Journal of Inflammation Research

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ORIGINAL RESEARCH

Advanced Lung Cancer Inflammation Index for Predicting Prognostic Risk for Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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Purpose: The decreased advanced lung cancer inflammation index (ALI), defined as body mass index (BMI) * albumin (Alb)/ neutrophil-to-lymphocyte ratio (NLR), is an independent prognostic risk factor for overall survival in gastric, lung, and colorectal cancers. This study aimed to investigate the value of ALI in predicting the risk of major adverse cardiovascular events (MACEs) in patients with acute coronary syndrome (ACS).

Patients and Methods: A total of 1624 patients with ACS undergoing percutaneous coronary intervention (PCI) were consecutively enrolled between January 2016 and December 2018. Follow-up data were collected at 1, 3, 6, and 12 months and annually thereafter. The primary endpoints were MACEs. All endpoints were defined as all-cause mortality, recurrent angina pectoris, restenosis/intra stent thrombosis, stroke, heart failure, and all-cause bleeding.

Results: The MACEs group and non-MACEs group showed significant differences in patients with age >65 years (28 [50.0%] vs 319 [23.7%]), history of heart failure (16 [28.6%] vs 127 [9.4%]), history of ischemic stroke (14 [25.0%] vs 186 [13.8%]), history of cardiogenic shock (6 [10.71%] vs 16 [1.19%]), left ventricular ejection fraction <40% (8 [14.29%] vs 33 [2.46%]), and ALI <343.96 (44 [78.65%] vs 680 [50.60%]) (all p<0.001). The optimal cut-off value for ALI was 334.96. The area under the curve (AUC) of the 1-, 2-, 3-, and 5-year was 0.560, 0.577, 0.665, and 0.749, respectively. The survival rate was significantly lower in the low ALI group than in the high ALI group (log-rank p<0.001). Low ALI was an independent risk factor for the long-term prognosis of patients with ACS after PCI, univariate HR: 3.671, 95% CI: 1.938–6.953, p<0.001; multivariate HR: 3.009, 95% CI: 1.57–5.769, p=0.001.

Conclusion: ALI score less than 334.96 is an independent prognostic risk factor for patients with ACS undergoing PCI and may be a novel marker for clinical practice.

Keywords: acute coronary syndrome, advanced lung cancer inflammation index, prognosis, percutaneous coronary intervention

Introduction

Recent research shows that more than 7 million people are newly diagnosed with acute coronary syndrome (ACS) each year.[1] Although great progress has been made in the diagnosis and treatment of ACSs, such as the development of percutaneous coronary intervention and dual antiplatelet therapy and the high prevalence of coronary computed tomographic angiography, ACS remains the leading cause of death worldwide.[2–5] Accurate assessment of prognostic risk and standard follow-up are widely recognized to be important approaches to improving patient survival.[6] In recent years, research attention has focused on different kinds of inflammatory indices, as a convenient and noninvasive measure for diagnosing and assessing prognostic risks.[7–9]

Received: 28 May 2023
Accepted: 15 August 2023
Published: 23 August 2023

The advanced lung cancer inflammation index (ALI) is a novel index that was firstly reported by Jafri et al in 2013.[10] This index is defined as body mass index (BMI) * albumin (Alb)/neutrophil-to-lymphocyte ratio (NLR). BMI is calculated as the height (m)/ weight (kg)^2. The NLR is involved in inflammation, and both BMI and albumin are associated with systemic nutritional status. Numerous studies have shown that inflammation and nutrient status are correlated with coronary heart disease (CAD).[11] The derived neutrophil-to-lymphocyte ratio is an novel independent predictor of mortality in patients undergoing PCI.[12] In oncology, decreased ALI is an independent prognostic risk factor for overall survival in gastric, lung, and colorectal cancers.[13–15] Our previous study using ALI-based nomograms also showed the diagnostic significance of ALI.[16]

However, the ability of ALI to predict the prognostic risk in patients with ACS undergoing PCI remains unknown. Thus, this study aimed to investigate the value of ALI in predicting the risk of MACEs in patients with ACS undergoing PCI.

Materials and Methods

Study Design and Population

This prospective cohort study was approved by the Ethics Committee of the Affiliated Hospital of Chengde Medical University (Number: LL2021036) and was conducted according to the tenets of the Declaration of Helsinki. All participants provided informed consent.

In this study, 1624 patients with ACS who underwent PCI were consecutively enrolled between January 2016 and December 2018 at the Affiliated Hospital of Chengde Medical University. The inclusion and exclusion criteria were based on our previous study.[12] Particularly, age was adjusted to >18 years. Patient data during hospitalization were collected by postgraduates who received professional education, using standard procedures. The diagnostic criteria for hypertension, type 2 diabetes mellitus, smoking, dyslipidemia, and ischemic stroke were as described in our previous study.[17] Details about PCI, premedication, and the definition of successful PCI have also been included in our previous study.[17] Dual antiplatelet therapy including ticagrelor or clopidogrel and other secondary prevention were administrated for the patients with ACS after PCI at least 12 months as suggested by "2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet, Therapy in Patients With Coronary Artery Disease". All laboratory data were collected within 24 hours after ACS diagnosis and before PCI. The specifications and models of the testing instruments can also be found in our previous study.[17]

