Prognostic value of pretreatment C-reactive protein/albumin ratio in nasopharyngeal carcinoma

A meta-analysis of published literature

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Abstract

**Background:** To explore the prognostic value of C-reactive protein/albumin ratio (CAR) in nasopharyngeal carcinoma (NPC), we conducted a comprehensive meta-analysis of relevant literature on the association between CAR and NPC outcome. In recent years, an increasing number of studies has been published analyzing the possible prognostic utility of C-reactive protein/albumin ratio (CAR) in nasopharyngeal carcinoma (NPC), but the results are still controversial.

**Methods:** A relevant literature search was performed by using the PubMed, Embase, Web of Science, Cochrane Library, CBM, Wanfang, VIP, and China National Knowledge Infrastructure databases to evaluate the prognostic value of CAR in patients with NPC. The last date of our primary search was December 5, 2017. This meta-analysis was conducted on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Pooled hazard ratio (HR) with 95% confidence interval (95% CI) was utilized to estimate the association of CAR and overall survival (OS) and distant metastasis-free survival (DMFS).

**Results:** Five studies that enrolled 5533 patients with NPC were finally quantified. Our findings revealed that high pretreatment CAR was significantly associated with poor OS (HR = 1.58, 95% CI = 1.36–1.83, P < .001) and DMFS (HR = 1.25, 95% CI = 1.09–1.44, P = .002). The findings from most subgroup meta-analyses were in line with those from the overall meta-analyses. No significant heterogeneity was observed among the included studies for OS and DMFS (P > .05); however, publication bias was found for OS (P < .05).

**Conclusion:** Our meta-analysis suggests that high pretreatment CAR indicates poor prognosis in NPC. Thus, pretreatment CAR serves as a prognostic marker in NPC and can be used to evaluate prognosis in clinical work.

**Abbreviations:** CAR = C-reactive protein/albumin ratio, CI = confidence interval, DMFS = distant metastasis-free survival, EBV = Epstein–Barr virus, GPS = Glasgow prognostic score, HA = human albumin, HR = hazard ratio, LDH = lactate dehydrogenase, NOS = Newcastle–Ottawa Scale, NPC = nasopharyngeal carcinoma, OS = overall survival.

**Keywords:** C-reactive protein/albumin ratio, meta-analysis, nasopharyngeal carcinoma, prognosis

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor arising from the nasopharyngeal epithelium.[1] There is a striking geographic and ethnic distribution of NPC, with high incidence in South China and East Asia. This phenomenon is not only related to the aggregation of NPC but also to genetic, dietary, and environmental factors, and Epstein–Barr virus (EBV) infection.[2–4] Radiation therapy is the preferred treatment method for NPC.[5] However, the long-term survival of most patients remains poor. To date, various biomarkers have been associated with the prognosis of NPC,[6–10] and these include lactate dehydrogenase (LDH), plasma EBV DNA, D-dimer, and inflammatory markers. However, these parameters do not provide sufficiently precise predictions of prognosis. Therefore, it remains important to identify accurate and easy-to-use biomarkers for NPC.

Previous research has reported that nutritional and immunological conditions are associated with postoperative prognosis, overall survival (OS), and disease-free survival of patients with NPC.[11,12] C-reactive protein (CRP) is a nonspecific, acute phase marker of inflammation that has been associated with poorer survival in numerous solid malignancies.[13–15] Albumin is the main substance that maintains the body’s nutrition. Hypoalbuminemia has been proved to be an independent predictor of poor survival in several types of cancers, including NPC.[16,17] Recently, the CRP/albumin ratio (CAR), a novel inflammation-based prognostic score, was reported as an independent prognostic marker for OS in several types of cancer.
as esophageal, gastric, pancreatic, and lung cancers. This report demonstrates that high CAR is associated with poor survival in patients with the aforementioned cancers. However, due to insufficient data on the relationship between CAR levels and risk of NPC, the prognostic role of CAR levels in patients with NPC remains unclear. Therefore, in this study, we evaluated this study of NPC, the prognostic role of CAR levels in patients with NPC following search terms:

