Volume 3 Issue 4, October 2021
ISSN: 2687-4245

Turkish Journal of Internal Medicine

Turkish Journal of Internal Medicine

http://www.tjim.org

e-ISSN:2687-4245

Aim and Scope

Turkish Journal of Internal Medicine (TJIM) is an international peer-reviewed scientific journal that publishes manuscripts describing both clinical and basic science research in medicine. Manuscripts must describe original data that has not been published previously nor submitted for publication elsewhere. Manuscripts that adhere to the TJIM submission guidelines and are deemed appropriate for the scope of the journal are sent to two reviewers who are specialists in the field. The reviewers' comments are then considered by the members of the TJIM Executive Editorial Board who discuss the suitability of each submission. The final decision for all submitted manuscripts rests with the Editor-in-Chief.

The journal publishes in the field of original research, case report, reviews, short report, short communication and letters to the editor are published only in English.

Editorial Board of TJIM complies with the criteria of the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME) , and Committee on Publication Ethics (COPE).

The journal is published quarterly (January, April, July and October).

No fee is required for publishing the manuscipt.

All articles are detected for similarity.

Abstracting & Indexing

The journal is abstracted and indexed with the following: The Directory of Open Access Journals (DOAJ), Google Scholar, Index Copernicus (Under Evaluation), ResearchGate, SciLit, CrossRef, ResearchBib, Asos Index, WorldCat, ROAD, Türkiye Atıf Dizini (Turkish Citation Index), TURK MEDLINE, DRJI (Directory of Research Journals Indexing).

Publisher

Turkish journal of Internal Medicine

Nizameddin KOCA

SBU Bursa Yüksek İhtisas SUAM

Yıldırm/BURSA-TURKEY

https://dergipark.org.tr/en/pub/tjim

Turkish Journal of Internal Medicine

Table of Contents

TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Letter to the Editor

Q Fever in the Differential Diagnosis of COVID-19 Infection

Sevil ALKAN[1], Alper SENER[1], Safiye Bilge GUCLU KAYTA[1], Anil AKCA[1]

[1]Department of Infectious Disease, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey

Turk J Int Med 2021;3(4):145-146
DOI: 10.46310/tjim.905105

Keywords: *Q Fever, COVID-19, Coxiella burnetii.*

Dear Editor,

Coronavirus Disease 2019 (COVID-19), which has disrupted most of the health services since the pandemic was declared since March 2020. The previously reported symptoms for COVID-19 possible case definition is quite wide. Fever, cough, shortness of breath, sore throat, headache, muscle aches, new loss of taste or smell, nausea or vomiting and diarrhea are among them.[1,2] Due to the variability of symptoms, it should be considered in differential diagnosis with many diseases. In addition, sometimes the increased workload of health workers can cause other diseases to be misdiagnosed or delayed.

A 60-year-old male livestock worker presented with complaints of fever, headache, abdominal pain, nausea, vomiting, cough and sputum for 4-5 days. The patient had nor an intravascular device neither immunosuppressive condition. In physical examination; fever: 39 °C, his general condition was moderate-poor, lethargic, and his consciousness was drowsy. Oropharynx was hyperemic. On physical examination, meningeal irritation findings were negative and there were no additional pathological features. White blood cell: 4,300/mm^3, lymphocyte count: 560/mm^3, neutrophil count: 3,260/mm^3 hemoglobin: 11.8 gr/dL, platelets: 127,000/mm^3, C-reactive protein: 17.7 gr/dL, erythrocyte sedimentation rate: 71/hour. Hepatic function test was normal. Postero-anterior chest radiography was normal. COVID-19 real time polymerase chain reaction (RT-PCR) test performed from the patient because the patient had signs of possible COVID-19 symptoms. The diagnosis of COVID-19 was ruled out due to insufficient scientific evidence as a result of negative COVID-19 PCR and absence of pulmonary radiological findings.

After obtaining the blood and urine cultures empirically, ceftriaxone 2x1 g IV treatment was initiated. Since central nervous system infection was not considered clinically, lumbar puncture was not performed to the patient. For differential

Received: March 30, 2021; Accepted: June 30, 2021; Published Online: October 29, 2021

Address for Correspondence:
Sevil Alkan, MD

Department of Infectious Disease, Canakkale Onsekiz Mart University, Faculty of Medicine, Canakkale, Turkey
E-mail: sevil3910@gmail.com

diagnosis; due to our endemic region, *Borrelia burgdorferi* IgM and IgG, *C. burnetii* Phase 1 IgM and IgG and Phase 2 IgM and IgG, West Nile Virus PCR, Brucella Rose Bengal and tube agglutination, laboratory tests were studied from the serum using the indirect fluorescent antibody test method. In addition, abdominal ultrasonography was performed. Blood and urine cultures were negative.

Finally, serology for Q fever by indirect immunofluorescence assay showed *C. burnetii* IgG Phase 1: negative; IgG phase 2: positive at 1/64 titer and of IgM phase 2: positive at 1/96 titer. The patient was diagnosed as acute Q fever disease. The treatment was changed to doxycycline tablet 2x100 mg/day. Transthoracic electrocardiography was performed to investigate cardiac valvular disease, no valvular pathology was detected. His complaints had regressed and discharged on the 10th day of hospitalization, with the completion of the doxycycline treatment to 14 days, with the recommendation of outpatient clinic control.

Coxiella burnetii is an intracellular gram-negative bacterium and is the causative agent of Q fever, a zoonosis first seen in Australia in 1937. It can cause endemics around the world. People usually get the disease by inhaling the contaminated aerosol produced by infected livestock. Contaminated milk, intradermal inoculation, sexual contact, blood transfusion, and transplacental may also occur as a mode of transmission.

Acute infection is typically asymptomatic but may manifest as a febrile flu-like illness, pneumonia, hepatitis, and central nervous system infection. During the course of the disease that cannot be distinguished from other pneumonia clinically; 2-10 fold increase in liver function tests, leukocytosis and thrombocytopenia, erythrocyte sedimentation rate and creatine kinase increase may be seen or laboratory findings may also be normal. An immunofluorescent antibody test, which is a serological reference method, should be requested from patients suspected for the diagnosis of Q fever.[3-7]

Q fever should be considered in the differential diagnosis, especially in endemic areas. While some of the acute Q fever cases are asymptomatic, symptoms such as limited fever, headache, muscle-joint pain and cough are observed in 90% .[3-9] Similar symptoms are present in the COVID-19 probable case definition. The disease may present at an early stage without pulmonary findings.[1,2] Also, the presented case had fever, headache, abdominal pain, nausea, vomiting, cough and sputum for 4-5 days, and as its pandemic period diagnosis could be confused with COVID-19. The diagnosis of presented case was confirmed by serologic methods, as we are in the endemic zone and we suspected Q fever.

Park et al.[9] reported a 37-year-old male patient with co-infection with COVID-19 and Q fever. Therefore, Q fever should be considered in the differential diagnosis of COVID-19 or co-infection, especially in endemic areas.

References

1. WHO COVID-19 Case definition. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.2. Accessed March 1, 2021.
2. COVID-19 Rehberi. Available at: https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html. Accessed March 1, 2021.
3. Eldin C, Mélenotte C, Mediannikov O, Ghigo E, Million M, Edouard S, Mege JL, Maurin M, Raoult D. From Q fever to Coxiella burnetii infection: a Paradigm Change. Clin Microbiol Rev. 2017 Jan;30(1):115-90. doi: 10.1128/CMR.00045-16.
4. Köksal E, Günal Ö, Kılıç SS. Q fever: An occupational disease. Klimik Derg. 2020 August 28;33(2):195-6 (in Turkish). doi: 10.5152/kd.2020.42.
5. Asan A. Q ateşi. In: Timurkaynak F, Yavuz SŞ, eds. KLİMİK 2015 XVII. Türk Klinik Mikrobiyoloji ve İnfeksiyon Hastalıkları Kongresi, Kongre Kitabı. 25-29 Mart 2015 Antalya;87-8.
6. Çelebi B, Baş B, Bali EA, Yavuz SŞ. First Isolation of Coxiella burnetii in Turkey from a Patient with Endocarditis; Antigen Production and Phase Change Study. Mikrobiyol Bul. 2019 Jul;53(3):274-84 (in Turkish). doi: 10.5578/mb.68336.
7. Coleman JJ, Manavi K, Marson EJ, Botkai AH, Sapey E. COVID-19: to be or not to be; that is the diagnostic question. Postgrad Med J. 2020;96(1137):392-8. doi: 10.1136/postgradmedj-2020-137979.
8. Vink M, Vink-Niese A. Could cognitive behavioural therapy be an effective treatment for long COVID and post COVID-19 fatigue syndrome? Lessons from the Qure Study for Q-Fever Fatigue Syndrome. Healthcare (Basel). 2020 Dec 11;8(4):552. doi: 10.3390/healthcare8040552.
9. Park HS, Bae PK, Jeong HW, Son BR, Shin KS. Serological evidence of Coxiella burnetii and SARS-CoV-2 co-infection: A case report. Ann Lab Med. 2021;41(5):510-3. doi: 10.3343/alm.2021.41.5.510.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Relation Between Microvascular and Macrovascular Hemodynamics in Normal Epicardial Coronary Arteries

Cafer PANC[1], Onur ERDOGAN[1], Remzi SARIKAYA[2], Mehmet KOCAAGA[3], Pelin KARACA OZER[4], Berrin UMMAN[4]

[1]Department of Cardiology, Istanbul Health Sciences University, Mehmet Akif Ersoy Cardiovascular and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
[2]Department of Cardiology, University of Health Sciences, Van Education and Research Hospital, Van, Turkey
[3]Yalova State Hospital, Yalova, Turkey
[4]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey

ABSTRACT

Background Cardiovascular risk factors affect both macrovascular and microvascular systems, resulting in negative results on the entire vascular tree. Aortic stiffness causes augmented systolic pressure, increased pulse pressure, increased myocardial oxygen demand, and consequently, coronary blood flow diminishes because of decreased diastolic augmentation. Deterioration in arterial stiffness and increased pressure pulsatility were shown in association with microvascular dysfunction. We investigated the relation between macrovascular parameters expressed by carotid-femoral pulse wave velocity (PWV), augmentation index (AI), and coronary microvascular parameters expressed by coronary flow reserve (CFR), index of microvascular resistance (IMR), and subendocardial viability ratio (SEVR)

Material and Methods We have included 58 consecutive patients (29 male, age 54 [34-71]) without any epicardial coronary stenosis in coronary angiography. Macrovascular and microvascular parameters were calculated with the measurements of tonometry, coronary flow reserve, and microvascular resistance.

Results PWV and SEVR had an inverse correlation (r=-0.328, p=0.007). The main reason for this correlation was a priorly positive correlation between PWV and systolic pressure-time integral (SPTI) (r=0.465, p<0.001).A positive correlation was noted between augmentation index (AI) and PWV (r=0.352, p=0.010); and an inverse significant correlation was noted between AI and SEVR (r=-0.383, p=0.003). PWV had a positive correlation with diastolic/systolic coronary flow velocity (r=0.42, p=0.04) and microvascular resistance (MR) (r=0.44, p=0.03) and a negative correlation with hyperemic mean coronary flow velocity (r=-0.416, p=0.043) and coronary flow reserve (CFR) (r=-0.419, p=0.04) in diabetic patient group (n=27). AI was inversely related to CFR (r=-0.41, p=0.04) in diabetic patient group. SEVR and CFR were well correlated in the same direction (r=0.569, p<0.001). SEVR was significantly lower in the patients with lower CFR (1.41±0.23 vs.1.58±0.24, p=0.01). SEVR had a significant negative correlation with MR (r=-0.321, p=0.016). SEVR was associated with arteriolar resistance index (r=0.413, p=0.002).

Conclusions Arterial stiffness is associated with coronary microvascular dysfunction in normal epicardial coronary arteries. The relation between the stiffness of the aorta, subendocardial myocardial perfusion, and coronary microvascular dysfunction in our study suggests that central arterial stiffness modulation may be a target for the treatment of coronary microvascular dysfunction.

Turk J Int Med 2021;3(4):147-155
DOI: 10.46310/tjim.871224

Keywords: *Pulse wave velocity, augmentation index, subendocardial viability ratio, index of microvascular, resistance, coronary flow reserve, normal coronary arteries, microvascular dysfunction.*

Received: February 02, 2021; Accepted: May 29, 2021; Published Online: October 29, 2021

Address for Correspondence:
Cafer Panc, MD
Department of Cardiology, Istanbul Health Sciences University, Mehmet Akif Ersoy Cardiovascular and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
E-mail: caferpanc@gmail.com

Introduction

Cardiovascular diseases are rapidly progressing in patients with risk factors, and the coexistence of these factors leads to more negative outcomes. Cardiovascular risk factors affect both macrovascular and microvascular systems, resulting in negative results on the entire vascular tree. A typical example of a macrovascular effect is an increase in arterial stiffness, and a typical example of a microvascular effect is remodeling in small-sized resistance arteries and a reduction in the vascular dilatation capacity.

In long-term epidemiological studies, increased arterial stiffness is an independent predictor of cardiovascular adverse events.[1] In many studies of arterial stiffness modeled by carotid-femoral pulse wave velocity (PWV) measurements in patients with hypertension, PWV is associated with all-cause and cardiovascular mortality.[2] As the aorta stiffens, the reflected wave returns in the systole rather than the diastole. Consequently, aortic stiffness causes augmented systolic pressure, increased pulse pressure, and increased myocardial oxygen demand. Coronary blood flow diminishes because of the decreased diastolic augmentation. Although there is no significant stenosis in coronary arteries, this decrease in coronary flow may cause impairment in the coronary microcirculation. The relation between arterial stiffness and coronary microcirculation has been investigated in experimental studies.[3-5] In the Framingham Heart Study, deterioration in arterial stiffness and increased pressure pulsatility were shown in association with microvascular dysfunction.[6] In another study, higher arterial stiffness was related to lower flow reserve calculated by flow-mediated dilatation beyond traditional risk factors.[7] Cooper et al.[8] also showed that a higher incidence of cardiovascular events was seen in patients with increased arterial stiffness and decreased hyperemic flow velocity.

We investigated the relation between macrovascular parameters expressed by carotid-femoral PWV, augmentation index (AI), and coronary microvascular parameters expressed by coronary flow reserve (CFR), index of microvascular resistance (IMR), and subendocardial viability ratio (SEVR).

Material and Methods

We included 58 patients who underwent elective coronary angiography because of stable angina or inducible ischemia in imaging studies and had no epicardial coronary artery stenosis. Non-invasive coronary flow reserve, coronary microvascular resistance, and arterial stiffness measurements were performed in all patients. CFR and IMR could not be calculated in one patient, and PWV could not be measured in 3 patients due to technical difficulties. We excluded patients with a history of myocardial infarction or coronary revascularization, cardiomyopathy, myocarditis, left ventricular systolic dysfunction (left ventricle ejection fraction <55%), moderate-severe valvular heart disease, chronic kidney and liver failure, active malignancy, active infection, and chronic obstructive pulmonary disease.

Patients with fasting blood sugar above 126 mg/dL and treated for known diabetes mellitus were considered diabetic. Patients with a systolic blood pressure above 140 mmHg, diastolic blood pressure above 90 mmHg, or those with a history of antihypertensive use were considered hypertensive. A fasting LDL level greater than 130 mg/dL or a history of statin use and a fasting triglyceride level above 150 mg/dL or with a history of antilipidemic drug use was considered as hyperlipidemia. All patients were included in the study after their written consent was obtained. The local ethics committee approved the study (2015/1283).

Measurement of Coronary Flow Reserve and Microvascular Resistance

CFR and coronary microvascular resistance studies were performed with VIVID 7 echocardiography device (GE, General Electronic). The mid-distal flow of the left anterior descending artery (LAD) was imaged with colored doppler with an optimal velocity of 12-15 cm/sec in the left ventricular apical 2-space long-axis view of the fourth or fifth left intercostal space in the left lateral decubitus position. Baseline diastolic average peak velocity (APVb), and diastolic deceleration time (DTb) of coronary flow were measured with pulsed-wave doppler, firstly. Then a dipyridamole infusion of 0.56 mg/kg was administered for 4 minutes. If the heart

rate increases less than 10% compared to baseline, an infusion of 0.28 mg/kg dipyridamole was added for 2 minutes. Then, hyperemic diastolic average peak velocity (APVh) and hyperemic diastolic deceleration time (DTh) were measured 2 minutes after the dipyridamole infusion was completed. Pre-and post-infusion blood pressures were measured at frequent intervals. CFR was calculated with the formula of APVh/APVb *(Figure 1).*

Resistance in arteries can be calculated with pressure difference divided by arterial flow (Resistance=ΔP/blood flow). The mean blood pressure measured from the peripheral artery is the same as the pressure that can be measured in any coronary area since it is studied in patients with proven absence of epicardial coronary artery stenosis. Coronary flow can be measured directly by doppler echocardiography from LAD. Microvascular resistance (MR), which is routinely calculated invasively, can be calculated by dividing mean blood pressure measured from the brachial artery by average peak velocity of coronary flow measured by echocardiography in patients with normal coronary arteries non-invasively. MR was calculated in baseline (MRb) and hyperemia (MRh) with the formula below:

Mean blood pressure (MBP)=diastolic blood pressure (DBP)+(systolic blood pressure [SBP]–DBP)/3

MR (cm.sn-1.mmHg)=MBP (mmHg)/average peak coronary flow velocity (cm/sec)

Arteriolar resistance index (ARI) is a significant indicator of resistance at the arterial level. ARI was calculated by the difference between the hyperemic and basal values of MR.

ARI=MRb – MRh

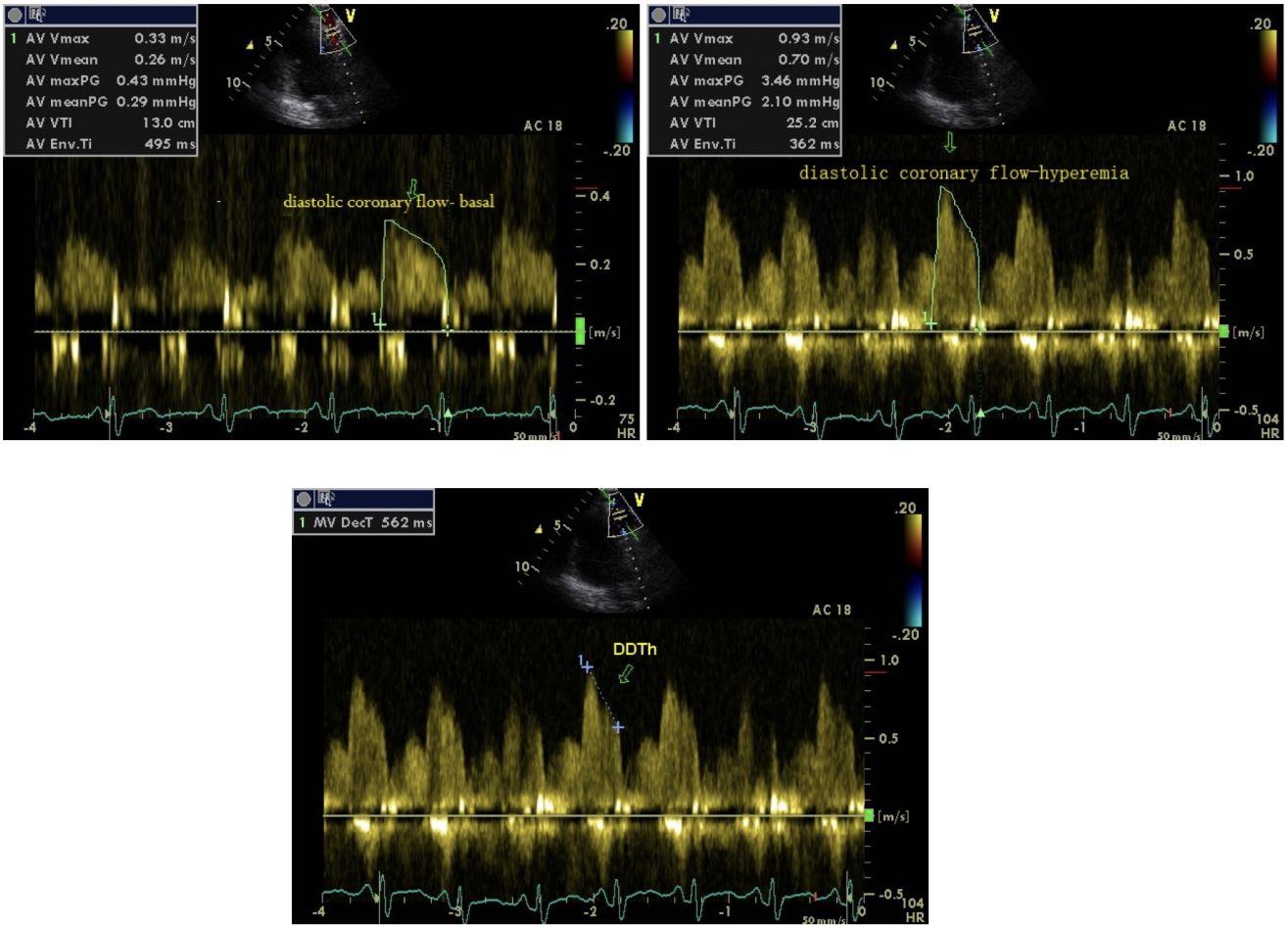

Figure 1. Hyperemic diastolic flow pattern, hyperemic diastolic deceleration time (DTh) and basal diastolic flow pattern obtained by pulsed wave doppler echocardiography from the mid-distal LAD in transthoracic echocardiography.

Measurement of Arterial Stiffness Parameters

Measurements were taken using SphygmoCor (AtCor Medical Pty. Ltd., Sydney) tonometry device. All measurements were made in ideal room conditions at the same time of the day, ten minutes after rest and lying in the supine position. Measurements were obtained by the applanation tonometry method. In this method, pressure trace was recorded pressing gently to the peripheral artery with a pressure transducer. Measurements were made on the radial artery because the pulse waveforms obtained from the superficial arteries were almost identical to the intra-arterial pressure waves. Pressure waveforms were transferred to the computer. SBP, DBP, mean arterial pressure (MAP), pulse pressure (PP), heart rate, augmentation index (AI), diastolic pressure-time integral (DPTI), systolic pressure-time integral (SPTI) parameters were calculated using "Pulse Wave Analysis (PWA)" with dedicated software of the device *(Figure 2)*.

PWV: The distance between the carotid artery and femoral artery was measured. The distance was calculated by the "direct measurement" method (direct carotid-femoral artery distance X 0.8) as indicated in the published consensus report.[9] PWV was calculated by dividing the time difference between the carotid artery and femoral artery by this distance.

Subendocardial viability ratio: The area under the systolic and diastolic portions of the central aortic pulse wave can be determined by pulse wave analysis. DPTI and SPTI were measured as the area under the diastolic and systolic portions of the pulse waves, respectively. SEVR was calculated from the ratio of DPTI to SPTI.

AI: AI was calculated from the central aortic waveform record as follows: Augmentation pressure (SBP – pressure at the first peak shoulder of the aortic pulse wave)/PPx100. AI was corrected for heart rate at 75 bpm as defined before.[10]

Statistical Analysis

Statistical analyses were performed using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 21.0 released 2012, IBM Corp., Armonk, New York, USA). Kolmogorov-Smirnov test was performed to detect the distribution of the variables. Normally distributed variables are presented as mean±standard deviation, and

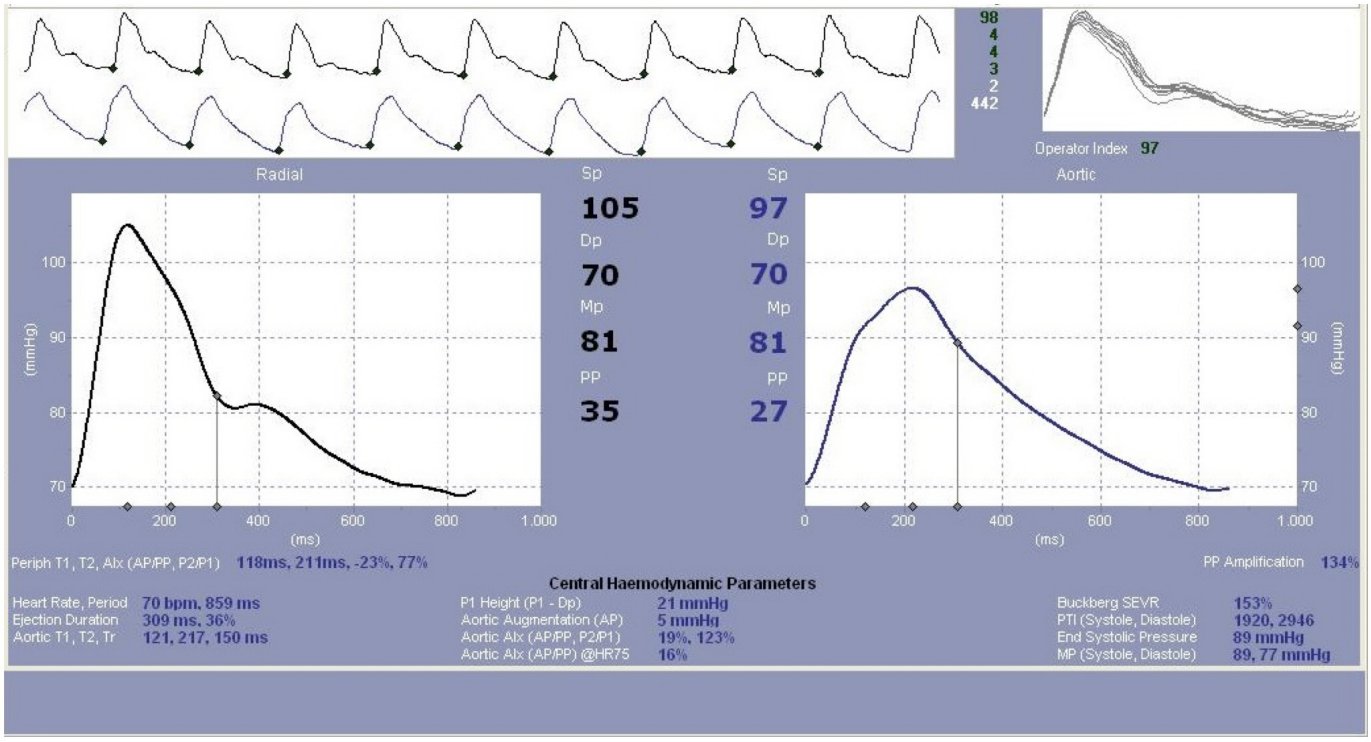

Figure 1. Central aortic pressure waveforms and hemodynamic parameters obtained by these waveforms

nonnormally distributed variables are presented as median (25^{th} to 75^{th} percentile). Categorical variables are expressed as numbers (%). The Student t-test was used to compare quantitative variables with normal distribution, and the Mann-Whitney U test was used to compare quantitative variables without normal distribution. The Pearson's chi-square and Fisher's exact tests were performed for categorical variables. Relations between coronary hemodynamic parameters and arterial hemodynamic parameters were assessed using Pearson or Spearman correlation analysis where appropriate. A p-value of <0.05 was considered significant.

Results

A total of 58 patients (29 males, mean age 54 [34-71]) were included in the study. 63% of the patients had hypertension (HT), 48% had diabetes mellitus (DM), 41% had hyperlipidemia (HL), and 17% had a smoking history. The general characteristics of the patients are shown in Table 1, measured microvascular parameters in Table 2, and macrovascular parameters in Table 3.

