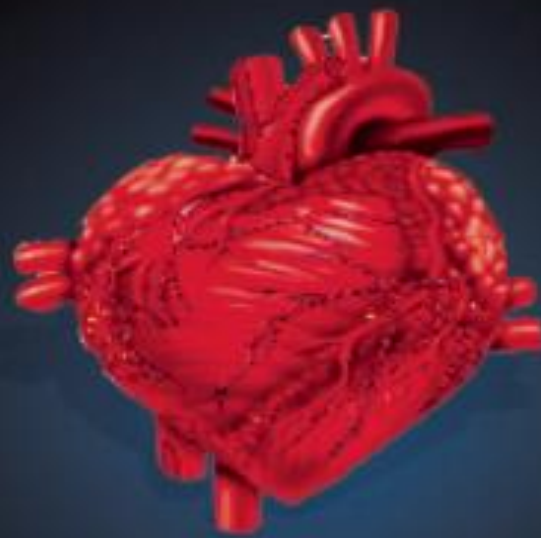


www.ijcva.com


ISSN: 2405-5181  
E-ISSN: 2405-519X

# INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

VOLUME 4 - ISSUE 4 - October - December 2015



 **CARDIOVASCULAR**  
ACADEMY SOCIETY

 Walters Kluwer

Medknow

# International Journal of the Cardiovascular Academy

## EDITORIAL BOARD

### EDITORS-IN-CHIEF

Prof. Dr. Oktay Ergene,  
9 Eylül University,  
Cardiology, Izmir-Turkey

### STATISTICS CONSULTANT

Prof. Dr. Vildan Mevsim,  
9 Eylül University, Department of Public  
Health, Izmir-Turkey

Prof. Dr. Mehdi Zoghi,  
Ege University, Cardiology, Izmir-Turkey

Prof. Dr. Ömer Kozan,  
Sağlık Bilimleri Üniversitesi, Dr Siyami Ersek  
Thoracic and  
Cardiovascular Surgery Training and Research  
Hospital,  
Cardiology, Izmir-Turkey

### EDITORIAL BOARD CHAIRS

Assoc. Prof. Dr. Ertuğrul Okuyan,  
Sağlık Bilimleri Üniversitesi, Bağcılar Training and  
Research Hospital, cardiology, Istanbul-Turkey

Assoc. Prof. Dr. Gönenç Kocabay,  
Cardiology, Istanbul-Turkey

Dr. Özgen Şafak,  
Burdur State Hospital, Cardiology, Burdur-Turkey

## ADVISORY BOARD MEMBERS

**Prof. Dr. Antonello Gavazzi**

Bergamo-Italy

**Prof. Dr. Tofiq Cahangirov**

Baku, Azerbaijan

**Prof. Dr. Elif Sade**

Ankara-Turkey

**Prof. Dr. Bülent Görenek**

Eskişehir-Turkey

**Assoc. Prof. Dr. Claudio Molinari**

Novara- Italy

**Dr. Cemil İzgi**

London, UK

**Assoc. Dr. Gulnaz Dadashova**

Baku, Azerbaijan

**Assoc. Prof. Dr. Hasan Güngör**

Aydın-Turkey

**Dr. Jyoti Bala**

Miami, Florida-USA

**Prof. Dr. Bülent Boyacı**

Ankara-Turkey

**Dr. Gerald Chi**

Boston, Massachusetts-USA

**Assist. Prof. Hatice Kemal**

Nicosia, Cyprus

**Prof. Dr. Tevfik Ecder**

Istanbul-Turkey

**Prof. Dr. Padmavathi Kora**

Hyderabad, Telangana-India

**Prof. Dr. Raimund Erbel**

Essen-Germany

**Dr. Saravanan Subramaniam**

Chapel Hill, North Carolina-USA

**Prof. Dr. Masatsugu Hori**

Osaka-Japan

**Dr. Firdovsi Ibrahimov**

Baku-Azerbaijan

**Assoc. Prof. Dr. Balambigai Subramanian**

Perundurai, Tamilnadu-India

**Prof. Dr. Nataša Marković- Nikolić**

Belgrade-Serbia

**Assoc. Prof. Babak Sharif-Kasahi**

Tehran-Iran

**Prof. Dr. Nazmi Narin**

Kayseri-Turkey

**Prof. Dr. Ilgin Karaca**

Elazığ-Turkey

**Dr. Raffaele Piccolo**

Switzerland

**Prof. Dr. Güliz Kozdağ**

Florida-USA

**Prof. Dr. Bambang Budi Siswanto**

Jakarta-Indonesia

**Dr. Ümit Yaşar Sinan**

Istanbul-Turkey

**Prof. Dr. Nurgül Keser**

Sakarya-Turkey

**Dr. Emanuele Bobbio**

Gothenburg-Sweden

**Dr. Chin Siang Ong**

Baltimore, Maryland-USA

**Prof. Dr. Massimo Santini**

Rome-Italy

**Dr. Pradeep Kumar**

Johannesburg, Gauteng, South Africa

**Dr. Yasmin Rustamova**

Baku, Azerbaijan

**Assoc. Prof. Dr. Tolga Aksu**

Kocaeli-Turkey

**Assoc. Prof. Mahdi Najafi**

Tehran-Iran

**Pratik Kalsaria**

Dallas, Texas-USA

**Assoc. Prof. Dr. Kaan Okyay**

Ankara-Turkey

# International Journal of the Cardiovascular Academy

## GENERAL INFORMATION

### The journal

International Journal of the Cardiovascular Academy or IJCA (ISSN: Print-2618-6012, Online 2405-8181) is a peer-reviewed journal published on behalf of the Turkish Cardiovascular Academy Society. The journal publishes information relating to Cardiologists, cardiothoracic surgeons, internists, radiologists, pulmonologists and physicians in training. The journal is published quarterly in March, June, September and December.

### Information for Authors

There are no page charges for submissions to the journal. Please check <http://www.ijcva.com/contributors.asp> for details. All manuscripts must be submitted online at <http://www.ijcva.com/>.

### Subscription Information

Copies are sent to the members of International Journal of the Cardiovascular Academy free of cost. A subscription to International Journal of the Cardiovascular Academy comprises 4 issues. Prices include postage. Annual Subscription Rate for non-members-

- Institutional: INR 6000 for India and  
USD 300 for outside India
- Personal: INR 4000 for India and  
USD 200 for outside India

For mode of payment and other details, please visit [www.medknow.com/subscribe.asp](http://www.medknow.com/subscribe.asp).

Claims for missing issues will be serviced at no charge if received within 60 days of the cover date for domestic subscribers, and 3 months for subscribers outside India.

The journal is published and distributed by Wolters Kluwer India Private Limited.

If any member/subscriber wishes to receive the copies by registered post or courier, kindly contact the publisher's office. Providing complete, correct and up-to-date address is the responsibility of the member/subscriber.

### Advertising policies

The journal accepts display and classified advertising. Frequency discounts and special positions are available. Inquiries about advertising should be sent to Wolters Kluwer India Private Limited, [advertise@medknow.com](mailto:advertise@medknow.com)

The journal reserves the right to reject any advertisement considered unsuitable according to the set policies of the journal.

The appearance of advertising or product information in the various sections in the journal does not constitute an endorsement or approval by the journal and/or its publisher of the quality or value of the said product or of claims made for it by its manufacturer.

### Copyright

The entire contents of the International Journal of the Cardiovascular Academy are protected under Indian and international copyrights.

The Journal, however, grants to all users a free, irrevocable, worldwide, perpetual right of access to, and a license to copy, use, distribute, perform and display the work publicly and to make and distribute derivative works in any digital medium for any reasonable non-commercial purpose, subject to proper attribution of authorship and ownership of the rights. The journal also grants the right to make small numbers of printed copies for their personal non-commercial use.

### Permissions

For information on how to request permissions to reproduce articles/information from this journal, please visit <http://www.ijcva.com/>

### Disclaimer

The information and opinions presented in the Journal reflect the views of the authors and not of the Journal or its Editorial Board or the Society or the Publisher. Publication does not constitute endorsement by the journal. Neither the International Journal of the Cardiovascular Academy nor its publishers nor anyone else involved in creating, producing or delivering the International Journal of the Cardiovascular Academy or the materials contained therein, assumes any liability or responsibility for the accuracy, completeness, or usefulness of any information provided in the International Journal of the Cardiovascular Academy, nor shall they be liable for any direct, indirect, incidental, special, consequential or punitive damages arising out of the use of the International Journal of the Cardiovascular Academy. The International Journal of the Cardiovascular Academy, nor its publishers, nor any other party involved in the preparation of material contained in the International Journal of the Cardiovascular Academy represents or warrants that the information contained herein is in every respect accurate or complete, and they are not responsible for any errors or omissions or for the results obtained from the use of such material. Readers are encouraged to confirm the information contained herein with other sources.

### Addresses

#### Editorial Office

Prof. Dr. Mehdi Zoghi  
Ege University, Faculty of Medicine Internal Medicine,  
Department of Cardiology  
Bornova, 3100, Izmir - Turkey  
Telephone: +90 232 - 3905458  
E-mail: [mehdi\\_zoghi@hotmail.com](mailto:mehdi_zoghi@hotmail.com)

#### Published by

Wolters Kluwer India Private Limited  
A-202, 2<sup>nd</sup> Floor, The Qube,  
C.T.S. No.1498A/2 Village Marol, Andheri (East),  
Mumbai - 400 059, India.  
Phone: 91-22-66491818  
Website: [www.medknow.com](http://www.medknow.com)

# International Journal of the Cardiovascular Academy

October-December 2018

Volume 4

Issue 4

## CONTENTS

### ORIGINAL ARTICLES

- Is there a Correlation between Systolic Heart Failure and Levels of Toll-Like Receptor-5 and N-Terminal Pro-B-Type Natriuretic Peptide?**  
*Cetin Mirzaoglu, Tarik Kivrak, Mehmet Balin, Mehmet Ali Kobat, Orhan Dogdu, Ilgin Karaca* ..... 65
- Predictive Values of Inflammatory Cell Ratios for Complexity of Coronary Artery Disease in Patients with Acute Coronary Syndrome**  
*Ahmet Karakurt, Cennet Yildiz* ..... 70
- Comparison of Anthropometric Indices in Predicting the Risk of Hypertension, Iran - 2014**  
*Hossein Lashkardoost, Fateme Hoseyni, Elham Rabbani, Farzane Qorbani Moqadam, Leila Hosseini, Salimeh Azizi, Andishe Hamedi* ..... 77
- The Predictors of Long-Term Hospitalization in Turkish Heart Failure Population: A Subgroup Analysis of Journey Heart Failure-TR Study: On Behalf of Journey Heart Failure-TR Investigators**  
*Umit Yasar Sinan, Mehmet Erturk, Erkan Yildirim, Duygu Koçyiğit, Ilgin Karaca, Faruk Ertas, Ahmet Celik, Fatih Aksoy, Hasan Ali Gumrukcuoglu, Umit Yuksek, Mahir Cengiz, Mehdi Zoghi* ..... 82
- Potential Factors Affecting the Anticoagulation Control in Patients Treated with Warfarin: Results WARFARIN-TR Study**  
*Salih Kilic, Ahmet Çelik, Ali Sabri Seyis, Ozge Kurmus, Kamil Tülüce, Zeynep Yapan Emren, Ali Kemal Kalkan, Mehdi Zoghi* ..... 86
- Association of Neutrophil to Lymphocyte Ratio with Lower Patency Rates among Patients with Infrapopliteal Arterial Disease Undergoing Balloon Angioplasty**  
*Abdulkadir Uslu, Regayip Zehir, Elnur Alizade, Ayhan Küp, Zubeyde Bayram, Ahmet Guner, Süleyman Barutcu* ..... 90

# International Journal of the Cardiovascular Academy on Web

<http://www.journalonweb.com/ijca>

The International Journal of the Cardiovascular Academy now accepts articles electronically. It is easy, convenient and fast. Check following steps:

## 1 Registration

- Register from <http://www.journalonweb.com/ijca> as a new author (Signup as author)
- Two-step self-explanatory process

## 2 New article submission

- Read instructions on the journal website or download the same from manuscript management site
- Prepare your files (Article file, First page file and Images, Copyright form & Other forms, if any)
- Login as an author
- Click on 'Submit new article' under 'Submissions'
- Follow the steps (guidelines provided while submitting the article)
- On successful submission you will receive an acknowledgement quoting the manuscript ID

## 3 Tracking the progress

- Login as an author
- The report on the main page gives status of the articles and its due date to move to next phase
- More details can be obtained by clicking on the ManuscriptID
- Comments sent by the editor and reviewer will be available from these pages

## 4 Submitting a revised article

- Login as an author
- On the main page click on 'Articles for Revision'
- Click on the link "Click here to revise your article" against the required manuscript ID
- Follow the steps (guidelines provided while revising the article)
- Include the reviewers' comments along with the point to point clarifications at the beginning of the revised article file.
- Do not include authors' name in the article file.
- Upload the revised article file against New Article File - Browse, choose your file and then click "Upload" OR Click "Finish"
- On completion of revision process you will be able to check the latest file uploaded from Article Cycle (In Review Articles-> Click on manuscript id -> Latest file will have a number with 'R', for example XXXX\_100\_15R3.docx)

## Facilities

- Submission of new articles with images
- Submission of revised articles
- Checking of proofs
- Track the progress of article until published

## Advantages

- Any-time, any-where access
- Faster review
- Cost saving on postage
- No need for hard-copy submission
- Ability to track the progress
- Ease of contacting the journal

## Requirements for usage

- Computer and internet connection
- Web-browser (Latest versions - IE, Chrome, Safari, FireFox, Opera)
- Cookies and javascript to be enabled in web-browser

## Online submission checklist

- First Page File (rtf/doc/docx file) with title page, covering letter, acknowledgement, etc.
- Article File (rtf/doc/docx file) - text of the article, beginning from Title, Abstract till References (including tables). File size limit 4 MB. Do not include images in this file.
- Images (jpg/jpeg/png/gif/tif/tiff): Submit good quality colour images. Each image should be less than 10 MB) in size
- Upload copyright form in .doc / .docx / .pdf / .jpg / .png / .gif format, duly signed by all authors, during the time mentioned in the instructions.

## Help

- Check Frequently Asked Questions (FAQs) on the site
- In case of any difficulty contact the editor

# Is there a Correlation between Systolic Heart Failure and Levels of Toll-Like Receptor-5 and N-Terminal Pro-B-Type Natriuretic Peptide?

Cetin Mirzaoglu, Tarik Kivrak<sup>1</sup>, Mehmet Balin<sup>1</sup>, Mehmet Ali Kobat<sup>1</sup>, Orhan Dogdu<sup>2</sup>, Ilgin Karaca<sup>1</sup>

Department of Cardiology, Elazig State Hospital, <sup>1</sup>Department of Cardiology, Firat University Hospital, <sup>2</sup>Department of Cardiology, Elazig Medical Park Hospital, Elazig, Turkey

## Abstract

**Objective:** Specific biomarkers are essential in the diagnosis of heart failure. Our trial aim is determined that relationship between toll-like receptor-5 (TLR-5) and N-terminal pro-B-type natriuretic peptide (NT-ProBNP) in patients with reduced ejection fraction. **Methods:** Two groups were formed in our study (normal and patient group). Among the two groups were investigated that relationship between TLR-5 and NT-ProBNP. **Results:** The plasma levels of both NT-ProBNP and TLR-5 are significantly higher in patients with congestive heart failure than healthy individuals. However, there is no definite correlation between plasma levels of NT-ProBNP and TLR-5 in patients with congestive heart failure. The high-level plasma TLR-5 is of prognostic value independent from the plasma NT-ProBNP levels, in these patients. **Conclusion:** As a conclusion, according to recent studies, the high plasma levels of NT-ProBNP and TLR-5 are mainly associated with high mortality and longer hospitalization rate in individuals with heart failure. Therefore, the higher is plasma levels of markers such as TLR-5 and NT-ProBNP, the worse is the overall prognosis in these patients. NT-ProBNP and TLR-5 are thought to be the cheapest and the most appropriate marker to be determined.

**Keywords:** N-terminal pro-B-type natriuretic peptide, systolic heart failure, toll-like receptor

## INTRODUCTION

Heart failure is a syndrome that occurs as a result of a decline in the ability of the heart to send enough blood to the tissues to meet the changing oxygen and metabolic needs of the body. Today, the clinic and echocardiographic findings of the patients have an essential role in the diagnosis of heart failure. However, new generation biochemical markers of cardiac ventricle origin may give important clues for the determination of heart failure, and further studies on finding newer cardiac markers are continuing worldwide. Many biochemical parameters are used in the diagnosis of heart failure.<sup>[1]</sup> The heart muscle is also an endocrine system besides its blood-pumping task. In this context, atrial natriuretic peptide is secreted from the atrium and brain natriuretic peptide (BNP) is emitted from the ventricle in response to the tension of myocyte cells in the atrium and ventricle walls of the heart. N-terminal pro-B-type natriuretic peptide (NT-ProBNP) is today meaningful for the preliminary diagnosis of heart failure. NT-ProBNP type

natriuretic peptide is a diuretic peptide synthesized in the ventricular myocardium but released into the plasma only in response to the left heart failure conditions such as the increase in the intraventricular volume, wall tension, and end diastolic pressure. Its specificity and sensitivity for diagnosing heart failure were published about 95% in the 2001 Practical Guideline of American College of Cardiology and American Heart Association. It is a valuable non-invasive method even for the heart failure cases who are still in the asymptomatic phase. It is also known that heart failure has inflammatory processes. Toll-like receptor-5 (TLR-5) as an inflammatory marker can give us illuminating information about this disease. The most commonly used method of diagnosis is

**Address for correspondence:** Dr. Tarik Kivrak,  
Department of Cardiology, Firat University Hospital, Elazig, Turkey.  
E-mail: tarikivrak@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Mirzaoglu C, Kivrak T, Balin M, Kobat MA, Dogdu O, Karaca I. Is there a correlation between systolic heart failure and levels of toll-like receptor-5 and N-terminal pro-B-type natriuretic peptide? *Int J Cardiovasc Acad* 2018;4:65-9.

### Access this article online

#### Quick Response Code:



**Website:**  
<http://www.ijcva.com>

**DOI:**  
10.4103/IJCA.IJCA\_41\_18

echocardiography (ECG). However, the need for experienced physicians, the cost and duration of ECG may be found less advantageous compared to biochemical parameters. Plasma NT-ProBNP and TLR-5 measurements seem more beneficial than ECG because they are inexpensive, easy to measure, measurable in a short time and easy to evaluate. In this study; we measured plasma NT-ProBNP and TLR-5 levels in patients who are diagnosed with clinical and echocardiographic heart failure. We investigated if the role of echocardiographic findings and these two biochemical markers are concordant in the diagnosis of heart failure. Hence in this study, comparison of two different methods in the diagnosis of heart failure is the issue. We tried to determine the superiority of these two approaches to diagnose heart failure; TLR-5 and NT-ProBNP method which is cheaper and more accessible, and ECG method which is expensive, time-consuming and requires the experienced physician.

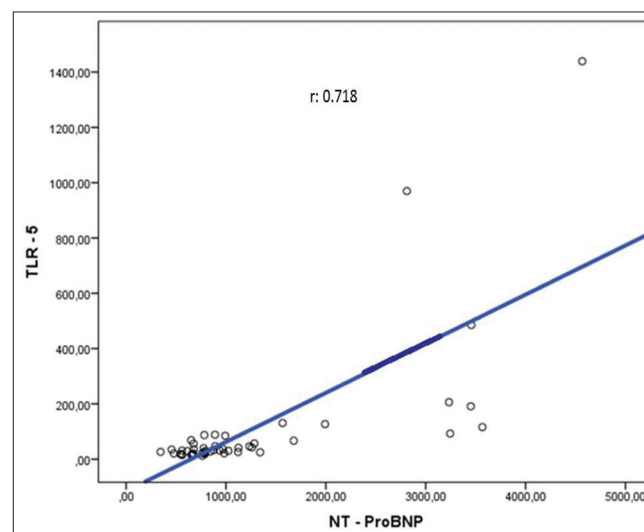
## METHODS

Patients admitted to the Cardiology outpatient clinic of the Firat University Research Hospital between May 2015, and May 2016 prospectively included in the study. We added in 17 female and 33 male to our research, totally 50 patients that we diagnosed heart failure and 25 males and 25 females, totally 50 healthy people as the control group was enrolled in the study. Ethics committee approval received from the Local Committee. Some of the patients who were admitted to our cardiology outpatient clinic with dyspnea in the effort, shortness of breath at night, tiredness, fatigue, anorexia, coughing, nausea, a manifestation of jugular veins, swelling in feet and legs, were diagnosed heart failure after a physical examination and clinical evaluations. ECG, chest radiography and ECG were performed to these patients. Blood samples were collected from heart failure patients with ejection fraction (EF)  $\leq 30\%$  in ECG; plasma NT-ProBNP, TLR-5, C-reactive protein (CRP), routine biochemical tests, and hemogram, sedimentation rate were studied. In the control group and all patients, detailed anamnesis was obtained, and physical examinations were performed. Patients with the chronic inflammatory disease, active infection, advanced liver disease, severe renal disease (creatinine  $\geq 2.5$ ), advanced heart valve disease, pulmonary artery pressure  $>35$  and chronic obstructive pulmonary disease (COPD) were excluded from the study. Blood samples were taken after a 10-12 h between 08:00 and 10:00. The samples were kept at room temperature for 30 min and then centrifuged at 4000 rpm (1600 g). BD vacutainer tubes were used for blood collection. Serum NT-ProBNP levels were studied by electrochemiluminescence assay using a modular Roche Hitachi E-70 analyzer (Roche Diagnostics, Germany). Routine biochemistry tests were performed spectrophotometrically on the Aerosat 2.0 (Abbott laboratory) instrument. In serum samples, TLR-5 was studied by using ELISA method following the directives of the manufacturer company (Hangzhou EastbioFarm Co. Ltd. Human TLR5 ELISA kit Catalog Number: CK-E90260).

