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2017 Troponin Study

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# Neutrophil-to-lymphocyte ratio and exercise intensity are associated with cardiac-troponin levels after prolonged cycling: the Indonesian North Coast and Tour de Borobudur 2017 Troponin Study

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## Abstract

**Purpose** The mechanism of cardiac-troponin elevation after exercise remains unclear. Studies have reported that leucocyte ratios are related to coronary artery disease. The present study explored the relationship between leucocyte ratios, exercise intensity, and post-exercise cardiac-troponin I (cTnI) levels.

**Methods** Ninety-two participants in a long-distance cycling tour were included in this study. Baseline and post-exercise blood samples were collected to determine cTnI concentrations. Biochemical parameters and leucocyte ratios were measured at baseline. Exercise intensity was examined by recording the heart rate (HR). Exercise intensity was determined as the percentage of peak HR to maximal predicted HR. Based on clinical cutoff points of the cTnI assay, cTnI levels were defined as < 10 ng/mL and ≥ 10 ng/mL.

**Results** Eighty-eight participants completed the cycling tour after a median time of 7.3 h, at a median intensity of 81.8% of maximal HR. cTnI concentrations increased from 5.2 ± 9.83 ng/mL at baseline to 13.6 ± 36.12 ng/mL post-exercise, with 31.8% of the study population having cTnI ≥ 10 ng/mL. Neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, recovery HR, mean and peak HR, and exercise intensity were associated with post-exercise cTnI levels in bivariate analysis. After adjustment for potential confounders, only NLR and exercise intensity were significantly related to post-exercise cTnI levels in the multivariable model.

**Conclusions** NLR and exercise intensity are significantly associated with post-exercise cTnI levels, suggesting that inflammatory factors may play a role in the magnitude of exercise-induced cTnI release beyond exercise intensity.

**Keywords** Cardiac stress · Lymphocyte · Neutrophil · Physical-exertion · Troponin

## Abbreviations

CAD Coronary artery disease  
CI Confidence interval

cTnI Cardiac-troponin I  
HR Heart rate  
MLR Monocyte-to-lymphocyte ratio

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NC	13 <sup>th</sup> coast
NEEDED	North Sea Race Endurance Exercise study
NLR	Neutrophil-to-lymphocyte ratio
OR	Odds ratio
SCD	Sudden cardiac death
TdB	Tour de Borobudur

## Introduction

Previous studies have shown that prolonged exercise may transiently increase the risk of acute cardiac events [1, 2]. Sixty-one cases of sport-related sudden cardiac death (SCD) have been reported in Madrid, Spain over 5 years [3], whereas 820 cases were reported in a population-wide study in France [2]. Interestingly, cycling activities comprised 36% of the SCD cases, which was substantially higher compared to football (23%), gymnastics (9%), running (7%), and other sport activities (4%) [3].

Detection of cardiac-troponin I (cTnI) in the blood is a highly sensitive and specific marker for cardiac injury and serves as the gold standard in the laboratory diagnosis of acute myocardial infarction [4, 5]. Previous studies reported cTnI elevations after different sport activities, including cycling [6–8]. Less race experience, younger age, and longer exercise duration appeared to be related to the magnitude of cTnI elevations after exercise [6, 9]. A previous study also confirmed that age, walking speed, and pre-existing cardiovascular diseases or risk factors are associated with post-exercise cTnI level [7]. Regarding the participants' age, one study reported that younger participants tended to have higher cTnI levels, suggesting important differences in metabolic adaptation to endurance exercise [6]. Conversely, another study reported that advanced age is related to higher post-exercise cTnI levels, indicating a decrease in metabolic function, as well as the presence of cardiovascular pathology. A study on the Quebrantahuesos tour reported that exercise intensity is responsible for the cTnI release after cycling [8]. Furthermore, the North Sea Race Endurance Exercise (NEEDED) study reported that exercise-induced cTnI elevations were higher in cyclists with subclinical coronary artery disease (CAD) [10].

