Prognostic Implication of Preoperative Serum Albumin to Carcinoembryonic Antigen Ratio in Colorectal Cancer Patients

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Research Article

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Abstract

Both preoperative serum albumin (ALB) and carcinoembryonic antigen (CEA) were previously reported as useful prognostic factors in colorectal cancer (CRC); however, the ALB to CEA ratio (ACR) and their individual prognostic efficacies have been less studied. In this study, a total of 156 CRC patients staged I-IV were retrospectively enrolled. Patients were divided into ACR-low or ACR-high subgroups, and the differences in progression-free survival (PFS) and overall survival (OS) were conducted by Kaplan-Meier curves, log-rank test and Cox proportional model. As a result, a total of 31.41% (49/156) of patients presented with ACR-low disease, and these patients had tumors with advanced T stages ($T_3 + T_4$) (P<0.01), larger tumor diameters (P<0.01) and distant metastases (P = 0.01) and a relatively lower lymphocyte to monocyte ratio (LMR) (P<0.01). The ACR was significant in predicting survival. When 5.98 was used as the cutoff point, it had a sensitivity of 58.50% and 61.50% and a specificity of 83.50% and 80.50% for PFS and OS, respectively. ACR displayed a superior prognostic efficacy than other tested markers for both PFS and OS (except LMR). Patients in the ACR-low group displayed significantly worse PFS (log rank = 35.75, P<0.01) and OS (log rank = 29.68, P<0.01) than those in the ACR-high group. Finally, ACR was an independent prognostic factor for both PFS (HR = 0.31, 95% CI: 0.17–0.56, P < 0.01) and OS (HR = 0.33, 95% CI: 0.16–0.66, P < 0.01). For conclusion, the ACR was a robust prognostic factor in CRC, and patients with a relatively low preoperative ACR had significantly worse survival.

Introduction

Colorectal cancer (CRC) is a classic solid tumor that causes many deaths worldwide[1], including in China[2]. Although early diagnosed cases could be cured by surgery, the majority of advanced cases are still incurable [3]. Identifying simple and reliable prognostic factors in the disease has become increasingly popular in recent years.

Albumin (ALB) acts as a carrier for practically all metabolites, drugs, hormones and products of toxic degradation in the human body[4], and its metabolism is affected by many exogenous and endogenous factors, including cancer cells[5]. Previously, several studies demonstrated the usefulness of individual ALB as a prognostic factor in many malignancies, including gastric cancer [6], nonsmall cell lung cancer [7], ovarian cancer [8], head and neck cancer [9] and, in particular, CRC [10–13]. Notably, the prognostic efficacy of ALB alone was inferior when compared with other markers[11]. In recent years, some innovative markers based on ALB, such as the albumin to globulin ratio[14–15], albumin to fibrinogen ratio[16], C-reactive protein to albumin ratio (CAR)[17–19] and others[20–22], have been frequently reported in cancer studies, including CRC. However, some of these parameters are not conventional prognostic factors and are not included in routine clinical tests, and more common markers are still needed.

Carcinoembryonic antigen (CEA) is a member of a family of glycoproteins anchored to the cell membrane of colonic epithelial cells and up to approximately 90% of colorectal cancer cells can release CEA [23, 24]. CEA is also a long-term established marker in the diagnosis, surveillance and prognosis of CRC.

Regrettably, only approximately 1/3 of patients have an abnormally elevated CEA at the time of diagnosis[25], which largely impairs its application in clinical practice. Interestingly, some investigators have attempted to further explore the prognostic value of CEA in patients whose levels fall into the normal range before surgery[26, 27]; however, the cutoff points were not consistent, and its value in postoperative surveillance in such a scenario was still mainly unclear. These studies also indicated that a single CEA assay was still insufficient for predicting patients' prognosis. Taking into consideration these results, it was plausible that combining ALB and CEA would have potential prognostic value in CRC, but studies addressing this topic have not been published.