All echocardiographic measurements were made in a left lateral decubitus position by a transthoracic approach using a General Electric Vivid PRO 7-color Doppler ECG device with a 2.5–3.5 MHz transducer. M-mode recordings were made at rate 50 mm/s, and Doppler recordings were made at rate 100 mm/s. M-mode and 2-D measurements were performed according to the recommendations of the American Society of ECG from parasternal long axis view. Statistical analysis of the study was made using the Statistical Package for Social Sciences 21 (Chicago, IL, USA) statistical program. Characteristics of the patients were summarized with basic statistics. Arithmetic means standard deviation were used for numerical parameters; while numbers and percentage values were used for categorical variables. In the comparisons, the Kolmogorov–Smirnov test was used to determine the distribution of all variable groups. Parametric statistical methods were used for variables with normal distribution, and non-parametric statistical methods were used for variables with skewed distribution. Student *t*-test (Independent Sample *t*-test) was used as a parametric test, and the Mann–Whitney U-test was used as a nonparametric test. Cross-tabulation statistics were used to compare categorical variables (Chi-square). In all analyzes, the statistical significance limit was accepted as  $P < 0.05$ .

## RESULTS

Age of patients was 68 ( $\pm 9$ ) years old in our study and 27.9 ( $\pm 9.3$ ) years old in the control group. There was the statistically significant difference between the groups regarding HT, diabetes mellitus (DM), hyperlipidemia, and coronary artery disease history ( $P < 0.001$ ). In the patient group, hypertension (%74), DM (%52), hyperlipidemia (%58), and coronary artery disease (%78) were found to be more frequent than the control group [Table 1]. When the mean hemogram and biochemistry values of patient and control



**Figure 1:** Relationship between TLR-5 and NT-ProBNP ( $r=0.718$ ,  $P<0.001$ )

groups were compared, a significant difference was found regarding laboratory values in the patient's group [Table 2]. There was the statistically significant difference between the two groups regarding echocardiographic values. In the patient group, many benefits were found to be higher; EF was found to be lower [Table 3]. In patients group, we determined that TLR and NT-ProBNP values are high [Table 4]. There was a positive correlation between TLR and NT-ProBNP ( $r = 0.718$ ,  $P < 0.001$ ) [Figure 1].

**Table 1: Basic demographic features**

	Patient Group (n=50)	Control Group (n=50)	P
Age	68±9	27,9±9,3	<0,001
Gender (Male)	33	25	0,06
Hypertension	%74	%4	<0,001
Diabetes Mellitus	%52	%1	<0,001
Hyperlipidemi	%58	%4	<0,001
Smoking	%12	%26	0,07
Coronary artery disease (%)	%78	%2	<0,001

**Table 2: Basic laboratory values**

	Patient Group (n=50)	Control Group (n=50)	P
Hemoglobin	12,6±1,8	14,1±1,3	<0,001
White Blood Cell	8,9±3	7,1±1,6	<0,001
Platletet	244,9±8,88	270,5±58,5	0,07
Sedimentation	29,1±12,5	6,8±3,7	<0,001
CRP	16,4±7,9	3,6±1,2	<0,001
Sodium	137,8±4,5	141,1±2,3	<0,001
Potassium	4,27±0,76	4,39±0,35	0,34
Urea	63,6±32,5	27,8±7,3	<0,001
Creatinine	1,45±1,1	0,7±0,15	0,003

**Table 3: Basic echocardiographic values**

	Patient Group (n=50)	Control Group (n=50)	P
Left Ventricle Diastolic Diameter (mm)	45,3±7,4	44,4±4,5	<0,001
Left Ventricle Systolic Diameter (mm)	41,6±8,4	24,7±4,7	<0,001
Intraventricular Diameter (mm)	11,6±1,7	9,1±1,6	<0,001
Posterior Wall Diameter (mm)	10,7±1,7	8,3±1,2	<0,001
Ejection Fraction (%)	29,4±4,3	63,3±3,4	<0,001
Left Atrium Diameter (mm)	42,8±7,7	30,2±3,2	<0,001
Basal Right Ventricle Diameter (mm)	24,5±4,1	21,4±2,2	<0,001

**Table 4: Group difference between TLR-5 and NT-ProBNP**

	Patient Group (n=50)	Control Group (n=50)	P
Toll Like Receptor-5	86,5±62,2	45,3±19,9	0,003
NT-ProBNP	1274±996	106±65	0,001

## DISCUSSION

Heart failure is an increasing health problem which has high morbidity and mortality.<sup>[1]</sup> The incidence of heart failure does not decrease in spite of progressive and successful developments in the treatment of etiologic factors such as ischemic heart disease and hypertension.

On the contrary, it is an increasingly common and significant public health problem.<sup>[2]</sup> The increase in the proportion of older adults in the community and developments of treatment of myocardial infarction have a considerable influence on this situation. As the diagnostic and therapeutic possibilities of myocardial infarction increase, the number of surviving patients increases and some of these people become chronic heart failure patients.<sup>[2]</sup> Despite the relatively younger population in our country, when it is considered that the average lifespan is prolonged and rate of cardiovascular diseases is increased, it seems that heart failure is a severe problem that needs to be addressed.

Since there are no symptoms specific to heart failure, to reduce morbidity and mortality, it becomes more important to diagnose early and start treatment soon for a differential diagnosis. Shortness of breath complaint can be seen in many diseases, especially COPD, and causes difficulties about distinguishing the disease that causes the primary charge in the patients, especially who have both heart failure and COPD diseases in the emergency department.<sup>[2]</sup> Here, the delay in diagnosis and treatment contributes to the morbidity and mortality of the patient.

Heart failure is a progressive disease, and besides, it is difficult to predict which patients have a high risk of death and cardiovascular event. Many parameters that are shown to be indicative of mortality, such as New York Heart Association (NYHA) classification, advanced age, and DM.<sup>[2]</sup> For this reason, there is a need for parameters that can show prognosis and patients with high mortality risk better. Similarly, starting an effective treatment to these patients in the early period and monitoring the effectiveness of the procedure is as important as determining the prognosis.

NT-ProBNP, which first appeared years ago but has been recently recognized as cardiologically important, is now meaningful for the preliminary diagnosis of heart failure. NT-ProB type natriuretic peptide (NT-ProBNP) is a diuretic peptide synthesized in the ventricular myocardium and released into the plasma in response to left heart failure conditions such as the increase in ventricular volume, wall tension, and end diastolic pressure. In the European Society of Cardiology guideline, it is published that the specificity and sensitivities of NT-proBNP for diagnosing heart failure were about 95%. It is a valuable non-invasive method even for identification of yet asymptomatic heart failure cases. In previous studies, Doust *et al.*,<sup>[3-5]</sup> Maisel<sup>[6]</sup> and Remme and Swedberg<sup>[7,8]</sup> have shown that NT-ProBNP can be used to diagnose symptomatic heart failure. Yoshimura *et al.*,<sup>[9]</sup> Wiecek *et al.*,<sup>[10]</sup> and Maisel

*et al.*<sup>[11]</sup> have shown that NT-ProBNP is correlated with the NYHA stage in their studies. The findings we obtained in our study were consistent with the results obtained in previous studies.

Regarding comparing NT-proBNP level with ECG, the survey of Kaan *et al.* is also essential and simultaneous plasma NT-proBNP levels were assessed in the cases to whom ECG performed to determine left the ventricular function.<sup>[12]</sup> Left ventricular dysfunction was detected in half of the facts in the group without known heart failure and previous left ventricular dysfunction, and plasma NT-proBNP levels were significantly higher in these cases. Abnormal echocardiographic findings were found in all patients in the group with known heart failure or previous left ventricular dysfunction, and the NT-proBNP levels of this group were found to be even higher. In addition to patients with heart failure with systolic dysfunction, plasma NT-proBNP levels also increase in patients with heart failure with diastolic dysfunction. In our study, consistent with the literature, NT-ProBNP values of the cases with EF <30% were statistically significantly higher than those with EF >50% ( $P < 0.001$ ), and there was a weak negative correlation between NT-ProBNP values and EF% ( $r = -0.360$   $P < 0.001$ ).

TLRs are a group of type 1 transmembrane proteins that provide the natural immune response against many pathogens. It was named “toll” because of its similarity to the receptor “toll gene,” which was first discovered in 1991 in *Drosophila melanogaster* and believed to have an important function in the immune system response. Today, these molecules which are homologous to the interleukin-1 receptor in humans are called “TLR.” These receptors are found in mast cells, dendritic cells, eosinophils, neutrophils, natural killer cells, natural killer T cells and particularly in macrophages; and they play a role in recognition of microorganisms and triggering the inflammation. Until now, 10 TLRs in the human and the bovine and 13 TLRs in the mouse have been identified, each of which can bind to one or more specific microbial molecules. 13 members have been recognized in the TLR family. Ligands of TLR1-TLR9 and TLR11 were determined; but the ligands of TLR10, TLR12, and TLR13 are not yet known. TLR5 recognizes bacterial flagellin, an essential structural component of bacterial flagella. The binding of TLR5 to flagellin results in an inflammatory signal as tumor necrosis factor- $\alpha$ . Therefore, that can be used as an inflammatory marker. It is known that other inflammatory markers (hs-CRP, N/L ratio) are high in systolic heart failure. TLR 5, as a new inflammatory biomarker, may also be a marker of decompensated systolic heart failure.

In our study, the values of both TLR-5 and NT-ProBNP were statistically significantly higher in patients with systolic heart failure (EF <30%) than in those without heart failure (EF >55%) ( $P < 0.001$ ). Besides, consistent with the literature, there was no significant correlation of NT-ProBNP and TLR-5 values between cases with heart failure and those

without heart failure ( $P > 0.05$ ). These results show that NT-ProBNP and TLR-5 levels are significantly higher in heart failure patients but, consistent with the literature, prognostic value of high TLR-5 is found to be a separate risk for heart failure independent of NT-ProBNP. Furthermore, there is a poor positive correlation between age and NT-ProBNP and TLR-5 values in our study.  $R = 0.246$   $P < 0.05$  and  $r = 0.223$   $P < 0.05$  (NT-ProBNP and TLR-5 values increase with increasing age). There is a poor positive correlation between urea and NT-ProBNP and TLR-5 values ( $r = 0.409$   $P < 0.001$  and  $r = 0.208$   $P < 0.01$ ). There is no significant correlation between fasting blood sugar, alanine aminotransferase, aspartate transaminase, gamma-glutamyl transferase, K, CL values and NT-ProBNP and TLR-5 levels. There was no statistically significant difference in NT-ProBNP and TLR-5 values between patients with and without arrhythmia or between the patients with and without wide QRS in ECG ( $P < 0.05$ ).

## CONCLUSION

Pro-BNP and TLR-5 levels were found to be significantly higher in patients with systolic heart failure than in those without heart failure. The high level of TLR-5, like NT pro-BNP, may be associated with mortality and number and duration of hospitalization. The routine use of this biomarker in systolic heart failure requires a large number of further studies involving more patients.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
2. McDonagh TA, Gardner RS, Clark AL, Dargie HJ. *Oxford Textbook of Heart Failure*. Oxford University Press; 2011. ISBN: 9780199577729.
3. Vanderheyden M, Bartunek J, Goethals M. Brain and other natriuretic peptides: Molecular aspects. *Eur J Heart Fail* 2004;6:261-8.
4. Vesely DL. Natriuretic peptides and acute renal failure. *Am J Physiol Renal Physiol* 2003;285:F167-77.
5. Doust JA, Glasziou PP, Pietrzak E, Dobson AJ. A systematic review of the diagnostic accuracy of natriuretic peptides for heart failure. *Arch Intern Med* 2004;164:1978-84.
6. Maisel A. B-type natriuretic peptide in the diagnosis and management of congestive heart failure. *Cardiol Clin* 2001;19:557-71.
7. Remme WJ, Swedberg K. Guidelines for heart evaluation and management of chronic heart failure. *J Am Cardiol* 1992;520:156-62.
8. Remme WJ, Swedberg K; Task Force for the Diagnosis and Treatment of Chronic Heart Failure, European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J* 2001;22:1527-60.
9. Yoshimura M, Yasue H, Okumura K, Ogawa H, Jougasaki M, Mukoyama M, *et al.* Different secretion patterns of atrial natriuretic peptide and brain natriuretic peptide in patients with congestive heart

- failure. *Circulation* 1993;87:464-9.
10. Wiecek SJ, Bailly KR, Thomas P. Clinical evaluation of the Triage B type natriuretic peptide assay for point of care testing of patients with congestive heart failure. *Clin Chem* 2000;46:77-8.
  11. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, *et al.* Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161-7.
  12. Kaan J, Hope J, Garcia A. A rapid bedside test for brain natriuretic peptide accurately predict cardiac function in patients referred for echocardiography. *J Am Coll Cardiol* 2000;135:419-20.

# Predictive Values of Inflammatory Cell Ratios for Complexity of Coronary Artery Disease in Patients with Acute Coronary Syndrome

Ahmet Karakurt, Cennet Yildiz<sup>1</sup>

Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, <sup>1</sup>Department of Cardiology, Bağcılar Tekden Hospital, İstanbul, Turkey

## Abstract

**Background:** The aim of this study was to investigate the relationship between neutrophil to lymphocyte ratio (NLR) platelet to lymphocyte ratio (PLR), mean platelet volume to lymphocyte ratio (MPVLR), MPV to platelet ratio (MPVPR) and the complexity of coronary artery disease (CCAD) in patients with acute coronary syndrome (ACS) using the SYNTAX score (SS) algorithm. **Materials and Methods:** A total of 599 patients with ACS undergoing coronary arteriography were enrolled and divided into three groups according to their SS: low SS group  $\leq 22$  (low-SSG,); intermediate SSG  $\geq 23$  and  $\leq 32$  (in-SSG,); and high-SSG  $\geq 33$  (high-SSG). Routine complete blood count parameters were analyzed at hospital admission. **Results:** There were significant differences between three groups in terms of PLR and MPVLR values ( $P = 0.007$  and  $P = 0.029$ ). Correlation analysis showed that PLR and MPVLR were positively correlated with CCAD ( $r = 0.095$ ,  $P = 0.018$  and  $r = 0.112$ ,  $P = 0.005$ , respectively). In multivariate logistic regression analysis, MPVLR was not an independent predictor of CCAD, whereas PLR was found to be a weak independent predictor of CCAD (odds ratio = 1.003 [1.001–1.006],  $P = 0.021$ ). Receiver operating characteristics analysis showed that PRL had low sensitivity (56.2%) and specificity (51.6%) for prediction of CCAD. **Conclusion:** Our study showed that NLR, MPVPR, and MPVLR were not independent predictors of CCAD in patients with ACS. PLR had such a weak relationship with CCAD that it could not be used for prediction of CCAD in these patients.

**Keywords:** Acute coronary syndrome, complexity of coronary artery diseases, inflammatory cell ratios

## INTRODUCTION

Atherosclerosis is a low-grade inflammatory disease that results in atherosclerotic plaque formation and progressive stenosis of the coronary arteries.<sup>[1-3]</sup> Inflammation plays an important role in all stages of atherosclerosis, from initiation and growth to complication of plaque including unstable angina pectoris (USAP), non-ST-elevation myocardial infarction (non-STEMI) and STEMI.<sup>[4,5]</sup>

The SYNTAX scoring (SS) system, based on qualitative and quantitative characterization of coronary artery disease (CAD) by including 11 angiographic variables that take into consideration lesion location and characteristics, is a valuable method for estimating the severity of CAD.<sup>[6]</sup> The severity of coronary artery lesions assessed by the SYNTAX score (SS) is associated with long-term mortality and major adverse cardiac event rates.<sup>[7-10]</sup>

Increased neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte (PLR), mean platelet volume (MPV), MPV to lymphocyte ratio (MPVLR), and MPV to lymphocyte ratio (MPVPR) have been shown to play a role in the pathophysiology of atherosclerotic disease. It has been reported that increased values of NLR, PLR, MPV, and MPVLR are associated with cardiovascular diseases.<sup>[11-15]</sup> In addition, these parameters have been shown to be related to the development of acute coronary syndrome (ACS) and found to be a predictor of morbidity and mortality in patients with ACS.<sup>[16-21]</sup> However, few reports have investigated so far the relationship between these parameters and the

**Address for correspondence:** Dr. Ahmet Karakurt,  
Department of Cardiology, Faculty of Medicine, Kafkas University,  
Kars 36100, Turkey.  
E-mail: karakurt38@hotmail.com

### Access this article online

Quick Response Code:



Website:  
<http://www.ijcva.com>

DOI:  
10.4103/IJCA.IJCA\_29\_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Karakurt A, Yildiz C. Predictive values of inflammatory cell ratios for complexity of coronary artery disease in patients with acute coronary syndrome. Int J Cardiovasc Acad 2018;4:70-6.

complexity (CCAD) in patients with ACS, with contrasting results.

Therefore, the aim of the current study was to evaluate the relationship between NLR, PLR, MPVLR, MPVPR, and CCAD in patients with ACS, using SS I algorithm.

## MATERIALS AND METHODS

### Study population

This study is a retrospective study based on medical record review. Between February 2014 and June 2017, 599 acute coronary disease patients who met all the inclusion criteria were admitted to our university hospital. None of the exclusion criteria were included in the study. Our study was in compliance with the Declaration of Helsinki, and it was approved by our university Local Research Ethics Committee.

ACS was diagnosed according to the criteria recommended by the 2015 ECS guidelines.<sup>[22]</sup> The study population composed of patients with USAP, non-STEMI, and STEMI. Diagnosis of USAP was based on the chest pain suggesting USAP with or without ischemic electrocardiographic findings. The diagnosis of non-STEMI was made when characteristic angina pectoris lasted longer than 20 min with/without associated ST-segment depression of  $\geq 0.1$  mV and/or T-wave inversion in two contiguous leads in the electrocardiogram and presence of increased troponin T level over the diagnostic cutoff value. STEMI was diagnosed in the presence of angina pectoris lasting more than 20 min that associated with ST-segment elevation of  $\geq 1$  mm in at least two contiguous limb leads or  $\geq 2$  mm in at least two contiguous chest leads.

Exclusion criteria consisted of patients with a history of trauma, surgery, malignancy, infectious diseases within 30 days before admission, hematologic disorders, rheumatologic diseases (systemic lupus erythematosus, rheumatoid arthritis, and Kawasaki disease), severe chronic or acute renal disease, hepatic failure, use of immunosuppressive agents within 3 weeks before study entry. Individuals with prior percutaneous or surgical revascularization were excluded from the study as SS had been validated only for patients with native CAD.

### Study protocol

Demographic characteristics and venous blood samples parameters were recorded from the patient's file. All subjects were evaluated with complete blood count (CBC), routine biochemical examination and ECG. The CBC parameters such as white blood count (WBC), hemoglobin (Hb), platelet count (PC), MPV, neutrophil, and lymphocyte were analyzed. The NLR, PLR, MPVLR, and MPVPR were calculated by dividing the absolute neutrophil count (NC) to the absolute lymphocyte count (LC), the absolute PC to absolute LC, MPV to the absolute LC, and MPV to the absolute PC, respectively. Fasting biochemical parameters such as the total cholesterol (TC), high-density lipoprotein, low-density lipoprotein (LDL), triglyceride (TG), and glucose levels were tested 1 day after hospital admission.

## Coronary angiography and SYNTAX score I

Coronary angiography was performed by standard Judkins techniques through femoral approach. An invasive cardiologist evaluated the angiographic CD records using the SS system. Patients' CCAD score was calculated using an online calculator (<http://www.syntaxscore.com/calculator/start.htm>). Patients were divided into three groups according to their SS: low SS group (SSG) ( $\leq 22$ ), intermediate SSG,<sup>[22-32]</sup> and high SSG ( $\geq 33$ ).<sup>[23]</sup>

### Statistical analysis

Data were tested for normal distribution and variance homogeneity using Levene's test. Categorical variables were expressed as absolute frequencies and percentages while continuous parametric variables were expressed as the mean and standard deviation, and continuous nonparametric variables were expressed as the median value and 25<sup>th</sup>–75<sup>th</sup> percentile. One-way ANOVA test was used to compare the continuous variables with parametric distribution. Kruskal–Wallis H-test was utilized to compare continuous variables with nonparametric distribution. Categorical variables were assessed by Chi-square test. Pearson correlation test was applied in the correlation analysis. Receiver operating characteristics (ROC) curve analysis was used for PLR and MPVLR. All statistical analyzes were performed by SPSS 23 (SPSS, Inc., Chicago, Illinois, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS

We conducted this single-center, medical record study through data retrieved between February 2014 and March 2018 at the cardiology department of the university hospital. A total of 599 (401 [66.9%] males and 198 [33.1%] females) patients with ACS were included in the study ( $P < 0.001$ ). Patients were stratified into three groups according to their SS: low-SSG ( $n = 436$ , 72.8%, mean age:  $61.26 \pm 11.21$ ), intermediate-SSG ( $n = 127$ , 21.2%, mean age:  $66.65 \pm 8.8$ ), and high-SSG ( $n = 36.6\%$ , mean age:  $73.47 \pm 8.6$ ).

