J Surg Med. 2019;3(8):588-592.
DOI: 10.28982/josam.606487

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Effect of cardiac rehabilitation on mortality related inflammatory markers

Egzersiz temelli kardiyak rehabilitasyonun mortalite ilişkili inflamatuar belirteçlere etkisi

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Ethics Committee Approval: Haydarpaşa Numune Research Hospital Ethics Committee approved the study (09.10.2017 HNEAH-KAEK 2017/KK/112).
Etik Kurul Onayı: Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu çalışmayı onayladı (09.10.2017 HNEAH-KAEK 2017/KK/112).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 8/24/2019
Yayın Tarihi: 24.08.2019

Abstract

Aim: Cardiac Rehabilitation (CR) is a rehabilitation method which decreases mortality in cardiac patients. The main goal of this study is to investigate the effect of CR on neutrophil-to-lymphocyte ratio (NLR) and thrombocyte-to-lymphocyte ratio (TLR), which are inflammatory markers directly related to mortality in cardiac patients. The secondary goal is to assess the effect of CR on functional capacity.

Methods: This retrospective cohort study consists of 211 CR patients who completed 30 sessions of tailored comprehensive CR programs. Their functional status and cardiovascular endurance were assessed with a 6- minute walk test and a cycle ergometer test. Inflammatory markers (TLR, NLR, sedimentation, CRP) were obtained from blood testing and demographic data were collected. After 30 sessions of CR all tests were repeated. No adverse events occurred during the exercise sessions.

Results: Among 211 patients enrolled in this the study, 114 (54%) were female and 97 (46%) were male. Mean age was 56.28 (10.25) years (min 21 - max 81 years). 94 (44.5%) patients were hypertensive, 24 (11.4%) had heart failure, 83 (39.3%) had coronary artery disease and 10 (4.7%) had arrhythmia. Mean range for the 6-minute walk test was 374.62 (61.75) meters before and 390.80 (62.87) meters after CR (P<0.001). Mean values of the maximum watts in cycle ergometer effort test were 50 watts before and 75 watts after CR (P<0.001). Before and after CR, NLR and TLR were 1.6, 1.4 and 107.59 (35.22), 101.46 (32.78), respectively (P<0.001). Sedimentation and CRP levels were 22.38 (11.55) mm/hour, 1.0 mg/dl before and 18.98 (10.06) mm/hour, 0.5 md/dl after rehabilitation, respectively (P<0.001).

Conclusion: CR can decrease the inflammatory markers TLR and NLR which are directly related to mortality in cardiac patients, while increasing the patients' functional capacity.

Keywords: Cardiac rehabilitation, Inflammation, Mortality

Öz

Amaç: Kardiyak rehabilitasyon kalp hastalarında mortaliteyi azaltan bir rehabilitasyon metodudur fakat bu etkisinin hangi parametreler üzerinden olduğuyla ilgili netlik yoktur. Nötrofil lenfosit ve trombosit lenfosit oranı kalp hastalarında mortaliteyle direk ilişkili inflamatuar belirteçlerdir. Bu çalışmanın amacı kardiyak rehabilitasyonun kalp hastalarında mortaliteyle direk ilişkili olan inflamatuar belirteçler (nötrofil lenfosit oranı, trombosit lenfosit oranı) üzerine olan etkilerini araştırmaktır. Çalışmanın ikincil hedefi ise kardiyak rehabilitasyonun aynı hasta grubunda fonksiyonel kapasite üzerine etkisini araştırmaktır.

Yöntemler: Bu çalışmaya 30 seans kardiyak rehabilitasyon programını tamamlayan 211 hasta dahil edilmiştir. Öncelikle hastaların fonksiyonel durumları 6 dakika yürüme testiyle, kardiyovasküler dayanıklılıkları bisiklet ergometer efor testi ile değerlendirilmiş, inflamatuar markerları (nötrofil lenfosit oranı, trombosit lenfosit oranı, sedimentasyon, CRP) kan testiyle bakılmış, demografik özellikleri kaydedilmiştir. 30 seans kardiyak rehabilitasyon sonrası bütün testler tekrar edilmiş ve istatistiksel analizleri yapılmıştır. Egzersiz seansları süresince herhangi bir yan etki gözlenmemiştir. Retrospektif bir kohort çalışmasıdır.

