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***Retrospective Study***

**Albumin-to-alkaline phosphatase ratio: A novel prognostic index of overall survival in cholangiocarcinoma patients after surgery**

Xiong JP *et al*. A novel prognostic index for cholangiocarcinoma

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**Abstract**

***AIM***

To clarify the prognostic significance of preoperative albumin-to-alkaline phosphatase ratio (AAPR) in cholangiocarcinoma (CCA) subjects receiving surgery.

***METHODS***

In this retrospective study, we included 303 CCA patients receiving surgery without preoperative therapy between from 2002 and 2014. Clinicopathological characteristics (including AAPR), were analyzed to determine predictors of post-operative overall survival (OS) and recurrence-free survival (RFS). In addition, univariate and multivariate Cox proportional hazards models were conducted, followed by application of time-dependent receiver operating curve to identify the optimal cutoff.

***RESULTS***

Univariate and multivariate analyses revealed both shortened OS [hazard ratio (HR): 2.88, 95%CI: 1.19-5.78] and RFS (HR: 2.31, 95%CI: 1.40–3.29) in patients with AAPR < 0.41 than those with AAPR ≥ 0.41, respectively. And the optimal cutoff of AAPR was 0.41. Of the 303 subjects, 253 (83.5%) had AAPR over 0.41. The overall 1-, 3- and 5-year survival rates were 70.2%, 38.0% and 16.5%, respectively in the low (< 0.41) AAPR group, which were significantly higher than those in the high (≥ 0.41) AAPR group (81.7%, 53.9%, and 33.4%, respectively) (*P* < 0.0001). Large tumor size, multiple tumors, and advanced clinical stage were also identified as significant predictors of poor prognosis.

***CONCLUSION***

Our outcomes showed that AAPR was a potential valuable prognostic indicator in CCA patients undergoing surgery, which, should be further confirmed by prospective studies. Moreover, it is necessary to investigate the mechanisms concerning the correlation of low AAPR with poor post-operative survival in CCA patients.

**Key words:** Albumin-to-alkaline phosphatase ratio; Cholangiocarcinoma; Prognosis; Surgery; Survival

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**Core tip:** Certain combinations of clinical features and laboratory indexes have been validated as prognostic indicators, including albumin to gamma-glutamyltransferase ratio, neutrophil-to-lymphocyte ratio as well as platelet to albumin ratio. Nevertheless, albumin-to-alkaline phosphatase ratio (AAPR), a novel indicator for the prognosis of hepatocellular carcinoma, has not been examined in cholangiocarcinoma (CCA). Hence, it is intriguing to confirm the potential application of AAPR in CCA. Our findings indicated AAPR as a potential prognostic indicator in CCA subjects undergoing surgery.

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INTRODUCTION

Cholangiocarcinoma (CCA), initially illustrated by Durand Fardel in 1840, is an aggressive cancer originated from biliary epithelial cells[1,2]. CCA represents the second most common primary hepatic carcinoma, accounting for 3% of all gastrointestinal malignancies as well as 10%-25% of liver malignancies[3,4]. Moreover, in recent decades, the incidence of CCA is still rising. Intriguingly, the epidemiology of extrahepatic CCA (ECC) and intrahepatic CCA (ICC) differs from each other, with a decreasing incidence of the former, but an increasing incidence of the latter in certain regions worldwide, including the United Kingdom and the United States (US)[5]. To be specific, in the past 20 years, the incidence of ICC has been elevated by 165%, while that of ECC has been declined by 14% in the US[6]. In addition, the prognosis of CCC is very poor. The relative survival rates of 1, 3 and 5 years have been reported to be 25%, 9.7% and 6.8%, respectively, almost without any change in recent decades[7,8].

