

Prognostic Roles of Inflammation- and Nutrition-Based Indicators for Female Patients with Cancer

Ming Yang¹⁻³, Qi Zhang¹⁻³, Yizhong Ge¹⁻⁴, Meng Tang¹⁻³, Chunlei Hu¹⁻³, Ziwen Wang¹⁻³, Xi Zhang¹⁻³, Mengmeng Song¹⁻³, Guotian Ruan¹⁻³, Xiaowei Zhang¹⁻³, Tong Liu¹⁻³, Hailun Xie¹⁻³, Heyang Zhang¹⁻³, Kangping Zhang¹⁻³, Qinqin Li¹⁻³, Xiangrui Li¹⁻³, Xiaoyue Liu¹⁻³, Shiqi Lin¹⁻⁴, Hanping Shi¹⁻³

¹Department of Gastrointestinal Surgery/Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, 100038, People's Republic of China; ²Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition, Beijing, 100038, People's Republic of China; ³Key Laboratory of Cancer FSMP for State Market Regulation, Beijing, 100038, People's Republic of China; ⁴The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, 325000, People's Republic of China

Correspondence: Hanping Shi, Department of Gastrointestinal Surgery/Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, 100038, People's Republic of China, Tel/Fax +86 10 6392 6983, Email shihp@ccmu.edu.cn

Purpose: The incidence, progression, and prognosis of cancer could be affected by inflammation and nutrition. Female patients have different inflammatory and nutritional states depending on their age and tumor types. It is important to screen for suitable prognostic indicators in female patients with cancer of different ages and tumor types.

Patients and Methods: Baseline clinicopathologic and laboratory characteristics of 1502 female patients with cancer were obtained from a multicenter cohort study. Concordance indices (C-indices) were used to evaluate the prediction accuracy of following inflammation- and nutrition-based indicators: advanced lung cancer inflammation index (ALI), systemic immune inflammation index (SII), modified geriatric nutritional risk index (mGNRI), albumin-to-globulin ratio (AGR), prognostic nutritional index (PNI), lymphocyte-to-C-reactive protein ratio (LCR), controlling nutritional status score (CONUT), modified Glasgow prognostic score (mGPS), and lymphocyte-to-C-reactive protein score (LCS).

Results: The most suitable indicators in different female populations with cancer had C-indices as follows: LCR (0.668; 95% CI, 0.644–0.693) for all females; AGR (0.681; 95% CI, 0.619–0.743) for young females; LCR (0.667; 95% CI, 0.628–0.706) for middle-aged females; ALI (0.597; 95% CI, 0.574–0.620) for elderly females; LCR (0.684; 95% CI, 0.621–0.747) for females with reproductive system cancer; and ALI (0.652; 95% CI, 0.624–0.680) for females with non-reproductive system cancer.

Conclusion: The most suitable indicators for the different female populations with cancer are summarized as follows: LCR for all females, AGR for young females, LCR for middle-aged females, ALI for elderly females, LCR for females with reproductive system cancer, and ALI for females with non-reproductive system cancer.

Keywords: female, cancer, prognosis, inflammation, nutrition

Introduction

As the leading cause of morbidity and mortality worldwide, cancer continues to represent an enormous social and economic burden to society.¹ The incidence, progression, and prognosis of cancer are affected by many factors, especially by inflammation and nutrition.²⁻⁵

Females vary in inflammatory and nutritional states at different ages. Elderly females have higher levels of inflammation than young females, but in younger females, malnutrition and iron deficiency anemia are more common.⁶ These conditions may be caused by physiological factors such as menstruation or external factors such as diet.^{7,8} It is worth noting that estrogen have impacts on female's inflammation and nutrition statuses.^{9,10} Erratic estrogen levels have impacts on perimenopausal female's inflammation and nutrition statuses, resulting in unstable inflammation

and nutrition statuses.¹¹ Compared with young and middle-aged females, most elderly females are post-menopausal. The lack of estrogen makes higher inflammatory levels and worse nutritional statuses in elderly females.^{9,10} The increment in age also has different degrees of impact on inflammatory and nutritional status.^{12,13}

Hence, we believe that physiological differences among female at different ages would affect inflammation and nutrition statuses in females with cancer and play important roles in cancer prognosis. In past decades, increasing numbers of factors influencing inflammation and nutrition have been discovered and developed to evaluate and improve the prognosis of patients with cancer.^{14–23} Therefore, we would like to compare the prognostic values of inflammation- and nutrition-based indicators and assessed the most suitable indicators in different female populations with cancer (young females, middle-aged females, elderly females). Moreover, the inflammatory and nutritional loads of female with reproductive system and non-reproductive system cancers are quite different.^{24,25} The most suitable indicators for females with reproductive system cancer and females with non-reproductive system cancer would also be evaluated in this study.

Materials and Methods

Study Population

We enrolled 22,783 patients with cancer from 14 hospitals for a multicenter cohort study. The patients with cancer in this study were assessed between January 1, 2012 and October 31, 2020. All patients were enrolled based on the following inclusion criteria: ≥ 18 years of age, a pathological diagnosis of cancer, willing and able to provide written informed consent, and consciousness throughout treatment with no communication disorders.

A comprehensive list of clinicopathological symptoms were used as exclusion criteria. There were 17,562 patients who lacked data for one or more critical variables and were excluded from this study: 12 patients were missing age data; 1795 patients were missing height data; 35 patients were missing serum albumin (Alb) levels; 151 patients were missing serum globulin (Glb) levels; 13,583 patients were missing C-reactive protein (CRP) data; 111 patients were missing fasting blood glucose (FBG) levels; 1749 patients were missing serum total cholesterol (TC) levels; 83 patients were missing neutrocyte (Neu) counts; 8 patients were missing lymphocyte (Lym) counts; and 35 patients were missing platelet (Plt) data (Figure 1). Among the 5222 patients preliminarily screened, those who meet the criteria of any of the following groups would be included in the final analysis: non-menopausal female < 45 years of age (young female group; 243 patients); non-menopausal and menopausal female ≥ 45 and < 55 years of age (middle-aged female group; 629 patients); and post-menopausal female > 55 years of age (elderly female group; 630 patients) (Figure 1).

We obtained approval for the study from the Medical Ethical Review Committees and Institutional Review Boards of the participating registered hospitals. The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>) and assigned a registration number ChiCTR1800020329.