2. Methods

2.1. Search strategy and eligibility criteria

This meta-analysis was carried out in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We systematically searched online databases, including PubMed, Embase, Web of Science, Cochrane Library, CBM, Wanfang, VIP, and China National Knowledge Infrastructure, to identify correlative studies published before October 15, 2017. Potentially interrelated reviews and Meta-Analyses statement. We systematically guidelines of the Preferred Reporting Items for Systematic

2.2. Data extraction and quality assessment

The following relevant parameters were extracted and summarized independently by 2 reviewers (XD Y and MT L) according to the prespecified selection criteria: first author, year of publication, sample size, sex, median age, cancer stage, treatment method, cutoff value of CAR, HR, and corresponding 95% CI for OS and/or DMFS, and Newcastle–Ottawa Scale (NOS) scores. Outcomes from multivariate analyses were superior to those from univariate analyses for inclusion, where both were presented. Quality was assessed by using the NOS, and studies with scores of 6 or higher were defined as high-quality studies. No ethical approval and consent from patients are required, as all analyses were based on previous published studies.

2.3. Statistical analysis

RevMan 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Stata 14.0 (Stata Statistical Software: Release 14; STATA Corp, College Station, TX) were utilized to conduct the meta-analysis. Data on the predictive ability of high CAR for OS rate were combined across studies by using fixed and random effects models for the synthesis of HR. A combined HR >1 with nonoverlapping 95% CI was considered indicative of a significant positive association with a diminished OS or DMFS. P < .05 was required for the overall HR to be considered significant. Between-study heterogeneity was explored by using Cochrane Q and I² tests. A fixed effects model was used in the absence of significant heterogeneity (I² < 50%); otherwise, a random effects model was utilized. Subgroup analyses for OS were conducted according to predefined parameters: outcome, sample size, and cut-off value of CAR. The comparison between subgroups was tested with the Q-test for heterogeneity. Publication bias of reports was assessed by using a funnel plot. Sensitivity analysis was performed by sequential omission of each individual study. Meta-regression analysis was not conducted due to the limited number of studies. This analysis is best suited to analyzing a minimum of 10 studies. All statistical tests were 2-sided, and statistical significance was defined by a P < .05.

3. Results

3.1. Search results and characteristics of included studies

By searching the aforementioned databases, 60 potentially relevant articles were identified. On the basis of the inclusion criteria, 5 eligible studies were finally enrolled in the current meta-analysis (Fig. 1). The predominant characteristics of the 5 eligible studies are summarized in Table 1. A total of 5533 patients were enrolled, ranging from 148 to 1572 patients per study (median 895). All studies were published after 2016. The outcomes analyzed in these studies were OS in 5 studies and DMFS in 2 studies. The CI differences of these 5 studies ranged from 0.54 to 2.37. The cutoff values of these studies varied from 0.037 to 0.189. The cutoff value of 1 study was not given in 1 study. All 5 studies were conducted in China and used a retrospective design. Two reviewers assessed the quality of the included studies, and the average NOS scores for both was 8. All included studies were defined as “good quality.”

