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Original Article

Predictors of febrile neutropenia in small cell lung cancer patients receiving concurrent chemoradiotherapy with etoposide and cisplatin: a focus on nutritional status, inflammation, and performance status

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Abstract: Small cell lung cancer (SCLC) is a rapidly proliferating malignancy with a poor prognosis, commonly treated with concurrent chemoradiotherapy based on the etoposide and cisplatin (EP) regimen; however, this treatment is often complicated by febrile neutropenia (FN), a potentially life-threatening condition that can compromise treatment efficacy and patient safety. The aim of this study was to identify risk factors for FN in SCLC patients undergoing EP-based concurrent chemoradiotherapy to enhance treatment outcomes and improve patient management. In this retrospective case-control study, data from 216 SCLC patients who underwent concurrent chemoradiotherapy with the EP regimen between September 2014 and January 2020 were analyzed. Patients were categorized into FN (n = 106) and non-FN (n = 110) groups. Various clinical factors, including body mass index (BMI), Eastern Cooperative Oncology Group Performance Status (ECOG PS), and pre-treatment laboratory values such as albumin, IL-6, and C-reactive protein (CRP), were examined. Statistical analyses, including univariate and multivariate logistic regression, were performed to identify independent risk factors for FN. Lower BMI (P = 0.016) and poorer ECOG Performance Status (P = 0.001) were associated with an increased risk of FN. Additionally, pre-albumin levels (P = 0.010), inflammatory markers CRP (P = 0.032), and IL-6 (P = 0.001) also showed significant associations, suggesting that nutritional status and systemic inflammation play important roles in the development of FN. Importantly, multivariate logistic regression analysis confirmed pre-albumin levels (P = 0.003), IL-6 level (P = 0.001), MASCC score (P < 0.001), and ECOG PS (P = 0.019) as independent factors for FN risk. These findings highlight the importance of nutritional status, systemic inflammation, and overall health condition in predicting FN occurrence, underscoring the need for integrated risk assessment and management strategies to mitigate FN risk in SCLC patients undergoing EP-based concurrent chemoradiotherapy.

Keywords: Febrile neutropenia, small cell lung cancer, chemoradiotherapy, etoposide, cisplatin, risk factors

Introduction

Small cell lung cancer (SCLC) is a highly aggressive neuroendocrine carcinoma characterized by rapid proliferation and early metastasis, accounting for roughly 10-15% of all lung cancer. Despite advances in therapeutic strategies, SCLC remains a clinical challenge due to its poor prognosis, with a 5-year survival rate below 7% [1-3]. Current treatment protocols predominantly rely on a combination of systemic chemotherapy and radiation therapy, with etoposide and cisplatin (EP) regimen emerging as a cornerstone in treating SCLC, particularly for patients with limited-stage disease [4]. While concurrent chemoradiotherapy offers potential survival benefits, it is often complicated by febrile neutropenia (FN) [5].

FN, defined as an absolute neutrophil count below 0.5 × 10^9/L accompanied by fever, is a significant and potentially life-threatening complication in cancer patients undergoing chemotherapy, necessitating prompt medical intervention. FN not only predisposes patients to severe infections but also frequently results in

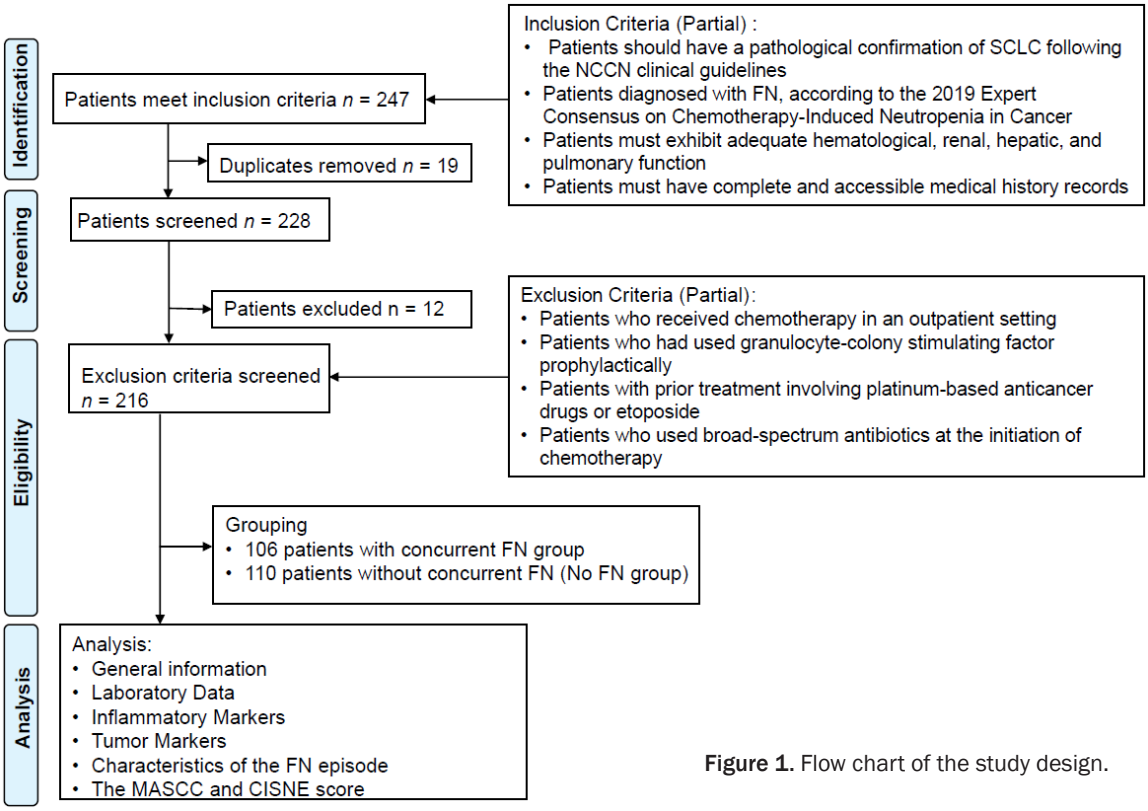

Figure 1. Flow chart of the study design.

chemotherapy dose reductions or delays, ultimately compromising treatment efficacy and adversely affecting patient prognosis [6-8]. Consequently, understanding and identifying the risk factors for FN in SCLC patients undergoing the EP regimen is imperative for improving treatment outcomes and patient safety.

Recent literature elucidates various risk factors contributing to FN, including patient-specific factors such as age, gender, functional status, nutritional status, and underlying comorbidities [9-11]. Other contributing factors include treatment-related, encompassing chemotherapy regimen, dose intensity, and the targeted volume of radiation therapy [12, 13]. Despite these recognized contributors, the specific risk profile for FN in SCLC patients receiving EP regimen warrants further investigation.

This study seeks to screen risk factors associated with FN in a cohort of SCLC patients undergoing concurrent chemoradiotherapy based on the EP regimen, aiming to inform tailored prophylactic and therapeutic strategies.

