotherapy between the two groups of patients. A: FEV_1 (%); B: FVC (%); C: PaO_2 (mmHg); D: $PaCO_2$ (mmHg). FEV_1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity. ns: No significant difference; *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$.

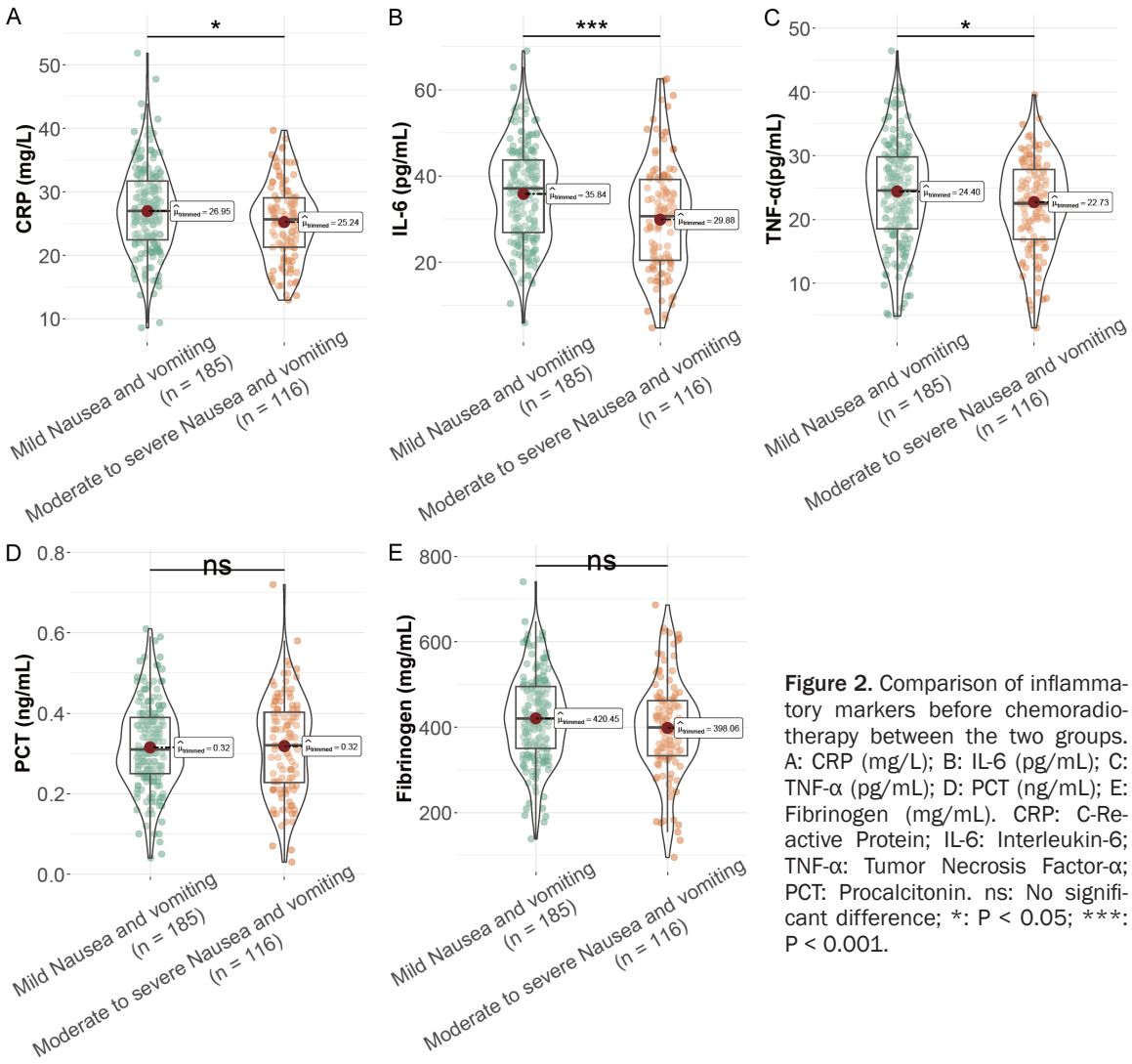

Figure 2. Comparison of inflammatory markers before chemoradiotherapy between the two groups. A: CRP (mg/L); B: IL-6 (pg/mL); C: TNF-α (pg/mL); D: PCT (ng/mL); E: Fibrinogen (mg/mL). CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α; PCT: Procalcitonin. ns: No significant difference; *: P < 0.05; ***: P < 0.001.

