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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,[18] such

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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 all eligible published reports to quantify the prognostic value of CAR in patients with NPC.

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 studies were identified using various combinations of the following search terms: "C-reactive protein/albumin ratio," "C-reactive protein albumin ratio," "CRP/Alb ratio," and "nasopharyngeal," "nasopharynx," "cancer," "tumor," "malignancy," or "carcinoma." The detailed search strategy used in PubMed was as follows: ((((C-reactive protein/Albumin ratio [Title/Abstract]) OR C-reactive protein Albumin ratio[Title/Abstract]) OR CRP/Alb ratio[Title/Abstract])) and (((((nasopharyngeal[Title/Abstract]) OR nasopharynx[Title/Abstract]) OR cancer[Title/Abstract]) OR carcinoma[Title/Abstract]) OR tumor [Title/Abstract]) OR malignancy[Title/Abstract]. The titles, abstracts, full texts, and reference lists of the retrieved articles were carefully reviewed to identify additional eligible studies. No additional restrictions were applied to the searches with regard to region or language. In addition, we traced the unpublished data through a search in Google and Baidu; however, no additional studies were found to be appropriate for inclusion.

Eligible studies met the following criteria: patients were pathologically diagnosed with NPC; there was a focus on the association between CAR and patients with NPC; and hazard ratios (HRs) describing the association between CAR and survival outcomes OS and/or distant metastasis-free survival (DMFS) were available or obtainable from other information presented.

The exclusion criteria were as follows: nonhuman experiments; review articles, letters, case reports, editorials or comments, and conference abstracts; duplicate publications; insufficient data for estimating HRs and 95% confidence intervals (95% CIs), and full text unavailability. Study selection was performed by 2 investigators independently according to the inclusion and exclusion criteria by screening the title, abstract, and full text. Any disagreement was resolved by consensus.

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.[19] 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.[20] Between-study heterogeneity was explored by using Cochrane Q and I^2 tests. A fixed effects model was used in the absence of significant heterogeneity ($I^2 < 50\%$); 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).[21–25] 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[21–25] and DMFS in 2 studies.[22,25] The CI differences of these 5 studies ranged from 0.54 to 2.37.[21–25] The cutoff values of these studies varied from 0.037 to 0.189. The cutoff value of 1 study was derived by using Cutoff Finder.[21] The receiver operating characteristic curve was used to determine the cutoff value for CAR in 3 studies.[22,23,25] The source of the CAR cutoff value was not given in 1 study.[24] 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 ($I^2 = 28.1\%$, P heterogeneity = .234; Fig. 2).

Considering the possible confounders, including CAR cut-off values and sample size, subgroup analyses were conducted to

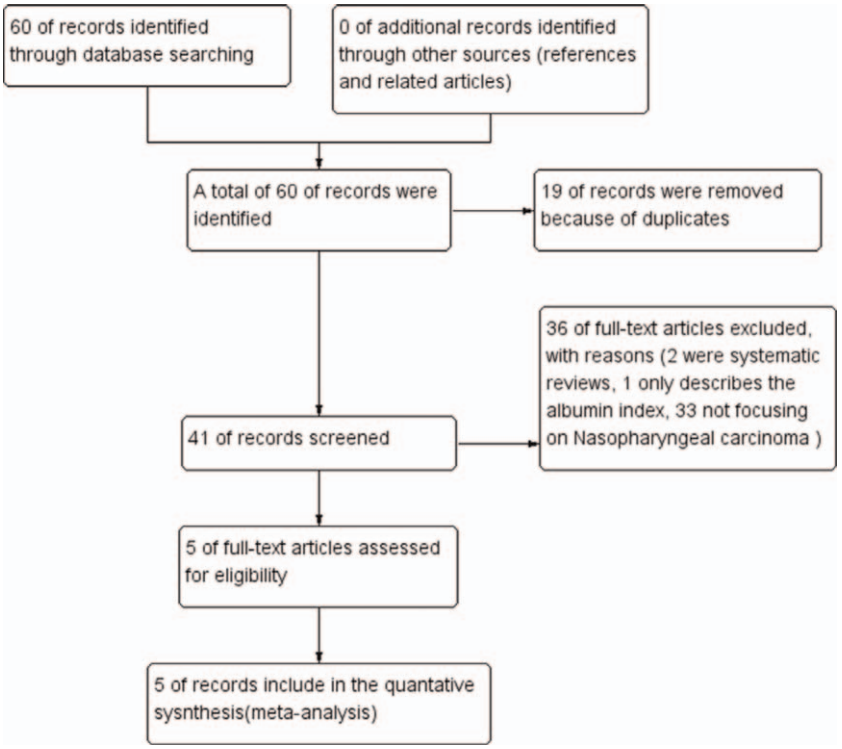

Figure 1. Flow diagram of the study selection process.

