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Development and validation of the systemic nutrition/inflammation index for improving perioperative management of non-small cell lung cancer

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Abstract

Background Systemic nutrition and inflammation status is recognized for its influence on cancer survival, yet its role in perioperative outcomes remains poorly defined. This study aimed to refine the assessment of systemic nutrition and inflammation status in non-small cell lung cancer (NSCLC) patients and to elucidate its impact on perioperative outcomes.

Methods All patients underwent video-assisted thoracoscopic lobectomy, with their nutrition and inflammation status assessed based on preoperative blood tests. The development cohort, comprising 1497 NSCLC patients from two centers, evaluated the predictive value of systemic nutrition/inflammation indicators for perioperative endpoints and formulated the systemic nutrition-inflammation index (SNII). The tertiles of SNII were used to classify the nutrition/inflammation risk as high (< 15.6), moderate (15.6–23.1), and low (> 23.1). An external validation cohort of 505 NSCLC patients was utilized to confirm the effectiveness of SNII in guiding perioperative management.

Results In the development cohort, the SNII tool, calculated as the product of total cholesterol and total lymphocytes divided by total monocytes, demonstrated a stronger correlation with perioperative outcomes compared to 11 existing nutrition/inflammation indicators. A low SNII score, indicative of high nutrition/inflammation risk, was independently predictive of increased complication incidence and severity, as well as prolonged chest tube duration and hospital stay. These findings were corroborated in the validation cohort. Upon combining the development and validation cohorts, the superiority of the SNII in predicting perioperative outcomes was further confirmed over the existing nutrition/inflammation indicators. Additionally, comprehensive subgroup analyses revealed the moderately variable efficacy of SNII across different patient populations.

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Conclusions This study developed and validated the SNII as a tool for identifying systemic nutrition and inflammation risk, which can enhance perioperative managements in NSCLC patients. Patients identified with high risk may benefit from prehabilitation and intensive treatments, highlighting the need for further research.

Keywords Non-small cell lung cancer, Nutrition, Inflammation, Perioperative management

Background

Lung cancer is the most prevalent malignancy and the leading cause of cancer-related mortality worldwide, with an estimated 2.48 million new cases and 1.82 million deaths reported in 2022 [1]. Lung adenocarcinomas now constitute the majority of non-small cell lung cancers (NSCLCs) [2, 3]. Anatomical resection remains a cornerstone for the radical treatment of NSCLCs, with video-assisted thoracoscopic surgery (VATS) lobectomy emerging as a mainstay of thoracic oncology [4, 5]. Despite advancements in surgical techniques and perioperative care, the incidence of complications following VATS lobectomy, reported at 20.0–30.0%, remains a significant concern [5, 6]. Certain patient populations continue to experience complications and slow recovery, leading to higher medical costs, diminished quality of life, and potential long-term morbidities. Identifying risk factors and implementing effective interventions are crucial from improving perioperative outcomes in NSCLC patients, an area of ongoing research focus.

Host properties of nutrition and inflammation significantly affect therapeutic outcomes in cancers and other diseases [7, 8]. However, their role in perioperative management has not been thoroughly explored. Traditionally, apart from the age, gender, and smoking factors, perioperative management for NSCLC patients has focused on local factors, such as comorbidities, cardiopulmonary function, and cancer characteristics, often overlooking nutrition and inflammation factors [9–12]. Recent studies have highlighted the impact of systemic nutrition and inflammation status on response to anticancer treatment, disease progression, and survival outcomes [2, 13–15]. The interaction between systemic nutrition and inflammation and the local tumor microenvironment has shown promise in NSCLCs [2] and gastrointestinal cancers [16, 17]. Considering the physical demands of VATS lobectomy, a patient's baseline nutrition and inflammation status can significantly influence perioperative outcomes and postoperative recovery. Addressing poor nutritional and inflammatory conditions through prehabilitation may enhance short-term postoperative outcomes. These considerations underscore the need for systematic investigation.

Several algorithms have been developed to assess systemic nutrition and inflammation based on routine blood tests (Additional file 1: Table S1), including the albumin-to-globulin ratio (AGR) [18], the advanced lung cancer inflammation index [15], the controlling nutritional status score (COUNT) [19], the geriatric nutritional risk index [20], the lymphocyte-to-monocyte ratio (LMR) [21], the neutrophil-to-lymphocyte ratio (NLR) [22], the neutrophil-to-platelet ratio [23], the platelet-to-lymphocyte ratio [24], the prognostic nutritional index [25], the systemic immune-inflammation index [26], and the systemic inflammation response index (SIRI) [27]. These indicators, derived from routinely tested biochemical and anthropometry parameters, have yet to be extensively evaluated for their predictive value in guiding perioperative managements, particularly in relation to complications and recovery in NSCLCs.

This study aimed to evaluate the predictive value of preoperative nutrition and inflammation indicators for perioperative outcomes in NSCLC patients undergoing VATS lobectomy. We have developed and validated the systemic nutrition-inflammation index (SNII), a composite biochemical indicator for assessing nutrition and inflammation risk, with the goal of facilitating more effective perioperative management.

Methods

Study design

This study encompassed both development and validation cohorts, as depicted in Fig. 1. For the development cohort, we amalgamated databases from two institutions: The First Affiliated Hospital of Zhengzhou University (cohort 1), with NSCLC patients undergoing VATS lobectomy from January 2018 to December 2020, and Peking University People's Hospital (cohort 2), with data from January 2014 to December 2016. Nutrition and inflammation parameters, derived from preoperative routine blood tests, were correlated with perioperative outcomes to develop the SNII tool. The external validation for the SNII was conducted using data from NSCLC patients who underwent VATS lobectomy at Henan Cancer Hospital (cohort 3) between January 2017 and December 2018. This study protocol was approved by the Ethics Committee Board of the First Affiliated Hospital of Zhengzhou University (2024-KY-1756–001) and the Ethics Committee Board of Peking University People's Hospital (2022PHB151-001). Data from all three cohorts were collected prospectively and analyzed retrospectively. Informed consent was previously obtained from all

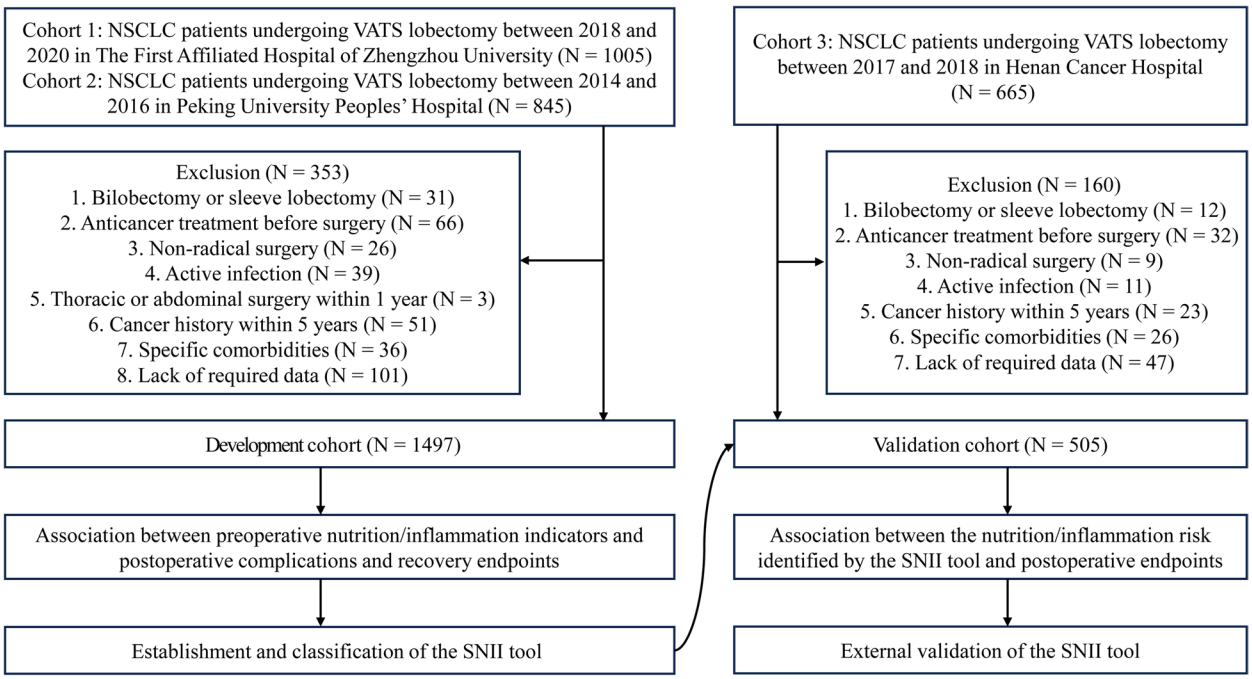

Fig. 1 Study design and patient recruitment flowchart. This flowchart illustrates the process of the study design and the recruitment of patients for both development and validation cohorts. SNII, the systemic nutrition-inflammation index; VATS, the video-assisted thoracoscopic surgery

patients for the establishment and utilization of institute databases. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [28].

