Clinical significance and prognostic value of C-reactive protein/albumin ratio in gastric cancer

Yan-jun Fu
Guilin Medical University Affiliated Hospital
Ke-zhi Li
Guangxi Medical University Cancer Hospital
Xin-qiang Liang
Guagnxi Medical University Cancer Hospital
Zhi-qing Liang
Guilin Medical University Affiliated Hospital
Bai jihong (glmubai@163.com)
Guilin Medical University

Research

Keywords: gastric cancer, C-reactive protein/albumin ratio, preoperative, prognosis

Posted Date: February 7th, 2020

DOI: https://doi.org/10.21203/rs.2.22877/v1

Abstract

Background

C-reactive protein/albumin ratio (CAR) is a novel prognostic biomarker in several malignancies. This study was aimed to evaluate the clinical significance and prognostic value of CAR in patients with gastric cancer.

Methods

The data of 205 gastric cancer patients who underwent surgery was retrospectively reviewed. The association with the clinical features and prognostic value of CAR in gastric cancer was analyzed. The data of this study was combined with previous studies to further determine the prognostic value of CAR in patients with gastric cancer.

Results

Cox analysis revealed that preoperative CAR was an independent prognosis indicator in patients with gastric cancer. High expression of CAR indicated a shorter survival time than those with lower expression. CAR has a higher prognostic value in the 1-, 3-, 5-years of overall survival in patients with gastric cancer. However, CAR has no significant difference regarding the gastric cancer patients' age, gender and TNM stage. The discriminated value of CAR in TNM stage of gastric cancer was moderate. A meta-analysis by combining previous data and our data showed that preoperative CAR was significantly associated with the overall survival of patients with gastric cancer.

Conclusions

This study demonstrated that preoperative CAR was an independent prognostic indicator in the patients with gastric cancer who underwent surgery.

Introduction

As one of the most common digestive malignant tumors, gastric cancer accounts for about 8% of all cancers [1]. Although the survival of some patients with gastric cancer was improved with the advancement of the therapeutic methods, those patients at later stage of cancer remain have a poor prognosis [2]. Therefore, finding effective prognostic indicators for these patients could help the clinicians to make proper treatment decisions.

Currently, some serum tumor indicators, such as CA125, CA153, CA199, have been applied to assess the diagnostic and prognostic values in patients with gastric cancer, but these indicators were subject to low sensitivity and specificity[3, 4]. Besides, some novel indicators that calculated from conventional biomarkers, such as neutrophil lymphocyte ratio (NLR) [5], platelet lymphocytes ratio (PLR) [6] and C-reactive protein/albumin ratio (CAR)[7, 8] have been reported to enhance the prognostic values in patients with various cancers. Among these indicators, the clinical significance and prognostic value of CAR in gastric cancer remained need to further elucidate.

CAR is a novel inflammation-based prognostic indicators, high expression of CAR was associated with poor outcome in various diseases, including sepsis[9], pancreatitis[10], and various cancers[11]. The prognostic value of CAR in patients with gastric cancer has also been explored [12–14]. However, the robustness of previous studies still needed to validate by more studies. Therefore, in order to derive a more precise assessment of the prognostic value of CAR in gastric cancer, we analyzed the data of gastric cancer and combine our data with previous data, which may further verify the value of CAR in gastric cancer.

Materials And Methods

Selection of gastric cancer patients

The data of patients with gastric cancer who underwent surgery was retrospectively analyzed at the Guangxi Medical University Cancer Hospital between January 2015 and October 2019. Inclusion criteria: (1) diagnosis of gastric cancer was confirmed by histologically method; (2) all the gastric cancer patients underwent surgical treatment. Patients who with autoimmune diseases, infectious diseases, severe hematologic diseases, or major organ failure were excluded. This study was approved by the ethics committee of the Guangxi Medical University Cancer Hospital.

Data collection and calculation

The clinical features of gastric cancer were collected, including patient's age, gender, tumor location, differentiation degree, tumor node metastasis (TNM) stage, the TNM stage was defined based on the American Joint Committee on Cancer criteria, AJCC criteria 7th edition [15]. The preoperative laboratory blood parameters, such as CRP, albumin, neutrophil lymphocytes, platelet, and the tumor biomarkers (CEA, CA125, CA153 and CA199) were collected. The NLR, PLR and CAR were calculated. The overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up.