Bulgular: Bu çalışmaya 211 hasta alınmıştır. Hastaların 114'ü (%54) kadın ve 97'si (%46) erkektir. Ortalama yaş 56,28 (10,25) yaştır (minimum 21 - maksimum 81 yaş). 94 (%44,5) hastada hipertansiyon, 24 (%11,4) hastada kalp yetmezliği, 83 (%39,3) hastada koroner arter hastalığı ve 10 (%4,7) hastada aritmi mevcuttu. 6 dakika yürüme testinde kardiyak rehabilitasyon öncesi ortalama mesafe 374,62 (61,75) metre olup rehabilitasyon sonrası bu mesafe 390,80 (62,87) metreye çıkmıştır (P<0,001). Bisiklet ergometer efor testinin maksimum watt ortalama değeri tedavi öncesi 50 watt iken tedavi sonrası 75 watt olmuştur (P<0,001). Nötrofil lenfosit oranı tedavi öncesi 1,6 iken tedavi sonrası 1,4 olarak saptanmıştır; trombosit lenfosit oranı ise rehabilitasyon öncesi 107,59 (35,22) iken rehabilitasyon sonrası 101,46 (32,78) olarak saptanış olup her ikisindeki düşüşte istatistiksel olarak anlamlıdır (P<0,001). Sedimentasyon ve CRP düzeyleri rehabilitasyon öncesi sırasıyla; 22,38 (11,55) mm/saat, 1,0 mg/dl iken rehabilitasyon sonrası, 18,98 (10,06) mm/saat ve 0,5 md/dl olarak değişmiştir (P<0,001).

Sonuç: Kardiyak rehabilitasyon mortaliteyle direk ilişkili belirteçler olan nötrofil lenfosit oranını ve trombosit lenfosit oranını düşürür ve aynı zamanda hastaların fonksiyonel kapasitelerini artırır.

Anahtar kelimeler: Kardiyak rehabilitasyon, İnflamasyon, Mortalite

How to cite / Atıf için: Kaya BB, Özbilgin N. Effect of cardiac rehabilitation on mortality related inflammatory markers. J Surg Med. 2019;3(8):588-592.

Introduction

Atherosclerosis plays a key role in cardiovascular disease progression. Leucocyte recruitment and pro-inflammatory cytokines promote atherogenesis [1]. Inflammation worsens and triggers plaque complications, which are mortal [2]. It also causes thrombosis in addition to atherogenesis, and thrombocytes further worsen the atherogenic process by adding plaque complications of their own [3]. Neutrophil-to-lymphocyte ratio (NLR) is an easily calculated parameter to assess the inflammatory state of the patients [4]. It is also proved in a systematic review that NLR can be used to predict mortality in major cardiac events in acute coronary syndrome [5]. Thrombocyte-to-lymphocyte ratio (TLR) is another parameter which is also related to mortality in cardiac patients [6-10]

Cardiac rehabilitation (CR) is a multi-component rehabilitation program for cardiac patients designed to maximize secondary prevention from heart disease [11]. It has internationally accepted core components which are nutritional counseling (NC), risk factor modification (RFM), psychosocial management (PM), patient education (PE) and exercise training (ET) [12]. A Cochrane review showed that exercise-based CR reduces mortality and morbidity by 20% for coronary artery disease patients [13]. Another systematic review focused on the effects of the core components of CR on mortality and morbidity. In this study the authors showed that each of PM, ET and RFM clearly reduce the hazard ratio of mortality and concluded that comprehensive CR has substantial benefits in reducing mortality and morbidity [14]. A recent study showed that elderly patients who attended a cardiac rehabilitation program after trans-catheter aortic valve implantation had decreased mortality at 6 months [15].