higher in the mild group, the difference was not statistically significant (P = 0.082). PaO_2 levels were markedly higher in the mild group (P < 0.001), while $PaCO_2$ levels were significantly lower (P = 0.005), indicating a correlation between better respiratory function and reduced symptom severity.

Comparison of inflammatory markers

CRP levels were significantly higher in the mild group than in the moderate to severe group (P = 0.013) (**Figure 2**). Similarly, IL-6 and TNF-α levels were elevated in the mild group (both P < 0.001). These results suggest a possible inverse relationship between inflammatory activity and CINV severity. In contrast, PCT levels did not differ significantly between groups (P = 0.986). Fibrinogen levels showed a non-significant trend toward being higher in the mild group (P = 0.069).

Univariate logistic regression analysis

Univariate logistic regression identified several factors associated with moderate to severe CINV (**Table 4**). A history of coronary heart disease increased the odds of severe symptoms (OR = 2.059, P = 0.041). Higher VAS anxiety scores were also predictive (OR = 1.992, P = 0.005). Each 1% increase in FEV_1 was associated with reduced risk (OR = 0.973, P = 0.002). Higher neutrophil counts were associated with greater severity (OR = 1.246, P = 0.038). Lower albumin levels were linked to more severe symptoms (OR = 2.060, P =

Table 4. Univariate logistic regression analysis of nausea and vomiting severity in patients with LSCC post-chemotherapy

	Coefficient	Std error	Wald	OR	P	AIC	BIC
History of coronary heart disease	0.722	0.354	2.041	2.059	0.041	401.144	408.558
VAS	0.689	0.248	2.779	1.992	0.005	397.300	404.714
Neutrophils ($\times 10^3/\mu L$)	0.220	0.106	2.079	1.246	0.038	400.903	408.318
Albumin (g/dl)	0.723	0.302	2.395	2.060	0.017	399.423	406.838
FEV_1 (%)	-0.022	0.009	-2.337	0.979	0.019	399.669	407.083
PaO_2 (mmHg)	-0.015	0.005	-3.314	0.985	< 0.001	393.664	401.078
$PaCO_2$ (mmHg)	0.069	0.025	2.750	1.071	0.006	397.486	404.900
CRP (mg/L)	-0.045	0.019	-2.392	0.956	0.017	399.379	406.794
IL-6 (pg/mL)	-0.039	0.010	-3.681	0.962	< 0.001	390.848	398.262
TNF-α (pg/mL)	-0.032	0.015	-2.056	0.969	0.040	401.017	408.431

FEV_1: Forced Expiratory Volume in one second; CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α.

Table 5. Multivariate logistic regression analysis of nausea and vomiting severity in patients with LSCC post-chemotherapy

	Coefficient	Std Error	Wald Stat	OR	OR CI Lower	OR CI Upper	P
History of coronary heart disease	1.048	0.399	2.623	2.851	1.303	6.236	0.009
VAS	0.566	0.273	2.072	1.761	1.031	3.007	0.038
Neutrophil ($\times 10^3/\mu L$)	0.171	0.119	1.436	1.187	0.939	1.499	0.151
Albumin (g/dl)	0.635	0.334	1.898	1.886	0.980	3.633	0.048
FEV_1 (%)	-0.020	0.010	-1.987	0.980	0.961	1.000	0.047
PaO_2 (mmHg)	-0.015	0.005	-3.097	0.985	0.975	0.994	0.002
$PaCO_2$ (mmHg)	0.068	0.028	2.465	1.071	1.014	1.131	0.014
CRP (mg/L)	-0.035	0.021	-1.694	0.966	0.927	1.005	0.090
IL-6 (pg/mL)	-0.039	0.011	-3.363	0.962	0.941	0.984	< 0.001
TNF-α (pg/mL)	-0.026	0.017	-1.514	0.974	0.942	1.008	0.130

FEV_1: Forced Expiratory Volume in one second; CRP: C-Reactive Protein; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-α.