Statistical analysis

Mann-Whitney U-test or Student's t-test was used to compare continuous variables between two groups when appropriated. The χ^2 test was used for categorical variables between groups. Kaplan-Meier curve and Log-Rank test was used to evaluate the survival time between two groups. Cox regression analysis was employed to identify the prognostic indicators in patients with gastric cancer. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) was applied to assess the prognostic value of CAR. All statistical tests were two-sided, and p-values < 0.05 were considered as statistically significant. The statistical analyses were performed using SPSS software (version 21.0), and R language (version 3.5.1).

Meta-analysis for the data

The performance of meta-analysis for the prognostic value of CAR in gastric cancer was conducted as our previous study[16]. Briefly, the relevant articles were retrieval and assess from the databases based on the certain criteria, and the data of these articles was extracted. STATA software (version 12.0) was used to combine these data and our data.

Results

Clinical characteristics of the study populations

A total of 205 patients with gastric cancer who underwent surgery treatment were finally selected in this study. The median age of the patients was 58 years. The median follow-up was 44 (1–64) months. 124 patients were alive, 81 patients were dead during the follow-up period. The detailed of patients with gastric cancer were showed in Table 1.

Table 1
Clinical characteristic of the patients with gastric cancer

Variables	Value
Age	58(26–85)
Gender	
Female/ male	79/126
Tumor Location	
Antrum/ Body/ Cardiac/fundus	154/22/21/8
Differentiation	
High/ Low/ middle	5/128/72
T stage	
T1/ T2/ T3/ T4	12/36/26/131
N stage	
N0/ N1/ N2/ N3/ Nx	50/50/46/35/24
M stage	
M0/ M1/Mx	161/40/4
Clinical stage	
I/ II/ III/ IV	12/44/105/44
CRP	2.15(0.1–171)
hsCRP	0.79(0.02–13.53)
Albumin	40(1.16–64.7)
CEA	2.07(0.2–1000)
CA125	11.5(2.33–1104)
CA153	9.16(1.1-136.5)
CA199	11.27(0.58–1000)
NLR	2.01(0.05–63.99)
PLR	163.64(11.45–812.2)
CAR	0.05(0-4.33)

NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocytes ratio; CAR: C-reactive protein/albumin ratio; hsCRP: high sensitivity CRP

Univariate and multivariate Cox regression analysis for the clinical features

The univariate Cox regression analysis was performed by including the clinical features including patients' gender, age, histological grade, TNM stage, laboratory variables. The results showed that patients' age, Albumin, CEA, CA125, CA153, CA199, hsCRP, N stage, M stage, NLR, CAR were independent prognostic factors for the survival of patients with gastric

cancer. Then the multivariate Cox regression analysis for these variables showed that only Albumin, CA199, hsCRP, M stage and CAR were independent prognostic biomarkers for the survival in patients with gastric cancer (Table 2).

Table 2
Identify prognostic biomarkers for patients with gastric cancer using Cox analysis

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value		P-value
Age	1.02(1.00-1.04)	0.017	HR (95%CI)	
ALB	0.93(0.91–0.95)	< 0.001	0.93(0.89–0.98)	0.010
CEA	1.00(1.00-1.03)	< 0.001		
CA125	1.00(1.00-1.005)	< 0.001		
CA153	1.02(1.01–1.03)	< 0.001		
CA199	1.01(1.00-1.03)	< 0.001	1.00(1.00–1.00)	0.001
hsCRP	1.14(1.07–1.22)	< 0.001	1.24(1.08–1.44)	0.002
N stage	10.07(2.32–43.63)	0.002		
M stage	6.14(3.93–9.60)	< 0.001	3.34(1.91–5.84)	0.003
NLR	1.03(1.01–1.05)	0.005		
CAR	1.37(1.04–1.82)	< 0.001	1.43(1.04–1.97)	0.045

Survival analysis and prognostic value of CAR in patients with gastric cancer

Using the median value as cut-off, which was 0.022, the Kaplan-Meier curve and Log-Rank test showed that, gastric cancer patients with high expression of CAR has shorter survival time than those with low expression (Fig. 1A). We next determined the prognostic value of CAR in gastric cancer patients in different survival time, and found that CAR has a good performance in predicting the 1-, 2-, and 3-years of survival in patients with gastric cancer, with the AUC as 0.717, 0.705 and 0.698, respectively (Fig. 1B).

