



Research Article

C-Reactive Protein to Albumin Ratio is an Indicator of Poor Prognosis for Patients with Biliary Tract Cancer

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Abstract

Objectives: This retrospective study evaluated the prognostic significance of the ratio of C-reactive protein (CRP) to albumin (Alb) in patients with biliary tract cancer (BTC).

Methods: A total of 178 patients with newly diagnosed BTC, who had been treated in our departments between January 2013 and September 2018, were enrolled in the study. All medical records were reviewed retrospectively. Patients who showed clinical evidence of infection or other inflammatory conditions were excluded. We investigated the correlation between the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), CRP to Alb ratio (CAR) and the overall survival (OS) rates for BTC patients. Both univariate and multivariate analyses were performed to identify clinicopathological variables associated with OS.

Results: The optimal cutoff level for the CAR was 0.66. An elevated CAR was associated with low OS ($p < 0.001$). In the multivariate analysis CAR, was independently associated with OS (HR 3.44, 95% CI: 2.05-5.79, $p < 0.001$). Median OS for CAR ≤ 0.66 and CAR > 0.66 were 22.0 months and 6.0 months, respectively. By contrast, NLR ($p = 0.12$) and PLR ($p = 0.85$) were not independently associated with OS.

Conclusion: The CAR might be an independent prognostic marker for patients with BTC, and might have value comparable with other established inflammation-based prognostic scores. The prognostic value of this novel inflammation-based prognostic score needs to be verified in patients with other types of cancer.

Keywords: Biliary tract cancer, C-Reactive protein to albumin ratio, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, prognostic score

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Biliary tract cancers (BTCs) are a heterogeneous group of epithelial cell malignancies arising from distinct anatomical locations of the biliary tree.^[1] BTCs are generally divided into intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), gallbladder cancer (GBCA) and periampullary cancer.^[2]

Though rare, the incidence and mortality of BTC are increasing worldwide.^[3] Survival outcomes of BTC remain dismal, with a 5-year overall survival (OS) rate of 30% for localized disease and 10% for patients with unresectable or metastatic disease.^[3] Most BTC cases are not accompanied by clinical symptoms until the disease reaches an

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advanced stage.^[4] A minority of BTC patients present with surgically resectable disease; however, the relapse rate is high.^[4] Therefore, a reliable predictor of survival is needed to allow for optimal treatment choices to be made and so improve patient outcomes.

Cancer treatment response not only depends on the tumor's characteristics, but also the patient's inflammatory response.^[5] Inflammation occurs during cancer pathogenesis in many adult patients and is an indicator of tumor development and progression.^[6] There is increasing data that a systemic inflammatory response is associated with poor outcomes in patients suffering from various types of cancers.^[6] Several common inflammation-based prognostic scores, including neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR), have been reported to have prognostic value in patients with many types of malignant solid tumors.^[8–11]

The C-reactive protein (CRP) to albumin (Alb) ratio (CAR) has also been reported as a novel inflammation-based prognostic marker in multiple types of tumors, including hepatocellular carcinoma, colorectal cancer, esophageal cancer, renal cancer, pancreatic cancer, non-small cell lung cancer, esophagogastric junction and gastric cancer.^[9,13–20] However, it was not evaluated in biliary tract cancers.

In the present study, we investigated the prognostic value of CAR in patients with BTC. We also evaluated NLR and PLR in these patients and compared them with the CAR.

Methods

Patients

One hundred seventy-eight patients with newly diagnosed biliary tract cancer, who were treated in the Department of Medical Oncology at the Bezmialem Vakif University Hospital, Afyon Kocatepe University School of Medicine Hospital, Trakya University School of Medicine Hospital, and Istanbul Okmeydanı Training and Research Hospital, between January 2013 and July 2018 were enrolled in the study. Eight patients were lost to follow-up. Forty-nine patients who showed clinical evidence of cholangitis were excluded. Patients who showed other inflammatory conditions were also excluded. In total, 121 patients with BTC met the conditions for inclusion and were evaluated. The diagnosis of BTC was confirmed either pathologically or by using images obtained from ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) or endoscopic retrograde cholangiopancreatography (ERCP). Tumor-related variables, such as the primary tumor site (intrahepatic bile duct, extrahepatic bile duct, gallbladder), and the extent of the disease

(locally advanced or metastatic) were also evaluated by these imaging techniques.

