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Original article

Inflammatory burden as a prognostic biomarker for cancer

Hailun Xie [a, b, c, 1], Guotian Ruan [a, b, c, 1], Yizhong Ge [a, b, c, 1], Qi Zhang [a, b, c], Heyang Zhang [a, b, c], Shiqi Lin [a, b, c], Mengmeng Song [a, b, c], Xi Zhang [a, b, c], Xiaoyue Liu [a, b, c], Xiangrui Li [a, b, c], Kangping Zhang [a, b, c], Ming Yang [a, b, c], Meng Tang [a, b, c], Chun-Hua Song [d], Hanping Shi [a, b, c, *]

[a] Department of Gastrointestinal Surgery/Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing, 100038, China
[b] Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition, Beijing, 100038, China
[c] Key Laboratory of Cancer FSMP for State Market Regulation, Beijing, 100038, China
[d] Department of Epidemiology, College of Public Health, Zhengzhou University, Zhenzhou, 450000, China

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SUMMARY

Background and aims: Systemic inflammation is the most representative host–tumor interaction in cancer. This study aimed to develop a novel inflammatory burden index (IBI) to assess the inflammatory burden of different cancers and predict the prognosis of patients with cancer.

Methods: A total of 6359 cancer patients admitted to multiple centers from 2012 through 2019 were included in this study. The IBI was formulated as C-reaction protein × neutrophil/lymphocyte. Survival differences between the groups were compared using the Kaplan–Meier method. Cox proportional hazard regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI). Logistic regression analysis was used to assess the association between the inflammatory burden index and outcomes.

Results: Cancers assessed by the IBI could be classified as high, moderate, or low inflammatory burden and had different prognostic stratification effects (46.5% vs 61.0% vs 83.0%; P < .001). Compared with other systemic inflammation biomarkers, the IBI had the highest accuracy in predicting survival. Patients with a high IBI had significantly lower survival rates than those with a low IBI (45.7% vs 69.1%; P < .001). For every standard deviation increase in the IBI, the risk of poor prognosis for patients with cancer increased by 10.3% (HR, 1.103; 95% CI, 1.072–1.136; P < .001). The IBI could be used as a useful prognostic supplement in the pathological stage. A high IBI was an independent high-risk factor that affected patient's physical condition, malnutrition, cachexia, and short-term outcomes and an independent risk factor for patients with cancer in both validation cohorts a (hazard ratio, 1.114; 95% confidence interval, 1.072–1.157; P < .001) and b (hazard ratio, 1.125; 95% confidence interval, 1.060–1.193; P < .001).

Conclusions: The IBI, as a novel indicator of systemic inflammation, is a feasible and promising predictive biomarker in patients with cancer and can be used to assess the inflammatory burden of different cancers.

1. Introduction

The morbidity and mortality associated with malignancy are rapidly increasing worldwide. China has the highest number of new cancer cases and cancer deaths worldwide. As the aging population increases, the cancer burden is expected to increase by 50% in 2040 compared with that in 2020, with nearly 30 million new cancer cases worldwide by then [1,2]. Therefore, effective, practical, and simple prognostic biomarkers are urgently needed to reduce cancer-related mortality and help formulate therapeutic interventions.

* Corresponding author. Department of Gastrointestinal Surgery/Department of Clinical Nutrition, Beijing Shijitan Hospital, Capital Medical University, Beijing International Science and Technology Cooperation Base for Cancer Metabolism and Nutrition, Beijing, 100038, China.
E-mail address: shihp@ccmu.edu.cn (H. Shi).
[1] Hailun Xie, Guotian Ruan, and Yizhong Ge contributed equally to this work and therefore share first authorship

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Pathological stages, lymph node metastasis, perineural/vascular invasion, and other tumor characteristics are widely considered as the main prognostic factors for cancer [3–5]. With the development of genomics research, we can gain insight into the biological characteristics of cancer [6–8]. However, most of these factors are obtained after invasive procedures (surgical removal of tissue). Furthermore, the detection cost is relatively high, which limits its application. In addition, focusing only on tumor characteristics cannot comprehensively evaluate the progression of malignancy. Many studies have demonstrated that host–tumor interactions profoundly affect the prognosis of patients with cancer [9,10]. Systemic inflammation is the most representative host–tumor interaction in patients with cancer and has been proven to play an important role in the occurrence, progression, metastasis, and therapeutic resistance of cancer. A high inflammatory burden in patients with cancer may be associated with poor prognosis [11,12]. Systemic inflammation in patients with cancer can manifest as changes in peripheral blood cells and inflammatory proteins, such as neutrophils, lymphocytes, and C-reactive protein (CRP). Based on these parameters, systemic inflammation biomarkers, including the neutrophil/lymphocyte ratio (NLR), lymphocyte/CRP, and CRP/albumin ratio have been shown to be independent prognostic factors for various malignancies [13–15]. Although an increasing number of systemic inflammation biomarkers have been demonstrated to affect the prognosis of cancer, the optimal systemic inflammation biomarkers for comprehensive evaluation of the inflammatory burden and prediction of the prognosis of patients with cancer remain unclear.