Participants

In both development and validation cohorts, patients with NSCLC, aged over 18 years, and undergoing anatomic VATS lobectomy were consecutively included. Exclusion criteria included (1) bilobectomy or sleeve lobectomy; (2) anticancer treatment before surgery; (3) non-radical resection; (4) active infection within 2 weeks before surgery; (5) history of thoracic or abdominal surgery within 1 year; (6) cancer history within 5 years; (7) liver or kidney dysfunction; (8) comorbidities of rheumatic, immune, hematologic, or lymphatic system; and (9) lack of required data.

Treatment strategy

Standard preoperative assessment included thoracic computed tomography, cardiopulmonary function tests, abdominal and adrenal gland ultrasonography, brain magnetic resonance imaging, and bone scans. Endobronchial ultrasound-guided transbronchial needle aspiration or mediastinoscopy biopsy was performed for mediastinal lymph node enlargement. Positron emission tomography/computed tomography was utilized to detect suspected metastasis. Staging or restaging of cancer was based on the American Joint Committee on Cancer 8th edition of the tumor, node, and metastasis (TNM) classification system. Anatomic VATS lobectomy with hilar and mediastinal lymph node dissection was the standard surgical approach. All procedures were performed by proficient thoracic surgeons. Postoperative care involved management of fluid and electrolyte balance, nutritional supplement, pulmonary exercises, and physical rehabilitation.

Nutrition/inflammation risk assessment

In the development cohort (Additional file 1: Table S2), systemic nutrition and inflammation parameters were assessed through preoperative routine blood tests conducted within 1 week prior to surgery. The basic nutrition/inflammation items measured included total protein, serum albumin, serum globulin, total cholesterol, hemoglobin, total neutrophils, total lymphocytes, total monocytes, and total platelets in peripheral blood. The existing systemic nutrition and inflammation indicators were determined by incorporating these nutrition/inflammation items, either with or without the inclusion of anthropometric parameters (Additional file 1: Table S1).

We began by evaluating the predictive power of the existing systemic nutrition and inflammation indicators for perioperative outcomes using receiver operating characteristic (ROC) curve analysis and

multivariate regression analysis (Table 1 and Additional file 1: Table S3). The independent predictive value of these established indicators was found to be relatively weak when adjusted for clinicopathological variables. To address this, we pinpointed the key foundational nutrition/inflammation items that demonstrated the strongest predictive potential for perioperative outcomes through multivariable analysis. Building on this, we created novel nutrition/inflammation indicators, the SNII, by integrating these key foundational variables through a method of variable division. This method involves the mathematical division of two or more related variables to yield a new metric, which not only mitigates potential biases in individual variables but also elucidates their interrelationships and interactions. In line with standard practices, we utilized the tertiles of SNII to stratify the nutrition/inflammation risk as low, moderate, and high, thus establishing novel classification systems.

Finally, we validated the predictive efficacy of the SNII classification systems for perioperative outcomes in an external cohort.

Endpoints

For both the development and validation cohorts, the primary endpoints were overall complications and duration of hospital stay following surgery. Secondary endpoints included specific complications, complication severity, chest tube duration, unscheduled readmission

Table 1 Predictive values of systemic nutrition/inflammation indicators for perioperative endpoints in the development cohort ($n = 1497$)

Parameters	Incidence of overall complications[a]			Length of postoperative hospital stay[b]			
	AUC (95% CI)	*P* values	Associations	6 days	8 days	12 days	Associations
The existing nutrition/inflammation indicators							
Biochemical groups							
PNI	0.534 (0.490–0.579)	0.13	Negative	0.556	0.551	0.519	Negative
COUNT	0.565 (0.520–0.611)	**0.004**	Positive	0.547	0.569	0.556	Positive
AGR	0.546 (0.500–0.592)	**0.044**	Positive	0.558	0.527	0.543	Positive
NLR	0.565 (0.522–0.609)	**0.004**	Positive	0.557	0.562	0.556	Positive
PLR	0.523 (0.480–0.567)	0.31	Positive	0.506	0.54	0.509	Positive
NPR	0.557 (0.513–0.600)	**0.013**	Positive	0.558	0.539	0.541	Positive
LMR	0.600 (0.559–0.641)	**< 0.001**	Negative	0.579	0.582	0.564	Negative
SIRI	0.582 (0.539–0.625)	**< 0.001**	Positive	0.570	0.569	0.557	Positive
SII	0.532 (0.486–0.577)	0.17	Positive	0.528	0.542	0.530	Positive
Biochemical and anthropometry groups							
GNRI	0.536 (0.490–0.582)	0.11	Negative	0.548	0.537	0.536	Negative
ALI	0.572 (0.528–0.615)	**0.002**	Negative	0.568	0.570	0.569	Negative
The basic nutrition/inflammation items							
Total protein, g/L	0.535 (0.489–0.581)	0.13	Negative	0.579	0.537	0.530	Negative
Serum albumin, g/L	0.511 (0.466–0.556)	0.63	Negative	0.541	0.522	0.502	Negative
Serum globulin, g/L	0.551 (0.504–0.599)	**0.024**	Negative	0.579	0.538	0.545	Negative
Total cholesterol, mmol/L	0.569 (0.526–0.612)	**0.002**	Negative	0.590	0.587	0.587	Negative
Hemoglobin, g/L	0.526 (0.479–0.573)	0.26	Positive	0.528	0.525	0.524	Positive
Total neutrophils, $\times 10^9$/L	0.536 (0.489–0.583)	0.11	Positive	0.541	0.530	0.533	Positive
Total lymphocytes, $\times 10^9$/L	0.559 (0.514–0.603)	**0.010**	Negative	0.523	0.552	0.529	Negative
Total monocytes, $\times 10^9$/L	0.553 (0.510–0.596)	**0.020**	Positive	0.551	0.538	0.530	Positive
Total platelet, $\times 10^9$/L	0.546 (0.502–0.591)	**0.042**	Negative	0.528	0.525	0.524	Negative
Newly proposed nutrition/inflammation indicator							
SNII	0.612 (0.571–0.653)	**< 0.001**	Negative	0.591	0.603	0.596	Negative

AGR albumin-to-globulin ratio, *ALI* advanced lung cancer inflammation index, *CI* confidence interval, *CONUT* controlling nutritional status score, *GNRI* geriatric nutritional risk index, *LMR* lymphocyte-to-monocyte ratio, *NLR* neutrophil-to-lymphocyte ratio, *NPR* neutrophil-to-platelet ratio, *PLR* platelet-to-lymphocyte ratio, *PNI* prognostic nutritional index, *SII* systemic immune-inflammation index, *SIRI* systemic inflammation response index, *SNII* systemic nutrition-inflammation index

[a] Receiver operating characteristic (ROC) curves were utilized to evaluate the predictive values of nutrition/inflammation indicators for the incidence of postoperative complications

[b] Time-dependent ROC curves were employed to assess the predictive value of nutrition/inflammation indicators concerning the length of postoperative hospital stay. Area under the curve (AUC) values are reported for these analyses. The specific time points analyzed were 6, 8, and 12 days post-surgery

within 30 days, and 90-day mortality. Intraoperative endpoints, such as operative time and estimated blood loss, were also assessed.

Postoperative complications were identified according to the Common Terminology Criteria for Adverse Events v5.0 [29], classified using the Clavien–Dindo classification [30], and quantified using the comprehensive complication index (CCI) [31]. Major complications were defined as those with a Clavien–Dindo classification of ≥ 2. Chest tubes were removed under conditions of no sign of leakage, normal drainage, and the drainage volume of less than 200 ml/day. Discharge criteria included stable vital signs, ability to tolerate oral feeding, absence of complications requiring hospital treatment, unassisted ambulation, and manageable pain with oral analgesics.

Patients were closely monitored for 30 days following discharge to identify any late complications, unscheduled readmission, or other issues. The initial follow-up appointment was scheduled routinely at 90 days postsurgery. The 90-day mortality rate, which is considered to be related to surgical complications, was evaluated and analyzed.