Demographic and clinical characteristics of these three groups are presented in Table 1. The mean patient age was significantly higher in the high-SSG group than that in the low- and in-SSGs ( $P < 0.001$ ). There was a significant difference in the number of male patients between the three groups ( $P = 0.01$ ). The prevalence of diabetes mellitus and hypertension differed significantly between these three groups ( $P < 0.001$  and  $P < 0.001$ , respectively). The mean of MCV, RDW, TC were significantly lower in the high-SSG group than that in the low- and in-SSG groups ( $P = 0.015$ ,  $P = 0.028$ ,  $P = 0.01$ ). Urea and uric acid were significantly higher in the high-SSG group than that in the low- and in-SSG groups. The median of left ventricle ejection fraction and B-type natriuretic peptide were significantly lower in the high-SSG group than those in the low- and in-SSG groups ( $P < 0.001$  and  $P = 0.004$ , respectively). However, the groups did not differ significantly with respect to body mass index; mean of SBP, diastolic blood pressure, pulse pressure, LDL, and TG.

**Table 1: Demographic and clinical characteristics of the low-, intermediate-, high-syntax score groups**

	Low-SSG (n=436)	In-SSG (n=127)	High-SSG (n=36)	P
Age (years)	61.26±11.21	66.65±8.8	73.47±8.6	<0.001
Gender male, n (%)	308 (66.5)	67 (52.8)	26 (72.2)	0.010
BMI (m <sup>2</sup> /kg)	28.43±4.75	28.67±5.5	27.79±3.91	0.732
DM, n (%)	144 (31.2)	85 (67.5)	21 (58.3)	<0.001
HT, n (%)	222 (48.1)	112 (88.9)	30 (83.3)	<0.001
SBP (mmHg)	121.8±24.69	125.45±20.86	122.54±19.48	0.424
DBP (mmHg)	76.02±13.2	78.24±12.77	76.54±13.18	0.359
PP (mmHg)	44.66±13.88	47.22±13.13	44.65±14.81	0.283
HGB (mg/dL)	14.08±5.73	13.07±1.65	12.9±2.04	0.164
HTC (fL)	40.71±5.32	39.13±4.57	38.94±5.33	0.015
MCV (fL)	86.92±7.14	86.94±6.06	87.23±7.85	0.978
RDW (%)	14.04±1.63	14.25±1.52	13.25±1.84	0.028
PGL (mg/dL)	137.81±71.1	168.37±77.55	142.03±81.44	<0.001
TC (mg/dL)	191.14±45.41	177.74±39.14	173.67±30.28	0.010
LDL (mg/dL)	124.28±89.43	109.63±34.64	108.87±28.15	0.132
HDL (mg/dL)	39.22±10.76	38.52±12.73	37.79±12.61	0.687
TG (mg/dL)	156.35±95.03	162.56±88.78	139.37±69.48	0.438
Na (mmol/L)	136.34±3.85	136.48±4.38	136.55±4.82	0.935
K (mmol/L)	4.28±0.54	4.45±0.51	4.32±0.53	0.024
GGT (U/L)	33.41±25.53	32.10±38.87	31.81±20.45	0.906
CB (mg/dL)	0.19±0.10	0.18±0.14	0.26±0.17	0.009
TB (mg/dL)	0.56±0.30	0.48±0.29	0.59±0.36	0.067
Urea (mg/dL)	30 (24-38)	35 (27-46)	39.45 (29.25-54)	<0.001
Uric acid (mg/dL)	5.4 (4.6-6.23)	5.2 (4.5-6.45)	5.75 (5.2-8.5)	0.094*
CK-MB (ng/mL)	57.45 (17.8-313.4)	132.2 (27.4-777.3)	264 (130.9-1241.8)	<0.001
T-I (ng/mL)	3.62 (1.64-10.31)	5.3 (2.11-14.69)	6.19 (2.67-33.88)	0.007*
BNP (pg/mL)	224.45 (82.29-704.05)	558.3 (136.9-1567.5)	1071.85 (230.25-4091.5)	0.004*
EF (%)	56 (50-60)	54 (45-58)	50 (40-57.75)	<0.001*
SS	15 (12.5-17.5)	27 (24.5-29)	36 (34-38)	<0.001*

\*Data are expressed as median (25<sup>th</sup>-75<sup>th</sup> percentiles). BMI: Body mass index, BNP: B-type natriuretic peptide, CB: Conjugated Bilirubin, CK-MB: Creatine kinase-MB, DBP: Diastolic blood pressures, DM: Diabetes mellitus, FGL: Fasting glucose level, HDL: High-density lipoprotein, SS: Syntax score, High SSG: High SS group, HT: Hypertension, HTC: Hematocrit, In SSG: Intermediate SS group, K: Potassium, LDL: Low-density lipoprotein, Low SSG: Low SS group, Na: Sodium, PP: Pulse pressure, RDW: Red cell distribution width, SBP: Systolic blood pressure, TB: Total Bilirubin, TC: Total cholesterol, TG: Triglyceride, T-I: Troponin-I, EF: Ejection fraction, GGT: Gamma glutamil transferaz, MCV: Mean corpuscular volume, HGB: Hemoglobin

The inflammatory markers, ratio of inflammatory markers, MPVLR, MPVPR, and CRP of the ACS patients according to the SS are presented in Table 2. WBC, NC, LC, and NLR did not differ statistically between the three groups.

Although PC, MPV, and MPVPR did not differ significantly between these three groups. PLR and MPVLR were higher significantly in high-SSG group than those in the low-SSG and intermediate-SSG groups ( $P = 0.007$  and  $P = 0.029$ , respectively).

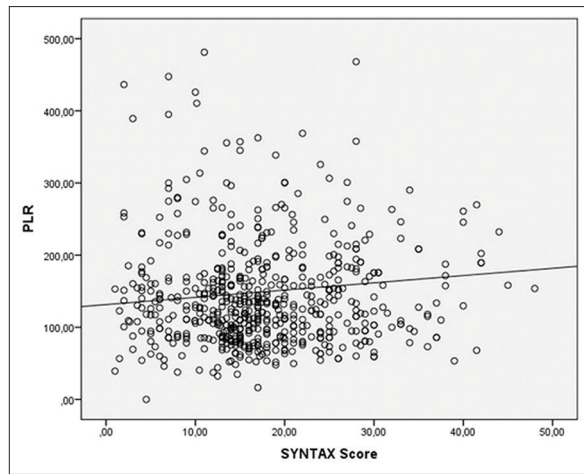
The high-SSG group had higher CRP levels ( $1.5 \pm 2.26$  mg/dl) than the intermediate-SSG group ( $1.22 \pm 1.57$  mg/dl), and the intermediate-SSG group had higher CRP levels than the low SSG ( $1.14 \pm 2.5$  mg/dl) ( $P < 0.001$ ).

Correlation analysis was performed to investigate the relationship between the SS and parameters (NLR, PLR, MPV, MPVLR, and MPVPR). A significant correlation was found between MPV, PLR, MPVLR, and SS ( $r = 0.094$ ,  $P = 0.019$ ;  $r = 0.095$ ,  $P = 0.018$  and  $r = 0.112$ ,  $P = 0.005$ , respectively) [Table 3, Figures 1 and 2].

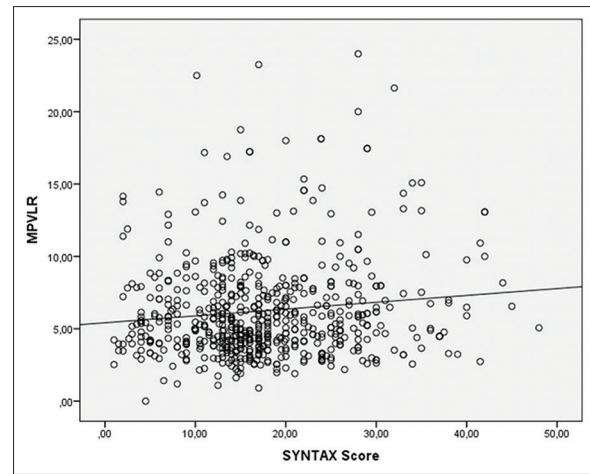
Univariate regression analysis showed statistically significant but weak correlations between PLR, MPVLR and CCAD ( $\beta = 0.009$  [95% confidence interval [CI]: 0.002–0.016],  $P = 0.018$  and  $\beta = 0.267$  [95% CI: 0.081–0.453],  $P = 0.005$ , respectively) [Table 4]. In addition, we performed multivariate regression analysis for variables that showed significance in the univariate model. Multivariate regression analysis revealed that MPVLR was not an independent predictor of CCAD (odds ratio [OR]. 1.070 [95% CI: 0.918–1.065],  $P = 0.761$ ), whereas PLR was a weak predictor for CCAD (OR: 1.003 [95% CI: 1.001–1.006],  $P = 0.021$ ) [Table 4]. In the ROC curves analysis, the (area under the curve [AUC]=0.560, 95% CI: 0.508–0.612,  $P = 0.023$ ), with optimal cutoff value of 127.65 (sensitivity: 56.2%, specificity: 51.6%) for predicting CCAD [Table 5 and Figure 3].

## DISCUSSION

In this study, we only included patients with ACS (USAP, non-STEMI, and STEMI). This study was designed to



**Figure 1:** Correlation between platelet to lymphocyte and SYNTAX score ( $r = 0.095$ ,  $P = 0.018$ )



**Figure 2:** Correlation between mean platelet volume to lymphocyte ratio and SYNTAX score ( $r = 0.112$ ,  $P = 0.005$ )

**Table 2: Complete blood count values and inflammatory cell ratios of the low-, intermediate-, high-syntax score groups**

	Low-SSG (n=436)	In-SSG (n=127)	High-SSG (n=36)	P
WBC (K/uL)	8.97±2.96	8.9013±2.82	8.46±2.45	0.596
NC (K/uL)	6.07±2.66	6.15±2.84	5.77±2.26	0.758
LC (K/uL)	2.08±1.17	1.96±0.90	1.73±0.87	0.139
PLT (K/uL)	9.97±1.48	10.29±1.54	9.86±1.28	0.085
MPV (fL)	242.75±70.37	255.87±87.13	245.67±82.67	0.218
NLR	3.74±2.98	4.11±3.89	4.63±3.91	0.179
PLR	142.87±79.76	163.23±111.55	181.35±126.04	0.007
MPVLR	6.04±3.40	6.70±4.06	7.36±3.89	0.029
MPVPR	4.52±1.84	4.44±1.61	4.43±1.45	0.881
CRP (mg/dL)	1.14±2.5	1.22±1.57	1.5±2.26	<0.001

CRP: C-reactive proteins, LC: Lymphocyte count, MPV: Main platelet volume, MPVLR: MPV to lymphocyte ratio, MPVPR: MPV to platelet ratio, NC: Neutrophil count, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, PLT: Platelet, SS: Syntax score, WBC: White blood count, High SSG: High SS group, In SSG: Intermediate SS group, Low SSG: Low SS group

investigate the relationship between NLR, PLR, MPVR, MPVLR, and CCAD in patients with ACS.

Main findings of our study were as follows: (1) although there was no correlation between NLR, MPVLR, and CCAD in ACS patients, (2) there was a weak positive correlation between PLR, MPVLR, and CCAD, (3) Univariate and multivariate regression analysis showed that MPVLR was not an independent predictor of CCAD, whereas PLR was a weak independent predictor of CCAD, and (4) PLR had a low sensitivity (56.2%) and specificity (51.6%) to predict intermediate and high anatomic CAD complexity (SS >22).

Ample research has shown that inflammation plays an important role in atherosclerotic CAD. Inflammatory cells are important at every stage of atherosclerotic lesions, their effector molecules accelerate progression of the lesions, and activation of inflammation can elicit ACS.<sup>[24,25]</sup> In recent years, NLR, PLR,

**Table 3: Correlation analysis between complete blood count values, inflammatory cell ratios, and syntax score of the patients**

	SS	
	r	P
WBC	-0.019	0.629
NC	0.007	0.860
LC	-0.056	0.159
PC	0.033	0.411
MPV	0.094	0.019
NLR	0.060	0.131
PLR	0.095	0.018
MPVLR	0.112	0.005
MPVPR	0.022	0.587
CRP	0.031	0.440

WBC: White blood count, NC: Neutrophil count, LC: Lymphocyte count, PC: Platelet count, MPV: Main platelet volume, MPVLR: MPV to lymphocyte ratio, MPVPR: MPV to platelet ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CRP: C-reactive proteins, SS: Syntax score

MPVLR, and MPVPR, derivate indexes of CBC assays, have emerged as the new prognostic markers for various diseases such as cardiovascular disorders, malignant diseases, stroke subtypes, transient ischemic attack and pulmonary diseases including cystic fibrosis, chronic obstructive pulmonary disease, and acute pulmonary embolism.<sup>[26-28]</sup> In this area, the most popular issue has certainly been CAD.

NLR and PLR have been shown to have a predictive value in the detection of CCAD in patients with stable CAD.<sup>[11,29-31]</sup> Furthermore, they have been used in prediction of major adverse cardiovascular events (a new episode or a recurrence of myocardial infarction, UASP, development or worsening of heart failure, re-hospitalization, stroke, in hospital and long-term mortality),<sup>[31]</sup> prognostication of CAD and evaluation of stent thrombosis risk.<sup>[32-36]</sup> However, few studies have investigated the relationship between inflammatory cell

**Table 4: Independent predictors of high syntax score in acute coronary artery syndrome**

	Univariate regression analysis		Multivariate regression analysis	
	$\beta$ (95% CI)	P	OR (95% CI)	P
NLR	0.159 (-0.048-0.365)	0.131	-	-
PLR	0.009 (0.002-0.016)	0.018	1.003 (1.001-1.006)	0.021
MPVLR	0.267 (0.081-0.453)	0.005	1.070 (0.918-1.065)	0.761
MPVPR	10.492 (-27.391-48.375)	0.587	-	-

OR: Odds ratio, MPV: Main platelet volume, MPVLR: MPV to lymphocyte ratio, MPVPR: MPV to platelet ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CI: Confidence interval

**Table 5: Receiver operating characteristic curves of platelet to lymphocyte ratio and main platelet volume to lymphocyte ratio for predicting coronary artery disease complexity using syntax score=22 cutoff value**

Test result variables	Area under the curve				
	Area	SD	P	95% CI	
				Lower bound	Upper bound
NLR	0.521	0.027	0.418	0.469	0.574
PLR	0,560	0.027	0.023	0.508	0.612
MPVLR	0.553	0.027	0.044	0.501	0.606
MPVPR	0.495	0.027	0.864	0.443	0.548

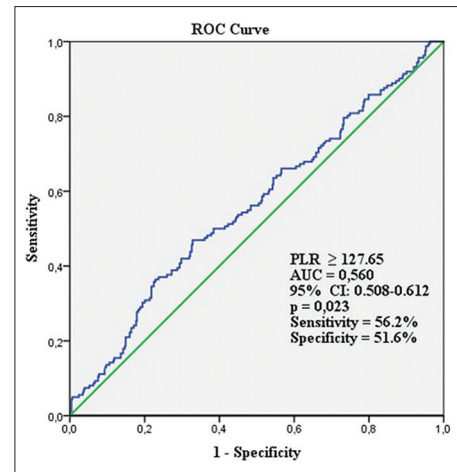
MPV: Main platelet volume, MPVLR: MPV to lymphocyte ratio, MPVPR: MPV to platelet ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SD: Standard deviation, CI: Confidence interval

ratios and CCAD in ACS patients, and findings of these studies were insufficient to predict CCAD.

Chen *et al.*<sup>[37]</sup> evaluated NLR in 2976 CAD patients and 571 healthy controls. CCAD was assessed using Gensini score. A cutoff value of 2.04 for NLR predicted severe CAD according to Gensini score. In that study, acute and chronic CAD were evaluated together; inflammatory response in chronic CAD was different from ACS; hence, the results of this study could not be generalized to ACS patients.

Another study performed by Soyly *et al.*<sup>[13]</sup> investigated the relationship between NLR and SS in patients with non-STEMI. Patients were divided into three groups according to their NLR (NLR <2.6, NLR = 2.6–4.5, and NLR >4.5). Patients with high-NLR had higher SS than those with intermediate and low-NLR. Moreover, high NLR values were strong predictors of the in-hospital mortality in non-STEMI patients. Although they found a positive correlation between NLR and SS ( $r=0.253$   $P=0.001$ ), independent predictive value of NLR for high SS was not investigated. The presence of correlation between NLR and SS did not mean that high NLR had a predictive value for CCAD.

Kurtul *et al.*<sup>[38]</sup> assessed the relationship between MPV, PLR and severity of CAD in patients with non-STEMI by using SS. NLR was found to be an independent predictor of severe



**Figure 3:** Receiver operating characteristics curves for the platelet to lymphocyte ratio value in the prediction of intermediate and high SYNTAX Score using = 22 cutoff value. AUC: Area under the curve, CI: Confidence interval

atherosclerosis (coefficient  $\beta = 0.380$ , 95% CI: 1.165–1.917,  $P < 0.001$ ), whereas MPV did not have such a predictive value (coefficient  $\beta = 1.010$ , 95% CI: 0.774–1.318,  $P = 0.941$ ).

Kurtul A *et al.*<sup>[12]</sup> divided the 1016 non-STEMI patients into two groups: group 1 composed of patients with low SS (SS <22), group 2 composed of patients with intermediate and high SS. They found a statistically significant difference with respect to PLR between the two groups, and a positive correlation was observed between PLR and SS ( $P < 0,001$ ). Increased PLR was an independent predictor for high SS in non-STEMI patients (OR = 1.018, 95% CI: 1.013–1.023,  $P < 0.001$ ). Moreover, in-hospital mortality was higher in group 2 than that in group 1 (OR = 1.004, 95% CI: 1.001–1.008,  $P = 0.032$ ).

In our study, except for a weak positive correlation between PLR and CCAD, no correlation was observed with any of the parameters measured. According to both univariate and multivariate analysis results, PLR was a weak predictor of CCAD in ACS patients. The ROC analysis results confirmed the limited predictive value of PLR for CCAD in patients with ACS. Our findings contradicted the previous studies,<sup>[13,37,38]</sup> except for the study by Kurtul *et al.*<sup>[12]</sup> which was partially in concordance with our results.

Recent research has shown that inflammation is an integral part of atherosclerotic CAD. The degree of inflammatory activity depends on the characteristics of the atherosclerotic lesion.<sup>[2]</sup> Plaque analysis has demonstrated less local and systemic inflammatory activity in silent atherosclerotic (noncomplicated and nonvulnerable) plaque than complicated plaque.<sup>[39]</sup> It has been shown that ACS patients have higher levels of inflammatory cells and mediators including T-cell, CRP, interleukin-6, fibrinogen, interleukin-7, interleukin-8, soluble CD40 ligand, and C-reactive protein-related protein pentraxin-3 compared to patients with stable CAD, both systemically and within the lesion, suggesting the role of these mediators in atherosclerotic

plaque rupture.<sup>[39-49]</sup> High levels of inflammatory mediators were associated with increased cardiovascular mortality and adverse cardiovascular events.<sup>[45-47]</sup> Increased levels of these mediators did not result from CCAD; rather they resulted from inflammatory response that was triggered by plaque rupture.<sup>[42-46]</sup> In the light of these data, it could be concluded that the presence of stable, non-complicated CAD was associated with both systemic and local low-grade inflammation. However, clinical forms of ACS were associated with high-grade inflammation, both systemically and locally. Overall, the existence of noncorrelation between NLR, PLR, MPVLR, MPVLR and CCAD was an expected result. Stable CAD patients with low-grade inflammatory activity might have higher CCAD; ACS patients with high-grade inflammatory activity might have lower CCAD, and vice versa. As the degree of inflammatory response depended on plaque complication (vulnerability, erosion, and rupture) in both patient groups, the circulating levels of inflammatory markers would differ between them.

### Study limitations

The present study had several limitations. First, our study was retrospective, cross-sectional, and was based on patient file data. However, our study population consisted of a sufficient number of patients with ACS. Second, NLR, PLR, MPVLR, and MPVPR were analyzed from the first blood samples at hospital admission rather than several samples at different time intervals. Third, these ratios were considerably affected by many factors, including dehydration, overhydration, diluted blood specimens, and *in vitro* blood specimen handling. Finally, the results of this study could be generalized for all ACS but not for USAP, non-STEMI, or STEMI. Therefore, a separate study was needed to evaluate the relationship between inflammatory markers and CCAD for each subgroup of patients.