Methods

Patient selection

This retrospective case-control study analyzed data from 216 patients diagnosed with both SCLC and FN, who received concurrent chemoradiotherapy with etoposide and cisplatin at the First People's Hospital of Shangqiu City between September 2014 and January 2020. The study focused on several clinical factors, including age, gender, Eastern Cooperative Oncology Group Performance Status (ECOG PS), body mass index (BMI), clinical stage, and history of thoracic surgery. Additionally, we assessed pretreatment laboratory parameters, such as neutrophil count, hemoglobin level, serum albumin, aspartate aminotransferase (AST), and total bilirubin. The study design flowchart is shown in **Figure 1**.

Efforts were made to ensure patient confidentiality, maintaining anonymity throughout the study. This study was approved by the Medical Ethics Committee of First People's Hospital of Shangqiu City. Informed consent was waived as

the research utilized anonymized patient data exclusively, thereby presenting no risk or adverse effect on patient care.

Inclusion criteria: 1) Patients with a pathological diagnosis of SCLC in accordance with the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for SCLC [14]; 2) Patients diagnosed with FN as defined by the Expert Consensus on the Diagnosis and Management of Chemotherapy-Induced Neutropenia in Cancer Patients (2019 Edition). FN is characterized by an absolute neutrophil count (ANC) of < 0.5 × 10^9/L, or expected to drop below this level within 48 hours, along with an oral temperature ≥ 38.3°C or a sustained temperature ≥ 38.0°C for more than one hour; 3) Patients with adequate hematological, renal, hepatic, and pulmonary function; 4) Patients with complete and accessible medical history records.

Exclusion criteria: 1) Patients who received chemotherapy in an outpatient setting; 2) Patients who received prophylactical granulocyte-colony stimulating factor (G-CSF); 3) Patients with a prior treatment involving platinum-based anticancer drugs or etoposide; 4) Patients who used broad-spectrum antibiotics at the initiation of chemotherapy.

Grouping and treatment methods

The patients were categorized into two groups: the FN group (n = 106), consisting of patients who developed concurrent febrile neutropenia (FN), and the No FN group (n = 110), consisting of patients who did not develop FN. FN occurrence was monitored for 21 days following the initiation of cisplatin and etoposide therapy, with the timeframe for FN occurrence limited to within 28 days from the first chemotherapy session.

EP Therapy Protocol: The treatment protocol involved an initial cycle of concurrent chemoradiotherapy, followed by three cycles of consolidation chemotherapy. All patients received a standardized chemotherapy regimen, which included cisplatin (X20010743, Lianyungang Hengrui Pharmaceutical Co., Ltd., China) administered at a dosage of 40-80 mg/m^2 on day 1, in combination with etoposide (H32025583, Jiangsu Hengrui Medicine Co., Ltd., China) at a dosage of 80-100 mg/m^2 on days 1-3. Thoracic radiation therapy (TRT) commenced concurrently with the first cycle of chemotherapy, starting on day 1. A total dose of 44 Gy was delivered through daily fractions of 2.0 Gy over 22 sessions (excluding weekends and holidays), utilizing the anteroposterior/posteroanterior (AP/PA) portal arrangement.

Data extraction

Data extraction was performed using a standardized form that included demographic information, clinical characteristics, laboratory results, and treatment outcomes. Two independent reviewers extracted the data from medical records, and discrepancies were resolved through discussion or consultation with a third reviewer. The data were validated by cross-referencing with electronic health records and ensuring consistency across multiple sources.

Outcome measures

The primary outcome measure was the occurrence of FN within 28 days from the start of chemoradiotherapy. Secondary outcomes included laboratory parameters such as neutrophil count, albumin levels, CRP, IL-6, and MASCC score. These outcomes were assessed to identify risk factors associated with FN.

Selection of parameters for risk factor analysis

To ensure that the identified risk factors reflect intrinsic patient characteristics rather than treatment-induced changes, only parameters that showed significant differences between the FN and non-FN groups in the pre-treatment phase were selected for risk factor analysis. These included BMI, ECOG PS, pre-albumin, CRP, IL-6, and MASCC score. Parameters reflecting changes or clinical characteristics during the FN episodes, as presented in this paper, were not used for this purpose to avoid introducing confounding factors into the risk assessment model. This approach ensures that the selected parameters represent baseline patient conditions and are more likely to be independent predictors of FN risk.

Assessment tool

The ECOG PS score: The ECOG Performance Status (PS) is a widely utilized scale for evaluating the impact of a patient's disease on their

daily functional abilities. This scale ranges from 0 to 5, with lower scores denoting better functional status and higher scores indicating greater disability. The inter-rater reliability of this assessment, as measured by Cohen's κ, was 0.486 [15]. The ECOG PS includes the following five categories.

0: Fully active. 1: Capable of mild physical exertion, though strenuous activities are restricted. 2: Mobile and can manage personal care independently but unable to engage in work-related activities; active for more than half of waking hours. 3: Only able to handle basic self-care tasks with limitations; and spends more than 50% of waking hours confined to bed or a chair. 4: Entirely incapacitated. 5: Deceased.

Complete blood count and biochemical profile: Fasting venous blood (5 ml) was collected from each patient before 8 a.m. Neutrophils, lymphocytes, platelets, and monocytes were detected using the DxH800 blood analyzer (Beckman Coulter, Inc., Brea, CA, USA). Albumin, potassium, blood glucose, blood lipids, as well as liver and renal functions were assessed with the BECKMAN Synchron ×20 fully automatic biochemical analyzer (Beckman Coulter, Inc., Brea, CA, USA). These evaluations were carried out within two days prior to the initiation of the first chemotherapy cycle.

Inflammatory and tumor markers: Fasting venous blood (4 ml) was collected into a disposable vacuum tube without anticoagulant. The sample was incubated at 37°C until full clotting, then centrifuged at 3,000 g for 10 minutes at 4°C. The serum was stored at -20°C until cytokine analysis. CRP and procalcitonin levels were measured using enzyme-linked immunosorbent assay (ELISA; SPS-15252, Shanghai Saipuisen Biotechnology Co., Ltd., China; XY-E10643, Shanghai Xinyu Biotechnology Co., Ltd., China). TNF-α, fibrinogen, and IL-6 levels were also quantified using ELISA kits (IL-6: BMS213-2TEN, Thermo Fisher Scientific Inc., USA; fibrinogen: DEC01969, Beijing Zhongke Quality Inspection Biotechnology Co., Ltd., China; TNF-α: PHC3016, Thermo Fisher Scientific Inc., USA). Neuron-specific enolase (NSE) and carcinoembryonic antigen (CEA) levels were measured with ELISA (NSE: CSB-E07961h, Huamei Biotech Co., Ltd., China; CEA: CSB-RA005165MA2HU, Huamei Biotech Co., Ltd., China). Additionally, Pro-gastrin-releasing peptide (Pro GRP) and cytokeratin 19 fragment (CYFRA 21-1) were assessed using ELISA (Pro GRP: FT-P32430R, Shanghai Fantai Biotechnology Co., Ltd., China; CYFRA 21-1: BJ005513, Shanghai Bangjing Industrial Co., Ltd., China).

