Int J Clin Exp Med 2015;8(10):19138-19143
www.ijcem.com /ISSN:1940-5901/IJCEM0014019

Original Article

Prognostic significance of Glasgow prognostic score in patients with stage II colorectal cancer

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Received August 5, 2015; Accepted October 10, 2015; Epub October 15, 2015; Published October 30, 2015

Abstract: Glasgow prognostic score (GPS), one information based prognostic score, has been previously shown to be a prognostic factor in varieties cancers mostly in advanced tumors. This study aimed to explore its value in patients with relatively early stage colorectal cancer (CRC). A total of 99 CRC patients with stage II from 2005 to 2010 operated in our hospital were enrolled in this study. C-reactive protein (CRP), albumin (ALB), Karnofsky Performance Status (KPS) score as well as a variety of biochemical variables before the operation was acquired from the database retrospectively. The value of GPS was calculated and its association with the clinical factors was further investigated. The prognostic significance was analyzed by univariate and multivariate analyses. Increased preoperative GPS was found associated with elevated carcinoembryonic antigen (CEA) and decreasing of KPS. Kaplan-Meier analysis and log-rank test revealed that a higher GPS predicted a higher risk of postoperative mortality in stage II CRC ($P < 0.001$). Furthermore, multivariate analysis demonstrated the GPS to be a risk factor for postoperative mortality (HR 3.215; P=0.025). The preoperative GPS might be a potential useful indicator for postoperative survival in patients with stage II CRC.

Keywords: Glasgow prognostic score, colorectal cancer, prognosis, CEA, KPS

Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with a cumulative lifetime risk of ~5% [1]. Now partly attributing to acquiring the western life style, the patients with CRC maintained an upward momentum in China. Although recent years have seen improvements in surgical techniques and adjuvant chemotherapy, the long-term survival of patients with this lesion, particularly advanced-stage cancers, remains unsatisfactory. Now, the predictor of outcome usually used in clinic is postoperative clinical stage, namely TNM. Stage II CRC is a relatively early subtype compared with its counterparts with lymph node or distance metastasis. However, despite an often long and better overall survival, there is marked heterogeneity in the duration of survival among these patients mostly according to whether having perforation, difference grades, detecting numbers of lymph node during operation and so on. Therefore, there have been continuing efforts to investigate the prognostic factors related to survival in these patients.

Recently, Glasgow prognostic score (GPS), an inflammation-based prognostic score which includes only serum C-reactive protein (CRP) and albumin (ALB) levels, was developed to aid in the assessment of cancer prognosis [2, 3]. An elevated GPS has been shown to be associated with worse prognosis for a number of different tumors [4-6]. Several previous studies have investigated the value of the GPS for postoperative prognostication of patients with advanced CRC [3, 7, 8]. However, whether GPS is suitable for predicting outcome in patients with relatively early stage CRC has not been fully elucidated. Thus, in the present study, we collected data retrospectively from 99 patients with stage II CRC cancer in our hospital and investigated the significance of the preoperative GPS for postoperative survival in these patients.

Patients and methods

Study subjects

After being explored the database of Taizhou People's Hospital, Jiangsu Province, China, all medical records of patients with CRC who undergone curative colorectomy from 2005 to 2010 were reviewed retrospectively. The criteria for cases inclusion were as follows: (1) pathologically confirmed CRC, (2) no prior chemotherapy or radiotherapy, (3) without presence of lymph node or distance metastatic disease, and (4) availability of clinical data at the initiation of therapy and follow-up. At the same time, patients who died within 30 days after surgery, or those who died of non-cancer related causes were excluded from the study. Furthermore, patients who had other malignancies or who had inflammatory diseases that might have increased CRP levels were also excluded from the study. As the result, a total of 99 CRC cases with stage II whose preoperative laboratory data for CRP and albumin were available enrolled into the study including some cases came from our last two retrospective researches which investigated the clinical significance of PLT count and CRP in CRC [9, 10]. The histological tumor subtype was determined according to the 1997 UICC classification. The pathological tumor staging was based on the 2002 TNM classification. The ethical committee of the Taizhou people's hospital approved the study. Written informed consents were obtained from all patients according to the guidelines approved by the Institutional Research Board.

