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ORIGINAL RESEARCH

# The Prognostic Significance Of Pretreatment Albumin/alkaline Phosphatase Ratio In Patients With Stage IB-IIA Cervical Cancer

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**Background:** Pretreatment albumin/alkaline phosphatase ratio (AAPR) has been discussed about its prognostic value in several malignancies, whereas its role in cervical cancer remains unclear. In this study, we attempt to explore the prognostic significance of the AAPR in stage IB-IIA cervical cancer patients who underwent a radical hysterectomy.

**Patients and methods:** A total of 230 cervical cancer patients were enrolled in this retrospective study. The threshold value of AAPR was determined by receiver operating characteristic (ROC) curve. Kaplan-Meier survival analysis and multivariate analysis were performed to identify independent prognostic predictors of disease-free survival (DFS) and overall survival (OS).

**Results:** The optimal cut-off value of the preoperative AAPR was 0.68. Patients with AAPR<0.68 showed obviously inferior OS and DFS than those with AAPR>0.68 according to Kaplan-Meier curves (DFS: P = 0.011; OS: P = 0.017). In multivariate analysis, the preoperative AAPR showed to be an independent predictive factor for disease-free survival (DFS: P = 0.015) and overall survival (OS: P = 0.019). Moreover, subgroup analysis revealed that the lower AAPR was correlated with worse prognosis in patients with histologic grade I-II; but in those with histologic grade III, there was no significant difference between the two groups.

**Conclusion:** Preoperative AAPR was a potentially valuable prognostic index in stage IB-IIA cervical cancer patients. Further prospective studies are required to validate its prognostic value.

**Keywords:** albumin-to-alkaline phosphatase ratio, uterine cervical neoplasms, prognosis, survival analysis

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## Introduction

Cervical carcinoma is the most common cancer of the female genital tract and the fourth primary cause of malignancy-related deaths among women, giving rise to approximately 527 600 new cases and 265 700 deaths each year worldwide, especially in low-and middle-income countries.[1] At present, radical hysterectomy followed by chemotherapy or chemoradiation has been widely accepted as effective treatments in patients with IB-IIA stage cervical cancer.[2,3] Nevertheless, once disease recurrence occurs, the prognosis is relatively poor because of limited clinical therapies.[4–6]

Established prognostic factors associated with recurrence, progression, or death include parametrial involvement (PMI), lymph node metastasis (LNM), and

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positive surgical margins, which require confirmation of postoperative pathology.[7] A simpler and more economic index to predict the clinical outcomes for early-stage cervical cancer patients effectively is required.

At the moment, certain laboratory indexes have been validated as prognostic indicators in cervical cancer, including C- reactive protein/albumin ratio (CAR), neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI).[8–10] The albumin (ALB) to alkaline phosphatase (ALP) ratio (AAPR) was first revealed as a prognostic index for hepatocellular carcinoma in 2015 as another available indicator for assessing the nutritional status, inflammation level, and immune response.[11] Subsequently, it has been reported as a novel prognostic factor in different malignant carcinomas, including nasopharyngeal carcinoma, pancreatic ductal adenocarcinoma, breast cancer, lung cancer, and cholangiocarcinoma.[12–17]

However, the pretreatment level of AAPR and their prognostic role in cervical cancer have not ever been evaluated. Hence, we retrospectively studied the prognostic significance of AAPR in cervical cancer patients with stage IB-IIA disease, followed by the correlation of AAPR with other clinicopathological features.

# Methods

## Patients

We retrospectively reviewed patients histologically confirmed cervical cell carcinoma (stage IB-IIA) at Tumor Hospital Affiliated to Nantong University from January 2008 to June 2014. Patients were treated with radical hysterectomy plus pelvic lymphadenectomy without neoadjuvant chemotherapy or preoperative radiotherapy. Adjuvant therapy after surgery was considered based on pathological risk factors. The exclusion criteria were listed in the following: 1. receiving conization before radical hysterectomy; 2. with incomplete pathological information; 3. with previous or coexisting cancers; 4. without available follow-up data; 5. with diseases that could affect ALB or ALP level, such us liver disease, bone disease and active infectious disease. Our study was approved by the Ethics Committee of Tumor Hospital Affiliated to Nantong University and were in accordance with the 1964 Helsinki Declaration and its amendments. Informed consent was not required as the study was based on retrospective anonymous patient data and was not involved with patient intervention or the use of human tissue samples.

## Data Collection

Baseline clinicopathological features and laboratory assessments were intensively reviewed and obtained from the hospital database. We recorded patient age, menstruation, FIGO (International Federation of Gynecology and Obstetrics) stage, tumor size, treatment regimens, and histopathological parameters for analysis. Besides, ALB and ALP levels were retrieved within seven days before radical surgery. The preoperative AAPR was calculated as follows: AAPR = pretreatment serum albumin level (g/L)/alkaline phosphatase level (U/L).