Relation Between Arterial Stiffness Parameters and SEVR

An inverse correlation was noted between PWV and SEVR (r=-0.328, p=0.007). This relationship was basically determined by the relationship of PWV and SPTI (r=0.465, p <0.001). A positive

Table 1. Patients' general characteristics

Variables	All study population (n=58)
Age (years)	54.97±8.5
Male	29 (50)
Hypertension	37 (63.8)
Diabetes Mellitus	28 (48.3)
Hyperlipidemia	24 (41.4)
Smoking	10 (17.2)
Body mass index (kg/m^2)	30.3±5.2
HbA1c (%)	7.06±1.4
Microalbumin/Creatinine (mg/g)	22.5±27.1
Creatinine (mg/dL)	0.84±0.19
Hemoglobin (g/dL)	13.2±1.3
HDL-Cholesterol (mg/dL)	45.3±12.3
LDL-Cholesterol (mg/dL)	132.5±27.8
Systolic blood pressure (mmHg)	125.4±15.2
Diastolic blood pressure (mmHg)	73.86±9.01
Carotid intima-media thickness (mm)	0.69±0.16
Ejection fraction (%)	68.9±2.7

Data are presented as number (%) or mean±SD. HbA_{1c}: glycosylated hemoglobin, SD: standard deviation.

Table 2. Microvascular parameters.

Parameters	Mean± SD
APVb (cm/sn)	23.93±5.60
DDTb (msn)	993±206
APVh (cm/sn)	51.74±13.31
sAPVh (cm/sn)	26.33±6.61
DDTh(msn)	743±197
CFR	2.19±0.48
MRb ($cm.sn^{-1}.mmHg$)	3.96±0.83
MRh ($cm.sn^{-1}.mmHg$)	1.76±0.47
Delta MR ($cm.sn^{-1}.mmHg$)	2.19±0.64

APVb: baseline average peak velocity, APVh: hyperemic average peak velocity, CFR: coronary flow reserve, DDTb: baseline diastolic deceleration time, DDTh: hyperemic diastolic deceleration time, MRb: baseline microvascular resistance, MRh: hyperemic microvascular resistance, sAPVh: systolic hyperemic average peak velocity.

Table 3. Macrovascular parameters.

Parameters	Mean±SD
PWV (m/sn)	8.37±2.06
AI (%)	25±11.01
DPTI (mmHg x sec)	3251.18±503.029
SPTI (mmHg x sec)	2261.12±414.813
SEVR (%)	1.46±0.22
Mean blood pressure (mmHg)	90.95±9.96
Pulse pressure (mmHg)	51.53±12.43

AI: augmentation index, DPTI: diastolic pressure-time integral, PWV: pulse wave velocity, SPTI: systolic pressure-time integral, SEVR: Subendocardial viability ratio.

correlation was noted between AI and PWV (r=0.352, p=0.010); and an inverse significant correlation was noted between AI and SEVR (r=-0.383, p=0.003).

Relation Between Coronary Microvascular Parameters and Arterial Stiffness Parameters

PWV and AI were not correlated with microvascular parameters in all groups or non-diabetic patients. PWV has a positive correlation with diastolic/systolic coronary flow velocity (r=0.42, p=0.04) and MR (r=0.44, p=0.03) and a negative correlation with diastolic deceleration time (DDT) (r=-0.399, p=0.05), hyperemic mean coronary flow velocity (r=-0.416, p=0.043) and CFR (r=-0.419, p=0.04) in diabetic patient group (n=27). AI was inversely related to CFR (r=-0.41, p=0.04) in diabetic patient group.

Relation Between SEVR and Coronary Microvascular Parameters

When the relation between SEVR and CFR was evaluated in the whole group, it was seen that the two parameters were well correlated in the same direction (r=0.569, p <0.001). SEVR was significantly lower in the patients with lower CFR (1.41±0.23 vs. 1.58±0.24, p=0.01) when CFR values were divided into two groups according to 2, which was considered categorically significant.[11] When SEVR and MR were evaluated, it was seen that the two parameters were significantly correlated in the opposite direction (p=0.016, r=-0.321). Delta MR (arteriolar resistance index-ARI), which is a significant indicator of resistance at the arterial level -calculated by the difference between the hyperemic and basal values of MR- and SEVR were shown to correlate significantly in the same direction (p=0.002, r=0.413).

Discussion

In this study, the effect of aortic stiffness, assessed by central hemodynamic parameters (PWV and AI) on myocardial supply/demand balance (SEVR) and coronary microcirculation hemodynamics (CFR and IMR), were investigated in patients with normal epicardial coronary arteries. The main findings of our study are as follows:

1. An increase in the severity of aortic stiffness determined by central hemodynamic parameters is associated with decreased subendocardial

perfusion (SEVR) despite normal coronary perfusion pressure (patients with normal coronary arteries). So, central aortic hemodynamic properties affect subendocardial microvascular perfusion.

2. PWV, an expression of the degree of arterial stiffness, is related to the structural and functional status assessed by objective parameters of coronary microcirculation in the diabetic patient group (CFR, ARI, MR). Increased aortic stiffness in diabetic patients affects microvascular hemodynamic parameters negatively despite normal epicardial coronary arteries.

3. A decrease in subendocardial perfusion ratio is associated with increased coronary microvascular resistance and a decrease in coronary flow reserve.

CFR is a measure of how much of the maximum flow quantity the microvessel can adapt to during myocardial rest.[12] Although the reduction in CFR is often considered a decrease in the dilatation capacity of the coronary microvasculature and, therefore, called microvascular dysfunction, another important indicator of the need for coronary flow during rest is energy the left ventricle consumes during systole. Any condition that causes the left ventricle to experience more hydraulic load during blood transfer to the aorta will increase baseline blood requirement and, therefore, a decrease in coronary flow reserve. Aortic stiffness, depending on age and various pathologies, causes blood to be drawn during systole to cause more aortic pressure elevation due to decreased aortic compliance.[13] This increase in hydraulic work, which is the product of pressure and stroke volume, requires more coronary flow (as shown in our work, PWV is related to SPTI). This causes the heart to use more quantity of CFR during the rest. Therefore, the increase in aortic stiffness is associated with a decrease in CFR, as demonstrated by the diabetic patient group. This situation, which leads to more dilatation of the prearteriolar sphincters during rest, also explains why there is a correlation between deltaMR and SEVR in our study (delta MR or ARI is a measure of the dilatation capacity of the prearteriolar sphincter, which represents the difference between baseline and hyperemic states of coronary microvascular resistance).[14] Essentially, in this situation, there is not any primary problem in the dilatation capacity of the coronary microvascular bed, and there is not any primary microvascular dysfunction. In accordance with our trial, Muroya et al.[15] showed that increased arterial stiffness is associated with microvascular dysfunction in non-obstructive coronary arteries.

Another disadvantage of aortic stiffness is increased systolic-diastolic fluctuation and pulsatile organ flow.[16] This creates a bigger problem, especially for coronary beds that are fed in the diastole. SEVR, which is an indicator of myocardial supply/demand balance and, therefore particularly, subendocardial perfusion, is related to the structural (MR) and functional (ARI) characteristics of the coronary microcirculation.[17] DPTI (mmHg x sec) accounts for the coronary diastolic pressure and diastolic time. Thus, it potentially indicates subendocardial blood flow supply. Reduced compliance with the lower diastolic flow (or lower DPTI) may cause objective ischemia because of supply/demand imbalance during exercise despite normal coronary arteries. In a previous study in normal coronary arteries, low CFR was associated with decreased SEVR as in our study.[18]

Another negative effect of arterial stiffness is that the pressure wave transmitted to the periphery during systole returns more rapidly than observed in the normal aorta.[19] In the optimal case, the reflected wave reaches the proximal aorta in the diastole and is less noticeable; but in the stiffened aorta, this wave returns in the systole and becomes more prominent. This means that more myocardial energy is needed to provide the same amount of cardiac output. Previous studies have demonstrated that lower levels of CFR in diabetic patients compared to non-diabetic patients in normal coronary arteries are explained with increased basal coronary flow rate, which is an indicator of increased myocardial energy requirement.[20-23]

One of the interesting findings of our study is the inverse relationship between hyperemic MR and SEVR. Since MR in resting is associated with coronary blood requirement, it is expected that there will not be a direct connection between the maximal dilatation capacity of the coronary bed -even if it is related to the afterload increase due to aortic stiffness. This association may be interpreted as an increase in the hyperemic

coronary microvascular resistance because of 1) aortic stiffness increasing microvascular resistance by microvascular destruction in various ways or 2) the mechanism causing the aortic stiffness leading to an increase in coronary resistance. First, a mechanism may be suggested that increased pulsatile stress has an adverse effect on the coronary bed. Mitchell et al.[16] investigated the effect of arterial stiffness on brain structure and function. Carotid pulse rate, pulsatility index, and carotid-femoral PWV increase were associated with an increase in silent subclinical infarcts detected by MRI. At the same time, increased pulsatility index was associated with lower total brain volume, lower memory scores, and decreased cognitive function. In another trial, the increased arterial pulsatile flow was associated with coronary microvascular dysfunction and cardiovascular events in non-obstructive coronary arteries.[24] Second, the similarities between the pathological changes in the micro and macrovascular structures can be suggested. Due to the elastic properties of the large arteries, the pulsatile flow is converted to continuous flow, and the microvascular structure provides metabolite and oxygen flow to the tissues. The microvascular structure is not only related to vascular resistance. At the same time, there are regions where wave reflections occur; especially in the elderly, these wave reflections are associated with an increase in the central aortic pressure. In a study by Safar et al.[25], the relation between the resistance of small subcutaneous arteries and blood pressure values in normotensive and hypertensive patients was evaluated. The most important determinants of small artery structure were clinical SBP, DBP, MBP, cardiac output, and PP, which indicated the compliance of the large arteries.

Conclusions

As a result, central aortic and coronary microvascular hemodynamics cannot be considered separately. Arterial stiffness is associated with coronary microvascular dysfunction in normal epicardial coronary arteries. The relation between the stiffness of the aorta, subendocardial myocardial perfusion, and coronary microvascular dysfunction in our study suggests that central arterial stiffness modulation may be a target for the treatment of coronary microvascular dysfunction.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IG, MTA, SC; Study Design: IG, MTA, SC; Supervision: IG, MTA, SC; Materials: MTA, IG; Data Collection and/or Processing: IG, MTA; Statistical Analysis and/or Data Interpretation: IG, SC; Literature Review: IG, MTA, SC; Manuscript Preparation: SC, IG; and Critical Review: MTA.

References

1. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness on survival in end-stage renal disease. Circulation 1999;99:2434-9.
2. Ben-Shlomo Y, Spears M, Boustred C, May M, Anderson SG, Benjamin EJ, Boutouyrie P, Cameron J, Chen CH, Cruickshank JK, Hwang SJ, Lakatta EG, Laurent S, Maldonado J, Mitchell GF, Najjar SS, Newman AB, Ohishi M, Pannier B, Pereira T, Vasan RS, Shokawa T, Sutton-Tyrell K, Verbeke F, Wang KL, Webb DJ, Willum Hansen T, Zoungas S, McEniery CM, Cockcroft JR, Wilkinson IB. Aortic pulse wave velocity improves cardiovascular event prediction: an individual participant meta-analysis of prospective observational data from 17,635 subjects. J Am Coll Cardiol. 2014 Feb 25;63(7):636-46. doi: 10.1016/j.jacc.2013.09.063.
3. Ohtsuka S, Kakihana M, Watanabe H, Sugishita Y. Chronically decreased aortic distensibility causes deterioration of coronary perfusion during increased left ventricular contraction. J Am Coll Cardiol. 1994 Nov 1;24(5):1406-14. doi: 10.1016/0735-1097(94)90127-9.
4. Saito M, Okayama H, Nishimura K, Ogimoto A, Ohtsuka T, Inoue K, Hiasa G, Sumimoto T, Higaki J. Possible link between large artery stiffness and coronary flow velocity reserve. Heart. 2008 Jun;94(6):e20. doi: 10.1136/hrt.2007.126128.
5. Watanabe H, Ohtsuka S, Kakihana M, Sugishita Y. Coronary circulation in dogs with an experimental decrease in aortic compliance. J Am Coll Cardiol. 1993 May;21(6):1497-506. doi: 10.1016/0735-1097(93)90330-4.
6. Mitchell GF, Vita JA, Larson MG, Parise H, Keyes MJ, Warner E, Vasan RS, Levy D, Benjamin EJ. Cross-sectional relations of peripheral microvascular function, cardiovascular disease risk factors, and aortic stiffness: the Framingham Heart Study. Circulation. 2005 Dec 13;112(24):3722-8. doi: 10.1161/CIRCULATIONAHA.105.551168.
7. Cooper LL, Musani SK, Washington F, Moore J, Tripathi A, Tsao CW, Hamburg NM, Benjamin EJ, Vasan RS, Mitchell GF, Fox ER. Relations of Microvascular

Function, Cardiovascular Disease Risk Factors, and Aortic Stiffness in Blacks: The Jackson Heart Study. J Am Heart Assoc. 2018 Oct 16;7(20):e009515. doi: 10.1161/JAHA.118.009515.
8. CooperLL,PalmisanoJN,BenjaminEJ,LarsonMG,Vasan RS, Mitchell GF, Hamburg NM. Microvascular Function Contributes to the Relation Between Aortic Stiffness and Cardiovascular Events: The Framingham Heart Study. Circ Cardiovasc Imaging. 2016 Dec;9(12):e004979. doi: 10.1161/CIRCIMAGING.116.004979.
9. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, Pannier B, Vlachopoulos C, Wilkinson I, Struijker-Boudier H; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. Eur Heart J. 2006 Nov;27(21):2588-605. doi: 10.1093/eurheartj/ehl254.
10. Aslanger E, Assous B, Bihry N, Beauvais F, Logeart D, Cohen-Solal A. Effects of Cardiopulmonary Exercise Rehabilitation on Left Ventricular Mechanical Efficiency and Ventricular-Arterial Coupling in Patients With Systolic Heart Failure. J Am Heart Assoc. 2015 Oct 13;4(10):e002084. doi: 10.1161/JAHA.115.002084.
11. Cortigiani L, Rigo F, Galderisi M, Gherardi S, Bovenzi F, Picano E, Sicari R. Diagnostic and prognostic value of Doppler echocardiographic coronary flow reserve in the left anterior descending artery in hypertensive and normotensive patients [corrected]. Heart. 2011 Nov;97(21):1758-65. doi: 10.1136/heartjnl-2011-300178.
12. Caiati C, Montaldo C, Zedda N, Bina A, Iliceto S. New noninvasive method for coronary flow reserve assessment: contrast-enhanced transthoracic second harmonic echo Doppler. Circulation. 1999 Feb 16;99(6):771-8. doi: 10.1161/01.cir.99.6.771.
13. McDonald DA, Nichols WW, O'Rourke MF, Hartley C. McDonald's blood flow in arteries : theoretic, experimental, and clinical principles. London; New York: Arnold ; Oxford University Press; 1997.
14. Chamuleau SA, Siebes M, Meuwissen M, Koch KT, Spaan JA, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. Am J Physiol Heart Circ Physiol. 2003 Nov;285(5):H2194-200. doi: 10.1152/ajpheart.01021.2002.
15. Muroya T, Kawano H, Koga S, Ikeda S, Yamamoto F, Maemura K. Aortic Stiffness Is Associated with Coronary Microvascular Dysfunction in Patients with Non-obstructive Coronary Artery Disease. Intern Med. 2020;59(23):2981-7. doi: 10.2169/internalmedicine.5401-20.
16. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson Ó, Garcia M, Aspelund T, Harris TB, Gudnason V, Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. Brain. 2011 Nov;134(Pt 11):3398-407. doi: 10.1093/brain/awr253.
17. Chemla D, Nitenberg A, Teboul JL, Richard C, Monnet X, le Clesiau H, Valensi P, Brahimi M. Subendocardial viability index is related to the diastolic/systolic time ratio and left ventricular filling pressure, not to aortic pressure: an invasive study in resting humans. Clin Exp Pharmacol Physiol. 2009 Apr;36(4):413-8. doi: 10.1111/j.1440-1681.2008.05084.x.
18. Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, Toutouzas K, Tsiamis E, Stefanadis C. Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. J Hum Hypertens. 2012 Jan;26(1):64-70. doi: 10.1038/jhh.2010.127.
19. Westerhof N, Stergiopulos N, Noble MI. Snapshots of hemodynamics: an aid for clinical research and graduate education: Springer Science & Business Media; 2010.
20. Knaapen P, Camici PG, Marques KM, Nijveldt R, Bax JJ, Westerhof N, Götte MJ, Jerosch-Herold M, Schelbert HR, Lammertsma AA, van Rossum AC. Coronary microvascular resistance: methods for its quantification in humans. Basic Res Cardiol. 2009 Sep;104(5):485-98. doi: 10.1007/s00395-009-0037-z.
21. Rizzoni D, Porteri E, Guelfi D, Muiesan ML, Valentini U, Cimino A, Girelli A, Rodella L, Bianchi R, Sleiman I, Rosei EA. Structural alterations in subcutaneous small arteries of normotensive and hypertensive patients with non-insulin-dependent diabetes mellitus. Circulation. 2001 Mar 6;103(9):1238-44. doi: 10.1161/01.cir.103.9.1238.
22. Iozzo P, Chareonthaitawee P, Di Terlizzi M, Betteridge DJ, Ferrannini E, Camici PG. Regional myocardial blood flow and glucose utilization during fasting and physiological hyperinsulinemia in humans. Am J Physiol Endocrinol Metab. 2002 May;282(5):E1163-71. doi: 10.1152/ajpendo.00386.2001.
23. Quiñones MJ, Hernandez-Pampaloni M, Schelbert H, Bulnes-Enriquez I, Jimenez X, Hernandez G, De La Rosa R, Chon Y, Yang H, Nicholas SB, Modilevsky T, Yu K, Van Herle K, Castellani LW, Elashoff R, Hsueh WA. Coronary vasomotor abnormalities in insulin-resistant individuals. Ann Intern Med. 2004 May 4;140(9):700-8. doi: 10.7326/0003-4819-140-9-200405040-00009.
24. Coutinho T, Mielniczuk LM, Srivaratharajah K, deKemp R, Wells GA, Beanlands RS. Coronary artery microvascular dysfunction: Role of sex and arterial load. Int J Cardiol. 2018 Nov 1;270:42-47. doi: 10.1016/j.ijcard.2018.06.072.
25. Safar ME, Rizzoni D, Blacher J, Muiesan ML, Agabiti-Rosei E. Macro and microvasculature in hypertension: therapeutic aspects. J Hum Hypertens. 2008 Sep;22(9):590-5. doi: 10.1038/jhh.2008.43.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

The Relationship Between Coronary Artery Disease and High-Sensitive Troponin T Changes During the Exercise Stress Test

Ismail GURBAK[1], Mustafa Tarik AGAC[2], Sukru CELIK[3]

[1]Department of Cardiology, University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
[2]Department of Cardiology, School of Medicine, Sakarya University, Sakarya, Turkey
[3]Department of Cardiology, University of Health Sciences, Ahi Evren Thoracic and Cardiovascular Surgery Training and Research Hospital, Trabzon, Turkey

ABSTRACT

Background The aim of this study was to investigate the relationship between coronary artery disease and changing of high sensitivity troponin T (hs-TnT) values during the exercise stress test (EST) in patients with suspected coronary artery disease (CAD).

Material and Methods We included 68 patients who underwent coronary angiography after positive EST. The hs-TnT values of all patients were measured before EST and at 4 hours after EST. Patients with coronary artery stenosis of 50% or more were divided into two groups (CAD [+]) and those without (CAD [-]). Hs-TnT values measured before and after EST were compared.

Results Among the 68 patients evaluated, 26 patients (39.3%) were identified as CAD (-) and 42 patients (61.7) as CAD (+). There was no significant difference between the two groups in the hs-TnT values before and after EST. There was a significant correlation between hs-TnT before exercise and pre-EST systolic blood pressure (SBP) (r=0.313, p=0.009) and hs-TnT before exercise and peak SBP during EST (r=0.241, p=0.038). There was a significant correlation between hs-TnT after EST and peak SBP during EST (r=0.398, p=0.001). Also, a strong negative correlation was found between the Duke treadmill score (DTS) calculated by the exercise test parameters and the Syntax score, which indicates the extent and severity of coronary artery disease (r=-0.521, p=0.0001).

Conclusions As a result of our study, it was observed that hs-TnT values did not contribute to the diagnosis of coronary artery disease. However, DTS evaluation performed before invasive coronary angiography can provide important information about coronary artery lesion complexity.

Turk J Int Med 2021;3(4):156-163
DOI: 10.46310/tjim.875638

Keywords: *Exercise stress testing, coronary artery disease, hs-troponin T, Syntax score.*

Received: February 06, 2021; Accepted: May 29, 2021; Published Online: October 29, 2021

Address for Correspondence:
Ismail Gurbak, MD
Department of Cardiology, University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey
E-mail: ismailgurbak@gmail.com

Introduction

Cardiovascular diseases continue to be the most common cause of death in the world. Especially coronary artery disease (CAD) is shown as the most important factor for increased mortality in the adult population.[1] Therefore, the importance of early diagnosis and treatment of CAD has been discussed in more detail in recent years.[2,3] Early diagnosis is an essential factor in the treatment and prognosis of the disease. For the diagnosis of stable CAD, 12-lead electrocardiogram (ECG), exercise test, coronary computed tomography angiography, and myocardial perfusion scintigraphy are the most frequently used examination tools.[2] Among these diagnostic tests, the exercise stress test (EST) is the most frequently used method for applicability and cost. However, due to low sensitivity and specificity, false positive and negative results can be encountered. For this reason, there are studies to increase the diagnostic power of this test with new parameters to be added to the EST examination. One of these parameters is high sensitive-troponin T (hs-TnT).

Hs-TnT is a cardiac biomarker used to diagnose acute coronary syndromes, especially in emergency rooms.[4] In previous studies, hs-TnT has been shown to predict heart failure and cardiovascular death, independent of other risk factors.[5] In stable coronary artery patients, it has been shown that when hs-troponin is above normal reference values, it increases the potential risk.[6]

The aim of this study is to investigate the relationship between CAD and hs-TnT values measured before and after EST in individuals with suspected CAD.

Material and Methods

Sixty-eight patients with the complaint of chest pain and having positive EST were included in this study. The demographic and clinical characteristics of the patients were recorded from routine polyclinic examinations. Informed consent was obtained from all members of the patient group participating in the study. The Ethics Committee approved the study's compliance with the Declaration of Helsinki and ethical rules.

Patients with clinical heart failure, severe valve disease, a permanent pacemaker, left bundle branch block, atrial fibrillation, history of cardiac surgery, percutaneous coronary intervention, and acute coronary syndrome were excluded from the study.

Exercise Stress Test Procotol

Routine 12-lead ECG were obtained from all the patients . Heart rate, blood pressure, and ECG were recorded at the end of each stage. The formula, Maximum Heart Rate (beats/minute)=220-age (years) was used for the target heart rate. Chest pain, decrease in systolic blood pressure (SBP) by ten mmHg or more compared to the initial blood pressure, development of bradycardia, downsloping of the ST segment in 2 or more consecutive leads, or a horizontal depression of 1 mm or more after 80 ms from the J junction, and ST-segment elevation were taken as the positive criteria of the test. ST-segment depression in the upsloping type without typical chest pain was not considered a positive criterion.[7] The equation for calculating Duke treadmill score (DTS) is as follows: DTS=exercise time-(5 x ST deviation)-(4x exercise angina). Exercise angina was assessed as one of three levels: 0, none; 1, nonlimiting; and 2, exercise-limiting.

Coronary Angiography

Coronary angiography (CAG) was performed with standard techniques. Before CAG, an informed consent form was obtained from all patients. All coronary angiographies were recorded in DICOM format on compact discs and then examined off-line and visually. The presence and severity of CAD were evaluated using the SYNTAX scoring method, special computer software with previously proven prognostic value.[8]

High-Sensitive Troponin T Measurement

Approximately 5-10 cc of blood was drawn from the peripheral venous route at the fourth hour after the EST. These blood samples were described as post-exercise blood samples. The blood samples of the patients who came for CAG on the day of their appointment were taken before the angiography while lying in the ward while at rest. Blood samples taken during this period were described as basal or non-exercise blood samples.

Blood samples taken under both conditions were subjected to centrifugation, and their sera were distinguished. Serum samples were stored under suitable conditions. It was then mass analyzed using the hs-TnT Elecsys kit (Roche Diagnostics, Mannheim, Germany). Values above 14 ng/L in the healthy population was considered abnormal.

Statistical Analysis

Data analysis was carried out by the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 15.0, Armonk, New York, USA). Data conforming to normal distribution are presented as mean (±) standard deviation and data not conforming to normal distribution are presented as median and quartiles. Categorical data was presented as frequency distribution and percentage. Yates corrected Chi-square test, and Fisher's exact test were used for comparison of categorical variables. Mann-Whitney U test was used to compare two independent groups that were not normally distributed. Student t-test was used to compare two groups that fit a normal distribution. Spearman correlation test was used for the relationship between the measurement and specified variables. The Kendall Tau correlation test was used for the relationship between categorical variables. Statistical significance value was accepted as $p<0.05$.

Results

The patients were divided into two groups as CAD (+) and CAD (-) according to their final coronary angiographical data (coronary artery stenosis of 50% or more). The main characteristics of both groups are summarized in Table 1. The CAD (+) group was older than the CAD (-) group (53.73±7.4 vs. 58.81±9.55, p=0.02). There was no statistically significant difference between the two groups in terms of gender, diabetes, hypertension, hyperlipidemia, family history of CAD, smoking, body mass index, LDL-HDL-total-cholesterol, triglyceride, creatinine, and glucose. with CAD (-) and CAD (+) were compared. CAD was detected in 42 of 68 patients whose EST was accepted as positive, and 26 patients did not have CAD. EST's positive predictive value was 61%. There was no statistically significant difference between the percentage increase hs-TnT, basal hs-TnT, post-EST hs-TnT, and Δh hs-TnT (ΔHs-Troponin T; after exercise hs-TnT - before exercise hs-TnT). There was no significant correlation between basal hs-TnT, post-EST hs-TnT, Δh hs-TnT, and SYNTAX score (*Table 2*). There was a significant correlation between hs-TnT before exercise and pre-EST SBP (r=0.313, p=0.009) and hs-TnT before exercise and peak SBP during EST (r=0.241, p=0.038).There was a significant correlation between hs-TnT after EST and peak SBP during EST (r=0.398, p=0.001) *(Table 3)*. Also, a strong negative correlation was found between the DTS and the Syntax score (r=-0.521, p=0.0001) *(Figure 1)*.

Figure 1. Corelation between duke treadmill score and syntax score.

