Review Article

Neutrophil-to-lymphocyte ratio in occlusive vascular diseases: the literature review of the past 10 years

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BACKGROUND: This study aims to evaluate the results of studies investigating neutrophil-to-lymphocyte ratio (NLR) and to identify the prognostic and diagnostic value of NLR in occlusive vascular diseases.

METHODS: With the aim of identifying the studies related to NLR, a search was performed on <http://www.ncbi.nlm.nih.gov/pubmed> by using the key words "neutrophil lymphocyte ratio" between January 2005 and December 2014. All of the original articles were evaluated according to date of publications, countries, clinics and topics. Studies about occlusive vascular diseases were evaluated according to their qualifications, review methods and results. SPSS for Windows 16.0 was used in data analysis and data were expressed as mean, standard deviation and percentage.

RESULTS: A total of 735 original research articles were investigated. The number of publications have shown a regular logarithmic increase over the years. Thirty-two percent of all publications were performed by clinics in Turkey and 56.4% were performed by general-oncological surgery and cardiology clinics. A total of 107 publications were identified to be about occlusive vascular diseases, 80.3% of these publications were found to be prognostic and 19.6% to be diagnostic, 82.2% of them were found to be planned as retrospective and 17.7% as prospective. In 95.3% of prognostic publications, there was a positive correlation between high NLR values at admission and poor prognosis. In 95.3% of diagnostic publications high NLR values at admission were identified to be significant diagnostically.

CONCLUSION: Elevated neutrophil-to-lymphocyte ratio at admission, could be used as a diagnostic and/or prognostic parameter in occlusive vascular diseases.

KEY WORDS: Neutrophil-to-lymphocyte ratio; Occlusive vascular diseases; Publication

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INTRODUCTION

Occlusive vascular diseases are destructive diseases associated with high morbidity and mortality. They are considered to be important reasons for presenting to emergency departments. Atherosclerosis plays an important role in the pathophysiology of occlusive vascular diseases. Coronary artery diseases, cerebrovascular diseases and peripheral arterial diseases are known as the three major syndromes of atherosclerosis.^[1] Atherosclerosis

is a progressive, complex and multifactorial disease characterized by the accumulation of lipids and fibrous elements in the large arteries and inflammation plays an important role in all stages of the atherosclerosis development.^[2,3] Inflammatory processes along with endothelial dysfunction initiate a progressive process within the arterial wall, resulting in the reduction or obstruction of blood supply to end organs of the body.^[2,4] The neutrophil-to-lymphocyte ratio (NLR) has been shown

to be a marker of inflammation and closely related to increased cardiovascular mortality and morbidity.^[5,6]

This study aims to evaluate the studies that investigating NLR and to identify the prognostic and diagnostic value of NLR as an inexpensive and easy-to-access parameter in occlusive vascular diseases.

METHODS

With the aim of identifying the studies published in journals within the scope of Index Medicus, where neutrophil lymphocyte ratio is investigated, a search was performed between the dates 1/1/2005 and 12/31/2014 by using the key words "neutrophil lymphocyte ratio" on <http://www.ncbi.nlm.nih.gov/pubmed> on May, 2015. PubMed database was chosen because of the fact that it is widely used all around the world and for its large content made up of 5 600 medical journals in various languages.^[7] The electronic publication date of the articles that have been published electronically but not submitted for printing yet was accepted as the date of publication in our study. As research methodology, studies were gathered under 4 main titles: original research article, review, case report and letter to the editor. Publications were required to be published as an original research article about NLR. Publications outside of medical science were excluded from the study.

All of studies gathered as original research articles were evaluated according to their date of publications, countries, clinics and reviewed topics. Additionally studies about occlusive vascular diseases were identified and evaluated according to their qualifications (diagnostic or prognostic), review methods (retrospective or prospective) and results. Full texts of all articles were obtained and information not within the data acquired from PubMed were completed from these articles. Two members of the research team (E.K., I.K.) reviewed the relevant literature according to the STARD Statement guidelines.^[8] Researchers used the STARD checklist to evaluate the results of the studies.