### CONCLUSION

ACS was almost always associated with rupture of an atherosclerotic plaque and outburst of systemic markers of inflammation. Since, patients with ACS might have both less complex CAD morphology and high levels of inflammatory response; they might have no correlation between them. Therefore, NLR, PLR, MPVLR, MPVPR could not be used for prediction of CCAD in patients with ACS.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

- Ross R. Atherosclerosis – An inflammatory disease. *N Engl J Med* 1999;340:115-26.
- Wong BW, Meredith A, Lin D, McManus BM. The biological role of inflammation in atherosclerosis. *Can J Cardiol* 2012;28:631-41.
- Wang T, Palucci D, Law K, Yanagawa B, Yam J, Butany J. Atherosclerosis: pathogenesis and pathology. *Diagn Histopathol* 2012;18:461-7.
- Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002;105:1135-43.
- Mulvihill NT, Foley JB. Inflammation in acute coronary syndromes. *Heart* 2002;87:201-4.
- Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K, *et al.* The SYNTAX score: An angiographic tool grading the complexity of coronary artery disease. *EuroIntervention* 2005;1:219-27.
- Yadav M, Palmerini T, Caixeta A, Madhavan MV, Sanidas E, Kirtane AJ, *et al.* Prediction of coronary risk by SYNTAX and derived scores: Synergy between percutaneous coronary intervention with taxus and cardiac surgery. *J Am Coll Cardiol* 2013;62:1219-30.
- Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, *et al.* A new tool for the risk stratification of patients with complex coronary artery disease: The clinical SYNTAX score. *Circ Cardiovasc Interv* 2010;3:317-26.
- Safarian H, Alidoosti M, Shafiee A, Salarifar M, Poorhosseini H, Nematipour E, *et al.* The SYNTAX score can predict major adverse cardiac events following percutaneous coronary intervention. *Heart Views* 2014;15:99-105.
- Girasis C, Garg S, Räber L, Sarno G, Morel MA, Garcia-Garcia HM, *et al.* SYNTAX score and clinical SYNTAX score as predictors of very long-term clinical outcomes in patients undergoing percutaneous coronary interventions: A substudy of SIRolimus-eluting stent compared with pacliTAXel-eluting stent for coronary revascularization (SIRTAX) trial. *Eur Heart J* 2011;32:3115-27.
- Akboga MK, Canpolat U, Yayla C, Ozcan F, Ozeke O, Topaloglu S, *et al.* Association of platelet to lymphocyte ratio with inflammation and severity of coronary atherosclerosis in patients with stable coronary artery disease. *Angiology* 2016;67:89-95.
- Kurtul A, Murat SN, Yarlioglu M, Duran M, Ergun G, Acikgoz SK, *et al.* Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. *Am J Cardiol* 2014;114:972-8.
- Soylu K, Gedikli Ö, Dagan G, Aydin E, Aksan G, Nar G, *et al.* Neutrophil-to-lymphocyte ratio predicts coronary artery lesion complexity and mortality after non-ST-segment elevation acute coronary syndrome. *Rev Port Cardiol* 2015;34:465-71.
- Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: Is there a practical index of platelet activity? *Clin Appl Thromb Hemost* 2003;9:177-90.
- Ornek E, Kurtul A. Relationship of mean platelet volume to lymphocyte ratio and coronary collateral circulation in patients with stable angina pectoris. *Coron Artery Dis* 2017;28:492-7.
- Park JJ, Jang HJ, Oh IY, Yoon CH, Suh JW, Cho YS, *et al.* Prognostic value of neutrophil to lymphocyte ratio in patients presenting with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2013;111:636-42.
- Bajari R, Tak S. Predictive prognostic value of neutrophil-lymphocytes ratio in acute coronary syndrome. *Indian Heart J* 2017;69 Suppl 1:S46-50.
- Gazi E, Bayram B, Gazi S, Temiz A, Kirilmaz B, Altun B, *et al.* Prognostic value of the neutrophil-lymphocyte ratio in patients with ST-elevated acute myocardial infarction. *Clin Appl Thromb Hemost* 2015;21:155-9.
- Azab B, Shah N, Akerman M, McGinn JT Jr. Value of platelet/lymphocyte ratio as a predictor of all-cause mortality after non-ST-elevation myocardial infarction. *J Thromb Thrombolysis* 2012;34:326-34.
- Cho KI, Ann SH, Singh GB, Her AY, Shin ES. Combined usefulness of the platelet-to-lymphocyte ratio and the neutrophil-to-lymphocyte ratio in predicting the long-term adverse events in patients who have undergone percutaneous coronary intervention with a drug-eluting stent. *PLoS One* 2015;10:e0133934.
- Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, *et al.* Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. *Am J Cardiol* 2010;106:470-6.
- Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, *et al.* 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment

- elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2016;37:267-315.
23. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al.* Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009;360:961-72.
  24. Libby P. Changing concepts of atherogenesis. *J Intern Med* 2000;247:349-58.
  25. Zakyntinos E, Pappa N. Inflammatory biomarkers in coronary artery disease. *J Cardiol* 2009;53:317-33.
  26. O'Brien CE, Price ET. The blood neutrophil to lymphocyte ratio correlates with clinical status in children with cystic fibrosis: A retrospective study. *PLoS One* 2013;8:e77420.
  27. Günay E, Sarınc Ulaşlı S, Akar O, Ahsen A, Günay S, Koyuncu T, *et al.* Neutrophil-to-lymphocyte ratio in chronic obstructive pulmonary disease: A retrospective study. *Inflammation* 2014;37:374-80.
  28. Kayrak M, Erdoğan HI, Solak Y, Akilli H, Gül EE, Yildirim O, *et al.* Prognostic value of neutrophil to lymphocyte ratio in patients with acute pulmonary embolism: A retrospective study. *Heart Lung Circ* 2014;23:56-62.
  29. Açar G, Fidan S, Uslu ZA, Turkdıy S, Avci A, Alizade E, *et al.* Relationship of neutrophil-lymphocyte ratio with the presence, severity, and extent of coronary atherosclerosis detected by coronary computed tomography angiography. *Angiology* 2015;66:174-9.
  30. Zhou D, Wang G, Fan Y, Wan Z, Liu X. Platelet to lymphocyte ratio is associated with the severity of coronary artery disease and clinical outcomes of percutaneous coronary intervention in the Chinese Han population. *Exp Ther Med* 2017;13:731-8.
  31. Dentali F, Nigro O, Squizzato A, Gianni M, Zuretti F, Grandi AM, *et al.* Impact of neutrophils to lymphocytes ratio on major clinical outcomes in patients with acute coronary syndromes: A systematic review and meta-analysis of the literature. *Int J Cardiol* 2018;266:31-7.
  32. Huang G, Zhao JL, Du H, Lan XB, Yin YH. Coronary score adds prognostic information for patients with acute coronary syndrome. *Circ J* 2010;74:490-5.
  33. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F, *et al.* Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. *Clin Chim Acta* 2008;395:27-31.
  34. Osadnik T, Wasilewski J, Lekston A, Strzelczyk J, Kurek A, Gonera M, *et al.* The platelet-to-lymphocyte ratio as a predictor of all-cause mortality in patients with coronary artery disease undergoing elective percutaneous coronary intervention and stent implantation. *J Saudi Heart Assoc* 2015;27:144-51.
  35. Poludasu S, Cavusoglu E, Khan W, Marmur JD. Neutrophil to lymphocyte ratio as a predictor of long-term mortality in African Americans undergoing percutaneous coronary intervention. *Clin Cardiol* 2009;32:E6-10.
  36. Ayça B, Akın F, Celik O, Sahin I, Yildiz SS, Avci II, *et al.* Neutrophil to lymphocyte ratio is related to stent thrombosis and high mortality in patients with acute myocardial infarction. *Angiology* 2015;66:545-52.
  37. Chen J, Chen MH, Li S, Guo YL, Zhu CG, Xu RX, *et al.* Usefulness of the neutrophil-to-lymphocyte ratio in predicting the severity of coronary artery disease: A Gensini score assessment. *J Atheroscler Thromb* 2014;21:1271-82.
  38. Kurtul S, Sarlı B, Baktir AO, Demirbas M, Saglam H, Doğan Y, *et al.* Neutrophil to lymphocyte ratio predicts SYNTAX score in patients with non-ST segment elevation myocardial infarction. *Int Heart J* 2015;56:18-21.
  39. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685-95.
  40. Liuzzo G, Goronzy JJ, Yang H, Kopecky SL, Holmes DR, Frye RL, *et al.* Monoclonal T-cell proliferation and plaque instability in acute coronary syndromes. *Circulation* 2000;101:2883-8.
  41. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836-43.
  42. Liu J, Sukhova GK, Sun JS, Xu WH, Libby P, Shi GP. Lysosomal cysteine proteases in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2004;24:1359-66.
  43. Liuzzo G, Biasucci LM, Gallimore JR, Grillo RL, Rebuzzi AG, Pepys MB, *et al.* The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;331:417-24.
  44. Biasucci LM, Vitelli A, Liuzzo G, Altamura S, Caligiuri G, Monaco C, *et al.* Elevated levels of interleukin-6 in unstable angina. *Circulation* 1996;94:874-7.
  45. Aukrust P, Müller F, Ueland T, Berget T, Aaser E, Brunsvig A, *et al.* Enhanced levels of soluble and membrane-bound CD40 ligand in patients with unstable angina. Possible reflection of T lymphocyte and platelet involvement in the pathogenesis of acute coronary syndromes. *Circulation* 1999;100:614-20.
  46. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. *Fragmin during instability in coronary artery disease*. *N Engl J Med* 2000;343:1139-47.
  47. Wilhelmssen L, Svärdsudd K, Korsan-Bengtson K, Larsson B, Welin L, Tibblin G, *et al.* Fibrinogen as a risk factor for stroke and myocardial infarction. *N Engl J Med* 1984;311:501-5.
  48. Peri G, Introna M, Corradi D, Iacuitti G, Signorini S, Avanzini F, *et al.* PTX3, A prototypical long pentraxin, is an early indicator of acute myocardial infarction in humans. *Circulation* 2000;102:636-41.
  49. Damás JK, Waehre T, Yndestad A, Otterdal K, Hognestad A, Solum NO, *et al.* Interleukin-7-mediated inflammation in unstable angina: Possible role of chemokines and platelets. *Circulation* 2003;107:2670-6.

# Comparison of Anthropometric Indices in Predicting the Risk of Hypertension, Iran - 2014

Hossein Lashkardoost, Fateme Hoseyni<sup>1</sup>, Elham Rabbani<sup>1</sup>, Farzane Qorbani Moqadam<sup>1</sup>, Leila Hosseini<sup>2</sup>, Salimeh Azizi<sup>3</sup>, Andishe Hamed<sup>3</sup>

Departments of Epidemiology and Biostatistics, <sup>1</sup>Public Health, <sup>2</sup>Cardiology and <sup>3</sup>Faculty of Nursing, North Khorasan University of Medical Sciences, Bojnurd, Iran

## Abstract

**Purpose:** The best anthropometric index has not been established to investigate the relationship between hypertension and obesity. Since a similar study was not conducted in Bojnurd, we began to investigate the comparison of anthropometric indices (body mass index, waist circumference, and waist-to-hip and waist-to-height ratios) in predicting the risk of hypertension. **Materials and Methods:** The present cross-sectional study was conducted on women referring to Bojnurd health centers. For analyzing the data, we used *t*-test, Chi-square, logistic regression, and the receiver operating characteristic curve in SPSS 19 software. **Results:** The prevalence of blood pressure was 53.4% (confidence interval = 46.8–60). All four anthropometric indicators were used as a screening tool for hypertension diagnosis; however, body mass index (BMI) had a higher sub-curved surface than other anthropometric indices (area under curve = 0.717). The cutoff point of BMI for predicting the risk of hypertension was 25.6. **Conclusions:** This study suggested that BMI as an anthropometric indicator to evaluate the risk of hypertension. Since a significant percentage of people are unaware of the existence of hypertension, continuing education is needed to encourage people to pay more attention to this problem.

**Keywords:** Body mass index, hypertension, waist circumference, waist-to-height ratio, waist-to-hip ratio

## INTRODUCTION

Urbanization, industrialization, and population growth have led to an increase in the prevalence of chronic diseases worldwide. Obesity as a risk factor for noncommunicable diseases is one of the most important public health problems worldwide.<sup>[1]</sup> Obesity refers to the abnormal accumulation of fat in the body tissue.<sup>[2]</sup> The prevalence of obesity is increasing, and obese people are prone to chronic diseases such as Type 2 diabetes, hypertension, cardiovascular disease, and some cancers.<sup>[3]</sup> Due to its economic burden, choosing the best measure to monitor the complications of obesity in the population is very important. Body mass index (BMI) is the most commonly used index for assessing obesity. Other anthropometric indices, such as waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratios (WHtR), have recently been suggested and are considered for the distribution of fat in the body.<sup>[4,5]</sup> The WC gives us information on how the body's fat is distributed, indicating abdominal obesity.<sup>[6]</sup> Some environmental factors, including obesity, are effective in high blood pressure. The prevalence of hypertension in obese people is higher than in normal people,<sup>[5]</sup> and it varies from one country to another,

from 10% to over 60% in different countries.<sup>[7]</sup> About 18% of global deaths have been attributed to hypertension. It causes one of the eight deaths in the world.<sup>[8]</sup> It is the most important health issue in developed and developing countries.<sup>[9]</sup> The prevalence of hypertension in the 25–64 years' Iranian population was 22.1% in 2015.<sup>[10]</sup> The risk of developing hypertension in individuals with abnormal BMI is proportional to the increase in WC.<sup>[5]</sup> North Khorasan Province has been ranked first regarding age-related blood pressure in women. The prevalence of hypertension in women of North Khorasan province is 42.7%.<sup>[11,12]</sup> Hence, using simple and inexpensive methods to diagnose, especially the distribution of obesity in the body, help us to identify people at high risk for chronic diseases such as blood pressure. By decreasing the prevalence of obesity, through prevention and education, we will see a

**Address for correspondence:** Mrs. Andishe Hamed, Shirvan Center of Higher Health Education, North Khorasan University of Medical Sciences, Shirvan, Iran.  
E-mail: ahamed1364@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Lashkardoost H, Hoseyni F, Rabbani E, Moqadam FQ, Hosseini L, Azizi S, *et al.* Comparison of anthropometric indices in predicting the risk of hypertension, Iran - 2014. *Int J Cardiovasc Acad* 2018;4:77-81.

### Access this article online

#### Quick Response Code:



**Website:**  
<http://www.ijcv.com>

**DOI:**  
10.4103/IJCA.IJCA\_27\_18

significant reduction in the prevalence of hypertension. Since a similar study has not been conducted in Bojnurd, this study was done to determine the best anthropometric index and determine the optimal cutoff point for each of these indicators to predict the risk of hypertension.

## MATERIALS AND METHODS

### Ethics

This article was approved by the code “93P767” in North Khorasan University of Medical Sciences, Iran. We get consent from each participant.

### Study design

The present study was a cross-sectional study, and the statistical population was women referring to health centers in Bojnurd. We used cross-sectional sample size formula, based on the prevalence of hypertension 30%, accuracy of 0.06%, and confidence level of 95% to estimate the sample size. Finally, we examined 230 people. We used multistage sampling methods from health centers of Bojnurd in five geographic regions of North, South, East, West, and Center. Then, we chose one center randomly from each region. We randomly selected the participants from the centers. Then, we conducted the coordination (on a telephone) for them who were willing to participate in the study after explaining the purpose of the study for them and getting consent; then, we measured anthropometric indices of each one in the health center. The criteria for entry were all women (married) referred to health centers, in which, they were willing to participate in the study. Excluded criteria were as follows: not having a history of exercise and exercise therapy to control or reduce weight gain. After obtaining satisfaction, the questions were asked by the trained person using a questionnaire and an interview. We measured hypertension, with pressure gauge. People, with systolic blood pressure  $\geq 140$  mmHg or diastolic pressure  $\geq 90$  mmHg, were considered as people with hypertension based on the definition of hypertension published by the Seventh Joint National Committee on Prevention. The weight of the participants was measured using an Omron digital scale manufactured in Japan. Furthermore, a meter was used to measure the height of the people in cm. The BMI was obtained as weight (in kg) divided by the square of the height (in  $m^2$ ). The hip circumference was also measured similar to the WC at the widest part of the buttocks, and then WHR calculated by dividing the WC to the hip circumference in cm. The WC was also divided by the height to obtain WHtR.

### Statistics

To analyze the data, we used *t*-test, logistic regression model, the receiver operating characteristic (ROC) curve and area under curve (AUC), Youden's Index (J), and the maximum potential effectiveness of a biomarker to measure the power of each anthropometric index in predicting the risk of hypertension in SPSS 19 software, version 19.0 (IBM Corp., Armonk, NY) by using 95% of confidence interval level.

## RESULTS

In this cross-sectional study, 230 women were enrolled in the study. The mean age of the women, who participate in the study, was  $41.1 \pm 15.2$  years, with an average pregnancy rate of  $3 \pm 0.14$ . The prevalence of blood pressure was 53.4% (confidence interval = 46.8–60). Demographic characteristics of the study are shown in Table 1.

The mean anthropometric indices of BMI, WC, WHR, and WHtR were higher in participants with hypertension than those without hypertension ( $P < 0.001$ ). There was a statistically significant difference in physical activity between the two groups ( $P = 0.02$ ). The odds ratio of hypertension obtained from anthropometric indices before and after adaptation for age variables, occupation, level of education, number of pregnancies, and physical activity is shown in Table 2.

In the first model, from four anthropometric indices, BMI, and WHR had a significant relationship with the risk of hypertension. After entering the confounding variables, BMI, WC, and WHtR showed a significant relationship, so that the risk of hypertension in people with  $BMI \geq 27$  greater than  $<27$ . To compare the predictive power of anthropometric indices, for the risk of hypertension, we used the ROC curve and the sub-curved surface (AUC) [Figure 1].

To determine the risk of hypertension, the best cutoff point for anthropometric indices is shown in Table 3. The best cutoff point for BMI was  $25.65 \text{ kg/m}^2$ . Furthermore, the cutoff point of WHtR was 0.52, and the cut-off point of WHR was 0.94.

**Table 1: Basic characteristics of the population studied**

Variables	With hypertension	Without hypertension	P
n	123	107	
Age	44.1 $\pm$ 16.5	37.4 $\pm$ 12.9	0.001
BMI	21.4 $\pm$ 2.5	24.3 $\pm$ 3.3	<0.001
WC	101.6 $\pm$ 9.7	92.06 $\pm$ 13.1	<0.001
WHtR	0.6 $\pm$ 0.07	0.57 $\pm$ 0.08	0.02
WHR	0.93 $\pm$ 0.06	0.87 $\pm$ 0.07	<0.001
Number of pregnancy			
$\leq 2$	46 (37.4)	59 (55.2)	0.018
2-5	57 (46.3)	39 (36.4)	
$> 5$	20 (16.3)	9 (8.4)	
Occupation			
Housewife	108 (87.8)	88 (82.2)	0.23
Employee	15 (12.2)	19 (17.8)	
Level of education			
Under diploma	90 (73.2)	55 (51.4)	0.003
Diploma	19 (15.4)	30 (28)	
Academic	14 (11.4)	22 (20.6)	
Regular exercise			
No	116 (94.3)	91 (85)	0.02
Yes	7 (5.7)	16 (15)	

\*Significant at 95% confidence level. BMI: Body mass index, WC: Waist circumference, WHtR: Waist-to-height ratio, WHR: Waist-to-hip ratio

The cut-off point of WC was 101, although WC had a lower surface area under the ROC curve than other anthropometric indices.

For comparison in pairs between BMI and WC,  $P = 0.0012$ ; however, the surface area under the ROC curve was higher in BMI. Similar to BMI versus WHR: 0.015 and BMI versus WHtR: 0.0057. For comparison in pairs between WC versus WHR,  $P = 0.12$ , WC versus WHtR: 0.2 and WHR versus WHtR: 0.38, which means WC, WHR, and WHtR had similar predictive power in the risk of hypertension.

