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] D t t G t t t S /D t t C N t t , B S t H t , C t M t , B , 100038, C
[b] B I t t S T C t B C M t N t t , B , 100038, C
[c] K L t C FSMP St t M t R t , B , 100038, C
[d] D t t E , C P H t , t , , 450000, C

ARTICLE INFO

A t t :
Received 10 February 2022
Accepted 18 April 2022

K :
Inflammatory burden
Systemic inflammation
Cancer
Prognostic

SUMMARY

B : 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.

M t : 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.

R t : 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

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. P t t

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. D t t -

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. O t

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. St t t

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. M t t fl t

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. C p t t t

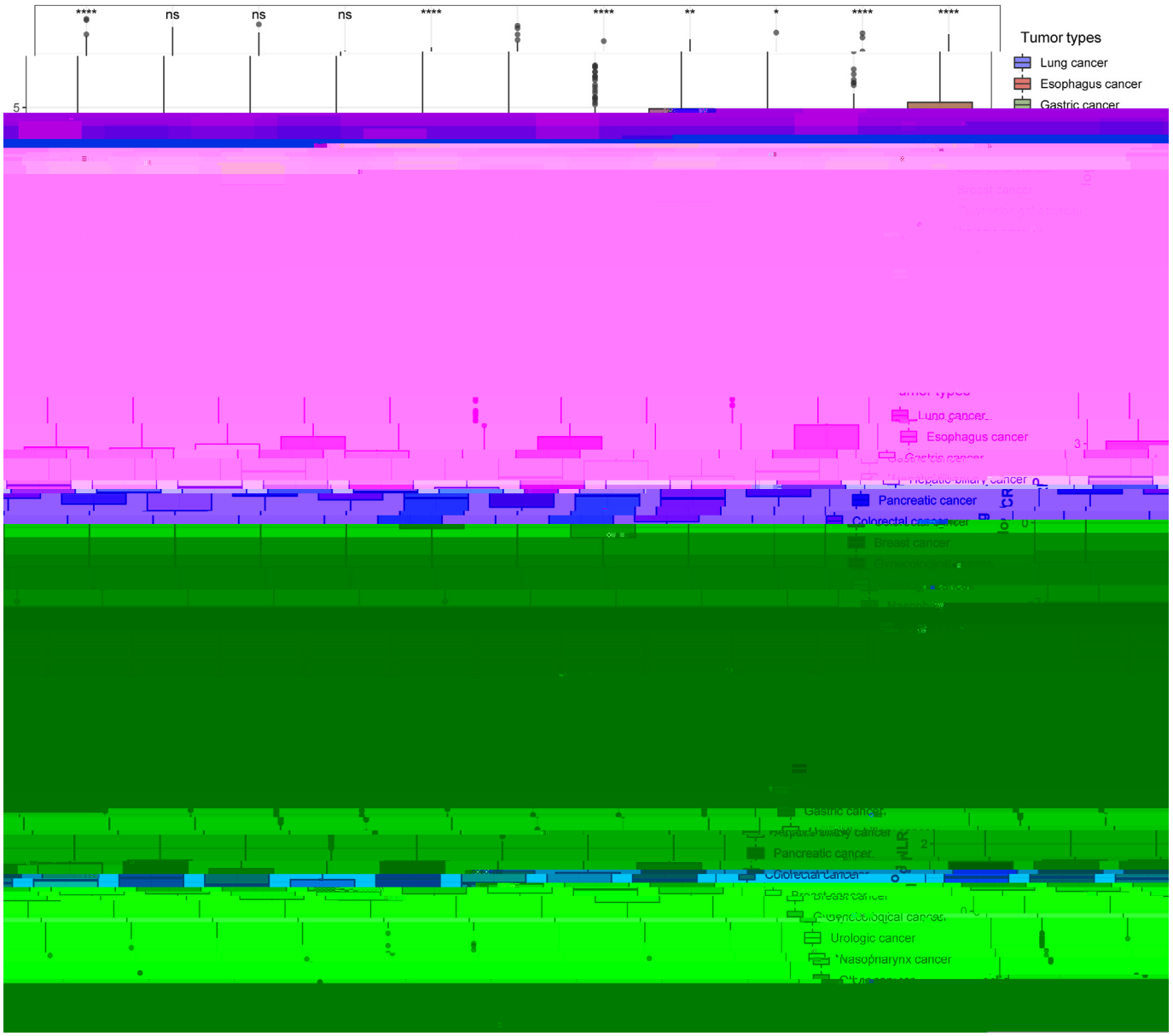

Fig. 1. The systemic inflammatory in different cancer. Notes: ns p-value

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. C t fl t t t t p t

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. R t t

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).