Statistical analysis

Data was analyzed using SPSS for Windows 16.0 (SPSS: An IBM Company, version 16.0, IBM Corporation, and Armonk, New York, USA). Data is expressed as mean, standard deviation and percentage.

RESULTS

Totally 1 338 studies were found after searching PubMed database. Among these studies, 79 were

identified as letters to the editor, 5 as case reports and 4 as reviews and they were excluded from the study. Of the remaining 1 250 studies, 116 were identified to be performed by veterinary department, 19 by biology department, 9 by dentistry, 4 by sport academy and 15 by various engineering departments and they were excluded from the study. After reviewing the remaining 1 087 publications, 352 of them were identified as irrelevant to NLR and they were excluded from the study. As a result, a total of 735 publications as original research articles reviewing NLR were included in the study.

Distribution by year of publication shows that, number of publications have shown a regular logarithmic increase, especially over the last 3 years there has been an important increase and 84.6% ($n=622$) of all publications were performed within the last 3 years. Distribution by year of publication is shown in Figure 1.

Evaluation of publication country shows that 32% ($n=240$) of all publications were performed in Turkey and the rest is as follows: China (13%, $n=97$), England (9%, $n=71$), Japan (9%, $n=68$) and USA (7%, $n=54$). Distribution of publications according to countries is shown in Figure 2.

Evaluation of clinics of publications reveal that 56.4% ($n=415$) of all publications were performed by general surgery-oncological surgery, cardiology

Figure 1. Distribution of publications according to the publication date.

Figure 2. Distribution of publications according to countries.

Figure 3. Distribution of publications according to clinics.

and oncology clinics. Distribution of the publications according to clinics is shown in Figure 3.

When evaluated in terms of topics of publications, it was found that 53% ($n=391$) of the publications were about oncological diseases and 23% ($n=172$) of the publications pertained to cardiovascular diseases. The rest of the disease groups is as follows: endocrine diseases (3.2%, $n=24$), nephrological diseases (2.9%, $n=22$) and infectious diseases (2.8%, $n=21$). Colorectal (18%, $n=73$) and liver cancers (12%, $n=50$) were the most frequently reviewed oncological diseases. Occlusive coronary artery disease was reviewed in 48% ($n=84$) of cardiovascular diseases. Diabetes mellitus was the most frequently reviewed endocrinological disease (62%, $n=15$). Eighty-one percent ($n=18$) of the publications about nephrological diseases were identified to review end-stage renal disease and dialysis topics. Sepsis (38%, $n=8$), Hepatitis B-C infections (28%, $n=6$) and malarial infections (14%, $n=3$) were the most reviewed infectious diseases.

A total of 107 publications were identified to be about occlusive vascular diseases, when the publications about cardiovascular diseases were evaluated. Eighty-four of them were found to review the topics of occlusive coronary diseases, 9 of peripheral arterial occlusion, 8 of ischemic cerebrovascular disease, and 6 of venous thromboembolism and pulmonary embolism.

When publications about occlusive vascular diseases were evaluated in terms of their qualifications and review methods, 86 (80.3%) of them were prognostic and 21 (19.6%) were diagnostic. Eighty-eight (82.2%) publications were retrospective studies and 19 (17.7%) were prospective. Sixty-eight of publications about occlusive coronary artery diseases were prognostic (56 retrospective, 12 prospective) and 16 were diagnostic

(15 retrospective, 1 prospective). All of the 9 studies reviewing peripheral arterial occlusion were prognostic (5 retrospective, 4 prospective). Six of the publications reviewing ischemic cerebrovascular disease were prognostic (5 retrospective, 1 prospective) and 2 were diagnostic (1 retrospective, 1 prospective). Three of the publications reviewing venous thromboembolism and pulmonary embolism were prognostic and 3 were diagnostic and all publications were found to be planned as retrospective.

After evaluating the results of all these publications about occlusive vascular diseases, it was found that in 95.3% ($n=82$) of prognostic publications, a positive correlation between high NLR values at admission and poor prognosis was identified but not an important difference was found in 4.6% ($n=4$). In 95.3% ($n=20$) of diagnostic publications high NLR values at admission were identified to be significant diagnostically and 4.7% ($n=1$) were found to have no significant difference.

