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ORIGINAL RESEARCH

The Role of Advanced Lung Cancer Inflammation Index in Predicting COPD Exacerbation Risks

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Background: The role of the Advanced Lung Cancer Inflammation Index (ALI) in chronic obstructive pulmonary disease (COPD) remains unclear, although it has been utilized to investigate various non-malignant conditions.

Methods: A prospective study involving Chinese patients with COPD was carried out in Hong Kong to examine the relationship between baseline ALI levels and the risk of acute exacerbations of COPD (AECOPD). ALI was evaluated across quartiles. Patients were prospectively recruited from respiratory clinic in Queen Mary Hospital and Grantham Hospital in 2021, follow up with patients was done until 8th March 2025 or the death date, whichever is earlier.

Results: Among 272 Chinese COPD patients recruited, 138 of them had moderate to severe AECOPD and 66 patients died in the follow-up period. Those in the Q1 ALI, when compared with Q4 (highest quartile), had significantly shorter time to moderate to severe AECOPD with adjusted hazard ratio of (aHR) 2.17 (95% CI = 1.29–3.65, p = 0.011), severe AECOPD (aHR 2.05, 95% CI = 1.18–3.55, p = 0.011) and overall survival (aHR 2.73, 95% CI = 1.21–6.15, p = 0.015). The same phenomenon was also observed in the patient subgroup with baseline blood eosinophil counts <300 cells/μL.

Conclusion: In this prospective study, it suggested that ALI can serve as a biomarker to predict the risk of moderate to severe AECOPD, as well as severe AECOPD and mortality. The phenomenon was also observed in the non-eosinophilic subgroup. This can allow clinicians to use this simple and repeatable biomarker as a way to prognosticate COPD patients and estimate AECOPD risks.

Keywords: COPD, COPD exacerbation, advanced lung cancer inflammation index, biomarkers

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent chronic respiratory condition characterized by diverse inflammatory endotypes and phenotypes.[1] Acute exacerbation of COPD (AECOPD) is a significant complication that contributes greatly to healthcare burden and economic costs.[2] Various biomarkers have been studied for predicting AECOPD risk, with the majority focusing on the type[3–6] or severity of the inflammation.[7–9] Indeed, as a chronic respiratory disease, the association between COPD with malnutrition, sarcopenia and frailty was also reported, which can impact disease progression and patient outcomes.[10–12] Using inflammatory markers alone may not be holistic enough to represent the general status of COPD patients. Therefore, nutritional markers have been incorporated into risk assessment tools for this population. For example, a high neutrophil-to-lymphocyte ratio/serum albumin was shown to be associated with increased all-cause mortality in critically ill COPD patients.[13] In a retrospective study utilizing data from the National Health and Nutrition Examination Survey, various nutrition-related indices were evaluated. The findings indicated that ALI to be one of the markers linked to an increased risk of COPD and all-cause mortality among COPD patients. Notably, ALI showed the strongest predictive capability for both COPD development and mortality in these analyses.[14] Notably, ALI showed the strongest predictive capability for both COPD development and mortality in these analyses.

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While ALI was developed for lung cancer patients initially,[15,16] its role has since been extended to be used for other malignancies.[17–20] Its applications beyond oncology include various cardiometabolic disorders.[21–24]

ALI is a simple and repeatable biomarker that is composed of nutritional and inflammatory parameters which allows comprehensive assessment of the clinical status of the patients. This can reflect both the nutritional deficit in chronic diseases like COPD, as well as the degree of systemic inflammation in COPD. However, the prognostic role of ALI in COPD, especially among various phenotypes as determined by blood eosinophil count, is still lacking.

Given the known inflammatory nature of COPD and its association with malnutrition, this study aims to explore the role of ALI, which incorporates body mass index, serum albumin, blood neutrophil and lymphocyte levels, in this context.

Materials and Methods

This prospective study was conducted at two regional hospitals and tertiary respiratory referral centers in Hong Kong – Queen Mary Hospital (QMH) and Grantham Hospital (GH).

The study enrolled Chinese patients aged ≥40 years or older with a smoking history of at least 10 pack-years, who were diagnosed to have COPD, and regular follow-up in the respiratory clinics at QMH or GH during 2021. Participants were recruited during routine outpatient visits while in a clinically stable condition. COPD diagnosis was confirmed with spirometry demonstrating post-bronchodilator airflow limitation, with forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio <70%.[25]

Patients were considered clinically stable if they had no recent symptom deterioration in past 120 days, no change in COPD maintenance treatment in past 90 days and had not experienced an acute exacerbation of COPD (AECOPD) and had not used systemic corticosteroids in the past 90 days. An AECOPD was defined as an acute worsening of respiratory symptoms beyond normal day-to-day variations, necessitating changes in medication. AECOPD severity was classified as mild if treated with short-acting bronchodilators only, moderate if treated with short-acting bronchodilators plus oral corticosteroids with or without antibiotics, and severe if hospitalization or emergency department visits were required.[25]

Patients with co-existing asthma—determined based on clinical history, prior diagnosis, and a significant bronchodilator reversibility on spirometry as supporting evidence in uncertain cases—were excluded. Additionally, individuals with bronchiectasis and interstitial lung disease identified through high-resolution computed tomography (HRCT), active or past malignancies, autoimmune diseases, or other conditions that could influence ALI values were also excluded. Written informed consent was obtained from all participants. At recruitment, data collected included demographic information, clinical history, physical examination findings, blood samples for complete blood count and serum albumin levels, and medication records. Regular use of inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), long-acting muscarinic antagonists (LAMA), theophylline, and roflumilast was defined as continuous use for ≥12 months before enrollment.