Follow-Up and Endpoints

Follow-up data were collected via a review of electronic medical records and/or clinic visits at 1, 3, 6, and 12 months and annually thereafter. The primary study endpoints were MACEs, including all-cause mortality and the requirement for rehospitalization with severe heart failure (HF). All-cause mortality was defined as death of any cause. Severe HF was defined as a New York Heart Association classification grade IV. All endpoints were defined as all-cause mortality, ACS recurrence/cardiac ischemia/angina, restenosis/intrastent thrombosis, stroke/transient ischemic attack, heart failure, all-cause bleeding.[18]

Statistical Analysis

The normality of distribution of continuous variables was confirmed using the Kolmogorov–Smirnov test, and normally and non-normally distributed variables were presented as the mean ± standard deviation and as the median with interquartile range, respectively. Differences in non-normally distributed continuous variables between the MACEs and non-MACEs groups, which was the same as the low and high ALI groups, were analyzed using the Mann–Whitney *U*-test. Meanwhile, categorical variables were presented as numbers (%) and compared using the $\chi 2$ test. Survival was estimated using the Kaplan–Meier method and compared between the groups using the Log rank test. The diagnostic value of ALI was evaluated using receiver operating characteristic (ROC) curves, and the optimal cut-off value was determined using Youden's index (sensitivity + specificity - 1). Before trend analysis, the ALI index was divided equally into three: T1, T2, and T3. Significant variables in the univariate Cox proportional hazard model (ie, those with P<0.3) were entered into a multivariate Cox hazard proportional model. In the univariate and multivariate Cox hazard proportional hazards models and p for trend, age was divided into four categories (<55, 56–65, 66–75, and >76

years) as ranking variables. The R package time ROC and survival were used to plot time-dependent ROC curves, and the R package rms was used to plot the restricted cubic spline (RCS). All statistical analyses were performed using SPSS (version 26; SPSS Inc., Chicago, IL, USA), GraphPad Prism 8.0 (GraphPad Software Inc, La Jolla, CA, USA) and R 4.2.2. P<0.05 was considered statistically significant.

Results

Patient Characteristics

Among the 1624 patients, 28 patients were excluded due to infectious diseases (n=19), blood system diseases (n=5), malignant tumors (n=4), and hypertrophic cardiomyopathy (n=1). In addition, 195 patients were lost to follow-up. Thus, 1400 patients who completed the follow-up were included in the final analysis. The median follow-up time was 1150 days. There were 56 patients who developed MACEs; among them, 51 patients died and 5 patients required rehospitalization for severe HF (Figure 1). Table 1 shows the characteristics of the patients in the MACEs (n=56) and non-MACEs (n=1344) groups. The MACEs group and non-MACEs group showed significant differences in the proportion of patients with age >65 years (28 [50.0%] vs 319 [23.7%]), history of HF (16 [28.6%] vs 127 [9.4%]), history of ischemic stroke (14 [25.0%] vs 186 [13.8%]), history of cardiogenic shock (6 [10.71%] vs 16 [1.19%]), left ventricular ejection fraction (LVEF) <40% (8 [14.29%] vs 33 [2.46%]), ALI <343.96 (44 [78.65%] vs 680 [50.60%]), in the levels of UA (13 [23.2%] vs 528 [39.3%]), albumin (39.8 [37.63–42.05] vs 41.82 [39.30–44.10]), and creatinine (82.64±30.25 vs 69.29±16.26) (all p<0.001). Patients in the MACEs group tended to be aged >65 years and have a history of HF (HF, ischemic stroke, and cardiogenic shock.

The optimal ALI cutoff value was 343.96, and 724 and 676 patients were assigned to the low and high ALI groups, respectively. The groups showed significant differences in the number of patients with male sex (567 [78.31%] vs 479 [70.86%]), dyslipidemia (364 [50.28%] vs 434 [64.20%]), type 2 diabetes mellitus (170 [23.448%] vs 190 [28.11%]), smoking history (401 [55.39%] vs 320 [47.33%]), history of HF (98 [13.54%] vs 45 [6.66%]), family history of CAD (92 [12.71%] vs 114 [16.86%]), UA (141 [19.48%] vs 400 [59.17%]), ST-elevation myocardial infarction (STEMI) (456 [62.98%] vs 168 [24.85%]), and MACEs (44 [6.08%] vs 12 [1.78%]) (all p<0.05). The WBC count (10.06±3.54 vs 7.28 ±2.18), Alb level (40.4 [37.91–42.80] vs 41.82 [39.30–44.10]), and creatinine (Cr) level (71.26±18.77 vs 68.29±15.26) were also significantly different between the low and high ALI groups (all p<0.05). Low ALI was associated with male sex, smoking, history of HF, family history of CAD, STEMI, high WBC count, high Cr levels, and LVEF <40% (Table 2).