Deadline for follow-up is July 9, 2019. We defined overall survival (OS) time as the period from the initial treatment to death due to cervical carcinoma or to the last follow-up date if the patient remained alive. The disease-free survival (DFS) time was defined as the interval from the initial treatment to relapse or death, or the last follow-up visit if no recurrence or death occurred.

## Statistical Analysis

Receiver operating curve (ROC) was utilized to evaluate the diagnostic performance of ALP, ALB and AAPR, and the largest Youden index (sensitivity + specificity-1) was selected as the optimal cut-off point. Independent-samples *t*-test or Mann–Whitney *U*-test was used to compare the difference of continuous variables between groups, and Chi-squared test or Fisher's exact test was employed for categorical variables. Survival data, including OS and DFS among the classification groups, were calculated using the Kaplan-Meier method and were compared using the log rank test. Univariate and multivariate Cox proportional hazards regression models were performed to identify the independent prognostic factors. Results were reported as hazard ratio (HR) and 95% confidence interval (CI). A two-sided $P < 0.05$ was considered to indicate statistical significance. All statistical analysis were obtained by using IBM SPSS software (Statistical Package for the Social Sciences; Version 25.0).

# Results

## Patient Clinic Characteristics

The study evaluated 484 patients (stage IB-IIA) who underwent a radical hysterectomy, and 230 patients were included finally (Figure 1).

The clinicopathological features of the patients were analyzed and shown in Table 1. The median age of the cohort at the time of diagnosis was 55 years (range: 29–79