ALI, which is a biomarker composed of nutritional and inflammatory parameters of high relevance to COPD, was determined using the formula: body mass index (kg/m^2) multiplied by serum albumin level (g/dL), divided by the neutrophil-to-lymphocyte ratio (NLR). BMI and serum albumin level reflected the nutritional status of the patients, which could be impaired in patients with chronic diseases such as COPD. NLR reflected the systemic inflammatory status of the patient and is relevant in COPD, which is a disease with chronic airway and systemic inflammation. Based on the quartiles of ALI values, patients were categorized into four distinct subgroups.

After enrollment, patients continued to receive standard-of-care provided by their attending healthcare teams. They were prospectively followed in the respiratory or COPD specialty clinics at QMH or GH every 16 to 26 weeks until March 8th, 2025. During follow-up visits, clinicians monitored symptoms, COPD control status, medication adherence, and recorded the date of the first moderate or severe AECOPD.

Patient data were accessed through the Electronic Patient Record (ePR) system maintained by the Hong Kong Hospital Authority. This system included comprehensive information on outpatient and inpatient episodes, such as demographic details, clinical notes, investigation results, and treatment records.

The primary outcome of this study was the time to the first moderate-to-severe AECOPD. The secondary outcomes included the time to severe AECOPD, overall survival (OS), and the annual frequency of moderate-to-severe AECOPDs or severe AECOPDs.

The study received approval from The University of Hong Kong and Hospital Authority Hong Kong West Cluster Institutional Review Board (approval reference number: UW 21–172). Informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Demographic and clinical data were summarized as frequencies, means ± standard deviations (SD), or medians with interquartile ranges (25th–75th percentile). Baseline characteristics were compared between patients with and without moderate-to-severe AECOPD during follow-up using independent *t*-tests. Cox regression was employed to assess the association between ALI quartiles and time to moderate-to-severe and severe AECOPD. When less than 50% of patients experienced the event, Weibull survival models estimated the median times to AECOPD and death.

Multivariable regression analyses adjusted for covariates including age, sex, FEV_1 (% predicted), baseline mMRC dyspnea score, number of moderate-to-severe AECOPDs in the year prior to recruitment, and use of the following medication: ICS, LAMA, LABA, theophylline, and roflumilast. Subgroup analyses were performed in patients with baseline blood eosinophil counts (BEC) <300 cells/μL and ≥300 cells/μL. The annual number of moderate-to-severe and severe AECOPDs across different ALI quartiles was compared using one-way ANOVA. A p-value of <0.05 (two-sided) was considered to be statistically significant. All analyses were conducted using SPSS version 28.

Results

In total, 348 Chinese patients with COPD were recruited. Forty-three were excluded as they had a past history of malignancy or have active malignancies. Twenty-one patients were excluded as they had co-existing bronchiectasis and four were excluded as they had interstitial lung disease. Eight subjects were excluded as ALI was not available due to lack of recorded BMI or serum albumin level. The patient selection flow diagram was illustrated in Figure 1.

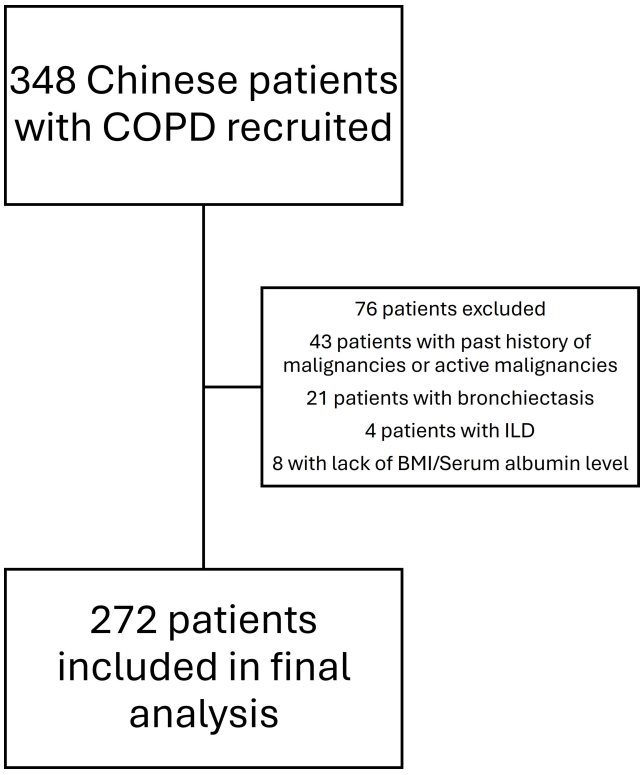

Figure 1 Patient selection flow diagram.

