Heliyon 9 (2023) e17776

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

The relationship between C-reactive protein to lymphocyte ratio and the prevalence of myocardial infarction in US adults: A cross-sectional study

Lu He, Hang Xie, Yajuan Du, Xuegang Xie, Yushun Zhang *

Department of Structural Heart Disease, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710061, China

ARTICLE INFO

Keywords:
C-reactive protein
Lymphocyte
Myocardial infarction
Cross-sectional
NHANES

ABSTRACT

Objective: C-reactive protein to lymphocyte ratio (CLR) has been identified as a novel inflammatory biomarker. However, the role of CLR in myocardial infarction is unclear. Thus, this study designs to investigate the association of CLR with the prevalence of myocardial infarction in a large multiracial population in the United States.

Methods: Participants from the National Health and Nutrition Examination Survey (NHANES) 2017–March 2020 Pre-pandemic were included in this cross-sectional study. Multivariable regression and subgroup analyses, controlling for demographic variables, were performed to examine the association between CLR and its quintiles and myocardial infarction. A smooth curve fitting was used to model the non-linear relationship between them.

Results: A total of 12,615 participants aged ≥18 years were recruited, of whom 609 (4.83%) self-reported a history of myocardial infarction. Compared to those in the lowest quartile of ln-transformed CLR (Q1), the myocardial infarction risks for subjects in Q2, Q3, and Q4 were 1.64, 1.71, and 1.79 times, respectively. Obvious upward trends were observed when ln-transformed CLR increased (P for trend <0.01). In continuous analyses, the fully adjusted odds ratios (OR) for myocardial infarction prevalence per ln-transformed increment in CLR was 1.46 (95% CI: 1.16–1.84, $P < 0.01$). Furthermore, a linear association was detected for ln-transformed CLR with the risk of myocardial infarction. Interaction test showed that the effect of CLR on myocardial infarction was significantly affected by age (P for interaction = 0.04).

Conclusions: Data from a large, cross-sectional cohort program show that CLR is positively associated with myocardial infarction prevalence. Our findings highlight that CLR may be a novel inflammation warning biomarker for myocardial infarction.

1. Introduction

Myocardial infarction (MI) is a serious heart disease with high mortality rates and poor outcomes worldwide. In recent years, reperfusion therapy, mainly primary percutaneous coronary intervention, has been associated with a dramatic reduction in MI-related deaths [1]. However, the incidence of MI continues to rise, emerging as one of the world's most pressing public health challenges in recent decades, with about 7 million patients diagnosed with MI yearly [2,3]. It is commonly accepted that during MI, myocardium blood flow is suddenly reduced as a result of plaque rupture and thrombus formation. When MI occurs, cardiomyocytes, as well as

* Corresponding author.
E-mail address: zys2889@sina.com (Y. Zhang).

https://doi.org/10.1016/j.heliyon.2023.e17776
Received 11 March 2023; Received in revised form 27 June 2023; Accepted 28 June 2023
Available online 29 June 2023

other heart cells, die from a lack of blood and oxygen [4]. At the same time, the inflammatory process begins with the infiltration of inflammatory cells. In addition, atherosclerosis is characterized by inflammation from the earliest stages. As atherosclerosis progresses, inflammation has been linked to strokes and acute myocardial infarctions [5]. Even the body can perform self-repair by eliciting a suitable inflammatory response for injured myocardial tissue, it is important to note that persistent excessive inflammatory response further exacerbates cardiomyocyte apoptosis and may result in serious adverse events that have a detrimental impact on the prognosis of the patient [6,7]. Therefore, these evidences clearly indicate that inflammation plays an important role in MI.

The C-reactive protein (CRP) is a classic inflammation marker used to monitor infections and inflammatory conditions. There is general agreement that lymphocytes are a major component of the immune response, and that excessive immune activation leads to a decrease in lymphocyte counts [8]. In routine clinical practice, leukocytes, neutrophils, lymphocytes, platelets, or CRP are usually measured as indicators of inflammation. Thus, a combination of these inflammatory biomarkers should have better reproducibility and accuracy than a single biomarker. Recently, there is good evidence that the ratio of C-reactive protein to lymphocytes (CLR), as a novel inflammatory biomarker, can be used for predicting both prognosis and diagnostic evaluation of various diseases. For example, increasing CLR indicates unfavorable outcomes for COVID-19 patients [9]. Furthermore, the CLR played a significant and independent role in predicting the outcome of patients with severe fever with thrombocytopenia syndrome [10]. Moreover, several studies have linked a high CLR to a poor prognosis for patients with malignant diseases [11–15]. However, the association between CLR and MI is not well described until now. The level of CLR reflects the balance between the systemic inflammatory and immune responses [16]. Given that both inflammation and immunity are important for cardiovascular disease, we believed CLR can be assumed to reflect systemic inflammatory and immune status in MI. To the best of our knowledge, there is no study investigating the association of CLR with MI. Therefore, the main goal of our study was to investigate whether higher CLR is linked to higher risk of MI in US adults using a cross-sectional design.

2. Methods

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES), utilizing a stratified, multistage probability sample of non-institutionalized civilians in US, is a long-term epidemiology survey to acquire fundamental data and assess health status (https://wwwn.cdc.gov/nchs/nhanes/default.aspx). The most recently released available data of the NHANES from March 2017 to 2020 Pre-pandemic was analyzed in this cross-sectional study. Data collected in the cross-sectional survey include demographics, diet, physical examination, and questionnaires. The NHANES starts with a home interview in which trained personnel ask questions and automated data are collected. After that, all the participants go to a mobile examination clinic, where qualified personnel collect anthropometric data and biological samples. NHANES survey data is freely accessible on the web for use by data researchers and other users. For more information about NHANES, please visit www.cdc.gov/nchs/nhanes/. NHANES project has been approved by the Ethics Review Committee of the National Center for Health Statistics and Research. It is a publicly accessible database, so ethical approval was not required.