In this study, we aimed to explore the prognostic value of the ALB to CEA ratio (ACR) as well as its prognostic efficacy when compared with individual ALB, CEA and other systemic inflammation markers in CRC.

Materials And Methods

Patient enrollment

From January 2011 to January 2018, patients with CRC treated in Hainan Hospital of Chinese PLA General Hospital were enrolled. Those meeting the following criteria were included: 1. age>18 y; 2. radical recession of the primary lesion; and patients were excluded based on any one of the following criteria: 1. neoadjuvant therapies; 2. missing laboratory tests within a week before surgery or key information in postoperative pathological reports; 3. multiple or recurrent malignancies or *in situ* lesions; 4. abnormal aminotransferase or bilirubin by liver function tests; and 5. loss to follow-up of less than 36 m. Other clinicopathological parameters were collected as previously reported [28,29], and the body mass index was calculated as body weight (kg) divided by height (m^2). Tumor size was cut off at 4 cm according to a previous report [30]. The study was approved by the ethics committee of Hainan Hospital of PLA General Hospital (ID: 301HLFYLS15), and written informed consent was received from the patients or their authorized relatives.

Determination of ACR and other systemic inflammation markers

Laboratory tests were performed between 6:00 and 9:00 am on peripheral venous blood within 1 week to 1 month before the surgery, and the latest results were used when more than one result was found. The ACR was calculated as ALB (Ref: 35–50 g/L) divided by CEA (Ref: 0–55 ng/mL) and then by 10^6 to make the results easier to read. In addition, other systemic inflammation markers, including the neutrophil to lymphocyte ratio (NLR)[31], lymphocyte to monocyte ratio (LMR)[32] and platelet to lymphocyte ratio (PLR)[33], were also determined according to previous reports.

Definition of progression-free survival (PFS) and overall survival (OS)

The follow-up was conducted by telephone, WeChat or by visit to the medical records at the hospital with an interval of 3–6 months for the first 2 years and 6–12 months for the following years. PFS was defined

as the point from the date of surgery until the date of first recurrence at any location, disease progression by imaging examinations according to the RECIST (version 1.1) [34] or death from any cause. OS was defined as the date of surgery until the date of death by any cause. The latest follow-up point was June 2021.

Statistical analysis

The statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). A receiver operating characteristic (ROC) curve analysis was used to determine the optimal discriminator value of ACR, and comparison of the areas under the curve (AUCs) was achieved by MedCalc v19.0.7 (MedCalc Software Ltd., Ostend, Belgium). The differences in clinicopathological parameters in the ACR subgroups were calculated by χ^2-test or Fisher's exact test and Student's t when appropriate. Survival differences for ACR-low or high groups were conducted by Kaplan–Meier (K-M) analysis followed by log-rank tests. Risk factors for survival were estimated by a Cox proportional hazards model. Double-sided $P<0.05$ was considered statistically significant.

Results

Demographic characteristics and the prognostic efficacy of ACR

As shown in Fig. 1, a total of 294 patients were registered, and 156 patients (100 males, 56 females) were ultimately included in the study. The mean age of the patients was 60.36 y (range: 24–85 y), and the mean follow-up was 47.61 m (range: 1–102 m). According to the ROC tests, ACR was significant for predicting PFS (AUC = 0.75, 95% CI: 0.368–0.83, $P < 0.01$) and OS (AUC = 0.74, 95% CI: 0.65–0.83, $P < 0.01$) (Fig. 2), and when 5.98 (according to the *Youden* index) was used as the cutoff point, it had a sensitivity of 58.50% and 61.50% and a specificity of 83.50% and 80.50% for PFS and OS, respectively. Next, further comparison of the prognostic efficacy of ACR with other markers indicated that ACR had a superior efficacy than individual ALB ($Z = 2.58$, $P = 0.01$), CEA ($Z = 2.17$, $P = 0.03$) and NLR ($Z = 2.63$, $P = 0.01$), LMR ($Z = 2.08$, $P = 0.01$), PLR ($Z = 3.03$, $P<0.01$) in PFS; and it also had a similar advantage over single ALB ($Z = 2.05$, $P = 0.04$), CEA ($Z = 2.04$, $P = 0.04$) and NLR ($Z = 2.29$, $P = 0.02$), PLR ($Z = 2.40$, $P = 0.02$) in OS except LMR ($Z = 1.72$, $P = 0.09$).

