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ORIGINAL ARTICLE

Prognostic significance of C-reactive protein to albumin ratio in colorectal cancer patients: a meta-analysis

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Abstract

Purpose Inconsistent results on the prognostic significance of C-reactive protein to albumin ratio (CAR) in colorectal cancer patients have been reported. This meta-analysis sought to assess the prognostic value of pretreatment CAR for survival outcomes in colorectal cancer patients.

Methods We conducted a systematic literature search of PubMed and Embase databases until February 16, 2019. Observational studies investigating the prognostic role of pretreatment CAR for survival outcome in patients with colorectal cancer were included. Outcome measures included overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS). Pooled hazard ratio (HR) with 95% confidence interval (CI) was utilized to summarize the prognostic significance of CAR for patient survival.

Results Nine retrospective studies involving 2492 colorectal cancer patients were identified. A fixed-effect model meta-analysis showed that high pretreatment CAR was an independent predictor of poor OS (HR 2.25; 95% CI 1.84–2.76) and DFS (HR 2.49; 95% CI 1.43–4.33). On the other hand, no significant association was observed between high CAR and PFS (HR 1.71; 95% CI 0.44–6.60). The predictive values of OS with high pretreatment CAR caused no significant changes in different sample sizes, countries, cut-off values of CAR, treatment methods, and study quality of subgroups.

Conclusion This meta-analysis suggests that CAR may be a powerful prognostic indicator for colorectal cancer prognosis. High pretreatment CAR is associated with poor OS and DFS in patients with colorectal cancer.

Keywords C-reactive protein/albumin ratio · Colorectal cancer · Disease-free survival · Overall survival · Meta-analysis

Introduction

Colorectal cancer is the third most commonly diagnosed malignancy in males and the second in females worldwide [1]. In spite of advances in surgical technique and chemotherapy, the 5-year survival probability of colorectal cancer achieved no considerable improvement [2]. Colorectal cancer is characterized by high inter-patient heterogeneity, which is a challenge for personalized medicine [3]. Biomarkers play a crucial role in personalization of therapies [4]. Therefore, identification of novel prognostic biomarkers is required to improve risk stratification.

Systemic inflammatory responses play a central role in carcinogenesis and cancer progression [5]. Inflammation-based scoring systems, including Glasgow prognostic score (GPS), platelet-lymphocyte ratio, and neutrophil-to-lymphocyte ratio have been widely utilized for cancer prognosis [6]. C-reactive protein (CRP) is a widely used systemic inflammatory index. The serum level of albumin can accurately reflect the nutritional status. GPS, which is based on the CRP and albumin level, is recognized as a strong prognostic biomarker in colorectal cancer patients [7]. CRP to albumin ratio (CAR) is a novel useful inflammation-based prognostic marker. Recently, several epidemiological studies [8–12] have reported that high CAR served as a good predictor of poor survival outcomes in colorectal cancer patients. However, conflicting results on the

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prognostic significance of CAR in these patients remained [13, 14].

No previous systematic review nor meta-analysis has specially focused on the association between pretreatment CAR and survival outcome in patients with colorectal cancer. Therefore, we conducted this meta-analysis to evaluate the prognostic utility of pretreatment CAR for survival outcomes in colorectal cancer patients.

Materials and methods

Data source and literature search

We conducted and reported this meta-analysis according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis [15]. A comprehensive computerized literature search was conducted on PubMed and Embase databases until February 16, 2019. The search terms used were as follows: ("C-reactive protein to albumin ratio" OR "C-reactive protein/albumin ratio" OR "C-reactive protein albumin ratio") AND ("carcinoma" OR "neoplasm" OR "tumor" OR "cancer") AND ("colorectal" OR "rectal" OR "colon") AND ("survival" OR "death" OR "mortality"). The detailed search strategy used in PubMed is provided in Supplemental Text S1. Reference lists of included articles and pertinent reviews were also manually searched for potential missing studies.

Study selection

The following inclusion criteria were used to identify the eligible studies: (1) retrospective or prospective epidemiological studies, (2) enrollment of patients with pathologically diagnosed colorectal cancer, (3) pretreatment CAR as exposure, and (4) outcome measures including overall survival (OS), disease-free survival (DFS), or progression-free survival (PFS). Exclusion criteria included the following: (1) reported unadjusted risk estimates of above clinical outcomes, (2) studies without survival data, and (3) conference abstracts, reviews, or comments.