Statistical analysis

Categorical data are presented as frequencies (percentages), while continuous data are shown as means (standard deviations, SDs) or medians (interquartile ranges, IQRs). Group differences were assessed using ANOVA, Pearson's chi-squared tests, Fisher's exact test, Mann–Whitney *U* tests, or Kruskal–Wallis tests as appropriate. ROC curves were utilized to evaluate the predictive accuracy of nutrition and inflammation indicators for perioperative endpoints, with the area under the curve indicating performance. Propensity score matching balanced patient baseline characteristics using a logistic regression model, with SNII-defined nutrition/inflammation risk as the matching indicator, considering variables such as age, sex, comorbidity, smoking history, lung function, tumor location, histology, and cancer stage. A 1:1 match was made with a caliper width of 0.2 of the standard deviation for the nearest propensity scores. Multivariable analysis was performed using logistic regression and the Cox proportional hazards regression models. Subgroup analysis of clinicopathological characteristics was conducted to identify vulnerable populations at risk from nutrition and inflammation effects. Odds ratios (ORs) and hazard ratios (HRs) with 95% confidence intervals (CIs) were reported. A two-tailed P value < 0.05 was considered significant. All analyses were conducted using IBM SPSS Statistics for Windows (version 22.0, IBM Corp., Armonk, NY, USA) and R tool (version 4.2.0, R Core Team, Vienna, Austria).

Results

Development cohort

Participants

The development cohort comprised 1497 NSCLC patients, with 805 from cohort 1 and 692 from cohort 2 (Fig. 1). Clinicopathological data are detailed in Additional file 1: Table S2. All patients underwent radical VATS lobectomy as the primary treatment, with an average age was 61.2 years (SD: 10.3). The cohort included 724 females (48.4%) and 773 males (51.6%), with 37.4% having a smoking history. Median operation time was 165 min (IQR: 135–200), and estimated blood loss was 50 ml (IQR: 30–100). Adenocarcinoma and squamous cell carcinoma (SCC) accounted for 81.8% and 14.0% of cases, respectively. Pathological TNM stage distribution was IA (44.4%), IB (24.6%), II (14.6%), and III (16.4%). Postoperative complications occurred in 182 patients (12.2%), with a median chest tube duration of 5 days (IQR: 3–7) and a postoperative hospital stay of 7 days (IQR: 5–9). Rates of unscheduled readmission within 30 days and 90-day mortality were 1.34% and 1.27%, respectively.

The existing nutrition/inflammation indicators and perioperative endpoints

The existing nutrition/inflammation indicators for the development cohort are detailed in Additional file 1: Table S2. Their predictive values for postoperative complications and hospital stay, as determined by ROC curves and multivariable regression analyses, are presented in Table 1 and Additional file 1: Table S3, respectively. The LMR, SIRI, COUNT, NLR, and AGR—particularly the LMR and SIRI—showed moderate predictive values for these endpoints in ROC curves and univariable regression analyses. However, after adjusting for demographic and surgical parameters, none of these established nutrition/inflammation indicators was found to be independently associated with the primary endpoints. Notably, both the LMR and SIRI include peripheral lymphocyte and monocyte parameters but with reversed ratios, highlighting the prognostic significance of these two parameters for the endpoints.

Establishment of the SNII for nutrition/inflammation risk assessment

We aimed to develop new systemic nutrition/inflammation indicators that have a stronger correlation with perioperative outcomes and are easy to use, based on readily available nutrition/inflammation items derived from routinely preoperative blood tests. The predictive values of these foundational nutrition/inflammation items for primary endpoints were assessed using ROC curves and multivariate regression analyses, as shown in Table 1

and Additional file 1: Table S4, respectively. These analyses identified total cholesterol, total lymphocytes, and total monocytes as the key predictive parameters. Notably, total lymphocytes and total monocytes are parameters that have been widely used in established nutrition/inflammation indicators (Additional file 1: Table S1), whereas total cholesterol has not been well recognized or utilized. Moreover, total lymphocytes and total cholesterol were found to be negatively associated with the incidence of overall complications and the length of postoperative hospital stay, whereas total monocytes were associated with an increase in complications and a prolongation of postoperative hospital stay. Consequently, we developed a novel nutrition/inflammation indicator, the SNII, by combining these three key predictive parameters using a variable division method: total cholesterol (mmol/L) × total lymphocytes / total monocytes. The median value of SNII in the development cohort was 19.1 (IQR: 13.9–25.6). Following conventional practices, we used the tertiles of SNII to categorize nutrition/inflammation risk into low (> 23.1), moderate (15.6–23.1), and high (< 15.6), thereby establishing a new classification system, with 497 patients in each group (Table 2).

SNII and clinicopathological characteristics

Groups classified by the SNII showed significant differences in age, gender, smoking history, Charlson comorbidity index, diabetes prevalence, lung function, cancer histology, and pathological stage (Table 2). Patients with high nutrition/inflammation risk was older, more males, had more smoking history, higher comorbidity index, increased diabetes prevalence, poorer lung function, higher SCC proportion, higher risk of vascular invasion, and more advanced pathological stage. After propensity score matching, 278 pairs were selected with no significant differences in baseline characteristics among groups.

SNII and perioperative endpoints

Intraoperatively, high nutrition/inflammation risk patients identified by the SNII showed increased operative time and blood loss, with no differences after propensity score matching (Table 2). Postoperatively, moderate and high-risk patients had increased overall complications rates, particularly cardiac, pulmonary, and hypoalbuminemia. Clavien–Dindo grades and CCI elevated with the increased SNII risk. A high or moderate SNII risk was also associated with prolonged chest tube duration and hospital stay and increased rates of 90-day mortality.

Propensity score matching confirmed that high-risk patients had increased complications, higher complication grades, larger CCI, and prolonged chest tube duration and hospital stay compared to moderate or low-risk patients (Table 2). However, patients with moderate and low SNII risk showed no significant differences in these endpoints after propensity score matching.

Multivariable analyses (Table 3) demonstrated that high nutrition/inflammation risk was independently associated with increased incidence of overall complications and major complications, prolonged chest tube duration, and extended hospital stay, after adjusting for demographics, surgical parameters, and cancer characteristics. Moderate SNII risk showed a non-significantly association with these endpoints.

Validation cohort

Participants

The validation cohort consisted of 505 NSCLC patients (Fig. 1). Clinicopathological characteristics are detailed in Additional file 1: Table S5. All patients underwent radical VATS lobectomy with an average age of 64.5 years (SD: 9.13). The cohort included 277 females (54.9%) and 228 males (45.1%), with 37.0% having a smoking history. Median operation time was 170 min (IQR: 140–196), and estimated blood loss was 50 ml (IQR: 40–70). Adenocarcinoma and SCC were presented in 78.8% and 13.1% of patients, respectively. Pathological TNM stage distribution was IA (62.2%), IB (12.5%), II (12.7%), and III (12.7%). Postoperative complications occurred in 104 patients (20.6%), with a median chest tube duration of 5 days (IQR: 4–8) and a postoperative hospital stay of 7 days (IQR: 6–8). Rates of unscheduled readmission within 30 days and 90-day mortality were 2.57% and 1.58%, respectively.

SNII and clinicopathological characteristics

The preoperative SNII median value was 18.4 (IQR: 12.0–25.4). Using the established SNII classification, systemic nutrition/inflammation risk was categorized as low, moderate, and high in 163 (32.3%), 163 (32.3%), and 179 (35.4%) patients, respectively (Table 4). Consistent with the development cohort, high-risk patients were older, more males, had more extensive smoking and drinking histories, increased prevalence of cardiovascular disease and diabetes, poorer lung function, a higher proportion of SCC, increased vascular invasion risk, and more advanced stages. After propensity score matching of 114 pairs, no significant differences in clinicopathological characteristics were observed between the high-risk and low-to-moderate risk groups.

Table 2 Clinicopathological characteristics and perioperative endpoints according to the classified systemic nutrition/inflammation risk in the development cohort