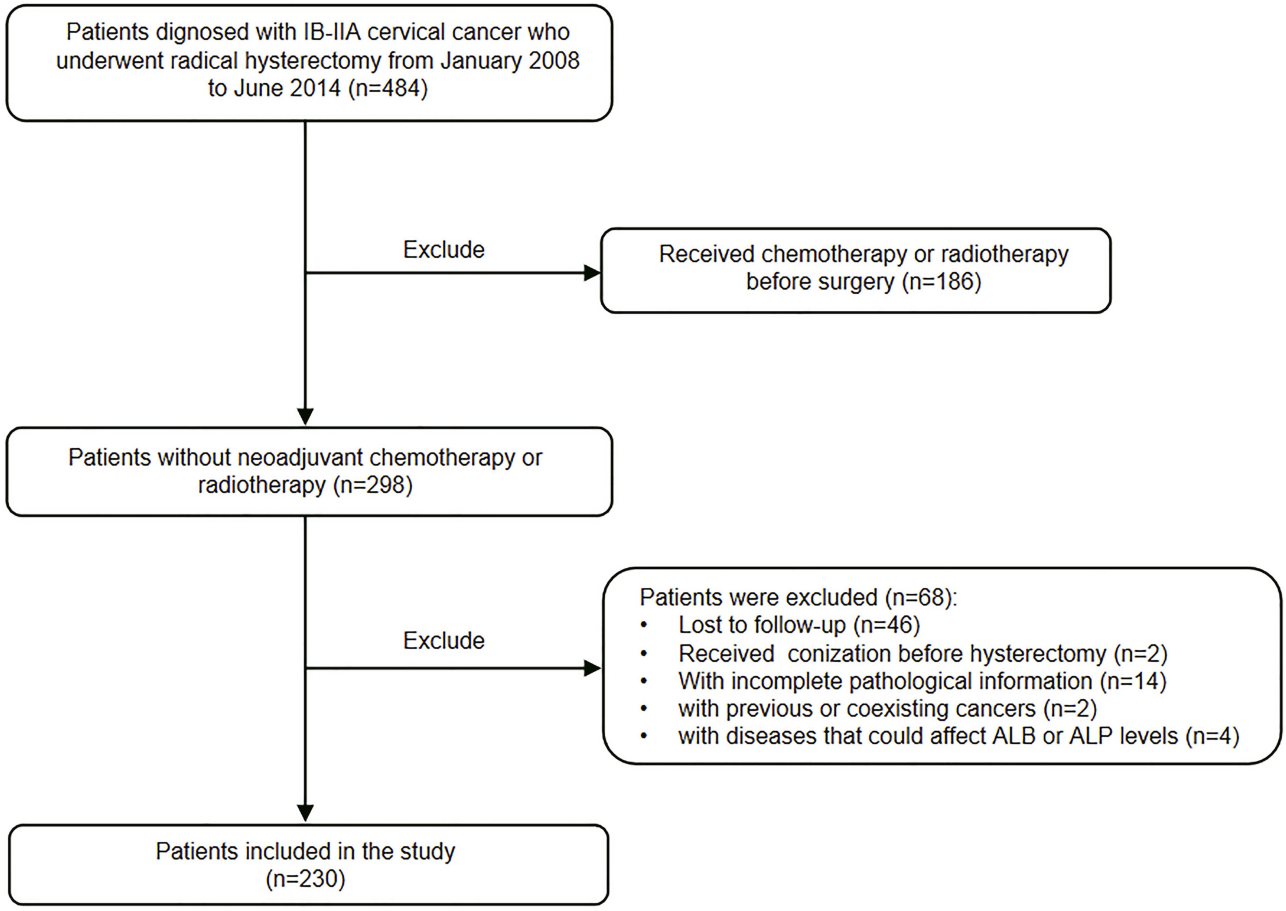


**Figure 1** Flow chart of patient selection.
**Abbreviations:** ALB, albumin; ALP, alkaline phosphatase.

years), and their median follow-up time was 81 months (range: 12–137 months). According to FIGO staging, there were 201 patients (87.4%) in IB and 29 patients (12.6%) in IIA.

## Relationship Between AAPR And Patient Characteristics

We used ROC curve analysis to determine the predictive significance of pretreatment values of ALB, ALP, and AAPR. Using OS as an endpoint, the area under the ROC curve was 0.631 (95% CI, 0.516–0.746; P=0.025) for ALB, 0.616 (95% CI, 0.501–0.732; P=0.046) for ALP and 0.654 (95% CI, 0.539–0.769; P=0.008) for AAPR, and the sensitivities (specificities) were 63.9% (60.7%), 75% (54.5%), 43.1% (85.7%), respectively (Figure 2). The respective optimal cutoff value for ALB, ALP, and AAPR were 45.5, 73.5, and 0.68, corresponding to maximum joint sensitivity and specificity. Then, 141 patients (61.3%) with AAPR< 0.68 and 89 patients (38.7%) with ALP≥ 0.68 were classified into low and high AAPR groups. The relationship between the preoperative AAPR and clinicopathological parameters of cervical cancer patients is shown in Table 1. According to the analysis, significant differences between the low and high preoperative AAPR groups were identified for age (P<0.001), menstruation (P<0.001), depth of invasion (P=0.045), and ALP level (P<0.001). However, there was no significant difference between FIGO stage (P=0.189), pathological type (P=0.054), tumor size (P=0.313), histologic grade (P=0.176), lymphovascular space invasion (P=0.875), LNM (P=0.748), vaginal invasion (P=0.770), adjuvant therapy (P=0.419) and ALB level (P=0.141).

## Survival Analysis

The 5-year overall survival (OS) rate and disease-free survival (DFS) rate in the AAPR-low group were significantly lower than those in the AAPR-high group (OS:

