Original Article

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# The C-reactive protein to albumin ratio is an excellent prognostic predictor for gallbladder cancer

**Yongjin Bao, Junsheng Yang, Yunfei Duan, Yuxiang Chen, Weibo Chen*, Donglin Sun***

Department of Hepatopancreatobiliary Surgery, The Third Affiliated Hospital of Soochow University, Changzhou, China.

**SUMMARY** A number of inflammation indicators based on C-reactive protein (CRP) and albumin have been widely used to predict the prognosis in several types of tumors, but their functions in gallbladder cancer (GBC) have rarely been explored. The aim of our study is to evaluate and compare the prognostic values of the C-reactive protein to albumin ratio (CAR), Glasgow prognostic score (GPS), modified Glasgow prognostic score (mGPS) and high-sensitivity modified Glasgow prognostic score (HS-mGPS) in patients with GBC. 144 GBC patients who received curative surgery in our hospital from January 2010 to May 2017 were enrolled in this research. The Kaplan-Meier analysis showed that the median OS of the patients in the high CAR group was significantly shorter than the patients in the low group ($p < 0.001$), and higher scores of GPS, mGPS and HS-mGPS were also associated with decreased OS, respectively. However, according to the Receiver Operating Characteristic (ROC) curve, the CAR was superior to the other prognostic scores in determining the prognosis for the GBC patients. In the multivariate analysis, CAR was verified as an independent risk factor for poor prognosis, together with tumor differentiation, T stage and postoperative complications. All in all, compared to the other three CRP-albumin-related prognostic predictors, CRA is a better indicator in predicting poor long-term outcomes in GBC patients after radical surgery.

***Keywords*** gallbladder cancer, C-reactive protein to albumin ratio, prognostic score, surgery

## 1. Introduction

Gallbladder cancer (GBC) is one of the most frequently diagnosed malignancies of the biliary system and ranks as the sixth most common cancer of the digestive system, notorious for its poor prognosis (*1-3*). According to the latest global cancer statistical analysis in 2018, about 219,000 cases were diagnosed with GBC, while 165,000 people died of it worldwide (*4*). Because of its nature of insensitivity to radiotherapy and chemotherapy, surgical resection is still the only possible curative treatment for GBC (*2,5*). However, due to the lack of effective early diagnostic methods and typical symptoms, most patients are diagnosed at advanced stages. Even with aggressive surgical intervention and other comprehensive therapies, the 5-year survival rate is still below 20% (*6*). Currently, risk factors associated with the prognosis of GBC include tumor stage, pathological grade, lymph node metastasis, vascular and nerve invasion, and tumor margin status (*7-9*). However, the above indicators can only be obtained after surgery. Therefore, it is important to find a simple and reliable preoperative risk factor to predict the prognosis of GBC.

Recently, more and more research has shown that the occurrence of tumors is closely related to inflammatory response. Inflammatory cytokines in the tumor microenvironment, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) (*10*), amplify the inflammatory effect and promote tumor growth by recruiting inflammatory cells to the tumor location. Therefore, many predictors based on inflammation indicators are widely adopted to predict the prognosis of various tumors (*11-13*). Among those immune-nutritional parameters, some C-reactive protein-albumin-related indexes have been identified as important prognostic factors in cancer patients, such as the C-reactive protein to albumin ratio (CAR), Glasgow prognostic score (GPS), modified Glasgow prognostic score (mGPS) and high-sensitivity modified Glasgow prognostic score (HS-mGPS) (*11,14-16*). Although the prognostic significance of those inflammation-based markers have been confirmed in a variety of tumors, their role in GBC is rarely reported. Therefore, this retrospective cohort study aimed to determine the prognostic effects of those inflammatory indicators and compare their predictive values in GBC patients after radical surgery.