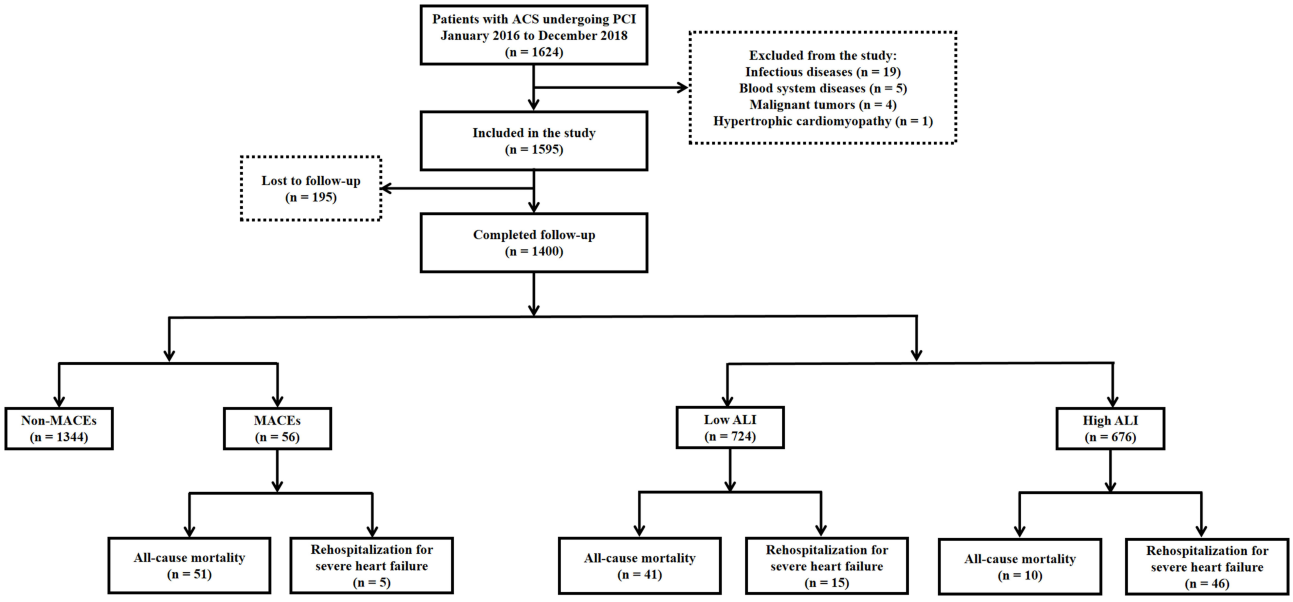

Figure 1 Patient selection flowchart.

Table 1 Baseline Patient Characteristics of the MACEs and Non-MACEs Groups

Variables	MACEs Group (n=56)	Non-MACEs Group (n=1344)	χ^2/Z	*p*-value
Clinicodemographic				
Male	39 (69.6%)	1007 (74.9%)	0.794	0.373
Age >65 years	28 (50.0%)	319 (23.7%)	19.893	<0.001
Dyslipidemia	35 (62.5%)	763 (56.8%)	0.720	0.396
Hypertension	34 (60.7%)	796 (59.2%)	0.049	0.824
Diabetes mellitus	14 (25.0%)	346 (25.7%)	0.016	0.901
Smoking	25 (44.6%)	696 (51.8%)	1.098	0.295
History of HF	16 (28.6%)	127 (9.4%)	21.434	<0.001
Ischemic stroke	14 (25.0%)	186 (13.8%)	5.469	0.019
Family history of CAD	5 (8.9%)	201 (15.0%)	1.556	0.212
UA	13 (23.2%)	528 (39.3%)	5.856	0.016
Non-STEMI	13 (23.2%)	222 (16.52%)	1.726	0.189
STEMI	30 (53.6%)	594 (44.20%)	1.913	0.167
Cardiogenic shock	6 (10.71%)	16 (1.19%)	31.526	<0.001
Laboratory data				
WBC count (10^9/L)	9.06±3.00	8.71±3.28	−1.338	0.181
Platelet count (10^9/L)	206.5 [176.75–238.5]	215.00 [180.00–250.00]	−1.201	0.230
TC (mmol/L)	4.40 (3.65–5.26)	4.43±1.06	−0.133	0.894
TG (mmol/L)	1.81 (0.93–2.24)	1.99±1.45	−1.339	0.181
HDL-C (mmol/L)	1.16 (0.91–1.29)	1.11±0.31	−0.613	0.540
LDL-C (mmol/L)	2.29 (1.86–3.13)	2.40±0.85	−0.395	0.693
ALB (g/L)	39.8 [37.63–42.05]	41.82 [39.30–44.10]	−2.700	0.007
Cr (μmol/L)	82.64±30.25	69.29±16.26	−3.485	<0.001
Serum uric acid (μmol/L)	342 [263.3–390.98]	326.2 [264.00–383.40]	−0.773	0.440
ALI <343.96	44 (78.657%)	680 (50.60%)	16.850	<0.001
Echocardiography, n (%)				
LVEDD >53 mm for males or LVEDD >50 mm for females	18 (32.14%)	332 (24.70%)	1.587	0.208
LVEF <40%	8 (14.29%)	33 (2.46%)	26.467	<0.001
Coronary angiography, n (%)				
1 vessel	15 (26.79%)	421 (31.32%)	0.516	0.472
2 vessels	20 (35.71%)	426 (31.70%)	0.400	0.527
3 vessels	21 (37.50%)	497 (36.98%)	0.131	0.718
Drugs (n, %)				
Aspirin	47 (83.93%)	1335 (99.33%)	100.479	<0.001
Clopidogrel	42 (75.00%)	1059 (78.79%)	0.461	0.497
Ticagrelor	4 (7.14%)	275 (20.46%)	5.976	0.015
β-blocker	31 (55.36%)	706 (52.53%)	0.172	0.678
ACEI/ARB	19 (33.93%)	631 (46.95%)	3.665	0.056
Statins	47 (83.93%)	1332 (99.11%)	83.829	<0.001
CCB	7 (12.50%)	226 (16.82%)	0.722	0.396
Diuretic	11 (19.64%)	93 (6.92%)	12.655	<0.001

Note: Data are presented as n (%) or as the median [range].

