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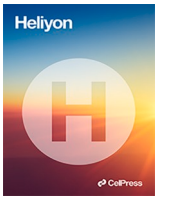

Research article

Association between the advanced lung cancer inflammation index and all-cause and cardiovascular mortality in patients with RA: Insights from NHANES data analysis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with significant mortality, which is primarily due to cardiovascular complications. Despite advancements in RA treatment, mortality rates remain high, highlighting the need for reliable prognostic markers. The advanced lung cancer inflammation index (ALI), which integrates inflammatory and nutritional biomarkers, has shown promise in predicting outcomes in various medical conditions. However, its role in RA prognosis remains unclear.

Methods: This study aimed to investigate the associations between the ALI and all-cause mortality, as well as cardiovascular mortality, in RA patients using data from the National Health and Nutrition Examination Survey (NHANES). A total of 1568 RA patients were included, and the ALI was calculated using body mass index (BMI), serum ALB, and the neutrophil-to-lymphocyte ratio. Comprehensive demographic, lifestyle, and metabolic data from the NHANES enabled adjustments for potential confounders. Multivariate Cox regression and sensitivity analyses were conducted to assess the associations between the ALI and mortality outcomes.

Results: Our findings demonstrate an inverse association between the ALI and both all-cause and cardiovascular mortality in RA patients. Furthermore, a nonlinear relationship was observed, with mortality risk increasing significantly below a certain ALI threshold. Stratified analyses revealed a protective effect of the ALI across various demographic and clinical subgroups, underscoring its potential as a prognostic marker in patients with RA.

Conclusion: The ALI holds promise as a valuable prognostic marker for identifying high-risk individuals and guiding personalized management strategies for patients with RA. However, further validation in prospective studies is warranted to confirm its clinical utility. Nonetheless, the potential implications of the ALI for improving the prognosis of patients with RA underscore the importance of its continued investigation in clinical practice.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent inflammation of the synovial membrane,

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which leads to progressive joint destruction, deformity, and disability. It affects approximately 1 % of the global population and has a profound impact on both the quality of life and life expectancy of affected individuals [1]. In addition to causing joint disease, RA can also cause complications such as osteoporosis, cardiovascular disease (CVD), and cancer [2–4]. CVD events are the main cause of death in rheumatoid patients and are closely associated with the degree of disease activity. The elevated cardiovascular risk in patients with RA is well documented and multifactorial. Chronic systemic inflammation, which is a hallmark feature of RA, plays a central role in the pathogenesis of atherosclerosis and CVD. Moreover, traditional cardiovascular risk factors such as hypertension, dyslipidaemia, diabetes mellitus (DM), and smoking are more prevalent among RA patients than in the general population. Additionally, the use of immunosuppressive medications such as corticosteroids and disease-modifying antirheumatic drugs (DMARDs) may further contribute to cardiovascular risk [5,6]. Despite advancements in the treatment of RA, mortality rates, particularly those associated with cardiovascular complications, have shown no improvement [7]. Consequently, there is an urgent need to identify novel biomarkers that can reliably predict all-cause mortality and cardiovascular mortality in RA patients.

In recent years, the advanced lung cancer inflammation index (ALI) has emerged as a promising prognostic marker in various medical conditions, including cancer, CVD, and chronic inflammatory disorders [8–10]. The ALI is a composite index that integrates multiple biomarkers of inflammation and nutritional status, including body mass index (BMI), serum albumin (Alb), and the neutrophil-to-lymphocyte ratio (NLR). These parameters reflect the complex interplay among systemic inflammation, immune function, and nutritional status, all of which are implicated in the pathogenesis of RA. One key feature of RA is the persistent activation of inflammatory pathways within synovial tissue. Proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) are abundantly produced by activated immune cells, including macrophages, T cells, and fibroblast-like synoviocytes (FLSs), within the inflamed synovium. These cytokines orchestrate a complex network of signalling cascades that drive inflammation, promote leukocyte recruitment, and stimulate the production of matrix-degrading enzymes such as matrix metalloproteinases (MMPs) and cathepsins.