## 2. Materials and Methods

### 2.1. Patients

We retrospectively reviewed 144 cases of resectable GBC patients registered between January 2010 and May 2017 who received curative surgery in the Third Affiliated Hospital of Soochow University. We collected all the patients' clinical characteristics, including demographics, degree of tumor differentiation, lymph node metastasis, pathologic TNM staging, laboratory data and follow-up data. The hematological parameters including C-reactive protein, albumin, Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 were extracted from blood samples within 1 week prior to surgery (the upper physiological values of CEA and CA19-9 are 10 U/mL and 37 U/mL) (*17*). TNM staging of GBC was described according to the 8th edition of the American Joint Committee on Cancer (AJCC-8th) manual. The inclusion criteria were as follows: *i*) patients with histological confirmed GBC; *ii*) patients who received radical surgery; and *iii*) patients aged > 18 years old. The exclusion criteria were: *i*) patients without complete clinical data or follow-up data; *ii*) patients with other malignancies; *iii*) patients with perioperative or non-neoplastic death; and *iv*) patients with acute inflammation, infectious diseases or autoimmune diseases.

An informed consent was obtained from all patients and the study was approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University.

### 2.2. Definition of the inflammation-based prognostic scores

In this research, the CAR was calculated as the serum CRP level divided by the serum albumin level. According to the ROC curve and the Youden index, the optimal cut-off value of CAR was 0.069. The value of GPS was calculated as follows: patients with both an elevated CRP level (> 10 mg/L) and hypoalbuminemia (< 35 g/L) were allocated a score of 2; patients with only one of the above-mentioned abnormalities were allocated a score of 1, and those without these abnormalities were allocated a score of 0. In addition, the mGPS score was defined as follows: patients with both high CRP level (> 10 mg/L) and low albumin (< 35 g/L) got a score of 2; patients with only a high CRP level got a score of 1 and those without a high CRP value regardless of albumin level got a score of 0. When it came to HS-mGPS, the threshold of CRP was set as 3 mg/L according to the report by Proctor (*18*).

### 2.3. Surgical strategy and follow-up

For patients at T1a stage, simple cholecystectomy could reach radical resection. For patients at T1b and T2 stage, we routinely perform a cholecystectomy and liver wedge-resection with a margin of 2 cm around the gallbladder and lymph node dissection at station N1. For patients at T3 stage, the gallbladder combined with liver S4b + S5 segment resection and lymph node dissection at station N2 were performed. For some patients at T4 stage, on the basis of radical resection of GBC, combined resection of affected organs and enlarged regional lymph node dissection were performed. In cases of incidental GBC, patients with stage T1b-T4 received reoperation and radical resection. Follow-up was performed by the outpatient clinics or phone calls, and the end of the follow-up period was the last follow-up visit (October 2020) or death.

### 2.4. Statistical analysis

The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off values of the CAR and evaluate the performance of each prognostic score, and the areas under the curve (AUC) were measured and compared using the method established by DeLong *et al.* (*19*) $\chi^2$ test , Mann-Whitney *U* test and Kruskal-Wallis test were used to determine the statistical associations of the clinicopathological factors. The primary outcome measure of this study was overall survival (OS), from the date of surgery to the date of death or last follow-up. The survival curve was constructed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed to evaluate the impact of the variables to OS in all patients. Variables shown to have significant prognostic value by univariate analysis were further assessed by multivariate analysis using a Cox's proportional hazards model. A *p*-value < 0.05 was considered to be a significant difference in all analyses. All statistical analyses were performed by SPSS version 20.0.

