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Original article

## Prognostic significance of preoperative albumin-to-globulin ratio in patients with cholangiocarcinoma

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### ABSTRACT

**Background.** – This study aimed to assess the prognostic value of the serum albumin to globulin ratio (AGR) in cholangiocarcinoma patients after surgery.

**Methods.** – We retrospectively enrolled 123 cholangiocarcinoma patients who underwent surgical treatment between June 2003 and September 2014 at the Third Affiliated Hospital of Sun Yat-sen University. Univariate and multivariate analyses using the Cox regression model were performed to determine the prognostic value of AGR.

**Results.** – Univariate analysis suggested that AGR was a predictive factor for (overall survival) OS but not for recurrence free survival (RFS). After adjustment for other risk factors, multivariate analysis showed that AGR remained independently associated with OS. The optimal cut-off point for AGR was determined to be 1.44. Kaplan–Meier curves showed that there was a significantly lower mean survival time in the low AGR group compared to the high AGR group. A low AGR was found to be significantly associated with high alkaline phosphatase, gamma-glutamyl transpeptidase, total bilirubin levels and an advanced American Joint Committee on Cancer TNM stage, but a low hemoglobin level.

**Conclusion.** – In summary, patients with higher AGRs have better outcomes than those with lower AGRs. Preoperative AGR can be a reliable marker for evaluating the prognosis of cholangiocarcinoma patients.

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## 1. Introduction

Cholangiocarcinoma arises from the malignant transformation of the bile duct epithelium and represents approximately 10% of all primary hepatobiliary cancers, accounting for approximately 2% of overall malignancies [1,2]. Based on the location along the biliary tree, it consists of three types: intrahepatic cholangiocarcinoma (IHC), perihilar cholangiocarcinoma (PHC) and distal cholangiocarcinoma (DCC). The prediction of a long-term prognosis for individuals with cholangiocarcinoma remains difficult. Currently, the American Joint Committee on Cancer (AJCC) TNM staging system is the most commonly used tool to stage cholangiocarcinoma and predict long-term survival. However, a few studies suggest that this

staging system poorly stratified cholangiocarcinoma patient survival, especially for those who underwent resection [3,4]. Additionally, the inclusion of tumor size as a factor in the staging system remains controversial. Thus, there is an urgent need to find noninvasive markers that can distinguish patients with better prognoses from those with more aggressive disease.

As two major constituents of human serum, albumin and globulin have garnered much attention as noninvasive prognostic markers for cancers. These factors play pivotal roles in the inflammatory process [5] and serum albumin is also an objective parameter that reflects long-term nutrition status. Previous studies have identified the preoperative albumin to globulin ratio (AGR) as a simple and useful biomarker for the determination of prognosis in several types of cancers [5–7]. However, the significance of the AGR in tumor recurrence and mortality in cholangiocarcinoma has not yet been addressed. In the present study, we evaluated the prognostic value of preoperative AGR for predicting tumor recurrence and survival in patients with cholangiocarcinoma after undergoing surgery.

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## 2. Materials and methods

### 2.1. Study design and population

The present study enrolled an unselected cohort of 123 cholangiocarcinoma patients who received radical surgery at the Third Affiliated Hospital of Sun Yat-sen University, between June 2003 and September 2014. The histological diagnoses were pathologically confirmed after surgery. Those without radical surgical intervention, unavailable baseline data, or with distant metastases were excluded from the study. This study was approved by the Clinical Ethics Review Board at the Third Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from all participants.

Globulin and albumin levels were measured on admission before treatment for all 123 patients. All were confirmed to have negative margin by pathological diagnosis. Medical records were reviewed, including demographic features, clinicopathological characteristics, laboratory test results and survival status. The AGR was calculated using the equation  $AGR = \text{albumin}/\text{globulin}$  and the tumors were staged based on the the7th AJCC staging system.

A CT scan was performed at 4 to 6-week intervals to determine tumor recurrence. The time of death from any cause was confirmed by telephone call up until November 2014. The primary endpoint was overall survival (OS), which was calculated from the day of diagnosis to the day of death from any cause, while recurrence free survival (RFS), the secondary endpoint, was defined as the time from the date of surgery to the date of the first recurrence or last follow-up in patients with no recurrence.

### 2.2. Statistical analysis

Continuous variables are presented as the median and were analyzed using the independent-samples *t* test or the Mann-Whitney *U* test. Categorical variables are presented as frequencies and percentages and were analyzed using the  $\chi^2$  test or the Mann-Whitney *U* test. Univariate analysis was performed for each variable with the potential to be a predictor using the Cox proportion-hazards model. Any variables deemed to be significant ( $P < 0.05$ ) were included in a multivariate Cox regression model. Albumin and globulin were excluded, as they were used in the calculation of AGR. In order to be able to compare values with different dimensions, the original data were standardized before we performed the hazard ratio (HR). Any independent prognostic factors were used to generate a mathematical model. In addition, the receiver operating characteristic (ROC) curves for novel prognostic factors to predict one-year disease control were plotted, whereupon the optimal cut-off values for each variable were determined. The area under the ROC curve (AUC) was calculated. A larger AUC meant better discriminatory ability. Survival rates were analyzed using the Kaplan–Meier method and compared using the log rank test. We then treated AGR as a dichotomous variable. The correlations were demonstrated between pretreatment AGR with clinicopathological characteristics. All statistical analyses were performed using SPSS version 17.0. A *P* value  $< 0.05$  was considered statistically significant.