0.017). Unexpectedly, higher levels of CRP, IL-6, and TNF-α were inversely associated with symptom severity (CRP: OR = 0.956, P = 0.017; IL-6: OR = 0.962, P < 0.001; TNF-α: OR = 0.969, P = 0.040), suggesting complex immunological modulation.

Multivariate logistic regression analysis

In the multivariate model (**Table 5**), the following factors remained independently associated with CINV severity: Coronary heart disease history (OR = 2.851, P = 0.009) Higher VAS anxiety scores (OR = 1.761, P = 0.038) Increased FEV_1% as a protective factor (OR = 0.980, P = 0.047) Higher albumin levels were associated with increased symptom severity (OR = 1.886, P = 0.048). Higher PaO_2 was protective (OR = 0.985, P = 0.002), whereas higher $PaCO_2$ was a risk factor (OR = 1.071, P = 0.014). CRP showed a marginally protective effect (OR = 0.966, P = 0.090). IL-6 remained a strong protective factor (OR = 0.962, P < 0.001). TNF-α approached statistical significance (OR = 0.972, P = 0.095). Neutrophil count was not significant in the adjusted model (OR = 1.187, P = 0.151).

Discussion

This study investigated the factors influencing the severity of CINV in patients with LSCC, offering important insight into its multifactorial nature. Understanding these contributing factors may enable the development of targeted interventions to mitigate CINV severity and improve patient outcomes.

One notable finding was the association between a history of coronary heart disease

and increased CINV severity. This relationship may be explained by several overlapping mechanisms. Cardiovascular health influences systemic inflammation and autonomic nervous system activity - both of which are implicated in the body's response to chemotherapy. CINV is largely mediated by the central nervous system through neurotransmitters such as serotonin and dopamine, which also regulate cardiovascular function [23]. Patients with coronary artery disease often exhibit heightened sympathetic activity, which may increase gastrointestinal sensitivity or alter central processing of nausea signals, thereby intensifying CINV [24, 25]. Moreover, endothelial dysfunction - a hallmark of coronary heart disease - can impair microcirculation in gastrointestinal tissues, resulting in localized hypoxia and metabolic disturbances that further exacerbate symptoms [26]. Oxidative stress, also driven by endothelial dysfunction, may worsen gastrointestinal discomfort. Previous research has shown that patients with cardiovascular comorbidities often experience more severe chemotherapy-related side effects due to reduced physiological reserves and impaired systemic compensation [27]. Future studies should explore whether cardiovascular optimization strategies can help attenuate CINV and enhance patients' resilience to chemotherapy.

Another important observation was the inverse association between pulmonary function indicators (e.g., FEV_1 and PaO_2) and CINV severity. Each percentage increase in FEV_1 was associated with a reduced risk of severe symptoms, suggesting a protective role of optimal respiratory function. Adequate pulmonary function ensures better oxygenation and metabolic homeostasis, thereby reducing physiological stress and improving chemotherapy tolerance [28, 29]. Conversely, impaired respiration can lead to carbon dioxide retention and respiratory acidosis, stimulating central chemoreceptors and enhancing nausea susceptibility [30]. Patients with chronic obstructive pulmonary disease, who exhibit similar respiratory deficits, are known to be more vulnerable to chemotherapy-related complications [31, 32], and similar mechanisms may apply to LSCC patients. Therefore, pre-treatment respiratory assessment is essential. Pulmonary rehabilitation and supplemental oxygen therapy may serve as effective supportive strategies to reduce CINV in patients with compromised lung function. Consistent with this, higher PaO_2 levels were protective, while elevated $PaCO_2$ levels were associated with more severe symptoms, reinforcing the role of respiratory physiology in modulating chemotherapy side effects.

