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ORIGINAL RESEARCH

Robust Predictive Performance of MLPAS and CCMLP for Clinical Outcome and Risk Stratification in Patients with Colorectal Cancer

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Background: There is no recognized biomarker is recommended to monitor or predict the prognosis of colorectal cancer (CRC) patients with negative detection of carcinoembryonic antigen (CEA) or carbohydrate antigen 19–9 (CA19-9) and to classify high recurrence-risk cases.

Methods: Discovery and two-stage validation cohorts, which included 2111 radically resected patients with stage II–III CRC, were enrolled in this study. We detected preoperative peripheral monocyte, platelet, albumin (Alb), pre-albumin (pAlb), CEA, and CA19-9 and investigated the prognostic and risk-stratified roles of twelve new inflammatory biomarkers in the three cohorts.

Results: In our study, monocyte-to-pAlb ratio (MPAR), monocyte-to-lymphocyte -to-Alb ratio (MLAR), monocyte-to-lymphocyte-to-pAlb ratio (MLPAR), monocyte- to-pAlb score (MPAS), lymphocyte-to-monocyte-Alb score (MLAS), lymphocyte-to monocyte-pAlb score (MLPAS), and platelet-to-lymphocyte-Alb score (PLAS) were significantly associated with both RFS and OS in three cohorts. MLPAS showed the best performance in predicting RFS and OS, and it was related to right-tumor location and significant cancer burden (≥5cm) in the overall population. Moreover, MLPAS is a robust prognostic biomarker in subgroups stratified by CEA or CA19-9. Patients with scores zero and two of the CEA-CA19-9-MLPAS score (CCMLP) showed the lowest and highest recurrence and death rates, respectively, and significant survival differences were observed between them.

Conclusion: MLPAS is an optimal, independent, and robust prognostic biomarker in the stage II–III CRC population, especially with negative CEA or CA19-9. The CCMLP could effectively classify high recurrence-risk patients who require more focus, monitoring, and treatment for the clinic.

Keywords: colorectal cancer, inflammation, prognosis, lymphocyte to monocyte-pre-albumin score, CEA-CA19-9-MLPAS score

Introduction

Primary radical resection is the way to cure patients with early-stage colorectal cancer (CRC).[1] However, approximately 22.24% and 43.09% of stage II and stage III CRC patients can be observed to have recurrence or distal metastasis in three years' follow-up.[2] So, accurately identifying patients with high-recurrence risk and efficient stratification of those who harbor unsatisfactory outcomes is essential for clinical treatment and decision-making.

Currently, carcinoembryonic antigen (CEA) is one of the most common biomarkers used to monitor recurrence and predict the survival of postoperative patients.[3] Its sensitivity ranged from 41% to 97% and specificity from 52% to 100%

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for CRC.[4] Unfortunately, a small number of patients with negative CEA detection and CEA neither classify the patients with high-recurrence risk nor predict the survival of these patients.[5,6] Carbohydrate antigen 19–9 (CA19-9) is the second most common biomarker to predict the survival of these postoperative patients. High and low CA19-9 detections can stratify patients with different outcomes.[6,7] However, the expected efficacy is unsatisfactory, and significant survival heterogeneity was observed in patients with either high or low CA19-9.[8] Hence, it is urgent to discover the ideal biomarker to monitor and predict CRC patients, especially for patients with negative CEA or CA19-9.

It is well known that cancer-elicited inflammation is a hallmark of malignancy, including CRC.[9] Systematic chronic inflammation can regulate the expression of albumin (Alb), and pre-albumin (pAlb). High circulating, monocyte (Mon) and platelet (Plt) counting, and low lymphocyte (Lym) counting are commonly detected in peripheral samples of CRC patients. Our previous study showed that new combined inflammatory ratios could help select patients who could benefit from adjuvant chemotherapy and bevacizumab-based target therapy and were superior to the single biomarker in predicting the prognosis of patients with early or advanced CRC.[10–13] Several inflammatory scores, such as the inflammation-Immunity-Nutrition score, Glasgow prognostic score, and Naples prognostic score, were also considered as independent prognostic biomarkers for CRC.[14–16] However, there is no study to report the prognostic role of Mon to Alb ratio (MAR), Mon to pAlb ratio (MPAR), ratio of Mon to Lym to Alb (MLAR), ratio of Mon to Lym to pAlb (MLPAR), Plt to Alb ratio (PAR), ratio of Plt to Lym to Alb (PLAR) in stage II–III CRC. The predicting efficacy of Mon-Alb score (MAS), Mon-pAlb score (MPAS), Lym to Mon-Alb score (MLAS), Lym to Mon-pAlb score (MLPAS), Plt-Alb score (PAS), and Plt to Lym-Alb score (PLAS) in the prognosis of these patients remains unknown.

In this study, we formed twelve inflammatory biomarkers, and three cohorts, including 2111 patients, were enrolled to investigate: 1) the prognostic role of these biomarkers in CRC; 2) the optimal prognostic biomarker between them, especially in subgroups with negative CEA or CA19-9; 3) the stratification role of the optimal prognostic biomarker in identifying the patients with high-recurrence risk and unsatisfactory outcome.

Materials and Methods

Population

In our study, 1413 patients recruited from the Second Affiliated Hospital of Nanchang University were randomly divided into discovery and internal validation cohorts in a 6:4 ratio following previous research.[17] An external validation cohort consisted of patients from Nanjing First Hospital, and the Second Hospital of Shandong First Medical University, respectively. All enrolled patients shall meet the following inclusion criteria: 1) clinical and pathological detection confirmed patients with stage II–III CRC according to the Chinese Protocol of Diagnosis and Treatment of Colorectal Cancer;[18] 2) the enrolled patients received radical resection; 3) all the patients participated voluntarily and signed the informed consent form. The patients who meet the following criteria shall be excluded: 1) combined with other malignancies, hematological or autoimmune diseases, as well as recent infections or injuries; 2) combined with benign chronic inflammatory intestinal disease; 3) age under 18 years old; 3) non-firstly clinical confirmation or performed clinical intervention ahead of clinical confirmation. The Ethics Committee of each hospital approves this study, and all eligible patients have signed the informed consent form.