### DISCUSSION

In this study, all four anthropometric indicators were significantly different between the two groups with and without hypertension;<sup>[13]</sup> however, BMI had a higher AUC than other anthropometric indices like study conducted by Fuchs.<sup>[14]</sup> However, in a study that conducted in Spanish, the AUC for BMI was significantly higher than the AUCs for WC and WHtR like this study (AUC = 0.717).<sup>[15]</sup> Some study shows WHtR is a better predictor for hypertension, which is contradicted with this study.<sup>[16]</sup>

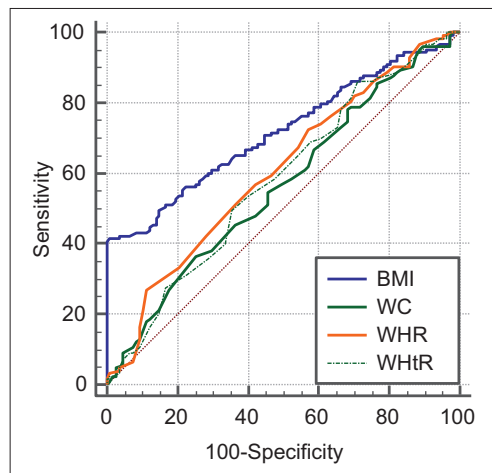
Waist-to-hip indices were a good predictor for the risk of hypertension in some studies, which was contradicted with this study.<sup>[17]</sup> However, such studies have shown that WC is most closely correlated with changes in blood pressure.<sup>[18,19]</sup> In this study, results showed that BMI, WC, and WHtR had a significant relationship with the risk of hypertension after controlling for confounders such as age, occupation, level of education, number of pregnancies, and physical activity. Furthermore, by analyzing ROC curves, it showed that BMI is the best prediction for the risk of hypertension compared to other anthropometric indicators. WHR, WC, and WHtR are also showed similar predictive power. In a cross-sectional study conducted by Liu, the AUC values did not differ between BMI, WC, and WHtR for prediction of hypertension, which was different with this study.<sup>[20]</sup>

In a meta-analysis study, in the world that compared WC, WHtR, and BMI indices, WHtR was the best indicator for measuring obesity.<sup>[21]</sup> In the study conducted by Zabetian in Tehran,<sup>[22]</sup> the cutoff point for WC was 94.5 as a predictor for the risk of cardiovascular disease. Furthermore, according to the National Committee of Obstetrics,  $WC \geq 90$  had been suggested for obesity, which was different with this study. This committee recommends a  $WC \geq 95$  cm for appropriate medical interventions. Our estimate is also up to 101. The cutoff points for BMI, WHR, and WHtR were 25.6, 0.52, and 0.94 in this study, respectively. Each population, depending on the race and ethnicity, has a different cutoff point for anthropometric indices related to the risk of developing diseases such as

**Table 2: The odds ratio of blood pressure regarding cutoff points for anthropometric indices**

Variables	OR (95%CI)	P	OR (95%CI)**	P
<b>BMI</b>				
<22	1		1	
23.5-25.6	1.5 (0.7-3.2)	0.23	1.2 (0.4-3.1)	0.67
$\geq 25.6$	7.6 (3.1-18.2)	<0.001	13.9 (4.5-43.1)	<0.001
<b>WC</b>				
<93	1		1	
93-97.9	1.06 (0.4-2.6)	0.88	0.2 (0.04-1.3)	0.11
$\geq 98$	1.2 (0.7-2.1)	0.41	0.07 (0.01-0.4)	0.005
<b>WHR</b>				
<0.86	1		1	
0.86-0.89	1.4 (0.5-3.4)	0.43	1.06 (0.3-3.5)	0.92
$\geq 0.9$	1.9 (1.1-3.6)	0.02	0.7 (0.2-2.2)	0.6
<b>WHtR</b>				
<0.50	1		1	
0.50-0.52	1.2 (0.5-2.6)	0.58	3.01 (0.7-12.7)	0.13
$\geq 0.52$	1.6 (0.8-2.9)	0.11	9.2 (1.3-62.6)	0.02

\*Significant at  $P < 0.05$ , \*\*After adjusting for confounders. BMI: Body mass index, WC: Waist circumference, WHtR: Waist-to-height ratio, WHR: Waist-to-hip ratio, OR: Odds ratio, CI: Confidence interval



**Figure 1: Comparison of receiver operating characteristic curves**

**Table 3: Areas under the receiver operating characteristic curve, cutoff points, sensitivity, and specificity of anthropometric measurements to predict hypertension**

Variables	AUC (95% CI)	P	Cut-off points	Sensitivity	Specificity	Youden's index
BMI	0.71 (0.65-0.77)	<0.001	25.65	40.65	100	0.4
WC	0.56 (0.49-0.62)	0.09	101	36.5	74.7	0.11
WHR	0.6 (0.53-0.66)	0.004	0.94	26.8	88.7	0.15
WHtR	0.58 (0.51-0.64)	0.03	0.52	86.1	28.9	0.15

AUC: Area under curve, BMI: Body mass index, WC: Waist circumference, WHtR: Waist-to-height ratio, WHR: Waist-to-hip ratio, OR: Odds ratio, CI: Confidence interval

blood pressure. Different cutoff points are estimated for anthropometric indices. These differences may be due to the differences in lifestyle because of the dietary habits and physical activity of the population under the study as well as the differences in the study outcomes found in the prediction models. Cutting points that show the highest probability of predicting the risk of hypertension based on sensitivity and specificity were similar to recommended values.<sup>[13,23]</sup> WC does not consider the person's height in the risk assessment, it was not significantly a good predictor for hypertension; therefore, it can be said that because the WHtR index considers the height of people in measuring body mass, in contrast to WC, is more sensitive than other anthropometric indices in identifying patients with hypertension. In this study, the prevalence of hypertension was 53.4%. In comparison with other parts of the country, the prevalence rate of hypertension was 23.7% in Tehran,<sup>[24]</sup> and 27.3% in Isfahan.<sup>[25]</sup> There is a significant difference in the prevalence of hypertension in different parts of the world. In the United States, it was 30.1%;<sup>[26]</sup> and in Canada, it was 21.6%.<sup>[27]</sup> The prevalence of hypertension in the study conducted by Ana was 44%.<sup>[13]</sup> Several studies have reported the increasing incidence of hypertension, especially in women in developing countries, including Iran. In this study, the abdominal obesity was one of the factors that influenced women's hypertension. Such studies confirm our results.<sup>[28,29]</sup> In this study, age had a major risk of hypertension. Such studies have reported similar results.<sup>[24,30]</sup> However, Anane's study did not report a significant relationship between the age and hypertension which may be due to differences in the age group of the study.<sup>[31]</sup> In the present study, there was a significant relationship between regular exercise and hypertension. Some studies reported inconsistent results with our study.<sup>[32,33]</sup> Maybe few people in the two study groups had reported doing exercise in their leisure time. However, such studies have shown that by reducing physical activity, the risk of hypertension would increase.<sup>[31,34]</sup> Hence, people, who do not have physical activity in the day, are twice more susceptible to having higher blood pressure. The present study shows that the number of pregnancies is one of the factors that increase the blood pressure in women. Such studies have reported similar results.<sup>[35]</sup> In this study, there was no significant relationship between female occupation and their education level with hypertension. The results of such studies contradicted our study.<sup>[31,33]</sup>

## CONCLUSION

Overall, this study indicated that BMI, WC, WHR, and WHtR had affected on blood pressure in women since BMI had better surface area under the ROC curve. Since a significant percentage of people are unaware of the existence of hypertension, and controls of this disorder are not appropriate in many people, continuing education is needed to encourage people to pay more attention to this problem. Since obesity and hypertension are important risk factors for cardiovascular disease, the need for nutritional education with a change

in attitude is necessary as a result of weight control and fitness. There were some limitations in this study. The main limitation of our study was its cross-sectional design, and it was impossible to show the cause–effect relationship. We propose a prospective study on a large population of men and women because this study has been done only on women.

## Acknowledgment

This article was approved by the code “93P767” in North Khorasan University of Medical Sciences, Iran. The authors would like to thank all participants who participate in the present study.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Poirier P, Lemieux I, Mauriège P, Dewailly E, Blanchet C, Bergeron J, *et al.* Impact of waist circumference on the relationship between blood pressure and insulin: The quebec health survey. *Hypertension* 2005;45:363-7.
2. Pi-Sunyer X. The medical risks of obesity. *Postgrad Med* 2009;121:21-33.
3. Huxley R, Mendis S, Zheleznyakov E, Reddy S, Chan J. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk – A review of the literature. *Eur J Clin Nutr* 2010;64:16-22.
4. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. *Am J Clin Nutr* 2004;79:379-84.
5. Kabalin M, Kolarić B, Marchesi VV, Perez N, Ostojic S, Rukavina T, *et al.* Body mass index, waist circumference and waist-to-hip ratio: Which anthropometric indicator is better predictor for the hypertension development in women population of the Island Cres. *Coll Antropol* 2012;36:363-8.
6. Siani A, Cappuccio FP, Barba G, Trevisan M, Farinara E, Lacone R, *et al.* The relationship of waist circumference to blood pressure: The olivetti heart study. *Am J Hypertens* 2002;15:780-6.
7. Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. *Lancet* 2008;371:1513-8.
8. World Health Organization. *The World Health Report 2002: Reducing Risks, Promoting Healthy Life.* Geneva, Switzerland: World Health Organization; 2002.
9. Demisse AG, Greffie ES, Abebe SM, Bulti AB, Alemu S, Abebe B, *et al.* High burden of hypertension across the age groups among residents of Gondar city in Ethiopia: A population based cross sectional study. *BMC Public Health* 2017;17:647.
10. Malekzadeh MM, Etemadi A, Kamangar F, Khademi H, Golozar A, Islami F, *et al.* Prevalence, awareness and risk factors of hypertension in a large cohort of Iranian adult population. *J Hypertens* 2013;31:1364-71.
11. Mohammadi M, Mirzaei M. Population attributable fraction of hypertension associated with obesity in Iran. *J Community Health Res* 2016;5:249-59.
12. Mohammadi M, Mirzaei M. Population-attributable fraction of hypertension associated with obesity, abdominal obesity, and the joint effect of both in the central provinces of Iran. *J Epidemiol Glob Health* 2017;7:71-9.
13. Rezende AC, Souza LG, Jardim TV, Perillo NB, Araújo YCL, de Souza SG, *et al.* Is waist-to-height ratio the best predictive indicator of hypertension incidence? A cohort study. *BMC Public Health* 2018;18:281.
14. Fuchs FD, Gus M, Moreira LB, Moraes RS, Wiehe M, Pereira GM, *et al.* Anthropometric indices and the incidence of hypertension:

- A comparative analysis. *Obes Res* 2005;13:1515-7.
15. Guasch-Ferré M, Bulló M, Martínez-González MÁ, Corella D, Estruch R, Covas MI, *et al.* Waist-to-height ratio and cardiovascular risk factors in elderly individuals at high cardiovascular risk. *PLoS One* 2012;7:e43275.
  16. Li WC, Chen IC, Chang YC, Loke SS, Wang SH, Hsiao KY, *et al.* Waist-to-height ratio, waist circumference, and body mass index as indices of cardiometabolic risk among 36,642 Taiwanese adults. *Eur J Nutr* 2013;52:57-65.
  17. Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference, waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The canadian heart health surveys. *Int J Obes Relat Metab Disord* 2001;25:652-61.
  18. Gustat J, Elkasabany A, Srinivasan S, Berenson GS. Relation of abdominal height to cardiovascular risk factors in young adults: The bogalusa heart study. *Am J Epidemiol* 2000;151:885-91.
  19. Silva DA, Petroski EL, Peres MA. Accuracy and measures of association of anthropometric indexes of obesity to identify the presence of hypertension in adults: A population-based study in Southern Brazil. *Eur J Nutr* 2013;52:237-46.
  20. Liu Y, Tong G, Tong W, Lu L, Qin X. Can body mass index, waist circumference, waist-hip ratio and waist-height ratio predict the presence of multiple metabolic risk factors in Chinese subjects? *BMC Public Health* 2011;11:35.
  21. Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y, *et al.* Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: A meta-analysis. *Am J Epidemiol* 2012;176:959-69.
  22. Zabetian A, Hadaegh F, Azizi F. Appropriate cut-off values of anthropometric variables in predicting a 7.6-year risk of cardiovascular disease in Iranian adult population. *J Isfahan Med Sch* 2009;27:1-18.
  23. Physical status: The use and interpretation of anthropometry. Report of a WHO expert committee. *World Health Organ Tech Rep Ser* 1995;854:1-452.
  24. Fazizi F, Esmailzadeh A, Mirmiran FP. Obesity and cardiovascular disease risk factors in Tehran adults: A population-based study. *East Mediterr Health J* 2004;10:887-97.
  25. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: A systematic review. *J Hypertens* 2004;22:11-9.
  26. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA* 2010;303:2043-50.
  27. McAlister FA, Wilkins K, Joffres M, Leenen FH, Fodor G, Gee M, *et al.* Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. *CMAJ* 2011;183:1007-13.
  28. Smith LP, Gilstad-Hayden K, Carroll-Scott A, Ickovics J. High waist circumference is associated with elevated blood pressure in non-hispanic white but not hispanic children in a cohort of pre-adolescent children. *Pediatr Obes* 2014;9:e145-8.
  29. Song YH. The association of blood pressure with body mass index and waist circumference in normal weight and overweight adolescents. *Korean J Pediatr* 2014;57:79-84.
  30. Okosun IS, Cooper RS, Rotimi CN, Osotimehin B, Forrester T. Association of waist circumference with risk of hypertension and type 2 diabetes in Nigerians, Jamaicans, and African-Americans. *Diabetes Care* 1998;21:1836-42.
  31. Afrifa-Anane E, Agyemang C, Codjoe SN, Ogedegbe G, de-Graft Aikins A. The association of physical activity, body mass index and the blood pressure levels among urban poor youth in Accra, Ghana. *BMC Public Health* 2015;15:269.
  32. Kim HK, Takahashi M, Konishi M, Tabata H, Nishimaki M, Xiang M, *et al.* P-46 Effects of increased daily physical activity on blood lipids and blood pressure in older adults. *BMJ* 2016;50(Suppl 1):A1-A90.
  33. Sarikhani Y, Heydari ST, Emamghorashi F, Jafari F, Tabrizi R, Karimpour S, *et al.* Associated factors and standard percentiles of blood pressure among the adolescents of Jahrom City of Iran, 2014. *Int J Pediatr* 2017;2017:1-6.
  34. Luke A, Bovet P, Plange-Rhule J, Forrester TE, Lambert EV, Schoeller DA, *et al.* A mixed ecologic-cohort comparison of physical activity & weight among young adults from five populations of African origin. *BMC Public Health* 2014;14:397.
  35. Amirkhizi F, Siasi F, Minaee s, Jalali M, Dorostimotlagh A, Chamri M. Study of blood pressure in rural women in Kerman province and its relationship with anthropometric status. *J Lorestan Univ Med Sci* 2008;10:31-8.

# The Predictors of Long-Term Hospitalization in Turkish Heart Failure Population: A Subgroup Analysis of Journey Heart Failure-TR Study: On Behalf of Journey Heart Failure-TR Investigators

Umit Yasar Sinan, Mehmet Erturk<sup>1</sup>, Erkan Yıldırım<sup>2</sup>, Duygu Koçyiğit<sup>3</sup>, Ilgin Karaca<sup>4</sup>, Faruk Ertas<sup>5</sup>, Ahmet Celik<sup>6</sup>, Fatih Aksoy<sup>7</sup>, Hasan Ali Gumrukcuoglu<sup>8</sup>, Umit Yuksek<sup>9</sup>, Mahir Cengiz<sup>10</sup>, Mehdi Zoghi<sup>11</sup>

Department of Cardiology, Istanbul University Institute of Cardiology, <sup>1</sup>Department of Cardiology, Ministry of Health Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital, Istanbul, <sup>2</sup>Department of Cardiology, Health Science University Erzurum Region Education and Research Hospital, Erzurum, <sup>3</sup>Department of Cardiology, Hacettepe University School of Medicine, Ankara, <sup>4</sup>Department of Cardiology, Firat University School of Medicine, Elazig, <sup>5</sup>Department of Cardiology, Dicle University School of Medicine, Diyarbakir, <sup>6</sup>Department of Cardiology, Mersin University School of Medicine, Mersin, <sup>7</sup>Department of Cardiology, Afyonkarahisar Dinar State Hospital, Afyonkarahisar, <sup>8</sup>Department of Cardiology, Lokman Hekim Van Hospital, Van, <sup>9</sup>Department of Cardiology, Izmir Odemis State Hospital, Izmir, <sup>10</sup>Department of Cardiology, Istanbul University Cerrahpasa School of Medicine, Istanbul, <sup>11</sup>Department of Cardiology, Ege University School of Medicine, Izmir, Turkey

## Abstract

**Background:** Heart failure (HF) is an important public health problem. We aimed to investigate the predictors of long-term hospitalization in Turkish HF population. **Materials and Methods:** Journey-HF-TR study is a multicenter, cross-sectional, noninvasive, and observational study that was conducted in intensive care unit (ICU), coronary care unit (CCU), and cardiology wards in seven geographical regions of Turkey. In this subgroup analysis, patients were classified as two groups according to in-hospital stay called the patient with the shorter length of stay (S-LOS) (in-hospital stay <5 days; S-LOS) and patients with longer LOS (L-LOS) (in-hospital stay ≥5 days; L LOS). **Results:** The study group was consisted of 1606 patients (57.2% male, mean age: 67. 8 ± 13.0 years old). One thousand and thirty seven patients, whom in-hospital stay duration were recorded in case report form, were included in this analysis. There were 487 patients (32.1%) in S LOS group and 1030 patients (67.9%) in L LOS group. In multivariate analysis, correlation was present for NYHA functional capacity, CKD, ACS related HF, right HF, cardiogenic shock, invasive and noninvasive ventilation, and hemodynamic monetarization. The longer in-hospital stay increases the probability of morbidity and mortality. **Conclusion:** We demonstrated that there was positive correlation between longer hospital stay and HF severity (NYHA III-IV), CKD, cardiogenic shock, right ventricular HF, and HF related to ACS. HFpEF patients have less in-hospital stay than HFrEF and HFmrEF patients.

**Keywords:** Acute heart failure, long in-hospital stay (length of stay), morbidity, mortality

## INTRODUCTION

Acute heart failure (AHF) is a life-threatening syndrome that constitutes a majority of the hospitalizations in cardiology clinics and intensive/coronary care units (CCUs) among patients aged above 65.<sup>[1]</sup> It can develop as a result of worsening symptoms of existing HF (acute decompensated chronic HF (ADCHF) or *de novo* development of these symptoms. As well as, it is a leading cause of morbidity and mortality, and it also increases the health-care costs.

Hospital length of stay (LOS) is defined as the actual number of days the patients remained in the hospital, determined from the day of admission to the day of discharge. Theoretically, longer LOS (L-LOS) identifies more severe patients and/or

**Address for correspondence:** Dr. Umit Yasar Sinan, Instructor, Department of Cardiology, Istanbul University Institute of Cardiology, Haseki Street, 29/31, Istanbul, Turkey. E-mail: drumityasar@hotmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Sinan UY, Erturk M, Yıldırım E, Koçyiğit D, Karaca I, Ertas F, *et al.* The predictors of long-term hospitalization in Turkish heart failure population: A subgroup analysis of journey heart failure-TR study: On behalf of journey heart failure-TR investigators. *Int J Cardiovasc Acad* 2018;4:82-5.

### Access this article online

#### Quick Response Code:



**Website:**  
<http://www.ijcva.com>

**DOI:**  
10.4103/IJCA.IJCA\_40\_18

complications occurring during hospitalization. It has been suggested a surrogate measure of hospital performance.<sup>[2,3]</sup> LOS is a key determinant of HF hospitalization costs. L-LOS is also associated with lower performance on quality of care measures and higher rates of subsequent readmission and mortality. Several studies revealed that possible determinants of L-LOS for HF patients include sociodemographic variables, medical comorbidity, disease severity (worse functional class and lower left ventricular ejection fraction [LVEF]), clinical presentation, inpatient treatment, inhospital progress, and development of iatrogenic complications.<sup>[3,4]</sup> Some medical comorbidities that were known in prolonging LOS are concurrent stroke, worsening of renal function, atrial fibrillation, respiratory problems requiring specific treatment, and malnutrition.<sup>[5,6]</sup>

We aimed to determine the predictors of long-term hospitalization in Journey HF-TR population.

## METHODS

Journey-HF-TR study is a multicenter, cross-sectional, noninvasive, and observational study that was conducted in intensive care unit (ICU), CCU, and cardiology wards in seven geographical regions of Turkey.<sup>[7]</sup> The patients hospitalized with the final diagnosis of AHF between September 2015 and 2016 were included in Journey-HF-TR study. According to LOS, patients were classified as patient with shorter LOS (S-LOS) (inhospital stay <5 days; S-LOS) and patients with L-LOS (inhospital stay  $\geq$ 5 days; L-LOS) in this subgroup analysis. Baseline and clinical characteristics, comorbidities, and laboratory data were collected during hospital admission. 12-lead electrocardiogram (ECG) and transthoracic echocardiography (TTE) were performed in all patients. Patients with systolic blood pressure higher than 140 mmHg and diastolic blood pressure higher than 90 mmHg or who were taking antihypertensive treatment were classified hypertensive (HT). Patients with fasting blood sugar higher than 125 mg/dl in two blood samples and glycated hemoglobin A1c (HbA1c) higher than 6.5% or who were taking antidiabetic medication were classified as diabetes mellitus (DM). Anemia was defined as Hb level is <13 g/dl in men and <12 g/dl in women according to the World Health Organization criteria. Chronic kidney disease (CKD) was defined as if glomerular filtration rate (GFR) is <60 ml/per min/1.73 m<sup>2</sup>. On TTE, patients were divided into three groups according to LVEF as patients with reduced EF (LVEF <40%), patients with midrange EF (LVEF: 40%-49%), and patients with preserved EF (LVEF >50%).

### Statistical analysis

Statistical analysis was performed using SPSS program (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as the mean  $\pm$  standard deviation or median (minimum-maximum) if not normally distributed. Categorical variables are presented in frequency (percentages). Univariate analysis was performed to identify the variables associated with LOS. Those variables with  $P < 0.25$  at

the univariate analysis were included in the multivariate model. A value of  $P < 0.05$  was considered to be statistically significant.