Abbreviations: MACEs, major adverse cardiovascular events; HF, heart failure; CAD, coronary artery disease; UA, unstable angina; STEMI, ST-segment elevation myocardial infarction; Non-STEMI, non-ST-segment elevation myocardial infarction; WBC, white blood cell; ALB, albumin; Cr, creatinine; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker; CCB, calcium channel blocker.

Receiver Operating Characteristic Curve, Time-Dependent ROC, and Survival Analysis

The AUC for ALI was 0.632 (p =0.001, 95% confidence interval [CI], 0.557–0.707). Based on the Youden's index, and the optimal diagnostic cutoff value for ALI was 330.49, with a sensitivity of 68.30% and a specificity of 55.50%.

Table 2 Baseline Characteristics of the Low and High ALI Groups

Variables	Low ALI Group (n=724)	High ALI Group (n=676)	χ^2/Z	*p*-value
Clinicodemographic				
Male	567 (78.31%)	479 (70.86%)	10.290	0.001
Age >65 years	195 (26.93%)	152 (22.49%)	3.711	0.054
Dyslipidemia	364 (50.28%)	434 (64.20%)	27.657	<0.001
Hypertension	413 (57.04%)	417 (61.69%)	3.121	0.077
Diabetes mellitus	170 (23.48%)	190 (28.11%)	3.916	0.048
Smoking	401 (55.39%)	320 (47.33%)	9.069	0.003
History of HF	98 (13.54%)	45 (6.66%)	18.039	<0.001
Ischemic stroke	106 (14.64%)	94 (13.91%)	0.154	0.694
Family history of CAD	92 (12.71%)	114 (16.86%)	4.813	0.028
UA	141 (19.48%)	400 (59.17%)	232.341	<0.001
Non-STEMI	127 (17.54%)	108 (15.98%)	0.613	0.434
STEMI	456 (62.98%)	168 (24.85%)	205.746	<0.001
Cardiogenic shock	13 (1.80%)	9 (1.33%)	0.487	0.485
MACEs	44 (6.08%)	12 (1.78%)	16.850	<0.001
Laboratory data				
WBC count (10^9/L)	10.06±3.54	7.28±2.18	−17.548	<0.001
Platelet count (10^9/L)	217.1±57.63	221.52±55.09	1.442	0.871
TC (mmol/L)	4.41±1.09	4.45±1.04	0.635	0.464
TG (mmol/L)	1.75±1.33	2.23±1.53	6.264	<0.001
LDL-C (mmol/L)	2.42±0.83	2.38±0.86	−0.758	0.472
HDL-C (mmol/L)	1.12±0.29	1.09±0.32	−2.239	0.225
ALB (g/L)	40.4 [37.91–42.80]	41.82 [39.30–44.10]	−2.700	0.007
Cr (μmol/L)	71.26±18.77	68.29±15.26	−3.237	0.011
Serum uric acid (μmol/L)	330.65±92.79	328.62±89.76	−0.416	0.977
Echocardiography, n (%)				
LVEDD>53mm (Male) or LVEDD>50mm (Female)	202 (27.90%)	148 (21.89%)	6.728	0.009
LVEF < 40%	31 (4.28%)	10 (1.48%)	9.658	0.002
Coronary angiography, n (%)				
1 vessel	212 (29.28%)	224 (33.14%)	2.422	0.120
2 vessels	234 (32.32%)	212 (31.36%)	0.148	0.700
3 vessels	278 (38.40%)	240 (35.50%)	1.257	0.262
Drugs (n, %)				
Aspirin	713 (98.48%)	669 (98.96%)	0.645	0.422
Clopidogrel	554 (76.52%)	547 (80.92%)	4.026	0.045
Ticagrelor	158 (21.82%)	121 (17.90%)	3.373	0.066
β-blocker	374 (51.66%)	363 (53.70%)	0.584	0.445
ACEI/ARB	342 (27.24%)	308 (45.56%)	0.395	0.530
Statins	713 (98.48%)	666 (95.52%)	0.004	0.951
CCB	76 (10.50%)	157 (23.22%)	40.821	<0.001
Diuretic	67 (9.25%)	37 (5.47%)	7.267	0.007

Note: Data are presented as n (%) or as the median [range].

Abbreviations: ALI, advanced lung cancer inflammation index; HF, heart failure; CAD, coronary artery disease; UA, unstable angina; non-STEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; MACEs, major adverse cardiovascular events; WBC, white blood cell; ALB, albumin; Cr, creatinine; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ACEI/ARB, angiotensin-converting enzyme inhibitor.

Figure 2A shows the time-dependent ROC. The 1-, 2-, 3-, and 5-year AUCs were 0.560, 0.577, 0.665, and 0.749, respectively. As shown in Figure 2B, the AUC and 95% CI tended to increase with time. The time-dependent AUC showed an increasing tendency, suggesting that the diagnostic efficiency of ALI increased with time.

The Kaplan–Meier curve (Figure 3) showed that compared with the high ALI group, the low ALI group had lower cumulative survival, and the difference was significant (log-rank $p < 0.001$).