Data extraction and quality assessment

Data were abstracted from the included studies by two independent authors. Abstracted data included the following: first author's last name, year of publication, region, study design, sample sizes, gender, mean/median age, cancer stage, types of treatment, high CAR cutoff value, follow-up length, outcome measures, and analyzed model. Newcastle–Ottawa Scale (NOS) for cohort studies was selected to judge the

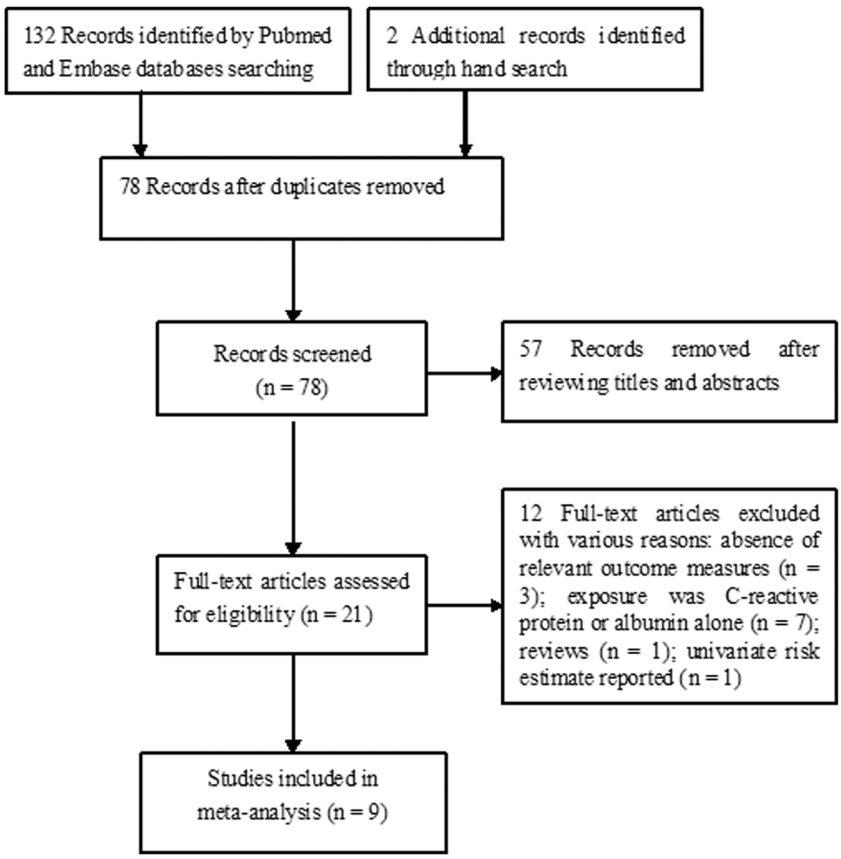

Fig. 1 Flowchart of the study selection process

methodological quality assessment of eligible studies [16]. High-quality studies were defined by NOS score of 7 points or higher. Disagreements in data extraction and quality assessment were resolved by consensus.

Statistical analysis

All statistical analyses were conducted with STATA version 12.0 (Stata Corp LP, TX, USA). The multivariable adjusted multivariable adjusted hazard ratio (HR) with 95% confidence interval (CI) were used to pool the prognostic value of high pretreatment CAR. Heterogeneity across studies was examined using the Cochrane Q statistic and quantified using the I^2 statistic. Statistically significant heterogeneity was deemed by $p < 0.1$ in Cochrane Q test or I^2 statistic $\geq 50\%$. We selected a random effect model in the presence of significant heterogeneity. Otherwise, a fixed-effects model was applied in pooling summary. Publication bias was scheduled using the Begg's rank correlation test [17] and Egger's linear regression test [18], where $p \leq 0.1$ was considered statistically significant. Furthermore, a trim-and-fill method was used to assess the possible influence of publication bias. Sensitivity analyses were conducted by omitting each study in turn. Subgroup analysis was performed on the basis of sample sizes (≥ 200 or < 200), country (China or Japan), treatment methods (chemotherapy or resection), cutoff value of CAR (> 0.1 or ≤ 0.1), and NOS scores (≥ 7 or < 7). As for small number of studies reported the PFS and DFS as outcome measures, we only analyzed the OS outcome in the subgroup analysis.