## 3. Results

### 3.1. Patient characteristics

The demographic characteristics of the 144 patients with GBC are shown in Table 1. Among these patients, 97 patients were female and 37 were male, the median age was 63 years. According to the pathological findings, the resected specimens included 82 (56.9%) well- or moderately- and 62 (43.1%) poorly-differentiated tumors. 27 (18.7%) of tumors had nerve and 42 (29.2%) had liver invasion. Referring to the AJCC-8th TNM staging of GBC, 24 (16.7%), 60 (41.7%), 51 (35.4%) and 9 (6.2%) tumors staged T1, T2, T3 and T4, respectively, and 100 (69.4%), 37 (25.7%) and 7 (4.9%) tumors staged N0, N1 and N2 stage, respectively. Finally, 55 (38.2%) tumors were classified as stages I-II and 89 (61.8%), III-IV. In regard to surgical complications, a total of 38 (26.4%) patients had postoperative complications, including bile

**Table 1. Correlations between the clinicopathologic parameters and each prognostic predictor**

| Factor | CAR | | *p* value | GPS | | | *p* value | mGPS | | | *p* value | HS-mGPS | | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | < 0.069 | ≥ 0.069 | | 0 | 1 | 2 | | 0 | 1 | 2 | | 0 | 1 | 2 | |
| Age | | | 0.709[a] | | | | 0.155[b] | | | | 0.273[b] | | | | 0.341[a] |
| ≤ 60 | 11 | 24 | | 25 | 6 | 4 | | 29 | 2 | 4 | | 13 | 16 | 6 | |
| > 60 | 38 | 71 | | 58 | 34 | 17 | | 80 | 11 | 18 | | 42 | 37 | 30 | |
| Gender | | | 0.869[a] | | | | 0.071[b] | | | | 0.843[b] | | | | 0.942[a] |
| Male | 13 | 24 | | 16 | 17 | 4 | | 27 | 6 | 4 | | 15 | 13 | 9 | |
| Female | 36 | 71 | | 67 | 23 | 17 | | 82 | 7 | 18 | | 40 | 40 | 27 | |
| Differentiation | | | 0.456[a] | | | | 0.355[a] | | | | 0.254[b] | | | | 0.081[b] |
| Well/moderate | 30 | 52 | | 50 | 23 | 9 | | 65 | 8 | 9 | | 30 | 36 | 16 | |
| Poor | 19 | 43 | | 33 | 17 | 12 | | 44 | 5 | 13 | | 25 | 17 | 20 | |
| T stage | | | 0.020[c] | | | | 0.047[c] | | | | 0.294[c] | | | | 0.095[c] |
| T1 | 14 | 10 | | 18 | 5 | 1 | | 21 | 2 | 1 | | 14 | 8 | 2 | |
| T2 | 21 | 39 | | 35 | 13 | 12 | | 44 | 3 | 13 | | 21 | 21 | 18 | |
| T3 | 11 | 40 | | 28 | 16 | 7 | | 39 | 5 | 7 | | 17 | 21 | 13 | |
| T4 | 3 | 6 | | 2 | 6 | 1 | | 5 | 3 | 1 | | 3 | 3 | 3 | |
| N stage | | | 0.146[c] | | | | 0.771[c] | | | | 0.147[c] | | | | 0.048[c] |
| N0 | 39 | 61 | | 58 | 30 | 12 | | 79 | 9 | 12 | | 42 | 37 | 21 | |
| N1 | 9 | 28 | | 22 | 7 | 8 | | 26 | 2 | 9 | | 12 | 15 | 10 | |
| N2 | 1 | 6 | | 3 | 3 | 1 | | 4 | 2 | 1 | | 1 | 1 | 5 | |
| TNM stage | | | < 0.001[a] | | | | 0.054[b] | | | | 0.011[b] | | | | 0.001[a] |
| I+II | 30 | 25 | | 38 | 13 | 4 | | 48 | 3 | 4 | | 31 | 16 | 8 | |
| III+IV | 19 | 70 | | 45 | 27 | 17 | | 61 | 10 | 18 | | 24 | 37 | 28 | |
| BMI (kg/m$^2$) | | | 0.447[a] | | | | 0.232[b] | | | | 0.493[b] | | | | 0.169[a] |
| < 25 | 37 | 66 | | 59 | 26 | 18 | | 77 | 7 | 19 | | 42 | 33 | 28 | |
| ≥ 25 | 12 | 29 | | 24 | 14 | 3 | | 32 | 6 | 3 | | 13 | 20 | 8 | |
| Nerve invasion | | | 0.151[a] | | | | 0.221[b] | | | | 0.559[b] | | | | 0.305[a] |
| Present | 6 | 21 | | 12 | 11 | 4 | | 19 | 4 | 4 | | 7 | 11 | 9 | |
| Absent | 43 | 74 | | 71 | 29 | 17 | | 90 | 9 | 18 | | 48 | 42 | 27 | |
| Liver invasion | | | 0.005[a] | | | | 0.291[b] | | | | 0.972[b] | | | | 0.079[a] |
| Present | 7 | 35 | | 23 | 15 | 4 | | 31 | 7 | 4 | | 11 | 21 | 10 | |
| Absent | 42 | 60 | | 60 | 25 | 17 | | 78 | 6 | 18 | | 44 | 32 | 26 | |
| Complications | | | 0.018[a] | | | | < 0.001[a] | | | | 0.070[b] | | | | 0.002[a] |
| Present | 7 | 31 | | 8 | 20 | 10 | | 24 | 4 | 10 | | 14 | 7 | 17 | |
| Absent | 42 | 64 | | 75 | 20 | 11 | | 85 | 9 | 12 | | 41 | 46 | 19 | |
| Serum CEA level (ng/mL) | | | 0.097[a] | | | | 0.713[a] | | | | 0.222[b] | | | | 0.312[a] |
| < 5 | 39 | 63 | | 61 | 27 | 14 | | 81 | 7 | 14 | | 43 | 35 | 24 | |
| ≥ 5 | 10 | 32 | | 22 | 13 | 7 | | 28 | 6 | 8 | | 12 | 18 | 12 | |
| Serun CA 19-9 level (U/mL) | | | 0.688[a] | | | | 0.385[a] | | | | 0.197[b] | | | | 0.910[a] |
| < 37 | 27 | 49 | | 42 | 20 | 14 | | 53 | 8 | 15 | | 28 | 28 | 20 | |
| ≥ 37 | 22 | 46 | | 41 | 20 | 7 | | 56 | 5 | 7 | | 27 | 25 | 16 | |