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Baseline Characteristics

The mean age of the included patients was 74.4 ± 8.6 years. There were more males (91.5%). The mean baseline FEV_1 was 1.36 ± 0.55 L (60.9 ± 22.5%). The mean ALI was 44.0 ± 30.7. The quartiles of ALI were Q1 (lowest): <25.2; Q2: 25.2–39.59; Q3: 39.6–55.3; and Q4: >55.3. The mean duration of follow-up was 40.7 ± 11.5 months. The results were summarized in Tables 1 and 2.

Table 1 Baseline Demographic and Clinical Characteristics According to AECOPD on Follow Up

	Whole Cohort (n = 272)	**No Moderate-to-Severe AECOPD on Follow Up (n = 134)**	**Had Moderate-to-Severe AECOPD on Follow Up (n = 138)**	***p-value***
Age (years), mean ± SD	74.4 ± 8.6	74.5 ± 8.6	74.3 ± 8.7	0.91
Male	249 (91.5%)	123 (91.8%)	126 (91.3%)	0.89
BMI (kg/m^2)	22.9 ± 4.4	23.3 ± 4.4	22.5 ± 4.3	0.11
FEV_1 (L), mean ± SD	1.36 ± 0.55	1.51 ± 0.55	1.22 ± 0.52	<0.001*
FEV_1 (% predicted), mean ± SD	60.9 ± 22.5	65.7 ± 22.5	54.3 ± 20.6	<0.001*
FVC (L), mean ± SD	2.79 ± 0.82	2.92 ± 0.85	2.67 ± 0.78	0.012*
FVC (% predicted), mean ± SD	92.3 ± 23.6	95.8 ± 23.7	88.9 ± 23.1	0.02*
FEV_1/FVC ratio (%), mean ± SD	49.6 ± 16.1	52.4 ± 12.4	47.0 ± 18.5	0.006*
mMRC dyspnoea scale				<0.001*
0	19 (7.0%)	16 (11.9%)	3 (2.2%)	
1	95 (34.9%)	51 (38.1%)	44 (31.9%)	
2	89 (32.7%)	46 (34.3%)	43 (31.2%)	
3	54 (19.9%)	20 (14.9%)	34 (24.6%)	
4	15 (5.5%)	1 (0.7%)	14 (10.1%)	
Number Exacerbations in past 12 months				0.049*
0	246 (90.4%)	128 (95.5%)	118 (85.5%)	
1	20 (7.4%)	6 (4.5%)	14 (10.1%)	
2	4 (1.5%)	0 (0%)	4 (2.9%)	
≥3	2 (0.7%)	0 (0%)	2 (1.4%)	
Baseline blood platelet count ($\times 10^9$ cells/L), mean ± SD	238 ± 78	240 ± 87	236 ± 69	0.71
Baseline blood neutrophil count ($\times 10^9$ cells/L), mean ± SD	4.66 ± 1.57	4.46 ± 1.46	4.85 ± 1.64	0.037
Baseline blood lymphocyte count ($\times 10^9$ cells/L), mean ± SD	1.90 ± 1.47	1.84 ± 0.67	1.96 ± 1.96	0.51
Baseline blood eosinophil count (cells/μL), mean ± SD	251 ± 218	262 ± 218	240 ± 219	0.42
Baseline serum albumin (g/dL), mean ± SD	4.3 ± 0.43	4.3 ± 0.3	4.3 ± 0.3	0.87
Baseline serum creatinine (mmol/L), mean ± SD	93.2 ± 34.2	95.7 ± 40.2	90.9 ± 27.0	0.25
ALI, mean ± SD	44.0 ± 30.7	46.0 ± 23.6	42.1 ± 36.2	<0.001*

(*Continued*)

Table 1 (Continued).

	Whole Cohort (n = 272)	**No Moderate-to-Severe AECOPD on Follow Up (n = 134)**	**Had Moderate-to-Severe AECOPD on Follow Up (n = 138)**	***p-value***
Treatment				
ICS	143 (52.6%)	47 (35.1%)	96 (69.6%)	<0.001*
LABA	196 (72.1%)	78 (58.2%)	118 (85.5%)	<0.001*
LAMA	213 (78.3%)	94 (70.1%)	119 (86.2%)	0.001*
Roflumilast	25 (9.2%)	5 (3.7%)	20 (14.5%)	0.002*
Theophylline	46 (16.9%)	29 (21.6%)	17 (12.3%)	0.07

Note: *Statistically significant.
Abbreviations: SD, standard deviation; mL, millilitre; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

Table 2 Baseline Demographic and Clinical Characteristics According to ALI in Quartile

