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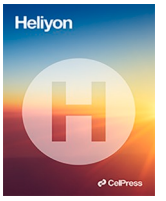

Research article

Prognostic value of lymphocyte to C-reactive protein ratio for cardiovascular and all-cause mortality in adults with congestive heart failure in the United States: NHANES 1999–2010

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ABSTRACT

Background: Lymphocyte to C-reactive protein ratio (LCR) is an emerging inflammatory biomarker, but its association with prognosis in individuals with congestive heart failure (CHF) remains unclear. We sought to evaluate the relationship between LCR and cardiovascular (CV) and all-cause mortality in individuals diagnosed with CHF.

Methods: We included 718 CHF individuals, using NHANES 1999–2010 data. ROC curves were used to compare the prognostic value of LCR, C-reactive protein, and lymphocyte counts for 3-year, 5-year, and 10-year CV and all-cause mortality risk. The population was divided into 4 groups based on the value of LCR according to the quartile. Prognosis analysis utilized the Kaplan-Meier method and Cox-regression analysis while accounting for NHANES recommended weights.

Results: Kaplan-Meier curves demonstrated a significantly worse prognosis in the low LCR group compared to the high LCR group (log-rank test; $p < 0.001$). For 3-year CV mortality, the multivariable-adjusted hazard ratios [95 % confidence interval] for LCR quartiles (Q 2,3,4 vs Q 1) were 0.43 (0.21–0.87), 0.38 (0.13–1.07), 0.34 (0.13–0.88), (P for trend = 0.033). For 3-year all-cause mortality, aHRs were 0.36 (0.22–0.60), 0.51 (0.29–0.89), 0.35 (0.18–0.64), (P for trend = 0.002). Similar findings were observed for 5- and 10-year CV and all-cause mortality.

Conclusions: Elevated LCR emerged as an independent prognostic factor for CV and all-cause mortality in individuals with CHF. Moreover, the implementation of anti-inflammatory therapy exhibits the potential to improve outcomes for decreased LCR patients with CHF.

1. Introduction

Congestive heart failure (CHF) has been recognized as the terminal stage of cardiovascular diseases, and remains a significant global burden with an estimated prevalence of approximately 1–2% worldwide and exceeding 10 % in individuals aged over 70 years [1–4]. This condition is associated with a dismal long-term prognosis, posing substantial challenges to medical systems [5,6]. Effective

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management strategies focusing on long-term follow-up are pivotal for improving patient outcomes. Therefore, the identification of a reliable, cost-effective, and readily available prognostic biomarker would greatly facilitate the prompt administration of targeted interventions to high-risk CHF patients and ultimately enhance their survival rates.

In recent decades, it has become increasingly evident that in addition to the recognized hemodynamic and neurohumoral hypotheses of heart failure, inflammation is also implicated in the pathogenesis and progression of CHF [7]. Similarly, cancer is a systemic disease characterized by activated inflammatory response and functional decline as hallmarks of disease progression. The lymphocyte/C-reactive protein ratio (LCR) has surfaced as an innovative prognostic indicator for this complex disease [8,9]. The LCR has also been reported to serve as a prognostic indicator for long-term outcomes in post-primary percutaneous coronary intervention individuals with ST-segment elevation myocardial infarction [10]. However, the long-term prognosis of patients with CHF and its correlation with LCR is still not fully understood.

In this research, our objective was to verify this novel systemic inflammatory biomarker as a valuable prognostic predictor for CHF individuals.

2. Materials and methods

2.1. Data source and study population

The Centers for Disease Control and Prevention initiated the National Health and Nutrition Examination Survey (NHANES) to investigate the health and nutritional data of Americans. The NHANES obtained ethical approval from the ethics review board of the National Center for Health Statistics, ensuring that all participants provided written informed consent.

In this retrospective cohort study, we examined the association of LCR with individuals who have been diagnosed with CHF, using data from the NHANES survey conducted from 1999 to 2010. The diagnosis of CHF was confirmed by asking participants if a healthcare professional had ever informed them of their condition. We collected comprehensive data encompassing demographics, physical examinations, laboratory analyses, and questionnaires. The study involved 1122 individuals diagnosed with CHF, while 152 participants who lacked lymphocyte and C-reactive protein (CRP) data, as well as 252 participants diagnosed with cancer and HIV, were excluded. Furthermore, there were no participants under the age of 18 and none were lost to follow-up, as a result, the study ultimately included 718 participants (Fig. 1).