We aimed to develop a novel inflammatory burden index (IBI) to assess the inflammatory burden of different cancers and predict the prognosis of patients with cancer as well as to verify its prognostic value in both the overall evaluation and internal validation in a large sample cohort.

2. Materials and methods

2.1. Patients

The patients were from the Investigation on Nutrition Status and Its Clinical Outcome of Common Cancers (INSCOC) project of China (registration number: ChiCTR1800020329), which prospectively recruited patients who were hospitalized at more than 40 clinical centers in China between June 2012 and December 2019. All patients were hospitalized due to the need for anticancer treatment (surgery, radiotherapy, and chemotherapy, etc.). The exclusion criteria were as follows: admission time <24 h; with missing pathological characteristics data; synchronous or metachronous double cancer; no peripheral blood cell and inflammatory protein data; severe or acute infection; continued use of anti-inflammatory drugs within the past 6 months; inability to make independent decisions or refusal to participate in this study. All patients provided written consent. This study was approved by the ethics committees of all participating institutions.

2.2. Data collection and follow-up

The collected serological tests included white blood cells, neutrophils, lymphocytes, platelets, red blood cells, hemoglobin, and CRP and albumin levels. All serological tests were performed before cancer treatment. Other baseline clinicopathological variables were the following: demographic data, including sex, age, height, weight, comorbidities (hypertension, diabetes), lifestyle (smoking, drinking), and family history; tumor characteristics, including cancer types, tumor-node-metastasis (TNM); treatment information, including surgery, radiotherapy, and chemotherapy. Patients were prospectively followed up by professionals from their admission until the last follow-up date (October 30, 2020) or the date of death for any cause.

2.3. Outcomes

The primary outcome was overall survival (OS), defined as the time interval between the date of cancer diagnosis and all-cause mortality or the last follow-up. The secondary outcomes were the functional status of the patients, which was assessed by the Karnofsky Performance Scale (KPS) score; the nutritional status of the patients, which was assessed by the Patient-Generated Subjective Global Assessment (PG-SGA); cancer cachexia, which was assessed according to the International Diagnostic Criteria for Cancer Cachexia [16]; and short-term outcome, which was defined as the prognostic outcome of the patient within 3 months after treatment.

2.4. Statistical analysis

Data are expressed as mean ± standard deviation or median [interquartile range] for continuous variables and as frequencies (proportions) for categorical variables. Differences between groups were compared using the Mann–Whitney U test, chi-square test, or Fisher's exact test. Optimal stratification was used to determine the threshold for continuous IBI using log-rank statistics. The receiver operator characteristic curve was used to compare the prognostic predictive value of systemic inflammation biomarkers. Restricted cubic splines were used to evaluate the nonlinear relationship between the IBI and all-cause mortality in patients with cancer. The Kaplan–Meier method was used to draw the survival curve, and the log-rank test was used to compare the survival rates of each group. Cox proportional hazard regression analysis was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of IBI change in cancer mortality under the model of independent effects. Patients with liver disorders and hematological system diseases or those with short-term deaths were also excluded in order to evaluate the robustness of the results as a sensitivity analysis. We performed a subgroup analysis and tested the interaction of exposure with these characteristics on the outcome. Logistic regression analysis was used to assess the association of the IBI with KPS, PGSGA, cachexia, and short-term outcomes, adjusted for different confounders. Two-sided P values < 0.05 were considered statistically significant. All statistical analysis was performed using R version 4.0.5 (http://www.r-Project.org).