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 inpatients 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 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

Table 1

Main characteristics of the included studies.

First author	Year	Area	Sample size	Male: Female	Median age	Cancer stage	Treatment	Cut-off value resource	Cut-off value for CAR	Study end points	NOS
Sun et al[21]	2017	China	148	124/24	45 (24–72)	I–IV (NA)	Chemotherapy	Cutoff Finder	0.189	OS	8
He et al[22]	2016	China	2685	2535/150	NR	I–III (NA)	Radiotherapy/ IMRT	Roc	0.064	OS /DMFS	8
Tao et al[23]	2016	China	719	495 /224	48 (14–81)	I–IV (AJCC)	Radiotherapy/ chemotherapy	Roc	0.141	OS	8
Li et al[24]	2016	China	409	288/121	45 (18–77)	I–IV (AJCC)	Radiotherapy/ chemotherapy	Unknown	0.037	OS	8
Zhang et al[25]	2016	China	1572	1172/400	45 (14–78)	I–IV (AJCC)	IMRT	Roc	0.05	OS /DMFS/DFS	8

AJCC = American Joint Committee on Cancer, CAR = C-reactive protein/albumin ratio, DFS = disease free survival, DMFS = distant metastasis-free survival, IMRT = intensity-modulated radiation therapy, NA = not available, NOS = Newcastle–Ottawa Scale scores, NR = not reported, OS = overall survival, Roc = receiver operating characteristic curve.

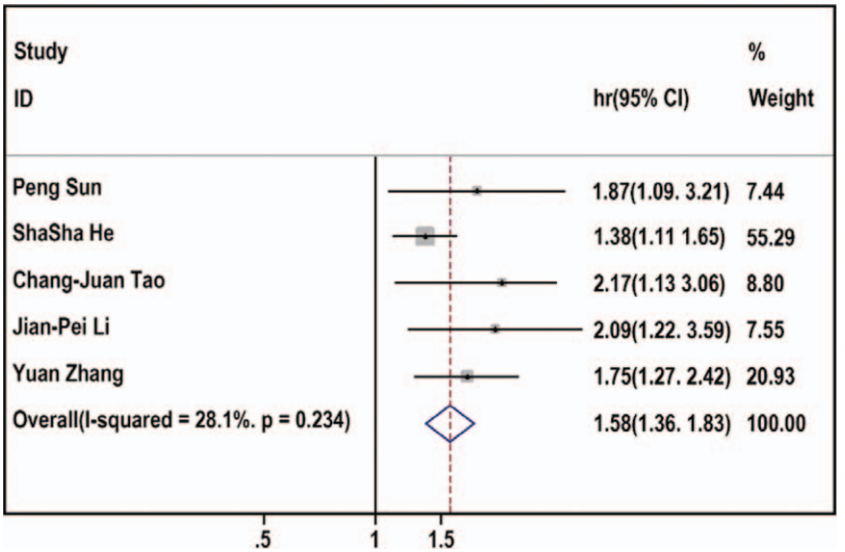

Figure 2. A forest plot of the association between CAR and OS in patients with NPC. *P* values are based on the Cochrane Q test for heterogeneity. The squares represent HRs for each study. The sizes of the squares and horizontal lines crossing the squares represent the weights of included studies in the meta-analysis and 95% confidence intervals, respectively. The blue hollow diamond gives the pooled HR from the fixed effects model; The center of this diamond denotes the HR, and the extremities denote the 95% confidence interval. CAR = C-reactive protein/albumin ratio, HR = hazard ratio, OS = overall survival.

incidence in South China. The World Health Organization classifies NPC into 3 types: nonkeratinizing, keratinizing, and basaloid squamous cell carcinoma.[26] 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.[27] The prognosis of NPC is associated with EBV, neutrophil-to-lymphocyte ratio, LDH, vascular endothelial growth factor, endothelin-1, and hemoglobin.[28–33] 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.[34,35] CRP is an acute phase protein that is mainly produced in the liver,[36] 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.[36–38] 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.[16,39,40] The CAR was initially used to assess the outcome of patients with acute medical admissions and sepsis.[41,42] 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.[43] 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

Table 2

Effect of CAR on nasopharyngeal carcinoma in different subgroups.