Patient Characteristics and Outcomes

The following demographic and clinicopathological data were collected within 24 hours of admission (Table 1): age; height; weight; type of cancer; smoking status; alcohol consumption; TNM stage; history of surgery; radiotherapy and chemotherapy; Karnofsky performance status score (KPS); Scored Patient-Generated Subjective Global Assessment (PG-SGA); Alb levels; Glb levels; CRP levels; FBG levels; TC levels; Neu counts; Plt counts; Lym counts; Neu-to-Lym ratio (NLR); Plt-to-Lym ratio (PLR); glucose-to-Lym ratio (GLR); advanced lung cancer inflammation index (ALI); systemic immune inflammation index (SII); CRP-to-Alb ratio (CAR); nutritional risk index (NRI); geriatric NRI (GNRI); modified GNRI (mGNRI); Alb-to-Glb ratio (AGR); prognostic nutritional index (PNI); Lym-to-CRP ratio (LCR); controlling nutritional status score (CONUT); modified Glasgow prognostic score (mGPS); and Lym-to-CRP score (LCS). The standard for smoking was smoking more than 20 cigarettes in a lifetime. The standard for drinking was regular drinking over the past year. TNM staging followed the guidelines of the American Joint Committee on Cancer.²⁶ Laboratory tests consisted of standardized tests used throughout China using the same protocol and reference range used nationwide. Patient death due to cancer was defined as the primary endpoint.

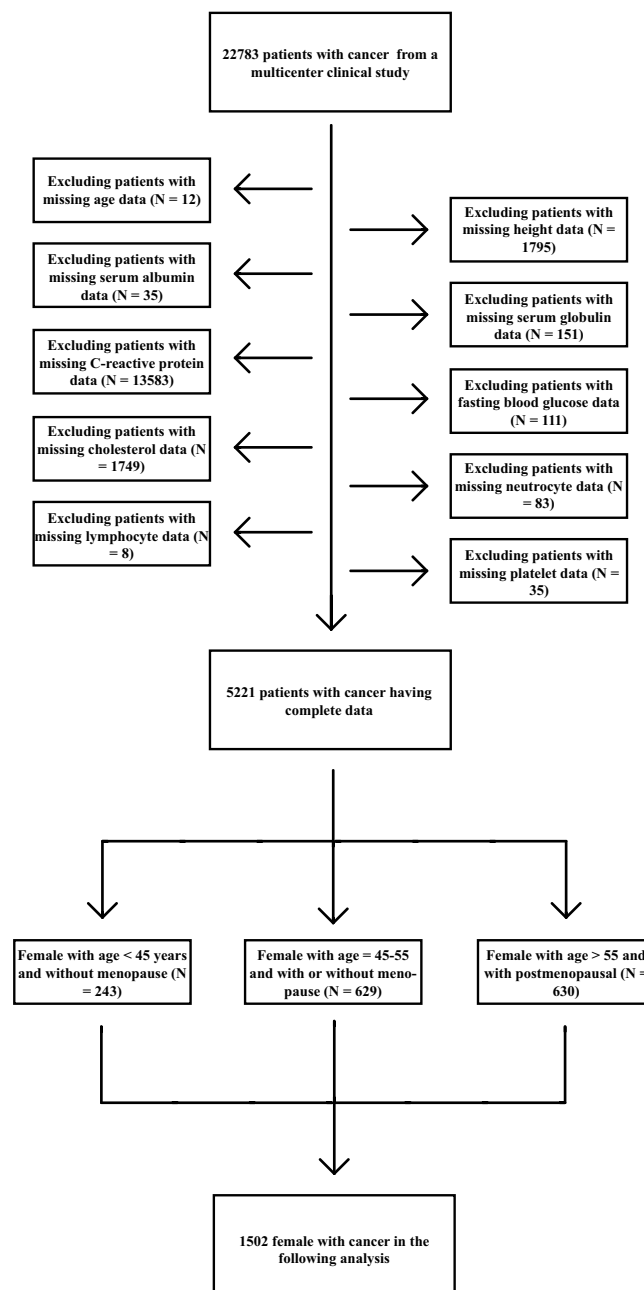


Figure 1 Flow diagram for the selection of female patients with cancer from a multicenter clinical database.

The calculation methods and criteria of the inflammation- and nutrition-based indicators were as follows: body mass index (BMI) = weight/height²; NLR = Neu/Lym; PLR = Plt/Lym; GLR = FBG/Lym; ALI = BMI × Alb/NLR; SII = Neu × Plt/Lym; and CAR = CRP/Alb.^{14,16,18,19,21,27-31} Ideal weight (WLo) was determined using the Lorentz equation for women:²⁰

$$(\text{Height} - 100) - [(\text{Height} - 150)/2.5]$$

Additional parameters included: NRI = 1.519 × Alb + 41.7 × Weight/WLo; GNRI = 1.489 × Alb + 41.7 × weight/WLo; mGNRI = 1.489/CRP + 41.7 × Weight/WLo; AGR = Alb/Glb; PNI = 10 × albumin + 0.005 × Lym; and LCR = Lym/CRP. The criteria for CONUT, mGPS, and LCS are presented in [Supplemental Tables 1–3](#), respectively.

Table I Characteristics of All Females with Cancer

Characteristics	Overall Female Patients
Age (years) ^b	54.00 [47.00, 63.00]
BMI (kg/m ²) ^b	22.37 [20.08, 24.77]
Smoking (Yes, %) ^{a, c}	179 (11.9)
Drinking (Yes, %) ^{a, d}	33 (2.2)
Cancer type (%) ^a	
Lung cancer	436 (29.0)
Gastric cancer	173 (11.5)
Hepatic cancer	23 (1.5)
Breast cancer	311 (20.7)
Esophageal cancer	24 (1.7)
Cervical cancer	54 (3.6)
Bladder cancer	2 (0.1)
Pancreatic cancer	41 (2.7)
Ovarian cancer	58 (3.9)
Nasopharyngeal cancer	28 (1.9)
Colorectal cancer	259 (17.2)
Endometrial cancer	11 (0.7)
Gastric stromal tumor	1 (0.1)
Biliary tract cancer	19 (1.3)
Other cancer	62 (4.1)
TNM stage (%) ^a	
I	187 (12.5)
II	265 (17.6)
III	370 (24.6)
IV	680 (45.3)
Surgery (%) ^a	855 (56.9)
Radiotherapy (%) ^a	196 (13.0)
Chemotherapy (%) ^a	1016 (67.6)
KPS ^b	90.00 [80.00, 90.00]
PG-SGA ^b	4.00 [2.00, 8.00]
Alb (g/L) ^b	39.70 [36.40, 42.58]
TC (mmol/L) ^b	4.67 [4.05, 5.33]
CRP (mg/L) ^b	3.23 [2.62, 9.60]
FBG (mmol/L) ^b	5.30 [4.82, 5.98]
Neu (×10 ⁹ /L) ^b	3.43 [2.46, 4.89]
Lym (×10 ⁹ /L) ^b	1.50 [1.10, 1.90]
Plt (×10 ⁹ /L) ^b	234.00 [182.00, 296.75]
NLR ^b	2.28 [1.54, 3.65]
PLR ^b	157.99 [114.17, 222.12]
GLR ^b	3.67 [2.75, 5.17]
ALI ^b	38.80 [22.88, 61.57]
SII ^b	533.43 [317.88, 928.57]
CAR ^b	0.09 [0.06, 0.25]
GNRI ^b	102.07 [94.79, 108.73]
mGNRI ^b	47.86 [42.46, 55.42]
AGR ^b	1.35 [1.17, 1.55]
PNI ^b	47.45 [43.60, 51.35]
NRI ^b	103.22 [95.82, 110.02]
LCR ^b	4134.75 [1298.14, 7395.56]