The study was conducted retrospectively by searching medical records of patients with the approval of the institutional review board of the hospital. As the data were retrospective in nature and analyzed anonymously, informed consent was not obtained from the patients.

Inflammation-Based Prognostic Scores and Other Variables

Values for NLR, PLR and CAR were calculated. Blood samples were obtained before the initial treatment to measure levels of CRP, albumin, total bilirubin, alkaline phosphatase (ALP), hemoglobin (Hb), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). In addition, white blood cell (WBC), neutrophil, lymphocyte and platelet (Plt) counts were determined. NLR and PLR were defined as absolute neutrophil count and platelet counts, respectively, divided by the absolute lymphocyte count.

Treatment and Follow-Up of Patients

Patients were treated and followed-up according to guidelines of the National Comprehensive Cancer Network (NCCN). The patients were treated with gemcitabine alone, gemcitabine and cisplatin, 5-fluorouracil and irinotecan (FOLFIRI), 5-fluorouracil/capecitabine and oxaliplatin (FOLFOX/XELOX) or best supportive care (BSC). The patients with obstructive jaundice underwent endoscopic retrograde biliary drainage or percutaneous transhepatic biliary drainage before the initial treatment. The patients were followed after the initial treatment with imaging techniques and analysis of tumor marker levels. For patients who showed tumor progression, palliative chemotherapy or best supportive care was provided. The end of the follow-up was the time of the last examination (July 2018) or death.

Statistical Analysis

Data were presented as median and interquartile ranges. Categorical variables were reported as frequencies and group percentages. Survival curves were plotted according to the Kaplan–Meier method, and any differences were analyzed using the log-rank test. Univariate and multivariate analyses were performed with a Cox proportional hazard model to identify the independent prognostic factors. All p values were two-sided, and a p value of <0.05 was considered statistically significant. ROC curve analysis was used to determine the predictive value of parameters, such as NLR, PLR, and CAR. A p value <0.05 was considered to be significant.

Results

Patient Characteristics

The clinicopathological characteristics of the patients are shown in Table 1. A total of 121 patients with BTC were identified on our institutional database. Fifty-eight (47.9%) patients were male and 63 (52.1%) patients were female. The median age of the patients was 65 (range 57–71) years. The primary tumor sites were the intrahepatic bile duct (43 patients; 35.5%), the extrahepatic bile duct (44 patients; 36.4%) and the gallbladder (34 patients; 28.1%). Fifty-one (42.1%) patients with obstructive jaundice underwent endoscopic retrograde or percutaneous transhepatic biliary

drainage. Palliative chemotherapy was administered in 61 (50.4%) patients: gemcitabine monotherapy, 22 (18.2%) patients; gemcitabine plus cisplatin, 32 (26.4%) patients; FOLFOX/XELOX regimen, 5 (4.1%) patients; FOLFIRI regimen, 1 (0.8%) patient. The remaining 60 (49.6%) patients received BSC. Eighty-seven (71.9%) patients had de novo metastases. The metastatic sites were liver (70 patients; 57.8%), lung (1 patient; 0.8%), lymph node (50 patients; 41.3%) and bone (4 patients; 3.3%). At the time of diagnosis most of the patients were stage 4 (90; 74.4%), while the remaining patients were stage 1-2 (11; 9.1%) and stage 3 (20; 16.5%). Median tumor size was 5.0cm in diameter (range 1.0-17.0 cm).