Association of CAR with the clinical features in gastric cancer

The association of CAR with the clinical features of gastric cancer, including patient's age, gender, histological grade, TNM stage, and clinical stage were analysis. However, no significant difference was found between the CAR with these clinical features ($P > 0.05$). Table 3.

Table 3
Association of CAR with the clinical features in gastric cancer

Gender	CAR value	P-value
Male	0.08(0.01–4.33)	0.507
Female	0.03(0.01–3.79)	
Age		
< 60 years	0.06(0.01–1.85)	0.475
≥ 60 years	0.05(0.01–4.33)	
T stage		
T1 + T2	0.04(0.01–4.33)	0.865
T3 + T4	0.07(0.01–3.79)	
N stage		
N0	0.04(0.01–4.33)	0.630
N1 + N2 + N3	0.06(0.01–3.79)	
M stage		
M0	0.05(0.01–4.33)	0.352
M1	0.09(0.01–1.85)	
Clinical stage		
I + II	0.04(0.01–4.33)	0.727
III + IV	0.08(0.01–3.79)	

Discrimination value of CAR in early or advance TNM stage of gastric cancer

To further evaluate the discriminated value of CAR in TNM stage of gastric cancer, the ROC method was used to calculate the AUC of CAR. As the results showed that, CAR could reach a moderate predictive value in the early T stage and M stage, with the AUC value as 0.624 and 0.649, respectively; but the discriminated in the early N stage was low, with the AUC value as 0. 544. See Fig. 2.

Meta-analysis for the prognostic value of CAR in gastric cancer

Seven studies[12–14, 17–20] with 1978 patients that evaluated the prognostic value of CAR in patients with gastric cancer were included the meta-analysis. The details of included studies were listed in Table 4. All the data of CAR in predicting the prognosis of patients was extracted from multivariant Cox regression. By combing these data with our data, we found that CAR was significantly associated with the survival of patients with gastric cancer (HR: 1.83, 95%CI: 1.58–2.12). The subgroup by dividing the cutoff value into < 0.1 or > 0.1 group showed that no significant difference between these two groups (P > 0.05). See Fig. 3. No publish bias was found across these studies (P > 0.05).

Table 4
Characteristics of included studies

First author	Year/country	Median age	Num. patients	HR (95%CI)	Design	Cut-off value	Treatment	Tumor stage	FU (month)
Kudou	2019/Japan	65	144	2.378(1.025–5.249)	R	0.10	surgery	I - IV	60
Liu	2013/China	59	455	1.626(1.191–2.219)	R	0.025	surgery	I - III	25
Toiyama	2016/Japan	67	384	2.21(1.19–4.11)	R	0.058	surgery	I - III	47.6
Mao	2017/China	59	337	1.78(1.20–2.65)	R	0.3778	surgery	I - IV	60
Toyokawa	2018/Japan	65	75	2.161(1.332–3.507)	R	0.03	surgery	II	120
Saito	2018/Japan	70	453	1.975(1.152–3.386)	R	0.0232	surgery	I - IV	61.9
Liu	2018/China	64.8	130	2.27(1.76–3.39)	R	0.44	surgery	I - IV	60
R: retrospective design; FU: follow up									

Discussion

Development and progression of cancer is a complicated process, and many factors have been showed to contribute to the gastric carcinogenesis. Among them, systemic inflammatory response and nutritional status are two important contributors[21]. Evidences showed that CAR was an important inflammation- based prognostic indicator that associated with various cancer survival outcomes[22, 23]. In the present study, we found that CAR was an independent prognostic indicator in patients with gastric cancer, which was in agreement with previous studies[12, 13, 20]. We also found that CAR has a higher prognostic value in predicting the 1-, 3-, 5- year survival of patients. However, inconsistent with previous studies[12, 14, 20], we failed to showed that CAR was associated with clinical features of gastric cancer, and the discriminated value for the early and advanced TNM stage was moderated, suggesting that the prognostic value of CAR might independent of the clinical features of gastric cancer.