(Continued)

Table 1 (Continued).

Characteristics	Overall Female Patients
CONUT (%) ^{a, e}	
Normal	685 (45.6)
Light	669 (44.6)
Moderate	132 (8.8)
Severe	16 (1.1)
mGPS (%) ^a	
0	1134 (75.5)
1	220 (14.6)
2	148 (9.9)
LCS (%) ^a	
0	349 (23.2)
1	956 (63.6)
2	197 (13.1)

Notes: ^aCategorical variables are presented as number (percentage). ^bContinuous variables are presented as median [interquartile range]. ^cThe standard is to smoke more than 20 cigarettes in a lifetime. ^dThe standard is regular drinking in the past year. ^eNormal: 0–1; Light: 2–4; Moderate: 5–8; Severe: 9–12.

Abbreviations: BMI, body mass index; KPS, Karnofsky performance status score; PG-SGA, Scored Patient-Generated Subjective Global Assessment; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; FBG, fasting blood glucose; TC, serum total cholesterol; Neu, neutrocyte; Lym, lymphocyte; Plt, platelet; NLR, Neu-to-Lym ratio; PLR, Plt-to-Lym ratio; GLR, FBG-to-Lym ratio; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; CAR, CRP-to-Alb ratio; GNRI, geriatric nutritional risk index; mGNRI, modified GNRI; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; NRI, nutritional risk index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

Statistical Analysis

Data were presented as simple percentages or medians and interquartile ranges (IQR). Chi-square tests or Fisher's exact tests were used to assess baseline characteristics. Continuous variables with normal distributions were assessed using Student's *t*-tests. Continuous variables with non-normal distributions were assessed using Mann-Whitney tests.

Lasso regression analyses were used to remove unsuitable indicators. Receiver operating characteristic (ROC) curves were used to obtain cut-off values for the indicators. Hazard ratios (HR) and associated 95% confidence intervals (CI) from three analysis models used in this study were determined using univariate and multivariate Cox proportional hazard regression analyses. Model 1 was not adjusted for any covariates. Model 2 was adjusted for age, BMI, type of cancer, smoking status, alcohol consumption, and TNM stage. Model 3 was adjusted for age, BMI, type of cancer, smoking status, alcohol consumption, TNM stage, history of surgery, radiotherapy and chemotherapy, KPS, and PG-SGA. Concordance indices (C-indices) and Area Under the Curves (AUCs) were used to compare the prognostic values of the indicators. C-indices were used to evaluate and select of prognostic models in terms of discrimination ability. AUC is a measure of the discriminative ability of prediction models. We further divided patients into 3 groups according to age (young, middle-aged, and elderly) and into 2 groups according to the type of cancer [reproductive system cancer (ovarian cancer, endometrial cancer, and cervical cancer) and non-reproductive system cancer (lung cancer, gastric cancer, hepatic cancer, breast cancer, esophageal cancer, bladder cancer, pancreatic cancer, nasopharyngeal cancer, colorectal cancer, and biliary tract cancer)] and repeated the above analyses using the three models.

The statistical significance threshold was set to 0.05. Analyses were performed using R (version 4.1.1) software.

Results

Patient Characteristics

The median age of patients in the study was 54 years (IQR, 47 to 63 years), the median BMI was 22.37 kg/m² (IQR, 20.08 to 24.77 kg/m²), the median KPS was 90 (IQR, 80 to 90), and the median PG-SGA was 4 (IQR, 2 to 8). Among the cohort, 12.5% (187/1502) were stage I, 17.6% (265/1502) were stage II, 24.6% (370/1502) were stage III, and 45.3% (680/1502) were stage IV. The baseline characteristics of patients are summarized in Table 1.

Lasso Regression Analyses and Prognostic Values of Indicators for Females with Cancer

Based on Lasso regression analyses of all the indicators, NLR, PLR, GLR, CAR, NRI, and GNRI were removed from further consideration in subsequent group and subgroup analyses.

The trend between the risk of death and indicators in females with cancer and different subgroups is shown in Supplemental Figures 1–6. The cut-off values of indicators were obtained using ROC curves (Supplemental Figure 7, Supplemental Table 4). Patients with higher SII or CONUT or lower ALI, mGNRI, AGR, PNI, or LCR had lower overall survival than patients with the lower SII or CONUT or higher ALI, mGNRI, AGR, PNI, or LCR (Figure 2, Table 2).