Table 1. Demographic and clinical characteristics of the subjects

	All (n=121)
Age, year Median (Interquartile range)	65 (57-71)
Gender, F/M	63/58
Tumor localization, n (%)	
Intrahepatic	43 (35.5)
Extrahepatic	44 (36.4)
Gallbladder	34 (28.1)
De novo metastatic, n (%)	87 (71.9)
Metastatic site, n (%)	
Liver	70 (57.8)
Lung	1 (0.8)
Lymph node	50 (41.3)
Bone	4 (3.3)
Biliary drainage, n (%)	51 (42.1)
Percutaneous transhepatic cholangiography, n (%)	6 (5.0)
Stage, n (%)	
Stage 1 or 2	11 (9.1)
Stage 3	20 (16.5)
Stage 4	90 (74.4)
Tumor size, cm	
Median (minimum-maximum)	5.0 (1.0-17.0)
Grade, n (%)	
Grade 2	27 (22.3)
Grade 3	14 (11.6)
Unknown	80 (66.1)
Best supportive care, n(%)	60 (49.6)
First line chemotherapy regimens, n(%)	
Gemcitabine	22 (18.2)
Cisplatin+gemcitabine	32 (26.4)
FOLFOX/XELOX	5 (4.1)
FOLFIRI	1 (0.8)
Second line chemotherapy regimens, n (%)	
Gemcitabine	2 (1.7)
Cisplatin+gemcitabine	2 (1.7)
FOLFOX/XELOX	17 (14.0)
FOLFIRI	7 (5.8)

Comparison of the prognostic value of parameters for identifying extended OS

The median follow-up was 8.8 months (range 3.1–16.6). At the end of the follow-up period, 18 (14.9%) patients were alive and 103 (85.1%) patients had died. The 1-, 3- and 5-year OS rates were 16.5, 14.1 and 7.1%, respectively. The comparison of OS with CAR, PLR and NLR values is shown in Table 2. A significant difference in OS was only found with CAR ($p<0.01$); NLR ($p=0.12$) and PLR ($p=0.85$) showed no correlation with OS.

Prognostic factors

In the univariate analysis, metastatic status ($p<0.001$), adjuvant chemotherapy ($p<0.01$) and CAR ($p<0.001$) correlated with OS (Table 3). Multivariate analysis with these parameters showed that only CAR (HR 3.44, 95% CI: 2.05-5.79, $p>0.001$) was independently associated with OS (Table 3).

Based on the optimal cutoff value of CAR (0.66), patients were divided into a CAR-Low group ($n=60$) and a CAR-High group ($n=61$). The clinical features of the 2 groups were compared by chi-square test. The 2 groups did not differ significantly in age, staging or tumor site. However, the

Table 2. The comparison of the overall survival according to the CAR, PLR, and NLR

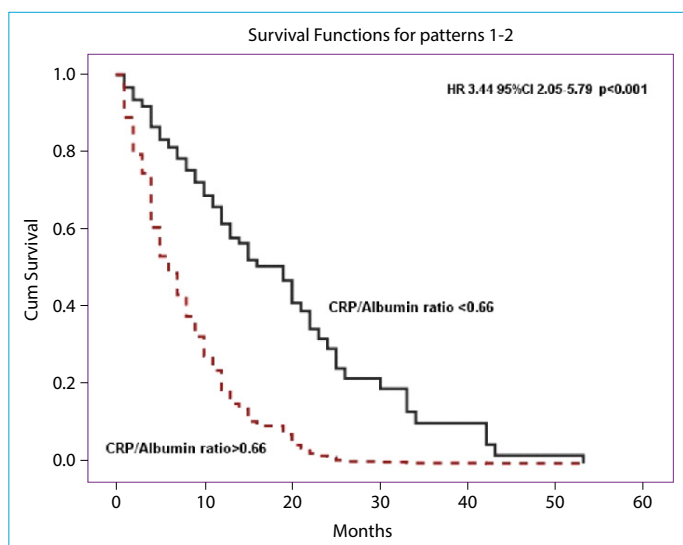
	Median OS (months)	SE	95% CI	P
CRP/Albumin ratio				
≤ 0.66	20.0	3.7	12.6-27.3	<0.001
>0.66	6.0	1.2	3.4-8.5	
NLR				
≤ 2.9	12.0	1.3	9.3-14.6	0.12
>2.9	7.0	2.6	1.7-12.2	
PLR				
≤ 155	11.0	1.9	7.2-14.7	0.85
>155	9.0	1.7	5.6-12.3	

Table 3. Univariate and multivariate analyses for overall survival

	Univariate analysis	Multivariate analysis		
	p	HR	95% CI	p
Age, ≥65 years	0.51			
Gender, Male	0.81			
Metastatic status	<0.001			
Surgery	0.02			
Adjuvant chemotherapy	<0.01	0.61	0.34-1.08	0.09
Palliative chemotherapy	0.30			
PLR, >155	0.85			
NLR, >2.9	0.12			
CRP/Albumin ratio, >0.66	<0.001	3.44	2.05-5.79	<0.001

CAR-High group had a higher percentage of men compared to the CAR-Low group, while the CAR-Low group had a lower treatment rate and percentage of BTC. Among clinical factors, median lymphocyte, Hb, CRP and Alb levels were higher in the CAR-Low group, whereas neutrophil, platelet, and globulin levels were higher in the CAR-High group.

Kaplan–Meier analyses and log-rank tests showed median OS in the CAR-High group (6 months) was significantly shorter than in the CAR-Low group (22 months; $p < 0.001$). Univariate COX regression analyses of age, sex, stage, treatment status, NLR, PLR, and CAR, showed that high CAR, adjuvant chemotherapy and metastatic status were significant adverse risk factors for OS in BTC patients (Table 3). Multivariate analysis showed that no adjuvant treatment (HR 0.61, 95% CI: 0.34-1.08, $p = 0.09$) affected OS. By contrast, CAR-High was independently associated with mortality (HR 3.44, 95% CI: 2.05-5.79, $p < 0.001$; Fig. 1).

**Figure 1.** Prognostic significance of CRP/Alb ratio in BTC.

Discussion

CAR was shown to be a prognostic index for patients with BTC, compared with several other inflammation-based scores, including NLR and PLR. While CAR was an independent risk factor for OS, NLR and PLR were not reliable prognostic factors for patients with BTC. As the first study to show a relationship between CAR and prognosis in patients with BTC, our results suggest that this new parameter could help in selecting optimal treatment regimens for patients with poor prognoses, who may need more supportive therapy and palliative care.

Accumulating evidence has indicated that cancer and inflammation are linked in patients suffering from various types of cancers.^[5-7] Specifically, inflammatory cytokines and chemokines are believed to facilitate cancer growth, invasion, metastasis and angiogenesis, subversion of the host immune response, and resistance to cytotoxic drugs.^[21,22] Moreover, the presence of a systemic inflammatory response, evidenced by an elevation of CRP levels, accompanies a decrease in the serum albumin concentration and a progressive loss of weight and lean tissue, resulting in a poor performance status and increasing mortality in cancer patients.^[23-25]

Several common inflammation-based parameters have been reported to have prognostic value in patients with many types of malignant solid tumors.^[9-11] Proctor et al.^[26] demonstrated that the prognostic scores based on CRP levels for a variety of tumor sites were superior to other inflammation-based prognostic scores. Since the CAR is based on only 2 standard laboratory measurements, it is a simple, readily available, and inexpensive prognostic marker for patients with cancer.

CAR has been reported as a novel inflammation-based prognostic marker for multiple types of cancer, including hepatocellular, colorectal, esophageal, renal, pancreatic, non-small cell lung, esophagogastric junction and gastric.^[9,13-20]

Initially, CAR was reported as a novel inflammation-based prognostic score to predict survival in patients with hepatocellular carcinoma.^[13] Its prognostic ability was found to be comparable with that of the modified Glasgow Prognostic Score (mGPS) and better than that of NLR. Since then, there has been an increasing number of studies describing the relationship between CAR and prognosis of malignant diseases (Table 4). These studies suggest that the prognostic ability of CAR could be superior to that of other inflammation-based prognostic scores.

The cut-off value of CAR is not yet clear. Various studies have utilized different cut-off values. For instance, CAR cut-

Table 4. Summary of C-reactive protein/albumin ratio study

First Author	Patients	Publication year	cutoff value of CAR	P
Kinoshita A. et al. ^[13]	Hepatocellular carcinoma (n=186)	2015	0.037	<0.001
Wei XL et al. ^[15]	Esophageal Squamous Cell Carcinoma (n=423)	2015	0.095	0.031
Chen Z et al. ^[16]	Clear Cell Renal Cell Carcinoma (n=406)	2015	0.060	<0.001
Liu X et al. ^[18]	Gastric Cancer (n=455)	2015	0.062	<0.001
Ishizuka M et al. ^[14]	Colorectal Cancer (n=627)	2016	0.038	<0.001
Haruki K et al. ^[17]	Pancreatic Cancer (n=113)	2016	0.03	0.023
Kensuke Kudou et al. ^[19]	Esophagogastric Junction and Upper Gastric Cancer (n=144)	2018	0.1	0.0439
Ni X-F et al. ^[20]	Non-Small Cell Lung Cancer (n=436)	2018	0.2357	<0.005
Yu X et al. ^[9]	pT1pN0 Esophageal Squamous Cell Carcinoma (n=160)	2018	0.023	0.040

n: number of patient; CAR: C-reactive protein/albumin ratio.

off value was 0.2357 in Ni X-F et al.'s study of Non-Small Cell Lung Cancer patients,^[20] while it was 0.023 in Yu X et al.'s study of pT1pN0 Esophageal Squamous Cell Carcinoma patients.^[9] We estimate that the calculation of different CAR cut-off values is expected in different types of cancer studies. However, in the same group of cancer patients, more work must be done to determine the value of a CAR cut-off.

In most of the studies reported, CAR was compared with the values such as NLR, PLR and mGPS/GPS, and it was stated that CAR could be a better prognostic factor than the other inflammation parameter.^[9,13-16] Cho KM et al.^[8] demonstrated that NLR and PLR to predict survival in BTC. However, in our study, the prognostic significance of NLR and PLR could not be demonstrated. Additionally, unlike other studies, the fact that mGPS/GPS is not considered as inflammation parameter may be considered as the missing aspect of our study

Our results were generally consistent with these previous studies and suggested that CAR was also superior to other inflammation-based parameters in predicting prognosis for patients with BTC.

Potential limitations of the current study were that it was retrospective, contained relatively few patients, and the cancers were heterogeneous in type. The predictive value of CAR should be verified in multicenter prospective studies, with more patients and longer follow-up times.

Conclusion

We have demonstrated that CAR is an independent prognostic marker for patients with BTC, and shown that it was

superior to other established inflammation-based parameters in terms of its prognostic ability. The prognostic value of this novel inflammation-based parameter needs to be verified in patients with other types of cancer. In addition, the usefulness of a combination of a CRP-based prognostic parameter and white cell-based prognostic score in predicting outcomes in cancer patients should be validated in future trials.

Disclosures

Ethics Committee Approval: Ethics Committee Approval: The study was approved by the Local Ethics Committee: Bezmialem Vakif University, Decision No: 22/405 Date: 19.11.2019.

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Conflict of Interest: None declared.

Authorship Contributions: Concept – T.D., O.K., M.A., A.S., A.A., M.B., H.M.T.; Design – T.D., M.A., A.S., A.A., M.B., H.M.T.; Supervision – T.D., O.K., A.S., A.A., M.B., H.M.T.; Materials – T.D., O.K., M.A., A.A., M.B.; Data collection &/or processing – T.D., O.K., M.A., A.S., M.B., H.M.T.; Analysis and/or interpretation – T.D., O.K., M.A., A.S., A.A., M.B.; Literature search – T.D., O.K., M.A., A.S., A.A., M.B., H.M.T.; Writing – T.D., O.K., M.A., A.S., A.A., H.M.T.; Critical review – T.D., O.K., M.A., A.S., A.A., M.B., H.M.T.

References

- Vasilieva LE, Papadimitriou SI, Dourakis SP. Modern diagnostic approaches to cholangiocarcinoma. *Hepatobiliary Pancreat Dis Int* 2012;11:349–59. [\[CrossRef\]](#)
- Imperatori M, D'Onofrio L, Marrucci E, Pantano F, Zoccoli A, Tonini G. Neoadjuvant treatment of biliary tract cancer: state of the art and new perspectives. *Hepatic Oncol* 2015;3:93–9.