We identified the outcomes (MI) using a Medical Condition Questionnaire. When an individual returned "yes" to the question "has a doctor ever told you that you had a heart attack (also called myocardial infarction)," we determined that a participant had MI. Previous epidemiological studies using NHANES data have employed self-reported MI measures, and the results of several studies have indicated that the self-reported measurement method is reliable [17–19]. The study involved 15,549 participants aged ≥18 years. Among these participants, we excluded participants who were pregnant women (n = 144), without CLR value (n = 2158), and participants who did not report myocardial infarction status (n = 632). A total of 12,615 participants were ultimately included in the analysis (Fig. 1). In the most recently released NHANES data, CRP concentrations were measured using a highly sensitive two-reagent, immunoturbidimetric system. The laboratory procedure was performed at University of Minnesota, Advanced Research and Diagnostic Laboratory based on high-sensitivity near-infrared particle immunoassay rates (https://wwwn.cdc.gov/nchs/data/nhanes/2017-2018/labmethods/HSCRP-J-MET-508.pdf). The high-sensitivity C-reactive protein (hs-CRP) can detect low levels of CRP using hypersensitive detection technology, and is a more sensitive inflammatory marker, which detecting slight increases in CRP levels even when within the normal range [20]. Thus, the hs-CRP was used in this study and was measured in mg/l.

2.2. Variables

Based on the existing literature and clinical relevance, variables with potential links to MI were gathered in this study. The sociodemographic characteristics including age, sex (male/female), ethnicity (Mexican Americans, non-Hispanic Black, non-Hispanic white, other races), waist circumference, body mass index (BMI), marital status (we defined married/living with partner as "married," widowed/divorced/separated/never married as "unmarried"), education level (less than high school, high school, above high school), and alcohol user status (never/mild/moderate/heavy). The history of malignancy, statins use, antihypertensive drugs, hypoglycemic drugs, anti-hyperlipidemic drugs, and cardiac disease (heart failure/coronary heart disease/angina/stroke) were determined from the Medical Conditions Questionnaire (MCQ) by self-reporting. Smoking status was divided into never smoker (smoked less than 100 cigarettes in life), former smoker (smoked over 100 cigarettes but not still smoking recently), and current smoker. Recreational activity was categorized as none, moderate, vigorous, moderate and vigorous. Diabetes was defined based on self-reported diabetes diagnosis, fasting plasma glucose (FPG) level ≥7.0 mmol/L, HbA1c ≥ 6.5%, or taking diabetes medication to lower blood sugar. It was defined as hypertension if the patient received a diagnosis by a physician, was taking antihypertensive medication, or had a mean systolic blood pressure greater than 140 mmHg or diastolic blood pressure ≥90 mmHg on examination. The estimated glomerular filtration rate

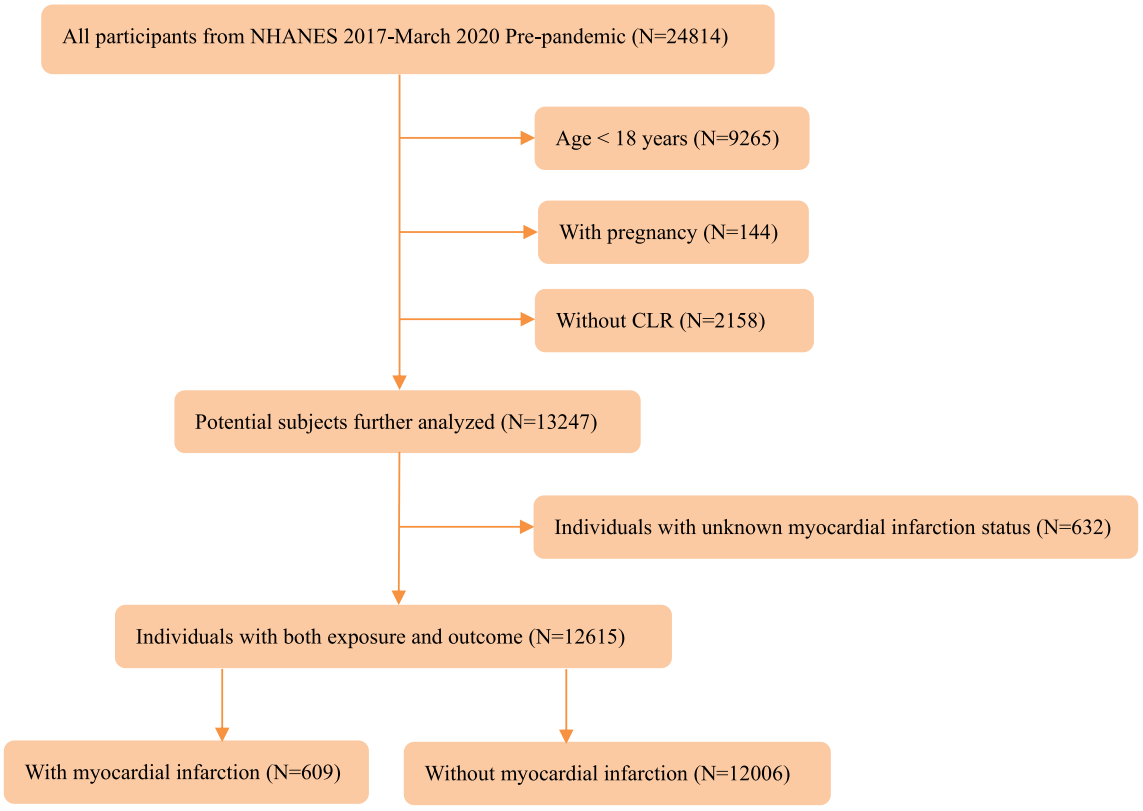

Fig. 1. Flow chart of the study population inclusion.

(eGFR) was calculated according to Chronic Kidney Disease Epidemiology Collaboration formula [21]. Baseline laboratory tests assessed were, bilirubin, creatinine, uric acid, total cholesterol, blood urea nitrogen, and high-density lipoprotein cholesterol (HDL-C).