Univariate analyses indicated that ALI, SII, AGR, LCR, mGPS, LCS, PNI, mGNRI, and CONUT were prognostic factors for females with cancer (all *P* for trend < 0.001). Multivariate analyses found that ALI (HR, 0.80; 95% CI, 0.72–0.88; *P* for trend < 0.001), SII (HR, 1.18; 95% CI, 1.08–1.30; *P* < 0.001), AGR (HR, 0.81; 95% CI, 0.74–0.89; *P* for trend < 0.001), LCR (HR, 0.78; 95% CI, 0.71–0.86; *P* for trend < 0.001), mGPS (HR, 1.35; 95% CI, 1.18–1.54; *P* for trend < 0.001), LCS (HR, 1.53; 95% CI, 1.29–1.81; *P* for trend < 0.001), PNI (HR, 0.83; 95% CI, 0.75–0.90; *P* for trend < 0.001), mGNRI (HR, 0.73;

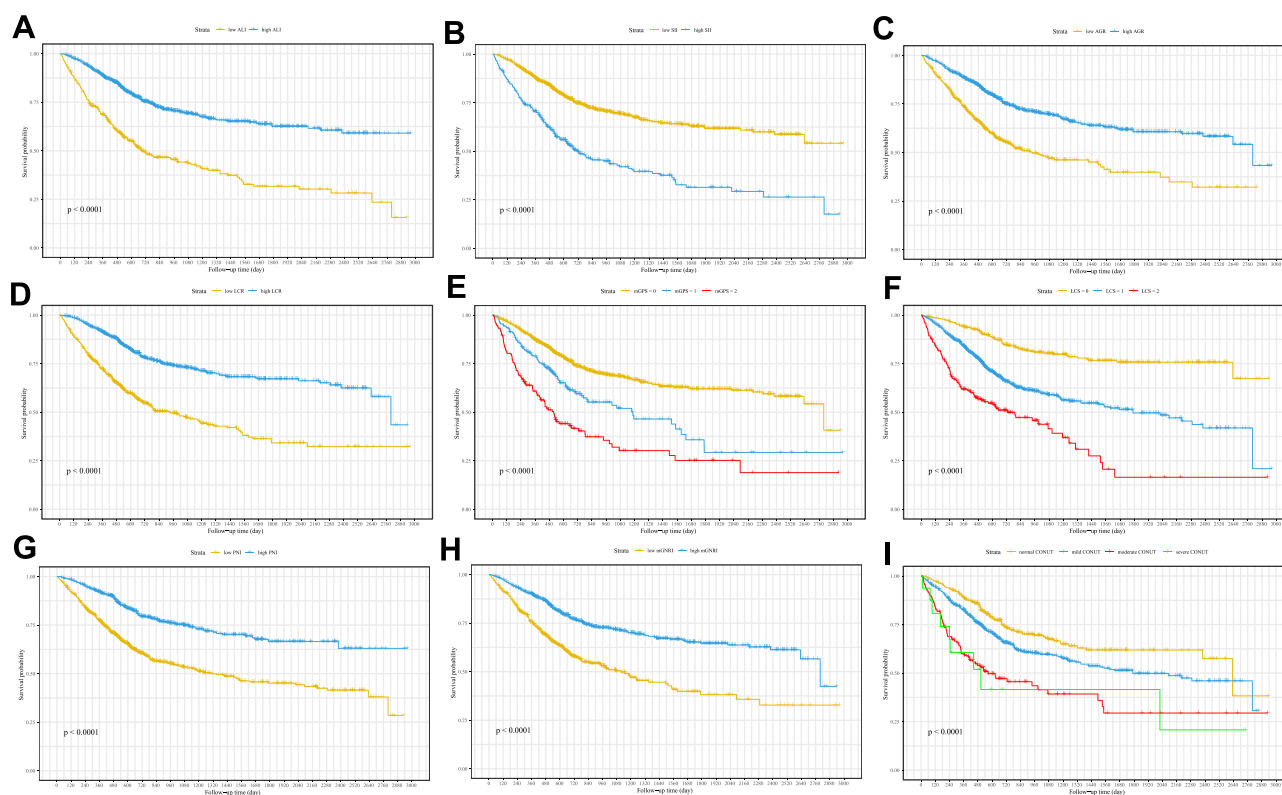


Figure 2 Kaplan-Meier curves of associations among indicators and OS in females with cancer. (A) ALI. (B) SII. (C) AGR. (D) LCR. (E) mGPS. (F) LCS. (G) PNI. (H) mGNRI. (I) CONUT.

Abbreviations: OS, overall survival; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; Lym, lymphocyte; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; mGNRI, modified GNRI; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

