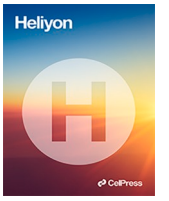
Heliyon 10 (2024) e39326

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Prognostic value of visceral protein ratios in patients with colon cancer

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ARTICLE INFO

Keywords:
Systemic inflammation
Malnutrition
Visceral protein ratios
Colon cancer
Prognostic

ABSTRACT

This study aimed to assess different combinations of visceral proteins and to elucidate their value in predicting progression-free survival (PFS) and overall survival (OS) in patients with colon cancer. The visceral protein ratios included the albumin-globulin ratio (AGR), prealbumin-globulin ratio (PGR), and albumin-prealbumin-globulin ratio (APGR). Compared with AGR and PGR, APGR had the best time-dependent area under the receiver operating characteristic curves for predicting the outcomes. High AGR/PGR/APGR levels were associated with an increased risk of mortality. High AGR (HR = 0.816, 95%CI: 0.719–0.925, p = 0.001), PGR (HR = 0.831, 95%CI: 0.724–0.953, p = 0.008), and APGR (HR = 0.789, 95%CI: 0.688–0.904, p < 0.001) were independent risk factors for PFS. For every SD increase in AGR, PGR, and APGR, the risk of poor OS in patients with colon cancer was reduced by 16.9 % (HR = 0.831, 95%CI, 0.733–0.943; p = 0.001), 15.1 % (HR = 0.849, 95%CI, 0.739–0.976; p = 0.021), and 19.1 % (HR = 0.809, 95%CI, 0.705–0.928; p = 0.002), respectively. Logistic regression models showed that AGR, PGR, and APGR were independent factors that affected recurrence. Visceral protein ratios are independent predictors of PFS and OS. Compared to the existing visceral protein ratios (AGR and PGR), APGR is a more accurate and sensitive indicator for predicting the outcomes of patients with colon cancer.

1. Introduction

Colorectal cancer (CRC) is a common cancer of the digestive system with high incidence and mortality rates [1]. CRC poses a significant public health burden in China. According to 2016 data, the number of CRC cases was close to 408,000. The number of deaths is as high as 196,000, ranking fourth among all malignancies after lung, stomach, and liver cancers [2]. The colon is the most

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https://doi.org/10.1016/j.heliyon.2024.e39326
Received 28 September 2023; Received in revised form 10 October 2024; Accepted 11 October 2024
Available online 17 October 2024

common site of CRC, and because its symptoms are not obvious, CRC often progresses to an advanced stage. In recent years, CRC treatment has progressed rapidly and is not limited to chemotherapy, radiotherapy, and surgery. The rise in immunotherapy and targeted therapy has greatly improved CRC prognosis. Despite progress in CRC treatment, the prognosis of advanced-stage CRC remains a concern. The 5-year survival rate of early-stage CRC patients can reach 90 %, whereas it is only 16 % for advanced-stage CRC with distant metastasis [3,4]. Therefore, the identification of reliable prognostic factors is crucial to guide clinical decisions and improve colon cancer outcomes.

Pathological tumor factors are important tools for assessing prognosis, making clinical decisions, and guiding treatment. Although the TNM staging system and pathological type have distinct effects on the prognosis, there are still some limitations to individual evaluations. Even at the same pathological stage, there may still be significant differences in prognosis among different individuals owing to the heterogeneity of the tumor and the influence of individual host immune and nutritional status. Therefore, more recent studies are exploring whether laboratory markers can be used as auxiliary prognostic factors. Furthermore, visceral proteins have become important research topics as serological indicators.

Visceral proteins mainly include albumin, globulin, and prealbumin, which reflect the protein-energy status of the body and participate in many important physiological functions [5,6]. In recent years, visceral proteins have also been suggested as indicators of systemic inflammation in cancer patients [7]. In an environment of inflammation, liver protein synthesis undergoes rearrangement, with the liver prioritizing acute-phase protein synthesis. Simultaneously, increased capillary permeability leads to the redistribution of visceral proteins inside and outside the blood vessels. These changes can lead to changes in serum visceral protein levels. These studies indicate that serum visceral proteins are effective indicators for evaluating nutritional status, systemic inflammation, disease severity, progression, and prognosis [6,8–10].