	Whole Cohort (n = 272)	**ALI Q1 (n = 68)**	**ALI Q2 (n = 67)**	**ALI Q3 (n = 70)**	**ALI Q4 (n = 67)**	***p-value***
Age (years), mean ± SD	74.4 ± 8.6	77.4 ± 7.9	74.6 ± 8.2	72.9 ± 9.2	72.7 ± 8.6	0.004*
Male	249 (91.5%)	62 (91.2%)	62 (92.5%)	64 (91.4%)	61 (91.0%)	0.99
BMI (kg/m^2)	22.9 ± 4.4	20.9 ± 3.6	22.8 ± 5.2	23.1 ± 3.4	24.8 ± 4.3	<0.001*
FEV_1 (L), mean ± SD	1.36 ± 0.55	1.17 ± 0.52	1.24 ± 0.46	1.50 ± 0.59	1.53 ± 0.55	<0.001*
FEV_1 (% predicted), mean ± SD	60.9 ± 22.5	56.8 ± 25.8	54.9 ± 18.0	64.0 ± 21.7	67.8 ±22.0	0.003*
FVC (L), mean ± SD	2.79 ± 0.82	2.58 ± 0.81	2.70 ± 0.76	2.95 ± 0.86	2.93 ± 0.81	0.026*
FVC (% predicted), mean ± SD	92.3 ± 23.6	91.1 ± 25.7	89.1 ± 21.8	92.5 ± 24.1	96.2 ± 22.7	0.39
FEV_1/FVC ratio (%), mean ± SD	49.6 ± 16.1	46.1 ± 14.3	46.9 ± 13.8	51.0 ± 12.5	54.6 ± 21.4	0.008*
mMRC dyspnoea scale						0.045*
0	19 (7.1%)	2 (2.9%)	5 (7.5%)	8 (11.4%)	4 (6.0%)	
1	95 (34.9%)	15 (22.1%)	25 (37.3%)	26 (37.1%)	29 (43.3%)	
2	89 (32.7%)	22 (32.4%)	21 (31.3%)	21 (30.0%)	25 (37.3%)	
3	54 (19.9%)	22 (32.4%)	12 (19.4%)	13 (18.6%)	7 (10.4%)	
4	15 (5.5%)	7 (10.3%)	4 (6.0%)	2 (2.9%)	2 (3.0%)	
Number Exacerbations in past 12 months						0.39
0	246 (90.4%)	60 (88.2%)	60 (89.6%)	66 (94.3%)	60 (89.6%)	
1	20 (7.4%)	5 (7.4%)	6 (9.0%)	4 (5.7%)	5 (7.5%)	
2	4 (1.5%)	3 (4.4%)	0 (0%)	0 (0%)	1 (1.5%)	
≥3	2 (0.7%)	0 (0%)	1 (1.5%)	0 (0%)	1 (1.5%)	
Baseline blood platelet count ($\times 10^9$cells/L), mean ± SD	238 ± 78	240 ± 95	241 ± 71	234 ± 55	236 ± 87	0.95

(*Continued*)

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Table 2 (Continued).

	Whole Cohort (n = 272)	ALI Q1 (n = 68)	ALI Q2 (n = 67)	ALI Q3 (n = 70)	ALI Q4 (n = 67)	*p-value*
Baseline blood neutrophil count ($\times 10^9$cells/L), mean ± SD	4.66 ± 1.57	5.55 ± 1.70	4.96 ± 1.61	4.34 ± 1.03	3.78 ± 1.26	<0.001*
Baseline blood lymphocyte count ($\times 10^9$cells/L), mean ± SD	1.90 ± 1.47	1.18 ± 0.40	1.67 ± 0.53	2.02 ± 0.50	2.74 ± 2.62	<0.001*
Baseline blood eosinophil count (cells/μL), mean ± SD	251 ± 218	272 ± 306	216 ± 137	246 ± 169	268 ± 223	0.43
Baseline serum albumin (g/dL), mean ± SD	4.3 ± 0.4	4.2 ± 3.6	4.3 ± 3.2	4.3 ± 2.6	4.4 ± 3.0	<0.001*
Baseline serum creatinine (mmol/L), mean ± SD	93.2 ± 34.2	90.9 ± 30.0	95.7 ± 44.3	94.6 ± 34.1	91.7 ± 26.2	0.82
ALI, mean ± SD	44.0 ± 30.7	18.8 ± 5.0	32.5 ± 4.4	47.1 ± 4.7	77.8 ± 42.8	<0.001*
Treatment						
ICS	143 (52.6%)	47 (69.1%)	39 (58.2%)	24 (34.3%)	33 (49.3%)	<0.001*
LABA	196 (72.1%)	52 (76.5%)	52 (77.6%)	43 (61.4%)	49 (73.1%)	0.13
LAMA	213 (78.3%)	54 (79.4%)	60 (89.6%)	53 (75.7%)	46 (68.7%)	0.029
Roflumilast	25 (9.2%)	9 (13.2%)	10 (14.9%)	3 (4.3%)	3 (4.5%)	0.051
Theophylline	46 (16.9%)	11 (16.2%)	15 (22.4%)	9 (12.9%)	11 (16.4%)	0.52

Note: *Statistically significant.
Abbreviations: SD, standard deviation; mL, millilitre; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICS, inhaled corticosteroid.

Time to Moderate-to-Severe AECOPD and Baseline ALI

A total of 138 patients developed moderate-to-severe AECOPD during follow-up. Patients in the Q1 ALI, when compared with Q4 (highest quartile) had significantly shorter time to moderate-to-severe AECOP with hazard ratio (HR) of 2.71 (95% CI = 1.69–4.37, p < 0.001) for Q1. The HRs were 1.62 (95% CI = 1.00–2.62, p = 0.05) for Q2 and 0.89 (95% CI = 0.53–1.50, p = 0.012) for Q3 (Figure 2).

The adjusted HRs (aHRs) were 2.17 (95% CI = 1.29–3.65, p = 0.011) for Q1, 1.14 (95% CI = 0.67–1.93, p = 0.64) for Q2 and 0.96 (95% CI = 0.55–1.67, p = 0.90) for Q3.