There are various studies on the effects of CR on mortality in the literature. However, to the best of our knowledge, there are no studies about the effect of CR on mortality related inflammatory parameters, except for a very recent concurrent study on a relatively limited number of patients with only a specific type of cardiac disease [16]. In this study, we investigate the mechanisms that lower mortality in a large number of CR patients with a broad range of cardiac pathologies, and focus on inflammatory markers (NLR, TLR) which are directly related to atherosclerosis and mortality.

The primary aim of this study is to assess the effects of 10-week long CR (30 sessions) on mortality-related inflammatory markers in cardiac patients. Secondary aim is to assess the effect of CR on functional capacity. We hypothesize that CR would have a positive impact on mortality related inflammatory markers and functional capacity in CR patients.

Materials and methods

Study design

A single center, retrospective cohort study was performed by evaluating all CR participants between 01.01.2017-11.11.2018 in a Cardiovascular and Thoracic Surgery University Hospital. Adult patients older than 18 years of age who were directed to the CR unit and completed all 30 sessions and tests were included in the study. Exclusion criteria were hematological diseases, systemic inflammatory diseases, acute and chronic infection, cancer, autoimmune diseases and steroid treatment. The study was approved by a local ethics committee (Ethical approval: Haydarpaşa Numune Research Hospital Ethics Committee, 09.10.2017 HNEAH-KAEK 2017/KK/112) and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the subjects. Patients' demographic data were collected.

Inflammatory markers

All patients were outpatient patients of the CR unit. Venous blood was drawn at the forearm after 8 hours fasting and was stored in plastic tubes containing EDTA. Absolute and relative white blood cell counts were generated automatically by Mindray BC6800. NLR was calculated as Neutrophil Absolute Count / Lymphocyte Count and TLR as Platelet Count / Lymphocyte Count. CRP was calculated with Architect C16000 with the turbidimetric method. The normal range of CRP was 0-0.5 mg/dl. Sedimentation was calculated with Alifax Test 1 THL automatically.

Functional capacity

Functional capacity was assessed with a 6-minute walk test. The patients were asked to walk as far as possible back and forth around the cones in 6 minutes in a 30 meters pathway. They were permitted to slow down or stop if needed. Conversation with patients during walking was avoided.

Submaximal cycle ergometer test was performed to evaluate endurance. Watts were increased by 25 in every two minutes. Borg scale was used to assess breath and muscle fatigue every two minutes. Arterial blood pressure (ABP) was measured at the beginning and every two minutes afterwards, automatically. Heart rate, SPO_2 and electrocardiogram were monitored continuously during test and recovery periods. In the case of angina, light headedness, confusion, cyanosis, dyspnea, hypoxia, significant muscle pain (Borg Scale $\geq$5) occurrence, ABP >180/100mmHg or reaching submaximal heart rate according to Karvonen formula, the test was stopped prematurely and the maximum watt was calculated.

Cardiac rehabilitation

Tailored CR program was planned for each individual patient according to their cycle ergometer test peak workload. For patients with a low initial test performance, low intensity interval training was prescribed. For those using beta blockers, the exercise program was prescribed independently from heart rate. All core components of CR were tailored to the patients' special needs. The CR program of each patient was evaluated after 10 sessions and updated according to their Borg scales assessed by a rehabilitation nurse during exercise sessions. Each exercise program began with warm-up and ended with recovery periods. Throughout the exercise, the patients' SPO_2, heart rate, ABP and electrocardiogram were continuously monitored. Before cycle ergometer program patients performed stretching exercises under supervision, and strengthening exercises were added to their programs after two weeks. These exercise sessions were designed to work large muscles of upper and lower extremity with 60-80% of maximum load at 10 repetitions for each muscle group.

All patients had NC from a dietitian, PM from a psychologist and patient education from a CR nurse, and

smokers were guided to tobacco cessation polyclinic. All tests were repeated in a week after completion of 30 sessions of CR.