3. Results

3.1. Measurements of serum systemic inflammation biomarkers

The systemic inflammatory response is characterized by the upregulation of inflammatory parameters and downregulation of anti-inflammatory parameters. We identified 5 key factors in serum parameters: upregulation in disease progression, including neutrophils, platelets, and CRP, and downregulation in disease progression, including lymphocytes and albumin. Subsequently, we comprehensively evaluated various combinations of inflammatory and anti-inflammatory parameters to determine the optimal biomarker for assessing the inflammatory burden and to predict the prognosis of patients with cancer (eFigure 1 in the Supplement). The formulas used to calculate these systemic inflammation biomarkers are presented in eTable 1 in the Supplement. In the comparison of the predictive performance of these inflammatory biomarkers by receiver operator characteristic curve and C-index (eFigure 2 in the Supplement), our newly developed IBI [= CRP (mg/dL) × neutrophil (/μL)/lymphocyte (/μL)] had the highest

accuracy in predicting adverse survival of patients with cancer (area under the curve, 0.649; C-index, 0.648).

3.2. Clinicopathological characteristics

A total of 6359 patients with cancer were included in the present study (eFigure 3 in the Supplement). Among the patients, 3842 (60.4%) were men and 2517 (39.6%) were women, and the mean age of the patients was 59.40 ± 11.24 years. The optimal cutoff value of the IBI determined by the optimal stratification method was 16. Based on this cutoff value, 3542 (55.7%) patients had a low IBI, and 2817 (44.3%) had a high IBI. Patients with high IBI were significantly associated with male sex, advanced age, low body mass index, high comorbidities, adverse lifestyle, advanced pathological stage, no treatment, hyperinflammatory status, low nutritional status, and poor outcomes. The mortality rate was approximately 23.4% higher, the length of hospitalization was nearly 2 days longer, and the hospitalization cost was nearly 9716.27 yuan (~1525 USD) higher in patients with high IBI than in with patients with low IBI (eTable 2 in the Supplement).

3.3. Distribution of inflammatory burden in different cancers

We explored the distribution of inflammatory burden in 10 common cancers using the newly constructed IBI and commonly used inflammatory parameters (CRP and NLR) (Fig. 1). Taking colorectal cancer as a reference, we divided cancers into 3 grades according to inflammatory burden: high inflammatory burden cancers (pancreatic cancer, lung cancer, and gynecological tumors), moderate inflammatory burden cancers (esophageal cancer, gastric cancer, hepatobiliary tumors, urinary system tumors, and colorectal cancer), and low inflammatory burden (breast cancer and nasopharyngeal cancer). The results of the different inflammatory burden assessment tools showed obvious consistency, and the IBI showed the most significant effect. In the stratified analysis of pathological stages, we found that the distribution of inflammatory burden of different cancers was generally consistent at different pathological stages, with breast cancer and nasopharynx cancer having the low inflammatory burden, and lung cancer, pancreatic cancer, and gynecological cancer having the high inflammatory burden (eFigure 4 in the Supplement).

Subsequently, we performed a survival analysis to assess survival differences in cancers with different levels of inflammatory burden. The results showed that cancers with high inflammatory burden had the worst prognosis, followed by those with moderate inflammatory burden, then those with low inflammatory burden (46.5% vs 61.0% vs 83.0%; log-rank $P < .001$) (eFigure 5 in the Supplement). Furthermore, we found that the IBI could distinguish the prognosis of cancers with different inflammatory burdens. Compared with patients with low IBI, patients with high IBI had worse survival (eFigure 6 in the Supplement). The inflammatory burden in patients with cancer increased progressively with age. Male patients had a heavier burden of inflammation than female patients. The inflammatory burden was closely related to pathological stage; that is, patients at advanced stages had a higher inflammatory burden than those at early stages (eFigure 7 in the Supplement).

3.4. Kaplan–Meier curves of inflammatory burden

The median follow-up time was 18.7 [interquartile range, 0.1–72.0] months. During the follow-up period, 2627 (41.3%) patients died. Patients with high IBI had significantly lower OS than those with low IBI (45.7% vs 69.1%; log-rank $P < .001$) (Fig. 2). We found that the IBI could further clearly distinguish the prognosis of patients with different pathological stages. Patients with high inflammatory burden had worse outcomes than those with low inflammatory burden at all pathological stages (eFigure 8 in the Supplement). These results suggest that the IBI could be used as a useful supplement to pathological stage in assessing the prognosis of patients with cancer. Subgroup survival analysis for common cancers, including lung cancer, esophageal cancer, gastric cancer, hepatic-biliary cancer, pancreatic cancer, colorectal cancer, breast cancer, gynecological cancer, urologic cancer, nasopharynx cancer, and other cancers, indicated that a high IBI was a poor prognostic factor for most cancers (eFigure 9 in the Supplement). In the subgroup analysis, we analyzed the clinical application range of IBI in different cancers. For example, IBI may be suitable for lung cancer patients with all stages, while for colorectal cancer, IBI may be more suitable for patients with advanced stages (eTable 3 in the Supplement).

