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A novel systematic inflammation related index is prognostic in curatively resected non-metastatic colorectal cancer

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ABSTRACT

Backgroud: To better identify patients with high mortality risk, we developed a systematic inflammation index (IPI) based on neutrophil to lymphocyte ratio (NLR) and albumin.
Methods: The performance of pretreatment IPI was evaluated in patients with surgically resected non-metastatic colorectal cancer. IPI was predefined and compared with Glasgow Prognostic Score (GPS)/modified GPS in terms of discrimination and calibration abilities.
Results: In multivariate analysis, patients with an IPI of 1 or 2 had 1.68(95%CI:1.15−2.44) or 3.56(95% CI:2.12−5.98)-fold increased cancer specific mortality risk(CSMR) respectively in comparison to patients with an IPI of 0. The prognostic significance was independent of tumor locations and nodal status. Compared with the GPS/mGPS, IPI had the higher c statistics and lower Akaike Information Criterion. IPI showed good calibration in predicting 1-year, 3-year and 5-year CSMR.
Conclusions: IPI is readily available, independently prognostic and may reflect the host inflammation, immune and nutritional status that could have impact on cancer progression.

1. Introduction

The association between cancer and inflammation is well recognized and substantiated.[1,2] An ongoing systematic host response would have impact on cancer progression.[3,4] Several blood-based systematic inflammation related index have been demonstrated as prognostic in a variety of cancers. Among them, the Glasgow Prognostic Score (GPS)/modified Glasgow Prognostic Score(mGPS), which are based on a combination of C-reactive protein (CRP) and albumin level, are the most extensively validated and recommended to be used in the routine clinical management of patients with cancer.[5–7] However, CRP testing is not routinely performed in the management of cancer patients in most clinical facilities. That hampers the widespread adoption of the GPS/mGPS. Neutrophil to lymphocyte ratio (NLR), is another extensively validated inflammation score[8–10] and has repeatedly been shown to outperform some of its counterparts.[11–15] NLR and CRP are equally good in some studies.[15] Calculation of NLR is quite easy with a full blood count test-the most common test in clinical practice. So far, the combined prognostic performance of NLR and albumin has not been investigated and how it fares when compared with the GPS/mGPS is quite intriguing. If they are equally fit, the new inflammation related index would be a reasonable substitute for the GPS/mGPS when CRP is not available.

Both GPS/mGPS[16] and NLR[8] has been shown as prognostic in colorectal cancer either in non-metastatic or metastatic settings. The aim of the present study was to evaluate the performance of a novel inflammation related prognostic index (IPI) based on NLR and albumin and to compare it with the GPS/mGPS in a cohort of non-metastatic colorectal cancer treated with curative resections.

2. Material and methods

2.1. Patients

The cancer registry database of Wuxi 4th People's Hospital (Wuxi Cancer Center) was established in December 2009. All information of cancer patients treated in this hospital was prospectively recorded in the registry since its establishment. A retrospective study was conducted in a cohort of consecutive colorectal cancer patients who underwent curative resection of

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primary colorectal cancers between January 2010 and December 2013 at the hospital. The inclusion criteria were as follows: 1) Patients who had histologically confirmed colorectal adenocarcinoma. 2) who underwent curative resection of primary tumors. 3) who had a full blood cell count and biochemical profile test within two weeks before surgery. Patients with any of the following criteria were excluded: 1) who had bowel obstruction or perforation with emergency presentation. 2) who had a history of chronic inflammatory diseases such as inflammatory bowel diseases and rheumatoid arthritis. 3) who was complicated with other acute inflammation diseases such as pneumonia. 4) who had neo-adjuvant treatment. 5) who had metastatic diseases found either pre-operatively or intra-operatively. 6) whose survival status could not be ascertained. 7) whose cause of death was not related to colorectal cancer. 8) who died within one month after surgery. 9) who had previously been diagnosed with other malignancy including colorectal cancer at different sites.

A standardized data form was created to retrieve the following information: demographic characteristics including name, age and sex; pathological characteristics including site of disease, histology, depth of primary tumor invasion(T), number of metastasized lymph nodes(N), histological grade, number of total lymph nodes sampled, number of tumor deposits (TDs), status of peri-neural invasion(PNI) and lympho-vascular invasion(LVI), and tumor necrosis; serum biomarkers including neutrophil count, lymphocyte count, albumin and CRP. Patients were staged according to the 7th edition of AJCC TNM staging manual.

Patients' survival status was checked every three months by staff from the Clinical Statistic Center of the hospital, relying on medical records platform or telephone contacts with patients.