Data Collection

The following clinical characteristics: gender, age, life history (smoking and drinking), and chronic diseases (diabetes, hypertension) were collected from the electronic medical record system in each hospital. Two senior pathological experts examined tumor pathological characteristics, such as tumor invasion, lymph node status or distal metastasis, cell differentiation, and tumor size.

Sample Collection and Laboratory Detection

We collected clinical samples, a 2mL EDTA anti-coagulation peripheral blood sample, a 2mL sodium citrate anti-coagulation plasma sample, and a 4mL serum sample at 7:00~9:00 am from each patient before clinical surgery. Peripheral blood cell counting, such as circulating neutrophil, monocyte, lymphocyte, and platelet counting, was measured by Sysmex HST-302 analyzer (Sysmex, Tokyo, Japan). AU5400 analyzer (Beckman Coulter, Tokyo, Japan)

was used to detect serum Alb and pAlb using bromocresol green colorimetry and immunoturbidimetric assay, respectively. The cancer biomarkers CEA and CA19-9 were detected by chemiluminescent immunoassay using the SIEMENS ADVIA Centaur XP machine (Siemens, Erlangen, Germany). We measured peripheral blood counting within two hours after sample collection, and the other detections were completed within six hours. The coefficients of variation within intra- and inter-assay of the detection was less than 10%.

According to the computational formula, we formed and calculated six inflammatory biomarkers, MAR, MPAR, MLAR, MLPAR, PAR, and PLAR, based on the detection results. We also established six inflammatory scores, MAS, MPAS, MLAS, MLPAS, PAS, and PLAS, and each of them was defined as score zero, one, and two according to the cut-off value of each parameter. The detailed formulas and defined scores are displayed in Table S1.

Follow-Up

We performed three years of follow-up in each eligible patient, three months in the first and second years and six months in the third year. The follow-up was conducted through clinical follow-up, telephone, email, and consultation of clinical records. Recurrence and distal metastasis were diagnosed by clinical imaging detection. The deadline for follow-up was Dec 31, 2023. The follow-up endpoints are recurrence-free survival (RFS) and overall survival (OS), and the times from surgery to clinical recurrence/distal metastasis or death and follow-up deadline were defined as RFS and OS, respectively.

Statistics

The optimal cut-off values of each inflammatory biomarker and six inflammatory ratios were defined using X-tile software (Yale University, New Haven, Connecticut) relying on RFS (Table S1). Binary variables were displayed as numbers and percentages, and the differences in each group were compared using the chi-square test and Fisher's exact test. Continuous variables were shown as average ± standard deviation (SD) and were compared using the Kruskal–Wallis *H*-test in intergroup analysis. We conducted the Kaplan–Meier curve (Log rank test) and the univariate and multivariate Cox regression model to identify independent factors in influencing RFS and OS for the patients, determining the hazard ratios (HR) and 95% confidence intervals (CI). We used time-dependent receiver operating characteristic (ROC) curves to assess and compare the effectiveness of these indicators in predicting prognosis. Statistical analysis was performed using SPSS. 27.0 (IBM Corp, Armonk, NY, USA), R4.3.3 (Institute for Statistics and Mathematics, Vienna, Austria), along with GraphPad Prism 10 (GraphPad Software Inc., San Diego, USA).

Results

According to inclusion and exclusion criteria, 2111 eligible patients were enrolled in this study. The discovery, internal, and external validation cohorts included 847, 566, and 698 cases. The detailed baseline characteristics are displayed in Table 1. In three cohorts, it shows significant differences in MAR, MAS, MPAR, MPAS, MLAS, PAR, PAS, PLAR, recurrence rate, and death rate. More than 75% of the patients received postoperative adjuvant chemotherapy in each cohort. The postoperative recurrence rates were 27.20%, 26.30%, and 36.80% in discovery, internal, and external validation cohorts. However, the death rates were similar in the three cohorts.

Table 1 Baseline Clinical Characteristics of the Eligible Patients in Three Cohorts

Parameters	Discovery Cohort N = 847, N (%)	Internal Validation Cohort N = 566, N (%)	External Validation Cohort N = 698, N (%)	*p*-Value
Gender (male)	499(58.90%)	350(61.80%)	453(64.90%)	0.06
Age (>60 year)	411(48.60%)	265(46.90%)	414(59.30%)	<0.01*
Smoking (yes)	139(16.40%)	100(17.70%)	87(12.40%)	0.03
Drinking (yes)	102(12.00%)	65(11.50%)	57(8.20%)	0.04
Diabetes (yes)	65(7.70%)	43(7.60%)	58(8.30%)	0.86
Hypertension (yes)	146(17.20%)	98(17.30%)	150(21.50%)	0.07

(*Continued*)

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Table 1 (Continued).