Inflammation plays a pivotal role in CAD pathogenesis [11]. Inflammatory cells, such as monocytes, macrophages, dendritic cells, and T cells, are commonly found in atherosclerotic lesions and are essential for their formation [12–14]. Other studies have also reported that inflammatory processes are involved in exercise-induced cardiac-troponin release [15–17]. Moreover, the neutrophil-to-lymphocyte ratio (NLR) and monocyte-to-lymphocyte ratio (MLR) have been reported as indicators of the presence of CAD [18, 19]; moreover, they were found to predict its severity [13, 20]. However, little is known about the relationship between

NLR/MLR and cTnI elevation after exercise. Therefore, we aimed to investigate whether NLR and MLR are independent predictors of cTnI elevation after long-distance cycling. We hypothesized that NLR and MLR are positively related to cTnI elevation after long-distance cycling.

## Methods

### Study participants

Consecutive sampling of amateur participants in two Indonesian long-distance cycling tours [the 2017 North Coast (NC) tour (<http://ina-northcoast-cyclingtour.com/index.html>) and the 2017 Tour de Borobudur (TdB) (<https://event.sambabikers.com/>)] was performed by voluntary confirmation. All amateur athletes were invited to participate in this prospective observational study via an online advertisement on the website of the cycling tours. After the minimum sample size was met, recruitment was stopped immediately. Initially, 114 potential participants agreed to participate; after exclusion of professional athletes and individuals with a history of CAD, a total of 92 participants were included in this study.

### Ethical approval

The study protocol was approved by the Ethical Committee of the Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Semarang, Indonesia. Informed consent was obtained from all participants. The study was registered in ClinicalTrials.gov under ID number NCT03310450. The study protocol conformed to the concepts of the Declaration of Helsinki. The study was funded by the Directorate of Research and Public Service, Ministry of Research, Technology and Higher Education of the Republic of Indonesia, which was not involved in the research procedures.

### Data collection

One day before the cycling tour, all participants completed a questionnaire on their personal characteristics and health conditions, including medical history. After completing the questionnaire, a 10-mL venous blood sample was obtained from the antecubital vein. The heart rate (HR) was monitored during exercise using a chest band HR monitor (Polar RC3 GPS®; Polar Corporation, Kempele, Finland). We defined mean HR as the average HR during cycling and the peak HR as the highest HR during cycling. The maximal predicted HR ( $HR_{max} = 208 - 0.7 \times \text{age}$ ), percentage of  $HR_{max}$  ( $\%HR_{max} = 100 \times \text{peak HR} / HR_{max}$ ), and exercise intensity ( $\text{Exercise intensity} = 100 \times \text{mean HR} / HR_{max}$ ) were calculated [21]. Immediately post-exercise (within less than

5 min), blood sampling was repeated in the same manner to measure post-exercise cTnI levels.

Obtained blood samples were analyzed in the laboratory. The whole blood sample's leucocyte ratios were analyzed on an automated blood cell counter (Sysmex Xn-350; Sysmex Corporation, Kobe, Japan). The other fractions of the whole blood were collected in serum-gel vacutainer tubes and allowed to clot for 45 min. After centrifugation, serum was aliquoted, frozen, and stored at  $-84^{\circ}\text{C}$  for future analysis. All analyses were conducted using the same calibration and setting to minimize variation. cTnI level was measured using a cTnI assay (E-EL-H0649; Elabscience, Houston, TX, USA). The assay detection limit was 0.39–25 ng/mL with an intra-assay precision coefficient of variance (CV) 4–10%; there was no significant inter-assay precision CV. A cTnI value of 10 ng/mL was used as a limit based on the 99th percentile reference value described elsewhere [22, 23]. Biochemical parameters [i.e., hemoglobin, total cholesterol, and high-density lipoprotein (HDL) cholesterol] were analyzed using an automated analyzer (Cobas C-501; Roche Diagnostics, NJ, USA).

### 13 Statistical analysis

All normally distributed numeric data are reported as mean  $\pm$  standard deviation and statistical significance was assumed at a  $p$  value  $< 0.05$ . Statistical analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 23.0; IBM Corp., Armonk, NY, USA). The normality of the data distribution was examined by the Kolmogorov–Smirnov test. When the data demonstrated a non-Gaussian distribution, natural logarithmic transformation was applied. If the data remained not normally distributed after transformation, non-parametric statistics were used and data were presented as median with interquartile range.

Paired Student's  $t$  test was used to test the significance of the differences between baseline and post-exercise cTnI levels. A post-exercise cTnI cutoff of 10 ng/mL was used to determine cyclists with high cTnI concentrations. Bivariate analyses were then conducted to determine parameters that were related to post-exercise high cTnI level. Binary logistic regression analysis using the enter method was used to identify factors that were significantly related to post-exercise cTnI levels. Based on our hypothesis and considering confounders, we included age, body mass index, medical history (i.e., history of hypertension, dyslipidemia, diabetes mellitus, and family history of CAD), total and HDL cholesterol levels, NLR, MLR, exercise duration, recovery HR, mean HR, peak HR,  $\%HR_{\max}$ , and exercise intensity in our model as potential determinants of post-exercise cTnI levels. Thereafter, all predictors with a  $p$  value  $< 0.10$  were included in the final regression model.

## Results

In 2017, 31 and 1180 cyclists completed the Indonesia NC tour and the TdB, respectively. NC participants cycled for 240 km with a total elevation of 826 m, during sunny weather with an average temperature of  $33^{\circ}\text{C}$  [ $28\text{--}41^{\circ}\text{C}$ ]. TdB participants were divided into two groups; the first group cycled for 140 km, with a total elevation of 2754 m, during drizzle and mostly rainy weather with an average temperature of  $26^{\circ}\text{C}$  [ $21\text{--}37^{\circ}\text{C}$ ]. The second TdB group cycled 100 km in sunny weather with an average temperature of  $30^{\circ}\text{C}$  [ $28\text{--}34^{\circ}\text{C}$ ].

Of 92 recruited amateur cyclists, four dropped out since they did not complete post-exercise examinations and were excluded from further analyses. The remaining 88 cyclists covered 240 km (NC240 K group,  $n = 28$ ), 140 km (TdB140 K group,  $n = 30$ ), and 100 km (TdB100 K group,  $n = 30$ ). Details of participant recruitment are described in Fig. 1. Table 1 provides an overview of the participants' characteristics. Family history of CAD, HDL cholesterol levels, and the neutrophil count were significantly different between the different touring groups ( $p < 0.05$ ). All other participant characteristics were comparable across groups. Table 2 provides an overview of exercise characteristics. As expected, exercise duration, resting HR, recovery HR, and exercise intensity were significantly different across groups ( $p < 0.05$ ). Peak HR and  $\%HR_{\max}$  did not differ across groups ( $p > 0.05$ ).

Baseline cTnI levels were significantly lower in the NC240 K group compared to the other groups (Fig. 2). A significant increase in cTnI levels from baseline ( $5.2 \pm 9.83$  [0.00–47.97] ng/mL) to post-exercise ( $13.6 \pm 36.12$  [0.00–245.05] ng/mL) was found in the entire study population ( $p = 0.021$ ) (Table 3). However, the exercise-induced increase in cTnI appeared to differ among the subgroups. Although a significant increase in cTnI levels was found in the NC240 K group ( $3.5 \pm 8.93$  [0.08–47.97] ng/mL– $25.0 \pm 61.39$  [0.11245.05] ng/mL,  $p = 0.001$ ), cTnI was not significantly elevated in the TdB140 K ( $5.2 \pm 9.98$  [0.0–25.10]– $6.6 \pm 10.36$  [0.0–27.0] ng/mL,  $p = 0.318$ ) and TdB100 K groups ( $6.6 \pm 10.56$  [0.0–26.30]– $10.1 \pm 10.44$  [0.0–26.89] ng/mL,  $p = 0.151$ ).

Cyclists with post-exercise cTnI levels  $< 10$  ng/mL ( $n = 60$ , mean age,  $46 \pm 10.9$  years) demonstrated lower neutrophil counts, NLR, and MLR, but higher lymphocyte counts (Table 4 and Fig. 3) compared to cyclists with post-exercise cTnI levels  $\geq 10$  ng/mL ( $n = 28$ ; mean age,  $44 \pm 12.8$  years). Furthermore, exercise intensity, mean HR, peak HR, and  $\%HR_{\max}$  were significantly higher in cyclists with cTnI levels  $\geq 10$  ng/mL.

All variables with  $p$  value  $< 0.10$  were included in the binary logistic regression analysis. These were neutrophil



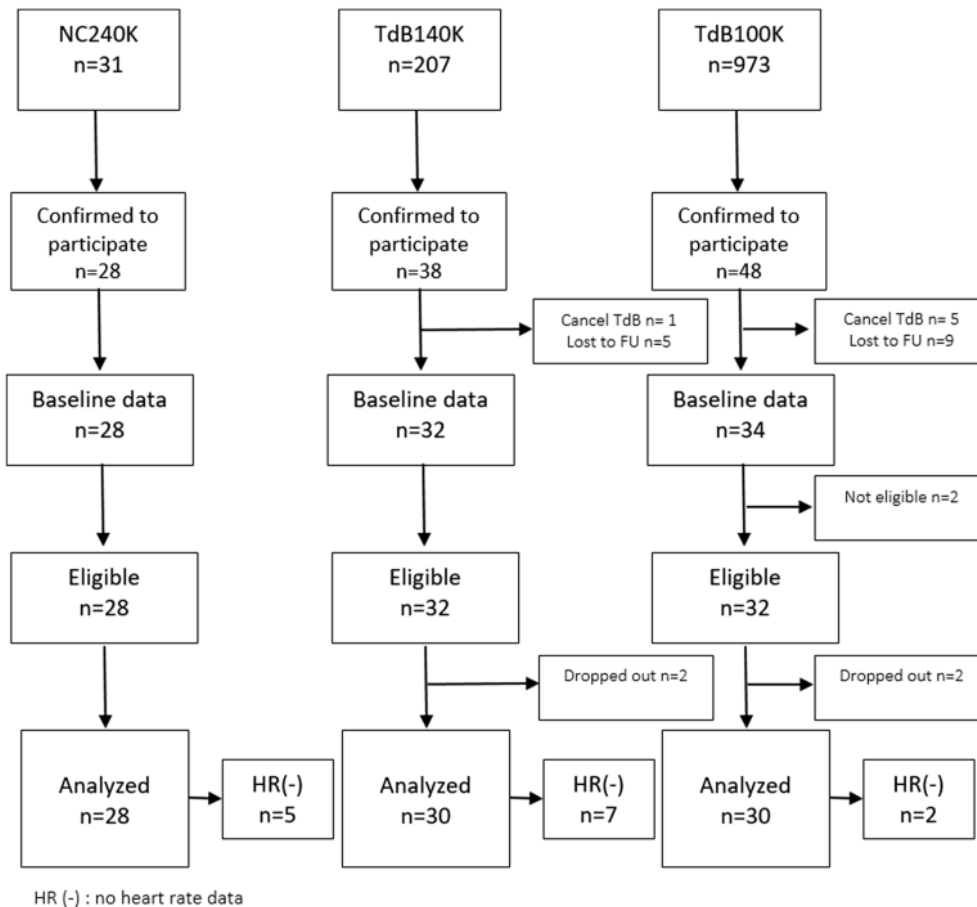


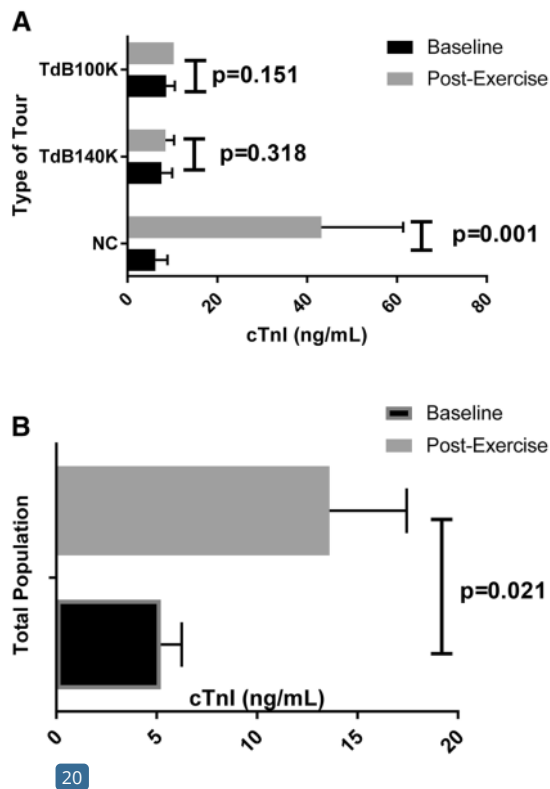
Fig. 1 Flow diagram of participant recruitment

and lymphocyte counts, NLR, MLR, recovery HR,  $r_{28}$  HR, peak HR,  $\%HR_{max}$ , and exercise intensity. NLR (odds ratio [OR]: 10, 95% confidence interval (CI): 1.17–8.56;  $p = 0.024$ ) and exercise intensity (OR: 1.09, 95% CI: 1.004–1.19);  $p = 0.040$ ) were the only parameters significantly associated with cTnI levels  $\geq 10$  ng/mL in the multivariable model ( $r = 0.213$ ,  $p < 0.05$ ). The association with neutrophil counts, lymphocyte counts, MLR, recovery HR, mean HR, peak HR, and  $\%HR_{max}$  did not reach statistical significance, and they were therefore excluded from the regression analysis as determinants of post-exercise cTnI levels.

## Discussion

To the best of our knowledge, the present study is the first to investigate the relationship between leucocyte ratios and cTn levels after prolonged exercise. The results showed that NLR and exercise intensity were related to post-exercise cTnI levels. Exercise intensity is a well-known determinant of post-exercise cTn level. Previous studies reported a consistent relationship between exercise intensity and post-exercise cTn level following prolonged walking [7], marathon running [24, 25], and prolonged cycling





**Fig. 2** Baseline and post-exercise cTnI levels by a type of tour and b total population. cTnI cardiac-troponin I

[8]. The observation that leucocyte ratios, especially NLR and MLR, are related to exercise-induced cTnI elevations is a novel finding suggesting that inflammation may play a role in the magnitude of exercise-induced troponin release from cardiomyocytes beyond exercise intensity.

Although exercise induced a significant increase in cTnI levels at the entire cohort level, cTnI levels did not increase significantly in TdB participants following 6.1 [3.5–9.8] h of cycling. A potential explanation for this finding may relate to the race's characteristics. NC participants cycled most of the race in a peloton, except in the last 30 km before the finish, whereas TdB participants cycled in some pelotons at their own pace. Indeed, the exercise intensity as revealed by %HR<sub>max</sub> was lower in TdB participants (TdB140 K 74.5% [45.58–90.98%] and TdB100 K 80.8% [53.73–92.16%]) compared to NC participants (84.3% [75.14–90.80]), which may explain the lack of increase in cTnI.

Many previous reports on cTn elevations after prolonged exercise were published; however, the potentially damaging effects of prolonged exercise on the heart remain unclear [1]. Although prolonged exercise has not been definitively shown to adversely affect cardiac function, the evidences on the elevation of certain markers in the blood after exercise indicate cardiac stress. Several previous studies reported that a simple parameter, NLR, can predict both the occurrence and the severity of coronary lesions [20, 26, 27]. An Indian study reported that patients with NLR > 5.25 had higher risk of SCD after 6 months of follow-up [26]. Another study also found that NLR > 3 correlated to CAD severity and predicted the existence of atherosclerosis or coronary lesions [27]. Finally, a study from Bosnia and Herzegovina also found a positive correlation between NLR and myocardial infarction

**Table 3** Baseline and post-exercise cTnI levels

cTnI levels	Tour category			Total n = 88	p
	NC240K n = 28	TdB140K n = 30	TdB100K n = 30		
Baseline (ng/mL, mean ± SD)	3.5 ± 8.93***	5.2 ± 9.98***	6.6 ± 10.56***	5.2 ± 9.83****	0.575*
Post-exercise (ng/mL, mean ± SD)	25.0 ± 61.39***	6.6 ± 10.36***	10.1 ± 10.44***	13.6 ± 36.12****	0.076*
Δhs-cTnI (mean ± SD)	21.5 ± 55.37	0.7 ± 12.00	3.5 ± 12.98	8.3 ± 33.78	0.079*
p (within group)	<b>0.001***</b>	0.318***	0.151***	<b>0.021****</b>	
Post-exercise cTnI level category					
≥ 10 ng/mL (n; %)	9; 32.1	8; 26.7	11; 36.7	28; 31.8	0.707**
< 10 ng/mL (n; %)	19; 67.9	22; 73.3	19; 63.3	60; 69.2	

Bold values are statistically significant

cTnI cardiac-troponin I, NC north coast, SD standard deviation, TdB Tour de Borobudur

\*Kruskal–Wallis test

\*\*Chi-squared test

\*\*\*Wilcoxon's test

\*\*\*\*Paired sample t test

**Table 4** Characteristics and parameters according to cTnI level

Variables	cTnI < 10 ng/mL n = 60	cTnI ≥ 10 ng/mL n = 28	p
Age (years, mean ± SD)	46 ± 10.9	44 ± 12.8	0.540*
BMI (kg/m <sup>2</sup> , mean ± SD)	24.2 ± 3.09	23.9 ± 2.98	0.347*
Medical history of			
Hypertension (n; %)	9; 69.2	4; 30.8	1.00**
Dyslipidemia (n; %)	21; 75	7; 25	0.489**
Diabetes mellitus (n; %)	9; 69.2	4; 30.8	0.834**
CAD in family (n; %)	3; 100	0; 0	0.566**
Total cholesterol level (mg/dL, mean ± SD)	2.09 ± 42.21	2.08 ± 33.4	0.445*
HDL cholesterol level (mg/dL, mean ± SD)	57.9 ± 16.82	58.1 ± 17.61	0.958*
Neutrophil count (10 <sup>6</sup> /L, mean ± SD)	51.6 ± 8.20	55.3 ± 7.85	<b>0.048*</b>
Lymphocyte count (10 <sup>6</sup> /L, mean ± SD)	37.1 ± 7.94	33.3 ± 7.29	<b>0.036*</b>
Monocyte count (10 <sup>6</sup> /L, mean ± SD)	7.5 ± 1.71	7.8 ± 1.20	0.352*
NLR (mean ± SD)	1.51 ± 0.594	1.78 ± 0.600	<b>0.049*</b>
MLR (mean ± SD)	0.21 ± 0.070	0.25 ± 0.068	<b>0.037*</b>
Resting HR (bpm; mean ± SD)	62.7 ± 8.81	62.5 ± 10.	0.47*
Recovery HR (bpm; median [range])	89 [59–133]	93 [57–168]	<b>0.043***</b>
Exercise duration (h; median [range])	7.3 [3.5–9.8]	7.3 [3.5–8.3]	0.472***
Mean HR (bpm; median [range])	134 [94–168]	149 [140–180]	<b>&lt; 0.001***</b>
Peak HR (bpm; median [range])	168 [116–233]	180 [153–229]	<b>0.007***</b>
%HR <sub>max</sub> (%; median [min–max])	77.5 [51.5–93.7]	85.2 [78.8–98.8]	<b>&lt; 0.001***</b>
Exercise intensity	79.3 [45.6–90.9]	84.57 [64.0–92.2]	<b>0.014***</b>

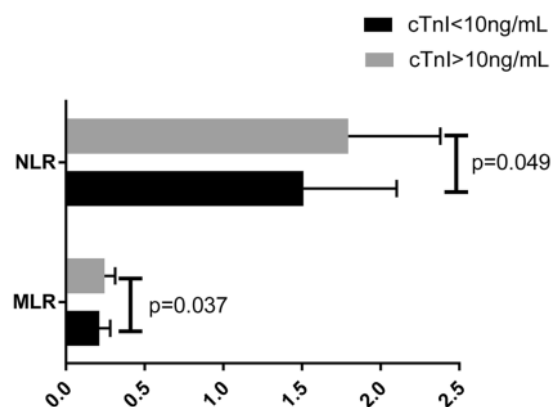
bold values are statistically significant

BMI body mass index, bpm beats per minute, CAD coronary artery disease, cTnI cardiac-troponin I, HDL high-density lipoprotein, HR heart rate, min minimum, MLR monocyte-to-lymphocyte ratio, NLR neutrophil-to-lymphocyte ratio, SD standard deviation

\*Independent sample *t* test

\*\*Chi-squared test

\*\*\*Mann–Whitney test



**Fig. 3** MLR/NLR and post-exercise cTnI levels. cTnI cardiac-troponin I, MLR monocyte–lymphocyte ratio, NLR neutrophil–lymphocyte ratio

and highlighted the pivotal role of NLR as an inflammatory marker in acute coronary syndrome (ACS) [20].

We found a significant relationship between NLR and post-exercise cTnI levels, albeit in a low-variance regression model, which means that other dominant parameters still influenced the post-exercise cTnI levels. Exercise-induced inflammation is a well-known phenomenon after prolonged exercise [28]. A systematic review showed changes in leucocyte count after exercise, including increased neutrophil counts and decreased lymphocyte counts [29]. These findings might be explained by the muscle damage induced by sport activities, wherein the mechanical overload causes accumulation of leucocytes in damaged myocytes [29]. Changes in the types of white cells, such as eosinophils, monocytes, neutrophils, and lymphocytes, seen in relation to CAD might be due to inflammation that has an important role in CAD pathophysiology [13].

A study of triathlon athletes found a dramatic increase in most circulating leucocytes' levels, especially



neutrophils, during the race [28]. The study also showed an increase in lymphocytes during high-intensity exercise, followed by lymphopenia after recovery [28]. Immune cell activity plays a pivotal role in the pathogenesis of atherosclerosis, which is a predisposing factor to CAD. Neutrophils play a role in non-specific inflammation by secreting various mediators, such as elastase, myeloperoxidase, and free radicals, which are implicated in the development of atherosclerosis. In this process, neutrophils adhere to the capillary endothelium, inhibiting capillary reperfusion of the ischemic areas. The release of autacoids, such as thromboxane-B2 and leukotriene-B4, induces vasoconstriction and thrombocyte aggregation. When ischemia occurs, including that induced by exercise [30, 31], neutrophils pool in the ischemic area and release proteolytic enzymes and reactive oxygen species which destroy the surrounding myocytes. This process results in the enlargement of the infarcted area through microvascular occlusion [32, 33]. A previous study also showed a relationship between a decrease in T-cell count and function during ACS and atherosclerotic plaque instability [34].

The amateur athletes included in the present study showed a rather significant variation in mean age ( $45.3 \pm 11.47$  years), with the youngest participant being 22 years old and the oldest being 71 years old. This condition described a wide age range of cycling tour participants in the community, therefore the age of the study subjects was not restricted. While younger age is reportedly related to the elevation of cTn [6, 7, 9], we did not find a significant relationship between age and cTnI levels, although younger participants tended to have higher cTnI levels (Table 4). This can be potentially explained by the dominant influence of exercise intensity on cTnI levels in this study. However, it must be noted that among the tour categories of different exercise intensities, the mean age of the participants appeared to be different, albeit not significantly (Table 1). This issue must be acknowledged since age is closely related to changes in the cardiovascular system [35].

The limitations in the present study's methodology include the lack of assessment of other inflammatory indicators, such as interleukin-6 and -10, and other mediators. Moreover, post-exercise NLR was not assessed; hence, the NLR could not be compared before and after prolonged cycling. Furthermore, we included participants from three different long-distance cycling tours; however, participant characteristics were comparable between the tours, and the tours' characteristics were included in the multivariable model to minimize their effect on study outcomes. Future studies should recruit larger number of participants and include assessment of novel inflammatory and cardiac injury parameters to understand these processes more thoroughly.

## Conclusions

NLR and exercise intensity are significantly related to post-exercise cTnI levels, suggesting that inflammatory factors play an important role in exercise-induced troponin release together with the amount of effort exerted by the athlete.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Ethical Committee of the Faculty of Medicine, Diponegoro University/Dr. Kariadi General Hospital, Semarang, Indonesia; approval number 607/EC/FK-RSDK/X/2017) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Informed consent** Written informed consent was obtained from all individual participants included in the study.

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