Table 2 Associations Between Indicators and OS in All Females with Cancer

Characteristics	Model 1 ^a	P value	Model 2 ^b	P value	Model 3 ^c	P value
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
ALI						
Continuous ^d	0.64 (0.57, 0.72)	< 0.001	0.77 (0.68, 0.87)	< 0.001	0.83 (0.73, 0.94)	0.004
High ^d	0.38 (0.32, 0.45)	< 0.001	0.55 (0.45, 0.67)	< 0.001	0.62 (0.51, 0.77)	< 0.001
Quartile 2 ^d	0.53 (0.42, 0.66)	< 0.001	0.67 (0.53, 0.85)	0.001	0.71 (0.56, 0.91)	0.006
Quartile 3 ^d	0.38 (0.30, 0.48)	< 0.001	0.55 (0.43, 0.72)	< 0.001	0.65 (0.49, 0.86)	0.002
Quartile 4 ^d	0.27 (0.20, 0.35)	< 0.001	0.42 (0.31, 0.56)	< 0.001	0.50 (0.36, 0.69)	< 0.001
P for trend	0.64 (0.59, 0.69)	< 0.001	0.75 (0.68, 0.82)	< 0.001	0.80 (0.72, 0.88)	< 0.001
SII						
Continuous ^d	1.35 (1.27, 1.44)	< 0.001	1.23 (1.14, 1.32)	< 0.001	1.18 (1.09, 1.27)	< 0.001
High ^e	2.51 (2.10, 3.01)	< 0.001	1.92 (1.59, 2.33)	< 0.001	1.72 (1.41, 2.10)	< 0.001
Quartile 2 ^e	1.27 (0.96, 1.68)	0.093	1.33 (0.99, 1.79)	0.062	1.29 (0.95, 1.74)	0.097
Quartile 3 ^e	1.20 (0.90, 1.60)	0.213	1.06 (0.78, 1.43)	0.731	0.95 (0.69, 1.29)	0.729
Quartile 4 ^e	2.88 (2.23, 3.71)	< 0.001	2.12 (1.61, 2.79)	< 0.001	1.78 (1.34, 2.38)	< 0.001
P for trend	1.42 (1.30, 1.54)	< 0.001	1.26 (1.15, 1.37)	< 0.001	1.18 (1.08, 1.30)	< 0.001
mGNRI						
Continuous ^d	0.64 (0.57, 0.72)	< 0.001	0.76 (0.66, 0.88)	< 0.001	0.80 (0.69, 0.92)	0.002
High ^f	0.46 (0.38, 0.55)	< 0.001	0.54 (0.42, 0.69)	< 0.001	0.59 (0.46, 0.76)	< 0.001
Quartile 2 ^f	0.64 (0.51, 0.81)	< 0.001	0.61 (0.46, 0.8)	< 0.001	0.64 (0.49, 0.84)	0.001
Quartile 3 ^f	0.48 (0.38, 0.61)	< 0.001	0.42 (0.30, 0.59)	< 0.001	0.47 (0.34, 0.67)	< 0.001
Quartile 4 ^f	0.29 (0.22, 0.38)	< 0.001	0.34 (0.22, 0.51)	< 0.001	0.40 (0.27, 0.60)	< 0.001
P for trend	0.67 (0.62, 0.73)	< 0.001	0.69 (0.6, 0.79)	< 0.001	0.73 (0.64, 0.84)	< 0.001
AGR						
Continues ^d	0.66 (0.60, 0.73)	< 0.001	0.75 (0.68, 0.83)	< 0.001	0.78 (0.70, 0.86)	< 0.001
High ^g	0.47 (0.39, 0.56)	< 0.001	0.60 (0.50, 0.73)	< 0.001	0.63 (0.52, 0.76)	< 0.001
Quartile 2 ^g	0.74 (0.59, 0.92)	0.008	0.80 (0.63, 1.02)	0.07	0.87 (0.68, 1.11)	0.257
Quartile 3 ^g	0.48 (0.38, 0.62)	< 0.001	0.55 (0.42, 0.72)	< 0.001	0.59 (0.45, 0.78)	< 0.001
Quartile 4 ^g	0.37 (0.29, 0.48)	< 0.001	0.54 (0.41, 0.70)	< 0.001	0.57 (0.44, 0.76)	< 0.001
P for trend	0.71 (0.66, 0.77)	< 0.001	0.79 (0.73, 0.87)	< 0.001	0.81 (0.74, 0.89)	< 0.001
PNI						
Continuous ^d	0.65 (0.60, 0.71)	< 0.001	0.76 (0.69, 0.83)	< 0.001	0.79 (0.72, 0.87)	< 0.001
High ^h	0.44 (0.36, 0.53)	< 0.001	0.61 (0.50, 0.76)	< 0.001	0.66 (0.53, 0.82)	< 0.001
Quartile 2 ^h	0.59 (0.47, 0.74)	< 0.001	0.66 (0.52, 0.84)	0.001	0.70 (0.55, 0.89)	0.004
Quartile 3 ^h	0.46 (0.36, 0.59)	< 0.001	0.64 (0.5, 0.83)	0.001	0.71 (0.55, 0.93)	0.013
Quartile 4 ^h	0.31 (0.24, 0.41)	< 0.001	0.48 (0.37, 0.64)	< 0.001	0.53 (0.40, 0.71)	< 0.001
P for trend	0.68 (0.63, 0.74)	< 0.001	0.80 (0.73, 0.87)	< 0.001	0.83 (0.75, 0.90)	< 0.001
LCR						
Continuous ^d	0.62 (0.51, 0.75)	< 0.001	0.76 (0.64, 0.91)	0.002	0.81 (0.68, 0.96)	0.013
High ⁱ	0.38 (0.32, 0.45)	< 0.001	0.55 (0.45, 0.66)	< 0.001	0.61 (0.50, 0.74)	< 0.001
Quartile 2 ⁱ	0.66 (0.53, 0.82)	< 0.001	0.82 (0.65, 1.04)	0.103	0.87 (0.69, 1.11)	0.268
Quartile 3 ⁱ	0.39 (0.30, 0.50)	< 0.001	0.55 (0.43, 0.71)	< 0.001	0.61 (0.47, 0.80)	< 0.001
Quartile 4 ⁱ	0.24 (0.19, 0.32)	< 0.001	0.43 (0.32, 0.58)	< 0.001	0.49 (0.36, 0.66)	< 0.001
P for trend	0.62 (0.57, 0.68)	< 0.001	0.75 (0.68, 0.82)	< 0.001	0.78 (0.71, 0.86)	< 0.001
CONUT						
Light ^j	1.42 (1.13, 1.80)	0.003	1.19 (0.93, 1.52)	0.176	1.18 (0.92, 1.52)	0.193
Moderate ^j	2.82 (2.08, 3.83)	< 0.001	2.24 (1.62, 3.11)	< 0.001	2.00 (1.42, 2.83)	< 0.001
Severe ^j	3.27 (1.65, 6.48)	0.001	2.36 (1.02, 5.44)	0.045	2.18 (0.93, 5.09)	0.073
P for trend	1.20 (1.15, 1.25)	< 0.001	1.44 (1.23, 1.69)	< 0.001	1.11 (1.06, 1.17)	< 0.001
mGPS						
1	1.83 (1.45, 2.32)	< 0.001	1.25 (0.98, 1.61)	0.076	1.21 (0.94, 1.55)	0.146
2	3.30 (2.61, 4.18)	< 0.001	2.19 (1.70, 2.82)	< 0.001	1.89 (1.45, 2.47)	< 0.001
P for trend	1.82 (1.62, 2.04)	< 0.001	1.44 (1.27, 1.64)	< 0.001	1.35 (1.18, 1.54)	< 0.001

(Continued)

Table 2 (Continued).

Characteristics	Model 1 ^a	P value	Model 2 ^b	P value	Model 3 ^c	P value
	HR (95% CI)		HR (95% CI)		HR (95% CI)	
LCS						
1	2.59 (1.98, 3.38)	< 0.001	1.70 (1.28, 2.27)	< 0.001	1.57 (1.18, 2.09)	0.002
2	5.26 (3.85, 7.20)	< 0.001	2.66 (1.9, 3.72)	< 0.001	2.35 (1.66, 3.31)	< 0.001
P for trend	2.26 (1.94, 2.62)	< 0.001	1.62 (1.38, 1.9)	< 0.001	1.53 (1.29, 1.81)	< 0.001