Serum CRP is an acute-phase protein, and reported to be a sensitive prognostic indicator in a variety of inflammatory diseases and cancers [24, 25]. On the other hand, serum albumin levels is an indicator of body nutrition status, low albumin levels indicts a malnutrition status and often second to patients with gastrointestinal cancers, especially those at advanced stage [26, 27]. CAR is calculated based on both serum CRP and hypoalbuminemia, which is consider more reliable than single one in predicting the outcome of the malignancy[28]. Although other inflammation-based prognostic indicators, such as NLR and PLR, have been showed to associate with the prognosis in patients with gastric cancer, however, the present study failed to confirm the prognostic value of them by using multivariant Cox regression analysis. These results suggesting that these two indicators might not stable in predicting the survival of patients with gastric cancer compared with CAR.

The TNM stage is one of the most important criteria in predicting the prognosis of patients with many kinds of cancers, and many studies reported that the inflammation-based prognostic indicators, including NLR, PLR and CAR were associated with the TNM stage in gastric cancer. For example, Toiyama et al[14] reported that CAR was significantly higher in gastric cancer with lymph-node metastasis, poor differentiation. Liu et al[18] also observed that CAR was associated with the lymph-node metastasis and clinical stage of gastric cancer. The similar result was found in Mao et al[12] report. However, in the present

study, we failed to show the association with the clinical features, including the TNM stage, which was similar to the Saito et al[13] report, indicating that the change of CAR might be independent of the TNM stage. Moreover, our results showed that CAR has a moderate value in discriminating the early or advanced TNM stage, especially the T stage and M stage, which may help to identify the patients who at high-risk and give them proper treatment.

Like other studies, our results were based on the single center, which may subject to several limitations, in order to achieve a more robust conclusion, we conducted a meta-analysis by combing our data with previous studies. As showed from the meta-analysis, which including seven studies with larger gastric cancer patients, CAR was showed to be significantly associated with the survival of patients with gastric cancer, which further confirmed the prognostic value of CAR in patients with gastric cancer. Considering the simplicity, noninvasive, cheapness, and easy availability of CAR, it is of great significance to apply this indicator in the routine clinical setting.

However, we acknowledge several potential limitations in present study, which might undermine the robustness of the conclusion. First, our study was a retrospective design, single center study, which might lead to selection bias. Second, many factors affect the serum levels of CRP and albumin, but we could not adjust these confounding factors in this study. Third, the postoperative therapy was different across the patients, which might also induce bias. Therefore, future larger-scale study with prospective design by addressing the aforementioned issues is warranted to validate our findings.

Conclusions

The present study demonstrates that preoperative CAR is an independent prognostic indicator in patients with gastric cancer after surgery, which may help to provide proper treatment for patients.

Declarations

Author contributions

Study concept and design: BJH and LZQ; Collection and assembly of data: FYJ, LXQ and LKE; Data analysis and interpretation: FYJ, LKZ, LXQ and LZQ; Manuscript writing and review: All authors

Funding

This study was partially supported by research funding from the National Natural Science Foundation of China (No.81260078); Guangxi Natural Science Foundation Grant (2014GXNSFAA118152).

Availability of data and materials

All data analyzed during this study are included in this published article.

