

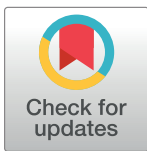
RESEARCH ARTICLE

Mid-arm muscle circumference: A significant factor of all-cause and cancer mortalities in individuals with elevated platelet-to-lymphocyte ratio

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Citation: Chang P-K, Chen W-L, Wu L-W (2018) Mid-arm muscle circumference: A significant factor of all-cause and cancer mortalities in individuals with elevated platelet-to-lymphocyte ratio. PLoS ONE 13(12): e0208750. <https://doi.org/10.1371/journal.pone.0208750>

Editor: Celena Scheede-Bergdahl, McGill University, CANADA

Received: June 3, 2018

Accepted: November 21, 2018

Published: December 13, 2018

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Data Availability Statement: The survey design and procedures (questionnaires, examinations, and laboratory components) of NHANES III are publicly available online at <http://www.cdc.gov/nchs/nhanes.htm>.

Funding: The authors received no specific funding for this work.

Competing interests: The authors have declared that no competing interests exist.

Abstract

Platelet-to-lymphocyte ratio (PLR) is an inflammatory maker, and high PLR is associated with mortality in several diseases. The predictors of mortality in individuals with high PLR is still lacking. Our aims were to assess if mid-arm muscle circumference (MAMC) can predict all-cause mortality, cancer mortality, and cardiovascular mortality in individuals with high PLR. Adult participants from the National Health and Nutrition Examination Survey III (1988–1994) were included. All participants were divided into low PLR and high PLR groups with the cut-off point being the median PLR level, and each group was evaluated for risk factors of mortality. MAMC was divided into tertiles and the general characteristics of the study population related to MAMC were evaluated. The study included 14,221 adults with 6,701 (47.1%) male and 7,520 (52.9%) female participants. The median PLR ratio was 122. Higher levels of systolic blood pressure, total triglycerides, total cholesterol, low-density lipoprotein, C-reactive protein, uric acid, and glucose, as well as a higher age, were associated with increased risk of mortality in both groups. After adjusting for all the covariates, in the higher PLR group, the highest MAMC tertile was significantly associated with lower hazard ratios for all-cause and cancer mortalities compared with the lowest MAMC tertile. However, this association was not observed in the low PLR group. The highest MAMC tertile showed protective effects from all-cause and cancer mortalities compared with the lowest MAMC tertile in individuals with $PLR \geq 122$. In conclusion, the highest MAMC tertile was significantly associated with decreasing HRs for all-cause and cancer mortalities compared with the lowest MAMC tertile in individuals with elevated PLR.

Introduction

The platelet-to-lymphocyte (PLR) ratio is a universally known indicator of systemic inflammation. Previous literature has demonstrated that higher PLR is associated with poor prognosis

and higher mortality in those with malignancies, cardiovascular diseases, and end-stage renal disease [1–4]. Anthropometric parameters have been widely used to screen for, or monitor, a disease. Mid-arm muscle circumference (MAMC) is calculated as: mid-upper arm circumference (MAC) (cm) - 0.3142 x triceps skinfold (TS) thickness (mm). It is a simple, inexpensive, and universally applicable measurement. MAMC correlates strongly with more accurate dual-energy X-ray absorptiometry measures of lean mass, and can represent lean mass well [5]. Meanwhile, sufficient muscle mass may be positively related to functional performance and survival [6–7]. Despite the growing interest and research, information on the relationships between anthropometric parameters and inflammatory markers is lacking. Therefore, the primary objective of this study was to examine the associations between PLR and MAMC. Furthermore, the secondary objective was to evaluate how MAMC levels affect all-cause mortality, cancer mortality, and cardiovascular mortality in people with low and high PLR. The data was obtained from the National Health and Nutrition Examination Survey (NHANES) III, which is a large-scale, nationally representative, and population-based database of adults in USA.

Materials and methods

Data source and participants

The National Health and Nutrition Examination III (1988–1994) was a complex multi-stage stratified study managed by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) [8]. NHANES III was a program to evaluate the health and nutritional statuses with household interviews and physical examinations of non-institutionalized adults in USA. It was conducted in accordance with the guidelines of the Declaration of Helsinki. A subsample of participants aged 20–90 years was identified from it with a mean follow-up of 14.3 years. The survey design and procedures (questionnaires, examinations, and laboratory components) of NHANES III are publicly available online at <http://www.cdc.gov/nchs/nhanes.htm>.