The following factors have been determined to be of prognostic significance, including multifocal disease, increased carbohydrate antigen 19-9 level, tumor, node and metastasis (TNM) staging classification, lymph node involvement, margin-positive resection and vascular evasion. In addition, certain combinations of clinical features and laboratory indexes have been validated as prognostic indicators, including albumin to gamma-glutamyltransferase ratio, neutrophil-to-lymphocyte ratio as well as platelet to albumin ratio[9-12]. Nevertheless, albumin-to-alkaline phosphatase ratio (AAPR), a novel indicator for the prognosis of hepatocellular carcinoma (HCC), has not been examined in CCA[13]. Hence, it is intriguing to confirm the potential application of AAPR in CCA.

Therefore, a retrospective cohort study was performed to identify the prognostic significance of AAPR in CCA subjects, followed by investigation of the correlation of AAPR with other clinicopathological features.

**MATERIALS AND METHODS**

***Study population and design***

In this retrospective study, we enrolled 303 patients with histologically diagnosed CCA from Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. The majority of CCA patients from Beijing were admitted to Peking Union Medical College Hospital (PUMCH) for diagnosis and therapy.

We obtained the list of CCA patients diagnosed from 2002 to 2014 by utilizing the patient informatics dataset of PUMCH, and further enrolled those receiving curative resection and pathologically confirmed. Curative dissection was considered as complete macroscopic removal of tumor, which was conducted in 156 subjects (51.5%).

***Data collection***

The calculation of AAPR of all subjects was based on preoperative blood value. Univariate Cox proportional hazards model was conducted of overall survival (OS) and recurrence-free survival (RFS). Specifically, OS was determined in all subjects (*n* = 303), while RFS was assessed only in those receiving curative surgery (*n* = 156). We examined the following factors with respect to OS and RFS: age, gender, hepatitis C virus (HCV), hepatitis B virus (HBV), alkaline phosphatase level (ALP), serum albumin level (ALB), tumor size, number of tumors, TNM stage (in accordance with the 8th American Joint Committee on Cancer staging system) and curative resection. Of note, curative resection was eliminated in evaluating RFS. Pre-operative laboratory indexes were acquired, and contiguous variables were included into the model.

***Ethical statement***

This study gained approval from the Institutional Review Board of PUMCH, and all participants signed written informed consent.

***Statistical analysis***

The primary endpoint was OS, defined as the duration from surgery to CCA-associated mortality. The secondary endpoint was RFS, defined as the duration from surgery to recurrence. Receiver operating curve (ROC) was employed to identify the optimal cut-off value of AAPR. Chi-squared test or Fisher’s exact test was employed for baseline characteristics comparison. Survival data were compared by Kaplan-Meier curve, along with log-rank test. Univariate and multivariate Cox proportional hazards regression models were performed for hazard ratios with corresponding 95%CIs. A two-sided *P* value < 0.05 was considered as statistical significance. SPSS version 20.0 (SPSS, Chicago, IL, USA) was employed for all statistical analysis.

**RESULTS**

***Patient characteristics***

The baseline clinical characteristics were presented in Table 1. In total, 303 CCA cases were enrolled in this research. The median age was 59 (range 29–83) years old. Overall, 168 subjects were males and 135 were females, with a male-to- female ratio being 1.2:1. Of the 303 CCA patients, 10.23 % (31 subjects) and 1.65 % (five subjects) were positive for HBV and HCV infection, respectively. The median follow-up duration was 21.0 mo. In total, 177 patients passed away during the study, with an estimated median OS of 16.8 mo (range: 1.0-75.0 mo). The 1-year, 3-year and 5-year survival rates were 75.6%, 48.7% and 26.8%, respectively.

***Selection of the optimal cutoff value for AAPR***

Time-dependent ROC curve was employed to examine the optimal cutoff of AAPR for prognosis. Consequently, an AAPR of 0.41 was considered as the optimal cutoff value for predicting prognosis, with sensitivity of 0.735 and septicity of 0.829. According to the cutoff value, 253 and 50 and subjects were assigned to the high- and low-AAPR groups, respectively.