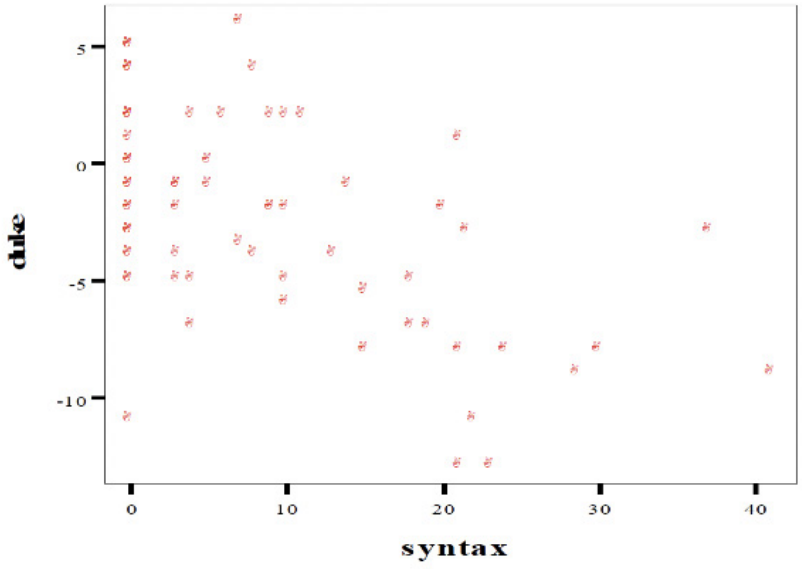

Table 1. Baseline characteristics of the study population

	CAD (-) (n=26)	CAD (+) (n=42)	p value
Gender, male (n%)	17 (65.4%)	36 (85.7%)	NS
Age (years)	53±7	58±9	0.024
BMI (kg/m²)	30±5	28.5±4	NS
Familial history (n%)	12 (46.2%)	17 (4.5%)	NS
Diabetes mellitus (n%)	8 (30.8%)	12 (28.6%)	NS
Hypertension (n%)	14 (53.8%)	26 (61.9%)	NS
Hyperlipidemia (n%)	10 (38.5%)	20 (47.6%)	NS
Smoking (n%)	3 (11.5%)	11 (26.2%)	NS
Biochemical parameters			
Total cholesterol (mg/dL)	197.4±59	210±35	NS
HDL-c (mg/dL)	41 (34/45)	40 (37/45)	NS
LDL-c (mg/dL)	141.4±41	145±31	NS
Triglyceride (mg/dL)	224±148	176±82	NS
Serum creatinine (mg/dL)	0.8 (0.67/1)	0.9 (0.8/1)	NS
Glucose (mg/dL)	106(96/121)	103 (95/118)	NS
Before exercise hs-TnT (ng/dL)	7 (5,10.2)	8 (6,12)	NS
After exercise hs-TnT (ng/dL)	10 (6,15.5)	11 (8,16.5)	NS
Delta hs-TnT (ng/dL)	1.5 (1,1.5)	2 (1,6)	NS
Percentage increase hs-TnT (ng/dL)	0.25 (0.09,0.48)	0.3 (0.1,0.5)	NS
Stress test parameters			
Heart Rate (beat/min)	86 (78,93)	82 (70,97.5)	NS
Before exercise SBP (mmHg±SD)	140 (130,150)	140 (130,15	NS
Before exercise DBP (mmHg±SD)	85 (80,90)	80 (75,90)	NS
Duration (minutes±SD)	7 (4.8,9)	7 (5.3,7.6)	NS
Maximum workload (METs±SD)	10 (7,10)	9 (7,10)	NS
Peak SBP (mmHg±SD)	181±25	180±29	NS
Heart rate recovery	30.2±13	27±9.1	NS
Duke treadmil score	-0.23±3.85	-3.67±4.4	0.002
Syntax score	-	10 (5.7,21)	-

BMI: body mass index, CAD: coronary artery disease, DBP: diastolic blood pressure, HDL-c: high-density lipoprotein cholesterol, METs: metabolic equivalent, LDL-c: low-density lipoprotein cholesterol, SBP: systolic blood presssure.

Table 2. Relation between hs-TnT values and Syntax score

	r	p
Before exercise hs-TnT (ng/dL)		
Syntax score	-0.073*	0.64
After exercise hs-TnT (ng/dL)		
Syntax score	0.029*	0.856
Δ hs-TnT (ng/L)		
Syntax score	0.097*	0.543
Before exercise hs-TnT (pg/dL) T ≥14 ng/L		
Syntax score	0.181**	0.167
After exercise hs-TnT (pg/dL) T ≥14 ng/L		
Syntax score	0.012**	0.928

hs-TnT: high sensitive troponin T.
*Spearman correlation test was used.
**Kendall tau correlation test was used.

Discussion

In this study, we investigated that the change in hs-TnT levels after EST and the use of stress test parameters together could be beneficial in identifying high-risk individuals and in the early diagnosis of CAD. In our study, CAD was detected in 42 of 68 patients whose EST was accepted as positive, and 26 patients did not have CAD. Similar to the literature, the limited role of EST positivity in determining the presence of CAD was found in our study. In our study, no significant relationship was found between CAD and the presence of diabetes, hypertension, smoking, and family history. In this study, we thought that the absence of a significant relationship between CAD and major clinical risk factors was due to the small number of our patients. However, many large angiographic studies have shown the relationship between CAD and risk factors. It has been demonstrated that it is useful to consider classical CAD risk factors in EST interpretation.

Early diagnosis of the acute coronary syndrome and prediction of prognosis based on a hs-TnT level have been clearly established in earlier studies; however, in the literature, there are not enough data for using change of hs-TnT during the EST as a diagnostic tool for CAD. In a study conducted by Omland *et al.*[9], a strong correlation was found between baseline hs-TnT value and prognosis in 3679 stable coronary artery patients at 5.2 years of follow-up. In the study conducted by Mingels *et al.*[10], the basal hs-TnT value of 1,088 patients with chest pain was examined, and cardiac events and cardiac mortality were significantly higher in the group with high hs-TnT group at 2.2 of follow-up. Ndrepepa *et al.*[11] showed a significant correlation was found between baseline hs-TnT levels and angiographic CAD in 904 stable coronary artery patients ($p<0.001$). The difference between our study and this study may be due to the difference in the number of patients and the patient population. Ndrepepa *et al.*[11] hypothesized that the increase in basal hs-TnT levels in patients with stable CAD may be due to myocardial ischemia in myocardial microcirculation with the embolization of thrombotic material formed by the dysrussion of silent plaques with physical activity.

In our study, it was found that the post-EST hs-TnT levels increased significantly compared

Table 3. Relation between hs-TnT values and stress test parameters

	r*	P
Maximum workload, METs Before exercise hs-TnT (pg/dL)	1.0	0.398
Maximum workload, METs After exercise hs-TnT (pg/dL)	-0.086	0.464
Peak HR (beats/minute) Before exercise hs-TnT (pg/dL)	0.051	0.667
Peak HR (beats/minute) After exercise hs-TnT (pg/dL)	-0.027	0.819
Duration (minutes) After exercise hs-TnT (pg/dL)	-0.137	0.243
Before exercise hs-TnT (pg/dL) Peak SBP (mmHg)	0.241	0.038
Before exercise hs-TnT (pg/dL) Before exercise SBP (mmHg)	0.313	0.009
After exercise hs-TnT (pg/dL) Peak SBP (mmHg)	0.398	0.0001
After exercise hs-TnT (pg/dL) Peak DBP (mmHg)	0.146	0.213

DBP: diastolic blood pressure, HR: heart rate, hs-TnT: high sensitive troponin T, METs: metabolic equivalent, SBP: systolic blood pressure.
*Spearman correlation test was used.

to the basal values. An increase in troponin levels has been reported after heavy exercise in various previous studies and case reports.[12,13] In studies conducted so far, troponin levels that increase with exercise have not been elucidated to be physiological or pathological. Frank *et al*.[14] found that this increase may be due to reversible cardiomyocyte membrane leakage due to oxidative stress induced by exercise and the circulation of cytosolic cTnT. König *et al*.[15] designed to evaluate whether the troponin increase mechanism due to exercise-induced myocardial stress is related to oxidative stress and inflammation. They showed that there is no correlation between the levels of markers. They reported that hs-Troponin increase only correlated with the increase in myoglobin, CK and CK-MB released from skeletal muscle. Hs-TnT is the third generation troponin and does not show cross-reaction with skeletal muscle. For this reason, they thought that hs-TnT release from the myocardium and myoglobin and CK, CK-MB release from skeletal muscle maybe by the same mechanism. Kurz *et al*.[16] and Axelsson *et al*.[17] reported that similar to our study, post-EST troponin values increased compared to basal troponin. In our study, we thought that this increase may be due to the transfer of cytosolic troponin into the circulation due to the temporary and reversible permeability increase in myocyte membrane permeability due to exercise-related metabolic stress.

In our study, the DTS from the stress test data was significantly more negative in the group with CAD. There was a negative correlation between DTS and Syntax score. Previous studies reported that major cardiac events were more common in patients with high Syntax scores.[18,19] In Mark *et al*.[20], they reported that the cardiac events were significantly higher in patients with a more negative DTS. Previous studies revealed a relationship between the ST-segment depression occurring during the exercise test, the number of leads with collapse, and the ST segment depression pattern and the presence of CAD. However, there is no study in the literature comparing the DTS and the syntax score. EST can give an idea about DTS, the presence, prevalence, and severity of CAD.

There are some limitations of our study. Our most important limitation is related to the number of patients. The hypothetical relationship between the presence and complexity of CAD and hs-TnT elevation due to exercise may have been overlooked due to the limited number of patients. Another issue concerns our methodology. Since our main goal was to investigate the relationship between CAD and CAD complexity and exercise-induced hs-TnT elevation, we only included EST-positive and potentially undergoing CAG. Therefore, we initially excluded the patient population with a negative EST test. The main reason for this initial exclusion is that we could not recommend CAG to the EST-negative group for ethical reasons. For this reason, our study data are far from representative of the entire stress test patient population. This methodological limitation prevented us from taking blood for hs-TnT before exercise, since we did not know which patient would have a positive EST at the beginning. For this reason, we found it appropriate to use the hs-TnT value taken at rest at a later time instead of hs-TnT before EST for comparison.

Conclusions

In our study, data could not reveal the relationship between the increase of hs-TnT, which is a biochemical marker we recommend to be added to EST, and the presence of CAD and its complexity. This suggests that exercise-induced hs-TnT elevation, even in patients with CAD, maybe due to other potential mechanisms other than ischemia, such as increased left ventricular afterload and increased wall tension. It is thought that additional studies are needed that include a higher number of patients and use biochemical markers such as BNP that reflect wall tension. However, a strong negative correlation was found between DTS and the extent and severity of CAD. DTS evaluation performed before invasive CAG can provide important information about coronary artery lesion complexity.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IG, MTA, SC; Study Design: IG, MTA, SC; Supervision: IG, MTA, SC; Materials: MTA, IG; Data Collection and/or Processing: IG, MTA; Statistical Analysis and/or Data Interpretation: IG, SC; Literature Review: IG, MTA, SC; Manuscript Preparation: SC, IG; and Critical Review: MTA.

References

1. Capewell S, Morrison CE, McMurray JJ. Contribution of modern cardiovascular treatment and risk factor changes to the decline in coronary heart disease mortality in Scotland between 1975 and 1994. Heart Br Card Soc. 1999;81(4):380-6. doi:10.1136/hrt.81.4.380.
2. Cassar A, Holmes DR, Rihal CS, Gersh BJ. Chronic coronary artery disease: diagnosis and management. Mayo Clin Proc. 2009;84(12):1130-46. doi:10.4065/mcp.2009.0391.
3. Reeh J, Therming CB, Heitmann M, Højberg S, Sørum C, Bech J, Husum D, Dominguez H, Sehestedt T, Hermann T, Hansen KW, Simonsen L, Galatius S, Prescott E. Prediction of obstructive coronary artery disease and prognosis in patients with suspected stable angina. Eur Heart J. 2019;40(18):1426-35. doi:10.1093/eurheartj/ehy806.
4. Hochholzer W, Reichlin T, Twerenbold R, Stelzig C, Hochholzer K, Meissner J, Haaf P, Schaub N, Steuer S, Bassetti S, Reiter M, Roost K, Freidank H, Winkler K, Mueller C. Incremental value of high-sensitivity cardiac troponin T for risk prediction in patients with suspected acute myocardial infarction. Clin Chem. 2011;57(9):1318-26. doi:10.1373/clinchem.2011.162073.
5. Hochholzer W, Valina CM, Stratz C, Amann M, Schlittenhardt D, Büttner HJ, Trenk D, Neumann FJ. High-sensitivity cardiac troponin for risk prediction in patients with and without coronary heart disease. Int J Cardiol. 2014;176(2):444-9. doi:10.1016/j.ijcard.2014.07.094.
6. Vavik V, Pedersen EKR, Svingen GFT, Tell GS, Schartum-Hansen H, Aakre KM, Nygård O, Vikenes K. Usefulness of Higher Levels of Cardiac Troponin T in Patients With Stable Angina Pectoris to Predict Risk of Acute Myocardial Infarction. Am J Cardiol. 2018;122(7):1142-47. doi:10.1016/j.amjcard.2018.06.027.
7. Lear SA, Brozic A, Myers JN, Ignaszewski A. Exercise stress testing. An overview of current guidelines. Sports Med Auckl NZ. 1999;27(5):285-312. doi:10.2165/00007256-199927050-00002.
8. Farooq V, Brugaletta S, Serruys PW. The SYNTAX score and SYNTAX-based clinical risk scores. Semin Thorac Cardiovasc Surg. 2011;23(2):99-105. doi:10.1053/j.semtcvs.2011.08.001.
9. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E; Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361(26):2538-47. doi:10.1056/NEJMoa0805299.
10. 1Mingels AM, Joosen IA, Versteylen MO, Laufer EM, Winkens MH, Wildberger JE, Van Dieijen-Visser MP, Hofstra L. High-sensitivity cardiac troponin T: risk stratification tool in patients with symptoms of chest discomfort. PloS One. 2012;7(4):e35059. doi:10.1371/journal.pone.0035059.
11. Ndrepepa G, Braun S, Schulz S, Mehilli J, Schömig A, Kastrati A. High-sensitivity troponin T level and angiographic severity of coronary artery disease. Am J Cardiol. 2011;108(5):639-43. doi:10.1016/j.amjcard.2011.04.012.
12. Mingels A, Jacobs L, Michielsen E, Swaanenburg J, Wodzig W, van Dieijen-Visser M. Reference population and marathon runner sera assessed by highly sensitive cardiac troponin T and commercial cardiac troponin T and I assays. Clin Chem. 2009;55(1):101-8. doi:10.1373/clinchem.2008.106427.
13. Middleton N, George K, Whyte G, Gaze D, Collinson P, Shave R. Cardiac troponin T release is stimulated by endurance exercise in healthy humans. J Am Coll Cardiol. 2008;52(22):1813-14. doi:10.1016/j.jacc.2008.03.069.
14. Fu FH, Nie J, George K, Tong TK, Lin H, Shi Q. Impact of a 21-km Run on Cardiac Biomarkers in Adolescent Runners. J Exerc Sci Fit. 2010;8(2):61-6. doi:10.1016/S1728-869X(10)60009-3.
15. König D, Neubauer O, Nics L, Kern N, Berg A, Bisse E, Wagner KH. Biomarkers of exercise-induced myocardial stress in relation to inflammatory and oxidative stress. Exerc Immunol Rev. 2007;13:15-36.
16. Kurz K, Giannitsis E, Zehelein J, Katus HA. Highly sensitive cardiac troponin T values remain constant after brief exercise- or pharmacologic-induced reversible myocardial ischemia. Clin Chem. 2008;54(7):1234-38. doi:10.1373/clinchem.2007.097865.
17. Axelsson A, Ruwald MH, Dalsgaard M, Rossing K, Steffensen R, Iversen K. Serial measurements of high-sensitivity cardiac troponin T after exercise stress test in stable coronary artery disease. Biomark Biochem Indic Expo Response Susceptibility Chem. 2013;18(4):304-9. doi:10.3109/1354750X.2013.776635.
18. Ellis SG, Chew D, Chan A, Whitlow PL, Schneider JP, Topol EJ. Death following creatine kinase-MB elevation after coronary intervention: identification of an early risk period: importance of creatine kinase-MB level, completeness of revascularization, ventricular function, and probable benefit of statin therapy. Circulation. 2002;106(10):1205-10. doi:10.1161/01.cir.0000028146.71416.2e.
19. Van Gaal WJ, Ponnuthurai FA, Selvanayagam J, Testa L, Porto I, Neubauer S, Banning AP. The Syntax score predicts peri-procedural myocardial necrosis during percutaneous coronary intervention. Int J Cardiol. 2009;135(1):60-5. doi:10.1016/j.ijcard.2008.03.033.
20. Mark DB, Shaw L, Harrell FE Jr, Hlatky MA, Lee KL, Bengtson JR, McCants CB, Califf RM, Pryor DB. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. N Engl J Med. 1991;325(12):849-53. doi:10.1056/NEJM199109193251204.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

The Influence of Gender and Age on Laparoscopic Sleeve Gastrectomy Short-Term Outcomes in Type-2 Diabetic Obese Patients

Onur ELBASAN[1], Pinar SISMAN[2], Hande PEYNIRCI[3], Aysegul YABACI[4], Canan ERSOY[5]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey
[2]Department of Endocrinology and Metabolism, Medicana Hospital, Bursa, Turkey
[3]Deparment of of Endocrinology and Metabolism, Istanbul Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital, Istanbul, Turkey
[4]Department of Biostatics, Bezmialem Vakif University Faculty of Medicine , Medicana Hospital, Istanbul, Turkey
[5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Bursa Uludag University Faculty of Medicine, Bursa, Turkey

ABSTRACT

Background Bariatric surgery has come out as an effective treatment for morbid obesity due to its effects as stabilized weight loss and remission of obesity related comorbidities like type 2 diabetes. Postoperative weight loss is affected by many factors and predictors of weight loss after bariatric surgery are controversial. This study has been performed to evaluate the impact of gender and age on the short-term outcomes of laparoscopic sleeve gastrectomy (LSG) in type 2 diabetic (T2D) obese patients.

Material and Methods In this retrospective study, the records of morbidly obese patients with a body mass index (BMI)≥40 kg/m^2, aged between 18-65 years old who underwent LSG and were followed-up for at least 6 months postoperatively were reviewed. Patients were subdivided into two groups according to age (≥50 y,<50 y), gender (female, male) and compared.

Results The study included 25 patients, 17 (68%) female and 8 (32%) male, 14 (56%) were in <50 years old group and 11 (44%) were in ≥50 years old group. At the postoperative 6th month, there was a significant decrease in weight, BMI, diastolic blood pressure, fasting blood glucose, postprandial glucose and HbA1c in both gender and age groups (p<0.05). A significant decrease was observed in triglyceride (TG) at 6th month in both gender. While a significant increase in high-density lipoprotein (HDL) was observed in patients aged ≥50 (p=0.028), no significant change was observed in the younger group. There was a positive correlation between change in total cholesterol(TCh), TG and age (respectively; r=0.436, p=0.030, r=0.528, p=0.007).

Conclusions LSG is an effective treatment method for morbid obesity for younger (<50 y) and advanced aged (≥50 y) T2D patients in both genders. The percentage changes in the decreament of TG in male gender and TCh in younger age were more prominent in short-term follow-up.

Turk J Int Med 2021;3(4):164-171
DOI: 10.46310/tjim.881201

Keywords: *Laparoscopic sleeve gastrectomy, age, gender, obesity, type 2 diabetes.*

Received: Februrary 16, 2021; Accepted: June 18 2021; Published Online: October 29, 2021

Address for Correspondence:
Onur Elbasan, MD
Division of Endocrinology and Metabolism, Department of Internal Medicine, Marmara University Faculty of Medicine, Istanbul, Turkey
E-mail: dronurelbasan@hotmail.com

Introduction

In the last decade, both type 2 diabetes and obesity have been increasing epidemically worldwide. In TURDEP II study performed in Turkey in 2010, the prevalence of diabetes was found to be 13.7% and obesity 32%.[1] Bariatric surgery has come out as an effective treatment for morbid obesity due to its effects as stabilized weight loss and remission of obesity related comorbidities like type 2 diabetes. Laparoscopic sleeve gastrectomy (LSG) has been increasingly applied in our country in parallel with the world due to its advantages such as relative technical simplicity, permanent weight loss, endoscopy feasibility, having the chance of revision, and the need for less vitamin support throughout life.[2] Although bariatric surgery is the most effective therapy for obesity, postoperative weight loss is affected by many factors. Bariatric surgery results can be implicated by many physiological, epidemiological and psychosocial parameters, but studies evaluating potential predictors of weight loss after bariatric surgery are controversial.[3,4] This study has been carried out to evaluate the impact of gender and age on the short-term outcomes of LSG in type 2 diabetic obese patients.

Material and Methods

The study was conducted after the approval of the local Ethics Committee in accordance with the Helsinki Declaration. In this retrospective study,the records of morbidly obese patients with a body mass index (BMI) ≥40 kg/m^2, aged between 18-65 years old who admitted to our Endocrinology and Metabolism outpatient clinics and underwent sleeve gastrectomy were reviewed. Patients who were followed up for at least 6 months postoperatively were included in the study. Gender, age, height, weight, BMI (calculated according to the formula=weight (kg)/height(m)^2), insulin usage, diastolic blood pressure (DBP), systolic blood pressure (SBP), fasting blood glucose (FBG), postprandial blood glucose (PPG), hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), total cholesterol (TCh), high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol and triglyceride (TG) were recorded retrospectively from files of the subjects. The percent of excess Body Mass Index Lost (%EBMIL) was calculated with the formula ([Preoperative BMI-current BMI]/[preoperative BMI-25])x100. Patients were subdivided into two groups according to age (≥50 y, <50 y), gender (female, male) and compared regarding changes in the mentioned parameters.

Statistical Analysis

Descriptive statistics for the numerical variables following nonnormal distribution were expressed as median (min-max). Shapiro-Wilk test was used to determine whether the data followed a normal distribution. In the comparison of two independent groups showing normal distribution, Independent Sample T test was used. Nonparametric tests were used for data that did not show normal distribution. Mann-Whitney U test was used to determine whether there was a significant difference between the mean values of independent data following nonnormal distribution in the presence of two groups. Wilcoxon test was used to determine whether there was a significant difference between the mean values of dependent data following nonnormal distribution. Pearson chi-square, Fisher Exact tests were used to determine whether there was a correlation between the categorical variables or whether they were independent of each other. The correlation between the numerical variables was determined using Spearman's Correlation Analysis. All statistical analyses were performed using IBM SPSS Statistics version 20.0 and a p-value of 0.05 was considered statistically significant.

Results

Gender

Twenty five patients fulfilling the criterias were included in our study. Among them, 17 (68%) were females and 8 (32%) were males. The median age was 50 (25-59) years for females and 42.5 (18-57) years for males. Initial BMI values were 50.8 kg/m^2 (42.1-78.1) and 45.2 kg/m^2 (40.4-52.5) for females and males respectively, significantly higher in the female gender (p=0.049). Baseline ALT values in males were significantly higher compared to females (p<0.001). In the preoperative evaluation, no significant difference was observed between

the two genders in terms of other demographic and laboratory parametersas well as insulin usage percentages and doses used *(Table 1)*.

At the postoperative 6th month, there was a significant decrease in weight, BMI, DBP, FBG, PPG and HbA1c values in both gender compared to baseline *(Table 2)*. Although there was a significant decrease in SBP (p=0.001) and ALT (p=0.003) values in female patients, no significant change was observed in males. Concerning lipid parameters, a significant decrease was observed in TG values at 6th month compared to baseline in both gender (p=0.014 for females, p=0.017 for males, respectively). There was no significant change in TCh, HDL and LDL values. Insulin treatment was discontinued at the postoperative 6th month in all males and in 3 of the 5 females. Insulin dose was significantly reduced in the other 2 female patients. %EBMIL was found to be 49.66±12.67 in females and 64±15.8 in males, and it was significantly higher in male gender (p=0.023). There was not any significant difference among genders in terms of the percentage changes of all parameters.

Age

When the patients were grouped according to age, 14 (56%) were in <50 years old group and 11 (44%) were in ≥50 years old group. Although at baseline the weights of the patients in <50 years old group were significantly higher than the other group (p=0.013), there was no significant difference between the groups in terms of BMI. There was also no difference among the groups in terms of parameters other than weight before the operation *(Table 1)*.

At the postoperative 6th month, there was a statistically significant decrease in weight, BMI, DBP, FBG, PPG, HbA1c, ALT and TG values compared to baseline in both groups (p<0.05). While a significant increase in HDL was observed in patients aged 50 and over (p=0.028), no significant change was observed in the <50 years old group. The percentage change of the TCh values in the patients aged <50 years was found to be significantly higher than the changes in patients aged 50-years and over (p=0.015). At the postoperative 6th month, insulin treatment was discontinued in 3 of 4 patients <50 years

Table 1. Baseline demographic and laboratory characteristics of patients in gender and age groups

	Female (n=17)	Male (n=8)	p^1	Age <50 years (n=14)	Age ≥50 years (n=11)	p^2
Age (year)	50 (25-59)	42.50 (18-57)	0.511	38±9.72	53.33±2.74	**<0.001**
Weight (kg)	130 (103-190)	137 (121-159)	0.884	140.5 (121-178)	121 (103-190)	**0.013**
BMI (kg/m^2)	50.8 (42.1-78.1)	45.2 (40.4-52.5)	**0.049**	51.4 (40.4-78.1)	46.2 (40.9-69.9)	0.183
Insulin usage (%)	5 (29.4%)	5 (62.5%)	0.194	4 (28.6%)	6 (54.5%)	0.241
Insulin dosage (U/day)	83 (42-150)	44 (10-100)	0.421	63.50 (10-150)	77 (10-100)	0.914
SBP (mmHg)	135 (120-170)	132.5 (125-170)	1	130 (120-170)	135 (120-170)	0.267
DBP (mmHg)	85 (70-100)	80 (80-90)	0.157	80 (70-100)	80 (80-90)	0.687
FBG (mg/dL)	133 (94-288)	149 (92-238)	0.932	125 (92-193)	165 (94-288)	0.075
PPG (mg/dL)	166 (124-307)	186 (111-347)	0.887	169 (111-347)	180 (124-307)	0.434
HbA1c (%)	7 (5.7-9.9)	7.7 (5.7-10.4)	0.977	6.55 (5.7-10.4)	8.3 (5.7-9.9)	0.222
ALT (IU/L)	22 (12-53)	55 (33-90)	**p<0.001**	37 (13-90)	22 (12-60)	0.183
LDL cholesterol (mg/dL)	126 (63-228)	118 (45-189)	0.475	118 (45-195)	161 (81-228)	0.149
HDL cholesterol (mg/dL)	40 (27-58)	39.5 (28-60)	0.887	39 (27-60)	41 (28-58)	0.609
TG (mg/dL)	215 (79-401)	179 (86-355)	0.977	222 (79-401)	187 (98-258)	0.373
TCh (mg/dL)	214 (114-306)	199.5 (129-268)	0.475	213 (114-269)	214 (148-306)	0.267

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, PPG: postprandial blood glucose, HbA1c: hemoglobin A1c, ALT: alanine aminotransferase, HDL: high-density lipoprotein, LDL: low density lipoprotein, TG: triglyceride, TCh: total cholesterol.
p^1 comparison of initial and parameters of in gender groups.
p^2 comparison of initial and parameters of in age groups.