The Multinational Association of Supportive Care in Cancer (MASCC) score: The MASCC scale was used to identify the risk of cancer patients developing FN. A MASCC score of 21 or higher indicates low risk. The reliability of the MASCC score was supported by a Cronbach's alpha of 0.72 [16].

The Clinical Index of Stable Febrile Neutropenia (CISNE) score: The CISNE score is a predictive tool used to assess the risk of serious complications in cancer patients who develop FN. The CISNE score ranges from 0 to 5 and is determined by considering factors such as age, neutrophil count, comorbidities, functional status, the site of infection. Higher scores indicate a greater risk of complications. The Cronbach's α was 0.78 [17].

Statistical analysis

Measurement data were represented as mean ± SD for normally distributed variables, and median (IQR) for non-normal distributions. Categorical data were shown as frequencies (%). Unpaired t-tests were used to compare continuous variables between two groups. Univariate and multivariate logistic regression analyses were performed to calculate the odds ratio (OR) and 95% confidence interval (CI) for each parameter (continuous variable). A p-value < 0.05 was considered with statistical significance. Analyses were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA) and R software version 3.0.2 (Free Software Foundation, Inc., Boston, MA, USA).

Sample size calculation

To ensure sufficient statistical power, we calculated the required sample size based on previous studies reporting similar outcomes. Assuming a prevalence of FN in SCLC patients treated with the EP regimen of approximately 50%, we aimed for a power of 80% and a significance level (α) of 0.05. Using the formula for comparing two proportions, we estimated that a total sample size of 84 patients (42 per group) would provide adequate power to detect a clini-

Table 1. Comparison of general information between two groups

Characteristic	FN group (n = 106)	No FN group (n = 110)	t/χ^2	P
Gender (F/M)	30 (28.30%)/76 (71.71%)	32 (29.09%)/78 (70.91%)	0.016	0.898
Age (years)	64.24 ± 8.45	63.84 ± 8.52	0.350	0.727
BMI (kg/m^2)	21.54 ± 3.62	22.71 ± 3.47	2.433	0.016
BSA (m^2)	1.53 ± 0.31	1.59 ± 0.32	1.307	0.193
Smoking history [n (%)]	64 (60.38%)	72 (65.45%)	0.597	0.440
Nutritional support [n (%)]	66 (62.26%)	70 (63.64%)	0.044	0.835
Weight loss [n (%)]			1.985	0.371
< 5%	89 (83.96%)	84 (76.36%)		
5-10%	10 (9.43%)	16 (14.55%)		
> 10%	7 (6.6%)	10 (9.09%)		
Previous thoracic surgery [n (%)]	11 (10.38%)	14 (12.73%)	0.291	0.589
Diabetes mellitus [n (%)]	35 (33.02%)	42 (38.18%)	0.627	0.428
Osteoporosis [n (%)]	6 (5.66%)	8 (7.27%)	0.232	0.630
COPD [n (%)]	17 (16.04%)	18 (16.36%)	0.004	0.948
Clinical stage [n (%)]			0.235	0.889
IIIA	26 (24.53%)	24 (21.82%)		
IIIB	58 (54.72%)	63 (57.27%)		
IV/postoperative recurrence	22 (20.75%)	23 (20.91%)		
Disease Stage [n (%)]			0.067	0.796
Limited	32 (30.19%)	35 (31.82%)		
Extensive	74 (69.81%)	75 (68.18%)		
Liver metastasis [n (%)]	23 (21.7%)	21 (19.09%)	0.226	0.634
Brain metastasis [n (%)]	52 (49.06%)	55 (50%)	0.019	0.890
Bone metastasis [n (%)]	21 (19.81%)	19 (17.27%)	0.231	0.631
ECOG PS			13.178	0.001
0	24 (22.64%) 30	34 (30.91%)	14/84/7	
1	70 (66.04%) 61	36 (32.73%)		
2	12 (11.32%) 15	40 (36.36%)		

F, female; M, male; BMI, body mass index; BSA, Body surface area; COPD, chronic obstructive pulmonary; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

cally meaningful difference between the FN and non-FN groups. This calculation was performed using G*Power software version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Germany). However, in our actual study, we included a larger cohort: FN group (n = 106) and No FN group (n = 110). The expanded sample size allowed for more robust statistical analysis and better representation of the patient population, enhancing the generalizability of our findings.

Results

General information

Patients in the FN group had a lower mean BMI of 21.54 ± 3.62 kg/m^2 compared to 22.71 ± 3.47 kg/m^2 in the no-FN group (t = 2.433, P = 0.016), indicating a potential association between lower BMI and increased risk of FN (**Table 1**). Additionally, the ECOG PS showed significant differences (χ^2 = 13.178, P = 0.001), with a higher proportion of patients in the FN group having ECOG PS scores of 1 and 2 compared to the non-FN group, suggesting that poorer ECOG PS scores may be associated with a higher incidence of FN. Other characteristics such as gender distribution, age, body surface area, smoking history, nutritional support, weight loss, previous thoracic surgery, comorbid conditions (including diabetes mellitus, osteoporosis, and chronic obstructive pulmonary disease), clinical stage, disease stage, and metastases to the liver, brain, and bone showed no statistically significant differences between the two groups (all P > 0.05). These findings highlight the importance of BMI and

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

Characteristic	FN group (n = 106)	No FN group (n = 110)	t	P
Neutrophil (× 10^3/μL)	3.35 ± 1.18	3.58 ± 1.07	1.502	0.135
Red blood cell (× 10^3/mL)	6.32 ± 1.04	6.12 ± 1.05	1.367	0.173
White blood cell (× 10^3/mL)	6.37 ± 1.21	6.52 ± 1.14	0.919	0.359
Hemoglobin, g/dL	11.88 ± 2.37	12.12 ± 2.15	0.761	0.448
Platelet (× 10^3/mL)	225.48 ± 56.45	238.54 ± 55.98	1.708	0.089
Lymphocyte (/μL)	6.42 ± 2.01	5.99 ± 1.95	1.605	0.110
Albumin (g/dl)	3.72 ± 0.36	3.86 ± 0.42	2.584	0.010
Creatinine (mg/dL)	7.01 ± 1.52	7.12 ± 1.27	0.556	0.579
AST (U/L)	20.12 ± 5.68	19.61 ± 5.21	0.696	0.487
ALT (U/L)	17.65 ± 3.59	16.83 ± 3.78	1.640	0.103
LDH (U/L)	178.44 ± 33.07	182.21 ± 32.54	0.845	0.399
BUN (mg/dl)	17.37 ± 3.51	16.81 ± 3.42	1.197	0.233
TC (mg/dl)	1.65 ± 0.53	1.58 ± 0.54	0.944	0.346
T-Bil (mg/dL)	0.62 ± 0.13	0.61 ± 0.11	0.594	0.553

AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase; TC, total cholesterol; T-Bil, total bilirubin.

ECOG PS as potential risk factors for developing FN in this patient population.

