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Cardiovascular Surgery and Interventions

Letter to the Editor Open Access

Response to Letter to the Editor: Effectiveness of remote endarterectomy in superficial femoral artery occlusion

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As the authors, we would like to express our gratitude for your interest in our article.[1] During the writing of the manuscript and the performance of the surgical procedures, we were fully aware that the use of saphenous vein grafts typically yields the most favorable outcomes. However, the patient who underwent 24 femoropopliteal bypasses also had a distal circulation deficiency. We anticipated delayed and potentially complicated wound healing at the site of saphenous vein harvest due to this condition. Consequently, we opted to use prosthetic grafts in this case.

Saphenous vein grafts were employed in patients under the age of 18 and those with a history of trauma, as these patients did not have a history of peripheral arterial disease. However, since our study specifically focused on peripheral arterial disease, these patients were excluded from our analysis.

We greatly appreciate your insightful comments, which contribute significantly to the ongoing discussion in the literature. We believe that our study makes a meaningful contribution to the field in its current form.

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Cardiovascular Surgery and Interventions

Letter to the Editor Open Access

Comment on "Effectiveness of remote endarterectomy in superficial femoral artery occlusion"

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I read the article, "*Effectiveness of remote endarterectomy in superficial femoral artery occlusion*" by Koçak et al.[1] with great interest. As the technology for angiographic interventions advances, there is a need for development in the open surgical field. The minimally invasive approach described by the authors provides a stronger option compared to angiographic interventions. I believe the comparison of remote endarterectomy with percutaneous transluminal angioplasty will provide further valuable information about remote endarterectomy surgery.

However, there are several concerns regarding the study design. It is mentioned that patients under 18 years of age and traumatic bypasses done with saphenous vein grafts were not included in the study,[1] but there is no comment on femoropopliteal bypasses performed using saphenous vein grafts. Furthermore, the absence of saphenous vein bypasses is surprising, given the Class I indication for saphenous vein grafts in the European Society for Vascular Surgery guidelines and better long-term patency rates.[2]

The anatomical indications for surgery are clearly described in the text; however, there is no information regarding clinical symptoms of the presented patients. The indications for surgery are limited according to most of the guidelines. Currently, optimal medical management and exercise are the first-line approaches, followed by revascularization if necessary.[2]

Another issue is that distal runoff is crucial for patients undergoing revascularization for peripheral arterial disease. Providing information on whether these 48 patients also had distal vascular disease would help the reader interpret the results thoroughly.[3] Once again, I would like to commend the authors for their great work.

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Cardiovascular Surgery and Interventions

Original Article Open Access

Revival of the modified Brock procedure: Mid-term outcomes and clinical significance in cyanotic congenital heart disease

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ABSTRACT

Objectives: This study aimed to provide a detailed account of the mid-term outcomes of the modified Brock procedure, a recently implemented procedure for patients with cyanotic congenital cardiac disease in our institution, with a particular focus on the clinical follow-up data.

Patients and methods: A total of 14 patients (7 males, 7 females; median age 4.5 years; range, 1 to 14.5 years) underwent the modified Brock procedure between January 2014 and January 2024. Relevant information was collected retrospectively, with a focus on the sizes of the pulmonary arteries.

Results: The preoperative median oxygen saturation and McGoon ratio were 71.5% (69.5 to 72.5%) and 1.35 (1.2 to 1.4), respectively. The postoperative course was uneventful. The median follow-up was seven years, and there was only one mortality two months after the operation. The complete repair was done in four patients during follow-up, with a median of 17.5 months after the initial procedure. The median McGoon ratio was 2 (1.9 to 2.125) in these patients. The postoperative median oxygen saturation was 93% (86.25 to 94.25%) and the median McGoon ratio was 1.6 (1.5 to 1.7) in patients awaiting complete repair surgery.

Conclusion: We concluded that the modified Brock procedure, when implemented with meticulous technique, is a viable choice in both short- and mid-term follow-up for palliative repair in patients with pulmonary artery anatomical constraints that preclude complete repair.

Keywords: Brock procedure, cyanotic, palliative surgery.

An additional source of pulmonary blood flow is required in symptomatic patients (severely cyanotic or spell) with ductus arteriosus-dependent cyanotic congenital heart diseases. All surgically created shunts require postoperative antiaggregant therapy and are associated with complications such as ongoing hypoxemia and the risk of occlusion. Furthermore, in some patients, the physiology of the shunt may be suboptimal, leading to diastolic runoff, which will eventually result in compromised coronary and visceral blood flow. Although it is well established that pulsatile pulmonary blood flow may result in enhanced pulmonary artery growth, shunts do not provide pulsatile blood flow in systole and diastole.[1]

Another palliative method described by Brock[2] involves a direct intervention on the stenotic pulmonary valve or infundibulum. Brock[3] was also the first to suggest that this procedure could also alleviate the pulmonary stenosis associated with tetralogy of Fallot (TOF).[2-5] The original technique has recently been revived with the use of modern cardiopulmonary bypass (CPB) techniques and surgical modifications. Studies showed that right ventricular outflow tract (RVOT)-directed palliative techniques appear to be safe and effective in achieving adequate pulmonary arterial growth until complete repair.[6-12]

In this study, we utilized a modified Brock procedure (patch enlargement of RVOT under CPB) as a palliative procedure of choice in patients with ductus-dependent cyanotic congenital heart diseases and hypoplastic pulmonary arterial bed. The study

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aimed to describe mid-term results with the modified Brock procedure with emphasis on the clinical follow-up data.

PATIENTS AND METHODS

In the retrospective study, 14 patients underwent the modified Brock procedure as a palliative procedure between January 2014 and January 2024. Patients with discontinuous pulmonary arteries that required unifocalization procedures and patients with functionally univentricular heart physiology were not included in the study. Consent was obtained from the participants after providing them with all the necessary information, and the study was approved by the institutional review board. We reviewed demographic data, disease characteristics, preoperative echocardiographic, and other available imaging (catheterization and computed tomography [CT]) data, pulmonary artery Z-scores, McGoon indices, operational data, and postoperative parameters, such as vasoactive inotropic scores, time to extubation, length of stay in the critical care and hospital. Z-scores were primarily evaluated through angiographical measurements; however, if these data were unavailable, data from CT angiography or echocardiography were utilized. All patients completed follow-up. During follow-up, echocardiographic and other imaging data, details of corrective surgeries, and morbidity and mortality rates were determined. All surgical decisions were made by the joint multidisciplinary team on a case-by-case basis. The overarching principle was to ensure that the pulmonary arterial tree grew to its full potential for optimal repair. A written informed consent was obtained from each patient. The study protocol was approved by the Hacettepe University Health Sciences Research Ethics Committee (date: 24.05.2024, no: SBA 24/1013). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Surgical technique

Surgical technique was standard and performed by the same surgeon in all cases (pulmonary atresia with intact ventricular septum [PA-IVS] patient had membranous atresia). After median sternotomy, CPB was initiated with aortic and bicaval cannulation. Anatomy was observed considering the branch pulmonary arteries, the morphology of the aortic arch, and the coronary arterial trajectories. To eliminate competitive flow, patent ductus arteriosus or any additional pulmonary blood flow was always ligated when accessible. Having arrested the heart, a mini right ventriculotomy was performed on the infundibulum. Obstructing muscle bundles were divided and resected if necessary. It should be noted that excessive resection was not required, and only limited resection was done at this stage. The pulmonary valve was evaluated with Hegar dilators going from RVOT to pulmonary artery. The aim was to achieve approximately 75% of the normal size of the RVOT and pulmonary artery to prevent pulmonary flooding and right ventricular (RV) distension due to excessive pulmonary regurgitation. Thus, if the annulus was smaller, the main pulmonary artery was incised, and a commissurotomy was performed. A transannular incision was never made to prevent pulmonary regurgitation. However, serial dilatations were performed with incremental sizes of Hegar dilators. Bovine pericardium or Dacron velour sheet was used to augment incisions. We did not prefer the use of autologous pericardium to prevent RVOT aneurysmal dilatation. Moreover, the nondistensible RVOT patch facilitated the transmission of RV contraction energy to the distal pulmonary vascular bed, minimizing energy loss associated with distending a redundant RVOT patch. The patches were then sized to fit around a Hegar dilator that was 75% of the normal size. This step was crucial to avoid overburdening the right ventricle and causing disproportionate pulmonary blood. Consequently, appropriate pulmonary blood flow was provided, and RV function was maintained. Direct pressure measurements were consistently performed after the cessation of CPB, and a minimum pressure gradient of 40 mmHg was desired throughout RVOT with pulsatile pulmonary artery flow, oxygen saturation (SO_2) of 75 to 85%, and FiO_2 (fraction of inspired oxygen) of 30 to 50% to represent a balanced, banded ventricular septal defect (VSD). Before leaving the operating room, the patient was specifically observed for the requirement for inhaled nitric oxide, elevated FiO_2, or vasopressor administration to maintain SO_2 levels between 75 and 85%, which clearly indicates insufficient pulmonary blood flow.[6-10] In this scenario, further modifications to the patch were executed as required.

Statistical analysis

Statistical analyses were performed using Jamovi version 2.3.18.0 software. Continuous data were presented as median and interquartile range.

RESULTS

At the time of operation, the median age and median weight were 4.5 years (1 to 14.5 years) and 17.5 kg (7.75 to 51.25 kg), respectively. The median body surface area was 0.64 m^2 (0.4 to 1.5 m^2). Diagnoses were TOF with hypoplastic pulmonary arteries in 12 (86%) patients, pulmonary atresia with intact ventricular septum in one (7%), and TOF with absent left pulmonary artery in one (7%). The preoperative median oxygen saturation, hemoglobin, and hematocrit levels were 71.5% (69.5 to 72.5%), 17.1 g/dL (15.1 to 18.4 g/dL), and 53.6% (45.9 to 58.15%), respectively. Table 1 summarizes the demographic and

Table 1
Demographic and clinical characteristics of the patients

	n	%	Median	IQR
Demographics				
Age (years)			4.5	1-14.5
Sex				
Male	7	50		
Weight (kg)			17.5	7.75-51.25
BSA (m^2)			0.64	0.4-1.5
Preoperative variables				
Diagnoses				
TOF	12	86		
TOF-absent LPA	1	7		
PA-IVS	1	7		
SO_2 (%)			71	69-72
Hemoglobin (g/dL)			17.1	15.1-18.4
PA Z-score (median, IQR)			–3	–3.95 - –2.75
McGoon index (median, IQR))			1.35	1.2-1.4
Intraoperative variables				
Bypass time (min)			85	60.5-109.5
Cross-clamp time (min)			39.5	26.25-52.75
Additional procedures				
Secundum ASD closure	2			
Pulmonary valve vegetectomy	1			
RVOT patch materials				
Dacron velour patch	7	50		
Bovine pericardial patch	7	50		
Postoperative variables				
MV time (h)			5	3-8
ICU stay (day)			4	4-5
In-hospital stay (day)			12	11.75-20.75
Vasoactive inotropic scores			15	5-25
SO_2 (%)			93	86.25-94.25
Hemoglobin (g/dL)			12.65	12.1-14.7
McGoon index (median, IQR)				
Patients had complete repair			2	1.9-2.125
Patients awaiting for complete repair			1.6	1.5-1.7

IQR: Interquartile range; BSA: Body survey area; TOF: Tetralogy of Fallot; LPA: Left pulmonary artery; PA: Pulmonary atresia; IVS: Intact ventricular septum; ASD: Atrial septal deffect; RVOT: Right ventricular outflow tract; MV: Mechanical ventilation; ICU: Intensive care unit.

Table 2
List of previous operations of the cohort

Previous procedures	n
Left mBTT shunt	5
Right mBTT shunt	4
Central shunt	3
Sano shunt	1
RVOT stent	2
Percutaneous balloon valvuloplasty	1

mBTT: modified Blalock-Taussig-Thomas shunt; RVOT: Right ventricular outflow tract.

clinical characteristics of the patients. Fourteen patients underwent a total of 16 previous catheter or surgical interventions (1.14 interventions per patient). Of those 16 interventions, only three were catheter-directed RVOT stent implantations. The remaining 13 were different types of systemic-pulmonary artery shunt procedures. A detailed list of previous operations is shown in Table 2. The preoperative median Z-score of the pulmonary artery was –3 (–3.95 to –2.75), and the median McGoon ratio was 1.35 (1.2 to 1.4).

In terms of operative details, the median durations of CPB and aortic cross clamp were 85 min (60.5 to 109.5 min) and 39.5 min (26.25 to 52.75 min), respectively. Three patients underwent an additional cardiac operation at the time of the Brock procedure. Two were the closure of secundum atrial septal defect (ASD) (to decrease the risk of pulmonary overcirculation in the setting of large VSD and large ASD after the procedure) and the other was the vegetectomy of the infected foci in the pulmonary valve. In terms of patch material used during the Brock procedure, half of the patients had Dacron velour sheet, and the other half had bovine pericardial patch.

In all patients but one, the postoperative course was uncomplicated. All patients required inotropic support, with a median vasoactive inotropic score of 15. We were able to extubate all patients, except for one, in a median duration of 5 h (3 to 8 h), and the median length of stay in the intensive care unit was 4 days (4 to 5 days). The median duration of hospital stay was 12 days (11.75 to 27.25 days). There was one mortality that occurred two months after the operation. This patient had TOF with a hypoplastic pulmonary artery previously palliated with RVOT stent implantation, which was complicated and required emergency surgical operation. The patient collapsed in the 6th hour after the operation, and extracorporeal cardiopulmonary resuscitation was performed with central venoarterial extracorporeal membrane oxygenation (ECMO) cannulation. The patient was successfully weaned off ECMO on the fourth day of the circuit run but died two months after the initial operation due to extubation failure, tracheostomy requirement, and septic sequela.

Follow-up was complete for the remaining 13 patients with a median follow-up of seven years (6 to 8 years). Degree of pulmonary valvular regurgitation was mild-moderate in nine (70%) and moderate-severe in four (30%). Of these 13 patients, only four underwent complete repair during follow-up. The time interval between the modified Brock procedure and the complete repair was eight months, 11 months, two years, and three years. The growth of the pulmonary arterial tree as shown by the McGoon ratio in these patients was 1.2 to 1.9, 1.5 to 2.1, 1.4 to 1.9, and 1.2 to 2.2. The median McGoon ratio was 2 (1.9 to 2.125). Only one reoperation was required in four patients who underwent complete repair. It was a pulmonary valve replacement four years after total correction. For nine patients who had not undergone complete repair, only one reoperation for reaugmentation of the previously placed Brock patch was performed three years postoperatively. The postoperative median oxygen saturation, hemoglobin, and hematocrit levels were 93% (86.25 to 94.25%), 12.65 g/dL (12.1 to 14.7 g/dL), and 39.7% (37.6 to 44.7%), respectively. The postoperative median McGoon ratio was 1.6 (1.5 to 1.7). None of the patients had cyanotic spells, and there was no mortality during follow-up.

DISCUSSION

After the introduction of the Blalock-Thomas-Taussig (BTT) shunt in 1944, it garnered significant interest from both surgeons and the general public, becoming a widely adopted palliation method until it was eclipsed by direct corrective surgery. Later, Lord Russell Claude Brock innovated a closed transventricular pulmonary valvotomy technique, subsequently incorporating closed infundibular excision with a custom valvutome, which directly addresses outflow restriction and represents a genuine partial repair of the deformity.[2-4,13] The procedure was the first direct intracardiac intervention prior to the

development of echocardiography and CPB; however, this operation has not been widely adopted since then due to concerns about long-term survival, including recurrence of RVOT obstruction, arrhythmias, sudden cardiac mortality, and gradual biventricular dysfunction and failure, despite favorable short-term results, as indicated by reports.[6-12]

Right ventricular outflow tract stents, which have recently gained in popularity and are promoted as providing better hemodynamics and perhaps lower death rates compared to modified BTT (mBTT) shunts or ductal stenting, could be regarded as a transcatheter synthesis of a variant Brock procedure with an intracardiac Sano-type shunt, executed without CPB.[14-17] Therefore, surgical palliative procedures targeting RVOT have gained popularity recently. We employed the modified Brock procedure for patients with hypoplastic pulmonary arteries that hindered their ability to endure a full repair, as this technique offers advantages over BTT shunts. First, it facilitates antegrade flow via the natural pathway, promoting optimal uniform and symmetrical growth of the pulmonary arteries without distortion and gradually prepares the pulmonary bed for increased pulmonary blood flow. In extreme cases of TOF, it may facilitate the possibility of total correction. Second, the infundibulum and the RV cavity can also undergo further growth. Third, there may be a reduction in coronary steal attributed to decreased diastolic runoff. Fourth, the operation can also be repeated if necessary and facilitates further catheter interventions.[11,12,18] In our cohort, we managed to safely palliate patients with hypoplastic pulmonary arteries with a median SO_2 above 90% at mid-term follow-up. Mortality was low (7%) with a straightforward postoperative course, and we were able to achieve complete repair in 30% of the patients during follow-up in a median of 17.5 months after the modified Brock procedure. Similarly, a retrospective study from Germany with 11 patients reported that there was no perioperative mortality, and 10 patients underwent elective complete repair.[8] They determined that palliative RVOT construction may offer the potential for complete repair in a severe form of TOF. The Paris group reported an early mortality rate of 2.7%, an interstage attrition rate of 6.6%, and successful biventricular repair in 84 (77%) patients with the use of a similar technique. They also reported that a Nakata index of 74 mm^2/m for the mBTT shunt and 102 mm^2/m for the right ventricle-to-pulmonary artery connection, indicating that the right ventricle-to-pulmonary artery connection appeared to facilitate superior pulmonary artery growth compared to the mBTT shunt.[9,10] Batlivala et al.[11] reported their experience of 17 patients who underwent modified RVOT procedure as palliation, and they concluded that it is a viable alternative that produces satisfactory results by preventing the possibility of sudden mortality associated with a shunt. Another study from China reported that the modified Brock procedure appears to be a more effective strategy that ensures safety and promotes satisfactory pulmonary arterial growth until complete repair compared to the mBTS procedure.[12]

On the other hand, disadvantages can be listed as the requirement of CPB and cardioplegia, and the challenging nature of the technique that requires precise division and resection (risk of pulmonary overflow).[18] If the valve is excessively opened, physiological issues may arise, particularly in the context of a large VSD, when a double outlet ventricle is present. In TOF, pulmonary stenosis prevents most left ventricular output from diverting to the low pressure pulmonary vascular system. The protective mechanism is abruptly removed when the valve is opened via the Brock technique. Subsequent extensive postoperative pulmonary mucosal edema, difficult tracheal extubation, and even heart failure are possible.[11,12,18,19] Therefore, it is crucial to open the pulmonary valve to an appropriate extent. Proper adjustment of the valve may produce sufficient pulmonary blood flow without significant blood shunting to the lungs. We did not encounter any of these problems as a result of our meticulous surgical technique, including restricted muscle resection, restricted RVOT enlargement, preservation of the annulus, and leaving a pressure gradient between the right ventricle and pulmonary artery. Furthermore, the fine-tuning of the RVOT patch size according to immediate hemodynamic parameters after weaning off CPB helped us prevent pulmonary overcirculation, which can result in sudden left ventricular dilation, bradycardia, and cardiac arrest. We strongly believe that all these preventive measures helped us achieve low mortality and straightforward postoperative recovery. Classically, it was often accepted that TOF management required total alleviation of obstruction in the RVOT. Recently, an emphasis has been placed on the preservation of the pulmonary valve and annulus, and a greater residual RVOT gradient

after surgery may be tolerated to prevent early and long-term complications.[19,20] Similar considerations are crucial when addressing RVOT for palliation, as frequently highlighted in previous articles.[6-12] As we managed to preserve the annulus in our cohort, we believe that pulmonary regurgitation would not be a significant problem after complete repair.

Although 30% of our cohort has undergone total repair, nine individuals were still awaiting full repair, with satisfactory growth of the pulmonary artery. Our institutional strategy for complete repair in patients with hypoplastic pulmonary arteries is to achieve a McGoon ratio of no less than 1.8. Consequently, although there was growth in pulmonary arteries, individuals awaiting complete repair still exhibited a McGoon ratio below 1.8. Their functional state and oxygen saturation levels were decent during the most recent follow-up. We employed a proactive approach during follow-up to assess pulmonary arterial growth. In terms of the reoperations following the modified Brock procedure, only one patient necessitated reaugmentation of the patch. Late reoperation for restrictive flow is typically not the result of an initial technical failure, as is widely recognized. It is often the result of the progressive relative stenosis of the initial procedure, which was caused by somatic growth, and the lack of development of the pulmonary artery to facilitate a full repair. Interestingly, few case reports have recently been published presenting long-term follow-up after the classical Brock procedure. One of the earliest patients who underwent the Brock procedure, a four-year-old child, was reported to have survived an additional 43 years without further surgical intervention.[21] Other patients have been reported to remain active and asymptomatic 43, 52, and even 63 years after the Brock procedure with good biventricular function.[22-24] Brock's[2] initial hypothesis that the pulmonary arteries would endure substantial development as a result of enhanced flow through the natural channel is also supported by these patients. This would suggest that a smaller number of patients would require total correction.[4,6,13]

This study was limited by the fact that it was conducted retrospectively and observationally at a tertiary referral center and with a small sample size over an extended period of time. The generalizability of our findings was also limited by the significant anatomical heterogeneity within the patient population. In addition, no comparison was made with other palliative procedures. Comprehensive statistical analysis was ultimately limited by the number of deaths, reoperations, and complications. It is imperative to collect additional data consistent with surgical techniques in a larger population of patients to derive association metrics.

In conclusion, we believe that palliative repair of RVOT with the modified Brock procedure appears to be a viable option and should be the primary palliative therapy, as opposed to conventional aortopulmonary shunts, for patients whose pulmonary artery anatomy prevents complete repair. The modified Brock procedure contributes to the preservation of RV function by maintaining an appropriate pressure gradient between the right ventricle and pulmonary artery, as well as enhancing pulmonary arterial growth through pulsatile flow. The potential drawback of pulmonary overcirculation was not a significant problem in our experience. Close follow-up of patients after palliative RVOT augmentation is essential.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

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Effect of coronary artery diseases on ocular perfusion

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ABSTRACT

Objectives: This study aimed to evaluate the ocular perfusion of patients with ischemic coronary artery disease (CAD) using optical coherence tomography angiography.