Differences in clinicopathological parameters in the ACR-low or ACR-high subgroups

By ROC tests, the patients were subsequently divided into ACR-low (< 5.98) or ACR-high (≥ 5.98) subgroups, and it was found that 31.41% (49/156) of cases were ACR-low.

As shown in Table 1, these patients apparently presented with advanced T stages ($T_3 + T_4$) ($P<0.01$), larger tumor diameters ($P<0.01$) and distant metastases ($P = 0.01$) and a relatively lower LMR ($P<0.01$).

Table 1
Different ACR among varied clinicopathological parameters

		ACR		
	Patient No.	**<5.98**	**≥ 5.98**	P
Age (y)				0.08
< 60	68	16	52	
≥ 60	88	33	55	
Gender				0.47
Female	56	20	36	
Male	100	29	71	
Tumor location				1.00
Right	36	11	25	
Left	110	38	82	
Histological grade				0.12
Well + moderate	127	36	91	
Poor	29	13	16	
Invasive depth				<0.01*
T_{1+2}	34	4	30	
T_{3+4}	122	45	77	
Tumor diameter (cm)				<0.01*
<4	64	12	52	
≥4	92	37	55	
Node involvement				0.23
N_0	91	25	66	
N_{1+2}	65	24	41	
Positive nodes no.	156	3.12 ± 5.78	1.64 ± 3.88	0.15
Distant metastasis				0.01*

*with significant statistical difference; no. number.

		ACR		
Yes	12	8	4	
No	144	41	103	
TNM stage				0.17
I + II	87	23	64	
III + IV	69	26	43	
Adjuvant therapies				0.02
Received	85	31	54	
None	52	9	43	
Unknown	19	9	10	
BMI (kg/m^2)	156	23.22 ± 4.78	23.89 ± 3.23	0.11
Preoperative measures				
NLR	156	3.18 ± 2.88	2.52 ± 2.75	0.17
LMR	156	3.43 ± 1.61	4.20 ± 1.69	<0.01*
PLR	156	165.91 ± 94.37	148.24 ± 87.25	0.25
*with significant statistical difference; no. number.				

Survival differences of ACR-low or ACR-high groups in PFS and OS

There were significant differences in the ACR-low or ACR-high subgroups in the 3-year PFS (63.27% *vs.* 20.56%, P<0.01) and OS (48.98% *vs.* 14.02%, P<0.01) rates. By K-M analyses, it was found that patients with ACR-low had a significantly worse PFS (ACR-low *vs.* high: 29.35 ± 24.73 m *vs.* 49.81 ± 21.43 m, Log Rank = 35.75, P<0.01) and OS (ACR-low *vs.* high: 35.22 ± 21.94 m *vs.* 53.28 ± 18.98 m, Log Rank = 29.68, P<0.01) than those with ACR-high (Fig. 3).

Univariate and multivariate analyses of the prognostic factors for PFS and OS

Univariate tests indicated that invasive depth, tumor diameter, node involvement, positive node number, distant metastasis, TNM stage, NLR, LMR and ACR were significant prognostic factors for PFS and OS (additional plus age and histological grade) (Table 2), and when all these factors were included in multivariate tests, the results indicated that the ACR was an independent prognostic factor for both PFS (HR = 0.31, 95% CI: 0.17–0.56, P<0.01) and OS (HR = 0.33, 95% CI: 0.16–0.66, P<0.01) (Table 3).