Laboratory data

The FN group had a lower mean pre-treatment albumin level of 3.72 ± 0.36 g/dL compared to 3.86 ± 0.42 g/dL in the non-FN group (t = 2.584, P = 0.010), suggesting that reduced albumin levels before intervention may be associated with an increased risk of FN (**Table 2**). Conversely, no statistically significant differences were found between the two groups in other pre-intervention laboratory parameters, including neutrophil count, red blood cell count, white blood cell count, hemoglobin, platelet count, lymphocyte count, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), total cholesterol (TC), and total bilirubin (T-Bil) (all P > 0.05). These findings highlight albumin as a potential biomarker for assessing the risk of FN in this patient cohort.

The mean post-treatment neutrophil count in the FN group was 1.59 ± 0.51 × 10^3/μL, significantly lower than the 3.14 ± 0.63 × 10^3/μL observed in the non-FN group (t = 19.929, P < 0.001), indicating a strong association between decreased neutrophil levels and the occurrence of FN (**Table 3**). Conversely, no significant differences were observed between the groups in other post-treatment laboratory parameters, including red blood cell count, white blood cell count, hemoglobin, platelet count, lymphocyte count, albumin, creatinine, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), blood urea nitrogen (BUN), total cholesterol (TC), and total bilirubin (T-Bil) (all P > 0.05). This highlights the significant role of neutrophil reduction in the development of FN in patients undergoing this treatment regimen.

Inflammatory markers

The FN group exhibited higher CRP levels at 27.15 ± 6.89 mg/L compared to 25.26 ± 6.01 mg/L in the non-FN group (t = 2.152, P = 0.032), as well as elevated IL-6 levels (35.81 ± 11.32 pg/mL vs 30.44 ± 12.62 pg/mL; t = 3.292, P = 0.001) (**Figure 2**). These findings suggest an association between heightened inflammatory response, as indicated by CRP and IL-6, and the development of FN. There were no significant differences between the two groups regarding tumor necrosis factor-α (TNF-α), procalcitonin (PCT), and fibrinogen levels (all P > 0.05). These results highlight CRP and IL-6 as potential inflammatory markers linked to FN in patients treated with the EP regimen.

Tumor markers

The mean levels of NSE were 10.88 ± 3.05 ng/mL in the FN group and 10.62 ± 2.91 ng/mL in the non-FN group (t = 0.649, P = 0.517) (**Table 4**). Pro-gastrin-releasing peptide (Pro GRP) levels were 21.21 ± 7.24 pg/mL in the FN group

Table 3. Comparison of laboratory data after chemoradiotherapy between two groups

Characteristic	FN group (n = 106)	No FN group (n = 110)	t	P
Neutrophil (× 10^3/μL)	1.59 ± 0.51	3.14 ± 0.63	19.929	< 0.001
Red blood cell (× 10^3/mL)	5.82 ± 1.05	5.87 ± 1.05	0.334	0.739
White blood cell (× 10^3/mL)	5.66 ± 1.24	5.72 ± 1.24	0.332	0.740
Hemoglobin, g/dL	11.45 ± 2.41	11.12 ± 2.34	1.019	0.309
Platelet (× 10^3/mL)	238.47 ± 55.84	242.54 ± 56.64	0.531	0.596
Lymphocyte (/μL)	6.13 ± 1.91	6.24 ± 2.02	0.402	0.688
Albumin (g/dl)	3.77 ± 0.32	3.84 ± 0.33	1.535	0.126
Creatinine (mg/dL)	7.25 ± 1.58	7.62 ± 1.55	1.733	0.084
AST (U/L)	18.36 ± 5.62	18.94 ± 5.47	0.776	0.439
ALT (U/L)	17.53 ± 4.01	16.82 ± 3.91	1.322	0.188
LDH (U/L)	179.58 ± 32.81	180.37 ± 33.48	0.175	0.862
BUN (mg/dl)	17.14 ± 3.47	16.63 ± 3.58	1.061	0.290
TC (mg/dl)	1.62 ± 0.52	1.6 ± 0.55	0.338	0.736
T-Bil (mg/dL)	0.56 ± 0.11	0.55 ± 0.12	0.181	0.857

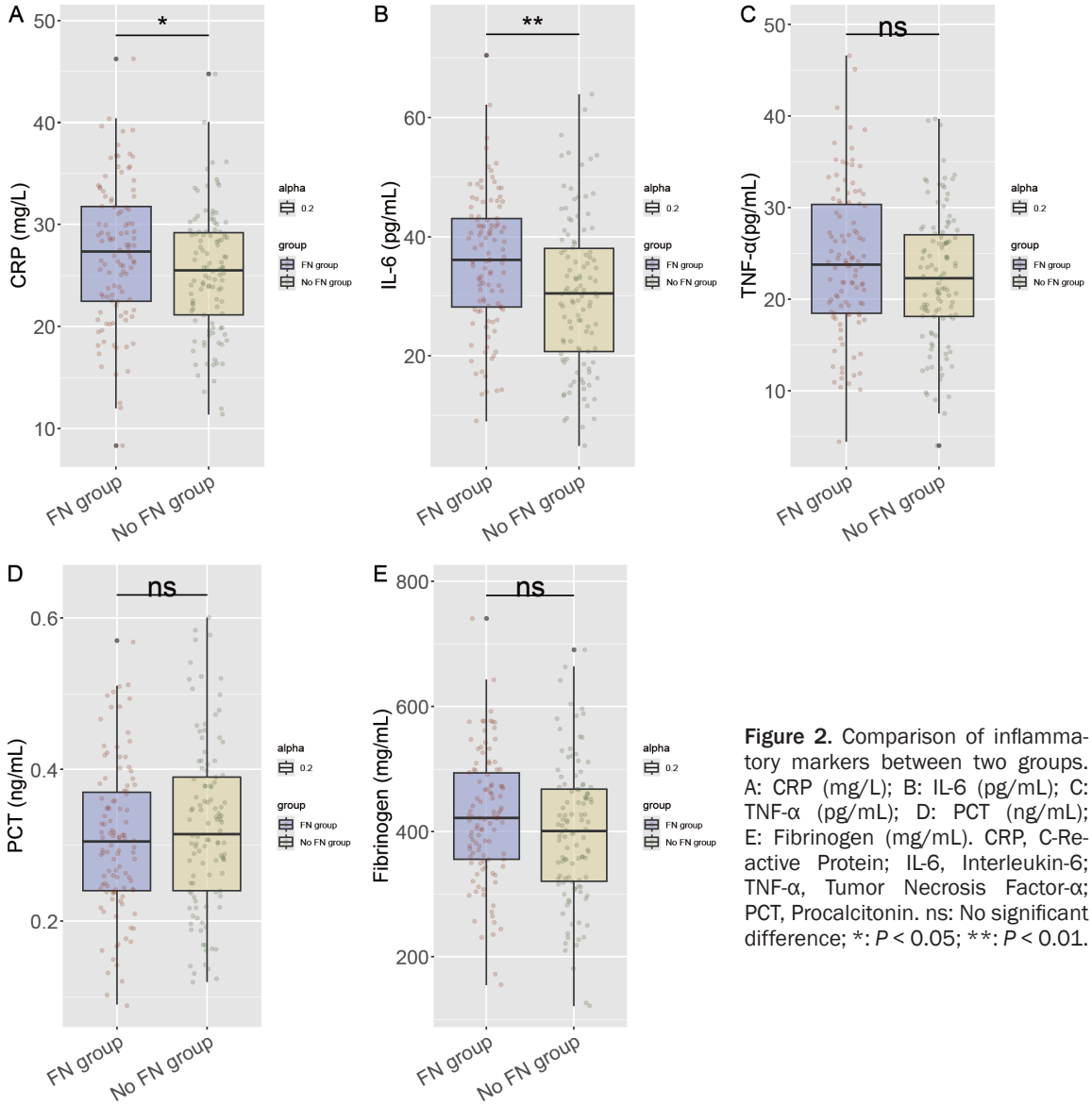

Figure 2. Comparison of inflammatory markers between two groups. A: CRP (mg/L); B: IL-6 (pg/mL); C: TNF-α (pg/mL); D: PCT (ng/mL); E: Fibrinogen (mg/mL). CRP, C-Reactive Protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; PCT, Procalcitonin. ns: No significant difference; *: $P < 0.05$; **: $P < 0.01$.