Table 2. Comparison of baseline and six month values of clinical and laboratory parameters in gender groups

Parameteres	Female (n=17)				Male (n=8)				
	Baseline	6th month	Δ	P*	Baseline	6th month	Δ	P**	P***
Weight (kg)	130 (103-190)	97 (79-156)	-0.25 (-0.32/-0.17)	**<0.001**	137 (121-159)	92.5 (85-125)	-0.27 (-0.45/-0.02)	**0.012**	0.374
BMI (kg/m^2)	50 (42.1-78.1)	38.3 (29.7-63.2)	-0.25 (-0.32/-0.17)	**<0.001**	45.2 (40.4-52.5)	31.5 (28.7-41.8	-0.21 (-0.45/-0.02)	**0.012**	0.374
SBP (mmHg)	135 (120-170)	120 (110-160)	-0.07 (-0.21/0.00)	**0.001**	132.5 (125-170)	130 (110-140)	-0.11 (-0.19/0.08)	0.092	0.798
DBP(mmHg)	85 (70-100)	80 (60-90)	-0.1 (-0.25/0.00)	**0.002**	80 (80-90)	75 (70-80)	-0.11 (-0.18/0.00)	**0.025**	0.932
FBG (mg/dL)	133 (94-288)	100 (73-184)	-0.27 (-0.61/0.16)	**0.001**	149 (92-238)	90.5 (74-127)	-0.18 (-0.54/1.00)	**0.025**	0.669
PPG (mg/dL)	166 (124-307)	124 (98-188)	-0.31 (-0.6/-0.01)	**<0.001**	186 (111-347)	118 (101-173)	-0.23 (-0.64/0.57)	**0.012**	0.932
HbA1c (%)	7 (5.7-9.9)	5.5 (4.7-6.8)	-0.26 (-0.53/-0.01)	**<0.001**	7.7 (5.7-10.4)	5.8 (5.3-6.7)	-0.21 (-0.43/-0.03)	**0.012**	0.798
ALT (IU/L)	22 (12-53)	14 (6-34)	-0.38 (-0.82/0.24)	**0.003**	55 (33-90)	33 (11-82)	-0.56 (-0.78/1.48)	0.176	0.406
LDL cholesterol (mg/dL)	126 (63-228)	139 (43-253)	0.17 (-0.32/0.54)	0.522	118 (45-189)	126.5 (48-189)	0.05 (-0.08/0.28)	0.237	0.344
HDL cholesterol (mg/dL)	40 (27-58)	44 (32-81)	0.07 (-0.15/1.06)	0.065	39.5 (28-60)	44.5 (30-52)	0.13 (-0.36/0.33)	0.623	0.977
TG (mg/dL)	215 (79-401)	135 (90-237)	-0.22 (-0.73/0.88)	**0.014**	179 (86-355)	91.5 (84-182)	-0.47 (-0.75/0.02)	**0.017**	0.086
TCh (mg/dL)	214 (114-306)	209 (95-354)	-0.02 (-0.22/0.31)	0.723	199.5 (129-268)	185 (96-249)	-0.03 (-0.26/0.11)	0.327	0.549

p* comparison of initial and sixth month parameters of female group.
p** comparison of initial and sixth month parameters of male group.
p*** comparison of Δfemale and Δmale.

of age, and in 5 of 6 patients >50 years of age. A significant reduction in dose was observed in patients who continued insulin. %EBMIL was 56.68±17.02 in the younger group and 51.62±12.8 in the elderly group, and no significant difference was observed (p=0.412). There was also not any significant difference between groups in terms of percentage changes of other parameters *(Table 3).*

When the relationship between the changes in the clinical and laboratory parameters of the patients and age is examined, there was a statistically significant and positive correlation between change in TCh, TG and age (respectively; r=0.436 p=0.030, r=0.528 p=0.007). There was no significant correlation between the change of other parameters and age.

Discussion

In this preliminary retrospective study, our results indicated that both females and males benefited from LSG concerning weight and metabolic parameters in both groups younger than and equal to or older than 50 years of age in a 6 months follow-up period. At the 6th month of the evaluation, the percentage changes in the decreament of TG in male gender and TCh in younger age were more prominent.

Although the beneficial effects of bariatric surgery are known, there is a significant difference in the demand for bariatric surgery in men and women, and it is known that bariatric surgery is performed more in women.[5] Studies have reported that 63-82% of cases undergoing bariatric surgery are women.[6] It is well recognised that men generally tend to underutilise healthcare services compared to women. The reasons for this are multifactorial, including social, economic and cultural motivations.[7,8] Besides these differences in demand, it is thought that there may be differences between the genders in the postoperative results of bariatric surgery.

Obesity and diabetic status differ between genders due to significant differences in fat storage and metabolism, insulin resistance, blood pressure, lipid profile, endothelial dysfunction and systemic inflammation.[9,10] But little is known about the influence of these findings on the outcome of obesity surgery. Bariatric Outcome Longitudinal Database (BOLD) study results show that bariatric surgery efficiency is higher for female patients.[11] A recently published study demonstrated that female gender is an independent predictor of greater weight loss and %EBMIL, 1 year after bariatric surgery.[12] In another study, LSG was

Table 3. Comparison of the baseline and sixth month values of clinical and laboratory parameters in age groups and comparison of their percent changes

Parameteres	Age <50 (n=14)				Age ≥50 (n=11)				
	Baseline	6th month	Δ	P*	Baseline	6th month	Δ	P**	P***
Weight (kg)	140.5 (121-178)	104 (85-144)	-0.28 (-0.45/-0.19)	**0.001**	121 (103-190)	92 (79-156)	-0.23 (-0.3/-0.17)	**0.003**	0.095
BMI (kg/m^2)	51.4 (40.4-78.1)	37.4 (28.7-63.2)	-0.28 (-0.45/-0.19)	**0.001**	46.2 (40.9-69.9)	36 (29.1-57.3)	-0.23 (-0.3/-0.17)	**0.003**	0.095
SBP (mmHg)	130 (120-170)	120 (110-160)	-0.07 (-0.21/0.08)	**0.008**	135 (120-170)	130 (115-140)	-0.07 (-0.18/0)	0.007	0.809
DBP (mmHg)	80 (70-100)	72.5 (60-90)	-0.11 (-0.25/0)	**0.004**	80 (80-90)	80 (70-85)	-0.11 (-0.13/0)	**0.011**	0.317
FBG (mg/dL)	125 (92-193)	87 (73-184)	-0.32 (-0.54/0.16)	**0.005**	165 (94-288)	111 (92-129)	-0.21 (-0.61/0.07)	**0.004**	0.727
PPG (mg/dL)	169 (111-347)	104 (98-188)	-0.31 (-0.64/-0.05)	**0.001**	180 (124-307)	130 (119-173)	-0.21 (-0.57/-0.01)	**0.003**	0.501
HbA1c (%)	6.55 (5.7-10.4)	5.4 (4.70-6.20)	-0.17 (-0.43/-0.03)	**0.001**	8.30 (5.7-9.9)	6 (4.7-6.8)	-0.26 (-0.53/-0.01)	**0.003**	0.851
ALT (IU/L)	37 (13-90)	15 (6-82)	-0.49 (-0.82/1.48)	**0.023**	22 (12-60)	14 (8-35)	-0.33 (-0.78/0.24)	**0.029**	0.317
LDL cholesterol (mg/dL)	118 (45-195)	122.5 (43-181)	0.003 (-0.32/0.28)	0.615	161 (81-228)	136 (117-253)	0.17 (-0.20/0.54)	0.169	0.647
HDL cholesterol (mg/dL)	39 (27-60)	41.5 (30-66)	0.06 (-0.36/0.35)	0.530	41 (28-58)	46 (34-81)	0.07 (-0.13/1.06)	**0.028**	0.244
TG (mg/dL)	222 (79-401)	113.5 (88-237)	-0.44 (-0.75/0.88)	**0.009**	187 (98-258)	135 (84-205)	-0.21 (-0.53/0.36)	**0.014**	0.183
TCh (mg/dL)	213 (114-269)	183.5 (95-264)	-0.13 (-0.26/0.14)	**0.026**	214 (148-306)	217 (184-354)	0.06 (-0.18/0.31)	0.286	**0.015**

p* comparison of initial and sixth month parameters of age <50 group.
p** comparison of initial and sixth month parameters of age ≥50group.
p*** comparison of Δ age<50 group and Δ age≥50group.

more effective in obese male than in obese female in terms of %EBMIL.[3] However, Kennedy-Dalby *et al.*[4] reported in a cohort study that there was no gender difference in terms of %EBMIL at 2-year follow-up. In our study, %EBMIL was found to be significantly higher in male in short-term, but the lower baseline BMI of males can be thought to contribute to this result.

The reason for the different response to bariatric surgery between males and females is still unclear.[13] Another study examining the weight loss and metabolic effects of bariatric surgery on women and men showed a significant decrease in BMI, weight loss percentage and HbA1c values for both genders in the first year after surgery, no significant difference was observed among both genders regarding the changes of parameters stated.[4] Although it is known that bariatric surgery provides significant weight control and resolution of type 2 diabetes even in the short term[14], many studies have shown that there is no difference between genders in respect of weight loss and type 2 diabetes improvement.[15,16] In our study, it was seen that there was a significant decrease in weight, BMI, FPG, PPG and HbA1c values in the 6th month of treatment compared to the baseline in females and males who had LSG. Besides, similar to the literature, there was no significant difference between genders with regard to the percentage changes of these parameters.

In different studies, it is emphasized that some differences between genders in bariatric surgery results may be associated with varying cardiovascular risk profiles.[17] In a study conducted in Europe, at the end of 1-year follow-up, there was a significant decrease in both SBP and DBP, but no difference was observed in respect to percentage changes between genders. In our study, there was no significant change in the value of SBP in men, while there was a significant decrease in DBP. There was also no difference between genders in terms of percentage changes in DBP. In another study, the cardiovascular effects of bariatric surgery in women and men were evaluated by calculating the total cholesterol/HDL ratio, and a significant decrease was detected in both sexes, but no significant difference was observed in percentage changes between genders.[4] In our study, there was a significant decrease in TG value at the 6th month compared to baseline in men and women underwent LSG, while no significant change was found in other lipid parameters. Nevertheless, the percentage of TG change was not significantly different between genders.

The number of patients suffering from obesity and its comorbidities increase with the age, especially in the population aged 50 years and over. Therefore, the treatment of morbid obesity has become increasingly important, especially in the elderly population. Studies show that the majority of the patients selected for bariatric surgery were younger than 50 years, despite the fact that the prevalence of obesity is higher in the older age groups.[18] Nevertheless, although sleeve gastrectomy is not more risky in the elderly population, its outcomes on weight loss and comorbidities in older patients are less known.[19] The effectiveness of bariatric surgery in the older ages has been previously investigated. For instance, in a study comparing the patients over 60 years with those under 50 years for up to 22 months after LSG showed better results in the younger age group for BMI% change.[20] In a study conducted in our country, it is stated that age may be the determining factor for weight loss after LSG and that weight loss is less in patients over the age of 40 years.[21] Many studies have shown that the mean excess of weight loss was lower for the older patients and those younger than 45 years tended to have greater %BMI loss and %EBMIL than the older patients.[22,23] Chang *et al*.[24] also indicated that age was identified as an independent risk factor for weight loss in long-term follow-up. However, Robert *et al*.[25] showed age not to be a predictive factor of weight loss failure at 1 year. A recent study in India revealed that %EBMIL at the 6th month postoperatively did not differ between those over and under 65 years of age.[26] In another research, which used an age of 55 years as the cut-off point, there was no significant difference in weight loss and BMI after 24 months of follow-up.[27] In a comparative study by Burchett *et al*.[28], there was not any significant difference in weight loss and comorbidities such as diabetes between older and younger age groups. In this study, cut-off value for age was determined as 50 years based on the previous studies in the literature. We also used 50 years as cut-off for age in our study. Our study indicated a significant decrease in weight, BMI, DBP, FBG, PPG and HbA1c in both age groups. However, in the short-term follow-up of 6 months, the change of these parameters and %EBMIL did not differ significantly between the groups in accordance with the literature.

It is known that therapeutic interventions in diabetic patients are more effective in elderly patients to improve hypercholesterolemia. In the Action for Health Diabetes (AHEAD) program, interventions were effective in inducing larger relative improvements in HDL and waist circumference among the older participants when compared with the youngers. Lifestyle changes have often been promoted to explain these better outcomes in older patient groups.[29] In our study, there was a significant decrease in TG in both age groups after LSG in diabetic obese patients, but no significant change was observed in LDL value. While in younger group HDL did not change significantly, there was a significant increase in HDL level in the elderly group (≥50 y). Although the percentage of TCh change is significantly higher in the young group compared to the older group, the percentage of TG and TCh decrease increases with age (positive corelation). These good results in the older group can be explained by the fact that these patients being more aware of the negative consequences induced by obesity on their health as reported in some studies.[30] This makes them more likely to have a better motivation to change lifestyle and adhere to postoperative follow-up instructions.

In conclusion, sleeve gastrectomy is an effective treatment method for morbid obesity for younger (<50 y) and advanced aged (≥50 y) type 2 diabetic patients in both genders. In our study, no difference was observed in terms of weight loss, SBP and DBP values and changes in glycemic and lipid parameters between genders in short-term 6 months follow-up. There is no significant difference between the younger and older age groups in terms of the parameters other than TCh that decreased in the <50 years old age group. On the other hand, there is a positive correlation between age and percentage decreases of TCh and TG. Studies involving longer follow-up periods and higher number of patients are needed to reveal the effect of gender and age on the results of bariatric surgery concerning weight, metabolic parameters and positive effects on type 2 diabetes.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OE, PS, HP, AY, CE; Study Design: OE, PS, HP, AY, CE; Supervision: OE, PS, HP, AY, CE; Funding: OE, CE; Materials: OE, HP, CE; Data Collection and/or Processing: OE, HP, PS; Statistical Analysis and/or Data Interpretation: AY, PS, CE; Literature Review: OE, PS, HP; Manuscript Preparation: OE, PS, CE; and Critical Review: OE, PS, CE.

References

1. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al. Twelve-year trends in prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013 Feb;28(2):169-80. doi: 10.1007/s10654-013-9771-5.
2. Palikhe G, Gupta R, Behera BN, Sachdeva N, Gangadhar P, Bhansali A. Efficacy of laparoscopic sleeve gastrectomy and intensive medical management in obese patients with type 2 diabetes mellitus. Obes Surg Doı 10.1007/S11695-015-1746-Z.
3. Perrone F, Bianciardi E, Benavoli D, Tognoni V, Niolu C, Siracusano A, Gaspari AL, Gentileschi P. Gender Influence on Long-Term Weight Loss and Comorbidities After Laparoscopic Sleeve Gastrectomy and Roux-en-Y Gastric Bypass: a Prospective Study With a 5-Year Follow-up. Obes Surg. 2016 Feb;26(2):276-81. doi: 10.1007/s11695-015-1746-z.
4. Kennedy-Dalby A, Adam S, Ammori BJ, Syed AA. Weight loss and metabolic outcomes of bariatric surgery in men versus women - A matched comparative observational cohort study. Eur J Intern Med. 2014 Dec;25(10):922-5. doi: 10.1016/j.ejim.2014.10.020.
5. Farinholt GN, Carr AD, Chang EJ, Ali MR. A call to arms: obese men with more severe comorbid disease and underutilization of bariatric operations. Surg Endosc. 2013 Dec;27(12):4556-63. doi: 10.1007/s00464-013-3122-1.
6. Padwal RS, Klarenbach SW, Wang X, Sharma AM, Karmali S, Birch DW, Majumdar SR. A simple prediction rule for all-cause mortality in a cohort eligible for bariatric surgery. JAMA Surg. 2013 Dec;148(12):1109-15. doi: 10.1001/jamasurg.2013.3953.
7. Smith JA, Braunack-Mayer A, Wittert G. What do we know about men's help-seeking and health service use? Med J Aust. 2006 Jan 16;184(2):81-3. doi: 10.5694/j.1326-5377.2006.tb00124.x.
8. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005 Mar;49(6):616-23. doi: 10.1111/j.1365-2648.2004.03331.x.
9. Horigan G, McGuigan K, Quinn L, Coates V. Does gender make a difference to self-management of diabetes in adults ≤55 years? A pilot study. University of Ulster. 2015. Available at: HYPERLINK "http://www.publichealth.hscni.net/sites/default/files/Shaping%20Services-Does%20gender%20make%20a%20difference%20to%20self%20management%20of%20diabetes%20in%20younger%20adults.pdf" www.publichealth.hscni.net/sites/default/files/Shaping%20Services-Does%20gender%20make%20a%20difference%20to%20self%20management%20of%20diabetes%20in%20younger%20adults.pdf. Accessed February 01, 2021.
10. Wannamethee SG, Papacosta O, Lawlor DA, Whincup PH, Lowe GD, Ebrahim S, Sattar N. Do women exhibit greater differences in established and novel risk factors between diabetes and non-diabetes than men? The British Regional Heart Study and British Women's Heart Health Study. Diabetologia. 2012 Jan;55(1):80-7. doi: 10.1007/s00125-011-2284-4.
11. van de Laar AW. Algorithm for weight loss after gastric bypass surgery considering body mass index, gender, and age from the Bariatric Outcome Longitudinal Database (BOLD). Surg Obes Relat Dis. 2014 Jan-Feb;10(1):55-61. doi: 10.1016/j.soard.2013.05.008.
12. Kitamura R, Chen R, Trickey A, Eisenberg D. Positive and Negative Independent Predictive Factors of Weight Loss After Bariatric Surgery in a Veteran Population. Obes Surg. 2020 Jun;30(6):2124-30. doi: 10.1007/s11695-020-04428-0.
13. Ketterer C, Heni M, Stingl K, Tschritter O, Linder K, Wagner R, Machicao F, Häring HU, Preissl H, Staiger H, Fritsche A. Polymorphism rs3123554 in CNR2 reveals gender-specific effects on body weight and affects loss of body weight and cerebral insulin action. Obesity (Silver Spring). 2014 Mar;22(3):925-31. doi: 10.1002/oby.20573.
14. Cingi A, Yardimci S, Yavuz D, Coskun M, Uygur MM, Coskun S. One Hundred Twenty-Eight Consecutive Sleeve Gastrectomies, Short-Term Outcomes, and Impacts on Type 2 Diabetes Mellitus. Indian J Surg. 2018 Oct:80(5):410-4. doi: 10.1007/s12262-017-1616-0.
15. Buchwald H, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009 Mar;122(3):248-256.e5. doi: 10.1016/j.amjmed.2008.09.041.
16. Arterburn DE, Courcoulas AP. Bariatric surgery for obesity and metabolic conditions in adults. BMJ. 2014 Aug 27;349:g3961. doi: 10.1136/bmj.g3961.
17. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med. 2002 Nov 14;347(20):1557-65. doi: 10.1056/NEJMoa021993.
18. Burns EM, Naseem H, Bottle A, Lazzarino AI, Aylin P, Darzi A, Moorthy K, Faiz O. Introduction of laparoscopic bariatric surgery in England: observational population cohort study. BMJ. 2010 Aug 26;341:c4296. doi: 10.1136/bmj.c4296.
19. O'Keefe KL, Kemmeter PR, Kemmeter KD. Bariatric surgery outcomes in patients aged 65 years and older at an American Society for Metabolic and Bariatric Surgery Center of Excellence. Obes Surg. 2010 Sep;20(9):1199-205. doi: 10.1007/s11695-010-0201-4.
20. Mizrahi I, Alkurd A, Ghanem M, Zugayar D, Mazeh H, Eid A, Beglaibter N, Grinbaum R. Outcomes of laparoscopic sleeve gastrectomy in patients older than 60 years. Obes Surg. 2014 Jun;24(6):855-60. doi: 10.1007/s11695-014-1177-2.
21. Aslaner A, Öngen A, Kosar M, Çakır T, Mayir B, Dogan U, Gündüz U, Cantilav G, Habibi M, Özdemir S, Oruç MT, Bülbüller N. Relation between weight loss and age after laparoscopic sleeve gastrectomy. Eur Rev Med Pharmacol Sci. 2015 Apr;19(8):1398-402.

22. Ritz P, Topart P, Benchetrit S, Tuyeras G, Lepage B, Mouiel J, Becouarn G, Pattou F, Chevallier JM. Benefits and risks of bariatric surgery in patients aged more than 60 years. Surg Obes Relat Dis. 2014 Jan 9;S1550-7289(14)00004-5. doi: 10.1016/j.soard.2013.12.012.
23. Contreras JE, Santander C, Court I, Bravo J. Correlation between age and weight loss after bariatric surgery. Obes Surg. 2013 Aug;23(8):1286-9. doi: 10.1007/s11695-013-0905-3.
24. Chang WW, Hawkins DN, Brockmeyer JR, Faler BJ, Hoppe SW, Prasad BM. Factors influencing long-term weight loss after bariatric surgery. Surg Obes Relat Dis. 2019 Mar;15(3):456-61. doi: 10.1016/j.soard.2018.12.033.
25. Robert M, Pasquer A, Espalieu P, Laville M, Gouillat C, Disse E. Gastric bypass for obesity in the elderly: is it as appropriate as for young and middle-aged populations? Obes Surg. 2014 Oct;24(10):1662-9. doi: 10.1007/s11695-014-1247-5.
26. Bhandari M, Mathur W, Fobi M, Kosta S. Outcomes of bariatric surgery in geriatric patients ≥65 years: single institution study. Obes Surg. 2019 May;29(5):1470-6. doi: 10.1007/s11695-019-03718-6.
27. Giordano S, Victorzon M. Laparoscopic Roux-en-Y gastric bypass is effective and safe in over 55-year-old patients: a comparative analysis. World J Surg. 2014 May;38(5):1121-6. doi: 10.1007/s00268-013-2399-5.
28. Burchett MA, McKenna DT, Selzer DJ, Choi JH, Mattar SG. Laparoscopic sleeve gastrectomy is safe and effective in elderly patients: a comparative analysis. Obes Surg. 2015 Feb;25(2):222-8. doi: 10.1007/s11695-014-1421-9.
29. Espeland MA, Rejeski WJ, West DS, Bray GA, Clark JM, Peters AL, Chen H, Johnson KC, Horton ES, Hazuda HP; Action for Health in Diabetes Research Group. Intensive weight loss intervention in older individuals: results from the Action for Health in Diabetes Type 2 diabetes mellitus trial. J Am Geriatr Soc. 2013 Jun;61(6):912-22. doi: 10.1111/jgs.12271.
30. Fabricatore AN, Wadden TA, Moore RH, Butryn ML, Heymsfield SB, Nguyen AM. Predictors of attrition and weight loss success: Results from a randomized controlled trial. Behav Res Ther. 2009 Aug;47(8):685-91. doi: 10.1016/j.brat.2009.05.004.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

The Relationship Between HbA1c and Contrast-Induced Nephropathy in Patients with Non-ST Elevation Myocardial Infarction and Non-Established Diabetes Mellitus

Onur BAYDAR[1]

[1]Department of Cardiology, Avicenna Hospital, Istanbul, Turkey

ABSTRACT

Background Diabetes Mellitus (DM) is an important cardiovascular risk factor and 50% of newly diagnosed diabetic patients have coronary artery disease. HbA1c levels in these patients have an effect on prognosis. Development of contrast agent-induced nephropathy (CIN) is common in patients who have undergone percutaneous coronary intervention (PCI) without ST elevation myocardial infarction (NSTEMI) and is associated with increased mortality and morbidity. In this study, the relationship between HbA1c and the development of CIN was investigated in NSTEMI patients who did not have a previous diagnosis of DM and receive treatment.

Material and Methods In this study, 359 (189, 52.6% male) patients who were not diagnosed with DM and did not receive treatment were retrospectively analyzed for NSTEMI diagnosis. HbA1c and creatinine values before and after the procedure were evaluated. CIN was defined as an increase of 25% or 0.5 mg/dL compared to the basal value in serum creatinine measured 48-72 hours after the procedure.

Results CIN was detected in 56 (15.6%) of all patients. Among the group with and without CIN; There was no difference between gender, amount of contrast material, pre-procedure eGFR, troponin and ejection fraction values. Only in the group with CIN, the patients were older and the number of hypertensive patients was significantly higher. As a result of coronary angiography, medical follow-up was made for 46 (12.7%) patients, coronary stent in 271 (74.7%) and coronary bypass in 40 (11%) patients. In addition, in-hospital mortality was detected in 17 (4.7%) patients. HbA1c and fasting glucose levels were found significantly higher in the group developing CIN (6.1±1.0 vs. 5.5±0.6 mg/dL, $p<0.001$, 133.8±65.9 vs. 110.9±48.7 mg/dL, $p=0.002$, respectively). But only the HbA1c value was determined to be an independent predictor in the logistic regression analysis of CIN (OR: 2.3, $p<0.001$, CI: 1.6-3.2).

Conclusions CIN was more common in NSTEMI patients with high HbA1c who were not diagnosed with DM and were not treated. In addition, HbA1c value was an independent predictor of CIN development.

Turk J Int Med 2021;3(4):172-176
DOI: 10.46310/tjim.882755

Keywords: *HbA1c, nephropathy, myocardial infarction.*

Received: February 18, 2021; Accepted: May 23, 2021; Published Online: October 29, 2021

Address for Correspondence:
Onur Baydar, MD*
Department of Cardiology, Istanbul Health Sciences University, Mehmet Akif Ersoy Cardiovascular and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey
E-mail: dr.onurbaydar@hotmail.com

Introduction

Percutaneous coronary intervention (PCI) in patients with non-ST-elevation myocardial infarction (NSTEMI) reduces ischemic complications and improves survival. Patients undergoing PCI are at high risk for contrast-induced nephropathy (CIN) and this has been associated with renal dysfunction, longer hospital stay, increased cardiovascular events and mortality.[1,2] So many factors such as hypovolemia, contrast volume, and baseline glomerular filtration rate (GFR) may contribute to the development of CIN.[3,4] Because of this, identifying patients at risk of CIN is important in patients undergoing PCI. Diabetes Mellitus (DM) is an important cardiovascular risk factor and 50% of newly diagnosed diabetic patients have coronary artery disease. HbA1c levels in these patients have an effect on prognosis. A recent study indicated that elevated HbA1c is an independent factor associated with CIN among patients without diabetes undergoing elective coronary angiography or PCI.[5] But there was not enough information in patients with NSTEMI. Therefore, in this study aimed to examine the effects of elevated HbA1c on CIN after coronary angiography in NSTEMI patients who did not have a previous diagnosis of DM and did not receive treatment.

Material and Methods

The study prospectively observed 359 consecutive patients with NSTEMI undergoing coronary angiography at the Avicenna Hospital Cardiology Depratment between January 2015 and January 2018. NSTEMI was defined according to the current guidelines.[6] Patients with severe valvular heart disease, severe or decompensated heart failure, need intra-aortic balloon pressure support, severe renal failure, and patients undergoing emergency cardiac surgery for revascularization, previously diagnosed with DM, and treated for DM (such as metformin, insulin etc.) were excluded. The study was approved by the Local Ethics Committee. In all patients, plasma glucose and Hba1c levels were assessed at hospital admission. Hypertension (HT) was defined as blood pressure >140/90 mmHg or being on treatment with antihypertensive medications. Also, diabetes mellitus (DM) was defined as fasting glucose levels >126 mg/dL or being on treatment with oral antidiabetic drugs or insulin. Finally, hyperlipidemia (HL) was defined by reference to current guidelines.[7] Serum creatinine concentration level was observed at hospital admission, every day for the following days and at hospital discharge. Estimated GFR (eGFR) was calculated using the modified formula of Levey et al.[8] CIN was defined as an increase in creatinine 25% or 0.5 mg/dL from the baseline value within the 48- 72-hour period following PCI.[9]

Statistical Analysis

All analyses were performed using SPSS version 22 for Windows (SPSS Inc, Chicago, Illinois). Numerical variables are presented as mean (standard deviation) (SD) and nominals as percentages. All variables were subjected to Kolmogorov Smirnov testing to determine whether they were normally distributed. The independent samples t test was used to compare the values of continuous variables between the 2 groups. Nonparametric values were compared using the Mann-Whitney U test. The chi-square test was used to compare categorical data. To evaluate the effects of various factors on CIN development, we performed multivariate regression analyses using the backward logistic regression (LR) method. Variables for which the unadjusted P was <0.05 was considered significant.