Study endpoints

The Primary endpoint was observation of changes in inflammatory markers (NLR, TLR, Sedimentation, CRP). Secondary endpoint of the study was observation of improvement in functional capacity.

Statistical analysis

NCSS (Number Cruncher Statistical System 2007 Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quarter, third quarter, frequency, percentage, minimum, maximum) were used to evaluate the study data. The normal distribution of quantitative data was evaluated with the Shapiro-Wilk test and graphical investigations. Dependent groups t-test was used for intra-group comparisons of quantitative variables showing normal distribution. Wilcoxon signed-ranks test was used for intragroup comparisons of quantitative variables that did not show normal distribution. The Mann-Whitney U test was used to compare two groups of data that were not normally distributed. Kruskal-Wallis test and double Bonferroni-Dunn test were used in the comparison of the groups with three or more normal distributions. Spearman Correlation Analysis was utilized to evaluate the relationships between variables. The threshold for statistical significance was $P<0.05$.

Results

Among 211 patients enrolled in this the study, 114 (54%) were female and 97 (46%) were male. Average age was 56.28 (10.25) years (min 21 - max 81 years). 94 (44.5%) patients were hypertensive, 24 (11.4%) had heart failure, 83 (39.3%) had coronary artery disease and 10 (4.7%) had arrhythmia. Demographic data of the patients is presented in Table 1. Mean range for the 6-minute walk test was 374.62 (61.75) meters before and 390.80 (62.87) meters after CR ($P<0.001$). Mean values of cycle ergometer effort test maximum watts were 50 watts before and 75 watts after CR ($P<0.001$). Before and after CR, NLR and TLR were 1.6, 1.4 and 107.59 (35.22) and 101.46 (32.78), respectively ($P<0.001$). Sedimentation and CRP levels were 22.38 (11.55) mm/hour, 1.0 mg/dl before and 18.98 (10.06) mm/hour, 0.5 md/dl after rehabilitation, respectively ($P<0.001$). The differences between inflammatory markers and functional capacity before and after CR are shown in Table 2. The changes in inflammatory markers NLR, TLR, Sedimentation and CRP are shown in detail in Figures 1, 2, 3 and 4, respectively. The changes in weight, BMI, functional capacity, sedimentation, and CRP did not significantly affect NLR and TLR (Table 3). NLR and TLR changes were independent from age and sex (Table 4).

Table 1: Demographic data

n=211		n	%
Sex	Female	97	46
	Male	114	56
Disease	Hypertension	94	44.5
	Heart Failure	24	11.4
	Coronary Artery Disease	83	39.3
	Arrhythmia	10	4.7
		Min-Max	Mean (SD)
Age (year)		21-81	56.28(10.15)
Weight(kg)	Before	50-130	80.64(13.32)
	After	50-133	79.44(13.15)

SD: Standard deviation

Table 2: Difference in inflammatory markers and functional capacity before and after CR

	Before Mean (SD)	After Mean (SD)	Difference Mean (SD)	*P*-value
‡NLR	1.6 (1.3, 2.2)	1.4 (1.2, 2)	-0.2 (-0.5, 0.1)	[b]<0.001**
TLR	107.59(35.22)	101.46(32.78)	-6.13(24.65)	[a]<0.001**
‡Sedimentation	20 (20, 20)	20 (14, 20)	0 (-9, 0)	[b]0.001**
‡CRP	1 (0.3, 1)	0.5 (0.2, 1)	0 (-0.5, 0)	[b]<0.001**
‡WBC	7.2 (6.3, 8.5)	6.8 (5.9, 8.1)	-0.5 (-1.2, 0.2)	[b]<0.001**
Platelet	255.33(55.43)	247.14(55.88)	-8.19(38.65)	[a]0.002**
Neutrophil	4.17(1.53)	3.84(1.20)	-0.33(1.15)	[a]<0.001**
Lymphocyte	2.53(0.80)	2.57(0.73)	0.04(0.56)	[a]0.344
MPV	8.14(1.45)	8.53(1.44)	0.39(1.27)	[a]<0.001**
6-minute walk test (meters)	374.62(61.75)	390.80(62.57)	16.18(43.77)	[a]<0.001**
‡Cycle Ergometer Test maximum watts	50 (50, 75)	75 (50, 100)	25 (0, 25)	[b]<0.001**