Table 4. Comparison of tumor markers between two groups

Characteristic	FN group (n = 106)	No FN group (n = 110)	t	P
NSE (ng/mL)	10.88 ± 3.05	10.62 ± 2.91	0.649	0.517
Pro GRP (pg/mL)	21.21 ± 7.24	22.45 ± 6.69	1.305	0.193
CEA (ng/mL)	2.56 ± 1.12	2.37 ± 1.02	1.304	0.193
CYFRA 21-1 (ng/mL)	1.72 ± 0.48	1.84 ± 0.55	1.670	0.096

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

Table 5. Comparison of characteristics of the FN episode between two groups

Characteristic	FN group (n = 106)	No FN group (n = 110)	χ^2	P
Productive cough [n (%)]	48 (45.28%)	33 (30%)	5.380	0.020
Urinary infection [n (%)]	11 (10.38%)	10 (9.09%)	0.102	0.750
Abnormal X-ray without pneumonia at the onset [n (%)]	19 (17.92%)	8 (7.27%)	5.600	0.018
Dehydration [n (%)]	15 (14.15%)	16 (14.55%)	0.007	0.934
Chills [n (%)]	17 (16.04%)	18 (16.36%)	0.004	0.948

and 22.45 ± 6.69 pg/mL in the non-FN group (t = 1.305, P = 0.193). Carcinoembryonic antigen (CEA) level was 2.56 ± 1.12 ng/mL in the FN group and 2.37 ± 1.02 ng/mL in the non-FN group (t = 1.304, P = 0.193). Similarly, cytokeratin 19 fragment (CYFRA 21-1) level was 1.72 ± 0.48 ng/mL in the FN group compared to 1.84 ± 0.55 ng/mL in the non-FN group (t = 1.670, P = 0.096). These results indicate that the tumor markers evaluated did not show a significant association with the occurrence of FN in patients receiving the EP regimen.

Characteristics of the FN episode

Productive cough was more frequent in the FN group, occurring in 48 patients (45.28%) compared to 33 patients (30%) in the non-FN group (χ^2 = 5.380, P = 0.020) (**Table 5**). Similarly, abnormal X-ray findings without pneumonia were noted in 19 patients (17.92%) in the FN group compared to 8 patients (7.27%) in the non-FN group (χ^2 = 5.600, P = 0.018). Conversely, no statistically significant differences were found between the two groups for urinary infection, dehydration, or chills (all P > 0.05). These results suggest that productive cough and abnormal X-ray findings without pneumonia may be associated with FN episodes in patients undergoing concurrent chemoradiotherapy with the EP regimen.

The MASCC and CISNE score

A MASCC score of ≥ 21 was observed in 63 patients (59.43%) in the FN group compared to 96 patients (87.27%) in the non-FN group (χ^2 = 21.537, P < 0.001), indicating that a lower MASCC score was associated with a higher incidence of FN (**Figure 3**). In contrast, the CISNE score did not demonstrate a statistically significant difference between the groups, with scores ≥ 3 found in 64 patients (60.38%) in the FN group and 55 patients (50.00%) in the non-FN group (χ^2 = 2.350, P = 0.125). These results suggest that the MASCC score may be a more reliable indicator of FN risk in patients undergoing concurrent chemoradiotherapy with the EP regimen.

Correlation analysis

The correlation analysis (**Table 6**) identified several factors significantly associated with the risk of FN in SCLC patients undergoing concurrent chemoradiotherapy based on the EP regimen. Specifically, BMI (rho = -0.145, P = 0.033), ECOG PS (rho = -0.137, P = 0.045), pre-Albumin levels (rho = -0.147, P = 0.031), CRP concentrations (rho = 0.143, P = 0.035), IL-6 levels (rho = 0.229, P < 0.001), and the MASCC score (rho = -0.316, P < 0.001) exhibited significant correlations with FN risk.

Receiver operating characteristic (ROC) curve analysis

To further evaluate the predictive performance of BMI, ECOG PS, pre-Albumin, CRP, IL-6, and MASCC score for identifying patients at risk of FN, ROC curve analyses were conducted to

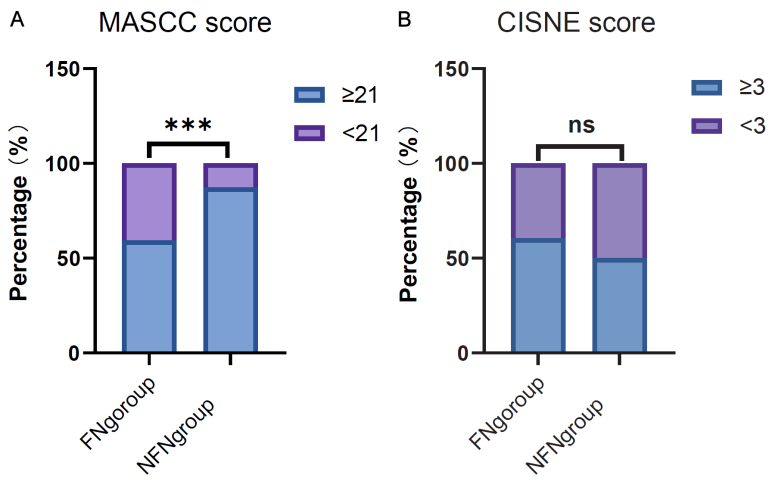

Figure 3. Comparison of the MASCC and CISNE score between two groups. A: MASCC score; B: CISNE score. MASCC score, Multinational Association of Supportive Care in Cancer score; CISNE score, clinical index of stable febrile neutropenia score. ***: $P < 0.001$; ns: No significant difference.