Parameters	Discovery Cohort N = 847, N (%)	Internal Validation Cohort N = 566, N (%)	External Validation Cohort N = 698, N (%)	*p*-Value
Radical operation (yes)	847(100%)	566(100%)	698(100%)	
Chemotherapy (yes)	650(76.70%)	450(79.50%)	537(77.00%)	0.44
Radiotherapy (yes)	67(7.90%)	39(6.90%)	36(5.20%)	0.13
Chemoradiotherapy (yes)	652(77.00%)	450(79.50%)	579(82.90%)	0.02
TNM stage (III)	417(49.20%)	302(53.40%)	331(47.40%)	0.10
T stage (T3-4)	769(90.80%)	512(90.50%)	664(95.10%)	<0.05
Tumor size (≥5cm)	365(43.10%)	241(42.60%)	294(42.10%)	0.93
Differentiation (G2)	91(10.80%)	66(11.70%)	103(14.70%)	0.13
Right hemicolon	214(25.30%)	146(25.80%)	186(26.70%)	0.81
Rectum	392(46.30%)	269(47.50%)	354(50.70%)	0.21
LN status (N1)	418(49.40%)	302(53.40%)	331(47.40%)	0.11
Adenocarcinoma	847(100.00%)	566(100.00%)	698(100.00%)	
CEA (>5ng/mL)	255(31.20%)	175(31.70%)	262(47.00%)	<0.01*
CA19-9 (>37U/mL)	150(18.40%)	118(21.50%)	94(17.60%)	0.22
MAR	8.77(5.99–12.04)	8.89(6.30–11.92)	10.15(7.07–14.49)	<0.01*#
High MAS	188(22.20%)	117(20.70%)	255(36.50%)	<0.01*
MPAR	1.69(1.16–2.67)	1.80(1.15–2.58)	2.05(1.44–3.10)	<0.01*#
High MPAS	205(24.20%)	140(24.70%)	278(39.80%)	<0.01*
MLAR	58.46(40.57–88.68)	56.70(40.40–82.27)	59.00(40.32–88.63)	0.52#
High MLAS	220(26.00%)	123(21.70%)	207(29.70%)	<0.05
MLPAR	11.43(7.36–20.18)	11.22(7.23–18.59)	11.04(7.13–19.55)	0.71#
High MLPAS	231(27.30%)	144(25.50%)	211(30.30%)	0.18
PAR	5.55(4.43–6.94)	5.68(4.46–7.03)	5.88(4.49–7.51)	0.04#
High PAS	207(24.40%)	135(23.90%)	239(34.30%)	<0.01*
PLAR	3.79(2.77–5.25)	3.62(2.72–5.19)	3.23(2.47–4.78)	<0.01*#
High PLAS	229(27.00%)	148(26.20%)	194(27.80%)	0.84
Recurrence rate	230(27.20%)	149(26.30%)	257(36.80%)	<0.01*
Death rate	125(14.80%)	95(16.80%)	168(24.10%)	<0.01*

Note: #compared with the rank-sum test; *$p < 0.001$.

Abbreviations: LN, lymph node status; MAR, monocyte to albumin ratio; MAS, monocyte- albumin score; MPAR,monocyte to pre-albumin ratio; MPAS, monocyte-pre-albumin score; MLAR, ratio of monocyte to lymphocyte to albumin; MLAS, lymphocyte to monocyte-albumin score; MLPAR, ratio of monocyte to lymphocyte to pre-albumin; MLPAS, lymphocyte to monocyte-pre- albumin score; PAR, platelet to albumin ratio; PAS, platelet-albumin score; PLAR, ratio of platelet to lymphocyte to albumin; PLAS, platelet to lymphocyte-albumin score.

In the discovery cohort, significant survival differences were observed in high- and low-groups stratified by cell differentiation, lymph node status (LN), CEA, CA19-9, MAR, MAS, MPAR, MPAS, MLAR, MLAS, MLPAR, MLPAS, PAR, PAS, PLAR, and PLAS in terms of RFS and OS in the analysis of Kaplan–Meier curve, respectively (Figure 1A and B). Moreover, LN, CEA, CA19-9, MAR, MAS, MPAR, MPAS, MLAR, MLAS, MLPAR, MLPAS, PAR, PAS and PLAS were still significantly associated with clinical outcomes of the patients with stage II–III CRC, respectively (Table 2).

In internal validation cohort, LN, CA19-9, MAS, MPAR, MPAS, MLAR, MLAS, MLPAR, MLPAS, PAR, PAS, PLAR, and PLAS were validated to be significantly associated with survival of the patients, respectively (Figure 1C and D, 2A and B). Moreover, the significant associations of CEA, CA19-9, MPAR, MPAS, MLAR, MLAS, MLPAR, MLPAS, and PLAS with the prognosis were still observed in the external validation cohort (Figures 1E and F, 2C and D).

Time-dependent ROC showed that MLPAS harbored the highest areas under the curve (AUCs) to predict 12 (AUC = 0.65 for RFS, AUC = 0.67 for OS), 24 (AUC = 0.64 for RFS, AUC = 0.64 for OS), and 36 (AUC = 0.63 for RFS, AUC = 0.64 for OS) months' survival in the overall population (Figure 3A and B). The AUCs of MLPAS are higher than CEA ($p < 0.01$) or CA19-9 ($p < 0.01$) in predicting one, two, and three years' of RFS and OS of the patients (Table S2). Furthermore, the distribution of left primary tumor locations is significantly higher in patients with low-MLPAS than in high-MLPAS patients