‡ Data are presented as median (first quarter, third quarter)
[a] Dependent groups t test, [b] Wilcoxon signed-ranks test, *$P<0.05$, **$P<0.01$

Table 3: The relation of NLR and TLR differences to other variables after cardiac rehabilitation

Before and after difference	Before and after difference			
	NLR		TLR	
	r	p	r	*P*-value
Weight (kg)	-0.109	0.115	0.034	0.628
BMI (kg/m^2)	-0.063	0.364	0.022	0.755
6-minute walk test (m)	0.066	0.342	-0.024	0.727
Cycle ergometer test maximum watt	-0.022	0.755	0.044	0.522
Sedimentation	0.019	0.785	0.031	0.650
CRP	0.036	0.601	0.007	0.923

r: Spearman's correlation coefficient, **$P<0.01$, *$P<0.05$

Table 4: Evaluation of NLR and TLR differences according to age and sex

		n	Before-After Difference NLR Median (Q1, Q3)	Before-After Difference TLR Median (Q1, Q3)
Age (year)	< 65 years	168	-0.14 (-0.5, 0.1)	-5.34 (-21.9, 9.4)
	≥ 65 years	43	-0.16 (-0.5, 0.1)	-3.08 (-30, 12.3)
	P-value		0,844	0,987
Sex	Male	97	-0.17 (-0.6, 0.1)	-3.30 (-20, 12.2)
	Female	114	-0.11 (-0.5, 0.1)	-5.34 (-23.5, 7.7)
	P-value		0,515	0,354

Mann Whitney U Test

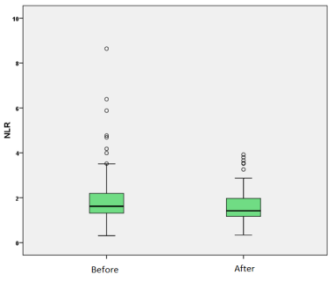

Figure 1: Changes in NLR before and after CR

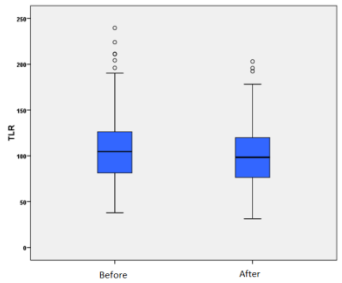

Figure 2: Changes in TLR before and after CR

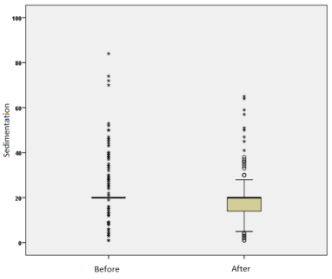

Figure 3: Changes in sedimentation before and after CR

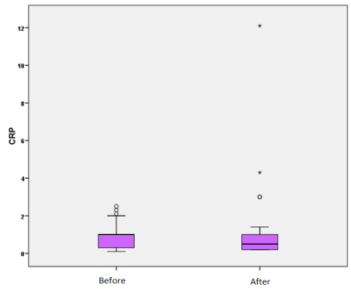

Figure 4: Changes in CRP before and after CR

Discussion

In our study, we investigated the underlying mechanism for the decrease of mortality rates in patients receiving CR. We focused on inflammatory markers which play a key role in atherosclerosis and thromboembolic events [1,2]. Our results show that NLR, TLR, which are mortality-related inflammatory markers, and CRP as well as sedimentation levels decrease and functional capacity increases with comprehensive CR.