Results

Search results and study characteristics

A total of 134 articles were identified based on our online databases and hand search. Among the articles, 56 duplicates were removed. A total of 57 articles were excluded after reviewing their titles and abstracts. After assessment of the full-text articles, 12 articles were further removed mainly due to the absence of relevant outcome measures and CRP or albumin alone as exposure. Nine studies [8–14, 19, 20] were finally included in this meta-analysis. Figure 1 shows the study selection process.

Table 1 summarizes the main characteristics of the eligible studies. All the included studies featured retrospective designs and were published from 2016 to 2019. Among the included studies, seven [8–12, 14, 20] were conducted in Japan and two studies [13, 19] were conducted in China. A total of 2492 colorectal cancer patients were included in our meta-analysis. The sample sizes of these studies ranged from 40 to 705. Three studies [8, 10, 13] selected patients with surgical resection; three studies [9, 14, 19] included patients with

Table 1 Summary of clinical studies included in meta-analysis

Author/year	Country	Study design	Patients (% men)	Mean/median age (years)	Treatment	Cutoff value of CAR	Outcome measures/HR (95% CI)	Follow-up (months)	Total NOS
Shibutani (a) 2016 [8]	Japan	Retrospective	Colorectal cancer 705 (58.3)	68 (26–90)	Resection	0.027	OS 1.67 (1.01–2.76) DFS 1.50 (1.05–2.14)	Up to 60	8
Shibutani (b) 2016 [9]	Japan	Retrospective	Unresectable metastatic colorectal cancer 99 (57.6)	63 (27–86)	Chemotherapy	0.183	OS 1.87 (1.06–3.30)	Up to 60	7
Ishizuka 2016 [10]	Japan	Retrospective	Colorectal cancer 627 (63.8)	73% cases > 60	Resection	0.038	OS 2.61 (1.62–4.21)	Median 29.6	8
Ni 2016 [19]	China	Retrospective	Metastatic colorectal cancer 148 (65.5)	60.2 (20–74)	Chemotherapy	0.671	OS 2.24 (1.45–3.47)	Median 12	6
Tominaga 2016 [11]	Japan	Retrospective	Colorectal cancer 136 (58.1)	63.8/62.4	Chemotherapy + resection	0.1	DFS 4.43 (1.94–10.15)	Up to 110	8
Ide 2017 [12]	Japan	Retrospective	Advanced rectal cancer 115 (71)	64 (33–83)	Chemotherapy + resection	0.049	OS 5.09 (2.31–11.58); DFS 4.98 (2.34–11.14)	65	7
Haruki 2017 [20]	Japan	Retrospective	Colorectal liver metastases 106 (76)	64.5 (39–87)	Chemotherapy + resection	0.04	OS 2.56 (1.42–4.61) DFS 1.73 (1.09–2.76)	60	8
Zhou 2018 [13]	China	Retrospective	Colorectal cancer 516 (64.1)	16–81	Resection	0.09	OS 1.59 (0.86–2.91) PFS 1.05 (0.71–1.56)	Median 21.72	7
Shibutani 2019 [14]	Japan	Retrospective	Metastatic colorectal cancer 40 (62.5)	47.5% cases > 68	Chemotherapy	0.122	OS 6.48 (1.37–30.5) PFS 4.53 (0.83–24.8)	Up to 36	6

HR, hazard ratio; *CI*, confidence interval; *CRP*, C-reactive protein; *CAR*, C-reactive protein (CRP)-to-albumin; *OS*, overall survival; *DFS*, disease-free survival; *PFS*, progression-free survival; *NOS*, Newcastle–Ottawa Scale