**Table 1** The Relationship Between The Preoperative AAPR And Clinicopathological Variables

| Variables | Total (n=230) | AAPR <0.68 | AAPR ≥0.68 | P-value |
|---|---|---|---|---|
| Age | | | | |
| ≤55 years | 115 (50%) | 52 (45.2%) | 63 (54.8%) | <0.001* |
| >55 years | 115 (50%) | 89 (77.4%) | 26 (22.6%) | |
| menopause | | | | |
| No | 98 (42.6%) | 41 (41.8%) | 57 (58.2%) | <0.001* |
| Yes | 132 (57.4%) | 100 (75.8%) | 32 (24.2%) | |
| FIGO stage | | | | |
| IB | 201 (87.4%) | 120 (59.7%) | 81 (40.3%) | 0.189 |
| IIA | 29 (12.6%) | 21 (72.4%) | 8 (27.6%) | |
| Pathological type | | | | |
| SCC | 192 (83.5%) | 123 (64.1%) | 69 (35.9%) | 0.054 |
| No-SCC | 38 (16.5%) | 18 (47.4%) | 20 (52.6%) | |
| Tumor Size | | | | |
| ≤2cm | 113 (49.1%) | 73 (64.6%) | 40 (35.4%) | 0.313 |
| >2cm | 117 (50.9%) | 68 (58.1%) | 49 (41.9%) | |
| Histologic grade | | | | |
| I-II | 124 (53.9%) | 81 (65.3%) | 43 (34.7%) | 0.176 |
| III | 106 (46.1%) | 60 (56.6%) | 46 (43.4%) | |
| Depth of invasion | | | | |
| <2/3 | 172 (74.8%) | 99 (57.6%) | 73 (42.4%) | 0.045* |
| ≥2/3 | 58 (25.2%) | 42 (72.4%) | 16 (27.6%) | |
| LVSI | | | | |
| No | 200 (87.0%) | 123 (61.5%) | 77 (38.5%) | 0.875 |
| Yes | 30 (13.0%) | 18 (60%) | 12 (40%) | |
| LNM | | | | |
| No | 196 (85.2%) | 121 (61.7%) | 75 (38.3%) | 0.748 |
| Yes | 34 (14.8%) | 20 (58.8%) | 14 (41.2%) | |
| Vaginal invasion | | | | |
| No | 218 (94.8%) | 133 (61.0%) | 85 (39.0%) | 0.770 |
| Yes | 12 (5.2%) | 8 (66.7%) | 4 (33.3%) | |
| Adjuvant therapy | | | | |
| No | 84 (36.5%) | 56 (66.7%) | 28 (33.3%) | 0.419 |
| Chemoradiotherapy | 57 (24.8%) | 31 (54.4%) | 26 (45.6%) | |
| Chemotherapy | 84 (36.5%) | 50 (59.5%) | 34 (40.5%) | |
| Radiotherapy | 5 (2.2%) | 4 (80%) | 1 (20%) | |
| ALB(g/L) | 46.3±4.2 | 46.0±4.4 | 46.8±4.0 | 0.141 |
| ALP(U/L) | 81.3±57.0 | 97.8±67.3 | 55.1±10.5 | <0.001* |

