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

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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 \( \chi^2 \) 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\(^\text{[16]}\). 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)          |
| 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)       |
| hsCRP                      | 0.79(0.02–13.53)       |
| 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               | HR (95%CI)         | P-value               |
| Age                 | 1.02(1.00-1.04)    | 0.017                 |                     |                       |
| 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.

| 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).

| 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 \cite{24, 25}. On the other hand, serum albumin levels is an indicator of body nutrition status, low albumin levels indicted a malnutrition status and often second to patients with gastrointestinal cancers, especially those at advanced stage \cite{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\cite{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 multivarient 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\cite{14} reported that CAR was significantly higher in gastric cancer with lymph-node metastasis, poor differentiation. Liu et al\cite{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\cite{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\cite{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

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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.

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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.