Despite its potential utility, the role of the ALI in predicting clinical outcomes in RA patients has not been fully elucidated. Therefore, the primary objective of this study was to investigate the associations between the ALI and both all-cause mortality and cardiovascular mortality in RA patients using data from the National Health and Nutrition Examination Survey (NHANES). The NHANES provides a unique opportunity to examine the relationship between the ALI and clinical outcomes in patients with RA within a nationally representative sample of the noninstitutionalized civilian population in the United States. By leveraging the rich epidemiological data available in the NHANES, we aimed to address a key question regarding whether the ALI is independently associated with all-cause mortality and cardiovascular mortality in RA patients after adjusting for traditional cardiovascular risk factors. Ultimately, our findings may have important implications for risk assessment, prognostication, and personalized management strategies in RA patients.

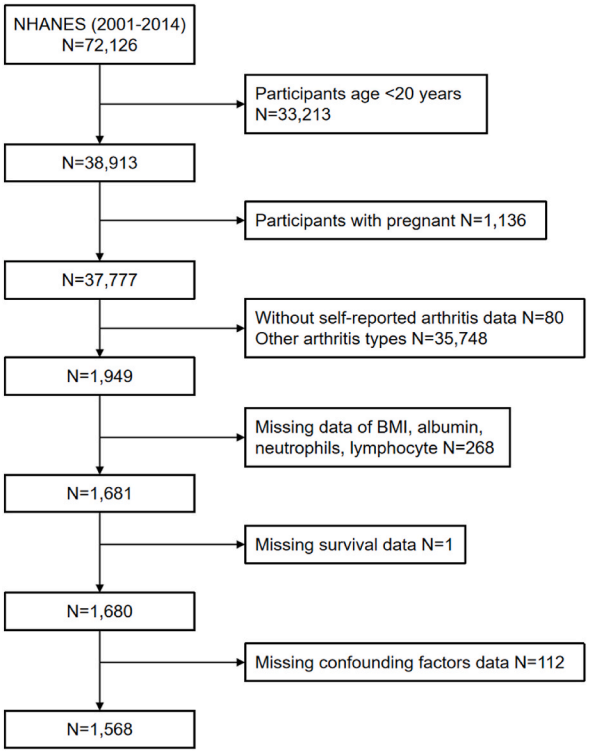

Fig. 1. Flowchart of the selection of the study participants.

2. Materials and methods

2.1. Study design and participants

The NHANES is a program conducted by the Centers for Disease Control and Prevention (CDC) in the United States. The NHANES is a nationally representative survey designed to assess the health and nutritional status of adults and children in the U.S. population. The NHANES data were collected through interviews and physical examinations conducted by trained health professionals. Participants are selected using a complex, stratified, multistage probability cluster sampling design, ensuring that the obtained data accurately represent the entire U.S. population. The survey received ethical approval from the National Center for Health Statistics (NCHS) Ethics Review Board, and informed consent was obtained from all adult participants [11]. This study included 38,913 participants aged 20 years and older from continuous NHANES (2001–2014) datasets. We excluded pregnant individuals, those without an RA diagnosis, individuals with missing albumin, lymphocyte, neutrophil, BMI and survival data, and those with incomplete confounding factor records. Ultimately, this study included a total of 1568 representative participants who met the inclusion criteria. A flowchart illustrating this process is shown in Fig. 1.

2.2. Diagnosis of RA

The diagnosis of RA was based on self-reported RA. These self-reports involve personal interview data collected at home by trained interviewers using the computer assisted personal interview (CAPI) system, and the questionnaire can be found in the Medical Conditions Questionnaire (MCQ). During the family interview, the interviewer asked the participants a series of questions, such as "Has a doctor or other health professional ever told you that you have arthritis?" and "Which type of arthritis was it?". We regarded patients with RA as those who answered "rheumatoid arthritis" to this question. Those who answered "Osteoarthritis", "Psoriatic Arthritis", "Other", or "Do not know" or who refused to answer were excluded from the analysis.

2.3. Definition of the advanced lung cancer inflammation index

According to previous reports [12], the ALI is negatively correlated with inflammation, with a low ALI indicating high inflammation and a high ALI indicating low inflammation. The formula for calculating the ALI is (BMI $\times$ Alb)/NLR, wherein BMI = weight in kilograms/(height in metres)^2, Alb = serum albumin in grams per decilitre, and NLR = absolute neutrophil count/absolute lymphocyte count [9]. A haematology analyser (Coulter® DxH 800 Analyser) was used to determine the lymphocyte and neutrophil counts, and the results are expressed as $\times$ 10^3 cells/μl [13].