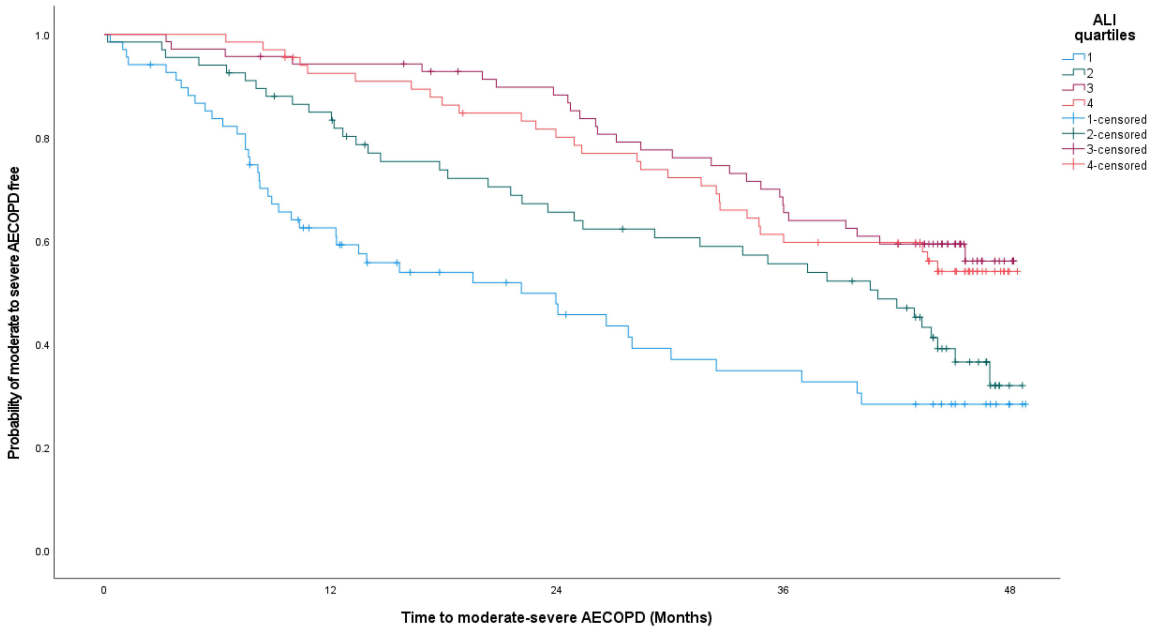
The median times to moderate-to-severe AECOPD were 25.1 months (95% CI = 19.5–30.7) in Q1, 34.3 months (95% CI = 29.4–39.3) in Q2, 46.9 months (95% CI = 39.1–54.7) in Q3 and 64.1 months (95% CI = 47.0–81.1) in Q4, respectively (p < 0.001 for comparison across quartiles).

Time to Severe AECOPD and Baseline ALI

A total of 128 patients developed severe AECOPD during the follow-up period. Patients in the Q1 and Q2 of ALI, when compared with Q4 (highest quartile), had significantly shorter times to severe AECOPD in the follow-up period with HR of 2.52 (95% CI = 1.53–4.16, p < 0.001) for Q1. The HRs were 1.86 (95% CI = 1.13–3.06, p = 0.05) for Q2 and 0.88 (95% CI = 0.51–1.53, p = 0.66) for Q3 (Figure 3).

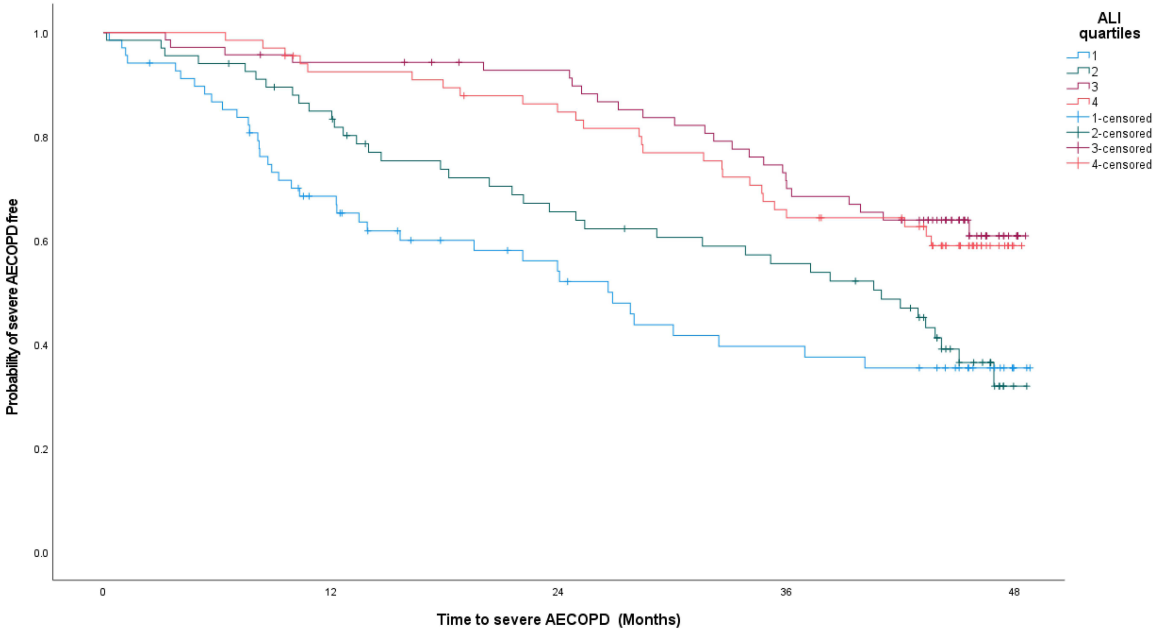
The aHRs were 2.05 (95% CI = 1.18–3.55, p = 0.011) for Q1, 1.31 (95% CI = 0.76–2.28, p = 0.006) for Q2 and 0.98 (95% CI = 0.54–1.77, p = 0.94) for Q3.