Results

CIN was detected in 56 (15.6%) of all patients. Among the group with and without CIN; There was no difference between gender, amount of contrast material, pre-procedure eGFR, troponin and ejection fraction values. Only in the group with CIN, the patients were older and the number of hypertensive patients was significantly higher *(Table 1)*. As a result of coronary angiography, medical follow-up was made for 46 (12.7%) patients, coronary stent in 271 (74.7%) and coronary bypass in 40 (11%) patients. Table 2 describes the medications of the cohort. In addition, in-hospital mortality was detected in 17 (4.7%) patients. HbA1c and fasting glucose levels were found significantly higher in the group developing CIN (6.1±1.0 vs. 5.5±0.6 mg/dL, p<0.001, 133.8±65.9 vs. 110.9±48.7 mg/dL, p:0.002, respectively). But only the HbA1c value was determined to be an independent predictor in the logistic regression analysis of CIN (OR: 2.3, p<0.001, CI: 1.6-3.2) *(Table 3)*.

Discussion

CIN is a frequent complication after invasive treatment of NSTEMI, even in patients with normal baseline renal function.[10] It is associated with increased in-hospital mortality and a prolonged hospitalization. Diabetic patients have twice the risk of cardiovascular events of that of healthy individuals. Cardiovascular disease is the leading cause of mortality in diabetic patients, accounting for 75% of mortalities.[11-13] In diabetes patients with cardiovascular disease who required coronary angiography or percutaneous coronary intervention, diabetes is a risk factor for acute renal injury after coronary angiography.[14] HbA1c is a product of Hb and blood glucose. It more accurately reflects long-term glycaemic control with blood glucose and helps to identify undiagnosed diabetic patients.[15] Moreover, chronic hyperglycemia associated with several adverse effects that endothelial dysfunction, increased cytokine activation, increased oxidative stress, impaired microcirculatory function and prothrombotic effects.[16-18] A study by Barbieri et al.[5] indicated that among patients without diabetes undergoing elective coronary angiography or PCI, elevated HbA1c but not glucose levels is a factor independently associated with CIN. Similar to these results, our study suggested that HbA1c and fasting glucose levels were significantly higher in the CIN group and only HBA1c is an independent predictor of CIN in NSTEMI patients. As diabetes is one of the most important risk factor for the development of CIN, this observation reinforced our findings and supports the importance of a correct management of this high risk subgroup of patients. On the other side, no relationship was found between fasting glycaemia and the occurrence of CIN.

Contrast volume is an important risk factor for

Table 1. Main characteristics of patients.

	Patients with CIN n: 56 (15.6%)	Patients without CIN n: 303 (84.4%)	p value
Age (years)	62.6±13.3	56.1± 10.2	<0.001
Male (n%)	31 (55.4&)	158 (52.1%)	0.65
Weight (kg)	76.0±4.4	75.8±5.9	0.86
HT (n%)	41 (73.2%)	177 (58.4%)	0.037
HL (n%)	23 (41.1%)	106 (35%)	0.38
Smoke (n%)	14 (25%)	87 (28.7%)	0.57
Contrast volume (mL)	228.3±15.5	228.6±17.4	0.91
Previous CABG (n%)	8 (27.4%)	83 (14.3%)	0.038
Creatinine (mg/dL)	1.1±0.1	1.0±0.08	<0.001
Peak troponin T level (ng/dL)	2.2±0.8	2.2±0.9	0.94
EF (n%)	53.2±7.4	53.9±7.7	0.52
eGFR (mL/min/1.73m^2)	86.5±22.7	89.6±15.1	0.21
HbA1c (%)	6.1±1.0	5.5±0.6	<0.001
Fasting glucose (mg/ dL)	133.8±65.9	110.9±48.7	0.002

HT: hypertension, HL: hyperlipidemia, CABG: coronary artery bypass grefting, EF: ejection fraction, GFR: glomerular filtration rate.

Table 2. Medications taken before the catheterization.

Medications	n (%)
Aspirin (n%)	170 (46.8%)
Clopidogrel (n%)	29 (8%)
Statins (n%)	122 (33.6%)
ACE-i/ARB (n%)	192 (52.9%)
Beta- Blockers (n%)	133 (36.6%)
CCB (n%)	38 (10.5%)
Nitrates (n%)	60 (16.5%)

ACE-i: angiotensin converting enzyme inhibitors, ARB: angiotensin receptor blocker, CCB: calcium channel blocker.

Table 3. Independent risk factors of CIN in logistic regression analysis.

Variables	OR (95% C.I)	p value
Weigth	0.99 (0.93-1.0)	0,80
Gender	1.2 (0.6-2.3)	0.54
Age	1.1 (0.7-1.5)	0,57
Fasting glucose	1,0 (0.99-1,0)	0,79
Hypertension	1.2 (0.5-2.6)	0.56
eGFR	0.99 (0.97-1,0)	0,96
HbA1c	2.3 (1.6-3.2)	<0.001

GFR: glomerular filtration rate.

CIN and dose minimization, on the background of a known baseline reduced renal function, may serve as an important strategy to limit the incidence of CIN.[16] We used higher contrast level that used during angiography than literature in our patients, we think that it is due to the high rate of patients undergoing PCI (74.7%). However, we did not find significant difference in terms of dose of contrast used in patients with and without CIN.

The present study supports the relationship between high HbA1c levels and the risk of acute renal dysfunction without established DM. This observation shows the importance the chronic elevation, as a predisposing factor for CIN. This findings should be investigated in future studies.

Conclusions

CIN was more common in NSTEMI patients with high HbA1c who were not diagnosed with DM and were not treated.In addition, HbA1c value was an independent predictor of CIN development.

Conflict of interest

The author declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception, Study Design, Supervision, Materials, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Literature Review, Manuscript Preparation, and Critical Review: OB.

References

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20. doi: 10.1016/S0140-6736(03)12113-7.
2. Marenzi G, Lauri G, Assanelli E, Campodonico J, De Metrio M, Marana I, Grazi M, Veglia F, Bartorelli AL. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. J Am Coll Cardiol. 2004 Nov 2;44(9):1780-5. doi: 10.1016/j.jacc.2004.07.043.
3. Ishihara M, Inoue I, Kawagoe T, Shimatani Y, Kurisu S, Nishioka K, Umemura T, Nakamura S, Yoshida M. Impact of acute hyperglycemia on left ventricular function after reperfusion therapy in patients with a first anterior wall acute myocardial infarction. Am Heart J. 2003 Oct;146(4):674-8. doi: 10.1016/S0002-8703(03)00167-4.
4. Nakamura T, Ako J, Kadowaki T, Funayama H, Sugawara Y, Kubo N, Momomura S. Impact of acute hyperglycemia during primary stent implantation in patients with ST-elevation myocardial infarction. J Cardiol. 2009 Apr;53(2):272-7. doi: 10.1016/j.jjcc.2008.11.011.
5. Barbieri L, Verdoia M, Schaffer A, Cassetti E, Di Giovine G, Marino P, Suryapranata H, De Lu-ca G. Pre-diabetes and the risk of contrast induced nephropathy in patients undergoing co-ronary angiography or percutaneous intervention. Diabetes Res Clin Pract. 2014 Dec;106(3):458-64. doi: 10.1016/j.diabres.2014.09.041.
6. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2011 Dec;32(23):2999-3054. doi: 10.1093/eurheartj/ehr236.
7. Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA. 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486.
8. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, Klag MJ, Mailloux LU, Manske CL, Meyer KB, Parfrey PS, Pfeffer MA, Wenger NK, Wilson PW, Wright JT Jr. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis. 1998 Nov;32(5):853-906. doi: 10.1016/s0272-6386(98)70145-3.
9. Thomsen HS. European Society of Urogenital Radiology (ESUR) guidelines on the safe use of iodinated contrast media. Eur J Radiol. 2006;60(3):307-13. doi: 10.1016/j.ejrad.2006.06.020.
10. Tepel M, Aspelin P, Lameire N. Contrast-induced nephropathy: a clinical and evidence-based approach. Circulation. 2006 Apr 11;113(14):1799-806. doi: 10.1161/CIRCULATIONAHA.105.595090.
11. Selvin E, Marinopoulos S, Berkenblit G, Rami T, Brancati FL, Powe NR, Golden SH. Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med. 2004 Sep 21;141(6):421-31. doi: 10.7326/0003-4819-141-6-200409210-00007.
12. Balkau B, Shipley M, Jarrett RJ, Pyorala K, Pyörälä K, Pyörälä M, Forhan A, Eschwège E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Poli-cemen Study. Diabetes Care. 1998;21:360-367. doi: 10.2337/diacare.21.3.360.
13. Xu Y, Wang L, He J, Bi Y, Li M, Wang T, Wang L, Jiang Y, Dai M, Lu J, Xu M, Li Y, Hu N, Li J, Mi S, Chen CS, Li G, Mu Y, Zhao J, Kong L, Chen J, Lai S, Wang W, Zhao W, Ning G; 2010 China Noncommunicable Disease Surveillance Group. Prevalence and control of diabetes in Chinese adults. JAMA. 2013 Sep 4;310(9):948-59. doi: 10.1001/jama.2013.168118.
14. McCullough PA, Wolyn R, Rocher LL, Levin RN, Oneill WW. Acute renal failure after coronary intervention: Incidence, risk factors, and relationship to mortality. Am J Med. 1997;103:368-375. doi: 10.1016/s0002-9343(97)00150-2.
15. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan DM, Peterson CM; American Diabetes Association. Tests of glycemia in diabetes. Diabetes Care. 2004 Jan;27 Suppl 1:S91-3. doi: 10.2337/diacare.27.2007.s91.
16. Yang Z, Laubach VE, French BA, Kron IL. Acute hyperglycemia enhances oxidative stress and exacerbates myocardial infarction by activating nicotinamide adenine dinucleotide phosphate oxidase during reperfusion. J Thorac Cardiovasc Surg. 2009 Mar;137(3):723-9. doi: 10.1016/j.jtcvs.2008.08.056.
17. Undas A, Wiek I, Stêpien E, Zmudka K, Tracz W. Hyperglycemia is associated with enhanced thrombin formation, platelet activation, and fibrin clot resistance to lysis in patients with acute coronary syndrome. Diabetes Care. 2008 Aug;31(8):1590-5. doi: 10.2337/dc08-0282.
18. Worthley MI, Holmes AS, Willoughby SR, Kucia AM, Heresztyn T, Stewart S, Chirkov YY, Zeitz CJ, Horowitz JD. The deleterious effects of hyperglycemia on platelet function in diabetic patients with acute coronary syndromes mediation by superoxide production, resolution with intensive insulin administration. J Am Coll Cardiol. 2007 Jan 23;49(3):304-10. doi: 10.1016/j.jacc.2006.08.053.

TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Original Article

A Retrospective Evaluation of Patients Hospitalized in the Internal Medicine Department at the Turkey Recep Tayyip Erdogan Somalia Mogadishu Training and Research Hospital

Oznur SARI[1], Ahmad Muhammad BASHIR[2]

[1]Department of Internal Medicine, Ministry of Health, General Directorate of Public Hospitals, Ankara, Turkey
[2]Department of Internal Medicine, Recep Tayyip Erdogan, Somalia Mogadishu Training and Research Hospital, Mogadishu, Somalia

ABSTRACT

Background There is limited data on the diagnosis and treatment practice of patients in internal medicine clinics in Somalia. The present study aims to evaluate the diagnostic distributions, demographic characteristics and clinical outcomes of inpatients treated in the department of internal medicine at our hospital.

Material and Methods The demographic characteristics, diagnoses, lengths of hospital stay, and mortality rates of patients hospitalized between January 2017 and June 2019 at the Department of Internal Medicine of the Turkey Recep Tayyip Erdogan Somalia Mogadishu Training and Research Hospital (service and intensive care) were evaluated.

Results A total of 3,246 patients, 1,759 (54.2%) males and 1,487 (45.8%) females, with an average age of 50.82±19.25 (18-101) years, were included in the study. While 76% of the patients were followed up in the general internal medicine service, 13.3% were monitored in the general intensive care unit and 10.7% in the emergency intensive care unit. When the indications for hospitalization were evaluated, the most common causes of hospitalization were chronic kidney disease (CKD) (29.4%) and acute kidney injury (AKI) (14.8%) and the internal problems associated with these conditions (electrolyte imbalance, hypervolemia and acid-base balance deterioration). Other important internal diseases requiring hospitalization were diabetes mellitus (DM)-related conditions (11.9%), anemia (5.2%), hypertensive (HT) emergencies (3.5%), gastrointestinal diseases (4.2%) viral hepatitis (2.1%) cases, conditions that required cancer-related hospitalization (3.6%), infectious diseases (3.3%), cardiovascular diseases (CVD) (3%), and other less frequent causes.

While 2,714 (83.6%) patients were discharged, 510 (15.7%) patients died and 22 (0.7%) patients left the hospital of their own accord. The mortality rates of the patients were found to be 38.6% in the general intensive care unit, 35.9% in the emergency intensive care unit and 25.5% in the general internal medicine service. Higher mortality rates were found in emergency and general intensive care patients compared to patients in the internal medicine service [OR: 7.4 (5.7-9.7), OR: 10.4 (8.2-13.3), respectively, ($p<0.001$)].

Conclusions It was determined that the majority of inpatients evaluated at the Turkey Recep Tayyip Erdogan Somalia Mogadishu Training and Research Hospital had preventable and treatable diseases in the early period. In the health system, which primarily aims to treat patients under current conditions, the development of primary care treatment plans in the future may deliver a significant decrease in mortality and morbidity rates by reducing the frequency and severity of CKD, DM, HT and CVD. There is a need for new and inclusive scientific studies in Somalia on this subject.

Turk J Int Med 2021;3(4):177-187
DOI: 10.46310/tjim.899718

Keywords: *Somalia, chronic kidney disease, diabetes mellitus, hypertension, internal disease, intensive care.*

Received: March 19, 2021; Accepted: May 23, 2021; Published Online: October 29, 2021

Address for Correspondence:
Oznur Sari, MD
Department of Internal Medicine, Ministry of Health, General Directorate of Public Hospitals, Ankara, Turkey
E-mail: oznurure@yahoo.com

Introduction

It has still not been possible to establish an adequate public health system in Somalia following decades of political turmoil, wars, poverty, and starvation. Infectious and parasitic diseases, especially malaria in infants and tuberculosis and cholera outbreaks in adults, are still important causes of death in this country. The lack of a competent and strong central government capable of providing adequate health system facilities has led to significant growth in the country's private health system. However, fees paid for health services make the sustainability of private health services impossible in a country where poverty is so prevalent. In recent years, with the help of foreign countries and international organizations, significant strategic gains have been achieved in this regard, resulting in the provision of equitable, affordable and effective basic health services for the general population.

Turkey has been offering inpatient and outpatient care services at Turkey Recep Tayyip Erdogan Somalia Mogadishu Training and Research Hospital (SMTERH) since August 2014, to help the people of Somalia in this regard. The hospital, which was brought into service with 201 beds, now has a total of 240 beds and undertakes not only the important task of patient treatment, but also the training of physicians and other healthcare professionals. Patients treated by the internal medicine service and intensive care units of the hospital are mostly those who have chronic illness-related complications because they cannot benefit from basic and preventive health services.

The present study aims to evaluate the diagnostic distributions, demographic characteristics and clinical outcomes of patients receiving inpatient treatment at the SMTERH Internal Diseases Clinic.

Material and Methods

In the study, the data of patients aged 18 and over, who were hospitalized between January 2017 and June 2019 at the SMTERH Internal Diseases Department, were obtained by retrospectively scanning the patient files. Information on patients' comorbid diseases was obtained from the patient files. The presence of documentation on drug use in the previous year was considered sufficient for the diagnosis of hypertension (HT), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD). Electrocardiogram, echocardiography, and cardiology clinical notes of patients in the previous 3 months were received for the diagnosis of heart failure (HF). Indications for admission to the inpatient clinics or intensive care units were recorded for metabolic acidosis, hypervolemia, hyperkalemia, severe uremic symptoms, and other causes (gastrointestinal bleeding, emergency surgical interventions, cerebrovascular event, and labor, etc.). The diagnoses of the patients were confirmed by the responsible internal medicine physician and the admission diagnoses were recorded as the first diagnoses.

Patient Follow-up

While the follow-up processes and treatments of the patients were managed by the responsible internal medicine physician during their stay in the hospital, the patients taken to intensive care units were followed up by the internal medicine physicians and anesthesiologists. Patients who needed hemodialysis due to renal failure were hemodialyzed with a temporary and/or permanent tunnel catheter in the hemodialysis (HD) unit of our clinic. In the case of non-invasive and invasive mechanical ventilation, patients were followed up in intensive care units. Patients in need of palliative treatment, analgesia and nutritional needs were given a temporary central venous catheter when necessary. COPD and heart failure patients also received oxygen and diuretic treatment in the internal medicine clinic due to the lack of relevant specialists.

Statistical Analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The conformity of univariate data to normal distribution was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U (Exact) test was used along with the Monte Carlo results to compare two independent groups according to the quantitative data. In comparing categorical variables with each other, the Pearson Chi-Square test was used with the Exact and Monte Carlo Simulation method and the Benjamini-Hochberg corrected p-value results were used in

comparing column ratios with each other and the results were shown in the table. The odds ratio was used with 95% confidence intervals to show how many times those with a risk factor were compared to those without one. Quantitative variables were expressed as mean±SD (standard deviation) and Median (percentile 25/percentile 75) in the tables, while categorical variables were shown as n (%). The variables were analyzed at a 95% confidence level and were considered significant when the p value was less than 0.05.

Results

A total of 3,246 patients, 1,759 (54.2%) males and 1,487 (45.8%) females, with an average age of 50.82±19.25 (18-101) years, were included in the study. While 76% of the patients were followed by the general internal medicine department, 13.3% were followed by the internal medicine department in the general intensive care unit and 10.7% in emergency intensive care *(Table 1)*.

While 2,714 (83.6%) patients were discharged, 510 (15.7%) patients died and 22 (0.7%) patients left the hospital of their own accord. The mean length of hospital stay was found to be 6.59±4.21 (3-81) days *(Table 1)*.

When the indications for hospitalization were evaluated, the most common reason for hospitalization was chronic kidney disease (CKD) (29.4%) and acute kidney injury (AKI) (14.8%) and internal problems associated with them (electrolyte imbalance, hypervolemia, and acid-base imbalance).

Other important internal diseases requiring hospitalization were found to be DM (11.9%) associated conditions, anemia (5.2%), hypertensive emergencies (3.5%), gastrointestinal diseases (4.2%) and viral hepatitis (2.1%), conditions requiring cancer-related hospitalization (3.6%), infectious diseases (3.3%), cardiovascular diseases (3%), and less frequently other causes *(Table 2)*.

There was no significant difference between the hospitalized patients in terms of age and gender distribution for mortality (p>0.05). The length of hospital stay was found to be higher in patients who died (p<0.001) *(Table 3)*. When the patients were evaluated according to discharge and mortality, it was found that mortality rates were the highest in general intensive care (38.6%), which was followed by emergency intensive care (35.9%) and the department of general internal medicine (25.5%). Higher mortality rates were found in emergency and general intensive care patients than in those in the department of internal medicine [OR:7.4 (5.7-9.7), OR: 10.4 (8.2-13.3), respectively, CI: 95%, (p<0.001)].

Table 1. Demographic findings.

	Mean±SD	Min	Q1	Q2	Q3	Max
Age (year)	50.82±19.25	18	35	51	65	101
Duration of hospital stay (day)	6.59±4.21	3	4	5	8	83
	n			%		
Gender						
Female	1,487			45.8%		
Male	1,759			54.2%		
Unit						
Emergency Intensive Care	347			10.7%		
Internal Medicine Department	2,467			76.0%		
Intensive Care	432			13.3%		
Form of discharge						
Discharged at one's own accord	22			0.7%		
Death	510			15.7%		
Discharge	2,714			83.6%		

SD: standard deviation, Q1: percentile 25, Q2: percentile 50 (median), Q3: percentile 75.

Table 2. Distribution of patients' diagnoses.

Diagnosis	n	%
Chronic kidney disease	1,001	29.4%
Acute kidney injury	503	14.8%
Diabetic emergencies	406	11.9%
Anemia	178	5.2%
Gastrointestinal system diseases	143	4.2%
Respiratory system diseases	132	3.9%
Electrolyte balance disorders	125	3.7%
Hypertensive emergencies	120	3.5%
Infectious diseases	111	3.3%
Cardiovascular system diseases	103	3.0%
Malignancy palliations	77	2.3%
Viral hepatitis	72	2.1%
Hematological benign diseases	49	1.4%
Hematological malignancies	45	1.3%
Other urinary system diseases	38	1.1%
Other miscellaneous causes	38	1.1%
Inflammatory bowel diseases	26	0.8%
Tuberculosis	24	0.7%
Other endocrine system diseases	17	0.5%
Rheumatological diseases	11	0.3%
Hypervolemic conditions	7	0.2%
Gall bladder and biliary tract diseases	6	0.2%
Stevens Johnson's syndrome	6	0.2%
Disruption and malnutrition in oral intake	5	0.1%
Acid-base balance disorders	3	0.1%

Table 3. Clinical outcomes of the patients.

	Form of discharge		
	Death (n=510) Median (Q1/Q3)	Discharge (n=2,736) Median (Q1/Q3)	p value
Age (year)	50 (33/70)	51 (35/65)	0.453[u]
Hospitalization (day)	6 (4/9)	5 (4/7)	<0.001[u]
	n (%)	n (%)	
Gender			
Female	235 (46.1)	1,252 (45.8)	0.923[pc]
Male	275 (53.9)	1,484 (54.2)	
Unit			
Emergency Intensive Care	130 (25.5) [B]	217 (7.9)	<0.001[pm]
Internal Medicine Service	183 (35.9)	2,284 (83.5)[A]	
Intensive Care	197 (38.6)[B]	235 (8.6)	

[u]Mann Whitney U test (Monte Carlo), [p]Pearson Chi-Square test ([c]Exact, [m]Monte Carlo), Q1: percentile 25, Q3: percentile 75.

Discussion

In the present study, more than half of the patients hospitalized in our department were found to have acute and chronic renal failure, as well as acid-base disorders, hypervolemia, and electrolyte imbalance. Due to the socioeconomic and sociocultural conditions of the environment in which our hospital is located, patients mostly apply to the hospital after apparent renal insufficiency due to the inadequacy of the diagnosis and treatment of HT, DM and failure to eliminate diet and treatment incompatibilities. Besides, there were many patients diagnosed with AKI due to gastroenteritis, malnutrition and, urinary system obstructions [stone, benign prostate hyperplasia (BPH), and infection] (14.8%). It would also be beneficial to discuss the hospitalized patients in terms of important health problems.

Acute and Chronic Renal Failure

CKD is a public health problem with a prevalence of 11-13% worldwide.[1] The number of patients with end-stage renal disease (ESRD) continues to increase throughout the world. Besides, the presence of CKD is associated with an increase in cardiovascular mortality as well as all-cause deaths in the general population. CKD in Sub-Saharan Africa (SSA) mainly affects young adults in their economically productive years and is the leading cause of death. Factors contributing to this bleak picture include late admission to hospital, limited renal replacement therapy (RRT), limited means used by healthcare professionals in preventing kidney diseases, and inadequate awareness of kidney disease in the community. However, in developing countries where approximately 85% of the world's population lives, CKD prevention programs are limited or their capacity mot viable. In SAA countries, HT, obesity, and DM are the three most common causes of CKD.[2] HT, proteinuria, dyslipidemia, obesity, and smoking are among the changeable factors. In addition,, there is no doubt that most infectious diseases such as malaria, schistosomiasis, hepatitis C and HIV increase the risk of developing CKD.[2]

Despite advanced treatment methods and transplantation options, high mortality and morbidity rates in ESRD patients are a serious public health problem.[3] Globally, approximately three million patients are currently receiving renal replacement therapy (RRT), and this number is expected to increase by 5 to 10 million by 2030.[4]

HD, the most frequently applied replacement therapy, is the most common method used in SSA with approximately 150 dialysis units spread across 13 countries. Most of the centers are in 4 countries: Nigeria, South Africa, Sudan, and Mauritius. In other countries in the sub-region such as Somalia, there are very few facilities.[5,6] Although CKD-related morbidity and mortality rates are high in low- and middle-income countries (LMICs), accurate epidemiological data on CVD in patients with CKD are still not available in these countries.[7]

In a study by Sachetti et al.[8], hypervolemia and hyperkalemia were identified as the most common causes requiring hospitalization of patients diagnosed with CKD. Similarly, electrolyte disturbances, deteriorations in acid-base balance and hypervolemia and hyperkalemia in most patients, which required urgent HD, were detected in the present study. Proper nutrition management, follow-up of chronic diseases such as comorbid DM and HT, regular drug use, referral to a nephrologist at the appropriate time and protection of vascular access routes for HD preparation also play an important role in CKD follow-up.[9]

Diabetes and Its Complications

DM is growing at an alarming rate worldwide and is becoming one of the most burdensome chronic diseases of our time. Following a rapid change in nutrition and active life- styles in developing countries, the development rate of DM is now considered to be of pandemic proportioms.[10,11] type 2 diabetes (T2D) accounts for 90-95% of all diabetes cases. In Somalia, diets rich in carbohydrates associated with intense fruit consumption, and inadequate physical activity increase the risk of developing DM However, due to insufficient glucose tolerance or insufficient practices for the early screening of DM, patients are admitted to the hospital with obvious DM and related complications.

Although the average age of patients diagnosed with T2D in the region where Somalia is located frequently corresponds with the reproductive years, most of them can be treated with oral antidiabetic

drugs and appropriate lifestyle changes according to American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD). Guidelines.[12] At the internal medicine clinic, those that are the most difficult to manage in this region are patients diagnosed with type 1 DM and type 2 DM, who need insulin. Due to the country's economic and infrastructure problems, access to suitable medication and maintaining insulin that requires a cold chain are major problems.

Short-acting crystalline insulin and mixture insulin preparations, which are not readily available on the market in Somalia, can be used in treatment. Although these treatments are relatively cost effective, problems present in terms of ease of use, treatment success and the risks of hypoglycemia compared to new generation insulin preparations. Moreover, the low rate of social security provision among patients means that access to insulin is overall quite limited. DM is a chronic disease, whose treatment should be monitored regularly, and care should be taken in terms of possible complications. In the present study, 11.9% of the patients were found to be hospitalized in our clinic due to DM and serious related complications. This figure covers only those patients in urgent need of hospitalization and can be regarded as the tip of the iceberg.

Considering the guidance recommendations, it is almost impossible for patients who need intensive insulin therapy to participate in the treatment process. Therefore, morbidity and mortality frequently develop in type 1 DM and type 2 DM patients due to the early effects of hyperglycemia. It is important for patients to continue treatment rather than insulin treatment selection methods. Patients with this condition must receive treatment in the later stages of the disease when complications such as diabetic ketoacidosis, hyperglycemic non-ketotic coma and diabetic end-organ injuries (retinopathy, nephropathy, neuropathy etc.) appear. Moreover, in terms of providing drugs used in DM and cold chain insulin treatment, Somalian patients have a higher risk of death, especially due to cerebrovascular diseases, where the main risk factors are DM, and HT.[13]

Acute and Chronic Viral Hepatitis

Viral hepatitis is an important public health problem, especially in developing countries. Chronic hepatitis-B virus (HBV) infection is quite common, especially in Asia and Sub-Saharan Africa. Viral hepatitis, especially HBV, is an important public health problem in Somalia. Approximately 15-40% of individuals with chronic HBV infection have an important risk for the development of cirrhosis, fulminant hepatitis, and hepatocellular carcinoma (HCC).[14,15] Analyzes on the global distribution of chronic HBV infection classify regions as low (<2%), intermediate (2-7%) and high (≥8%) prevalence regions according to the prevalence of HBsAg.[16] Somalia is a country with a high rate of HBV seroprevalence globally with a value >8. Viral hepatitis complications continue their natural course, especially due to insufficient screening and vaccination programs for HBV and HAV infections.