2.4. All-cause and cardiovascular-cause mortality

The NHANES dataset is linked to the National Death Index (NDI) records, providing updated mortality follow-up data through December 31, 2019 (accessible at https://www.cdc.gov/nchs/data-linkage/mortality-public.htm). Our analysis primarily focused on all-cause and cardiovascular-cause mortality among participants from 2001 to 2014. Cardiovascular causes of death are defined by ICD-10 codes (codes I00–I09, I11, I13, and I20–I51). The number of person-years of follow-up was calculated as the time interval between the NHANES Mobile Examination Center (MEC) date and either the date of death or the end of the follow-up period (December 31, 2019), whichever event occurred first.

2.5. Definition of covariates

Covariates mainly included demographic data, lifestyle factors, and metabolic factors. We included age, sex, and race to adjust for differences in demographic data. The race variable was categorized as non-Hispanic White, non-Hispanic Black, Mexican American, or other races. We primarily used smoking and alcohol status to account for lifestyle differences. Smoking status was defined based on the number of cigarettes smoked as follows: never (smoked fewer than 100 cigarettes in life), former (smoked more than 100 cigarettes in life and not smoking at all at present), and current (smoking more than 100 cigarettes in life and smoking some days or every day). Alcohol status was defined as follows: never (had< 12 drinks in lifetime), former (had ≥12 drinks in 1 year and did not drink last year, or did not drink last year but drank ≥12 drinks in lifetime), and now (≥1 drink per day for females, 2 drinks per day for males binge drinking ≥2 days per month).

Metabolic risk factors included BMI, DM, hypertension, cancer, chronic kidney disease (CKD), and arteriosclerotic cardiovascular disease (ASCVD). The presence of any one criterion indicated a diagnosis of DM. For the diabetes questionnaire, participants were asked, "Have you ever been informed by a doctor or health care professional that you have diabetes or hyperglycaemia?" The following diagnostic criteria were established by the Diabetes Association for the diagnosis: fasting glucose ≥7.0 mmol/L, 2-h oral glucose tolerance test (OGTT) blood glucose ≥11.1 mmol/L, glycated haemoglobin (HbA1c) ≥ 6.5 %, or random blood glucose ≥11.1 mmol/L. Participants who were taking antidiabetic drugs or insulin were also included in this diagnosis. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, use of blood pressure control medication or being told by a doctor that the patient had hypertension. Cancer was defined if participants reported that they had ever been told by a doctor that they had cancer or malignancy. CKD is defined as an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2 or a urinary albumin to creatinine ratio (uACR) greater than 30 mg/g [14]. The diagnosis of ASCVD was based on self-reported questions

from the MCQ: MCQ160C— "Have you ever been told you have coronary heart disease (CHD)?"; MCQ160D— "Have you ever been told you have angina/angina pectoris?"; MCQ160E— "Have you ever been told you have had a heart attack?"; or MCQ160F— "Have you ever been told you have had a stroke?" [15]. In our study, the inclusion of data from multiple NHANES cycles necessitated the adjustment of the NHANES cycle year as a confounding factor.

2.6. Statistical analyses

The statistical analyses were conducted by using R software (version 4.3.1). Given the inclusion of haematological indicators in our study, we opted to measure MEC weight. Weighted means and standard errors (SEs) were used to present continuous variables, while weighted percentages were used for categorical variables. Baseline characteristics were compared using t tests for continuous variables and chi-square tests for categorical variables. K–M curves were generated to illustrate the survival probabilities based on different ALI categories. We examined the association between the ALI and mortality in RA patients using weighted multivariate Cox regression models. The following five models were used to progressively adjust for demographic factors, lifestyle factors, and metabolic factors to validate the relationship between ALI and mortality: a crude model with no covariates adjusted; Model 1 adjusted for age, sex, and race; Model 2 adjusted for age, sex, race, and BMI; Model 3 adjusted for age, sex, race, BMI smoking status, and alcohol consumption status; and Model 4 adjusted for age, sex, race, BMI smoking status, alcohol consumption status, cancer status, hypertension status, DM status, CKD status, ASCVD status and NHANES cycle year.