The median times to severe AECOPD were 28.3 months (95% CI = 21.9–34.7) in Q1, 38.2 months (95% CI = 32.6–43.9) in Q2, 51.6 months (95% CI = 42.6–60.7) in Q3 and 69.7 months (95% CI = 50.3–89.1) in Q4, respectively (p < 0.001 for comparison across quartiles).



Number of patients at risk					
ALI quartiles					
1	68	38	23	16	2
2	67	55	40	33	1
3	70	65	58	43	5
4	67	60	51	38	1

Figure 2 Kaplan–Meier curve of the time to moderate-to-severe AECOPD among patients with ALI at different quartiles.



Number of patients at risk					
ALI quartiles					
1	68	42	27	19	2
2	67	55	40	33	1
3	70	65	61	46	6
4	67	60	54	41	1

Figure 3 Kaplan–Meier curve of the time to severe AECOPD among patients with ALI at different quartiles.

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Overall Survival and Baseline ALI

A total of 66 patients died during the follow-up period. Among the 66 deaths, 40 died of respiratory causes, 12 died of cardiac causes, 8 died of malignancies and 6 died of other causes. Patients in the Q1 of ALI, when compared with Q4 (highest quartile), had significantly shorter OS with HR of 3.67 (95% CI = 1.79–7.51, p < 0.001) for Q1. The HRs were 1.67 (95% CI = 0.76–3.68, p = 0.20) for Q2 and 0.97 (95% CI = 0.40–2.33, p = 0.95) for Q3 (Figure 4).

The aHRs were 2.73 (95% CI = 1.21–6.15, p = 0.015) for Q1, 1.24 (95% CI = 0.51–3.02, p = 0.64) for Q2 and 0.79 (95% CI = 0.30–2.05, p = 0.62) for Q3.

The median OS was 56.0 months (95% CI = 40.9–71.1) in Q1, 83.0 months (95% CI = 63.1–102.9) in Q2, 123.0 months (95% CI = 79.8–166.1) in Q3 and 182.2 months (95% CI = 87.7–276.7) in Q4, respectively (p < 0.001 for comparison across quartiles).

Annual Number of Moderate-to-Severe AECOPD and Severe AECOPD

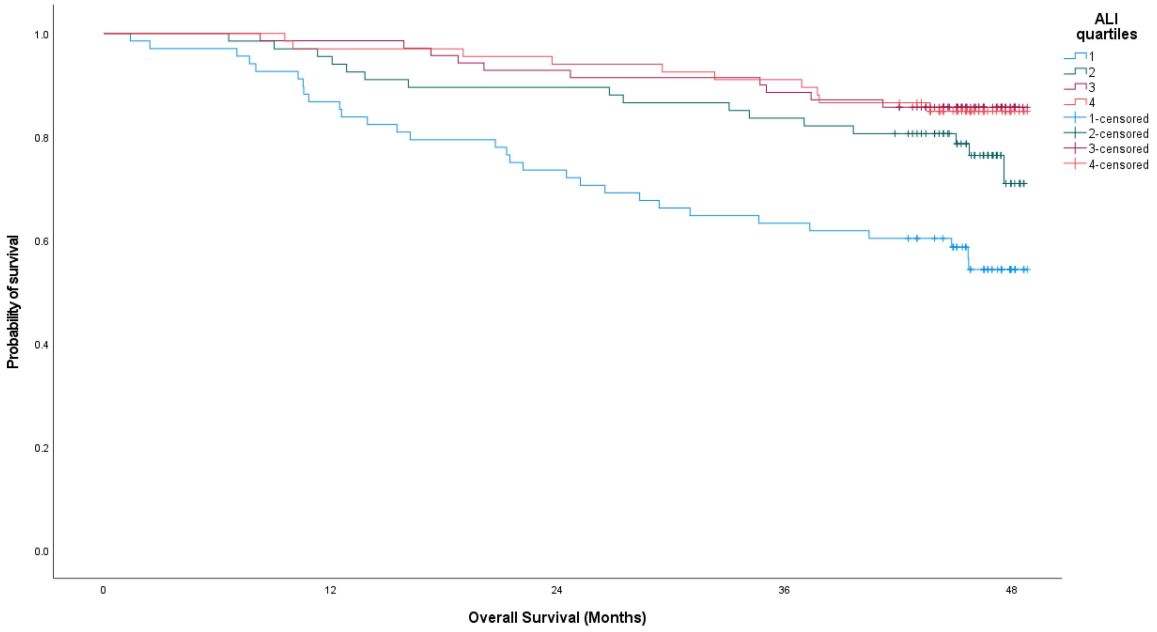
The median annual number of moderate-to-severe AECOPD was 0.27 [0–1.27] for Q1, 0.26 [0–0.73] for Q2, 0 [0–0.27] for Q3 and 0 [0–0.49] for Q4 (p = 0.022 and 0.050 in univariate and multivariable comparison across quartiles).

The median annual number of moderate to severe AECOPD was 0.26 [0–0.96] for Q1, 0.52 [0–0.73] for Q2, 0 [0–0.27] for Q3 and 0 [0–0.27] for Q4 (p = 0.012 and 0.025inunivariate and multivariable comparison across quartiles).

Subgroup Analysis

Subgroup analysis was performed on patients with eosinophilic and non-eosinophilic phenotypes, defined with baseline BEC <300 cells/μL and ≥300 cells/μL. These were the subgroups considered to have distinct phenotypes by the GOLD recommendations.[26]

There were 205 patients with non-eosinophilic COPD. Patients in the Q1 ALI, when compared with Q4 (highest quartile) had significantly shorter time to moderate-to-severe AECOPD in the follow-up period. The aHRs were 2.37



Number of patients at risk

ALI quartiles					
1	68	59	50	43	6
2	67	64	60	56	8
3	70	69	65	62	8
4	67	65	63	61	7

Figure 4 Kaplan–Meier curve of overall survival among patients with ALI at different quartiles.

(95% CI = 1.28–4.40, p = 0.006) for Q1, 1.25 (95% CI = 0.68–2.29, p = 0.48) for Q2 and 1.05 (95% CI = 0.55–2.01, p = 0.89) for Q3 (Supplementary Figure 1).

The median times to moderate-to-severe AECOPD were 23.5 months (95% CI = 17.7–29.3) in Q1, 32.4 months (95% CI = 27.3–37.5) in Q2, 44.6 months (95% CI = 36.3–52.9) in Q3 and 61.4 months (95% CI = 42.9–79.9) in Q4, respectively (p < 0.001 for comparison across quartiles).

Patients in the Q1 ALI, when compared with Q4 (highest quartile) had significantly shorter time to severe AECOPD in the follow-up period. The aHRs were 2.12 (95% CI = 1.11–4.05, p = 0.023) for Q1, 1.41 (95% CI = 0.75–2.63, p = 0.48) for Q2 and 0.99 (95% CI = 0.50–1.96, p = 0.98) for Q3 (Supplementary Figure 2).

The median time to severe AECOPD was 26.6 months (95% CI = 20.0–33.3) in Q1, 35.9 months (95% CI = 30.1–41.7) in Q2, 48.3 months (95% CI = 39.0–57.6) in Q3 and 65.0 months (95% CI = 45.0–85.1) in Q4, respectively (p < 0.0001 for comparison across quartiles).

Patients in the Q1 of ALI, when compared with Q4 (highest quartile), had significantly shorter overall survival. The aHRs were 2.70 (95% CI = 1.13–6.45, p = 0.026) for Q1, 0.83 (95% CI = 0.30–2.27, p = 0.72) for Q2 and 0.80 (95% CI = 0.28–2.27, p = 0.667) for Q3 (Supplementary Figure 3).

The median OS was 52.8 months (95% CI = 38.1–67.6) in Q1, 75.6 months (95% CI = 57.5–93.7) in Q2, 108.2 months (95% CI = 70.0–146.4) in Q3 and 154.8 months (95% CI = 72.9–236.7) in Q4, respectively (p < 0.001 for comparison across quartiles).

The mean annual number of moderate-to-severe AECOPD was 1.03 ± 2.08 for Q1, 0.55 ± 0.77 for Q2, 0.27 ± 0.65 for Q3 and 0.39 ± 0.82 for Q4 (p = 0.002 and 0.005 in univariate and multivariable comparison across quartiles). The median annual number of moderate to severe AECOPD were 0.27 [0–1.06] for Q1, 0.26 [0–0.79] for Q2, 0 [0–0.28] for Q3 and 0 [0–0.41] for Q4 (p = 0.038 and 0.050 in univariate and multivariable comparison across quartiles).

There were 67 patients with eosinophilic COPD. There was no statistically significant difference in the time to moderate-to-severe AECOPD, time to severe AECOPD, annual number of moderate-to-severe AECOPD, annual number of severe AECOPD and overall survival with p-value >0.05.

Discussion

Our study demonstrates the prognostic role ALI in COPD with the risk of AECOPD.

The lowest ALI quartile was shown to be associated with risks of both moderate-to-severe AECOPD and severe AECOPD. The overall survival was also the lowest among the patient subgroup with lowest ALI quartile. The annual number of moderate-to-severe and severe AECOPD was also higher in the lowest ALI quartile. Our findings suggest the potential role of this simple and readily available biomarker in prognostication of COPD.

