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ORIGINAL RESEARCH

The Association of Inflammatory Related Markers with the Prognosis in Elderly Patients with Colorectal Cancer

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Background: Colorectal cancer (CRC) is a common malignancy, especially among older adults. Inflammation has been implicated in cancer progression, making inflammatory indices potential prognostic markers. This study aimed to evaluate the prognostic significance of the Glasgow prognostic score (GPS), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/C-reactive protein ratio (LCR), and C-reactive protein/albumin ratio (CAR) in older adults with CRC.

Methods: This population-based, retrospective observational study included patients aged ≥ 65 years with colorectal adenocarcinoma who were admitted to Taichung Veterans General Hospital (Chiayi branch) between 2017 and 2022. Demographic and clinicopathological characteristics, and results of inflammatory indices were collected from medical records for all patients. Receiver operating characteristic (ROC) curve analyses were performed to determine the optimal cutoffs of the inflammatory indices in predicting overall mortality. Associations between the inflammatory indices, overall survival (OS) and progression-free survival (PFS) were determined using univariate and multivariable Cox proportional hazard regression analyses, with model performance evaluated using the C-index.

Results: Data of 106 patients were analyzed. After adjusting for confounders, GPS ≥1 (vs 0) significantly predicted poor OS (adjusted hazard ratio [aHR]: 3.80, 95% confidence interval [CI]: 1.30–11.10, p= 0.015, C-index= 0.825) and PFS (aHR: 3.19, 95% CI: 1.34–7.57, p= 0.008, C-index= 0.785). CAR ≥1.0 (vs <1) significantly predicted poor OS (aHR: 2.36, 95% CI: 1.01–5.48), p=0.046, C-index= 0.825) and PFS (aHR: 2.33, 95% CI: 1.14–4.76, p= 0.020, C-index= 0.786).

Conclusion: Among hospitalized older adults with CRC in Taiwan, high GPS and CAR, but not NLR, PLR or LCR, are potentially useful prognostic indicators for poor OS and PFS.

Keywords: Colorectal cancer, CRC, prognosis, mortality, inflammation index, Taiwan

Introduction

Colorectal cancer (CRC) is a relatively prevalent malignancy, ranking as the second most commonly diagnosed cancer in females and the third most commonly diagnosed cancer in males worldwide, which accounts for 10% of all cancer cases globally.[1] The older adult population bears the greatest burden of CRC, with nearly 70% of cases occurring in individuals aged 65 years or older and 40% in those aged over 75 years.[2,3] While older patients with pT4 disease face a higher risk of postoperative complications, the impact of age on survival outcomes remains unclear. Prognosis in older individuals may be affected by factors such as disease stage, tumor location, existing health conditions, and treatment type.[4]

The lack of early symptoms and reluctance to undergo colonoscopy contribute to a significant number of CRC patients being diagnosed at an advanced stage, resulting in poor overall survival (OS)[5]. Currently, the TNM staging system is widely used to predict OS and recurrence in patients with CRC. However, prognosis varies considerably among patients with the same TNM stage,[6] posing a challenge for clinicians in determining the most appropriate treatment strategies. Consequently, enhancing prognostic prediction depends on incorporating additional potential biomarkers into clinical practice. Notably, RAS mutational status serves as a vital biomarker for predicting responses to anti-EGFR

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antibodies and is associated with CRC's oncological aggressiveness, site-specific recurrence risk, and pathologic response to chemotherapy. Additionally, miRNAs, acting as tumor regulators, are under exploration for their diagnostic, prognostic, and predictive roles in CRC.[7]

The link between inflammation and cancer has long been recognized, since cancer often arises in areas of chronic inflammation and an abundance of inflammatory cells are found in biopsies of tumor tissue.[8] Moreover, the relationship between cancer-related inflammation and tumor progression is well-established.[9] Therefore, evaluating preoperative inflammatory indices may serve as a valuable tool in predicting tumor development and prognosis.

Cancer-related inflammation encompasses a complex interplay between cytokines, immune cells, and inflammatory mediators originating from both the tumor and the host.[10,11] The extent of inflammation is revealed by serum leukocyte levels, neutrophils, lymphocytes, platelets, and acute-phase proteins such as C-reactive protein (CRP).[12] These factors, either individually or combinations of these factors, may have different levels of accuracy in predicting prognosis. Several inflammatory indices are used in oncology, including the Glasgow prognostic score (GPS),[13] neutrophil-lymphocyte ratio (NLR),[14] platelet-lymphocyte ratio (PLR),[15] lymphocyte/C-reactive protein ratio (LCR),[16] and C-reactive protein/albumin ratio (CAR).[17] In one study, the LCR, for example, better predicted the prognosis of patients with stage IV cancer than other markers.[18] A GPS of 2 was associated with shorter OS of patients with advanced gastric cancer compared to longer PFS associated with disease control by chemotherapy immediately before nivolumab (DCBC)—both potential biomarkers for nivolumab monotherapy in gastric cancer patients.[19] Indications are that each index may provide valuable insight into patients' inflammatory state, making it potentially able to predict CRC prognosis.

In Taiwan, as of January 2022, individuals aged 65 years and older accounted for 16.91% of the total population.[20] As the older population increases and Taiwan transitions toward an aging society, an urgent need arises to identify more reliable and easy-to-use biomarkers in predicting the outcomes of CRC among older patients. Therefore, this study aimed to determine the prognostic significance of five inflammatory indices (ie, GPS, NLR, PLR, LCR, and CAR) calculated from routinely performed blood tests in older adult inpatients with CRC in a regional hospital in Taiwan.

Patients and Methods

Study Design and Sample

This retrospective, single-center study included hospitalized patients aged 65 years and older, diagnosed with CRC and admitted to the Chiayi Branch, Taichung Veterans General Hospital between January 2017 and December 2022. Patients younger than 65 years, first diagnosed with CRC before 2017, lacking complete data of inflammatory indices of interest, lost to follow-up, treated with endoscopic mucosal resection (EMR), with concurrent appendicitis or a gastrointestinal stromal tumor (GIST), or transferred to another hospital after surgery were excluded.

Patient Characteristics and Measures of Inflammatory Indices

Patients' baseline characteristics were obtained from patients' medical records, including sex, age, body weight, and standing height. The Eastern Cooperative Oncology Group (ECOG) scale was also used to evaluate patients' daily activity and performance.

Levels of CRP and albumin, and neutrophil, lymphocyte, and platelet counts were measured in the clinical laboratory using routine blood samples from the peripheral vein. Five inflammatory indices were calculated. The GPS assigned a score of 2 to patients with elevated CRP levels (>1.0 mg/dl) and hypoalbuminemia (<3.5 g/dl), while giving a score of 1 to those with only one of these abnormalities, and a score of 0 to those without positive inflammatory indices.[19] The NLR was determined by dividing the absolute level of neutrophils by that of lymphocytes. The PLR was calculated by dividing the absolute level of platelets by that of lymphocytes. The LCR was calculated by dividing the absolute level of lymphocytes by the level of C-reactive protein. The CAR was determined by dividing CRP by the albumin measurement.

Study Outcomes

The primary outcomes were patients' overall survival (OS) and progression-free survival (PFS).

Statistical Analysis

Descriptive statistics are presented as counts (n) and percentages (%) for categorical data, and as mean ± standard deviation (SD) or median with interquartile range (IQR: Q1-Q3) for continuous data as appropriate due to normality assumption. A receiver operating characteristic (ROC) curve analysis was utilized to establish the optimal cutoff values (ie, with the highest Youden index) of all studied inflammatory indices in predicting OS.

Univariate and multivariable Cox proportional hazard (PH) regression analysis were performed to assess the impact of the inflammatory indices on OS and PFS, based on the cutoff values derived from ROC curve analyses. Any factors with p-value <0.15 in univariable analysis were entered into the multiple Cox PH model for adjustment. C-index was calculated to evaluate the performance of the multiple Cox regression models.

All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using the IBM SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA) and the R package, "survival" for calculating the C-index.

Results

Patient Selection and Characteristics

The flowchart of patient selection is shown in Figure 1. The data of 106 older adult patients with CRC were included in the analysis. Table 1 shows patients' baseline characteristics. During the follow-up period, 44 patients (41.5%) presented with cancer progression, and 36 patients (34.0%) died. Patients' mean age was 78.4 years (SD=9.2) and 68.9% were male. The distributions of ECOG from grade 0 to grade 4 were 7.5%, 50.0%, 15.1%, 17.0% and 10.4%, respectively. Regarding inflammatory indices scores, 59 patients (55.7%) scored 1 in GPS, while 39 patients (36.8%) scored 0, and the others scored 2 (7.5%). The median values were 4.4 (IQR: 2.6–7.3) for NLR, 201.0 (IQR: 137.4–296.2) for PLR, 700.6 (IQR: 220.0–2396.3) for LCR, and 0.6 (IQR: 0.2–1.9) for CAR. The tumors of these patients were mostly located at the

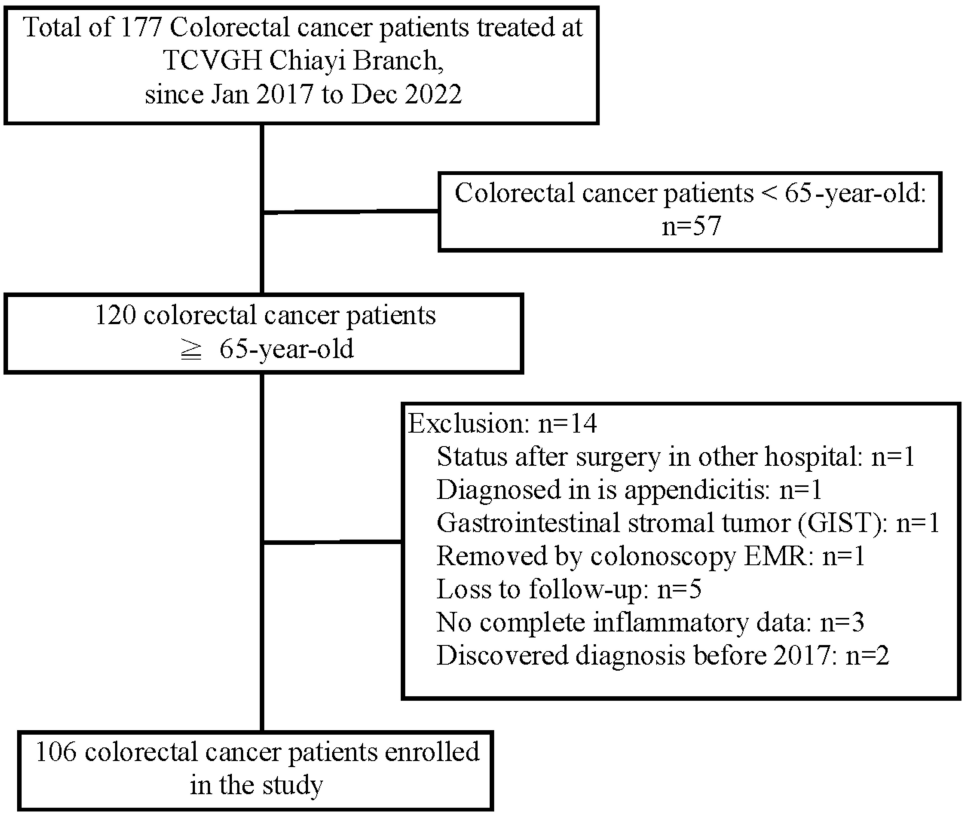

Figure 1 Flow chart of patient selection.

Table 1 Baseline Characteristics of Study Population

	Mean ± SD or Median (IQR) or N (%)
Age (years)	78.4 ± 9.2
65–74	41 (38.6)
75–84	36 (34.0)
>84	29 (27.4)
Sex	
Male	73 (68.9)
Female	33 (31.1)
BMI[a] (kg/m^2)	22.19 ± 3.8
<18.5	17 (17.7)
18.5–24	50 (52.1)
>24	29 (30.2)
Smoking	14 (13.2)
Inflammatory indices	
GPS	
0	39 (36.8)
1	59 (55.7)
2	8 (7.5)
NLR	4.4 (2.6–7.3)
<4.7	59 (55.7)
≥4.7	47 (44.3)
PLR	201.0 (137.4–296.2)
<341.6	88 (83.0)
≥341.6	18 (17.0)
LCR	700.6 (220.0–2396.3)
<520.6	46 (43.4)
≥520.6	60 (56.6)
CAR	0.6 (0.2–1.9)
<1.0	62 (58.5)
≥1.0	44 (41.5)
Clinical status	
ECOG	
0	8 (7.5)
1	53 (50.0)
2	16 (15.1)
3	18 (17.0)
4	11 (10.4)
Tumor location	
Cecum	5 (4.7)
Ascending colon	26 (24.3)
Transverse colon	3 (2.8)
Descending colon	6 (5.6)
Sigmoid colon	37 (34.6)
Rectum and Anus	29 (27.1)
TNM Stage[b]	
T	
T1	9 (8.7)
T2	8 (7.7)
T3	66 (63.5)
T4	21 (20.2)

(*Continued*)

Table 1 (Continued).

	Mean ± SD or Median (IQR) or N (%)
N	
N0	48 (46.2)
N1	34 (32.7)
N2	22 (21.2)
M	
M0	78 (75.0)
M1	26 (25.0)
Stage (by AJCC)	
I	10 (9.6)
II	33 (31.7)
III	35 (33.7)
IV	26 (25.0)
Received surgery (Yes)	70 (66.0)
Diagnosis year	
2017–2019	43 (40.6)
2020–2022	63 (59.4)
Follow-up (months)	15.6 (4.0–24.9)

Notes: [a]Ten patients lacked baseline data. [b]Two patients lacked baseline stage information.
Abbreviations: SD, standard deviation; IQR, interquartile range, expressed as (Q1, Q3); GPS, Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio, PLR, platelet/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; C-reactive protein/albumin ratio; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer.

sigmoid colon (34.6%), followed by rectum and anus (27.1%). About 66.0% received surgical treatment. The distribution of cancer stage classified by American Joint Committee on Cancer (AJCC), from stage I to stage IV were 9.6%, 31.7%, 33.7% and 25%. The median follow-up time was 15.6 months (IQR: 4.0–24.9).

ROC Curve Analysis on Discriminative Ability of Inflammatory Indices for OS

Results of ROC curve analysis of the inflammatory indices in predicting overall mortality are depicted in Supplementary Figure S1. The area under ROC curve (AUC) and optimal cutoff values of the five inflammatory indices were: GPS ≥1 (AUC= 0.665, p=0.006); NLR ≥4.7 (AUC=0.639, p=0.020); PLR ≥341.6 (AUC=0.540, p=0.496); LCR <520.6 (AUC=0.673, p=0.004); and CAR ≥ 1.0 (AUC=0.706, p=0.001).

Associations Between the Inflammatory Indices and Survival Outcomes

Table 2 presents the results of univariate analysis, demonstrating associations between the inflammatory indices, other study variables, and OS and PFS. Higher GPS (≥1), NLR (≥4.7), PLR (≥341.6), and CAR (≥1.0) were associated with increased risk of overall mortality and disease progression (all HR>1, p<0.05). In contrast, LCR ≥ 520.6 was associated with decreased HR for overall mortality (HR: 0.32, 95% CI: 0.16–0.63) and disease progression (HR: 0.35, 95% CI: 0.19–0.64). Aside from the inflammatory indices, age, BMI, ECOG, received surgery vs not, and advanced disease were significantly associated with both overall mortality and disease progression (all p<0.05).

Table 3 shows the results of multivariable analysis. After adjusting for age, BMI, ECOG, received surgery vs not and advanced cancer, the adjusted HR of GPS ≥1 (vs 0) was 3.80 (95% CI: 1.30–11.10) for overall mortality and 3.19 (95% CI:1.34–7.57) for disease progression. The adjusted HR for CAR ≥1.0 (vs <1.0) was 2.36 (1.01–5.48) for overall mortality and 2.33 (1.14–4.76) for disease progression. In contrast, NLR, PLR and LCR at given cutoff values were not associated with OS or PFS. Figures 2 and 3 show the cumulative survival curves for OS and PFS of the indices by given cutoff values, respectively.

The c-index was used to validate the model's ability to accurately rank risk associated with outcomes. Accordingly, the multiple Cox PH models demonstrated good discriminative ability for OS (all c-index >0.8) and PFS (all c-index >0.75).

Table 2 Univariate Cox Analysis of Associations Between Inflammatory Indices, Other Covariates, and OS and PFS

	OS		PFS	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
GPS (≥1 vs 0)	**3.94 (1.63–9.53)**	**0.002**	**3.21 (1.54–6.73)**	**0.002**
NLR (≥4.7 vs <4.7)	**2.42 (1.23–4.79)**	**0.011**	**2.47 (1.34–4.57)**	**0.004**
PLR (≥341.6 vs <341.6)	**4.07 (1.86–8.92)**	**<0.001**	**2.97 (1.41–6.23)**	**0.004**
LCR (≥520.6 vs <520.6)	**0.32 (0.16–0.63)**	**0.001**	**0.35 (0.19–0.64)**	**<0.001**
CAR (≥1.0 vs <1.0)	**3.50 (1.76–6.98)**	**<0.001**	**3.17 (1.71–5.86)**	**<0.001**
Age	**1.04 (1.01–1.08)**	**0.012**	**1.04 (1.01–1.07)**	**0.012**
Sex (Female vs Male)	1.37 (0.69–2.72)	0.370	1.43 (0.77–2.66)	0.256
BMI[a]	**0.87 (0.79–0.96)**	**0.005**	**0.89 (0.81–0.97)**	**0.010**
Smoking (Yes vs No)	0.63 (0.19–2.07)	0.448	0.48 (0.15–1.56)	0.224
ECOG				
0	Ref		Ref	
1	2.33 (0.31–17.77)	0.413	1.58 (0.37–6.77)	0.541
2	2.91 (0.34–24.99)	0.330	1.80 (0.36–8.92)	0.473
3	5.39 (0.66–43.96)	0.116	3.15 (0.67–14.91)	0.148
4	**18.05 (2.20–148.35)**	**0.007**	**8.06 (1.68–38.73)**	**0.009**
Received surgery (Yes vs No)	**0.12 (0.05–0.25)**	**<0.001**	**0.15 (0.07–0.29)**	**<0.001**
TNM Stage (by AJCC)[b]				
I	Ref		Ref	
II	4.67 (0.60–36.38)	0.141	2.29 (0.51–10.38)	0.282
III	2.10 (0.25–17.51)	0.491	2.36 (0.53–10.50)	0.258
IV	**15.20 (1.98–116.84)**	**0.009**	**8.96 (2.01–39.98)**	**0.004**
Advanced disease (metastatic vs non-metastatic)[c]	**5.27 (2.63–10.56)**	**<0.001**	**4.30 (2.24–8.23)**	**<0.001**

Notes: P-values < 0.05 are shown in bold. [a]Ten patients lacked baseline data. [b]Two patients lacked baseline stage information. [c]Based on AJCC M stage, 2 missing data would be classified as non-metastatic.

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, Hazard ratio; CI, confidence interval; GPS, Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio, PLR, platelet/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; C-reactive protein/albumin ratio; ECOG, Eastern Cooperative Oncology Group.

Table 3 Multivariable Cox Analysis of Associations Between Inflammatory Indices, OS and PFS

	OS			PFS		
	aHR (95% CI)	***P* value**	**C-index**	**aHR (95% CI)**	***P* value**	**C-index**
GPS (≥1 vs 0)	**3.80 (1.30–11.10)**	**0.015**	0.825	**3.19 (1.34–7.57)**	**0.008**	0.785
NLR (≥4.7 vs <4.7)	1.25 (0.49–3.22)	0.642	0.816	1.69 (0.76–3.77)	0.199	0.767
PLR (≥341.6 vs <341.6)	0.86 (0.29–2.48)	0.774	0.818	0.76 (0.29–1.99)	0.578	0.773
LCR (≥520.6 vs <520.6)	0.57 (0.24–1.33)	0.193	0.822	0.56 (0.27–1.17)	0.123	0.780
CAR (≥1.0 vs <1.0)	**2.36 (1.01–5.48)**	**0.046**	0.825	**2.33 (1.14–4.76)**	**0.020**	0.786

Notes: All models were adjusted for p<0.15 in univariate analysis, including age, BMI, ECOG, received surgery vs not and advanced cancer. P-values < 0.05 are shown in bold.

Abbreviations: OS, overall survival; PFS, progression-free survival; aHR, adjusted Hazard ratio; CI, confidence interval; GPS, Glasgow prognostic score; NLR, neutrophil/lymphocyte ratio, PLR, platelet/lymphocyte ratio; LCR, lymphocyte/C-reactive protein ratio; C-reactive protein/albumin ratio; ECOG, Eastern Cooperative Oncology Group.

Associations Between the Cancer Stage and the Inflammatory Indices

Owing that cancer stage is a critical factor highly associated with mortality and progression, an additional association analysis between the cancer stage and the inflammatory indices was conducted. The results are summarized in Supplemental Table 1. Throughout the stages, a noticeable increase was observed in the prevalence of high GPS (≥1), rising from 40% at Stage I to 84.6% at Stage IV (p =0.024). Similarly, the proportion of high CAR also exhibited an upward trend, escalating from 30% at Stage I to 65.4% at Stage IV (p =0.024). Conversely, the proportion of high LCR (≥520.6) demonstrated a decline with advancing cancer stages, shifting from 70% at Stage I to 34.6% at Stage IV (p =0.016).

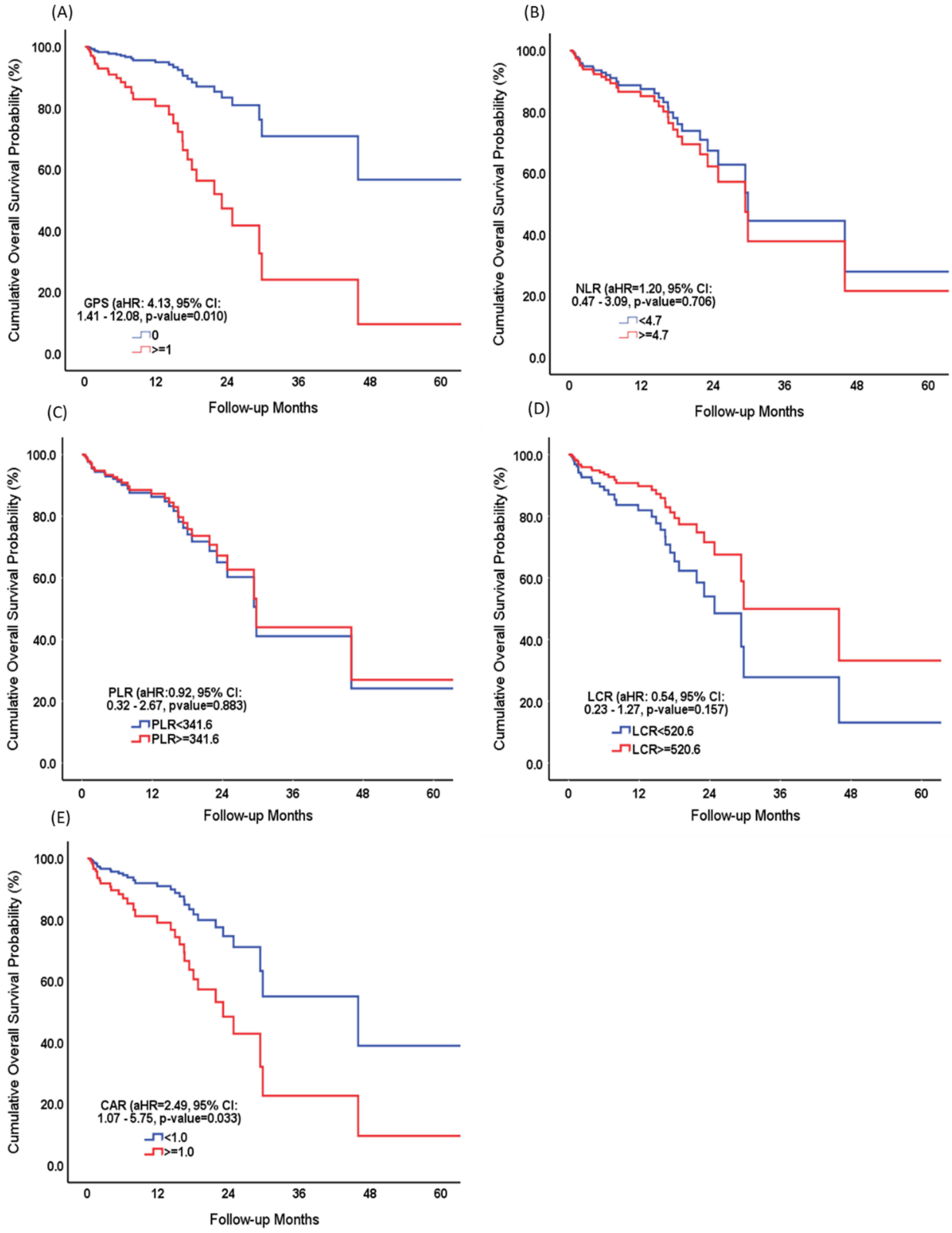

Figure 2 Estimated survival curves for the impact of the inflammatory indices on OS. (**A**) GPS, (**B**) NLR, (**C**) PLR, (**D**) LCR, (**E**) CAR. Adjusted for age, BMI, ECOG, surgery vs no surgery and advanced cancer.

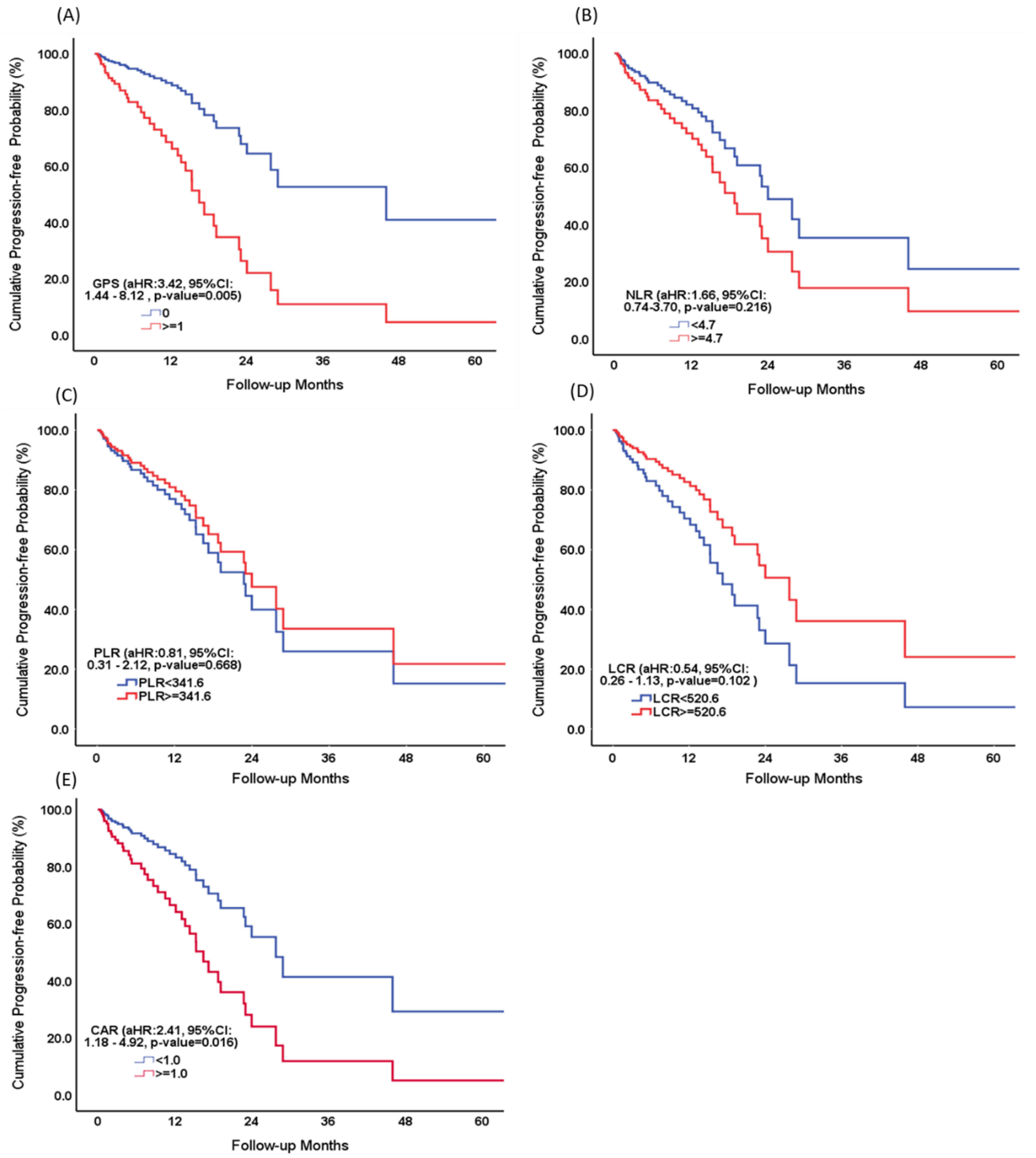

Figure 3 Estimated survival curves for the impact of the inflammatory indices on PFS. (**A**) GPS, (**B**) NLR, (**C**) PLR, (**D**) LCR, (**E**) CAR. Adjusted for age, BMI, ECOG, surgery vs no surgery and advanced cancer.

Discussion

The present study revealed that, among hospitalized older patients with CRC in Taiwan, GPS ≥1 and CAR ≥1.0 were independently associated with poor OS and PFS, indicating the potential clinical utility of these indices as prognostic biomarkers. However, it appears that NLR, PLR, and LCR at given cutoffs do not independently predict CRC mortality in this patient population. The observed correlations between tumor stage and inflammatory indices, specifically the

increase in GPS and CAR and decline in LCR with advancing stage, underscore the utility of these markers in refining prognostic assessments and tailoring treatment for older CRC patients.

The inflammation-based GPS has been studied as a predictor of tumor behavior and prognosis for different cancers, including CRC.[21–23] The score is derived from elevated serum CRP and decreased albumin concentration, reflecting patients' systemic inflammatory response, and is also suggested to reflect patients' nutritional status.[19] In the present study, after adjusting for patient factors such as age, received surgery vs not, and advanced disease as potential confounders, higher GPS (≥1 vs 0) significantly predicted poor OS and PFS in older adults with CRC. This is consistent with previous studies in which both GPS and the modified GPS (mGPS) have been shown to be significant and objective independent prognostic indicators in CRC.[13] Recent studies that analyzed inflammatory markers in patients with CRC after curative surgery reported that high scores for GPS were significantly associated with cause-specific survival and disease-free survival (DFS).[24,25] Another recent study showed that a GPS of 1 or 2 independently affected survival in CRC patients.[26] In addition to its predictive ability for postoperative survival, the GPS score prior to surgical treatment has also been shown to be a prognostic factor for survival in patients receiving palliative chemotherapy.[27] For example, GPS was identified as a predictive factor for adjuvant chemotherapy in patients who had undergone curative surgery for gastric cancer, again reflecting patients' immune response and nutritional status.[28]

CAR was shown in the present study to be better able than other potential markers to distinguish overall mortality and disease progression in the included older patients with CRC. CAR values represent the interactive relationship between C-reactive protein and albumin, reflecting systemic inflammatory response and dystrophy. A meta-analysis of nine studies with over 3000 patients with CRC found that pretreatment CAR results were associated with poor OS and DFS.[29] Also, in patients with soft tissue sarcoma, the use of CAR preoperatively showed superior prognostic ability compared to other commonly used inflammatory indices (GPS, NLR, PLR) and was independently associated with OS and DFS.[17] Influential patient factors included larger tumor size, higher grade tumors, and advanced cancer, emphasizing that more aggressive tumor behavior increases the prognostic value of some biomarkers. A study of patients with ovarian cancer found that elevated CAR scores were associated with advanced stages, residual tumor after surgical intervention, ascites and high values for serum carbohydrate antigen (CA-125), indicating that a highly predictive CAR value was associated with tumor progression.[30] Accordingly, while the measurement of given inflammatory indices may support them as being independently associated with OS and DFS, the importance of patient factors in the predictive effectiveness of these markers urges us to use them not only as prognostic indicators but also as clinically significant indications for individualizing treatment strategies. Furthermore, studies have indicated that there is a notable increase in the expression of PD-L1 in immune cells in CRC with deficient mismatch repair (MMR) compared to tumors with proficient MMR, with no differences among the different MMR-deficient molecular subtypes. The process of identifying faulty DNA MMR includes the use of immunohistochemistry (IHC) and/or microsatellite instability (MSI) tests. However, effectively interpreting the diverse characteristics of MSI testing to obtain meaningful data presents significant challenges.[31]