**Notes:** Independent-Samples T test or Mann–Whitney *U*-test was employed for continuous variables. Chi-squared test or Fisher's exact test was employed for categorical variables. *P<0.05.

**Abbreviations:** AAPR, albumin/alkaline phosphatase ratio; FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; LVSI, lympho-vascular space invasion; LNM, lymph node metastasis; ALB, albumin; ALP, alkaline phosphatase.

83.0% VS 95.5%, P =0.005; DFS: 80.1% VS 93.3%, P=0.006). The Kaplan-Meier survival curves demonstrated that AAPR <0.68 was significantly associated with worse OS and DFS (Figure 3).

Univariate and multivariate analyses were performed to identify the prominently independent prognostic factors in cervical cancer (Table 2). The results showed that AAPR was indicated as an independent prognostic index for OS (HR,

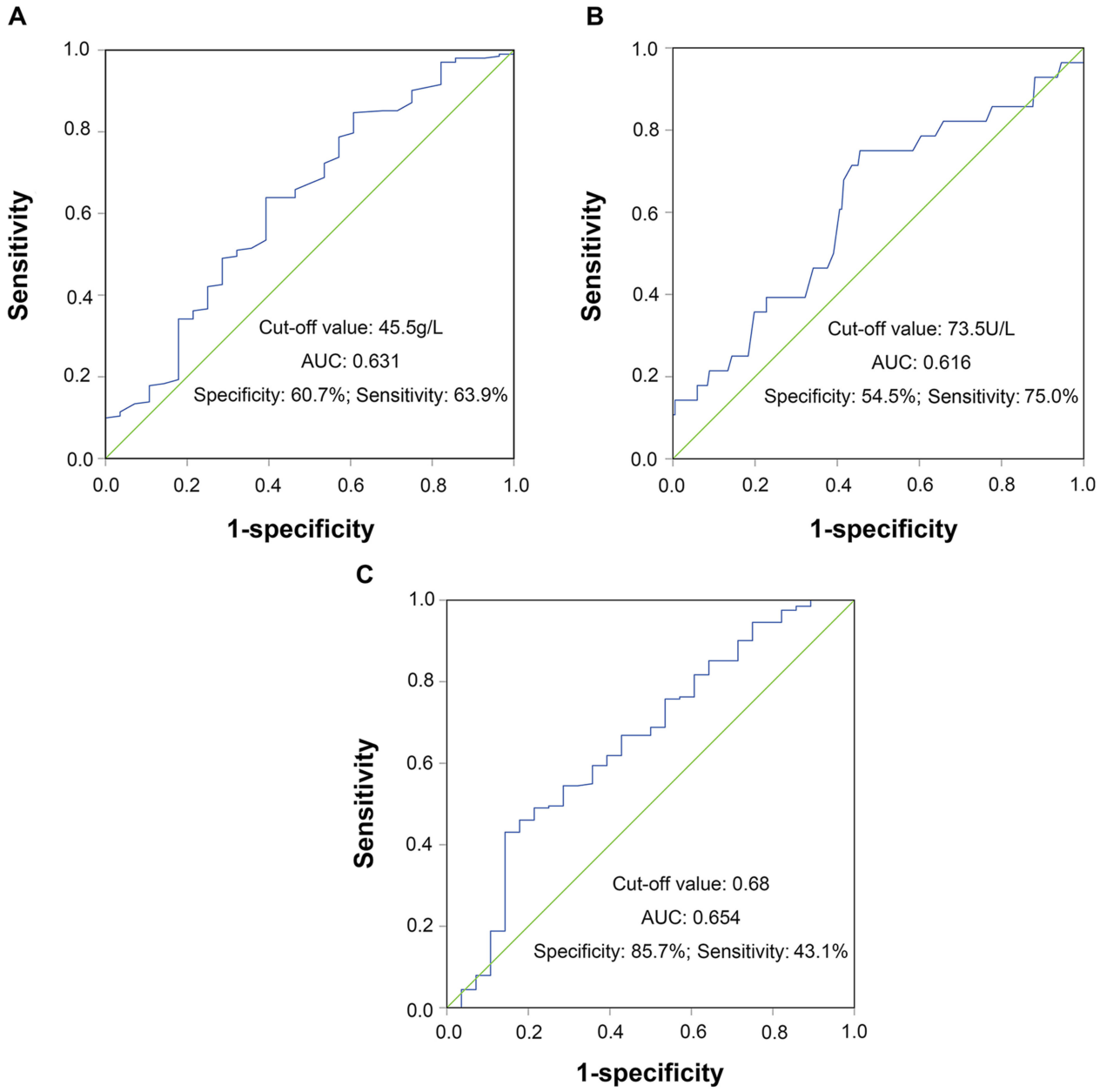


**Figure 2** Receiver operating characteristics curve analysis based on ALB (**A**), ALP (**B**), and AAPR (**C**) for overall survival.
**Abbreviations:** ALB, albumin; ALP, alkaline phosphatase; AAPR, albumin/alkaline phosphatase ratio.

0.331; 95% CI, 0.135–0.809; P= 0.015) and DFS (HR, 0.387; 95% CI, 0.176–0.853; P= 0.019). Additionally, other factors, including FIGO stage, pathological type, and adjuvant therapy, were also determined to be independent prognostic predictors for OS and DFS in multivariate analysis.

Moreover, subgroup analysis suggested that AAPR <0.68 was significantly related to inferior prognosis in patients with histologic grade I-II; however, in patients with histologic grade III, there was no difference between the two groups (Figure 4).

## Discussion

In this retrospective study, we demonstrated that AAPR was an independent predictor in cervical cancer patients receiving radical hysterectomy. Our results showed that AAPR levels under 0.68 were associated with poor OS and DFS. To our knowledge, this is the first study analyzing the association of AAPR with cervical cancer.

ALB, as a stable and flexible serum protein, is generally considered a biomarker for liver function and nutritional

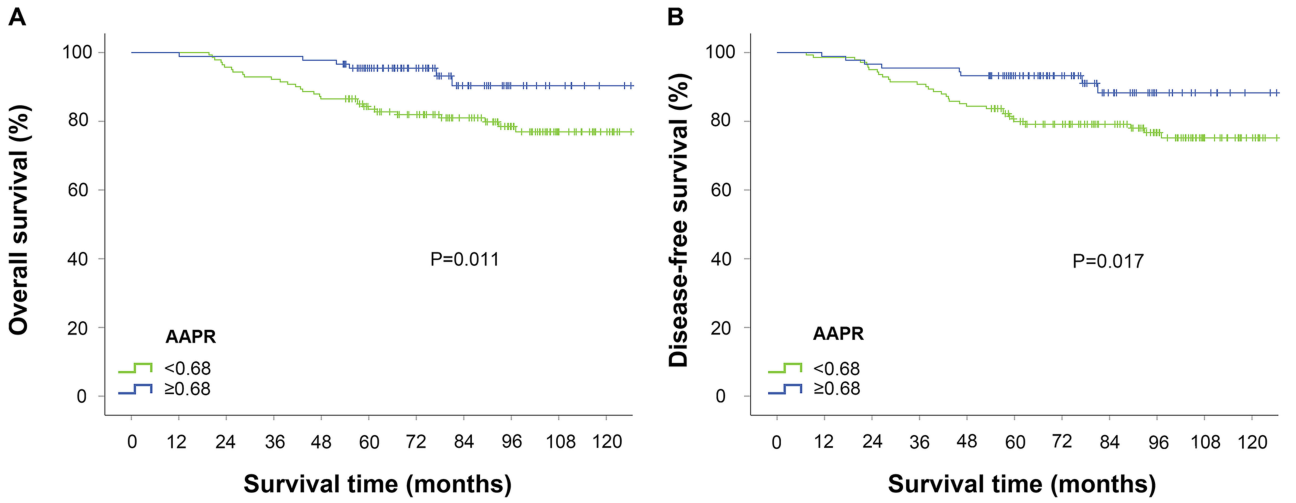


**Figure 3** Kaplan-Meier curves stratified according to AAPR value for the overall survival (**A**) and disease-free survival (**B**). The P-values were determined by the log rank test.
**Abbreviation:** AAPR, albumin/alkaline phosphatase ratio.