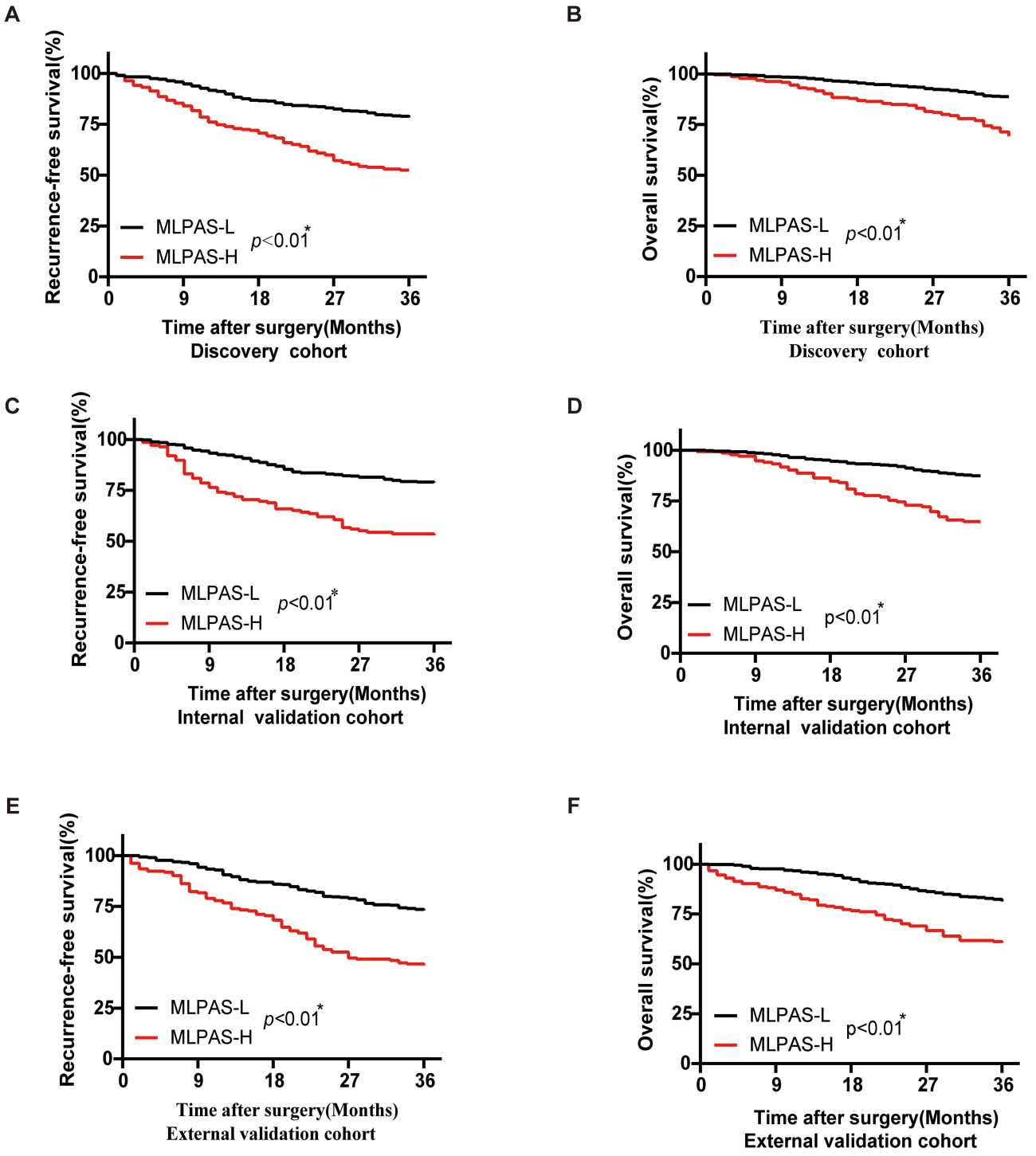

Figure 1 Kaplan–Meier curve of MLPAS in the three cohorts. (**A** and **B**) recurrence-free survival and overall survival in the discovery cohort, respectively; (**C** and **D**) recurrence-free survival and overall survival in the internal validation cohort, respectively; (**E** and **F**) recurrence-free survival and overall survival in the external validation cohort, respectively.
Notes: *$p < 0.001$.

($p < 0.01$). Patients with high MLPAS harbored a significantly enormous cancer burden (≥5cm) compared to patients with low MLPAS ($p < 0.01$) (Figure 3C and D). However, no distribution difference between high- and low-MLPAS was observed in the subgroups stratified by TNM stage, cell differentiation, or LN.

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Table 2 Kaplan–Meier Curve and Cox Regression Analysis in Discovery Cohort

Parameters	Recurrence-Free Survival			Overall Survival		
	p-Value	Crude HR (95% CI)	Adjusted HR (95% CI)	*p*-Value	Crude HR (95% CI)	Adjusted HR (95% CI)
Gender (male)	0.32	1.15(0.88–1.49)	1.09(0.82–1.46)	0.68	0.93(0.65–1.32)	0.91(0.62–1.34)
Age (>60 year)	0.15	1.21(0.93–1.57)	1.33(1.01–1.76)	<0.05	1.78(1.24–2.56)	1.95(1.32–2.88)
Smoking (yes)	0.40	1.16(0.83–1.61)	1.05(0.64–1.71)	0.63	1.12(0.71–1.78)	1.06(0.53–2.11)
Drinking (yes)	0.24	1.24(0.86–1.80)	1.30(0.89–1.91)	0.37	1.26(0.76–2.07)	1.19(0.71–2.00)
Diabetes (yes)	0.64	0.89(0.53–1.48)	0.74(0.43–1.28)	0.90	1.04(0.55–1.99)	0.79(0.40–1.57)
Hypertension (yes)	0.55	0.90(0.63–1.28)	0.75(0.52–1.09)	0.80	1.06(0.67–1.67)	0.86(0.54–1.38)
Chemotherapy (yes)	0.25	0.84(0.63–1.13)	0.66(0.48–0.90)	<0.05	0.68(0.47–0.99)	0.59(0.39–0.90)
Radiotherapy (yes)	0.14	1.37(0.90–2.10)	1.56(0.99–2.48)	0.76	0.90(0.46–1.78)	1.40(0.69–2.84)
T stage (T3-4)	0.18	1.42(0.85–2.36)	2.57(1.50–4.39)	0.38	1.36(0.69–2.67)	2.44(1.17–5.10)
Tumor size (≥5cm)	0.87	0.98(0.75–1.27)	1.11(0.83–1.47)	0.16	1.29(0.90–1.83)	1.46(1.01–2.12)
Differentiation (G2)	<0.05	1.81(1.26–2.62)	1.35(0.92–1.98)	<0.01*	2.19(1.38–3.48)	1.62(0.99–2.65)
LN status (N1)	<0.01*	2.50(1.89–3.29)	3.28(2.43–4.43)	<0.01*	2.34(1.61–3.40)	3.17(2.10–4.80)
CEA (>5ng/mL)	<0.01*	2.02(1.55–2.63)	1.73(1.30–2.29)	<0.01*	2.46(1.73–3.51)	1.82(1.25–2.65)
CA19-9 (>37U/mL)	<0.01*	2.29(1.71–3.05)	2.15(1.58–2.91)	<0.01*	2.77(1.90–4.04)	2.62(1.77–3.88)
High MAR	<0.01*	1.62(1.24–2.11)	1.48(1.12–1.95)	<0.05	1.75(1.23–2.50)	1.47(1.01–2.14)
High MAS	<0.01*	2.11(1.60–2.77)	1.88(1.41–2.50)	<0.05	1.75(1.20–2.56)	1.53(1.03–2.27)
High MPAR	<0.01*	2.98(2.27–3.89)	2.65(2.00–3.52)	<0.01*	2.97(2.08–4.24)	2.57(1.77–3.73)
High MPAS	<0.01*	3.01(2.31–3.92)	2.61(1.97–3.44)	<0.01*	2.55(1.78–3.63)	2.17(1.50–3.15)
High MLAR	<0.01*	1.87(1.42–2.47)	1.73(1.29–2.32)	<0.01*	2.23(1.55–3.21)	1.99(1.36–2.90)
High MLAS	<0.01*	2.14(1.64–2.79)	2.07(1.57–2.74)	<0.01*	2.33(1.63–3.33)	2.08(1.44–3.01)
High MLPAR	<0.01*	2.37(1.82–3.09)	2.18(1.65–2.88)	<0.01*	2.79(1.97–3.97)	2.41(1.68–3.47)
High MLPAS	<0.01*	2.67(2.05–3.47)	2.45(1.86–3.22)	<0.01*	3.03(2.13–4.30)	2.58(1.79–3.70)
High PAR	<0.01*	1.69(1.25–2.29)	1.68(1.22–2.32)	<0.05	1.75(1.17–2.63)	1.54(1.01–2.37)
High PAS	<0.01*	1.66(1.26–2.19)	1.72(1.29–2.30)	<0.05	1.81(1.25–2.61)	1.79(1.23–2.62)
High PLAR	<0.05	1.46(1.11–1.92)	1.46(1.10–1.94)	<0.05	1.53(1.06–2.20)	1.64(1.00–2.68)
High PLAS	<0.01*	1.67(1.27–2.18)	1.71(1.29–2.27)	<0.05	1.79(1.25–2.56)	1.72(1.18–2.50)