## RESULTS

The study group was consisted of 1606 patients (57.2% male, mean age: 67.8  $\pm$  13.0 years old). The initial functional capacity was New York Heart Association (NYHA) III-IV in 75.2% of patients. The median stay in CCU/ICU was 3 days, and total hospitalization duration was 7 days. The total inhospital mortality was 7.6% in the overall population.

One thousand and thirty-seven patients, whom inhospital stay duration were recorded in case report form, were included in this analysis. There were 487 patients (32.1%) in S-LOS group and 1030 patients (67.9%) in L-LOS group. Interestingly, the patients in S-LOS group were older than the patients in L-LOS group (69.1  $\pm$  13.0 and 67.0  $\pm$  13.0 years old,  $P < 0.05$ ). There was much more male in L-LOS group (55.6% and 44.4%,  $P < 0.05$ ).

The prevalence of HT, DM, AF, coronary artery disease, and anemia was similar between two groups. CKD was the unique comorbidity that was much more seen in patients with L-LOS than patients with S-LOS (30.1% and 22.8%,  $P = 0.003$ ). The clinical presentation (*de novo* AHF or ADCHF) was similar between groups. Patients with L-LOS were much more presented with acute pulmonary edema (32.3% and 28.3%), cardiogenic shock (4.1% and 1.8%), and right ventricular failure (28.6% and 20.7%) [Table 1].

Patients with L-LOS had much more severe disease. The prevalence of patients with advanced stage HF (NYHA III-IV) was higher in L-LOS group than S-LOS group (52.3% and 22.5%,  $P < 0.001$ ). Acute coronary syndrome (ACS)-related AHF was one of the contributing factors of long-term hospitalization. While the contributing factor was ACS in 16.3% of patients with L-LOS, 11.7% of patients with S-LOS were hospitalized due to ACS-related AHF ( $P < 0.05$ ). Hemodynamic monetarization (18.0% and 11.9%), noninvasive (18.3% and 10.9%), and invasive ventilation (7.7% and 3.1%) were the other causes of longer hospitalization ( $P < 0.01$  for all three variable).

On physical examination, systolic blood pressure (130.3  $\pm$  29.9 and 127.1  $\pm$  30.9 mmHg), diastolic blood pressure (82.4  $\pm$  12.2 and 80.1  $\pm$  11.4 mmHg), and heart rate (95.3  $\pm$  23.3 and 93.2  $\pm$  23.5 per min) were similar between S-LOS and L-LOS patient groups ( $P > 0.05$  for all three variables). On ECG, QRS duration also was similar between two groups (106.6  $\pm$  25.9 and 105.7  $\pm$  40.8 msn;  $P < 0.05$ ) [Table 2].

On laboratory, natriuretic peptide levels (N-terminal pro B-type natriuretic peptide) and GFR and Hb levels were also similar between two groups (respectively, 6701  $\pm$  978 and 8129  $\pm$  188 pg/ml, 49.7  $\pm$  28.7 and 49.4  $\pm$  31.4 ml/min/1.73 m<sup>2</sup>, and 12.3  $\pm$  2.1 and 12.1  $\pm$  2.1 g/dl;  $P > 0.05$  for all three variables) [Table 2].

The mean EF was  $35.5 \pm 12.9$  in S-LOS group patients,  $32.1 \pm 12.1$  in L-LOS group patients ( $P > 0.05$ ). While HF patients with preserved EF (HFpEF) was much more in patients with S-LOS (21% and 16%;  $P < 0.001$ ), HF patients with reduced EF (HFrEF) (64% and 67%) and HF patients with midrange EF (HFmrEF) (15% and 17%) were similar between group ( $P < 0.05$ ). There was no correlation between EF and L-LOS. As we know, HFpEF patients generally have more comorbidities and are older than other two groups. On the other hand, HFpEF patients have better systolic and diastolic BP than other EF groups. In advance stage, HF disease having lower BP is more problematic and causes L-LOS and higher mortality. Although we did not perform such statistical analysis, it may be the reason for S-LOS in HFpEF patients.

Univariate analysis showed correlation between LOS and male sex, advanced stage HF (NYHA III-IV), CKD, cardiogenic shock, pulmonary edema, right HF, invasive and noninvasive mechanical ventilation requirement, and hemodynamic monetarization requirement. In multivariate analysis, this correlation still was present for NYHA functional capacity, CKD, ACS-related HF, right HF, cardiogenic shock, invasive and noninvasive ventilation requirement, and hemodynamic monetarization requirement.

## DISCUSSION

In this study, we demonstrated that there was positive correlation between L-LOS and male sex, HF severity (NYHA III-IV), CKD, pulmonary edema, cardiogenic shock, right ventricular HF, HF related to ACS, invasive or noninvasive mechanical ventilation requirement, and hemodynamic monitor requirement. After multivariate analysis, this correlation remained constant for NYHA functional capacity, CKD, ACS-related HF, right HF, cardiogenic shock, invasive and noninvasive ventilation requirement, and hemodynamic monetarization requirement. Although the mean EF was similar between two groups, the prevalence of LOS was similar between patients with HFrEF and HFmrEF and had shorter in patients with HFpEF patients.

AHF is a life-threatening clinical syndrome that constitutes a majority of the hospitalizations among patients aged above 65 years.<sup>[1]</sup> The LOS in AHF patients is a surrogate for the quality of health-care service.<sup>[2,3]</sup> The L-LOS increases subsequent hospital readmission and mortality. It also increases health-care costs.

AHF patients with multiple comorbidities (HT, DM, AF, CKD, and anemia) have L-LOS.<sup>[3,4]</sup> Especially, anemia and worsening of renal failure during in-hospital stay are possible determinants of L-LOS for AHF patients.<sup>[8-10]</sup> Iron deficiency without the presence of anemia is an important consequence of HF. It causes worse prognosis and advanced stage disease in HF patients.<sup>[11]</sup> In our study population, we did not check the patient's ferritin and transferrin saturation, but Hb levels and prevalence of anemia were similar in S-LOS and

**Table 1: Demographical and clinical characteristics of two groups**

Parameters	L-LOS (n=1030)	S-LOS (n=487)	P
Sex, male (%)	55.6	44.4	0.04*
Age (years)	67.0±13.0	69.1±13.0	0.03*
NYHA III-IV (%)	52.3	22.5	<0.001
HT (%)	67.6	65.5	0.4
DM (%)	43.0	40.7	0.3
AF (%)	39.4	36.6	0.3
Anemia (%)	57.2	54.4	0.5
CKD (%)	30.1	22.8	0.003*
Clinical presentation (%)			
ADCHF	81.7	79.5	0.2
De novo AHF	18.3	20.5	0.3
APE	32.3	28.3	0.04*
CS	4.1	1.8	0.04*
RHF	28.6	20.7	0.002*
ACS	16.3	11.7	0.04*
Hemodynamic monitor	18.0	11.9	<0.01
NIV	18.3	10.9	<0.01
MV	7.7	3.1	<0.01

\* $P < 0.05$  is significant. NYHA: New York Heart Association, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, CKD: Chronic kidney disease, ADCHF: Acute decompensated chronic heart failure, AHF: Acute heart failure, ACS: Acute coronary syndrome, NIV: Noninvasive ventilation, APE: Acute pulmonary edema, CS: Cardiogenic shock, RHF: Right heart failure, MV: Mechanical ventilation, S-LOS: Shorter length of stay, L-LOS: Longer length of stay

**Table 2: Physical examination, electrocardiogram, laboratory, and echocardiographic features of groups**

Parameters	L-LOS	S-LOS	P
SBP (mmHg)	130.3±29.9	127.1±30.9	0.5
DBP (mmHg)	82.4±12.2	80.1±11.4	0.5
HR (bpm)	95.3±23.3	93.2±23.5	0.9
QRS duration (msn)	106.6±25.9	105.7±40.8	0.06
NT pro-BNP (pg/ml)	6701±978	8129±188	0.4
GFR (ml/pm/1.73 m <sup>2</sup> )	49.7±28.7	49.4±31.4	0.06
Hb (g/dl)	12.3±2.1	12.1±2.1	0.3
EF (%)	32.1±12.1	35.5±12.9	0.2
EF groups (%)			
HFrEF	67	64	0.3
HFmrEF	17	15	0.3
HFpEF	16	21	<0.001

S-LOS: Shorter length of stay, L-LOS: Longer length of stay, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, NT-proBNP: N-terminal pro B-type natriuretic peptide, GFR: Glomerular filtration rate, Hb: Hemoglobin, EF: Ejection fraction, HF: Heart failure, HFrEF: HF patients with reduced EF, HFmrEF: HF patients with mid-range EF, HFpEF: HF patients with preserved EF

L-LOS patient's groups. The mean GFR value was below 60 ml/min/1.73 m<sup>2</sup>. The prevalence of CKD patients was higher in L-LOS group. The prevalence of other comorbidities (HT, DM, AF, etc.) was similar between the two groups. ACS is an important clinical situation, especially for *de novo* AHF. Most of the patients with ACS-related AHF benefit from

revascularization therapy. In our study group, ACS-related AHF caused longer hospital stay.

NYHA functional classification has been used to describe the severity of symptoms and exercise intolerance. The term advanced HF (NYHA III-IV) is used to characterize patients with severe symptoms, recurrent decompensation, and severe cardiac dysfunction.<sup>[11]</sup> The prevalence of NYHA III-IV patients was higher in L-LOS group than S-LOS group. Cardiogenic shock and pulmonary edema are the two most serious clinical presentation of AHF. They increase LOS and in-hospital mortality. We demonstrated correlation between L-LOS and pulmonary edema and cardiogenic shock, but after multivariate analysis, this correlation was just continued for cardiogenic shock. Right HF is an important consequence of HF patients. Right ventricular dysfunction predicted poor outcomes in patients with stable CHF.<sup>[12]</sup> Yamin *et al.* showed right ventricular dysfunction as a predictor of longer hospital stay in patients with acute decompensated HF.<sup>[13]</sup> Likewise, right HF was one of the determinants of L-LOS in patients with ADCHF in our study. Invasive or noninvasive mechanical ventilation is necessary for hypoxemic HF patients. It reflects the hypoxemia due to volume overload, especially in lung parenchyma. Hemodynamic monetarization is necessary for the management of inotropic or vasodilator therapy in patients with hypertensive or hypotensive HF. The requirement of respiratory support and hemodynamic monetarization was higher in L-LOS group than S-LOS group.

## CONCLUSION

Our study is the largest scale study to investigate the determinants of longer hospital stay in Turkish HF population that was hospitalized due to AHF. It gives important clues to improve health-care quality and shorten the LOS in Turkey. L-LOS is an important surrogate subsequent hospital readmission and mortality. Since our study is retrospective in nature, we do not have an idea about the prevalence of hospital readmission and mortality among patients with L-LOS. Prospective studies are necessary to present this relation.

Our study has several limitations. Surveys based on voluntary participation and recruitment of patients have obvious limitations that have to be acknowledged. Although participant sites were encouraged to enroll patients, as consecutively as possible, the study population may not represent the general population. The registry data are based on only by documentation of medical history, and management during hospitalization and the follow-up data are not obtained.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, *et al.* Heart disease and stroke statistics-2014 update. *Circulation* 2014;129:e28-92.
2. Heidenreich PA, Sahay A, Kapoor JR, Pham MX, Massie B. Divergent trends in survival and readmission following a hospitalization for heart failure in the veterans affairs health care system 2002 to 2006. *J Am Coll Cardiol* 2010;56:362-8.
3. Cotter G, Davison BA, Milo O, Bourge RC, Cleland JG, Jondeau G, *et al.* Predictors and association with outcomes of length of hospital stay in patients with acute heart failure: Results from VERITAS. *J Card Fail* 2016;22:815-22.
4. Wright SP, Verouhis D, Gamble G, Swedberg K, Sharpe N, Doughty RN, *et al.* Factors influencing the length of hospital stay of patients with heart failure. *Eur J Heart Fail* 2003;5:201-9.
5. Aziz EF, Javed F, Pratap B, Musat D, Nader A, Plumi S, *et al.* Malnutrition as assessed by nutritional risk index is associated with worse outcome in patients admitted with acute decompensated heart failure: An ACAP-HF data analysis. *Heart Int* 2011;6:e2.
6. Kyle UG, Schneider SM, Pirlich M, Lochs H, Hebuterne X, Pichard C. Does nutritional risk, as assessed by nutritional risk index, increase during hospital stay? A multi-national population based study. *Clin Nutr* 2005;24:516-24.
7. Sinan UY, Ekmekçi A, Özbay B, Akçay FA, Bekar L, Koza Y, *et al.* The real life data of hospitalized patients with heart failure: On behalf of journey HF-TR study investigators. *Anatol J Cardiol* 2018. Doi:10.14744/Anatol J Cardiol.2018.50880.
8. Caughey MC, Avery CL, Ni H, Solomon SD, Matsushita K, Wruck LM, *et al.* Outcomes of patients with anemia and acute decompensated heart failure with preserved versus reduced ejection fraction (from the ARIC study community surveillance). *Am J Cardiol* 2014;114:1850-4.
9. Shirakabe A, Hata N, Kobayashi N, Shinada T, Tomita K, Tsurumi M, *et al.* Prognostic impact of acute kidney injury in patients with acute decompensated heart failure. *Circ J* 2013;77:687-96.
10. Reynolds K, Butler MG, Kimes TM, Rosales AG, Chan W, Nichols GA. Relation of acute heart failure hospital length of stay to subsequent readmission and all-cause mortality. *Am J Cardiol* 2015;116:400-5.
11. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, *et al.* 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC). Developed with the special contribution of the heart failure association (HFA) of the ESC. *Eur J Heart Fail* 2016;18:891-975.
12. Gajanana D, Seetha Rammohan H, Alli O, Romero-Corral A, Purushottam B, Ponamgi S, *et al.* Tricuspid annular plane systolic excursion and its association with mortality in critically ill patients. *Echocardiography* 2015;32:1222-7.
13. Yamin PP, Rharjo SB, Putri VK, Hersunarti N. Right ventricular dysfunction as predictor of longer hospital stay in patients with acute decompensated heart failure: A prospective study in Indonesian population. *Cardiovasc Ultrasound* 2016;14:14-25.

# Potential Factors Affecting the Anticoagulation Control in Patients Treated with Warfarin: Results WARFARIN-TR Study

Salih Kilic, Ahmet Çelik<sup>1</sup>, Ali Sabri Seyis<sup>2</sup>, Ozge Kurmus<sup>3</sup>, Kamil Tülüce<sup>4</sup>, Zeynep Yapan Emren<sup>5</sup>, Ali Kemal Kalkan<sup>6</sup>, Mehdi Zoghi<sup>7</sup>

Department of Cardiology, Doctor Ersin Arslan Research and Training Hospital, Gaziantep, <sup>1</sup>Department of Cardiology, Faculty of Medicine, Mersin University, Mersin, <sup>2</sup>Department of Cardiology, Istinie University Liv Hospital, Istanbul, <sup>3</sup>Department of Cardiology, Ufuk University, Faculty of Medicine, Ankara, <sup>4</sup>Department of Cardiology, Karsiyaka State Hospital, <sup>5</sup>Department of Cardiology, Tepecik Research and Training Hospital, <sup>6</sup>Department of Cardiology, Faculty of Medicine, Ege University, Izmir, <sup>7</sup>Department of Cardiology, Sandikli State Hospital, Afyon, Turkey

## Abstract

**Background:** In the present study, we aimed to evaluate the factors that might be caused by adequate anticoagulation control in patients treated with warfarin for any reason. **Methods:** The WARFARIN-TR (The Awareness, Efficacy, Safety, and Time in Therapeutic Range of Warfarin in Turkish Population) study included 4987 patients using warfarin between January 1, 2014 and December 31, 2014. Time in therapeutic range (TTR) was calculated according to F. R. Roosendaal's algorithm with linear interpolation. The study population divided into two groups; adequate international normalized ratio (INR) control when TTR  $\geq 70\%$  (Group 1,  $n = 1068$ , 21.4%) and inadequate INR control when TTR  $< 70\%$  (Group 2,  $n = 3919$ , 78.6%). All demographic and clinic characteristics of the patients were compared to determine possible factors that might be cause adequate warfarin use. **Results:** The mean age of the study population was  $60.7 \pm 13.5$  years, and there was no significant difference between groups. The mean TTR value of Group 1 was significantly higher than Group 2 ( $80 \pm 8.5$  vs.  $40.9 \pm 17.2$ ;  $P < 0.001$ ). The traditional cardiovascular risk factors were similar between groups except hypertension (Group 1 51.4% and Group 2 56.4%;  $P = 0.004$ ) and chronic kidney disease (Group 1 8.3% and Group 2 5.5%;  $P = 0.001$ ). There were no significant differences between groups regarding bleeding. The awareness of warfarin use was significantly higher in Group 1 patients than Group 2 patients. Multivariate logistic regression analysis revealed that age (odds ratio [OR], 1.007;  $P = 0.014$ ), hypertension (OR, 0.821;  $P = 0.01$ ), atrial fibrillation (OR, 1.180;  $P = 0.033$ ), chronic kidney disease (OR, 1.697;  $P < 0.001$ ), to know warfarin use reason (OR, 1.699;  $P < 0.001$ ), and know to food-drug interaction with warfarin (OR, 1.583;  $P < 0.001$ ) were independent predictors of adequate coagulation. **Conclusion:** Our study demonstrated that a low proportion of patients taking warfarin achieve an adequate TTR in daily practice. Furthermore, the patients with adequate TTR are more aware of warfarin use.

**Keywords:** Adequate anticoagulation, warfarin, warfarin awareness

## INTRODUCTION

Warfarin is an effective oral anticoagulant which is used for the prevention of thromboembolic events especially in patients with atrial fibrillation (AF) and prosthetic valve. Warfarin reduces the stroke by 64% compared to the placebo in patients with AF, and it is the unique treatment for prosthetic valve patients.<sup>[1,2]</sup> The efficacy and safety of warfarin are dependent on maintenance of the international normalized ratio (INR). The target INR values alter according to the reason of warfarin use; the TTR should be above 70% for optimal efficacy and safety of warfarin use.<sup>[3-6]</sup> The risk of total mortality and major bleeding increases with TTR value below 70%.<sup>[3,5]</sup> However, many studies from Turkey

have shown that the number of patients with TTR value above 70% is very low in daily practice. Previous studies have shown that many factors may cause a low rate of TTR in different study populations.

In the present study, we aimed to evaluate the factors that might be caused by adequate anticoagulation control in patients treated with warfarin in the WARFARIN-TR (The Awareness,

**Address for correspondence:** Dr. Salih Kilic, Department of Cardiology, Doctor Ersin Arslan Research and Training Hospital, Sahinbey, Gaziantep, Turkey. E-mail: kilicshh@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Kilic S, Çelik A, Seyis AS, Kurmus Ö, Tülüce K, Emren ZY, *et al.* Potential factors affecting the anticoagulation control in patients treated with warfarin: Results WARFARIN-TR study. *Int J Cardiovasc Acad* 2018;4:86-9.

### Access this article online

#### Quick Response Code:



**Website:**  
<http://www.ijcva.com>

**DOI:**  
10.4103/IJCA.IJCA\_43\_18

Efficacy, Safety, and Time in Therapeutic Range of Warfarin in Turkish Population) population study.

## METHODS

The design, conduct, and both main and subgroup results of the WARFARIN-TR study have been presented previously.<sup>[7-9]</sup> In brief, WARFARIN-TR study is a multi-center prospective observational study included 42 centers from 24 cities in seven regions of Turkey. Patients ( $n = 4987$ , mean age:  $60.7 \pm 13.5$  years, 44.9% male) attended follow-ups for 12 months. Of the total number of patients, 2124 (42.6%) had a mechanical valve, 1918 (38.4%) had nonvalvular AF, and 985 (19%) had other conditions as warfarin indications. The patients' data were recorded during routine clinic follow-up, and the INR values were recorded from the hospital records. The patients' INR data were extracted for the period of January 1, 2014–December 31, 2014. TTR was calculated as the proportion of days with INR values between the target INR (2.0–3.0 or 2.5–3.5). The safety and efficacy of warfarin therapy are dependent on maintaining the INR within the target is 2.5 (range 2.0–3.0) for patients with a mechanical aortic valve, nonvalvular AF, and other reasons. The target of INR value was 3 (2.5–3.5) in patients with a mechanical mitral valve and/or mechanical heart valves in both the aortic and mitral position.<sup>[10]</sup> TTR was calculated according to F. R. Roosendaal's algorithm with linear interpolation.<sup>[11]</sup>

For the hypothesis of the present study, we divided patients into two groups; adequate INR control when  $TTR \geq 70\%$  (Group-1,  $n = 1068$ , 21.4%) and inadequate INR control when  $TTR < 70\%$  (Group-2,  $n = 3919$ , 78.6%). All demographic and clinic characteristics of the patients were compared to determine possible factors that might be cause adequate warfarin use.

### Statistical analysis

The continuous variables were presented as mean  $\pm$  standard deviation, and the categorical variables were expressed as number and percentage (%). The continuous variables were compared with the Student's *t*-test or the Mann–Whitney U-test. Chi-square test or Fisher's exact test were used to compare categorical variables. The homogeneity of the variances was tested with Levene's test. To determine the independent predictors of  $TTR \geq 70\%$ , the logistic regression analysis was structured. The possible factors that identified with univariate analyses were entered into the logistic regression analysis. The Statistical Package for the Social Sciences (SPSS for Windows, Version 20.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.  $P < 0.05$  was determined as statistically significant.