Approval and consent to participate

This study was approved by the ethics committee of the Guangxi Medical University Cancer Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F: **Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.** *Int J Cancer* 2015, **136:**E359-386.
2. Hundahl SA, Phillips JL, Menck HR: **The National Cancer Data Base Report on poor survival of U.S. gastric carcinoma patients treated with gastrectomy: Fifth Edition American Joint Committee on Cancer staging, proximal disease, and the "different disease" hypothesis.** *Cancer* 2000, **88:**921-932.
3. Tian SB, Yu JC, Kang WM, Ma ZQ, Ye X, Cao ZJ, Yan C: **Combined detection of CEA, CA 19-9, CA 242 and CA 50 in the diagnosis and prognosis of resectable gastric cancer.** *Asian Pac J Cancer Prev* 2014, **15:**6295-6300.
4. Feng F, Tian Y, Xu G, Liu Z, Liu S, Zheng G, Guo M, Lian X, Fan D, Zhang H: **Diagnostic and prognostic value of CEA, CA19-9, AFP and CA125 for early gastric cancer.** *BMC Cancer* 2017, **17:**737.
5. Mellor KL, Powell A, Lewis WG: **Systematic Review and Meta-Analysis of the Prognostic Significance of Neutrophil-Lymphocyte Ratio (NLR) After R0 Gastrectomy for Cancer.** *J Gastrointest Cancer* 2018, **49:**237-244.
6. Xu Z, Xu W, Cheng H, Shen W, Ying J, Cheng F: **The Prognostic Role of the Platelet-Lymphocytes Ratio in Gastric Cancer: A Meta-Analysis.** *PLoS One* 2016, **11:**e0163719.
7. Tanaka H, Tamura T, Toyokawa T, Muguruma K, Kubo N, Sakurai K, Ohira M: **C-reactive protein elevation ratio as an early predictor of postoperative severe complications after laparoscopic gastrectomy for gastric cancer: a retrospective study.** *BMC Surg* 2019, **19:**114.
8. Xu BB, Lu J, Zheng ZF, Xie JW, Wang JB, Lin JX, Chen QY, Cao LL, Lin M, Tu RH, et al: **The predictive value of the preoperative C-reactive protein-albumin ratio for early recurrence and chemotherapy benefit in patients with gastric cancer after radical gastrectomy: using randomized phase III trial data.** *Gastric Cancer* 2019, **22:**1016-1028.
9. Ranzani OT, Zampieri FG, Forte DN, Azevedo LC, Park M: **C-reactive protein/albumin ratio predicts 90-day mortality of septic patients.** *PLoS One* 2013, **8:**e59321.
10. Yilmaz EM, Kandemir A: **Significance of red blood cell distribution width and C-reactive protein/albumin levels in predicting prognosis of acute pancreatitis.** *Ulus Travma Acil Cerrahi Derg* 2018, **24:**528-531.
11. Wu J, Tan W, Chen L, Huang Z, Mai S: **Clinicopathologic and prognostic significance of C-reactive protein/albumin ratio in patients with solid tumors: an updated systemic review and meta-analysis.** *Oncotarget* 2018, **9:**13934-13947.
12. Mao M, Wei X, Sheng H, Chi P, Liu Y, Huang X, Xiang Y, Zhu Q, Xing S, Liu W: **C-reactive protein/albumin and neutrophil/lymphocyte ratios and their combination predict overall survival in patients with gastric cancer.** *Oncol Lett* 2017, **14:**7417-7424.
13. Saito H, Kono Y, Murakami Y, Shishido Y, Kuroda H, Matsunaga T, Fukumoto Y, Osaki T, Ashida K, Fujiwara Y: **Prognostic Significance of the Preoperative Ratio of C-Reactive Protein to Albumin and Neutrophil-Lymphocyte Ratio in Gastric Cancer Patients.** *World J Surg* 2018, **42:**1819-1825.
14. Toiyama Y, Shimura T, Yasuda H, Fujikawa H, Okita Y, Kobayashi M, Ohi M, Yoshiyama S, Hiro J, Araki T, et al: **Clinical Burden of C-Reactive Protein/Albumin Ratio Before Curative Surgery for Patients with Gastric Cancer.** *Anticancer Res* 2016, **36:**6491-6498.
15. Edge BS, Byrd D: **AJCC Cancer Staging Manual. 7th ed.** *New York: Springer* 2010.