Notes: *p*-value: the value of Kaplan–Meier curve; multivariate cox regression was adjusted by gender, age, smoking, alcohol, diabetes, hypertension, radiotherapy, chemotherapy, T stage, tumor size, differentiation, node lymph status; *$p < 0.001$.

Abbreviations: LN, lymph node status; MAR, monocyte to albumin ratio; MAS, monocyte- albumin score; MPAR, monocyte to pre-albumin ratio; MPAS, monocyte-pre-albumin score; MLAR, ratio of monocyte to lymphocyte to albumin; MLAS, lymphocyte to monocyte-albumin score; MLPAR, ratio of monocyte to lymphocyte to pre-albumin; MLPAS, lymphocyte to monocyte-pre-albumin score; PAR, platelet to albumin ratio; PAS, platelet-albumin score; PLAR, ratio of platelet to lymphocyte to albumin; PLAS, platelet to lymphocyte-albumin score.HR, hazard ratio; CI, confidence interval; High MAR, MPAR, MLAR, MLPAR, PAR, PLAR, value larger than the cut-off value; High MAS, MPAS, MLAS, MLPAS, PLAS, score higher than score zero.

In patients with negative CEA, the recurrence rate was 24.03%, and the rate within the high-MLPAS cases was significantly higher than in the low-MLPAS patients ($p < 0.01$ for 42.01% vs 17.77%). Recurrence rates were 26.46%, 43.48%, and 19.63% in CA19-9-negative patients and patients with high- or low-MLPAS, respectively (Table S3). The survival of patients with low-MLPAS was superior to that of high-MLPAS patients in subgroups with either negative CEA or CA19-9 or both negative CEA and CA19-9 (Figure 4A–F). Moreover, significant survival differences were also observed in high- and low-MLPAS patients with positive CEA or CA19-9.

According to the cut-off values of CEA, CA19-9, and MLPAS, we established a new prognostic score named CCMLP. Among them, 43.58%, 55.25%, 1.17% of the patients were defined as score zero, one, and two of CCMLP, respectively. The recurrence rates of the patients with CCMLP scores zero, one, and two were 16.03%, 38.62%, and 71.43%, respectively, and the rate in score zero and two patients is low and significantly high compared to CEA, CA19-9, or MLPAS as well as combined CEA or CA19-9 and MLPAS scores (Table S3). The death rates were 8.08%, 25.78%, and 47.26% in each subgroup stratified by CCMLP (Table S3). The Kaplan–Meier curve showed that the patients with scores zero and two harbored the best and worst outcomes (Figure 4G–J), and significant clinical outcome differences were observed in comparison of the score one vs score 0