***AAPR as an independent prognostic factor***

The OS and RFS of patients in both AAPR groups were displayed in Figure 1. Specifically, the overall 1-, 3-, and 5-year survival rates were 70.2%, 38.0%, and 16.5%, respectively in the low (< 0.41) AAPR group, which were significantly lower than those in the high (≥ 0.41) AAPR group (81.7%, 53.9%, and 33.4%, respectively) (*P* < 0.0001) (Figure 1A). The RFS was significantly prolonged in the high AAPR group compared to that in the low AAPR group (*P* = 0.017) (Figure 1B). The median OS and RFS in the high AAPR groups were 48.5 (95%CI: 40.5-56.4) and 39.2 mo (95%CI: 31.1-47.3), respectively. Similarly, the median OS and RFS in the low AAPR groups were 30.3 mo (95%CI: 21.3-39.3) and 18.5 mo (95%CI: 11.1-25.8), respectively.

The significant prognostic indicators for OS determined by univariate and multivariate analyses were demonstrated in Table 2. Low AAPR level, large tumor size, HBV infection, multiple numbers of tumors, advanced clinical stage, and non-curative resection were identified as predictors of poor prognosis (Table 2).

The significant indicators for RFS indicated by univariate and multivariate analyses were shown in Table 3. Low AAPR level, large tumor size, multiple tumors, and advanced clinical stage were identified as significant predictors of poor prognosis (Table 2).

**DISCUSSION**

In this research, we mainly investigated the prognostic significance of AAPR in CCA patients receiving surgery, which is considered as the first study analyzing the association of AAPR with CCA. The results indicate that AAPR is an independent prognostic factor for CCA subjects, and those with AAPR level under 0.41 harbors shortened OS as well as RFS.

Liver function examination is a cost-effective and easy-to-obtain laboratory examination in clinical practice. Serum ALB and ALP levels are the two major indexes, and the former generally reflects the hepatic protein synthesis, mainly affected by primary chronic liver function damage as well as systemic immune response of liver cancer or the inflammatory microenvironment[14]. ALB is the most abundant serum protein, capable of stabilizing cell growth and DNA replication, maintaining diverse biochemical variations, which plays an antioxidant role in tumorigenesis[15]. Hence, low ALB levels not only indicate insufficient liver function, but reflect a lack of human defense capabilities, thereby leading to great infectious lesion and poor response to anti-cancer therapeutics. And ALB has been considered as a common biomarker to predict the survival rate of diverse malignant tumors, including colorectal cancer, HCC, prostate cancer[16-18]. ALP is a hydrolase enzyme, existing in all tissues of the body, while mainly exists in liver, bile duct, bone, kidney and placenta[19]. Pregnancy or certain pathological situations, including CCA, biliary cirrhosis, liver injury, liver cancer as well as bone metastasis, would lead to increased levels of ALP[20-22]. ALP level is an independent prognostic indicator for HCC patients[23]. In addition, ALP is included as a parameter in the Chinese University Prognostic Index system, which is one of the staging systems to predict survival[24]. The concept of AAPR was initially proposed by Anthony, who demonstrated AAPR as an independent prognostic indicator for OS as well as disease-free survival in HCC patients undergoing radical operation[25]. Therefore, we speculated that a combination of ALB and ALP might harbor novel prognostic significance, which could better be used for survival prediction of CCA subjects. In this study, AAPR (cutoff value: 0.41) was utilized for survival prediction in CCA subjects. As a result, univariate and multivariate analyses demonstrated that an AAPR under 0.41 was related to poor prognosis. Moreover, a low AAPR might indicate the malnutrition status, suppressive immunity, as well as relatively serious lesions (including liver or bone metastasis).

Our study had several strengths. Firstly, to our knowledge, it is the first study concerning the validation of the prognostic value of AAPR in CCA subjects undergoing surgery. And its results may be of interest to CCA researchers and be of help to clinicians aiming to develop approaches of preventing the development of CCA. Secondly, ALB and ALP are both simple but different and objective variables, which are more easily applied in clinical practice. Moreover, we also examined the correlation of AAPR with other clinicopathological features, which indicated that advanced clinical stage, low AAPR level, large tumor size as well as multiple numbers of lesions were significantly associated with poor prognosis.