3.5. Relationship between inflammatory burden and survival

We observed a significant nonlinearity between the IBI and the survival of patients with cancer (P value for nonlinearity <0.001). With increased IBI, the prognosis of patients was significantly reduced, but after a certain level, the fluctuation effect tended to flatten (eFigure 10 in the Supplement). After adjusting for confounders, multivariate Cox proportional risk regression analysis revealed that the IBI was an independent prognostic factor for patients with cancer. For every standard deviation increase in the IBI, the risk of poor prognosis for patients with cancer increased by 10.3% (HR, 1.103; 95% CI, 1.072–1.136; log-rank $P < .001$). When the IBI was divided into quintiles, the lowest quintile Q1 was used as a reference. Q2, Q3, and Q4 were positively associated with a poor prognosis ($P < .001$). Under the model of independent effects, the HRs for survival were 1.154 (1.015, 1.311), 1.520 (1.347, 1.716), and 2.128 (1.892, 2.395), respectively (Table 1). Patients with liver disorders, hematological system diseases and those with short-term deaths for sensitivity analysis were excluded. The results showed that the IBI was still an independent biomarker affecting the prognosis of patients with cancer, and sensitivity analyses had little effect on the findings (eTable 4 in the Supplement). Subgroup analysis showed that a high IBI was an independent risk factor for prognosis in most subgroups. It is worth noting that the IBI has an obvious interaction with family history, pathological stage, and surgery. That is, the inflammatory burden has a great impact on the prognosis of patients with a family history, no surgical treatment, and with advanced pathological stages (eFigure 11 in the Supplement).

3.6. Relationship between inflammatory burden and secondary outcomes

We explored the relationship between the IBI and secondary outcomes in patients with cancer, including daily function, malnutrition, cachexia, and adverse short-term outcomes (eTable 5 in the Supplement). Compared with patients with low IBI, those with a high IBI were more likely to have decreased daily function. A high IBI is an independent risk factor that affects daily function in patients with cancer. Compared with those with low IBI (Q1), the incidence of life dysfunction in patients with high IBI (Q4) was more than 3 times higher (odds ratio [OR], 4.424; 95% CI, 3.505–5.584; log-rank $P < .001$). Similarly, the IBI is an independent factor affecting malnutrition and cachexia in patients with cancer. Patients with high IBI (Q4 vs Q1) had more than 4 and 2 times the risk of malnutrition (OR, 4.103; 95% CI, 3.458–4.870; log-rank $P < .001$) and cachexia (OR, 2.439; 95% CI, 2.066–2.880; log-rank $P < .001$), respectively. In addition, the incidence of