Notes: ^aModel 1 was not adjusted for any covariates. ^bModel 2 was adjusted for age, body mass index, type of cancer, smoking status, alcohol consumption and TNM stage. ^cModel 3 was adjusted for age, body mass index, type of cancer, smoking status, alcohol consumption, TNM stage, history of surgery, radiotherapy and chemotherapy, Karnofsky performance status score and Scored Patient-Generated Subjective Global Assessment. ^dContinuous: as continuous variable; Low: < 23.727; High: ≥ 23.727; Quartile 1: < 22.875; Quartile 2: 22.875 ~ < 38.805; Quartile 3: 38.805 ~ < 61.579; Quartile 4: ≥ 61.579. ^eContinuous: as continuous variable; Low: < 930.286; High: ≥ 930.286; Quartile 1: < 317.797; Quartile 2: 317.797 ~ < 533.433; Quartile 3: 533.433 ~ < 929.343; Quartile 4: ≥ 929.343. ^fContinuous: as continuous variable; Low: < 46.858; High: ≥ 46.858; Quartile 1: < 42.460; Quartile 2: 42.460 ~ < 47.856; Quartile 3: 47.856 ~ < 55.432; Quartile 4: ≥ 55.432. ^gContinuous: as continuous variable; Low: < 1.232; High: ≥ 1.232; Quartile 1: < 1.173; Quartile 2: 1.173 ~ < 1.354; Quartile 3: 1.354 ~ < 1.546; Quartile 4: ≥ 1.546. ^hContinuous: as continuous variable; Low: < 48.700; High: ≥ 48.700; Quartile 1: < 43.600; Quartile 2: 43.600 ~ < 47.450; Quartile 3: 47.450 ~ < 51.350; Quartile 4: ≥ 51.350. ⁱContinuous: as continuous variable; Low: < 3212.291; High: ≥ 3212.291; Quartile 1: < 1297.710; Quartile 2: 1297.710 ~ < 4134.754; Quartile 3: 4134.754 ~ < 7399.381; Quartile 4: ≥ 7399.381. ^jNormal: 0–1; Light: 2–4; Moderate: 5–8; Severe: 9–12.

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; Lym, lymphocyte; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; mGNRI, modified geriatric nutritional risk index; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

95% CI, 0.64–0.84; *P* for trend < 0.001), and CONUT (HR, 1.11; 95% CI, 1.06–1.17; *P* for trend < 0.001) were independent prognostic factors for females with cancer (Table 2). The associations between indicators and overall survival in different subgroups are shown in Figure 3.

Survival Prediction Values of Indicators and Inflammatory and Nutritional Status Evaluation

LCR showed the highest prognostic ability for females with cancer, followed by ALI, PNI, mGNRI, SII, LCS, AGR, CONUT, and mGPS (Figure 4).

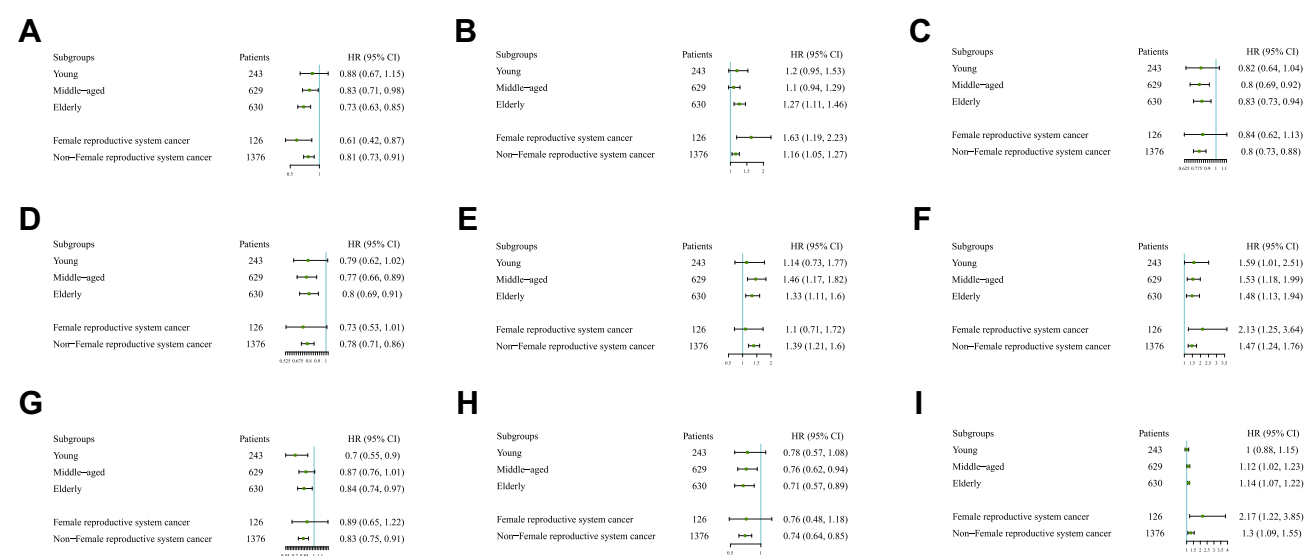


Figure 3 Associations between indicators and OS in different subgroups. (A) for ALI. (B) for SII. (C) for AGR. (D) for LCR. (E) for mGPS. (F) for LCS. (G) for PNI. (H) for mGNRI. (I) for CONUT. (A–I) were adjusted for age, body mass index, type of cancer, smoking status, alcohol consumption, TNM stage, history of surgery, radiotherapy, and chemotherapy, Karnofsky performance status score and Scored Patient-Generated Subjective Global Assessment.

Abbreviations: OS, overall survival; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; Lym, lymphocyte; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; mGNRI, modified geriatric nutritional risk index; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