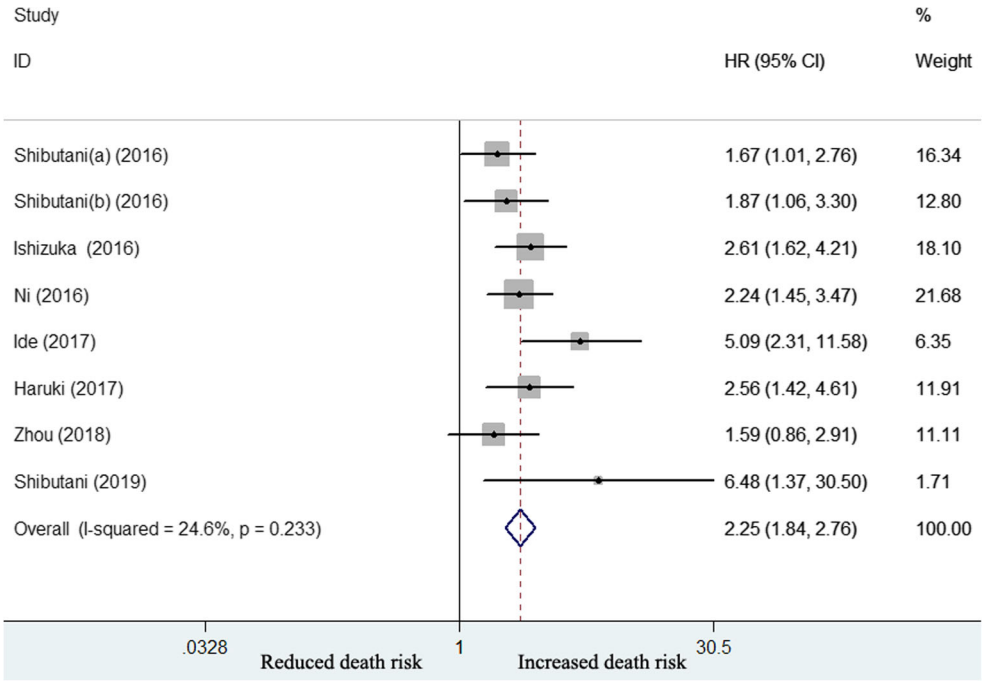

Fig. 2 Forest plots showing HR and 95% CI of OS for high versus low C-reactive protein to albumin ratio

chemotherapy, and the remaining studies enrolled patients with chemotherapy and surgical resection. The cutoff values for high pretreatment CAR ranged from 0.027 to 0.671. The NOS scores of the included studies ranged from 6 to 8, suggesting a relatively high quality.

Overall survival

Eight studies [8–10, 12–14, 19, 20] provided data on pretreatment CAR and OS. As shown in Fig. 2, a fixed-effect model was used given the lack of significant heterogeneity across studies ($I^2 = 24.6\%$; $p = 0.233$). Meta-analysis showed that high pretreatment CAR was associated with poorer OS (HR 2.25; 95% CI 1.84–2.76) compared with the low CAR category. Sensitivity analyses confirmed that any single study slightly affected the pooling results (data not shown). No evidence of publication bias was observed according to the Begg's test ($p = 0.386$) and Egger's test ($p = 0.129$). Trim-and-fill analysis showed there was one missing study in the funnel plot (Fig. 3). However, imputing this missing study caused no significant alteration in the original prognostic significance (HR 2.21; 95% CI 1.02–4.79; $p = 0.045$). Subgroup analyses confirmed the prognostic significance in our predefined subgroups (Table 2). Strong effects of high pretreatment CAR on OS were noted in metastatic colorectal cancer, chemotherapy, Japan, and sample sizes < 200 subgroups.

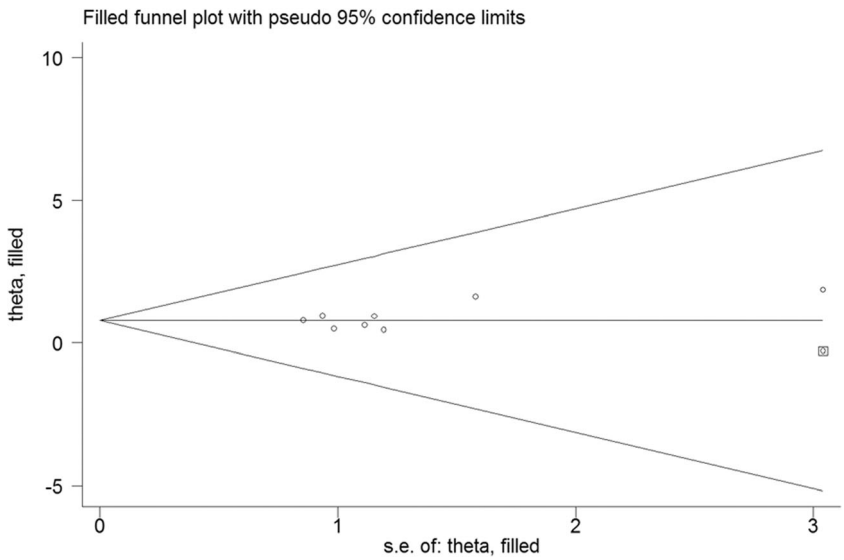

Fig. 3 Funnel plot of high C-reactive protein to albumin ratio with OS. The circles alone are real studies and the circle enclosed in box is 'filled' study