In addition to GPS and CAR as prognostic indicators in CRC and other cancers, different combinations of the inflammatory indices NLR, PLR, and LCR with other markers have been shown across multiple studies to have different levels of clinical significance and prognostic value for various cancers. Among the first parameters evaluated for prognostic ability in CRC patients, the systemic immune-inflammation index (SII) was reported to be a more powerful tool for predicting OS and PFS in patients with CRC who underwent radical surgery compared to NLR and PLR values.[12] Using a similar construct as the present study, but reaching entirely different results, a previous retrospective study of patients with CRC analyzed the prognostic value of NLR, PLR, lymphocyte-to-monocyte ratio (LMR), and albumin/globulin ratio (AGR) using regression analysis, finding that these indices were independently and significantly associated with shorter OS and DFS.[14] In another previous study, high scores for these factors preoperatively were also associated with the poor response of solid tumors to surgical treatment and with poor survival outcomes.[32] However, these results are in direct contrast with our recent results in older adult CRC patients. In the present study, NLR, PLR and LCR at given cutoff values were not independently associated with OS or PFS, and all results were validated by c-indexes, indicating that these factors were reliable for projecting the prognosis of select patients with CRC. Although the results of the above previous studies do not agree with the present results for all parameters, the discrepancies can be explained by differences in patient factors between the study populations, particularly the inclusion of more patients in

those studies with aggressive advanced cancer compared to the present study, and also whether or not they underwent surgery. By design all patients in the present study were also older adults and age was significantly associated with both overall mortality and disease progression. The importance of patient factors cannot be overlooked when analyzing the predictive value of inflammatory indices in patients with CRC.

Results of the present study have furthered the understanding of how inflammatory mediators behave in cancer development and particularly how older patients' inflammatory response reflects the tumor microenvironment. The prognostic ability of the inflammatory indices is especially valuable in this context. The immune systems of patients with CRC, as with other cancers, display an anti-tumor response to the disruption of tissue homeostasis, thereby infiltrating tumors with lymphocytes.[5] The infiltrating lymphocytes contribute to cancer growth and metastasis as well as to the immunosuppression associated with such malignancies.[8] Inflammation follows as a necessary part of repairing damage at the cellular level while the tumor rearranges the stromal environment.[11] Local immune cells help to assess the prognosis of individual cases, using cell counts from the inflammatory environment of the tumor site where leukocytes from the patients are found in both the supporting stroma and nearby areas. In some cancers, T-cells are associated with improved disease-specific and disease-free survival, while fewer T-cells, or a high frequency of non-T cells representing granulocytes, are associated with a poor immune response and poorer survival rates.[9] Pro-inflammatory cytokines like tumor necrosis factor and interleukins (IL-6, IL-17) are noted in CRC. Although the role of these factors in health is to help maintain gut homeostasis, in CRC they activate key oncologic transcription factors that promote cancer cell proliferation and resistance to apoptosis. In response, T-cells produce anti-inflammatory cytokines (IL-10), chemokines and transforming growth factor—a suppressive process that drives inflammation.[33] Although this mechanism does not apply directly or precisely to all cancers, since other cell types and genetic factors may be involved, it does describe the basis of the tumor inflammatory microenvironment—supporting the potential use of inflammatory indices as biomarkers for CRC.

Strength and Limitations

This is the first study to demonstrate the predictive significance of routinely performed hematologic inflammatory indices on the prognosis of older Taiwanese adults with CRC. Results of the indices are clinically applicable and can be helpful for risk stratification of older adult patients with CRC.

This study also has several limitations. First, the retrospective study design limits generalization of results to other populations and selection bias cannot be ruled out. Also, this single-center study with a relatively small sample size of only Taiwanese patients may include biases and may also limit the generalization of results to other populations. Second, the tumor locations were diverse, which may lead to diverse therapeutic outcomes. Also, some patients underwent surgery and some did not, and even though we stratified patients by surgery or not, outcomes cannot be compared between the two groups because results of the biomarkers would be necessarily different. Larger prospective cohort studies stratifying tumor conditions and patients' age are still needed to obtain more solid evidence and confirm results of the present study.

Conclusions

In Taiwan, among older adult patients with CRC, the inflammatory indices GPS and CAR independently predict poor survival outcomes. These indicators serve as predictive factors for CRC prognosis among the defined population. Future prospective multicenter studies with larger sample size are highly recommended.

Data Sharing Statement

Data are available from corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study protocol was approved by the Institutional Review Board (IRB) of Taichung Veterans General Hospital and complies with the Declaration of Helsinki. All written inform consents were obtained from each patient.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author has declared that no competing interests exist.

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