2.2. Measurement of inflammation biomarkers and definition of LCR

The Beckman Coulter® MAXM instrument was used for conducting complete blood count measurements from 1999 to 2006 and in 2009–2010, while the Beckman Coulter® HMX instrument was utilized in 2007–2008 at the Mobile Examination Center. Professional researchers utilized the Beckman Coulter® technique in order to acquire complete blood count parameters, which involved counting and sizing. Additionally, a sample processing device that automatically diluted and mixed samples was employed. Hemoglobinometry was measured using a single-beam photometer. The VCS technology was utilized to conduct the differentiation of white blood cells (WBC). The counts of lymphocytes and white blood cells were expressed as × 1000 cells/mm3. The latex nephelometry was used for the quantification of CRP. The exposure factor was LCR, which was determined as the ratio of lymphocyte count to C-reactive protein level.

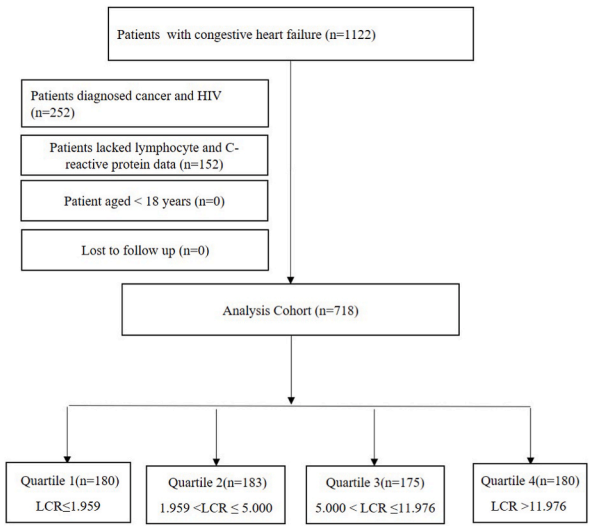

Fig. 1. Participants flow diagram.

2.3. Study endpoints

The study outcomes encompassed cardiovascular (CV) and all-cause mortality at 3-year, 5-year, and 10-year follow-up intervals. CV and all-cause mortality during follow-up were the endpoints for all survival analyses. The determination of the cause of death was based on data obtained from connected records of death certificates sourced from the National Death Index. Follow-up duration was defined as the period between the date of examination at the mobile center and either the date of mortality or the end of the mortality period (More details are accessible at https://www.cdc.gov/nchs/data-linkage/mortality-public.htm.).

2.4. Potential covariates

The demographic variables that were included were age (years), gender (male or female), race (non-Hispanic white, non-Hispanic black, Mexican American, or others), drinking (never, former, current), smoking status (never, former, current) and body mass index. Laboratory data were obtained from the NHANES 1999–2010 laboratory data files, including measurements of white blood cell count, lymphocyte count, platelet count, and the levels of hemoglobin, serum albumin, C-reactive protein, triglycerides, total cholesterol,

Table 1
Baseline characteristics of the study groups.

Characteristic	Overall (n = 718)	Q 1 LCR≤1.959 (n = 180)	Q 2 1.959 <LCR ≤5.000 (n = 183)	Q 3 5.000 < LCR ≤11.976 (n = 175)	Q 4 LCR >11.976 (n = 180)	P value
Age, (years)	64.36(0.72)	64.84(1.26)	66.29(1.30)	65.50(1.27)	61.13(1.36)	0.03
Female	303(42.2)	89(57.50)	78(43.65)	68(42.70)	68(34.07)	0.01
Race						0.7
Mexican American	107(14.9)	24(3.85)	23(3.30)	27(4.13)	33(5.05)	
Non-Hispanic Black	170(23.68)	52(19.30)	40(13.53)	42(14.51)	36(12.88)	
Non-Hispanic White	379(52.79)	92(68.77)	100(71.50)	93(74.14)	94(71.92)	
Other Hispanic	40(5.57)	8(3.98)	14(6.64)	8(1.81)	10(6.18)	
Other Race	22(3.06)	4(4.10)	6(5.04)	5(5.40)	7(3.97)	
Smoking status, n (%)						
Never	274(38.16)	63(39.06)	67(35.17)	74(39.91)	70(37.71)	0.91
Prior	302(42.06)	81(41.52)	75(37.91)	73(40.30)	73(42.27)	0.91
Current	142(19.78)	36(19.43)	41(26.91)	28(19.79)	37(20.02)	0.53
Drinking status, n (%)						
Never	96(14.52)	27(14.70)	26(14.69)	22(12.68)	21(11.22)	0.79
Prior	295(44.63)	87(56.00)	66(38.77)	71(36.98)	71(36.35)	0.01
Current	270(40.85)	51(29.31)	71(46.55)	73(50.34)	75(52.43)	0.004
SBP, (mmHg)	128.27(0.96)	128.41(2.21)	129.03(1.65)	126.98(2.25)	128.60(2.08)	0.91
DBP, (mmHg)	67.68(0.75)	67.09(1.27)	65.48(1.27)	67.98(1.64)	69.96(1.48)	0.15
BMI, (kg/m^2)	31.13(0.38)	34.01(0.95)	32.05(0.52)	30.63(0.55)	28.24(0.58)	<0.001
WBC, (10^3 cells/μL)	7.58(0.11)	7.95(0.18)	7.54(0.18)	7.51(0.20)	7.32(0.23)	0.13
Lymphocyte, (10^3 cells/μL)	1.99(0.04)	1.73(0.07)	1.92(0.06)	2.02(0.06)	2.26(0.07)	<0.001
HGB, (g/dL)	13.86(0.09)	13.16(0.14)	13.93(0.16)	14.14(0.16)	14.24(0.17)	<0.001
Platelet count, (10^6 cells/μL)	246.80(4.09)	260.99(8.11)	249.52(8.66)	236.43(5.74)	239.68(6.85)	0.08
Albumin, (g/dL)	4.11(0.02)	3.90(0.03)	4.05(0.04)	4.18(0.03)	4.30(0.03)	<0.001
C-reactive protein, (mg/dL)	0.80(0.05)	2.20(0.15)	0.60(0.02)	0.28(0.01)	0.09(0.01)	<0.001
TG, (mmol/L)	1.88(0.07)	1.73(0.15)	2.07(0.14)	1.94(0.21)	1.75(0.13)	0.28
TC, (mmol/L)	4.87(0.06)	4.71(0.09)	5.03(0.11)	4.93(0.10)	4.83(0.12)	0.07
LDL-C, (mmol/L)	2.79(0.06)	2.74(0.12)	2.81(0.10)	2.78(0.14)	2.83(0.11)	0.93
HDL-C, (mmol/L)	1.26(0.02)	1.23(0.04)	1.22(0.03)	1.25(0.04)	1.34(0.05)	0.29
Creatine, (mg/dL)	1.26(0.06)	1.49(0.14)	1.27(0.11)	1.17(0.05)	1.10(0.07)	0.13
eGFR ($mL/min/1.73m^2$)	68.69(1.47)	65.15(2.95)	67.17(2.45)	66.28(1.95)	75.46(2.68)	0.04
Urid acid, (mg/dL)	6.40(0.09)	6.86(0.22)	6.41(0.17)	6.49(0.18)	5.88(0.15)	0.01
CHD, n (%)	447(63.58)	112(60.38)	118(68.04)	108(62.05)	109(59.62)	0.58
DM, n (%)	320(44.63)	100(53.16)	84(46.39)	74(35.47)	62(27.85)	<0.001
HT, n (%)	567(78.97)	143(73.21)	147(72.89)	139(76.45)	138(67.09)	0.51
Anemia, n (%)	158(22.01)	54(28.64)	45(19.23)	31(15.79)	28(11.79)	0.01
Stroke, n (%)	141(19.72)	30(19.86)	45(19.83)	33(18.58)	33(15.81)	0.86
Beta blockers, n (%)	349(48.68)	93(54.47)	94(51.67)	87(47.86)	75(42.07)	0.29
ACEI/ARB, n (%)	389(54.25)	92(46.98)	97(51.61)	103(56.32)	97(49.88)	0.57
Statin, n (%)	212(29.57)	42(26.63)	49(24.43)	55(30.99)	66(37.56)	0.12
CCB, n (%)	192(26.78)	50(21.61)	58(28.05)	44(22.78)	40(21.48)	0.59
Diuretics, n (%)	378(52.72)	118(68.34)	94(49.43)	95(51.87)	71(36.06)	<0.001

Continuous variables are expressed as mean (SE).
Abbreviation: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WBC, white blood cell; HGB, hemoglobin; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; DM, diabetes mellitus; HT, hypertension; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blockers.

high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatine, and uric acid. All those measurements were taken only once time during the NHANES survey. The estimated glomerular filtration rate (eGFR) was determined by employing the modification of diet in renal disease 4-component study equation. The diagnostic criteria for hypertension (HT) were a medical diagnosis of HT and the administration of antihypertensive medication. Additionally, the diagnosis could be made if an individual had a mean measurement of systolic blood pressure ≥140 mmHg or a mean measurement of diastolic blood pressure ≥90 mmHg. The diagnostic criteria for diabetes mellitus (DM) included either a medical diagnosis of diabetes, a hemoglobin A1c (HbA1c) level exceeding 6.5 %, or the utilization of diabetes medication or insulin. The determination of the presence of coronary heart disease (CHD) and stroke was based on affirmative responses to the inquiry, "Has a medical professional ever diagnosed you with a heart attack, CHD, angina, or stroke?". The diagnostic criteria for anemia are as follows: hemoglobin levels below 120 g/L in women and below 130 g/L in men. (The measurement techniques for these variables and the definitions of diseases are readily accessible at www.cdc.gov/nchs/nhanes/.)

2.5. Statistical analysis

All statistical analyses were conducted using complex sampling weighted analysis, employing the recommended NHANES weights. Continuous variables are expressed as mean and standard error, while categorical variables are summarized as numbers and percentages. Differences in baseline characteristics among groups were analyzed by the weighted ANOVA test for continuous variables and the chi-squared test was employed to analyze the categorical data.

The construction of the receiver operating characteristic (ROC) curve aimed to assess and compare the prognostic value of LCR, C-reactive protein, and lymphocyte counts for CV and all-cause mortality risk at 3-, 5-and 10-year follow-up intervals. The participants were categorized into four cohorts based on the LCR value according to the quartile. The survival curves were generated through the Kaplan-Meier method for the 10-year CV and all-cause mortality, and the survival differences among groups were compared using the log-rank test. Relevant variables exhibiting statistically significant differences from the baseline data were identified and incorporated into a univariate analysis (Supplemental Table S1, Supplemental Table S2). Multivariate Cox regression analyses were employed to control for the variables initially identified through univariate analysis and independently assess the prognostic significance of LCR in terms of CV and all-cause mortality risk at 3-, 5-, and 10-year follow-up intervals among patients with CHF. P for trend was conducted to evaluate the trend of the association. An investigation was carried out using restricted cubic splines to examine the correlation between LCR and the long-term prognosis of patients with CHF and LCR was log-transformed due to non-normal distribution.

All statistical analyses were conducted through the Survey package in R software (version 4.2.1; R Foundation for Statistical Computing, Vienna, Austria). All P values reported in the analyses were computed using two-sided tests, and a significance level of $p < 0.05$ was adopted.

3. Results

3.1. Baseline characteristics

The study included 718 participants. The participants' baseline characteristics are presented in Table 1. The participants were divided into four groups: quartile (Q) 1 (LCR ≤1.959), Q 2 (LCR >1.959 and LCR ≤5.000), Q 3 (LCR >5.000 and LCR ≤11.976) and Q 4 (LCR >11.976). The average age of the study population was found to be 64.4 ± 0 0.7 years old. Females and individuals of advanced age were more likely to have lower LCR levels. Lymphocyte count, hemoglobin level, serum albumin, and eGFR were significantly lower among those with low LCR levels compared to those with high LCR levels. However, body mass index, CRP, and uric acid showed an opposite trend. Higher LCR quartiles had a higher prevalence of drinking history but a lower prevalence of DM and anemia. There was also significantly lower use of diuretics as well as long-term CV and all-cause mortality rates among individuals in the high LCR quartiles. More detailed information regarding participants' baseline characteristics is provided in Table 1. The ROC curve analysis demonstrated that LCR mostly exhibited higher AUC values for CV and all-cause mortality at the 3-, 5-, and 10-year follow-up compared to absolute lymphocyte count and C-reactive protein levels, which indicated that the prognostic value of LCR surpasses that of absolute lymphocyte and C-reactive protein levels (Supplemental Fig. S1, Supplemental Fig. S2).

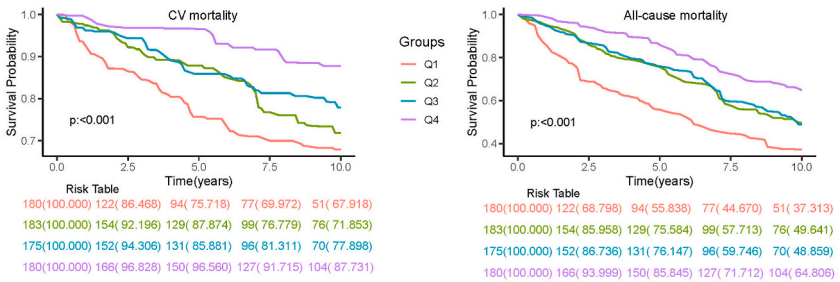

Fig. 2. Kaplan-Meier curves for long-term CV and all-cause mortality.

3.2. The Kaplan–Meier survival analysis for CV and all-cause mortality

Reaching a follow-up period exceeding 10 years, this cohort experienced a total of 69 (9.61 %), 104 (14.48 %) and 162 (22.56 %) cardiovascular-related deaths at the 3-, 5-, and 10-year marks, respectively, while all-cause mortality accounted for the deaths of 152 (21.17 %), 221 (30.78 %), and 392 (54.6 %) patients over the same periods. Kaplan-Meier survival analysis revealed that individuals in high LCR quartiles exhibited significantly lower rates of long-term CV and all-cause death compared to those in low LCR quartiles, as determined by log-rank testing (Fig. 2).

3.3. Associations of LCR with CV and all-cause mortality

Multivariable Cox regression analysis demonstrated that LCR was independently associated with 3-, 5- and 10-year CV and all-cause mortality in CHF patients. For 3-year CV mortality, the multivariable-adjusted hazard ratios (aHRs) [95 % confidence interval (CI)] for LCR quartiles (Q 2,3,4 vs Q 1) were 0.43 (0.21–0.87), 0.38 (0.13–1.07), 0.34 (0.13–0.88), (P value for trend = 0.033). For 3-year all-cause mortality, aHRs were 0.36 (0.22–0.60), 0.51 (0.29–0.89), 0.35 (0.18–0.64), (P value for trend = 0.002) (Table 2).

For 5-year CV mortality, the multivariable aHRs (95 % CI) for LCR quartiles (Q 2,3,4 vs Q 1) were 0.41 (0.22–0.77), 0.42 (0.17–1.00), 0.18 (0.07–0.46), (P value for trend = 0.001). For 5-year all-cause mortality, aHRs were 0.43(0.29–0.64), 0.57 (0.34–0.93), 0.44 (0.25–0.78), (P value for trend = 0.014) (Table 2).

For 10-year CV mortality, the multivariable aHRs (95 % CI) for LCR quartiles (Q 2,3,4 vs Q 1) were 0.65 (0.36–1.16), 0.39 (0.20–0.78), 0.33 (0.17–0.64), (P value for trend = 0.001). For 10-year all-cause mortality, aHRs were 0.63 (0.43–0.93), 0.69

Table 2
Multivariable Cox regression analysis for CV and all-cause mortality.

Groups	HR	95 % CI	P-value
3-year CV mortality[a]			
Q1	ref		
Q2	0.43	0.21–0.87	0.02
Q3	0.38	0.13–1.07	0.07
Q4	0.34	0.13–0.88	0.03
p for trend			0.033
5-year CV mortality[b]			
Q1	ref		
Q2	0.41	0.22–0.77	0.01
Q3	0.42	0.17–1.00	0.05
Q4	0.18	0.07–0.46	<0.001
p for trend			0.001
10-year CV mortality[c]			
Q1	ref		
Q2	0.65	0.36–1.16	0.14
Q3	0.39	0.20–0.78	0.01
Q4	0.33	0.17–0.64	0.001
p for trend			0.001
3-year all-cause mortality[d]			
Q1	ref		
Q2	0.36	0.22–0.60	<0.0001
Q3	0.51	0.29–0.89	0.02
Q4	0.35	0.18–0.64	<0.001
p for trend			0.002
5-year all-cause mortality[e]			
Q1	ref		
Q2	0.43	0.29–0.64	<0.0001
Q3	0.57	0.34–0.93	0.02
Q4	0.44	0.25–0.78	0.005
p for trend			0.014
10-year all-cause mortality[f]			
Q1	ref		
Q2	0.63	0.43–0.93	0.02
Q3	0.69	0.49–0.97	0.04
Q4	0.53	0.35–0.81	0.003
p for trend			0.008

[a] Adjusted for age, current drinking, albumin, eGFR, urid acid, anemia, use of diuretics.
[b] Adjusted for age, body mass index, current drinking, albumin, eGFR, urid acid, anemia, use of diuretics.
[c] Adjusted for age, body mass index, current drinking, eGFR, urid acid, diabetes mellitus, anemia, use of diuretics.
[d] Adjusted for age, current drinking, albumin, eGFR, urid acid, diabetes mellitus, anemia, use of diuretics.
[e] Adjusted for age, current drinking, albumin, eGFR, urid acid, diabetes mellitus, anemia, use of diuretics.
[f] Adjusted for age, body mass index, current drinking, albumin, eGFR, urid acid, diabetes mellitus, anemia, use of diuretics.

(0.49–0.97), 0.53 (0.35–0.81), (P value for trend = 0.008) (Table 2).

The restricted cubic splines analysis revealed that there are significant linear associations between LCR and both long-term CV and all-cause death rates in CHF patients, highlighting that elevated levels of LCR are linked to a reduction of risk for CV and all-cause death rates within this population (Fig. 3).

4. Discussion

In our study, we identified a novel systemic immune-inflammatory indicator, namely the LCR, which demonstrated independent predictive significance in relation to CV and all-cause death rate among CHF patients. Thus, the utilization of the LCR index in community health examinations may serve as a prospective biomarker for predicting poor prognosis among patients with CHF. The findings of this research revealed that higher LCR quartiles showed a notable correlation with reduced risk, ranging from 57 % to 66 %, 58 %–82 %, and 61 %–67 % for 3-, 5- and 10-year CV mortality, respectively. Similarly, all-cause mortality decreased by approximately 49 %–65 %, 43 %–57 %, and 31 %–47 % over the same periods. This report appears to be the first study to investigate the significance of the LCR index in community health examinations conducted among patients diagnosed with CHF, as far as our current knowledge extends.

In recent decades, there has been mounting evidence to suggest that, in addition to the well-established hemodynamic and neurohumoral hypotheses of heart failure, inflammation may also contribute significantly to the pathogenesis and progression of the disease. This recognition has led to the emergence of the cytokine hypothesis [11–14]. Multiple researches have indicated that the activation of both innate and adaptive immune systems could occur as a result of myocardial injury in individuals with CHF, thereby triggering a systemic inflammatory response [15]. Subsequently, there was an upregulation of proinflammatory cytokines and chemokines, as well as the infiltration of neutrophils and monocytes into the myocardium following injury, thereby contributing to a transient adaptation to cardiac stress, commonly referred to as physiological inflammation [16]. If myocardial damage persists, the prolonged presence of inflammation can eventually result in impaired function and remodeling of the left ventricle [17]. Furthermore, in studies involving acute heart injury in experimental models, it has been definitively established that the involvement of inflammatory cells plays a crucial part in the development of acute heart failure [18]. Prior studies have identified several systemic inflammatory markers as independent prognostic factors in patients with acute heart failure [19,20]. The understanding of the mechanism for systemic inflammation in acute heart failure individuals is relatively well understood. However, the significance of systemic inflammatory indicators in CHF has not been thoroughly elucidated. This research sought to investigate the significance of systemic inflammatory markers in the emergence and progression of CHF, in order to enhance the understanding of possible targets for therapy and the development of strategies for mitigating risks, which are tailored to individual levels of risk.

The activation of the immune system is a vital characteristic of CHF, as persistent and unresolved low-grade inflammation exacerbates the advancement of the condition [21]. The escalation of edema in the bowel wall may lead to the liberation of bacterial

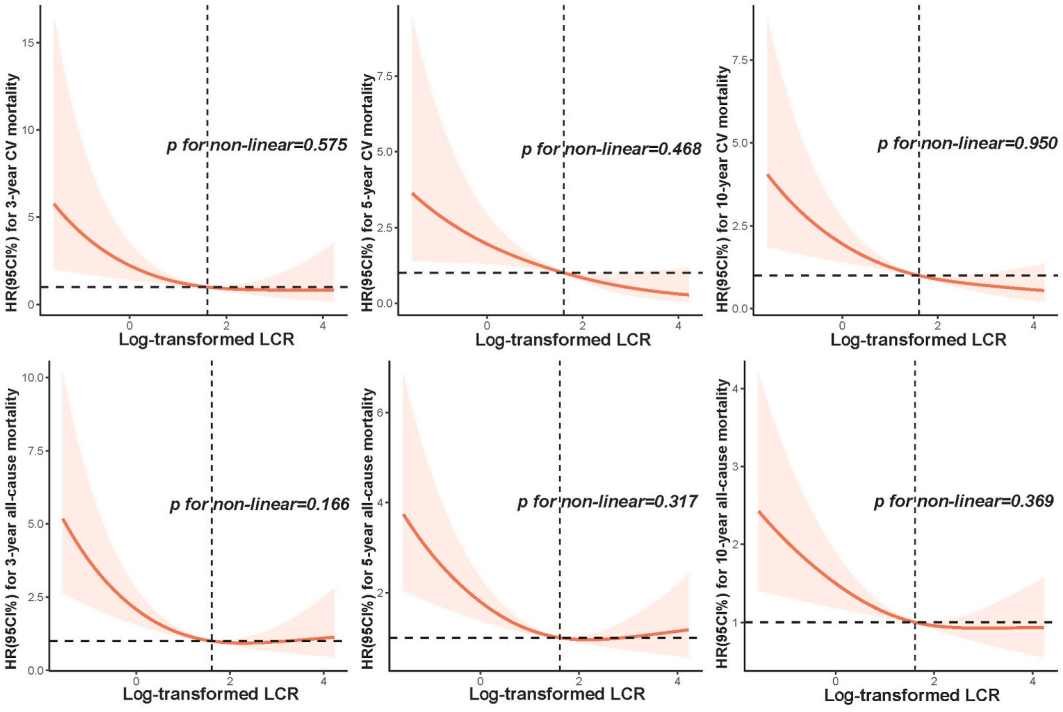

Fig. 3. Restricted spline curve for the LCR hazard ratio.

endotoxins from the gastrointestinal tract into the bloodstream [22]. Circulating endotoxins elicited the secretion of proinflammatory cytokines by peripheral blood mononuclear cells, a phenomenon that has been observed in both individuals with moderate HF and healthy individuals [23]. The cytokine hypothesis is a widely debated theory in academic discourse. Myocardial stress response is triggered in ischemic cardiac injury, causing the release of proinflammatory cytokines. These cytokines play a significant role in initiating myocyte hypertrophy, myocardial dysfunction, and left ventricular remodeling. Additionally, the reduced cardiac output exacerbates this detrimental effect by promoting ischemia and hypoperfusion, further increasing the release of inflammatory cytokines [24]. Systemic inflammation is a prevalent pathological feature of CHF, with some patients exhibiting evidence of monocyte-macrophage and lymphocyte activation [7,25]. Inflammation promotes adverse ventricular remodeling, which is predictive of poor prognosis independent of traditional predictors such as the New York Heart Association class or left ventricular ejection fraction [26,27]. Other composite systemic inflammation indicators, including the neutrophil to lymphocyte count ratio and platelet to lymphocyte count ratio, have been recognized as predictors for long-term poor prognosis in CHF patients [28,29]. This study's analysis demonstrated that LCR was also found to be a significantly independent prognostic factor for adverse long-term endpoints in patients with CHF.

The role of LCR in predicting the long-term prognosis of patients with CHF remains uncertain, despite several proposed mechanisms. On one hand, lymphocytes play a crucial role in regulating systemic inflammation, which has been shown to reduce myocardial fibrosis and adverse remodeling [10,30]. Conversely, an augmented inflammatory response can lead to excessive release of endogenous catecholamines and cortisol resulting in decreased levels of lymphocytes [31–33]. A low relative lymphocyte count has been identified as a valuable predictor for poor long-term outcomes among CHF patients [34]. On the other hand, C-reactive protein serves as a sensitive indicator of inflammation and is frequently elevated in patients with CHF [35]. Higher levels of CRP are often accompanied by higher New York Heart Association functional class [25]. CRP may exacerbate CHF in various ways. It can activate the complement system and stimulate cytokine release, leading to myocyte apoptosis and left ventricular remodeling [25]. Additionally, CRP may inhibit nitric oxide production and angiogenesis, promoting the development of diverse cardiovascular diseases [36]. Furthermore, CRP has a direct proinflammatory effect on human endothelial cells that contributes to atherosclerosis development [37]. High levels of CRP have been linked to poor long-term prognosis in CHF patients [38,39].

LCR serves as an affordable, easily calculable biomarker that is readily accessible for follow-up and management purposes. More importantly, it is applicable to the screening of high-risk populations in the community. Despite continuous advancements in pharmacological and device therapies for patient management, the long-term prognosis of CHF remains unfavorable. Chronic low-grade inflammation plays an essential part in the pathophysiology of CHF, with numerous studies reporting its predictive value for adverse outcomes in CHF patients. Despite the potential of anti-inflammatory therapy as an effective method to enhance the long-term prognosis for patients with CHF, its efficacy has been limited thus far [15]. However, this study's findings suggest that LCR may offer a new avenue for anti-inflammatory therapies.

The objective of this research was to evaluate the predictive capacity of LCR for long-term CV and all-cause mortality in patients with CHF. However, it is important to acknowledge certain limitations. Firstly, the diagnosis of comorbidities primarily depended on self-reported data, potentially introducing recall bias. Secondly, only CV and all-cause death were examined as outcomes in this study which limits our capacity to assess the significance of LCR with respect to other outcomes such as rehospitalization, acute heart failure, and malignant arrhythmias. Thirdly, due to a single blood draw being taken during this study period, we were unable to monitor changes over time in lymphocyte counts or C-reactive protein levels or their impact on long-term follow-up. Fourthly, in our study, we focused on excluding participants with cancer and HIV that severely impact immune function and prognosis. While we did not exclude participants with other conditions such as chronic inflammatory diseases, acute and chronic infections, autoimmune diseases, hematological disorders, recent surgeries or trauma, and the use of immunosuppressive or anti-inflammatory medications. Finally, despite adjusting for numerous confounding factors in our analysis there remains potential for residual unmeasured confounding variables.

5. Conclusion

LCR is an innovative and independent prognosticator for long-term CV and all-cause mortality in individuals with CHF. Its incorporation into risk stratification algorithms can aid in identifying high-risk individuals for targeted interventions, ultimately improving patient outcomes. However, conducting prospective multicenter cohort studies is essential for obtaining more robust evidence and confirming the validity of our discoveries.

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Ethics and consent

The NHANES research protocols were approved by the NCHS Research Ethics Review Board and all participants provided written informed consent (More information are readily accessible at www.cdc.gov/nchs/nhanes/.).

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Yong Lin: Writing – review & editing, Writing – original draft, Funding acquisition. **Kunming Bao:** Writing – review & editing, Writing – original draft, Software. **Dongjun Bao:** Methodology, Data curation. **Feng Luo:** Data curation. **Zhidong Huang:** Visualization, Software, Methodology. **Chunhua Guo:** Supervision, Project administration, Funding acquisition, 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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Not appliable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38416.

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