However, there were certain limitations in our study. Firstly, the single-center property and retrospective design were the major limitations of this research. Despite strict adherence to inclusion and exclusion criteria, selection bias might remain in this retrospective study. Secondly, the cut-off NLR values might not have been optimal and external validation is still needed. Thirdly, the absence of validation cohorts contributed to the failed validation of AAPR as an independent factor for CCA subjects. AAPR is combined by ALB and ALP, the low level of which might indicate a condition of inactive immune response, liver failure, malnourish as well as formation of invasive cancer, all of which might be correlated with the poor prognosis of CCA. Anyhow, more basic research and prospective studies are necessary to further elucidate the molecular mechanism the relationship between AAPR and prognosis.

In conclusion, our findings indicated AAPR as a potential prognostic indicator in CCA subjects undergoing surgery. In view of its low cost, usability and prognostic power, AAPR should be included in future research projects and clinical trials However, larger scale, multi-center studies are required for further validation.

**ARTICLE HIGHLIGHTS**

***Research background***

Several staging systems and various serum markers have been investigated to provide prognostic information, including the tumor, node and metastasis staging system, margin-positive resection, lymph node metastasis, multifocal disease, an elevated carbohydrate antigen 19-9 level, and vascular involvement. Some combined indexes of clinical characteristics and laboratory biomarkers have also been proven to be prognostic factors, such as the platelet to albumin Ratio, neutrophil-to-lymphocyte ratio and Albumin to gamma-glutamyltransferase ratio. However, the albumin-to-alkaline phosphatase ratio (AAPR), which is a novel prognostic factor for hepatocellular carcinoma (HCC), has not yet been studied in cholangiocarcinoma (CCA).

***Research motivation***

The AAPR has been recently revealed as a prognostic index for HCC, whereas its role in CCA remains unclear.

***Research objectives***

To clarify the prognostic value of the preoperative blood AAPR in patients undergoing surgery for CCA patients. And its results may be of interest to CCA researchers and of help to clinicians aiming to develop a means of preventing the development of CCA. Besides, serum albumin level (ALB) and alkaline phosphatase level (ALP) are both simple but differentiated and objective variables, which are more easily applied in clinical practice.

***Research methods***

We conducted a retrospective cohort study that included 303 patients with histologically confirmed CCA from Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China. Using the patients’ informatics database of Peking Union Medical College Hospital, we compiled a list of all patients who had been diagnosed with CCA between 2002 and 2014. The patients who had undergone a primary attempt at curative resection and whose diagnoses were confirmed by pathological examination were involved in this study. Curative resection was defined as complete macroscopic removal of the tumor and was performed in 156 patients (51.5%). AAPR of all the patients in this study were calculated on the basis of preoperative blood value. Univariate analysis in overall survival (OS) and recurrence-free survival (RFS) was performed, using the Cox proportional hazards model. The overall survival was evaluated in all the 303 patients, and the RFS was evaluated only in 156 patients who underwent curative resection. The primary endpoint was OS. OS is from the date of surgery to the date of cholangiocarcinoma-associated death. The secondary endpoint was RFS. RFS was calculated from the date of surgery to the date of recurrence. The most appropriate cut-off values of AAPR were determined by receiver operating characteristic curve. Baseline characteristics were compared using Chi-squared test or Fisher’s exact test. Survival data were calculated using the Kaplan-Meier method and were compared using the log-rank test. Univariate and multivariate survival analyses were conducted using the Cox proportional hazards regression methodology.

***Research results***

The overall 1-, 3-, and 5-year survival rates were 70.2%, 38.0%, and 16.5% in the low (< 0.41) AAPR group and 81.7%, 53.9%, and 33.4% in the high (≥ 0.41) AAPR group, which was a significant difference (*P* < 0.0001). The median OS (95%CIs) and RFS (95%CIs) in the AAPR ≥ 0.41 group were 48.5 mo (40.5-56.4) and 39.2 mo (31.1-47.3), respectively. In the AAPR < 0.41 group, the median OS (95%CI) and RFS (95%CI) were 30.3 mo (21.3-39.3) and 18.5 mo (11.1-25.8), respectively. The recurrence-free survival rate was significantly higher in the high AAPR group than in the low AAPR group (*P* = 0.017). The main limitation of this study is its single-center and retrospective design. More prospective studies and basic research are still needed to further elucidate the molecular mechanism of AAPR related to prognosis.