status. Moreover, it was reported with the ability to stabilize cell growth and DNA proliferation, exert antioxidant effects against carcinogens and modulate immune reaction, which plays a vital role in tumorigenesis.[18–20] Therefore, a low level of ALB might correlate with insufficient hepatic function, decreased immune capability, and inadequate anticancer response. Several previous reports have shown the prognostic value of ALB in malignant tumors, including breast cancer, kidney cancer, lung cancer and colorectal cancer.[15,21–23] ALP is known as a phosphate monoester hydrolase and mainly concentrate in the liver, bone, bile duct, kidney, and placenta.[24,25] It is commonly recognized to have high diagnosis specificity in bone metastasis and has been reported in certain bony metastasis malignancies.[26–28] Additionally, ALP was found to influence inflammation through regulation of purinergic signaling and induce an inhibitory immune response.[29] Besides, ALP can be generated and released into the blood directly by tumor cells and regulates tumor growth.[30] Therefore, evaluation of ALP might manifest as a heavy tumor burden and have prognostic value in cancer patients.[31,32]

As reported, the majority of cervical cancer cases are associated with persistent human papillomavirus (HPV) infections and chronic inflammation it induced.[33,34] The weakened systematic and local immune response plays an important role in the process.[35] Furthermore, approximately 62–88% of gynecological cancer patients are prone to experience malnutrition.[36] Prior studies have shown that nutrient deficiency and systematic inflammatory response might play a critical role in the pathogenesis and progression of human carcinomas and were correlated with inferior prognosis in patients undergoing resection for solid tumors.[8,37–39] Zheng et al have demonstrated that ALB is an independent prognostic indicator in early operable cervical cancer.[40] Moreover, a recent published article found that high levels of ALP could influence tumorigenesis and predict outcomes in cervical cancer patients.[41] In our present study, the AUC of AAPR was similar to that of ALB and ALP. However, AAPR has several advantages in cervical cancer patients compared with the other two indices. On one hand, both ALB and ALP can be influenced by other non-cancer-related conditions, and AAPR could minimize the potential basis. On the other hand, AAPR was proven to be an independent prognostic factor related with OS and DFS rather than ALB and ALP in multivariate survival analysis. As an integrated indicator, AAPR would be more reliable and might enhance its prognostic value and reflect nutritional status and immune response of patients, as well as the severity and progression of disease in a more effective way. A 0.68 cut-off value for AAPR was applied to divide patients into two groups. According to the chi-square test, the pretreatment AAPR was significantly related with age, menopause, and depth of invasion. Deep stromal invasion is considered to be an intermediate-risk factor in the management of cervical cancer. Preoperative indices in predicting the depth of invasion may benefit patients in treatment selection, especially for early-stage cervical cancer. Patients with AAPR under 0.68 were more likely to have a poor prognosis with the possibility of impaired immune-nutritional status, inadequate response to the surgical stress and increased susceptibility to infection,