Subgroup	No. of studies	No. of patients	HR	95% CI	*P* for HR	*Q*	*P* (heterogeneity)	I^2 (%)
Outcome						4.99	.025	
OS	5	5533	1.58	1.36–1.83	<.001	5.57	.234	28.1
DMFS	2	4257	1.25	1.09–1.44	.002	2.11	.146	52.7
Sample size						1.55	.213	
<500	2	557	1.98	1.35–2.90	<.001	0.09	.769	0.0
≥500	3	4976	1.52	1.29–1.78	<.001	3.93	.140	49.1
Cut-off value of CAR						2.10	.147	
<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.

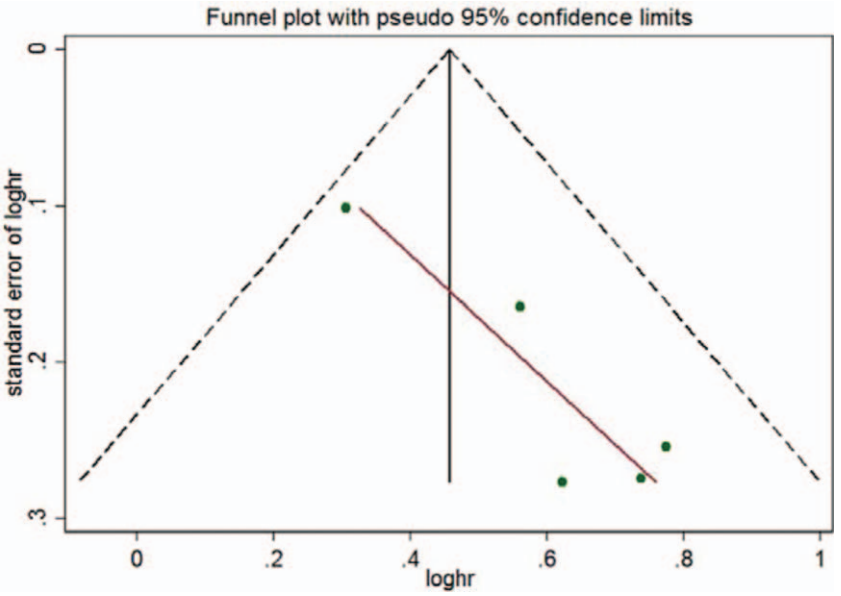

Figure 3. Funnel plots providing a graphic estimate of bias for overall studies. Each point represents a separate study. The 2 sloping lines represent 95% confidence interval.

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-

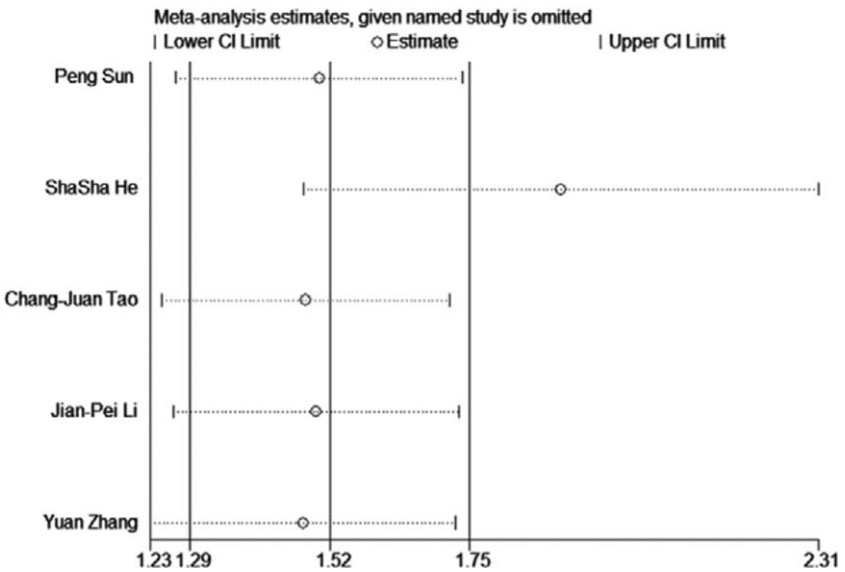

Figure 4. Sensitivity analysis of the influence of each individual study on the pooled HRs by omitting individual studies. The middle vertical line indicates the combined HR, and the other 2 vertical lines represent the corresponding 95% confidence intervals. The middle small circle and 2 ends of the 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.