3.2. Prognostic value of OS in patients with NPC

Five studies comprising 5533 patients provided HRs for OS between CAR and patients with NPC. The pooled results showed that high pretreatment CAR was significantly associated with poor OS (HR = 1.58, 95% CI = 1.36–1.83, P < .001) in patients with NPC, and no significant heterogeneity was observed between studies (I² = 28.1%, P heterogeneity = .234; Fig. 2). Considering the possible confounders, including CAR cut-off values and sample size, subgroup analyses were conducted to
identify parameters that were potentially related to OS in patients with NPC. In the subgroup of CAR cutoff values found by merging 3 studies with cutoff values < 0.1, high pretreatment CAR was significantly associated with poor OS (HR = 1.51, 95% CI = 1.28–1.77, \( P < .001 \), fixed-effects model; \( I^2 = 39.5\% \)). The same outcome was also shown in a meta-analysis of studies with cutoff values ≥ 0.1 (HR = 2.03, 95% CI = 1.40–2.93, \( P < .001 \), fixed-effects model; \( I^2 = 0.0\% \)), indicating that CAR was a reliable prognostic biomarker for OS in patients with NPC. Furthermore, stratifications by sample size (≥500 or < 500) showed that differences in sample size did not influence the relation between CAR and OS (both \( P < .001 \)), suggesting that CAR is a reliable prognostic value for NPC outcomes, regardless of sample size (Table 2).

3.3. Prognostic value of DMFS in patients with NPC

In total, 3 studies that enrolled 4475 patients assessed the prognostic effect of high pretreatment CAR on DMFS. The combined data showed that high pretreatment CAR was significantly associated with poor DMFS (HR = 1.25, 95% CI = 1.09–1.44, \( P = .002 \)) in patients with NPC, and this pooled result was stable, in that no significant heterogeneity was observed between studies (\( I^2 = 52.7\% \), \( P_{\text{heterogeneity}} = .146 \), Table 2).

3.4. Test for publication bias and analysis of sensitivity

A funnel plot for OS showed apparent asymmetry, indicating that significant publication bias existed (\( P = .015 \), Fig. 3).

In order to assess the stability of the results of the current meta-analysis, we performed a sensitivity analysis in which 1 study at a time was excluded. The sensitivity analysis showed that no single study affected the pooled HRs in the present meta-analysis (Fig. 4), suggesting the general stability of our meta-analysis.

4. Discussion

NPC is a malignant nasopharyngeal, mucosal epithelial tumor, which is also called the “Canton tumor,” because of its high...
incidence in South China. The World Health Organization classifies NPC into 3 types: nonkeratinizing, keratinizing, and basaloid squamous cell carcinoma. Radiotherapy is the preferred method of treatment for NPC. However, for patients with more highly differentiated carcinoma, with a later course of disease and recurrence after radiotherapy, surgical resection and chemotherapy are also indispensable treatments. Local recurrence and distant metastasis of NPC after radiotherapy are the main causes of death from this disease. Risk factors for NPC consist of EBV infection, intake of salt-preserved fish, smoking, chronic sinonasal tract inflammation, several types of human leukocyte antigens, and genetic variations. The prognosis of NPC is associated with EBV, neutrophil-to-lymphocyte ratio, LDH, vascular endothelial growth factor, endothelin-1, and hemoglobin. However, few of these parameters can be applied easily and/or precisely in clinical practice. Therefore, it remains urgent to identify accurate and easy-to-use biomarkers for NPC.

Accumulating evidence has demonstrated that inflammation plays a critical role in the pathogenesis of tumors, and that proinflammatory tumor microenvironments are closely related to cancer development and progression. CRP is an acute phase protein that is mainly produced in the liver and has been proved to be an independent predictor of poor survival in many malignancies, such as hepatocellular carcinoma, upper urinary tract urothelial carcinoma, and colorectal cancer. Albumin is an important indicator reflecting the patients’ nutritional status and has been used for prognostic assessment of patients with ovarian cancer, advanced hepatobiliary cancer, and NPC. The CAR was initially used to assess the outcome of patients with acute medical admissions and sepsis. Moreover, previous studies have demonstrated that CAR is superior prognostically for various cancers than are the established inflammation-based prognostic indices Glasgow prognostic score (GPS), modified GPS, and prognostic nutritional index. Given that there are no published articles published concerning CAR’s role in NPC, we conducted this meta-analysis to explore the association between CAR and NPC prognosis.