**Table 2** Univariate And Multivariate Analyses Of Survival In Cervical Cancer Patients

| Variables | Overall Survival | | | | Disease-Free Survival | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate Analysis[a] | | Multivariate Analysis[b] | | Univariate Analysis[a] | | Multivariate Analysis[b] | |
| | HR(95% CI) | P-value | HR(95% CI) | P-value | HR(95% CI) | P-value | HR(95% CI) | P-value |
| Age | | | | | | | | |
| ≤55 years | 1 | 0.101 | | | 1 | 0.047* | | |
| >55 years | 1.776(0.894–3.526) | | | | 1.935(1.010–3.706) | | | |
| menopause | | | | | | | | |
| No | 1 | 0.062 | | | 1 | 0.039* | | |
| Yes | 2.011(0.965–4.188) | | | | 2.078(1.037–4.161) | | | |
| FIGO stage | | | | | | | | |
| IB | 1 | <0.001* | 1 | 0.001* | 1 | 0.002* | 1 | 0.008* |
| IIA | 3.607(1.766–7.368) | | 3.488(1.681–7.239) | | 2.922(1.459–5.853) | | 2.628(1.294–5.338) | |
| Pathological type | | | | | | | | |
| SCC | 1 | 0.019* | 1 | 0.007* | 1 | 0.022* | 1 | 0.009* |
| No-SCC | 2.420(1.158–5.056) | | 2.934(1.340–6.420) | | 2.250(1.122–4.516) | | 2.644(1.280–5.462) | |
| Tumor Size | | | | | | | | |
| ≤2cm | 1 | 0.755 | | | 1 | 0.653 | | |
| >2cm | 1.112(0.572–2.160) | | | | 1.153(0.619–2.147) | | | |
| Histologic grade | | | | | | | | |
| I-II | 1 | 0.974 | | | 1 | 0.786 | | |
| III | 0.989(0.509–1.923) | | | | 1.090(0.586–2.027) | | | |
| Depth of invasion | | | | | | | | |
| <2/3 | 1 | 0.007* | | | 1 | 0.042* | | |
| ≥2/3 | 2.500(1.278–4.890) | | | | 1.944(1.024–3.692) | | | |
| LVSI | | | | | | | | |
| No | 1 | 0.432 | | | 1 | 0.379 | | |
| Yes | 1.423(0.591–3.429) | | | | 1.443(0.638–3.263) | | | |
| LNM | | | | | | | | |
| No | 1 | 0.027* | | | 1 | 0.077 | | |
| Yes | 2.366(1.105–5.067) | | | | 1.958(0.930–4.123) | | | |
| Vaginal invasion | | | | | | | | |
| No | 1 | 0.060 | | | 1 | 0.094 | | |
| Yes | 2.724(0.957–7.754) | | | | 2.424(0.860–6.830) | | | |
| Adjuvant therapy | | | | | | | | |
| No | 1 | <0.001* | 1 | <0.001* | 1 | <0.001* | 1 | 0.003* |
| Chemoradiotherapy | 1.753(0.807–3.807) | | 1.651(0.739–3.688) | | 1.606(0.751–3.433) | | 1.507(0.690–3.291) | |
| Chemotherapy | 0.382(0.136–1.072) | | 0.304(0.105–0.879) | | 0.644(0.279–1.489) | | 0.539(0.228–1.275) | |
| Radiotherapy | 8.744(2.834–26.981) | | 5.637(1.724–18.434) | | 8.413(2.739–25.838) | | 6.123(1.912–19.610) | |
| ALB(g/L) | | | | | | | | |
| <45.5 | 1 | 0.030* | | | 1 | 0.091 | | |
| ≥45.5 | 0.479(0.246–0.933) | | | | 0.585(0.314–1.089) | | | |
| ALP(U/L) | | | | | | | | |
| <73.5 | 1 | 0.013* | | | 1 | 0.027* | | |
| ≥73.5 | 2.543(1.218–5.312) | | | | 2.114(1.088–4.106) | | | |
| AAPR | | | | | | | | |
| <0.68 | 1 | 0.016* | 1 | 0.015* | 1 | 0.021* | 1 | 0.019* |
| ≥0.68 | 0.337(0.139–0.813) | | 0.331(0.135–0.809) | | 0.402(0.185–0.873) | | 0.387(0.176–0.853) | |

**Notes:** [a]Univariate Cox proportional hazards regression models; [b]Multivariate Cox proportional hazards regression models; *P<0.05.

**Abbreviations:** FIGO, International Federation of Gynecology and Obstetrics; SCC, squamous cell carcinoma; LVSI, lympho-vascular space invasion; LNM, lymph node metastasis; ALB, albumin; ALP, alkaline phosphatase; AAPR, albumin/alkaline phosphatase ratio.