In Somalia, the number of skilled health personnel is insufficient due to decades of civil war. Limited access to modern laboratory facilities creates significant screening and diagnostic challenges for viral hepatitis cases.[17] A study (1992) on the prevalence of serological markers for HBV and HCV in 596 children in a residential institution in Somalia reported a prevalence of 16% for HBsAg and 1.5% for anti-HCV.[15-18] In another study conducted with 62 Somalian patients with chronic liver disease, including primary HCC, prevalence rates were reported as 37.1% for HBsAg and as 40.3% for anti-HCV.[19,20] While these patients probably do not need virus suppressing medications, they will still need training on transmission, continuous monitoring for progression to cirrhosis, and HCC screening. No studies on viral hepatitis epidemiology have been reported in Somalia since 1992, and the data available on the prevalence of HBV and HCV in Somalia is notably limited. In the present study, it was found that 72 (2.1%) patients received inpatient treatment in our service for acute and chronic viral hepatitis, and 163 (4.8%) patients were frequently treated for hepatitis complications (cirrhosis, esophagus varicose and HCC). Since we do not have current seroprevalence rates in this study, we did not have a chance to make a more detailed analysis.

Hypertension and Cardiovascular Diseases

Cardiovascular diseases (CVD) continue to be the leading cause of death worldwide and are constantly increasing in prevalence.[21,22] Various changeable risk factors such as HT, DM dyslipidemia, obesity, smoking, unhealthy nutrition, and the harmful use of alcohol have an impact on the development of CVD.[23,24] Epidemiological and demographic transitions continue in LMICs such as Somalia, resulting in an increased burden in non-communicable diseases. Somaliland (formerly Northern Somalia) has a population of about 4.5 million, about 53% of whom live in urban areas.[25,26] Significant CVD risk factors in men include smoking, unhealthy nutrition, and HT, while in women, multiple unplanned pregnancies and a sedentary lifestyle are factors.[27,28]

Causes of death in Somalia are preventable diseases (maternal and infant deaths, nutritional deficiencies and infections) (64%), CVD (10%), cancer types (4%), chronic respiratory diseases (1%), diabetes (1%), other non-communicable diseases (8%), and accidents and injuries (12%). Preventable deaths constitute 24% of all mortalities.[29]

In Somalia, South Asia and India in particular, smokeless tobacco use is very common, with usage rates higher , in low-social-income groups, and those with lower levels of education.[30] Chewing khat t (the local fresh tobacco leaf type), a common habit in Somalia, is associated with various health problems associated with chronic diseases such as high blood pressure and coronary heart disease.[31,32] In the present study, 103 (3%) patients were being followed-up in our clinic due to CVD. This frequency was lower than expected and patients hospitalized in the cardiology clinic in our hospital were evaluated in relation to each other.

Pregnancy-related Complications

According to the joint estimates of the World Health Organization (WHO), the United Nations International Children's Emergency Fund (UNICEF) and the United Nations Population Fund (UNFPA), 293,000 women die every year as a result of pregnancy-related complications. The majority (99%) of all maternal deaths occur in LMICs, and more than half of these deaths occur in SSA. In LMICs the majority of maternal deaths can be prevented by timely and adequate intervention.[33]

In Somalia, a woman's life-long risk of death is estimated to increase by 5% due to pregnancy.[34] Somalia is one of the top five countries with the highest maternal mortality in the world, along with the Central African Republic, Chad, Nigeria, Sierra Leone and South Sudan.[35] In Somalia, the registration system for maternal deaths makes any possible review problematic. Therefore, it is estimated that maternal and infant mortality rates are even higher than current estimates.[34]

Pregnant women get help from people who practice traditional birthing methods instead of from experienced health personnel in a health center, and give birth at home. As a result, many preventable and treatable complications, especially postpartum bleeding, develop.[35] Hemorrhage developing during or after birth accounts for more than half (64.3%) of maternal deaths.[33,36,37] Health education programs should be implemented in order to change people's health-seeking behaviors.[38] In addition to anemia and postpartum hemorrhage-related complications in our clinic, hypertensive conditions of pregnancy were also considerable. Due to insufficient bed capacity in our hospital and in the overall region, we followed up postpartum hemorrhage patients with our obstetrician in our intensive care units.

Cancer and Palliative Care

Although infectious diseases are still one of the leading causes of death in SSA, the emergence of non-communicable diseases, especially cancer, is a major challenge for health systems. Health systems in this region are mainly for acute illness and maternal and infant health care. This fails to serve the needs of those with chronic diseases that require complex intervention maintenance throughout continued care.[39] Obstetric problems, nutrition and infectious diseases account for 69% of the mortality rate in Somalia, while cancers make up 4%.[40]

Palliative care services provide a more realistic public health approach for patients with cancer when cancer patients apply to health services with inadequate treatment options for the primary disease and most treatments for cancer improvement are beyond the reach of patients.[41]

In underdeveloped countries, such as Somalia, patients often apply in the late stages of the disease, regardless of the type of cancer, i.e. when chemotherapy, surgical treatment, or radiotherapy cannot provide additional therapeutic benefit. In many parts of SSA, access to cancer screening and basic treatment services is insufficient. However, the global cancer burden is expected to increase further due to an increasing and aging population, especially in less developed countries where approximately 82% of the world population lives.[42]

Although the importance of establishing cancer registry systems to identify etiological causes in cancer development, improve cancer biology studies and implement necessary interventions to prevent cancers is well established, unfortunately, adequate cancer registry records have not been established in many underdeveloped countries such as Somalia.[43,44] In this case, palliative care offers a realistic approach to fair, accessible, and cost-effective interventions.[42] Support therapy and palliative treatment were applied to a total of 122 (3.6%) cancer patients (solid and hematological) diagnosed in our hospital. Although new regulations in relation to cancer diagnosis and treatment approaches have been introduced in Somalia in recent years, the role of palliative treatment in these transition stages is important.

Chronic Respiratory Tract Diseases

LMICs are responsible for an estimated 12% of noncommunicable diseases caused by respiratory problems, especially asthma and COPD.[45] COPD was shown to be the third most common cause of death in the world between 1990 and 2010.[46] It is reported that approximately 90% of COPD-related deaths occur in LMICs.[47]

However, there is limited epidemiological evidence regarding the prevalence of COPD mortality and morbidity in LMICs and further studies are required. In Somalia, adverse conditions such as insufficient diagnosis of asthma and COPD due to insufficient health care and insufficient primary health care services, delayed treatment, and deficiencies in disease prevention present.[48,49] In Somalia, where access to adequate healthcare is quite difficult, even relatively simple needs such as that for nasal oxygen and antibiotherapy can often go unmet. A total of 132 (3.9%) inpatients in our hospital were treated for bacterial pneumonia and COPD-related complications.

Limitations

Since the present study was performed retrospectively in a relatively small patient population, it is difficult to evaluate patients in detail and to make a a more general assessment given the results obtained. Also, patient characteristics differ since patients of different departments that are not available in our hospital had to be hospitalized in the internal medicine service. Although some of our inpatients were diagnosed with infectious diseases and tuberculosis, it was thought that the number of these patients was lower than expected because they were mostly followed up in the department of infectious diseases. In addition, the presence of relatively higher number of patients diagnosed with CVD is related to their follow-up at the internal medicine clinic during periods when there is no cardiology specialist. The fact that the file recording system and the medications used by patients in the past could not be questioned in detail before social security institutions can be considered as another limitation of the study. With further prospective and wide-ranging studies, the relationship between hospitalization indications and mortality and morbidity could be better evaluated in this patient group.

Conclusions

It will likely be difficult for Somalia to create an adequate health service until the constantly changing socio-political climate stabilizes and the economy improves. The high frequencies of HT, DM, CKD and CVD in the region, which can be prevented or the complications of which can be reduced in the early period, has shown that there is a lot of work to be done in this regard. However, there have been some quite promising developments in recent years. The aid provided to Somalia, particularly from Turkey, but also from other countries on a regular basis, has increased over the last decade and a more comprehensive approach to strengthening health

systems under the guidance of most development agencies is evident. Mogadishu Turkish Hospital has started to accept patients since August 2014. The 205-bed hospital is in the status of a Training and Research Hospital. In other words, it is important not only for treating patients, but also for training physicians and other healthcare professionals. There is also a lodging, nursing school and mosque in the campus area. In this region, other hospitals affiliated to the United Arab Emirates and the United Nations, besides Turkey, also provide similar services. An important contribution of the Turkish hospital is that it provides the Somalian citizens in this region with the opportunity to obtain medical education and profession. This, in conjunction with efforts to create a regulatory framework for medical training and healthcare services is promising.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception, Study Design, Supervision, Materials, Data Collection and/or Processing, Statistical Analysis and/or Data Interpretation, Literature Review, Manuscript Preparation, and Critical Review: OS, AMB.

References

1. Capewell S, Morrison CE, McMurray JJ. Contribution 1. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FDR. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):1-18. doi:10.1371/journal.pone.0158765.
2. Stanifer JW, Egger JR, Turner EL, Thielman N, Patel UD. Neighborhood clustering of non-communicable diseases: results from a community-based study in Northern Tanzania. BMC Public Health. 2016;16(1):226. doi:10.1186/s12889-016-2912-5.
3. McCullough KP, Morgenstern H, Saran R, Herman WH, Robinson BM. Projecting ESRD Incidence and Prevalence in the United States through 2030. J Am Soc Nephrol. 2019;30(1):127-35. doi:10.1681/ASN.2018050531.
4. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao M, Lv J, Garg AX, Knight J, Rodgers A, Gallagher M, Kotwal S, Cass A, Perkovic V. Worldwide access to treatment for end-stage kidney disease: a systematic review. Lancet. 2015;385(9981):1975-82. doi:10.1016/S0140-6736(14)61601-9.
5. Ene-Iordache B, Perico N, Bikbov B, Carminati S, Remuzzi A, Perna A, Islam N, Bravo RF, Aleckovic-Halilovic M, Zou H, Zhang L, Gouda Z, Tchokhonelidze I, Abraham G, Mahdavi-Mazdeh M, Gallieni M, Codreanu I, Togtokh A, Sharma SK, Koirala P, Uprety S, Ulasi I, Remuzzi G. Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross-sectional study. Lancet Glob Heal. 2016;4(5):e307-19. doi:10.1016/S2214-109X(16)00071-1.
6. Ojo A. Addressing the global burden of chronic kidney disease through clinical and translational research. Trans Am Clin Climatol Assoc. 2014;125:226-9.
7. Stanifer JW, Muiru A, Jafar TH, Patel UD. Chronic kidney disease in low- and middle-income countries. Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc. 2016;31(6):868-74. doi:10.1093/ndt/gfv466
8. Sacchetti A, Stuccio N, Panebianco P, Torres M. ED hemodialysis for treatment of renal failure emergencies. Am J Emerg Med. 1999;17(3):305-7. doi:10.1016/S0735-6757(99)90131-6.
9. Lee J, Lee JP, An JN, Kim SG, Kim Y-L, Yang CW, Kang S-W, Kim N-H, Kim YS, Oh YK, Lim CS. Factors Affecting the Referral Time to Nephrologists in Patients With Chronic Kidney Disease: A Prospective Cohort Study in Korea. Medicine (Baltimore). 2016;95(19):e3648. doi:10.1097/MD.0000000000003648.
10. Gele AA, Pettersen KS, Kumar B, Torheim LE. Diabetes Risk by Length of Residence among Somali Women in Oslo Area. J Diabetes Res. 2016;2016:5423405. doi:10.1155/2016/5423405.
11. Joseph JJ, Echouffo-Tcheugui JB, Golden SH, Chen H, Jenny NS, Carnethon MR, Jacobs D, Burke GL, Vaidya D, Ouyang P, Bertoni AG. Physical activity, sedentary behaviors and the incidence of type 2 diabetes mellitus: the Multi-Ethnic Study of Atherosclerosis (MESA). BMJ Open Diabetes Res & Care. 2016;4(1):e000185. doi:10.1136/bmjdrc-2015-000185.
12. American Diabetes Association (ADA). Standard of medical care in diabetes - 2017. Diabetes Care. 2017 Jan;40(Suppl 1):S4-128. doi: 10.2337/dc17-S003.
13. Fedeli U, Ferroni E, Pigato M, Avossa F, Saugo M. Causes of mortality across different immigrant groups in Northeastern Italy. PeerJ. 2015 May 21;3:e975. doi: 10.7717/peerj.975.
14. Lok ASF, McMahon BJ. Chronic hepatitis B: Update 2009. Hepatology. 2009;50(3):661-62. doi:10.1002/hep.23190.
15. Rossi C, Shrier I, Marshall L, Cnossen S, Schwartzman K, Klein MB, Schwarzer G, Greenaway C. Seroprevalence of chronic hepatitis B virus infection and prior immunity in immigrants and refugees: a systematic review and meta-analysis. PLoS One. 2012;7(9):e44611. doi:10.1371/journal.pone.0044611.
16. Alter MJ. Epidemiology and prevention of hepatitis B. Semin Liver Dis. 2003;23(1):39-46. doi:10.1055/s-2003-37583.
17. Hassan-Kadle MA. The Diagnostic Challenges, Possible Etiologies and Lack of Researches of Hepatocellular Carcinoma in Somalia. Open J Gastroenterol. 2017;07(03):115-23. doi:10.4236/ojgas.2017.73013.
18. Bile K, Mohamud O, Aden C, Isse A, Norder H, Nilsson L, Magnius L. The risk for hepatitis A, B, and C at two institutions for children in Somalia with different socioeconomic conditions. Am J Trop Med Hyg. 1992;47(3):357-64. doi:10.4269/ajtmh.1992.47.357.

19. Bile K, Aden C, Norder H, Magnius L, Lindberg G, Nilsson L. Important role of hepatitis C virus infection as a cause of chronic liver disease in Somalia. Scand J Infect Dis. 1993;25(5):559-64. doi:10.3109/00365549309008543.
20. Hassan-Kadle MA, Osman MS, Ogurtsov PP. Epidemiology of viral hepatitis in Somalia: Systematic review and meta-analysis study. World J Gastroenterol. 2018;24(34):3927-57. doi:10.3748/wjg.v24.i34.3927.
21. Yuyun MF, Sliwa K, Kengne AP, Mocumbi AO, Bukhman G. Cardiovascular Diseases in Sub-Saharan Africa Compared to High-Income Countries: An Epidemiological Perspective. Glob Heart. 2020;15(1):15. doi:10.5334/gh.403.
22. Paolo F, Michelle C, Miller A. Cardiovascular disease and hypertension in sub-Saharan Africa : burden , risk and interventions. Intern Emerg Med. 2016;11(3):299-305. doi:10.1007/s11739-016-1423-9.
23. Mind ONMY. Tackling the Growing Burden of ardiovascular Diseases in Sub-Saharan Africa. Published online 2018:2449-51. doi:10.1161/CIRCULATIONAHA.118.037367.
24. Hamid S, Groot W, Pavlova M. Trends in cardiovascular diseases and associated risks in sub-Saharan Africa: a review of the evidence for Ghana, Nigeria, South Africa, Sudan and Tanzania. Aging Male. 2019;22(3):169-176. do i:10.1080/13685538.2019.1582621.
25. Ministry of National Planning and Development: Somaliland In Figure 2015. Published online 2015.
26. 26. Leather A, Ismail EA, Ali R, Abdi YA, Abby MH, Gulaid SA, Walhad SA, Guleid S, Ervine IM, Lowe-Lauri M, Parker M, Adams S, Datema M, Parry E. Working together to rebuild health care in post-conflict Somaliland. Lancet (London, England). 2006;368(9541):1119-25. doi:10.1016/S0140-6736(06)69047-8.
27. Peltzer K, Phaswana-Mafuya N. Fruit and vegetable intake and associated factors in older adults in South Africa. Glob Health Action. 2012;5:1-8. doi:10.3402/gha.v5i0.18668.
28. Lachat C, Otchere S, Roberfroid D, Abdulai A, Seret FMA, Milesevic J, Xuereb G, Candeias V, Kolsteren P. Diet and physical activity for the prevention of noncommunicable diseases in low- and middle-income countries: a systematic policy review. PLoS Med. 2013;10(6):e1001465. doi:10.1371/journal.pmed.1001465.
29. Organization WH. Noncommunicable Diseases Country Profiles 2018. World Health Organization; 2018.
30. Hossain MS, Kypri K, Rahman B, Arslan I, Akter S, Milton AH. Prevalence and correlates of smokeless tobacco consumption among married women in rural Bangladesh. PLoS One. 2014;9(1):e84470. doi:10.1371/journal.pone.0084470.
31. Tesfaye F, Byass P, Wall S, Berhane Y, Bonita R. Association of smoking and khat (Catha edulis Forsk) use with high blood pressure among adults in Addis Ababa, Ethiopia, 2006. Prev Chronic Dis. 2008;5(3):A89.
32. Ageely HMA. Health and socio-economic hazards associated with khat consumption. J Family Community Med. 2008;15(1):3-11.
33. Alkema L, Broaddus E, Chou D, Mathers C, Moller AB, Say L. Trends in maternal mortality 2010 - 2015, WHO. WHO Doc. Published online 2015:92.
34. Aden JA, Ahmed HJ, Östergren PO. Causes and contributing factors of maternal mortality in Bosaso District of Somalia. A retrospective study of 30 cases using a Verbal Autopsy approach. Glob Health Action. 2019;12(1). doi:10.1080/16549716.2019.1672314.
35. Pasha O, McClure EM, Saleem S, Tikmani SS, Lokangaka A, Tshefu A, Bose CL, Bauserman M, Mwenechanya M, Chomba E, Carlo WA, Garces AL, Figueroa L, Hambidge KM, Krebs NF, Goudar S, Kodkany BS, Dhaded S, Derman RJ, Patel A, Hibberd PL, Esamai F, Tenge C, Liechty EA, Moore JL, Wallace DD, Koso-Thomas M, Miodovnik M, Goldenberg RL. A prospective cause of death classification system for maternal deaths in low and middle-income countries: results from the Global Network Maternal Newborn Health Registry. BJOG. 2018;125(9):1137-43. doi:10.1111/1471-0528.15011.
36. Pacagnella RC, Cecatti JG, Parpinelli MA, Sousa MH, Haddad SM, Costa ML, Souza JP, Pattinson RC. Delays in receiving obstetric care and poor maternal outcomes: results from a national multicentre cross-sectional study. BMC Pregnancy Childbirth. 2014;14:159. doi:10.1186/1471-2393-14-159.
37. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, Gülmezoglu AM, Temmerman M, Alkema L. Global causes of maternal death: A WHO systematic analysis. Lancet Glob Heal. 2014;2(6):323-33. doi:10.1016/S2214-109X(14)70227-X.
38. Castro R, Campero L, Hernández B, Langer A. A study on maternal mortality in Mexico through a qualitative approach. J Womens Health Gend Based Med. 2000;9(6):679-690. doi:10.1089/15246090050118206.
39. Samb B, Desai N, Nishtar S, Mendis S, Bekedam H, Wright A, Hsu J, Martiniuk A, Celletti F, Patel K, Adshead F, McKee M, Evans T, Alwan A, Etienne C. Prevention and management of chronic disease: a litmus test for health-systems strengthening in low-income and middle-income countries. Lancet (London, England). 2010;376(9754):1785-97. doi:10.1016/S0140-6736(10)61353-0.
40. WHO. Global status report on noncommunicable diseases 2014. World Health. Published online 2014:176. doi:ISBN 9789241564854.
41. Kimani KN, Namukwaya E, Grant L, Murray SA. Cancer and palliative care in Africa. Eur J Cancer Care (Engl). 2017;26(1):2-5. doi:10.1111/ecc.12655.
42. World TF, Assembly H, Activity P. WHA58.22 Cancer prevention and control.:103-7.
43. Meyskens FLJ, Mukhtar H, Rock CL, Cuzick J, Kensler TW, Yang CS, Ramsey SD, Lippman SM, Alberts DS. Cancer Prevention: Obstacles, Challenges and the Road Ahead. J Natl Cancer Inst. 2016;108(2). doi:10.1093/jnci/djv309.
44. Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, Abdel-Rahman O, Abdelalim A, Abdoli A, Abdollahpour I, Abdulle ASM, Abebe ND, Abraha HN, Abu-Raddad LJ, Abualhasan A, Adedeji IA, Advani SM, Afarideh M, Afshari M, Aghaali M, Murray CJL et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019;5(12):1749-68. doi:10.1001/jamaoncol.2019.2996.
45. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, Casey DC, Charlson FJ, Chen AZ, Coates MM, Coggeshall M, Dandona L, Dicker DJ, Erskine HE, Ferrari AJ, Fitzmaurice C, Foreman K, Forouzanfar MH, Fraser MS, Murray CJL et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death,1980-2015: a systematic analysis for the Global Burden of Disease Study

2015. Lancet. 2016;388(10053):1459-544. doi:10.1016/S0140-6736(16)31012-1.
46. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, AlMazroa MA, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Murray CJ et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128. doi:10.1016/S0140-6736(12)61728-0.
47. Khan MA, Ahmed M, Anil S, Walley J. Strengthening the delivery of asthma and chronic obstructive pulmonary disease care at primary health-care facilities: study design of a cluster randomized controlled trial in Pakistan. Glob Health Action. 2015;8:28225. doi:10.3402/gha.v8.28225.
48. Uzaslan E, Mahboub B, Beji M, Nejjari C, Tageldin MA, Khan JA, Nafti S, Obeidat NM, Sayiner A, Wali S, Rashid N, El Hasnaoui A. The burden of chronic obstructive pulmonary disease in the Middle East and North Africa: Results of the BREATHE study. Respir Med. 2012;106:S45-59. doi:10.1016/S0954-6111(12)70014-8.
49. Jumbe Marsden E, Wa Somwe S, Chabala C, Soriano JB, Vallès CP, Anchochea J. Knowledge and perceptions of asthma in Zambia: a cross-sectional survey. BMC Pulm Med. 2016;16:33. doi:10.1186/s12890-016-0195-3.

TURKISH JOURNAL OF INTERNAL MEDICINE

ISSN:2687-4245

Original Article

Evaluation of Serum Neutrophil to Lymphocyte Ratio in the Results of Thyroid Fine Needle Aspiration; Can It Discriminate a Clinical Benefit for the Atypia of Undetermined Significance?

Ozlem OZDEMIR[1], Hamza CINAR[2], Cagri AKALIN[3], Muruvvet AKCAY CELIK[4]

[1]Department of Internal Medicine, School of Medicine, Ordu University, Ordu, Turkey
[2]Department of General Surgery, School of Medicine, Abant Izzet Baysal University, Bolu, Turkey
[3]Department of General Surgery, School of Medicine, Ordu University, Ordu, Turkey
[4]Department of Pathology, School of Medicine, Ordu University, Ordu, Turkey

ABSTRACT

Background Thyroid biopsy results are evaluated according to The Bethesda System for reporting thyroid cytopathology worldwide. The most ambiguous result from these categories is the Bethesda-III which is defined as "atypia of undetermined significance" (AUS). Neutrophil to lymphocyte ratio (NLR) is still evaluated in thyroid disorders and malignancy. The purpose of this study was to evaluate the NLR results in Bethesda categories and whether the NLR can discriminate a clinical benefit for the AUS category.

Material and Methods In this retrospective study, 1771 patients who had fine needle aspiration biopsy were examined. Demographic characteristics, NLR, Bethesda scores, operation rates and postoperative histopathological results were recorded.

Results The categories were; Bethesda-I for 298 (16.8%), Bethesda-II for 1320 (74.5%), Bethesda-III for 60 (3.4%), Bethesda-IV for 27 (1.5%), Bethesda-V for 36 (2%), Bethesda-VI for 30 (1.7%) results respectively. The mean NLR was 2.68. There was no statistically significant difference between groups in terms of NLR ($p=0.250$). Overall, 226 (12.76%) patients were underwent thyroidectomy. The AUS group was found by 3.4%, operation rate was 21.66% and malignancy rate was 23.07%. There was a statistically significant difference between Bethesda scores and malignancy rates ($p<0.001$). There was no statistically significant difference between the postoperative results in terms of NLR ($p=0.973$).

Conclusions The NLR does not differ according to the Bethesda categories neither the postoperative histopathological results. It is not a predictive parameter for the benign or malignant differentiation. We think that NLR cannot discriminate a clinical benefit for the surgery decision in the follow-up of the AUS category.

Turk J Int Med 2021;3(4):188-194
DOI: 10.46310/tjim.898205

Keywords: *Neutrophil to lymphocyte ratio, Bethesda categories, fine needle aspiration biopsy, atypia of undetermined significance, thyroid malignancy.*

Turkish Journal of Internal Medicine

Received: March 18, 2021; Accepted: May 23, 2021; Published Online: October 29, 2021

Address for Correspondence:
Ozlem Ozdemir, MD
Department of Internal Medicine, School of Medicine, Ordu University, Ordu, Turkey

E-mail: ozlemtfl@hotmail.com

Introduction

Thyroid nodule is a frequent problem in the clinical practice. While the detection rate of the nodule by the palpation is about 4% due to the inability to recognize the small ones, this rate is up to 68% by the thyroid ultrasonography (USG).[1] Malignancy rate in thyroid nodule is about 5-10% that is why a careful examination is required.[1] The gold standard diagnostic method for the thyroid nodule is fine-needle aspiration biopsy (FNAB) and cytopathologic evaluation. The Bethesda System for reporting thyroid cytopathology (TBSRTC) has been used increasingly since 2007 to classify thyroid nodules and this system broadly classifies thyroid nodules into six categories stratified by risk of malignancy.[2] In these categories, atypia of undetermined significance (AUS) or follicular lesion of undetermined significance (FLUS) category is still the most ambiguous and it is not benign neither malignant.

This category introduce the suspicious, atypical cytological or architectural features, but do not diagnose follicular neoplasm (FN) or suspicious for a follicular neoplasm (SFN), suspicious for malignancy (SM) status.

Systemic inflammatory response was found to be related to cancer pathophysiology in recent years.[3-5] Neutrophil to lymphocyte ratio (NLR) is an indicator of systemic inflammatory response and has been associated with the pathogenesis, development, progression, metastasis and even respond to treatment in solid tumors especially.[6-8] Many studies evaluating NLR in terms of thyroid malignancy give dissimilar results.[9-13] On the other hand, the value of NLR in the benign or malignant differentiation in the AUS category is not clear.

The aim of this study is to examine the FNAB results, to compare the Bethesda categories in terms of NLR, to evaluate the pathology results in patients who underwent thyroidectomy, and to see whether NLR is effective in the benign-malignant differentiation in the AUS category.

Material and Methods

Study Design

This study is a retrospective-cohort study. The results of the patients with thyroid nodule who were admitted to Education and Research Hospital of Medicine Faculty of University Ordu and Ordu State Hospital between May 2018 and December 2019 were evaluated. Demographic information and medical histories related to disease were obtained from patient files. This study was approved by the Ethics Committee of the Medicine Faculty of University Ordu (Number 2018-111).

Patient Selection

Patients older than 18 years old with thyroid nodule and normal thyroid function tests, without any diagnosed thyroid disease were included in the study. Any systemic disease, malignancy and drug use were also in exclusion criteria.

Data Collection

Age, gender, hemogram parameters, FNAB and postoperative histopathological results were analyzed.