We performed a sensitivity analysis by converting continuous ALI to categorical ALI. The ALIs were divided into 4 quantiles based

Table 1
Baseline characteristics.

Variable	Total	Q1	Q2	Q3	Q4	Pvalue
	N = 1568	N = 392	N = 392	N = 392	N = 392	
		[2.89–40.28]	(40.28–60.12]	(60.12–83.28]	(83.28–606.49]	
Age (yr), Mean (SE)	56.98 (0.45)	60.99 (0.94)	57.51 (0.88)	54.73 (0.84)	54.60 (0.78)	<0.0001
Gender						0.6
Female n (%)	911 (59.37)	207 (57.23)	227 (61.24)	228 (57.50)	249 (62.05)	
Male n (%)	657 (40.63)	185 (42.77)	165 (38.76)	164 (42.50)	143 (37.95)	
Race						<0.0001
Mexican American n (%)	237 (6.15)	46 (5.01)	76 (7.60)	65 (6.36)	50 (5.49)	
Non-Hispanic White n (%)	715 (69.90)	214 (75.39)	203 (72.56)	185 (74.16)	113 (55.00)	
Non-Hispanic Black n (%)	451 (15.78)	83 (9.91)	77 (10.64)	101 (13.36)	190 (31.69)	
Other n (%)	165 (8.17)	49 (9.70)	36 (9.20)	41 (6.12)	39 (7.82)	
Marital status						0.03
Married or living with partner n (%)	854 (61.23)	198 (57.94)	227 (64.04)	234 (66.91)	195 (54.47)	
Single n (%)	714 (38.77)	194 (42.06)	165 (35.96)	158 (33.09)	197 (45.53)	
Educational level						0.01
Below high school n (%)	567 (25.77)	128 (23.91)	144 (25.09)	139 (24.46)	156 (30.42)	
High school or equivalent n (%)	369 (26.73)	110 (33.48)	103 (30.94)	83 (21.43)	73 (20.80)	
Above high school n (%)	631 (47.48)	153 (42.61)	145 (43.97)	170 (54.10)	163 (48.79)	
BMI (kg/m2), Mean (SE)	30.21 (0.25)	27.01 (0.40)	29.11 (0.42)	31.11 (0.52)	34.06 (0.52)	<0.0001
Alcohol status						0.63
Never n (%)	260 (13.27)	69 (13.80)	64 (12.78)	62 (13.30)	65 (13.20)	
Former n (%)	437 (26.40)	110 (28.39)	108 (25.17)	94 (23.00)	125 (29.91)	
Now n (%)	871 (60.32)	213 (57.81)	220 (62.05)	236 (63.70)	202 (56.88)	
Smoking status						0.43
Never n (%)	675 (40.15)	162 (37.75)	165 (39.01)	166 (39.51)	182 (45.09)	
Former n (%)	499 (30.57)	124 (30.22)	119 (28.41)	131 (33.27)	125 (30.04)	
Now n (%)	394 (29.28)	106 (32.03)	108 (32.58)	95 (27.22)	85 (24.87)	
Hypertension						0.003
No n (%)	538 (40.72)	124 (37.59)	141 (42.02)	163 (48.58)	110 (32.75)	
Yes n (%)	1030 (59.28)	268 (62.41)	251 (57.98)	229 (51.42)	282 (67.25)	
T2DM						0.03
No n (%)	1102 (77.70)	282 (79.17)	289 (78.03)	279 (81.55)	252 (70.68)	
Yes n (%)	466 (22.30)	110 (20.83)	103 (21.97)	113 (18.45)	140 (29.32)	
Cancer						0.07
No n (%)	1338 (83.44)	319 (79.38)	326 (81.29)	339 (84.58)	354 (89.20)	
Yes n (%)	230 (16.56)	73 (20.62)	66 (18.71)	53 (15.42)	38 (10.80)	
CKD						<0.0001
No n (%)	1104 (75.76)	225 (61.80)	267 (73.39)	307 (84.15)	305 (83.95)	
Yes n (%)	464 (24.24)	167 (38.20)	125 (26.61)	85 (15.85)	87 (16.05)	
ASCVD						0.02
No n (%)	1207 (78.26)	277 (71.52)	300 (79.02)	317 (83.31)	313 (78.71)	
Yes n (%)	361 (21.74)	115 (28.48)	92 (20.98)	75 (16.69)	79 (21.29)	
Status						<0.0001
Assumed alive n (%)	1094 (74.22)	216 (60.77)	263 (72.15)	302 (81.24)	313 (83.24)	
Assumed deceased n (%)	474 (25.78)	176 (39.23)	129 (27.85)	90 (18.76)	79 (16.76)	

on the weighted sample distribution, and the lowest quantile was used as a reference. A restricted cubic spline (RCS) model with three equally spaced nodes was used to investigate the nonlinear association between ALI and mortality. To explore the threshold effect of the ALI on the risk of death from RA and to determine the point of infection, we used smooth curve transformation and generalized additive models. Finally, we performed stratification and interaction analyses according to age, sex, race, BMI, smoking status and alcohol consumption status. A P value less than 0.05 was considered to indicate a significant difference.

3. Results

3.1. Baseline characteristics

A total of 1568 individuals met the inclusion criteria in this study, representing 7,320,692 US. RA patients. The average age was 57 years, 59.37 % of the participants were female, and 69.90 % were non-Mexican whites. During follow-up, 25.78 % of the individuals died. Participants with higher ALI were younger, more likely to be non-Hispanic black, and had fewer deaths. In addition, there were significant differences in BMI, marital status, educational level, T2DM status, hypertension status, CKD status and ASCVD status ($p < 0.05$). The clinical characteristics of the participants by ALI quartiles are shown in Table 1.

3.2. ALI and all-cause mortality in patients with RA

Crude Kaplan–Meier analyses revealed that the risk of all-cause mortality in RA patients decreased with increasing ALI (Fig. 2A). According to the multivariate Cox regression analysis, the ALI was inversely associated with mortality (HR = 0.987, 95 % CI = 0.982–0.991), and the results were robust after adjusting for different confounding factors (HR = 0.992, 95 % CI = 0.987–0.998) (Table 2). According to the sensitivity analysis, compared with that in the lowest quartile, the risk of all-cause mortality in the highest quartile decreased by 67.2 % (HR = 0.328, 95 % CI = 0.236–0.456, $p < 0.0001$) in the crude model and by 48.7 % (HR = 0.513, 95 % CI = 0.333–0.790, p = 0.002) in Model 4 (Table 2). Moreover, as the ALI increased, the all-cause mortality rate clearly decreased ($P < 0.001$ for trend).

According to the RCS model, there was a nonlinear relationship between the ALI and mortality ($p < 0.05$); when the ALI was less than 110, the mortality rate increased significantly, and when the ALI was greater than 110, the mortality rate did not change significantly (Fig. 2B). Finally, we conducted a stratified analysis, and the ALI had a protective effect in all strata (HR < 1). This protective effect was particularly significant in RA patients who were older than 60 years, female, obese or overweight ($p < 0.05$) (Supplementary Table 1).