Table 6. Correlation analysis of various factors with FN

Characteristic	rho	P
BMI (kg/m^2)	-0.145	0.033
ECOG PS	-0.137	0.045
pre-Albumin (g/dl)	-0.147	0.031
CRP (mg/L)	0.143	0.035
IL-6 (pg/mL)	0.229	$P < 0.001$
MASCC score [n (%)]	-0.316	$P < 0.001$

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRP, C-Reactive Protein; IL-6, Interleukin-6; MASCC score, Multinational Association of Supportive Care in Cancer score.

determine their optimal cut-off values. The areas under the ROC curves (AUCs) and corresponding Youden indices were calculated. For BMI, an AUC of 0.584 was observed, with an optimal cut-off value of 20.71 kg/m^2, yielding a Youden index of 0.143. Regarding ECOG PS, the AUC was 0.426, and the optimal cut-off was set at -Inf, resulting in a Youden index of 0. For pre-Albumin, the AUC was 0.585, with an optimal cut-off value of 3.685 g/dL and a Youden index of 0.163. For CRP, the AUC was 0.583, and the optimal cut-off value was determined to be 31.42 mg/L, leading to a Youden index of 0.183. IL-6 showed a higher discriminatory power, with an AUC of 0.632 and an optimal cut-off value of 31.8 pg/mL, achieving a Youden index of 0.233. Finally, the MASCC score had the lowest AUC among all parameters at 0.361, with an optimal cut-off value of -Inf and a Youden index of 0. These findings suggest that IL-6 level has the highest discriminatory power for predicting FN. The cut-off values derived from the ROC analysis can serve as reference points for clinical decision-making to identify high-risk patients for FN (**Figure 4**).

Univariate logistic regression analysis

The univariate logistic regression analysis identified several factors significantly linked to the risk of FN in patients with SCLC undergoing concurrent chemoradiotherapy based on the EP regimen (**Table 7**). Specifically, BMI (kg/m^2) (OR = 0.910, 95% CI: 0.840-0.982, $P = 0.017$), ECOG PS (OR = 0.686, 95% CI: 0.477-0.977, P = 0.039), pre-Albumin levels (g/dl) (OR = 0.402, 95% CI: 0.194-0.807, $P = 0.012$), CRP concentrations (mg/L) (OR = 1.047, 95% CI: 1.004-1.093, $P = 0.034$), IL-6 levels (pg/mL) (OR = 1.038, 95% CI: 1.015-1.063, $P = 0.002$), and the MASCC score (OR = 0.214, 95% CI: 0.105-0.414, $P < 0.001$) all showed significant associations with FN risk.

Multivariate logistic regression analysis

Multivariate logistic regression analysis identified significant independent associations between several factors and the risk of FN in patients with SCLC undergoing concurrent chemoradiotherapy based on the EP regimen (**Table 8**), including pre-Albumin level (OR = 0.287, 95% CI: 0.127-0.648, $P = 0.003$), IL-6 level (OR = 1.044, 95% CI: 1.017-1.073, $P = 0.001$), and MASCC score (OR = 0.187, 95% CI: 0.088-0.39, $P < 0.001$). ECOG PS also showed a significant association with FN risk (OR = 0.615, 95% CI: 0.410-0.922, $P = 0.019$). In contrast, BMI ($P = 0.071$) and CRP ($P = 0.265$) did not demonstrate significant associations with FN risk. The significant reduction in FN risk associated with higher pre-Albumin levels and lower IL-6 concentrations, alongside the protective effect of a higher MASCC score and better ECOG PS, suggests that nutritional status, systemic inflammation, overall health condition,

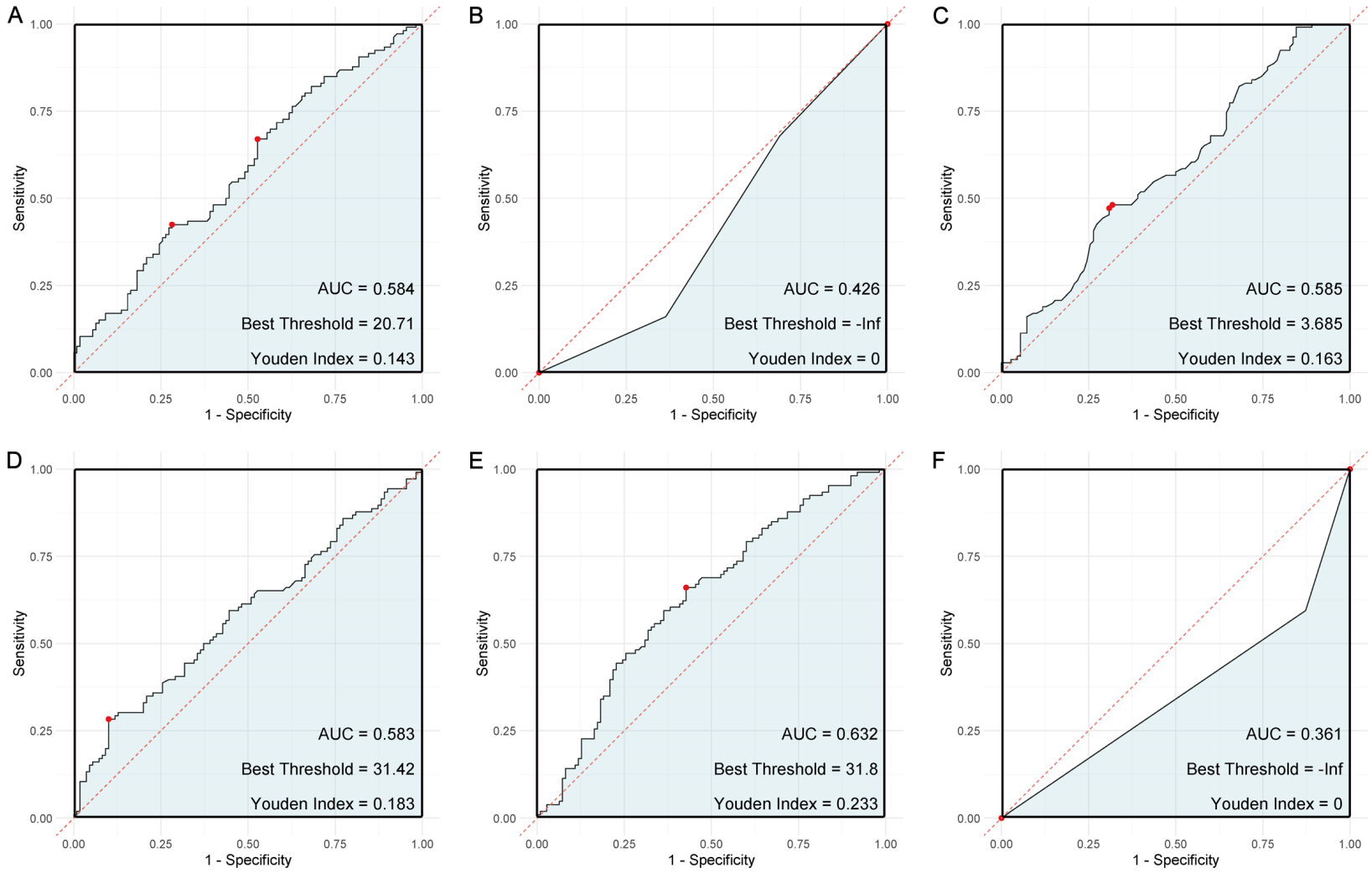

Figure 4. ROC curves for BMI, ECOG PS, pre-Albumin, CRP, IL-6, and MASCC score. A: BMI; B: ECOG PS; C: pre-Albumin; D: CRP; E: IL-6; F: MASCC score. BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRP, C-Reactive Protein; IL-6, Interleukin-6; MASCC score, Multinational Association of Supportive Care in Cancer score.