Single markers, such as albumin, globulin, and prealbumin, may not comprehensively reflect changes in energy metabolism and systemic inflammation. Therefore, it is necessary to perform a combined evaluation of visceral protein levels. In this study, we examined different combinations of visceral proteins and elucidated their roles in the stratification and clinical decision-making in patients with colon cancer.

2. Materials and methods

2.1. Patients

The study enrolled patients admitted to the First Affiliated Hospital of Guangxi Medical University, who underwent continuous, potentially curable CRC resection. The inclusion criteria included: 1) the primary cancer site was colon, patient underwent radical surgery, and postoperative pathological diagnosis confirmed colon adenocarcinoma; 2) complete serological test data were available; and 3) complete clinicopathologic data were available. The exclusion criteria included: 1) unclear primary tumour site, 2) lost to follow-up, and 3) patients received neoadjuvant chemoradiotherapy before surgery. 4) Severe liver and kidney dysfunction were observed preoperatively.

2.2. Collection and detection

The following clinicopathological and laboratory data were collected: gender, age, height, weight, body mass index (BMI), comorbidities, radiotherapy, and chemotherapy. The tumor pathological data included TNM stage (8th edition of the American Joint Commission on Cancer), tumor location, maximum tumor diameter, perineural/vascular invasion, pathological type, and differentiation.

After admission, 4 mL of fasting venous blood was collected from patients preoperatively, and within 1 h of blood collection, analysis was conducted using a fully automatic biochemical analyzer for the assessment of visceral proteins, which included albumin (g/dL), globulin (g/dL), and prealbumin (g/dL). According to previous literature [11,12], the albumin-globulin ratio (AGR) is characterized as the proportion of albumin (g/dL) to globulin (g/dL). Similarly, the prealbumin-globulin ratio (PGR) is described as the ratio of prealbumin (g/dL) to globulin (g/dL). In addition, we developed an albumin-prealbumin-globulin ratio (APGR), which is defined as albumin (g/dL) * prealbumin (g/dL)/globulin (g/dL). Serum carcino-embryonic antigen (CEA) $\geq$5 U/mL was considered abnormal CEA.

The main follow-up methods were telephone consultations and regular outpatient reexaminations. The follow-up mainly included the postoperative recovery of patients, whether recurrence or metastasis occurred (if so, the time of recurrence or metastasis was recorded), and whether death occurred. The final follow-up was July 2022. For the survival outcome, we used overall survival (OS) and progression-free survival (PFS) as indicators.

2.3. Statistical analysis

Categorical data were reported as frequencies (percentages) and compared using Pearson's chi-squared test (two-tailed). Continuous data were expressed as medians (ranges) or means (standard deviations) and analyzed using Student's t-test. The maximum principle of the Youden index was employed to ascertain the optimal threshold for visceral protein ratios. The prognostic predictive abilities of visceral protein ratios were compared using time-dependent area under the receiver operating characteristic curves (AUCs). Three knots of Restricted Cubic Splines (RCS) were employed to effectively model and illustrate the relationship between visceral protein ratios and mortality. Survival curves were generated utilizing the Kaplan-Meier approach. Cox proportional

hazards models (backward stepwise) were applied to determine hazard ratios (HR) along with their corresponding 95 % confidence intervals (95 % CIs). Logistic regression analysis was employed to evaluate the association between visceral protein ratios and recurrence, while calculating the risk ratio (OR) and 95 % CIs. Statistical significance was defined at a nominal threshold of 0.05. The analysis was conducted using R version 4.2.1, accessible at http://www.r-project.org/.