## 3. Results

### 3.1. Characteristics of the entire cohort

Demographic and clinicopathological characteristics of the 123 patients, including 67 (54.5%) males and 56 (45.5%) females, are summarized in Table 1. Among these patients, 22 (17.9%) had DCC, 36 (29.3%) had PCC and 65 (52.8%) had ICC. Lymph node metastases were found in 40 patients (32.5%) at the initial diagnosis and no distant metastases were discovered for any of the

study subjects. Overall, 22 (17.9%) patients received percutaneous transhepatic cholangial drainage (PTCD) before surgery and 25 (20.3%) received adjuvant chemotherapy after surgery. During the median follow-up of 443 days, there were a total of 73 deaths (59.3%). Among these patients, the one-year OS rate was 75%, while the RFS rate was 78.9%, (Table 1).

### 3.2. Predictive value of AGR

The univariate Cox regression revealed that AGR ( $HR = 0.654$ , 95% CI 0.499–0.856,  $P = 0.002$ ), tumor size ( $HR = 1.398$ , 95% CI 1.128–1.733,  $P = 0.002$ ), and AJCC TNM stage ( $HR = 1.569$ , 95% CI 1.225–2.010,  $P < 0.001$ ) were all associated with OS, as expected. Patients with higher AGRs presented with significantly more favorable prognoses. According to the hazard ratio, it seemed that AGR was a protective factor and might provide stronger prognostic information than either albumin ( $HR = 0.781$ , 95% CI 0.612–0.995,  $P = 0.046$ ) or globulin ( $HR = 1.337$ , 95% CI 1.041–1.717,  $P = 0.023$ ) alone. However, AGR did not seem to have any prognostic value for tumor recurrence ( $P = 0.146$ ). Multivariate analysis was then performed in order to delineate various prognostic indicators. We included variables associated with survival status in the univariate Cox analyses. After adjusting for other risk factors the multivariate analysis showed that AGR ( $HR = 0.731$ , 95% CI 0.555–0.963,  $P = 0.026$ ) remained independently associated with OS. Furthermore, tumor size and AJCC TNM stage seemed to be independent predictive factors of both OS and tumor recurrence (Tables 2 and 3). The three independent factors identified through multivariate analysis were combined to generate a new prognostic score, which we named the death risk score. This was calculated as follows:  $-0.313 \times AGR + 0.243 \times \text{tumor size} + 0.303 \times \text{AJCC TNM stage}$ . The associated parameter estimates (regression coefficients or weights) and *P* values are shown in Table 2.

### 3.3. Identification of the optimal cut-off value

ROC curves were used to determine the optimal cut-off value for predicting one-year survival. The predictive value of AGR was 1.44 (with a sensitivity of 75.0%, specificity of 46.7% and area under the ROC curve of 0.620) (Supplementary Table 1). This cut-off was used to determine whether the patients were included in the high ( $> 1.44$ ) or low ( $< 1.44$ ) AGR groups. Similarly, an albumin cut-off of 41.8 g/L, a globulin cut-off of 30.5 g/L, a tumor size cut-off of 47 mm, an AJCC TNM stage cut-off of III, and a death risk score of 0.28 were selected as the optimal cut-off points for survival analyses, in order to divide the patients into high- and low-risk subsets. ROC analysis presented similar results with Cox regression and revealed that AGR was a significant predictor for one-year survival after surgery. Moreover, the death risk score, which included a combination of tumor size, AGR and AJCC TNM stage, demonstrated an improved predictive value for OS, since the AUC was recorded as 0.687 and seemed to be the highest (Supplementary Table 1, Supplementary Fig. 2). Survival rates were then analyzed using the Kaplan–Meier method. As shown in Fig. 1, the medium survival times in the high and low AGR groups were 480 and 384 days, respectively. The elevated postoperative AGR group exhibited significantly better OS ( $HR = 0.564$ , 95% CI 0.346–0.921,  $P = 0.022$ ). The death risk score, consistent with the results above, demonstrated the highest HR, thus showing the best discriminatory ability (Supplementary Fig. 1) ( $HR = 2.555$ , 95% CI 1.593–4.098,  $P < 0.001$ ).

### 3.4. Association of AGR with the clinicopathological features of cholangiocarcinoma

Based on the optimal cut-off value, 51 out of 123 patients (41.4%) had a high AGR and 72 (58.6%) had a low AGR. The patients

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