Table 2 Subgroup analyses of overall survival

Subgroup	Number. of studies	Pooled hazard ratios	95% confidence interval	Heterogeneity between studies
Sample sizes				
≥ 200	3	1.97	1.46–2.66	$p = 0.329$; $I^2 = 10.0\%$
< 200	5	2.52	1.91–3.31	$p = 0.224$; $I^2 = 29.7\%$
Country of origin				
China	2	1.99	1.40–2.84	$p = 0.370$; $I^2 = 0.0\%$
Japan	6	2.39	1.86–3.06	$p = 0.166$; $I^2 = 36.1\%$
Type of cancer				
Metastatic CRC	4	2.29	1.71–3.07	$p = 0.501$; $I^2 = 0.0\%$;
All CRC	3	1.97	1.46–2.66	$p = 0.329$; $I^2 = 10.0\%$
Treatments				
Resection	3	1.97	1.46–2.66	$p = 0.329$; $I^2 = 10.0\%$;
Chemotherapy	3	2.21	1.58–3.10	$p = 0.336$; $I^2 = 8.4\%$
Cutoff value of CAR				
> 0.1	3	2.21	1.58–3.10	$p = 0.336$; $I^2 = 8.4\%$
≤ 0.1	4	2.27	1.76–2.93	$p = 0.131$; $I^2 = 43.6\%$
NOS points				
≥ 7	5	2.27	1.82–2.82	$p = 0.214$; $I^2 = 29.5\%$;
< 7	2	2.17	1.27–3.69	$p = 0.140$; $I^2 = 54.0\%$

CAR, C-reactive protein (CRP)-to-albumin; CRC, colorectal cancer

Disease-free survival and progression-free survival

Four studies [8, 11, 12, 20] provided data on DFS and two studies [13, 14] reported data regarding PFS. As shown in Fig. 4, the meta-analysis indicated that high pretreatment CAR was associated with poorer DFS (HR 2.49; 95% CI 1.43–4.33; $I^2 = 74.3\%$; $p = 0.009$) in a random effect model. However, a random effect model meta-analysis showed that there was no significant association between high pretreatment CAR and PFS (HR 1.71; 95% CI 0.44–6.60; $I^2 = 63.0\%$; $p = 0.100$). Leave-out one study sensitivity analyses further confirmed the robustness of our pooling results (data not shown).