Table 2
Univariate and multivariate analyses of different parameters for PFS

	Univariate			Multivariate		
	P	HR	95%CI	P	HR	95%CI
Age (years)						
<60	1					
≥60	0.16	1.51	0.85–2.67			
Gender						
Female	1					
Male	0.32	1.35	0.75–2.43			
Tumor location						
Right						
Left	0.26	1.51	0.74–3.10			
Histological grade						
Well + moderate	1					
Poor	0.15	1.61	0.84–3.06			
Invasive depth						
T_{1+2}	1			1		
T_{3+4}	< 0.01*	5.81	1.81–18.67	0.04*	3.34	1.02–11.01
Tumor diameter (cm)						
<4	1					
≥4	0.13	1.56	0.88–2.79			
Node involvement						
N_0	1					
N_{1+2}	0.03*	1.86	1.08–3.21			
Positive nodes no.	< 0.01*	1.11	1.06–1.16	0.03*	1.05	1.01–1.10

*with significant statistical difference

	Univariate			Multivariate		
Distant metastasis						
Yes	1					
No	< 0.01*	7.89	3.88–16.02	< 0.01*	3.04	1.40–6.61
TNM stage						
I + II	1					
II + IV	< 0.01*	2.19	1.26–3.80			
Adjuvant therapies						
Received	1					
None + Unknow	0.07	1.69	0.96-3.00			
BMI (kg/m^2)	0.39	0.97	0.89–1.05			
Preoperative measures						
NLR	< 0.01*	1.09	1.03–1.15	< 0.01*	1.09	1.03–1.16
LMR	< 0.01*	0.77	0.64–0.93			
PLR	0.17	1.00	1.00–1.00			
ACR						
<5.98	1					
≥5.98	< 0.01*	0.21	0.12–0.37	< 0.01*	0.31	0.17–0.56
*with significant statistical difference						

Table 3. Univariate and multivariate analyses of different parameters for PFS

	Univariate			Multivariate		
	P	HR	95%CI	P	HR	95%CI
Age (years)						
<60	1					
≥60	0.02*	2.28	1.13-4.59			
Gender						
Female	1					
Male	0.45	1.30	0.66-2.57			
Tumor location						
Right						
Left	0.37	1.45	0.64-3.29			
Histological grade						
Well+moderate	1					
Poor	0.04*	2.02	1.01-4.06			
Invasive depth						
T_{1+2}	1					
T_{3+4}	0.01*	13.49	1.85-98.31			
Tumor diameter (cm)	0.02*	1.16	1.03-1.30			
4	1					
≥4	0.03	2.19	1.07-4.50			
Node involvement						
N_0	1					
N_{1+2}	0.01*	2.21	1.17-4.17			
Positive nodes no.	<0.01*	1.14	1.09-1.20	<0.01*	1.08	1.02-1.13
Distant metastasis						
Yes	1			1		
No	<0.01*	8.71	4.01-18.94	<0.01*	4.41	1.92-10.10

TNM stage						
I+II	1					
II+IV	<0.01*	2.57	1.34-4.89			
Adjuvant therapies						
Received	1					
None+Unknow	0.43	1.30	0.68-2.48			
BMI (kg/m^2)	0.40	0.96	0.88-1.05			
Preoperative measures						
NLR	<0.01*	1.10	1.04-1.17	<0.01*	1.10	1.03-1.18
LMR	0.03*	0.79	0.63-0.98			
PLR	0.23	1.00	1.00-1.01			
ACR						
5.98	1					
≥5.98	<0.01*	0.20	0.10-0.38	<0.01*	0.33	0.16-0.66

*with significant statistical difference

Discussion

In the present study, we found that ACR was a useful prognostic marker in CRC, and patients with a relatively low preoperative ACR had a worse prognosis than those with a high preoperative ACR. The prognostic efficacy of ACR was significantly better than that of individual ALB, CEA and other systemic inflammation markers and was an independent risk factor for survival. To the best of our knowledge, this is the first report concerning the role of ACR in cancer.