Methods

Information on patients' and tumor characteristics, such as age, sex, KPS, histological grade, vascular and perineural invasion, CRP value, as well as serum carcinoembryonic antigen (CEA) and albumin level, was obtained from our hospital's database. Routine laboratory measurements of CRP and albumin and tumor markers such as CEA (cutoff value, 10 μg/L) were carried out before initial treatment. The limit of detection of the CRP assay was < 0.3 mg/L, with the upper limit of normal values being < 10 mg/L. Serum CRP was measured by using an automatic nephelometer (Beckman Coulter image, Fullerton, CA, USA), according to the manufacturer's instructions. The coefficients of variation for these methods, over the range of measurements, were < 5%, as established by routine quality control. The GPS was formed from albumin and CRP as previously described [2, 6]. Briefly, patients with both an elevated CRP (> 10 mg/L) and hypoalbuminemia (< 35 mg/L) were assigned a score of 2. Patients in whom only one of these biochemical abnormalities was present were assigned of 1. Patients in whom neither of these abnormalities was present were assigned a score of 0. The Karnofsky Performance Status (KPS) was used as an observer-rated measure of functional ability and assessed by a single investigator. Follow-up information, including cause of death, was ascertained through a review of clinic notes and direct or family contact. The designed during of follow-up was 5 years.

Statistical analysis

Continuous variables were presented as the median and range. Categorical variables were presented as the number. Differences between groups were performed with the one-way ANOVA for quantitative variables, with the chi-square test for categorical clinical variables, and with the Fisher exact test when appropriate. Overall survival (OS) was measured from the date of diagnosis until the date of death or final follow up. Survival curves were obtained according to the Kaplan-Meier method. Comparison of survival curves was carried out using the log-rank test. Variables significant at $P < 0.05$ in univariate analysis were further included in multivariate analysis. Multivariate survival analysis of the group variables was performed using the Cox proportional hazard model. To remove a variable from the model, the corresponding *P*-value had to be greater than 0.10. Analysis was performed using SPSS software 19.0 (SPSS Inc., Chicago, IL, USA) and two-tailed values of $P < 0.05$ were accepted as significant.

Results

Patient characteristics

According to the inclusion criteria, during 2005 to 2010, a total of 99 consecutive stage II CRC patients with completely available baseline characteristics were included in this study. Thirty five patients were males and 64 patients were females. Of this included patients, twenty

Table 1. Association between pretreatment GPS with clinic-pathological variables in patients with II stage CRC

	GPS			
	0 (55)	1 (29)	2 (15)	*P* value
Age (year)	64.42±10.09	59.31±11.81	62.47±10.09	> 0.05
Gender				
Male	18	11	6	0.822
Female	37	18	9	
CRP				
> 10 mg/L	0	10	15	0
≤ 10 mg/L	55	19	0	
ALB				
> 35 g/L	55	10	0	0
≤ 35 g/L	0	19	15	
Vascular invasion				
Negative	40	22	10	0.81
Positive	15	7	5	
Perinueral invasion				
Negative	40	18	9	0.481
Positive	15	11	6	
Histology				
High	15	8	2	0.58
Moderate	28	15	7	
Low	12	6	6	
CEA				
> 10 μg/L	7	10	9	0.001
≤ 10 μg/L	47	20	6	
KPS	83.09±10.16	81.03±13.72	68.67±18.46	0.001

Abbreviation: GPS= Glasgow Prognostic Score; CRP= C-reactive protein; ALB= albumine; CEA= carcinoembryonic antigen; KPS= Karnofsky Performance Status.

five had elevated CRP levels and 34 with hypoalbuminemia. Fifteen cases with both elevated CRP level and hypoalbuminemia were given a GPS of 2. Besides, twenty seven people had positive vascular invasion and 32 patients with perinueral invasion. The follow-up time was 60 months. None of the patients was lost to follow-up.