DISCUSSION

In 12 prognostic studies evaluating the severity of coronary artery disease, the relationship between NLR values at admission and the severity of angiographically determined coronary artery disease was reviewed by using scoring systems like Syntax, Gensini, Electrocardiographic Ischemic Grade and Grace. In all these publications, a significant positive correlation between high NLR values at admission and the severity of coronary artery disease was found. In a prognostic study conducted by Açar et al^[9] the relationship between the CT angiographically determined expansion and severity of coronary atherosclerotic plaques and NLR values at admission were reviewed. It was reported that high NLR values in clinical practice could be a useful parameter in evaluating cardiovascular risk. In another study conducted by Arbel et al^[10] the severity of coronary artery disease was identified by an interventional cardiologist and the relationship between NLR values at admission and the severity of coronary artery disease was evaluated. In this study a positive correlation between NLR values at admission and the severity of coronary artery disease was found. A study conducted by Kalay et al^[11] reviewed 394 patients with recurring need of coronary angiography and NLR values of patients were determined before angiography. According to angiography reports, patients were separated into two groups as progressive and non-progressive coronary

artery diseases. This study reported that high NLR values could be the determinant of coronary atherosclerosis progression. In 2 prognostic studies about coronary artery diseases, the relationship between NLR values at admission and coronary atherosclerotic plaque components was reviewed. In both studies, high NLR values at admission were identified to be more with rupture-prone coronary atherosclerotic plaque components.^[12,13] In 4 prognostic studies, the relationship between NLR values at admission and angiographically determined coronary thrombus load were examined. While 3 of these studies found high NLR values to be associated with coronary thrombus formation, Tanboga et al^[14] found that patients with high NLR values were identified to have high thrombus load but it was reported to be statistically non-significant. And 5 prognostic studies reviewed the relationship between NLR values at admission and coronary arteries that developed infarct. In all of these studies spontaneous reperfusion development was associated with low NLR values at admission and high NLR values were identified in the group that didn't develop spontaneous reperfusion.

In 23 of 24 publications reviewing the relationship between short and/or long term mortality of coronary artery disease and NLR values at admission, pre-intervention high NLR values were found to be associated with short and/or long term mortality significantly. A study conducted by Kruk et al^[15] found no significant relationship between pre-intervention NLR values and early stage mortality. One of these studies, reported pre-intervention high NLR values to be associated with high VF rates and in another study high NLR values during presentation were associated with impaired myocardial perfusion.^[16,17] In two of these studies, high NLR values at admission were associated with high mortality and heart failure.^[18,19] And a positive correlation was found between high NLR values at admission and stent thrombosis in another study.^[20] Two of the studies, reviewed the relationship between NLR values at admission and after intervention and prognosis. He et al^[21] found high average NLR values to be associated with poor prognosis and Núñez et al^[22] found maximum NLR values to show a positive correlation with poor prognosis. In 7 studies reviewing mortality and prognosis in coronary artery diseases, primary pre-intervention NLR values and post-intervention coronary blood flow velocity were reviewed and in all of these publications high NLR values during presentation were found to be associated with post-intervention "no-reflow" phenomenon and poor prognosis. In a prospective