BMI: body mass index; CAR: C-reactive protein to albumin ratio; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; GPS: Glasgow prognostic score; HS-mGPS: high-sensitivity modified Glasgow prognostic score; mGPS: modified Glasgow prognostic score. [a]: Chi-square test; [b]: Mann-Whitney *U* test; [c]: Kruskal-Wallis test.

leakage in 11 (7.6%), abdominal abscess in 7 (4.9%), incision infection in 4 (2.8%), postoperative bleeding in 3 (2.1%), and lung infection in 14 (9.0%).

### 3.2. Prognostic role of the CRP-albumin-related indicators

As shown in Table 1, 49 patients were classified as the low CAR group (CAR < 0.069) and 95 patients as the high CAR group (CAR ≥ 0.069). Patients in the high CAR group tended to have postoperative complications ($p = 0.018$), liver invasion ($p = 0.005$) and advanced tumor status such as T stage ($p = 0.020$) and TNM stage ($p < 0.001$). Of the 144 patients, 83 had a GPS of 0, 40 had a GPS of 1 and 21 had a GPS of 2. The GPS was significantly correlated with T stage ($p = 0.047$) and postoperative complications ($p < 0.001$). In subgroup analysis of the mGPS, the 109 patients had a mGPS score of 0, 13 had a score of 1, and another 22 had a score of 2. There was significant association between higher score of mGPS and advanced TNM stage ($p = 0.011$). In contrast, the numbers of patients in HS-mGPS 0/1/2 was 55, 53 and 36, respectively. A higher score of HS-mGPS was associated with higher N stage ($p = 0.048$), TNM stage ($p = 0.001$) and postoperative complications ($p = 0.002$).