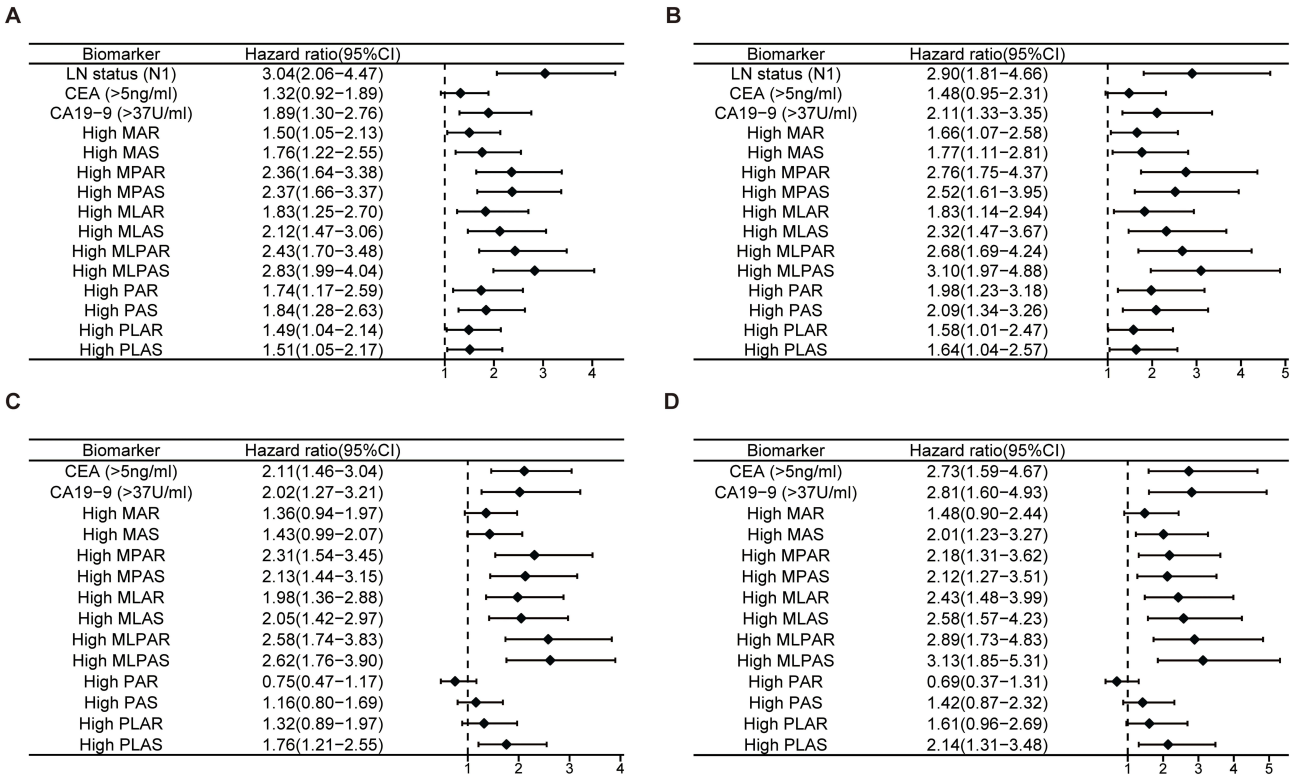

Figure 2 Forest plot of LN status, CEA, CA19-9, and the twelve inflammatory biomarkers in the internal and external validation cohorts. (**A**) recurrence-free survival in the internal validation cohort; (**B**) overall survival in the internal validation cohort; (**C**) recurrence-free survival in the external validation cohort; (**D**) overall survival in the external validation cohort.

[adjusted HR (95% CI) = 2.56 (2.03–3.22) for RFS; adjusted HR (95% CI) = 3.41 (2.44–4.77) for OS] and score two vs score 0 [adjusted HR (95% CI) = 10.86 (5.89–20.00) for RFS; adjusted HR (95% CI) = 9.53 (4.35–20.92) for OS] (Table 3).

Discussion

It is unknown what the prognostic and stratifying role of MLPAS is in patients of stage II–III CRC, particularly in cases with negative CEA or CA19-9. Our study observed that three new inflammatory ratios (MPAR, MLAR, MLPAR) and four new inflammatory scores (MPAS, MLAS, MLPAS, PLAS) were independent predictive biomarkers for the prognosis of patients in the three cohorts. MLPAS was the best factor in predicting the clinical outcome of the patients, especially in the CEA or CA19-9 negative subgroup. Moreover, CCMLP could effectively identify postoperative patients with the lowest and the highest risk of recurrence and death.

As we know, CRC is a kind of metabolic wasting disease accompanied by metabolic reprogramming, contributing to malnutrition, hypoalbuminemia, sarcopenia, or even cachexia.[19,20] Moreover, high systematic chronic inflammation, which CRC elicits, is commonly observed in middle- or advanced-stage disease, showing elevated counting of peripheral neutrophils, monocytes, platelets, and lymphocytopenia.[2,12,21] Our previous studies showed that the Neu to Lym ratio and fibrinogen to pAlb ratio were independent prognostic biomarkers for CRC.[22,23] Xie also reported that combined neutrophil/lymphocyte ratio and C-reaction protein index could serve as an effective biomarker to predict the survival of cancer.[24] In this study, we found that three new ratios (MPAR, MLAR, MLPAR) and four scores (MPAS, MLAS, MLPAS, PLAS) were significantly associated with the prognosis of stage II–III CRC patients in discovery, internal, and external validation cohorts, demonstrating that these new inflammatory biomarkers were robust and independent biomarkers to predict the outcome of the patients. MLPAS harbored the highest predicted efficacy among these biomarkers for predicting the clinical outcome of the patients, implying that it is an optimal and ideal prognostic factor. Significant associations were observed not only in patients with positive CEA or CA19-9 but also in the negative