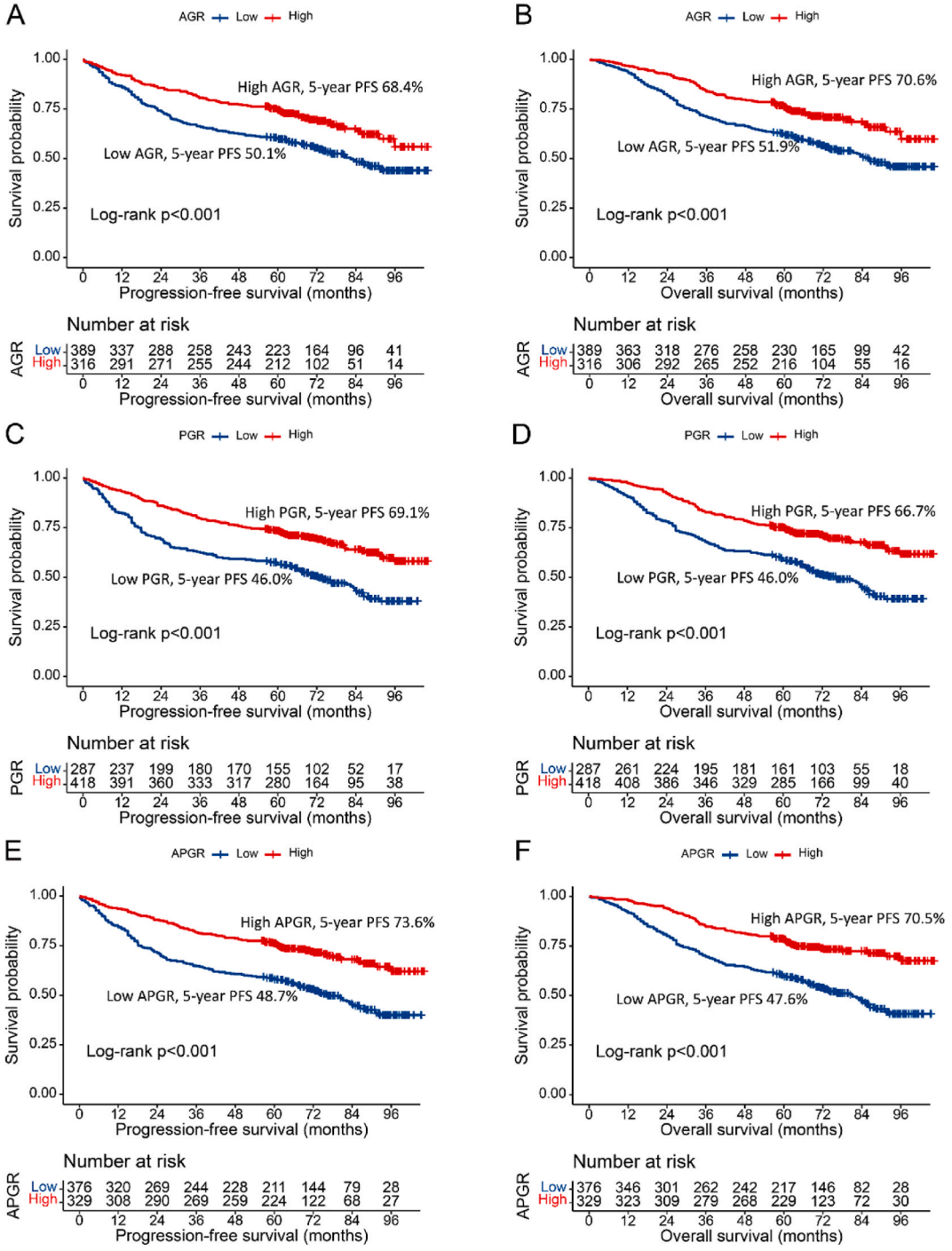

Fig. 1. Kaplan-Meier curve of visceral proteins ratio in patients with colon cancer.
Notes: A, PFS curve of AGR; B, OS curve of AGR; C, PFS curve of PGR; D, OS curve of PGR; E, PFS curve of APGR; F, OS curve of APGR.

3. Results

3.1. Demographic and clinicopathological characteristics

This study included a total of 705 patients diagnosed with colon cancer, comprising 443 men (62.8 %) and 262 women (37.2 %), with an average age of 58.1 years (±13 years). There were 343 patients (48.7 %) with TNM stages III-IV. Perineural and vascular invasion occurred in 9.8 % and 18.9 % of patients, respectively. The median maximum tumor diameter was 5.0 cm (4.0–6.0 cm). The median levels for albumin, globulin, and prealbumin were 38.00 (35.10–40.80), 26.40 (23.60–29.60), and 188.70 (145.30–232.60), respectively. During the observation period, 182 patients (25.8 %) experienced recurrence and 280 patients (39.7 %) died (Table S1).