Table 7. Univariate logistic regression analysis of each factor and FN

Characteristic	Std Error	Wald	*P* Value	OR	95% CI
BMI (kg/m^2)	0.040	-2.379	0.017	0.910	0.840-0.982
ECOG PS	0.183	-2.068	0.039	0.686	0.477-0.977
pre-Albumin (g/dl)	0.362	-2.517	0.012	0.402	0.194-0.807
CRP (mg/L)	0.022	2.117	0.034	1.047	1.004-1.093
IL-6 (pg/mL)	0.012	3.158	0.002	1.038	1.015-1.063
MASCC score [n (%)]	0.348	-4.437	< 0.001	0.214	0.105-0.414

OR, odds ratio; CI, confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRP, C-Reactive Protein; IL-6, Interleukin-6; MASCC score, Multinational Association of Supportive Care in Cancer score.

Table 8. Multivariate logistic regression analysis of each factor and FN

Characteristic	Std Error	Wald	P	OR	95% CI
BMI (kg/m^2)	0.045	-1.807	0.071	0.923	0.845-1.007
ECOG PS	0.207	-2.351	0.019	0.615	0.410-0.922
Pre-Albumin (g/dl)	0.416	-3.003	0.003	0.287	0.127-0.648
CRP (mg/L)	0.024	1.114	0.265	1.027	0.980-1.077
IL-6 (pg/mL)	0.014	3.189	0.001	1.044	1.017-1.073
MASCC score [n (%)]	0.387	-4.329	< 0.001	0.187	0.088-0.39

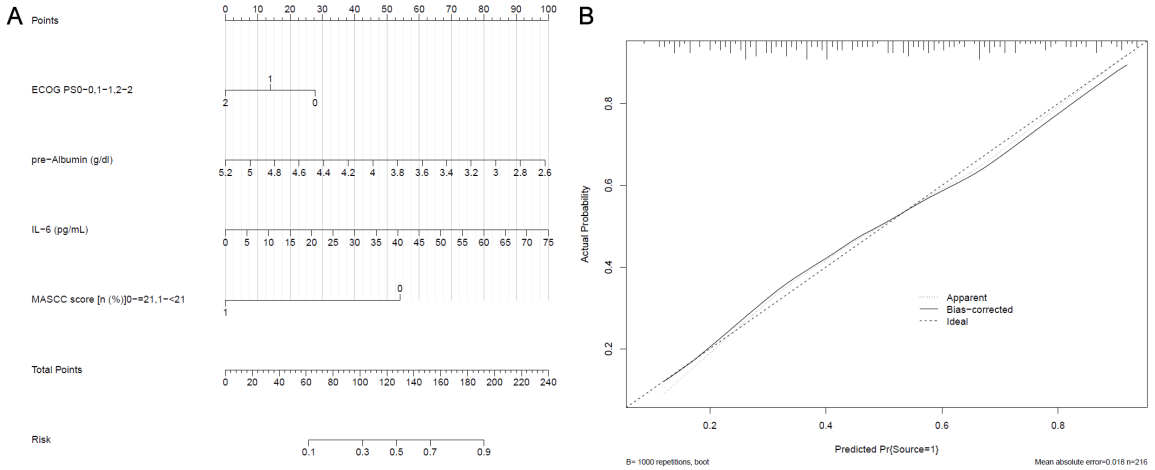

Figure 5. Nomogram and calibration plot for predicting febrile neutropenia risk.

and comorbidity burden are critical determinants for FN development in this patient population. These findings underscore the importance of monitoring and managing these factors to mitigate FN risk in SCLC patients undergoing concurrent chemoradiotherapy.

Nomogram construction and decision curve analysis

To facilitate the clinical application of our findings, a nomogram was constructed based on the significant independent factors identified in the multivariate logistic regression analysis (**Figure 5**). The nomogram integrated BMI, ECOG PS, pre-Albumin, CRP, IL-6, and MASCC score to predict individual risk for FN in patients with SCLC undergoing concurrent chemoradiotherapy. Calibration plots were used to verify the consistency between predicted probabilities from the nomogram and actual observation rates.

Furthermore, decision curve analysis (DCA) was performed to evaluate the potential clinical impact of using the nomogram compared to treat-all or treat-none strategies (**Figure 6**). Panels A-F illustrate the net benefit across a