Characteristics	Assessment and classification of nutrition/inflammation risk using the systemic nutrition-inflammation index										
	Before propensity score matching				After propensity score matching						
	Low risk ($n=499$)	Moderate risk ($n=499$)	High risk ($n=499$)	*P* value	Low risk ($n=278$)	Moderate risk ($n=278$)	High risk ($n=278$)	*P* values			
								All	H vs. L	M vs. L	H vs. M
Demographic data											
Age, years	60.0 ± 9.43	60.3 ± 10.7	63.2 ± 10.5	**<0.001**	60.3 ± 10.6	60.5 ± 10.1	61.0 ± 10.4	0.70	0.95	0.76	0.59
Gender (female)	353 (70.7)	238 (47.7)	133 (26.7)	**<0.001**	132 (47.5)	132 (47.5)	133 (47.8)	1.00	0.93	1.00	0.92
Smoking history	110 (22.0)	180 (36.1)	270 (54.1)	**<0.001**	95 (34.2)	99 (35.6)	110 (39.6)	0.39	0.19	0.72	0.34
Charlson comorbidity index ≥ 3	66 (13.2)	72 (14.4)	105 (21.0)	**0.002**	39 (14.0)	45 (16.2)	50 (18.0)	0.45	0.20	0.48	0.57
Comorbidities											
Cardiovascular disease	61 (12.2)	64 (12.8)	84 (16.8)	0.074	36 (12.9)	33 (11.9)	40 (14.4)	0.68	0.62	0.70	0.38
Pulmonary disease	24 (4.81)	23 (4.61)	35 (7.01)	0.18	15 (5.40)	12 (4.32)	17 (6.12)	0.63	0.72	0.55	0.34
Diabetes	40 (8.02)	46 (9.22)	71 (14.2)	**0.003**	26 (9.35)	26 (9.35)	34 (12.2)	0.44	0.27	1.00	0.27
Pulmonary function											
FEV1, %	97.6 (85.2–109.0)	95.0 (82.7–106.1)	91.1 (77.7–103.0)	**0.003**	94.1 (77.1–108.2)	93.0 (81.3–106.1)	91.4 (76.1–103.3)	0.48	0.37	0.87	0.25
FEV1/FVC, %	79.1 (74.9–82.6)	78.5 (72.9–82.5)	77.4 (70.9–82.0)	**0.003**	78.3 (74.0–82.2)	78.5 (73.2–82.8)	78.1 (71.6–82.1)	0.55	0.32	0.98	0.37
DLCO, %	88.1 (78.4–97.9)	87.6 (76.9–96.6)	83.7 (71.7–95.0)	**0.001**	87.0 (77.9–96.5)	87.1 (74.9–98.7)	85.8 (73.3–97.4)	0.31	0.13	0.48	0.39
Body mass index, kg/m^2	24.1 ± 3.13	24.1 ± 3.04	24.0 ± 3.22	0.95	24.5 ± 3.31	24.1 ± 3.03	24.1 ± 3.32	0.31	0.17	0.21	0.84
Surgical parameters											
Operative time, min	160 (135–195)	165 (135–200)	170 (140–205)	**0.014**	165 (140–205)	170 (140–210)	178 (140–210)	0.35	0.16	0.34	0.61
Estimated blood loss, ml	50 (30–100)	50 (30–100)	50 (40–100)	**<0.001**	50 (30–100)	50 (30–100)	50 (40–100)	0.11	0.10	0.16	0.22
Lymph node dissection stations	7 (6–8)	7 (6–7)	6 (6–7)	0.99	6 (6–8)	7 (6–8)	7 (6–7)	0.65	0.84	0.41	0.46
No. of harvested lymph nodes	15 (11–20)	15 (11–20)	15 (12–22)	**0.045**	16 (12–20)	15 (11–20)	15 (12–21)	0.28	0.44	0.41	0.11
Cancer characteristics											
Tumor location: right/left	314/185 (62.9/37.1)	297/202 (59.5/40.5)	319/180 (63.9/36.1)	0.32	186/92 (66.9/33.1)	181/97 (65.1/34.9)	171/107 (61.5/38.5)	0.40	0.19	0.65	0.38

Table 2 (continued)

Characteristics	Assessment and classification of nutrition/inflammation risk using the systemic nutrition-inflammation index										
	Before propensity score matching				After propensity score matching						
	Low risk ($n=499$)	Moderate risk ($n=499$)	High risk ($n=499$)	*P* value	Low risk ($n=278$)	Moderate risk ($n=278$)	High risk ($n=278$)	*P* values			
								All	H vs. L	M vs. L	H vs. M
Histology: AD/SCC/others	448/33/18 (89.8/6.61/3.61)	408/70/21 (81.8/14.0/4.21)	369/106/24 (73.9/21.2/4.81)	**<0.001**	241/26/11 (86.7/9.35/3.96)	235/34/9 (84.5/12.2/3.24)	231/37/10 (83.1/13.3/3.60)	0.60	0.34	0.61	0.90
Multiple primary cancer	60 (12.0)	46 (9.22)	53 (10.6)	0.36	30 (10.8)	32 (11.5)	24 (8.63)	0.51	0.39	0.79	0.26
Pleural invasion	144 (28.9)	127 (25.5)	150 (30.1)	0.22	81 (29.1)	84 (30.2)	92 (33.1)	0.58	0.31	0.78	0.47
Vascular invasion	83 (16.6)	76 (15.2)	110 (22.0)	**0.013**	40 (14.4)	42 (15.1)	36 (12.9)	0.76	0.62	0.81	0.46
Pathological TNM stage IA/IB/II/III	235/124/59/81 (47.1/24.8/11.8/16.2)	238/126/68/67 (47.7/25.3/13.6/13.4)	191/119/92/97 (38.3/23.8/18.4/19.4)	**<0.001**	125/73/34/46 (45.0/26.3/12.2/16.5)	117/72/45/44 (42.1/25.9/16.2/15.8)	114/73/44/47 (41.0/26.3/15.8/16.9)	0.62	0.34	0.51	0.77
Postoperative complications											
Cardiac complications	4 (0.802)	14 (2.81)	17 (3.41)	**0.017**	2 (0.719)	11 (3.96)	14 (5.04)	**0.011**	**0.002**	**0.012**	0.54
Supraventricular arrhythmia	2 (0.401)	12 (2.40)	15 (3.01)	**0.008**	1 (0.360)	9 (3.24)	13 (4.68)	**0.007**	**0.001**	**0.025**	0.38
Cardiac ischemia/infarction	1 (0.200)	1 (0.200)	0	0.61	0	1 (0.360)	0	0.37	–	1.00	1.00
Heart failure	2 (0.401)	2 (0.401)	2 (0.401)	1.00	2 (0.719)	2 (0.719)	1 (0.360)	0.82	1.00	1.00	1.00
Pulmonary complications	20 (4.01)	37 (7.41)	39 (7.82)	**0.026**	15 (5.40)	21 (7.55)	30 (10.8)	0.060	**0.020**	0.30	0.19
Pneumonia	5 (1.00)	10 (2.00)	13 (2.61)	0.17	4 (1.44)	7 (2.52)	10 (3.60)	0.27	0.10	0.36	0.46
ARDS	1 (0.200)	0	0	0.37	–	–	–	–	–	–	–
Respiratory failure	2 (0.401)	3 (0.601)	3 (0.601)	0.88	2 (0.719)	3 (1.08)	3 (1.08)	0.88	1.00	1.00	1.00
Fistula of lung	12 (2.40)	24 (4.81)	21 (4.21)	0.12	10 (3.60)	13 (4.68)	17 (6.12)	0.38	0.17	0.52	0.45
Fistula of bronchus	0	1 (0.200)	3 (0.601)	0.17	0	0	1 (0.360)	0.38	1.00	–	1.00
Atelectasis	2 (0.401)	4 (0.802)	4 (0.802)	0.67	0	1 (0.360)	3 (1.08)	0.17	0.25	1.00	0.62
Gastrointestinal complications	3 (0.601)	2 (0.401)	8 (1.60)	0.090	2 (0.719)	0	7 (2.52)	**0.013**	0.18	0.48	**0.022**
Digestive ulcer	1 (0.200)	0	2 (0.401)	0.37	1 (0.360)	0	1 (0.360)	0.61	1.00	1.00	1.00
Duodenal perforation	0	1 (0.200)	0	0.37	–	–	–	–	–	–	–

Table 2 (continued)