Follow-up data on all-cause mortality, cancer mortality, and cardiovascular mortality

The mortality data of the NHANES III study is from a probabilistic match between NHANES III and the National Death Index (NDI) records. NDI is available publically and contains de-identified death-certificate data, updated through 31 December 2006.

The cause of death was identified according to the guidelines of the International Statistical Classification of Disease, Injuries and Causes of Death; the 9th revision was used for those who died before 1999 and 10th revision for all others. NHANES procedures harmonized the differences in definitions and causes of death, all of which have been demonstrated to be comparable.

We included deaths from all causes; we included deaths due to malignant neoplasms, which were coded from C00–C97 in the International Classification of Diseases, 10th Edition (ICD-10) for cancer specific mortality, while for cardiovascular (CV) mortality, we included diseases of the heart and circulation system (ICD-10 = I00–I178).

Measurement of PLR and definition of the MAMC tertiles group

Platelet-to-lymphocyte ratio (PLR) is the ratio of the absolute platelet count to the absolute lymphocyte count. In NHANES III, complete blood count (CBC) was performed automatically using the Coulter method with different generations of Coulter counters. In the present study, PLR cut-off point was the median PLR of the participants.

The data of MAC was collected according to the standard procedures defined by Lohman and colleagues and was based on the age of the participant [9]. They were divided into tertiles and the lowest tertile was used as the reference group. All participants were divided into low PLR and high PLR groups with the cut-off point being the median PLR level, and each group was divided into three subgroups (lowest, middle, and highest) based on their MAMC level. The tertiles were as follows: T1 (15.3–24.1 cm), T2 (24.2–28.1 cm), and T3 (28.2–44.1 cm) in the low PLR group, and T1 (13.8–23.3 cm), T2 (23.4–27.3 cm), and T3 (27.4–41.1 cm) in the high PLR group.

Covariates

The participants were interviewed for self-reporting of general characteristics and previous medical histories regarding the following variables: age, race/ethnicity, sex, smoking status, and physician-diagnosed previous clinical illnesses (congestive heart failure–CHF, stroke, asthma, malignancy, and type 2 diabetes mellitus–DM). Diabetes was defined as self-report history, fasting plasma glucose ≥ 126 mg/dL, OGTT 2-h plasma glucose ≥ 200 mg/dL, or random serum glucose ≥ 200 mg/dL. The biochemistry profiles were collected from the blood samples, which were then assessed by the Lipoprotein Analytical Laboratory at Johns Hopkins University, Baltimore, Maryland, USA. The plasma glucose level was assessed via the hexokinase enzymatic method. Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels were measured using the Hitachi 704 Analyzer, and serum C-reactive protein (CRP) levels were measured using latex-enhanced nephelometry. Other biochemical profiles, such as serum albumin, aspartate transaminase (AST), alanine transaminase (ALT), uric acid (UA), and total bilirubin were measured by using Beckman Synchron LX20.

Statistical analysis

The statistical analyses were performed using SPSS version 18 (SPSS, Inc., Chicago, IL, USA). Continuous data were compared using the Independent t-test or Wilcoxon Rank sum test, and presented as means \pm standard errors (SE). Categorical data were compared using the Chi-square test and presented as number and percentages (%). The p values of less than 0.05 were considered to be statistically significant.

The association between MAMC tertiles and all-cause, cardiovascular, and cancer mortalities were evaluated by Cox proportional hazard models. An extended-model approach was used for adjusted covariates. Model 1 was not adjusted for any variables; model 2 was adjusted for race, sex, and body mass index (BMI); model 3 was adjusted for the variables in model 2 and systolic blood pressure, serum triglycerides, and serum fasting glucose; and model 4 was adjusted for the variables of models 2 and 3, and smoking, congestive heart failure, stroke, gout, and malignancy.

Ethics statement

The National Center for Health Statistics Institutional Review Board approved the NHANES III study, and all participants in the NHANES III provided written informed consent. This study was exempt from IRB review because we analyzed an open available online database. All methods in this study were performed based on the relevant guidelines and regulations.

Results

The study included 14,221 adults with 6,701 (47.1%) male and 7,520 (52.9%) female participants. The median PLR ratio in this population was 122. The participants were divided into

two groups; low PLR group (PLR<122) and high PLR (PLR≥122) group. The mean MAMC was 26.3 ± 3.9 cm and mean age was 47.5 ± 18.7 years in the lower PLR group. The mean MAMC was 25.6 ± 3.8 cm and the mean age was 47.8 ± 19.4 years in the high PLR group. In our study, the mean follow-up duration was 14.3 years.

The clinical characteristics of the participants of the low PLR group related to mortality are depicted in Table 1. In this group, higher levels of age, systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum levels of TG, TC, LDL, CRP, total bilirubin, UA, glucose, and AST were associated with increased risk of mortality. Other factors that were associated with increased risk of mortality included male sex, non-Hispanic white ethnicity, and associated conditions like congestive heart failure, stroke, asthma, malignancy, diabetes mellitus, and smoking. However, higher serum levels of HDL, albumin, and ALT were associated with decreased risk of mortality.

The clinical characteristics of the participants of the high PLR group related to mortality are depicted in Table 2. In this group, higher levels of age, SBP, and serum TG, TC, LDL, CRP, UA, and glucose were associated with increased risk of mortality. Additional factors that

Table 1. Characteristics of participants with low platelet-to-lymphocyte ratio (<122).

Characteristics of Study Participants	Non-mortality	Mortality	Total	P value
	n = 5,447	n = 1663	n = 7110	
Continuous variables, mean (SE)				
MAMC (cm)	26.2 (4.0)	26.3 (3.6)	26.3 (3.9)	0.630
Age (years)	41.4 (15.2)	67.4 (14.9)	47.5 (18.7)	<0.001
BMI (kg/m ²)	27.6 (5.9)	27.5 (5.5)	27.5 (5.8)	0.577
SBP (mmHg)	121.2 (18.4)	141.3 (25.0)	125.9 (21.8)	<0.001
DBP (mmHg)	72.4 (12.7)	73.8 (14.2)	72.7 (13.1)	<0.001
Serum TG (mg/dL)	148.3 (115.1)	174.5 (125.5)	154.5 (118.1)	<0.001
Serum total Cholesterol (mg/dL)	202.3 (43.6)	217.4 (48.5)	205.9 (45.2)	<0.001
LDL cholesterol (mg/dL)	126.1 (38.4)	136.9 (40.7)	128.6 (39.2)	<0.001
HDL cholesterol (mg/dL)	49.9 (15.1)	48.5 (16.2)	49.6 (15.3)	0.001
Serum CRP (mg/dL)	0.4 (0.6)	0.5 (0.6)	0.4 (0.6)	<0.001
Serum total bilirubin (mg/dL)	0.6 (0.3)	0.6 (0.4)	0.6 (0.4)	<0.001
Serum UA (mg/dL)	5.3 (1.4)	5.9 (1.6)	5.5 (1.5)	<0.001
Serum glucose (mg/dL)	97.2 (31.6)	116.1 (54.1)	101.6 (38.9)	<0.001
Albumin (g/dL)	4.2 (0.4)	4.0 (0.4)	4.1 (0.4)	<0.001
AST (U/L)	22.9 (16.0)	25.3 (24.5)	23.5 (18.4)	<0.001
ALT (U/L)	20.2 (19.6)	17.2 (18.7)	19.5 (19.4)	<0.001
Categorical variables, N (%)				
Male	2604 (47.8)	966 (58.1)	3570 (50.2)	<0.001
Non-Hispanic white	1933 (35.5)	896 (53.9)	2829 (39.8)	<0.001
Congestive heart failure	82 (1.5)	170 (10.2)	252 (3.5)	<0.001
Stroke	57 (1)	135 (8.1)	192 (2.7)	<0.001
Asthma	340 (6.2)	124 (7.5)	464 (6.5)	0.041
Malignancy	118 (2.2)	116 (7.0)	234 (3.3)	<0.001
Type 2 diabetes mellitus	302 (5.5)	341 (20.5)	643 (9.0)	<0.001
Smoking	488 (9.0)	326 (19.6)	814 (11.4)	<0.001

Abbreviation: N, number; SD, standard deviation; MAMC, mid-arm muscle circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Serum TG, serum total triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Serum CRP, serum C-reactive protein; Serum UA, serum uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

<https://doi.org/10.1371/journal.pone.0208750.t001>

Table 2. Characteristics of participants with high platelet-to-lymphocyte ratio (≥ 122).

Characteristics of Study Participants	Non-mortality	Mortality	Total	P value
	n = 5389	n = 1722	n = 7111	
Continuous variables, mean (SE)				
MAMC (cm)	25.6 (3.9)	25.5 (3.5)	25.6 (3.8)	0.443
Age (years)	41.1 (15.3)	69.0 (15.1)	47.8 (19.4)	<0.001
BMI (kg/m ²)	26.9 (5.6)	26.5 (5.4)	26.8 (5.6)	0.007
SBP (mmHg)	119.9 (18.2)	141.8 (25.0)	125.2 (22.1)	<0.001
DBP (mmHg)	72.1 (12.4)	72.7 (15.5)	72.3 (13.2)	0.145
Serum TG (mg/dL)	128.6 (102.0)	154.5 (142.3)	134.9 (113.6)	<0.001
Serum total Cholesterol (mg/dL)	202.0 (42.9)	218.4 (47.0)	206.0 (44.5)	<0.001
LDL cholesterol (mg/dL)	124.7 (36.7)	137.2 (42.5)	127.4 (39.0)	<0.001
HDL cholesterol (mg/dL)	52.6 (15.0)	52.6 (17.7)	52.6 (15.7)	0.976
Serum CRP (mg/dL)	0.5 (0.8)	0.7 (1.3)	0.5 (0.9)	<0.001
Serum total bilirubin (mg/dL)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.847
Serum UA (mg/dL)	5.1 (1.4)	5.7 (1.6)	5.3 (1.5)	<0.001
Serum glucose (mg/dL)	95.1 (27.3)	111.4 (51.9)	99.1 (35.6)	<0.001
Albumin (g/dL)	4.2 (0.4)	4.0 (0.4)	4.1 (0.4)	<0.001
AST (U/L)	21.3 (12.7)	21.6 (14.4)	21.4 (13.2)	0.375
ALT (U/L)	17.6 (14.3)	13.9 (14.2)	16.7 (14.4)	<0.001
Categorical variables, N (%)				
Male	2103 (39)	1028 (59.7)	3131 (44)	<0.001
Non-Hispanic white	1933 (35.5)	896 (53.9)	2829 (39.8)	<0.001
Congestive heart failure	78 (1.4)	158 (9.2)	236 (3.3)	<0.001
Stroke	37 (0.7)	134 (7.8)	171 (2.4)	<0.001
Asthma	377 (7.0)	145 (8.4)	522 (7.3)	0.048
Malignancy	106 (2.0)	190 (11.0)	296 (4.2)	<0.001
Type 2 diabetes mellitus	223 (4.1)	258 (15.0)	481 (6.8)	<0.001
Smoking	458 (8.5)	303 (17.6)	761 (10.7)	<0.001

Abbreviation: N, number; SD, standard deviation; MAMC, mid-arm muscle circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Serum TG, serum total triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Serum CRP, serum C-reactive protein; Serum UA, serum uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

<https://doi.org/10.1371/journal.pone.0208750.t002>

increased the risk of mortality included male sex, non-Hispanic white ethnicity, and conditions such as congestive heart failure, stroke, asthma, malignancy, diabetes mellitus, and smoking. However, high levels of BMI, and serum albumin and ALT were associated with decreased risk of mortality.

Table 3 presents the clinical characteristics of the participants of the low PLR group related to MAMC tertiles. In these participants, higher levels of BMI, SBP, DBP, TC, TG, LDL, total bilirubin, UA, glucose, albumin, AST, and ALT were associated with higher MAMC tertiles. However, higher levels of HDL were associated with lower MAMC tertiles. Higher percentages of male participants and those with diabetes mellitus and smoking were associated with higher MAMC tertiles. Higher percentages of non-Hispanic white participants were associated with lower MAMC tertiles. Higher levels of age and higher percentages of congestive heart failure and malignancy were found in the second tertile of MAMC.

Table 4 shows the clinical characteristics of the participants of the higher PLR group related to MAMC tertiles. In these participants, higher levels of BMI, DBP, and serum TG, LDL, total bilirubin, UA, glucose, albumin, AST, and ALT were associated with higher MAMC tertiles.

Table 3. Characteristics of participants with low platelet-to-lymphocyte ratio (<122) according to mid-arm muscle circumference tertiles.

Characteristics of the study participants	Tertiles of mid-arm muscle circumference (cm)			Total	P for trend
	T1 (15.3–24.1 cm)	T2 (24.2–28.1 cm)	T3 (28.2–44.1 cm)		
Continuous variables, mean (SE)					
MAMC (cm)	21.7 (1.4)	25.8 (1.2)	30.4 (2.1)	26.3 (3.9)	<0.001
Age (years)	45.4 (19.7)	50.5 (19.8)	46.6 (16.7)	47.5 (18.8)	<0.001
BMI (kg/m ²)	24.1 (4.1)	27.3 (4.9)	29.5 (5.3)	27.1 (5.3)	<0.001
SBP (mmHg)	120.1 (23.1)	127.5 (22.2)	128.5 (19.2)	125.6 (21.8)	<0.001
DBP (mmHg)	68.1 (13.0)	72.1 (12.9)	76.8 (11.7)	72.7 (13.0)	<0.001
Serum TG (mg/dL)	128.9 (101.6)	153.7 (110.0)	175.4 (132.9)	154.3 (118.2)	<0.001
Serum total cholesterol (mg/dL)	203.4 (47.8)	206.7 (45.3)	206.8 (43.2)	205.7 (45.3)	0.017
LDL-cholesterol (mg/dL)	122.0 (39.4)	129.3 (39.9)	132.3 (37.9)	128.4 (39.2)	<0.001
HDL-cholesterol (mg/dL)	56.1 (16.3)	49.5 (14.8)	44.6 (13.2)	49.7 (15.4)	<0.001
Serum CRP (mg/dL)	0.4 (0.5)	0.4 (0.6)	0.4 (0.6)	0.4 (0.6)	0.100
Serum total bilirubin (mg/dL)	0.5 (0.3)	0.6 (0.3)	0.7 (0.4)	0.6 (0.4)	<0.001
Serum UA (mg/dL)	4.6 (1.3)	5.5 (1.4)	6.1 (1.4)	5.4 (1.5)	<0.001
Serum glucose (mg/dL)	95.5 (35.6)	102.9 (38.8)	104.7 (39.4)	101.3 (38.3)	<0.001
Albumin (g/dL)	4.1 (0.4)	4.1 (0.4)	4.2 (0.4)	4.1 (0.4)	<0.001
AST (U/L)	20.8 (14.4)	23.7 (20.4)	25.5 (18.8)	23.5 (18.3)	<0.001
ALT (U/L)	15.3 (16.1)	18.6 (17.2)	23.4 (22.2)	19.4 (19.2)	<0.001
Categorical variables, N (%)					
Male	120 (5.8)	1158 (50.9)	2228 (87.7)	3506 (50.9)	<0.001
Non-Hispanic white	938 (45.3)	927 (40.7)	896 (35.3)	2761 (40.1)	<0.001
Congestive heart failure	46 (2.2)	99 (4.4)	97 (3.8)	242 (3.5)	0.007
Stroke	47 (2.3)	76 (3.3)	58 (2.3)	181 (2.6)	0.085
Asthma	125 (6.0)	144 (6.3)	177 (7.0)	446 (6.5)	0.481
Malignancy	70 (3.4)	92 (4.0)	64 (2.5)	226 (3.3)	0.027
Type 2 diabetes mellitus	129 (6.2)	222 (9.8)	258 (10.2)	609 (8.8)	<0.001
Smoking	33 (1.6)	255 (11.2)	514 (20.2)	802 (11.6)	<0.001

Abbreviation: N, number; SEs, standard errors; MAMC, mid-arm muscle circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Serum TG, serum total triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Serum CRP, serum C-reactive protein; Serum UA, serum uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

<https://doi.org/10.1371/journal.pone.0208750.t003>

However, higher HDL was associated with lower MAMC tertiles. Higher levels of age, SBP, and serum TC and CRP were found in the second tertile of MAMC. Higher percentages of male participants and those with smoking habit were associated with higher MAMC tertiles. Higher percentages of non-Hispanic white participants and those with malignancies were associated with lower MAMC tertiles. The maximal percentage of patients with congestive heart failure, stroke, and diabetes mellitus were found in the second tertile of MAMC.

We further investigated the relationship between MAMC and all-cause mortality, cancer mortality, and CV mortality according to the low and high PLR values. The results of multivariable adjusted analyses for all-cause mortality, cancer mortality, and CV mortality associated with MAMC in the two PLR groups are shown in Table 5. After adjusting for all the covariates (model 4), in the high PLR group, the highest MAMC tertile was significantly associated with decreasing hazards ratios (HRs) for all-cause and cancer mortalities compared with the lowest MAMC tertile. However, this association was not observed in the low PLR group. Furthermore, higher MAMC tertiles were not significantly associated with decreasing CV mortality after adjusting for covariates in both the groups.

Table 4. Characteristics of participants with high platelets-to-lymphocytes ratio (≥ 122) according to mid-arm muscle circumference tertiles.

Characteristics of the study participants	Tertiles of mid-arm muscle circumference (cm)			Total	P for trend
	T1 (13.8–23.3 cm)	T2 (23.4–27.3 cm)	T3 (27.4–41.1 cm)		
Continuous variables, mean (SE)					
MAMC (cm)	21.7 (1.4)	25.7 (1.2)	30.3 (2.1)	25.6 (3.8)	<0.001
Age (years)	46.7 (20.2)	51.1 (20.1)	46.0 (17.0)	48.0 (19.4)	<0.001
BMI (kg/m ²)	23.9 (4.0)	27.0 (4.8)	29.0 (5.2)	26.5 (5.1)	<0.001
SBP (mmHg)	120.3 (23.2)	128.1 (23.2)	127.5 (18.5)	125.1 (22.2)	<0.001
DBP (mmHg)	68.1 (13.185)	72.5 (12.6)	76.8 (12.3)	72.2 (13.2)	<0.001
Serum TG (mg/dL)	116.2 (91.4)	135.8 (102.6)	156.2 (141.9)	134.7 (113.4)	<0.001
Serum total cholesterol (mg/dL)	202.9 (44.5)	207.9 (46.3)	207.8 (42.5)	206.1 (44.6)	<0.001
LDL cholesterol (mg/dL)	122.0 (38.4)	129.2 (38.2)	131.8 (37.9)	127.3 (38.4)	<0.001
HDL cholesterol (mg/dL)	57.5 (15.5)	52.0 (15.9)	47.6 (14.2)	52.7 (15.8)	<0.001
Serum CRP (mg/dL)	0.5 (1.0)	0.6 (0.9)	0.5 (0.8)	0.5 (0.9)	<0.001
Serum total bilirubin (mg/dL)	0.5 (0.3)	0.6 (0.3)	0.7 (0.3)	0.6 (0.3)	<0.001
Serum UA (mg/dL)	4.5 (1.2)	5.3 (1.4)	6.1 (1.4)	5.3 (1.5)	<0.001
Serum glucose (mg/dL)	93.7 (31.3)	101.3 (37.1)	102.9 (37.9)	99.0 (35.6)	<0.001
Albumin (g/dL)	4.1 (0.4)	4.1 (0.4)	4.2 (0.4)	4.1 (0.4)	<0.001
AST (U/L)	19.4 (10.1)	21.4 (15.3)	23.8 (13.6)	21.4 (13.2)	<0.001
ALT (U/L)	13.4 (9.8)	16.0 (14.1)	21.5 (17.4)	16.7 (14.2)	<0.001
Categorical variables, N (%)					
Male	150 (5.9)	1133 (48.2)	1819 (87.8)	3102 (44.6)	<0.001
Non-Hispanic white	1227 (48.3)	1037 (44.1)	833 (40.2)	3097 (44.5)	<0.001
Congestive heart failure	60 (2.4)	106 (4.5)	67 (3.2)	233 (3.3)	0.001
Stroke	50 (2.0)	79 (3.4)	39 (1.9)	168 (2.4)	0.005
Asthma	167 (6.6)	177 (7.5)	162 (7.8)	506 (7.3)	0.226
Malignancy	132 (5.2)	106 (4.5)	52 (2.5)	290 (4.2)	<0.001
Type 2 diabetes mellitus	118 (4.6)	201 (8.5)	145 (7.0)	464 (6.7)	<0.001
Smoking	43 (1.7)	257 (10.9)	456 (22)	756 (10.9)	<0.001

Abbreviation: N, number; SEs, standard errors; MAMC, mid-arm muscle circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Serum TG, serum total triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Serum CRP, serum C-reactive protein; Serum UA, serum uric acid; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

<https://doi.org/10.1371/journal.pone.0208750.t004>

Discussion

PLR is an inexpensive and routinely available valuable maker for nonspecific inflammatory conditions [10]. Previous reports have shown that inflammation plays a critical role in cancer progression [11], coronary artery disease [12], chronic kidney disease [13], heart failure [14], and all-cause mortality [15]. Recently, studies demonstrated that PLR is an inflammatory biomarker, prognostic factor, and mortality predictor in patients with malignancy, cardiovascular diseases, and end-stage renal diseases [1–4]. The mechanisms of the influence of PLR on prognoses in patients with malignancies, cardiovascular diseases, and end-stage renal disease is still incompletely understood. The increased inflammatory response may promote production of acute phase proteins and cytokines, and lead to the differentiation of megakaryocytes into platelets [16–18]. Platelets play a critical role in thrombosis and inflammation. The increased platelet counts may lead to the release of pro-inflammatory cytokines and further result in a pro-thrombotic state, which will lead to further platelet activation and thrombosis [19–20]. Platelets also play a critical role in cancer cell proliferation and migration through production of metalloproteinases and growth factors [21–22]. Lymphocytes also play a major role in

Table 5. Cox proportional hazards ratios of all-cause, cardiovascular, and cancer mortalities according to mid-arm muscle circumference in American individuals.

PLR (<122)				PLR (≥122)			
Models ^a	Tertiles of MAMC	Hazard Ratio (95%CI)	P-value	Models ^a	Tertiles of MAMC	Hazard Ratio (95%CI)	P-value
All-cause mortality							
Model 1	T2 vs. T1	1.83 (1.57–2.12)	<0.001	Model 1	T2 vs. T1	1.51 (1.32–1.73)	<0.001
	T3 vs. T1	1.20 (1.02–1.40)	0.026		T3 vs. T1	0.94 (0.81–1.10)	0.453
Model 2	T2 vs. T1	1.11 (0.94–1.31)	0.211	Model 2	T2 vs. T1	0.97 (0.84–1.13)	0.734
	T3 vs. T1	0.95 (0.78–1.15)	0.608		T3 vs. T1	0.82 (0.67–0.99)	0.041
Model 3	T2 vs. T1	1.09 (0.92–1.28)	0.326	Model 3	T2 vs. T1	0.95 (0.81–1.10)	0.472
	T3 vs. T1	0.90 (0.74–1.09)	0.273		T3 vs. T1	0.79 (0.65–0.96)	0.016
Model 4	T2 vs. T1	1.09 (0.92–1.28)	0.337	Model 4	T2 vs. T1	0.91 (0.78–1.06)	0.244
	T3 vs. T1	0.89 (0.73–1.08)	0.238		T3 vs. T1	0.76 (0.62–0.92)	0.006
Cancer mortality							
Model 1	T2 vs. T1	1.77 (1.31–2.40)	<0.001	Model 1	T2 vs. T1	2.04 (1.53–2.71)	<0.001
	T3 vs. T1	1.20 (0.88–1.64)	0.254		T3 vs. T1	1.30 (0.95–1.78)	0.097
Model 2	T2 vs. T1	1.05 (0.75–1.47)	0.769	Model 2	T2 vs. T1	0.96 (0.70–1.33)	0.803
	T3 vs. T1	0.86 (0.58–1.28)	0.463		T3 vs. T1	0.61 (0.41–0.90)	0.013
Model 3	T2 vs. T1	1.06 (0.76–1.47)	0.748	Model 3	T2 vs. T1	0.91 (0.66–1.27)	0.585
	T3 vs. T1	0.87 (0.58–1.29)	0.486		T3 vs. T1	0.58 (0.39–0.86)	0.007
Model 4	T2 vs. T1	1.06 (0.76–1.48)	0.743	Model 4	T2 vs. T1	0.88 (0.63–1.22)	0.473
	T3 vs. T1	0.86 (0.57–1.28)	0.444		T3 vs. T1	0.58 (0.39–0.86)	0.008
CV mortality							
Model 1	T2 vs. T1	2.00 (1.59–2.51)	<0.001	Model 1	T2 vs. T1	1.58 (1.29–1.93)	<0.001
	T3 vs. T1	1.17 (0.92–1.49)	0.201		T3 vs. T1	0.96 (0.76–1.21)	0.719
Model 2	T2 vs. T1	1.08 (0.84–1.38)	0.563	Model 2	T2 vs. T1	1.08 (0.87–1.35)	0.486
	T3 vs. T1	0.94 (0.70–1.25)	0.657		T3 vs. T1	1.07 (0.80–1.42)	0.656
Model 3	T2 vs. T1	1.05 (0.82–1.34)	0.716	Model 3	T2 vs. T1	1.04 (0.84–1.30)	0.711
	T3 vs. T1	0.87 (0.65–1.17)	0.356		T3 vs. T1	1.03 (0.78–1.38)	0.817
Model 4	T2 vs. T1	1.06 (0.83–1.36)	0.645	Model 4	T2 vs. T1	0.98 (0.78–1.22)	0.845
	T3 vs. T1	0.87 (0.64–1.17)	0.339		T3 vs. T1	0.95 (0.71–1.27)	0.728

^a Adjusted covariates

Model 1 = Unadjusted.

Model 2 = adjusted for sex, race, and body mass index.

Model 3 = Model 2 + adjusted for systolic blood pressure, serum triglycerides, and serum fasting glucose.

Model 4 = Model 3 + adjusted for history of smoking, congestive heart failure, stroke, gout, and malignancy.

<https://doi.org/10.1371/journal.pone.0208750.t005>

inflammation; under stressful conditions, the activation of hypothalamic-pituitary-adrenal axis results in secretion of cortisol, which results in decreased lymphocyte count [23–24].

Since the relationships between high PLR, mortality, and clinical outcomes in several diseases have been proven, we should attempt to identify the potential factors to decrease the mortality in individuals with high PLR. Patients with lower MAMC may have reduced lean muscle mass and decreased muscle strength, which may be due to decreased physical activity

or an underlying medical disease [7, 25]. In previous studies, MAMC has been demonstrated to be associated with physical function, life quality [7], male all-cause mortality [26], and mortality in patients on hemodialysis [5].

In our study, we examined a nationally demonstrative sample of American adults to determine whether MAMC influences mortality outcomes in low and high PLR groups. We observed a statistically significant decrease in the HRs for all-cause and cancer mortalities in the highest MAMC tertile compared with those in the lowest MAMC tertile after adjusting for covariates; however, this association was not observed in the low PLR group. Individuals with high PLR are believed to be in a state of systemic inflammation and one of the reasons for our results is that higher MAMC may have a protective effect from mortality in such individuals. However, patients with lower MAMC may be suffering from weakness, chronic illness, or malnutrition; therefore, the underlying condition may result in a higher mortality rate in individuals with chronic inflammation. Previous studies reported that physical performance was associated with MAMC [27] and physical activity may aid in the prevention and treatment of sarcopenic obesity [28]. As mentioned above, proper exercise may help control inflammation, and it plays an important role in lowering the mortality risk in individuals with high PLR. Routine exercise maintains muscle mass and strength, and it also improves inflammatory conditions by reducing the levels of pro-inflammatory cytokines [29–31]. Therefore, we may suppose that proper exercising modulates inflammation and leads to decreased mortality risk in the population with high PLR.

There are several limitations to our study. First, the cross-sectional nature of our survey and the fact that the anthropometric and blood examination data were collected only at the follow-up time may have resulted in bias. Second, the large amount of data was collected from self-reporting and, therefore, maybe have a recall bias. Third, even after adjusting for many confounding variables, some confounding bias may still be present. Fourth, the native design of NHANES database is not fit for a global population.

Conclusion

In conclusion, the highest MAMC tertile was significantly associated with decreasing HRs for all-cause and cancer mortalities compared with the lowest MAMC tertile in individuals with $PLR \geq 122$. Clinical care should focus on maintaining muscle mass and muscle strength by means of increasing physical activity and controlling the underlying chronic inflammatory disease to decrease the mortality rate. Future studies should focus on the longitudinal investigation of the changes in MAMC and the change in the influence of MAMC on mortality in individuals with high PLR.

Author Contributions

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