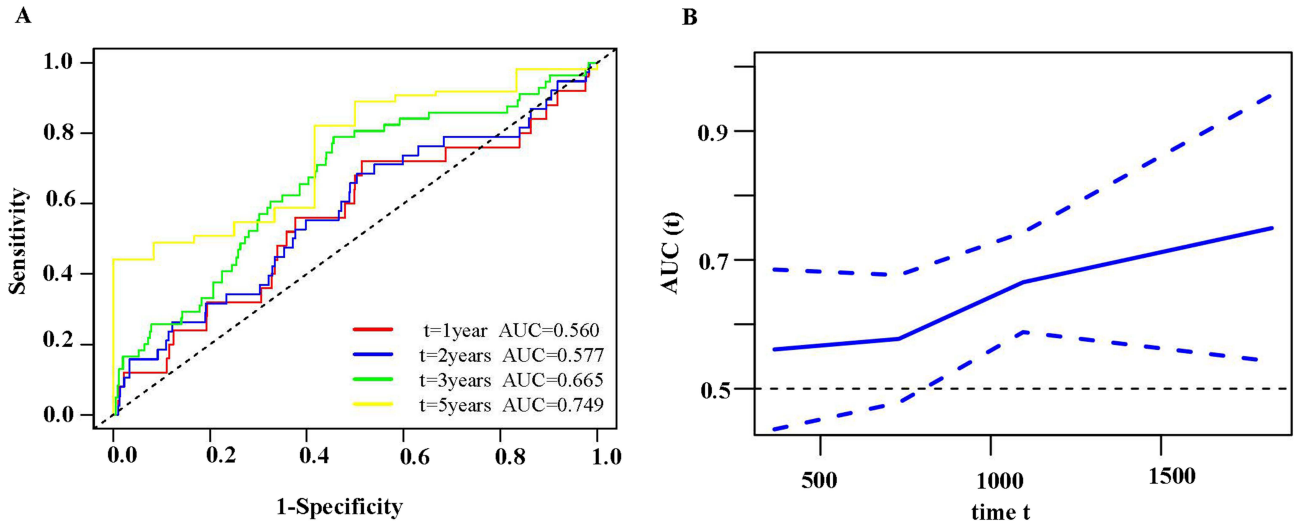

Figure 2 (**A**) Time-dependent receiver operating characteristic plotted by R. (**B**) AUC tends to increase with time.

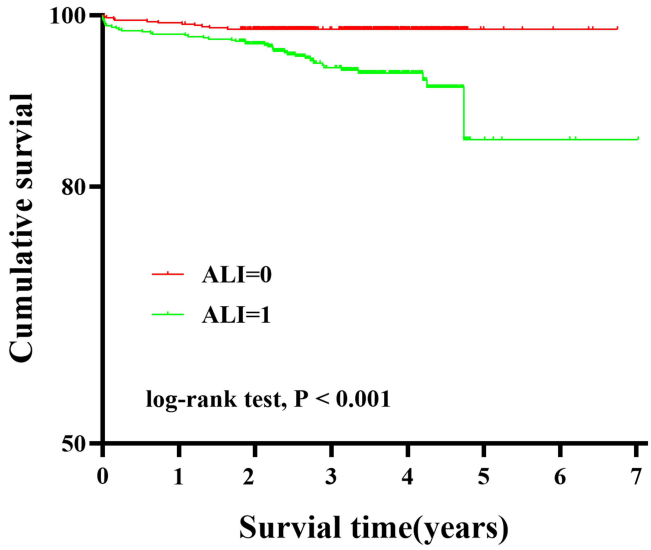

Figure 3 Kaplan–Meier curves of cumulative survival by ALI in ACS patients undergoing PCI (log-rank p < 0.001).

Univariate and Multivariate Cox Hazard Proportional Models

The univariate Cox proportional hazard model showed that a low ALI (<343.96) was an independent risk factor for patients with ACS undergoing PCI (HR: 3.671, 95% CI: 1.938–6.953, P<0.001). Thus, it was entered into the multivariate Cox hazard proportional model. The other significant factors were age category (p<0.001), STEMI diagnosis (p=0.14), history of ischemic stroke (p=0.022), history of HF (p<0.001), family history of CAD (p=0.187), occurrence of cardiogenic shock (p<0.001), left ventricular end-diastolic diameter (LVEDD) >53% for males or LVEDD <50% for females (p=0.225), LVEF <40% (p<0.001). Age, occurrence of cardiogenic shock, LVEF <40%, and ALI <343.96 were finally selected in the multivariate Cox hazard proportional model through adjusted variables, and the variables that effectively influenced the prognosis of ACS patients were selected. The results showed that age category (per 1 category) (HR: 1.59, 95% CI: 1.156–2.187, P=0.004), cardiogenic shock (HR: 6.115, 95% CI: 2.422–15.442, P<0.001), LVEF <40% (HR: 3.626, 95% CI: 1.61–8.168, P=0.002), and ALI <343.96 (HR: 3.009, 95% CI: 1.57–5.769, p=0.001) were independent predictor of MACEs (Table 3, Figure 4). In addition, the multivariate Cox proportional hazards model also demonstrated that a low ALI (<343.96) was an independent risk factor for patients with ACS undergoing PCI.