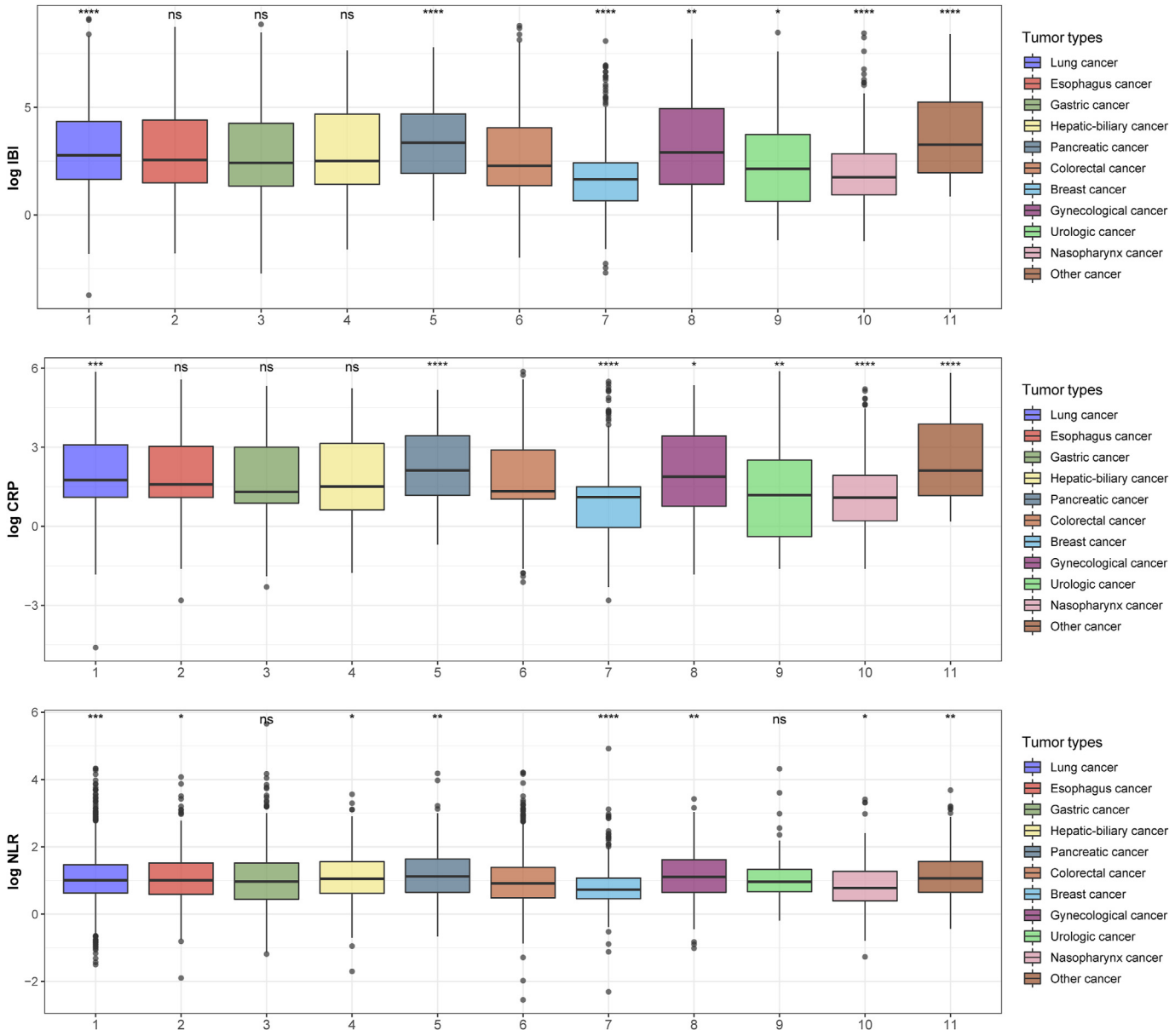

Fig. 1. The systemic inflammatory in different cancer. Notes: ns p-value > 0.05, * p-value < 0.05, **** p-value < 0.001.

adverse short-term outcomes in patients with a high IBI was also significantly increased (OR, 4.807; 95% CI, 3.295–7.011; log-rank $P < .001$).

3.7. Combination of inflammatory burden and nutrition in the prognosis assessment

The results of the combined analysis of the inflammatory burden and nutrition suggested that the IBI could assist nutritional assessment tools in more detailed prognostic stratification (eFigure 12A and B in the Supplement). Compared with neither, patients with malnutrition and high inflammation had a 33.1% higher risk of death. Under the model of independent effects, a patient with both malnutrition and high inflammation was estimated to have a much worse overall prognosis (HR, 2.260; 95% CI, 2.018–2.531; $P < .001$) (eTable 6 in the Supplement, PG-SGA). Moreover, patients with cachexia and high inflammatory burden had a worse prognosis, with an approximately doubled risk of death (HR, 2.021; 95% CI, 1.809–2.258; $P < .001$) (eTable 6 in the Supplement, cachexia).

3.8. Randomized internal validation

Subsequently, we randomly assigned the total population to validation cohorts A (4452 cases) and B (1907 cases), with a 7:3 ratio based on computer-generated random numbers (eTable 7). The prognosis of patients with a high IBI was significantly worse than that of patients with a low IBI (Figure 3A and B). High IBI was an independent risk factor for patients with cancer in both validation cohorts A (HR, 1.114; 95% CI, 1.072–1.157; log-rank $P < .001$) and B (HR, 1.125; 95% CI, 1.060–1.193; log-rank $P < .001$) (Table 2). The IBI could also distinguish patients with poor prognosis at different pathological stages in both validation cohorts a and b (eFigure 13A and B in the Supplement).