16. Fu YJ, Li KZ, Bai JH, Liang ZQ: **C-reactive protein/albumin ratio is a prognostic indicator in Asians with pancreatic cancers: A meta-analysis.** *Medicine (Baltimore)* 2019, **98:**e18219.
17. Kudou K, Saeki H, Nakashima Y, Kamori T, Kawazoe T, Haruta Y, Fujimoto Y, Matsuoka H, Sasaki S, Jogo T, et al: **C-reactive protein/albumin ratio is a poor prognostic factor of esophagogastric junction and upper gastric cancer.** *J Gastroenterol Hepatol* 2019, **34:**355-363.
18. Liu X, Sun X, Liu J, Kong P, Chen S, Zhan Y, Xu D: **Preoperative C-Reactive Protein/Albumin Ratio Predicts Prognosis of Patients after Curative Resection for Gastric Cancer.** *Transl Oncol* 2015, **8:**339-345.
19. Toyokawa T, Muguruma K, Tamura T, Sakurai K, Amano R, Kubo N, Tanaka H, Yashiro M, Hirakawa K, Ohira M: **Comparison of the prognostic impact and combination of preoperative inflammation-based and/or nutritional markers in patients with stage II gastric cancer.** *Oncotarget* 2018, **9:**29351-29364.
20. Liu HC, Chen YJ, Xu YF, Xu ZH, Xu CY: **Effect of preoperative ratio of C reactive protein to albumin on prognosis of patients with gastric cancer.** *Chin J Lab Diagnose* 2018, **22:**27-29.
21. Abdi E, Latifi-Navid S, Zahri S, Yazdanbod A, Pourfarzi F: **Risk factors predisposing to cardia gastric adenocarcinoma: Insights and new perspectives.** *Cancer Med* 2019, **8:**6114-6126.
22. Liu Y, Chen S, Zheng C, Ding M, Zhang L, Wang L, Xie M, Zhou J: **The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer.** *BMC Cancer* 2017, **17:**285.
23. Uchimoto T, Komura K, Fujiwara Y, Saito K, Tanda N, Matsunaga T, Ichihashi A, Tsutsumi T, Tsujino T, Yoshikawa Y, et al: **Prognostic impact of C-reactive protein-albumin ratio for the lethality in castration-resistant prostate cancer.** *Med Oncol* 2019, **37:**9.
24. Chen IM, Johansen AZ, Dehlendorff C, Jensen BV, Bojesen SE, Pfeiffer P, Bjerregaard JK, Nielsen SE, Andersen F, Hollander NH, et al: **Prognostic value of combined detection of serum interleukin-6, YKL-40, and C-reactive protein in patients with unresectable pancreatic cancer.** *Cancer Epidemiol Biomarkers Prev* 2019.
25. Khedher S, Fouthaili N, Maoui A, Lahiani S, Salem M, Bouzid K: **The Diagnostic and Prognostic Values of C-Reactive Protein and Procalcitonin during Bacterial Infections in Decompensated Cirrhosis.** *Gastroenterol Res Pract* 2018, **2018:**5915947.
26. Takeda K, Umezawa R, Takahashi N, Matsushita H, Kozumi M, Ishikawa Y, Yamamoto T, Takeda K, Jingu K: **Impact of change in serum albumin level during and after chemoradiotherapy in patients with locally advanced esophageal cancer.** *Esophagus* 2018, **15:**190-197.
27. Lim WS, Roh JL, Kim SB, Choi SH, Nam SY, Kim SY: **Pretreatment albumin level predicts survival in head and neck squamous cell carcinoma.** *Laryngoscope* 2017, **127:**E437-E442.
28. Dupre A, Malik HZ: **Inflammation and cancer: What a surgical oncologist should know.** *Eur J Surg Oncol* 2018, **44:**566-570.