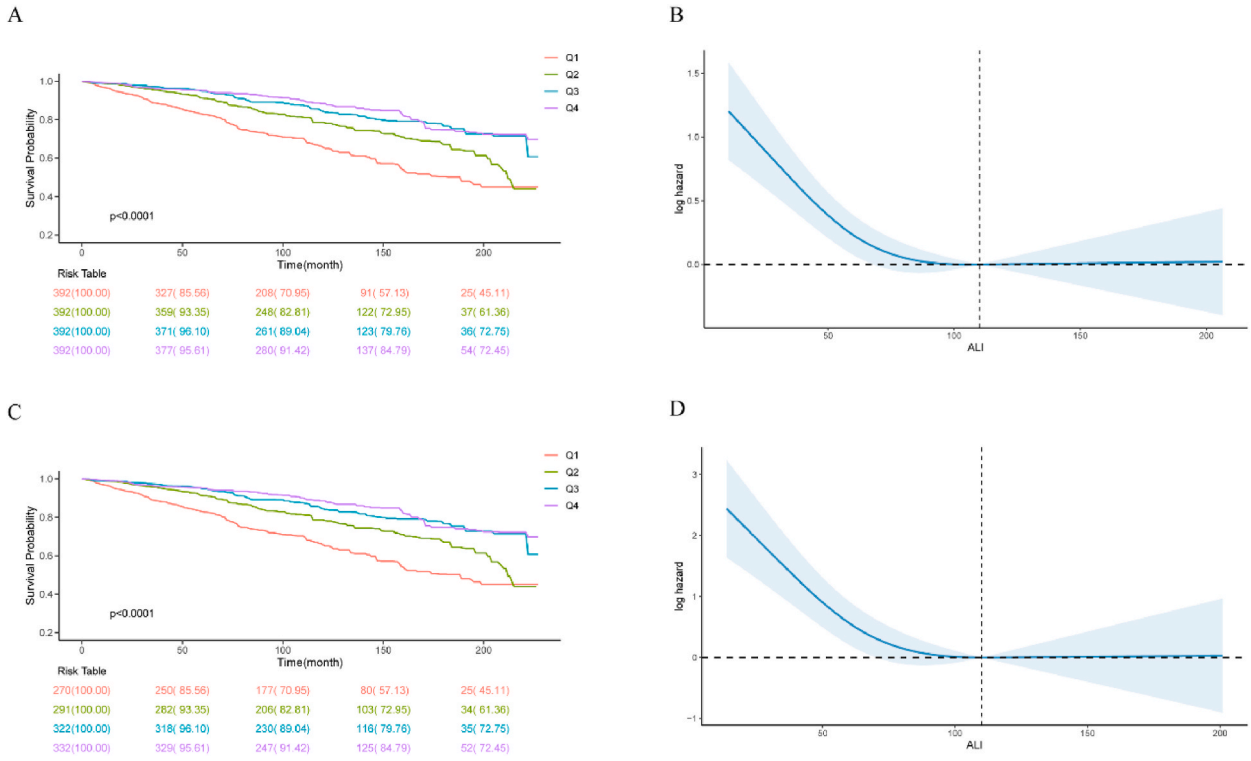

Fig. 2. (A) All-cause mortality survival curve. (B) RCS model analysis of the nonlinear association between the ALI and all-cause mortality. (C) Cardiovascular mortality survival curve. (D) RCS model analysis of the nonlinear association between the ALI and cardiovascular mortality.

Table 2
Association of the ALI with all-cause mortality in patients with RA.

	crude model	Model 1	Model 2	Model 3	Model 4
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
ALI (continuous variable)	0.987 (0.982,0.991)	0.991 (0.986,0.996)	0.991 (0.985,0.996)	0.991 (0.986,0.997)	0.992 (0.987,0.998)
Stratified by ALI quartiles					
Q1	ref	ref	ref	ref	ref
Q2	0.605 (0.455,0.804)	0.663 (0.489,0.901)	0.660 (0.486,0.897)	0.698 (0.516,0.945)	0.719 (0.537,0.961)
Q3	0.388 (0.292,0.515)	0.544 (0.400,0.739)	0.540 (0.399,0.732)	0.568 (0.418,0.772)	0.623 (0.455,0.853)
Q4	0.328 (0.236,0.456)	0.454 (0.310,0.663)	0.447 (0.303,0.659)	0.471 (0.312,0.712)	0.513 (0.333,0.790)
p for trend	<0.0001	<0.0001	<0.0001	<0.0001	<0.001

Crude model: no covariates were adjusted; Model 1: age, sex, and race were adjusted; Model 2: age, sex, race, and BMI were adjusted; Model 3: age, sex, race, BMI, alcohol status, and smoking status were adjusted; Model 4: age, sex, race, BMI, alcohol status, smoking status, cancer status, hypertension status, DM status, CKD status, ASCVD status, and NHANES cycle year were adjusted.

3.3. ALI and cardiovascular mortality in patients with RA

Crude Kaplan–Meier analyses revealed that the risk of cardiovascular mortality in RA patients decreased with increasing ALI (Fig. 2C). According to the multivariate Cox regression analysis, the ALI was inversely associated with cardiovascular mortality (HR = 0.979, 95 % CI = 0.970–0.989), and the results were robust after adjusting for different confounding factors (HR = 0.979, 95 % CI = 0.968–0.990) (Table 3). According to the sensitivity analysis, compared with that in the lowest quartile, the risk of cardiovascular mortality in the highest quartile decreased by 77.5 % (HR = 0.225, 95 % CI = 0.121–0.419, $p < 0.0001$) in the crude model and by 80.4 % (HR = 0.196, 95 % CI = 0.086–0.446, $p < 0.001$) in Model 4 (Table 3). Moreover, as the ALI increased, the cardiovascular mortality rate has a clear downward trend ($P < 0.0001$ for trend).