Characteristics	Assessment and classification of nutrition/inflammation risk using the systemic nutrition-inflammation index										
	Before propensity score matching				After propensity score matching						
	Low risk ($n=499$)	Moderate risk ($n=499$)	High risk ($n=499$)	*P* value	Low risk ($n=278$)	Moderate risk ($n=278$)	High risk ($n=278$)	*P* values			
								All	H vs. L	M vs. L	H vs. M
Gastroparesis	0	1 (0.200)	1 (0.200)	0.61	0	0	1 (0.360)	0.37	1.00	–	1.00
Ileus	1 (0.200)	0	0	0.37	–	–	–	–	–	–	–
Liver function damage	1 (0.200)	0	5 (1.00)	**0.030**	1 (0.360)	0	5 (1.80)	**0.029**	0.22	1.00	0.072
Specific complications											
Hypoalbuminemia	2 (0.401)	9 (1.80)	13 (2.61)	**0.019**	1 (0.360)	3 (1.08)	8 (2.88)	**0.037**	**0.044**	0.62	0.13
Chylothorax	2 (0.401)	7 (1.40)	7 (1.40)	0.21	1 (0.360)	3 (1.08)	5 (1.80)	0.26	0.22	0.62	0.72
Wound infection	2 (0.401)	1 (0.200)	3 (0.601)	0.61	1 (0.360)	1 (0.360)	2 (0.719)	0.78	1.00	1.00	1.00
Thrombosis/thrombus/embolism	1 (0.200)	1 (0.200)	3 (0.601)	0.45	1 (0.360)	0	3 (1.08)	0.17	0.62	1.00	0.25
Other complications	4 (0.802)	3 (0.601)	7 (1.40)	0.39	4 (1.44)	0	3 (1.08)	0.15	1.00	0.13	0.25
Overall complications	36 (7.21)	63 (12.6)	83 (16.6)	**<0.001**	25 (8.99)	32 (11.5)	59 (21.2)	**<0.001**	**<0.001**	0.33	**0.002**
Clavien–Dindo grades I/II/III/IV/V	11/10/9/5/1 (2.20/2.00/1.80/1.00/0.200)	19/32/7/2/3 (3.81/6.41/1.40/0.401/0.601)	24/44/9/4/2 (4.81/8.82/1.80/0.802/0.401)	**<0.001**	9/8/3/4/1 (3.24/2.88/1.08/1.44/0.360)	5/19/4/1/3 (1.80/6.83/1.44/0.360/1.08)	15/33/6/3/2 (5.40/11.9/2.16/1.08/0.719)	**<0.001**	**<0.001**	0.31	**0.003**
CCI, median (10–90% range)	0 (0–0)	0 (0–8.66)	0 (0–20.9)	**<0.001**	0 (0–0)	0 (0–13.1)	0 (0–20.9)	**<0.001**	**<0.001**	0.29	**0.003**
Recovery endpoints											
Chest tube duration, days	4 (3–6)	5 (3–7)	5 (3–7)	**<0.001**	4 (3–6)	4 (3–6)	6 (3–8)	**0.003**	**0.002**	0.84	**0.005**
Postoperative hospital stay, days	6 (5–8)	7 (5–9)	7 (6–10)	**<0.001**	7 (5–8)	6 (5–8)	7 (6–10)	**<0.001**	**<0.001**	0.43	**<0.001**
Unscheduled readmission within 30 days	6 (1.20)	5 (1.00)	9 (1.80)	0.52	5 (1.80)	4 (1.44)	6 (2.16)	0.82	0.76	0.74	0.40
90-day mortality	2 (0.401)	6 (1.20)	11 (2.20)	**0.039**	2 (0.719)	5 (1.80)	8 (2.88)	0.16	0.056	0.45	0.52

Data are mean ± standard deviation, number (percentage), or median (interquartile range)

Differences between groups were assessed using ANOVA, Pearson's chi-squared tests, Fisher's exact test, Mann–Whitney *U* tests, or Kruskal–Wallis tests

For propensity score matching, nutrition/inflammation risk classified by the systemic nutrition-inflammation index was the intervention indicator, and the confounding covariates were age, gender, smoking history, Charlson comorbidity index, lung function, tumor location, cancer histology, and pathological stage. Pairs of low, moderate, and high risk with a nearest propensity score were matched 1:1:1 with a caliper width of 0.2 of standard deviation

AD adenocarcinoma, *ARDS* acute respiratory distress syndrome, *CCI* comprehensive complication index, *DLCO* diffusing capacity for carbon monoxide, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *SCC* squamous cell carcinoma

SNII and perioperative endpoints

High nutrition/inflammation risk patients identified by the SNII showed increased operative time and estimated blood loss compared to low-to-moderate risk patients, with no differences after propensity score matching (Table 4). The incidence rate of overall complications was significantly higher in the high-risk group, with elevated Clavien–Dindo grades and increased CCI, persisting after propensity score matching. High-risk patients also had prolonged chest tube duration, larger drainage volume, and longer hospital stay, with significant differences in chest tube duration and hospital stay remaining after matching, but not in drainage volume. Additionally, patients with high nutrition/inflammation risk showed trends of increased incidence of unscheduled readmission within 30 days and 90-day mortality.

Comparisons of SNII with the existing nutrition/inflammation indicators

By combining the development and validation cohorts, we compared the predictive values of the SNII for perioperative endpoints with those of established nutrition/inflammation indicators known for their moderate predictive values, such as the LMR, SIRI, COUNT, NLR, and AGR (Fig. 2). The ROC curves indicated that the SNII showed superior predictive power for the incidence of overall complications, major complications, cardiac complications, pulmonary complications, unscheduled readmissions within 30 days, and 90-day mortality when compared to other nutrition/inflammation indicators. Additionally, time-dependent ROC curves revealed a stronger association between the SNII and the length of postoperative hospital stay (at the 8-day timepoint) and chest tube duration (at the 6-day timepoint) than was observed with other nutrition/inflammation indicators.

Comprehensive subgroup analysis of the SNII classification system

Combining development and validation cohorts, high nutrition/inflammation risk identified by SNII correlated with increased complication risk and prolonged hospital stay across most subgroups defined by age, gender, smoking history, comorbidity index, specific comorbidities, body mass index (BMI), cancer histology, and pathological stage (Fig. 3). Notably, the correlation between the risk identified by SNII and primary endpoints was significantly reduced in patients with a history of smoking or a Charlson comorbidity index of 3 or higher, compared to those without these factors. In patients with cardiovascular disease, pulmonary disease, or diabetes, a high SNII risk was associated with the occurrence of adverse endpoints, although this association was either significant or not, possibly due to the relatively small sample size in these subgroups. Moreover, the link between high SNII risk and adverse endpoints remained significantly among patients with different BMIs, although this significance tended to decrease with increasing BMI. In patents with SCC, high nutrition/inflammation risk was not significantly associated with endpoints. Furthermore, moderate nutrition/inflammation risk was associated with postoperative endpoints in specific populations, such as those without comorbidities and those with lung adenocarcinomas.

Discussion

This study evaluated the impact of preoperative systemic nutrition and inflammation risk on the perioperative outcomes of NSCLC patients undergoing VATS lobectomy. The SNII, derived from routine preoperative blood parameters, was established and validated for its correlation with postoperative complications and recovery. It demonstrates potential in simplifying the assessment of systemic nutrition and inflammation states, thereby enhancing perioperative management in NSCLC patients.

Previous researches have extensively documented the correlation between patients' systemic nutrition and inflammation profiles and survival outcomes, with less emphasis on perioperative recovery. In the context of NSCLC, elevated nutrition/inflammation risk has been associated with diminished response to cancer treatments [13, 14], earlier recurrence [2], and poor survival rates [15]. Similar adverse effects have been reported in small cell lung cancer [32], gastrointestinal cancers [21, 27, 33], and urogenital cancers [34–36]. For perioperative outcomes, high nutrition/inflammation risk has been identified as a predictor for severe complications and infections in patients with esophageal and gastric cancer undergoing surgical resection [33, 37]. This study, focusing on NSCLC patients undergoing VATS lobectomy, compared the predictive capabilities of existing systemic nutrition/inflammation indicators for perioperative endpoints and integrated total lymphocytes, total monocytes, and total cholesterol into the novel SNII tool to enhancing performance.

The SNII's predictive efficacy for perioperative outcomes was confirmed across both development and validation cohorts through multivariable analysis, propensity score matching, ROC curve analysis, and subgroup analysis. A low SNII score, indicative of high systemic nutrition/inflammation risk, was independently associated with the occurrence and severity of complications, as well as extended chest tube duration and hospital stay. The SNII provided a comprehensive assessment of nutritional, inflammatory, and immune status by incorporating total lymphocytes, total monocytes, and total

Table 3 Multivariable analysis investigating the association between systemic nutrition/inflammation risk and postoperative endpoints in the development cohort ($n = 1497$)

Endpoints	SNII risk	Univariable analysis		Multivariable analysis [OR/HR (95% CI)]					
		OR/HR (95% CI)	*P* value	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
Overall complications[a]	High	2.57 (1.70–3.88)	**< 0.001**	1.64 (1.05–2.56)	**0.031**	1.67 (1.04–2.67)	**0.034**	1.68 (1.05–2.70)	**0.031**
	Moderate	1.86 (1.21–2.86)	**0.005**	1.54 (0.97–2.40)	0.058	1.58 (0.99–2.52)	0.057	1.56 (0.98–2.50)	0.062
	Low (reference)	–	–	–	–	–	–	–	–
Major complications (Clavien–Dindo grades ≥ 2)[a]	High	2.54 (1.57–4.13)	**< 0.001**	1.75 (1.05–2.91)	**0.032**	1.75 (1.04–2.93)	**0.035**	1.83 (1.07–3.15)	**0.028**
	Moderate	1.83 (1.10–3.05)	**0.019**	1.61 (0.96–2.70)	0.069	1.57 (0.93–2.66)	0.091	1.64 (0.95–2.83)	0.075
	Low (reference)	–	–	–	–	–	–	–	–
Chest tube duration[b]	High	0.719 (0.611–0.846)	**< 0.001**	0.769 (0.642–0.922)	**0.004**	0.819 (0.685–0.979)	**0.029**	0.802 (0.675–0.952)	**0.012**
	Moderate	0.782 (0.665–0.919)	**0.003**	0.829 (0.698–0.985)	**0.033**	0.859 (0.723–1.020)	0.083	0.855 (0.722–1.012)	0.068
	Low (reference)	–	–	–	–	–	–	–	–
Length of postoperative hospital stay[b]	High	0.708 (0.625–0.802)	**< 0.001**	0.821 (0.718–0.939)	**0.004**	0.823 (0.713–0.949)	**0.007**	0.823 (0.713–0.949)	**0.008**
	Moderate	0.826 (0.729–0.936)	**0.003**	0.878 (0.773–0.997)	**0.045**	0.890 (0.778–1.017)	0.087	0.895 (0.783–1.024)	0.11
	Low (reference)	–	–	–	–	–	–	–	–