planned study, Papa et al^[6] monitored the patients with stable coronary artery disease and found that cardiac mortality was significantly higher in the patients with high NLR values. In another prospective study conducted by Shah et al,^[23] 7 363 healthy US citizens were examined for 14.1 years and the mortality associated with coronary artery diseases was identified to be more in the asymptomatic general population with high NLR values. A study by Park et al^[24] observed 325 patients with coronary artery disease with primary intervention and reviewed NLR, neutrophil and leukocyte values of the patients during presentation and after 24 hours. A total of 25 patients were identified to be dead after 24 hours and NLR and neutrophil values in these patients were increased and leukocyte values were decreased after 24 hours. High NLR values 24 hours after presentation were associated with significantly higher mortality and a more intense treatment has to be given to those patients. A study by Çiçek et al^[25] evaluated PLR and NLR values during presenting. High PLR and NLR values were reported to be associated with significant mortality when used together. And a study by Cho et al^[26] reported that high Hb and NLR values were associated with significant mortality in coronary artery diseases when evaluated together. Boles et al^[27] reviewed the development of coronary artery ectasia and short term prognosis. In AMI patients developing coronary artery ectasia, NLR values were identified to be lower compared to AMI patients not developing ectasia and also inflammatory response between the patients with developing and not developing coronary artery ectasia were reported to be different but this was indicated to have no prognostic value. Çanga et al,^[28] found an association between high osteoprotegerin value at admission and poor prognosis after primary intervention as well as high NLR values in patients with acute coronary syndrome. In a study by Tanındı et al,^[29] primary pre-intervention NLR, total bilirubin and uric acid values in patients with acute coronary syndrome and arterial stenosis and central arterial wave reflection were evaluated. This study reported that NLR, total bilirubin and uric acid values in coronary artery diseases in the presence of especially acute coronary syndrome could be used in the risk classification of patients according to arterial stenosis. In a study by Doğdu et al,^[30] the relationship between hematological parameters in patients with multivessel coronary artery disease and left ventricular systolic dysfunction was reviewed. This study found a positive correlation between impaired left ventricular systolic functions and high NLR values in patients with multivessel coronary artery disease.

In a similar way with our study, Guasti et al^[31] performed a systemic literature review and identified 21 publications reviewing the relationship between the clinical results in patients with acute coronary syndrome and/or cardiac revascularization and NLR values and evaluated the clinical results accordingly. In this study, determining role of inflammatory markers in terms of risk classification in patients with acute coronary syndrome and/or cardiac revascularization was indicated in a similar way with our study. And again in a similar study, Wang et al^[32] evaluated the results of 13 studies reviewing the relationship between NLR values in patients who underwent angiography or cardiac revascularization and the mortality or cardiovascular incidents. This study reported the NLR value to be a determinant of mortality and cardiovascular incidents.

In a total of 6 studies evaluating NLR values for diagnostic purposes, NLR values were significantly higher in patients with acute coronary artery disease. In a study conducted by Parajapati et al,^[33] NLR values were significantly higher in coronary artery patients with low HDL levels. Mayyas et al^[34] found that NLR values were significantly higher in patients who had myocardial infarction compared to patients with stable coronary artery disease. This study also found higher NLR values in patients with ST-elevation myocardial infarction compared to patients with non-ST-elevation myocardial infarction. Demir et al^[35] found that NLR values in patients with coronary total occlusion were significantly increased compared to coronary artery patients and the control group. Korkmaz et al^[36] found that NLR values in patients with troponin positive coronary artery were significantly higher compared to patients with troponin negative coronary artery disease. This indicated that high NLR values could be a parameter to foresee troponin positive patients in emergency departments.

In 5 studies reviewing acute coronary syndromes for diagnostic purposes, coronary collateral circulation was evaluated in patients with coronary artery disease. In all of these studies, patients with poor coronary collateral circulation had significantly higher NLR values. Two of these studies evaluated patients with coronary chronic total occlusion and three of these studies evaluated patients with stable coronary artery disease. Karabay et al^[37] described the relationship between the development of coronary artery aneurysm after stent implantation in patients with ST-elevation myocardial infarction treated with primary percutaneous coronary intervention and pre-intervention NLR values. In this study NLR values in patients with coronary artery aneurysm were significantly

higher compared to patients without aneurysm. Another study by Kaya et al^[38] reviewed the relationship between contrast-induced nephropathy in patients who received primary percutaneous coronary intervention and NLR values. In this study, NLR values were significantly higher in patients with contrast-induced nephropathy. And in a study by Turak et al,^[39] the relationship between stent restenosis in patients with coronary stent implantation and pre-intervention NLR values was reviewed. In this study pre-intervention NLR values were reported to be a strong and independent determinant of stent restenosis in patients with stable and unstable angina pectoris. Kocaman et al^[40] reviewed the relationship between the traditional cardiovascular risk factors and leukocyte subgroups and reported a significant positive correlation between NLR and age. A study conducted by Nordestgaard et al^[41] investigated the characteristics of various biomarkers to determine a myocardial infarction that can develop in 4 years. In this study while alpha 1 antitrypsin, C reactive protein, creatinine, serum iron and fibrinogen were identified to be associated with increased myocardial infarction, it was indicated that there is no such correlation with NLR.

All the studies reviewing NLR and peripheral arterial occlusion were found to be prognostic. In 7 of these studies pre-operative high NLR values during presentation were significantly associated with poor prognosis in peripheral arterial occlusive diseases. A prospective study by Kullar et al^[42] reviewed the relationship between post-operative NLR values and graft failure that can develop afterwards and post-operative high NLR values were found to be associated with graft failure. Another study by Demirtaş et al^[43] prospectively reviewed 50 patients with the diagnosis of new peripheral arterial occlusion. In this study pre-operatively taken complete blood count parameters were examined according to Fontaine's classification. Consequently in this study while RDW and MPV values in peripheral arterial occlusion were identified to increase with the severity of atherosclerosis disease, NLR values showed no significant change.

Six of the studies evaluating the relationship between ischemic cerebrovascular disease and NLR were reported to be prognostic. In 5 of these studies, high NLR values at admission were found to be associated with poor prognosis in patients with ischemic cerebrovascular disease. A study by Brouns et al^[44] reviewed the relationship between kynurenine/tryptophan ratio at admission in patients with ischemic cerebrovascular disease and inflammatory response due to stroke severity

and infarction. High kynurenine/tryptophan ratio was found to be associated with high stroke severity and infarction volume. Also in this study a positive correlation was reported between high kynurenine/tryptophan ratio and NLR. Two studies evaluating the relationship between ischemic cerebrovascular disease and NLR were identified to be diagnostic. In one of these studies Lee et al^[45] reported that increased C-reactive proteins is one of the major acute phase reactants in ischemic cerebrovascular disease and evaluated the relationship between C-reactive proteins and MPV, erythrocyte sedimentation rate and NLR in patients with ischemic cerebrovascular disease. In this study they found a significant correlation between C-reactive protein and MPV, Erythrocyte Sedimentation Rate and NLR and indicated that NLR values could be used in patients with cerebral infarction. Akıl et al^[46] evaluated the relationship between ischemic cerebrovascular disease diagnosis and echocardiographic epicardial fat thickness and NLR. In this study epicardial fat thickness in ischemic cerebrovascular disease patients and NLR values were identified to be increased compared to the control group. There was also a correlation between epicardial fat thickness and NLR values.

Three of the studies reviewing the relationship between NLR, venous thromboembolism and pulmonary embolism were prognostic. In all of these studies high NLR values during presentation were found to be associated with poor prognosis. In one of these studies, Akgüllü et al^[47] indicated high NLR values at admission to be a more powerful prognostic determinant than Simplified Pulmonary Embolism Severity Index score. Three of the studies reviewing the relationship between NLR, venous thromboembolism and pulmonary embolism were diagnostic. In all of these studies increased NLR values at admission were identified to have a diagnostic role in Pulmonary Embolism. In a study by Bakirci et al,^[48] NLR values in patients with deep vein thrombosis and pulmonary embolism were found to be significantly higher compared to the control group. There was also a positive correlation between high NLR levels and venous thromboembolism severity. In another study by Keskin et al,^[49] pulmonary embolism development in patients with cancer patients receiving chemotherapy was associated with high NLR values.

There are several potential limitations in this study. This study is limited within the PubMed database and does not include reviews published in some of the international and national journals. This is the most important limitation of this study; however, data acquired

from PubMed database includes a significant part of the existing literature, so it was thought that it doesn't constitute an impediment to have an opinion about the whole literature.

Elevated neutrophil-to-lymphocyte ratio at admission, could be used as a diagnostic and/or prognostic parameter in occlusive vascular diseases. However, more prospective studies about this topic are required.

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Contributors: Egemen K proposed the study and wrote the first draft. All authors read and approved the final version of the paper.

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