### 3.3. Survival analysis

During the follow-up, 101 patients died and 43 patients were censored at the last follow-up. According to the Kaplan-Meier analysis, the median OS of the patients

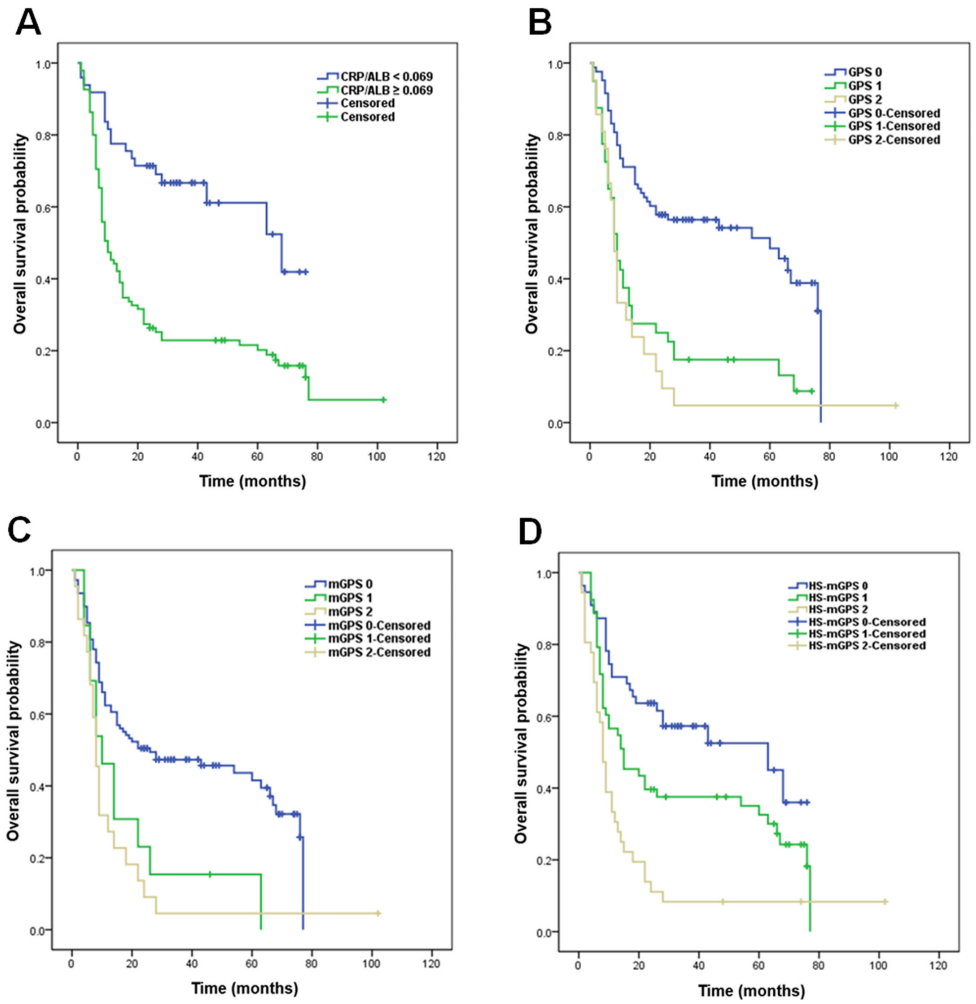


**Figure 1. Kaplan–Meier curve demonstrated significant prognostic difference among the 144 GBC patients who underwent curative resection according to the (A) CAR, (B) GPS, (C) mGPS and (D) HS-mGPS.**

in the high CAR group was significantly shorter than the patients in the low CAR group ($p < 0.001$, Figure 1A). Meanwhile, higher scores of GPS, mGPS and HS-mGPS were also correlated with worse prognosis ($p < 0.001$; Figure 1B, 1C, and 1D). Univariate analysis demonstrated that nerve invasion, tumor differentiation, liver invasion, T stage, N stage, and TNM stage were significantly correlated with shorter OS. Moreover, CAR, GPS, mGPS, HS-mGPS, postoperative complications, serum CEA level and CA 19-9 level were all associated with reduced OS in univariate analysis. The multivariate analysis showed that tumor differentiation, T stage, CAR and postoperative complications were independent prognostic factors of GBC (Table 2).