2.3. Statistical analysis

In the NHANES, a complex multistage sampling design was used, and appropriate sampling weights were employed for the statistical analysis. Continuous variables between MI and non-MI groups were expressed as a survey-weighted mean (95% CI) and categorical variables were presented as a survey-weighted percentage (95% CI). To rule out the possibility of collinearity, we employed the collinearity test when the variance inflation factor was greater than 5. A potential variable was included based on their associations with the MI or caused more than 10% change in any effect measure [22]. Because of non-normal distribution of CLR, the data were natural logarithm (LN) transformed before statistical analysis. The smooth curve fittings, based on generalized additive model, were performed to examine the linear or non-linear relationship of ln-transformed CLR with MI with full adjustment. In analyses investigating associations with MI prevalence, the CLR were used as a continuous variable, scaled per 1-unit increment in ln-transformed, or divided into quartiles, using multivariable logistic regression models with various adjustments to measure odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In the crude model, no confounding factors were adjusted; Model 1 was adjusted for sex, age, BMI, race, waist circumference, and education level; Model 2 was further adjusted for history of malignancy, history of coronary heart disease, history of heart failure, history of angina, history of stroke, smoke, recreational activity, diabetes, hypertension, eGFR, creatinine, uric acid, total cholesterol, HDL cholesterol, statins use, and antidiabetic drugs. Finally, stratified analyses were conducted according to sex, age (<60 years or ≥60 years), BMI (<25, 25–30 or > 30 kg/m^2), malignancy (yes or no), coronary heart disease (yes or no), heart failure (yes or no), stroke (yes or no), angina (yes or no), recreational activity (yes or no), hypertension (yes or no), smoking habits (never, former, now), statins use (yes or no), and eGFR (<60, 60–90,≥90 ml/min/1.73 m^2). Statistical significance of interactions was tested by generating interaction terms between CLR and different subgroups and using Wald tests for dichotomous variables and likelihood ratio tests for continuous variables. A forest plot was used to display the effects of different subgroups and the significance of interactions. In order to examine the statistical significance of the interaction, we generated interaction terms between CLR and different subgroups, and used Wald tests to check for binary variables, and likelihood ratio tests to check for multi-level variables. Given that hs-CRP ≥10 mg/L was an abnormal stress state [23], we conducted sensitivity analyses to assess the reliability of the results after excluded these participants. We further investigated the possibility of unmeasured confounding between CLR and MI by calculating E-values. The e-value quantifies the magnitude of an unmeasured confounder that would be necessary to nullify the observed association between CLR and MI [24].

3. Results

3.1. Baseline characteristics

A total of 12,615 participants were included in the study, comprising 609 and 12,006 individuals with and without MI, respectively. As shown in Fig. 2, the incidence of MI increased (from 2.85% to 6.50%) with the increase of quarters of CLR (P for trend <0.01). Overall, substantial differences were noticed in both baseline demographic and clinical characteristics between participants with MI and participants without MI (Table 1). Compared with the individuals without MI, participants in the MI group were older, more often men, had a higher proportion of malignancy, coronary heart disease, heart failure, angina, stroke, smoke, diabetes, hypertension, statins use, hypoglycemic drugs, anti-hyperlipidemic drugs, and higher level of creatinine, uric acid, blood urea nitrogen (all $P < 0.05$). Moreover, the total cholesterol, HDL cholesterol, and eGFR of the participants with MI was significantly lower compared with that of those without MI (all $P < 0.05$).

3.2. Positive relationship of CLR and the presence of MI

Due to the skewed distribution of CLR, we transform it with natural logarithm to make it closer to the normal distribution. Through generalized additive models and smoothed curve fitting, and after adjusting for various potential confounders, we found a linear relationship between ln-transformed CLR and MI in this study (Fig. 3).

However, this relationship was only found in the population aged over 60 years when participants were divided into different age groups (Fig. 4).

Three logistic regression models were created. Table 2 displays the relationship between CLR and MI in three models. In the crude model, the continuous ln-transformed CLR demonstrated an 84.8% (95% CI: 58.3%–115.9%) higher OR of MI with each 1-unit increase of ln-transformed CLR. Besides, this association still exists after adjusting for different variables, and the ORs for Model 1 and Model 2 were 1.49 (1.24–1.79) and 1.46 (1.16–1.84), respectively. Furthermore, when using as categorical variables, the associations of CLR for MI risks were in line with the trends in the continuous analyses. After all subjects were divided into quantiles according to the levels of ln-transformed CLR, and we found that individuals in Q2, Q3, and Q4 were associated with a higher risk of MI compared with individuals in the Q1 (the lowest quartile) of ln-transformed CLR in the crude model (all $P < 0.05$). After adjust for sex, age, BMI, race, waist circumference, and education level, compared to those in the Q1, the prevalence of MI for subjects in the Q2, Q3, and Q4 was 1.36, 1.60 and 1.65 times, respectively (all $P < 0.05$). After full adjustment, ln-transformed CLR remained positive associated with MI risk, with the ORs of 1.64 (1.15, 2.35) in Q2, 1.71 (1.20, 2.45) in Q3, and 1.79 (1.24, 2.58) in Q4 compared with the Q1 group (all $P < 0.05$). Furthermore, the incidence of MI increased with the increase of quarters of ln-transformed CLR in all models (all P for trend <0.05).

The associations between ln-transformed CLR and MI risks were generally significant in multiple subgroups.

As demonstrated in Fig. 5, the positive associations were more pronounced among participant who were males, older (aged $\geq$60 years), BMI between 25 and 30 kg/m^2, eGFR between 60 and 90 ml/min/1.73 m^2, with history of malignancy, hypertension, former smoker, and performed recreational activity, as well as participant without history of coronary heart disease, heart failure, angina, and statins use. Interaction tests revealed that age (<60 years or $\geq$60 years) influenced the association between CLR and MI after adjustment (P for interactions = 0.04). Considering the opposite directionality of the association, these results may have clinical implications. We further performed a sensitivity analysis after excluding subjects with hs-CRP $\geq$10 mg/L. The results of the sensitivity analysis were in agreement with those of the main analysis. The results of the sensitivity analysis showed that Ln-transformed CLR, whether used as a continuous or categorical variable, was still positively associated with MI (Table S1, all $P < 0.05$). We eventually

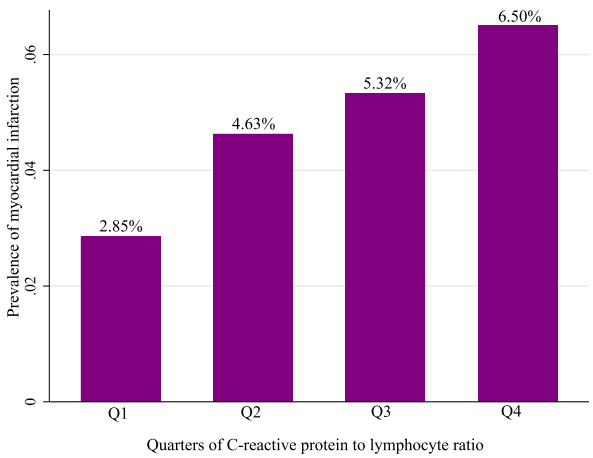

Fig. 2. Association between quarters of C-reactive protein to lymphocyte ratio and the prevalence of myocardial infarction.