3.2. Distribution of visceral protein ratios

The AGR value ranged from 0.32 to 3.05, with a median of 1.43 (95 % CI:1.24–1.62). The median AGR in patients who experienced recurrence was 1.37, whereas the median AGR in patients without recurrence was 1.45 (Fig. S1A). The median AGR in patients who died was significantly lower than that in those who survived (1.37 and 1.49, respectively) (Fig. S1D). The PGR value ranged from 0.96 to 19.74, with a median of 7.22 (95 % CI:5.23–9.13). The PGR of patients with recurrence was lower than that of patients without recurrence (6.53 vs. 7.46) (Fig. S1B). Similarly, the PGR of the patients who died was significantly lower than that of the patients who survived (6.33 vs. 7.78) (Fig. S1E). The APGR value ranged from 17.09 to 915.79, with a median of 275.23 (95%CI:182.54–358.62). The APGR of patients who experienced recurrence/death was also significantly higher than that of patients without recurrence/survival (243.69 vs. 288.68; 237.04 vs. 306.03) (Figs. S1C and F).

Based on the maximum principle of the Youden index, the ideal cut-off for the AGR was determined to be 1.474, yielding an AUC of 0.619 ($p < 0.001$) (Fig. S2A). For the PGR, the optimal cut-off value was found to be 6.585, with an AUC of 0.626 ($p < 0.001$) (Fig. S2B). Additionally, the APGR had an optimal cut-off of 287.242, achieving an AUC of 0.643 ($p < 0.001$) (Fig. S2C). Table S2 summarizes the relationship between visceral protein ratios and clinicopathological variables. Low visceral protein ratios were significantly associated with advanced age, low BMI, advanced M stage, large tumor diameter, and high CEA levels. As the visceral

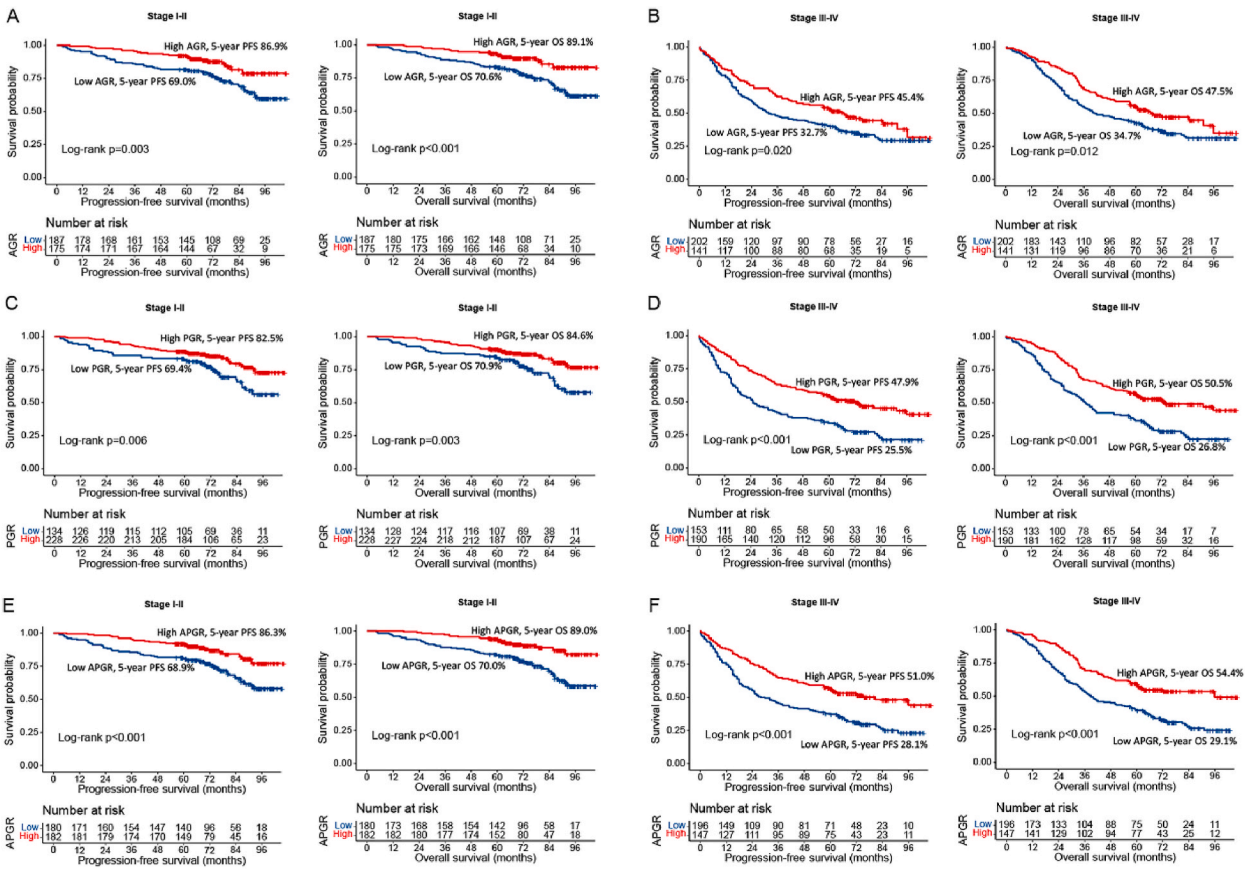

Fig. 2. Kaplan-Meier survival curves categorized by visceral protein ratios according to different TNM stage.
Notes: A, PFS and OS curve of AGR at Stage I-II; B, PFS and OS curve of AGR at Stage III-IV; C, PFS and OS curve of PGR at Stage I-II; D, PFS and OS curve of PGR at Stage III-IV; E, PFS and OS curve of APGR at Stage I-II; F, PFS and OS curve of APGR at Stage III-IV.

protein ratio increased, recurrence and mortality rates also increased.

3.3. Survival analysis of AGR, PGR, and APGR

Using Kaplan-Meier survival analysis, the AGR had a significant prognostic stratification effect on the 5-year PFS and OS (PFS, 50.1 % vs. 68.4 %, $p < 0.001$; OS, 51.9 % vs. 70.6 %, $p < 0.001$) (Fig. 1A and B). Compared with patients in the high PGR group, those in the low PGR group had significantly worse 5-year PFS and OS (PFS, 46.0 % vs. 69.1 %, $p < 0.001$; OS, 46.0 % vs. 66.7 %, $p < 0.001$) (Fig. 1C and D). Similarly, patients in the low APGR group had significantly lower 5-year PFS and OS than those in the high APGR group (PFS: 48.7 % vs. 73.6 %, $p < 0.001$; OS: 47.6 % vs. 70.5 %, $p < 0.001$) (Fig. 1E and F). In the analysis of subgroups, the AGR demonstrated a notable ability to stratify prognosis and distinguish between patients at various stages. However, it is important to highlight that this prognostic differentiation was less pronounced in individuals with advanced tumors (Fig. 2A and B). The PGR could also differentiate patients at different stages, but the prognostic stratification effect of the PGR was weaker in early stage patients (Fig. 2C and D). Patients with low APGR had significantly worse prognoses at different stages than those with high APGR. When compared to AGR and PGR, APGR exhibited notable benefits in forecasting the prognosis of patients across various stages, successfully providing effective prognostic stratification for both early and advanced cases (Fig. 2E and F). Furthermore, CEA subgroup analysis revealed that AGR was capable of effectively stratifying patients with elevated CEA levels, but it was less effective for those with normal levels (Fig. S3A). PGR and APGR effectively stratified patients with both normal and high CEA levels (Figs. S3B and C).

3.4. The prognostic value of AGR, PGR, and APGR

RCS analysis showed that the association between AGR, PGR, and APGR levels and the risk of PFS and OS was an inverted L-shaped curve (Fig. S4). High AGR, PGR, and APGR levels were associated with increased PFS risk. In the multivariate-adjusted Cox proportional risk model, high AGR (HR = 0.816, 95%CI:0.719–0.925, $p = 0.001$), PGR (HR = 0.831, 95%CI:0.724–0.953, $p = 0.008$), and APGR (HR = 0.789, 95%CI:0.688–0.904, $p < 0.001$) levels were independent risk factors for PFS (Table 1). As AGR, PGR, and APGR levels increased, the HR for OS mortality gradually decreased. For every SD increase in AGR, PGR, and APGR, the risk of poor OS was reduced by 16.9 % (HR = 0.831, 95%CI, 0.733–0.943; $p = 0.001$), 15.1 % (HR = 0.849, 95%CI, 0.739–0.976; $p = 0.021$), and 19.1 % (HR = 0.809, 95%CI, 0.705–0.928; $p = 0.002$), respectively (Table 2). The multivariate subgroup analysis indicated that AGR served as a reliable predictor for both PFS and OS across the majority of subgroups (Fig. S5). Additionally, PGR emerged as a valuable marker for survival prediction in most of the analyzed subgroups (Fig. S6). Furthermore, reduced levels of APGR were notably linked to unfavorable prognoses in most subgroups (Fig. S7).

3.5. The relationship among AGR, PGR, APGR, and recurrence

In the univariate analysis, it was observed that AGR, PGR, and APGR were significantly linked to recurrence (all $p < 0.001$). After controlling for potential confounders, AGR was identified as an independent predictor of recurrence (OR = 0.779, 95%CI = 0.637–0.954, $p = 0.016$). Furthermore, multivariate logistic regression analyses revealed that PGR also acted as an independent variable influencing recurrence rates in these patients. Notably, for each standard deviation increase in APGR, the likelihood of recurrence decreased by 31.9 % (OR = 0.681, 95 % CI = 0.548–0.846, $p < 0.001$) (Table S3).

3.6. The discrimination of the AGR, PGR, and APGR for survival

We compared the ability of the AGR, PGR, and APGR to predict the prognosis of patients with colon cancer using the time-dependent AUC. Overall, the APGR had the best predictive ability, followed by the PGR and AGR. For the 3-year PFS, the AUC of AGR, PGR, and APGR were 0.603, 0.616, and 0.622, respectively (Fig. 3A). Furthermore, for the 5-year PFS, the AUC of AGR, PGR, and APGR decreased slightly, but APGR still had the best predictive value (0.589 vs. 0.604 vs. 0.614) (Fig. 3B). For the 3-year OS, the AUC

Table 1
Association between visceral protein ratios and overall survival of patients with colon cancer.

Markers	Model a		Model b		Model c	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
AGR (Continuous)	0.789 (0.705,0.884)	<0.001	0.836 (0.745,0.938)	0.002	0.831 (0.733,0.943)	0.004
AGR (High)	0.580 (0.452,0.744)	<0.001	0.636 (0.493,0.821)	0.001	0.647 (0.497,0.843)	0.001
PGR (Continuous)	0.727 (0.645,0.82)	<0.001	0.83 (0.731,0.943)	0.004	0.849 (0.739,0.976)	0.021
PGR (High)	0.503 (0.398,0.637)	<0.001	0.629 (0.489,0.81)	<0.001	0.674 (0.516,0.881)	0.004
APGR (Continuous)	0.716 (0.635,0.808)	<0.001	0.795 (0.701,0.901)	<0.001	0.809 (0.705,0.928)	0.002
APGR (High)	0.456 (0.354,0.587)	<0.001	0.545 (0.417,0.714)	<0.001	0.581 (0.437,0.772)	<0.001

Notes.
Model a: No adjusted.
Model b: Adjusted for gender, age, and BMI.
Model c: Adjusted for gender, age, BMI, hypertension, diabetes, T stage, N stage, tumor size, perineural invasion, vascular invasion, pathological type, differentiation, radiotherapy, chemotherapy.

Table 2
Association between visceral protein ratios and progression-free survival of patients with colon cancer.

Markers	Model a		Model b		Model c	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
AGR (Continuous)	0.786 (0.702,0.88)	<0.001	0.827 (0.736,0.928)	0.001	0.816 (0.719,0.925)	0.001
AGR (High)	0.606 (0.476,0.772)	<0.001	0.661 (0.516,0.846)	0.001	0.662 (0.513,0.855)	0.002
PGR (Continuous)	0.733 (0.652,0.825)	<0.001	0.83 (0.732,0.94)	0.003	0.831 (0.724,0.953)	0.008
PGR (High)	0.522 (0.415,0.656)	<0.001	0.636 (0.497,0.813)	<0.001	0.657 (0.506,0.854)	0.002
APGR (Continuous)	0.723 (0.643,0.813)	<0.001	0.791 (0.699,0.895)	<0.001	0.789 (0.688,0.904)	0.001
APGR (High)	0.498 (0.39,0.635)	<0.001	0.59 (0.455,0.765)	<0.001	0.612 (0.465,0.805)	<0.001

Notes.
Model a: No adjusted.
Model b: Adjusted for gender, age, and BMI.
Model c: Adjusted for gender, age, BMI, hypertension, diabetes, T stage, N stage, tumor size, perineural invasion, vascular invasion, pathological type, differentiation, radiotherapy, chemotherapy.