According to the RCS model, there was a nonlinear relationship observed between the ALI and cardiovascular mortality ($p < 0.05$); when the ALI was less than 110, the cardiovascular mortality rate increased significantly, and when the ALI was greater than 110, the cardiovascular mortality rate did not change significantly (Fig. 2D).

4. Discussion

RA is an autoimmune disease characterized by joint pain, swelling, deformity, and limited mobility. In addition to joint involvement, RA patients also have higher mortality rates, especially cardiovascular-related mortality [16]. However, there is currently a lack of effective prediction methods for identifying people at high risk of death in the early stages of the disease. For the first time, we conducted a prospective cohort study using data from 2001 to 2014 from the NHANES database and found that the ALI may be an effective indicator for predicting the prognosis of RA patients. A total of 1568 RA participants, representing 7,320,692 US. RA patients were included in this study. During a median follow-up of 119 months, 25.78 % of the participants with RA died (6.24 % from cardiovascular-related deaths and 6.07 % from cancer-related deaths). We found that the ALI was inversely associated with all-cause mortality and cardiovascular mortality in RA patients. As the ALI decreases by 1-unit, all-cause mortality decreases by 0.7 %, and cardiovascular mortality decreases by 2 %. More interestingly, we found that when the ALI was <110, the mortality rate of RA patients increased significantly, while when the ALI was >110, the mortality rate was relatively stable. This nonlinear relationship suggests a critical threshold below which mortality risk significantly increases, emphasizing the importance of the ALI as a predictive tool for identifying high-risk individuals.

Jafri et al. first proposed the concept of the ALI, which reflects the degree of inflammation and prognosis in patients with metastatic non-small cell lung cancer in 2013 [8]. Moreover, compared with other inflammation/nutritional indicators, the ALI can better predict the prognosis of lung cancer patients [12]. In recent years, in addition to lung cancer, an increasing number of studies have suggested that the ALI is closely associated with the prognosis of other diseases. Studies have proven that increased ALI is significantly associated

Table 3
Association of the ALI with cardiovascular mortality in patients with RA.

	crude model	Model 1	Model 2	Model 3	Model 4
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
ALI (continuous variable)	0.979 (0.970,0.989)	0.983 (0.973,0.994)	0.978 (0.968,0.989)	0.979 (0.968,0.989)	0.979 (0.968,0.990)
Stratified by ALI quartiles					
Q1	ref	ref	ref	ref	ref
Q2	0.546 (0.322,0.925)	0.637 (0.384,1.059)	0.556 (0.332,0.931)	0.621 (0.372,1.036)	0.534 (0.310,0.921)
Q3	0.256 (0.130,0.502)	0.364 (0.178,0.743)	0.306 (0.156,0.604)	0.344 (0.178,0.668)	0.371 (0.194,0.711)
Q4	0.225 (0.121,0.419)	0.309 (0.154,0.622)	0.209 (0.104,0.421)	0.208 (0.099,0.438)	0.196 (0.086,0.446)
p for trend	<0.0001	<0.001	<0.0001	<0.0001	<0.0001

Crude model: no covariates were adjusted; Model 1: age, sex, and race were adjusted; Model 2: age, sex, race, and BMI were adjusted; Model 3: age, sex, race, BMI, alcohol status, and smoking status were adjusted; Model 4: age, sex, race, BMI, alcohol status, smoking status, cancer status, hypertension status, DM status, CKD status, ASCVD status, and NHANES cycle year were adjusted.

with reduced mortality in patients with digestive tract tumours [17–19], diabetes [20], and CVD [10,21,22]. Currently, there are also several inflammatory/nutritional biomarkers that are associated with the prognosis of RA patients, such as the NLR [23,24], controlled nutritional status score (CONUT) and nutritional risk index (NRI) [25]. However, these indicators can only reflect inflammation or nutritional status alone and cannot simultaneously reflect both levels.