### 3.4. Comparison of prognostic performance among each prognostic score

The ROC curve demonstrated that the CAR was superior to the other prognostic scores in predicting 1- and 3-year OS. The AUC values of CAR at 1 year (0.785) and 3 years (0.798) was significantly higher than GPS (1 year: 0.684, $p = 0.0122$; 3 years: 0.615, $p < 0.0001$), mGPS (1 year: 0.644, $p < 0.0001$; 3 years: 0.601, $p < 0.0001$), and HS-mGPS (1 year: 0.684, $p = 0.0019$; 3 years: 0.704, $p = 0.0080$) (Figure 2A and 2B).

## 4. Discussion

Currently, the 8th edition of the TNM staging system for tumors released by AJCC is considered to be the most practical prognostic indicator of GBC. Nevertheless, some experts have suggested that the staging system lacks individual specificity because it focuses too much on the anatomical extent of disease and ignores the effects of biological factors (*20,21*). In this study, we revealed that CAR is an effective predictor of OS and superior to the other CRP-albumin-related indicators in predicting the prognosis of the GBC patients after radical surgery.

Actually, the development of tumors is a complex process, not only dependent on the biological features of tumor cells, but also closely related to the host's inflammatory response. It has already been well recognized that inflammation stimulates tumor progression and metastasis (*22,23*). In the case of GBC,

**Table 2. Univariate and multivariate analysis for overall survival**

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *p* value | HR (95% CI) | *p* value |
| Age (years) | | 0.309 | | |
| ≤ 60 | 1.000 | | | |
| > 60 | 1.272 (0.800-2.021) | | | |
| Gender | | 0.079 | | |
| Female | 1.000 | | | |
| Male | 0.673 (0.433-1.046) | | | |
| BMI (kg/m$^2$) | | 0.212 | | |
| < 25 | 1.000 | | | |
| ≥ 25 | 1.312 (0.857-2.011) | | | |
| Nerve invasion | | < 0.001 | | 0.747 |
| Absent | 1.000 | | 1.000 | |
| Present | 2.471 (1.560-3.916) | | 0.902 (0.482-1.687) | |
| Differentiations | | < 0.001 | | 0.022 |
| Well/moderate | 1.000 | | 1.000 | |
| Poor | 2.226 (1.419-3.322) | | 1.754 (1.083-2.840) | |
| Liver invasion | | < 0.001 | | 0.421 |
| Absent | 1.000 | | 1.000 | |
| Present | 2.388 (1.401-3.666) | | 1.085 (0.467-2.413) | |
| T stage | | < 0.001 | | < 0.001 |
| T1+T2 | 1.000 | | 1.000 | |
| T3+T4 | 2.845 (2.190-3.695) | | 4.374 (2.323-8.236) | |
| N stage | | < 0.001 | | 0.240 |
| N0 | 1.000 | | 1.000 | |
| N1 | 2.681 (1.711-4.198) | | 1.482 (0.845-2.601) | |
| N2 | 4.170 (1.866-9.317) | | 1.961 (0.727-5.289) | |
| TNM stage | | < 0.001 | | NG |
| I+II | 1.000 | | | |
| III+IV | 3.543 (2.675-7.413) | | | |
| CAR | | < 0.001 | | 0.003 |
| < 0.069 | 1.000 | | 1.000 | |
| ≥ 0.069 | 2.706 (1.474-5.148) | | 2.647 (1.434-5.560) | |
| GPS | | < 0.001 | | 0.070 |
| 0 | 1.000 | | 1.000 | |
| 1 | 2.658 (1.697-4.162) | | 0.347 (0.134-0.902) | |
| 2 | 3.125 (1.820-5.364) | | 1.435 (0.151-13.602) | |
| mGPS | | < 0.001 | | 0.143 |
| 0 | 1.000 | | 1.000 | |
| 1 | 1.715 (0.984-3.631) | | 0.915 (0.335-2.500) | |
| 2 | 2.528 (1.529-4.179) | | 2.039 (0.784-5.302) | |
| HS-mGPS | | < 0.001 | | 0.108 |
| 0 | 1.000 | | 1.000 | |
| 1 | 1.772 (1.077-2.917) | | 1.217 (0.494-2.385) | |
| 2 | 3.360 (1.993-5.666) | | 2.253 (1.076-5.541) | |
| Complications | | < 0.001 | | 0.028 |
| Absent | 1.000 | | 1.000 | |
| Present | 3.688 (2.401-5.653) | | 1.741 (0.543-4.723) | |
| Serum CEA level | | 0.012 | | 0.273 |
| < 5 | 1.000 | | 1.000 | |
| ≥ 5 | 1.735 (1.147-2.626) | | 0.742 (0.435-1.265) | |
| Serum CA 19-9 level | | 0.009 | | 0.756 |
| < 37 | 1.000 | | 1.000 | |
| ≥ 37 | 1.805 (1.142-2.644) | | 1.085 (0.650-1.809) | |