Multivariate analyses were conducted to establish the independent association between systemic nutrition/inflammation risk and postoperative endpoints, after controlling for confounding clinicopathological parameters. The models varied based on the inclusion of different clinicopathological characteristics as follows: model 1 included adjustments for demographic data (age, gender, smoking history, Charlson comorbidity index, and lung function); model 2 further incorporated adjustments for surgical data (operation time, estimated blood loss, and lymph node dissection); and model 3 encompassed adjustments for demographic and surgical data, as well as cancer characteristics (tumor location, histology, and cancer stage)

SNII systemic nutrition/inflammation index

[a] Multivariate logistic regression analyses were conducted with the backward conditional method and results are reported as odds ratios (ORs) and 95% confidence intervals (CIs)

[b] Multivariate Cox's proportional hazards regression analyses were conducted with the backward conditional method and results are reported as hazard ratios (HRs) and 95% CIs

cholesterol. Lymphocyte counts, primarily comprising T cells, B cells, and NK cells, reflect immune system preservation [38, 39], while monocyte counts indicate inflammation levels [40]. The low lymphocyte-to-monocyte ratio may signal heightened inflammation and compromised immunity. Total cholesterol serves as a robust indicator of nutrition status [41], with low levels associated with increased mortality risk following general surgeries [42] and in the elderly patients with cancer and infection [43]. Higher cholesterol levels may indicate better resilience to acute attacks and chronic diseases [44]. Consequently, the SNII demonstrated superior predictive performance for adverse perioperative endpoints compared to existing nutrition/inflammation indicators. Specifically, an independent association between the SNII classification system and the occurrence of overall complications, as well as prolonged postoperative hospital stays, was validated. This association was not observed with existing nutrition/inflammation indicators, thereby confirming the necessity and superiority of the SNII tool.

Comprehensive subgroup analyses confirmed the robust predictive performance of the SNII classification system in forecasting adverse perioperative endpoints for NSCLC patients, while also revealing heterogeneity in its application across different patient groups (Fig. 3). Notably, the association between SNII and perioperative endpoints was less pronounced in subgroups with a smoking history and in SCC patients. It is well-documented that smoking contributes to an increased risk of malnutrition and inflammation [45, 46], and this study further supports these findings. The smoking history and high nutrition/inflammation risk may cooperatively lead to adverse perioperative endpoints. Moreover, smoking is recognized as a risk factor for the development of lung SCC [47]. The considerable disparity in the prevalence rates of low and high SNII risk among these patients may overshadow the association. The small sample size of SCC patients in this study necessitates further investigation. Additionally, although the association between SNII risk and perioperative outcomes was attenuated in patients with a high Charlson comorbidity index, this association remained significant among patients with specific comorbidities, including cardiovascular disease and pulmonary disease, even when considering the relatively small sample size. Intriguingly, the association between the SNII classification system and perioperative

Table 4 Clinicopathological characteristics and perioperative endpoints according to the classified systemic nutrition/inflammation risk in the validation cohort

Characteristics	Assessment and classification of nutrition/inflammation risk using the systemic nutrition-inflammation index						
	Before propensity score matching				After propensity score matching		
	Low risk ($n=163$)	Moderate risk ($n=163$)	High risk ($n=179$)	*P* value	Low-to-moderate risk ($n=114$)	High risk ($n=114$)	*P* value
Demographic data							
Age, years	63.1 ± 9.33	64.1 ± 9.51	66.0 ± 9.14	**< 0.001**	65.2 ± 9.03	65.3 ± 9.91	0.77
Gender (female)	123 (75.5)	97 (59.5)	57 (31.8)	**< 0.001**	41 (36.0)	45 (39.5)	0.59
Smoking history	26 (16.0)	51 (31.3)	110 (61.5)	**< 0.001**	59 (51.8)	59 (51.8)	1.00
Drinking history	12 (7.36)	21 (12.9)	30 (16.8)	**0.031**	21 (18.4)	15 (13.2)	0.28
Charlson comorbidity index	2 (2–3)	2 (2–3)	2 (2–3)	0.28	2 (2–3)	2 (2–3)	0.75
Comorbidities							
Cardiovascular disease	25 (15.3)	18 (11.0)	52 (29.1)	**< 0.001**	21 (18.4)	30 (26.3)	0.15
Pulmonary disease	6 (3.68)	7 (4.29)	11 (6.15)	0.53	7 (6.14)	9 (7.89)	0.60
Diabetes	13 (7.96)	29 (17.8)	29 (16.2)	**0.023**	14 (12.3)	19 (16.7)	0.35
FEV1, %	109 (90.1–117.0)	95.2 (88.3–99.7)	96.2 (78.6–111.2)	**0.001**	99.4 (88.3–111.3)	105 (80.3–117.1)	0.74
FEV1/FVC, %	78.4 (75.5–80.9)	75.0 (72.6–79.8)	73.6 (69.1–80.5)	**0.001**	75.9 (72.7–78.6)	74.7 (70.2–83.7)	0.87
DLCO, %	83.9 (71.5–94.5)	88.9 (80.4–95.3)	79.1 (63.4–90.6)	**0.021**	88.9 (75.9–94.0)	80.8 (76.9–91.7)	0.52
Body mass index, kg/m^2	23.7 ± 3.43	23.9 ± 2.94	24.0 ± 3.52	0.61	23.8 ± 3.13	24.0 ± 3.51	0.64
Surgical parameters							
Operative time, min	165 (140–195)	165 (133–191)	175 (150–220)	**< 0.001**	176 (151–215)	174 (141–196)	0.31
Estimated blood loss, ml	40 (40–70)	40 (40–70)	70 (40–100)	**< 0.001**	50 (40–70)	55 (40–70)	0.45
Cancer characteristics							
Tumor location: right/left	95/68 (58.3/41.7)	109/54 (66.9/33.1)	105/74 (58.7/41.3)	0.19	72/42 (63.2/36.8)	67/47 (58.8/41.2)	0.50
Histology: adenocarcinoma/SCC/others	146/11/6 (89.6/6.75/3.68)	134/15/14 (82.2/9.20/8.59)	118/40/21 (65.9/22.3/11.7)	**< 0.001**	91/15/8 (79.8/13.2/7.02)	82/21/11 (71.9/18.4/9.65)	0.38
Multiple primary cancer	17 (10.4)	16 (9.82)	7 (3.91)	**0.046**	7 (6.14)	5 (4.39)	0.55
Pleural invasion	10 (6.13)	17 (10.4)	28 (15.6)	**0.018**	16 (14.0)	22 (19.3)	0.29
Vascular invasion	56 (34.4)	44 (27.0)	51 (28.5)	0.31	42 (36.8)	40 (35.1)	0.78
Pathological TNM stage IA/IB/II/III	109/16/20/18 (66.9/9.82/12.3/11.0)	120/18/9/16 (73.6/11.0/5.52/9.82)	85/29/35/30 (47.5/16.2/19.6/16.8)	**< 0.001**	59/19/14/22 (51.8/16.7/12.3/19.3)	56/17/26/15 (49.1/14.9/22.8/13.2)	0.75
Postoperative complications							
Supraventricular arrhythmia	3 (1.84)	0	5 (2.79)	0.11	0	5 (4.39)	0.070
Pneumonia	5 (3.07)	3 (1.84)	11 (6.15)	0.096	1 (0.877)	7 (6.14)	0.072
Subcutaneous emphysema	9 (5.52)	10 (6.13)	25 (14.0)	**0.008**	10 (8.77)	17 (14.9)	0.15
Fistula of lung	7 (4.29)	4 (2.45)	18 (10.1)	**0.007**	8 (7.02)	16 (14.0)	0.084
Fistula of bronchus	0	0	7 (3.91)	**0.002**	0	7 (6.14)	**0.021**
Pleural effusion	10 (6.13)	17 (10.4)	22 (12.3)	0.15	9 (7.89)	15 (13.2)	0.20
Hypoalbuminemia	3 (1.84)	5 (3.07)	12 (6.70)	0.055	2 (1.75)	8 (7.02)	0.052
Chylothorax	3 (1.84)	0	2 (1.12)	0.24	2 (1.75)	0	0.48