## RESULTS

Of the 4987 patients included in the Warfarin-TR study, only one in fifth had adequate anticoagulation control (Group 1,  $n = 1068$ , 21.4%). Baseline demographic and clinical characteristics of the two groups are summarized in Table 1.

**Table 1: Baseline clinical and demographic characteristics of groups**

Variables	Group 1 ( $n=1068$ ), $n$ (%)	Group 2 ( $n=3919$ ), $n$ (%)	<i>P</i>
Age (year) and mean $\pm$ SD	60.6 $\pm$ 13.5	60.8 $\pm$ 13.3	0.638
Female	582 (54.5)	2167 (55.3)	0.641
TTR (%) and mean $\pm$ SD	80 $\pm$ 8.5	40.9 $\pm$ 17.2	<0.001
Number of INR monitoring 1 year and mean $\pm$ SD	10.3 $\pm$ 3.5	10.2 $\pm$ 2.8	0.294
Hypertension	549 (51.4)	2209 (56.4)	0.004
Diabetes mellitus	229 (21.4)	811 (20.7)	0.594
Current smoker	214 (20.0)	821 (20.9)	0.515
Hyperlipidemia	237 (22.2)	832 (21.2)	0.497
Atrial fibrillation	641 (60.0)	2231 (56.9)	0.070
Heart failure	242 (22.7)	979 (25.0)	0.118
Antiplatelet agent use	243 (22.8)	962 (24.5)	0.225
Coronary artery disease	240 (22.5)	916 (23.4)	0.536
Pulmonary embolism	53 (5.0)	196 (5.0)	0.959
Deep venous thrombosis	43 (4.0)	231 (5.9)	0.018
Cerebrovascular event	101 (9.5)	364 (9.3)	0.866
Chronic kidney disease	89 (8.3)	215 (5.5)	0.001
Following doctor (cardiologist)	1018 (95.3)	3611 (92.3)	<0.001
Any bleeding event	198 (18.4)	807 (20.6)	0.138
Major bleeding	33 (3.1)	12 (3.2)	0.869
Minor bleeding	165 (15.4)	682 (17.4)	0.132
Warfarin use reason			
NVAf	433 (40.5)	1485 (37.9)	0.078
MHV	456 (42.7)	1666 (42.5)	
Other	179 (16.8)	768 (19.8)	

MHV: Mechanical heart valve, NVAf: Nonvalvular atrial fibrillation, SD: Standard deviation, TTR: Time in therapeutic range, INR: International normalized ratio

The mean age of the study population was  $60.7 \pm 13.5$  years, and there was no significant difference between the two groups. The mean TTR value of Group 1 was significantly higher than Group 2 ( $80 \pm 8.5$  vs.  $40.9 \pm 17.2$ ;  $P < 0.001$ ). The traditional cardiovascular risk factors were similar between groups except hypertension (Group 1 51.4%, Group 2 56.4%;  $P = 0.004$ ) and chronic kidney disease (Group 1 8.3%, Group 2 5.5%;  $P = 0.001$ ). There were no statistically significant differences between groups regarding warfarin use reason. Although majority of the patients were followed by a cardiologist, the number of patients who followed by a cardiologist were significantly higher in Group 1 than Group 2 (95.3% vs. 92.3%;  $P < 0.001$ ). Even though any bleeding and minor bleeding events were higher in Group 2 than Group 1, it was not statistically significant. Furthermore, the major bleeding rate was similar between groups [Table 2]. The awareness of warfarin use which determined with three questions, known to use warfarin, known to the reason of warfarin use, and known to food-drug interactions with warfarin, was significantly higher in Group 1 than Group 2 [Figure 1]. Multivariate logistic regression analysis revealed that age (odds ratio [OR], 1.007; 95% confidence interval [CI], 1.002–1.013;  $P = 0.014$ ),

hypertension (OR, 0.821; 95% CI, 0.707–0.955;  $P=0.01$ ), AF (OR, 1.180; 95% CI, 1.014–1.374;  $P=0.033$ ), chronic kidney disease (OR, 1.697; 95% CI, 1.301–2.215;  $P < 0.001$ ), to known warfarin use reason (OR, 1.699; 95% CI, 1.341–2.153;  $P < 0.001$ ), and known to food-drug interaction with warfarin (OR, 1.583; 95% CI, 1.350–1.857;  $P < 0.001$ ) were independent predictors of adequate coagulation [Table 3].

## DISCUSSION

Our study that reflecting daily practice determined that only one-fifth of the patients who use warfarin for any reason have adequate coagulation. In addition, the mean TTR value of groups was dramatically different. This result showed that the patients with adequate coagulation control had highly good control; however, the patients with inadequate coagulation have extremely poor control. Moreover, our results revealed that the awareness of warfarin use of patients with adequate coagulation was significantly higher than inadequate coagulation, and it is independent predictors of adequate coagulation.

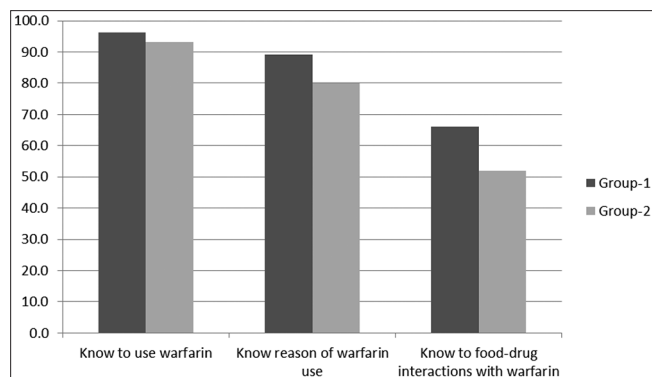
**Table 2: Comparison of bleeding ratio between groups**

Bleeding type	Group 1 (n=1068), n (%)	Group 2 (n=3919), n (%)	P
Any bleeding event	198 (18.4)	807 (20.6)	0.138
Major bleeding	33 (3.1)	12 (3.2)	0.869
Minor bleeding	165 (15.4)	682 (17.4)	0.132

**Table 3: Predictors of time in therapeutic range  $\geq 70\%$  in multivariate logistic regression analysis**

Variable	OR	95% CI	P
Age	1.007	1.002-1.013	0.014
Hypertension	0.821	0.707-0.955	0.010
Atrial fibrillation	1.180	1.014-1.374	0.033
Chronic kidney disease	1.697	1.301-2.215	<0.001
To know warfarin use reason	1.699	1.341-2.153	<0.001
Know to food-drug interaction with warfarin	1.583	1.350-1.857	<0.001

CI: Confidence interval, OR: Odds ratio



**Figure 1: Comparison of awareness of warfarin use**

Our results are fairly consistent with previous studies that conducted in Turkish patients.<sup>[12-14]</sup> In their study, Turk *et al.* reported that the mean TTR was 42.3%  $\pm$  18.4% in patients with valvular and nonvalvular AF. In the same study, 44% of patients had TTR <40%.<sup>[12]</sup> Ertaş *et al.* conducted a study that included 2242 patients with at least one AF episode reported that only 41.3% of all patients had adequate INR levels.<sup>[13]</sup> Furthermore, the study conducted by our group have shown that although mean TTR level was favorable in warfarin specialized outpatients clinic (68.8% $\pm$ 15.88), it was unfavorable in general cardiology outpatients clinic (51.6% $\pm$ 23.04).<sup>[14]</sup> Even though the mean TTR of general cardiology outpatient's clinic is higher than other studies that conducted by Turk and Ertaş, it is so far from adequate value. Furthermore, this study has shown the importance of follow-up clinic. In WARFARIN-TR study, we did not evaluate the effect of specialized and general outpatient's clinic separately. However, we recorded the physician that follow-up patients. Although the majority of patients followed up by a cardiologist, the number in Group 1 was significantly higher than Group 2. Previous studies have shown that comorbidities such as diabetes mellitus, hypertension, and heart failure might be associated with inadequate TTR control.<sup>[15,16]</sup> On the contrary of previous studies, in this study, there were no significant differences between groups regarding traditional cardiovascular risk factors except hypertension and chronic kidney disease. Chronic kidney disease is an independent predictor of adequate coagulation. This might be explained by the patients with chronic kidney disease tightly follow-up by their physicians both for kidney function and warfarin use. On the other hand, hypertension is significantly higher in Group 2 that may explain by an explanatory mechanism is the possible interaction between warfarin and drugs administered to hypertension. The awareness of warfarin use is important in achieving the optimal TTR. As we emphasized, above the follow-up, clinics are play an important role in adequate coagulation.<sup>[14,17,18]</sup> Previous studies have shown that significantly higher TTR level is reached with INR specialized outpatient clinics rather than general clinics follow-up coagulation.<sup>[14,17,18]</sup> An advantage of INR specialized outpatient clinics is frequent reminding of food-drug interaction with warfarin that might result in better TTR value. In the present study, we showed that the awareness of warfarin use was an independent predictor of adequate coagulation. The safety and efficacy of warfarin therapy depend critically on maintaining the INR within the therapeutic range.<sup>[19-22]</sup> Many studies found that a vast number of bleeding events occurred when the INR was outside the therapeutic range.<sup>[22,23]</sup> Similarly, to the previous studies, in this study, the number of any bleeding and minor bleeding were higher in Group 2 than Group 1; however, it was not statistically significant. In contrast to the previous studies, the major bleeding rate was similar between groups. The low number of bleeding might be due to short follow-up periods of patients and also incomplete declarations of patients.

## CONCLUSION

Our study demonstrated that a low proportion of patients taking warfarin achieve an adequate coagulation in daily practice. Furthermore, patients with adequate coagulation were more aware of warfarin use.

## Limitations

The main limitation of our study was that we did not evaluate the stroke rate of the patient during the study period. Another limitation is that due to the study conducted in outpatient clinics, it might be caused by limited answers of patients in some busy outpatient clinics.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, *et al.* Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;349:1019-26.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
- White HD, Gruber M, Feyzi J, Kaatz S, Tse HF, Husted S, *et al.* Comparison of outcomes among patients randomized to warfarin therapy according to anticoagulant control: Results from SPORTIF III and V. *Arch Intern Med* 2007;167:239-45.
- Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, *et al.* 2012 focused update of the ESC guidelines for the management of atrial fibrillation: An update of the 2010 ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012;33:2719-47.
- Gallagher AM, Setakis E, Plumb JM, Clemens A, van Staa TP. Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. *Thromb Haemost* 2011;106:968-77.
- Cove CL, Hylek EM. An updated review of target-specific oral anticoagulants used in stroke prevention in atrial fibrillation, venous thromboembolic disease, and acute coronary syndromes. *J Am Heart Assoc* 2013;2:e000136.
- Çelik A, İzci S, Kobat MA, Ateş AH, Çakmak A, Çakılı Y, *et al.* The awareness, efficacy, safety, and time in therapeutic range of warfarin in the Turkish population: WARFARIN-TR. *Anatol J Cardiol* 2016;16:595-600.
- Kılıç S, Çelik A, Çekirdekçi E, Altay S, Elçik D, Akboğa MK, *et al.* The prevalence and risks of inappropriate combination of aspirin and warfarin in clinical practice: Results from WARFARIN-TR study. *Balkan Med J* 2018. [Epub ahead of print].
- Kılıç S, Çelik A, Çakmak HA, Afşin A, Tekkeşin AI, Açıksarı G, *et al.* The time in therapeutic range and bleeding complications of warfarin in different geographic regions of Turkey: A subgroup analysis of WARFARIN-TR study. *Balkan Med J* 2017;34:349-55.
- Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic therapy and prevention of thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141:7S-47S.
- Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236-9.
- Türk UO, Tuncer E, Alioğlu E, Yuksel K, Pekel N, Ozpelit E, *et al.* Evaluation of the impact of warfarin time in therapeutic range on outcomes of patients with atrial fibrillation in Turkey: Perspectives from the observational, prospective WATER registry. *Cardiol J* 2015;22:567-75.
- Ertaş F, Kaya H, Kaya Z, Bulur S, Köse N, Gül M, *et al.* Epidemiology of atrial fibrillation in Turkey: Preliminary results of the multicenter AFTER study. *Turk Kardiyol Dern Ars* 2013;41:99-104.
- Kılıç S, Soner Kemal H, Yüce EI, Şimşek E, Yağmur B, Memişoğlu Akgül N, *et al.* Comparison of warfarin use in terms of efficacy and safety in two different polyclinics. *Anatol J Cardiol* 2017;18:328-33.
- Melamed OC, Horowitz G, Elhayany A, Vinker S. Quality of anticoagulation control among patients with atrial fibrillation. *Am J Manag Care* 2011;17:232-7.
- Ciurus T, Cichocka-Radwan A, Lelonek M. Factors affecting the quality of anticoagulation with warfarin: Experience of one cardiac centre. *Kardiochir Torakochirurgia Pol* 2015;12:334-40.
- Fitzmaurice DA, Hobbs FD, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: A randomized, controlled trial. *Arch Intern Med* 2000;160:2343-8.
- Wilson SJ, Wells PS, Kovacs MJ, Lewis GM, Martin J, Burton E, *et al.* Comparing the quality of oral anticoagulant management by anticoagulation clinics and by family physicians: A randomized controlled trial. *CMAJ* 2003;169:293-8.
- Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandembroucke JP, Briët E, *et al.* Optimal oral anticoagulant therapy in patients with mechanical heart valves. *N Engl J Med* 1995;333:11-7.
- Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994;120:897-902.
- A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) study group. *Ann Neurol* 1997;42:857-65.
- Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke prevention in atrial fibrillation III randomised clinical trial. *Lancet* 1996;348:633-8.
- Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. *N Engl J Med* 1996;335:540-6.

# Association of Neutrophil to Lymphocyte Ratio with Lower Patency Rates among Patients with Infrapopliteal Arterial Disease Undergoing Balloon Angioplasty

Abdulkadir Uslu, Regayip Zehir, Elnur Alizade, Ayhan K p, Zubeyde Bayram, Ahmet Guner, S leyman Barutcu<sup>1</sup>

Department of Cardiology, Kartal Kosuyolu Heart Research and Training Hospital, Istanbul, <sup>1</sup>Department of Cardiology, Van Research and Education Hospital, Van, Turkey

## Abstract

**Introduction:** Percutaneous endovascular methods have emerged to the contemporary revascularization choice in patients with infrapopliteal (IP) arterial disease. However, restenosis remains to be the Achilles' heel of this minimally invasive revascularization techniques. We aimed to analyze the association between preprocedural (neutrophil to lymphocyte ratio) Neutrophil-to-Lymphocyte ratio (NLR) and subsequent patency in a cohort of patients with symptomatic IP disease undergoing balloon angioplasty. **Methods:** All patients primarily treated with angioplasty of at least one IP artery causing severe symptoms or critical limb ischemia (CLI) (Rutherford category 1–6) between January 2014 and August 2015 were analyzed. The baseline demographic, clinical, and angiographic features admission laboratory test results were obtained from hospital files and computer records. NLR was calculated as the preprocedural ratio of neutrophils to lymphocytes. **Results:** The study population involved 42 (43.8%) CLI patients and 52 (54.2%) claudicants. The most frequent target vessel was the posterior tibial artery. Primary patency at 1 month was 81.9% and 62.7% at 6 months. NLR (odds ratio: 0.04,  $P = 0.03$ ) independently predicted patency at 1 month but did not have a role on arterial patency after 1 month. Only smoking (odds ratio: 4.8,  $P = 0.01$ ) associated with patency at 6 months. **Conclusion:** Preprocedural NLR was an independent risk factor for IP arterial patency at short-term. It may be used as a risk factor for subsequent amputation or recurrent interventions.

**Keywords:** Critical limb ischemia, infrapopliteal, neutrophil-to-lymphocyte ratio, patency, percutaneous transluminal angioplasty

## INTRODUCTION

Infrapopliteal (IP) occlusive disease is a severe and diffuse form of peripheral artery disease (PAD) and requires challenging revascularization procedures. Patients suffering from severe lifestyle-limiting claudication or critical limb ischemia (CLI) due to atherosclerosis of the crural arteries are often frailer and have higher amputation and mortality rates.<sup>[1]</sup> Percutaneous endovascular methods have emerged to the contemporary revascularization choice in these high-risk patients. Production of uninterrupted blood flow to the foot to allow wound healing, alleviation of pain, and preservation of limb mobility are the primary goals of interventions on the IP.<sup>[2]</sup> The main drawbacks with regard to endovascular interventions of these end arteries were the vessel patency, complications, and technical failure. Because of small caliber and high calcification and occlusion rates, below the knee

arteries is subject to a higher risk of restenosis and thrombosis than the other vascular districts. Percutaneous transluminal angioplasty (PTA) remains a reasonable primary treatment approach for IP despite high re-stenosis and re-intervention rates. Loss of arterial patency after intervention delays ischemic wound healing and achievement of ambulatory status and subsequently hinders improvement of clinical outcome.<sup>[3]</sup>

Neutrophil-to-lymphocyte ratio (NLR), an inflammatory biomarker, related to adverse vascular endpoints in the atherosclerotic spectrum of diseases.<sup>[4]</sup> It correlates with

**Address for correspondence:** Dr. Ahmet Guner,

Kartal Kosuyolu Heart and Research Hospital, Denizler Street, Kartal, 34846  
Istanbul, Turkey.  
E-mail: ahmetguner488@gmail.com

### Access this article online

Quick Response Code:



Website:  
<http://www.ijcv.com>

DOI:  
10.4103/IJCA.IJCA\_32\_18

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Uslu A, Zehir R, Alizade E, K p A, Bayram Z, Guner A, *et al.* Association of neutrophil to lymphocyte ratio with lower patency rates among patients with infrapopliteal arterial disease undergoing balloon angioplasty. *Int J Cardiovasc Acad* 2018;4:90-5.

biomarkers of proinflammatory state and reflects both the neutrophilia of inflammation and the relative lymphopenia of the cortisol-induced stress response. Elevated NLR has been associated with a high risk for CLI in PAD patients and higher mortality in patients with PAD who present with CLI.<sup>[5,6]</sup> NLR also predicts intimal proliferation and resultant restenosis in coronary arteries.<sup>[7]</sup> However, its predictive role on vessel patency after IP angioplasty in patients with symptomatic IP has not been demonstrated yet. Therefore, we aimed to assess the association between NLR and the 1 and 6 months patency rates in patients with IP after IP intervention. We hypothesized that preprocedural NLR would be associated with patency rate early after intervention but not thereafter.

## METHODS

This retrospective observational study was conducted at the Kartal Kosuyolu Heart Training and Research Hospital. All patients primarily treated with PTA of at least one IP artery causing severe symptoms or CLI (Rutherford category 1–6) between January 2014 and August 2015 were analyzed. A total of 134 patients (93 males) of mean age 65 years with 166 limbs were evaluated. Significant stenosis of inflow arteries if present had to be treated successfully before enrollment. The success rate was 93.2% (125 patients), and technically successful angioplasty of *de novo* lesions were included. CLI defined as the presence of chronic ischemic rest pain, ulcers, or gangrene attributable to objectively proven IP.<sup>[8]</sup> Technical success of IP PTA was described as recanalization with the antegrade flow and 30% or less residual stenosis of below the knee artery. PTA was performed through anterograde (ipsilateral or contralateral) or retrograde approach at the discretion of the treating interventional cardiologist. Stents were implanted if flow-limiting complications occurred. Unless contraindicated, all patients received aspirin, clopidogrel, statin and cilostazol after successful recanalization of the vessel. ON a 1-month course of combination antiplatelet therapy consisting of aspirin (100 mg) and clopidogrel (75 mg) were administered. Patients who failed to take the prescribed medication during follow-up were excluded from the study. Previous peripheral artery bypass graft surgery affecting the target limb, procedural complications requiring further surgical revascularization or immediate amputation postprocedure, amputation of treated limb above the metatarsal level and death of the patient during follow-up and patients with hematological, inflammatory or rheumatological diseases, and those treated with steroids or anti-inflammatory drugs were the exclusion criteria. Fourteen patients underwent amputation, 6 patients died during 6 months of follow-up. Primary patency of vessel attempted was accepted as the endpoint and evaluated at 1 and 6 months. Loss of patency defined as restenosis (>50%) or occlusion of the artery intervention on detected by computed tomography angiography or duplex scan. Peak systolic velocity ratio  $\geq 2.4$  value calculated on duplex ultrasound has been clinically established to represent >50% restenosis.<sup>[9]</sup> Primary patency was reported as continual patency with no procedure at the treated site or on a segment adjacent to it. The baseline demographic,

clinical, and angiographic features admission laboratory test results (including absolute neutrophil and lymphocyte counts) were obtained from hospital files and computer records. Blood samples were collected in calcium-ethylenediaminetetraacetic acid tubes. Blood counts were measured with an auto-analyzer. Neutrophil-to-lymphocyte ratio was calculated as the ratio of neutrophils to lymphocytes in the peripheral blood. Other routine laboratory parameters were also measured in our hospital's laboratory, from the blood samples obtained on the admission of the patients. NLR was calculated as the preprocedural ratio of neutrophils to lymphocytes. C-reactive protein (CRP) levels were measured on Cobas Integra analyzer (Roche Diagnostics, Istanbul, Turkey) using the turbidimetric method. The study was carried out according to the Declaration of Helsinki and was approved by the Local Ethics Committee. Written consent was obtained from all the patients.