BODE index is one of the most commonly used and well validated scoring systems to prognosticate patients with COPD.[27] However, the need for a 6-minute walk test may not be feasible among patients with limited mobility. Also, seeing that COPD is a chronic inflammatory disease, the lack of parameters used to assess inflammation limits our ability to determine the inflammatory status of COPD. Two sides of the same coin, attempts have been made to find inflammatory markers to assess COPD.[9,28–30] While some biomarkers do reflect the degree of systemic inflammation, they do not reflect the component of nutritional status, which also becomes impaired in COPD patients.[31,32] ALI is relatively more reliable as it can serve as a biomarker that integrates both inflammatory and nutritional elements in COPD. ALI could be a simple, easily repeatable and comprehensive prognostic marker in COPD to predict AECOPD risks and mortality. ALI involves NLR as the denominator, which reflects the systemic inflammatory status, mostly related to neutrophilic inflammation which is also the predominant pathophysiological mechanism in COPD. The numerator includes BMI and albumin level, which are important nutritional parameters that may be impaired among patients with more advanced chronic respiratory diseases.[33] The findings in this study also suggested that ALI could predict AECOPD risks when assessed in quartiles. Patients with the lowest ALI quartile would likely represent those patients with the worst nutritional status and the highest degree of neutrophilic inflammation, or both, thus having the highest risks of AECOPD and the shortest overall survival. They also had the highest annual number of AECOPD.

In the subgroup analysis, we also demonstrated the role of ALI in patients with non-eosinophilic phenotype, as in the whole cohort. However, in the eosinophilic subgroup, due to small sample size, the same phenomenon was not observed.

According to the GOLD guidelines,[26] patients are classified into eosinophilic and non-eosinophilic subgroups, each exhibiting distinct phenotypes and different risks of AECOPD. The non-eosinophilic subgroup, which comprised the majority of patients in this study, is characterized by neutrophilic airway inflammation. Our study demonstrated that ALI, which reflects the degree of neutrophilic inflammation alongside nutritional aspects, can predict AECOPD risk. A higher ALI may indicate poorer nutritional status and an elevated level of systemic neutrophilic inflammation, which could indirectly reflect the degree of airway neutrophilic inflammation, thus translating into AECOPD risks. Unfortunately, due to limited sample size, we could not establish the same association within the eosinophilic group. Larger-scale studies are necessary to confirm whether similar findings are applicable to this phenotype.

AECOPD are among the most common and significant complications of COPD, often leading to increased morbidity, hospitalization, and healthcare utilization. As understanding of COPD phenotypes advances, personalized therapies are being developed to reduce symptoms and risk of AECOPD.[34,35] The choice of treatment to prevent AECOPD is largely based on number of AECOPD episodes. However, because AECOPD is associated with adverse long-term outcomes including future AECOPD and disease progression, predicting AECOPD risk proactively is crucial. Currently, blood eosinophil count is among the most frequently used biomarkers for assessing AECOPD risks.[36] Nonetheless, this marker does not address non-eosinophilic phenotypes, which constitute the majority of COPD patients. Our findings could potentially fill this gap by introducing ALI as a biomarker to predict AECOPD risk in non-eosinophilic COPD.

ALI reflects both the pathophysiology and overall health status of COPD patients, which may have its relevance observed in this study. Importantly, it also reminds clinicians to not only focus on the extent and severity of COPD but also the negative nutritional impact from COPD, as indicated by low BMI and serum albumin levels—often a consequence of chronic inflammation. Given its simplicity, ALI could be integrated into routine COPD assessment and can be monitored serially to evaluate disease progression.

However, our study has several limitations that should be acknowledged. First, we only include Chinese COPD patients, which may limit the generalizability of the findings, though disease pathophysiology and prognosis are largely the consistent across ethnicities. Second, lung function tests were performed at different times for each patient, and only one ALI measurement was taken at recruitment. As such, we do not have serial ALI measurement tin this study. Since BMI and blood parameters can change over time, serial ALI measurement and assessing its role in COPD should be considered in a separate study. Serial ALI will allow clinicians to see if interventions in COPD that affect the nutritional and inflammatory component in ALI will result in change in AECOPD risks, which could strengthen the role of ALI in COPD prognostication. Lastly, the relatively small sample size of this study warrants larger, multi-ethnic studies to test, validate and expand upon the observations noted in this study. Although we already showed positive findings in this study, long-term validation and further exploration of ALI's role in different phenotypes are still worthwhile. While phenotypes as defined by blood eosinophil count have been assessed, other phenotypes such as chronic bronchitis and emphysema shall also be examined in future studies.

Conclusion

ALI, which constituted of nutritional and inflammatory parameters, can serve as a biomarker to predict the risks of moderate-to-severe AECOPD, severe AECOPD, as well as mortality. Notably, this predictive association was also observed in non-eosinophilic subgroups, specifically among non-eosinophilic COPD patients. ALI can be considered to be used as a simple and repeatable biomarker to prognosticate COPD patients and estimate AECOPD risks.

Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors did not use any AI tools/service.

Data Sharing Statement

All available data are presented in the manuscript, and no additional data will be provided. Due to the ethical restrictions imposed by the Institutional Review Board (IRB) regulations and rules on patient data privacy in this study, the supporting research data is not available upon request.

Ethics Approval and Consent to Participate

The study was approved by the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (approval reference number: UW 21-172). Informed consent was obtained from all participants prior to their inclusion in the study.

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. Guarantor of the article: James Chung Man Ho.

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Disclosure

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