The relationship between clinicolaboratory characteristics and GPS was given in **Table 1**. In this study, GPS was not affected by age, gender, histological grades as well as the vascular and perineural invasion. However, with increasing GPS, there was a reduction of KPS and an elevation of CEA level.

Survival

Kaplan-Meier analysis and log-rank test demonstrated significant differences among patients with GPS of 0, 1 and 2 (P < 0.001), with the mortality rate higher for patients with a higher GPS (**Figure 1**). The mean 5 year overall survival rate of patients with a GPS of 0, 1 and 2 was 83.6%, 75.9% and 33.3%, respectively.

Univariate and multivariate analysis of postoperative mortality were indicated in **Table 2**. In present study, ten factors were included in the univariate analysis. The univariate analysis showed that eight factors were significantly associated with overall survival including CRP, ALB, GPS, histological grade, vascular and perineural invasion, CEA and KPS. On the further multivariate analysis, factors with *P* value < 0.05 in univariate analysis were included. Multivariate analysis revealed a significant association between postoperative mortality and GPS (hazard ratio (HR), 3.215; 95% CI, 1.158-8.925; P=0.025), vascular invasion (HR, 4.425; 95% CI, 1.382-14.166; P=0.012), KPS (HR, 0.891; 95% CI, 0.838-0.947; P=0.000) and the CEA (HR, 6.749; 95% CI, 1.498-28.024; P=0.012) (**Table 2**).

Discussion

At present, so many basic researches have been used to explore molecular prognostic indicators to predict the outcome of the patients with CRC [11]. However, it is a pity that till now there were little factors could be used in clinic meaningfully and easily. Actually, pathological TNM is currently considered the gold standard for predicting postoperative outcome, but it can only be properly evaluated postoperatively. Moreover, completely different outcome always be found in cases with same stage, and so this always contributed to the difficulty and bias for predicting survival preoperatively.

Based on several recent studies including our previous research, it was widely accepted that

Table 2. Univariate and multivariate analysis of the clinicpathological parameters in stage II CRC

	Overall survival				
	Univariate analysis	Multivariate analysis			
Variables	*P* value	Hazard ratio	95.0% CI		*P* value
			Lower	Upper	
Age	0.441				
Gender	0.799				
CRP	0	1.178	1.036	1.879	0.034
ALB	0.019	1.576	0.875	2.837	0.129
GPS	0	3.215	1.158	8.925	0.025
Vascular invasion	0	4.425	1.382	14.166	0.012
Perineural invasion	0	1.207	0.411	3.547	0.732
Histology grades	0	2.438	0.919	6.47	0.074
KPS	0	0.891	0.838	0.947	0
CEA	0	6.479	1.498	28.024	0.012

Abbreviation: GPS= Glasgow Prognostic Score; CRP= C-reactive protein; ALB= albumine; CEA= carcinoembryonic antigen; KPS= Karnofsky Performance Status.

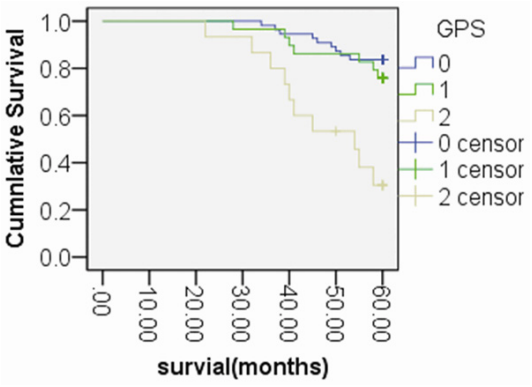

Figure 1. Survival of patients according to the GPS. The mean 5 year overall survival rate of patients with a GPS of 0, 1 and 2 was 83.6%, 75.9% and 33.3%, respectively (P < 0.001).