Notably, we observed a paradoxical association between serum albumin levels and CINV severity, where higher albumin predicted worse symptoms. While hypoalbuminemia typically correlates with poor prognosis, our finding may reflect a unique pharmacodynamic interaction in LSCC patients receiving cisplatin-based regimens. Cisplatin is primarily bound and transported by albumin; so elevated albumin levels could increase drug-binding capacity, prolonging systemic exposure to cause gastrointestinal toxicity [33]. Concurrently, hyperoncotic states induced by high albumin may exacerbate intestinal mucosal dehydration through osmotic shifts, sensitizing the gut epithelium to chemotherapy-induced damage [34]. This highlights a need for personalized nutritional assessment: albumin optimization (rather than maximization) may be warranted in LSCC patients undergoing EP chemotherapy [35].

Equally unexpected was the protective role of elevated inflammatory markers (CRP, IL-6, TNF-α) against severe CINV. This inverse relationship challenges conventional views that inflammation universally exacerbates chemotherapy toxicity. Mechanistically, pre-existing mild inflammation may induce neuro-adaptive responses: IL-6 can suppress $5\text{-}HT_3$ receptor expression in the dorsal vagal complex, reducing emetic signaling [36]. Furthermore, inflammation may induce compensatory gastrointestinal adaptations or modulate blood-brain barrier permeability, influencing the central effects of chemotherapeutic agents [37]. These findings challenge the conventional belief that inflammation universally worsens chemotherapy side effects, suggesting instead that inflammatory responses may exert biphasic effects - potentially beneficial at certain levels or stages [38]. Further mechanistic studies are needed to clarify this paradox and to evaluate whether selective modulation of inflammatory mediators can be leveraged for CINV prevention.

Furthermore, anxiety - an important psychological factor influencing CINV - highlights the critical mind-body connection in symptom perception and management. Anxiety may amplify

symptom awareness and lower the threshold for negative expectancy, engaging complex neuronal circuits and stress-associated neurotransmitters [39, 40]. Therefore, managing anxiety through pharmacologic or psychological interventions prior to chemotherapy may help reduce CINV by modulating physiological reactivity and enhancing psychological resilience [41]. These findings underscore the need for a holistic, patient-centered approach to symptom management in LSCC patients. Integrating cardiovascular and pulmonary assessments, nutritional evaluation, and comprehensive psychological support could significantly improve treatment outcomes and overall patient well-being.

However, this study had several limitations. First, the sample was restricted to patients with LSCC, which may limit the generalizability of the findings to other cancer types. Second, anxiety and symptom severity were assessed using self-reported scales, which may be subject to reporting bias and inter-individual variability. Third, the observational design precluded causal inference regarding the relationship between the identified factors and CINV severity. Additionally, possible confounders - including variability in chemotherapy regimens, concomitant medications, and unmeasured comorbidities - were not fully controlled and may have influenced the observed associations. The paradoxical roles of albumin and inflammatory markers warrant validation in prospective trials with pharmacodynamic assessments. Future studies should include larger, more diverse populations, adopt longitudinal or prospective designs, and incorporate objective biomarkers to strengthen the evidence base. Randomized controlled trials will be essential to evaluate the effectiveness of integrated interventions for mitigating CINV. By applying a multidisciplinary model, we can better enhance both the quality of life and clinical outcomes of LSCC patients receiving chemotherapy.

Conclusion

This study identified key factors associated with CINV severity in LSCC patients, including physiological indicators, inflammatory biomarkers, and comorbid conditions. These findings reveal a complex interplay between biological systems and the body's response to chemotherapy. Notably, pre-chemotherapy anxiety levels were significantly linked to greater CINV severity and were associated with higher VAS scores and more frequent prior chemotherapy exposure, underscoring the relevance of psychological state in treatment response.

An integrated approach combining pharmacological management with psychosocial support is essential to address both biological and psychological determinants of CINV. Such a strategy has the potential to improve patient resilience, reduce symptom burden, and enhance overall quality of life. As advances in oncology continue to improve survival outcomes, equal emphasis must be placed on supportive care innovations to ensure comprehensive cancer treatment for patients with LSCC.

Disclosure of conflict of interest

None.

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