Figures

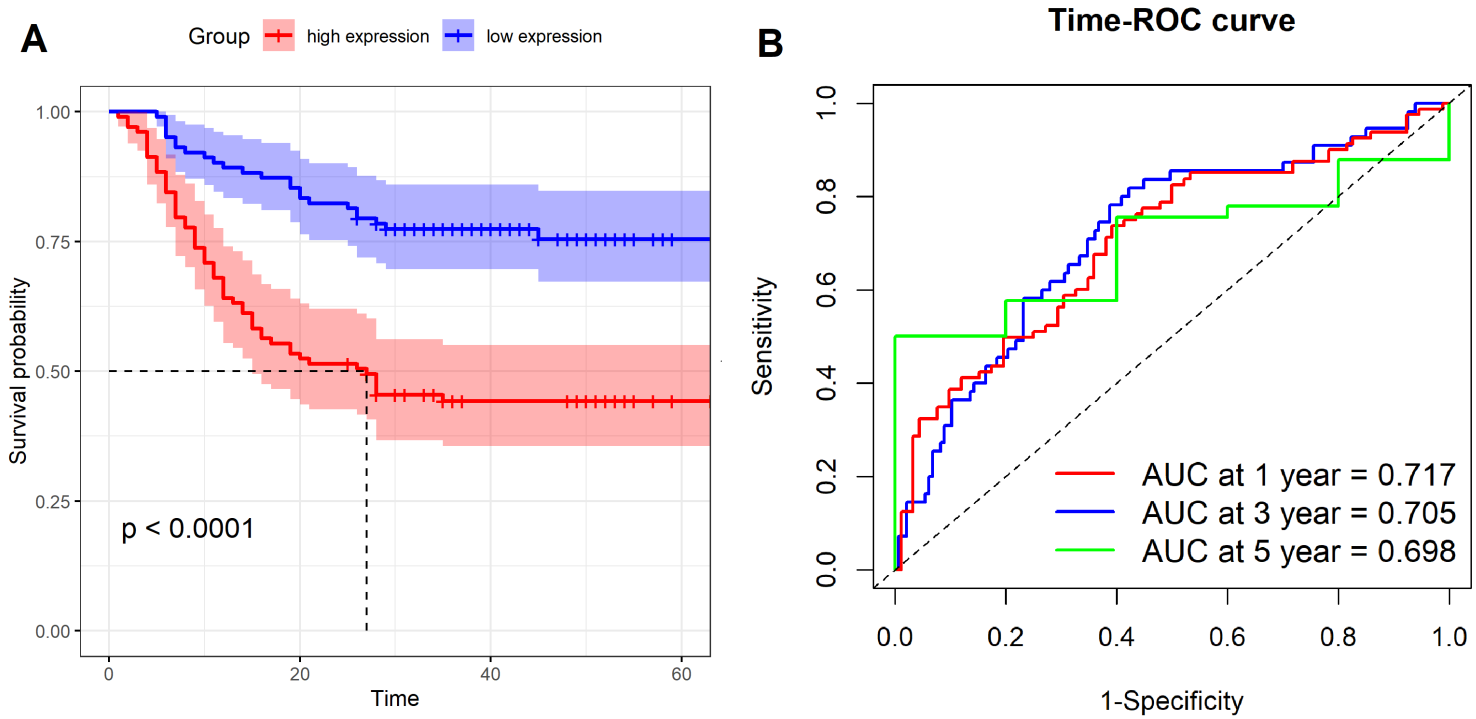

Figure 1

(A) Kaplan-Meier curve for the CAR in patients with gastric cancer using median value as cut-off; (B) The prognostic value of CAR in predicting the 1-, 2-, and 3-years of survival in patients with gastric cancer.