Table 3 Cox Hazard Proportional Model for Predictive Factors of MACEs

Variables	Univariate HR (95% CI)	p-value	Multivariate HR (95% CI)	p-value
Age category	1.975 (1.508–2.588)	<0.001	1.934 (1.470–2.544)	<0.001
STEMI	1.485 (0.878–2.511)	0.14		
Ischemic stroke	2.029 (1.108–3.716)	0.022		
History of HF	3.981 (2.227–7.117)	<0.001		
Family history of CAD	0.539 (0.215–1.350)	0.187		
Cardiogenic shock	8.317 (3.552–19.471)	<0.001	6.868 (2.774–17.006)	<0.001
LVEDD >53 mm for males or LVEDD >50 mm for females	1.415 (0.808–2.480)	0.225		
LVEF <40%	6.875 (3.241–14.583)	<0.001	3.861 (1.741–8.562)	0.001
ALI <343.96	3.671 (1.938–6.953)	<0.001	3.335 (1.750–6.353)	<0.001

Abbreviations: HR, hazard ratio; STEMI, ST-segment elevation myocardial infarction; HF, heart failure; CAD, coronary artery disease; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; ALI, advanced lung cancer inflammation index.

P for Interaction

The independent association between ALI and prognosis was assessed in various subgroups of age (>65 or ≤65 years), cardiogenic shock (yes or no), and LVEF (<40% or ≥40%). The results (Figure 5) were as follows: age >65 years vs age ≤65 years: HR: 3.095 (95% CI: 1.253–7.642) vs HR: 3.919 (95% CI: 1.588–9.672); occurrence of cardiogenic shock vs non-occurrence of cardiogenic shock: HR: 1.438 (95% CI: 0.262–7.876) vs HR: 4.046 (95% CI: 2.022–8.094); LVEF ≥40% vs LVEF <40%: HR: 3.908 (95% CI: 1.946–7.847) vs HR: 1.063 (95% CI: 0.214–5.273), all p for interaction >0.05.

P for Trend and Restricted Cubic Spline

Patients with low ALI have more adverse events.[16,19,20] Therefore, T3 was selected as a reference. Model 1 consisted of only the ALI index, and the results were as follows: T1 vs T3: HR: 3.221, (95% CI:1.514–6.853), p=0.002 and T2 vs T3: HR: 2.255 (95% CI: 1.027–4.952), p=0.043. The p value for trend was 0.01 (Table 4). Model 2 was adjusted for age, cardiogenic shock, and LVEF, and the results were as follows: T1 vs T3: HR: 2.400 (95% CI: 1.001–5.758, p=0.05) and T2 vs T3: HR: 1.012 (95% CI: 0.398–2.575), p=0.980. The p value for trend was 0.026 (Table 4). Two RCS models were generated to visualize the relationship between ALI and the prognostic risk. Model 1 (Figure 6A) was adjusted for ALI,

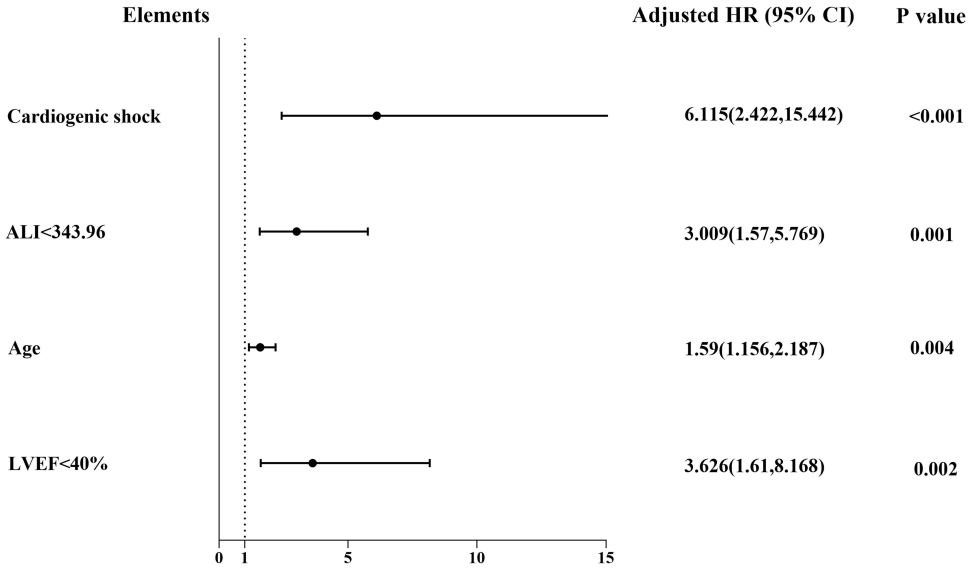

Figure 4 Forest graphs according to Cox proportional hazards regression model to test the risk factors for MACEs.