Table 1
Weighted baseline characteristics of participants by categories of myocardial infarction: NHANES 2017–March 2020 Pre-Pandemic.

Characteristics (weighted)	Without myocardial infarction	With myocardial infarction	*P*-value
Age (years)	47.96 (46.82,49.10)	64.59 (62.92,66.27)	<0.01
BMI (kg/m^2)	29.79 (29.26,30.32)	30.96 (29.52,32.40)	0.14
Waist circumference (cm)	100.71 (99.32,102.09)	107.54 (104.02,111.06)	<0.01
Bilirubin (mg/dl)	0.47 (0.45,0.49)	0.49 (0.46,0.53)	0.23
Creatinine (mg/dl)	0.88 (0.87,0.89)	1.02 (0.96,1.08)	<0.01
Uric acid (mg/dl)	5.37 (5.31,5.44)	5.92 (5.69,6.15)	<0.01
Blood urea nitrogen (mg/dl)	14.89 (14.55,15.22)	18.24 (16.86,19.63)	<0.01
Total cholesterol (mg/dl)	189.49 (185.99,192.98)	170.94 (159.51,182.38)	<0.01
HDL cholesterol (mg/dl)	53.78 (52.81,54.75)	46.60 (45.22,47.98)	<0.01
eGFR (ml/min/1.73 m^2)	94.32 (92.69,95.96)	77.28 (72.95,81.61)	<0.01
Sex			<0.01
Female	52.06 (49.79,54.33)	32.07 (22.90,42.88)	
Male	47.94 (45.67,50.21)	67.93 (57.12,77.10)	
Race			0.06
Mexican American	9.14 (6.16,13.35)	3.74 (1.80,7.63)	
Non-Hispanic Black	10.79 (7.86,14.64)	9.25 (5.28,15.71)	
Non-Hispanic White	62.65 (57.21,67.78)	71.44 (59.16,81.20)	
Others	17.42 (14.19,21.20)	15.57 (8.41,27.03)	
Education level			0.09
Less than high school	10.96 (9.30,12.86)	17.09 (9.92,27.85)	
High school or GED	27.17 (24.01,30.57)	29.46 (21.23,39.28)	
Above high school	61.88 (57.61,65.97)	53.45 (42.79,63.80)	
Marital status			0.49
Unmarried	37.34 (34.44,40.35)	41.17 (30.06,53.26)	
Married	62.66 (59.65,65.56)	58.83 (46.74,69.94)	
Malignancy			<0.01
No	89.59 (88.01,90.99)	77.38 (68.57,84.28)	
Yes	10.41 (9.01,11.99)	22.62 (15.72,31.43)	
Coronary heart disease			<0.01
No	97.85 (96.91,98.50)	40.25 (31.78,49.34)	
Yes	2.15 (1.50,3.09)	59.75 (50.66,68.22)	
Heart failure			<0.01
No	98.76 (98.43,99.02)	69.10 (57.39,78.78)	
Yes	1.24 (0.98,1.57)	30.90 (21.22,42.61)	
Angina			<0.01
No	98.39 (97.90,98.77)	70.12 (57.31,80.39)	
Yes	1.61 (1.23,2.10)	29.88 (19.61,42.69)	
Stroke			<0.01
No	97.37 (96.54,98.00)	80.05 (72.35,86.02)	
Yes	2.63 (2.00,3.46)	19.95 (13.98,27.65)	
Smoke			<0.01
Never	58.34 (55.34,61.28)	31.83 (24.75,39.86)	
Former	24.58 (22.81,26.44)	45.72 (36.80,54.92)	
Now	17.08 (14.99,19.40)	22.46 (14.37,33.32)	
Alcohol user			0.79
None	8.40 (7.21,9.75)	9.80 (4.13,21.49)	
Mild	46.24 (42.93,49.58)	45.29 (29.45,62.14)	
Moderate	22.16 (20.15,24.31)	17.77 (10.69,28.06)	
Heavy	23.21 (20.01,26.76)	27.15 (16.49,41.28)	
Recreational activity			0.05
None	45.13 (41.50,48.81)	54.07 (42.15,65.55)	
Moderate	26.02 (22.63,29.71)	31.39 (20.94,44.15)	
Vigorous	7.68 (6.27,9.38)	4.03 (1.54,10.12)	
Moderate & Vigorous	21.18 (18.39,24.25)	10.51 (4.56,22.39)	
Diabetes			<0.01
No	86.08 (84.78,87.29)	52.57 (39.58,65.23)	
Yes	13.92 (12.71,15.22)	47.43 (34.77,60.42)	
Hypertension			<0.01
No	60.80 (57.56,63.95)	25.49 (15.56,38.85)	
Yes	39.20 (36.05,42.44)	74.51 (61.15,84.44)	
Statins use			<0.01
No	83.74 (81.15,86.04)	33.40 (21.40,48.02)	
Yes	16.26 (13.96,18.85)	66.60 (51.98,78.60)	
Hypoglycemic drugs			<0.01
No	89.98 (89.17,90.73)	63.49 (52.75,73.03)	
Yes	10.02 (9.27,10.83)	36.51 (26.97,47.25)	
Anti-hyperlipidemic drugs			<0.01
No	82.05 (79.61,84.26)	32.47 (20.60,47.11)	
Yes	17.95 (15.74,20.39)	67.53 (52.89,79.40)	

For continuous variables: survey-weighted mean (95% CI), *P*-value was by survey-weighted linear regression.
For categorical variables: survey-weighted percentage (95% CI), *P*-value was by survey-weighted Chi-square test.

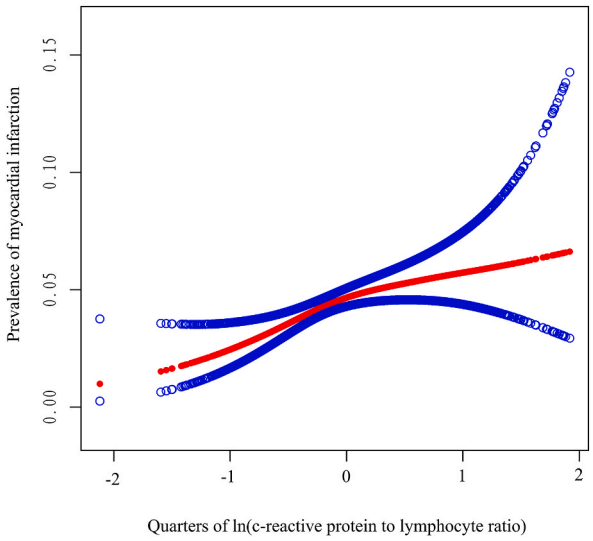

Fig. 3. The smooth curve between quarters of ln-transformed c-reactive protein to lymphocyte ratio and the risk of myocardial infarction. The solid red line represents the smooth curve, while the blue lines represent the 95% confidence interval. Sex, age, BMI, race, waist circumference, education level, history of malignancy, history of coronary heart disease, history of heart failure, history of angina, history of stroke, smoke, recreational activity, diabetes, hypertension, eGFR, creatinine, uric acid, total cholesterol, HDL cholesterol, statins use, and antidiabetic drugs were adjusted. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

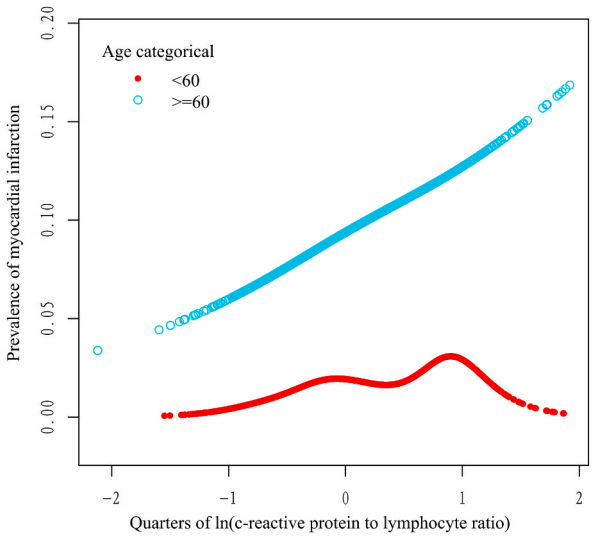

Fig. 4. Subgroup analysis stratified by age between quarters of ln-transformed c-reactive protein to lymphocyte ratio and the risk of myocardial infarction. Sex, age, BMI, race, waist circumference, education level, history of malignancy, history of coronary heart disease, history of heart failure, history of angina, history of stroke, smoke, recreational activity, diabetes, hypertension, eGFR, creatinine, uric acid, total cholesterol, HDL cholesterol, statins use, and antidiabetic drugs were adjusted.

produced an E-value to measure the sensitivity to unmeasured confounding. The negative association between CLR and MI was influenced only when the unmeasured covariates had ORs greater than >1.71 (the corresponding CI is at least 1.37) for both CLR and MI (Fig. S1). Thus, the results of the sensitivity analysis showed that the conclusions drawn in the present study are reliable and consistent. Since CRP and lymphocyte alone showed association with prevalence of MI, thus the receiver operating characteristic (ROC) curve was plotted and the area under curve (AUC) value was calculated to evaluate the predictive ability of lymphocyte, CRP, and CLR for MI. Of the three indexes examined, the highest AUC was CLR. However, the statistical difference between lymphocyte, CRP, and CLR was not significant (Fig. S2).

Table 2
Associations of the ln-transformed C-reactive protein to lymphocyte ratio with myocardial infarction risk.

	Non-adjusted	Adjust I	Adjust II
CLR ln transform	1.85 (1.58, 2.16) <0.01	1.49 (1.24, 1.79) <0.01	1.46 (1.16, 1.84) <0.01
CLR ln transform quartiles			
Q1	1 (Reference)	1 (Reference)	1 (Reference)
Q2	1.65 (1.27, 2.16) <0.01	1.36 (1.02, 1.82) 0.038	1.64 (1.15, 2.35) <0.01
Q3	1.91 (1.48, 2.49) <0.01	1.60 (1.20, 2.14) <0.01	1.71 (1.20, 2.45) <0.01
Q4	2.37 (1.84, 3.05) <0.01	1.65 (1.23, 2.22) <0.01	1.79 (1.24, 2.58) <0.01
P for trend	<0.01	<0.01	<0.01

Non-adjusted model adjust for: none.
Adjust I model adjust for: sex, age, BMI, race, waist circumference, education level.
Adjust II model adjust for: sex, age, BMI, race, waist circumference, education level, history of malignancy, history of coronary heart disease, history of heart failure, history of angina, history of stroke, smoke, recreational activity, diabetes, hypertension, eGFR, creatinine, uric acid, total cholesterol, HDL cholesterol, and statins use.