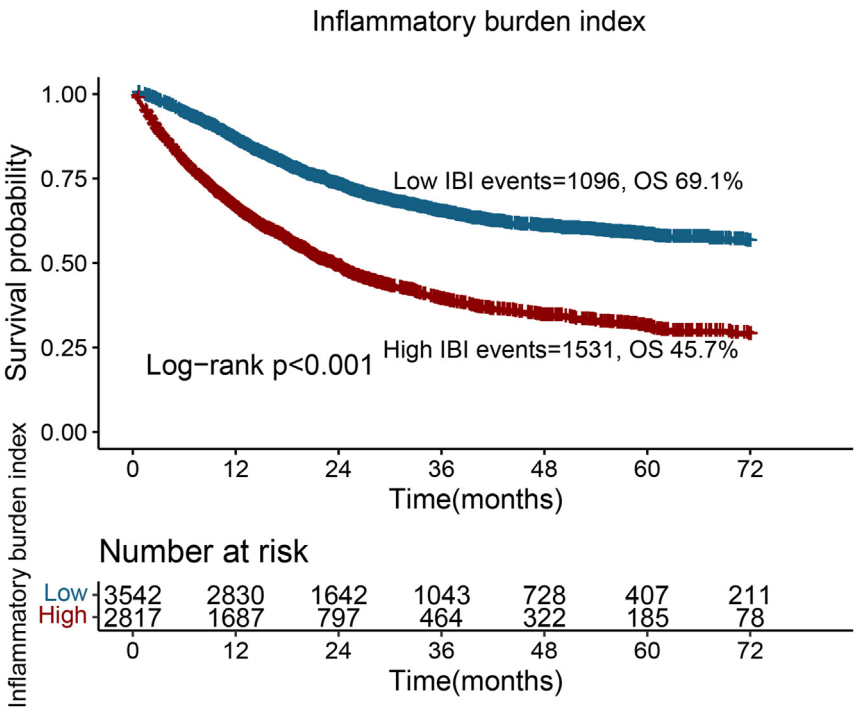

Fig. 2. Kaplan–Meier curve of Inflammatory burden index in patients with cancer.

Table 1
Association between inflammatory burden index and overall survival of patients with patients with cancer.

IBI	Model a	p value	Model b	p value	Model c	p value
Continuous (per SD)	1.145 (1.113,1.178)	<0.001	1.097 (1.065,1.129)	<0.001	1.103 (1.072,1.136)	<0.001
Cutoff value		<0.001		<0.001		<0.001
C1 (<16)	Ref		Ref		ref	
C2 (≥16)	2.342 (2.166,2.531)		1.829 (1.69,1.98)		1.706 (1.574,1.85)	
Quartiles						
Q1 (<4.08)	Ref		Ref		ref	
Q2 (4.08–11.37)	1.373 (1.209,1.559)	<0.001	1.207 (1.062,1.371)	0.004	1.154 (1.015,1.311)	0.029
Q3 (11.37–65.47)	2.238 (1.988,2.519)	<0.001	1.670 (1.481,1.883)	<0.001	1.520 (1.347,1.716)	<0.001
Q4 (≥65.47)	3.239 (2.891,3.63)	<0.001	2.342 (2.085,2.63)	<0.001	2.128 (1.892,2.395)	<0.001
p for trend		<0.001		<0.001		<0.001

Notes:
Model a: No adjusted.
Model b: Adjusted for age, sex, BMI, TNM stage.
Model c: Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

4. Discussion

This study proposed, for the first time, a tool for assessing the inflammatory burden in patients with cancer and confirmed that it was a powerful prognostic indicator for patients with cancer. Compared with other inflammatory markers, it is a more reliable biomarker for predicting poor prognosis in patients with cancer. Second, we performed inflammatory burden grading for different cancers for the first time and achieved good prognostic stratification. We assessed a variety of outcomes, including OS, life function, nutritional status, short-term outcome, length of hospitalization, and hospitalization expenses, which provide a good reference for comprehensively evaluating the prognostic value and clinical application prospects of the IBI in cancer. Finally, we confirmed the clinical significance of our newly developed IBI in the prognostic assessment of cancer using internally randomized validation cohorts.

Systemic inflammation caused by complex host–tumor interactions plays a vital role in the development of cancer, and it is also considered to be the 7th hallmark of cancer [9,10,17,18]. There is increasing evidence that blood-borne systemic inflammation biomarkers are effective predictors of the prognosis of various cancers [13,19,20]. Pro-inflammatory cytokines are upregulated as part of the inflammatory response. They create an inflammatory microenvironment suitable for tumor proliferation, invasion, and microvascularization by mediating the recruitment of circulating white blood cells to tumors, thereby promoting the development and progression of tumors. They also induce the synthesis of acute phase proteins, such as CRP, and reduce albumin production in the liver [10,21,22]. Therefore, systemic inflammation is typically characterized by increased circulating neutrophils, platelets, and CRP and decreased levels of circulating lymphocytes and albumin. Based on these basic inflammatory biomarkers, we developed an IBI that comprehensively reflects the inflammatory state of patients with cancer. Subsequently, we found that the IBI was a more reliable prognostic marker for cancer than other combinations of inflammatory biomarkers. This may be because IBI measures the balance between acute and immune inflammation by combining