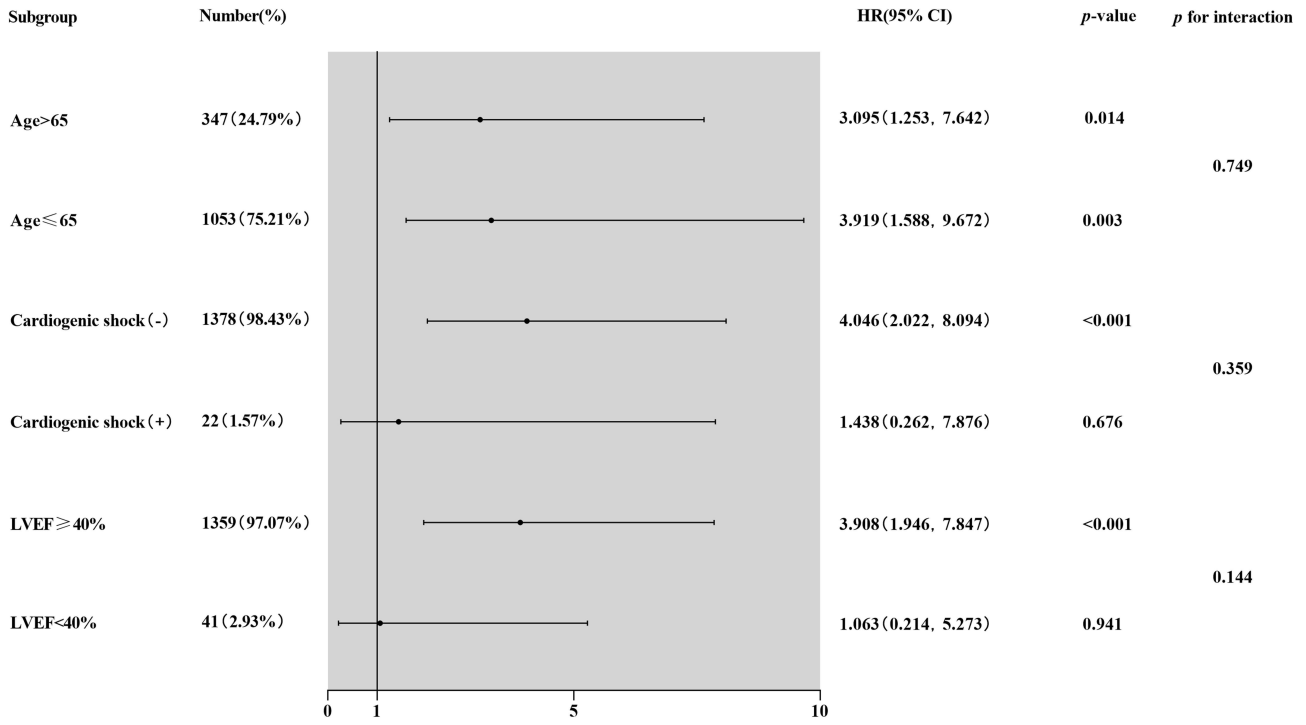

Figure 5 Forest graphs based on subgroup analysis for the effect of different factors in patients with ACS undergoing PCI.

and Model 2 (Figure 6B) was adjusted for age (<55 years=1, 56–65 years=2, 66–75 years=3, >76 years=4), cardiogenic shock (occurrence=1, non-occurrence=0), and LVEF (>40%=0, <40%=1). In both models, the ALI values with an HR close to 1 were 330.49. As shown in the figure, when ALI was <330.49, a low ALI was an independent risk factor in both Models 1 ($P_{nonlinear}$ =0.058) and 2 ($P_{nonlinear}$ = 0.143).

Discussion

The predictive ability of ALI for the prognostic risk in patients with ACS undergoing PCI remains unknown. The main findings of our research were as follows. First, low ALI was correlated with poor prognosis and was an independent risk factor for ACS patients undergoing PCI. Second, patients with ACS who underwent PCI had low ALI and a lower cumulative survival rate than those in the control group. Third, the diagnostic efficiency of ALI increased with time. Fourth, ALI was a better predictor of MACEs in patients with ACS who underwent PCI. Finally, low ALI was significantly associated with male sex, smoking, history of HF, family history of CAD, STEMI, higher WBC count, higher Cr level, and LVEF <40%. To the best of our knowledge, this is the first study to analyze the correlation between this novel index and prognosis in patients with ACS who underwent PCI.

Table 4 Cox Hazard Proportional Models of MACEs Risk According to Tertiles of ALI

ALI Tertiles	Model 1		Model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
T1	3.221 (1.514–6.853)	0.002	2.400 (1.001–5.758)	0.05
T2	2.255 (1.027–4.952)	0.043	1.012 (0.398–2.575)	0.980
T3	1 (Reference)	-	1 (Reference)	-
p for trend	0.01		0.026	

Note: Model 1: Unadjusted. Model 2: Adjusted for age category, cardiogenic shock, and LVEF.
Abbreviations: ALI, advanced lung cancer inflammation index; HR, hazard ratio; LVEF, left ventricular ejection fraction.

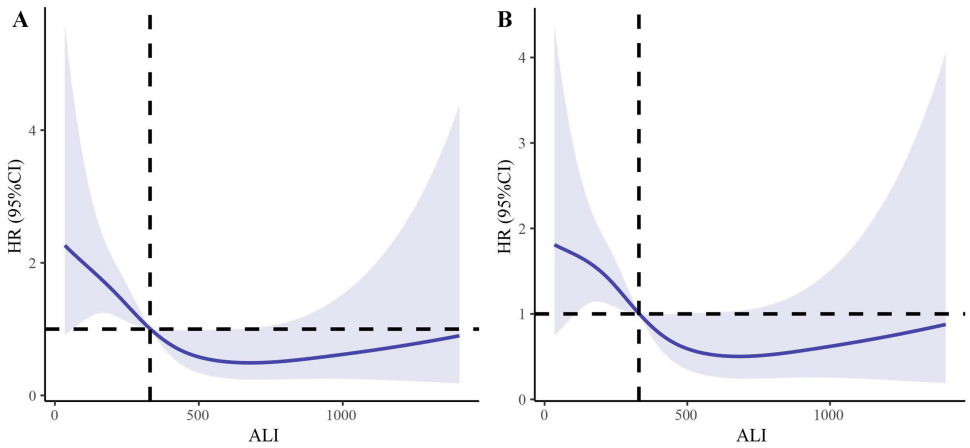

Figure 6 Restricted cubic spline (RCS). (**A**) Model 1 is adjusted for ALI. (**B**) Model 2 is adjusted for CKD stage, age stage, cardiogenic shock, and LVEF.