BMI: body mass index; CAR: C-reactive protein to albumin ratio; CA 19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: Confidence interval; GPS: Glasgow prognostic score; HR: Hazard ratio; HS-mGPS: high-sensitivity modified Glasgow prognostic score; mGPS: modified Glasgow prognostic score.

chronic cholecystitis always causes DNA damage and repeated tissue proliferation releases cytokines and growth factors, which induce canceration of cells. Therefore, the increase of peripheral blood inflammation indicators could reflect the inflammatory response status caused by tumor growth and invasion to a certain extent.

CRP is an acute phase response protein produced by the liver and regulated by a variety of pro-inflammatory cytokines. It is an important response indicator of the body's non-specific inflammatory response and an increased CRP is associated with

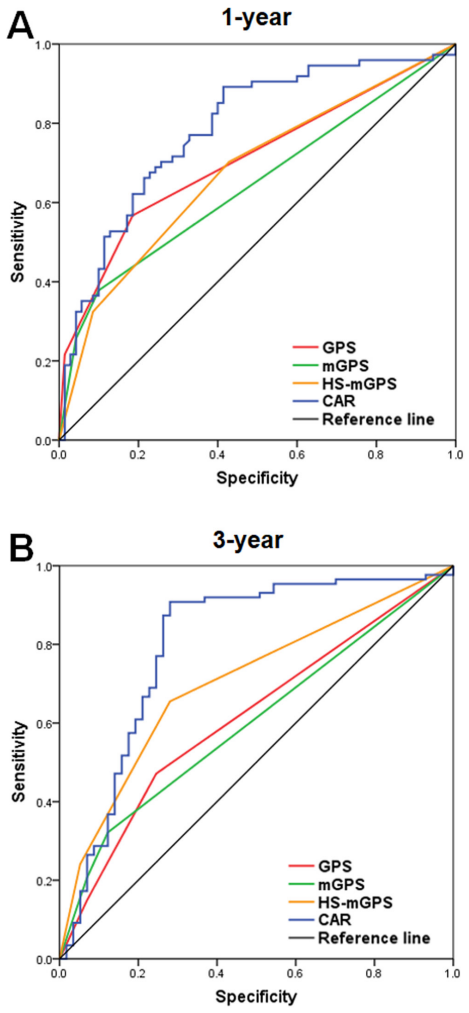


**Figure 2. Comparison of the areas under the ROC curves for outcome prediction among the four CRP-albumin-related prognostic scores (CAR, GPS, mGPS, and HS-mGPS) at (A) 1 year and (B) 3 years.**