Author contributions

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Writing – review & editing: Hongjian Liu, Minfu He, Xiumin Zhang.

References

[1] Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 2005;365:2041–54.
[2] Jia WH, Qin HD. Non-viral environmental risk factors for nasopharyngeal carcinoma: a systematic review. Semin Cancer Biol 2012;22: 117–26.
[3] Hildesheim A, Wang CP. Genetic predisposition factors and nasopharyngeal carcinoma risk: a review of epidemiological association studies, 2000-2011: Rosetta Stone for NPC: genetics, viral infection, and other environmental factors. Semin Cancer Biol 2012;22:107–16.
[4] Su CK, Wang CC. Prognostic value of Chinese race in nasopharyngeal cancer. Int J Radiat Oncol Biol Phys 2002;54:752–8.
[5] Chen W-S, Li J-J, Hong L, et al. Comparison of MRI, CT and 18F-FDG PET/CT in the diagnosis of local and metastatic of nasopharyngeal carcinomas: an updated meta analysis of clinical studies. Am J Transl Res 2016;8:4532–47.
[6] Wang WY, Twu CW, Chen HH, et al. Long-term survival analysis of nasopharyngeal carcinoma by plasma Epstein-Barr virus DNA levels. Cancer 2013;119:963–70.
[7] Chen WH, Tang LQ, Wang FW, et al. Elevated levels of plasma D-dimer predict a worse outcome in patients with nasopharyngeal carcinoma. BMC Cancer 2014;14:583.
[8] Zhou GQ, Tang LL, Mao YP, et al. Baseline serum lactate dehydrogenase levels for patients treated with intensity-modulated radiotherapy for nasopharyngeal carcinoma: a predictor of poor prognosis and subsequent liver metastasis. Int J Radiat Oncol Biol Phys 2012;82:e359–65.
[9] Li JP, Chen SL, Liu XM, et al. A novel inflammation-based stage (I Stage) predicts overall survival of patients with nasopharyngeal carcinoma. Int J Mol Sci 2016;17:pii: E1900.
[10] Li XH, Chang H, Xu BQ, et al. An inflammatory biomarker-based nomogram to predict prognosis of patients with nasopharyngeal carcinoma: an analysis of a prospective study. Cancer Med 2016; 6:310–9.
[11] Zhang W, Ye B, Liang W, et al. Preoperative prognostic nutritional index is a powerful predictor of prognosis in patients with stage III ovarian cancer. Sci Rep 2017;7:9548.
[12] Yang L, Xia L, Wang Y, et al. Low Prognostic Nutritional Index (PNI) predicts unfavorable distant metastasis-free survival in nasopharyngeal carcinoma: a propensity score-matched analysis. PLoS One 2016;11: e158853.
[13] Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011;48:155–70.
[14] Kinoshita A, Onoda H, Imai N, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol 2015;22:803–10.
[15] McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 2013;39:534–40.
[16] Du XJ, Tang LL, Mao YP, et al. The pretreatment albumin to globulin ratio has predictive value for long-term mortality in nasopharyngeal carcinoma. PLoS One 2014;9:e94473.
[17] McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Curr Opin Clin Nutr Metab Care 2009;12:223–6.
[18] Xu H, Ma Y, Deng F, et al. The prognostic value of C-reactive protein/albumin ratio in human malignancies: an updated meta-analysis. Onco Targets Ther 2017;10:3059–70.
[19] Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Metaanalyses. Appl Eng Agric 2012;18:727–34.
[20] Knosel T, Chen Y, Hotovy S, et al. Loss of desmocollin 1-3 and homeobox genes PITX1and CDX2 are associated with tumor progression and survival in colorectal carcinoma. Int J Colorectal Dis 2012; 27:1391–9.
[21] Sun P, Chen C, Xia Y, et al. The ratio of C-reactive protein/albumin is a novel inflammatory predictor of overall survival in cisplatin-based treated patients with metastatic nasopharyngeal carcinoma. Dis Markers 2017;2017:6570808.
[22] He S, Wang Y, Chen H, et al. C-reactive protein/albumin ratio (CAR) as a prognostic factor in patients with non-metastatic nasopharyngeal carcinoma. J Cancer 2016;7:2360–6.
[23] Tao C-J, Chen Y-Y, Jiang F, et al. The C-reactive protein/albumin ratio is an independent prognostic factor for overall survival in patients with nasopharyngeal carcinoma receiving intensity-modulated radiotherapy. J Cancer 2016;7:2005–11.
[24] Li J-P, Chen S-L, Liu X-M, et al. A novel inflammation-based stage (I Stage) predicts overall survival of patients with nasopharyngeal carcinoma. Int J Mol Sci 2016;17:pii: E1900.
[25] Zhang Y, Zhou G-Q, Liu X, et al. Exploration and validation of C-reactive protein/albumin ratio as a novel inflammation-based prognostic marker in nasopharyngeal carcinoma. J Cancer 2016;7:1406–12.
[26] Tumours of the nasopharynx. In: Barnes L, Eveson John W, Reichart P, Sidransky D (eds). World Health Organization Classification of Tumours, Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press; 2005;781–106.
[27] Takenaka Y, Kitamura T, Oya R, et al. Prognostic role of neutrophil–lymphocyte ratio in nasopharyngeal carcinoma: a meta-analysis. PLoS One 2017;12:e0181478.
[28] Tsao SW, Tsang CM, Lo KW. Epstein-Barr virus infection and nasopharyngeal carcinoma. Philos Trans R Soc Lond B Biol Sci 2017; 372:1732.
[29] Yin J, Qin Y, Luo Y, et al. Prognostic value of neutrophil-to lymphocyte ratio for nasopharyngeal carcinoma: a meta-analysis. Medicine 2017;96: e7577.
[30] Chen Z, Guo Q, Lu T, et al. Pretreatment serum lactatez dehydrogenase level as an independent prognostic factor of nasopharyngeal carcinoma in the intensity-modulated radiation therapy era. Med Sci Monitor 2017;23:437–45.
[31] Tan J, Jiang L, Cheng X, et al. Association between VEGF–460T/C gene polymorphism and clinical outcomes of nasopharyngeal carcinoma treated with intensity-modulated radiation therapy. Onco Targets Ther 2017;10:909–18.
[32] Luo DH, Chen QY, Liu H, et al. The independent, unfavorable prognostic factors endothelin A receptor and chemokine receptor 4 have a close relationship in promoting the motility of nasopharyngeal carcinoma cells via the activation of AKT and MAPK pathways. J Transl Med 2013;11:203.
[33] Guo S-S, Tang L-Q, Chen Q-Y, et al. Is hemoglobin level in patients with nasopharyngeal carcinoma still a significant prognostic factor in the era of intensity-modulated radiotherapy technology? PLoS One 2015;10: e0136033.
[34] Fernandes JV, Cobucci RN, Jatoba CA, et al. The role ofthe mediators of inflammation in cancer development. Pathol Oncol Res 2015;21:527–34.