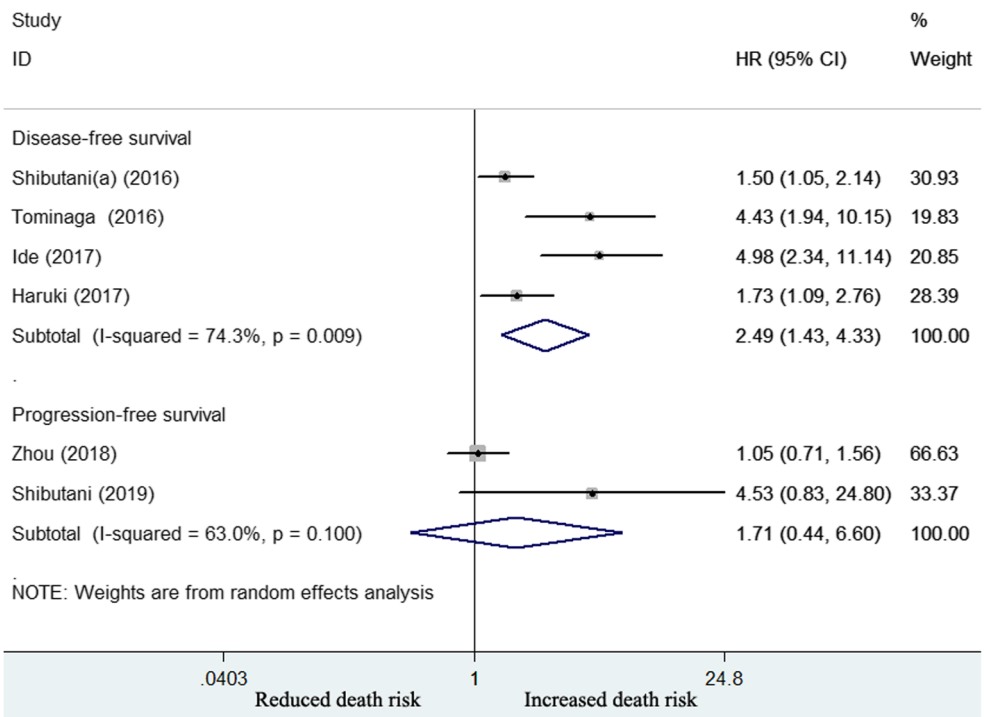

Fig. 4 Forest plots showing HR and 95% CI of DFS and PFS for high versus low C-reactive protein to albumin ratio

Discussion

To address the prognostic value of CAR in colorectal cancer patients, we conducted this meta-analysis on the most recent literature to quantitatively summarize the association of pretreatment CAR with survival outcomes. Our meta-analysis indicates that high pretreatment CAR is associated with poor OS and DFS. Colorectal cancer patients with high pretreatment CAR face more than twofold higher risk of death than those with low CAR. Subgroup analysis and sensitivity analyses further confirmed the robustness of the prognostic significance of high CAR. Therefore, determination of baseline CAR has potential to improve risk stratification of colorectal cancer.

Increasing inflammation-related predictors including the neutrophils to lymphocytes, platelets to lymphocytes, and GPS or modified GPS have been developed in recent years. GPS and CAR are calculated based on the combination of CRP and albumin level. GPS is determined by its categorical value. On the contrary, CAR is established on the continuous range of values. CAR has been reported to be superior to GPS or modified GPS in terms of prognostic values [8, 9, 12, 20]. Therefore, CAR may be superior to GPS for predicting survival.

Apart from pretreatment CAR, dynamic change in post-treatment CAR was also identified as being a good predictor for survival [13]. Importantly, normalization of the CRP/ALB ratio after the treatment tended to be correlated with an improved OS [9]. In addition, CAR could predict grade 3 or 4 side effects of adjuvant chemotherapy in stage III colorectal cancer patients [11]. Thus, high CAR may also predict the risk of side effects or tolerance of the therapy.

However, the molecular mechanisms underlying the prognostic utility of CAR in colorectal cancer remain unclear. One possible explanation is that cancer-related inflammatory response may be linked to tumor progression and recurrence [21]. Therefore, biomarkers of systemic inflammation can predict the post-treatment prognosis. CRP, the most widely used inflammatory marker, has been demonstrated as an independent predictor of survival in colorectal cancer patients [22]. Serum albumin level can represent the nutritional status and immune function. Hypoalbuminemia is recognized as an indicator of malnutrition and cachexia. On the other hand, serum albumin level also reflects the consequence of the inflammatory state. Pretreatment low albumin level was associated with reduced survival in cancer patients [23]. CAR, a combination of CRP and albumin, may synergistically improve the prognostic value.

Nevertheless, the findings of the current meta-analysis should be interpreted in light of several potential limitations. First, all the included studies were retrospective cohort designs and are prone to selection bias. Factors affecting enrollment of participants into these retrospective cohort studies are relatively correlated with the outcome of interest and loss of records of individuals. Second, all the included studies were conducted in East Asia. Hence, application of current findings in Western colorectal cancer patients should be interpreted with caution. Third, no uniform cutoff value is available for defining high CAR. We failed to determine an optimal cutoff value for high CAR as this meta-analysis only analyzed the study level data. Finally, coexistence of other comorbidities may have affected serum CRP and albumin level.