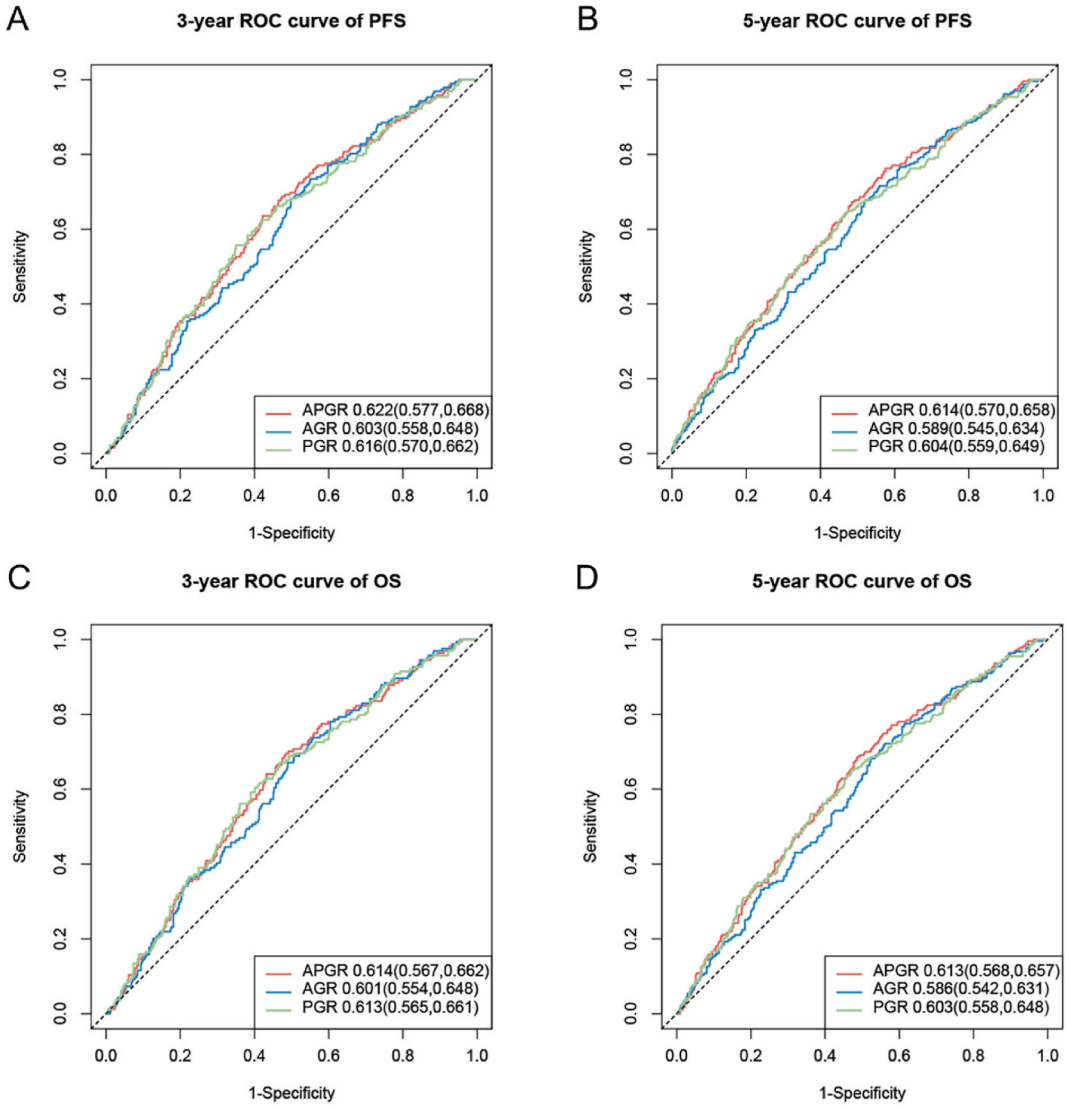

Fig. 3. Comparison of the ability of the visceral protein ratios in predicting PFS/OS.
Notes: A, 3-year ROC curve of PFS; B, 5-year ROC curve of PFS; C, 3-year ROC curve of OS; D, 5-year ROC curve of OS.

of AGR, PGR, and APGR were 0.601, 0.613, and 0.614, respectively (Fig. 3C). For 5-year OS, the AUC of APGR was still superior to those of PGR and AGR (0.613 vs. 0.603 vs. 0.586) (Fig. 3D).

4. Discussion

Systemic inflammation is pivotal in the onset, progression, and response to treatment of tumors, and it has been demonstrated to have an independent association with cancer prognosis [13–16]. The decline in a patient's nutritional status is closely linked to disease progression and is a significant factor contributing to unfavorable treatment outcomes. In perioperative patients, malnutrition not only significantly raises the risk of postoperative complications but is also associated with a poor long-term prognosis [17–19]. Visceral proteins are important indicators of nutritional and inflammatory status in clinical practice. Prealbumin is a small plasma molecular protein that can more sensitively reflect the nutritional status of the body owing to its fast metabolism [20]. Albumin is one of the main plasma protein that provides nutrients and maintains blood volume [21,22], whereas globulin plays a crucial role in the body's immune system [23,24].

In this study, we investigated the prognostic significance of various combinations of visceral proteins in individuals with colon cancer. Alongside the AGR and PGR, we introduce the APGR as a novel marker that could offer greater accuracy and sensitivity in predicting colon cancer outcomes. In comparison to the current visceral protein ratios (AGR and PGR), the APGR demonstrates superior performance in forecasting the outcomes for colon cancer patients. This ratio can be utilized for a thorough assessment of prognosis and offers more effective direction for clinical management.

Individuals exhibiting low visceral protein ratios tended to be older, have a lower BMI, later stage, larger tumor sizes, elevated CEA levels, higher recurrence rates, and higher mortality rates. This indicates that visceral protein ratios can reflect information such as the patient's physical condition, nutritional status, and tumor-invasive phenotype. Low AGR, PGR, and APGR ratios may indicate malnutrition, rapid metabolic depletion, or systemic inflammation.

Kaplan-Meier survival analysis showed that these visceral protein ratios were effective prognostic indicators. In addition, we found that visceral protein ratios could play a good prognostic role in patients with the same pathological stage, suggesting that visceral protein ratios are a strong complement to TNM stage and could be used to differentiate prognosis in patients with the same pathological stage. Notably, compared with the AGR and PGR, the APGR performs particularly well in distinguishing the prognosis of patients with early- and late-stage colon cancer. A diminished ratio of AGR, PGR, or APGR was found to be independently linked to unfavorable PFS and OS in individuals diagnosed with colon cancer. Additionally, the logistic regression analysis reinforced that low levels of AGR, PGR, or APGR serve as independent risk factors for the recurrence of colon cancer. These findings indicate that visceral protein ratios, particularly APGR, hold significant potential as effective indicators for evaluating the prognosis of colon cancer patients.

It is essential to recognize the limitations inherent in this research. To begin with, the study was a retrospective analysis carried out at a single institution, which resulted in a limited sample size. Additionally, the investigation focused solely on widely utilized visceral protein markers in clinical settings. Lastly, the findings of this study necessitate further confirmation and prospective assessments to validate the results.

5. Conclusion

Our research demonstrates that ratios of visceral proteins act as independent indicators of PFS and OS in individuals with colon cancer. Notably, lower levels of AGR, PGR, and APGR correlate with diminished PFS and OS outcomes in these patients. Among the visceral protein ratios analyzed, APGR shows superior performance in forecasting the prognosis of colon cancer patients, suggesting it could serve as a more precise and sensitive measure for predicting their outcomes.

CRediT authorship contribution statement

Hailun Xie: Writing – original draft, Formal analysis, Data curation. **Lishuang Wei:** Writing – original draft, Formal analysis, Data curation. **Mingxiang Liu:** Data curation. **Yanren Liang:** Data curation. **Qiwen Wang:** Data curation. **Shuangyi Tang:** Validation, Supervision. **Jialiang Gan:** Validation, Supervision, Conceptualization.

Novelty & impact statements

Visceral proteins, including albumin, globulin, and prealbumin, reflect the protein-energy status of the body and participate in many important physiological functions. This study has found that visceral protein ratios are independent predictors of progression-free survival (PFS) and overall survival (OS) in patients with colon cancer.

Ethics approval and consent to participate

This study followed the Helsinki declaration. All participants signed an informed consent form and this study was approved by the Institutional Review Board of the hospital (Registration number: NO.2022-KY-(043)). Due to the retrospective nature of this study, the requirement of consent to participate in the study was waived.

Data availability

Data will be made available on request.

Consent for publication

All authors consent for publication.

Funding

This study was supported by the Guangxi College Students' Innovation and Entrepreneurship Training Program (No.202110598306), Guangxi medical and health appropriate techology development and application project (No. S2021095), and Young Elite Scientists Sponsorship Program by CAST (2022QNRC001).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank the members for their substantial work on data collection and patient follow-up.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39326.

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