The ALI was calculated based on the serum ALB concentration, BMI and NLR. The components of ALI reflect the intricate interplay between inflammation, malnutrition, and the immune response in RA progression. ALB levels, which are indicative of nutritional status, decline in the presence of systemic inflammation and cachexia, which are commonly observed in advanced stages of malnutrition. Patients with active RA often have low albumin levels, which is mainly due to the high level of transferrin receptor (HSA) absorption at the inflamed site [26]. ALB not only reflects nutritional status but is also associated with inflammation within the body. Studies have shown that low ALB levels are closely associated with an increase in proinflammatory factors (such as TNF and CRP) within the body [27]. Concurrently, BMI, which is another component of the ALI, serves as a clinical marker for malnutrition and disease severity. BMI is positively correlated with the occurrence and activity of RA [28,29]. Moreover, patients with RA who have a high BMI have a greater risk of developing complications, especially regarding a greater incidence of cardiovascular diseases [30]. However, there is controversy regarding the impact of BMI on all-cause and cardiovascular mortality in RA patients. The findings of several studies have indicated that RA patients with a higher BMI exhibit a decreased mortality risk compared to those with a normal BMI [31–33]. The obesity paradox can provide an explanation for this seemingly contradictory phenomenon. Although obesity is recognized as being a risk factor for CVD events, patients with higher BMI often exhibit improved outcomes. This intriguing observation may be attributed to the enhanced anti-inflammatory effect mediated by adiponectin synthesis in obese individuals [34].

The NLR reflects the balance between inflammatory and immune responses. RA is a chronic low-grade inflammatory metabolic disease. Previous studies have reported that the normal NLR ranges from 1.65 to 2.11 [35]; in this study, the NLR of RA patients was 2.43. Activated white blood cells release active oxygen through neutrophils and cytokines, thereby promoting systemic inflammation and endothelial damage. The abovementioned results indicate that a higher NLR indicates a worse prognosis for RA patients. Compared to individual biomarkers such as the NLR, CONUT score and NRI, the ALI provides a more holistic approach, representing both inflammation and nutritional status simultaneously. This comprehensive evaluation enables a more nuanced understanding of disease progression and prognosis, facilitating risk stratification and tailored interventions to optimize patient outcomes. Moreover, our study highlights the potential clinical implications of the ALI for guiding personalized management strategies for RA patients. By identifying individuals at greater risks of adverse outcomes, clinicians can implement proactive measures, including intensified monitoring, lifestyle interventions, and targeted therapies, to mitigate cardiovascular risk and improve overall prognosis. Furthermore, the incorporation of the ALI into routine clinical practice may enhance risk assessment algorithms and prognostic models, ultimately guiding treatment decisions and improving long-term outcomes in patients with RA.

This study had several limitations to consider. First, the use of data from the NHANES database, while offering a representative sample of the U.S. population, may limit the generalizability of the results to RA patients in other countries or regions. Additionally, the reliance on self-reported diagnosis of RA introduces the potential for diagnostic errors or omissions. Although ALI has been extensively studied in other diseases, its application in RA patients requires further validation. Despite adjusting for multiple risk factors, potential confounding factors such as treatment regimens and disease activity may influence the observed association between the ALI and mortality. The retrospective observational design limits causal inference, necessitating further prospective studies to elucidate the underlying involved mechanisms. Moreover, the selected thresholds for the ALI may not be optimal, highlighting the need for future research to determine the most accurate threshold for predicting the prognosis of RA patients. Overall, although this study provides initial insights, addressing these limitations is essential for validating the clinical utility of the ALI in managing patients with RA.

In conclusion, our study provides compelling evidence supporting the prognostic value of the ALI in predicting all-cause and cardiovascular mortality in RA patients. By elucidating the complex interplay between inflammation and nutritional status, ALI offers a valuable tool for risk stratification and personalized management strategies in patients with RA, ultimately improving patient outcomes and quality of life. Further prospective studies are warranted to validate these findings and explore the utility of the ALI in guiding clinical decision-making in patients with RA.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The public data can be found at the National Center for Health Statistics (https://www.cdc.gov/NCHS/NHANES/INDEX.HTM). All data generated or analysed during this study are included in this published article.

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CRediT authorship contribution statement

Xiaoyuan Tian: Writing – original draft, Validation, Methodology, Investigation. **Zhenan Qu:** Writing – original draft, Validation, Investigation, Formal analysis. **Yulan Sun:** Software, Formal analysis. **Bocheng Zhang:** Writing – review & editing, Conceptualization.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33673.

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