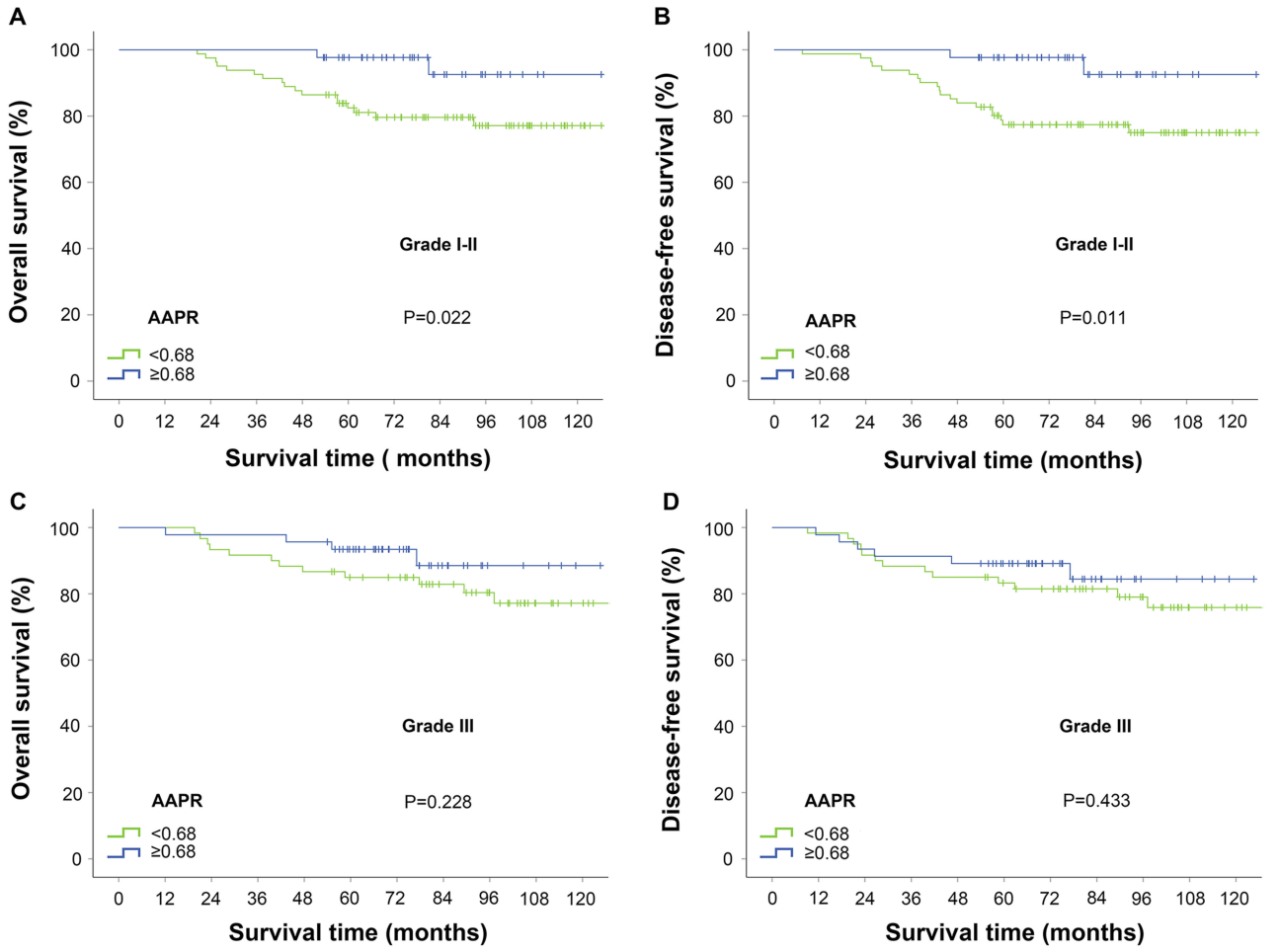


**Figure 4** Kaplan-Meier curves for survival outcomes stratified according to APPR value in patients with histologic grade I–II and III. (**A**) Overall survival and (**B**) disease-free survival for patients with histologic grade I–II; (**C**) Overall survival and (**D**) disease-free survival for patients with histologic grade III. The P-values were determined by the log rank test.
**Abbreviation:** AAPR, albumin/alkaline phosphatase ratio.

indicating the demands for increased nutritional intake, favourable anti-inflammatory therapy and improved systematic immunity. What's more, receiving immunotherapy according to clinical guidance is likely to provide a good therapeutic response in these patients. Besides, we explored the role of AAPR in subgroups with different histologic grades. Our results showed that the low AAPR contributed to worse survival outcomes in well and moderate differentiated cervical cancer; but in terms of poorly differentiated disease, there was no significant relationship between them, which was consistent with the result obtained in upper tract urothelial carcinoma.[39] The result gave us a prompt that patients with low AAPR level should have their cancer status and physical condition evaluated more carefully compared with the high-AAPR group, especially in well and moderate differentiated patients.

In our study, adjuvant therapy was found to be an independent prognostic index for OS and DFS. Although various guidelines recommend radiation therapy or concurrent chemoradiation therapy as the standard adjuvant therapy to reduce recurrence in patients with high or intermediate risk factors after radical hysterectomy, adjuvant therapies remain controversial.[42] Adjuvant chemotherapy alone may potentially reduce adverse events with the same efficacy as RT.[43] In our study, adjuvant chemotherapy was considered according to different pathological risk factors.

There were some limitations in this study. First, this was a retrospective study conducted in a single centre with a relatively small sample size, which may have caused selection bias though both inclusion and exclusion criteria were strictly performed. Second, only stage IB-IIA cervical cancer patients who received surgery were included. Patients in different FIGO stages are needed to discuss in the future regardless of treatment options. Third, the cut-off AAPR value obtained from ROC curves might not have been optimal in other independent cohorts, and external validation is

still needed. The underlying mechanisms of the correlation between AAPR and prognosis remain unknown, and further basic research are needed.

In conclusion, the preoperative AAPR is a novel derived indicator in stage IB-IIA cervical cancer patients with radical surgery. A low AAPR level was independently associated with inferior OS and DFS. However, larger scale, multi-centre, and prospective studies are required to confirm the prognostic role of AAPR.

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## Disclosure

The authors report no conflicts of interest in this work.

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