Previously, both individual ALB and CEA were reported as conventional prognostic markers in CRC. In a study which included 69 nonmetastatic and 57 metastatic CRC patients, Wei et al. found that ALB was significantly reduced in metastatic patients and was an independent prognostic factor for PFS [10]. Li et al. studied 312 stage I-III CRC patients and found that low ALB correlated with shortened PFS and OS [11]. In line with these results, Almasaudi et al. performed a study on 795 CRC patients and found that hypoalbuminemia was associated with poorer cancer-specific survival and OS [35]. Lakemeyer et al. conducted a study with 1487 staged I-IV CRC and found that an elevated CEA (> 5 ng/mL) could predict significantly worse OS [36]. Additionally, Egenvall et al. carried out a study on 2509 staged II-III CRC and found that an elevation of CEA (> 5 ng/mL) either before or after treatment could predict an increased risk of recurrence as well as cancer-specific mortality and OS[37]. In addition, Beom et al. studied 2021 staged

I-III CRC with a normal preoperative CEA level (< 5 ng/mL) and demonstrated that a relatively high CEA (> 2.1 ng/mL) correlated with significantly poor disease-free survival (DFS) [27]. Interestingly, all these studies consistently indicated that a lower ALB or a relatively higher CEA could be associated with poor survival in patients, which could be partially interpreted as equal to a lower ACR in our study. Additionally, as indicated in previous studies, a lower ALB was more commonly found in cases with metastasis[10, 38] or large tumor diameter and advanced T stages [38–40]. The significant differences in invasive depth, tumor diameter and distant metastasis in the ACR-low and ACR-high subgroups in our study were also in line with these results to some extent.

Furthermore, serum albumin levels have long been regarded as a reflection of nutritional status in patients, and serum albumin metabolism could be significantly altered in the context of cancer. Except for those who underwent surgery that presented with a decreased synthesis rate of ALB [41], the generation of ALB could be purely suppressed by the activation of a series of inflammatory cytokines, including IL-1, IL-6 and TNFα, in cancer patients [18, 35, 42]. Notably, CEA was found to be positively associated with IL-6 [43, 44]. Based on these results, it was plausible that patients with a high preoperative CEA could have a low ALB (equal to a low ACR in our study) in CRC. Additionally, since a high CEA was produced by drug-resistant cancer cells in CRC[45], these patients were also likely to have a poor prognosis.

Notably, individual ALB or CEA was insufficient for their prognostic efficacy in CRC, particularly when compared with other markers. For example, in Li et al.'s study, the AUCs for PFS and OS of ALB were 0.644 and 0.611, respectively, and ALB alone was not an independent prognostic factor when compared to PLR[11]; similarly, Artaç M et al. studied 90 metastatic CRC patients treated with the bevacizumab plus FOLFIRI regimen and found that ALB was not a risk factor for PFS when compared with NLR[46]. For CEA, Björkman K et al. investigated 322 staged I-IV CRC and found that CA125 was superior to CEA in predicting disease-specific survival (DSS)[47]. In recent years, some authors have tried to combine ALB or CEA with other markers to further improve their prognostic efficacy. For ALB, Matsuoka et al. collected 133 stage III CRC and explored the prognostic value of pre- and postoperative CAR, which was found to be an independent prognostic factor for recurrence-free survival and OS, but its AUC was only 0.63 and was the highest of the assessed markers (NLR, PLR) [48]. Yamamoto et al. studied 523 staged I-IV CRC and combined ALB with cholinesterase as a new prognostic indicator. The results suggested that patients in both ALB and cholinesterase high groups would have a better DSS than others; however, the AUCs of the combined groups were not compared with individual ALB (0.71) and cholinesterase (0.69) in their study[22]. Some authors tried to combine CEA with Ki-67 [49], p53 [50], tumor budding [51], CD44v6 [52], peritoneal carcinomatosis index [53], D-dimer [54] and NLR[55] to generate new prognostic indicators, but these studies did not compare the AUC of the new indicators with individual CEA. In our study, we found that ACR displayed the largest AUC when compared with individual ALB, CEA and NLR, LMR, PLR both for PFS and OS, which supports its priority in prognosis prediction in CRC.

The present study has some limitations. First, it was retrospectively conducted at a single center, and the relatively small sample size may attenuate the statistical power and lead to biased findings. Second, other factors could also influence PFS and OS. For example, some of the patients, including those with

stage II disease with high recurrence or metastasis risks or those with stage III-IV disease, will accept subsequent therapies after surgery. Nonetheless, additional studies with increased cases could resolve these drawbacks and confirm the results of our study in the future.

Conclusion

Overall, our results indicated for the first time that ACR was a robust prognostic factor in CRC, and patients with a relatively low preoperative ACR had significantly worse survival.

Declarations

Conflict of interests

The authors have no conflicts of interest to declare.

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Figures

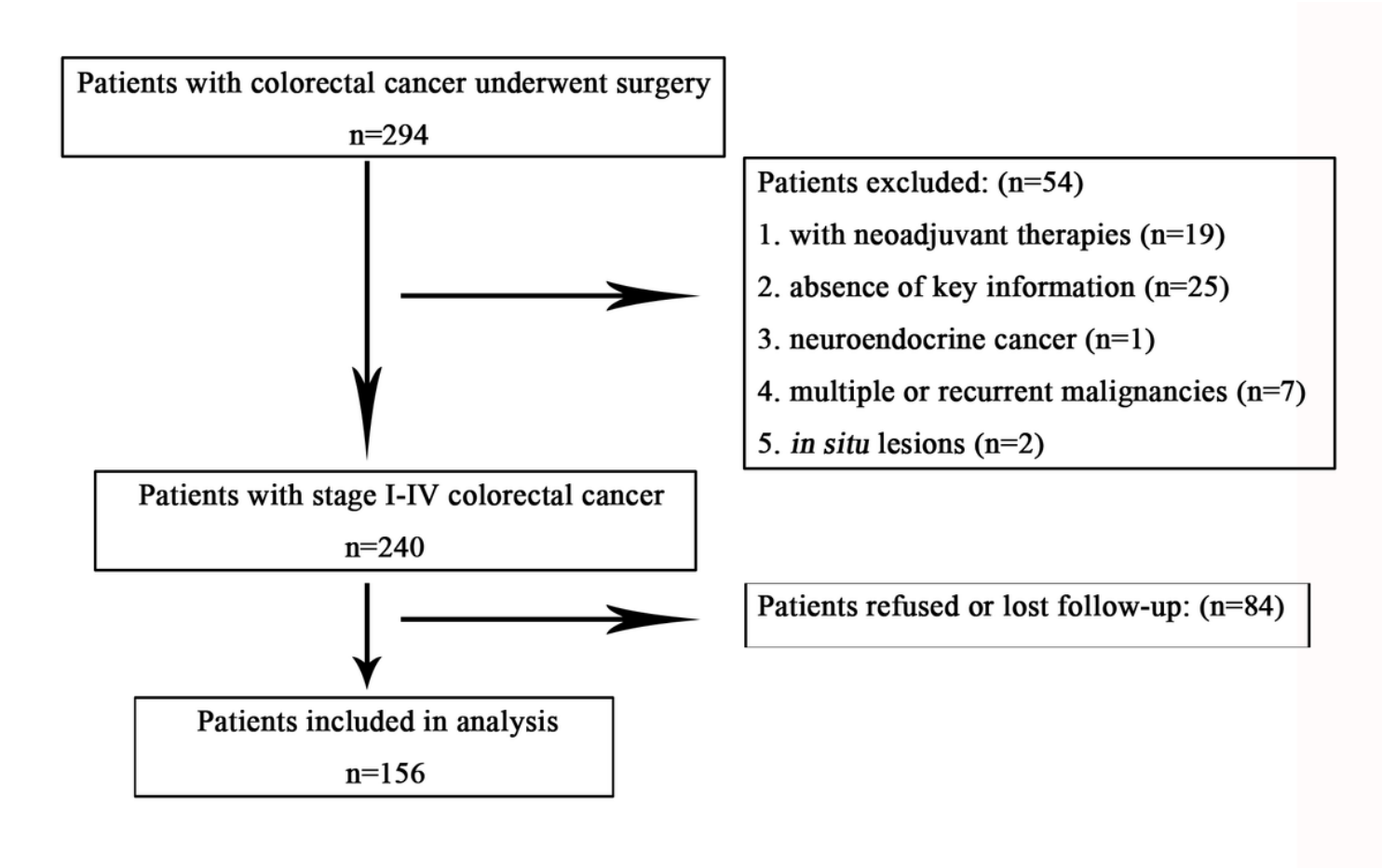

Figure 1

Flow diagram of the study.

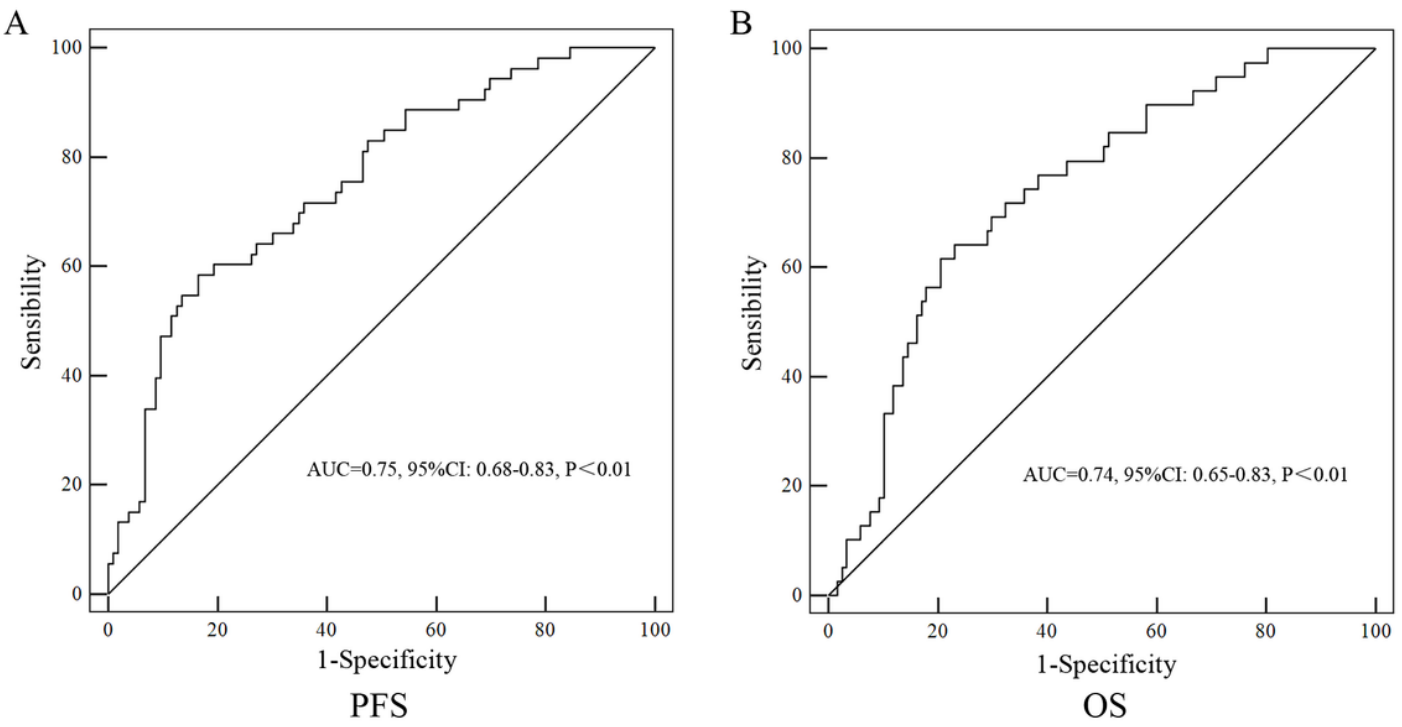

Figure 2

ROC tests of ACR for PFS and OS