Table 4 (continued)

Characteristics	Assessment and classification of nutrition/inflammation risk using the systemic nutrition-inflammation index						
	Before propensity score matching				After propensity score matching		
	Low risk ($n=163$)	Moderate risk ($n=163$)	High risk ($n=179$)	*P* value	Low-to-moderate risk ($n=114$)	High risk ($n=114$)	*P* value
Wound infection	0	9 (5.52)	4 (2.23)	**0.007**	5 (4.39)	2 (1.75)	0.44
Thrombosis/embolism	0	3 (1.84)	0	**0.042**	1 (0.877)	0	1.00
Overall complications	20 (12.3)	27 (16.6)	57 (31.8)	**< 0.001**	18 (15.8)	42 (36.8)	**< 0.001**
Clavien–Dindo grades I/II/IIIa	2/13/5 (1.23/7.98/3.07)	13/10/4 (8.0/6.13/2.45)	19/23/15 (10.6/12.8/8.38)	**< 0.001**	6/9/3 (5.26/7.89/2.63)	10/19/13 (8.77/16.7/11.4)	**< 0.001**
CCI	0 (0–8.66)	0 (0–8.66)	8.66 (0–20.9)	**< 0.001**	0 (0–8.66)	8.66 (0–22.6)	**< 0.001**
Recovery endpoints							
Chest tube duration, days	4 (4–5)	5 (4–6)	6 (4–7)	**< 0.001**	5 (4–6)	5 (4–7)	**0.021**
Drainage volume, ml	1050 (750–1500)	850 (611–1300)	1225 (800–2300)	**< 0.001**	1050 (800–1750)	1290 (794–2300)	0.19
Postoperative hospital stay, days	7 (6–7)	7 (6–8)	8 (6–9)	**< 0.001**	7 (6–8)	8 (6–10)	**0.013**
Unscheduled readmission within 30 days	3 (1.84)	2 (1.23)	8 (4.47)	0.13	2 (1.75)	8 (7.02)	0.052
90-day mortality	1 (0.613)	1 (0.613)	6 (3.35)	0.062	1 (0.877)	6 (5.26)	0.055

Data are mean ± standard deviation, number (percentage), or median (interquartile range)

Differences between groups were assessed using ANOVA, Pearson's chi-squared tests, Fisher's exact test, Mann–Whitney *U* tests, or Kruskal–Wallis tests

For propensity score matching, nutrition/inflammation risk classified by the systemic nutrition-inflammation index was the intervention indicator, and the confounding covariates were age, gender, smoking history, Charlson comorbidity index, lung function, tumor location, cancer histology, and pathological stage. Pairs of low-to-moderate and high risk with a nearest propensity score were matched 1:1 with a caliper width of 0.2 of standard deviation

CCI comprehensive complication index, *DLCO* diffusing capacity for carbon monoxide, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *SCC* squamous cell carcinoma

endpoints weakened with increasing BMI, despite similar classification proportions. The growing prevalence of comorbidities associated with higher BMI [48], especially in patients who are overweight or obese, may attenuate the association between SNII risk and adverse outcomes. These heterogeneities highlight the need to tailor the SNII classification system to accommodate these specific subpopulations, thereby enhancing its effectiveness in guiding perioperative management strategies.

The precise mechanisms by which systemic nutrition and inflammation risk influences perioperative outcomes are not fully understood. Elevated nutrition/inflammation risk, indicated by a low SNII, may stem from factors such as aging, smoking, comorbidities, and cancer itself [11], which were particularly evident in our study cohorts. The interplay between nutrition, inflammation, and immunity is complex and continuous [9]. Chronic inflammation can lead to immune senescence and suppression, as well as nutritional depletion and wasting of body composition [10–12]. A compromised nutritional status is closely linked to weakened immune function, as the immune response requires substantial nutrient support, especially energy and amino acids [49, 50]. Consequently, poor systemic nutrition/inflammation status often coincides with impaired immunity. Patient with high nutrition/inflammation risk may exhibit poor nutrition, inflammation, and immunity properties, which can lead to diminished surgical tolerance and impaired tissues repair, immune response, and metabolic mobilization under the stress of surgery [51]. Infectious complications, such as the pneumonia observed in this study, may arise from compromised immunity and heightened inflammation. An increased incidence risk of infection complications has also been observed in major surgeries for esophageal cancers and gastric cancer patients with poor nutrition and inflammation status [33, 37]. Another example is the occurrence of healing complications, such as lung and bronchus fistula noticed in this study. The connection between nutrition/inflammation risk and the likelihood of anastomotic leaks has been observed in gastrointestinal surgeries [52–54]. A higher incidence of hypoalbuminemia also suggests impaired protein mobilization during the metabolic stress of surgery, which can negatively affect tissue repair and anastomotic healing [51, 55]. Even in the absence of overt complications, the recovery of postoperative function in major organs and

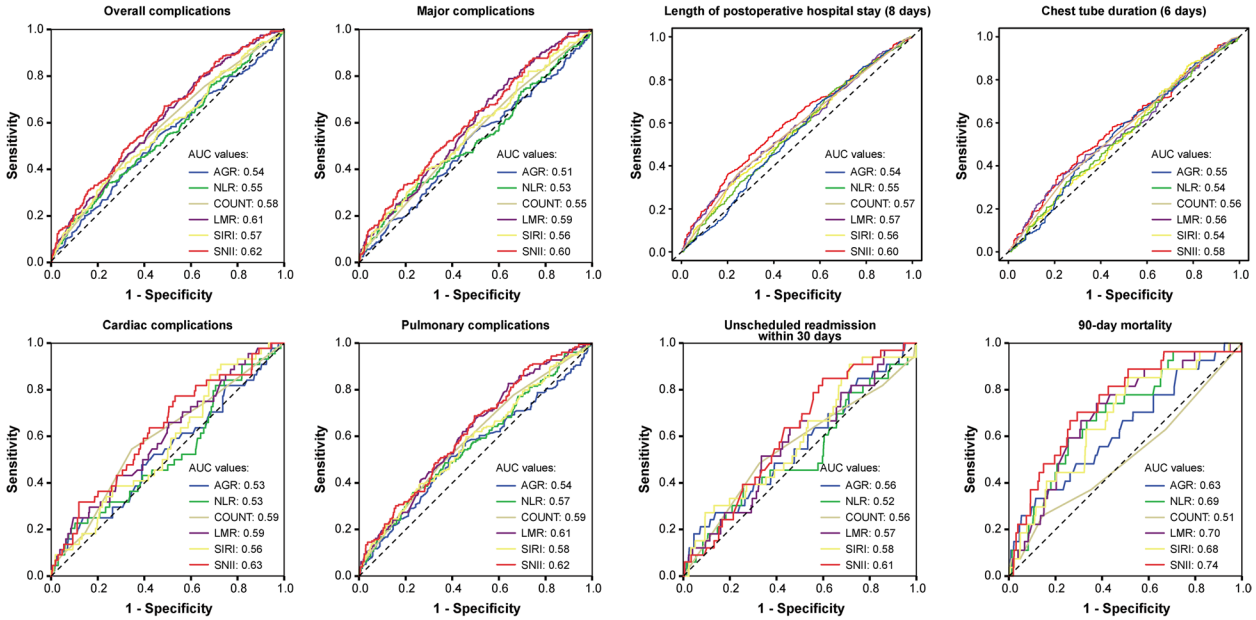

Fig. 2 Comparisons of predictive values of the systemic nutrition-inflammation index (SNII) and selected established nutrition/inflammation indicators for perioperative endpoints. Receiver operating characteristic (ROC) curves were utilized to evaluate the predictive values of these indicators for the incidence of postoperative complications, unscheduled readmissions within 30 days, and 90-day mortality. Time-dependent ROC curves were employed to assess the predictive value of these indicators concerning the length of postoperative hospital stay (at the 8-day timepoint) and chest tube duration (at the 6-day timepoint). AGR, albumin-to-globulin ratio; AUC, area under the curve; CONUT, controlling nutritional status score; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SIRI, systemic inflammation response index

systems may be delayed in patients at risk. All these factors can contribute to an extended duration of chest tube use, delayed in hospital discharge, and increased 90-day mortality rate, which in turn incurs significant medical and economic costs.