CR is known to reduce mortality in cardiac patients with different diagnoses [13-15]. There are a list of core components of CR which are internationally agreed upon: NC, RFM, PM, PE and ET [12]. In a systematic review and network meta-analysis of 148 randomized controlled trials of 50,965 patients, researchers investigated which components are directly linked to decrease in mortality. They concluded that PM, ET, RFM each clearly reduced the hazard of mortality, while PE, ET and PM each reduced the hazard of morbidity. As a result, authors concluded that comprehensive CR has substantial benefits in reducing mortality and morbidity [14]. In our study, patients received all core components of cardiac rehabilitation.

While most studies in the literature focused on the decrease in mortality due to CR, the pathophysiological mechanisms that are at the heart of this reduction are not fully understood.

In cardiac diseases, atherosclerosis, inflammation, and leukocyte recruitment play a major role [1]. Inflammation leads the metabolism to a procoagulant state with help of thrombocytes, causing thrombosis [3]. In light of this knowledge, NLR and TLR are investigated as markers of inflammation and mortality in many cardiac diseases. They are also related to the non-dipper status of the hypertensive patients, resulting in more cardiovascular complications [4,6-9,17]. In a recent study, Fest et al. [18] followed up 8715 individuals for 12 years (2002-2014) to assess NLR association with mortality in the general population and concluded that NLR is a strong and independent risk factor for mortality in elderly population.

In our study we also focused on inflammatory markers (NLR, TLR) as they are directly related to mortality. We showed that after a 30-session comprehensively tailored CR program, the mean NLR value of the patients participating in the program showed a statistically significant decrease of 14.3% from its baseline value. Likewise, the mean TLR value showed a statistically significant decrease of 6% after CR. We further report a statistically significant decrease in other mortality related inflammatory markers, namely, CRP and sedimentation, for 211 patients who attended the comprehensive CR program.

A recent independent and concurrent study also investigated the effect of CR on inflammatory markers in 68 ST-elevated myocardial infarction patients and claimed that chronic inflammation may regress with CR. The limitations of the study, as stated by the authors, were the relatively low cohort number and evaluation of only ST-elevated patients [16]. In comparison, our study had a homogeneous group of cardiac patients and a significantly larger sample size (211 patients).

Another significant result of our study is that the changes in inflammatory markers are irrespective of age and sex. Hence, we claim that regardless of age and gender, everyone can take advantage of CR with the goal of decreasing mortality. Our results which evaluate the increase in functional capacity are also promising. The average range of the 6-minute walk test was extended by more than 15 meters after rehabilitation. The functional capacity, as measured by the cycle ergometer test, increased by 50% on average, as it was 50 watts before and 75 watts after CR. We conclude that functional capacity significantly increases with CR. This data is also compatible with current literature [19].

Inflammation has a significant role in atherosclerosis [1,2]. Elevated inflammatory markers such as thrombocyte-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are linked to high mortality and morbidity in cardiac patients [4,6-9]. Cardiac rehabilitation has been proven to reduce mortality, morbidity and also increase functional capacity in cardiac patients [13-15,19].

The reason cardiac rehabilitation decreases mortality has not yet been shown via blood analysis. We aimed to investigate the effect of cardiac rehabilitation on mortality related inflammatory markers. According to our findings, a comprehensively tailored cardiac rehabilitation program can statistically significantly decrease neutrophil-to-lymphocyte and thrombocyte-to-lymphocyte ratios independent from age and gender, in a wide range of cardiac pathologies. This study shows the vital importance of referring patients diagnosed with cardiac pathologies to a cardiac rehabilitation clinic irrespective of age and gender.

Limitation

This study is a retrospective cohort study, which is its limitation. A prospective study on mortality and functional status with long-time follow up of patients is needed for further enlightenment on this subject.

Conclusion

We conclude that CR decreases the inflammatory markers (TLR, NLR) which are directly related to mortality in cardiac patients while increasing patients' functional capacity. The decrease in mortality-related inflammatory markers is independent from age and gender.