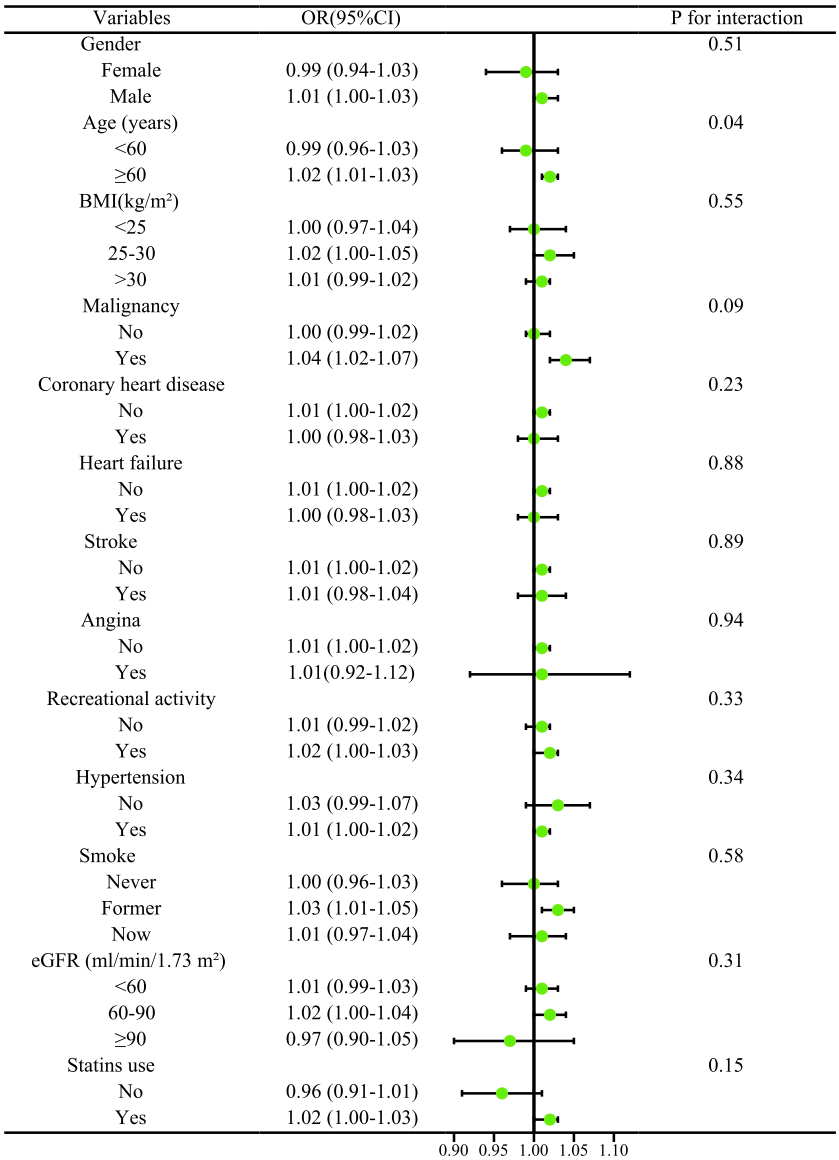

Fig. 5. Subgroup analysis of the association of C-reactive protein to lymphocyte ratio with myocardial infarction.

4. Discussion

In a representative sample of US adults, the present study demonstrated that CLR were positively and obviously associated with MI after adjusting for multiple covariates in the adults based on NHANES. Multiple sensitivity analyses and subgroup analysis confirmed the robustness of the results. As far as we know, this is the first cross-sectional study with a relatively large sample size to examine the connection between CLR and MI risk.

The CLR has recently been linked to adverse outcomes in certain clinical situations. As a new inflammatory biomarker, CLR has demonstrated its essential role in diagnostic and prognostic prediction for COVID-19 pneumonia [16,25]. A recent study using NHANES III data indicated that hs-CRP $\geq$0.5 mg/dl was an independent risk factor for all-cause mortality, cardiovascular mortality, and cancer specific mortality in patients with metabolic associated fatty liver disease after adjusting for risk factors [26]. Apart from infectious diseases, CLR is employed as a significant biomarker to assess the prognosis in cancer patients [11,12,14,27]. These studies suggested that a combination of CRP and lymphocyte measured in routine examinations, can be utilized to reflect systemic inflammatory and immune status and may serve as a convenient and precise prognostic indicator for various diseases. CRP is an acute phase protein, which is synthesized by the liver and activated by various cells under the influence of the body under trauma or inflammatory factors [28]. CRP is nonspecific and its levels are increased in all inflammatory conditions. Previous studies have demonstrated that CRP is a widely accepted universal inflammatory marker, and CRP levels rise in response to cell damage or tissue injury [29,30]. Lymphocytes play a role in stimulating the proliferation and control of endothelial cells and immune defense, which will be consumed in large amounts when the body is traumatized [31]. A reduction in the lymphocyte count may be associated with apoptosis and impairment of immune cells [32]. Thus, the CLR can reflect the balance between systemic inflammatory and immune status. Furthermore, hs-CRP allows for the identification of lower CRP levels, and can assist in pinpointing more precise issues and chronic inflammation over the long term [33]. As a result, elevated hs-CRP results can be a useful early warning sign of cardiovascular disease and atherosclerosis in patients who are not exhibiting any symptoms [34,35]. Numerous studies in the literature have demonstrated that even a slight increase in CRP concentration is linked to a poor prognosis in various chronic diseases [36,37]. These above evidences suggest that CLR may also be associated with cardiovascular diseases, particularly MI.

MI is a very common clinical syndrome characterized by obstruction of a blood vessel by a blood clot or narrowing of the blood-vessel channel. The molecular mechanisms of MI still remain unclear; inflammation plays a crucial role in the occurrence and development of MI [38]. However, the underlying relationship between CRP and MI is still uncertain. Numerous potential explanations exist for the clinical role of elevated CRP levels in relation to the risk of MI. First, hs-CRP is a well-known indicator of senescence and aging, which is characterized by the accumulation of senescent cells that secrete proinflammatory cytokines, chemokines and other mediators that lead to inflammatory microenvironments in many tissues and organs [39]. As people age, the prevalence of coronary artery disease rises significantly. Senescent cells accumulate in tissues, including the heart, and are linked to age-related pathologies such as myocardial infarction [40]. Second, the level of CRP is linked to endothelial dysfunction and may be indicative of the progression of atherosclerosis. A recent study found that endothelial dysfunction and high-sensitivity C-reactive protein, in conjunction, significantly raised the likelihood of developing heart failure [41]. For clinical applications, CRP appears to be the most promising inflammatory biomarker, and numerous population-based studies have indicated that initial CRP levels can be used to predict future cardiovascular events [42]. Third, as is well known, lymphocytes are responsible for determining the specificity of the immune system's reaction to infectious microorganisms and other foreign materials. Excessive inflammation and immune responses are of great importance throughout the entire MI process [43]. Excessive immune activation leads to a decrease in lymphocyte counts [8]. As a result, it will also lead to the increase of CLR.

These above evidences can explain the correlation between CRP and risk of MI.

The findings of this study are important because it suggests that maintaining low CLR may be an important consideration for reduce MI risk. Our study contributes to the scarce data on age differences in the link between CLR and MI risk. Our findings revealed that participants aged over 60 years have a greater risk of MI. However, the association is not significant in population aged less than 60 years. These findings suggest that age differences (elderly individuals aged 60 and over) may exist when examining the CLR on MI risk. This is consistent with the fact that aging is associated with decreased immunity and linked to a higher risk of MI. Elderly individuals are not only more likely to experience an MI, but are also more likely to develop heart failure [44,45].