The ALI index combines both inflammation and nutritional status,[21] and includes BMI, serum albumin levels, and NLR. Nutrition plays an important part in CAD.[22,23] This index was first used to assess the degree of systemic inflammation in non-small cell lung cancer. A previous study using propensity score matching showed great prognostic value of ALI in gastric cancer and renal cell carcinoma.[24,25] Compared with other indices, ALI has better predictive performance for the MACEs risk in patients with ACS undergoing PCI because it combines anthropometric, nutritional, and inflammatory status.[21] Atherosclerosis is the original pathological change in CAD and is regarded as inflammatory and oxidative stress.[26] Many studies have confirmed the significance of anti-inflammatory therapy, such as canakinumab and low-dose methotrexate, in CAD patients.[27–29] Clinical trials have suggested that inflammation plays an important role in CAD. Particularly, neutrophils, neutrophil extracellular traps, and lymphocytes are correlated with atherosclerosis.[30] The disturbed equilibrium among lipid accumulation, immune responses, and clearance is regulated by leukocyte trafficking and homeostasis controlled by chemokines and their receptors. Animal experiments have shown that CD4+ T cells are commonly found in atherosclerotic plaques.[31] Therefore, NLR is regarded as an independent prognostic factor for coronary artery disease.[32,33]

We used several approaches to investigate the correlation between ALI values and prognostic risk. The results of the multivariate Cox proportional hazards model showed that ALI, as a novel index to predict MACEs risk, had the same efficiency as other classical prognostic risk factors (HR: 3.009, 95% CI: 1.57–5.769). In addition, age, occurrence of cardiogenic shock, and LVEF <40% were the main factors influencing the prognosis. Particularly, the risk of MACEs increased per 1 category increase in age. The p value for the interaction analysis method was used to identify the bias produced by different variables. Classical factors, such as age (>65 or ≤65 years), cardiogenic shock (yes or no), and LVEF (<40% or ≥40%), were included in our study. The results showed no significant differences in age, cardiogenic shock, or left heart function. This indicated that ACS patients undergoing PCI with a low ALI had an increased incidence of MACEs regardless of age (>65 or ≤65 years), occurrence or non-occurrence of cardiogenic shock, and LVEF <40% or ≥40%.

Both the p-value for trend and RCS methods were used to analyze the correlation between ALI and MACEs, and the dependent and independent variables were the J shape, U shape, or linear shape. When performing p for trend, we used model 1 (adjusted only for ALI) and model 2 (adjusted for age category, cardiogenic shock, and LVEF) in the analysis. Interestingly, the results showed that the association between ALI and MACEs initially decreased and then increased. Model 1 suggested that from T1 to T2, HR presented a decreasing tendency, while in model 2, T1 still presented the same results. Both models demonstrated that a low ALI was a dependent risk factor for prognosis in patients with ACS undergoing PCI. The RCS plot indicated similar conclusions that a low ALI of <330.49 was a dependent risk factor. Although when RCS was performed (Figure 6, model 1 adjusted for ALI alone, model 2 adjusted for age, cardiogenic shock, and LVEF), the curve showed that the HR of patients with ACS undergoing PCI increased sharply when the ALI

value was < 330.49. This supported that patients with ACS undergoing PCI who have an ALI value <330.49 have a high prognostic risk. Further studies are needed to elucidate the association between ALI and ACS.

Limitations

Firstly, our data were obtained from a single center in China, and the sample size was relatively small. Therefore, multicenter studies with larger sample size are needed. Secondly, the correlation between the ALI index and MACEs requires further investigation using the RCS analysis method to further examine whether the associated is linear, J shaped, or U shaped. Thirdly, future studies are needed to compare the prognosis among different subtypes of the ACS. Finally, there was great heterogeneity in antiplatelet therapy including clopidogrel and ticagrelor, so the conclusion may be conservative in the present study.

Conclusion

ALI, as a novel inflammation index, is independently associated with a higher risk of all-cause mortality and severe HF requiring rehospitalization in patients with ACS undergoing PCI. This index combines inflammatory and nutritional statuses, is more convenient and effective, and can be widely used to predict the risk of MACEs in patients with ACS undergoing PCI.

Abbreviations

ACS, acute coronary syndrome; ALI, advanced lung cancer inflammation index; AUC, area under the curve; BMI, body mass index; CAD coronary heart disease; Cr, creatinine; HF, heart failure; LVEF, left ventricular ejection fraction; MACEs, major adverse cardiovascular events; NLR, neutrophil-to-lymphocyte ratio; PCI, percutaneous coronary intervention; RCS, restricted cubic spline; ROC, receiver operating characteristic; STEMI, ST-elevation myocardial infarction.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Acknowledgments

The authors would like to thank the doctors and nurses of the Cardiology Research Team at the Affiliated Hospital of Chengde Medical University for their assistance.

Funding

This study was supported by the Natural Science Foundation of Hebei Province (grant number H2021406071) to Dr. Lixian Sun.

Disclosure

The authors report no conflicts of interest in this work.

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