Number Cruncher Statistical System (NCSS) 2007 (NCSS, LLC, Kaysville, Utah, USA) program was used for statistical analysis. Continuous variables are presented as mean values + standard deviation, whereas categorical ones are presented as percentage. Student's *t*-test was used for comparing parameters which show normal distribution and Mann–Whitney U-test was used for comparing variables that do not show normal distribution. Pearson Chi-square test was used for comparing categorical variables. Freedom from restenosis and freedom from occlusion based on the time to the first event for each target lesion. Multivariate logistic regression analysis carried out to identify independent predictors of patency. Variables with unadjusted  $P < 0.1$  by univariate analysis were identified and forced in the full model. Significance was determined at level for  $P < 0.05$ .

## RESULTS

The demographic and clinical characteristics and laboratory results of the study population are summarized in Table 1. There were no significant differences between the two groups in terms of basic clinical features. After exclusions, we identified 94 patients (62 male) who underwent PTA to 144 IP lesions during the study. Study population involved 42 (43.8%) CLI patients and 52 (54.2%) claudicants. Patients divided into two groups according to patency at 1 month. Primary patency at 1 month was 81.9% (restenosis in 17 patients), significantly different between the claudicant and CLI cohorts ( $P = 0.001$ ). Clinical characteristics of patients and lesion features with respect to vessel patency at 1 month are summarized in Table 1. Renal failure (glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup>) ( $P = 0.017$ ), dialysis ( $P = 0.001$ ) and smoking ( $P < 0.001$ ) were more common in the restenotic group. The most frequent target vessel was the posterior tibial artery in both groups and lesion features did not differ between groups. Preinterventional NLR and CRP levels were significantly higher in the stenotic group. On multivariate analysis CRP (odds: 0.07,  $P = 0.02$ ) and NLR (odds: 0.04,  $P = 0.03$ ) independently predicted patency at 1 month [Table 2]. To evaluate the trend for increase of restenosis rate for increasing NLR and CRP

**Table 1: Clinical characteristics of patients and lesion features with respect to vessel patency at 1 month**

Characteristics	Infrapopliteal vessel restenosis ( <i>n</i> =17), <i>n</i> (%)	Patent infrapopliteal vessel ( <i>n</i> =77), <i>n</i> (%)	<i>P</i>
Age, years	61.3±8.1	62.1±8.6	0.72
Male sex	14 (82.4)	48 (62.3)	0.16
Diabetes	8 (47.1)	38 (48.4)	0.53
BMI (cm <sup>2</sup> )	22.1±2	24.3±4	0.67
Arrhythmia	4 (23.5)	17 (22.1)	0.89
Congestive heart failure	2 (11.8)	19 (24.7)	0.24
Coronary artery disease	5 (29.4)	33 (42.9)	0.30
CABG or PCI	5 (29.4)	26 (33.8)	0.73
Hypertension	16 (94.1)	66 (87.5)	0.34
Hyperlipidemia	4 (23.5)	33 (42.9)	0.14
Renal insufficiency	8 (47.1)	15 (19.5)	0.017
Dialysis	5 (29.4)	3 (3.9)	0.001
Stroke	4 (23.5)	9 (11.7)	0.20
Current smoker	14 (82.6)	26 (33.8)	<0.001
Medication (cilastazol + statin)	87	83	>0.22
Chronic obstructive pulmonary disease	3 (17.6)	17 (22.1)	0.68
Clinic presentation			
Claudicants	3 (17.6)	49 (63.9)	0.001
Critical limb ischemia	14 (82.4)	28 (36.4)	
Rutherford category			
1	0	7 (9.1)	0.01
2	0	13 (16.9)	
3	3 (17.6)	29 (30.9)	
4	4 (23.5)	13 (13.8)	
5	10 (58.8)	28 (29.8)	
6	0	4 (4.3)	
Previous higher level revascularisation	3 (17.6)	29 (37.9)	0.11
Target artery, <i>n</i> (total)			
Anterior tibial	7 (27)	31 (114)	0.28
Peroneal	4 (27)	28 (114)	
Posterior tibial	9 (27)	32 (114)	
Tibioperoneal trunk	7 (27)	23 (114)	
Lesion length, cm	7±2.1	6.4±3	0.51
Baseline stenosis, %	79±13	75±12	0.21
Total occlusions	3 (17.6)	21 (27.3)	0.41
Calcification	4 (23.5)	19 (24.7)	0.91
Hemoglobin (mg/dL)	14±1.2	13±1.8	0.13
White blood cells (10 <sup>9</sup> /L)	10±2	9.8±1.9	0.44
Fasting glucose (g/dl)	173±81	143±64	0.11
NLR	6.0±1.1	2.9±1	<0.001
CRP, mg/L	5.6±2.2	2.0±0.8	<0.001

CABG: Coronary artery bypass graft, CRP: C reactive protein, NLR: Neutrophil-lymphocyte ratio, PCI: Percutaneous coronary intervention, BMI: Body mass index

Jonckheere-Terpstra test was performed and showed statistical significance ( $P < 0.001$  for both). Seventy-seven patients with patent vessels were followed up until 6 months and patency re-evaluated. Patency at 6 months was 62.7% (restenosis in 35 patients). 18 patients developed restenosis after the 1<sup>st</sup> month. Patients divided into two groups according to patency at 6 months. Stent was implanted in 7 patients in the whole patient population. Clinical characteristics of patients and lesion features with respect to vessel patency at 6 months are presented in Table 3. Patients with CLI had also higher restenosis rate at 6 months ( $P = 0.013$ ). There was no difference between

groups in vessel diameter, baseline stenosis, the prevalence of chronic occlusion, or extent of lesion calcification. Coronary artery disease ( $P = 0.02$ ), smoking ( $P = 0.001$ ), and CRP levels ( $P = 0.004$ ) were significantly different between groups. On multivariate analysis only smoking (odds ratio: 4.8,  $P = 0.01$ ) associated with patency at 6 months [Table 4].

## DISCUSSION

This study allowed evaluation the role of system inflammation on arterial patency rates after successful PTA for IP. The

findings of the present study show that NLR provides relevant information regarding the risk of restenosis at 1 month.

**Table 2: The predictors of the patency at 1 month in the multivariable logistic regression analyses**

Parameters	OR (95% CI)	P
Clinic presentation	0.73 (0.03-17.1)	0.84
Current smoker	0.31 (0.01-9.9)	0.51
Dialysis	0.02 (0-7.4)	0.21
NLR	0.04 (0.002-0.74)	0.03
CRP	0.07 (0.008-0.70)	0.02

CRP: C reactive protein, NLR: Neutrophil-lymphocyte ratio, OR: Odds ratio, CI: Confidence interval

Admission NLR was found to be an independent predictor of early restenosis rate.

Restenosis after IP angioplasty is frequent and not fully understood. Preprocedural identification of patients who are likely to benefit from PTA and those who might need recurrent or a more definitive intervention is crucial for the management of IP. The occurrence of restenosis during the wound healing process early after angioplasty would hamper limb salvage. Most of the data on its pathophysiological mechanisms come from the experience on coronary arteries due to their morphological similarities with crural arteries. Barotraumatic vessel dilatation triggers an intense

**Table 3: Clinical characteristics of patients and lesion features with respect to vessel patency at 6 months**

Characteristics	Infrapopliteal vessel restenosis (n=18), n (%)	Patent infrapopliteal vessel (n=59), n (%)	P
Age, years	64.3±10	61.4±8	0.22
Male sex	11 (61.1)	37 (62.7)	0.90
Diabetes	11 (61.1)	27 (45.7)	0.25
Arrhythmia	2 (11.1)	15 (25.1)	0.20
Congestive heart failure	5 (27.8)	14 (23.7)	0.72
Coronary artery disease	12 (66.7)	21 (35.6)	0.02
CABG or PCI	9 (50)	17 (28.8)	0.09
Hypertension	15 (83.3)	51 (86.4)	0.74
Hyperlipidemia	6 (33.3)	27 (45.8)	0.35
Renal insufficiency	5 (27.8)	10 (16.9)	0.31
Dialysis	1 (5.6)	2 (3.4)	0.67
Stroke	1 (5.6)	8 (13.6)	0.35
Current smoker	12 (66.7)	14 (23.7)	0.001
Medication (cilastazol + statin)	87	83	>0.22
Chronic obstructive pulmonary disease	4 (22.2)	13 (22)	0.98
Clinic presentation			
Claudicants	7 (38.9)	42 (71.2)	0.013
Critical limb ischemia	11 (61.1)	17 (28.8)	
Rutherford category			
1	3 (16.7)	4 (6.8)	0.11
2	1 (5.6)	12 (20.3)	
3	10 (55.6)	16 (27.1)	
4	1 (5.6)	8 (13.6)	
5	2 (11.1)	16 (27.1)	
6	1 (5.6)	3 (5.1)	
Previous higher level revascularization	7 (38.9)	22 (37.3)	0.90
Target artery, n (total)			
Anterior tibial	6 (22)	25 (91)	0.13
Peroneal	7 (22)	21 (91)	
Posterior tibial	8 (22)	24 (91)	
Tibioperoneal trunk	1 (22)	21 (91)	
Lesion length, cm	6.2±1.7	6.5±3.3	0.67
Baseline stenosis, %	76±13	75±12	0.60
Total occlusions	7 (38.9)	14 (23.7)	0.20
Calcification	4 (22.2)	15 (25.4)	0.78
Hemoglobin (mg/dL)	13.1±2	13.3±1.7	0.69
White blood cells (10 <sup>9</sup> /L)	9.9±2	9.8±2	0.79
Fasting glucose (g/dl)	134±39	146±70	0.47
NLR	3.1±1.1	2.8±0.9	0.36
CRP, mg/L	2.4±0.6	1.9±0.8	0.004

CABG: Coronary artery bypass graft, CRP: C reactive protein, NLR: Neutrophil-lymphocyte ratio, PCI: Percutaneous coronary intervention

**Table 4: The predictors of the patency at 6 months in the multivariable logistic regression analyses**

Parameters	OR (95% CI)	P
Current smoker	0.21 (0.72-0.059)	0.01
Clinical presentation	2.4 (0.68-8.6)	0.17
Coronary artery disease	2.9 (0.81-10.3)	0.09
CRP	0.57 (0.28-1.1)	0.17

CRP: C reactive protein, OR: Odds ratio, CI: Confidence interval

local inflammatory reaction that leads to proliferation and migration of smooth muscle cells, ending up with neointimal thickening and restenosis.<sup>[10]</sup> Besides this local vascular inflammation, the preexisting systemic inflammatory state also contributes to the restenotic process. The extent of vascular inflammation in response to PTA was associated with restenosis risk.<sup>[11]</sup> Violi *et al.* reported that increased levels of inflammatory markers were associated with poor long-term prognosis in patients with PAD.<sup>[12]</sup> The concentrations of inflammatory markers such as CRP, fibrinogen and some cytokines were found to be higher in a nonselective PAD patients population with restenosis.<sup>[13]</sup> However, it remains indeterminate whether these markers before PTA independently indicates increased risk for restenosis or causally conduce to its occurrence. Neither of them is of clinical utility in this context. NLR and CRP are widely used inflammatory markers reflecting both severity and extent of PAD.<sup>[14,15]</sup> Higher levels of these markers long after angioplasty indicates lower arterial patency rate and support the thesis that systemic inflammation is involved in the pathogenesis of postangioplasty restenosis. Neutrophil-derived myeloperoxidase promotes atherogenesis and neointimal proliferation.<sup>[16]</sup> Relatively low lymphocyte count is an expected finding in IP since it is more aggressive atherosclerosis and generates more pronounced cortisol-induced stress response. Relative lymphopenia was independently associated with higher mortality in CLI.<sup>[17]</sup> Previously, cardiovascular events have been reported to be associated with inflammatory markers and a less frequent cardiovascular event has been reported in patients with hs-crp levels <2 mg/dl.<sup>[18]</sup>

NLR accepted as a systemic indicator of vascular atherosclerotic burden. Preprocedural NLR was shown to be a powerful and independent predictor of restenosis in coronary arteries.<sup>[19]</sup> Spark *et al.* prospectively analyzed 149 patients with IP and found that admission NLR was significantly associated with limb salvage rates and mortality.<sup>[6]</sup> Furthermore, NLR provides useful information about postoperative mortality and graft patency after vascular surgery. Recently, Chan *et al.* re-evaluated role of NLR in patients CLI undergoing PTA in a retrospective fashion and found out that admission NLR was a predictor of clinical outcomes but did not correlate with patency rates at 1 year.<sup>[17]</sup> They both used the same NLR cut-off value (5.25) for comparison. We also did not find any association between admission NLR and arterial patency beyond 1 month.

Recent studies have emphasized the weight of IP patency toward clinical outcomes of IP patients during long-term follow-up. In a recent study published by Joshi *et al.* the authors showed that the presence and extent of acute coronary arterial occlusion is associated with exacerbated vascular atherosclerotic inflammation and re-occlusion at 1 month but not afterward.<sup>[20]</sup> Similarly, Bleda *et al.* elucidated that CRP values both on admission and at 1 month representing the ongoing inflammatory process had a strong association with 1-year revascularization events, and suggested pre-PTA CRP levels to determine patients at increased risk for poorer outcomes after lower extremity endovascular therapy.<sup>[21]</sup> Based on the findings of the present study, we thought that vascular inflammatory load might be associated with arterial patency rates only early after a successful intervention. After creating and maintaining straight-line blood flow to the extremities, patient mobility, and limb salvage can occur. Although local inflammatory reaction at vessel wall increases early after the intervention, systemic vascular inflammation would probably subside. None of the inflammatory markers was independently described as risk factor for restenosis, 6 months after femoral PTA. Similarly, successful lower extremity angioplasty with the reestablishment of peripheral arterial perfusion improves systemic vascular endothelial functions and reduces inflammatory cell counts at 1 month of follow-up.<sup>[22]</sup> We adopted strict exclusion criteria to avoid possible confounding factors capable of increasing systemic inflammatory status such as failure of limb salvage after the first attempt, amputation or re-intervention. Consistent with previous studies, patency rate at 6 months was not related to baseline systemic inflammatory burden in our cohort. We identified only smoking as an independent predictor of restenosis at 6 months. Smoking is the major risk factor associated with the development and progression of the peripheral arterial disease and vascular inflammatory reaction induced by smoking may contribute to restenosis process.<sup>[23]</sup>

Our finding that periprocedural NLR predicts early loss of primary patency also raises the question of whether anti-restenosis concepts targeting systemic vascular inflammatory load before the time of intervention could improve vessel patency after angioplasty.

Some limitations of this study should be taken into account before reviewing our results. This study represents single-center experience and lack long-term follow-up data. Furthermore, the retrospective nature of the investigation is an inherited weakness. Angiographically verified restenosis of IP arteries was shown to correlate with IP lesion length in the literature. Mean lesion length was similar to previous articles and was 6.5 cm in this study.<sup>[24]</sup> However, we did not identify any lesion characteristics as independent predictors of short and mid-term. Exclusion criteria, relatively short follow-up time and design of our investigation may help to explain this difference. In addition, our study is a cross-sectional study and studies with more patient populations are required.

Elevated NLR at the time of IP balloon angioplasty is associated with significantly decreased arterial patency at 1 month. Supporting the hypothesis that vascular inflammation is a key factor in the restenotic process, we identified preprocedural NLR as an independent risk factor for IP arterial patency at short-term. Like other studies, inflammatory markers did not correlate with restenosis on crural arterial territory mid-term. Hence, preprocedural NLR may also be a risk factor for subsequent amputation or need for surgical revascularization early after PTA among patients with IP.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

- Rand T, Uberoi R. Current status of interventional radiology treatment of infrapopliteal arterial disease. *Cardiovasc Intervent Radiol* 2013;36:588-98.
- Sigala F, Kontis E, Hepp W, Filis K, Melissas J, Mirilas P, *et al.* Long-term outcomes following 282 consecutive cases of infrapopliteal PTA and association of risk factors with primary patency and limb salvage. *Vasc Endovascular Surg* 2012;46:123-30.
- Iida O, Soga Y, Kawasaki D, Hirano K, Yamaoka T, Suzuki K, *et al.* Angiographic restenosis and its clinical impact after infrapopliteal angioplasty. *Eur J Vasc Endovasc Surg* 2012;44:425-31.
- Verdoia M, Barbieri L, Di Giovine G, Marino P, Suryapranata H, De Luca G, *et al.* Neutrophil to lymphocyte ratio and the extent of coronary artery disease: Results from a large cohort study. *Angiology* 2016;67:75-82.
- Gary T, Pichler M, Belaj K, Hafner F, Gerger A, Froehlich H, *et al.* Neutrophil-to-lymphocyte ratio and its association with critical limb ischemia in PAOD patients. *PLoS One* 2013;8:e56745.
- Spark JI, Sarveswaran J, Blest N, Charalabidis P, Asthana S. An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia. *J Vasc Surg* 2010;52:632-6.
- Balli M, Taşolar H, Çetin M, Tekin K, Çağlıyan ÇE, Türkmen S, *et al.* Use of the neutrophil to lymphocyte ratio for prediction of in-stent restenosis in bifurcation lesions. *Eur Rev Med Pharmacol Sci* 2015;19:1866-73.
- Elsayed S, Clavijo LC. Critical limb ischemia. *Cardiol Clin* 2015;33:37-47.
- Ranke C, Rieder M, Creutzig A, Alexander K. A nomogram of duplex ultrasound quantification of peripheral arterial stenoses. Studies of the cardiovascular model and in angiography patients. *Med Klin (Munich)* 1995;90:72-7.
- Tiroch KA, Byrne RA, Kastrati A. Pharmacological prevention and management of restenosis. *Expert Opin Pharmacother* 2010;11:1855-72.
- Joviliano EE, Piccinato CE, Dellalibera-Joviliano R, Moriya T, Évora PR. Inflammatory markers and restenosis in peripheral percutaneous angioplasty with intravascular stenting: Current concepts. *Ann Vasc Surg* 2011;25:846-55.
- Violi F, Criqui M, Longoni A, Castiglioni C. Relation between risk factors and cardiovascular complications in patients with peripheral vascular disease. Results from the A.D.E.P. study. *Atherosclerosis* 1996;120:25-35.
- Kotschy D, Kotschy M, Maslowski L, Socha P, Kwapisz J, Czyżewska-Buczyńska A, *et al.* Inflammatory markers in peripheral arterial diseases patients after endovascular revascularization with new restenosis. *Acta Angiol* 2014;20:47-59.
- Vainas T, Stassen FR, de Graaf R, Twiss EL, Herngreen SB, Welten RJ, *et al.* C-reactive protein in peripheral arterial disease: Relation to severity of the disease and to future cardiovascular events. *J Vasc Surg* 2005;42:243-51.
- Amrock SM, Weitzman M. Multiple biomarkers for mortality prediction in peripheral arterial disease. *Vasc Med* 2016;21:105-12.
- Tiyerili V, Camara B, Becher MU, Schrickel JW, Lütjohann D, Mollenhauer M, *et al.* Neutrophil-derived myeloperoxidase promotes atherogenesis and neointima formation in mice. *Int J Cardiol* 2016;204:29-36.
- Chan C, Puckridge P, Ullah S, Delaney C, Spark JI. Neutrophil-lymphocyte ratio as a prognostic marker of outcome in infrapopliteal percutaneous interventions for critical limb ischemia. *J Vasc Surg* 2014;60:661-8.
- Lorenzatti A, Servato ML. Role of anti-inflammatory interventions in coronary artery disease: Understanding the canakinumab anti-inflammatory thrombosis outcomes study. *Eur Cardiol* 2018;13:38-41.
- Turak O, Ozcan F, Isleyen A, Tok D, Sokmen E, Buyukkaya E, *et al.* Usefulness of the neutrophil-to-lymphocyte ratio to predict bare-metal stent restenosis. *Am J Cardiol* 2012;110:1405-10.
- Joshi NV, Toor I, Shah AS, Carruthers K, Vesey AT, Alam SR, *et al.* Systemic atherosclerotic inflammation following acute myocardial infarction: Myocardial infarction begets myocardial infarction. *J Am Heart Assoc* 2015;4:e001956.
- Bleda S, de Haro J, Varela C, Acin F. C-reactive protein and endovascular treatment of lower limb peripheral artery disease: An independent prognostic factor. *J Endovasc Ther* 2015;22:233-9.
- Husmann M, Dörffler-Melly J, Kalka C, Diehm N, Baumgartner I, Silvestro A, *et al.* Successful lower extremity angioplasty improves brachial artery flow-mediated dilation in patients with peripheral arterial disease. *J Vasc Surg* 2008;48:1211-6.
- Schillinger M, Exner M, Mlekusch W, Haumer M, Sabeti S, Ahmadi R, *et al.* Effect of smoking on restenosis during the 1<sup>st</sup> year after lower-limb endovascular interventions. *Radiology* 2004;231:831-8.
- Baumann F, Willenberg T, Do DD, Keo HH, Baumgartner I, Diehm N, *et al.* Endovascular revascularization of below-the-knee arteries: Prospective short-term angiographic and clinical follow-up. *J Vasc Interv Radiol* 2011;22:1665-73.