The strengths of our study include the contribution of new evidence on the relationship between the CLR and MI risk, as well as the examination of age differences in this relationship. Besides, the study was based on a large, nationally representative sample of adults in the United States, and the study population was well-characterized and relatively homogeneous, allowing us to accurately control for confounding factors and their effects on the results. Furthermore, the multiple potential confounders were adjusted carefully, and a new method was used to select the variables. Moreover, the results of the sensitivity analyses provide additional support for the main findings. An hs-CRP level above 10 mg/L is reported a stressful condition and was excluded in the sensitivity analyses. This allowed us to obtain more precise results and accurately describe the correlation between hs-CRP and MI in individuals in a normal state. However, it is important to note that there are several potential limitations to this study that should be taken into account. First, our findings, which are based on US adults, may not be applicable to other populations, thus limiting the generalizability of our results. Second, due to the cross-sectional nature of this study, we could only infer an association and not a causal relationship. Third, the self-reported MI may introduce a subjective bias in our results. In NHANES database, we can't distinguish between ST-segment elevation MI and non-ST-segment elevation MI. Finally, due to the presence of unmeasured confounding factors, we could not eliminate all potential residual confounders. However, E-value supports the stability of our results.

5. Conclusions

In a large nationally representative survey individual among US adults, our results found that CLR was independently associated with higher prevalence of MI in a linear manner in US adults. CLR may be a novel inflammation warning biomarker for myocardial infarction. Age differences may exist when examining the relationship between CLR and MI. However, further prospective studies should be conducted to verify their association.

Author contribution statement

Lu He, Hang Xie, Yajuan Du, Xuegang Xie and Yushun Zhang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Data availability statement

Data associated with this study has been deposited at Publicly available dataset was analyzed in this study. The National Health and Nutrition Examination Survey dataset are publicly available at https://www.cdc.gov/nchs/nhanes/index.htm.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17776.

References

[1] B. Ibanez, Targeting inflammation to improve long-term outcome in ST-segment elevation myocardial infarction survivors, Eur. Heart J. Acute Cardiovasc. Care 11 (2) (2022) 124–126.
[2] G.A. Roth, G.A. Mensah, C.O. Johnson, G. Addolorato, E. Ammirati, L.M. Baddour, et al., Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study, J. Am. Coll. Cardiol. 76 (25) (2020) 2982–3021.
[3] H.D. White, D.P. Chew, Acute myocardial infarction, Lancet 372 (9638) (2008) 570–584.
[4] L. Shao, Y. Shen, C. Ren, S. Kobayashi, T. Asahara, J. Yang, Inflammation in myocardial infarction: roles of mesenchymal stem cells and their secretome, Cell Death Discov. 8 (1) (2022) 452.
[5] P.M. Ridker, M. Cushman, M.J. Stampfer, R.P. Tracy, C.H. Hennekens, Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men, N. Engl. J. Med. 336 (14) (1997) 973–979.
[6] I.M. Seropian, S. Toldo, B.W. Van Tassell, A. Abbate, Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction, J. Am. Coll. Cardiol. 63 (16) (2014) 1593–1603.
[7] S. Huang, N.G. Frangogiannis, Anti-inflammatory therapies in myocardial infarction: failures, hopes and challenges, Br. J. Pharmacol. 175 (9) (2018) 1377–1400.
[8] Y.C. Twu, M.R. Gold, H.S. Teh, TNFR1 delivers pro-survival signals that are required for limiting TNFR2-dependent activation-induced cell death (AICD) in CD8 + T cells, Eur. J. Immunol. 41 (2) (2011) 335–344.
[9] F.A. Lagunas-Rangel, Neutrophil-to-lymphocyte ratio and lymphocyte-to-C-reactive protein ratio in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis, J. Med. Virol. 92 (10) (2020) 1733–1734.
[10] F. Qian, W. Zhou, Y. Liu, Z. Ge, J. Lai, Z. Zhao, et al., High C-reactive protein to lymphocyte ratio predicts mortality outcomes of patients with severe fever suffering from thrombocytopenia syndrome: a multi-centre study in China, J. Med. Virol. 95 (2) (2023), e28546.
[11] Z. Fan, G. Luo, Y. Gong, H. Xu, Y. Qian, S. Deng, et al., Prognostic value of the C-reactive protein/lymphocyte ratio in pancreatic cancer, Ann. Surg. Oncol. 27 (10) (2020) 4017–4025.
[12] İ. Mungan, E.B. Bostancı, E. Türksal, B. Tezcan, M.N. Aktaş, M. Can, et al., The predictive power of C-reactive protein- lymphocyte ratio for in-hospital mortality after colorectal cancer surgery, Cancer Rep (Hoboken) 4 (3) (2021), e1330.
[13] L.H. Lu, C. Zhong, W. Wei, S.H. Li, J. Mei, J.W. Zou, et al., Lymphocyte-C-reactive protein ratio as a novel prognostic index in intrahepatic cholangiocarcinoma: a multicentre cohort study, Liver Int. 41 (2) (2021) 378–387.
[14] J.J. Hwang, J.Y. Hur, W. Eo, S. An, D.H. Kim, S. Lee, Clinical significance of C-reactive protein to lymphocyte count ratio as a prognostic factor for survival in non-small cell lung cancer patients undergoing curative surgical resection, J. Cancer 12 (15) (2021) 4497–4504.
[15] S. Koyuncu, O. Ismail, The role of C-reactive protein to lymphocyte ratio in the differentiation of acute and perforated appendicitis, Ulus Travma Acil Cerrahi Derg 26 (5) (2020) 760–764.
[16] C. Cillóniz, A. Torres, C. Garcia-Vidal, E. Moreno-Garcia, R. Amaro, N. Soler, et al., The value of C-reactive protein-to-lymphocyte ratio in predicting the severity of SARS-CoV-2 pneumonia, Arch. Bronconeumol. 57 (2021) 79–82.
[17] R. Micha, J.L. Peñalvo, F. Cudhea, F. Imamura, C.D. Rehm, D. Mozaffarian, Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States, JAMA 317 (9) (2017) 912–924.
[18] N.S. Shah, M.D. Huffman, H. Ning, D.M. Lloyd-Jones, Trends in myocardial infarction secondary prevention: the national health and nutrition examination surveys (NHANES), 1999-2012, J. Am. Heart Assoc. 4 (4) (2015).
[19] N.S. Parikh, S. Salehi Omran, H. Kamel, M.S.V. Elkind, J. Willey, Symptoms of depression and active smoking among survivors of stroke and myocardial infarction: an NHANES analysis, Prev. Med. 137 (2020), 106131.
[20] T.R. Price, C.M. Friedenreich, P.J. Robson, H. Li, D.R. Brenner, High-sensitivity C-reactive protein, hemoglobin A1c and breast cancer risk: a nested case-control study from Alberta's Tomorrow Project cohort, Cancer Causes Control 31 (12) (2020) 1057–1068.