***Research conclusions***

In this study, we focused exclusively on the prognostic value of the AAPR in patients with CCA receiving surgery. This is the first study focusing on validating the prognostic potential of AAPR in patients with CCA receiving surgery. And its results may be of interest to CCA researchers and of help to clinicians aiming to develop a means of preventing the development of CCA. ALB and ALP are both simple but differentiated and objective variables, which are more easily applied in clinical practice. Moreover, this study investigated the relationship between AAPR and other clinical factors. And the present study indicated that low AAPR level, large tumor size, multiple tumors, advanced clinical stage were identified as significant predictors of poor prognosis. To our knowledge, this is the first study to analyze the correlation between the AAPR and CCA. The results indicate that the AAPR is an independent prognostic indicator for patients with CCA; patients with an AAPR less than 0.41 exhibited inferior OS and RFS. Both univariate analysis and multivariate analysis showed that an AAPR less than 0.41 is associated with poor prognosis. A low AAPR may reflect the patient’s malnutrition status, impressed immunity, and relatively severe disease condition such as liver or bone metastasis.

***Research perspectives***

Our present study suggested that AAPR was a potentially valuable prognostic index in patients with CCA receiving surgery. In view of its low cost, usability and prognostic power, AAPR should be included in the design of future clinical trials and research projects. And a lack of validation cohorts limits the further confirmation of AAPR as an independent indicator for patients with CCA. Larger scale and multi-center research is still warranted for further confirmation.

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B

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**Figure 1 Kaplan-Meier survival curves for patients with cholangiocarcinoma stratified by albumin-to-alkaline phosphatase ratio.** A: Cholangiocarcinoma (CCA) patients with a preoperative albumin-to-alkaline phosphatase ratio (AAPR) lower than 0.41 were associated with significantly poorer overall survival compared with CCA patients with a preoperative AAPR larger than 0.41; B: CCA patients with a preoperative AAPR lower than 0.41 were associated with significantly poorer recurrence free survival compared with CCA patients with a preoperative AAPR larger than 0.41. OS: Overall survival; RFS: Recurrence free survival; AAPR: Albumin-to-alkaline phosphatase ratio.

**Table 1 Clinicopathological characteristics of patients with cholangiocarcinoma *n* (%)**

|  |  |
| --- | --- |
| **Characteristics** | **Total (*n* = 303)** |
| Age (yr) | |
| < 60 | 150 (49.5) |
| ≥ 60 | 103 (50.5) |
| Sex | |
| Female | 135 (44.55) |
| Male | 168 (55.46) |
| Infectious diseases | |
| HBV | 31 (10.23) |
| HCV | 5 (1.65) |
| Serum albumin level [median (cIQ values)] | 38.7 (25.0- 49.0) |
| ALP [median (IQ values)] | 315 (42.0- 6778.0) |
| AAPR |  |
| ≥ 0.41 | 253 (83.5) |
| < 0.41 | 50 (16.5) |
| Tumor size | |
| < 3 | 233 (76.9) |
| ≥ 3 | 70 (23.1) |
| Number of tumors | |
| 1 | 278 (91.7) |
| ≥ 2 | 25 (8.3) |
| Curative resection | 156 (51.5) |
| Stage (III+ IV) | 98 (32.3) |

AAPR: Albumin-to-alkaline phosphatase ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CCA: Cholangiocarcinoma; ALP: Alkaline phosphatase; IQ values: Interquartile values.