Patients and methods: A total of 62 patients (49 male, 13 female; mean age: 62.9±9.1 years; range, 35 to 78 years) with a diagnosis of CAD were enrolled in this study. The data were compared with 61 healthy controls (35 male, 26 female; mean age: 68.1±3.9 years; range, 46 to 76 years). Coronary artery disease diagnosis was defined as patients who underwent percutaneous coronary intervention after coronary angiography. Optical coherence tomography angiography was used to assess the choroid thickness, superficial capillary plexus, and deep capillary plexus vascular density parameters of each patient.

Results: Choroid thickness was lower in the CAD group compared to the control group, but this decrease was not statistically significant. The results showed a significant decrease in superficial capillary plexus and deep capillary plexus parameters in CAD patients compared to healthy controls.

Conclusion: Patients with CAD showed decreased flow density compared to healthy controls. The study concludes that CAD patients exhibit reduced ocular perfusion, which can be detected using optical coherence tomography angiography. This noninvasive technique could be an effective tool for monitoring ocular perfusion and detecting vascular abnormalities in patients with CAD.

Keywords: Coronary artery disease, microvascular changes, ocular perfusion, optical coherence tomography angiography.

Coronary artery disease (CAD) is the most important cause of mortality and morbidity worldwide. Diagnosis requires a sequential approach, and the most currently accessible techniques to directly explore coronary vasculature are invasive. Precipitating factors of CAD include atherosclerosis, vasospasm, and a progressive chronic inflammatory process of arterial wall thickening or stenosis.[1] Several studies have shown a potential correlation between the coronary artery and many peripheral vessels in the human body, such as the cerebral, renal, and ocular vasculature.[2-4] Therefore, recent studies have suggested that ocular perfusion could serve as a promising marker for systemic vascular health.

The human retina, consisting of 10 layers, is supplied by two vascular beds: the retinal vessels and the choriocapillaris. The retinal vessels supply the inner layers of the retina that facilitate visual function, while the choriocapillaris provides oxygen and nutrients to the outer layers. The retinal vasculature, with blood vessels of a similar size to the coronary microvasculature, can be used as a representative of the subclinical coronary stenosis process. Due to the distinctive structure of the eyeball, fundus vasculopathy can be precisely detected by several examination techniques, including ophthalmoscopy, funduscopy, fundus photography, and fundus fluorescein angiography. Although fundus fluorescein angiography remains the gold standard in analyzing vascular and capillary

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beds despite its injection-related inconvenience and fluorescein side effects, optical coherence tomography angiography (OCTA), a novel noninvasive imaging modality that has gained importance in recent years due to its capability of imaging the microvasculature of retinal and choroidal vessels for diagnosing ophthalmological and systemic diseases. The evaluation and quantification of vascular density and blood flow across various anatomical layers of the fundus can be accomplished using OCTA.[5] This noninvasive imaging technique has proven useful as an early diagnostic tool for numerous ocular angiopathies, including age-related macular degeneration,[6,7] diabetic retinopathy,[8] and hypertensive retinopathy.[9] In addition, it also has the potential to provide insights into the microvascular changes that occur in different systemic diseases, including CAD.[10] The retinal microvasculature has been proposed as a proxy for coronary circulation in various publications, although there is still contrasting evidence on the strength of this relationship. This study aimed to investigate vascular changes in the retina and choroid of participants diagnosed with CAD through coronary angiography using OCTA.

PATIENTS AND METHODS

This prospective, cross-sectional, observational case-control study involving 62 patients (49 male, 13 female; mean age: 62.9±9.1 years; range, 35 to 78 years) with CAD and 61 age- and sex-matched healthy controls (35 male, 26 female; mean age: 68.1±3.9 years; range, 46 to 76 years). The CAD diagnosis was defined as patients who underwent percutaneous coronary intervention after coronary angiography by the same expert specialist. Patients diagnosed with acute coronary syndrome were not included in the study. Approximately half of the patients underwent right coronary artery intervention (n=29, 46.8%). Circumflex artery intervention was performed in 18 (29%) patients, and left anterior descending artery intervention was performed in 15 (24.2%) patients. Twenty-five (40.3%) patients underwent elective percutaneous intervention on the other untreated coronary artery. After an ophthalmic examination for ocular diseases, OCTA was performed on all patients. Optical coherence tomography angiography was performed using a commercially available OCTA device (AngioVue; Optovue Inc., Fremont, CA, USA). The superficial capillary plexus (SCP) and deep capillary plexus (DCP) vascular density parameters were measured and analyzed using the built-in AngioRetina software. Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the İzmir University of Economics Clinical Research Ethics Committee (date 11.01.2023, no: 2023/1). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria included the following: *(i)* a definite diagnosis of CAD for the CAD group; *(ii)* being between 18 and 70 years of age; *(iii)* not having any previous disease that may affect the blood supply to the eye; *(iv)* not having any diseases that would prevent eye measurement. Coronary artery disease patients with moderate and high myopia/hyperopia (≥3 diopters or axial length ≥26 mm), any kind of glaucoma, dioptric media opacity that may affect OCTA imaging, and a history of any intraocular surgery or other fundus diseases were excluded. Patients with firm evidence of macular edema were also excluded. The control subjects had a best corrected visual acuity of 16/20 or better and underwent an ophthalmic examination to exclude glaucoma, cataract, fundus diseases, or other systemic diseases.

Optical coherence tomography angiography was performed to capture retinal and choroidal images using an AngioVue OCTA instrument (wavelength: 840 nm) and Avanti System version 2016.1.0. Optovue AngioVue software version 2016.1.0 (Optovue Inc., Fremont, CA, USA) was used to perform measurements of vessel density. The OCTA imaging software automatically fitted the examined zones based on the actual picture by the same examiner. In addition, the software automatically adjusted the specified margins while concurrently measuring the density of vessels. For OCTA, 100,000 A-scans are acquired per second to obtain images of the macula with a 3×3 mm^2. Five divided areas with the macula at the center are displayed, and the blood vessel density of each area is indicated as a percententage. The diameter of the inner circle is 1 mm, and the diameter of the outside circle is displayed at 3 mm (Figures 1, 2). The avascular zone of the fovea (mm^2) was then analyzed in the SCP and DCP OCTA of the macula. All patients were imaged in the same stage and under the same

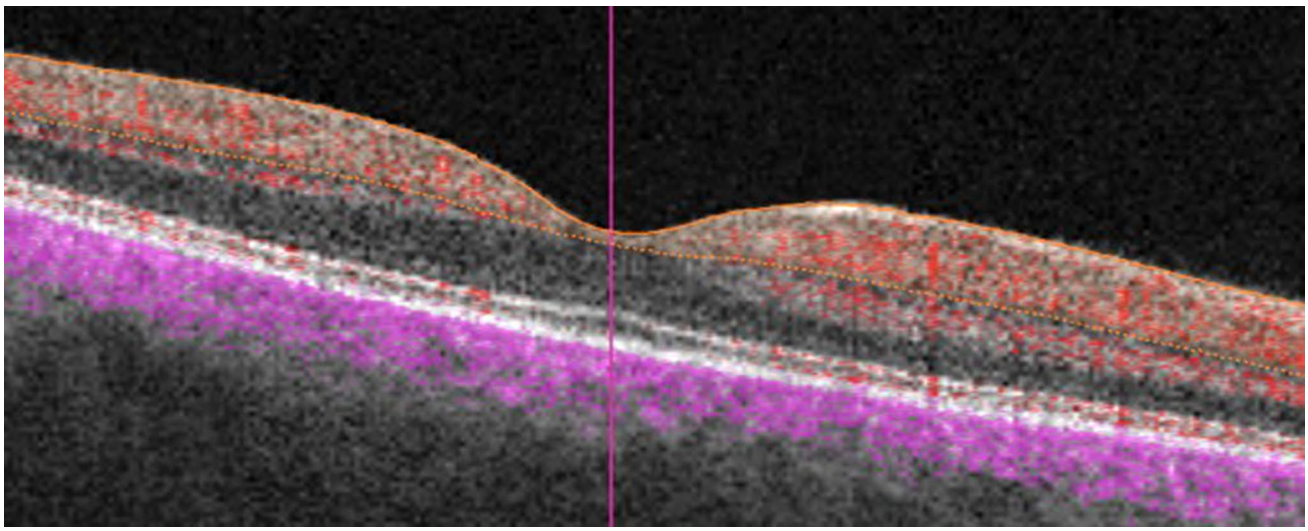

Figure 1. Cross-sectional image showing structural optical coherence tomography in the background and superficial vascular plexus data as a yellow overlay.

situations. Data reassessment was conducted by two independent, blinded examiners, followed by a final decision by a third blinded investigator in cases where discrepancies or disagreements arose during the assessments.

Statistical analysis

The statistical analysis of the study was performed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Continuous variables that were examined, including vessel density, were presented as means ± standard deviation (SD). The differences between the two groups were evaluated through the chi-square test and two sample t-test. All statistical tests were two-tailed, and *p*-values <0.05 were considered statistically significant.

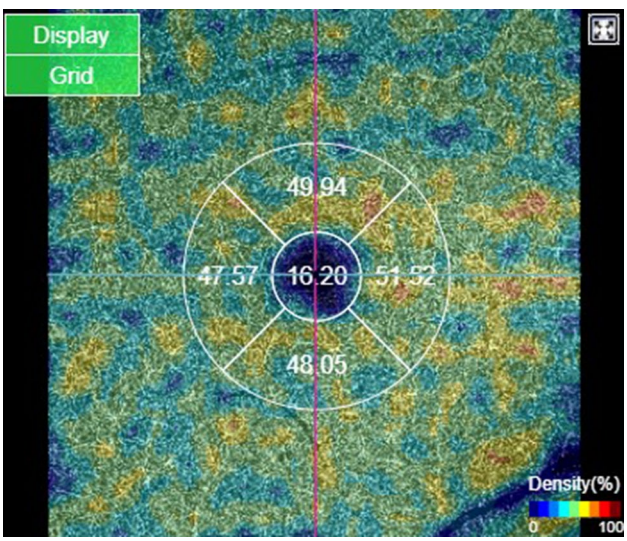

Figure 2. Vascular density in five regions, including the fovea (1-mm diameter), temporal, inferior, nasal, and superior quadrants (1-mm annular ring).

RESULTS

There were no significant differences in age, sex, or intraocular pressure between the two groups (Table 1). Patients diagnosed with CAD and volunteers participating in the control group did not have systemic diseases, such as hypertension, diabetes mellitus, heart failure, moderate/severe heart valve disease, thyroid dysfunction, or liver and kidney failure. No statistically significant difference was detected in total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglyceride levels in blood samples between the groups. No statistically significant differences were detected between the patient group and the control group in terms of echocardiographic parameters. Choroid thickness was lower in the CAD group compared to the control group, but this decrease was not statistically significant (286.42±78.93 µm *vs.* 309.32±72.93 µm). Superficial capillary plexus was significantly lower in the CAD group compared to the control group (15.4±2.1% *vs.* 16.9±3.4%; p=0.003). Deep capillary

Table 1
Demographic features and intraocular pressure of the study and control groups

	CAD group (n=62)			Control group (n=61)		
	n	%	Mean±SD	n	%	Mean±SD
Age (year)			62.9±9.1			68.1±3.9
Sex						
Female	13	20.9		26	42.6	
Male	49	79.1		35	57.4	
Intraocular pressure (mmHg)			16.05±3.13			14.55±3.50

CAD: Coronary artery disease; SD: Standard deviation.

plexus was also considerably lower in the CAD group compared to the control group (14.4±2.4% *vs.* 16.8±5.0%; p=0.001; Table 2).

DISCUSSION

Previous studies have provided limited data supporting the association between retinal microvasculature changes and CAD. In one such study, Tabatabaee et al.[3] demonstrated a strong correlation between retinal arterial atherosclerosis and the extent and severity of CAD using fundus photography. In addition, Wong et al.[11] confirmed the link between retinal arteriolar narrowing and the development of CAD by measuring the diameters of individual arterioles and venules on retinal photographs.

Arnould et al.[10] carried out a study where they compared the superficial retinal layer (SRL) vascular length (VL) of 44 healthy individuals to that of 237 patients who had been hospitalized for acute coronary syndrome. They found that in the parafoveal zone (excluding the central fovea), there was a significant decrease in SRL VL after matching 44 healthy individuals with 44 hospitalized patients.[10,12] The study established a connection between the retinal microvascular features and the cardiovascular risk profile of hospitalized patients. Patients with a lower VL were generally older and had a higher incidence of high blood pressure and diabetes mellitus. They also had a lower left ventricular ejection fraction and worse biological parameters, such as higher blood glucose, glycated hemoglobin A1c (HbA1c), creatinine, and N-terminal probrain natriuretic peptide. The study also identified two independent parameters, namely left ventricular ejection fraction and the burden of cardiovascular risk factors assessed by the American Heart Association risk score, which were negatively associated with the VL. Additionally, Arnould et al.[10] found moderate correlations between VL and two risk scores: Global Registry of Acute Coronary Events and the Reduction of Atherothrombosis for Continued Health. They also investigated the relationship between OCTA measured VL and hemodynamic variables in patients with myocardial infarction both during the acute phase and three months after cardiac rehabilitation.[13,14]

Table 2
Choroid thickness, SCP, and DCP perfusion in the study and control groups

	CAD group	Control group
	Mean±SD	Mean±SD
OCTA choroid (μm)	286.42±78.93	309.32±72.93
OCTA SCP (%)	15.4±2.1*	16.9±3.4*
OCTA DCP (%)	14.4±2.4*	16.8±5.0*

SCP: Superficial capillary plexus; DCP: Deep capillary plexus; CAD: Coronary artery disease; SD: Standard deviation; OCTA: Optical coherence tomography angiography; * p<0.05.

The study did not reveal any notable distinctions between the two time points or the OCTA parameters and cardiac hemodynamic variables, whether they were acute or chronic, such as left ventricular ejection fraction, aortic blood flow, systolic blood pressure, diastolic blood pressure, and cardiac output. This implies that the regulation of retinal microvasculature is not influenced by that of systemic circulation, indicating that it is self-regulated. However, it is important to note that the study did not assess the VL in the deep retinal layer (DRL), and the number of participants in the study was limited.[13]

Wang et al.[15] conducted a study that used OCTA to examine the relationship between vessel density, blood flow in the retina and choroid, and CAD. Their findings indicated a significant reduction in vessel density and flow area in most zones, except for SRL and DRL in the fovea in CAD patients. The researchers further analyzed the correlation between the changes in fundus microvasculature and the Gensini score, which reflects the severity of stenosis, in each coronary artery branch. They discovered that the degree of stenosis in the left main coronary artery, proximal left circumflex artery, and right coronary artery had a significant negative association with VD changes in the SRL and DRL. Proximal stenosis of the left anterior descending artery had a negative relationship with VD in the DRL. In terms of choroidal flow changes, negative correlations were found between this parameter and the severity of stenosis in the left main coronary artery, proximal left circumflex artery, and right coronary artery.[15]

In summary, the research outcomes indicate that OCTA has the potential to offer valuable insights into microvascular alterations linked to cardiovascular diseases and the capability to identify diminished ocular perfusion among patients with CAD. According to this investigation, there was a significant decline in the SCP and DCP vessel density metrics in CAD patients compared to their healthy counterparts. These findings indicate that patients with CAD experience a reduction in ocular perfusion, which may be associated with systemic vascular dysfunction.[10] Additionally, several investigations have highlighted the correlation between OCTA parameters and the severity or progression of CAD, suggesting that OCTA could serve as a noninvasive biomarker with clinical utility for predicting the risk of cardiovascular disease.[14]

The use of OCTA as a means of monitoring ocular perfusion and identifying vascular irregularities in patients with CAD could be a viable option. Nevertheless, additional investigations are required to validate these results and explore the possible contributions of OCTA in managing CAD patients. The conclusions of our research indicate that OCTA could be employed as a screening method for the prompt detection of CAD in populations with a high risk of the condition.

Furthermore, we found that OCTA is a reliable and noninvasive method for detecting early-stage CAD in high-risk patients showing reduced retinal vessel density, choroidal vessel density, and flow area. Therefore, early interventions such as percutaneous coronary intervention should be actively pursued to prevent myocardial infarction in such patients. Regular ophthalmic follow-up for high-risk patients may also effectively reduce the morbidity of ocular complications.

Previous studies have assessed the relationship between retinal vascular changes and CAD. For instance, a study including 109 CAD patients demonstrated a strong correlation between the degree of retinal arterial atherosclerosis and the severity and extent of CAD.[16] Some studies have also suggested that the diameter of retinal vessels, particularly arterioles, may predict the risk of CAD and stroke-related deaths in middle-aged individuals, which suggests that microvascular changes may contribute to the development of CAD.[15,17]

Our study revealed a decrease in both the SCP and DCP among patients with CAD. These results indicate that minor modifications in retinal vascularization could potentially function as early warning signals of cardiovascular disease, allowing cardiologists to intervene promptly. As a result, implementing this approach may prove successful in minimizing the frequency of myocardial infarctions.

Several theories have been suggested to account for these findings. Atherosclerotic alterations in the fundus vessels have been linked to thickening of the microvascular wall, lipid buildup, fibrosis, and calcification of larger arteries. Consequently, retinal arteriolar narrowing triggers premature microvascular injury. Individuals with CAD exhibit similar pathological characteristics in their coronary arteries as those found in the fundus vessels. As a result, changes in retinal or choroidal microvasculature may mirror systemic macrovascular modifications, particularly in instances of coronary artery stenosis.[15,16]

Although coronary angiography is the recognized benchmark for diagnosing cardiovascular diseases, it has some disadvantages, including adverse reactions and injuries caused by the contrast agent. Consequently, in some cases, there is a preference for less invasive techniques. One such approach is coronary computed tomography angiography, which offers several benefits over traditional angiography.

Nevertheless, it is unsuitable for some vulnerable patients. In these instances, OCTA provides a novel, noninvasive, drug-free diagnostic alternative.[15,18,19]

Several limitations were present in our study, including a homogeneous population, a relatively limited sample size, and a lack of long-term follow-up. Additionally, our study exhibited low statistical power due to its relatively limited sample size.

In conclusion, this study revealed a reduction in vessel density across various retinal layers in CAD patients, despite the absence of any observable clinical symptoms. These outcomes imply that CAD individuals may experience retinal vascular harm at an early stage. Optical coherence tomography angiography proves to be an effective and precise diagnostic method for detecting early-stage retina and choroid damage in CAD patients. Further comprehensive and longitudinal investigations are essential to substantiate these findings.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the research, acquisition of data, analysis and interpretation of the data, Statistical analysis and Obtaining financing, writing of the manuscript: C.T., S.G., T.O., O.U.F.; Critical revision of the manuscript for content: C.T., T.O., O.U.F.

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Cardiovascular Surgery and Interventions

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The utility of Vitamin D levels in predicting the severity of coronary artery disease in obese patients

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ABSTRACT

Objectives: This study aimed to investigate the relationship between Vitamin D (25-hydroxy [OH]D, 25[OH]D) levels and the severity of coronary artery disease (CAD), as measured by the SYNTAX score, in obese patients undergoing angiography for stable angina pectoris.

Patients and methods: This retrospective study included 120 obese patients (61 males, 59 females; mean age: 61.7±10.5 years) who underwent coronary angiography between May 2012 and June 2023. Obesity was defined as a body mass index >30 kg/m^2. Serum Vitamin D levels were measured within six months before angiography, and CAD severity was assessed using the SYNTAX score. Patients were categorized into three groups based on their SYNTAX scores: <23, 23-32, and ≥33.

Results: The 25(OH)D levels were significantly lower in the group with the highest SYNTAX scores. Multivariable regression analysis identified 25(OH)D levels as an independent predictor of the SYNTAX score (odds ratio=0.809, 95% confidence interval 0.743-0.881, p<0.001). A strong negative correlation was observed between 25(OH)D levels and SYNTAX scores (r=0.77, p<0.001). Additionally, a serum 25(OH)D level of 13.87 ng/mL could predict high SYNTAX scores with 81% sensitivity and 80.6% specificity.

Conclusion: This study demonstrates a significant association between low 25(OH)D levels and higher SYNTAX scores, indicating more severe CAD in obese individuals. Vitamin D deficiency may be an independent predictor of CAD severity in this population.

Keywords: Coronary artery disease, obesity, SYNTAX score, Vitamin D, 25(OH)D

Obesity is a growing global health issue, defined by a body mass index (BMI) over 30 kg/m^2. According to World Health Organization data, 16% of adults were obese in 2022. Its prevalence has more than doubled compared to 1990. Obesity is well-known to contribute to coronary artery disease (CAD) by accelerating atherosclerosis through mechanisms such as insulin resistance and inflammation.[1] It raises the risk of CAD by contributing to other traditional cardiovascular risk factors, such as diabetes and hypertension.[1]

Vitamin D deficiency is another significant public health issue due to its widespread prevalence.[2] The serum 25-hydroxy (OH)D (25[OH]D) level is measured to assess Vitamin D status, and low levels of 25(OH)D can lead to a range of health issues, mainly bone disorders. Beyond skeletal problems, low 25(OH)D levels have been associated with an increased risk of chronic diseases, such as cardiovascular diseases and the severity of CAD.[3,4] Importantly, Vitamin D deficiency is more prevalent among obese individuals, who are already at a heightened risk for CAD.[5]

Both obesity and Vitamin D deficiency may independently contribute to an increased risk of cardiovascular disease. The coexistence of these two conditions may further exacerbate the severity of CAD. It is known that Vitamin D deficiency is more common in obese people than in those with normal BMI. Therefore, this study aimed investigate the relationship between Vitamin D status and the severity of CAD, as measured by the SYNTAX score, in obese

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patients who underwent angiography for stable angina pectoris.

PATIENTS AND METHODS

In this study, files of patients who underwent angiography due to stable angina pectoris at the Gazi University Faculty of Medicine between May 2012 and June 2023 were retrospectively scanned. One hundred twenty patients (61 males, 59 females; mean age: 61.7±10.5 years) who had their 25(OH)D levels tested within six months before coronary angiography for various reasons, such as general health check-ups or osteoporosis risk evaluation, and who were classified as obese (BMI >30 kg/m^2) were included. Serum 25(OH)D levels were measured from venous blood samples using the Architect 25(OH) Vitamin D analysis kit (Abbott Laboratories, Chicago, United States of America). The SYNTAX score was calculated to determine the extent of CAD from the angiography images of the patients. The SYNTAX score calculation was performed using the international calculation method (www.syntaxscore.com). Patients were divided into three groups based on their SYNTAX score: a score of ≤22 was classified as mild disease, a score between 23 and 32 as moderate disease, and a score ≥33 as severe disease. Exclusion criteria were age under 18 years, acute coronary syndrome, evidence of acute or chronic infection, systemic inflammatory or autoimmune disease, history of using glucocorticoid therapy within the past three months, trauma, recent major surgery, active malignancy, hypo-or hyperthyroidism, hematological diseases, and severe liver or renal failure. None of the patients had a genetic condition that would affect their 25(OH)D levels, and it was also confirmed that no patient was receiving oral Vitamin D therapy. Patients without documented 25(OH)D levels within the last six months were excluded from the study. The study protocol was approved by the Gazi University Faculty of Medicine Ethics Committee (date: 10.09.2024, no: 2024-1441). Written informed consent was acquired from all participants. The study was conducted in accordance with the criteria of the Declaration of Helsinki.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The normality of the distribution of the data was assessed using a Kolmogorov-Smirnov test. Data were presented as frequency (percentage), median and interquartile range, (IQR) or mean ± standard deviation (SD). Categorical variables were subjected to comparison using the chi-square test. Continuous variables between study groups were compared using one-way analysis of variance or the Kruskal-Wallis test. Multivariable logistic regression analysis was utilized to identify factors contributing to the SYNTAX score. The correlation between 25(OH)D levels and the SYNTAX score was evaluated using Pearson's test. The capacity of 25(OH)D value in predicting a high SYNTAX score was analyzed using receiver operating characteristic curve analysis. All statistical analyses were performed two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Forty-five of the patients had a SYNTAX score ≤22, 38 had a score between 22 and 32, and 37 had a score ≥33. Age, sex, BMI, hypertension, and diabetes rates were similar between the groups (p>0.05 for all parameters). In addition, no statistical difference was found between the groups in terms of hemogram and biochemistry values. Moreover, 25(OH)D levels were the lowest in the group with the highest SYNTAX score, while 25(OH)D levels were the highest in the group with the lowest SYNTAX score (34.7±3.9 ng/mL *vs.* 17.5±7.5 ng/mL *vs.* 11.6±6.5 ng/mL; Table 1).

In the multivariable regression analysis, 25(OH)D levels were found to be an independent predictor of the SYNTAX score (odds ratio=0.809, 95% confidence interval 0.743-0.881, p<0.001; Table 2). There was a strong negative correlation between the SYNTAX score and 25(OH)D levels (r=0.77, p<0.001; Figure 1). Additionally, a serum 25(OH)D level of 13.87 ng/mL could predict a SYNTAX score with 81% sensitivity and 80.6% specificity (Figure 2).

DISCUSSION

This study revealed a significant relationship between 25(OH)D levels and the severity of CAD in obese patients. Our findings suggest that lower 25(OH)D levels are associated with increased coronary lesion complexity and severity. Furthermore, 25(OH)D levels were an independent predictor of SYNTAX scores in obese patients.

Table 1
Baseline clinical and laboratory parameters of the study population (n=120)

	SYNTAX score <22 (n=45)					SYNTAX score 22-32 (n=38)					SYNTAX score ≥33 (n=37)					
	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			61.7±1.5					61.2±1.7					62.2±1.8			0.914
Sex Male	23	51				22	58				16	43				0.447
BMI (kg/m^2)			34.7±2.2					35.2±2.2					34.6±2.1			0.490
Smokers	11	24				9	24				10	27				0.940
Hypertension	19	42				15	40				188	49				0.712
Diabetes mellitus	15	33				12	32				16	43				0.521
Glucose (mg/dL)				106	89.5-145				99	88.7-157				107	89.2-132.5	0.944
Urea (mg/dL)			18±5.4					18.3±7.2					17.4±5.1			0.831
Creatinine (mg/dL)			0.9±0.2					0.8±0.2					0.9±0.2			0.620
Sodium (mEq/L)			140.2±3.1					140.1±2.3					140.3±2.2			0.936
Potassium (mmol/L)			4.2±0.3					4.3±0.3					4.2±0.3			0.243
Total cholesterol (mg/dL)			178.6±65					193.5±60.3					192.9±50.8			0.433
Triglyceride (mg/dL)			48.5±10.8					50.7±16.7					48.6±13.4			0.828
HDL (mg/dL)				47	41-55.5				47.5	38.7-59.5				45	37-60.5	0.734
LDL (mg/dL)			93.6±44.5					103.2±43.6					106.5±38.1			0.348
Hemoglobin (g/dL)			13.8±1.8					13.4±1.5					13.6±1.6			0.586
Platelet count (×10^3)			258.9±92.8					242.1±77.5					228.5±58.9			0.286
White blood cells (×10^3)			7.5±1.8					7.8±2.3					7.6±2.8			0.693
25(OH)D (ng/mL)			34.7±3.9					17.5±7.5					11.6±6.5			<0.001
Ejection fraction (%)			63.8±3.9					63.2±5.7					61.5±7.1			0.177

SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; 25(OH)D: Vitamin D.

Table 2
Multivariable logistic regression analyses showing the independent predictors of the presence of a SYNTAX score ≥33 in obese patients

	Multivariable analysis			
		95% CI		
	OR	Lower	Upper	*p*
Age	1.057	0.999	1.119	0.054
Sex	0.345	0.114	1.047	0.060
Hypertension	1.310	0.438	3.916	0.630
Diabetes mellitus	1.494	0.473	4.716	0.494
Smoking	1.205	0.332	4.370	0.776
Low-density lipoprotein	1.002	0.989	1.016	0.750
25(OH)D	0.809	0.743	0.881	<0.001

CI: Confidence interval; OR: Odds ratio; 25(OH)D: Vitamin D.

Previous studies have shown an inverse relationship between serum 25(OH)D levels and obesity.[5-8] Several hypotheses have been proposed to explain how obesity leads to Vitamin D deficiency. The most likely mechanism is believed to be the volumetric distribution of Vitamin D. Since adipose tissue acts as a reservoir for Vitamin D, obese patients tend to have lower serum concentrations compared to lean individuals, even when their overall 25(OH)D levels are similar.[9,10] Additionally, obese individuals tend to respond less effectively to Vitamin D supplements.[11] Another possible mechanism is the impairment of 25-hydroxylation caused by hepatic steatosis, a condition commonly observed in obese individuals. This impairment leads to a reduction in the conversion of Vitamin D into its active form.[9] Other hypotheses include poor dietary habits, reduced sun exposure, and variations in gene expression that affect Vitamin D metabolism.[9]

Our results also align with observational studies identifying a link between serum 25(OH)D levels and CAD.[12,13] A comprehensive meta-analysis of prospective studies involving over 18,000 participants demonstrated that the serum 25(OH)D level was

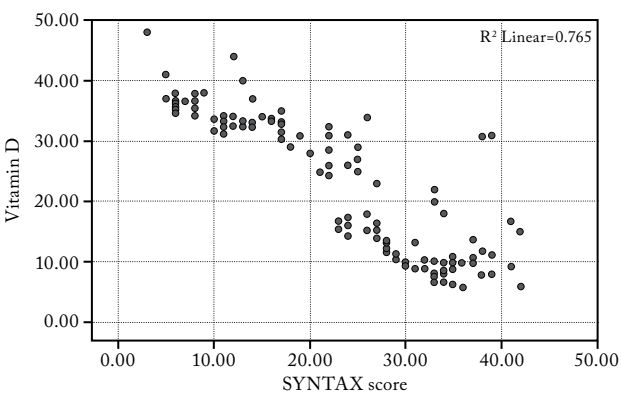

Figure 1. Correlation between 25(OH)D levels and SYNTAX scores in the study population.
25(OH)D: Vitamin D.

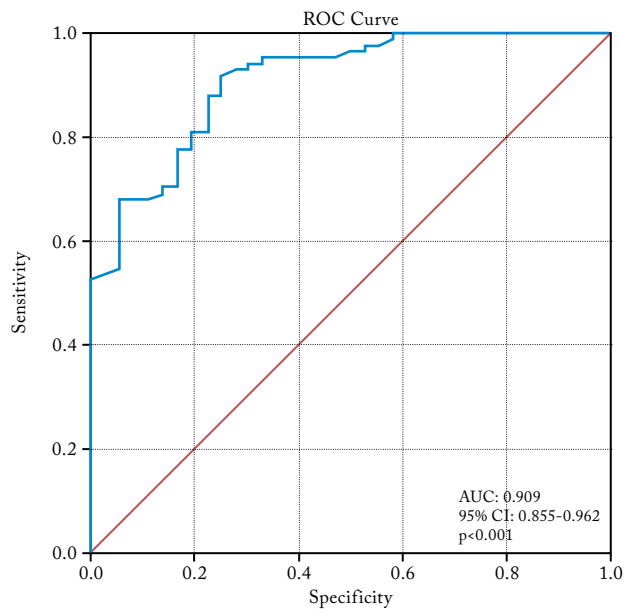

Figure 2. Receiver operating characteristic curve analysis of the 25(OH)D level for the detection of high SYNTAX scores (<33 *vs.* ≥33 comparison).
25(OH)D: Vitamin D.

inversely associated with the risk of cardiovascular events and cardiovascular mortality.[14] Verdoia et al.[4] demonstrated that lower 25(OH)D levels were associated with the severity of CAD. Similarly, a study involving 348 patients undergoing coronary angiography found that lower serum 25(OH)D levels were independently associated with higher SYNTAX scores, indicating more severe coronary lesions.[15] Notably, our findings extend these observations specifically to obese patients, confirming that low 25(OH)D levels are associated with increased coronary lesion complexity and severity.

Vitamin D appears to play a protective role in atherosclerosis through multiple mechanisms. It prevents endothelial dysfunction by increasing nitric oxide production, reducing oxidative stress, and inhibiting inflammatory cytokines and adhesion molecules.[16] Vitamin D also regulates vascular tone and angiogenesis.[16] In vascular smooth muscle cells, it has antiproliferative effects and impacts processes such as cell migration and fibrosis.[16] Another potential mechanism by which Vitamin D might influence myocardial infarction risk is through its effect on vascular calcification, as evidenced by the negative relationship between levels of 1,25-dihydroxyvitamin D and vascular calcification.[17] Vitamin D modulates immune responses by shifting the balance from proatherogenic T helper 1 cells to antiatherogenic T helper 2 profiles.[16] It also influences atherosclerosis by improving systemic conditions that contribute to it, such as insulin sensitivity, beta cell function, and lipid profiles.[16] Furthermore, it suppresses the renin-angiotensin-aldosterone system.[16]

Obesity is associated with a chronic, low-level inflammatory state that affects several metabolic and vascular pathways, such as insulin resistance, endothelial function, and lipid metabolism, all of which are also influenced by Vitamin D.[18] Additionally, obesity has been linked to increased inflammation in epicardial adipose tissue, which significantly correlates with the pathogenesis of CAD.[19] In obese individuals, low 25(OH)D levels can worsen these conditions, leading to increased atherosclerosis and higher cardiovascular risk. This is primarily assumed to be because low 25(OH)D levels fail to counteract oxidative stress.[20] However, it is unclear whether these factors are impaired simultaneously or whether there is a causal relationship.

There were some limitations to this study. First, as a cross-sectional study, the causal relationship between 25(OH)D levels and the severity of coronary artery stenosis could not be established. Second, 25(OH)D levels were measured only once within six months before angiography, which might not reflect seasonal or lifestyle changes. Third, the number of patients in the study was relatively low.

In conclusion, this study demonstrates a significant association between low serum 25(OH)D levels and higher SYNTAX scores, indicating more severe CAD in obese individuals. Additionally, in obese patients, Vitamin D levels were an independent predictor of SYNTAX scores.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization, investigation, writing-original draft, review, and editing: B.C.; Data curation, investigation, methodology, review and editing: B.A.Y.; Methodology, formal analysis, supervision, writing-review and editing: M.C.

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Cardiovascular Surgery and Interventions

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Effects of vascular endothelial growth factor inhibitors on systemic arterial blood pressure: Evaluation by ambulatory blood pressure measurement

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ABSTRACT

Objectives: This study aimed to determine the effects of vascular endothelial growth factor (VEGF) inhibitors on arterial blood pressure levels by performing ambulatory blood pressure measurement evaluation before and after the treatment.

Patients and methods: In this prospective study, A total of 33 patients (13 males, 20 females; mean age: 58.3±10.6 years; range, 33 to 82 years) were selected among those who applied to the cardiology clinic for cardiac evaluation before VEGF inhibitor treatment between September 2020 and November 2021. Twenty-four-hour ambulatory blood pressure examinations were performed before the treatment, and after four to six weeks of treatment (30 days for oral medications; after the third cycle for bevacizumab), ambulatory blood pressure examinations were repeated.

Results: With the evaluation of mean, ambulatory blood pressure measurement results, an increase was found in systolic and diastolic measurements during the day, night, and over 24 h. A statistically significant increase was observed in mean systolic, mean diastolic, daytime systolic, and daytime diastolic measurements.

Conclusion: Findings demonstrate that VEGF inhibitors increased the mean arterial blood pressure (all day mean, day time, and night time) and both systolic and diastolic pressures regardless of hypertension history. In this context, patients receiving VEGF inhibitor therapy should be more closely followed in their oncological evaluation.

Keywords: Ambulatory blood pressure measurement, hypertension side effects, VEGF inhibitors.

Hypertension is a common condition in the daily cardiology practice. Therefore, its management, treatment, and preventive measures are relatively well-defined. Although the diagnosis and treatment of hypertension might slightly differ in different sources and guidelines, a consensus can be reached regarding clinical studies and possible complications of hypertension.[1,2] Along with increasing the coordination and awareness between clinical branches, knowledge and experience of noncardiac hypertensive conditions have been increasing. With the progression of oncological science and research, new drugs and treatment protocols are emerging day by day. However, the usage of these drugs also creates possible side effects. Vascular endothelial growth factor (VEGF) inhibitors' clinical use started in 2004 with the USA Food and Drug Administration approval for the usage of bevacizumab in colorectal carcinoma. They are effective molecules that are increasingly used in cancer treatment by preventing the formation of new vessels.[3,4]

Vascular endothelial growth factor is one of the primary regulators of angiogenesis and triggers and promotes endothelial cell growth following its activation. Vascular endothelial growth factor molecules are encoded by a family of genes, including VEGF-A, VEGF-B, VEGF-C, and VEGF-D, as well as placental growth factor. These are mainly required

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for blood and lymphatic vessel formation.[4] Vascular endothelial growth factor inhibitors were developed to decrease tumor angiogenesis and destabilize existing tumor vascularization by blocking tumor blood flow.[5] Vascular endothelial growth factor causes increased nitric oxide (NO) production by stimulating endothelial NO synthase through the activation of VEGF receptor 2. Therefore, inhibition of the VEGF pathway and decreased NO bioavailability are believed to cause vasoconstriction and the development of hypertension.[6,7]

The clinical appearance of hypertension is relatively well-known. Some signs and symptoms can verify hypertension development besides the arterial blood pressure measurements. For instance, side effects such as headache, fatigue, developing retinopathy, or vascular complications, as well as some unusual metabolical parameters regarding newly developing hypertension, such as asymmetric dimethylarginine levels.[8] Furthermore, sometimes an infective state like the COVID-19 (coronavirus disease 2019) pandemic can cause hypertension-related symptoms.[9] These might be explained by psychological or diet-related factors or the infection itself. Nevertheless, none of the above could make the hypertension side effect diagnosis without obvious evidence. Therefore, with a molecule that relates to the hypertension side effect, these signs and measurements of the arterial blood pressure should be assessed regularly.

This study aimed to determine the effects of VEGF inhibitors on arterial blood pressure levels by performing ambulatory blood pressure measurement evaluation before and after the treatment.

PATIENTS AND METHODS

In this prospective study, the patients included in the study group were selected from patients who were referred to the cardiology outpatient clinic at the Manisa Celal Bayar University Faculty of Medicine between September 2020 and November 2021 after an assessment by the oncology outpatient clinic and were decided to commence a VEGF inhibitor treatment. A total of 57 patients who were diagnosed with colorectal, ovarian, renal cell, breast, gastrointestinal stromal tumor, and rectum carcinoma were included in our study. However, within the first assessments, a total of 24 patients were excluded. Among these patients, those who already had a hypertension diagnosis, those taking antihypertensive drugs, and those who were diagnosed with systolic or diastolic heart failure were excluded. Subsequently, some patients were excluded due to a hypertensive state at the first ambulatory measurement during the follow-up. Among these patients, there were no additional symptoms, except for headaches some patients had described. All the patients who had hypertension were treated with oral antihypertensive drugs according to the guidelines, and subsequently, all the arterial blood pressure measurements were controlled within normal ranges. Finally, 33 patients (13 males, 20 females; mean age: 58.3±10.6 years; range, 33 to 82 years) were included in the study. The baseline characteristics and demographic characteristics of the patients are summarized in Table 1. Twenty-four-hour ambulatory blood pressure measurements were performed before the treatment, and the results were evaluated. Blood tests were requested during the patient's routine outpatient examinations. After approximately four to six weeks of treatment (30 days for oral medications; after the third cycle for bevacizumab treatment), 24-h ambulatory blood pressure measurements were repeated, and the results before and after the treatments were compared. Twent-four-hour ambulatory blood pressure measurements were performed with hourly measurements during the day and night (12 daytime and 12 nighttime measurements). Valid measurements from 22 to 24 hours were accepted for evaluation. The study protocol was approved by the Manisa Celal Bayar University Ethics Committee (date: 31.12.2020, no: E-85252386-050.04.04-10360). Written informed

Table 1
Baseline characteristics of patients (n=33)

	n	%	Mean±SD
Age (year)			58.3±10.6
Sex			
Female	20	60.6	
Body mass index (kg/m^2)			27.59±3.63
Comorbidities			
Diabetes mellitus	10	10.3	
Coronary artery disease	5	15.2	
Chronic kidney disease	1	3	
Smoking	3	9.1	
Medications			
Bevacizumab	28	84.84	
Sunitinib	4	12.12	
Sorafenib	1	3	

SD: Standard deviation.

consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA), and figures were constructed using GraphPad Prism version 8 (GraphPad Software, La Jolla, CA, USA). The Shapiro-Wilk test was used to assess whether the continuous variables were distributed normally. Categorical variables were summarized with the use of frequencies and proportions and were compared with the use of Pearson's chi-square test or Fisher exact test in cases where applicability conditions were not met. Continuous variables were summarized as mean ± standard deviation (SD) and were compared using paired or unpaired Student's t-tests or nonparametric Wilcoxon rank-sum tests if the normal distribution of the variables could not be demonstrated. A p-value <0.05 was considered statistically significant.

RESULTS

Basal blood values of the patients were examined before and after the treatment. The mean hemoglobin values were 12.5±1.6 before the treatment and 12.7±1.5 after the treatment (p=0.132). The mean creatinine values were 0.72±0.2 before the treatment and 0.71±0.2 after the treatment (p=0.718). Similarly, glucose and other electrolytes of the patients, along with other hemogram parameters were examined, and no statistically significant change was found before and after the treatment. Blood values changes are summarized in Table 2.

The patients included in the study were receiving bevacizumab, sunitinib, and sorafenib treatment. The number of patients who received treatment was 28 patients with bevacizumab, four patients with sunitinib, and one patient with sorafenib. When the ambulatory blood pressure measurements were evaluated, after the VEGF inhibitor treatment, it was observed that a total of 12 patients had blood pressure measurements above the hypertension limit values. Of these, 10 were receiving bevacizumab, and two were receiving sunitinib. When the patient's mean ambulatory blood pressure measurement results were evaluated, an increase was found in all the systolic and diastolic measurements during the day, night, and over 24 h. The mean systolic (118.3±10.9 - 123.8±14.5, p=0.017), mean diastolic (69.8±8.2 - 73.4±10.0, p=0.018), daytime systolic (120.5±10.9 - 126.3±14.1, p=0.011), and daytime diastolic (72.1±8.1 - 75.8±10.1, p=0.023) measurements showed a statistically significant increase (Table 3).

When the blood pressure values were examined before and after VEGF inhibitor treatment, there was a statistically significant increase in the mean systolic (117.8±11.6 - 123.6±17.2, p=0.044), mean diastolic (69.7±7.9 -73.6±11.0, p=0.049), and daytime mean

Table 2
Laboratory parameters of the study population

	Pretreatment		Posttreatment		
	n	%	n	%	*p*
Glucose (mg/dL)	103	36	102	33	0.922
Creatinine (mg/dL)	0.67	0.27	0.69	0.34	0.879
Sodium (mEq/L)	138	1.5	139	2.7	0.119
Potassium (mEq/L)	4.2	0.3	4.2	0.6	0.139
AST (u/L)	21	9.5	22	13	0.875
ALT (u/L)	16	19	16	17	0.868
Hemoglobin (g/dL)	13	2	13.3	1.9	0.203
CRP (mg/dL)	0.56	0.77	0.63	0.78	0.903

AST: Aspartate transaminase; ALT: Alanine aminotransferase; CRP: C-reactive protein. Changes of parameters from pre-treatment to post-treatment were analyzed using paired samples Wilcoxon signed-rank test.

Table 3
Comparison of ambulatory blood pressure parameters before and after treatment with VEGF inhibitors

	Pretreatment	Posttreatment	Delta		
	Mean±SD	Mean±SD	Mean±SD	*p*	Cohen's d
24-h-systolic ABP (mmHg)	118.33±10.92	123.81±14.54	5.48±11.58	**0.017**	0.439
24-h-diastolic ABP (mmHg)	69.85±8.26	73.43±10.04	3.58±7.18	**0.018**	0.434
Daytime systolic ABP (mmHg)	120.52±10.96	126.36±14.17	5.84±12.0	**0.011**	0.469
Daytime diastolic ABP (mmHg)	72.17±8.19	75.87±10.11	3.70±8.38	**0.023**	0.417
Nighttime systolic ABP (mmHg)	113.43±11.94	117.66±16.59	4.60±14.19	0.081	0.325
Nighttime diastolic ABP (mmHg)	64.74±8.47	67.15±10.32	2.67±8.71	0.098	0.307

SD: Standard deviation; ABP: 24h-ambulatory blood pressure; Changes of parameters from pretreatment to posttreatment were analyzed using paired samples Student's t-test. Delta: value at posttreatment subtracted from the value at pretreatment. P<0.05 was regarded significant (bold type). Cohen´s d is reported for the effect size.

systolic (119.6±11.4 - 125.6±16.7, p=0.049) values in females and the mean diastolic (70.0±9.0 - 73.1±8.7, p=0.017) values in males. All day, daytime, and nighttime blood pressure changes are shown in Figure 1.

DISCUSSION

The findings of this study showed a progression in ambulatory blood pressure measurements. Compared to the pretreatment measurements, there was a statistically significant increase in the mean systolic, mean diastolic, daytime systolic, and daytime diastolic blood pressure measurements throughout the day after the treatment. In addition, when the distribution of these data was examined according to sex, we found a statistically significant increase in mean all day systolic and diastolic and daytime systolic measurements in females, as well as in daytime diastolic measurements in males. Some previous studies mentioned sex differences in ambulatory blood pressure measurement differences. One study found that diastolic pressures were higher in males than females.[10] Another ambulatory blood pressure study revealed that males had higher mean ambulatory diastolic and mean arterial blood pressures than females.[11] However, there were no studies that specifically mentioned sex differences in patients using VEGF inhibitors and its hypertension side effects. This topic needs further evaluation.

The incidence of hypertension after VEGF inhibitor treatment was observed in a total of 10 patients, with the ambulatory blood pressure limit values taken as the basis (mean 130/80 mmHg for mean measurement, 135/85 mmHg for mean daytime, and 120/70 mmHg for mean night time). Ten of 28 patients taking bevacizumab and two of four taking sunitinib were hypertensive. However, because the number of patients who received sorafenib and sunitinib treatment in the study was very small, it is not possible to draw conclusion about such a proportional relationship. For bevacizumab, this rate was found to be 35%, and this rate is similar to previous studies in the literature.[12] However, the design of our study and the difference from most previous studies was not to just determine the number of patients who crossed the absolute hypertension limit as the endpoint. Moreover, the ambulatory measurements of patients who did not exceed the hypertensive limit were compared before and after treatment. Additionally, the mean arterial blood pressure measurements of the whole patient group, with the normotensive patients included, showed statistically significant progression.

Hypertension is one of the common side effects that encountered with the usage of VEGF inhibitors.[13] It was determined that the hypertension side effect was observed from the first week at the beginning of the treatment.[14] In a different study with 313 patients comparing IFL (irinotecan, fluorouracil, and leucovorin) treatment and IFL + bevacizumab treatment, the hypertension side effect was observed approximately 2.75 times more in patients with bevacizumab treatment added.[15] In another study with VEGF inhibitors, the patients were evaluated with ambulatory

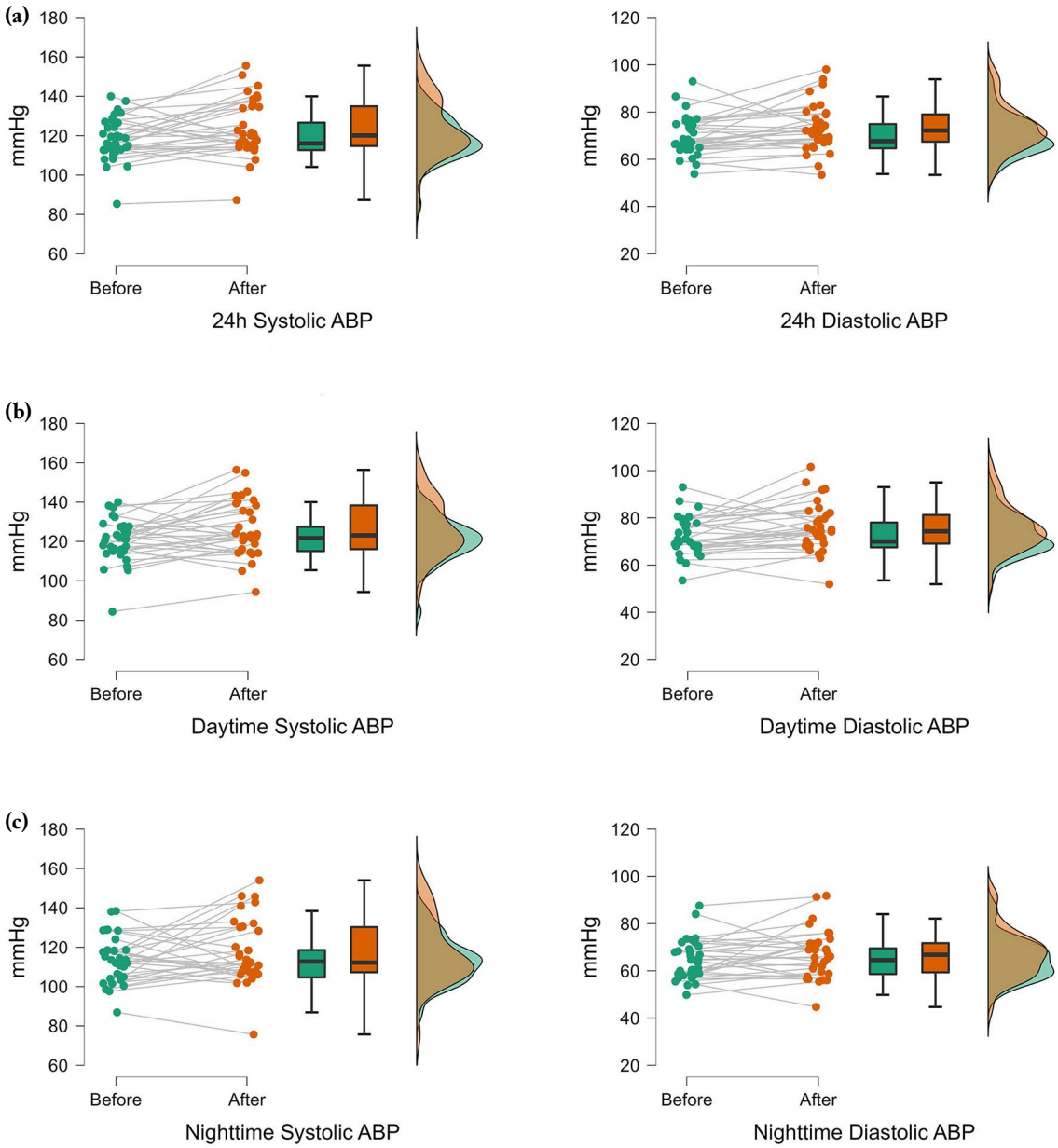

Figure 1. All day, daytime, and nighttime blood pressure measurement changes.

blood pressure measurements and were found to be hypertensive within six to 10 days after the treatment. Furthermore, it was found that this hypertensive effect started in the first 24-h of the treatment.[16] However, within the results of other trials, regardless of the specific molecules, with VEGF inhibitor-related hypertension, the rise of arterial blood pressure was observed by four weeks, and it could be reversible.[6,17]

Ambulatory mean arterial blood pressure changes with sunitinib were previously demonstrated before and after treatment, and an increase of 10.8 mmHg in mean systolic blood pressure and 8 mmHg in mean diastolic blood pressure was observed in that study.[12] In a study, in which bevacizumab treatment was given intraocularly and ambulatory blood pressures were measured before the treatment after 72 h, it was observed that

the arterial blood pressure values progressed.[18] However, when the literature was reviewed, it was observed that similar ambulatory blood pressure measurement evaluations before and after treatment with systemic bevacizumab treatment were not performed as much. In this sense, we believe that our study is important, although more voluminous clinical studies are needed in the future in terms of the number of patients.

It was observed that VEGF inhibitors increased the mean arterial blood pressure (all day mean, daytime, and nighttime measurements) and both systolic and diastolic blood pressure, regardless of hypertension history. When the results obtained by ambulatory blood pressure measurement are evaluated, it should be noticed that even if the blood pressure was below the limit values determined by the guidelines for the diagnosis of hypertension, the progression could have occurred after the treatment. Although it is thought that ambulatory blood pressure measurement brings more burden in terms of time and finance, it could be more cost-effective. For instance, in the case of white coat hypertension, it ensures that patients are correctly diagnosed (not misdiagnosed as hypertension) and that antihypertensive medication that would not normally be required is not prescribed. In addition, it is stated that adjusting antihypertensive treatment according to ambulatory blood pressure measurement rather than office blood pressure results in less antihypertensive drug prescribing without affecting the target organ involvement rate, and thus may be more cost-effective.[19]

This study had several limitations, including its small sample size. The most important factor is that it is a single-center study and the oncology clinic has limited patient capacity. These results need to be verified by further studies with a larger number of patients.

In conclusion, it should be kept in mind that, as in patients in our study group, in cases where the incidence of hypertension side effects significantly increases with treatment, ambulatory blood pressure measurement should be considered in the foreground. Moreover, although office blood pressure measurements may be normal in the pretreatment evaluations, there may be a progression in the arterial blood pressure values during the follow-up of patients during their treatment. Patients should be informed about this issue and encouraged to adapt to their follow-up and lifestyle changes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, writing the article: E.O.B., F.E., N.C.; Control/supervision: N.C.; Data collection and/or processing, literature review, materials: E.O.B., F.E.; Analysis and/or interpretation, critical review: E.O.B., N.C.; References and fundings: E.O.B.

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The relationship between proteinuria and ambulatory blood pressure in hypertensive patients

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ABSTRACT

Objectives: The study aimed to investigate the relationship between proteinuria and blood pressure (BP) determined with ambulatory BP monitoring (ABPM) in patients who applied to the nephrology clinic due to hypertension.

Patients and methods: A total of 163 patients (84 males, 79 females; mean age: 55.7±16.6 years; range, 18 to 80 years) were included in the cross-sectional study between January 2022 and January 2023. The amount of proteinuria was measured from 24-h urine samples. The ABPM values were measured using noninvasive multitasking BP recorders.

Results: A total of 53.4% (n=87) of the patients had dipper, 29.4% (n=48) had non-dipper, and 17.2% (n=28) had reverse-dipper hypertension (HT). Dipper HT, albumin, and glomerular filtration rate were significantly lower in those with proteinuria compared to those without proteinuria. Age, creatinine, HT duration, 24-h, daytime, and nighttime systolic BP, nighttime diastolic BP, nighttime mean BP, non-dipper HT (all p<0.001), 24-h diastolic BP (p=0.015), daytime mean BP (p=0.005), and reverse-dipper HT (p=0.001) were significantly higher in the group with proteinuria.

Conclusion: Elevated ABPM values, non-dipper HT, and reverse-dipper HT were detected in patients who had high proteinuria. Creatinine and 24-h urine protein excretion were found to be higher in patients with non-dipper HT and reverse-dipper HT. The progression of proteinuria can be slowed down by strict BP control in hypertensive patients with proteinuria.

Keywords: Ambulatory blood pressure monitoring, hypertension, proteinuria.

Hypertension (HT) is a risk factor affecting more than one billion people worldwide and leads to high mortality, but control rates are low.[1] It is already known that effective control of blood pressure (BP) reduces cardiovascular disease and renal morbidity and mortality.

Different methods are used to monitor the BP levels of patients. These are office BP measurement, home BP measurement, and ambulatory BP monitoring (ABPM). Constanti et al.[2] reported that office BP measurement is limited to a comprehensive BP check. An important aspect of the information provided with the ABPM is the ability to measure the degree of BP variability over 24 h, which was shown to be a significant and independent risk factor for cardiovascular disease morbidity and mortality.[3] Variability in BP includes short-term and circadian components. The drop in BP over time causes large variability among individuals. Elevated BP in the early morning hours, when cardiovascular events occur most frequently, can be detected early with ABPM.[4] Microalbuminuria is among the organ damages associated with HT, and its prevalence was reported to be between 8 and 15% in the nondiabetic patient population. Determination of microalbuminuria facilitates the approach to treatment and risk assessment for hypertensive patients.[5] Patients who have HT often

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also have renal damage. This condition manifests itself as microalbuminuria. The relationship between microalbuminuria and HT is explained by endothelial dysfunction or chronic low-grade inflammation. This occurs because BP fluctuation, particularly at night, increases glomerular perfusion pressure, causes endothelial cell damage in glomerular capillaries, increases microalbuminuria, and causes progressive renal damage.[4] Microalbuminuria is also associated with chronic low-grade inflammation, which can be a cause and a consequence of endothelial dysfunction. Furthermore, endothelial dysfunction and low-grade inflammation not only cause atherothrombosis but may also be independently associated with cardiovascular disease risks. When BP fluctuates, the sympathetic nervous system is stimulated, endocrine regulation is disrupted, and renal damage is triggered.[6] Although previous studies were conducted to evaluate ABPM in hypertensive patients, this study aimed to investigate the relationship between proteinuria levels and BP fluctuations determined with ABPM.

PATIENTS AND METHODS

The cross-sectional study was conducted with a total of 163 patients (84 males, 79 females; mean age: 55.7±16.6 years; range, 18 to 80 years) who were diagnosed with HT at the Ankara Bilkent City Hospital, Department of Nephrology, between January 2022 and January 2023. Those who were over 18 years of age, without diabetes, not under treatment with steroids or other immunosuppressive drugs, and without malnutrition, active malignancy, active infection, a history of myocardial infarction, cerebrovascular disease in the last six months, unstable angina, or other major diseases were included in the study. The study protocol was approved by the Ankara City Hospital Ethics Committee (date: 09.12.2020, no: E1-20-1355). Written informed consent was obtained from all participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. Venous blood samples were taken from the patients between 8:00 and 9:00 in the morning after an 8- to 10-h fast. Serum creatinine levels were analyzed with the spectrophotometric method by using the Beckman Coulter commercial kits on the Beckman Coulter AU5800 autoanalyzer (Beckman Coulter, Inc., Brea, CA, U.S.A). The glomerular filtration rate (GFR) value was determined with the Modification of Diet in Renal Disease criteria.Proteinuria was measured using the 24-h proteinuria levels. The patients were divided into four groups according to the amount of proteinuria in 24-h urine: proteinuria <200 mg/day, proteinuria 200-1000 mg/day, proteinuria 1000-3000 mg/day, and proteinuria >3000 mg/day (at nephrotic level).

Ambulatory BP measurements were conducted using noninvasive multitasking BP recorders (TM2425; A&D, Tokyo, Japan). Blood pressure was recorded at 15-min intervals between 07:00 and 21:00 and at 30-min intervals between 21:00 and 07:00. Mean systolic BP (SBP) and diastolic BP (DBP) values were calculated for each participant. Mean BP (MBP) was calculated as the sum of DBP and one-third of the pulse pressure. Daytime and nighttime BP were obtained as the mean values during daytime and nighttime, respectively. Daytime and nighttime BP ratios were then analyzed in each participant. Since the technique could cause errors, SBP >250 mmHg or <70 mmHg, DBP >130 mmHg or <30 mmHg, and pulse pressure >160 mmHg or <20 mmHg were not measured.

The patients were divided into three stages according to the BP levels specified in the 2018 European Society of Cardiology/European Society of Hypertension guidelines for HT.[7] Stage 1 HT was accepted as SBP 140-159 mmHg or DBP 90-99 mmHg, Stage 2 HT was accepted as SBP 160-179 or DBP 100-109, and Stage 3 HT was accepted as SBP ≥180 mmHg or DBP ≥110. In this classification made with the ABPM, a ≥10% decrease in the BP value measured at night compared to the daytime value was defined as dipper HT, a decrease of <10% was defined as non-dipper HT, and a nighttime increase in BP was defined as reverse-dipper HT.[8]

Statistical analysis

The data were evaluated with the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Results were expressed as mean ± standard deviation (SD) and median (min-max) for quantitative variables. Categorical data were presented as frequency (percentage). Normal distribution was examined with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Three and above one-way variance test was used to compare normally distributed data according to groups. Multiple comparisons were examined with the Tamhane T2 and Duncan tests. The Mann-Whitney U test was used to compare nonnormally distributed

data between two groups. The Kruskal-Wallis H test was used to compare nonnormally distributed data between three or more groups, and multiple comparisons were examined with the Dunn test with Bonferroni correction. Multiple comparisons were examined with the Bonferroni-corrected Z test. Nonnormally distributed data was examined with the Spearman rho correlation coefficient. Factors affecting the presence of proteinuria were examined by logistic regression analysis. A p-value <0.05 was accepted as statistically significant.

RESULTS

The median duration of HT was 60 (1-480) months. The mean creatinine level was 1.29±0.94 mg/dL, the mean GFR was 75.85±34.36 mL/min/1.73 m^2, and the mean 24-h urine protein was 829.8±1591.14 mg. Stage 1 HT was detected in 49.3% of the patients, Stage 2 HT was detected in 31%, and Stage 3 HT was detected in 19.7%. The mean 24-h SBP was 128 mmHg, daytime SBP was 129 mmHg, and nighttime SBP was 123 mmHg.

Table 1
Demographic and laboratory characteristics of the patients (n=163)

	n	%	Mean±SD	Median	Min-Max
Age (year)			50.7±16.6		
Sex					
Female	79	48.5			
Male	84	51.5			
HT duration (month)				60	1-480
Stage 1 HT	35	49.3			
Stage 2 HT	22	31			
Stage 3 HT	14	19.7			
Creatinine (mg/dL)			1.29±0.94		
GFR (mL/min/1.73 m^2)			75.85±34.36		
Albumin			43.98±4.53		
24-h urine protein (mg/24 h)			829.8±1591.14		
Daytime DBP (mmHg)			80.26±11.94		
Nighttime DBP (mmHg)			76.78±13.23		
Daytime SBP (mmHg)			129.76±16.6		
24-h DBP (mmHg)			79.68±11.89		
Nighttime SBP (mmHg)			125.89±19.35		
24-h SBP (mmHg)			128.88±16.79		
24-h MBP (mmHg)			102.51±13.5		
Daytime MBP (mmHg)			103.26±13.32		
Nighttime MBP (mmHg)			99.36±14.76		
Dipper HT					
No	76	46.6			
Yes	87	53.4			
Non-dipper HT					
No	115	70.6			
Yes	48	29.4			
Reverse-dipper HT					
No	135	82.8			
Yes	28	17.2			

SD: Standard deviation; HT: Hypertension; GFR: Glomerular filtration rate; DBP: Diastolic blood pressure; SBP: Systolic blood pressure; MBP: Mean blood pressure.

Table 2
Comparison of laboratory and ABPM measurements of patients with and without proteinuria

	Group without proteinuria				Group with proteinuria												Statistic	*p*
	n	%	Mean±SD	Median (Min-Max)	n	%	Mean±SD	Median (Min-Max)	n	%	Mean±SD	Median (Min-Max)	n	%	Mean±SD	Median (Min-Max)		
Age (year)			46.96±17.15				53.2±16.75				53.71±15.18				56.8±12.21		2.106	0.069d
Sex																	0.867	0.851f
Female	36	50			26	51			12	42.9			4	40				
Male	36	50			25	49			16	57.1			6	60				
Stage 1 HT	24a	68.6			7ab	35			2b	18.2			2ab	40			14.634	0.014f
Stage 2 HT	8a	22.9			9a	45			4a	36.4			1a	20				
Stage 3 HT	3a	8.6			4ab	20			5b	45.5			2ab	40				
Creatinine (mg/dL)				0.86 (0.4-1.83)b				0.98 (0.42-5)ab				1.44 (0.59-4.9)a				1.88 (0.4-5.5)a	23.171	<0.001e
GFR (ml/min/1.73 m²)				95 (1.02-135)b				75 (8-149)ab				55.5 (0.27-108)a				36 (10-125)a	24.404	<0.001e
Albumin				46 (30-52)c				44 (34-50)b			44 (30-49)ab					39 (25-44)a	30.223	<0.001e
Daytime DBP (mmHg)			78.2±10				79.98±12.89				84.36±14.59				84.9±8.17		2.378	0.072d
Night DBP (mmHg)			72.58±9.23b				77.52±14.44ab				82.93±16.67a				85.5±9.44a		8.008	0.031d
24-h DBP mmHg			76.99±9.31b				79.79±12.93ab				84.39±14.82a				85.1±8.52a		3.971	0.015d
Daytime SBP (mmHg)				124 (98-152)b				132 (92-182)ab				131 (113-187)a				139 (113-185)a	15.842	0.021e
Night SBP (mmHg)			117.35±10.67b				127.65±19.02a				138.86±25.36a				141±20.58a		12.167	<0.001d
24-h SBP mmHg			122.77±11.18b				129.29±16.66ab				138.86±20.53a				142.2±20.02ab		8.164	<0.001d
24-h MBP (mmHg)			97.89±9.43b				103.45±13.93ab				109.36±17.04a				111.4±13.04ab		7.142	0.001d
Daytime MBP (mmHg)			99.51±10.09b				103.49±13.51ab				109.5±16.89a				111.3±12.92ab		5.026	0.005d
Night MBP (mmHg)				92 (67-121)b				102 (73-153)a				108 (72-150)a				108 (86-135)a	27.177	<0.001e
Dipper HT																	29.610	<0.001f
No	17	23.3			34	65.4			18	64.3			7	70				
Yes	56a	76.7			18b	34.6			10b	35.7			3b	30				
Non-dipper HT																	17.489	0.001f
No	63	86.3			28	53.8			18	64.3			6	60				
Yes	10a	13.7			24b	46.2			10ab	35.7			4ab	40				
Reverse-dipper HT																	7.235	0.057f
No	66	90.4			42	80.8			20	71.4			7	70				
Yes	7	9.6			10	19.2			8	28.6			3	30				

SD: Standard deviation; a-c: There is no difference between groups with the same letter (Bonferroni correction Z test, Dunn test, Tamhane's T2 test and Duncan test); d: One-way variance test; e: Kruskall Wallis H test, f: Fisher's exact test,

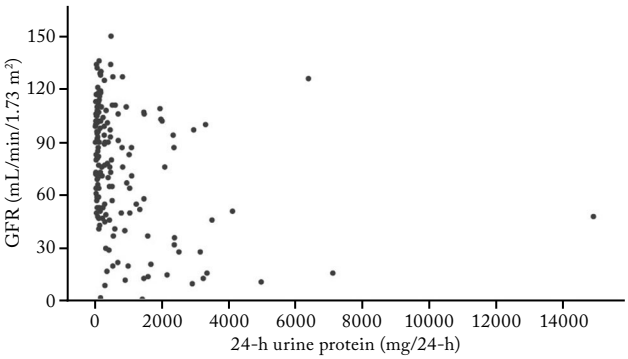

Figure 1. Relationship between proteinuria and GFR.
GFR: Glomerular filtration rate.

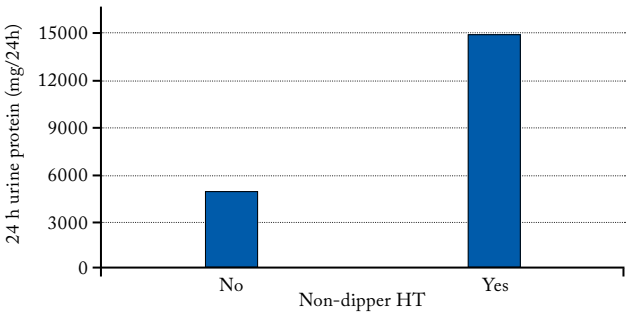

Figure 2. Relationship between proteinuria and non-dipper HT.
HT: Hypertension.

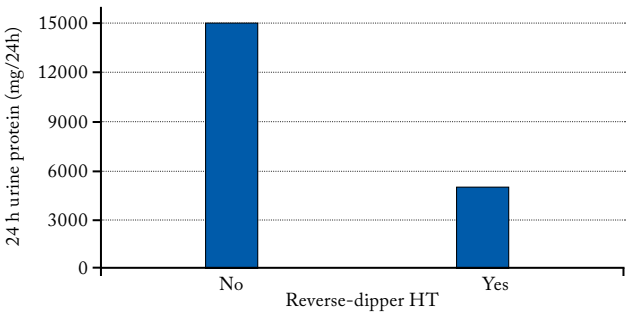

Figure 3. Relationship between proteinuria and reverse-dipper HT.
HT: Hypertension.

The mean 24-h DBP was 79.68±11.89 mmHg, daytime DBP was 80.26±11.94 mmHg, and nighttime DBP was 76.78±13.23 mmHg. The mean 24-h MBP was 102.51±13.5 mmHg, daytime MBP was 103.26±13.32 mmHg, and nighttime MBP was 99.36±14.76 mmHg. Dipper HT was detected in 53.4% of the patients, non-dipper HT in 29.4%, and reverse-dipper HT in 17.2% (Table 1).

The dipper HT, albumin, and GFR were significantly lower in those with proteinuria compared to those without proteinuria. Age, creatinine, HT duration, 24-h SBP, daytime SBP, nighttime SBP, DBP, and MBP, non-dipper HT (all p<0.001), 24-h DBP (p=0.015), daytime MBP (p=0.005), and reverse-dipper HT (p=0.001) were significantly higher in the group with proteinuria (Table 2). A significant relationship was detected in the univariate regression analysis between proteinuria and creatinine, GFR (Figure 1), albumin, 24-h SBP, daytime SBP, nighttime SBP, daytime MBP, nighttime MBP, dipper HT, non-dipper HT (p<0.001 for all; Figure 2), reverse-dipper HT (p=0.025; Figure 3), and age (p=0.011). However, no relationship was detected with DBP. In multivariate logistic regression analysis, a relationship was found between proteinuria and albumin (p=0.027), night SBP (p=0.001), and 24-h SBP (p=0.028; Table 3). When the patients were divided into dipper, non-dipper, and reverse-dipper HT, the duration of HT was shorter and GFR and albumin were higher in those with dipper HT. Twenty-four-hour urine proteinuria, nighttime SBP, 24-h SBP, and nighttime MBP were lower in those with dipper HT.

DISCUSSION

In the present study, the SBP, DBP, and MBP values that were determined with ABPM were higher in hypertensive patients who had proteinuria. It was also found that the development of non-dipper HT and reverse-dipper HT was more frequent in those who had proteinuria. Creatinine and urine protein levels were higher and there were more advanced stages of HT in patients who had non-dipper HT and reverse-dipper HT.

Rational management of HT begins with accurate measurement of BP. European[7] and American[9] guidelines recommend the use of ABPM in all patients using antihypertensive medications. The reasons for this recommendation of these guidelines include the differential diagnosis of causes such as whitecoat HT, masked HT, orthostatic HT, chronic renal failure, autonomic dysfunction, diabetes mellitus, and endocrine HT, as well as determining the time of hypertensive drug use. Additionally, a relationship

Table 3
Identifying factors associated with proteinuria using logistic regression analysis

	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	1.026	1.006-1.046	0.011	1.027	0.934-1.13	0.578
Sex						
Female	1.119	0.601-2.084	0.723			
HT duration (month)	1.006	1.001-1.010	0.015			
Creatinine (mg/dL)	4.311	1.992-9.327	<0.001	15.35	0.014-17398.799	0.447
GFR (mL/min/1.73 m^2)	0.978	0.968-0.988	<0.001	1.037	0.93-1.156	0.511
Albumin	0.811	0.736-0.895	<0.001	0.756	0.59-0.968	0.027
Daytime DBP (mmHg)	1.028	0.999-1.057	0.055			
Night DBP (mmHg)	1.050	1.021-1.080	0.001			
Daytime SBP (mmHg)	1.041	1.017-1.065	0.001	2.771	0.573-13.409	0.205
Night SBP (mmHg)	1.059	1.033-1.084	<0.001	1.297	1.109-1.516	0.001
24-h SBP mmHg	1.048	1.024-1.074	<0.001	0.858	0.748-0.984	0.028
24-h DBP mmHg	1.038	1.008-1.068	0.012			
24-h MBP (mmHg)	1.055	1.026-1.086	<0.001			
Daytime MBP (mmHg)	1.044	1.016-1.073	0.002			
Night MBP (mmHg)	1.071	1.040-1.104	<0.001			
Dipper HT (Ref.: no)	0.160	0.080-0.320	<0.001	0.24	0.004-14.049	0.492
Non-dipper HT (Ref.: no)	4.604	2.095-10.118	<0.001	0.245	0.014-4.318	0.337
Reverse-dipper HT (Ref.: no)	2.870	1.144-7.197	0.025			

OR: Odds ratio; CI: Confidence interval: Wald backward stepwise method.

was detected with the progression of microvascular diseases.[10] Ambulatory BP measurement was shown to be more effective in indicating the development of target organ damage.[11,12] Therefore, ABPM was used to determine the BP values of the patients in the present study. Furthermore, the ABPM was found to be the most useful and effective method in diagnosing HT, and it is also the best method in determining the time of taking antihypertensive medication.[7]

In the present study, the relationship between ABPM and 24-h urinary protein excretion was examined in patients who applied to the nephrology clinic with complaints of HT. Similar to the literature data, as the proteinuria level of the patients increased, an increase in creatinine levels and a decrease in GFR were detected.[13] The reason for this relationship was the increase in glomerular perfusion pressure, which may result in endothelial cell damage in the glomerular capillaries, resulting in microalbuminuria and progressive renal damage, similar to the study reported by Ying et al.[13]

Hermida et al.[14] reported that non-dipper or reverse-dipper HT was more common in patients who had resistant and uncontrolled HT. When the renal functions of dipper HT, non-dipper HT, and reverse-dipper HT patients were compared, GFR was found to be lower in patients who had non-dipper and reverse-dipper HT at significant levels. Hermida et al.[15] reported that non-dipper HT was more common in patients who had chronic renal failure, similar to our study, and GFR was lower and creatinine was elevated in those with non-dipper HT.

As a result of the increased BP at night, there is increased peripheral resistance and thickness of the glomerular basement membrane, which causes cell damage in the vascular endothelium, increasing albumin/protein excretion.[16] It was found in the present study that as proteinuria increased, dipper HT

and non-dipper HT developed in patients. Similar to our study, Farrag et al.[17] and Guo et al.[18] reported that the frequency of non-dipper HT increased as proteinuria increased and proteinuria was elevated in patients who had non-dipper HT. A recent study that investigated the bidirectional relationship of proteinuria and BP argued that proteinuria and BP might influence each other, suggesting that increase in proteinuria will cause higher BP and vice versa.[19] Similarly, the present study found that SBP, DBP, and MBP values that were determined with ABPM were elevated in patients who had proteinuria. Mettimano et al.[20] reported a significant relationship between proteinuria and 24-h SBP, daytime SBP, and nighttime SBP values. O'Seaghdha et al.[21] reported that this relationship was contradictory to DBP. Similar to our study, Hirayama et al.[22] reported a relationship between proteinuria and SBP but not with DBP. Differences between studies might be due to the differences in patient age. The ages of the patients in our study were higher compared to those in the Asian study and other referenced studies.[21,22] Low DBP levels reflect improved arterial stiffness in the elderly, which may be a risk factor associated with poor renal prognosis.[20] In other words, it may be a more practical method to follow up patients in the elderly with SBP.

This study had some limitations. First, since the study was conducted at a cross-sectional design, changes over time in the relationship between proteinuria and HT were not investigated. Second, proteinuria was assessed with 24-h urine collection, and spot urine protein-to-creatinine ratio was not examined. Third, the number of patients was insufficient since the study was conducted within a short period.

In conclusion, the development of non-dipper HT and reverse-dipper HT was more common in those with proteinuria compared to those without proteinuria. Renal dysfunction and proteinuria were more common in patients who have non-dipper or reverse-dipper HT. Advanced stage HT development was detected in those who have non-dipper HT and reverse-dipper HT compared to those with dipper HT. Ambulatory BP monitoring was more useful than other tests in hypertensive patients with proteinuria, and proteinuria could be controlled with strict BP control in such patients. However, further multicenter studies with a larger number of patients are needed.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, data collection and/or processing, literature review, writing the article, materials, other: B.A.D.; Design, analysis and/or interpretation, critical review, references and fundings: M.İ.D.; Control/supervision: A.Ö.

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Redo transcatheter aortic valve implantation: Our single-center experience and mid-term outcomes

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ABSTRACT

Objectives: In this study, we present our mid-term outcomes on redo transcatheter aortic valve implantation (TAVI).

Patients and methods: Between June 2012 and May 2019, a total of eight TAVI-in-TAVI patients (2 males, 6 females; mean age: 73.8±3.9 years; range, 66 to 79 year) were retrospectively analyzed. All patients were evaluated for comorbidity, characteristics of the first TAVI valve, indications for redo-TAVI, transthoracic echocardiographic parameters, mortality, pacemaker requirement, and valve function during follow-up.

Results: Five (62.5%) of the patients required a redo-TAVI procedure due to severe aortic regurgitation, while three (37.5%) required a redo-TAVI procedure due to degeneration of the first TAVI valve. The first TAVI valves of the patients were two Portico™, four CoreValve™ and two Edwards SAPIEN™. In redo-TAVI procedures of the patients, four CoreValve™, two Portico™, and two MyVal™ valves were used. The median time after the first procedure was 62 months. One patient had hypertensive pulmonary edema during the procedure and was intubated, and in-hospital mortality occurred due to infectious causes during intensive care follow-up. There was no in-hospital mortality and no need for pacemaker in other patients. There was no mortality at a median follow-up of 31 months after redo-TAVI procedures.

Conclusion: Redo-TAVI procedure is a feasible intervention and can be successfully done in selected patients requiring reintervention due to valve degeneration or severe aortic regurgitation.

Keywords: Aortic stenosis, redo, transcatheter aortic valve implantation.

Transcatheter aortic valve implantation (TAVI) is a well-established and widely used procedure for the treatment of severe aortic stenosis.[1] Although initially limited to high-risk patients, TAVI has demonstrated its efficacy in low-risk patients in recent years.[2-6]

With the widespread use of TAVI in Türkiye and the increase in valve durability, the number of patients undergoing TAVI has increased. Therefore, there has been a certain increase in the number of patients who need TAVI-in-TAVI (redo-TAVI). Our clinic is among the first facilities in our country to complete TAVI procedures.[7]

In the present study, we aimed to evaluate mid-term outcomes on redo-TAVI procedures.

PATIENTS AND METHODS

This single-center, descriptive, retrospective study was conducted at Dokuz Eylül University, Faculty of Medicine, Department of Cardiology between June 1st, 2012 and May 31st, 2019. A total of 441 patients with symptomatic severe aortic

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stenosis who were admitted to our hospital were deemed eligible for TAVI. Of these patients, eight (2 males, 6 females; mean age: 73.8±3.9 years; range, 66 to 79 year) who were TAVI-in-TAVI cases were included in the study. A written informed consent was obtained from each patient. The study protocol was approved by the Dokuz Eylül University Non-Invasive Ethics Committee (date: 03/01/2024, no: 2024/01-22). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were analyzed for comorbidity, characteristics of the first TAVI valve, indications for redo-TAVI, transthoracic echocardiographic parameters, mortality, pacemaker requirement, and valve function during follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of variables was evaluated with the Kolmogorov-Smirnov test, and the homogeneity of variance was evaluated with the Levene test. Continuous variables were presented in mean ± standard deviation, while categorical variables were presented in number and frequency.

RESULTS

Of eight patients included in the study, two (25%) had coronary artery disease and three (37.5%) had chronic renal failure. Demographic, clinical, and laboratory data of the patients are given in Table 1.

Five (62.5%) of the patients required a redo-TAVI procedure due to severe aortic regurgitation and three (37.5%) of the patients required a redo-TAVI procedure due to degeneration of the first TAVI valve. The first TAVI valves of the patients were two Portico™ valves (St. Jude Medical, Minneapolis, MN, USA), four CoreValves™ (Medtronic Inc., Minneapolis, MN, USA), and two Edwards SAPIEN™ (Edwards Lifesciences Inc., Irvine, CA, USA). One patient had two valves in the first procedure due to pop-out-related valve-in-valve (Figure 1). Aortic gradients, aortic regurgitation, and time passed after the first procedure before the redo-TAVI procedure are given in Table 2. In the TAVI-in-TAVI procedures of the patients, four CoreValve™ (Medtronic Inc., Minneapolis, MN, USA), two Portico™ valves (St. Jude Medical, Minneapolis, MN, USA) and two MyVal™ (Meril Life Sciences Pvt. Ltd., India) were used (Table 2). The median time after the first procedure was 62 (range, 19 to 89) months.

Before redo-TAVI, computed tomography (CT) was repeated both to evaluate the initial valve structure and to select a new valve. All patients underwent

Tablo 1
Comorbidities and laboratory values of the redo-TAVI patients

Variables	n	%	Mean±SD
Age			73.8±3.9
Sex			
Male	2	25	
Coronary artery disease	2	25	
Diabetes mellitus	3	37.5	
Hypertension	8	100	
Chronic kidney disease	3	37.5	
Creatinin			1.30±0.57
Sodium			138.33±4.22
Potassium			4.22±0.25
Albumin			2.85±0.39
White blood cells			9.42±1.29
Hemoglobin			10.33±1.20

TAVI: Transcatheter aortic valve implantation; SD: Standard deviation.

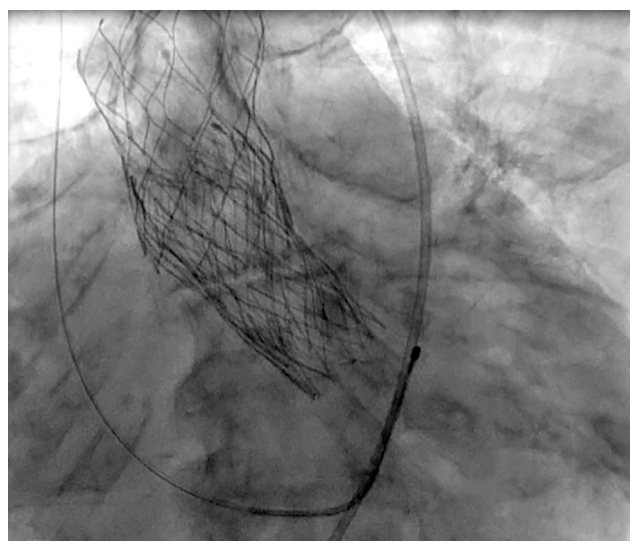

Figure 1. Post redo-TAVI aortography image for patient 1.
TAVI: Transcatheter aortic valve implantation.

Table 2
TAVI valves and echocardiographic characteristics of patients

Patients	First TAVI valve	LVEF (%)	Aortic gradient	Aortic regurgitation	Passed time after first TAVI (month)	Second TAVI valve
1	29 mm Portico + 27 mm Portico	60	70/39	Moderate	46	26 mm Corevalve
2	29 mm Edwards	35	25/11	Severe	60	27 mm Portico
3	29 mm Corevalve evolute-R	50	38/20	Severe	32	29 mm Portico
4	29 mm Edwards	20	88/53	Moderate	72	29 mm Corevalve
5	29 mm Portico	40	36/18	Severe	89	29 mm Corevalve
6	29 mm Corevalve evolute-R	50	29/11	Severe	19	34 mm Corevalve
7	29 mm Corevalve evolute-R	22	7/3	Severe	59	26 mm Meril Myval
8	29 mm Corevalve evolute-R	55	71/49	Mild	121	26 mm Meril Myval

TAVI: Transcatheter aortic valve implantation; LVEF: Left ventricular ejection fraction.

the procedure through the femoral artery. One patient had hypertensive pulmonary edema during the procedure and was intubated and in-hospital mortality occurred due to infectious causes during intensive care follow-up (Patient No. 2). There was no in-hospital mortality and pacemaker requirement in other patients. In seven patients, post-procedural echocardiographic valve evaluation revealed a median aortic gradient of 17/8 mmHg and no more than mild aortic regurgitation. Coronary artery occlusion was not seen in any case. There was no mortality at a median follow-up of 31 months after TAVI-in-TAVI procedures.

DISCUSSION

Transcatheter aortic valve implantation is an increasingly widespread method in the treatment of severe aortic stenosis.[8] However, the primary uncertainty regarding the long-term follow-up of TAVI is its durability. Advancements in TAVI valve design and deployment methods may enhance long-term durability.[9] With the increase in long-term durability, we expect an increase in redo-TAVI procedures in the near future.

The Valve Academic Research Consortium-3 identifies four primary mechanisms which contribute to the dysfunction of bioprosthetic valves for TAVI: *(i)* endocarditis; *(ii)* structural valve deterioration (SVD); *(iii)* valve thrombosis; and *(iv)* non-SVD.[10]

The recommendation for redo-TAVI versus surgical aortic valve replacement (SAVR) in patients with SVD and non-SVD depends on multiple criteria. Recent data from the United States indicate that the 30-day mortality rate for redo-TAVR is lower than that of SAVR.[11,12]

In their study, Şentürk et al.[7] showed that the number of true SVD was low in patients who underwent TAVI, confirming that the durability of TAVI valves was high. In our study, the indications for redo-TAVI were mainly due to paravalvular leak rather than SVD. In patients with paravalvular leak compared to those with SVD, the need for redo-TAVI has occurred earlier. This also highlights the necessity for the first TAVI procedure to be optimal for durability.

While preparing for a redo-TAVR procedure, it is essential to take into careful consideration the structure of the dysfunctional first TAVI valves. These TAVI valves differ in terms of the form and size of the metal stent frame, as well as the location of the leaflets inside the frame.[13]

Inserting a new TAVI valve into a defective TAVI valve leads the leaflets of the first valve

to remain in the open position. This basically transforms a portion of the initial valve into an enclosed cylindrical conduit. The vertical dimension of the enclosed cylinder is usually known as the neoskirt height. The neoskirt height is strongly influenced by the particular stent frame type and the precise positioning of the leaflets. The height of a neoskirt has a direct influence on the likelihood of possible coronary blockage.[14-17] Several parameters, including as TAVI valves design, implant depth, and TAVI valve choice for redo-TAVR, increase the possibility of coronary blockage. Performing cardiac CT is a standard procedure to assess the risk of coronary occlusion while managing a failing bioprosthetic valve with TAVI.

Currently, there is insufficient evidence to inform TAVI valve selection for redo-TAVR. The choice of TAVI valve device for redo-TAVR depends on the characteristics and location of the first TAVI valve, the underlying reason of failure, and its surrounding anatomical structure.[18-20]

There is a limited number of empirical evidence available on the practice of redo-TAVI in real-life scenarios. TAVI accounted for 0.46% of the 133,250 TAVI operations in the Medicare database from 2012 to 2017. In addition, it included 0.33% of the 63,876 procedures in the redo-TAVI worldwide registry, which are the two largest published series. In selected patients, redo-TAVI is usually safe and successful, with minimal procedural complications and significant relief in symptoms. Survival rates at 30 days are similar to those reported in other valve-in-valve transcatheter aortic valve replacements (TAVRs) performed in patients with intermediate-to-high surgical risk. The mortality rate ranges from 2.9 to 6.0%, the stroke rate ranges from 1.4 to 1.8%, and the pacemaker rate ranges from 4.2 to 9.6%.[13] However, the survival rate at one year is lower, ranging from 13.5 to 22%.[13] This could be due to the higher risk of mortality in this particular population, which affects the overall outcomes.[11-14,19]

Although TAVI can be performed in degeneration of surgical aortic valves, initial TAVI preserves the patient's surgical chances and provides the opportunity to perform percutaneous procedures in the future.[21] Younger patients undergoing open SAVR may be encouraged to start using bioprostheses more, instead of mechanical valves in the near future, given the availability of this effective technique for replacing a malfunctioning surgical bioprosthesis. It is well-known that the mortality of redo surgery is high compared to redo-TAVI.[22,23]

The main limitation to this study is that it has a single-center and retrospective design with a relatively small sample size. Of note, although different surgeons performed the first and second TAVI procedures, all were experienced in TAVI.

In conclusion, with the widespread use of TAVI procedures and increased valve durability, patients are followed for longer periods of time currently. Some patients require reintervention due to valve degeneration or severe aortic regurgitation. Redo-TAVI can be performed in these patients. Redo-TAVI procedure is feasible and successful. However, further large-scale, long-term, prospective studies are required to further assess its effectiveness and safety.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Sutureless aortic valve replacement in high-risk patients with infective endocarditis

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ABSTRACT

Objectives: This study aims to investigate whether sutureless aortic valve replacement (AVR) is a safe and technically feasible method in patients with infective endocarditits (IE).

Patients and methods: Between September 2019 and March 2023, a total of 10 consecutive patients (4 males, 6 females; mean age: 61.5±17.7 years; range, 29 to 80 years) who underwent sutureless AVR due to aortic valvular IE were retrospectively analyzed. Sutureless AVR was preferred in patients in whom suturing became complex after radical debridement. The pre, peri-, and postoperative results, and follow-up data of the patients were evaluated.

Results: The mean EuroSCORE was 23.85±20.4. The mean ejection fraction was 55.5±12.2%. Seven (70%) patients had prosthetic valve endocarditis, and three (30.0%) patients had native valve endocarditis. Eight (80%) patients had a history of cardiovascular surgery. Concomitant cardiac intervention was performed in four patients. Periprocedural mortality was observed in two patients. None of the patients required permanent pacemaker implantation. Infective endocarditis developed in one patient during follow-up, but reintervention was not needed.

Conclusion: Our study results suggest that sutureless AVR can yield favorable outcomes with low paravalvular leak rates and satisfactory hemodynamic performance and with no major adverse event in IE. We advocate the consideration of sutureless aortic valve replacement as a viable alternative in the management of IE, emphasizing the importance of meticulous execution and expertise to achieve favorable results.

Keywords: Aortic valve replacement, heart valve, infective endocarditis, prosthesis.

Infective endocarditis (IE) is a rare condition. Despite advancements in early diagnosis, new medical treatments, comprehensive antibiotics regimens, and accumulated experiences with surgical approaches, it is still associated with a high mortality rate and can present itself under various conditions.[1] Acute, subacute, and chronic states can manifest different symptoms in different organ systems with different severities. At the time of referral to a cardiac surgeon, IE has already caused multiorgan impairments such as valvular destruction, septic embolism to the central nervous system or peripheral vascular system, or abscesses in the skeletomuscular system.[2,3] Multiorgan dysfunction is already a high-risk factor for cardiac surgery, and the addition of the risks of re-exploration has led to high mortality in today's patient population.[4-6]

Surgical aortic valve replacement (SAVR) is a treatment method for advanced aortic valvular IE. In this approach, infected and damaged valvular tissue should be excised meticulously. Insufficient debridement of the aortic valve and its surrounding tissue can cause fatal complications such as reinfection, the formation of new vegetation and its embolism, paravalvular leakage (PVL), aortic pseudoaneurysm and even dislodgement of the aortic prosthesis. However, the high surgical risk scores of IE patients force surgeons to invent novel techniques or adapt existing techniques to lower the risk of these procedures.

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The development of new strategies to minimize the effects and shorten the duration of cardiopulmonary bypass (CPB) and arterial cross-clamp (AXC) is vital for reducing the risk of any cardiac surgery, not only in high-risk IE patients.[7-10]

Sutureless aortic valve replacement (Su-AVR) was introduced as a less invasive and rapid surgical approach for treating aortic valvular pathologies. It can be preferable in patients with calcified aortic valves and roots and small aortic annuli. The absence of the ring in sutureless valves leads to better hemodynamics, lower transvalvular gradients, and a better effective orifice area associated with a lower rate of patient–prothesis mismatch.[3,4] Additionally, owing to its hemodynamic advantages, Su-AVR significantly reduces the CPB and AXC times due to the simplicity of the procedure, and there is no significant difference in mortality or morbidity between Su-AVR and SAVR.[5,6]

In the current literature, despite the limited number and small sample sizes of studies reporting on the application of Su-AVR in patients with endocarditis, positive outcomes have been documented.[7] In the present study, we aimed to investigate whether sutureless AVR was a safe and technically feasible method in patients with IE.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Koşuyolu High Specialization Education and Research Hospital, Department of Cardiovascular Surgery between September 2019 and July 2023. A total of 141 patients underwent Su-AVR. Among these patients, 10 (4 males, 6 females; mean age: 61.5±17.7 years; range, 29 to 80 years) who had active IE were included. A Perceval™-S (CORCYM, previously LivaNova, Saluggia, Italy) aortic valve prosthesis was used in all the patients. Seven of those presented with IE caused by previously implemented valvular prostheses. The other three patients presented with native valve endocarditis. A written informed consent was obtained from each patient. The study protocol was approved by the Koşuyolu High Specialization Education and Research Hospital Ethics Committee (date: 06.02.2024; no: 2024/03/774). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were evaluated preoperatively by our institution's interdisciplinary Heart Team, which consists of cardiovascular surgeons, cardiologists, radiologists, pulmonologists, and infectious disease specialists. The Modified Duke criteria were used for differential diagnosis in association with cardiac imaging. Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were performed for all patients to identify possible vegetation, abscesses, or fistulas. Whole-body computed tomography (CT) was performed to detect possible septic embolism or IE-related complications.

Data were meticulously gathered from various reliable sources. Extensive preoperative information was obtained by scrutinizing medical records from relevant departments, such as cardiology, internal medicine, pulmonology, and nephrology. Furthermore, these physical records were cross-checked with the National Electronic Health Record to ensure precision. Postoperative data were extracted from both intensive care unit (ICU) and general ward records, supplemented by consultation with National Electronic Health Records.

Surgical technique

In our institution, we usually normally prefer to perform standard sternotomy for these patients, due to the possibility of complex disease. In only one patient, we performed upper reversed-T sternotomy due to anatomical suitability, the lack of abscess or pseudoaneurysm formation around the aortic root and the patient's insistent preference. In all cases, arterial cannulation was performed from the distal ascending aorta. In eight patients, double-stage venous cannulation from the right atrium was performed; in two patients, left atrial exploration was performed and bicaval cannulation was performed. Routinely, a venting cannula from the right superior pulmonary vein (RSPV) was used. Routinely isothermic blood cardioplegia was administered every 20 min in antegrade fashion. Proper deairing was performed and monitored via TEE via the aortic root via an aortic venting needle and from the RSPV with the patient in the Trendelenburg position.

Aortotomy was performed, and the native or prosthetic valve was decalcified and excised. Special care was taken to perform radical excision and debridement of all the vegetation and infected tissues. Of note, Su-AVR was performed in the patients as the complete excision of annular tissue in the valve,

resulting from endocarditis-induced destruction, left no available suture space. One patient underwent patch reconstruction at the level of the non-coronary cusp with the pericardium to the aortic annulus to achieve a proper site for fitting the valve and suturing space.

All patients in the study underwent sutureless valve replacement via a bioprosthetic nitinol-stented Perceval™ prosthesis. After the valve was sized, the Perceval™ sutureless aortic valve was placed in a standard manner over three guiding sutures (4-0 polypropylene) positioned at the lowest level of each resected and decalcified cusp. Then, the valve prosthesis was parachuted into the aorta, sliding on the guiding sutures and maintaining alignment with the aorta. After it was determined that the valve was in the correct position and fitted into the annulus, the balloon was expanded for 30 sec by 3 or 4 atm for all prosthesis sizes, if needed. Sterile 37°C saline was applied for the stabilization of the stent.

The aortotomy was closed with 4/0 continuous Prolene sutures with care to avoid intervening with the stents of the valve.

Antibiotic therapy and IE prophylaxis

All patients were treated with intravenous antibiotic therapy consisting of cefepime, vancomycin, and rifampicin, according to our standard regimen. The treatment regimen was usually planned to start four weeks before surgery and continue for two weeks after surgery, for a total of six weeks. Antibiotic therapy was changed according to sensitivity if a causative organism was isolated.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). In this study, categorical data were presented as percentages, representing the proportion of individuals in each category, while numerical data were expressed as mean values with their corresponding standard deviations (SD).

RESULTS

The mean EuroSCORE value was 23.85±20.4%. The mean ejection fraction was 55.5±12.2%. Seven (70%) patients had prosthetic valve endocarditis (PVE) and three (30%) patients had native valve endocarditis. Eight (80%) patients had a history of cardiovascular surgery. Among those eight patients, seven (87.5%) had a history of intervention in a cardiac valve. All patients suffered from multiple comorbidities (Table 1).

The intraoperative data of the patients are listed in Table 2. One of our operations was performed urgently due to severe aortic insufficiency and hemodynamic instability. In our study group, five of our patients needed concomitant surgery. Concomitant previous cardiac intervention was performed in five of the patients (50%). The mean CPB time was 159.7±36.4 min, and the mean AXC time was 83±24.3 min.

Postoperative outcomes are given in Table 3. The mean peak gradient of the aortic valve was 26.3±12.7 mmHg. In our study group, one patient needed postoperative re-exploration for bleeding. Three patients suffered from sepsis postoperatively, and one of them died due to septic shock on postoperative Day 74. This patient developed pneumonia after surgery, and the isolated microorganisms were different from those isolated via blood culture before surgery. Pneumonia progresses to sepsis and eventually causes patient death. In our study group, none of our patients experienced a stroke or transient ischemic attack. Although three of our patients had new-onset atrial fibrillation, none of them needed permanent pacemaker (PPM) implantation. None of the patients had a PVL on echocardiographic examination.

In total, two of our patients died in the early postoperative period (30-day mortality). The first patient was a 65-year-old male who had a history of coronary artery bypass grafting (CABG) and lung bullectomy. This patient also experienced chronic renal failure and was receiving dialysis. Additionally, the patient had vertebrobasilar insufficiency, peripheral arterial disease, and chronic obstructive pulmonary disease (under inhaler therapy). The patient's ejection fraction was 35%, with severe aortic regurgitation caused by a destructured valve but without any evidence of vegetative-obstructive material. Blood cultures revealed the presence of *Staphylococcus epidermidis* and *Staphylococcus lentus*. The patient's EuroSCORE II was 70.8%, indicating an extremely high risk of mortality. An urgent redo procedure involving isolated Su-AVR (Perceval™-S XL) implantation was performed. The patient was discharged from the ICU on postoperative

Table 1
Demographic data of the patients

Characteristics	n	%	Mean±SD
Age (year)			61.5±17.7
Sex			
Male	4		
Female	6		
Body mass index			26.59±4.37
Carotid disease	6	60	
Peripheral arterial disease	1	10	
Preoperative stroke	2	20	
Arterial hypertension	4	40	
Pulmonary hypertension	8	80	
Ischemic cardiomyopathy	2	20	
Atrial fibrillation	2	20	
Conduction abnormality	0	0	
Chronic obstructive pulmonary disease	1	10	
Type 2 diabetes mellitus (insulin-dependent)	2	0	
Chronic renal failure*	2	20	
Dialysis	1	10	
Reop surgery	8	80	
Previous surgery			
CABG	1		
AVR	3		
AVR+MVR	3		
AVR+Ascending aorta replacement	1		
LV ejection fraction (%)			55.5±12.2
Type of aortic valve dysfunction			
Aortic regurgitation	5	50	
Severe	4	40	
Moderate	1	10	
Aortic stenosis	9	9	
Severe	7	7	
Moderate	2	20	
Peak aortic valve gradient (mmHg)			70.1±27.8
Mean aortic valve gradient (mmHg)			28.8±16.9
End systolic/end diastolic diameter (cm)			3.73±5.45
Native aortic valve/prosthetic aortic valve	3/7	30/70	
Types of bacteria in hemocultures			
Staphylococcus aureus	4	40	
Coagulase negative *Staphylococcus*	4	40	
Enterococcus	1	10	
Enterobactericia	1	10	
EuroSCORE II			23.85±20.4

SD: Standard deviation; CABG: Coronary artery bypass grafting; AVR: Aortic valve replacement; MVR: Mitral valve replacement; LV: Left ventricle; * Chronic kidney failure is defined as a glomerular filtration rate <60 mL/min/1.73 m^2.

Table 2
Intraoperative characteristics

Variables	n	%	Mean±SD
Urgent procedure	1	10	
Emergent procedure	0	0	
Concomitant procedures	5	50	
CABG	2	20	
MVR	2	20	
Aortic root patch repair	1	10	
Intraoperative findings			
Vegetation/thrombus	7	70	
Abscess	1	10	
Destruction of aortic valvular tissue	4	40	
Aortic root pseudoaneursym	1	10	
Perceval size			
S	4	40	
M	3	30	
L	1	10	
XL	2	20	
CPB time (min)			159.7±36.4
AXC time (min)			83±24.3
Intraoperative complication	1*		
Second AXC	1*		
Using a second sut-AVR valve	1*		
Use of inotropes or vasopressors			
Dobutamine	8	80	
Noradrenaline	5	50	
Adrenaline	2	20	
Milrinone	0	0	
Vasopressine	0	0	
ECMO	0	0	

SD: Standard deviation; CABG: Coronary artery bypass grafting; MVR: Mitral valve replacement; S: Small; M: Medium; L: Large; XL: X-large; CPB: Cardiopulmonary bypass; AXC: Arterial cross-clamp; ECMO: Extracorporeal membrane oxygenation; AVR: Aortic valve replacement; * Patient presented with an aortic root abscess and pseudoaneurysm; even though complete debridement was performed, sufficient aortic root tissue was present, so the Sut-AVR valve was implemented. However, after the removal of the AXC and during weaning from CPB, a tear was detected at the aortic root. The surgical team was unable to control the bleeding, a second AXC was administered, and root repair with a pericardial patch was performed. The sutureless valve was removed to perform the procedure. The root was repaired successfully, and a second sutureless valve was deployed.

Day 4. However, the patient was readmitted to the ICU with dyspnea six days after being transferred to the ward and was electively reintubated. A chest X-ray revealed pulmonary infiltration and pleural effusion. Although extubation was attempted several times during follow-up, the patient had weak muscle strength and poor respiratory effort and was unable to tolerate it, leading to a tracheostomy being performed at three weeks. Due to inadequate oral intake, a percutaneous endoscopic gastrostomy (PEG) was placed on postoperative Day 55. After Day 60, the patient developed hemodynamic instability and sepsis. On Day 65, the patient progressed to septic shock, and despite all interventions, the patient was lost on postoperative Day 74.

The second patient was an 80-year-old female with a history of a bioprosthesis AVR. The patient presented with two large vegetations (13×7 mm and 5×4 mm) on her prosthesis. The patient also had mild pulmonary hypertension (57 mmHg)

Table 3
Postoperative outcomes

Variables	n	%	Mean±SD
Re-exploration for bleeding	1	10	
Stroke/transient ischemic attack	0/0	0/0	
Transient ischemic attack	0	0	
Erythrocyte concentrate transfusion (mean unit per patient)			5±2.7
Sepsis	3	30	
Pneumonia	3	30	
Myocardial infarction	0	0	
Atrial fibrillation	3	30	
Pacemaker (permanent/transitory)	0	0	
Acute kidney failure (need for transitory CRRT)	1	10	
Chronic kidney failure (A new onset/worsening in CKD stage)	0	0	
Paravalvular leakage	0	0	
Peak/mean transaortic gradient (mmHg)			26.3±12.7/13.8±5.6
Time on ventilator (h)			17±9.2
Inotrope or vasopressors (mean administration duration in days)			
Dobutamine (day)	8	4.2	
Noradrenaline (day)	5	3.6	
Adrenaline (day)	3	4	
Milrinone	0	0	
Vasopressine (day)	2	0.8	
ICU stay (day)			5±1.4
Postoperative in-hospital stay (day)			15.5±4.2
In-hospital mortality	20		

SD: Standard deviation; CRRT: Continuous renal replacement therapy; ICU: Intensive care unit; CKD: Chronic kidney disease.

Table 4
One-year follow-up outcomes

Variables	n	%	Mean±SD
Peak gradient of the aortic valve (mmHg)			25.3±11.3
Mean gradient of the aortic valve (mmHg)			13.7±6.3
Paravalvular leak (total)	2		
Mild	2		
Moderate	None		
Severe	None		
Reintervention	10*	1	
Infective endocarditis	1.0**	10	
Transient ischemic attack	0	0	
Stroke	0	0	
Survival	70	7	

SD: Standard deviation; * Reintervention was due to Infective Endocarditis in the mitral valve, which was not present in the first case; ** The same bacteria were isolated from the hemocultures, which was considered a relapse of the infection.

caused by severe mitral regurgitation. The patient underwent a redo Su-AVR (Perceval™-S, M) and mitral ring annuloplasty. The patient developed systemic inflammatory response syndrome and acute kidney failure postoperatively. The patient was unresponsive to the treatment and inotropes and died on postoperative Day 3.

The mean follow-up was 13.4±8.7 months. Table 4 outlines the one-year follow-up outcomes of the cohort. The mean peak gradient of the aortic valve during follow-up was 25.3±11.3 mmHg. Although intraoperative TEE and early postoperative TTE revealed no PVL, PVL was present in these two patients at follow-up after discharge. Both instances of PVL were mild, and intervention was deemed unnecessary. One of the patients in whom PVL was detected previously underwent a concomitant aortic root repair procedure. The PVL was identified post-discharge and was classified as mild, with no associated hemodynamic complications or hemolysis. The patients remain alive and continue to attend routine follow-ups every six months.

Readmission was necessary in one case. This patient was diagnosed with IE with the Duke criteria (1 major: a common causative microorganism was isolated in three separate blood cultures; 2 minor: history of IE, fever greater than 38°C). There was no vegetation or valvular dysfunction present. The patient received six weeks of antibiotic therapy, and there was no sign of infection afterward. Transient ischemic attack (TIA) or stroke was not observed in any patient within one year.

On follow-up, we lost a 37-year-old female with a previous history of concomitant aortic and mitral valve replacement and who was discharged from the hospital on postoperative Day 10. With this patient and the two patients who were lost during the early postoperative period, our overall one-year survival rate was 70%.

DISCUSSION

In this study, we present our experience with the use of Su-AVR for IE at the aortic valve. A total of 10 high-risk patients with a mean EuroSCORE II of 23.85±20.4% underwent Su-AVR. Our study results showed that Su-AVR could be a an alternative and technically feasible option for selected patients with IE at aortic valve.

Table 5
Studies evaluating Su-AVR in IE

Study	Year	Number of patients	EuroSCORE II (mean)	Valve type	Stroke	PVL discharge (%)	PPM (%)	Postoperative mortality (%)	Follow up time/ mortality %
Mosquera, et al.[7]	2023	36	24.9	Perceval	5	8 Trivial-mild	8	13.9	1 year 27.9 5 year 38.6
Zubarevich, et al.[6]	2022	13	28.7	Perceval	0	0	0	23.1	6 month 46.2
Roselló-Díez, et al.[13]	2017	9	16.3	Perceval	NA	33.3 Trivial-mild	11.1	22.2	6 month 22.2
Weymann, et al.[10]	2017	9	(median) 29.5	Perceval	0	0	0	0	(median) 7 months 11.1
Lio, et al.[17]	2015	5	25.8	Perceval	0	NA	0	20	NA

AVR: Aortic valve replacement; IE: Infective endocarditis; PVL: Paravalvular leak; PPM: Permanent pacemaker; NA: Not applicable.

Infective endocarditis is a unique pathology in the vast world of cardiac surgery. Most valvular pathologies have specific symptoms and a predictable course of development. How they affect cardiac physiology and hemodynamics is predictable. The effects of valvular pathologies on other organ systems are also highly predictable. However, the ability of IE to influence different valves with different pathologies and its ability to spread not only in cardiac structures, but also in other organ systems makes it highly challenging to manage.[2-6] Radical excision of the valvular structure and debridement of the surrounding structure are the main steps of IE surgery. This debridement process and the possibility of the involvement of other cardiac structures make IE surgery a high-risk procedure, and its results are highly dependent on the surgeon's experience and how complicated the pathology is. In addition to the complexity of the surgery, other existing end-organ impairments, either dependent on or independent of IE, increase the in-hospital mortality rates to 15 to 30%.[6]

As a clinical approach, for non-IE patients, we may prefer Su-AVR to achieve better valve hemodynamics and ease of surgery in some patients who are considered to be at high risk and have a narrowed aortic annulus. For IE patients, we resect infected tissues diligently and carefully to avoid complicated situations such as reinfection and abscess formation. Our strategy is usually to use a bioprosthetic valve in IE patients. After the aortic annulus is examined and the damaged valvular apparatus and vegetation are resected, a bioprosthetic valve, a sutureless valve or sometimes a change in the whole aortic root, such as the Bentall operation, can be performed.

In cases where the aortic annulus is severely damaged or where an abscess develops, the annulus may need to be reconstructed. In such cases, after massive debridement, deformities in the aortic root may lead to complete changes in the aortic root. Additionally, placing single or pledgeted sutures and a stented valve may become challenging in cases where the annulus has been reconstructed. Zubarevich et al.[7] and Mosquera et al.[8] reported that 15.3% and 44% of patients, respectively required pericardial patch repair. In our series, a pericardial patch was utilized in only one patient (10%).

The reason for mortality in two patients was unrelated to the prosthesis used, but rather to the complexity of the procedures and multimorbidity of the patients. Many of our patients also presented with prosthesis endocarditis (70%). Prothesis endocarditis has a high mortality rate compared with non-endocarditis valvular surgery.[9] In the current literature, prosthesis endocarditis has an estimated mortality rate of approximately 20 to 80%.[10] In-hospital mortality rates for patients with IE undergoing Su-AVR range from 0 to 23.2%.[7,11] Differences in mortality rates may vary depending on the patient's clinical condition, deformities in terms of the severity of destruction at the aortic annulus and aortic root, and comorbidities.

As previously discussed, PVE has significantly higher mortality than native valvular endocarditis. Glaser et al.[12] conducted the most robust studies on PVE after SAVR. In this study, PVE occurred in 3.53% of the patients; however, mortality rates were not reported. Andrade et al.[10] also published their results on PVE after SAVR. The percentage of PVE after SAVR was 3.7%, similar to that reported by Glaser et al.[12] In the study of Andrade et al.,[10] 40.6% of the PVEs occurred in the aortic position. One-year mortality was 22% in patients with endocarditis in all valvular positions after SAVR. In another study, Sepehripour et al.[13] published the results of the Su-AVR in its early stages. In the aforementioned study, PVE was seen at a rate of 2.1 to 3.1% after Su-AVR. This result was also reported for non-endocarditis patients. In our study, only one patient (10%) was diagnosed with IE after Su-AVR. However, the diagnosis was based on the Duke criteria (the patient had positive hemocultures, persistent fever >38°C, a prosthetic valve and underwent surgery due to IE during the first operation), and no vegetation was found on the prosthesis or other cardiac structures.

In our study group, no cases of PVL were observed at the time of discharge. However, during the follow-up period, two patients were found to have mild-to-trace PVL, which did not require intervention. In the literature, Zubarevich et al.[7] and Weymann et al.[11] reported no cases of PVL before discharge in their series. On the other hand, Roselló-Díez et al.[14] and Mosquera et al.[8] reported pre-discharge PVL rates of 33.2% and 8%, respectively, in their series of IE patients who underwent Su-AVR, none of whom required intervention or experienced progression. Considering this complicated patient group, we believe that

this non-progressive, mild paravalvular leak is acceptable in this patient group given the very good hemodynamic performance of the valves.

Conduction problems are common in aortic valvular surgeries. Although the need for PPM implantation is uncommon, it leads to a longer hospital stay, a need for additional invasive procedures, and an increase in the number of foreign bodies, which increases the risk for future infections. The reported postoperative PPM implementation for SAVR varies between 3% and 10%. Clemence et al.[15] reported that the need for PPM implementation was significantly greater in patients with aortic valvular endocarditis. Vogt et al.[16] reported that Su-AVR has an increased risk of needing PPM: 8.1% for Su-AVR and 2.7% for SAVR. Robich et al.[17] reported a need for PPM implementation after SAVR increased over time. Although it is not entirely clear, one possible reason might be patients' advanced age and comorbidities. However, they also reported that Su-AVR had lower rates of needing PPM, when concomitant mitral valve surgery was performed than when concomitant SAVR and mitral valve surgery were performed. However, a greater risk for a PPM-dependent AV block has been reported in both endocarditis patients and in Su-AVR patients. In the aortic valve endocarditis series in which Su-AVR was implanted, the rates of PPM varied between 0 and 11.2%.[14,18] Zubarevich et al.[7] reported that none of their patients needed PPM implementation. Our study shows a similar result. None of our patients required PPM implementation. Postoperative tachyarrhythmia rates are also similar, with a slightly lower incidence in our study (53.8% in Zubarevich et al., 30% in our study). The pre, peri-, and postoperative findings of recent studies of Su-AVR in patients with aortic valve IE are summarized in Table 5.

As previously mentioned, sutureless aortic valves are not routinely preferred in endocarditis surgery; however, they represent an alternative valve type that can be utilized in complex cases. Although the absence of sutures or pledgets in sutureless valves may appear advantageous in terms of reducing the risk of infection, it is crucial to acknowledge the potential for undesirable outcomes due to paravalvular leaks that may occur when these valves are implanted in a destructed annulus. Therefore, while sutureless valves may not be routinely employed in cases of infectious endocarditis, they can be considered as an alternative approach particularly in cases where annular area is suitable for sutureless valve implantation easily and suturing in the annular region is problematic.

The main limitations to this study are that it is a single-center, retrospective study with a relatively small sample size and no randomization. Due to the small cohort size, no specific statistical analyses were able to be performed. Additionally, the follow-up time was relatively short. The safety and efficiency of this approach can be validated with prospective studies with larger cohorts and long-term follow-up.

In conclusion, the standard surgical approach for IE at the aortic valve is AVR with a bioprosthetic valve. In cases of IE where radical resection leaves no suture area available, Su-AVR may serve as a rapid, reliable, and technically feasible option. Additionally, it may be preferred in selected high-risk patients with elevated comorbidities due to IE owing to its ability to provide short durations of CPB and cross-clamping. Our study demonstrated that Su-AVR resulted in low PVL rates and favorable hemodynamic outcomes. Additionally, there were no major adverse events related to the sutureless valve during follow-up after Su-AVR in IE patients. Taken together, we believe that Su-AVR can be recognized as an alternative approach in the management of IE in selected cases with anatomical suitability by surgeons, and positive results can be achieved when this procedure is carried out meticulously and with expertise.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Wrote the original draft: M.M.O., D.C., B.G.; Conceptualization: T.O., M.A.; Visualization: S.S., O.A.; Data collection: H.H., A.G., B.G.; Supervision, editing: K.K.

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Prognostic predictive value of CHA2DS2-VA score in patients with permanent atrial fibrillation

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ABSTRACT

Objectives: This study aims to investigate the prognostic value of the CHA_2DS_2-VA score in patients with permanent atrial fibrillation (AF).

Patients and methods: Between January 20223 and June 2023, a total of 917 patients with permanent AF (446 males, 471 females; mean age: 70.2±9.7 years; range, 27 to 89 years) were retrospectively analyzed. The patients were divided into two groups based on their CHA_2DS_2-VA scores: high-risk (score ≥2, n=743) and low-risk (score <2, n=174). Data on one-year all-cause mortality were collected through follow-ups and interviews.

Results: In the univariate analysis, CHA_2DS_2-VA score, age, sex, systolic blood pressure (SBP), left ventricular ejection fraction (LVEF), chronic obstructive pulmonary disease (COPD), chronic kidney disease, hemoglobin, neutrophil, and lymphocyte counts were found to be significant predictors of mortality. Multivariate analysis revealed that only age, sex, SBP, COPD, LVEF, and hemoglobin were independent predictors. There was a significant relationship between CHA_2DS_2-VA score and one-year all-cause mortality (p=0.002).

Conclusion: Our study results showed that the CHA_2DS_2-VA score was associated with one-year all-cause mortality in AF patients, but it was not an independent predictor when evaluated with all parameters affecting mortality. In the management of AF patients, the CHA_2DS_2-VA score may be useful not only in determining oral anticoagulation strategy, but also in the approach of clinicians to AF patients, considering that it may be a predictor of mortality.

Keywords: All-cause mortality CHA_2DS_2-VA score, permanent atrial fibrillation.

Atrial fibrillation (AF) is the most prevalent persistent arrhythmia, which significantly and adversely affects the quality of life and increases mortality and morbidity rates.[1] Preventing thromboembolism is the main goal to reduce the overall mortality rate associated with AF. Indeed, compared to a placebo or control, oral anticoagulation with Vitamin K antagonists (VKAs) dramatically lowers stroke and systemic embolism by 64%, while also significantly lowering all-cause mortality by 26.[2] Numerous extensive randomized studies have shown that non-Vitamin K oral anticoagulants (NOACs) are safe and effective.[3-6] Over the last decade, NOAC use has become widespread due to the impact of these studies and as NOAC use does not require international normalized ratio (INR) monitoring.

One commonly used metric to estimate the risk of thromboembolic events in individuals with AF was the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 and sex category [female]). Physicians widely used the CHA_2DS_2-VASc score, since it is straightforward: it does not require an online calculation, each point is assigned to a binary risk factor, and it does not require laboratory or radiographic testing. Numerous conventional coronary artery disease (CAD) risk

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factors are also included in the CHA_2DS_2-VASc score. Therefore, independent of the occurrence of AF, the CHA_2DS_2-VASc score is a good predictor of both in-hospital and long-term unfavorable cardiovascular events. All-cause mortality, non-fatal myocardial infarction, acute stent thrombosis, no-reflow phenomenon, non-fatal stroke, pulmonary embolism, and other adverse cardiovascular events have been linked to high CHA_2DS_2-VASc scores.[7-13]

In the final European Society of Cardiology (ESC) consensus, the sex component was removed from the CHA_2DS_2-VASc score, and this score was renamed CHA_2DS_2-VA. In the present study, we aimed to investigate the prognostic value of the CHA_2DS_2-VA score newly defined by the ESC in patients with permanent AF.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at University of Health Sciences, Gazi Yaşargil Training and Research Hospital, Department of Cardiology between January 2023 and June 2023. All patients over the age of 18 who were admitted to our clinic and diagnosed with permanent AF were included in the study. Initially, a total of 1,032 patients were reviewed. Patients who were restored to sinus rhythm for any reason (n=14), patients whose data were inaccessible (n=67), patients with active infection (n=23), and patients with malignancy or receiving chemotherapy (n=11) were excluded from the study. Finally, a total of 917 patients (446 males, 471 females; mean age: 70.2±9.7 years; range, 27 to 89 years) who met the inclusion criteria were recruited. The study flowchart is shown in Figure 1. A written informed consent was obtained from each patient. The study protocol was approved by the University of Health Sciences, Gazi Yaşargil Training and Research Hospital (No: 275-12/12/2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Demographic and echocardiographic characteristics of the patients, oral anticoagulation drug regimens, and one-year follow-up results were evaluated. Stroke risk was calculated using the CHA_2DS_2-VA score, while bleeding risk was calculated using the HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly), when applicable. The patients were, then, divided into two groups according to the CHA_2DS_2-VA scores newly defined by the ESC.[14] Patients with a CHA_2DS_2-VA score ≥2 were included in the high-risk group (n=743), and those with a CHA_2DS_2-VA score <2 were included in the low-risk group (n=174). Follow-up data were collected by telephone interviews or clinic visits. The primary outcome measure was one-year all-cause mortality.

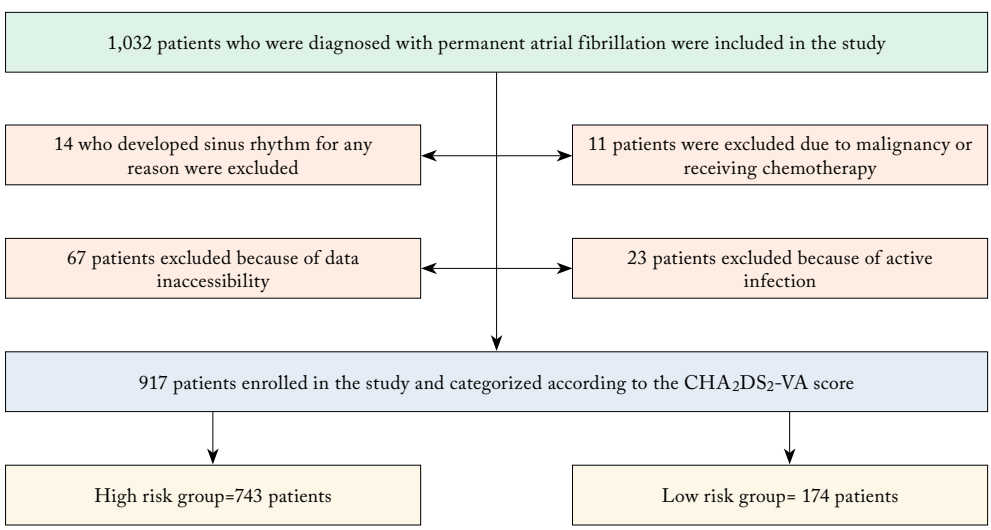

Figure 1. Study flowchart.

Definitions

Systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or the use of antihypertensive medication were considered as hypertension (HT). A fasting blood glucose level of ≥126 mg/dL, the use of anti-diabetic drugs, or a glycated hemoglobin (HbA1c) result in higher than 7% were considered diabetes mellitus (DM). Current smoking was the definition of smoking. The INR levels were measured at each center's local laboratory. The Cockroft-Gault formula was used to determine glomerular filtration rates.[15] Glomerular filtration rate (GFR) <60 mL/min/1.73 m² or signs of kidney damage, or both, for a minimum of three months was considered chronic kidney disease (CKD).

The CHA_2DS_2-VA score was calculated according to the criteria published by the ESC in the latest guideline. The CHA_2DS_2-VA ranges from 0 to 8 (ESC). While calculating the CHADS-VA score, 1 point is given for ages 65-74, 1 point for heart failure, 1 point for HT, 1 point for DM, 1 point for a history of vascular disease, 2 points for age 75 and over, and 2 points for the history of stroke, transient ischemic attack, or systemic thromboembolism.[13]

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 27.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of variables was analyzed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were expressed in mean ± standard deviation (SD) or median (interquartile range), while categorical variables were expressed in number and frequency. Depending on the distributions, the Mann-Whitney U test or Student t-test were used to compare continuous variables. For continuous variables, univariate analysis was used, while the chi-square or Fisher exact test was utilized for categorical variables. The association between survival and CHA_2DS_2-VA score over a 12-month follow-up period was examined using the Kaplan-Meier test. The variables influencing mortality for one-year were assessed using univariate Cox regression analysis. Parameters with a p value of <0.05 in the univariate Cox regression analyses were included in the multivariate Cox regression analyses. A p value of <0.05 was considered statistically significant.

RESULTS

In this study, patients with a CHA_2DS_2-VA score of ≥2 were included in the high-risk group (n=743), and patients with a CHA_2DS_2-VA score of <2 were included in the low-risk group (n=174). No significant difference was observed between the groups in terms of body mass index (BMI), heart rate, smoking, hemoglobin, platelet, and albumin ($p<0.05$ for all).

Mean age (71.9±9 *vs.* 62.8±8.8 years, p<0.001), CHA_2DS_2-VA score (3.12±1.16 *vs.* 0.75±0.43, p<0.001), SBP (129±17.6 *vs.* 125.9±16.9 mmHg, p=0.035), DBP (78.3±11.6 *vs.* 75.2±11.1 mmHg, p=0.002), and HAS-BLED score (2 [1] *vs.* 1 [1], p<0.001) were higher in the high-risk group. Additionally, as expected, the number of patients with HT (539 [72.5] *vs.* 76 [43.7], p<0.001), DM (174 [23.4] *vs.* 13 [7.5], p<0.001), ischemic cerebrovascular disease (CVD) (57 [7.7] *vs.* 4 [2.3], p=0.010), hemorrhagic CVD (4 [0.5] *vs.* 2 [1.1], p=0.368), chronic obstructive pulmonary disease (COPD) (147 [19.8] *vs.* 24 [13.8], p=0.040), CKD (556 [74.8] *vs.* 110 [63.2], p=0.002), heart failure with reduced ejection fraction (HFrEF) (209 [28.1] *vs.* 17 [9.8], p<0.001) and one-year mortality rates (69 [9.3] *vs.* 4 [2.3], p=0.002) were higher in the high-risk group. Also, the mean left ventricular ejection fraction (LVEF) (49.9±10.8 *vs.* 54.5±8.6%, p<0.001) and GFR (39.1 [33] *vs.* 52.4 [43] mL/min/1.73 m², p<0.001) were statistically significantly lower in the high-risk group (Table 1).

Univariate Cox regression analyses were performed to investigate predictors of one-year all-cause mortality. In these analyses, CHA_2DS_2-VA score (hazard ratio [HR]=1.368, 95% confidence interval [CI]: 1.180-1.585, p<0.001), age (HR=1.057, 95% CI: 1.029-1.086, p<0.001), female sex (HR=3.630, 95% CI: 2.109-6.246, p<0.001), SBP (HR=0.982, 95% CI: 0.968-0.996, p=0.009), LVEF (HR=0.961, 95% CI: 0.941-0.981, p<0.001), COPD (HR=1.972, 95% CI: 1.196-3.251, p=0.008), CKD (HR=1.792, 95% CI: 1.004-3.215, p=0.014), hemoglobin (HR=0.867, 95% CI: 0.772-0.973, p=0.015), neutrophil (HR=1.060, 95% CI: 1.036-1.085, p<0.001), and lymphocyte (HR=0.930, 95% CI: 0.930-0.957, p<0.001) were statistically significant predictors of one-year all-cause mortality (Table 2).

Table 1

Baseline characteristics of total population

	High risk group					Low risk group					Total					
Parameters	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Age (year)			71.9±9					62.8±8.8					70.2±9.7			**<0.001**
Sex																**<0.001**
Female	351	47.2				120	69				471	51.4				
CHA_2DS_2-VA score			3.12±1.16					0.75±0.43					2.7±1.4			**<0.001**
Body mass index (kg/m^2)			28.3±3.8					28±3.9					28.2±3.8			0.410
Heart rate (min)			88.6±17.5					88±18.5					88.5±17.7			0.696
Systolic blood pressure (mmHg)			129±17.6					125.9±16.9					128.4±17.5			**0.035**
Diastolic blood pressure (mmHg)			78.3±11.6					75.2±11.1					77.7±11.6			**0.002**
LVEF (%)			49.9±10.8					54.5±8.6					50.4±10.6			**<0.001**
GFR (mL/min)-IQR				39.1	33				52.4	43				41.4	35	**<0.001**
HAS-BLED score-IQR				2	1				1	1				2	1	**<0.001**
Hemoglobin (g/dL)			13±2					13.2±1.9					13.1±2			0.318
Platelet (10^3/μL)			230.7±72					232.1±64.5					231±70.6			0.812
Neutophile (10^3/μL)			64.2±9.8					60.1±9.7					63.4±9.9			**<0.001**
Lymphocyte (10^3/μL)			24.7±8.7					28±9.4					25.3±9			**<0.001**
Glucose (mg/dL)			120.6±41.7					105.8±23					117.7±39			**<0.001**
Urea (mg/dL)			34.3±15.4					28.1±13.5					33.1±15.3			**<0.001**
Creatinin (mg/dL)-IQR				0.9	0.41				0.8	0.23				0.9	0.34	**<0.001**
Albumin (g/dL)			4.06±0.52					4.05±0.49					4.1±0.53			0.873
Total cholesterol (mg/dL)			174.9±42					181.1±44					176.3±42			**0.043**
HFrEF	209	28.1				17	9.8				226	24.6				**<0.001**
CKD	556	74.8				110	63.2				666	72.6				**0.002**
Smoker	118	15.9				24	13.8				142	15.5				0.493
Hypertension	539	72.5				76	43.7				615	67.1				**<0.001**
Diabetes mellitus	174	23.4				13	7.5				187	20.4				**<0.001**
Ischemic CVD/TIA	57	7.7				4	2.3				61	6.7				**0.010**
Hemorrhagic CVD	4	0.5				2	1.1				6	0.7				0.368
COPD	147	19.8				24	13.8				171	18.6				**0.040**
One-year mortality	69	9.3				4	2.3				73	8				**0.002**

SD: Standard deviation; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; GFR: Glomerular filtration rate; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; TIA: Transient ischemic attack; COPD: Chronic obstructive pulmonary disease. Low risk group; patients with a CHA2DS2-VA score <2; High risk group; patients with a CHA2DS2-VA score ≥2; P value of <0.05 shows statistical significance.

Table 2
Cox Regression analysis of 1-year all-cause mortality

	Univariable			Multivariable		
Parameters	HR	95% CI	*p*	HR	95% CI	*p*
CHA_2DS_2-VA score	1.368	1.180-1.585	**<0.001**	1.040	0.863-1.254	0.679
Age	1.057	1.029-1.086	**<0.001**	1.035	1.005-1.065	**0.022**
Sex / Female	3.630	2.109-6.246	**<0.001**	2.978	1.662-5.337	**<0.001**
Body mass index	0.949	0.892-1.009	0.092			
Heart rate	0.992	0.979-1.006	0.255			
Systolic blood pressure	0.982	0.968-0.996	**0.009**	0.984	0.970-0.997	**0.019**
LVEF	0.961	0.941-0.981	**<0.001**	0.977	0.954-1.000	**0.047**
COPD	1.972	1.196-3.251	**0.008**	1.759	1.040-2.974	**0.035**
CKD	1.792	1.004-3.215	**0.014**	1.133	0.607-2.112	0.695
Smoking	2.208	0.585-7.279	0.154			
Hypertension	1.072	0.654-1.756	0.783			
Diabetes mellitus	1.294	0.760-2.204	0.342			
Ischemic CVD/TIA	1.280	0.555-2.951	0.562			
Hemoglobin	0.867	0.772-0.973	**0.015**	0.870	0.774-0.978	**0.019**
Glucose	0.999	0.992-1.005	0.638			
Platelet	1.000	0.996-1.003	0.786			
Neutrophile	1.060	1.036-1.085	**<0.001**	1.033	0.995-1.072	0.091
Lymphocyte	0.930	0.930-0.957	**<0.001**	0.989	0.943-1.036	0.632
Albumin	0.853	0.550-1.323	0.477			

HR: Hazard ratio; CI: Confidence interval; LVEF: Left ventricular ejection fraction; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; CVD: Cerebrovascular disease; TIA: Transient ischemic attack.

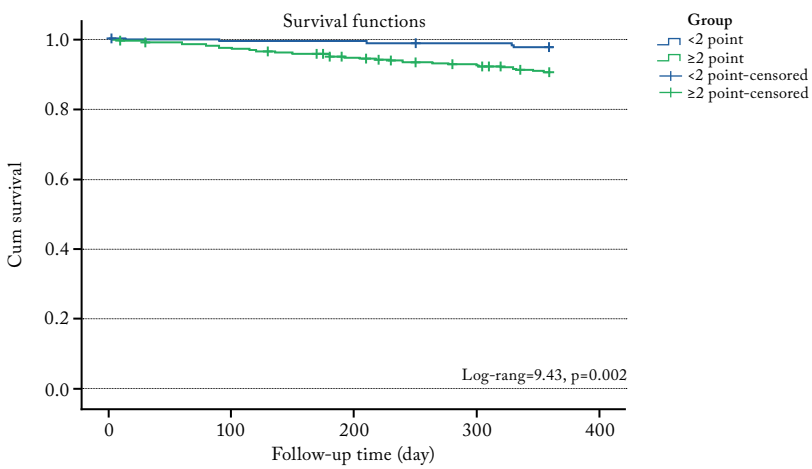

Figure 2. Kaplan-Meier analysis of relationship between CHA2DS2-VA score and 1-year all-cause mortality.

In the multivariate Cox regression analyses, only age (HR=1.035, 95% CI: 1.005-1.065, p=0.022), female sex (HR=2.978, 95% CI: 1.662-5.337, p<0.001), SBP (HR=0.984, 95% CI: 0.970-0.997, p=0.019), COPD (HR=1.759, 95% CI: 1.040-2.974, p=0.035), LVEF (HR=0.977, 95% CI: 0.954-1.000, p=0.047), and hemoglobin (HR=0.870, 95% CI: 0.774-0.978, p=0.019) were found to be independent predictors (Table 2).

The Kaplan-Meier analysis was performed to identify the relationship between CHA_2DS_2-VA score and one-year all-cause mortality. As a result of the analysis, the relationship between CHA_2DS_2-VA score and one-year all-cause mortality was statistically significant (log-rank=9.43, p=0.002) (Figure 2).

DISCUSSION

In the current study, we investigated the effect of CHA_2DS_2-VA score on one-year all-cause mortality in patients with permanent AF. Our study results showed a statistically significant relationship between the CHA_2DS_2-VA score and one-year mortality. However, the CHA_2DS_2-VA score was not an independent predictor of one-year all-cause mortality in patients with permanent AF. In addition, age, LVEF, COPD, female sex, hemoglobin level, and SBP were independent predictors of one-year all-cause mortality in permanent AF patients.

In previous studies investigating AF prognosis, results regarding the effect of sex are confusing. In the study by Dagres et al.,[16] male patients were more likely to have CAD and idiopathic AF, whereas female patients were older and more likely to have DM, thyroid disease, valvular heart disease, and HT. Overall, women were more likely than males to have comorbidities, be at the highest risk for stroke, and had symptoms. Other long-term morbidities and mortality rates were similar. The results from the Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) study, which included over 28,000 patients, showed that the unadjusted rate of all-cause mortality was only slightly higher in women than in men and, after adjustment for baseline risk factors, the rate of all-cause mortality was similar between women and men.[17] According to Emdin et al.'s[18] meta-analysis of more than 4,000,000 patients, women with AF had a greater relative risk of heart failure, cardiovascular death, stroke, all-cause mortality, and cardiac events than males.[18] In our study, similar results were found in the meta-analysis study conducted by Emdin et al.[18] in female AF patients. However, the effect of sex on mortality in AF patients is debatable. Many studies have shown that female patients have more comorbidities, more suffer from obesity, and are older patients. The outcomes of the female sex are expected to be worse, although its effect on mortality is still unclear.