3. Howlader N NA, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, et al. Cronin KA SEER Cancer Statistics Review 2016;1975–2013.
4. Wang SJ, Lemieux A, Kalpathy-Cramer J, Ord CB, Walker GV, Fuller CD, Kim JS, Thomas CR. Jr Nomogram for predicting the benefit of adjuvant chemoradiotherapy for resected gallbladder cancer. *J Clin Oncol* 2011;29:4627–32. [\[CrossRef\]](#)
5. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol* 2013;88:218–30. [\[CrossRef\]](#)
6. Park JH, Watt DG, Roxburgh CS et al. Colorectal cancer, systemic inflammation, and outcome: staging the tumor and staging the host. *Ann Surg* 2016;263:326–36. [\[CrossRef\]](#)
7. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol* 2010;6:149–63. [\[CrossRef\]](#)
8. Cho KM, Park H, Oh DY et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and their dynamic changes during chemotherapy is useful to predict a more accurate prognosis of advanced biliary tract cancer. *Oncotarget* 2017;8:2329–41. [\[CrossRef\]](#)
9. Yu X, Wen Y, Lin Y et al. The value of preoperative Glasgow Prognostic Score and the C-reactive protein to albumin ratio as prognostic factors for long-term survival in pathological T1N0 esophageal squamous cell carcinoma. *J Cancer* 2018;9:807–15. [\[CrossRef\]](#)
10. Gao GD, Sun B, Wang XB et al. Neutrophil to lymphocyte ratio as prognostic indicator for patients with esophageal squamous cell cancer. *Int J Biol Markers* 2017;32:e409–14. [\[CrossRef\]](#)
11. Song Y, Yang Y, Gao P et al. The preoperative neutrophil to lymphocyte ratio is a superior indicator of prognosis compared with other inflammatory biomarkers in resectable colorectal cancer. *BMC Cancer* 2017;17:744. [\[CrossRef\]](#)
12. Lu C, Gao P, Yang Y et al. Prognostic evaluation of platelet to lymphocyte ratio in patients with colorectal cancer. *Oncotarget* 2017;8:86287–95. [\[CrossRef\]](#)
13. 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. [\[CrossRef\]](#)
14. Ishizuka M, Nagata H, Takagi K et al. Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal cancer. *Ann Surg Oncol* 2016;23:900–7. [\[CrossRef\]](#)
15. Wei XL, Wang FH, Zhang DS et al. A novel inflammation-based prognostic score in esophageal squamous cell carcinoma: the C-reactive protein/albumin ratio. *BMC Cancer* 2015;15:350.
16. Chen Z, Shao Y, Fan M et al. Prognostic significance of preoperative C-reactive protein: albumin ratio in patients with clear cell renal cell carcinoma. *Int J Clin Exp Pathol* 2015;8:14893–900.
17. Haruki K, Shiba H, Shirai Y et al. The C-reactive protein to albumin ratio predicts long-term outcomes in patients with pancreatic cancer after pancreatic resection. *World J Surg* 2016;40:2254–60. [\[CrossRef\]](#)
18. Liu X, Sun X, Liu J et al. Preoperative C-reactive protein/albumin ratio predicts prognosis of patients after curative resection for gastric cancer. *Transl Oncol* 2015;8:339–45. [\[CrossRef\]](#)
19. Kensuke Kudou, Hiroshi Saeki, Yuichiro Nakashima et al. C-reactive protein/albumin ratio is a poor prognostic factor of esophagogastric junction and upper gastric cancer. *Journal of Gastroenterology and Hepatology* 2018.
20. Ni X-F, Wu J, Ji M, et al. Effect of C-reactive protein/albumin ratio on prognosis in advanced non-small-cell lung cancer. *Asia-Pac J Clin Oncol* 2018;1–8.
21. Heikkila K, Ebrahim S, Lawlor DA. A systematic review of the association between circulating concentrations of C reactive protein and cancer. *J Epidemiol Community Health* 2007;61:824–33. [\[CrossRef\]](#)
22. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;454:436–44. [\[CrossRef\]](#)
23. Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer* 2013;13:759–71.
24. McMillan DC. The systemic inflammation-based Glasgow prognostic score: a decade of experience in patients with cancer. *Cancer Treat Rev* 2013;39:534–40. [\[CrossRef\]](#)
25. Roxburgh CS, McMillan DC. Cancer and systemic inflammation: treat the tumour and treat the host. *Br J Cancer* 2014;110:1409–12. [\[CrossRef\]](#)
26. Proctor MJ, Morrison DS, Talwar D, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. *Eur J Cancer* 2011;47:2633–41. [\[CrossRef\]](#)