Laboratory and Pathological Parameters

Hemogram parameters taken before FNAB were evaluated. White blood cell count (WBC), neutrophil count (N), lymphocyte count (L), were obtained from the complete blood count report. NLR was calculated as the neutrophil count divided by the lymphocyte count.

FNAB and post-surgery specimens were evaluated by the same pathologists in our hospital. According to TBSRTC, the results of FNAB were divided into six groups: I- Nondiagnostic (ND), II- Benign, III- AUS/FLUS, IV- FN/SFN, V- SM, and VI- Malignancy.

Statistical Analysis

Analysis of data used the Statistical Package for the Social Sciences 22 (SPSS, Inc, Chicago IL, USA). Continuous variables were expressed as descriptive statistics; mean, standard deviation, minimum and maximum values. Categorical variables were expressed as number and percentage. Mann-Whitney U test was used for continuous

variables. Chi-square test was used to determine the relationship between categorical variables. P values of <0.05 were considered statistically.

Results

In this study, 1771 patients were analyzed. Mean age was 54.12±13 years old. As 1,465 (82.72%) of the patients were female, 306 (17.28%) were males. The categories were; Bethesda-I for 298 (16.8%), Bethesda-II for 1,320 (74.5%), Bethesda-III for 60 (3.4%), Bethesda-IV for 27 (1.5%), Bethesda-V for 36 (2%), Bethesda-VI for 30 (1.7%) patients respectively. There was no difference in term of gender but a significantly statistical difference in term of age between the groups (p=0.026). Descriptive parameters are given in Table 1. The mean NLR value was 2.68 (0.59-16.80); 3.12 (0.69-15.7) for males and 2.59 (0.59-16.80) for females. The median value of NLR was found to be 2.11.

There was no statistically significant difference between Bethesda groups in terms of NLR (p>0.05) *(Table 2)*.

It was detected that 226 (12.76%) patients were underwent thyroidectomy during the follow-up period.

These patients were 33 (11.07%) of 298 in Bethesda-I, 87 (6.59%) of 1,320 in Bethesda-II, 13 (21.66%) of 60 in Bethesda-III, and all of the Bethesda-IV, Bethesda-V, Bethesda-VI groups. The postoperative histopathological results were found benign in 133 patients and malign in 93. No significant difference was found between the benign and malign results in terms of NLR. Postoperative histopathological results were given in Table 3.

The malignancy rates in patients with thyroidectomy were 12.5% in Bethesda-I, 26.43% in Bethesda-II, 23.07% in Bethesda-III, 40.74% in Bethesda-IV, 61.1% in Bethesda-V, and 93.3% in Bethesda-VI groups. There was a statistically significant difference between Bethesda scores and malignancy rates (p<0.001). No statistically significant difference was found between the patients with thyroidectomy in Bethesda groups in terms of NLR *(Table 4)*.

Discussion

In this study, 1,465 (82.7%) of 1,771 patients with thyroid nodule were female and 306 (17.3%) were males. According to TBSRTC, the results were in benign (Bethesda-II) category for 1,097 (74,93%)

Table 1. Demographic characteristics of the groups

Variables	Bethesda-I (n=298)	Bethesda-II (n=1320)	Bethesda-III (n=60)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
Age (mean±sd) (range)	54.33±13.4 (23-91)	54.15±13.1 (21-95)	56.32±14.0 (27-86)	52.70±17.2 (24-84)	55.78±14.9 (16-88)	45.97±14.9 (15-77)	0.026
Gender							
Female	235	1098	49	25	33	25	
Male	63	222	11	2	3	5	0.165

sd: standart deviation, p<0.05 is considered to be significant

Table 2. NLR values of the groups

Variables	Bethesda-I (n=298)	Bethesda-II (n=1320)	Bethesda-III (n=60)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
NLR (mean±sd) (range)	2.69±1.70 (0.67-11.9)	2.71±1.78 (0.59-16.8)	2.47±1.78 (0.74-9.14)	2.28±0.91 (1.17-4.40)	2.29±1.61 (0.70-8.90)	2.80±1.63 (0.72-6.70)	0.250

sd: standart deviation, p<0.05 is considered to be significant, NLR: Neutrophil to lymphocyte ratio

Table 3. Postoperative histopathological results according to Bethesda Scores

Pathology Results	Bethesda-I (n=33)	Bethesda-II (n=87)	Bethesda-III (n=13)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	Total N=226
Benign							
Multinoduler goiter	11	18	2	6	3	-	43
Colloidal nodule	2	2	1	1	3	-	9
Nodular hyperplasia	9	33	4	3	2	-	51
Follicular adenoma	6	2	1	1	2	1	13
Hashimoto's thyroditis	-	1	-	1	1	-	3
Lymphocytic thyroiditis	-	4	1	1	1	-	7
Adenomatous hyperplasia	-	3	-	1	1	-	5
Diffuse hyperplasia	-	-	-	1	1	-	2
Granulomatous thyroiditis	-	1	-	1	-	1	3
Malign							
Papillary cancer	4	20	2	7	16	24	70
Hurtle cell neoplasia	-	1	1	2	4	-	8
Oncocytic cell nodule	1	1	1	2	1	-	6
Mucoepidermoid carcinoma	-	-	-	-	1	2	3
Medullary carcinoma	-	1	-	-	-	2	3
Total	33	87	13	27	36	30	226

women and 222 (72.07%) men. It is known that thyroid nodules are approximately 4 times more common and benign in women than men.[1] We found similar results in this study. Although the Bethesda-VI age was significantly lower than the other groups, it was compatible with the ages at which thyroid cancer was seen and was not in the primary aim of our study.

In this study, no significant difference was found between Bethesda groups in terms of NLR. Many studies of the NLR in the thyroid diseases are mostly on its evaluation in benign-malign differentiation and offers contrasting results. In the study of Kocer *et al.*[9], NLR was significantly higher in the papillary thyroid cancer group than the multinodular goiters group. Similarly, Çadırcı *et al.*[10] reported a significant difference in NLR between the differentiated thyroid cancer and healthy groups. In another study, mean NLR of malign nodule group was significantly higher than both those in benign nodule that therefore it was suggested that elevated NLR may be an indicator of underlying malign nodular disease in preoperative period.[11] In contrast, Yaylaci *et al.*[12] reported that NLR was not different in patients with benign nodular goiter and papillary thyroid cancer. In a meta-analysis conducted by Liu *et al.*[13], it was concluded that the benign nodules and the differentiated thyroid cancers did not differ in terms of NLR.

In the Bethesda-VI category 30 results were detected but the malignant results increased to 93 cases according to the postoperative pathology results. Thus, malignancy rate was found to be 5.24% in this study. This rate is similar to the expected rate in the population as 5-10%. Also, malignancy rates in patients with thyroidectomy were similar to those stated in TBSRTC only it

Table 4. NLR values of those operated on according to Bethesda groups

Variables	Bethesda-I (n=33)	Bethesda-II (n=87)	Bethesda-III (n=13)	Bethesda-IV (n=27)	Bethesda-V (n=36)	Bethesda-VI (n=30)	P value
NLR (mean±sd) (range)	2.61±1.75 (0.70-7.65)	2.553±1.40 (0.84-8.91)	2.49±1.20 (1.12-5.30)	2.29±0.97 (1.19-4.40)	2.58±1.25 (1.38-5.60)	2.91±1.76 (0.72-6.70)	0.973

sd: standart deviation, p<0.05 is considered to be significant, NLR: Neutrophil to lymphocyte ratio

was found to be higher in the group Bethesda-II (26.43%).[14] We can think that the operation was decided according to the other malignancy criteria by the follow up although the FNAB result was benign. In this study 60 (3.4%) patients were detected as Bethesda-III. However, more recent studies have shown that the incidence of the Bethesda-III category was to be high as 10-12%.[15-16] Essentially, AUS/FLUS implies an intermediate histologic grade between the benign and malignant grades. Therefore, it is the most undecided FNAB result about the malignancy diagnosis. In our study, 13 (21.6%) patients underwent surgery in AUS category and malignancy rate was detected as 23,07%. In the study by Erivwo *et al*.[17], malignancy rate was found to be 29.8% in AUS category. Ryu *et al*.[18] reported this rate as 35.3% and Mileva *et al*.[19] reported as 36.1%. We think that the fallibility of the ratio may occur due to the different experiences and competencies of pathology and radiology specialists.

In this study, we found ten benign and only three malign histopathological results in patients with thyroidectomy in the AUS group. NLR comparison between these groups could not be made due to the low number of patients. In a study of the patients who underwent thyroidectomy with AUS and SM categories, a comparison was made between benign and malignant groups in terms of NLR and no significant difference was found.[20] On the other hand, some studies have shown that the other criteria are much important than the NLR as well as the pathological results in the malignancy diagnosis and surgical decision of the AUS category. In the study of Ryu et al.[18], the increase in age was found to be parallel with the increase in the risk of thyroid malignancy in the patients with Bethesda-III category by the follow-up. In the study of Remonti *et al*.[21] it was reported that microcalcification and central vascularization provides by 96% the malignancy diagnosis in Bethesda-III category.

There are some studies in which the NLR was evaluated in the thyroid malignancy based on thyroiditis. Kocer *et al*.[9] reported that there was no difference in NLR between papillary thyroid cancer groups with and without lymphocytic thyroiditis on the basis. Similarly, in the study of Eroglu *et al*.[22], NLR was evaluated in nodular hyperplasia, thyroiditis, papillary ca and papillary ca with thyroiditis. No statistical difference was found between the groups in terms of NLR. Ari *et al*.[23] found that the mean NLR was significantly higher in the thyroiditis group and non-significantly higher in the papillary cancer group than in the healthy group. However, no significant difference was found between the thyroiditis and papillary cancer groups. In our study, postoperative histopathological results revealed 3 granulomatous and 3 Hashimato thyroiditis and 7 lymphocytic thyroiditis. In the AUS group, there was only one lymphocytic thyroiditis. Unfortunately, the low number of thyroiditis was insufficient for us to compare the effect of thyroiditis on NLR in this study.

We recognize certain limitations to our study. Firstly and major limitation was the retrospective design and relatively small simple size in AUS category. Secondly, the number of patients in the groups was heterogeneous, which may have statistically negatively affected our results. Thirdly, it was limited to a certain geographical region; therefore, the results may not be generalizable. Despite these limitations, there is an advantage of this study such as there are a limited number of studies in the literature that examine the relationship between the AUS category and NLR, but this relationship is not clear yet. We hope that it can make a concept for the future studies.

Conclusions

In conclusion, the present study showed that NLR does not differ according to Bethesda categories.

Additionally, the patients who underwent thyroidectomy also did not show any difference in NLR from those who did not. Moreover, there was no difference in NLR between benign and malignant postoperative histopathologic results. We think that it is not possible to say that NLR has a predictive role in making the decision of follow-up or surgery in the AUS category.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: OO; Study Design: OO, HC; Supervision: OO; Materials: OO, HC, CA, MCA; Data Collection and/or Processing: OO, HC, CA, MCA; Statistical Analysis and/or Data Interpretation: CA; Literature Review: OO; Manuscript Preparation: OO; and Critical Review: OO, HC, CA.

References

1. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination. Eur J Clin Invest. 2009 Aug;39(8):699-706. doi: 10.1111/j.1365-2362.2009.02162.x.
2. Cibas ES, Ali SZ. The 2017 Bethesda system for reporting thyroid cytopathology. Thyroid. 2017 Nov;27(11):1341-6. doi: 10.1089/thy.2017.0500.
3. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001 Feb 17;357(9255):539-45. doi: 10.1016/S0140-6736(00)04046-0.
4. Moore MM, Chua W, Charles KA, Clarke SJ. Inflammation and cancer: causes and consequences. Clin Pharmacol Ther. 2010 Apr;87(4):504-8. doi: 10.1038/clpt.2009.254.
5. Diakos CI, Charles KA, McMillan DC, Clarke SJ. Cancer-related inflammation and treatment effectiveness. Lancet Oncol. 2014 Oct;15(11):e493-503. doi: 10.1016/S1470-2045(14)70263-3.
6. Walsh SR, Cook EJ, Goulder F, Justin TA, Keeling NJ. Neutrophil-lymphocyte ratio as a prognostic factor in colorectal cancer. J Surg Oncol. 2005 Sep 1;91(3):181-4. doi: 10.1002/jso.20329.
7. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg. 2010 Aug;200(2):197-203. doi: 10.1016/j.amjsurg.2009.08.041.
8. Nakamura N, Kinami S, Fujii Y, Miura S, Fujita J, Kaida D, Tomita Y, Miyata T, Fujita H, Ueda N, Iida Y, Kosaka T. The neutrophil/lymphocyte ratio as a predictor of peritoneal metastasis during staging laparoscopy for advanced gastric cancer: a retrospective cohort analysis. World J Surg Oncol. 2019 Jun 25;17(1):108. doi: 10.1186/s12957-019-1651-3.
9. Kocer D, Karakukcu C, Karaman H, Gokay F, Bayram F. May the neutrophil/lymphocyte ratio be a predictor in the differentiation of different thyroid disorders? Asian Pac J Cancer Prev. 2015;16(9):3875-9. doi: 10.7314/apjcp.2015.16.9.3875.
10. Çadirci K, Yıldız F, Keskin H, Bayrak M, Özmen HK, Durmaz SA, Çarlioglu A. Investigation of the neutrophil/lymphocyte and monocyte to high-density lipoprotein cholesterol ratios in differentiated thyroid cancers. J Health Sci Med. 2020;3(2):172-5. doi: 10.32322/jhsm.689142.
11. Sit M, Aktas G, Erkol H, Yaman S, Keyif F, Savli H. Neutrophil to lymphocyte ratio is useful in differentiation of malign and benign thyroid nodules. P R Health Sci J. 2019 Mar;38(1):60-3.
12. Yaylaci S, Tosun O, Sahin O, Genc AB, Aydin E, Demiral G, Karahalil F, Olt S, Ergenc H, Varim C. Lack of variation in inflammatory hematological parameters between benign nodular goiter and papillary thyroid cancer. Asian Pac J Cancer Prev. 2016;17(4):2321-3. doi: 10.7314/apjcp.2016.17.4.2321.
13. Liu JF, Ba L, Lv H, Lv D, Du JT, Jing XM, Yang NJ, Wang SX, Li C, Li XX. Association between neutrophil-to-lymphocyte ratio and differentiated thyroid cancer: a meta-analysis. Sci Rep. 2016 Dec 12;6:38551. doi: 10.1038/srep38551.
14. Ling J, Li W, Lalwani N. Atypia of undetermined significance/follicular lesions of undetermined significance: What radiologists need to know. Neuroradiol J. 2021 Apr;34(2):70-9. doi: 10.1177/1971400920983566.
15. Garg S, Naik LP, Kothari KS, Fernandes GC, Agnihotri MA, Gokhale JC. Evaluation of thyroid nodules classified as Bethesda category III on FNAC. J Cytol. 2017 Jan-Mar;34(1):5-9. doi: 10.4103/0970-9371.197590.
16. Sullivan PS, Hirschowitz SL, Fung PC, Apple SK. The impact of atypia/follicular lesion of undetermined significance and repeat fine-needle aspiration: 5 years before and after implementation of the Bethesda System. Cancer Cytopathol. 2014 Dec;122(12):866-72. doi: 10.1002/cncy.21468.
17. Erivwo P, Ghosh C. Atypia of undetermined significance in thyroid fine-needle aspirations: Follow-Up and Outcome Experience in Newfoundland, Canada. Acta Cytol. 2018;62(2):85-92. doi: 10.1159/000486779.
18. Ryu YJ, Jung YS, Yoon HC, Hwang MJ, Shin SH, Cho JS, Lee JS, Kim HK, Kang HC, Lim HS, Yoon JH, Park MH. Atypia of undetermined significance on thyroid fine needle aspiration: surgical outcome and risk factors for malignancy. Ann Surg Treat Res. 2014 Mar;86(3):109-14. doi: 10.4174/astr.2014.86.3.109.
19. Mileva M, Stoilovska B, Jovanovska A, Ugrinska A, Petrushevska G, Kostadinova-Kunovska S, Miladinova D, Majstorov V. Thyroid cancer detection rate and

associated risk factors in patients with thyroid nodules classified as Bethesda category III. Radiol Oncol. 2018 Sep 27;52(4):370-6. doi: 10.2478/raon-2018-0039.
20. Bayır Ö, Karagöz T, Öcal B, Çakal E, Saylam G, Korkmaz MH. Predictive role of neutrophil- lymphocyte and platelet-lymphocyte ratios in thyroid nodules with cytological diagnosis of "undetermined significance" and "suspicious for malignancy". ENT Updates. 2017;7(1):28-32. doi:10.2399/jmu.2017001003.
21. Remonti LR, Kramer CK, Leitão CB, Pinto LC, Gross JL. Thyroid ultrasound features and risk of carcinoma: a systematic review and meta-analysis of observational studies. Thyroid. 2015 May;25(5):538-50. doi: 10.1089/thy.2014.0353.
22. Eroglu AH, Karayol SS, Guvendic B, Adalid Y. Predictive value of inflammatory cell ratios in incidental thyroid papillary carcinoma. Fam Pract Palliat Care. 2019 Dec;4(3):85-8. doi: 10.22391/fppc.518251.
23. Ari A, Gunver F. Comparison of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in patients with thyroiditis and papillary tumors. J Int Med Res. 2019 May;47(5):2077-83. doi: 10.1177/0300060519838392.

TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Original Article

How Screening Plays Role in COVID-19 Management? Results of a Cross-Sectional Study on COVID-19 Patients Signs and Symptoms

Mahdieh ARDANEH[1], Fatemeh TAVAKOLI-FAR[2,3], Atefeh PAYANDEH[3,4], Ehsan AMIRI-ARDEKANI[5,6,7]

[1]Department of Epidemiology, School of Health, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Faculty of Pharmacy, Ayatollah Amoli Branch, Islamic Azad University, Amol, Iran
[3] Student Association of Indigenous Knowledge, Shiraz University of Medical Sciences, Shiraz, Iran
[4] Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran
[5] Department of Phytopharmaceuticals (Traditional Pharmacy), Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[6] Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran
[7] Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

ABSTRACT

Background Today, COVID-19 outbreak has become a global alert. So, lots of medical complications and socioeconomic and mental burdens have arisen following the outbreak of the disease. There is no adequate general strategy for total control of the virus's widespread. According to this, preventive or early diagnostic measures are crucial. In this study, we designed a questionnaire in the context of the 4,030 telephonic platform to assess the most common symptoms of COVID-19 in Iran.

Material and Methods A questionnaire that had been designed with 20 common and rare symptoms of COVID-19 was filled out by 115 operators of 4,030, a 24-hour call center to answer the Iranians' questions associated with COVID-19 and screen probable COVID-19 cases.

Results Common COVID-19 symptoms among people included cough, dyspnea, sore throat, myalgia, headache, anosmia, fever, dysgeusia, chilling, lethargy, and fatigue. Also, less common symptoms were rhinorrhea, sneeze, vomiting, diarrhea, nasal congestion, eyesore, stomach ache, jaw pain, dry mouth, and abdominal cramps.

Conclusions Our study showed that the most common symptoms of COVID-19 in Iran include cough, dyspnea, sore throat, myalgia, headache, anosmia, fever, dysgeusia, chilling, lethargy, and fatigue. Some symptoms may incident due to over-use of disinfectants, or aggravated by fear of infection, or misdiagnosed with other issues such as food poisoning, flu, panic attacks, and allergies. Consequently, It seems that screening can help find new cases who haven't refered to hospitals and health care centres, and this can result in COVID-19 improving, COVID-19 management, and decreasing the costs of patients and health systems.

Turk J Int Med 2021;3(4):195-200
DOI: 10.46310/tjim. 984243

Keywords: *COVID-19, diagnosis strategy, screening, symptoms, call center.*

Received: August 24, 2021; Accepted: September 02, 2021; Published Online: October 29, 2021

Address for Correspondence:
Ehsan Amiri-Ardekani

Department of Phytopharmaceuticals (Traditional Pharmacy), Faculty of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
E-mail: ehsanamiri@sums.ac.ir

Introduction

Emerging infectious diseases cause serious public health issues that affect populations and governments. Since December 2019, a current explosion of pneumonia was identified with a novel coronavirus, severe acute respiratory syndrome (SARS) coronavirus-2, recorded in Wuhan, Hubei Province, China.[1,2] As the enormous spread of COVID-19, World Health Organization (WHO) declared this outbreak a global pandemic on March 11, 2020. The first Iranian case of COVID-19 was confirmed on February 19, 2020, in Qom city.[3] As of June 17, 2021; 3,060,135 confirmed cases and 82,480 deaths were reported in Iran.[4]

The most common clinical manifestations which set up criteria for testing COVID-19 infection include fever, cough, shortness of breath, myalgia, and rare symptoms including headache, confusion, sore throat, diarrhea, chest pain, rhinorrhea, nausea, and vomiting.[5] Also, mortality rates were higher in older patients than young adults and kids.[6] Expectedly, the case mortality is reported higher in critically infected patients, reaching 87.5-100% among those older than 70 years.[7]

Besides mentioned problems, some complications due to COVID-19 infection may occur. Persistence of some symptoms after discharge, such as dyspnea and asthenia[8], acute and late neurological[9], cardiovascular[10], and pulmonary complications[11] are reported during and after the COVID-19 infection. So, the appropriate follow-up after discharge is required for preventing or improving these complications. In addition, the proper screening to find the symptomatic/asymptomatic patients helps to prevent the widespread of the virus by isolating or quarantining the patients. Also, an effective screening may prevent the progression of the disease by early diagnosis and treatment; however, a purely effective pharmacotherapy regimen for COVID-19 is not available.

Diagnosing COVID-19 depends on the following criteria: clinical symptoms, epidemiological history, positive CT images, and positive pathogenic testing.[12] Tools enabling rapid screening of the COVID-19 infection with high accuracy can be crucially helpful to the healthcare professionals. The primary clinical test currently in use for diagnosing of COVID-19 is the reverse transcription-polymerase chain reaction (RT-PCR), which is expensive, less sensitive, and requires specialized medical personnel.[13]

Due to the prevalence of coronavirus in Iran and the increase in the number of people infected with this virus and public concern in this regard, the need to establish a 24-hour call center to answer questions and provide effective training, reducing stress and concerns, and preventing and combating the virus is an inevitable necessity. In this regard, the Ministry of Health and Medical Education of Iran has established a 24-hour call center called 4,030 platform to answer questions and provide services to people in the field of COVID-19.[14]

There is currently no approved medicine for COVID-19 treatment and vaccination has not been universal yet. Undoubtedly, in the current situation, a call center has a very prominent and important role in providing counseling, education, prevention, reducing anxiety and dealing with the coronavirus, answering ambiguities, and preventing gossip by providing correct and scientific answers to people's questions.[14]

Herein, due to the critical role of the early diagnosis in the COVID-19 pandemic and its effects on public health, we reported the results of our analysis of the clinical manifestation of COVID-19 in Iranian people and discussed the role of screening platforms in COVID-19 management.

Material and Methods

Study Design

Data of symptoms of callers were gathering in the context of a national telephonic COVID-19 diagnosis and follow-up platform called 4,030 that was established in March 2020. The people who answered the phone were medical doctors, pharmacists, nurses, health care providers, and other positions related to the health system, voluntarily registered in this system from all over Iran. These people, as operators, had trained in issues related to the diagnosis of COVID-19 symptoms and were answering caller's questions about COVID-19 around the clock.

Setting

In this cross-sectional study, an online questionnaire with 20 questions according to approved COVID-19 symptoms in medical evidence was filled out by 4,030 operators based on symptoms of callers from 15 to 19 December 2020.

Participants

115 operators who counseled at least 100 callers daily, and were aware of the symptoms of the disease answered 20 questionnaire questions based on the frequency of observed symptoms. Frequent was determined as reported more than 5 times from every 100 calls.

Laboratory and Pathological Parameters

Questionnaire variables were designed based on the most common symptoms that were presented by reputable global sites at the time of our study.

The variables were questioned included sore throat, cough, dyspnea or shortness of breath, headache, myalgia, vomiting, diarrhea, anosmia, dysgeusia, abdominal cramps, nasal congestion, rhinorrhea, sneeze, ophthalmia, jaw pain, stomach ache, lethargy and fatigue, fever, dry mouth, and chilling.

Statistical Analysis

Statistical analysis used for this study was measured using quantitative frequency indices and the number and percentage of SPSS version 22.

Table 1. Symptoms reported by operators from screened people

Symptoms	People with symptom n (%)	People without symptom n (%)
Sore throat	68 (60%)	47 (40%)
Cough	84 (74%)	31 (26%)
Dyspnea or shortness of breath	77 (67%)	38 (33%)
Headache	58 (51%)	57 (49%)
Myalgia	71 (62%)	44 (38%)
Vomiting	31 (27%)	84 (73%)
Diarrhea	40 (35%)	75 (65%)
Anosmia	68 (60%)	47 (40%)
Dysgeusia	61 (54%)	54 (46%)
Abdominal cramps	20 (18%)	95 (82%)
Nasal congestion	26 (23%)	89 (77%)
Rhinorrhea (rhinitis)	19 (17%)	96 (83%)
Sneeze	19 (17%)	96 (83%)
Ophthalmia (eyesore)	18 (16%)	97 (84%)
Jaw pain	3 (3%)	112 (97%)
Stomachache	28 (25%)	87 (75%)
Lethargy and fatigue	68 (60%)	47 (40%)
Fever	75 (66%)	40 (34%)
Dry mouth	35 (31%)	80 (69%)
Chilling	69 (60%)	46 (40%)

Results

Descriptive Data

More than 50% of 4,030 experts confirmed that the most common COVID-19 symptoms include cough, dyspnea, sore throat, myalgia, headache, anosmia, fever, dysgeusia, chilling, lethargy, and fatigue. Also, more than 50% of 4,030 experts determined that rhinorrhea, sneeze, vomiting, diarrhea, nasal congestion, eyesore, stomach ache, jaw pain, dry mouth, and abdominal cramps had the least prevalence among people suspected of COVID-19.

Outcome data

The results of patients' symptoms are provided in table 1.

Discussion

The increase in the number of patients and the lack of appropriate treatments led us to identify patients in the early stages of the disease through the 4,030 platform. The reported symptoms were recorded in a questionnaire.

The analysis of 21 studies involving COVID-19 patients exhibited that most patients with clinical disease manifested sore throat (43.9%), dyspnea (52.7%), cough (62.6%), and fever (75.3%), as the frequently recorded symptoms. Other described manifestations were less common (20-38%) and included myalgia, fatigue, diarrhea, vomiting/nausea, nasal congestion, anorexia, and headache. The least frequently mentioned symptoms (<20%) were abdominal pain, anosmia, dysgeusia, dizziness, and chest pain.[5] Based on our study results, the most reported symptoms to the 4,030 operators were consistent with the global manifestation of COVID-19. Our result showed that most people who had called the 4,030 were infected by COVID-19, which is a high number. Also, most of the symptoms developed 11 days after infection. However, this chiefly depends on age and comorbidities that is not possible for us to include these items in the questionnaire.[5]

Since reported from September 2020, the B.1.1.7 variant in the UK[15], cough, fatigue, weakness, myalgia, sore throat, headache, and fever are more common than other variants, and anosmia and dysgeusia are less common in the UK variant. In the UK variant, the most informed symptoms include all reported symptoms, involving reporting symptoms compatible with COVID-19 while not naming specific symptoms, and the classic symptoms such as cough, fever, dyspnea, but were less likely to report a loss of taste and smell. There was no evidence of a difference between the percentages of reporting gastrointestinal symptoms.[16] The comparison between the symptoms of the UK variant and our results showed that the UK variant may have been present in Iran during that period. Also, the B.1.617 variant called the "Indian variant" had been detected in October 2020 in India. There is no evidence that B.1.617 has different symptoms from B.1.1.7.[17] Therefore, it is possible that this variant also existed in Iran while filling out the questionnaire. Generally, one of the screening advantages is its role in analyzing the common virus variant and its congestion in society.