**Table 2 Univariate and multivariate analyses of factors in relation to overall survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Univariate** | | **Multivariate** | |
| **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Age (yr) | 1.3 (0.6–2.1) | 0.650 |  |  |
| ≥ 60 |  |  |  |  |
| ≥ 60 |  |  |  |  |
| Sex | 0. 98 (0.64- 1.76) | 0.300 |  |  |
| Female |  |  |  |  |
| Male |  |  |  |  |
| Infectious diseases | | | | |
| HBV | 1.85 (1.10- 2.47) | *P* < 0.001 | 1.31 (1.42–1.92) | < 0.001 |
| HCV | 1.67 (0.23- 12.03) | 0.486 |  |  |
| Serum albumin level | 0.84 (0.59- 1.21) | 0.278 |  |  |
| ≥ 35 g/L |  |  |  |  |
| < 35 g/L |  |  |  |  |
| ALP | 2.46 (0.98- 6.18) | 0.054 |  |  |
| ≥ 20 ng/mL |  |  |  |  |
| < 20 ng/mL |  |  |  |  |
| AAPR | 3.56 (1.28- 9.92) | 0.035 | 2.88 (1.19-5.78) | 0.002 |
| ≥ 0.41 |  |  |  |  |
| < 0.41 |  |  |  |  |
| Tumor size | 3.14 (1.80- 6.05) | 0.021 | 2.71 (1.72-4.79) | 0.012 |
| ≥ 5 cm |  |  |  |  |
| < 5 cm |  |  |  |  |
| Number of tumors | 2.82 (1.17- 4.28) | 0.013 | 2.30 (1.95-3.20) | < 0.001 |
| ≥ 2 |  |  |  |  |
| 1 |  |  |  |  |
| Curative resection | 0.49 (0.17- 0.85) | 0.007 | 0.35 (0.29-0.42) | 0.001 |
| Yes |  |  |  |  |
| No |  |  |  |  |
| Stage (III+ IV) | 2.02 (1.34–3.12) | < 0.001 | 1.81 (1.24–2.49) | < 0.001 |

HR: Hazard ratio; AAPR: Albumin-to-alkaline phosphatase ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CCA: Cholangiocarcinoma; ALP: Alkaline phosphatase.

**Table 3 Univariate and multivariate analyses of factors in relation to recurrence free survival**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variables** | **Univariate** | | **Multivariate** | |
| **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Age (yr) | 1.31 (0.89-2.91) | 0.381 |  |  |
| ≥ 60 |  |  |  |  |
| ≥ 60 |  |  |  |  |
| Sex | 1.0 (0.5–1.8) | 0.300 |  |  |
| Female |  |  |  |  |
| Male |  |  |  |  |
| Infectious diseases |  |  |  |  |
| HBV | 1.91 (0.73-5.21) | 0.212 |  |  |
| HCV | 2.45 (0.61–5.21) | 0.374 |  |  |
| Serum albumin level | 0.89 (0.34-2.34) | 0.171 |  |  |
| ≥ 35 g/L |  |  |  |  |
| < 35 g/L |  |  |  |  |
| ALP | 1.96 (0.73–5.32) | 0.212 |  |  |
| ≥ 20 ng/mL |  |  |  |  |
| < 20 ng/mL |  |  |  |  |
| AAPR | 2.52 (1.38–4.75) | 0.002 | 2.31 (1.40–3.29) | < 0.001 |
| ≥ 0.41 |  |  |  |  |
| < 0.41 |  |  |  |  |
| Tumor size | 3.62 (1.73–7.69) | 0.010 | 1.92 (1.70–2.16) | < 0.001 |
| ≥ 5 cm |  |  |  |  |
| < 5 cm |  |  |  |  |
| Number of tumors | 2.47 (1.21–5.23) | 0.009 | 2.20 (1.41–4.87) | 0.002 |
| ≥ 2 |  |  |  |  |
| 1 |  |  |  |  |
| Stage (III+ IV) | 2.73 (1.81–3.55) | 0.003 | 2.32 (1.26–3.53) | < 0.001 |

HR: Hazard ratio; AAPR: Albumin-to-alkaline phosphatase ratio; HBV: Hepatitis B virus; HCV: Hepatitis C virus; CCA: Cholangiocarcinoma; ALP: Alkaline phosphatase.