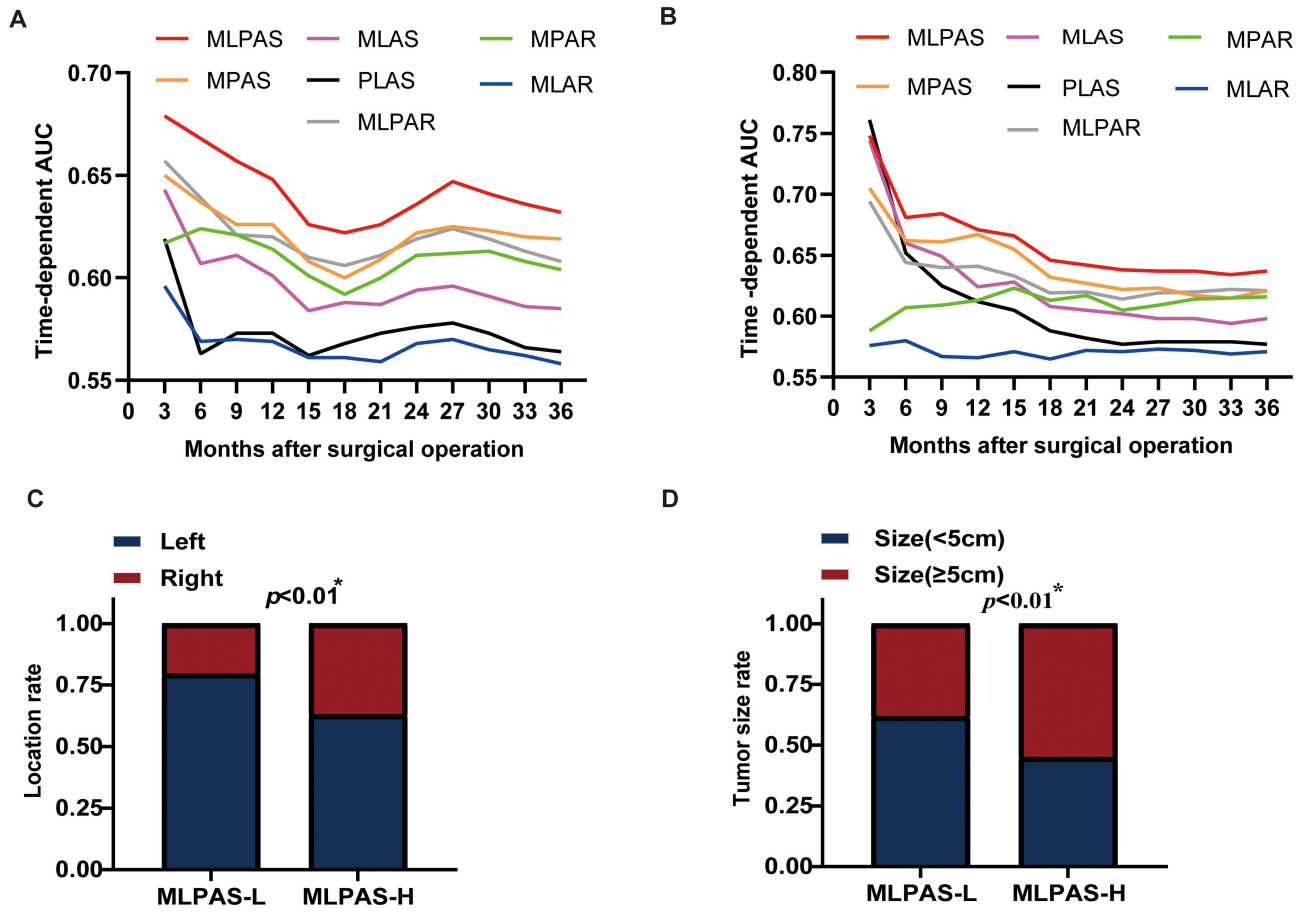

Figure 3 Prognostic area under time-dependent ROC (AUROC) of seven new inflammatory biomarkers and association of MLPAS with primary tumor location and cancer burden in the overall population. (**A**) recurrence-free survival; (**B**) overall survival; (**C**) MLPAS and primary tumor location; (**D**) MLPAS and cancer burden.
Notes: *p < 0.001.

patients, revealing that MLPAS was superior to CEA and CA19-9, and it could be recognized as a supplementary biomarker for cancer biomarkers to predict the outcome, particular for the patients with negative results.

MLPAS is a new inflammatory score for the Lym to Mon ratio and pAlb. Cytotoxic T lymphocytes and B lymphocytes are the main components consistent with tumor-infiltrating lymphocytes and play an essential role in anti-tumor characteristics, contributing to a favorite clinical outcome in CRC regardless of microsatellite instability status.[25] Tumor-associated macrophages, differentiated from circulating monocytes, can accelerate CRC tumorigenesis via IL-6 and IL-8 secretion.[26,27] Serum Alb, especially pre-Alb, is the optimal factor reflecting the nutritional status in patients, and inflammatory reactions can contribute to hypoalbuminemia, leading to poor survival.[28] Moreover, MLPAS was significantly correlated with CRC characteristics, including primary tumor location and cancer burden. The association between these clinical features and the progression of CRC consequently affects the prognosis of patients with CRC. Thus, MLPAS is an optimal biomarker to reflect systematic inflammation and predict clinical outcomes in patients with CRC.

No widely recognized solution exists to classify the postoperative progression patients or the best survival cases.[29] Exosomes, circulating tumor cells, and circulating tumor DNA detections were reported to stratify CRC patients relying on microfluidics-based methods, nanoparticles, electrochemical biosensors, respectively.[30–32] However, the high detection requirements of these biomarkers restrict their popularization and application, especially in many primary medical units. In this study, we newly formed CCMLP, and we found that the recurrence and death rates among patients with CCMLP zero score were the lowest compared to negative CEA, CA19-9, MLPAS, or combined two of them. On the contrary, the highest recurrence and death rates were found in patients with triple-positive biomarkers (MLPAS score two), and the highest recurrence and death rates were approximately 4.5-fold and six-fold compared to the lowest rates,