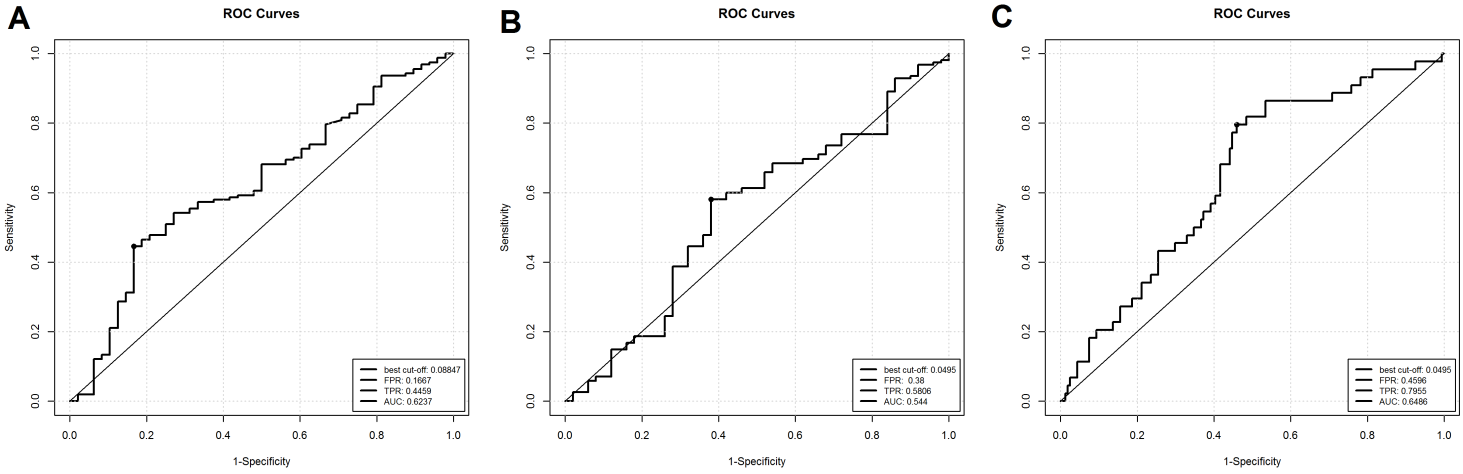

Figure 2

Discriminated value of CAR in early or advance TNM stage of gastric cancer. (A) T stage; (B) N stage; (C) M stage

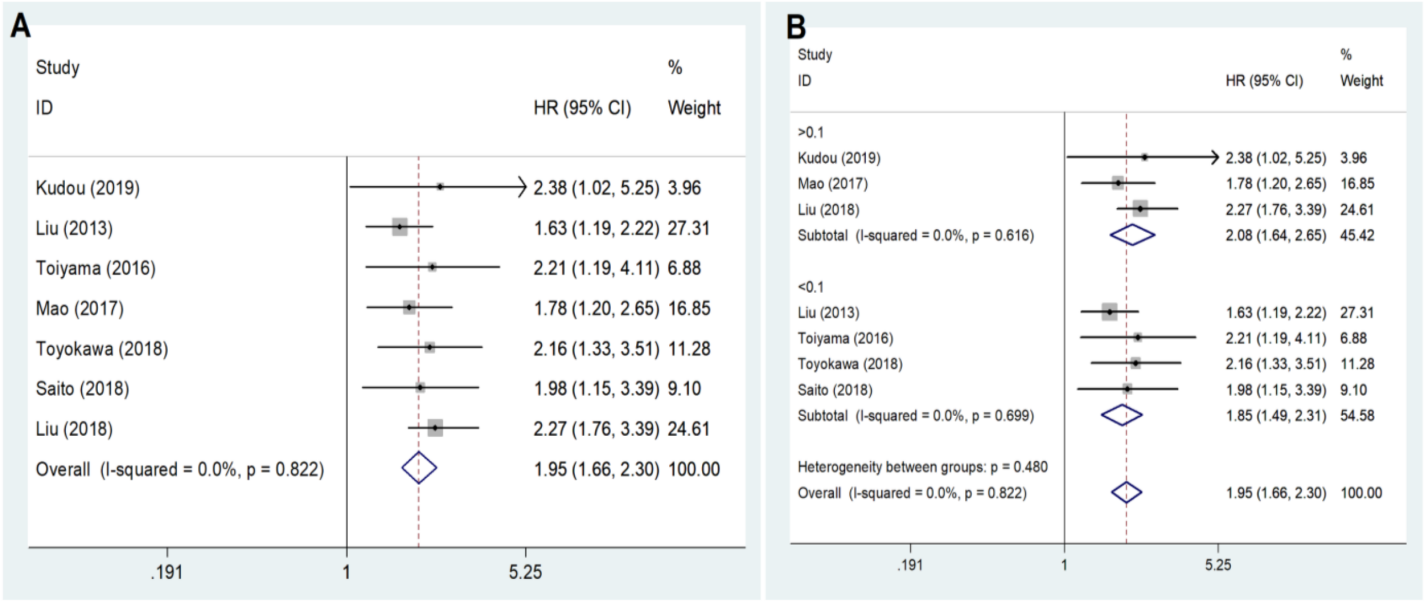

Figure 3

(A) Forest plot of hazard ratio (HR) for the association of CAR with overall survival (OS) in patients with gastric cancers; (B) Forest plot of HR for the association of CAR with OS in gastric cancers with different cutoff value.