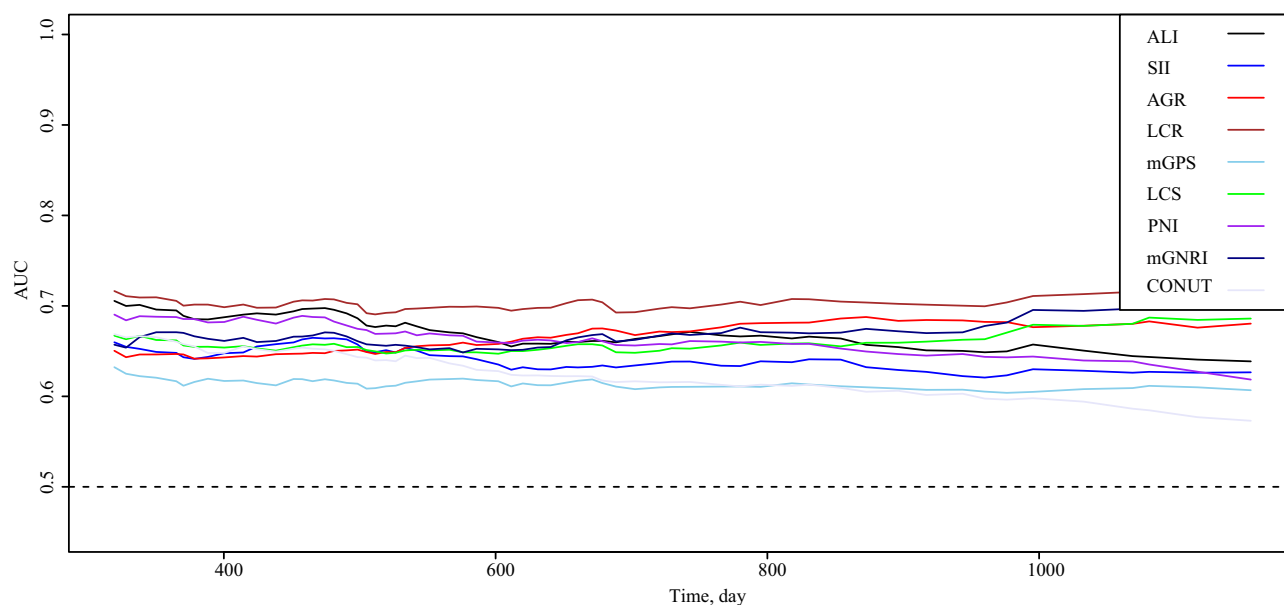


Figure 4 AUCs of indicators in females with cancer.

Abbreviations: AUCs, area under the curves; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; Lym, lymphocyte; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; mGNRI, modified geriatric nutritional risk index; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

The C-indices of LCR (0.668; 95% CI, 0.644–0.693), ALI (0.657; 95% CI, 0.632–0.683, $P = 0.345$), PNI (0.651; 95% CI, 0.625–0.676, $P = 0.024$), mGNRI (0.632; 95% CI, 0.606–0.657, $P = 0.004$), SII (0.629; 95% CI, 0.602–0.655, $P = 0.002$), LCS (0.624; 95% CI, 0.602–0.646, $P < 0.001$), AGR (0.622; 95% CI, 0.595–0.649, $P = 0.001$), CONUT (0.618; 95% CI, 0.591–0.645, $P < 0.001$), and mGPS (0.597; 95% CI, 0.574–0.620, $P < 0.001$) are presented in [Table 3](#).

LCR was used to evaluate the inflammatory levels of different subgroups, and PNI was used to evaluate the nutritional levels of different subgroups ([Supplemental Figures 8 and 9](#)).

Survival Prediction and Comparison Among Indicators for Young, Middle-Aged, or Elderly Female Patients

AGR showed the highest prognostic ability for young females with cancer, followed by mGNRI, LCR, PNI, LCS, ALI, SII, mGPS, and CONUT ([Supplemental Figure 10](#)). LCR showed the highest prognostic value for middle-aged females

Table 3 C-Indices of Indicators in Females with Cancer

Characteristics	C-Index (95% CI)	P value
LCR	0.668 (0.644, 0.693)	-
ALI	0.657 (0.632, 0.683)	0.345
PNI	0.642 (0.615, 0.668)	0.024
mGNRI	0.632 (0.606, 0.657)	0.004
SII	0.629 (0.602, 0.655)	0.002
LCS	0.624 (0.602, 0.646)	<0.001
AGR	0.622 (0.595, 0.649)	0.001
CONUT	0.618 (0.591, 0.645)	<0.001
mGPS	0.597 (0.574, 0.620)	<0.001

Abbreviations: C-indices, concordance indices; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; Lym, lymphocyte; LCR, Lym-to-CRP ratio; ALI, advanced lung cancer inflammation index; PNI, prognostic nutritional index; mGNRI, modified geriatric nutritional risk index; SII, systemic immune inflammation index; LCS, Lym-to-CRP score; AGR, Alb-to-Glb ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score.

with cancer, followed by ALI, mGNRI, LCS, PNI, AGR, SII, mGPS, and CONUT ([Supplemental Figure 11](#)). For elderly female patients, ALI had the highest prognostic value, followed by LCR, SII, PNI, CONUT, mGPS, AGR, LCS, and mGNRI ([Supplemental Figure 12](#)). The C-indices of indicators are presented in [Supplemental Table 5](#).

Survival Prediction and Comparison Among Indicators for Female Patients with or without Non-Reproductive System Cancer

SII showed the highest prognostic ability for female patients with reproductive system cancer, followed by LCR, ALI, LCS, AGR, PNI, CONUT, mGNRI, and mGPS ([Supplemental Figure 13](#)). ALI showed the highest prognostic ability for female patients with non-reproductive system cancer, followed by LCR, PNI, SII, mGNRI, AGR, LCS, mGPS, and CONUT ([Supplemental Figure 14](#)). The C-indices of indicators are presented in [Supplemental Table 6](#).

Discussion

In this study, we investigated the correlation between 15 inflammation and nutrition-based indicators with cancer prognoses in females to determine the prognostic values of these indicators. Of the 15 indicators, 9 were found to be prognostic indicators for females with cancer by Lasso analysis. These indicators were also found to be independent prognostic factors for females with cancer by multivariate analysis. LCR was the most suitable prognostic indicator for all females with cancer, followed by ALI, PNI, mGNRI, SII, LCS, AGR, CONUT, and mGPS.

Patients were divided into 3 groups (young, middle-aged, and elderly) according to age or into 2 groups according to the type of cancer (reproductive system cancer and non-reproductive system cancer). In each subgroup, we compared the prognostic value of these indicators and determined the most suitable prognostic factors for different populations. We used LCR to evaluate the inflammatory levels of the different subgroups and PNI to evaluate the nutritional levels of the different subgroups. By comparing the prognostic values of these indicators with the LCR and PNI levels in different patient populations, we could determine the appropriate prognostic indicators for each subgroup.

Indicators are composed of nutrition-related indices (BMI, Lym, WLo, and TC), inflammation-related indices (CRP, Neu, Glb, and Plt), and Alb, which are related to both nutrition and inflammation.^{14,16,18,19,21,27–31} We divided the nine indicators into three categories: nutrition-related indicators (PNI, CONUT), inflammation-related indicators (LCR, SII, LCS), and indicators that take into account nutrition and inflammation (ALI, mGNRI, AGR, and mGPS).^{14,16,18,19,21,27–31}

Inflammation affects the occurrence and development of cancer through different pathways.^{32,33} As evidence has accumulated linking inflammation with cancer development, additional indicators of cancer-related inflammation have been discovered. Cancer patients with higher SII or lower LCR or LCS have significantly worse prognoses than those with lower SII or higher LCR or LCS.^{18,23,28–31} Cancer patients are prone to malnutrition and an increased risk of death because inflammation influences the absorption and utilization of nutrients by cancer cells.³⁴ Patients with higher PNI or lower CONUT have a lower risk of death than those with lower PNI or higher CONUT.^{20,21,27} Changes in inflammation and nutritional statuses have mutual effects on each other.^{13,35,36} The mutual interactions between inflammation and nutritional statuses accelerate cancer progression and lead to a worse cancer prognosis for patients.³⁷