Conclusion

This meta-analysis suggests that colorectal cancer patients with high pretreatment CAR present poorer OS and DFS. Pretreatment CAR may serve as a promising predictor of prognosis in patients with colorectal cancer. Considering the limitations of this meta-analysis, future well-designed prospective studies should be conducted to verify these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68(6):394–424
2. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69(1):7–34
3. Molinari C, Marisi G, Passardi A, Matteucci L, De Maio G, Ulivi P (2018) Heterogeneity in colorectal cancer: a challenge for personalized medicine? Int J Mol Sci 19(12) pii: E3733 https://doi.org/10.3390/ijms19123733
4. Lemery S, Keegan P, Pazdur R (2017) First FDA approval agnostic of cancer site - when a biomarker defines the indication. N Engl J Med 377(15):1409–1412
5. Mantovani A, Allavena P, Sica A, Balkwill F (2008) Cancer-related inflammation. Nature 454(7203):436–444
6. Bugada D, Allegri M, Lavand'homme P, De Kock M, Fanelli G (2014) Inflammation-based scores: a new method for patient-targeted strategies and improved perioperative outcome in cancer patients. Biomed Res Int 2014:142425

7. Lu X, Guo W, Xu W, Zhang X, Shi Z, Zheng L, Zhao W (2019) Prognostic value of the Glasgow prognostic score in colorectal cancer: a meta-analysis of 9,839 patients. Cancer Manag Res 11: 229–249
8. Shibutani M, Maeda K, Nagahara H, Iseki Y, Ikeya T, Hirakawa K (2016) Prognostic significance of the preoperative ratio of C-reactive protein to albumin in patients with colorectal cancer. Anticancer Res 36(3):995–1001
9. Shibutani M, Maeda K, Nagahara H, Iseki Y, Hirakawa K, Ohira M (2016) The significance of the C-reactive protein to albumin ratio as a marker for predicting survival and monitoring chemotherapeutic effectiveness in patients with unresectable metastatic colorectal cancer. SpringerPlus 5(1):1798
10. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Shibuya N, Kubota K (2016) Clinical significance of the C-reactive protein to albumin ratio for survival after surgery for colorectal Cancer. Ann Surg Oncol 23(3):900–907
11. Tominaga T, Nonaka T, Sumida Y, Hidaka S, Sawai T, Nagayasu T (2016) The C-reactive protein to albumin ratio as a predictor of severe side effects of adjuvant chemotherapy in stage III colorectal cancer patients. PLoS One 11(12):e0167967
12. Ide S, Toiyama Y, Okugawa Y, Oki S, Yasuda H, Fujikawa H, Yoshiyama S, Hiro J, Kobayashi M, Ohi M, Araki T, Kusunoki M (2017) Clinical significance of C-reactive protein-to-albumin ratio with rectal cancer patient undergoing chemoradiotherapy followed by surgery. Anticancer Res 37(10):5797–5804
13. Zhou ZQ, Pang S, Yu XC, Xue Q, Jiang HY, Liang XJ, Liu L (2018) Predictive values of postoperative and dynamic changes of inflammation indexes in survival of patients with resected colorectal cancer. Current medical science 38(5):798–808
14. Shibutani M, Nagahara H, Fukuoka T, Iseki Y, Matsutani S, Wang EN, Maeda K, Hirakawa K, Ohira M (2019) Prognostic significance of the C-reactive protein-to-albumin ratio in patients with metastatic colorectal cancer treated with trifluridine/thymidine phosphorylase inhibitor as later-line chemotherapy. Anticancer Res 39(2):1051–1057
15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097
16. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P The Newcastle-Ottawa scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 20 Feb 2019
17. Begg CB, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101
18. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315(7109): 629–634
19. Ni XF, Wu P, Wu J, Ji M, Shao YJ, Zhou WJ, Jiang JT, Wu CP (2016) C-reactive protein/albumin ratio as a predictor of survival of metastatic colorectal cancer patients receiving chemotherapy. Int J Clin Exp Pathol 9(5):5525–5534
20. Haruki K, Shiba H, Horiuchi T, Sakamoto T, Gocho T, Fujiwara Y, Furukawa K, Misawa T, Yanaga K (2017) Impact of the C-reactive protein to albumin ratio on long-term outcomes after hepatic resection for colorectal liver metastases. Am J Surg 214(4):752–756
21. Grivennikov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. Cell 140(6):883–899. https://doi.org/10.1016/j.cell.2010.01.025
22. Woo HD, Kim K, Kim J (2015) Association between preoperative C-reactive protein level and colorectal cancer survival: a meta-analysis. Cancer causes & control : CCC 26(11):1661–1670
23. Gupta D, Lis CG (2010) Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 9:69