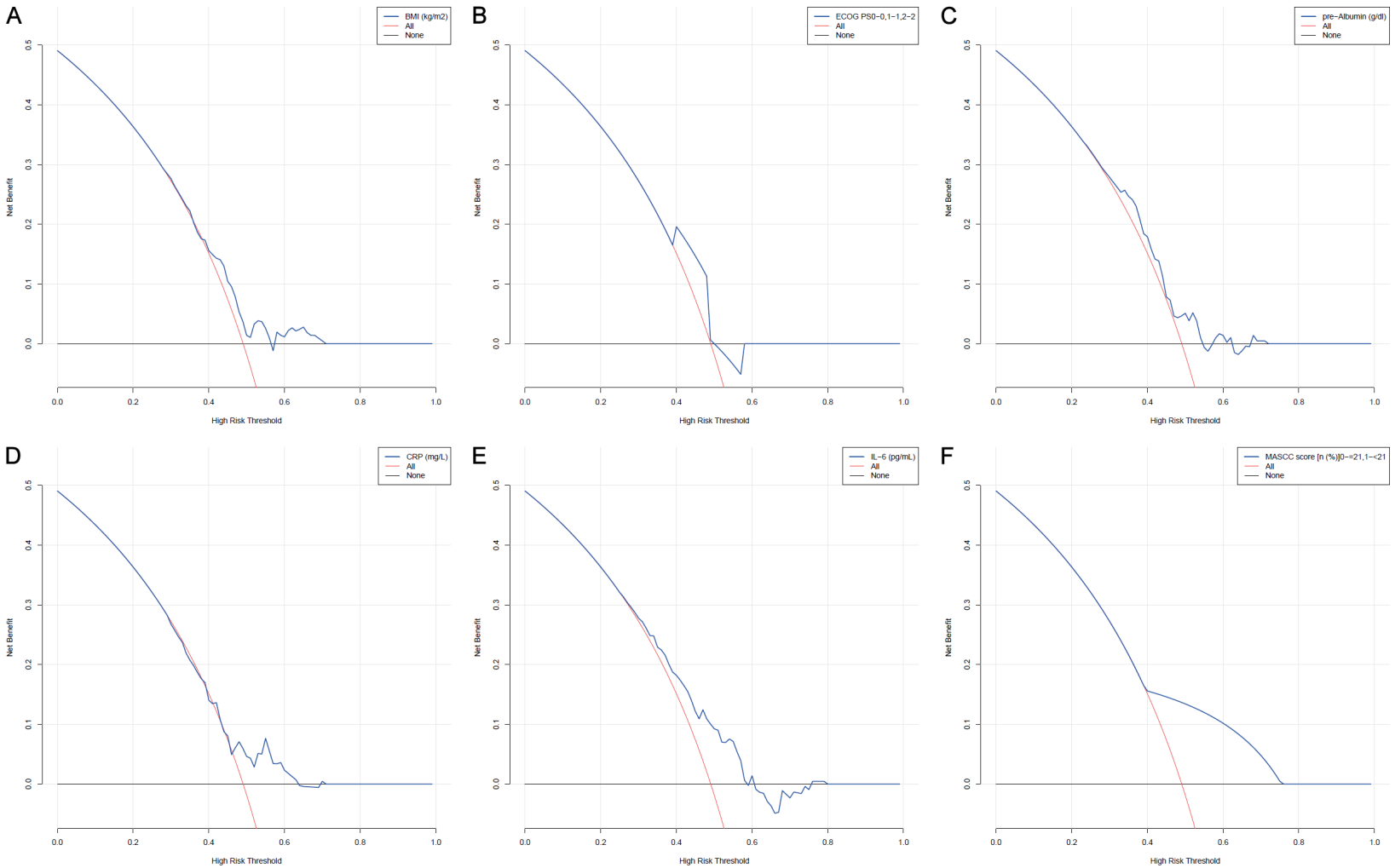

Figure 6. Decision Curve Analysis (DCA) of six predictive factors for febrile neutropenia. A: BMI; B: ECOG PS; C: pre-Albumin; D: CRP; E: IL-6; F: MASCC score. BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRP, C-Reactive Protein; IL-6, Interleukin-6; MASCC score, Multinational Association of Supportive Care in Cancer score.

range of threshold probabilities for each variable included in the nomogram. These analyses provide evidence that incorporating these variables into clinical decision-making may offer substantial benefits over existing approaches.

Discussion

Small cell lung cancer (SCLC) remains a challenging disease owing to its aggressive behavior and restricted treatment options. The concurrent chemoradiotherapy regimen involving etoposide and cisplatin (EP regimen) stands as a cornerstone in the therapeutic management of SCLC [14, 18]. However, the occurrence of FN during this treatment poses a substantial hurdle that compromises treatment efficacy and increases morbidity [19, 20]. This study provides a thorough assessment of potential risk factors for FN in SCLC patients undergoing this regimen, offering insights into clinical and biochemical parameters that may predict the development of FN.

One of the pivotal findings from our analysis is the significant association between BMI and FN risk, with lower BMI correlating to an increased susceptibility to FN. Previous studies have reported similar associations, suggesting that malnutrition can impair immune function and increase susceptibility to infections [5]. Malnutrition-related immunosuppression could enhance susceptibility to infections, especially in the context of chemotherapy-induced myelosuppression. Moreover, lower BMI may reflect generalized cachexia, which is common in cancer patients and is associated with systemic inflammation and further neutrophil suppression [21]. These observations are consistent with established knowledge that nutritional interventions could help mitigate FN risk, although further studies are needed to validate this hypothesis.

Another significant factor identified was ECOG PS, which was also strongly associated with FN development. A higher ECOG PS indicates reduced functional reserve, which could deteriorate further with the systemic stress induced by intensive chemoradiation. A lower performance status often reflects a compromised physiological state, predisposing patients to increased chemotherapy toxicity, including FN [22-24]. This association supports clinical strategies that emphasize the meticulous selection of patients for aggressive modalities, considering their baseline functional capacities and possible need for dose adjustments.

Albumin levels emerged as a critical biochemical parameter linked with FN. Albumin was not only a marker of nutritional status but also an acute phase reactant that reflects the patient's inflammatory state. Reduced albumin levels were common in acute and chronic illnesses, correlating with poor prognosis and heightened risk for chemotherapy complications. Consistent with our findings, previous studies have identified hypoalbuminemia as a risk factor for FN [25, 26]. Hypoalbuminemia might indicate decreased hepatic protein synthesis capability or increased protein loss due to systemic inflammation, both of which could impair hematopoietic function, leading to FN [27-29]. This association suggests a potential role for pretreatment nutritional assessment and interventions to optimize albumin levels and potentially reduce FN risk.

Inflammatory markers, specifically CRP and IL-6, presented a direct relationship with FN risk. In line with our initial expectation, higher levels of these markers were associated with an increased likelihood of FN. This finding contrasts with some studies that report an inverse relationship between inflammation and FN [30, 31]. Our results suggest that elevated CRP and IL-6 might signify a pre-existing heightened inflammatory state, which could exacerbate the adverse effects of chemotherapy. Alternatively, these markers' elevation could indicate ongoing systemic inflammation, increasing the vulnerability to neutropenia. Further investigation is needed to understand the exact biological mechanisms involved.

The MASCC risk index demonstrated remarkable predictive value for FN risk, with low scores correlating with increased FN likelihood. Our findings align with previous studies that have validated the MASCC score's effectiveness in predicting FN [32]. The MASCC score, which considers various clinical indicators, underscores the importance of comprehensive risk stratification in managing FN. Its robust association suggests it as a valuable tool for clinicians in predicting and mitigating FN risk, guiding intervention strategies such as the use of prophylactic antimicrobials or growth factors.

The score integrates multiple risk facets, providing a holistic view of the patient's vulnerability, and highlights the significance of multidimensional risk assessment in oncology practice.

While the univariate analyses identified several risk factors for FN, the multivariate model narrowed them down to MASCC score and IL-6 level. This refinement indicates that while many factors contribute to FN risk, their effects were interdependent, and more prominent factors like MASCC score encapsulate multiple dimensions of patient risk. These findings point towards the necessity for multi-parametric approaches in risk stratification that go beyond basic demographic and laboratory assessments, incorporating dynamic clinical indices that reflect systemic resilience and vulnerability. Compared to previous studies [33, 34], our multivariate analysis emphasizes the critical role of MASCC score and IL-6 in FN prediction.

Despite these valuable insights, several limitations of the study must be acknowledged. The retrospective design inherently limits the ability to establish causation and may introduce selection bias, as our data relied on existing medical records, which might not capture all relevant variables uniformly. Furthermore, the study was conducted within a single institution, potentially affecting the generalizability of the findings to broader populations. The reliance on laboratory parameters and clinical indices also raises concerns about variability in assessment standards and timing. Finally, despite the large sample size, the study did not account for all potential confounders such as genetic predispositions or socio-economic factors that could influence FN risk. Future prospective, multicenter studies with standardized data collection methods are needed to validate these findings and improve the generalizability of the risk factors identified.

Conclusion

In conclusion, our study identifies several significant independent predictors of febrile neutropenia (FN) in small cell lung cancer (SCLC) patients receiving concurrent chemoradiotherapy based on the EP regimen. Lower pre-albumin levels, higher IL-6 concentrations, poorer ECOG Performance Status, and a lower MASCC score are critical determinants for FN development. These findings underscore the importance of monitoring and managing nutritional status, systemic inflammation, and overall health condition to mitigate FN risk. Our results support an integrated approach to risk assessment that includes nutritional optimization, inflammatory modulation, and comprehensive evaluation of patient performance status. Future research should aim to validate these findings in larger, multicenter studies and explore how these insights can be translated into clinical practice to improve patient outcomes and safety during intensive cancer treatments.

Disclosure of conflict of interest

None.

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