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 infl

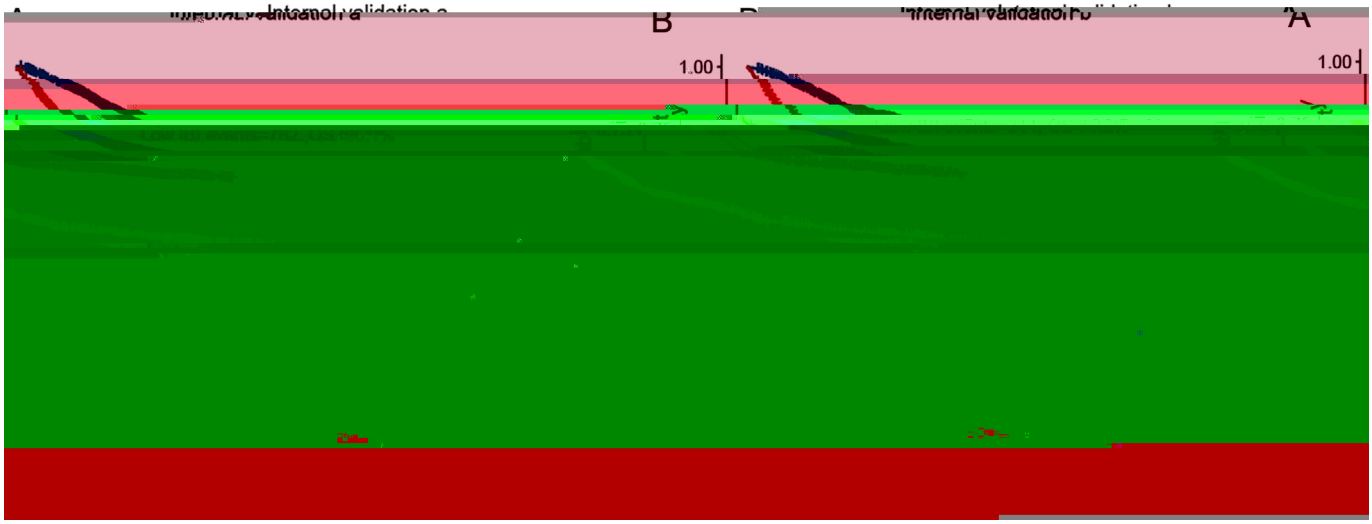

Fig. 3. Kaplan–Meier curve of inflammatory burden in patients with cancer at internal validation cohorts. Notes: A, Validation cohort a; B, Validation cohort b.

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.

Funding statement

This study was supported by the National Key Research and Development Program to Dr. Hanping Shi (No. 2017YFC1309200) and the Beijing Municipal Science and Technology Commission (SCW2018-06).

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.

Acknowledgements

We thank all the patients and their families for participating in the study.

Appendix A. Supplementary data

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

References

[1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA A Cancer J Clin 2021;71:209–49.

[2] Cancer TIAfRo. The International Agency for Research on Cancer (IARC); 2021. The latest global cancer burden in 2020, https://www.iarc.who.int/faq/latest-global-cancer-data-2020-qa/.

[3] van Roessel S, Kasumova GG, Verheij J, Najarian RM, Maggino L, de Pastena M, et al. International validation of the eighth edition of the American joint committee on cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg 2018;153:e183617.

[4] Hashimoto T, Makino T, Yamasaki M, Tanaka K, Miyazaki Y, Takahashi T, et al. The pattern of residual tumor after neoadjuvant chemotherapy for locally advanced esophageal cancer and its clinical significance. Ann Surg 2020;271:875–84.

[5] Samejima J, Yokose T, Ito H, Nakayama H, Nagashima T, Suzuki M, et al. Prognostic significance of blood and lymphatic vessel invasion in pathological stage IA lung adenocarcinoma in the 8th edition of the TNM classification. Lung Cancer 2019;137:144–8.

[6] Sparano JA, Crager MR, Tang G, Gray RJ, Stemmer SM, Shak S. Development and validation of a tool integrating the 21-gene recurrence score and clinical-pathological features to individualize prognosis and prediction of chemotherapy benefit in early breast cancer. J Clin Oncol 2021;39:557–64.

[7] Berger MF, Mardis ER. The emerging clinical relevance of genomics in cancer medicine. Nat Rev Clin Oncol 2018;15:353–65.

[8] Weber J, Braun CJ, Saur D, Rad R. In vivo functional screening for systems-level integrative cancer genomics. Nat Rev Cancer 2020;20:573–93.

[9] Crusz SM, Balkwill FR. Infl

[20] Song M, Zhang Q, Tang M, Zhang X, Ruan G, Zhang X, et al. Associations of low hand grip strength with 1 year mortality of cancer cachexia: a multicentre observational study. J Cachexia Sarcopenia Muscle 2021.
[21]