A definite issue is to magnify mild-to-moderate and non-serious signs and symptoms. Symptoms of food poisoning, panic attack, medication side effects, anxiety, allergies, and minor flu may misunderstand by some symptoms of COVID-19. Also, the incidence of a symptom similar to the symptoms of COVID-19, if accompanied by indoctrination and fear of COVID-19 infection, may aggravate these symptoms and cause misdiagnosis of the disease without diagnostic tests. High prevalence of some symptoms such as dyspnea, cough, and headache may be due to over-use of disinfectants such as bleach and alcohol in high percentage. Therefore, it is difficult to make a definitive diagnosis only based on symptoms without knowing a person's medical and social history.

Follow-up of patients with this disease becomes of note. We need to know how many of the 4,030 callers tested positive for COVID-19 and are among COVID-19 definitive cases. One of the crucial roles of 4,030 is to advise patients with mild-to-moderate COVID-19 symptoms to do home quarantine to prevent the spread of the disease to family members and other people. Also, 4,030 operators recommend individuals who have more severe symptoms or report a history of close contact with the COVID-19 patients to perform definitive diagnostic tests and follow the protocols. 4,030 operators can also differentiate

the symptoms of the disease from the signs of other difficulties such as food poisoning, panic attacks, and other mentioned problems, and accordingly guide the patients to stay at home and take measures or refer them to the physician for a clinical examination and tests if needed.

One caveat to close with is that the recommendation for early diagnosis to slow down the virus's rapid spread depends on the notion that no treatment is available efficiently. In lack of successful treatment, knowing how to manage the health of society through preventive and primary care is the most potent defense at the first step. In the second step, monitoring the symptomatic patients is considered. In the third and last step, following the patient up after recovery of illness or discharge is noteworthy to prevent the probable complications.

Limitations

Unfortunately, the study did not include factors such as age, sex, medical history, medication use, and social activities. This study was also limited by the absence of clarifying that how long it took to develop symptoms in infected people.

Future Research

We believe that screening can play a crucial role in or COVID-19 pandemic management as it can facilitate patients' diagnosis. Due to limitations, our recommendation to researchers is to involve the actual number of patients, age, sex, medical history, comorbidities, and the duration of symptoms incidence in their research to achieve more valuable results. Also, follow-up and monitoring of patient's symptoms should be on the agenda. All in all, we think screening and following up can help to manage COVID-19 and decrease its mortality rate and health system costs.

Conclusions

Our study has shown that the most common symptoms of COVID-19 in Iran include cough, dyspnea, sore throat, myalgia, headache, anosmia, fever, dysgeusia, chilling, lethargy, and fatigue. Some symptoms may incident due to over-use of disinfectants, or aggravated by fear of infection, or misdiagnosed with other issues such as food poisoning, flu, panic attacks, and allergies. The existence of B.1.617 and B.1.1.7 variants in Iran is still controversial and requires definitive diagnostic tests to confirm.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: MA, EAA; Study Design: MA, EAA; Supervision: EAA; Data Collection and/or Processing: MA; Statistical Analysis and/or Data Interpretation: MA, FTF, AP, EAA; Manuscript Preparation: FTF, AP; and Critical Review: AP, EAA.

References

1. Zu ZY, Jiang MD, Xu PP, Chen W, Ni QQ, Lu GM, Zhang LJ. Coronavirus Disease 2019 (COVID-19): A Perspective from China. Radiology. 2020 Aug;296(2):E15-E25. doi: 10.1148/radiol.2020200490.
2. Tavakoli-Far F, Ardekani EA. Spike protein and its proteases role in SARS-COV-2 pathogenicity and treatment; a review. Proc Shevchenko Sci Soc Med Sci. 2021 Apr 7;64(1):52-61. doi: 10.25040/ntsh2021.01.05.
3. Tuite AR, Bogoch II, Sherbo R, Watts A, Fisman D, Khan K. Estimation of Coronavirus Disease 2019 (COVID-19) Burden and Potential for International Dissemination of Infection From Iran. Ann Intern Med. 2020 May 19;172(10):699-701. doi: 10.7326/M20-0696.
4. Worldometer. Reported Cases and Deaths by Country or Territory; Iran. Available at: www.worldometers.info/coronavirus/country/iran/. Accessed June 17, 2021.
5. McArthur L, Sakthivel D, Ataide R, Chan F, Richards JS, Narh CA. Review of Burden, Clinical Definitions, and Management of COVID-19 Cases. Am J Trop Med Hyg. 2020 Aug;103(2):625-38. doi: 10.4269/ajtmh.20-0564.
6. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 May 12;323(18):1775-6. doi: 10.1001/jama.2020.4683.
7. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Yu Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020 May;8(5):475-81. doi: 10.1016/S2213-2600(20)30079-5.
8. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11;324(6):603-5. doi: 10.1001/jama.2020.12603.
9. Xiong W, Kwan P, Zhou D, Del Felice A, Duncan JS, Sander JW. Acute and late neurological complications

of COVID19: the quest for evidence. Brain. 2020 Dec 1;143(12):e99. doi: 10.1093/brain/awaa294.
10. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020 Jul;38(7):1504-7. doi: 10.1016/j.ajem.2020.04.048.
11. Jonker PKC, van der Plas WY, Steinkamp PJ, Poelstra R, Emous M, van der Meij W, Thunnissen F, Bierman WFW, Struys MMRF, de Reuver PR, de Vries JPM, Kruijff S; Dutch Surgical COVID-19 Research Collaborative. Perioperative SARS-CoV-2 infections increase mortality, pulmonary complications, and thromboembolic events: A Dutch, multicenter, matched-cohort clinical study. Surgery. 2021 Feb;169(2):264-74. doi: 10.1016/j.surg.2020.09.022.
12. Wang S, Kang B, Ma J, Zeng X, Xiao M, Guo J, Cai M, Yang J, Li Y, Meng X, Xu B. A deep learning algorithm using CT images to screen for Corona virus disease (COVID-19). Eur Radiol. 2021 Aug;31(8):6096-104. doi: 10.1007/s00330-021-07715-1.
13. CChowdhury MEH, Rahman T, Khandakar A, Mazhar R, Kadir MA, Mahbub ZB, Islam KR, Khan MS, Iqbal A, Emadi NA, Reaz MBI. Can AI Help in Screening Viral and COVID-19 Pneumonia?. IEEE Access. 2020 Jul 20;8:132665-76. doi: 10.1109/ACCESS.2020.3010287.
14. https://call4,030.ir. Accesed May 17, 2021.
15. World Health Organization. Weekly epidemiological update on COVID-19 - 25 May 2021. Available at: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---25-may-2021. Accessed June 17, 2021.
16. Steel K, Davies B. Coronavirus (COVID-19) Infection Survey: characteristics of people testing positive for COVID-19 in England. 27 January 2021.
17. Page ML. Indian COVID-19 variant (B.1.617). 2021; Available at: www.newscientist.com/definition/indian-covid-19-variant-b-1-617/. Accessed June 17, 2021

TURKISH JOURNAL OF INTERNAL MEDICINE
ISSN:2687-4245
Case Report

Langerhans Cell Histiocytosis in Bone: A Case Report

Orkide KUTLU[1], Gizem Meral[2], Hasan Eruzun[1], Ozlem BULUZ[3], Ayca Zeynep KUTLU[4], Deniz OZCAN[5], Suat Erol CELIK[2]

[1]Department of Internal Medicine, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey
[2]Department of Neurosurgery, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey
[3]Department of Family Medicine, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey
[4]Istanbul University, School of Medicine, Istanbul, Turkey
[5]Department of Family Medicine, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey

ABSTRACT

Langerhans cell histiocytosis (LCH) is a rare disease in which histiocytic infiltrations can be seen in bone, skin, lymph nodes, lungs, liver, spleen, bone marrow, central nervous system and endocrine glands. Pulmonary LCH has been closely associated with smoking while there is no data on genetic, viral or neoplastic etiology. In LCH with multiple system involvement, unifocal/multifocal infiltrations occur in two or more organs together with systemic symptoms such as weight loss and fever. In histology, Langerhans cells that do not contain phagocytic material in their cytoplasm, have a folded "coffee bean" appearance in their nucleus, express histiocyte markers CD1a, S100 and C207 and contain Birbeck granules under electron microscope. In treatment, if there is a risk of collapse in spinal or femoral bone lesions, surgery and radiotherapy can be applied for stabilization; if necessary, chemotherapy can be applied in multisystem disease. Here, we reported an LCH patient with a malignant shaped lytic lesion in the thoracic spine and adjacent bone.

Turk J Int Med 2021;3(4):201-206
DOI: 10.46310/tjim.876279

Keywords: *Langerhans cell histiocytosis, bone.*

Received: March 08 2021; Accepted: September 03, 2021; Published Online: October 29, 2021

Address for Correspondence:
Ozlem BULUZ

Department of Family Medicine, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey
E-mail: hasret_aksu2007@hotmail.com

Introduction

Langerhans cell histiocytosis (LCH) is a rare disease that can be seen as granulomatous histiocyte infiltrates in almost every tissue such as lymph nodes, lungs, liver, spleen, bone marrow, central nervous system, endocrine organs, mainly osteolytic bone lesions and/or skin lesions. Its incidence in adults has been reported as 1-2 per million. It is more prevelant in males, specifically in northern European Caucasians and between the ages of 1-3. Although pulmonary LCH is closely associated with smoking, extrapulmonary LCH is not associated with smoking.[1]

In the pathophysiology of LCH, the increase in regulatory T cells and various cytokines such as IL-17, IL-2 and growth factors was thought to be a reactive condition secondary to a defect in the immune regulatory system. In 2010, however, a BRAF-V600E mutation was reported in more than half of the LCH patient samples and ERK phosphorylation in all cases. After these developments, LCH is thought to be a clonal myeloid neoplasm. LCH is now defined as an inflammatory myeloid neoplasm in the revised 2016 Histiocyte Association Classification. Patients with BRAF-V600E mutation constitute the group with risky organ involvement multisystem disease, resistant to chemotherapy or high reactivation rate. Up-regulation of TGF-beta, BCL2, ICAM, CD14, CD2, osteopontin and vanin, which are genes that bring and activate T cells to the area of inflammation in LCH, have also been shown.[2,3]

In histology, granulomatous infiltration consisting of eosinophils, CD8 positive T cells and multinuclear giant cells is observed with heterogeneous collection of Langerhans cells in the tissue involved. Langerhans cells are myeloid dendritic cells with a slightly eosinophilic cytoplasm, few vacuoles, no phagocytic material, a "coffee bean" nucleus, expressing the histiocyte markers CD1a, S100 and CD207 (langerin), and containing Birbeck granules in electron microscopy. Birbeck granules are intracytoplasmic, rod-shaped organelles with enlargement at the tip, tennis racket-like organelles.[1,4]

The names: Hand Schüller-Christian disease, Letterer Siwe disease, Histiocytosis X, diffuse reticuloendotheliosis were used in the past for LCH. However, they are no longer used, instead the term "eosinophilic granuloma" continues to be used for the disease with isolated lytic appearance in the bone. Here, we wanted to report that we diagnosed LCH in a patient with a malignant lytic lesion in the thoracic vertebra and adjacent bone, since it is very rare in the practice of internal medicine.

Case Report

A 51-year-old male patient was admitted to our internal medicine outpatient clinic with the complaint of localized pain in the back that had been intensified for the last 3 months and had been bothering him for 1 year. The general condition of the patient, who had no known chronic disease, was good, his vital signs were stable, and system examinations were normal. LDH was 281 U/L (125-220). Other laboratory findings were unremarkable. In thoracic spinal CT-MR examinations, a lytic, destructive 66x37 mm mass lesion causing compression on the spinal cord and a nodular lesion area on the lateral of the 6th rib were observed in the costovertebral junction at the level of the 7th rib on the right, at the vertebral corpus-pedicle transverse process-articular facets *(Figure 1)*. In PET-CT, intensely increased FDG uptake was observed in the lesion with irregular borders (SUVmax: 10.5) and the lesion at the 6th rib (SUVmax: 8.0). Abdominal CT was normal. Total laminectomy at T6-T7 level, extradural total tumor resection, subtotal excision of the 6th-7th ribs was performed. Spinal stabilization was achieved, and the patient was discharged on the 7th postoperative day. No additional involvement was observed in bone scintigraphy. There was radiological regression in the postoperative 2nd month imaging of the patient *(Figure 2)*.

In the pathological examination, cells with oval vesicular nuclei, as well as ones with oval vesicular nuclei that have nicks and grooves in the nuclei were observed among the bone trabeculae, which had spread to the soft tissue, infiltrated the trabeculae and contained dense eosinophil leukocytes. Lastly it was rich in mixed type

Figure 1. T2A axial and sagittal sections of preoperative MRI. A mass destructs the right costovertebral angle at the level of the T7 vertebra, showing infiltration in the right transverse process/intraarticular facets, and compressing the spinal cord.

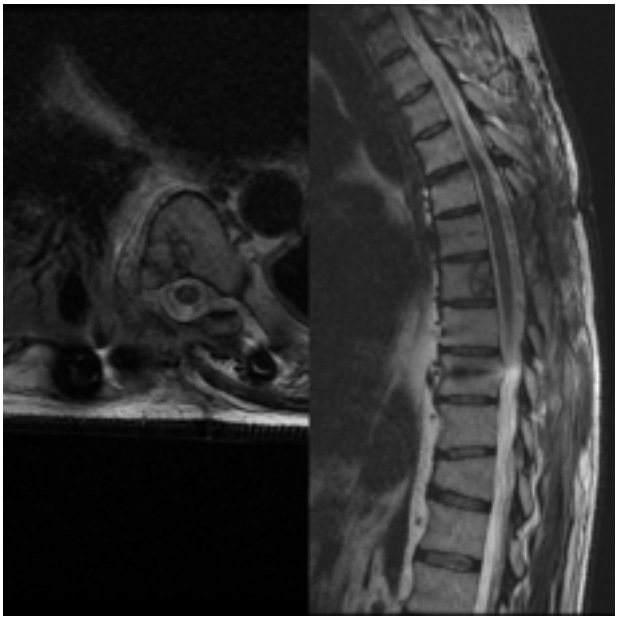

Figure 2. Aortic dissection images with multi-slice computerized tomographic angiography.

inflammatory cells *(Figure 3)*. CD1a (Thermo/Ab-5): positive, S100 (BioGenex/15E2E2): positive, CD68 (Biocare/KP1): positive were detected in cells with oval and vesicle nuclei. The findings were evaluated as compatible with Langerhans cell histiocytosis *(Figure 4)*. With the decision of the council, a total of 2000 cgy radiotherapy was administered to the patient in 10 sessions with the IMRT technique. The patient, who was in remission after treatment, was followed up.

Discussion

Patients with LCH may have unifocal or multifocal involvement in bone, skin, lymph nodes, lungs, CNS, thyroid and rarely the thymus. In LCH with single system involvement, systemic symptoms such as weight loss and fever are generally not seen. In multisystem LCH, there are two or more organ involvements that can be associated with risky organ involvement. The organs at risk are the hematopoietic system, liver and/or spleen, indicating a poor prognosis. While most patients wait 1-4 years for a correct diagnosis, some may be diagnosed 5-20 years after childhood-onset diabetes insipidus.[5]

Patients with bone involvement may be asymptomatic or complain of localized pain in the sensitive area. Huang *et al*.[6] reported that in 30 cases of eosinophilic granuloma diagnosed in their center, the cervical than thoracic regions were affected most frequently in the vertebral column. Radiographically, soft tissue mass is most commonly seen around the lytic lesion in the bone. The most commonly affected area of the vertebra is the corpus, and the lesion may compress the spinal cord, and collapse may occur with epidural invasion/pathological fracture.

Phillips *et al*.[7] evaluated the effectiveness of FDG-PET scans in identifying areas of active disease and evaluating response to therapy in patients with LCH. As a result of their studies, they showed that PET-CT is superior to other imaging studies such as X-ray, CT, and MRI in determining the extent of the disease and the response to treatment. In our patient, a multifocal disease with single system bone involvement was observed as a

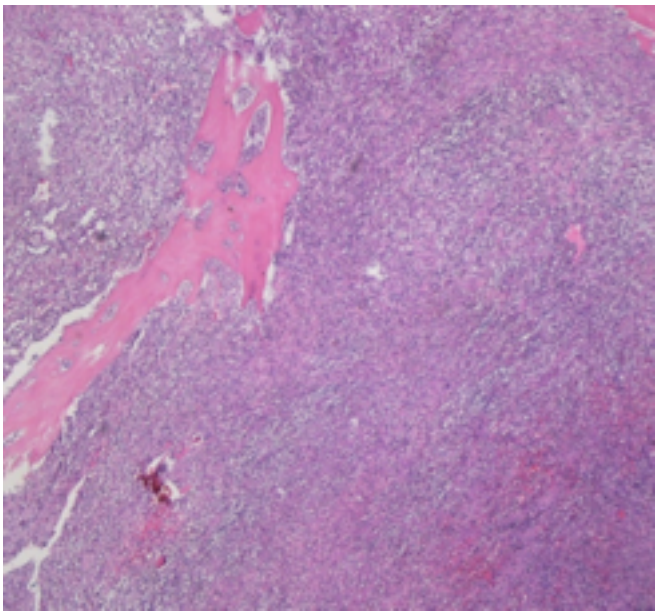

Figure 3. Cells infiltrating bone trabeculae, spreading to soft tissue with rich in mixed-type inflammatory are seen. HE x40 magnification.

result of PET-CT taken before the operation, and a treatment plan was made.

The BRAF–V600E mutation detected in more than half of LCH cases elucidated the pathogenesis of the disease. The BRAF protein is a component of the MAPK (RAS-RAFMEK-ERK) signaling pathway, which leads to the activation of transcription factors required for cell growth and proliferation. V600E is the most common mutation in BRAF and is the trigger for the development of malignancy.[8-10] Liquid biopsy, which allows detection of BRAF-V600E mutations in cell-free DNA extracted from peripheral blood plasma of LCH patients, using allele-specific real-time PCR or digital droplet PCR techniques, is promising as a potential biomarker for early detection in high-risk LCH.[11]

Since LCH is a very rare disease and different organs can be affected in the disease, its diagnosis is difficult. By histology and immunophenotyping, it should be differentiated from other histiocytic diseases, metastatic solid tumors, hematopoietic neoplasms such as lymphoma and myeloma, hemophagocytic lymphohistiocytosis, macrophage activation syndrome and lastly, Erdheim-Chester/Rosai-Dorfman disease.[12]

Although the treatment may vary according to the number of organs and lesions involved in a single organ system disease, curettage of the bone lesion, topical treatments for skin lesions can be combined with methotrexate (20 mg/m^2/week), mercaptopurine (50 mg/m^2/day), single agent prednisolone or vinblastine when necessary. If there is a risk of collapse in spinal or femoral bone lesions, surgery and/or intralesional corticosteroid and radiotherapy can be applied for stabilization. Since there was a risk of spinal cord compression in our patient, an operation was performed to eliminate the risk, and then radiotherapy was applied.

In multisystem disease, patients should be referred to clinical study groups. Since the discovery of the BRAF-V600E mutation, the pathophysiology of LCH has been largely resolved, making the feasibility of targeted therapies such as BRAF or MEK inhibitors possible. It has been possible to expand the treatment options with a BRAF inhibitor (vemurafenib, dabrafenib) and a MEK1/2 inhibitor (trametinib).[13-15] In the treatment of LCH, patients should be directed to centers where clinical trials of combined chemotherapy and targeted therapies are performed, and treatment results should be closely monitored.

Conflict of Interests

Authors declare that there are none.

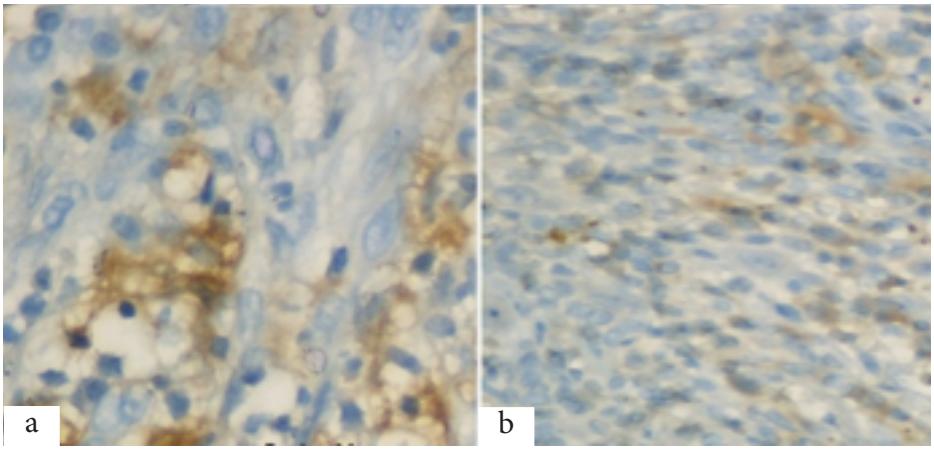

Figure 4. Positive staining is seen with immunohistochemical methods for CD1a (a) and S100 (b) which are specific for Langerhans cells. CD1a x400 magnification (a), S100 x400 magnification (b).

Authors' Contribution

Study Conception: OK, SEC; HE; Study Design: OB, AZK, DO; Supervision: OK, HE, SEC; Fundings: DO, HE, SEC; Materials: OK, OB, AZK; Data Collection and/or Processing: OO, MT, TDH, KA; Statistical Analysis: OK, GM; Data Interpretation: OB, AZK, DO; Literature Review: OK; TDH; Manuscript Preparation: AZK, OK, GM; Critical Review: OK, HE, GM.

References

1. De Young B, Egeler RM, Rollins BJ. Langerhans cell histiocytosis. In: Fletcher CD, Bridge JA, Hogendoorn PC, Mertens F, eds. WHO Classification of Tumours of Soft Tissue and Bone. 4th ed. Lyons: International Agency for Research on Cancer; 2013:356.
2. Senechal B, Elain G, Jeziorski E, Grondin V, Patey-Mariaud de Serre N, Jaubert F, Beldjord K, Lellouch A, Glorion C, Zerah M, Mary P, Barkaoui M, Emile JF, Boccon-Gibod L, Josset P, Debré M, Fischer A, Donadieu J, Geissmann F. Expansion of regulatory T cells in patients with Langerhans cell histiocytosis. PLoS Med. 2007 Aug;4(8):e253. doi: 10.1371/journal.pmed.0040253.
3. Berres ML, Lim KP, Peters T, Price J, Takizawa H, Salmon H, Idoyaga J, Ruzo A, Lupo PJ, Hicks MJ, Shih A, Simko SJ, Abhyankar H, Chakraborty R, Leboeuf M, Beltrão M, Lira SA, Heym KM, Bigley V, Collin M, Manz MG, McClain K, Merad M, Allen CE. BRAF-V600E expression in precursor versus differentiated dendritic cells defines clinically distinct LCH risk groups. J Exp Med. 2014 Apr 7;211(4):669-83. doi: 10.1084/jem.20130977.
4. Minkov M, Pötschger U, Grois N, Gadner H, Dworzak MN. Bone marrow assessment in Langerhans cell histiocytosis. Pediatr Blood Cancer. 2007 Oct 15;49(5):694-8. doi: 10.1002/pbc.21227.
5. Götz G, Fichter J. Langerhans'-cell histiocytosis in 58 adults. Eur J Med Res. 2004 Nov 29;9(11):510-4.
6. Huang W, Yang X, Cao D, Xiao J, Yang M, Feng D, Huang Q, Wu Z, Zheng W, Jia L, Wu S. Eosinophilic granuloma of spine in adults: a report of 30 cases and outcome. Acta Neurochir (Wien). 2010 Jul;152(7):1129-37. doi: 10.1007/s00701-010-0644-3.
7. Phillips M, Allen C, Gerson P, McClain K. Comparison of FDG-PET scans to conventional radiography and bone scans in management of Langerhans cell histiocytosis. Pediatr Blood Cancer. 2009 Jan;52(1):97-101. doi: 10.1002/pbc.21782.
8. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, Kuo FC, Ligon AH, Stevenson KE, Kehoe SM, Garraway LA, Hahn WC, Meyerson M, Fleming MD, Rollins BJ. Recurrent BRAF mutations in Langerhans cell histiocytosis. Blood. 2010 Sep 16;116(11):1919-23. doi: 10.1182/blood-2010-04-279083.
9. Kobayashi M, Tojo A. Langerhans cell histiocytosis in adults: Advances in pathophysiology and treatment. Cancer Sci. 2018 Dec;109(12):3707-13. doi: 10.1111/cas.13817.
10. Go H, Jeon YK, Huh J, Choi SJ, Choi YD, Cha HJ, Kim HJ, Park G, Min S, Kim JE. Frequent detection

of BRAF(V600E) mutations in histiocytic and dendritic cell neoplasms. Histopathology. 2014 Aug;65(2):261-72. doi: 10.1111/his.12416.

11. Héritier S, Hélias-Rodzewicz Z, Lapillonne H, Terrones N, Garrigou S, Normand C, Barkaoui MA, Miron J, Plat G, Aladjidi N, Pagnier A, Deville A, Gillibert-Yvert M, Moshous D, Lefèvre-Utile A, Lutun A, Paillard C, Thomas C, Jeziorski E, Nizard P, Taly V, Emile JF, Donadieu J. Circulating cell-free BRAFV600E as a biomarker in children with Langerhans cell histiocytosis. Br J Haematol. 2017 Aug;178(3):457-67. doi: 10.1111/bjh.14695.
12. Allen CE, Ladisch S, McClain KL. How I treat Langerhans cell histiocytosis. Blood. 2015 Jul 2;126(1):26-35. doi: 10.1182/blood-2014-12-569301.
13. Haroche J, Cohen-Aubart F, Emile JF, Arnaud L, Maksud P, Charlotte F, Cluzel P, Drier A, Hervier B, Benameur N, Besnard S, Donadieu J, Amoura Z. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013 Feb 28;121(9):1495-500. doi: 10.1182/blood-2012-07-446286.
14. Diamond EL, Subbiah V, Lockhart AC, Blay JY, Puzanov I, Chau I, Raje NS, Wolf J, Erinjeri JP, Torrisi J, Lacouture M, Elez E, Martínez-Valle F, Durham B, Arcila ME, Ulaner G, Abdel-Wahab O, Pitcher B, Makrutzki M, Riehl T, Baselga J, Hyman DM. Vemurafenib for BRAF V600-Mutant Erdheim-Chester Disease and Langerhans Cell Histiocytosis: Analysis of Data From the Histology-Independent, Phase 2, Open-label VE-BASKET Study. JAMA Oncol. 2018 Mar 1;4(3):384-8. doi: 10.1001/jamaoncol.2017.5029.
15. Papapanagiotou M, Griewank KG, Hillen U, Schimming TT, Moeller LC, Führer D, Zimmer L, Roesch A, Sucker A, Schadendorf D, Livingstone E, Schilling B. Trametinib-induced remission of an MEK1-mutated langerhans cell histiocytosis. JCO Precis Oncol. 2017 May 18;1:1-5. doi: 10.1200/PO.16.00070.

http://www.tjim.org
https://dergipark.org.tr/tr/pub/tjim