[21] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro 3rd, H.I. Feldman, et al., A new equation to estimate glomerular filtration rate, Ann. Intern. Med. 150 (9) (2009) 604–612.
[22] V.W. Jaddoe, L.L. de Jonge, A. Hofman, O.H. Franco, E.A. Steegers, R. Gaillard, First trimester fetal growth restriction and cardiovascular risk factors in school age children: population based cohort study, BMJ 348 (2014) g14.
[23] M.B. Pepys, G.M. Hirschfield, C-reactive protein: a critical update, J. Clin. Invest. 111 (12) (2003) 1805–1812.
[24] S. Haneuse, T.J. VanderWeele, D. Arterburn, Using the E-value to assess the potential effect of unmeasured confounding in observational studies, JAMA 321 (6) (2019) 602–603.
[25] T. Damar Çakırca, A. Torun, G. Çakırca, R.D. Portakal, Role of NLR, PLR, ELR and CLR in differentiating COVID-19 patients with and without pneumonia, Int. J. Clin. Pract. 75 (11) (2021), e14781.
[26] J. Huang, M. Wang, Y. Wu, R. Kumar, S. Lin, Serum high-sensitive C-reactive protein is a simple indicator for all-cause among individuals with MAFLD, Front. Physiol. 13 (2022), 1012887.
[27] T. Taniai, K. Haruki, R. Hamura, Y. Fujiwara, K. Furukawa, T. Gocho, et al., The prognostic significance of C-reactive protein-to-lymphocyte ratio in colorectal liver metastases, J. Surg. Res. 258 (2021) 414–421.
[28] S.P. Ballou, I. Kushner, C-reactive protein and the acute phase response, Adv. Intern. Med. 37 (1992) 313–336.
[29] L.N. Ma, X.Y. Liu, X. Luo, Y.C. Hu, S.W. Liu, Y.Y. Tang, et al., Serum high-sensitivity C-reactive protein are associated with HBV replication, liver damage and fibrosis in patients with chronic hepatitis B, Hepato-Gastroenterology 62 (138) (2015) 368–372.
[30] C. Sjöwall, K. Cardell, E.A. Boström, M.I. Bokarewa, H. Enocsson, M. Ekstedt, et al., High prevalence of autoantibodies to C-reactive protein in patients with chronic hepatitis C infection: association with liver fibrosis and portal inflammation, Hum. Immunol. 73 (4) (2012) 382–388.
[31] W. Wang, Y. Wang, C. Qu, S. Wang, J. Zhou, W. Cao, et al., The RNA genome of hepatitis E virus robustly triggers an antiviral interferon response, Hepatology 67 (6) (2018) 2096–2112.
[32] J.H. Kwon, J.W. Jang, Y.W. Kim, S.W. Lee, S.W. Nam, D. Jaegal, et al., The usefulness of C-reactive protein and neutrophil-to-lymphocyte ratio for predicting the outcome in hospitalized patients with liver cirrhosis, BMC Gastroenterol. 15 (2015) 146.
[33] Y.Y. Luan, Y.M. Yao, The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases, Front. Immunol. 9 (2018) 1302.
[34] S.S. Bassuk, N. Rifai, P.M. Ridker, High-sensitivity C-reactive protein: clinical importance, Curr. Probl. Cardiol. 29 (8) (2004) 439–493.
[35] S.W. Oh, J.D. Moon, S.Y. Park, H.J. Jang, J.H. Kim, K.B. Nahm, et al., Evaluation of fluorescence hs-CRP immunoassay for point-of-care testing, Clin. Chim. Acta 356 (1–2) (2005) 172–177.
[36] X. Qian, S. He, J. Wang, Q. Gong, Y. An, H. Li, et al., Prediction of 10-year mortality using hs-CRP in Chinese people with hyperglycemia: findings from the Da Qing diabetes prevention outcomes study, Diabetes Res. Clin. Pract. 173 (2021), 108668.
[37] S. Kurl, S.Y. Jae, A. Voutilainen, J.A. Laukkanen, The combined effect of blood pressure and C-reactive protein with the risk of mortality from coronary heart and cardiovascular diseases, Nutr. Metabol. Cardiovasc. Dis. 31 (7) (2021) 2051–2057.
[38] G.K. Hansson, A.K. Robertson, C. Söderberg-Nauclér, Inflammation and atherosclerosis, Annu. Rev. Pathol. 1 (2006) 297–329.
[39] Bruserud Ø, A.K. Vo, H. Rekvam, Hematopoiesis, inflammation and aging-the biological background and clinical impact of anemia and increased C-reactive protein levels on elderly individuals, J. Clin. Med. 11 (3) (2022).
[40] A. Walaszczyk, E. Dookun, R. Redgrave, S. Tual-Chalot, S. Victorelli, I. Spyridopoulos, et al., Pharmacological clearance of senescent cells improves survival and recovery in aged mice following acute myocardial infarction, Aging Cell 18 (3) (2019), e12945.
[41] R. Maio, M. Perticone, E. Suraci, A. Sciacqua, G. Sesti, F. Perticone, Endothelial dysfunction and C-reactive protein predict the incidence of heart failure in hypertensive patients, ESC Heart Fail. 8 (1) (2021) 399–407.
[42] V. Della Corte, A. Tuttolomondo, R. Pecoraro, D. Di Raimondo, V. Vassallo, A. Pinto, Inflammation, endothelial dysfunction and arterial stiffness as therapeutic targets in cardiovascular medicine, Curr. Pharmaceut. Des. 22 (30) (2016) 4658–4668.
[43] Y.P. Wang, Y. Xie, H. Ma, S.A. Su, Y.D. Wang, J.A. Wang, et al., Regulatory T lymphocytes in myocardial infarction: a promising new therapeutic target, Int. J. Cardiol. 203 (2016) 923–928.
[44] A.P. Maggioni, A. Maseri, C. Fresco, M.G. Franzosi, F. Mauri, E. Santoro, et al., Age-related increase in mortality among patients with first myocardial infarctions treated with thrombolysis. The Investigators of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2), N. Engl. J. Med. 329 (20) (1993) 1442–1448.
[45] S. Ding, G. Niu, X. Xu, J. Li, X. Zhang, H. Yin, et al., Age is a critical risk factor for severe fever with thrombocytopenia syndrome, PLoS One 9 (11) (2014), e111736.