The current meta-analysis consists of 5 articles containing records of 5533 patients with NPC. The combined HR for OS showed significantly poor OS when it was associated with high pretreatment CAR, which was similar to results obtained in the DMFS analyses. Moreover, no significant heterogeneity was observed across the studies, indicating that these results were consistent.

**Table 2**

| Subgroup             | No. of studies | No. of patients | HR     | 95% CI      | P for HR | Q     | P (heterogeneity) | I² (%) |
|----------------------|----------------|-----------------|--------|-------------|----------|-------|-------------------|--------|
| Outcome              |                |                 |        |             |          |       |                   |        |
| OS                   | 5              | 5533            | 1.58   | 1.36–1.83   | <.001    | 5.57  | .234              | 26.1   |
| DMFS                 | 2              | 4257            | 1.25   | 1.09–1.44   | .002     | 2.11  | .146              | 52.7   |
| Sample size          |                |                 |        |             |          |       |                   |        |
| <500                 | 2              | 557             | 1.98   | 1.35–2.90   | <.001    | 0.99  | .769              | 0.0    |
| ≥500                 | 3              | 4976            | 1.52   | 1.29–1.78   | <.001    | 3.93  | .140              | 49.1   |
| Cut-off value of CAR |                |                 |        |             |          |       |                   |        |
| <0.1                 | 3              | 4666            | 1.51   | 1.28–1.77   | <.001    | 2.62  | .269              | 39.5   |
| ≥0.1                 | 2              | 867             | 2.03   | 1.40–2.93   | <.001    | 0.16  | .686              | 0.0    |

95% CI = 95% confidence interval, CAR = C-reactive protein/albumin ratio, DMFS = distant metastasis-free survival, HR = hazard ratio, No. = number, OS = overall survival.
moderate. We also performed subgroup analyses stratified by outcome, sample size, and CAR cutoff value. Notably, the results of the subgroup analyses that had been stratified by outcome and sample size were in agreement with the results of our overall analyses, which further verifies the prognostic value of CAR for predicting survival in patients with NPC. In subgroup analyses of CAR, we found that CAR cutoff values did not have any substantial effects on the association between CAR and OS, indicating that CAR is a reliable biomarker for the prognosis of NPC.

Some limitations of this meta-analysis should be considered. First, a small number of studies were included, especially in the subgroup analyses, which, therefore, may not provide sufficient power to estimate the association between CAR and risk of NPC. Second, the cutoff values for CAR were diverse among individual studies, which could have caused heterogeneity. Third, all patients included in the studies were Chinese; thus, patients from other regions were not considered. Finally, although significant publication bias was detected in our study, our overall results were not affected, indicating that the prognostic effect of CAR on NPC is reliable.

Apart from the above limitations, this study has a special advantage, that is, to the best of our knowledge, it is the first meta-analysis that evaluated the association between pretreat-

**Figure 3.** Funnel plots providing a graphic estimate of bias for overall studies. Each point represents a separate study. The 2 sloping lines represent 95% confidence interval.

**Figure 4.** Sensitivity analysis of the influence of each individual study on the pooled HRs by omitting individual studies. The middle vertical line indicates the combined HR, and the other 2 vertical lines represent the corresponding 95% confidence intervals. The middle small circle and 2 ends of the dotted lines indicate pooled HR and 95% confidence intervals, respectively, when the corresponding study listed on the left was omitted during each round of analysis.
ment CAR and survival status in patients with NPC. Our results reveal that high pretreatment CAR is associated with diminished OS and DMFS in these patients. However, our data should be interpreted with caution because the sample size was small. Therefore, further investigations of CAR inhibitions will provide a new prospect for clinical practice.

5. Conclusion

Our meta-analysis suggests that high pretreatment CAR can be a valuable prognostic biomarker for outcomes in patients with NPC. However, our findings need to be interpreted cautiously because of the aforementioned limitations. To strengthen our findings, prospective studies are needed to validate the relationship between pretreatment CAR and survival outcome of patients with NPC.

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