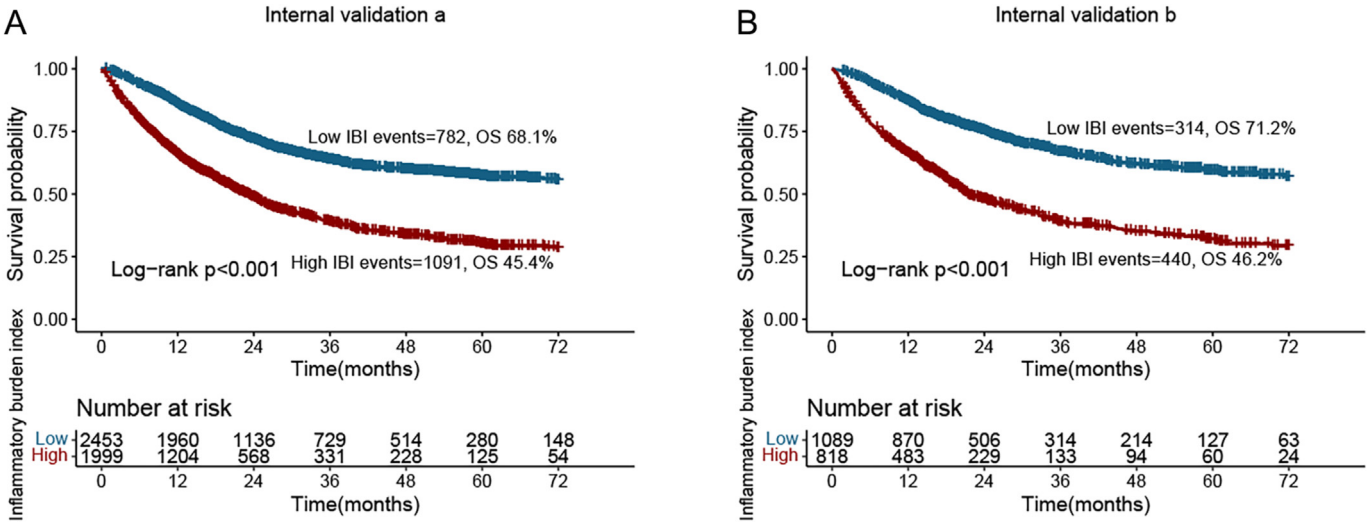

Fig. 3. Kaplan–Meier curve of inflammatory burden in patients with cancer at internal validation cohorts. Notes: A, Validation cohort a; B, Validation cohort b.

Table 2
Association between inflammatory burden index and overall survival of patients with cancer at validation cohorts.

Validation cohort a						
IBI	Model a	p value	Model b	p value	Model c	p value
Continuous (per SD)	1.165 (1.122,1.209)	<0.001	1.103 (1.063,1.145)	<0.001	1.114 (1.072,1.157)	<0.001
Cutoff value		<0.001		<0.001		<0.001
C1 (<16)	ref		ref		ref	
C2 (≥16)	2.283 (2.082,2.504)		1.789 (1.629,1.965)		1.666 (1.514,1.832)	
Quartiles						
Q1 (<4.16)	ref		ref		ref	
Q2 (4.16–11.88)	1.369 (1.178,1.591)	<0.001	1.163 (1,1.353)	0.05	1.110 (0.954,1.292)	0.178
Q3 (11.88–69.09)	2.263 (1.967,2.604)	<0.001	1.655 (1.436,1.907)	<0.001	1.495 (1.295,1.725)	<0.001
Q4 (≥69.09)	3.209 (2.803,3.675)	<0.001	2.286 (1.991,2.625)	<0.001	2.078 (1.807,2.391)	<0.001
p for trend		<0.001		<0.001		<0.001
Validation cohort b						
IBI	Model a	p value	Model b	p value	Model c	p value
Continuous (per SD)	1.146 (1.087,1.209)	<0.001	1.116 (1.054,1.182)	<0.001	1.125 (1.060,1.193)	<0.001
Cutoff value		<0.001		<0.001		<0.001
C1 (<16)	ref		ref		ref	
C2 (≥16)	2.485 (2.149,2.874)		1.924 (1.659,2.232)		1.800 (1.547,2.093)	
Quartiles						
Q1 (<3.88)	ref		ref		ref	
Q2 (3.88–10.44)	1.388 (1.091,1.767)	0.008	1.258 (0.987,1.602)	0.064	1.202 (0.942,1.533)	0.139
Q3 (10.44–59.47)	2.207 (1.764,2.760)	<0.001	1.698 (1.354,2.13)	<0.001	1.559 (1.240,1.961)	<0.001
Q4 (≥59.47)	3.525 (2.854,4.354)	<0.001	2.527 (2.036,3.136)	<0.001	2.273 (1.821,2.838)	<0.001
p for trend		<0.001		<0.001		<0.001