The SNII tool addresses the need for a straightforward assessment of systemic nutrition/inflammation status during perioperative management. Its classification system, particularly for identifying high-risk patients, proved consistent across development and validation cohorts in terms of diagnostic proportion and association with clinicopathological characteristics and perioperative endpoints. The SNII's correlation with factors such as older age, male, smoking, comorbidities, poor lung function, SCC, vascular invasion, and advanced cancer stage supports its efficacy in detecting adverse situations. In clinical practice, we recommend using the SNII at admission to assess surgical risk and manage strategies, allowing time for interventions. High-risk patients may require more rigorous treatment strategies, including meticulous surgical techniques, optimal medical resources, early antimicrobial therapy, and aggressive nutritional support. A preoperative intervention targeting poor nutrition and inflammation status over 2 weeks could be beneficial. The role of physical exercise in boosting immune function is well-established [56, 57], and a balanced nutritional formula with regular physical activity may improve nutrition and immunity [58, 59]. However, the effectiveness of specific drugs to enhance patient profiles requires further investigation. For patients with advanced cancer, interventions during neoadjuvant therapy may be beneficial, as this therapy can significantly compromise a patient's nutritional and inflammatory status [60]. Furthermore, a high nutrition/inflammation risk, reflecting deteriorated intrinsic patient conditions [7–9], can adversely affect therapeutic outcomes in various major surgeries and other stress events, such as major trauma and infectious diseases. The SNII tool thus holds the potential to guide not only the perioperative management of major surgeries for various solid tumors but also the management of major trauma and other stress events. However, factors such as population characteristics, primary diseases, and surgical approaches can influence the predictive values of SNII tool for therapeutic outcomes. Within this study's NSCLC patient cohorts, SNII values were shown to be influenced by age, gender, smoking history, comorbidities, and cancer characteristics. Therefore, the SNII classification system, which was established based on NSCLC

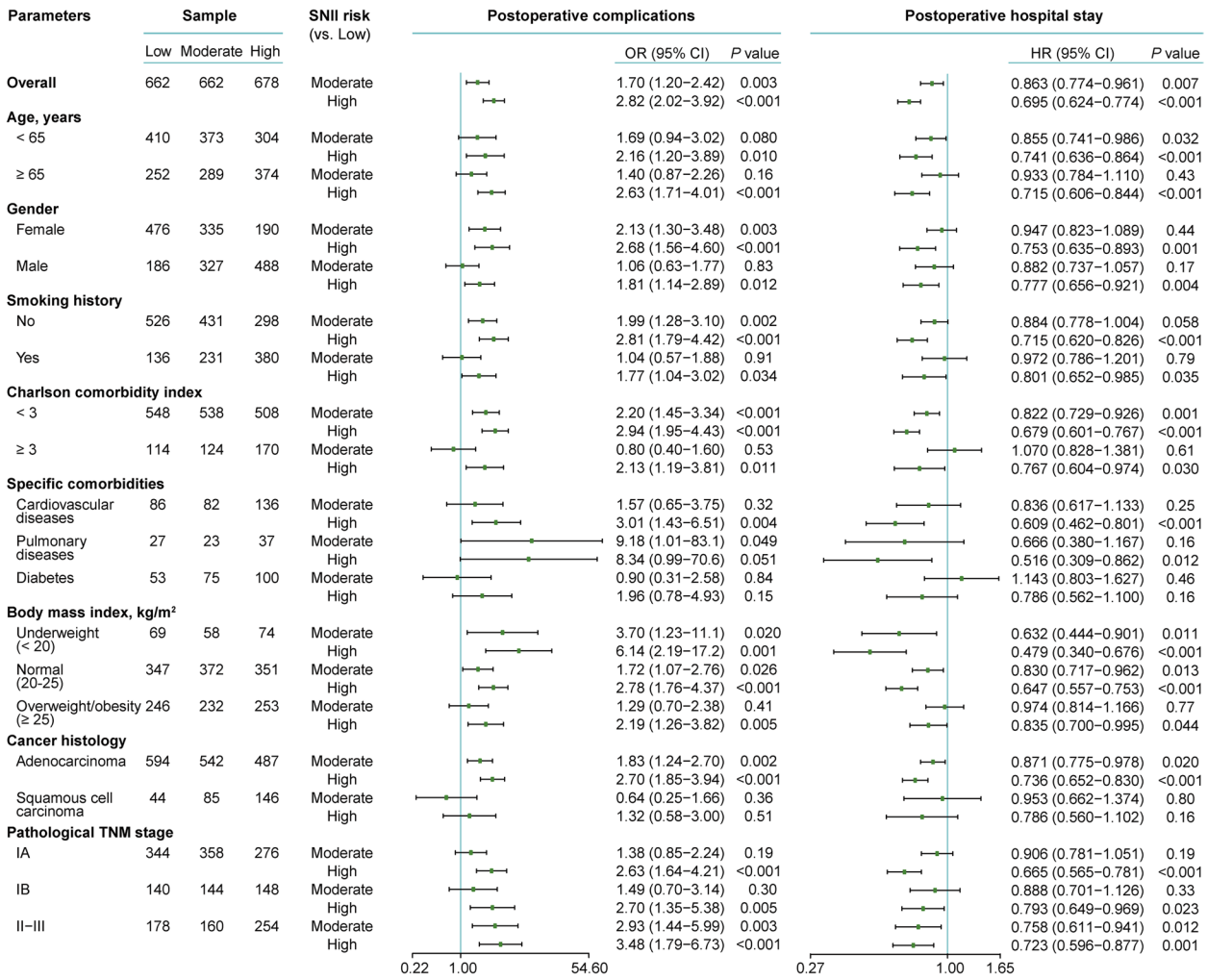

Fig. 3 Forest plots of subgroup analysis for systemic nutrition/inflammation risk and perioperative outcomes across different patient populations. Systemic nutrition/inflammation risk was assessed and classified using the systemic nutrition-inflammation index (SNII). CI, confidence interval; HR, hazard ratio; OR, odds ratio

patients undergoing VATS lobectomy in this study, particularly the thresholds used, may require adjustments to fit diverse application scenarios and ensure robust predictive power. Despite the extensive work involved, these issues can only be resolved in future studies that target different populations and application scenarios.

Our study's findings should be interpreted with caution due to several limitations. Although based on a large sample from multiple centers, the study was retrospective. The SNII's role in assessing surgical risk and guiding perioperative management needs further validation in clinical settings. The impact of neoadjuvant therapy on the SNII's utility in locally advanced NSCLC patients requires further examination. Apart from the reported confounding factors, other potential influences, such as psychosocial status and specific comorbidities, could affect the performance of SNII tool in perioperative management. Further studies should aim to tailor the SNII classification system to fit specific subpopulations and diverse application scenarios, thereby enhancing its effectiveness in guiding medical management strategies. Benefits of interventions targeting systemic nutrition/inflammation risk also warranted additional research. Moreover, further scientific inquiry is needed to elucidate the mechanisms linking nutrition/inflammation risk to adverse perioperative outcomes.

Conclusions

This study introduces the SNII tool for assessing systemic nutrition/inflammation risk in NSCLC patients and validated its predictive power for postoperative complications and recovery. The SNII is recommended for preoperative nutrition/inflammation assessment and subsequent integration into perioperative management strategies. High-risk patients may benefit from more aggressive treatments, while the methods and effectiveness of interventions require further exploration. Future studies should tailor the SNII classification system to fit specific subpopulations and diverse application scenarios.

Abbreviations

AGR	The albumin-to-globulin ratio
BMI	Body mass index
CCI	Comprehensive complication index
CI	Confidence interval
COUNT	The controlling nutritional status score
HR	Hazard ratio
IQR	Interquartile ranges
LMR	The lymphocyte-to-monocyte ratio
NLR	The neutrophil-to-lymphocyte ratio
NSCLC	Non-small cell lung cancer
OR	Odds ratio
ROC	Receiver operating characteristic curve
SCC	Squamous cell carcinoma
SD	Standard deviation
SIRI	The systemic inflammation response index
SNII	The systemic nutrition-inflammation index
VATS	The video-assisted thoracoscopic surgery

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-03925-2.

Additional file 1: Tables S1–S5. Table S1 Calculation of systemic nutrition/inflammation indicators. Table S2 Characteristics of the included patients in the development cohorts. Table S3 Prognostic values of clinicopathological characteristics for perioperative endpoints in non-small cell lung cancer patients. Table S4 The association between foundational nutrition/inflammation items and perioperative endpoints in non-small cell lung cancer patients. Table S5 Characteristics of the included patients in the validation cohort.

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Not applicable.

Authors' contributions

PW, YL, XP, XL1, and XL2 contributed to study design, data analysis, and data interpretation. SW, QH, XC, YY, RZ, and MQ contributed to data collection and data analysis. All authors contributed to manuscript writing. PW, YL, XL1, and XL2 verified the underlying data. All authors had full access to all the data in the study and accept responsibility to submit for publication. All authors read and approved the final manuscript.

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Data availability

All data generated or analyzed during this study are included in this published article (and its Supplementary Information files).

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee Board of the First Affiliated Hospital of Zhengzhou University (2024-KY-1756–001) and the Ethics Committee Board of Peking University People's Hospital (2022PHB151-001). Informed consent was previously obtained from all patients for the establishment and utilization of institute databases.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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