the elevation of serum CRP level was a reliable indicator of poor outcome in certain cancers involving gastric, HCC, renal as well as colorectal cancer [7, 12-14]. At present, the mechanism by which a systemic inflammatory response might influence cancer survival was poorly understood. Some people considered that inflammation could promote tumor angiogenesis, invasion, and metastasis through recruitment of regulatory T lymphocytes and chemokines, activation of interleukin-6 and tumor necrosis factor alpha, secretion of CRP, induction of neutrophilia, subversion of adaptive immune response, and aberration of response to chemotherapeutic agents [15-17]. In addition, in the patients with gastrointestinal cancer, although it was recognized that there might be reduced caloric intake due to stenosis of the digestive tract, several recent reports showed that the systemic inflammatory response plays a major role in the progressive nutritional and functional decline of patients with cancer [18]. Therefore, hypoalbuminemia is likely to develop secondary to increases in serum CRP levels [19]. And the relation of low albumin concentrations and poorer survival in patients with GI cancer was dependent on the elevated CRP level. In patients with colorectal cancer, low albumin concentration was also reported to be associated with a poorer outcome [8, 20]. In the present study, although with relatively lesser proportion, hypoalbuminemia was found significantly correlated with the survival of the patients. These theoretical backgrounds above have led to the proposal of several inflammation-based prognostic scores in patients with cancer over the last 10 years [15]. The GPS, which is based on both serum elevation of CRP and hypoalbuminemia, may enable a better appreciation of effects of the tumor on both ongoing systemic inflammation and malnutrition. In this retrospective study, we analyzed individual clinical data for 99 patients with stage II CRC who underwent en bloc colorectomy in our hospital. Our results demonstrated that GPS might be an independent marker for poor prognosis in patients with relatively early CRC. Multivariate analysis further revealed a significant association between over survival OS and GPS and CEA. These results indicated that the GPS might predict postoperative survival for patients with relatively early CRC. Considering the GPS can be achieved easily before operation, we suggested that it could be a perfect complementary factor to the conventional tumor marker like CEA in early stage CRC. In addition, in view of some previous studies have found the prognostic value of GPS in advanced CRC [21-24], to our knowledge, this research was a rare study focused on the specific subset with II stage in CRC. Through the present result in our study, we could predict

that not only had clinical values in advanced CRC patients, the GPS also could be seen as a significant prognosticator in relatively early cases.

As we known, stage II cases is a distinct type in CRC with relatively better outcome need no further adjuvant chemotherapy except for some cases with so called high risk factors, such as perforation, no adequate lymph nodes as well as poor histological grade and so on. However, most factors only could be acquired after operation and even some patients with same stage at last had different outcome. The findings of the present study which showed that the GPS might be a novel and simple biomarker in patients with early CRC could translate to potential improvements in the therapy of CRC. In this study, the patients with GPS of 2 had a tendency to have a poorer median overall survival than the patients with normal CRP and or normal albumin level, further adjuvant chemotherapy might be needed in these patients. However, some preclinical and clinical studies have showed that impaired nutritional status and elevated levels of acute-phase plasma proteins have been associated with increased toxicity from chemotherapy [25]. Furthermore, in this group of the patients, increased GPS might be associated with the poor KPS. So, it remains to be established whether patients with a higher GPS need more active therapy. Sometimes, anti-inflammatory therapy or nutritional support might have a beneficial effect on prognosis in these patients. In our opinion, the GPS level should be seemed as an compensatory indicator to the conventional prognosticators in CRC, and comprehensive consideration of the total factors involving clinical stages, performance status, CEA level as well as GPS and so on is more suitable for additional therapies.

A potential limitation of this study was that it was a retrospective, single-centre study. Therefore, a large-scale prospective validation study is needed to confirm the results.

In conclusion, the preoperative GPS is a simple and useful prognostic factor for postoperative survival in patients with early CRC. The GPS may be used together with traditional risk factors to individual treatment strategies and the follow-up of patients with relatively early CRC.

Disclosure of conflict of interest

None.

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