References

1. Libby P. Inflammation in atherosclerosis. Nature. 2002;420:868–74.
2. Libby P, Ridker PM and Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54:2129–38.
3. De Caterina R, D'Ugo E. and Libby P. Inflammation and thrombosis - testing the hypothesis with anti-inflammatory drug trials. Thromb Haemost. 2016;116:1012–21.
4. Gibson PH, Croal BL, Cuthbertson BH, Small GR, Ifezulike AI, Gibson G, et al. Preoperative neutrophil lymphocyte ratio and outcome from coronary artery bypass grafting. Am Heart J. 2007;154(5):995–1002.
5. Dong CH, Wang ZM, Chen SY. Neutrophil to lymphocyte ratio predict mortality and major adverse cardiac events in acute coronary syndrome: A systematic review and meta-analysis, Clinical Biochemistry. 2018;52:131-6.
6. Pourafkari L, Wang CK, Tajlil A, Afshar AH, Schwartz M, Nader ND. Platelet–lymphocyte ratio in prediction of outcome of acute heart failure. Biomarkers in Medicine. 2018;12:63–70.
7. Ommen SR, Hammill SC, Gibbons RJ. The relative lymphocyte count predicts death in patients receiving implantable cardioverter defibrillators. Pacing Clin Electrophysiol 2002;25(10):1424–8.
8. Acanfora D, Gheorghiade M, Trojano L, Furgi G, Pasini E, Picone C, et al. Relative lymphocyte count: a prognostic indicator of mortality in elderly patients with congestive heart failure. Am Heart J. 2001;142(1):167–73.
9. Zouridakis EG, Garcia-Moll X, Kaski JC. Usefulness of the blood lymphocyte count in predicting recurrent instability and death in patients with unstable angina pectoris. Am J Cardiol. 2000;86(4):449–51.
10. Ommen SR, Gibbons RJ, Hodge DO, Thomson SP. Usefulness of the lymphocyte concentration as a prognostic marker in coronary artery disease. Am J Cardiol. 1997;79(6):812–4.
11. Leon AS, Franklin BA, Costa F, Balady GJ, Berra KA, Stewart KJ, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: An American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2005;111:369–76.
12. Balady GJ, Williams MA, Ades P, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: A scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. Circulation. 2007;115:2675–82.

13. Anderson L, Thompson DR, Oldridge N, Zwisler A, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease. Cochrane Database of Systematic Reviews. 2016(1):CD001800.
14. Kabboul NN, Tomlinson G, Francis TA, Sherry LG, Gabriela C, Valeria R, et al. Comparative Effectiveness of the Core Components of Cardiac Rehabilitation on Mortality and Morbidity: A Systematic Review and Network Meta-Analysis. J Clin Med. 2018;7(12):514.
15. Butter C, Groß J, Haase-Fielitz A, Helen S, Cornelia D, Peter B, Michael N. Impact of Rehabilitation on Outcomes after TAVI: A Preliminary Study. J Clin Med. 2018;7(10):326.
16. Fest J, Ruiter TR, Groot Koerkamp B, Dimitris Rizopoulos M, Arfan I, Casper H J van Eijck, et al. The neutrophil-to-lymphocyte ratio is associated with mortality in the general population: The Rotterdam Study Eur J Epidemiol. 2019;34:463.
17. Turgay Yıldırım, Ö, Akşit, E, Aydın F, Hüseyinoglu Aydın A , Dağtekin E .Can neutrophil to lymphocyte ratio and platelet to lymphocyte ratio be used as biomarkers for non-dipper blood pressure? J Surg Med. 2019;3(1):4-7.
18. Zengin İ , Arı S. Effect of cardiac rehabilitation on neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in ST elevation myocardial infarction patients. Eur Res J. 2019;early pub doi: 10.18621/eurj.447027
19. Pasquali SK, Alexander KP, Coombs LP, Lytle BL, Peterson ED. Effect of cardiac rehabilitation on functional outcomes after coronary revascularization. Am Heart J. 2003;145(3):445–51.

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Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine