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Patent Foramen Ovale: A Practical and Imaging Based Morphological Classification

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Abstract

Objectives: Patent foramen ovale (PFO) has been implicated in cryptogenic stroke, transient ischemic attacks, migraine with auras, decompression sickness and severe refractory hypoxemia. Recently published data provided sufficient evidence for the percutaneous closure of PFO in the embolic stroke of an undetermined source. After a suspicion for a paradoxical cerebral embolism, a transthoracic echocardiography, transcranial doppler study, and transesophageal echocardiography using contrast bubble injection are indicated. Detection of PFO is possible during contrast bubble injection with or without Valsalva maneuver in transesophageal echocardiography. Three- or two-dimensional transesophageal echocardiography (TEE) give opportunity to obtain detailed information about complex anatomical variations in PFO morphologies including atrial septal aneurysm, large tunnel, increased height of PFO, lipomatous hypertrophy. Ideal device selection is important for the appropriate closure of PFO. A standardized classification is needed to define PFO morphologies when selecting the device size. In our study, we aimed to create a common language for different and high-risk morphologies with two-dimensional (2D) and three-dimensional (3D) TEE in patients with cryptogenic stroke that would be helpful in transcatheter PFO closure.

Materials and Methods: One hundred eleven one patients with the diagnosis of cryptogenic stroke and with high "The Risk of Paradoxical Embolism" (RoPE) score (>7) were included in the study. From the recorded images, interatrial septum was evaluated retrospectively with 2D and 3D TEE. Also, transcranial doppler, contrast bubble injection in TEE, 12-lead electrocardiography was performed. The amount of shunting during bubble study was recorded. According to analysis with 2D and 3D TEE technique, we classified the subtypes of different PFO morphologies into two main types and subgroups according to atrial septal aneurysm.

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Abstract

Results: 2D and 3D transesophageal echocardiography was applied to all patients before and during the PFO closure procedure. The amount of shunting was severe in 64 patients (57.7%) patients. PFO tunnel was found to be spontaneously open in 64 patients. Most of patients had long PFO tunnel and mean tunnel length was 11.47±2.26 mm. The mean atrial septal defect (ASD) size accompanying PFO was 3.17±1.64 mm (large ASD). There were atrial septal defects accompanying PFO in 28 (25.2 %) patients. The mean of opening length of PFO (height of PFO) which can induce severe shunting was 4.06±1.6 mm. Atrial septal aneurysm was existed in 22 (19.8 %) patients. The total amount of other then simple morphologies which carry high risk features were higher. We found that the most frequent device selected by the operator was multi-fenestrated septal occluder (cribriform). The multi-fenestrated septal occluder devices were implanted in 69.4% of patients. The more complex anatomy led the operator for to choose mostly multi-fenestrated devices.

Conclusion: After defining PFO morphologies and categorizing the different types, we would be able to express the same morphological classification which could be easily and repetitively used. With the usage of a well-known classification, device type selection could be standardized for optimization of percutaneous transcatheter closure of PFO while minimizing the complications and increasing procedural success.

Keywords: Patent foramen ovale, cryptogenic stroke, percutaneous closure of patent foramen ovale

Introduction

Patent foramen ovale (PFO) is one of the anatomical variants of the interatrial septum and considered to be a subclass of ostium secundum defects. Blood flow through the foramen ovale permits the passage of oxygenated blood from the right atrium into the left atrium in fetal circulation. Two membranes, septum secundum and septum primum, are part of the interatrial septum and fuse soon after birth with the increase in left atrial pressure. However, in 15-35% of patients this fusion does not occur and may serve as a conduit for paradoxical embolization. The flap valve of PFO allows only a right-to-left shunt, either when the right atrial pressure exceeds the left atrial pressure during a short interval of cardiac cycle or following a straining maneuver (Valsalva Maneuver). The size and morphology show a great variability among patients. Associated defects such as atrial septal aneurysm (ASA), atrial septal defects (ASD) make the morphology of the interatrial septum more complicated[1]. Although mostly encountered as innocent, PFO has been reported to be associated with cryptogenic stroke, migraine, peripheral embolism, platypnea-orthodexia syndrome and Alzheimer's dementia[2]. A cryptogenic stroke is defined as an ischemic stroke with an unknown cause which constitutes one-third of all stroke patients. Association between cryptogenic stroke and the presence of PFO causing paradoxical emboli have been demonstrated in several studies[3]. Young population are mostly affected by PFO-related embolic events. PFO is found to be the cause in 40-56% of stroke patients under the age of 55. However, it is still controversial whether PFO is an incidental finding in some of the cryptogenic stroke patients. Percutaneous PFO closure and antithrombotic therapy are available options for secondary prevention in PFO-related strokes[3,4]. Many studies and metanalyses tried to demonstrate that a device-closure strategy could be superior to a medical-therapy strategy. Hypermobile atrial septum, channel length or height of PFO, presence of ASA or degree of shunt from PFO that are identified in transesophageal echocardiography (TEE) may contribute to the ischemic cerebrovascular events. The Risk of Paradoxical Embolism (RoPE) score calculator is used to define stroke risk estimation in PFO patients for decision of PFO closure. A new risk estimation system with the use of PFO features (ASA or long tunnel length) and ROPE score simultaneously was also defined in a recent study[5,6].

Different morphologic features of PFO may predispose to cerebrovascular events and frequently associated with cryptogenic stroke[7-9]. Morphologic definitions and classifications of PFO are based on limited autopsy studies and may not be applicable to the clinical practice[10,11]. Two-dimensional (2D) or three-dimensional (3D) TEE provides accurate imaging of the interatrial septum and help defining the detailed morphology of the PFO which could be high risk for cerebrovascular events. On the other hand, anatomical variations seen in patients undergoing transcatheter device closure may influence device selection and procedural success. Inappropriate closure procedure could be a result of a complex anatomical feature. 2D TEE with agitated saline contrast is currently gold standard for diagnosis of PFO[1,9]. 3D TEE allows direct visualization of the entire fossa ovalis with surrounding structures and also bubbles crossing fossa ovalis. A standardized definition and classification of PFO morphology including accompanying structures is needed for the decision of percutaneous PFO closure procedure, device selection or sizing in PFO closure procedures. An ideal device selection is important to facilitate apposition and fusion of the septum primum and septum secundum.

We aimed to propose a practical new classification of different morphologies with 2D and 3D TEE in patients with cryptogenic stroke to create a common language when defining a high risk PFO type based on the data of our series. We believe such classification will be helpful in practice of PFO closure and fill a gap.

Materials and Methods

One hundred eleven one patients who were referred to cardiology department and evaluated by TEE between 2014 and 2020 with the diagnosis of cryptogenic stroke and with high RoPE score (≥7) were included in this study. All patients were confirmed for embolic ischemic stroke with magnetic resonance imaging (MRI). MRI of the brain with three sequences (T2 sequence, diffusion-weighted imaging, and fluid-attenuated inversion recovery) was used to diagnose acute stroke. Patients with carotid artery stenosis, uncontrolled diabetes or hypertension, a high-risk source of cardioembolism such as atrial fibrillation or major structural cardiac anomaly and prothrombotic disorder were excluded. Before evaluating the defect in interatrial septum by 2D and 3D TEE, extensive workup consisting of transcranial doppler, echocardiography, 12-lead electrocardiography was performed. Also, with bubble study, the amount of shunting across the PFO was evaluated during transcranial doppler and echocardiography.

Recorded images with the General Electric Vivid E9 (GE Health Medical, Horten, Norway) were used. The 2D and 3D TEE images were evaluated retrospectively. Definition and characterization of PFO morphologies were classified according to the additional defects detected with PFO, spontaneous opening of PFO tunnel (spontaneous or provokable right-to-left shunt), PFO size (maximum separation between septum primum and septum secundum overlap at the point of entry into the left atrium), presence of interatrial septal aneurysm, thickness of primum and secundum septum (lipomatous hypertrophy), passage of agitated saline from PFO tunnel with Valsalva or spontaneously. The length of tunnel was noted. The degree of right-to-left shunting, at rest and during the Valsalva maneuver, was defined as mild when 3 to 9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared, and severe if >30 microbubbles appeared. Bubbles appearing in the left atrium (shunt occurring) within the third cardiac cycle was taken as a cut off time. All saline injections were performed from antecubital vein[8]. Atrial septal aneurysm was diagnosed as 15-mm of total septal tissue excursion or a 10-mm protrusion into either atrium from the septal midline[11,12]. According to analysis with 2D and 3D TEE technique, we classified the subtypes of different PFO morphologies causing cryptogenic stroke as follows:

Type I- A tunnel morphology without ASD or ASA

a. Closed PFO tunnel opened and passage of agitated saline with Valsalva maneuver (Figure 1)

b. A spontaneously opened PFO tunnel, passage of bubbles without Valsalva maneuver (Figure 2)

Type II- More complicated morphology with ASD, ASA or lipomatous hypertrophy

a. PFO tunnel with small ASD next to the tunnel (Figure 3)

b. PFO tunnel with multiple defects or a large ASD (defined as greater than 3 mm) (Figure 4a,b)

c. PFO with atrial septal aneurysm and increase in PFO size with Valsalva maneuver (Figure 5a,b)

d. PFO with atrial septal aneurysm with increase in PFO size with Valsalva maneuver and ASD (Figure 6)

e. PFO with atrial septal aneurysm and/or lipomatous hypertrophy (Figure 7a,b)

Percutaneous PFO closure procedures were performed to all patients included in the study. The devices were implanted under fluoroscopic and 2D/3D TEE echocardiographic guidance according to standard technique while the patient was under general anesthesia. The type of device was chosen with decisions of interventional cardiologist and echocardiographer according to morphologies.

Statistical Analysis

Data analyses and statistical analyses were performed by using SPSS 23 for Windows (SPSS Inc., Armonk, NY, USA). Distribution of data was assessed by using Shapiro-Wilk test or Kolmogorov-Smirnov test. Numerical variables were presented as mean ± standard deviation or median (quartile deviation), and categorical variables were presented as percentages.

Results

One hundred eleven one patients (age ranged between: 18-68 years, 36.9% male and 63.1% female) who had a cerebrovascular event were evaluated. 2D and 3D transesophageal echocardiography was applied to all patients before and during the PFO closure procedure. All patients had been evaluated with magnetic resonance imaging showing different number and location of ischemic lesions. After shared decision making and consultation with neurology, PFO closure was decided in patients who had ischemic lesions in MRI. All patients had high RoPe score (RoPE ≥7) Passage of intravenously injected microbubbles in transcranial doppler with different types of severity was demonstrated in all patients. During TEE imaging, mild shunt was demonstrated in two patients (1.8%) and moderate shunt was in 45 patients (40.5%). The amount of shunt after saline injection in TEE was severe 64 (57.7%) patients. The baseline demographic and clinical characteristics of patients were summarized in Table 1.

There were atrial septal defects accompanying PFO in 28 (25.2%) patients. The mean ASD size accompanying PFO was 3.17±1.64 mm. Mean tunnel length was 11.47±2.26 mm. A simple PFO tunnel was found to be open spontaneously in 26 (49.4 %) patients. Opening length of PFO (height of PFO) which can induce severe shunting was 4.06±1.6 mm. Lipomatous hypertrophy was detected in five (4.5%) patients and atrial septal aneurysm was existed in 22 (19.8%) patients. PFO tunnel was found to be spontaneously open in 64 patients. The distribution of different morphologies according to new classification is shown in Figure 8.

The total amount of other morphologies which carry high risk features other than Type Ia were higher.

Table 1. Baseline demographic and clinical characteristics of patients

Demographic and clinical characteristics	Patients (n=111)
Age (years)	18-68
Gender (%) Male Female	 36.9% 63.1%
RoPE score	≥7
Severe shunt from PFO tunnel (%)	57.7%
Spontaneous right-to-left shunting from PFO (%)	57.6%
PFO with ASD (%)	25.2%
PFO with ASA (%)	19.8%
Mean tunnel length (mm)	11.47±2.26
Mean ASD size (mm)	3.17±1.64
Mean PFO height (mm)	4.06±1.6

RoPE: The risk of paradoxical embolism, ASD: Atrial septal defect, ASA: Atrial septal aneurysm, PFO: Patent foramen ovale, n: Number

All patients were evaluated with TEE imaging during percutaneous PFO closure. The device types and size of the selected devices were evaluated. We found that the most frequent device diameter selected by the operator was multi-fenestrated septal occluder (cribriform) (9-ASD-MF-025) Amplatzer Multi-Fenestrated Septal Occluder. The second most used device was Amplatzer 9-PFO-025. Other devices which were selected are shown in Figure 9.

The multi-fenestrated septal occluder devices were implanted in 69.4% of patients. All devices were successfully implanted and there were no complications after device implantation.

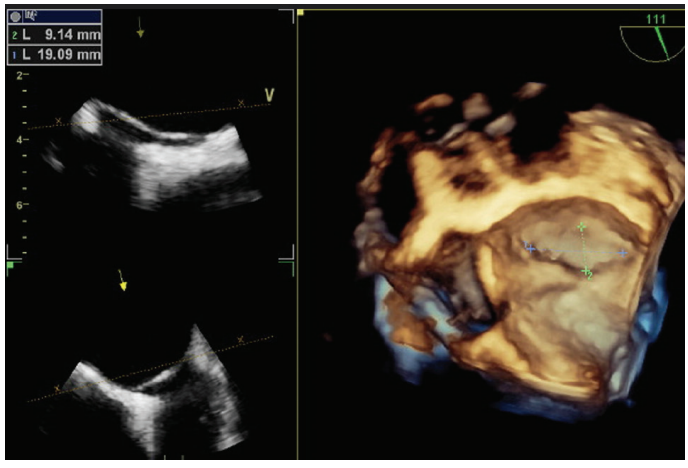

Figure 1. Type Ia

Discussion

In this study we analyzed the structural differences in PFO morphology with TEE and we propose a standardized definition for the additional defects. Although mostly left undetected due to its asymptomatic nature, PFO can potentially lead to paradoxical embolism with either transient or continuous right-to-left shunt. Three randomized clinical trials and meta-analyses of all the available studies showed that in selected patients with cryptogenic stroke, PFO closure is superior to medical therapy for the secondary prevention of stroke[13-15]. Appropriate patient selection should be carried out by a team composed of cardiologists and stroke neurologists. Retrospective analysis from recent studies developed a model for risk estimation which is a Risk of Paradoxical Embolism (RoPE) score. A high RoPE score identify patients with PFO-mediated cryptogenic stroke (CS). However, this score is limited in determining risk of anatomical features. Two categories for anatomical characteristics of PFO were defined as simple and complex including amount of shunt, multiple openings, length and thickness of tunnel. Some anatomical features may prevent appropriate closure, increase the risk of complications and may cause incomplete PFO closure[1,5,13].

PFO should be considered as an anatomical variant. Morphologic feature of PFO had mostly been defined from the heart specimen observations. Any failure in the

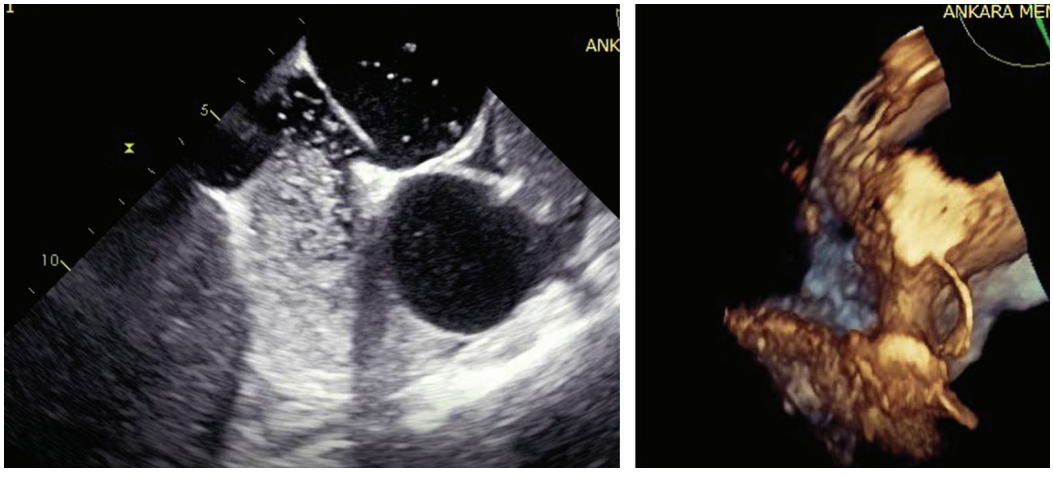

Figure 2. Type Ib

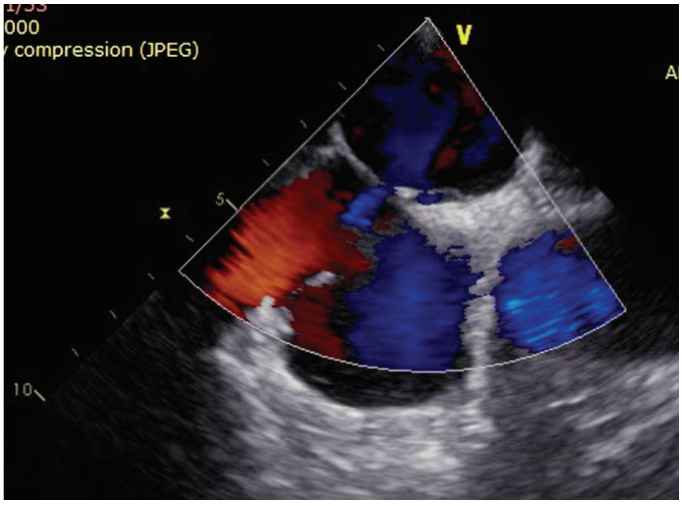

Figure 3. Type IIa. A small ASD next to the tunnel
ASD: Atrial septal defect

dynamic feature of the flap valve competence in addition to the differences in surrounding structures may affect the risk profile of PFO triggering CS[14-17]. Today TTE, TEE, intracardiac echocardiography and TCD provides detailed information about additional structures accompanying PFO. All these modalities can improve image quality with or without administration of a contrast agent. In some of the cases the distinction between ASD and PFO is not simple. Some authors suggested that large left and right atrial openings of the PFO with a short tunnel should be considered as ASD. An additional defect of ASD would cause a left to right shunt[1,18].

The majority of PFOs cannot be detected at rest and contrast bubble study during Valsalva maneuver is

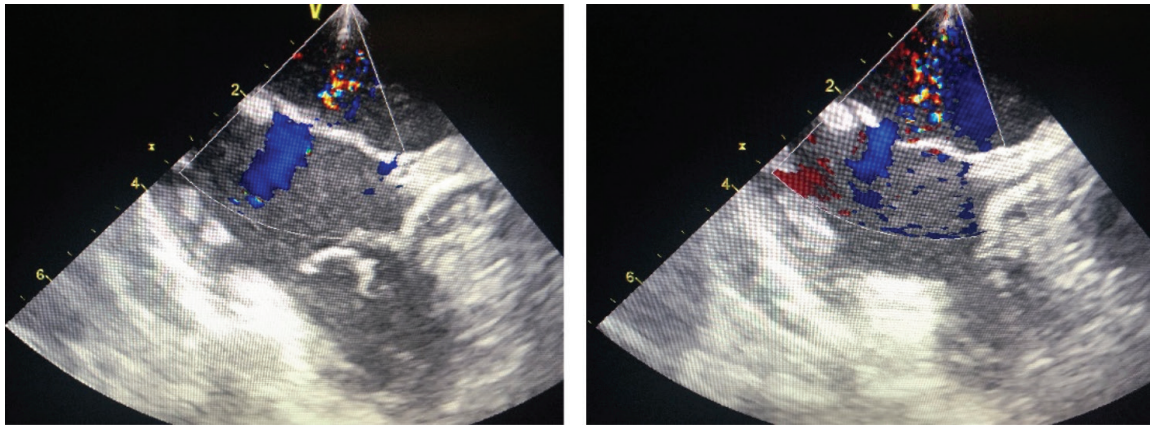

Figure 4a, b. Type IIb (multiple defects with PFO)
PFO: Patent foramen ovale

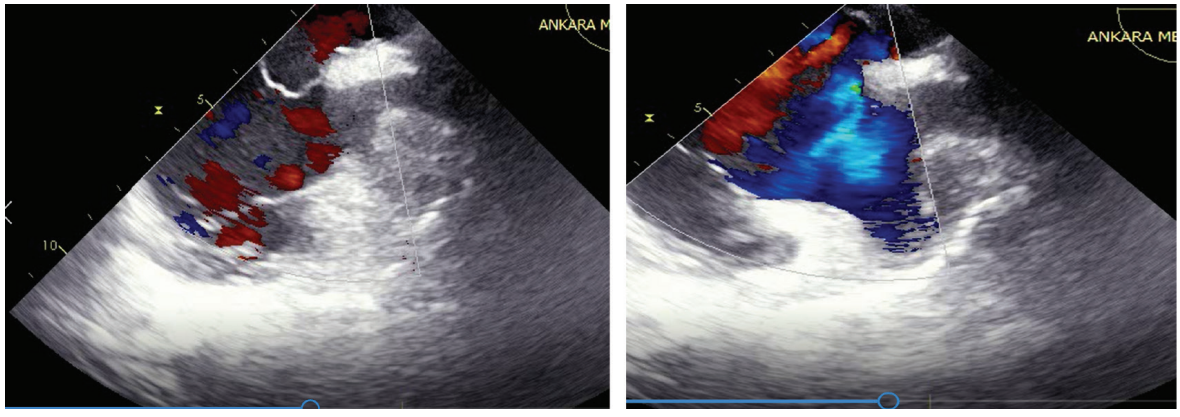

Figure 5. a) Type IIc ASA and PFO tunnel before Valsalva. **b)** ASA and increase in PFO size after Valsalva
ASA: Atrial septal aneurysm, PFO: Patent foramen ovale

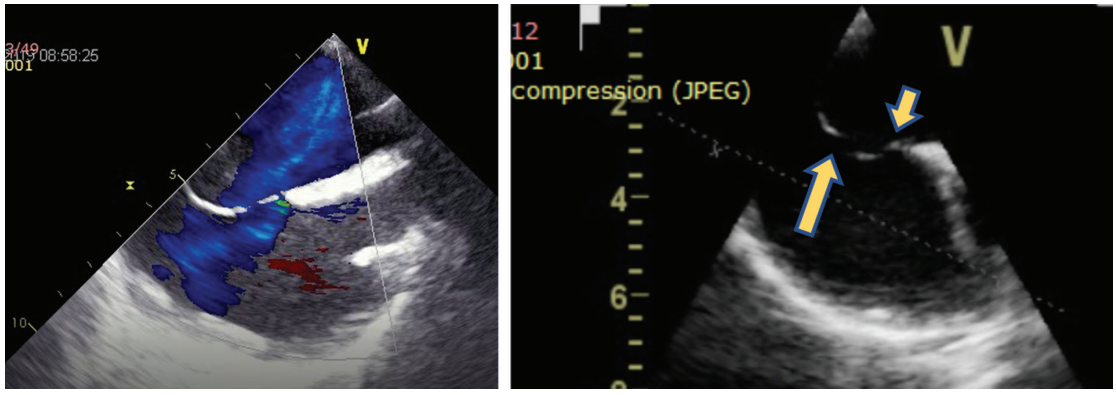

Figure 6. a) Type IId:ASA and ASD. **b)** ASD and PFO with ASA

ASD: Atrial septal defect, PFO: Patent foramen ovale, ASA: Atrial septal aneurysm

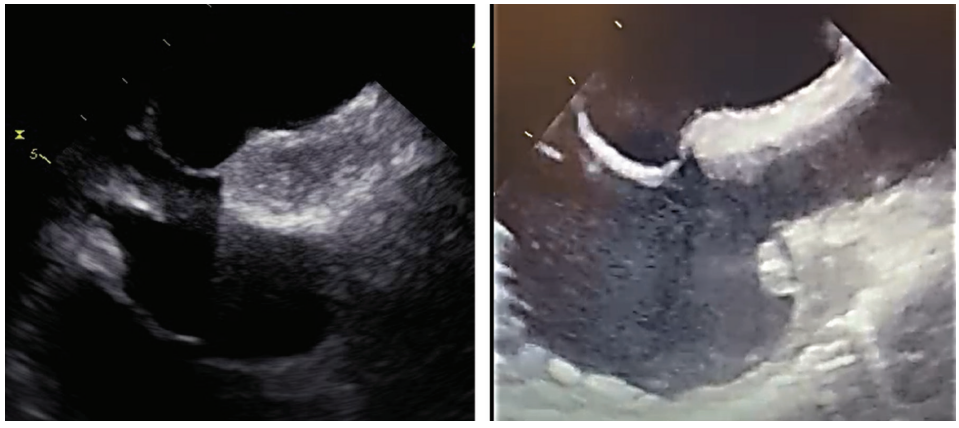

Figure 7. a) Type IIe Lipomatous hypertrophy and PFO. **b)** Type IIe ASA and PFO

PFO: Patent foramen ovale, ASA: Atrial septal aneurysm

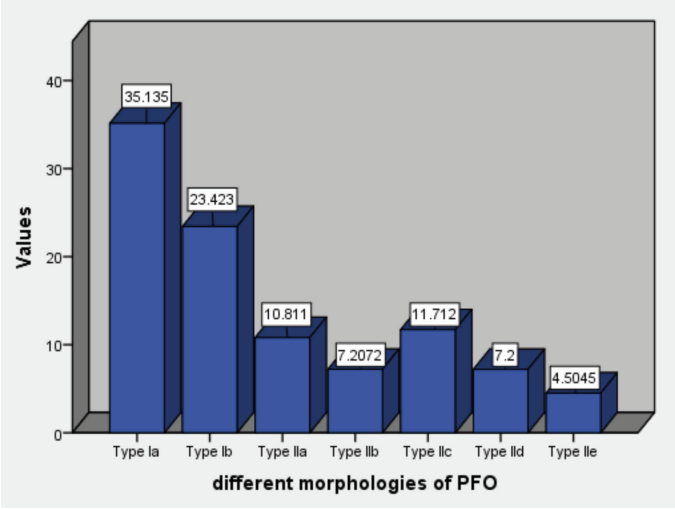

Figure 8. The distribution of different morphologies according to new classification

PFO: Patent foramen ovale

essential[19]. In our study, we performed contrast test with agitated saline bubbles in transthoracic echocardiogram which is a simple technique to suspect PFO. Following TTE, every patient had been taken to TEE and TCD. In our series Type Ia morphology, as a simple tunnel opening with Valsalva was the most common type of PFO. Presence of additional features in morphology that accompanies PFO, increases the risk of paradoxical embolism. In a study, the height of PFO tunnel, thickness of septum secundum and septal excursion distance (septal mobility), ASA was found to be greater in symptomatic patients with cryptogenic stroke or transient ischaemic attack (TIA)[20]. Moreover, the presence of ASA was found to be more important than the degree of shunting with regard to stroke recurrence[21].

A long tunnel PFO, ASA or septal excursion, large right to left shunts at rest and during Valsalva were frequently observed in patients with CS. PFO with two or more accompanying factors should be considered as high risk PFO causing higher probability for CS[19]. In our study, we found that the sum of all different morphologies was greater than simple defects (64.8%). We categorized PFO types into two main groups. ASA accompanying other PFO morphologies like ASD was used to define PFO subtypes. Patients with a long-tunnel morphology (>8-10 mm) have been found to have predisposition to clot formation[1,7,22]. In our study, the mean tunnel length was found to be 11.47±2.26 mm which pointed a high risk in paradoxical embolism. We claim that such morphological definitions made by 3D TEE and 2D TEE would provide us information about exact therapeutic indications for prevention of CS and navigate us through decision in transcatheter PFO closure.

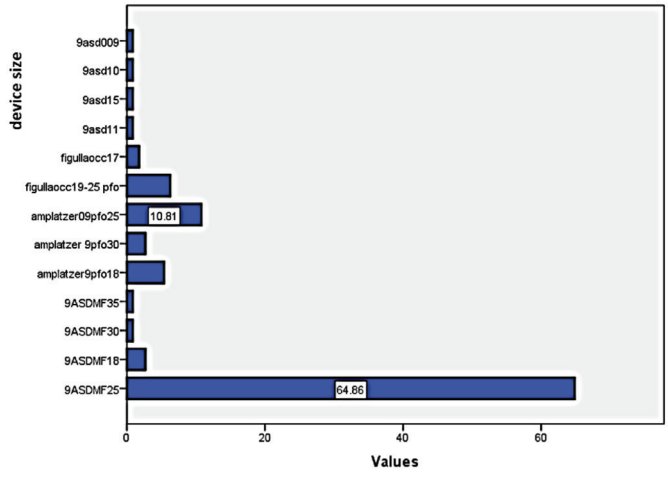

Figure 9. The type of selected devices

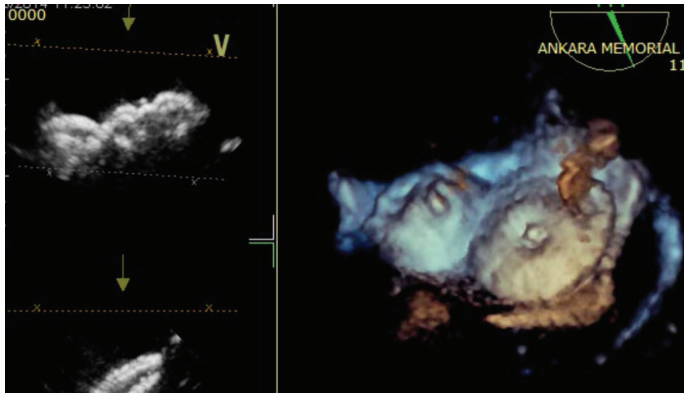

Figure 10. Closure of multiple defects accompanying PFO
PFO: Patent foramen ovale

In our series, the mean length of PFO height (PFO size) was 4.06±1.6 mm. While categorizing Type IId and Type IIe morphologies, we used PFO height (PFO size) parameter. Schuchlenz et al.[23] has found a relation between PFO size and risk for cerebrovascular events. They suggested that a PFO size (maximal separation between septum primum and secundum) greater and equal to 4 mm was associated with ischemic stroke or TIA. When taken into account ASD with PFO as a risk factor, additional defects such as small ASD near PFO tunnel or large ASD apart from PFO tunnel, which we had defined under type II defects, could be an increasing risk mimicking the risk of PFO height.

Recurrence rate of paradoxical cerebral embolism is reported to be between 3.4% and 11%. Percutaneous closure of a PFO with different types of devices are feasible in patients with presumed paradoxical embolism[24,25]. Recently, most PFO closure devices are ASD closure devices modified for PFO anatomy[26]. Selection of a device type should be made according to morphologies accompanying PFO. Sievert et al.[26] defined three distinct morphologies during a course of device closure study in order to place an "in tunnel" PFO closure system. In this categorization type1 consisted of simple tunnel anatomy, type 2 included defects with aneurysmal septum primum that maintains a stable length (a minimum of 4 mm) of tunnel that is not aneurysmal and remains stable overlapping the septum secundum. Type III had an aneurysmal septum primum that has no stable length of tunnel to allow placement of an "in-tunnel" PFO closure system. In our classification, we defined overall morphology when most of the defects included the complex anatomical variances including ASA, ASD, lipomatous hypertrophy and we have showed that multi-fenestrated devices were more successfully implanted in complicated anatomies.

We also prevented device embolization by defining the full morphology especially in the presence of ASA or ASD. Two device strategy sometimes could be applied in the presence of multiple defects accompanying PFO (Figure 10).

Study limitations

Long term follows up of our patients are needed in order to find out if the device selection would affect the prognosis of patients, recurrence of CS or complications after device implantation. In this study, every patient had cryptogenic stroke; we did not have any control group.

Conclusion

Characterization and defining types of PFO provides us using the same language for standardized shared decision making and proper patient selection in PFO closure. Considering highly variable anatomical morphology with respect to size, tunnel length, redundancy of septum, thickness of septum secundum and relationship to neighboring structures, one type of device might not be suitable for optimal treatment of PFOs. We suggest that by defining PFO morphologies and categorizing the different types, we would express the same morphological classification which could be easily and repetitively used. After this classification, the appropriate device type selection could be standardized for optimization of percutaneous transcatheter closure of PFO while minimizing the complications and increasing the procedural success. Further studies are required for decision making in PFO closure and comparison with medical therapies.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from Bursa Yüksek İhtisas University Non-Interventional Clinical Research Ethics Committee on 08.04.2022 with decision number 20220504.

Informed Consent: The authors declare no conflict of interest.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Yetiş Sayın B, Oto A, Concept: Yetiş Sayın B, Oto A, Design: Yetiş Sayın B, Oto A, Data Collection and/or Processing: Yetiş Sayın B, Analysis and/or Interpretation: Yetiş Sayın B, Oto A, Literature Search: Yetiş Sayın B, Oto A, Writing: Yetiş Sayın B, Oto A.

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Diffusion-weighted Imaging Versus Doppler Ultrasound in the Diagnosis of Calf Deep Vein Thrombosis

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Abstract

Objectives: Doppler ultrasound (DUS) is the primary diagnostic tool used in lower extremity deep vein thrombosis (DVT). However, its accuracy may decrease in the calf-located DVT. This study aims to examine the contribution of diffusion-weighted imaging (DWI) to the diagnosis of acute calf DVT (CDVT).

Materials and Methods: Consecutive patients with clinical suspicion of acute onset CDVT, referred to our department between January 1, 2018 and September 1, 2018, were recruited. Patients were initially evaluated with DUS. Same day magnetic resonance imaging (MRI) [axial T1 and T2-weighted, gradient echo, diffusion, and apparent diffusion coefficient (ADC) sequences with 1.5 T MRI] were performed for comparison. The ADC value was measured independently by two radiologists. Second-look DUS was performed as a confirmatory diagnostic method for patients with incompatible MRI and initial DUS findings.

Results: Thirty-four patients were recruited during the study period. Restricted diffusion was defined significantly more often in patients with acute DVT (11/13 vs. 2/21, $p<0.001$). ADC value was 1.08×10^{-3} mm^2/s ±0.575 and 2.7×10^{-3} mm^2/s ±0.639 in patients with and without thrombus ($p<0.001$). Twelve patients had inconsistent results requiring a second look DUS (ultimately 7 false positive, 4 false-negative cases due to initial DUS), and MRI had a false-positive result in 1 patient.

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Abstract

Conclusion: DWI could detect acute DVT with ADC mapping. Diffusion MRI of the lower extremity may contribute to the diagnosis of thrombi isolated to the deep veins of the calf, especially in selected patients with inconclusive or sub-optimal DUS findings.

Keywords: Diffusion-weighted imaging, calf deep vein thrombosis, MRI, apparent diffusion coefficient, Doppler ultrasound

Introduction

Acute deep vein thrombosis (DVT) of the lower extremity is an urgent pathology that can be complicated and has a high mortality and morbidity risk in both the community and in-hospital care and should be treated promptly[1]. Although the clinical significance and management of isolated calf DVT (CDVT) are controversial, the blood clot can extend from crural deep veins to proximal (above the knee) and migrate to the lungs causing pulmonary thromboembolism and hence requires an accurate and timely diagnosis for clinical-decision making. Doppler ultrasound (DUS) is a non-invasive, safe, easily applicable, cost-effective primary diagnostic tool used in DVT diagnosis. However, the diagnostic accuracy of DUS may decrease due to secondary factors such as soft tissue edema, obesity, poor patient cooperation, and inexperienced operator as deep crural veins are often thin or have slow flow[2]. While the sensitivity of DUS diagnosis is lower in distal DVT (71.2%), it is higher in proximal venous thrombosis (96.5%)[3].

The use of magnetic resonance imaging (MRI) for direct thrombus imaging and MR venography has been previously documented[4-9]. Technological advances in fat saturation pulse sequences and surface coils have made DWI applicable to the whole body[10-12]. Most studies evaluating the detectability of acute DVT by diffusion MRI have a limited number of patients or are experimental[13-15]. This study aims to evaluate the capability of echo-planar diffusion MRI in CDVT detection as a second-line imaging method.

Materials and Methods

Patient Characteristics

Consecutive patients with clinically suspected acute onset CDVT, referred to our department between January 1, 2018 and September 1, 2018, were recruited prospectively. Patient data on age, gender, history of surgery in the lower extremity within the last month, and results of imaging studies were gathered.

Acquisition Protocol

Patients referred to the radiology department with a clinical suspicion of acute CDVT, received a standard of care lower extremity DUS, and then were referred for study protocol MRI after informed consent. A second look DUS was performed as a confirmatory diagnostic method by a different senior radiologist blinded to MRI results but had access to the first study and clinical records, including the ongoing inpatient stay.

The non-contrast MRI protocol consisted of T1 and T2 weighted, gradient-echo, diffusion-weighted sequences, and ADC map were applied to the patients with a 12-channel body-phased array coil on a 1.5 Tesla scanner (Magnetom Symphony, Siemens, Germany) in axial and coronal sections, including both lower extremities. MRI parameters are listed in Table 1.

Ethics

This study was approved by Acıbadem University Faculty of Medicine Ethics Committee (decision no: 2018-18/17, date: 22.11.2018).

Image Analysis and Patient Records

The region of interest was drawn on ADC maps corresponding to T1-weighted, T2-weighted, gradient-echo, and diffusion-weighted sequences from the thrombus level and the regular vessel, which was the equivalent of the same vessel in the other extremity, and ADC values were measured independently by two radiologists. Other sequences were evaluated with consensus. In MRI, additional findings (increased vessel diameter, subcutaneous and muscular edema) were evaluated.

Statistical Analysis

The data was analyzed using SPSS 26.0 (IBM Corp, Armonk, NY, USA). Chi-square test and Fisher's exact test were used to evaluate the factors associated with acute DVT and the relationship between the history of surgery and the presence of acute DVT.

Table 1. Magnetic resonance imaging (MRI) parameters

Cor TIRM	TR/TE, 4960/63; TI, 230 ms; slice thickness/gap, 5 mm/1; FOV, 500 mm; matrix, 448x336; Average 1; scan time, 3 min
TSE-T2WI-FS	TR/TE, 4420/109, slice thickness/gap, 7 mm/2.5; FOV, 430 mm; matrix, 320x180; average 3; scan time, 2.5 min
TSE-T1WI	TR/TE, 400/11, slice thickness/gap, 7 mm/2.5; FOV, 430 mm; matrix, 320x180; average 2; scan time, 2 min
T2 FL2D	TR/TE, 500/12.5; slice thickness/gap, 7 mm/2.5; FOV, 380 mm; flip angle 20°, matrix, 320x195; scan time, 1.5 min
Ep 2d-diff	TR/TE, 9300/81; slice thickness/gap, 7 mm/2.5; FOV, 500 mm; flip angle 20°, matrix, 320x195; b-values, 0, 400, and 800 s/mm^2; scan time, 5 min
The total scanning time	14 min

Turbo inversion recovery magnitude (TIRM), inversion time (TI), field of view (FOV), Fat-suppressed turbo spin-echo T2-weighted imaging (TSE-T2WI-FS), Turbo spin-echo T1-weighted imaging (TSE-T1WI), T2 fast low angle shot two-dimensional sequence (T2 FL2D), Two-dimensional echo planar-diffusion (Ep 2d-diff)

Kappa test was used to evaluate the compliance between MRI and DUS in diagnosing acute DVT. The interclass correlation coefficient was used to evaluate the compliance between radiologists.

In evaluating the relationship between the standard or pathological status of the measurement results, the distribution characteristics of the measurement values were determined by the Shapiro-Wilk test; then, the intergroup difference was evaluated with the Mann-Whitney U test.

Results

Thirty-four patients (male: 16, female: 18) were included in the study. The mean age was 46.3±14.1 (20-77). Six patients had a history of lower extremity surgery within the last month.

During the initial scans, 16 and 14 patients had positive findings for CDVT in DUS and MRI, respectively. Of those patients, nine had concurrent positive findings per both modalities (Figures 1-3). The result breakdown of the initial scans is provided in Table 2.

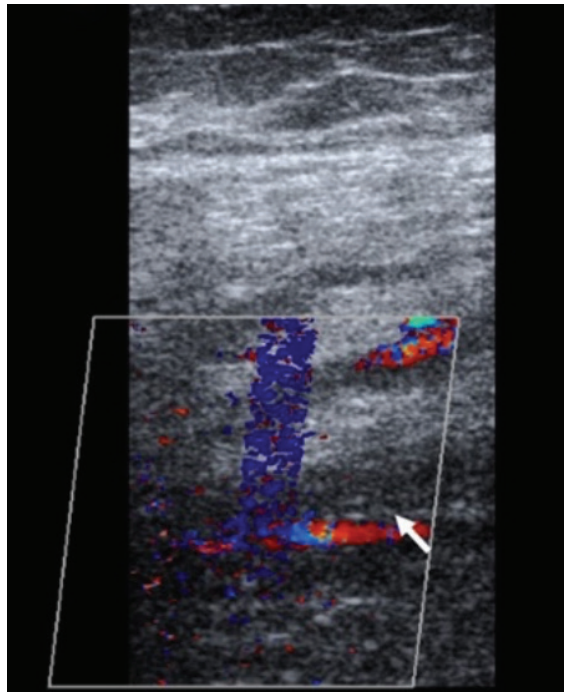

Figure 1. Doppler US of a recently operated 48-year-old female with deep venous thrombosis of the posterior tibial vein
US: Ultrasonography

Twelve out of 34 patients had inconsistent results between DUS and MRI and thus required a second look DUS per the study protocol (Table 3). In seven cases where DUS was compatible with CDVT but had negative findings on MRI, a second look DUS confirmed MRI results. Slow flow (n=3) and partial subacute-chronic thrombus formation (n=4) were detected in the second look DUS, partially explaining the false-positive results of the initial DUS.

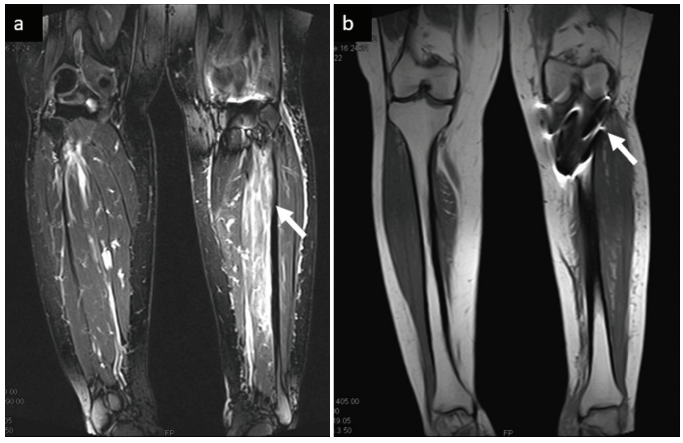

Figure 2. In the same patient, T2-weighted image **(a)** shows hyperintense signals compatible with extensive edema, and T1-weighted image **(b)** reveals surgery material on the left cruris

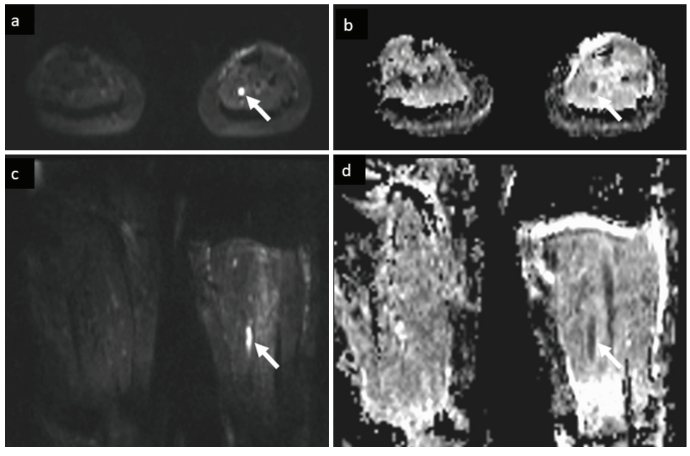

Figure 3. DWI (b=800) with ADC map defines acute thrombosis of posterior tibial vein as restricted diffusion on axial **(a,b)** and coronal **(c,d)** images

DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient

Table 2. The result breakdown of the initial scans

	DUS (+)	DUS (-)	Total
MRI (+)	n=9	n=5	n=14
MRI (-)	n=7	n=13	n=20
Total	n=13	n=18	n=34

DUS: Doppler ultrasound, MRI: Magnetic resonance imaging, n: Number

Five patients had negative DUS results but positive findings in the study MRI protocol. Four of those patients did have evidence of acute CDVT in the second-look DUS. Three of those patients had extensive subcutaneous tissue and muscle edema, partially explaining the missed diagnosis. The remaining one patient did have positive findings in DWI and ADC map, which was evaluated as leveling secondary to slow flow in the vessel lumen in the T2-weighted sequence in MRI.

Ultimately 13 patients were found to have acute CDVT at the completion of the second look DUS. Three out of six patients who had lower extremity surgery within the last month were diagnosed with acute CDVT.

Of 13 patients with acute DVT, affected veins were popliteal vein (n=2), anterior tibial vein (n=2), peroneal vein (n=11), posterior tibial vein (n=13) and gastrocnemius veins (GV) (n=4). Acute DVT was observed in both the medial and lateral GV in two of the cases with acute DVT in the GV and only in the medial GV in two of them.

Restricted diffusion was observed significantly more often in patients with acute DVT (11/13 vs. 2/21, $p<0.001$). Findings of T1-weighted, T2-weighted, and gradient-echo

Table 3. Inconsistent results between DUS and MRI required a second look DUS, including possible reasoning

	Second look DUS (n)	Results of second look DUS
DUS (+) MRI (-)	**7**	**DVT (-) n=7:** n=3; slow flow n=4; partial subacute-chronic thrombus formation
DUS (-) MRI (+)	**5**	**DVT (+) n=4:** n=3 extensive subcutaneous and muscle edema **1 DVT (-)**
Total (n)	**12**	

DUS: Doppler ultrasound, MRI: Magnetic resonance imaging, DVT: Deep vein thrombosis, n: Number

sequences were comparably distributed in DVT and non-DVT groups (Table 4).

Mean ADC values were significantly lower in patients with acute DVT when compared to those without ($1.08x10^{-3}$ mm^2/s ±0.575 vs. $2.7x10^{-3}$ mm^2/s ±0.639, $p<0.001$). All ADC value measurements were 93.6-100% compatible between the two radiologists.

Discussion

DVT is a common condition that can be seen both de novo and as a complication due to various factors (surgery, prolonged immobilization, trauma) and may cause death due to pulmonary embolism or result in post-thrombotic syndrome due to long-term sequelae[16,17]. Whereas clinical significance and management of distal DVT are more controversial compared to proximal DVT, in order to initiate appropriate treatment, the acuity of the thrombus needs to be known[18]. DUS is a practical, non-invasive, safe, easily applicable, and cost-effective primary diagnostic tool with high diagnostic accuracy in lower extremity DVT[19]. However, since it is an examination depending on the radiologist's experience and the patient's physical condition, false negative and positive results may occur[2].

MRI has the potential to be safely used in the diagnosis of acute DVT, even in cases of renal insufficiency or contrast allergy. Although DUS and MR venography are widely used as non-invasive diagnostic methods, DWI can provide information about thrombus age that DUS and MR venography cannot provide[13,20].

We showed that DWI is a useful tool in CDVT diagnosis together with ADC mapping in cases of either inconclusive or sub-optimal DUS findings. As evidenced by smaller case series[13,14] and our prospective study, DWI and ADC mapping findings were significantly different in DVT patients. Those were used as an indicator of the need for a second look DUS, were involved in both rule out and rule in situations.

DUS may be more susceptible to either patient factors (poor cooperation, muscle-soft tissue edema, DVT in

Table 4. MRI findings of patients with and without acute DVT

	Acute DVT (+) (n=13)	Acute DVT (-) (n=21)	p*
T1			**NS**
Isointense	4	5	
Hypointense	0	1	
Hyperintense	9	15	
T2			**NS**
Isointense	0	1	
Hypointense	5	5	
Hyperintense	7	14	
Periphery hyperintense center hypointense	1	0	
Slow flow	0	1	
Gradient-echo			**NS**
Hypointense	2	1	
Hyperintense	1	16	
Periphery hyperintense center hypointense	9	0	
Periphery hypointense center hyperintense	1	2	
Slow flow	0	2	
DWI			**<0.001**
Hypointense	2	19	
Hyperintense	11	2	
ADC			**<0.001**
Hypointense	13	1	
Hyperintense	0	20	
Vascular diameter			**NS**
Normal	4	17	
Increased	9	1	
Decreased	0	3	
Subcutaneous edema			**0.002**
-	1	13	
+	12	8	
Muscle edema			**<0.001**
-	1	16	
+	12	5	

NS: Not significant, DWI: Diffusion-weighted imaging, ADC: Apparent diffusion coefficient, DVT: Deep vein thrombosis, MRI: Magnetic resonance imaging

crural veins, obesity) or operator inexperience[2]. Twenty out of 34 of our study patients had subcutaneous edema, and 17 had muscular edema complicating the conduction of optimal imaging. While subcutaneous and muscle edema was observed in eight and five of those without acute DVT, respectively, were present in 12 patients with acute DVT ($p=0.002$, $p<0.001$). Since factors that may result in a suboptimal study is found more frequently in CDVT patients, diffusion MRI of the lower extremity may contribute to the diagnosis, especially in patients with thickened extremities and edema where the calf deep venous system cannot be optimally evaluated sonographically.

Acute thrombi in the lower extremity deep veins[13-15] were usually shown as hyperintense on DWI as in cerebral vein and portal vein thrombi[14,21,22]. However, tumors and inflammatory lesions, normal structures such as peripheral nerves in the lower extremities, lymphatic system, and bone marrow may show similarly restricted diffusion[10]. Therefore, evaluating DWI in combination with other sequences and clinical and laboratory findings will prevent false-positive cases. Multiparametric MRI (combined T2-weighted sequence and ADC) was also shown to be an effective method for distinguishing venous thrombus and acute and chronic pulmonary thromboembolism in autopsy samples[23]. We used T1-weighted and gradient-echo sequences in addition to DWI, ADC, and T2-weighted sequences to double-check for false positivity. Acute thrombus signal intensity was observed as restricted diffusion in DWI, and factors that could cause other sequences accounted for false positivity. In our study, false positivity secondary to slow flow (leveling in T2-weighted sequence in MRI) was observed in only one patient. However, T1-weighted, T2-weighted, and gradient-echo sequences were comparable among those with and without DVT.

Phinikaridou et al.[20] conducted a mouse model of DVT in the inferior vena cava and reported that *in vivo* magnetization transfer and DWI could be useful in thrombus staging. The study mentioned above showed that ADC values were the highest on the 7th and 14th days of thrombus and were lower in erythrocyte-rich and collagen-rich thrombi. Also, Wu et al.[15] compared acute DVT (≤14 days) and nonacute DVT (>14 days), they found ADC values lower in acute DVT than non-acute DVT. In our study, ADC values were important in discriminating false positivity for acute DVT in the initial DUS also (Table 3).

In the study of Bendick et al.[2], involving 112 patients, compared DUS and MR venography and revealed the necessity of questioning the results of DUS in case of suspicion of a thrombus in the crural deep veins. In their study, they mostly attributed the false-negative results of DUS to the thrombus's location (crural veins), presence of either non-occlusive thrombus or acute thrombus masked by severe chronic thrombus and operator dependency. In our study, four patients were evaluated as false negative in the first DUS. We attributed this to the localization of the thrombus in the crural deep veins and the presence of extensive edema.

ADC measurement results in our study showed superior operator correlation than DUS in the detection of thrombus in the crural deep veins. Non-senior radiologists and resident doctors who are expected to evaluate under emergency conditions can easily differentiate acute DVT in DWI in suspicious cases. Our study revealed that DWI in the lower extremity is more effective than DUS in evaluating proximal crural deep veins.

This study is limited since MRI is sensitive to flow artifacts caused by slow flow and relatively small case size. DWI, which is a rapid, non-contrast, and non-invasive examination in diagnosing acute DVT in selected cases or in hospitals where MRI appointment density is not high, can be used as a second-line imaging method. However, future studies in larger patient groups are needed to support our study results.

Conclusion

DWI can detect acute DVT with ADC mapping. Diffusion MRI may contribute to the diagnosis of CDVT as an alternative or complementary diagnostic tool in specific patient populations with inconclusive results or

high clinical suspicion where optimal visualization and evaluation cannot be achieved in the DUS of calf deep venous system.

Ethics

Ethics Committee Approval: This study was approved by Acıbadem University Faculty of Medicine Ethics Committee (decision no: 2018-18/17, date: 22.11.2018).

Informed Consent: Informed consents were obtained.

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Authorship Contributions

Surgical and/or Medical Practices: Bilgi Z, Concept: Tekin ZN, Türk A, Barutçu Ö, Design: Tekin ZN, Türk A, Barutçu Ö, Data Collection and/or Processing: Tekin ZN, Türk A, Barutçu Ö, Analysis and/or Interpretation: Tekin ZN, Türk A, Bilgi Z, Literature Search: Tekin ZN, Türk A, Bilgi Z, Barutçu Ö, Writing: Tekin ZN, Bilgi Z.

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Research Article

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Comparison of Ischemia-modified Albumin and Exercise Stress Test in Stable Angina Pectoris

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Abstract

Objectives: We aimed to compare ischemia modified albumin (IMA) and exercise stress test to determine myocardial ischemia in stable angina pectoris and investigate the diagnostic value of IMA in non-exercised patients.

Materials and Methods: One hundred and eight patients who applied to the cardiology outpatient clinic with chest pain and were diagnosed with ischemia on myocardial perfusion scintigraphy were included in the study. They were divided into groups with and without coronary artery disease (CAD) according to the results of coronary angiography and with and without ischemia according to the stress electrocardiogram (ECG) results. In addition, IMA levels of the patients were measured, and an exercise stress test was performed.

Results: The IMA was found to be 1.06±0.23 in patients with CAD and 1.12±0.18 in patients without CAD (p=0.08). Statistically, between the groups, IMA determined no significant evidence for ischemia in stable angina pectoris.

Conclusion: No significant difference was found between exercise ECG and IMA in the study of patient groups to determine myocardial ischemia in patients with stable angina pectoris. That is why it has been concluded that the measurement of IMA does not help determine myocardial ischemia in immobile patients and that it cannot be used in place of a stress ECG test.

Keywords: Ischemic modified albumin, exercise stress test, stable angina pectoris

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Introduction

Ischemic heart disease is a term that refers to the inability of enough blood and oxygen to reach the myocardium and the resulting clinical manifestations. Many pathologies that cause an imbalance between myocardial oxygen demand and supply can lead to myocardial ischemia[1]. Ischemic heart disease is the most common cause of death in developed countries. Deaths due to cardiovascular diseases are still approximately twice as high as all cancer deaths and the sum of all non-cardiovascular deaths[2]. Ischemic heart disease may present with different clinical manifestations and present with stable typical or atypical angina in approximately one-third of its cases. Acute clinical manifestations include acute coronary syndromes (unstable angina pectoris, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction) and sudden death with fatal ventricular arrhythmias. Its chronic forms are stable angina pectoris or stable clinical pictures with silent ischemia[3]. In recent years, the determination of changes in serum albumin structure in ischemia conditions has enabled the discovery of a new serum cardiac ischemia marker. The last amino-terminal in the albumin structure is the region where transition metals such as cobalt, copper and nickel are attached[4]. Hypoxia, acidosis, free radical damage and membrane disruption that occurs with ischemia reduce the binding of these transition metals to the N-terminus of albumin[5-7]. This albumin, which has changed its structure, is called "ischemia modified albumin" (IMA). Measurement of IMA level is known as albumin-cobalt binding capacity measurement and includes spectrophotometric measurement of cobalt unbound to albumin. The increase in IMA concentrations is used to evaluate coronary ischemia as a marker of myocardial ischemia[7-9].

The exercise test is a physiological stress test frequently used to reveal cardiovascular abnormalities that do not exist at rest and determine cardiac function adequacy[10]. Exercise electrocardiography is one of the most commonly used non-invasive methods for evaluating patients with suspected or proven cardiovascular disease. In addition to being non-invasive, its significant advantages are that it has few side effects and does not contain radiation.

This study aimed to compare IMA and exercise stress tests in the determination of myocardial ischemia in patients with stable angina pectoris and investigate the diagnostic value of IMA measurement in patients who are immobile or unable to perform the exercise test.

Materials and Methods

In this study, 108 (62 men/46 women) patients who applied to the cardiology outpatient clinic of our hospital with the complaint of chest pain between December 2018 - May 2019 and whose myocardial perfusion scintigraphy were interpreted as ischemia and who indicated coronary angiography were included in this study. The patients were divided into two groups according to the results of coronary angiography. Those with 50% or more stenosis in one or more of the coronary arteries were considered coronary artery disease (CAD) (+), while those with normal coronary artery were considered CAD (-). Detailed physical examinations were performed by questioning the medical histories of the patients. After 12-lead surface electrocardiograms (ECG) were taken, blood samples were taken for IMA, centrifuged and serum separated. Serum samples were stored at -70 °C. Exercise ECG testing was performed on all participants in the study group and was also used as part of the myocardial perfusion scintigraphy (MPS) application protocol. The patients did not do any physical activity before the exercise test. After blood was drawn from the patients, an exercise test was performed according to the Bruce protocol. Patients with a previous diagnosis of severe aortic stenosis, severe valvular pathologies, coronary artery bypass graft surgery history, previous myocardial infarction, heart failure with reduced ejection fraction (HFrEF), heart failure with mid-range ejection fraction (HFmrEF), ventricular tachycardia, chronic renal failure (glomerular filtration rate of <60 mL/min), acute pericarditis or myocarditis, skeletal muscle disease, systemic infection, and known malignancy were excluded from the study.

Venous blood samples were taken after 12 hours of fasting for biochemical analysis. In biochemical analysis, serum lipids, total cholesterol, high-density lipoprotein (HDL), light density lipoprotein (LDL), troponin, blood urea nitrogen (BUN), uric acid, creatinine, sodium, potassium, magnesium, calcium, phosphorus, glucose and serum albumin levels viewed. Hemoglobin, white blood cell and platelet levels were measured in the complete blood count. IMA levels were measured by the colorimetric method. Spekol 1300 brand spectrophotometer was used for the measurements. Materials used cobalt 2 chloride ($CoCl_2$) solution, dithiothreitol (DTT) solution (1.5 g/dL), isotonic NaCl solution (0.9 g/dL). Working procedure 50 mL of 1 g/L cobalt chloride solution was added to 200 mL of patient serum, mixed, and incubated for 10 minutes at room temperature. Then 50 mL of 1.5 g/L DTT solution was added and mixed. It was then incubated for 2 minutes at room temperature. 1 mL of 0.9 g/L NaCl solution was added. Sample blanks were similarly prepared by adding distilled water instead of adding DTT. The absorbances of the test mixtures were read at 470 nm with the Beckman DU 530 Life Science UV/Vis Spectrophotometer. Results are reported in absorbance units (ABSUs).

According to Bruce protocol, an exercise stress test was performed with TEPA TM-PRO 2000 brand device. Routine 12-lead ECGs of all patients were taken before exercise. Heart rate, blood pressure and ECG were recorded at the end of each stage. The formula [maximum heart rate (beats/minute) = 220-age (year)] was used for target heart rate. At the end of the test, the patients were placed in the supine position. Routine hemodynamic parameters were followed for 3-5 minutes in this position. When changes were observed to terminate the test, they were followed closely until they returned to normal. Chest pain on exertion test, decrease in systolic blood pressure of 10 mmHg or more from baseline blood pressure, development of bradycardia or severe arrhythmia, downsloping of the ST segment in two or more consecutive leads or horizontally 1 mm or more 80 ms after the J junction. The presence of excessive collapse or elevation was taken as the criteria for being positive for the test. Upslopping type ST-segment depression without typical chest pain was not accepted positively.

Statistical Analysis

Statistical analyses were performed using the IBM SPSS V23 (IBM Corp, Armonk, NY, USA) statistical analysis program. The data were presented as mean, standard deviation, median, minimum, maximum percentage, and number. The normal distribution of continuous variables was considered using the Shapiro-Wilk W-test where the sample size was <50, and the Kolmogorov-Smirnov test in the case where it was >50. For comparisons between two independent groups, the Independent Samples t-test was used dec the normal distribution condition was met, and the Mann-Whitney U test was used in case it was not met. In comparisons of 2x2 between categorical variables, the Pearson chi-square test was used if the expected value (>5), dec dec-squared yates test was used if the expected value was between (3-5), and the expected value (<3) was used Fisher's Exact test. Multiple groups were evaluated by the Anovis method. The level of statistical significance was taken as $p<0.05$.

Results

The demographic characteristics of the patients are shown in Table 1. There were 62 males and 46 females in the study group, and the mean age was 57±11 years. While 31.5% (34 patients) of the patients had a diagnosis of hypertension, 14.8% (16 patients) had diabetes. Coronary artery disease was detected in 53.7%

Table 1. Demographic characteristics of the study group

	Frequency	%
Gender		
Female	46	42.6
Male	62	57.4
Coronary artery disease	58	53.7
Hypertension	34	31.5
Diabetes mellitus	16	14.8
Effort ECG test (+)	56	51.9

ECG: Electrocardiography

(58 patients) of the patients (more than 50% of these patients had stenosis in their coronary angiographs). In comparison, the coronary arteries were normal in 46.3% (50 patients). Patients were divided into groups according to their current demographic characteristics: those with or without coronary artery disease, patients with suspected ischemia due to exercise ECG, and patients who were not considered. The results of stress electrocardiography and IMA were compared among these patients. Demographic characteristics of the biochemical parameters studied from the blood samples taken from the patients are given in Table 2.

The mean troponin values of the patients were found to be 0.006±0.012 mg/dL and were considered normal. Mean creatinine values were 0.94±0.56 mg/dL. Mean albumin values were 3.99±0.4 mg/dL, and no hypoalbuminemia was observed in the follow-up. In the study, arrhythmia (atrial fibrillation) was observed in the electrocardiography of only two patients; the ECGs of the others were normal sinus rhythm.

Table 2. Biochemical parameters of the study population (n=108)

Parameters	Mean ± SD
IMA (ABSU)	1.09±0.21
Troponine (mg/dL)	0.006±0.012
Creatinine (mg/dL)	0.94±0.56
Albumin (mg/dL)	3.99±0.40
Sodium (mmol/L)	138±3
Potassium (mmol/L)	4.12± 0.41
Magnesium (mg/dL)	1.95±00.28
Calcium (mg/dL)	9.15±0.58
Phosphorus (mg/dL)	3.38±0.75
Uric acid (mg/dL)	5.46±1.95
Blood urea nitrogen (mg/dL)	18.58±8.10
LDL - cholesterol (mg/dL)	135±62
HDL - cholesterol (mg/dL)	44±11
Triglyceride (mg/dL)	192±123
Glucose (mg/dL)	123±66
Hemoglobin (g/dL)	14.33±1.80
White blood cell (mg/dL)	8139±2186
Platelet (10^3/mL)	259±62

IMA: Ischemia modified albumin, LDL: Low-density lipoprotein, HDL: High-density Lipoprotein, ABSU: IMA levels as absorbance unit, SD: Standard deviation, n: Number

No statistically significant difference was found between those with and without coronary artery disease regarding IMA levels. IMA values were found to be 1.06±0.23 in patients with coronary artery disease and 1.12±0.18 in patients without coronary artery disease (p=0.08) (Table 3).

When the patients were divided into groups as those whose exercise ECG result was not considered ischemia (negative) and whose exercise ECG result was thought to be ischemia (positive) and were compared, no difference was observed in terms of gender in these groups. Exercise ECG was positive in 41.1% of hypertensive patients and negative in 21.2% (p=0.02). There was no significant difference between positive and negative rates on exercise ECG in diabetic patients (p=0.48). IMA levels were measured as 1.08±0.25 and 1.10±0.17 in patients with positive and negative exercise ECGs, respectively, and no statistically significant difference was observed between the two groups (p=0.08) (Table 4).

The comparisons between the exercise stress test results and the patients divided into four groups according to whether they were diagnosed with coronary artery disease in their coronary angiograms are shown in Table 5 and Table 6.

Table 3. Comparison of those with and without coronary artery disease on coronary angiography

	CAD (-) (%) (n=50)	CAD (+) (%) (n=58)	p value
Gender			
Male	48 (n=24)	65.5 (n=38)	0.06
Female	52 (n=26)	34.5 (n=20)	0.06
Hypertension	18 (n=9)	43.1 (n=25)	**0.005**
Diabetes mellitus	12 (n=6)	17.2 (n=10)	**0.44**
Effort ECG test (+)	22 (n=11)	77.6 (n=45)	**0.001**
IMA (mean ± SD)	1.12±0.18	1.06±0.23	0.08

Significant p values are shown in bold.
CAD: Coronary artery disease, ECG: Electrocardiography, SD: Standard deviation, n: Number

In the patient groups with positive exercise ECG results (80.4% of 56 patients (n=45)) and 25% (n=13) of 52 patients with negative exercise ECG results, coronary artery disease was diagnosed in these groups. However, IMA was not statistically significant (p=0.51).

Discussion

Early diagnosis and treatment of coronary artery disease is an essential condition in terms of mortality and morbidity. In studies conducted so far, it has been determined that IMA can be used to diagnose acute coronary syndromes, especially in emergency services[11-13]. However, there is no study on the use of IMA in stable CAD. In our study, IMA and exercise testing were compared in patients with and without stable CAD. The significant increase in IMA in acute coronary syndromes aroused the idea that determining the level of IMA may be beneficial in the early diagnosis of stable CAD, and this study was planned.

Table 4. Demographic characteristics of patients with positive and negative exercise ECG

	Effort ECG test (-) (%) (n =52)	Effort ECG test (+) (%) (n=56)	p value
Gender			
Male	46.2 (n=24)	67.9 (n=38)	
Female	53.8 (n=28)	32.1 (n=18)	**0.02**
Hypertension	21.2 (n=11)	41.1 (n=23)	0.48
Diabetes mellitus	15.4 (n=8)	14.3 (n=18)	**0.01**
IMA (mean ± SD)	1.10±0.17	1.08±0.25	0.08

Significant p values are shown in bold.
ECG: Electrocardiography, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Table 5. Comparison of stress ECG and IMA in patients with coronary artery disease

	CAD (+), (%) (n=58)	IMA (mean ± SD)	p value
Effort ECG test (+)	80.4 (n=45)	1.06±0.123	0.51
Effort ECG test (-)	25 (n=13)	1.07±0.170	0.51

ECG: Electrocardiography, CAD: Coronary artery disease, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Table 6. Comparison of stress ECG and IMA with patients without coronary artery disease

	CAD (-), (%) (n=50)	IMA (mean ± SD)	p value
Effort ECG test (+)	19.6 (n=11)	1.16±0.221	0.51
Effort ECG test (-)	75 (n=39)	1.10±0.174	0.51

ECG: Electrocardiography, CAD: Coronary artery disease, IMA: Ischemia modified albumin, SD: Standard deviation, n: Number

Previous studies have shown that increased IMA levels in patients evaluated in the emergency department with chest pain complaints are associated with short-term major cardiac events[14,15]. In our study, patients with stable angina were prioritized, and patients with the acute coronary syndrome were omitted. However, the idea that IMA levels after exertion can be used in the follow-up rather than the diagnosis of stable coronary heart disease was one of the main ideas of our study.

Sinha et al.[16] measured IMA and troponin T in 208 patients who presented to the emergency department with chest pain. They reported that the sensitivity for acute coronary syndrome reached 95% by evaluating IMA values of 85 U/mL and above, positive troponin T and ECG together. In the study of Mutrie et al.[15], a sensitivity of 85% was found when IMA and troponin I were evaluated together in acute coronary syndromes. Serum levels of cardiac troponin rise approximately 2-4 hours after the onset of ischemia[17]. Nevertheless, for IMA, this time is expressed in minutes[18]. Since the patients in our study were patients with stable angina pectoris, troponin values were negative. In the study of Lippi et al.[19] on healthy aerobic athletes, no change was found in troponin levels after excessive exercise. In our study, except for a few patients, the initial ECGs of all patients were average in terms of acute ischemia and arrhythmia. Ischemia occurring during the exercise test can be detected by the appearance of hemodynamic findings such as chest pain, hypotension, bradycardia, and arrhythmia during the test and only electrocardiographically determined. These ECG changes often appear as ST-segment depression or elevation. In our study, ST-segment elevation was not observed in any patients. Sensitivity and specificity of the relationship between effort test positivity and CAD. When all studies performed so far in the American

College of Cardiology (ACC) and the American Heart Association (AHA) guidelines were examined, including a group of 24,074 patients, the sensitivity was 68%, and the specificity was 77%[20]. However, nearly 30% of false-negative results have been reported in the exercise test[21].

Therefore, sometimes even severe CAD cases can have evaluation errors because the effort test is normal. Therefore, we think that determining post-exercise IMA levels and high-risk individuals in the future may play an essential role in the diagnosis, follow-up, and treatment of stable coronary heart disease. However, there are contradictory and opposing views that IMA does not increase only due to cardiac origin after exertion. Some studies show that IMA increases in the blood with ischemia that may occur in peripheral ischemia, especially in the extremity muscles. When Lippi et al.[19] compared IMA levels with professional cyclists and the sedentary control group, they found 100±13 U/mL and 94±6 U/mL, respectively ($p<0.05$)[20]. In Lippi's study, the participants were exercised first at low exercise and then at a high workload, and blood was drawn for IMA after exertion at the end of a 12-24-hour rest period. There was no information about the patients' baseline ECGs in this study, and myocardial ischemia was not included in the exclusion criteria. In our study, patients had myocardial ischemia, which was confirmed by MPS. As a result of the Lippi study, he claimed that the elevation of IMA might be due to irreversible muscle necrosis due to excessive exercise. If the increase in IMA is due to muscle necrosis, it could not be explained why it did not increase in the sedentary group subjected to the same workload. There is no cut-off value for IMA levels due to muscle ischemia in the literature. In our study, on the other hand, no exercise was difficult enough to cause muscle necrosis in patients. In addition, stable CADs without myocardial necrosis were included in the study, and no statistically significant increase was found in post-exercise IMA levels in those without CAD. Roy et al.[22], in a study conducted in a group with 23 consecutive peripheral arterial diseases, reported a significant difference in IMA levels in the treadmill effort test at baseline and peak exercise. In this patient group, myocardial ischemia was investigated by dobutamine stress echocardiography (ECHO) they applied later, and wall motion disorder was not detected in any of the patients. No significant difference was found between serum IMA levels measured at baseline and peak heart rate during dobutamine stress ECHO[22]. However, theoretically, IMA elevation may occur due to oxygen radicals that may occur during peripheral ischemia. However, we think coronary ischemia should be excluded first in future studies.

In a study by Apple et al.[23] on 14 marathon runners, they found a biphasic response to baseline in IMA levels. Initial IMA levels decreased significantly in the measurement immediately after exertion and returned to normal levels in the first hour. Therefore, they argued that the reliability of IMA in the diagnosis of post-exercise myocardial ischemia is low[23]. However, during strenuous exercise, hemoconcentration and excessive lactate production occur during exertion. The excess lactate formed may cause low IMA levels by cross-reacting during the albumin binding test. An exercise stress test cannot be considered a demanding exercise test like marathon running. Excessive proteinuria occurs during strenuous exercise such as a marathon. Therefore, the result in Apple et al.'s[23] study may be due to excessive exercise-induced urinary proteinuria. In our study, serum lactate levels were not evaluated. The number of patients in our study was relatively high compared to Apple et al.'s[23] study. However, no disease group that could cause proteinuria was included in our study.

In conclusion, our study observed that measuring IMA levels in stable coronary artery patients and in immobile patients who could not perform an exercise ECG did not make a statistically significant contribution to the diagnosis of myocardial ischemia. Several previous studies investigated the relationship between IMA and myocardial ischemia in diagnosing asymptomatic coronary heart disease using MPS and pharmacological stress echocardiography methods. However, it is difficult

to say that scintigraphy and stress echocardiography show one hundred percent coronary artery disease. Furthermore, no study has been found in the literature comparing IMA levels with exercise ECG in patients with stable angina. Our study is a first in this regard.

Study Limitations

One of the limitations of our study is that patients whose MPS results were interpreted in favor of ischemia present with average coronary artery results, and the study was affected in this direction because of false-positive results of scintigraphy. Another aspect was that our study group was limited to only stable coronary artery patients. Therefore, our findings cannot be applied to all patients with acute coronary syndrome.

Conclusion

Ischemic heart disease is a severe health problem worldwide, as in our country. Diagnostic tests used today are primarily used to diagnose and determine the extent of ischemia and necrosis area. The high levels of troponin and Creatine kinase-MB, which are among the available biomarkers, are very useful in diagnosing and determining the width of the necrosis area. In patients with acute coronary syndrome without necrosis and stable angina pectoris, these tests are insufficient for diagnosis. They are not sufficient to determine the prevalence of CAD. IMA levels increase in the early stages of ischemia in patients with acute coronary syndrome presenting with NSTEMI/USAP clinic and may indicate ischemia. As a result of our study, it was observed that IMA, whose sensitivity and specificity are significant in the diagnosis of CAD, is not a significant biomarker in predicting myocardial ischemia in patients with stable angina. Compared with the exercise ECG, IMA was not significant in demonstrating myocardial ischemia in patients. It has been determined that IMA is not a significant biochemical marker in demonstrating myocardial ischemia in immobile or unable to exercise patients with stable angina pectoris.

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Ethics

Ethics Committee Approval: Atatürk University Faculty of Medicine approved compliance with the study with the Declaration of Helsinki and the ethical rules of the Medicine Ethics Committee (decision number: 06/27, date: 04.10.2018).

Informed Consent: Signed consent form was received from patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Özmen M, Karakelleoğlu Ş, Design: Özmen M, Karakelleoğlu Ş, Analysis and/or Interpretation: Özmen M, Karakelleoğlu Ş, Ardahanlı İ, Literature Search Özmen M, Karakelleoğlu Ş, Ardahanlı İ, Writing: Özmen M, Ardahanlı İ.

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Research Article

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Effect of Admission Hyperglycemia on Mortality in Diabetic and Non-diabetic Geriatric Patients with Non-ST-segment Elevation Myocardial Infarction

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Abstract

Objectives: High level of admission plasma glucose (APG) in myocardial infarction is associated with an increased risk of death in previous studies; however, most studies that evaluated this relationship were conducted before the guideline-based definition of hyperglycemia. This study was designed to assess the prognostic significance of APG and admission hyperglycemia in patients with and without diabetes mellitus (DM).

Materials and Methods: Five hundred and twenty-seven geriatric patients with non-ST segment elevation myocardial infarction (NSTEMI) were enrolled in the study. Patients were divided into four groups according to APG and DM status: those with DM, those with APG <144 mg/dL were named group 1, and those with APG ≥144 mg/dL were named group 2. Those without DM, those with APG <180 mg/dL were called group 3, and those with APG≥ 180 mg/dL were named group 4.

Results: Hyperglycemia was common in diabetic and nondiabetic patients threatening 29% of the study population. Patients without hyperglycemia (Groups 1 and 3) had the least mortality rates in one-month follow-up. In one-year follow-up, the patients with hyperglycemia (Group 2 and 4) had higher mortality rates (22.6% and 23.3%, respectively) than those with no-hyperglycemia groups. In regression analysis, hyperglycemia was independently associated with one-month and one-year mortality. In receiver operating characteristics curve analysis, the discriminative value of APG for one-month and one-year mortality was good in the groups.

Conclusion: APG may be used to predict one-month and one-year death irrespective of DM status. Therefore, DM and admission hyperglycemia could not be considered and treated as similar situations.

Keywords: Diabetes mellitus, acute myocardial infarction, non-ST-segment myocardial infarction, hyperglycemia, mortality

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Introduction

Patients with Diabetes Mellitus (DM) have a higher risk of coronary artery disease and acute myocardial infarction (AMI) than the nondiabetic population. These patients more commonly encounter cardiovascular mortality[1]. Increased admission plasma glucose (APG) can be seen in the acute phase of AMI, ranging from 3% to 71% in patients without DM[2]. High plasma glucose levels might result from circulating stress hormones and pancreatic β-cell insufficiency that becomes apparent after a stressful event. Therefore, high APG levels might represent underlying metabolic derangement in most patients with AMI and be considered detrimental to jeopardized myocardium[3].

Several studies investigated the effect of APG on mortality and morbidity in patients with ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). They demonstrated that high glucose levels increased the risk of mortality, stent thrombosis, recurrent AMI, and some studies showed inconsistent results on long-term mortality[1,4-6]. However, most of these studies were conducted before the percutaneous coronary intervention (PCI) era, and those patients were more commonly treated with thrombolytic therapy[1,3,4,7-10]. The primary treatment strategy in patients with AMI is PCI in the current era. There is a lack of evidence to establish the association between APG levels and outcomes in diabetic and nondiabetic patients with AMI undergone PCI.

In previous studies, various plasma glucose levels were defined as a cut-off value. However, according to a meta-analysis by Capes et al.[9] and American Diabetes Association (ADA) guideline, a plasma glucose level above 144 mg/dL in nondiabetic patients and a level above 180 mg/dL in diabetic patients were defined as hyperglycemia. These cut-off levels were not widely implemented in the previous studies[9,11-13].

The current study examined the utility of guideline-based hyperglycemia levels and the effect of APG levels on one-month and one-year mortality in patients with NSTEMI with and without DM. In the present study, the patients were categorized according to DM and hyperglycemia status, and the outcomes were compared between the groups and subgroups.

Materials and Methods

Study Population and Definitions

This retrospective study evaluated 568 consecutive geriatric patients with confirmed NSTEMI who were admitted to the emergency department of a tertiary hospital. The study duration was 18 months, from April 2017 to October 2018. NSTEMI was defined according to the European Society of Cardiology Guideline[14]. Patients were excluded with had followings: treated with thrombolytic therapy, no performed coronary angiography during the hospitalization, and no recorded glucose level in admission to the emergency department. Thirty-seven patients were excluded from the study based on the exclusion criteria, and four patients were not included in the study due to data loss after hospitalization. Therefore 527 patients with NSTEMI were enrolled in the study. A study flow chart was demonstrated in Figure 1. The primary endpoints were the one-month and one-year incidence of all-cause mortality.

Sociodemographic characteristics of the patients and necessary clinical information were obtained at the time of admission to the emergency department. Transthoracic echocardiography (TTE) evaluations of the patients were performed using the Vivid 7 system (GE Vingmed Ultrasound AS, Horten, Norway). The patients' left ventricular ejection fraction (LVEF) was calculated by the Simpson method[15]. The study obtained local ethics committee approval, and the Helsinki Declaration principles were followed at all stages.

Diabetes Mellitus was defined as having a history of DM or following a DM-specific diet or using oral glucose-lowering medication and/or insulin, or HbA1c ≥6.5%. Hyperglycemia at admission was defined as blood glucose above 140 mg/dL upon patient admission to the hospital[11,12]. According to previous studies and a meta-

analysis by Capes et al.,[9] the prognostic cut-off is 144 mg/dL for patients without DM and 180 mg/dL for those with DM[3,9,16,17]. Patients were divided into four groups according to APG and DM status: those with DM, those with APG <144 mg/dL were named group 1, and those with APG ≥144 mg/dL were named group 2. Those without DM, those with APG <180 mg/dL were called group 3, and those with APG ≥180 mg/dL were named group 4.

Coronary Angiography, SYNTAX, Gensini and Grace Scores

The patients underwent coronary angiography (CAG) by either the femoral or radial approach using the standard Seldinger's technique. The synergy between percutaneous coronary intervention with Taxus and cardiac surgery (SYNTAX) score is a scoring system that emerged by scoring the lesions with 50% or more stenosis in vessels with a diameter of 1.5 mm and above in the images obtained by conventional CAG. Its relationship with mortality has been demonstrated (http://www.syntaxscore.com). Another scoring system used in the anatomical classification of coronary artery disease is Gensini scoring. Scoring is based on the extent of the lesion and the coronary artery in which it is located, and non-critical stenosis is also included in the scoring[18].

Global Registry of Acute Coronary Events (GRACE) scoring is a mortality predictive scoring system that uses clinical parameters such as age, heart rate, systolic blood

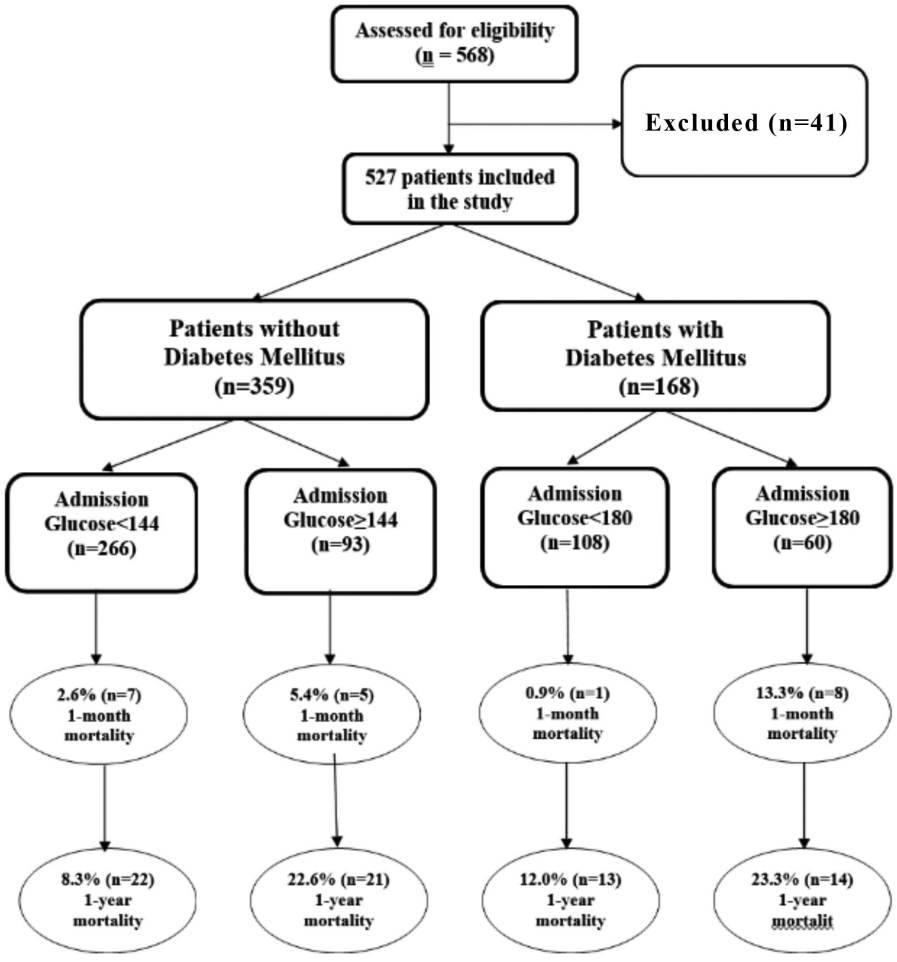

Figure 1. Flow chart of the study

pressure, baseline creatine level, history of congestive heart failure, in-hospital percutaneous coronary intervention, history of AMI, cardiac enzyme levels, ST-segment depression on admission electrocardiography (ECG)[19]. This study used single serum levels of cardiac troponin I (cTnI) 0.1 ng/mL as the elevated cardiac enzyme. ST-segment depression was defined as decreased ST segment 0.5 mV below the isoelectric line in any ECG lead.

Statistical Analysis

Analyses of the study were performed using SPSS version 22.0 (IBM SPSS, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation and categorical variables as numbers and percentages. After evaluating the parametric assumptions, the intergroup comparison of continuous variables was compared using a one-way analysis of variance. The statistical difference between the groups was assessed with the Tukey post-hoc test. Pearson's chi-square was used to compare categorical variables. Survival analyzes of the four groups were evaluated using the Kaplan-Meier survival method. The log-rank test was used to analyze the differences between groups. Multivariate analyzes were evaluated with the Cox proportional regression model. The hazard ratio (HR) was used for the groups' relative risk of death. In multivariate models, confounders in multivariate analysis were considered predictors of 1-month and 1-year mortality. P value <0.05 was considered statistically significant.

Results

Patients' baseline characteristics are listed in Table 1. The groups were similar in terms of age, current smoking, prior stroke, and anticoagulant therapy. There was a higher rate of female subjects, chronic kidney disease, hypertension, atrial fibrillation, previous peripheral arterial disease, coronary artery disease, renin-angiotensin system blockers, and P2Y12 inhibitors used in the DM group (Groups 3 and 4) compared to the non-DM group (Groups 1 and 2). Patients with DM and hyperglycemia (Group 4) had a significantly higher rate of chronic lung disease, hypertension, and using aspirin than the other three groups. The number of patients using calcium channel blockers was higher in both DM and non-DM groups without hyperglycemia (Groups 1 and 3).

Patients' clinical characteristics, treatment strategy, discharge medication, and outcomes were summarized in Table 2. The groups were similar in terms of ST-segment deviation, revascularization, admission heart rate, GRACE score, and hospitalization duration. The patients with DM and hyperglycemia (Group 4) had higher admission systolic blood pressure, SYNTAX I, SYNTAX II and Gensini scores, HbA1C and APG levels compared to the other groups. Additionally, Group 4 had lower LVEF, hemoglobin and estimated glomerular filtration rate (eGFR) levels compared to other groups. Whereas the patients with hyperglycemia (Group 2 and 4) were more commonly treated with conservative strategy, the patients with non-DM and hyperglycemia (Group 1) more commonly underwent PCI, and were less commonly treated with conservative strategy and coronary artery bypass grafting (CABG). According to discharge medication, P2Y12 inhibitor use was more common in groups 1 and 3 due to the revascularization strategy. Anticoagulant therapy was more commonly used in DM because the existence of DM would increase the CHA2DS2-VASc score. Statins were less commonly used in patients with DM and hyperglycemia (Group 4), probably due to side effects.

Group 4 had a higher mortality rate (13.3%) in one-month follow-up, whereas Group 3 had a lower mortality rate (0.9%) compared to the other two groups. Patients without hyperglycemia at admission (Groups 1 and 3) had the least mortality rate. In one-year follow-up, the patients with hyperglycemia (Groups 2 and 4) had higher mortality rates (22.6% and 23.3%, respectively) compared to the patients who had no hyperglycemia. Overall survivals for Groups 1, 2, 3 and 4 were 89.0%, 72.0%, 87.0% and 63.3% respectively. Therefore, during the one-year follow-up, Group 4 had lower overall survival than the other three groups, and Group 2 had lower overall survival compared to Groups 1 and 2. Kaplan-Meier overall cumulative risk

of groups regarding mortality was demonstrated in Figure 2, and the log-rank test p value was <0.001. According to receiver operating characteristics (ROC) curve analysis, the admission glucose level of 157 mg/dL was identified as an effective cut-off point for one-month mortality [area under the curve (AUC): 0.86; 95% confidence interval (CI): 0.68-0.85, p<0.001], and it had a sensitivity of 76% and specificity of 71%. The discriminative value of admission glucose for one-month mortality was also good in DM and non-DM groups (AUC was 0.74 for patients with DM and 0.76 for patients with non-DM) (Figure 3). Additionally, the admission glucose level of 138 mg/dL was identified as an effective cut-off point for one-year mortality (AUC: 0.67; 95% CI: 0.60-0.74, p<0.001), and it had a sensitivity of 72% and specificity of 62%. The discriminative value of APG for one-month mortality was also good in DM and non-DM groups (AUC was 0.60 for patients with DM and 0.67 for patients with non-DM) (Figure 4).

Table 3 presents the study population's one-month and one-year univariate and multivariable Cox regression analyses. Univariate predictors of one-month mortality were GFR <60 mL/min/1.73 m^2, LVEF <50% and hyperglycemia. By multivariate regression analysis, the two independent factors that increased the risk of one-month mortality were GFR <60 mL/min/1.73 m^2 (HR:

Table 1. Baseline characteristics of groups according to diabetes mellitus and hyperglycemia status

Variables	No diabetes mellitus		Diabetes mellitus		p value
	Group 1 Glucose <144 mg/dL (n=266)	Group 2 Glucose ≥144 mg/dL (n=93)	Group 3 Glucose <180 mg/dL (n=108)	Group 4 Glucose ≥180 mg/dL (n=60)	
Age, year	76.44±6.60	76.37±7.06	75.45±6.10	77.01±6.92	0.458
Female gender	100 (37.6%)$^{£β}$	43 (46.2%)$^{£β}$	71 (65.7%)$^{*#}$	40 (66.7%)$^{*#}$	<0.001
Current smoking	44 (16.5%)	7 (7.5%)	13 (12.0%)	5 (8.3%)	0.085
Chronic lung disease	22 (8.3%)^{β}	13 (14.0%)^{β}	10 (9.3%)β	17 (28.3%)$^{*#£}$	<0.001
Chronic kidney disease	165 (62.0%)$^{£}$	58 (62.4%)$^{£}$	92 (85.2%)$^{*#β}$	41 (68.3%)$^{£}$	<0.001
Hypertension	174 (65.4%)$^{£β}$	60 (64.5%)$^{£β}$	90 (83.3%)$^{*#}$	53 (88.3%)$^{*#}$	<0.001
Atrial fibrillation	40 (15.0%)$^{£β}$	18 (19.4%)$^{£}$	37 (37.3%)$^{*#}$	16 (26.7%)*	<0.001
Prior PAD	14 (5.3%)$^{£β}$	4 (4.3%)$^{£β}$	0 (0%)$^{*#β}$	8 (13.3%)$^{*#£}$	0.002
Prior CAD	121 (45.5%)$^{#}$	20 (21.5%)$^{*£β}$	50 (46.3%)$^{#}$	35 (58.3%)$^{#}$	<0.001
Prior PCI	56 (21.1%)$^{#}$	8 (8.6%)$^{*£}$	30 (27.8%)$^{#}$	10 (16.7%)	0.006
Prior stroke	13 (4.9%)	0 (0%)	5 (4.6%)	4 (6.7%)	0.146
Admission medications					
Aspirin	128 (48.1%)	34 (36.6%)^{β}	46 (42.6%)^{β}	37 (61.7%)$^{#£}$	0.017
P2Y12 inhibitors	66 (24.8%)$^{#β}$	9 (9.7%)$^{*£β}$	28 (25.9%)$^{#}$	23 (38.3%)$^{*#}$	<0.001
Warfarin	21 (7.9%)	16 (17.2%)	9 (8.3%)	8 (13.3%)	0.056
NOAC	20 (7.5%)	4 (4.3%)	8 (7.4%)	4 (6.7%)	0.755
RAS blockers	127 (47.7%)$^{£β}$	37 (39.8%)$^{£β}$	69 (63.5%)$^{*#}$	38 (63.3%)$^{*#}$	<0.001
Beta blockers	149 (56.0%)	38 (40.9%)	61 (56.5%)	32 (53.3%)	0.072
CCB	95 (35.7%)^{β}	24 (25.8%)$^{£β}$	44 (40.7%)$^{#}$	11 (18.3%)$^{*£}$	0.008

The p value indicates the statistical difference between the 4 groups.
*p<0.05, vs. group 1
$^{#}$p<0.05, vs. group 2
$^{£}$p<0.05, vs. group 3
^{β}p<0.05, vs. group 4
CAD: Coronary artery disease, CCB: Calcium channel blockers, NOAC: Novel anticoagulation drugs, PAD: Peripheral arterial disease, PCI: Percutaneous coronary intervention, RAS: Renin-angiotensin system, n: Number

Table 2. Clinical characteristics of groups according to Diabetes Mellitus and hyperglycemia status

Variables	No diabetes mellitus		Diabetes mellitus		p value
	Group 1 Glucose <144 mg/dL (n=266)	Group 2 Glucose ≥144 mg/dL (n=93)	Group 3 Glucose <180 mg/dL (n=108)	Group 4 Glucose ≥180 mg/dL (n=60)	
ST segment deviation	74 (27.8%)	26 (28.0%)	39 (36.1%)	23 (38.3%)	0.213
Revascularization	188 (70.7%)	56 (60.2%)	74 (68.5%)	38 (63.3%)	0.261
Hear rate (beat/min)	82.29±20.14	84.78±15.85	83.25±18.74	87.56±19.17	0.427
Systolic blood pressure (mmHg)	132.22±22.66$^{\beta}$	131.29±20.23$^{\beta}$	129.87±14.32$^{\beta}$	139.56±19.19$^{*\#£}$	0.026
Diastolic blood pressure (mmHg)	77.71±12.04	76.34±10.40	75.00±13.96	79.30±9.38	0.097
LVEF (%)	51.86±9.65$^{\beta}$	49.24±9.46	50.87±8.65$^{\beta}$	45.88±9.02$^{*£}$	<0.001
SYNTAX Score	10.66±9.22$^{\beta}$	10.62±9.98$^{\beta}$	10.26±9.17$^{\beta}$	16.72±13.43$^{*\#£}$	0.001
SYNTAX II-1 Score	37.63±9.08$^{\beta}$	40.04±9.84$^{\beta}$	40.29±8.81$^{\beta}$	47.30±13.90$^{*\#£}$	<0.001
SYNTAX II-2 Score	36.56±9.19$^{£\beta}$	36.78±8.47$^{£\beta}$	32.83±6.35$^{*\#\beta}$	41.93±10.53$^{*\#£}$	<0.001
Grace Score	136.83±21.25	141.78±29.52	134.43±18.18	142.00±24.20	0.088
Gensini Score	29.02±20.18$^{\beta}$	25.11±22.60$^{\beta}$	30.45±20.68$^{\beta}$	41.59±31.24$^{*\#£}$	0.002
HbA1C	5.98±0.93$^{\beta}$	5.90±0.41$^{\beta}$	5.95±0.67$^{\beta}$	8.18±2.62$^{*\#£}$	<0.001
Glucose	105.05±18.05$^{\#£\beta}$	189.56±58.66$^{*£\beta}$	125.37±32.73$^{*\#\beta}$	244.36±43.58$^{*\#£}$	<0.001
Hemoglobin (mg/dL)	13.11±1.95$^{£\beta}$	13.12±1.74$^{£\beta}$	12.06±1.96$^{*\#}$	11.96±1.78$^{*\#}$	<0.001
eGFR (mL/min/1.73 m^2)	56.71±18.37$^{\beta}$	53.45±19.36	51.82±15.86	48.27±21.52*	0.005
Treatment strategy					
Conservative	78 (29.3%)	37 (39.8%)	34 (31.5%)	22 (36.7%)	0.020
PCI	171 (64.3%)	43 (46.2%)	58 (53.7%)	31 (51.7%)	
CABG	17 (6.4%)	13 (14.0%)	16 (14.8%)	7 (11.6%)	
Hospitalization days	6.44±6.77	7.75±6.95	6.01±4.25	6.68±4.97	0.227
Discharge medications					
Aspirin	235 (88.3%)$^{\#}$	69 (74.2%)*	90 (83.3%)	48 (80.0%)	0.011
P2Y12 inhibitors	222 (83.5%)$^{\#}$	61 (65.6%)$^{*£}$	90 (83.3%)$^{\#}$	46 (76.7%)	0.002
Warfarin	21 (7.9%)$^{\#\beta}$	16 (17.2%)*	13 (12.0%)	10 (16.7%)*	0.045
NOAC	16 (6.0%)$^{£\beta}$	8 (8.6%)$^{£}$	24 (22.2%)$^{*\#}$	8 (13.3%)*	<0.001
RAS blockers	117 (66.5%)	55 (59.1%)$^{£\beta}$	80 (74.1%)$^{\#}$	47 (78.3%)$^{\#}$	0.038
Beta-Blockers	241 (90.6%)	79 (84.9%)	97 (89.8%)	50 (83.3%)	0.251
Statins	190 (71.4%)$^{\beta}$	64 (68.8%)$^{\beta}$	76 (70.4%)$^{\beta}$	22 (36.7%)$^{*\#£}$	<0.001
Follow-up time (months)	11.8±2.2$^{\beta}$	10.7±3.4	11.3 ± 2.5$^{\beta}$	10.9 ± 4.4$^{*£}$	<0.001
One-month mortality	7 (2.6%)$^{\beta}$	5 (5.4%)$^{£}$	1 (0.9%)$^{\#\beta}$	8 (13.3%)$^{*£}$	<0.001
One-year mortality	22 (8.3%)$^{\#\beta}$	21 (22.6%)$^{*£}$	13 (12.0%)$^{\#\beta}$	14 (23.3%)$^{*£}$	<0.001

Abbreviations: CABG: Coronary artery bypass grafting, eGFR: Estimated glomerular filtration rate, LVEF: Left ventricular ejection fraction, NOAC: Novel anticoagulation drugs, PCI: Percutaneous coronary intervention, RAS: Renin-angiotensin system.
p value indicates the statistical difference between the 4 groups.
$^{*}P < 0.05$, vs. Group 1
$^{\#}P < 0.05$, vs. Group 2
$^{£}P < 0.05$, vs. Group 3
$^{\beta}P < 0.05$, vs. Group 4

9.66, 95% CI: 1.28-72.4) and hyperglycemia (HR: 4.16, 95% CI: 1.71-10.09). Univariate predictors of one-year mortality were female gender, the age between 65-74 years, ST-segment deviation, eGFR <60 mL/min/1.73 m^2, LVEF <50%, hyperglycemia and SYNTAX score. By multivariate regression analysis, the four independent factors that increased the risk of one-year mortality were the age between 65-74 years (HR: 5.77, 95% CI: 2.49-13.35), ST-segment deviation (HR: 2.65, 95% CI: 1.51- 4.65), LVEF<50% (HR: 5.77, 95% CI: 2.49-13.35) and hyperglycemia (HR: 1.87, 95% CI: 1.10-3.19). DM was associated neither with one-month nor one-year mortality.

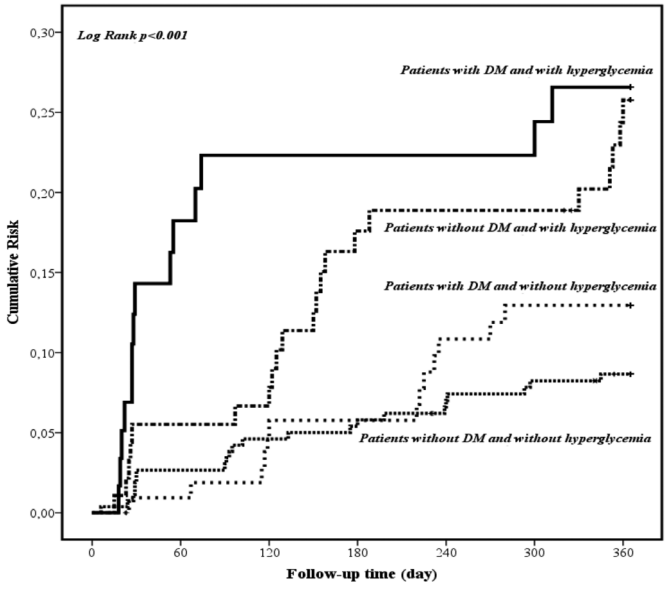

Figure 2. Kaplan-Meier overall cumulative risk of groups regarding mortality

DM: Diabetes mellitus

Discussion

Two significant results were obtained in this study, in which we evaluated the short-term and long-term effects of APG levels in NSTEMI patients. First, hyperglycemia was common in diabetic and nondiabetic patients, threatening approximately 29% of all NSTEMI patients. Second, hyperglycemia was independently associated with short and long-term overall death in both diabetic and nondiabetic patients. The present study demonstrated that patients who were not diagnosed with DM at the time of AMI admission but whose APG levels were in the diabetic range had a similar mortality trend in patients with a previous diagnosis of diabetes. Additionally, the diabetic-hyperglycemic group (Group 4) was more commonly associated with some

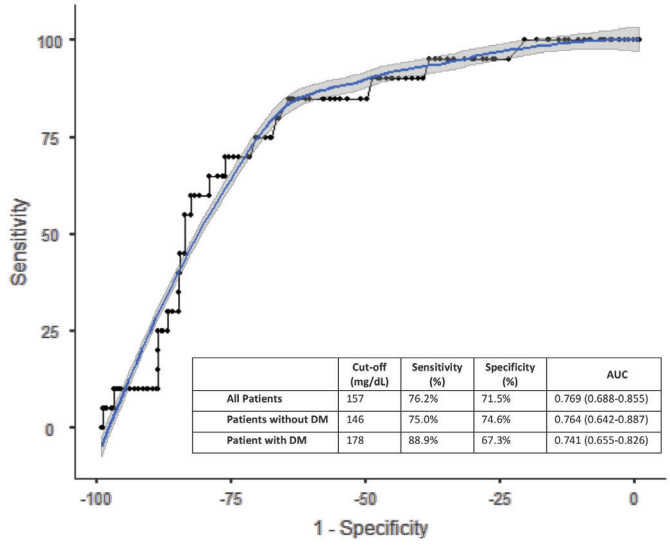

Figure 3. ROC curve of APG one-month mortality

ROC: Receiver operating characteristics, APG: Admission plasma glucose, AUC: Area under the curve, DM: Diabetes mellitus

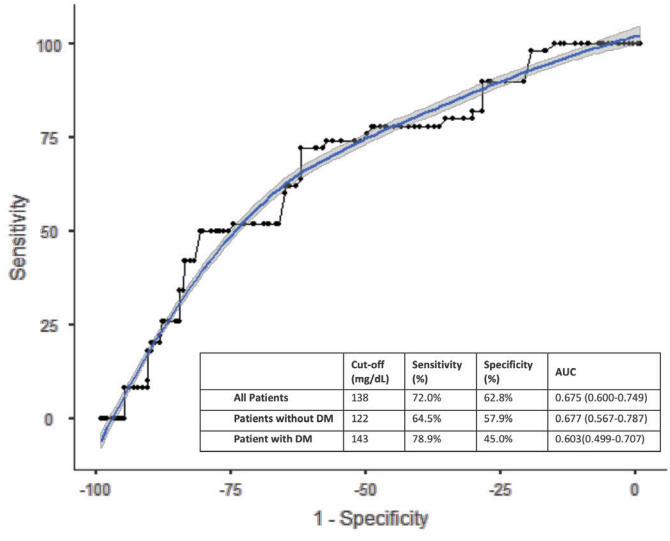

Figure 4. ROC curve of APG mortality from one month to one year

ROC: Receiver operating characteristics, APG: Admission plasma glucose, AUC: Area under the curve, DM: Diabetes mellitus

unfavorable clinical and angiographic characteristics such as lower LVEF, lower eGFR and higher SYNTAX and Gensini scores.

This study not only confirms the association between APG level and mortality after NSTEMI, but also expresses the importance of this variable as a predictor of long-term mortality in diabetic and nondiabetic patients. We showed that patients without a diagnosis of DM but with APG levels in the diabetic range have a similarly high risk of death as patients with DM.

There are some possible underlying mechanisms of the high APG levels in patients with AMI, such as growth hormone and activation of stress hormones (noradrenaline, glucagon, cortisol)[7,9,20]. During ischemia, glucose level increases as a compensatory mechanism to protect myocardial contraction and prevent myocyte necrosis[21]. The other possible mechanism in STEMI patients is that high glucose levels facilitate platelet adhesion and aggregation by accelerating inflammatory processes and directly activating the glycation of coagulation factors[22-24]. Thus, a vicious cycle occurs between myocardial ischemia and glucose.

According to literature and previous studies, some authors demonstrated an association between microvascular coronary obstruction and high APG levels[16,17,25-27]. Straumann et al.[25] examined the predictive value of APG in patients who underwent primary PCI, and they classified the patients according to plasma glucose levels at admission: <7.8 mmol/L, 7.8 to 11 mmol, and >11.0 mmol/L. However, their categorization strategy was not based on a guideline, and they did not stratify the patients according to their diabetes diagnosis[25]. Kosiborod et al.[16] evaluated a national sample of elderly patients with AMI, and in

Table 3. Predictors of One-month and One-year mortality: Cox regression analysis

Predictors	Univariable		Multivariable	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
One-Month Mortality				
Gender (female)	0.453 (0.183-1.123)	0.087		
Age (65-74 years)	0.974 (0.410-2.311)	0.952		
ST-segment deviation	2.075 (0.881-4.887)	0.095		
Diabetes mellitus	1.633 (0.688-3.875)	0.266		
eGFR<60 (mL/min/1.73 m²)	9.886 (1.327-73.660)	0.025	9.662 (1.288-72.492)	0.027
LVEF <50%	3.022 (1.172-7.789)	0.022	2.232 (0.858-5.803)	0.100
Hyperglycemia	4.130 (1.712-9.966)	0.002	4.164 (1.717-10.099)	0.002
SYNTAX score	1.034 (0.989-1.082)	0.142		
One-year mortality				
Gender (female)	0.372 (0.223-0.620)	<0.001	0.850 (0.479-1.508)	0.578
Age (65-74 years)	2.849 (1.609-5.043)	<0.001	5.776 (2.499-13.350)	<0.001
ST-segment deviation	2.146 (1.342-3.431)	<0.001	2.654 (1.515-4.650)	0.001
Diabetes mellitus	1.382 (0.854-2.236)	0.188		
eGFR<60 (mL/min/1.73 m²)	2.524 (1.356-4.700)	0.004	0.884 (0.451-1.732)	0.719
LVEF <50%	3.875 (2.324-6.461)	<0.001	2.654 (1.515-4.650)	0.001
Hyperglycemia	2.680 (1.677-4.282)	<0.001	1.876 (1.102-3.193)	0.020
SYNTAX score	1.032 (1.008-1.057)	0.008	1.020 (0.998-1.042)	0.065

eGFR: Estimated glomerular filtration rate, LVEF: Left ventricular ejection fraction, SYNTAX: Synergy between percutaneous coronary intervention with taxus and cardiac surgery, CI: Confidence interval

their analysis, APG was categorized into ≤110, >110 to 140, >140 to 170, >170 to 240, and >240 mg/dL) for its association with mortality in patients with and without recognized DM. Although they did not determine a single cut-off value for hyperglycemia, their patient population was not homogenous. Additionally, they classified the patients as having recognized DM if their medical records contained documentation of a previous history of DM. However, they could not use HbA1C levels to differentiate the patients better. Zhao et al.[28] reported a meta-analysis in 2015 which included 13 studies and demonstrated a significant relationship between the APG levels and long-term mortality. However, they did not find any relationship with short-term mortality[28]. Furthermore, they only included studies that enrolled the patients with STEMI. There is no convincing data on this subject.

The utilization of HbA1C levels in routine clinical practice made an enormous contribution to the rapid detection of DM. The patients without any medication on DM or documented DM might be in a group of old onset DM with no hospital records. The lack of utilization of HbA1C levels in most previous studies might have caused an underestimation of the rate of the diabetic patient population[3-6,16,17,25,26,29]. We checked HbA1C levels in all patients to diagnose DM accurately, which was not done in most previous studies.

Additionally, most studies evaluating the effect of APG levels on clinical outcomes in patients with AMI were reported before the investigations to determine a single cut-off value by meta-analyses, large-scale studies, clinical guidelines, and the statement of the definition "hyperglycemia" by ADA[2,30-33]. In the current study, hyperglycemia was defined as admission APG measurement >140 mg/dL in nondiabetic patients in accordance with the 2013 ADA Standard of Medical Care Criteria which are based on some studies with large patient populations.

Study Limitations

Our study has several limitations. First, due to a relatively low number of patients in subgroups, we did not further check the discriminative value of APG levels in different treatment strategies. Second, we could not reach the socioeconomic status, immunological and infectious status, obesity, and physical activity data and could not adjust the analysis for these confounders. Third, we did not evaluate the patients' further glucose measurements during the hospitalization and the therapeutic interventions for hyperglycemia.

Conclusion

Our study evaluated the effect of APG and the newly generated term of "hyperglycemia" in overall patients with NSTEMI, and confirmed that APG might be an important prognostic indicator of short and long-term mortality, and novel hyperglycemia cut-off values might be used as a simple prognostic threshold in these patients. As far as we know, the present study is the first to evaluate recommended cut-off APG separately in patients with NSTEMI regardless of the treatment strategy. Furthermore, we investigated the association of APG with several widely used angiographic and clinical scores. Our results warrant further investigations with large-scale studies.

Ethics

Ethics Committee Approval: Haydarpaşa Numune Training and Research Hospital Ethics Committee approval (no: 2017/117, date: 05.09.2018) was obtained for the study.

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and/or Medical Practices: Demir-Gündoğmuş P, Keskin Ü, Concept: Demir-Gündoğmuş P, Design: Demir-Gündoğmuş P, Keskin Ü, Data Collection and/or Processing: Demir-Gündoğmuş P, Keskin Ü, Analysis

and/or Interpretation: Demir-Gündoğmuş P, Literature Search: Demir-Gündoğmuş P, Keskin Ü, Writing: Demir-Gündoğmuş P, Keskin Ü.

Conflict of Interest: The authors have no conflict of interest to declare.

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Cystatin C and Its Temporal Change May Predict Development and Recovery of Cardio-renal Syndrome Type 1 in Acute Heart Failure

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Abstract

Objectives: Cardio-renal syndrome type 1 (CRS1) complicates 40% of patients hospitalized for acute decompensated heart failure (ADHF) and is associated with poor prognosis. Factors associated with the development and recovery of CRS1 have not been completely understood, and the value of cystatin C in this context has not been studied.

Materials and Methods: We evaluated the predictive value of cystatin C levels at admission and 24th hour and delta-cystatin C (cystatin C change in the first 24 hours of admission) in the development and reversibility of CRS1 in patients hospitalized for ADHF. One hundred ten consecutive patients hospitalized for ADHF were enrolled.

Results: Admission cystatin C [odds ratio (OR): 30.97, confidence interval (CI): 9.28-139.60, p<0.001], delta-cystatin C (OR: 41.26, CI: 7.75-93.55, p<0.001), furosemide dose given in first 24 hours of admission (OR: 1.941, CI: 1.541-4.112, p=0.009), and systolic pulmonary artery pressure (OR: 0.927, CI: 0.874-0.983, p=0.011) were independent predictors of

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Abstract

CRS1. A ROC curve analysis showed that an admission cystatin C level at a cut-off point of 1.385 could detect AKI with 77.1% sensitivity and 77.4% specificity. Among 48 patients in the AKI group, renal function was recovered in 31 (64.6%). Delta-cystatin C (OR: 0.088, CI: 0.018-0.441, p=0.001), systolic pulmonary artery pressure (OR: 0.917, CI: 0.621-0.982, p=0.005), and furosemide dose given in first 24 h of admission (OR: 0.877, CI: 0.541-0.998, p=0.04) were independent predictors of recovery of renal function while admission creatinine and creatinine change in 24 hours were not.

Conclusion: This study demonstrated the potential value of cystatin C and delta-cystatin C in CRS1. Further studies are required to determine the clinical utility of these findings.

Keywords: Cardio-renal syndrome type 1, cystatin C, acute decompensated heart failure, acute kidney injury

Introduction

Cardio-renal syndrome type 1 (CRS1) is a term used to describe acute kidney injury (AKI) due to worsening cardiac functions[1]. It complicates almost 40% of patients hospitalized for acute decompensated heart failure (ADHF) and is associated with higher morbidity and mortality[2]. Although creatinine is the main test to recognize AKI, it is far from being a perfect marker since it increases 48 hours after renal injury when half of the renal function is lost. It is affected by age, muscle mass and many other factors[3,4]. Novel renal markers, such as cystatin C, may detect AKI earlier than serum creatinine when a renal injury is still reversible. However, it remains unclear whether such biomarkers are also suitable for the prediction of recovery after established AKI[5].

Cystatin C is a small protein molecule produced by virtually all nucleated cells in the human body. It is suitable for estimating renal function because its production rate is nearly constant. It is freely filtered from the glomerular membrane and completely reabsorbed without being secreted from the proximal tubular cells. Moreover, its level is not influenced by sex, age, race, muscle mass, infection, liver function, and inflammation. It can be detected earlier than creatinine in renal injury. After renal injury cystatin C level increases in 8 hours, peaks at 24 hours, and decreases at 48 hours[6-10]. In previous studies, cystatin C was found to be associated with contrast-induced nephropathy, renal injury after cardiac surgery, and prognosis in acute or chronic heart failure and acute coronary syndrome[11-15]. Furthermore, Lassus et al.[5] suggested that cystatin C may be a useful marker of early AKI in patients hospitalized for ADHF in their study. However, the predictive value of cystatin C and temporal change in cystatin in AKI recovery in ADHF has not been investigated so far.

The present study aims to evaluate the predictive value of cystatin C levels at admission and 24th hour and cystatin C change in 24 hours in the development and reversibility of acute kidney injury in patients hospitalized for ADHF.

Materials and Methods

Study Population

In this observational study, we prospectively enrolled 110 consecutive patients hospitalized for decompensated heart failure. Patients with acute coronary syndrome in the last 30 days, chronic kidney disease, renal transplant, rheumatologic or auto-immune disease, acute infection, thyroid dysfunction, and malignity were excluded from the study. Patients who received intravenous diuretic therapy or radiopaque contrast media in the last 15 days and who received aminoglycosides, metformin and non-steroid anti-inflammatory drugs in the last 7 days were also excluded. The Institutional Ethics Committee of Gazi University approved the study protocol (09.06.2014/297), and all participants have given informed consent.

Analysis of Patient Data and Laboratory Analysis

Demographic parameters, symptoms, physical examination findings, medications, and the patients' medical history were recorded. A transthoracic echocardiographic examination was performed at admission. The left ventricular ejection fraction was calculated by Modified Simpson's method. Routine serum biochemical parameters including creatinine, blood urea nitrogen, electrolytes, glucose and hepatic transaminases were checked at admission, 24th and 48th hour of admission, and when respective clinicians of the patients required after then. Venous blood samples were taken at admission and 24th hour to measure cystatin C. An immune nephelometric N latex cystatin C assay (Siemens healthcare products, Germany) were used with normal cystatin C levels between 0.53-0.95 mg/L.

Definitions

Acute kidney injury was defined as an increase in serum creatinine level ≥0.3 mg/dL or ≥50% above baseline value during the hospital stay[16]. In patients who developed acute kidney injury, a discharge creatinine value below 125% of admission was defined as recovery from acute kidney injury[17]. Estimated glomerular filtration rate was calculated by the modification of diet in renal disease (MDRD) equation. Creatinine and cystatin C changes in the first 24 h of the admission were defined as delta-creatinine and delta-cystatin C. Patients with ongoing antihypertensive treatment or a systolic blood pressure 140 mmHg or diastolic blood pressure ≥90 mmHg were accepted as hypertensive. Patients on antidiabetic medications or fasting glucose levels >126 mg/dl were defined as diabetic. As ischemic etiology of heart failure was defined as the presence of heart failure with a history of myocardial infarction or coronary revascularization or presence of a ≥50% stenosis in an epicardial coronary artery.

Statistical Analysis

IBM SPSS Statistics version 22.0 for Windows (IBM Corp., Armonk, NY, USA) was used for all statistical calculations. Continuous variables were presented as mean and standard deviation or median and interquartile range as appropriate. Categorical variables were presented as numbers and proportions. Distribution patterns of variables were tested with The Kolmogorov-Smirnov test. The student's t-test was used to compare data with normal distribution, and the Mann-Whitney U test was used for non-normally distributed data. The optimum cut-off level of cystatin C to predict CRS1 was determined with receiver-operating characteristics (ROC) curve analysis. A multivariable stepwise logistic regression analysis was used to examine the association of development and recovery of acute kidney injury with other variables. If a variable has a p value <0.1 in univariate logistic regression analysis, it was included in the multivariate model. A two-tailed p value <0.05 was defined as significant.

Results

The mean age of the 110 participants was 65.06, and 55 (50 %) of them were males. Forty-eight (43.6%) of the participants developed AKI. Age, gender, heart failure etiology, and rates of hypertension (HT) and diabetes mellitus (DM) were similar between patients with and without AKI. Patients in AKI group had higher body mass index (34.12±7.12 vs. 30.32±6.41, p=0.041), higher systolic blood pressure (131.74±26.42 vs. 121.33±17.80, p=0.019) and higher systolic pulmonary artery pressure (38.79±15.89 vs. 37.57±14.00, p=0.003). Daily furosemide dose before admission was significantly higher in the AKI group (94.85±83.49 vs. 50.83±42.56, p=0.036). In AKI group, ALT (20.78±11.16 vs. 15.19±7.94, p=0.003), admission creatinine (1.13±0.25 vs. 1.00±0.17, p=0.002), 24th hour creatinine (1.02±0.46 vs. 1.21±0.92, p<0.001), delta creatinine (0.02±0.01 vs. 0.08±0.06, p=0.001), admission cystatin C (1.32±0.68 vs. 1.24±0.28, p=0.002), 24th hour cystatin C (1.56±0.58 vs. 1.26±0.34, p=0.001) and delta-cystatin C (0.24±0.44 vs. 0.02±0.21, p<0.002) were significantly higher. Furosemide dose given in the first 24 h of admission was also higher in the AKI group (128.47±102.63 vs. 106.55±80.88, p=0.002) (Table 1). In multivariate logistic

Table 1. Demographic, clinical and laboratory characteristics of study patients

Variables	All patients (n=110)	No CRS1 (n=62)	CRS1 (n=48)	p value
Age (years)	65.06±29.65	64.43±31.42	65.86±28.18	0.801
Male gender, n (%)	55 (50)	26 (41.9)	29 (60.4)	0.055
BMI (kg/m^2)	31.51±6.94	30.32±6.41	34.12±7.12	**0.041**
Hypertension, n (%)	92 (83.6)	52 (83.9)	40 (83.3)	0.940
Diabetes, n (%)	59 (53.6)	32 (51.6)	27 (56.2)	0.629
Ischemic etiology, n (%)	80 (72.7)	44 (70.9)	36 (75.0)	0.332
Atrial fibrillation, n (%)	75 (68.2)	42 (67.7)	33 (68.8)	0.853
Previous medication, n (%)				
ACE-I/ARB	89 (80.9)	52 (83.8)	37 (77.1)	0.577
Beta-blocker	83 (75.5)	48 (77.4)	35 (72.9)	0.548
MRA	35 (31.8)	22 (35.5)	13 (27.1)	0.348
Furosemide	81 (73.6)	48 (77.4)	33 (68.8)	0306
Thiazide	27 (24.5)	14 (22.6)	13 (27.1)	0.767
Digoxin	24 (21.8)	12 (19.4)	12 (25.0)	0.477
Daily furosemide dose before admission (mg/day)	70.03±62.28	50.83±42.56	94.85±83.49	**0.036**
HF Hospitalization in last year	1.73±2.05	2.13±2.54	1.24±0.971	0.055
Hospitalization duration (days)	11.77±7.78	12.06±7.22	11.40±8.51	0.657
LVEF (%)	35.95±15.24	36.47±13.32	35.29±16.28	0.146
Systolic PAP (mmHg)	38.10±15.21	37.57±14.00	38.79±15.89	**0.003**
Heart rate (min^{-1})	87.84±21.02	85.74±21.31	90.86±20.45	0.222
Systolic BP (mmHg)	125.68±22.31	121.33±17.80	131.74±26.42	**0.019**
Diastolic BP (mmHg)	74.56±12.74	74.67±13.02	74.42±12.20	0.923
Hemoglobin (g/dL)	11.46±2.27	11.69±2.49	11.16±1.95	0.219
WBC (x1000/µL)	7.74±2.01	7.90±2.19	7.53±1.76	0.351
AST (IU/L)	26.00±11.90	26.03±12.63	25.96±10.94	0.974
ALT (IU/L)	17.54±9.78	15.19±7.94	20.78±11.16	**0.003**
CRP (mg/L)	23.84±46.80	27.41±56.22	19.28±16.28	0.374
Na (mmol/L)	136.69±5.36	135.58±5.54	138.17±4.80	0.052
Cystatin C (mg/L)	1.27±0.34	1.24±0.28	1.32±0.68	**0.002**
Cystatin C 24h (mg/L)	1.39±0.52	1.26±0.34	1.56±0.58	**0.001**
Delta-cystatin C (mg/L)	0.12±0.29	0.02±0.21	0.24±0.44	**<0.001**
BUN (mg/dL)	25.57±9.62	25.04±9.73	25.25±9.18	0.509
BUN 24h (mg/dL)	34.36±14.75	30.42±7.63	39.46±18.04	**0.001**
Maximum BUN (mg/dL)	43.54±1687	37.27±8.13	51.66±21.36	**0.001**
Creatinine (mg/dL)	1.06±0.22	1.00±0.17	1.13±0.25	**0.002**
Creatinine 24h (mg/dL)	1,10±0.68	1.02±0.46	1.21±0.92	**<0.001**
Maximum creatinine (mg/dL)	1.32±0.49	1.09±0.26	1.62±0.54	**<0.001**
Delta-creatinine (mg/dL)	0.04±0.03	0.02±0.01	0.08±0.06	**0.001**
Furosemide dose-first 24 h (mg)	114.94±88.28	106.55±80.88	128.47±102.63	**0.002**

Significant p values are shown in bold.
ACE-I: Angiotensin-converting enzyme inhibitor, ALT: Alanine transaminase, ARB: Angiotensin receptor blocker, AST: Aspartate transaminase, BP: Blood pressure, BMI: Body mass index, BUN: Blood urea nitrogen, CRP: C-reactive protein, CRS1: Cardio-renal syndrome type 1, HF: Heart failure, LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, PAP: Pulmonary artery pressure, WBC: white blood cell

regression analysis, admission cystatin C level [odds ratio (OR): 30.97, confidence interval (CI): 9.28-139.60, p<0.001] and delta-cystatin C (OR: 41.26, CI: 7.75-93.55, p<0.001) were found as independent predictors for development of AKI. Furosemide dose is given in the first 24 h of admission (OR: 1.941, CI: 1.541-4.112, p=0.009), and systolic pulmonary artery pressure (OR: 0.927, CI: 0.874-0.983, p=0.011) were other independent predictors. Although baseline creatinine level and delta-creatinine were predictive of AKI in univariate analysis, they lost their significance in multivariate analysis (Table 2). The receiver-operating characteristic (ROC) curve analysis showed that cystatin C at a cut-off point of 1.385 could detect the occurrence of AKI with 77.1% sensitivity and 77.4% specificity (Figure 1).

Among 48 patients in AKI group, renal function was recovered in 31 (64.6%) during hospital stay. There is not any significant difference between patients with recovered and unrecovered renal function regarding age, gender, heart failure etiology and rates of HT and DM. Admission cystatin C level (1.33±0.72 vs. 1.30±0.60, p=0.661), maximum creatinine level (1.64±0.63 vs. 1.61±0.51, p=0.184) and delta-creatinine (0.08±0.07 vs. 0.08±0.04, p=0.988) were similar between groups. While systolic blood pressure (140.89±26.97 vs. 114.67±14.57, p=0.001) and admission creatinine (1.21±0.23 vs. 0.98±0.19, p=0.001) were higher, hospitalization due to heart failure in last year (0.92±0.58 vs. 1.79±1.25, p=0.006), systolic pulmonary artery pressure (32.48±9.56 vs. 50.29±18.76,p ≤0.001), cystatin C at 24th hour of admission (1.38±0.47 vs. 1.89±0.63, p=0.003), delta-cystatin C (0.05±0.06 vs. 0.59±0.21, p=0.001) and furosemide dose given in first 24 h of admission (124.60±114.18 vs. 135.52±89.92, p=0.001) were significantly lower in patients with recovered renal function. Need for hemodialysis (17.6% vs. 16.1%, p=0.222) and time to hemodialysis (132.4±64.58 h vs. 138.5±78.33 h, p=0.265) were similar between groups (Table 3). In multivariate logistic regression analysis, cystatin c change in 24 h was found as an independent predictor of recovery of renal function in patients with AKI (OR: 0.088, CI: 0.018-0.441, p=0.001). Systolic pulmonary artery pressure (OR: 0.917, CI: 0.621-0.982, p=0.005), p=0.033) and furosemide dose given in first 24 h of admission (OR: 0.877, CI: 0.541-0.998, p=0.04) were other independent predictors (Table 4).

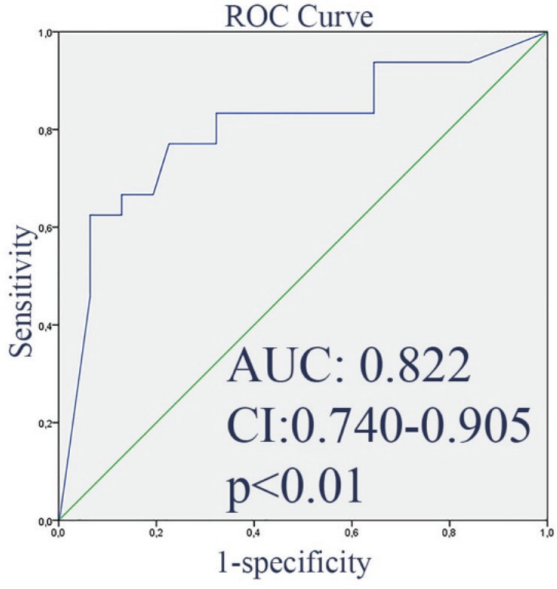

Figure 1. The receiver operating characteristic curve analysis for admission Cystatin C in predicting cardio-renal syndrome type 1

AUC: Area under the curve, CI: confidence interval, ROC: Receiver operating characteristics

Discussion

The present study demonstrated for the first time that the change in cystatin C level in the first 24 h of admission is associated with the development and recovery of CRS1 in patients hospitalized for acute heart failure. In addition, admission cystatin C level was associated with the development of CRS1 in these patients. Admission creatinine and creatinine change in the first 24 h of admission were not independent predictors of CRS1 and its recovery.

Pathophysiological mechanisms underlying CRS1 are not entirely understood. Advanced age and pre-existing chronic kidney disease are essential, but classical risk factors of AKI such as hypotension and hypovolemia are uncommon in this population[18]. Although renal venous HT and renal hypoperfusion are thought to be the major

mechanism of CRS1, previous studies showed that LVEF is not associated with CRS 1 and renal deterioration is not correlated with cardiac output, filling pressures and systemic vascular resistance[19]. It is probably due to the fact that endogenous vasoactive substances such as endothelin, nitric oxide, prostaglandins, natriuretic peptides, and vasopeptidase inhibitors interact with renal perfusion independent of central hemodynamics[20-21]. Even so, it is known that elevated central venous pressure causes increased renal venous and interstitial pressures, leading to the kidney's inability to maintain the glomerular filtration rate resulting in hypoxia renin-angiotensin-aldosterone system activation[22]. Cardio-renal syndrome type1 is rarely seen before hospital admission. It is thought to be a particular evidence of the effect of in-hospital medication on renal function in these patients. High-dose furosemide is associated with a worse renal prognosis. However, it is not clear whether the need for higher doses of furosemide is a cause or a consequence of advanced heart failure or blunt diuretic response due to pre-existing renal failure[23]. In our study, we found out that the furosemide dose given in the first 24 h of admission is associated with CRS1.

Age and chronic kidney disease were shown to be associated with recovery of AKI in different populations. However, it is still unclear whether demographic and clinical factors associated with the development of CRS1 are also helpful for predicting the recovery of CRS1[24,25]. The effect of the presence of chronic kidney disease on the prediction of CRS1 and its recovery was not evaluated in our study since patients with CKD were excluded. However, admission creatinine was not associated with CRS1 and its recovery in our study. We did not find an association between age and development and recovery of CRS1. Schiffl[26] and Alsultan[27] did not find such an association in patients with AKI requiring renal replacement therapy either.

Cystatin C is an important marker of prognosis in AHF[28,29]. Previous studies showed that cystatin C is a

Table 2. Predictors of CRS1 in multivariate logistic regression analysis

Variables	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	0.995 (0.958-1.033)	0.799	-	
Gender (male)	2.113 (0.981-4.553)	0.56	-	
Hypertension	0.962 (0.348-2.658)	0.940	-	
Diabetes mellitus	1.205 (0.565-2.570)	0.629	-	
Daily furosemide dose before admission	0.642 (0.274-1.505)	0.308	-	
Furosemide dose-first 24 h	2.762 (1.841-3.546)	0.002	1.941 (1.541-4.112)	0.009
Hospitalization (1 year)	0.774 (0.594-1.010)	0.059	0.850 (0.555-1.303)	0.456
Systolic blood pressure	1.023 (1.003-1.044)	0.027	0.958 (0.944-1.026)	0.462
BUN	1.014 (0.974-1.055)	0.506	-	
ALT	1.065 (1.018-1.114)	0.006	1.079 (0.995-1.158)	0.057
Creatinine	23.74 (2.79-201.73)	0.004	16.85 (0.565-502.70)	0.103
Delta-creatinine	27.41 (3.98-321.14)	0.003	18.21 (0.873-345.78)	0.098
Cystatin C	24.59 (6.35-95.23)	<0.001	30.97(9.28-139.60)	<0.001
Delta-cystatin C	22.26 (4.523-109.57)	<0.001	41.26 (7.75-93.55)	<0.001
LVEF	0.981 (0.955-1.007)	0.146	1.028 (0.971-1.089)	0.344
Systolic PAP	0.961 (0.935-0.988)	0.004	0.927 (0.874-0.983)	0.011

ALT: Alanine transaminase, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, PAP: Pulmonary artery pressure, OR: Odds ratio, CI: Confidence interval

Table 3. Demographic, clinical and laboratory characteristics of patients with recovered and non-recovered acute kidney injury

Variables	All CRS1 (n=48)	AKI has not recovered (n=17)	AKI recovered (n=31)	p value
Age (years)	65.86±28.18	66.38±26.48	65.58±28.62	0.564
Gender (male), n (%)	29 (60.4)	10 (58.8)	19 (61.3)	0.867
BMI (kg/m^2)	34.12±7.12	35.42±9.06	31.74±6.01	0.145
Hypertension, n (%)	40 (83.3)	12 (70.6)	28 (90.3)	0.079
Diabetes, n (%)	27 (56.2)	12 (70.6)	15 (48.4)	0.138
Ischemic etiology, n (%)	36 (78.0)	13 (76.4)	23 (74.19)	0.336
Atrial Fibrillation, n (%)	33 (68.8)	11 (64.7)	22 (70.9)	0.165
Previous medication, n (%)				
ACE-I/ARB	37 (77.1)	13 (76.47)	24 (77.41)	0.453
Beta-blocker	35 (72.9)	13 (76.47)	22 (70.96)	0.381
MRA	13 (27.1)	5 (29.4)	8 (25.8)	0.788
Furosemide	33 (68.8)	15 (88.2)	18 (58.1)	0.031
Thiazide	13 (27.1)	6 (29.4)	7 (22.6)	0.601
Digoxin	12 (25.0)	3 (176)	9 (29.0)	0.384
Daily furosemide dose before admission (mg/day)	94.85±83.49	80.00±63.696	107.22±72.75	0.568
HF hospitalization in last year	1.24±0.971	1.79 ±1.25	0.92±0.58	**0.006**
Hospitalization duration (days)	11.40±8.51	12.94±8.70	10.55±8.42	0.357
LVEF (%)	35.29±16.28	34.76 ±17.65	35.58 ±15.76	0.870
Systolic PAP (mmHg)	38.79±15.89	50.29±18.76	32.48±9.56	**<0.001**
Heart rate (min^{-1})	90.86±20.45	91.53±13.4	90.50±± 23.6	0.877
Systolic BP (mmHg)	131.74±26.42	114.67±14.57	140.89±26.97	**0.001**
Diastolic BP (mmHg)	74.42±12.20	70.67±9.61	76.43±13.11	0.142
Hemoglobin (g/dL)	11.16±1.95	11.97±2.10	10.71±1.73	0.051
WBC (x1000/µL)	7.53±1.76	8.11±2.57	7.22±1.03	0.096
CRP (mg/L)	19.28±16.28	31.24±15.98	13.09±17.07	0.055
Na (mmol/L)	138.17±4.80	139.25±5.10	137.61±4.61	0.272
Cystatin C (mg/L)	1.32±0.68	1.30±0.60	1.33±0.72	0.661
Cystatin C 24h (mg/L)	1.56±0.58	1.89±0.63	1.38±0.47	**0.003**
Delta-cystatin C (mg/L)	0.24±0.44	0.59±0.21	0.05±0.06	**0.001**
BUN (mg/dL)	25.25±9.18	30.18±9.83	24.09±8.18	0.26
BUN 24h (mg/dL)	39.46±18.04	46.35±24.37	35.68±12.31	0.49
Maximum BUN (mg/dL)	51.66±21.36	56.12±26.77	49.21±18.49	**0.001**
Creatinine (mg/dL)	1.13±0.25	1.15±0.19	1.12±0.28	**0.02**
Creatinine 24h (mg/dL)	1.21±0.92	1.23±0.76	1.20±0.97	**0.01**
Maximum creatinine (mg/dL)	1.62±0.54	1.64±0.63	1.61±0.51	0.184
Delta-creatinine (mg/dL)	0.08±0.05	0.08±0.07	0.08±0.04	0.988
Furosemide dose-first 24 h (mg)	128.47±102.63	135.52±89.92	124.60±114.18	**0.001**
Hemodialysis	8 (16.7)	3 (17.6)	5 (16.1)	0.222
Time to hemodialysis	136.3±71.26	132.4±64.58	138.5±78.33	0.265

Significant p values are shown in bold.
ACE-I: Angiotensin-converting enzyme inhibitor, AKI: Acute kidney injury, ALT: Alanine transaminase, ARB: Angiotensin receptor blocker, AST: Aspartate transaminase, BMI: Body mass index, BP: Blood pressure, BUN: Blood urea nitrogen, CRP: C-reactive protein, CRS1: Cardio-renal syndrome type 1, HF: Heart failure, LVEF: Left ventricular ejection fraction, MRA: Mineralocorticoid receptor antagonist, PAP: Pulmonary artery pressure, WBC: White blood cell

more reliable marker of renal function than creatinine post cardiopulmonary bypass and detected reduced glomerular filtration rate at an earlier stage after cardiac catheterization[30,31]. Lassus et al.[5] demonstrated that cystatin C is a useful marker of AKI in AHF, and a rise in cystatin C >0.3 mg/L within 48 h after hospitalization was associated with longer hospital stay and higher in-hospital mortality. A study by Carrasco-Sanchez et al.[32] also showed the usefulness of cystatin C in predicting AKI and prognosis in AHF. In contrast, Breidthardt et al.[33] suggested that plasma cystatin C levels cannot adequately predict CRS1 in AHF. Results of the present study confirm the usefulness of cystatin C in predicting CRS1 in AHF. In addition to previous studies, the potential utility of the cystatin C change in the first 24 h in the prediction of CRS was demonstrated.

The value of the novel renal markers in the recovery of AKI has recently been investigated in some studies. In one of them, among neutrophil gelatinase-associated lipocalin (NGAL), the mRNA expressions of kidney injury molecule-1, interleukin-18, alpha-1-microglobulin, sodium/hydrogen exchanger-3, beta-2 microglobulin and N-acetyl-β-D-glucosaminidase, only alpha-1-microglobulin was correlated with the degree of improvement in renal failure[34]. In another, plasma NGAL predicted the failure of renal recovery in community-acquired pneumonia[35]. Urine NGAL and urine hepatocyte growth factor were also showed promise in the prediction of renal recovery[36,37]. Furthermore, Gharaibeh et al.[38] suggested that cystatin C decreases one day earlier than creatinine in most hospitalized patients with AKI, and Leem et al.[39] showed that admission serum cystatin C was associated with recovery of AKI in patients with sepsis-induced kidney injury. In their study on CRS1 patients, Basu et al.[40] suggested that a composite of urine NGAL and plasma cystatin C is superior to serum creatinine for predicting transient AKI in children after cardiopulmonary bypass. Unfortunately, none of the studies above were performed on AHF patients. Results of the present study demonstrated the potential usefulness of cystatin C and

Table 4. Predictors of the recovery from acute kidney injury in multivariate logistic regression analysis

	Univariable		Multivariable	
Variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Age	1.055 (0.986-1.127)	0.119	-	
Male Gender	1.108 (0.332-3.703)	0.867	-	
Diabetes mellitus	0.391 (0.111-1.375)	0.143	-	
Body mass index	1.425 (0.998-1.942)	0.174	-	
Atrial fibrillation	3.800 (1.068-13.520)	0.039	2.480 (0.984-15.648)	0.088
Systolic blood pressure	1.092 (1.031-1.158)	0.003	1.088 (1.025-1.188)	0.09
AST	0.990 (0.937-1.046)	0.718	-	
Hemoglobin	0.663 (0.445-0.989)	0.044	0.758 (0.328-1.055)	0.101
WBC	0.741 (0.512-1.073)	0.112	-	
Sodium	0.938 (0.541-1.357)	0.188	-	
LVEF	1.003 (0.967-1.041)	0.867	-	
Systolic PAB	0.908 (0.854-0.965)	0.002	0.917 (0.621-0.982)	0.005
Cystatin	1.228 (0.501-3.012)	0.653	-	
Delta-cystatin C	0.057 (0.008-0.409)	0.002	0.088 (0.018-0.441)	0.001
Creatinine	0.632 (0.319-0.868)	0.032	0.741 (0.289-0.827)	0.063
Delta-creatinine	0.982 (0.241-1.368)	0.122	-	
Furosemide dose-first 24 h	0.842 (0.565-0.922)	0.038	0.887 (0.541-0.998)	0.04

AST: Aspartate transaminase, BUN: Blood urea nitrogen, LVEF: Left ventricular ejection fraction, PAP: Pulmonary artery pressure, WBC: White blood cell

its change with time in the prediction of CRS1 and its recovery.

The present study has several limitations. It is a retrospective and single-center study. However, all consecutive patients hospitalized for ADHF in a time frame were included in the study to overcome the limitations of the retrospective design. Moreover, BNP or pro-BNP levels were not measured. Thus, we do not have biochemical evidence about the severity of the heart failure in patients with and without CRS1.

Conclusion

Admission cystatin C may predict CRS1, and a change in cystatin C level in the first 24 h of admission is associated with the development and recovery of CRS1 in patients hospitalized for acute heart failure. Cystatin C may be used as a predictor of renal function beyond creatinine in AHF because neither admission creatinine nor its change in the 24th hour was associated with CRS and its recovery in our study population. Further studies are required to elucidate the role of cystatin C and its temporal change in predicting renal outcomes in ADHF.

Ethics

Ethics Committee Approval: The Institutional Ethics Committee of Gazi University approved the study protocol (decision no: 297, date: 09.06.2014).

Informed Consent: All participants gave informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Design: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Data Collection and/or Processing: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Analysis and/or Interpretation: Açıkgöz E, Açıkgöz SK, Özilhan MO, Özlem G, Özdemir HM, Literature Search: Açıkgöz E, Açıkgöz SK, Özilhan MO, Candemir M, Gökalp G, Çakmak-Karaaslan Ö, Nurkoç SG, Koçak A, Özlem G, Özdemir HM, Writing: Açıkgöz E, Açıkgöz SK, Özdemir HM.

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The Correlation Between Education Levels and Lifestyles of Patients Admitted Cardiology Clinics: A Subgroup Analysis of Medlife-TR Study

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Abstract

Objectives: The lifestyle, dietary habits, and cardiovascular (CV) risk perception of patients with CV risk factors and/or diseases in Turkish population may vary with education. We aimed to reveal the relationship between education level and lifestyles in patients who participated in the Medications and Lifestyles of Patients with Cardiovascular Risk Factors and/or Diseases in Turkish Population (MedLife-TR) study.

Materials and Methods: This study was conducted between November 2018 and March 2019 with 2793 patients. The male gender ratio was 47.91%, and the female gender ratio was 52.09%. The participants first completed a self-administered questionnaire in four sections: baseline characteristics, awareness of CV risk factors and their CV risk levels,

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Abstract

lifestyle habits (exercise, diet, eating….) and use of drugs. This was a multicenter, national and observational study that included 27 centers in Turkey. Fisher-Freeman-Halton test was used for comparison of qualitative data. A p-value <0.05 was considered statistically significant.

Results: According to the education level of patients, CV risk perception and eating habits vary as education level increases. The ratio of patients to exercise regularly was low. But as the level of education increases, the rate of regular exercise increases (p<0.001). The rate of using herbal products (p=0.086) or vitamins (p=0.384) did not change as the level of education increased. The university-level group stated that smoking was the highest risk factor for CV disease (28.33%). However, the other groups, especially the uneducated group (42.92%) think that hypertension is the most risk factor for CV diseases. The consumption of fast-food products such as hamburgers, pizza, and fries increased as the education level increased. The rate of skipping breakfast (17.69%) was higher in the university-level group than the other groups (p<0.001).

Conclusion: Statistically significant differences were observed between education level and lifestyle of patients with CV risk factors and/or diseases. As the education level increases, the rate of skipping breakfast and the consumption of fast-food products increase; however, the rate of regular exercise and diet increases.

Keywords: Lifestyles, education levels, dietary habits, cardiovascular risk perception

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death worldwide. The association between low socioeconomic status and CVD mortality risk is well documented. Some studies show that the socioeconomic death gradient in cardiovascular (CV) mortality was steeper in women than men when education was used to indicate social standing[1,2]. The education is considered one of the lifelong socioeconomic indicators of the individual[3]. Most prospective studies conducted on European populations have found an increased incidence of coronary heart disease (CHD) among less-educated individuals[4,5].

Some of the causes of social disparity in CHD mortality are the unequal distribution of risk factors such as smoking, low physical activity, unhealthy diet and lifestyle. However, several studies show that behavioral risk factors contribute to the socioeconomic gradient in CHD[6-8]. The educational disparity in CV diseases is evident in many countries, particularly those in northern Europe. Education has been cited as a good indicator of social position in epidemiological studies[9,10].

The World Health Organization (WHO) stated that the determinants of health were physical, social and economic environment and individual characteristics[11]. Studies have shown that the patients' socioeconomic status is also associated with the risk of CV disease[10-12]. Education is a more specific factor[13]. There is a lack of data on the effects of patients' education levels on a diet, physical activity, smoking cessation, and use of pharmacological treatments as recommended.

The lifestyle, dietary habits and CV risk perception of patients with CV risk factors and/or diseases in the Turkish population may vary with the level of education. So, we aimed to reveal the relationship between education level and lifestyles in patients who participated in the Medications and Lifestyles of Patients with Cardiovascular Risk Factors and/or Diseases in Turkish Population (MedLife-TR) study[14].

Materials and Methods

Patients admitted to the cardiology outpatient clinics for diagnostic or therapeutic purposes, who were over 18 years of age and agreed to participate in the study

were included in the study. The patients included in the study were divided into four groups according to their education level; elementary-middle school education (group I), high school (group II), university-level (group III), and uneducated (group IV). A total of 2793 patients participated in this study. There were 1360 patients in group I, 446 patients in group II, 294 patients in group III, and 693 patients in group IV. The participants signed informed consent and completed a self-administered questionnaire in the following sections: baseline characteristics, awareness of CV risk factors and individual CV risk, lifestyle habits, medical behaviors and CV medication. From different country regions, 27 sites in Turkey were in cluded in this study. Patients were enrolled between November 2018 and March 2019. Actual CV risk levels according to Framingham risk score were calculated by the physicians. The ethics committee approval of this multicenter, national, cross-sectional, and observational study was obtained from University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Research and Training Hospital on 16.09.2019 with the decision number 2019-18-07.

Patients who did moderate exercise at least 3 days a week (at least 30 minutes per day) were considered to be regular exercisers. Those who used antihypertensive drugs or had blood pressure (BP) >140/90 mmHg in at least two measurements during the examinations were considered as hypertensive[15]. BP measurements were made in outpatient clinics with a validated digital sphygmomanometer. Patients who used antidiabetic drugs or insulin or had a fasting blood glucose level higher than 126 mg/dL were considered diabetic[16]. According to lipid guidelines, hyperlipidemia was diagnosed in patients who took lipid-lowering drugs or had higher lipid levels[17].

History of CV interventions (percutaneous coronary interventions or bypass grafting), myocardial infarction, cerebrovascular diseases, peripheral arterial disease, moderate/severe valvular disease, dysrythmia, renal diseases, medication history (including over the counter drugs) were questioned and in the case report form. The investigative cardiologist evaluated the electrocardiography of each patient.

Statistical Analysis

All statistical analyses were conducted using MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Continuous variables were presented as mean, standard deviation, and data on frequency were presented as percentages (%) for categorical variables. Chi-square analysis was used for correlation between categorical variables. Where appropriate, categorical variables were evaluated by Fisher's exact and Fisher-Freeman-Halton test. $P<0.05$ was considered statistically significant.

Results

According to the education level of patients, CV risk perception and eating habits vary as education level increases. In this study the ratio of patients to exercise regularly was low. But as the level of education increases, the rate of regular exercise increases ($p<0.001$). The rate of regular exercise in patients with high school and university education were 43.05% and 43.88%, respectively.

Regardless of the level of education, the majority of patients did not use any method to lose weight. However, as the level of education increases, the rate of diet and exercise increases. The proportion of those who do not apply any method to lose weight were higher in uneducated group (67.53%) and elementary-middle school group (49.12%) than in other groups ($p<0.001$). The rate of using herbal products ($p=0.086$) or vitamins ($p=0.384$) did not change as the level of education increased. As the education level of the patients increased, the frequency of going to physician controls and using more than five and more drugs decreased.

The patient group with university-level education considers smoking (28.33%) as the riskiest for CV disease. However, the other groups, especially the uneducated group (42.92%) think that hypertension (HT) was the riskiest for CV diseases. The majority of the uneducated

group considered the least risky factor for CV diseases as genetic diseases (24.96%), whereas the majority of the university-level group considered age progression (22.11%). The other groups think immobility was the least risky for CV diseases (Figure 1). Patients with high school (43.15%) and university (41.16%) level education thought that cholesterol drugs were harmful compared to other groups (p<0.001) (Figure 2).

The consumption of fast-food products such as hamburgers, pizza, and fries increased as the education level increased. The rate of using butter (23.13%) and olive oil (38.44%) at home were higher in the university

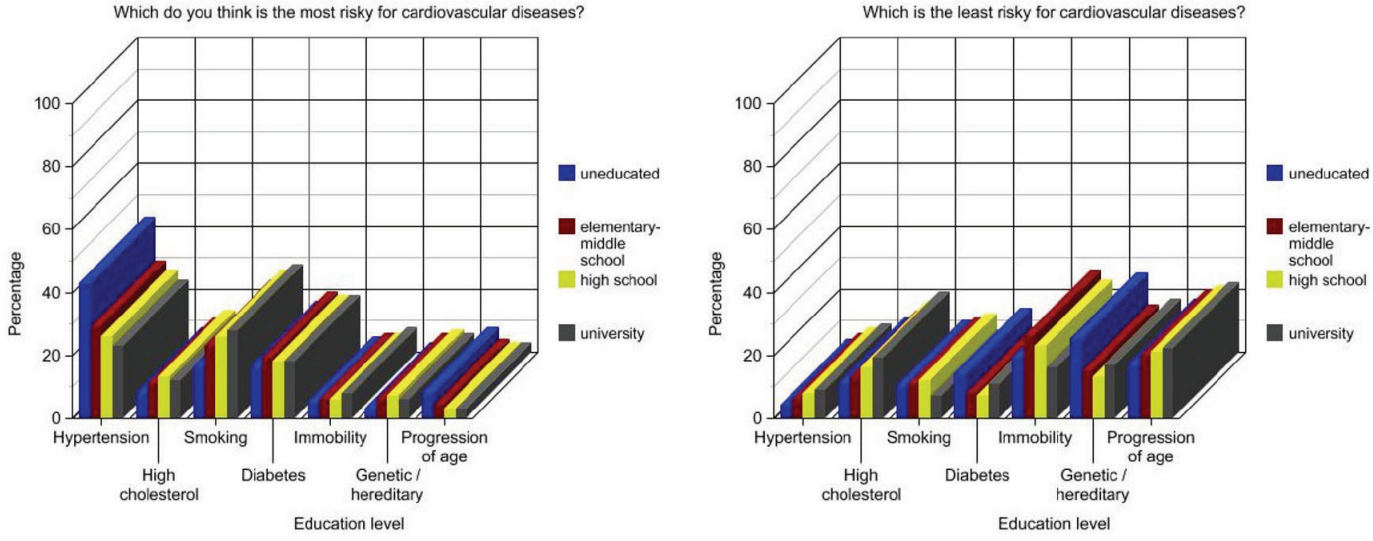

Figure 1. Distribution of factors that the study population considers the riskiest and least risky for CVD. The patient group with university-level education considers smoking (28.33%) as the riskiest for CVD. However, the other groups, especially the uneducated group (42.92%) think that hypertension is the riskiest for CVD

CVD: Cardiovascular diseases

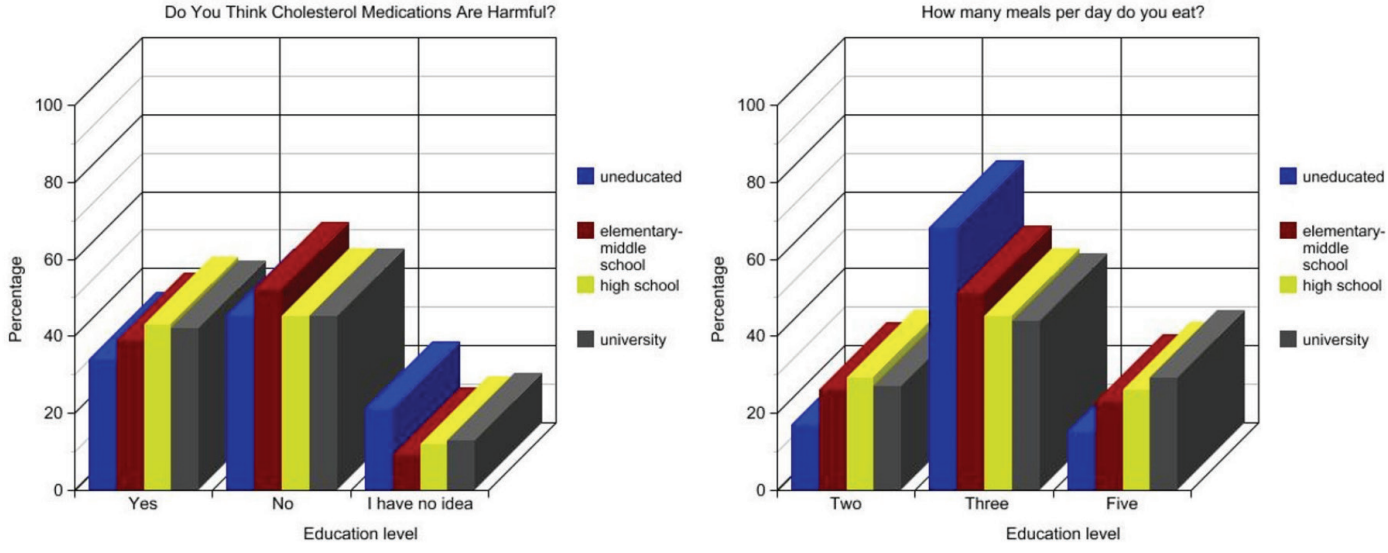

Figure 2. Graph of the distribution of those who think that cholesterol drugs were harmful in the study population and the comparison of the number of daily meals. Patients with high school and university level education thought that cholesterol drugs were harmful compared to other groups

education group than the other groups (p<0.001). However, the rate of using sunflower oil (55.44%) was lower at the group of university-level compared to other groups (p<0.001). As the level of education increases, the rate of eating three meals per day decreases (p<0.001). In the patient group receiving education at university level, the rate of skipping morning breakfast (17.69%) is higher than the other groups (p<0.001) (Table 1).

Discussion

Our study concluded that patients' perceptions of nutrition, lifestyle, and awareness of CV risk varied according to education level. Some of the interesting results of our study were that as the level of education increases, the rate of skipping breakfast and consumption of fast-food products were increased, and cholesterol drugs were thought to be harmful. In addition, the rates of regular exercise and dieting were increased.

Despite the decline in CV mortality rates in many countries, the number of patients with CV disease increases. In addition to creating physical and psychological effects on patients, this situation also causes an increase in costs to the health system[18]. Low physical activity and irregular diet cause an increase in CV disease rate. However, there were not enough information about the effects of common eating behaviors on CV disease.

The habit of eating breakfast was associated with a lower risk of HT. It has also been shown that it can prevent blood vessel occlusion, bleeding and CV events[19,20]. In a study examining the relationship between breakfast frequency and the 10-year risk of atherosclerotic CVD, it was shown that participants who never had breakfast were more likely to be in the high-risk group compared to participants who had breakfast >5 times a week. Even breakfast consumption, even once a week could prevent

Table 1. The relationship between the lifestyle, dietary habits and perception of cardiovascular risk in patients with education level

		Elementary-middle school	High school	University	Uneducated	p-value
Are you doing regular exercise (3 days a week, at least 30 minutes)?	Yes	475 (34.93)	192 (43.05)	129 (43.88)	203 (29.29)	**<0.001**
Do you use vitamins?	Yes	218 (16.03)	75 (16.82)	52 (17.69)	132 (19.05)	0.384
Do you use herbal products?	Yes	203 (14.94)	50 (11.21)	51 (17.35)	93 (13.42)	0.086
How do you the most follow the information you are wondering about your disease?	- Asking my doctor - From TV programs - Newspapers/ journals (s) from health corners - Researching by the Internet* - Not interested	1110 (81.62) 87 (6.40) 7 (0.51) 79 (5.81) 77 (5.66)	310(69.51) 48(10.76) 11 (2.47) 51 (11.43) 26 (5.83)	199 (67.69) 32 (10.88) 2 (0.68) 35 (11.90) 26 (8.84)	522 (75.32) 41 (5.92) 2 (0.29) 15 (2.16) 113 (16.31)	**<0.001**
How often do you apply to a doctor?	<3 monthly* Once in 3-month 3-6 months >6 months	262 (19.28) 393 (28.92) 558 (41.06) 146 (10.74)	83 (18.61) 127 (28.48) 163 (36.55) 73 (16.37)	55 (18.71) 74 (25.17) 124 (42.18) 41 (13.95)	204 (29.44) 262 (37.81) 179 (25.83) 48 (6.93)	**<0.001**
How do you define yourself in terms of cardiovascular diseases?	Low risk Medium risk High risk	457 (33.60) 649 (47.72) 254 (18.68)	174 (39.10) 195 (43.82) 76 (17.08)	124 (42.18) 117 (39.80) 53 (18.03)	121 (17.46) 386 (55.70) 359 (26.84)	**<0.001**
Do you use additional table salt for your meals?	Yes	547 (40.22)	193 (43.27)	133 (45.24)	359 (51.80)	**<0.001**
Do you skip morning breakfast?	Yes	115 (8.46)	52 (11.66)	52 (17.69)	39 (5.63)	**<0.001**
How often do you consume fast food (hamburger, pizza, fried potato, etc.)?	- Once a week - More than once a week* - Once in a month - I never eat	141 (10.37) 80 (5.88) 308 (22.65) 831 (61.10)	67 (15.02) 55 (12.33) 118 (26.46) 206 (46.19)	51 (17.35) 35 (11.90) 84 (28.57) 124 (42.18)	92 (13.28) 34 (4.91) 222 (32.03) 345 (49.78)	**<0.001**

The values in the table are given as n (%). * showed that the result with the most significant difference in meaning

CVD[21]. One of the interesting results of our study was that the rate of skipping breakfast in patients with university-level education was higher than in the other groups.

Psychological variables such as stress, personality, anxiety and lifestyle, HT, obesity, lack of exercise, smoking and high blood cholesterol contribute to the development of CV disease[22]. On the relationship between educational differences and the incidence of major CV events, in a study that included 5084 participants with no previous CV event, it was found that lower education was associated with higher mean body mass index (BMI), higher prevalence of diabetes and smoking in men. Less-educated women had higher mean systolic BP, BMI and high-density lipoprotein cholesterol and were more likely to have diabetes. Men and women in the lower education class had a 2-fold increase in the incidence of ischemic stroke and CHD, respectively, after controlling for major risk factors[23].

The WHO has stated that 80-90% of people who have died from CHD since 1990 have one or more lifestyle-related risk factors[6]. Lifestyle is a person's way of life. Lifestyle is one of the main factors that show a strong relationship with CHD[7,24]. A healthy lifestyle and diet have been found to have positive effects on blood cholesterol[8,24]. Another interesting result of our study was that the higher the education level groups more than consumption of fast-food products such as hamburger, pizza and french fries, and the use of butter (23.13%) and olive oil (38.44%) compared to other groups.

Often referred to as the "gold standard" for treating high levels of LDL, statins are one of the most widely used drugs globally. In our study, the underlying reason why cholesterol drugs are thought to be harmful in patients with high school and university education compared to other groups may be due to the fact that there was more medical misinformation that appears to be "real" on the internet. The rate of searching for health-related information on the internet was higher in these groups compared to the low-educated/non-educated group.

Diet, sleep patterns, smoking and alcohol consumption habits affect health[8,22]. Tobacco use, whether smoking or chewing tobacco, increases the risk of CV disease[25]. In our study, as the level of education increases, the number of patients who think that smoking was the most important risk factor for CV disease were increases. However, patients with lower education thought that HT was the most important risk factor.

Study Limitations

The survey in our study was conducted before the coronavirus disease-2019 (COVID-19) pandemic that occurred in recent years. COVID-19 pandemic may have increased the awareness of patients about their disease. Although this situation caused a limitation in our study, we do not think it significantly impacted our study since we aimed to reveal the relationship between education level and CV risk perception/lifestyle. Since the patient population included in the study was the patients who applied to cardiology outpatient clinics, the study results may not reflect the entire population.

Conclusion

Statistically significant differences were observed between education level and lifestyle of patients with CV risk factors and/or diseases. Perception of CV risk varies with education level. As the education level increases, the rate of skipping breakfast and the consumption of fast-food products increase; however, the rate of regular exercise and diet increases.

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Ethics

Ethics Committee Approval: Ethics committee approval of our study was obtained from the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee on 16.09.2019 with the decision number 2019-18-07.

Informed Consent: Signed voluntary consent forms were obtained from all patients included in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Kış M, Design: Kış M, Data Collection and/or Processing: Kış M, Öz A, Yenerçağ M, Analysis and/or Interpretation: Öz A, Bekar L, Tanık VO, Supervision: Kış M, Tanık VO, Literature Search: Kış M, Öz A, Bekar L, Tanık VO, Karabulut D, Yenerçağ M, Yıldırımlı MK, Kudat H, Zoghi M, Writing: Kış M.

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