Young females have lower systemic inflammation compared to young males, which may be due to the protective effect of female hormones.⁹ Females have a higher incidence of malnutrition and iron-deficiency anemia than males, which may be due to the effects of menstruation and diet.^{7,8} Our results showed that compared with middle-aged and elderly females, young females have lower inflammatory levels and better nutritional statuses. We believe that although the nutritional statuses of young females are unstable, their status remains at a higher level compared with middle-aged and elderly women. Nutrition status still has a greater impact on the cancer prognosis of young females than inflammation status. In comparison with inflammation, the nutritional status of females with cancer is more apparent. Our results show that AGR is the most appropriate prognostic indicator in young females with cancer. Nutritional supplements could reverse this trend.³⁸ We recommend using the nutrition-related prognostic index AGR to predict patients' survival and to provide nutritional interventions.

The inflammation and nutritional statuses of middle-aged females differ from those of young females. Because most middle-aged females are in perimenopause, their hormone levels are in flux.¹¹ The inhibitory effect of estrogen on

inflammation is weakened, and anorexia caused by perimenopause affects the nutritional status of females with cancer.^{9,39,40} Cancers in patients with low estrogen levels progress faster than those with normal levels of estrogen, which help inhibit cancer progression.⁴¹ In addition, inflammatory levels in cancer patients increase with age as their nutritional statuses continue to deteriorate.^{12,42}

We found that the most suitable prognostic indicator for middle-aged females with cancer was LCR. The level of inflammation in cancer patients had a greater impact on their prognosis than nutritional status. LCR may be a more suitable prognostic factor for middle-aged females with cancer and reducing the inflammatory state of these patients may bring greater clinical benefits.

Compared with young and middle-aged populations, elderly females are always in a state of low-level systemic inflammation.⁴⁰ This is due to physiological changes and the loss of estrogen brought on by increased age. This reduces the inhibition of cancer growth.⁴¹ Due to the reduction of nutritional intake caused by a decreased appetite and the increase in nutritional consumption caused by systemic inflammation, the nutritional statuses of elderly females are worse than those of young and middle-aged females.^{16,43} We show that elderly females have the highest inflammatory load and the lowest nutritional status. Indicators of inflammatory and nutritional status were the most appropriate prognostic factors for elderly female patients. Our results showed that ALI was the most suitable prognostic indicator for elderly females with cancer. For elderly females with cancer, comprehensive interventions such as reducing inflammation, increasing nutrition, getting reasonable exercise, and enhancing immunity are desirable.

To provide more accurate prognostic indicators, we divided patients into 2 groups, one with reproductive system cancer and the other with non-reproductive system cancer. Inflammation is a fundamental cause of the occurrence and development of both reproductive system cancer and non-reproductive system cancer.^{44–47} However, patients with reproductive system cancer have higher levels of inflammation than those with non-reproductive system cancer.⁴⁴ Nutritional consumption caused by high inflammatory levels is a critical source of malnutrition in patients with cancer.⁴⁸ Our results show that patients with reproductive system cancers have higher levels of inflammation and worse nutritional status than those with non-reproductive system cancer. For female patients with reproductive system cancer, an index measuring inflammation is consistent with the most suitable prognostic index (LCR), and a treatment scheme should focus on reducing systemic inflammation. However, for patients with non-reproductive system cancer, an index that incorporates measures of both nutrition and inflammation provides the most suitable prognostic index (ALI). For these patients, a combination of anti-inflammatory and nutritional supplements is a desirable treatment strategy.

Our study had several limitations. The sample sizes were relatively small, which may have affected the statistical power of the study. In addition, we could not conduct a subgroup analysis based on each cancer type. Studies with larger sample sizes for each cancer type and more clinical factors may improve the prognostic prediction for females with cancer. Laboratory data were acquired using standard laboratory test protocols, which were limited compared to more advanced testing techniques. Although there was no measurement of hormone levels in our study, previous studies had shown that compared with males, females have more intense hormonal changes throughout their lives and are more vulnerable and more likely to be affected by age-related changes in hormone levels.^{49,50} Studies with more clinical factors (such as hormone) should be carried out in the future.

Conclusion

In summary, LCR showed the highest prognostic ability for females with cancer, followed by ALI, PNI, mGNRI, SII, LCS, AGR, CONUT, and mGPS. For young females with cancer, we recommend using AGR to predict patient survival. For middle-aged females with cancer, inflammatory index (LCR) may be a more suitable prognostic factor. For elderly females with cancer, ALI was the most suitable prognostic indicator. We formulated individualized treatment plans for different populations according to their inflammatory and nutritional statuses to maximize the improvement of the populations' prognoses.

Abbreviations

BMI, body mass index; KPS, Karnofsky performance status score; PG-SGA, Scored Patient-Generated Subjective Global Assessment; Alb, serum albumin; Glb, serum globulin; CRP, C-reactive protein; FBG, fasting blood glucose; TC, serum total cholesterol; Neu, neutrocyte; Lym, lymphocyte; Plt, platelet; NLR, Neu-to-Lym ratio; PLR, Plt-to-Lym ratio; GLR, FBG-to-Lym ratio; ALI, advanced lung cancer inflammation index; SII, systemic immune inflammation index; CAR, CRP-to-Alb ratio; GNRI, geriatric nutritional risk index; mGNRI, modified GNRI; AGR, Alb-to-Glb ratio; PNI, prognostic nutritional index; NRI, nutritional risk index; LCR, Lym-to-CRP ratio; CONUT, controlling nutritional status score; mGPS, modified Glasgow prognostic score; LCS, Lym-to-CRP score.

Data Sharing Statement

All data needed to evaluate the conclusions in the paper are present in the paper and/or the [Supplementary Materials](#). Additional data related to this paper may be requested from the corresponding author (Prof. Hanping Shi).

Ethics Approval and Informed Consent

We obtained approval for the study from the Medical Ethical Review Committees and Institutional Review Boards of the participating registered hospitals. The study was conducted in accordance with the guidelines of the Declaration of Helsinki. The study was registered with the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>) and assigned a registration number ChiCTR1800020329.

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Disclosure

The authors report no conflicts of interest in this work.

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