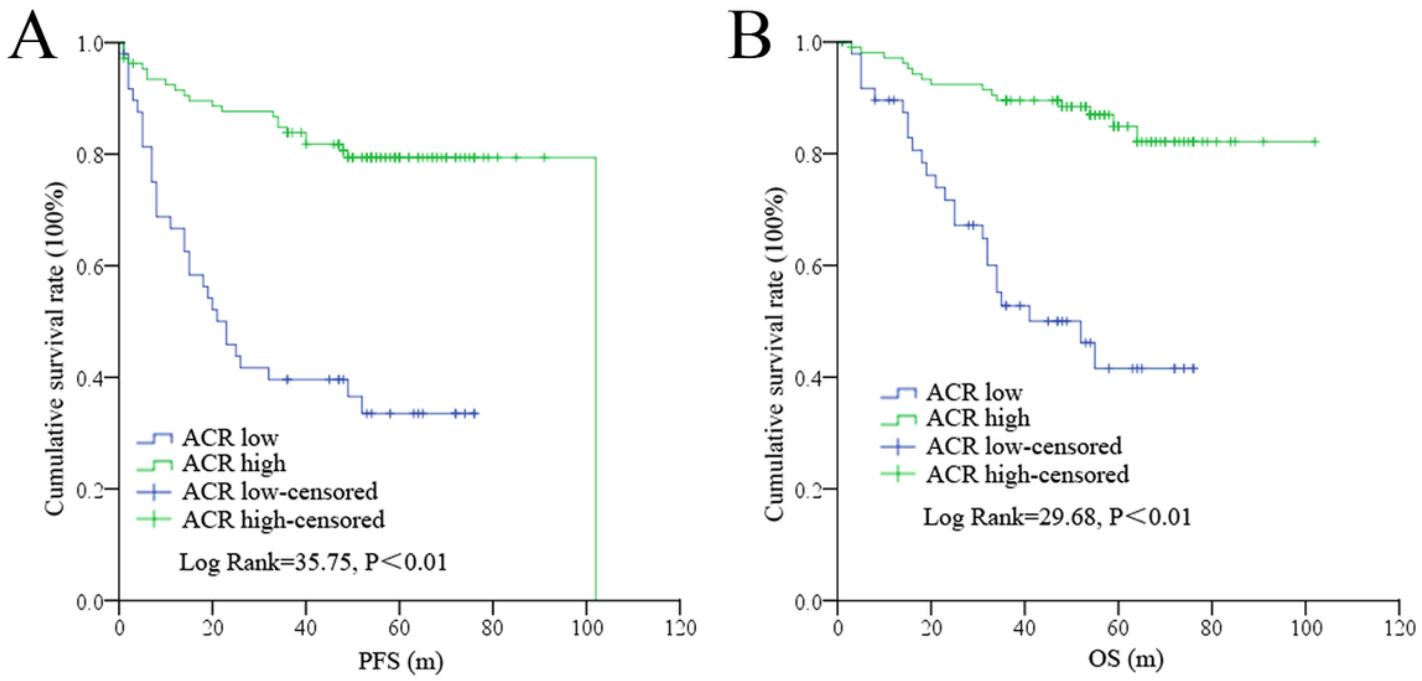

Figure 3

Impact of ACR-low or -high on PFS and OS in the patients.