Notes:
Model a: No adjusted.
Model b: Adjusted for age, sex, BMI, TNM stage.
Model c: Adjusted for age, sex, BMI, TNM stage, tumor type, surgery, radiotherapy, chemotherapy, hypertension, diabetes, smoking, drinking, family history.

the strengths of CRP, neutrophils, and lymphocytes. Serum CRP is the most representative clinical marker of acute systemic inflammation [23]. Neutrophils secrete inflammatory mediators and chemokines to create a tumor microenvironment suitable for tumor proliferation, invasion and microvascularization, promoting the occurrence and development of tumors [24,25]. Lymphocytes play an important role in cancer immune surveillance, inhibiting tumor cell proliferation and growth through cytokine-mediated cytotoxicity [26]. The ratio of neutrophil to lymphocyte is considered as a biomarker of immune systemic inflammation [27–29].

The clinical outcome of patients with cancer is determined not only by tumor characteristics reflecting the degree of disease progression but also by host-related factors, such as the host's systemic inflammation response [22,30]. Comparison of the distribution of adverse events in the high- and low-IBI groups showed that a high IBI was closely related to poor physical condition, functional status, progressive pathological stages, and to greater proneness to adverse outcomes (higher mortality, longer hospital stay, and higher hospitalization expenses). In the multivariate survival analysis, the IBI was a strong prognostic predictor of cancer and could be used as a useful supplement to the pathological stage in prognostic assessment. Randomized internal validation of the newly developed IBI showed that a high IBI remained an independent risk factor for cancer outcomes. Moreover, a high IBI was also an independent high-risk factor that affected the patient's physical condition, malnutrition, cachexia, and short-term outcomes.

The intensity of the interaction between different cancers and the host differs, leading to different inflammatory burdens in

patients with different cancers. In this study, we have, for the first time, clarified that different cancers have different inflammatory burdens and performed inflammatory grading for conventional cancers. For cancers with high inflammatory burden, such as pancreatic cancer and lung cancer, continuous monitoring of inflammatory burden is particularly important, and anti-inflammatory therapy is recommended if necessary. The IBI not only distinguished the outcomes of patients with different inflammatory grades but also provided significant prognostic stratification in most cancers. In the era of precision medicine, these analyses provide more individualized and targeted references for efficacy monitoring, prognostic guidance, and therapeutic intervention for cancer patients with different levels of inflammation.

This study has the following advantages. First, to our knowledge, this is the first study that explored the distribution of the inflammatory burden in cancers. Second, we evaluated the clinical significance of inflammatory burden in patients with cancer in terms of OS, daily function, nutritional status, short-term outcomes, length of hospital stay, and hospitalization expenses. Finally, this is a large-scale prospective cohort study, which guarantees the accuracy of the results. However, this study has several limitations. Systemic inflammation biomarkers were only assessed at a single time point, and their changes over time and response to treatment were not assessed. Because some patients had other cancers, such as lymphoma and melanoma, the inflammatory burden of these cancers cannot be evaluated in this study. Finally, although internal randomization validation was performed in this study, further external, multicenter studies are needed to verify our results.

5. Conclusion

The IBI, as a novel indicator of systemic inflammation, is a feasible and promising predictive biomarker in patients with cancer and could be used to assess the inflammatory burden of different cancers, which, in turn, could provide individual and targeted references for efficacy monitoring, prognosis guidance, and therapeutic intervention.

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Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Author contributions

Hanping Shi, and Hailun Xie: designed the study and had primary responsibility for the final content; Hailun Xie, Guotian Ruan and Yizhong Ge: analyzed the data; Hailun Xie, Guotian Ruan and Yizhong Ge: wrote the paper; Qi Zhang, Heyang Zhang, Shiqi Lin, Mengmeng Song, Xi Zhang, Xiaoyue Liu, and Kangping Zhang: acquired the data; Ming Yang, Meng Tang, and Chun-Hua Song: critically revised the manuscript for important intellectual content; and all authors: read and approved the final manuscript. The authors report no conflicts of interest. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2022.04.019.

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