All the patients in the present study gave informed consent to the usage of their social-demographic and clinical information in scientific investigations. This study was approved by the hospital's institutional review board and conformed to the provisions of the Declaration of Helsinki.

2.2. Definitions of inflammation indexes

The IPI was developed based on NLR and albumin (Table 1). The IPI used albumin similarly to the GPS (vs the modified GPS), that is either low albumin OR low NLR was worthy of a IPI score of 1. The reference cutoff value for NLR was pre-specified as 3, which was adopted by other researchers and proved to be prognostic across different cohorts.[17–21] The reference cutoff value for CRP and albumin was the same as defined by the GPS/mGPS (Table 1).

Table 1
Definitions of IPI, GPS and mGPS.

Index	Definition
IPI	
0	Both NLR≤3 and Albumin≥35
1	Either NLR≤3 or Albumin<35
2	Both NLR>3 and Albumin<35
GPS	
0	Both CRP≤10 and Albumin≥35
1	Either CRP ≤10 or Albumin<35
2	Both CRP >10 and Albumin<35
mGPS	
0	CRP≤10
1	Both CRP >10 and Albumin≥35
2	Both CRP >10 and Albumin<35

Abbreviations: IPI: inflammation related prognostic index; GPS: Glasgow Prognostic Score; mGPS: modified Glasgow Prognostic Score; NLR: neutrophil to lymphocyte ratio; CRP: C-reactive protein.

2.3. Statistical analysis

The primary endpoint was cancer specific survival(CSS), which was defined as the time from the day of surgery to death from colorectal cancer or the last date of follow up. Only Cases with missing information less than 5% were used in the analysis. The relationship of IPI with other characteristics was checked by one-way ANOVA test or chi square test. The relationship between OS and predictive factors was assessed with univariate and multivariate Cox proportional hazards regression analysis. A multivariate analysis was performed including all the variables with $P < 0.10$ from the univariate analysis and using backward selection for the best predictor set (significance level 0.1). The distributions of survival were obtained by the Kaplan-Meier method and compared with the two-sided log-rank test.

Internal validation was performed with bootstrap resampling strategy (100 resamples). The discrimination and calibration performance of PI and the GPS/mGPS was compared.[22] The discrimination performance was measured using Harrell's C statistic and AIC. The higher Harrell's C statistic and the lower AIC, the better performance (sensitivity and specificity) the model has. A c statistic of 0.5 indicates that the model has no discriminative ability, and a c statistic of 1 indicates that the model perfectly distinguishes between those who died and remained alive by a specific time frame. Calibration refers to the accuracy of prediction of event probabilities at any time after the time origin, and was evaluated with calibration curves in which predicted outcomes versus observed outcomes were graphically depicted.[23]

All hypothesis tests were two-sided with $p < 0.05$ as statistically significant. All statistical analysis was performed using STATA 14.0 (STATA Corp, Texas, USA).

3. Results

3.1. Cohort characteristics

Initially, a consecutive of 1032 patients with resected colorectal cancer were screened for eligibility. Patients inclusion and exclusion were illustrated in Fig. 1. A final total of 571 patients were eligible for the analysis. The baseline demographic, biochemical and pathological characteristics of the cohort were listed in Table 2. Most patients had stage III disease, followed by stage II disease. More than eighty percent of patients had 12 or more lymph nodes sampled. More than sixty patients received adjuvant treatment with either fluoropyrimidine-based chemotherapy or radiotherapy.

Patients were largely followed up in accordance with National Comprehensive Cancer Network (NCCN) guidelines. Physical examination and serum carcinoembryonic antigen (CEA) were performed every 3–6 months for the first 2 years, then every 6 months from the third to fifth year, and annually thereafter. Chest/abdominal/pelvis CTs were performed annually for 5 years. Colonoscopy was performed for the first year after treatment and repeated in the third year and then every 5 years. The last follow up was conducted around June 2016. With a median follow up period of 42 months, a total of 142 colorectal cancer specific deaths (25%) occurred. The estimated 1-year, 3-year and 5-year cancer specific survive rate for the cohort was 94.7%(95%CI: 92.5–96.3), 80.1%(95% CI: 76.5–83.2),69.2%(95%CI: 63.8–74.0) respectively.

3.2. Prognostic analysis

In univariate survival analysis, both IPI and the GPS/mGPS was prognostic, along with age, CRP, albumin, NLR, T stage, N stage, TNM stage, lympho-vascular invasion (LVI), histological grade, number of metastasized lymph nodes and tumor deposits (Table 3). A side by

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