[35] Oliva N, Carcole M, Beckerman M, et al. Regulation of dendrimer/dextran material performance by altered tissue microenvironment in inflammation and neoplasia. Sci Transl Med 2015;7:272ra211.
[36] Sieghart W, Pinter M, Hucke F, et al. Single determination of C-reactive protein at the time of diagnosis predicts long-term outcome of patients with hepatocellular carcinoma. Hepatology 2013;57:2224–34.
[37] Aziz A, Rink M, Gakis G, et al. Preoperative C-reactive protein in the serum: a prognostic biomarker for upper urinary tract urothelial carcinoma treated with radical nephroureterectomy. Urol Int 2014; 93:352–60.
[38] Erlinger TP, Platz EA, Rifai N, et al. C-reactive protein and the risk of incident colorectal cancer. Jama 2004;291:585–90.
[39] Ayhan A, Günakan E, Alyazıcı İ, et al. The preoperative albumin level is an independent prognostic factor for optimally debulked epithelial ovarian cancer. Arch Gynecol Obstet 2017;296:989–95.
[40] Song A, Eo W, Kim S, et al. Significance of serum ferritin as a prognostic factor in advanced hepatobiliary cancer patients treated with Korean medicine: a retrospective cohort study. BMC Complement Altern Med 2018;18:176.
[41] Fairclough E, Cairns E, Hamilton J, et al. Evaluation of a modified early warning system for acute medical admissions and comparison with C-reactive protein/albumin ratio as a predictor of patient outcome. Clin Med (Lond) 2009;9:30–3.
[42] Ranzani OT, Zampieri FG, Forte DN, et al. C-reactive protein/albumin ratio predicts 90-day mortality of septic patients. PLoS One 2013;8: e59321.
[43] Liu Y, Chen S, Zheng C, et al. The prognostic value of the preoperative c-reactive protein/albumin ratio in ovarian cancer. BMC Cancer 2017; 17:285.