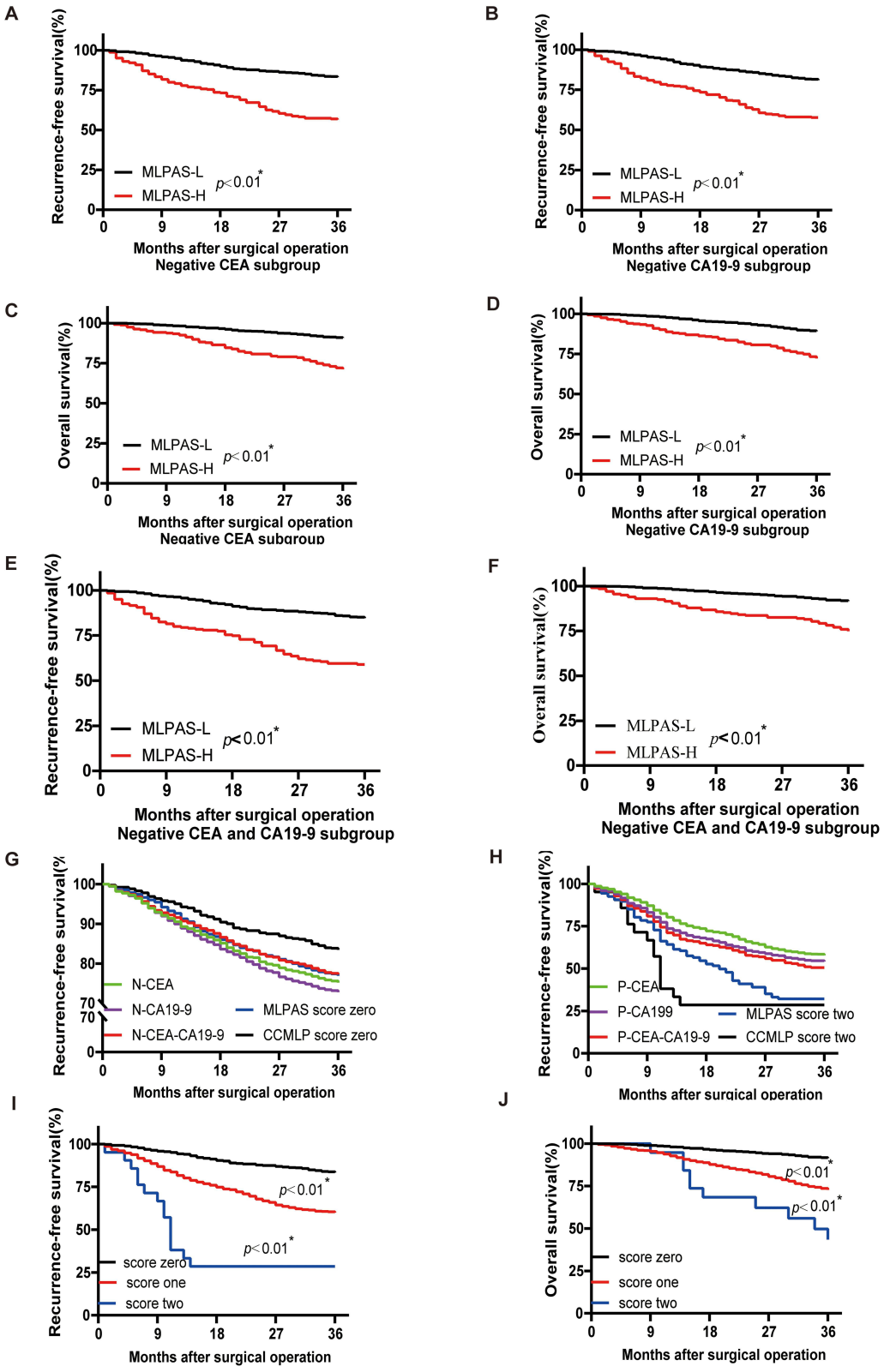

Figure 4 Kaplan–Meier curve of CEA, CA19-9, MLPAS, CCMLP in the overall population. (**A** and **C**) MLPAS in negative CEA subgroup; (**B** and **D**) MLPAS in negative CA19-9 subgroup; (**E** and **F**) MLPAS in both negative CEA and CA19-9 subgroup (**G**) RFS comparison in subgroups with negative CEA, CA19-9, MLPAS, both negative CEA and CA19-9, and CCMLP (score zero); (**H**) RFS comparison in subgroups with positive CEA, CA19-9, and MLPAS (score two), and CCMLP (score two); (**I** and **J**) clinical outcome comparison in subgroups stratified by CCMLP score.

Notes: *$p < 0.001$.

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Table 3 Kaplan–Meier Curve and Cox Regression Analysis of CCMLP in Overall Population

CCMLP	Recurrence-Free Survival			Overall Survival		
	p-Value	Crude HR (95% CI)	Adjusted HR (95% CI)	*p*-Value	Crude HR (95% CI)	Adjusted HR (95% CI)
Score zero		1	1		1	1
Score one	<0.01*	2.84(2.32–3.48)	2.56(2.03–3.22)	<0.01*	3.59(2.73–4.74)	3.41(2.44–4.77)
Score two	<0.01*	9.43(5.48–16.23)	10.86(5.89–20.00)	<0.01*	8.75(4.48–17.10)	9.53(4.35–20.92)

Notes: CCMLP, CEA-CA19-9-MLPAS score; score zero: CEA ≤ 5.0, CA19-9 ≤ 37.0 and MLPA score = 0; score one: Single CEA ≤ 5.0 or CA19-9 ≤ 37.0 or MLPA score≥1; score two: CEA > 5.0, CA19-9 > 37.0 and MLPA score = 2; *p*-value: the value of Kaplan–Meier curve; *$p < 0.001$; multivariate cox regression was adjusted by gender, age, smoking, alcohol, diabetes, hypertension, radiotherapy, chemotherapy, T stage, tumor size, differentiation, node lymph status.

respectively. Moreover, CCMLP was an independent and robust biomarker for predicting the survival of patients in the overall population. These results illustrate that CCMLP could identify subgroups with significant differences in outcome, and it helped to distinguish a class of patients with high-recurrence risk who need clinical focus and real-time monitoring.

The new inflammatory indexes, estimated based on peripheral blood counting and circulating Alb or pAlb detection, are simple, economical, practical, and easy to popularize. In our large sample size and multiple center study, we first reported that MLPAS was a robust and independent prognostic score for patients with both negative- and positive CEA or CA19-9 patients. It is also the first time to report a new biomarker CCMLP, and we confirmed that the newly combined score could serve as a new classification system based on chronic inflammation. However, some limitations should be addressed as follows: 1) we did not obtain comprehensive treatment data, such as the detailed chemotherapy regimen and cycle, as well as clinical response data; 2) we did not detect some other important biomarkers, for example, circulating tumor cell, due to the shortage of research fund; 3) some studies showed postoperative detection was the better choice for prediction of the patients, we only detected the preoperative sample, and it is still a question for preoperative or postoperative detection; 4) cancer-elicited inflammation may vary according to its molecular subtype. However, we did not obtain the molecular characteristics, such as mutation of *RAS, BRAF*, and microsatellite instability status, in these patients. Thus, the prognostic roles of MLPAS and CCMLP in subgroups stratified by these molecular characteristics remain unclear.

In summary, MLPAS is a robust, independent, economical, and practical inflammatory indicators for patients with either negative or positive CEA or CA19-9. CCMLP is helpful in precise inflammatory classification and identifying a clinical focus and high-risk populations.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

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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 authors declare no conflicts of interest in this work.

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