unsatisfactory prognosis in a variety of tumors (*24,25*). In addition to CRP, serum albumin is also involved in systemic inflammation and hypoproteinemia is always considered to be a sign of poor long-term survival in cancer patients (*26,27*). The GPS is an objective indicator reflecting the inflammatory response and nutritional status, which combines the serum CRP value and albumin levels. It was first used to predict the prognosis of patients with lung cancer (*28*). Later, Inoue *et al.* (*29*) modified the prognostic score and named mGPS. Proctor *et al.* (*30*) found that the mGPS is superior to other inflammation-based prognostic scores such as NLR, PLR and PNI in predicting the prognosis of patients with various tumors. Furthermore, in a retrospective study by Tomoyuki *et al.* (*15*), they proved that a high preoperative mGPS was an independent prognostic indicator of poor survival in GBC. However, in this study, the mGPS has limited value in predicting the prognosis of patients with GBC. We found that in addition to the mGPS, the other three indicators are all related to the occurrence of postoperative complications. We believe the major reason is that only a small number of patients have CRP values greater than 10 mg/L, thus, it may be difficult to clarify the relationship between the mGPS and each variable. In order to solve the uneven distribution of preoperative parameters, Proctor *et al.* proposed HS-mGPS, which has a lower CRP threshold (> 3 mg/L). There is some research reported that the HS-mGPS is a better prognostic indicator than mGPS (*16,31,32*), and this conclusion is also verified in our study.

Recently, much research demonstrated that the CAR is significantly correlated with tumor progression and plays a vital function in assessing the prognosis of tumor patients (*14,33*). Although the CAR is also composed of CRP and albumin, the difference is that the CAR is a continuous variable. Kinoshita *et al.* (*33*) believed that systems, which score the serum CRP and albumin levels separately may underestimate or overestimate the effects of CRP and albumin, so their predictive ability may not be as good as CAR. As demonstrated in our study, an increased CAR and a higher score for GPS, mGPS and HS-mGPS were all associated with higher tumor malignancy and shorter OS. However, according to the ROC analysis, the AUC values of CAR are significantly higher than the GPS, mGPS and HS-mGPS in predicting the 1-year and 3-year overall survival. The result indicates that the predicted value of CAR is more accurate and reliable than the other three indicators.

It was previously reported that a high serum level of CA 19-9 was an independent risk factor for poor prognosis in patients with GBC (*34*). In this research, although univariate analysis verified that CA 19-9 was a risk factor for poor prognosis, the result of multivariate analysis showed that the independent risk factors for poor prognosis of GBC patients were high CAR, poor tumor differentiation, advanced T stage and postoperative complications, rather than CA 19-9 (In this study, we didn't include the TNM stage into the multivariate analysis because it is colinear with T stage and N stage). Considering that tumor stage and differentiation need to be evaluated postoperatively, CAR can be easily measured preoperatively, and the price is much lower than CA 19-9. Therefore, it can be adopted as an effective tool for predicting the GBC prognosis before surgery.

However, there are still some limitations in our study. First of all, this is a single-center retrospective study with a small sample size, and insufficient sample size may lead to selection bias. Secondly, the subjects of this study are patients undergoing radical surgery, and only a small proportion of patients had preoperative jaundice. Therefore, we did not analyze the relationship between those indicators and preoperative jaundice. Third, since this study is restricted to Asians, the results may not apply to other races. Hence, a multi-center

prospective study is necessary to validate our results.

In conclusion, our study demonstrated that the CAR is the best prognostic predictor among the CRP-albumin-related markers for GBC patients. It's not only associated with tumor progression but also is an independent risk factors for poor prognosis.

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*Address correspondence to:
Donglin Sun and Weibo Chen, Department of Hepatopancreatobiliary Surgery, The Third Affiliated Hospital of Soochow University, 185 Juqian Street, Changzhou, Jiangsu 213003, China.
E-mail: czyysdl@163.com (Sun DL), cwb_med@163.com (Chen WB)

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