According to Goldhaber et al.,[19] compared to patients under 65 years of age, the HRs for major adverse clinical outcomes within 24 months of follow-up for overall mortality, cardiovascular and non-cardiovascular mortality, non-hemorrhagic stroke or systemic embolism, major bleeding, myocardial infarction/acute coronary syndrome, and new or worsening heart failure increased with older age category. Many comorbidities and frailties are expected in older patients. It is not surprising that many diseases are predictors of mortality in this patient group. In our study, similar to previous studies,[19,20] age was an independent predictor of one-year mortality.

Previous studies have demonstrated that anemia is associated with poor prognosis and death in patients with AF.[21,22] Anemia was revealed to be an independent predictor of major adverse cardiac and cerebrovascular events as well as all-cause mortality by the Atrial Fibrillation Undergoing Coronary Stenting (AFCAS) registry.[22] Additionally, compared to AF patients who were not anemic, anemia was linked to a considerably higher risk of severe bleeding events, stroke, thromboembolic events, and all-cause death, according to the Danish registry.[21] In our study, in line with these studies, low hemoglobin level was an independent predictor of one-year all-cause mortality.

Heart failure has also been shown to increase one-year mortality in patients with AF in previous studies. A significant relationship was demonstrated between heart failure and mortality in the study conducted by Fauchier et al.[1] The Randomized Evaluation of Long-term Anticoagulant Therapy: dabigatran vs. warfarin (RELY-AF) study[23] and XANTUS (Xarelto® for Prevention of Stroke in Patients with Atrial Fibrillation)[24] real-life data also showed that heart failure was associated with

one-year all-cause mortality in patients with AF. The difference between our study and these studies is the mortality rate in patients. In our study, the one-year all-cause mortality rate was 8% and the mortality rate was higher compared to other studies. We believe that the reason for this is that we only included permanent AF patients in our study. Permanent AF is seen in more frail and older patients than other types of AF, and worse clinical outcomes are expected in permanent AF.

In Denmark, an observational study examined whether death rates differed for patients with AF and COPD based on the order of diagnosis.[25] After five years, more than half of these patients died, showing poor prognosis. Patients diagnosed with AF before COPD had a 26% lower death risk than those with COPD diagnosed first. Earlier COPD diagnosis increased mortality risk. In the meta-analysis study by Ye et al.,[26] AF patients with COPD were found to be associated with increased overall mortality, increased cardiovascular mortality, and more frequent bleeding complications compared to AF patients without COPD. Our study found similar results to previous studies. Taken together, it should be kept in mind that COPD is a risk factor in predicting mortality, given the fact that it is frequently seen in AF patients.

Nonetheless, there are some limitations to this study. First, this study is a single-center and retrospective study. Therefore, the results cannot be generalized. Second, since our study is retrospective, some bias could not have been completely eliminated. Third, in the multivariate analyses, some other parameters could have been included; however, we have missing data. Finally, we have no data on hemorrhagic or ischemic CVD that developed during follow-up in the patients, and since we are unaware of the causes of death, only predictors of all-cause death were analyzed.

In conclusion, our study results showed that the CHA_2DS_2-VA score was associated with one-year all-cause mortality in AF patients, but it was not an independent predictor when evaluated with all parameters affecting mortality. In the management of AF patients, the CHA_2DS_2-VA score may be useful not only in determining oral anticoagulation strategy, but also in the approach of clinicians to AF patients, considering that it may be a predictor of mortality.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Plasma matrix metalloproteinase-9 level in prediction of myocardial fibrosis improved by magnetic resonance imaging in patients with hypertrophic cardiomyopathy

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ABSTRACT

Objectives: This study aimed to compare plasma matrix metalloproteinase-9 (MMP-9) levels of hypertrophic cardiomyopathy (HCM) patients with and without fibrosis.

Patients and methods: Fifty-three HCM patients (33 males, 20 females; mean age: 52.4±10 years; range, 42 to 63 years) diagnosed by transthoracic echocardiography and cardiac magnetic resonance imaging (CMR) between January 2015 and March 2018 were included in the prospective study. They were divided into two groups according to CMR: patients with and without fibrosis. Plasma MMP-9 levels were compared.

Results: In this study, serum MMP-9 levels were significantly higher in HCM patients with myocardial fibrosis in CMR than those without fibrosis (p<0.001). Left ventricular mass index (OR=1.056, 95% CI: 1.004-1.112, p=0.035) and MMP-9 levels (OR=1.031, 95% CI: 1.013-1.049, p=0.003) were independent predictors of myocardial fibrosis.

Conclusion: Serum MMP-9 level has high sensitivity and specificity for prediction of myocardial fibrosis on CMR in HCM patients. It is known that myocardial fibrosis is associated with major adverse cardiac events. Therefore, it would be appropriate to closely monitor HCM patients with high serum MMP-9 levels.

Keywords: Cardiomyopathy, fibrosis, hyperthrophic, magnetic resonance imagination, MMP-9.

Pathologic events that occur in the heart muscle are usually called cardiomyopathy. Cardiomyopathy may occur due to systemic diseases such as valve disease (aortic stenosis and mitral regurgitation) and hypertension. Cardiomyopathies arising from the heart muscle itself are called primary cardiomyopathy. Hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy, and restrictive cardiomyopathy are examples of primary cardiomyopathies.

Hypertrophic cardiomyopathy is a primary heart muscle disease that occurs in the absence of another cardiac or systemic disease to cause hypertrophy, usually showing increased contractile function, involving mostly the interventricular septum of the undilated left ventricle and causing myocardial hypertrophy. Although HCM can be observed at any age, it most commonly occurs between 40 and 50 years of age. The disease affects males and females alike. Its general prevalence in the population is 0.2%, and it is the most common of the inherited cardiac disorders. Mortality is high in younger patients. Although the majority of HCM patients are asymptomatic, they are usually diagnosed during routine screening of relatives with HCM. The first symptom of patients may be sudden cardiac death. Annual mortality due to HCM is 1%, and mortality is two to four times higher annually in cases diagnosed under 14 years of age.[1,2]

Matrix metalloproteinases (MMPs) are primary matrix-destructive proteases that have the ability to degrade all protein components of the extracellular

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matrix. They are members of the zinc- and calcium-dependent endopeptidase family and are characterized by three histidine residues that bind a zinc ion in the catalytic site. Matrix metalloproteinases are also divided into six categories according to their substrate recognition and cleavage mechanism: collagenases, stromelysins, matrilysins, gelatinases, membrane-bound MMPs, and MMPs without group designation. Gelatinases have two types of members: MMP-2 (gelatinase A) and MMP-9 (gelatinase B).[3]

Cardiac magnetic resonance (CMR) imaging studies have demonstrated that myocardial fibrosis can be visualized by late gadolinium enhancement (LGE). However, CMR is expensive, often not available, and not feasible in patients with ferromagnetic implants or claustrophobia. Thus, alternative biomarkers for myocardial fibrosis are needed. This study aimed to examine the association between serum levels of MMP-9 and myocardial fibrosis detected by cardiac magnetic resonance imaging (CMR) in individuals diagnosed with HCM.

PATIENTS AND METHODS

This prospective included 53 patients (33 males, 20 females; mean age: 52.4±10 years; range, 42 to 63 years) who were diagnosed with HCM by echocardiography at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital, Department of Cardiology, between January 2015 and March 2018. Patients with left ventricular (LV) ejection fraction <50%, those undergoing cardiac surgery, and those who had chronic kidney disease were excluded. Echocardiography was performed in all patients who were compensated. A written informed consent was obtained from each patient. The study protocol was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training Research Hospital Ethics Committee (date 10.04.2018, no: 2018-10). This study was performed in accordance with the principles of the Declaration of Helsinki.

A 12-lead electrocardiogram was performed at 25 mm/sec with the patient at rest in supine position. Resting heart rate was then measured from electrocardiogram data. The measurement of the QRS complex time and PR interval (determined by the largest values and recorded from surface vectors) was performed by experienced cardiologists focused on patients' echocardiographic characteristics.

Blood samples for plasma MMP-9 level were taken from the antecubital vein and collected in EDTA tubes placed on ice. Each pooled sample was centrifuged at 2000 g for 5 min and at 4°C for 30 min. Then the separated plasma was kept at −40°C until the observation time. The MMP-9 level was measured with an assay device (Roche Diagnostics GmbH, Mannheim, Germany).

Images were acquired using 1.5 T scanners (MAGNETON Aera; Siemens Healthcare, Erlangen, Germany) with full myocardial coverage. Balanced steady-state free-precession sequences were used to obtain breath-hold cine images in three long-axis planes, followed by a contiguous stack of short-axis slices from the atrioventricular ring to the apex. Late enhancement images were acquired 10 min after the administration of 0.1 mmol/kg intravenous gadolinium contrast agent (gadopentetate dimeglumine/gadobutrol; Bayer AG, Berlin, Germany) with an inversion recovery-prepared gradient-echo sequence. Inversion times were optimized to null normal myocardium with images acquired in two orthogonal phase-encoding directions to exclude artefact.

Images were transferred to a workstation (Leonardo; Siemens Medical Solutions, Erlangen, Germany) for analysis. For the functional analysis, a commercially available software program, Argus (Siemens Healthcare, Erlangen, Germany), was used. The endocardial and epicardial borders were traced manually using both software systems, and functional analysis was performed. Using the Argus (Siemens Healthcare, Erlangen, Germany) software for each study, the end-diastolic and end-systolic phases were determined. For the detection of each phase, the largest and narrowest diameters of the ventricular cavity at the middle of the ventricle were used. The endocardial and epicardial borders were traced manually in short axis images in both phases. The borders of the endocardium were traced using the intensity difference between the chamber when filled with blood and the moderate intensity of the myocardium. The papillary muscles were included in the LV volumetric analysis. While the epicardial border was being detected, the interventricular septum was included in the LV volume. The most basal slice that was surrounded by at least 50% of the myocardium with filled blood was defined as the basal segment of the left ventricle. This was included in the LV chamber volume. The apex was defined as the last slice with a visible lumen throughout the entire cardiac cycle. The end-systolic

volume (ESV), end-diastolic volume (EDV), and ejection fraction were determined according to the Simpson's rule. The elapsed time from inputting of the data to obtaining the results was calculated for each patient.

The CMR images were reanalyzed and documented using the 17-segment cardiac model recommended by the American Heart Association to improve standardization of the results. The left ventricle was evaluated from the short-axis images from basal, mid, and apical segments. The basal and mid cavity were divided into six equal segments: anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral. The apical segment was divided into four segments: anterior, septal, inferior, and lateral. The apical cap was termed the apex and constituted the 17th segment. Left gadolinium enhancement, validated by a visual assessment and each segment on a two-point scale (segmental fibrosis score; 0= absent LGE, 1= present LGE), was graded using the Kaandrop method and with employee-owned linear frequencies and nonischemic dilated cardiomyopathy increasing irregularly in patients. The cardiac fibrosis index was calculated by the algorithm of percentage of fibrotic segments: (fibrotic segments/17) ×100. Patients were subgrouped based on the presence and absence of fibrosis in any segment of the left ventricle.

Statistical analysis

All analyzes were performed using the IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The variables were examined using visual (histograms and probability plots) and analytical methods (the Kolmogorov-Simirnov test) to determine whether they were normally distributed. Descriptive analyses were presented with the values and standard deviations for normally distributed variables and with median (interquartile range) for nonnormally distributed variables. Comparison of parametric values between the two groups was done with the independent sample t-test. Comparison of nonparametric values between the two groups was done with the Mann-Whitney U test. Categorical variables were compared with the chi-square test. Spearman's test and point biserial correlation coefficient were calculated to examine the relationship between the variables. Logistic regression analysis was used to evaluate predictors of myocardial fibrosis in patients with HCM. Variables with a p-value <0.1 in univariate analysis were included in the backward stepwise multivariate logistic regression analysis model, and odds ratios (ORs) for 95% confidence intervals (CIs) were calculated. Receiver operating characteristic curve analysis was drawn for MMP-9 to predict the presence of myocardial fibrosis. Sensitivity and specificity values were presented when a significant cutoff value was observed. A two-way p-value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical patient characteristics are listed in Table 1. Patients with myocardial fibrosis had high wall thickness (p=0.017) and low LV ESV (p=0.007). There was no difference between the groups regarding age, sex, incidence of hypertension, diabetes, history of coronary artery disease, LV mass, LV outflow trace gradient, and LV EDV. Serum MMP-9 levels were found to be significantly higher in the fibrosis group compared to the nonfibrosis group (1618±62 vs. 1531±50, p <0.001; Table 2). In the HCM group, MMP-9 was positively correlated with the number of regions with LGE (r=0.649, p<0.001).

Table 1
Graphical and clinical patient characteristics in HCM (n=53)

Variables	n	%	Mean±SD
Age (year)			52.4±10
Sex			
Male	33	62.2	
Hypertension	22	41.4	
Diabetes mellitus	11	20.7	
CAD	11	20.7	
Familial HCM	4	7.5	
LVOT gradient	16	30.1	
LV mass (g/m^2)			97.7±16
LV EF (%)			70.7±9
LVEDV (mL/m^2)			74.6±11
LVESV (mL/m^2)			20.7±5
LGE	25	47.2	
MMP-9 (ng/mL)			1572.5±74

HCM: Hypertrophic cardiomyopathy; SD: Standard deviation; CAD: Coronary artery disease; LVOT: Left ventricular outflow tract; LV: Left ventricle; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; LGE: Late gadolinium enhancement; MMP-9: Matrix metalloproteinase 9.

Table 2
Comparison of demographic data according to the presence of myocardial fibrosis

	Fibrosis + (n=25)			Fibrosis – (n=28)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			51.8±12			52.8±9	0.729
Sex							
Male	16	64		17	60.7		0.807
NYHA class I, II, III, IV	12	48		17	60.7		0.390
Hypertension	15	60		16	57.1		0.835
Diabetes mellitus	22	88		20	71.4		0.183
CAD	17	68		25	89.2		0.090
Family history	22	88		27	96.4		0.333
LVOT gradient	9	36		7	25		0.550
Angina pectoris	15	60		24	85.7		0.060
Maximal LVWT (mm)			23.1±3			21.1±3	0.017
LV mass (g/m^2)			101.7±15			94.2±16	0.090
LVEDV (mL/m^2)			73.2±9			76±12	0.362
LVESV (mL/m^2)			18.8±4			22.4±4	0.007
LV EF (%)			68.5			72.6	0.122
LGE			2.9±1.3			0	<0.001
MMP-9 (ng/mL)			1618±62			1531±50	<0.001

SD: Standard deviation; NYHA: New York Heart Association; CAD: Coronary artery disease; LVOT: Left ventricular outflow tract; LVWT: Left ventricular wall thickness; LV: Left ventricle; LVEDV: Left ventricle end-diastolic volume; LVESV: Left ventricle end-systolic volume; EF: Ejection fraction; LGE: Late gadolinium enhancement; MMP-9: Matrix metalloproteinase 9.

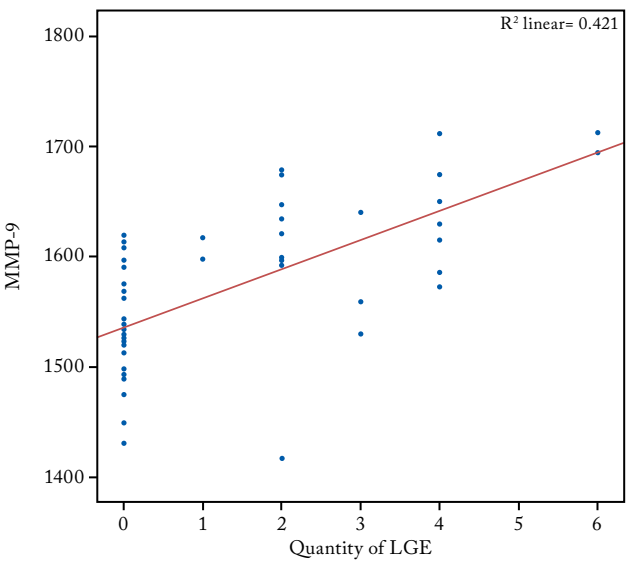

Figure 1. Myocardial correlation graph with serum MMP-9 level between the number of areas with fibrosis.
MMP-9: Matrix metalloproteinase 9; LGE: Late gadolinium enhancement.

There was a mildly significant correlation between MMP-9 levels and LVESV (r=–0.350, p=0.010; Figure 1).

Significant univariate predictors of myocardial fibrosis were history of coronary artery disease, LV mass index, and MMP-9. The results of the

Table 3
Left ventricular mass index, LVESV, and MMP-9 ORs

	OR	95% CI	*p*
LVMI	1.056	1.004-1.112	0.035
CAD	2.098	0.244-1.834	0.500
LVESV	0.955	0.801-1.139	0.606
MMP-9	1.031	1.013-1.049	0.003

LV: Left ventricle; LVESV: Left ventricle end-systolic volume; MMP-9: Matrix metalloproteinase 9; ORs: Odds ratios; CI: Confidence interval; LVMI: Left ventricle mass index; CAD: Coronary artery disease.

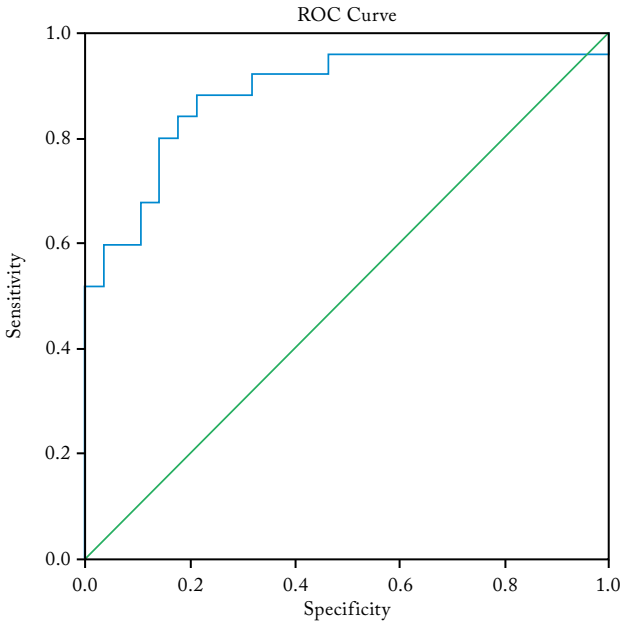

Figure 2. Receiver operating characteristic curve of serum MMP-9 level for detection of myocardial fibrosis in patients with hypertrophic cardiomyopathy (area under the curve=0.884, 95% CI: 0.787-0.981, p<0.001; blue line serum MMP-9 level, green line reference line).

ROC: Receiver operating characteristic; MMP-9: Matrix metalloproteinase 9; CI: Confidence interval.

multivariate logistic regression analysis are presented in Table 3. Receiver operating characteristic analysis yielded a cutoff value of 1580.5% for MMP-9 to predict myocardial fibrosis, with 84% sensitivity and 83% specificity (AUC =0.884, 95% CI: 0.787-0.981, p<0.001; Figure 2).

DISCUSSION

The results of our study indicate a substantial elevation in serum MMP-9 levels in HCM patients exhibiting myocardial fibrosis detected by CMR in comparison to those who did not display fibrosis. Additionally, a noteworthy correlation was found between interventricular septum thickness, as identified by CMR, and cardiac fibrosis. Furthermore, the study demonstrated a positive correlation between the serum MMP-9 level and the quantity of myocardial fibrosis of the left ventricle.

Hypertrophic cardiomyopathy is a hereditary cardiovascular disease characterized by myocardial hypertrophy and impaired diastolic function, which can result in adverse clinical outcomes, including heart failure, arrhythmias, and sudden cardiac death.[1] Myocardial fibrosis, the deposition of excess collagen in the myocardial interstitium, is a common feature of HCM and contributes to the progression of disease.[2] Cardiac magnetic resonance imaging has emerged as a reliable tool for detecting and quantifying myocardial fibrosis in HCM patients, and its role in risk stratification and management has been well-established.[3] The presence and extent of myocardial fibrosis detected by CMR have been shown to correlate with poor clinical outcomes, including heart failure, ventricular arrhythmias, and sudden cardiac death, providing important prognostic information for HCM patients.[4] Consequently, the identification of fibrosis-related factors has become a major research focus, as these may serve as potential therapeutic targets to mitigate disease progression and improve patient outcomes. Current guidelines recommend the use of CMR to assess the presence and extent of myocardial fibrosis in HCM patients, with fibrosis over 15% indicating a high risk of sudden cardiac death and consideration for implantable cardioverter-defibrillator placement.[5] As a consequence, there has been an escalation in the significance attributed to factors related to fibrosis, alongside an increase in efforts aimed at identifying the parameters that could predict the presence and extent of myocardial fibrosis in HCM patients.

Matrix metalloproteinases are a group of endopeptidases that require zinc and are involved in tissue remodeling processes that include the degradation of the collagen network in cardiovascular disease. Among the MMPs, MMP-9, also called type IV collagenase or gelatinase B, is a key player in the tissue remodeling of the extracellular matrix, particularly in the migration of cardiac fibroblasts. Prior research has revealed a relationship between MMP-9 levels and cardiovascular events, including heart failure, atherosclerosis, and myocardial infarction.[6-9] Specifically, Roldán et al.[10] discovered a correlation between cardiac fibrosis and serum MMP-9 levels. Other investigations have also reported a connection between MMP-9 levels and heart failure severity, clinical status deterioration, and atherosclerotic plaque formation and destabilization.[11,12] Additionally, macrophages have been identified as a strong source of MMP-9, and patients with acute myocardial infarction or stable angina exhibited higher levels of MMP-9 in macrophages than those in control groups.[13-15]

Previous research has demonstrated that MMP-9 activity is significantly higher in high-pressure arteries compared to normal-pressure arteries.[16,17] Hypertension-induced cardiac hypertrophy is a key risk factor for various cardiovascular disorders, including diastolic and systolic heart failure, atrial fibrillation, and sudden cardiac death.[18] An association has been reported between increased MMP-9 activity and compensatory hypertrophy of the heart. Specifically, Li et al.[16] observed elevated MMP-9 activity during compensatory hypertrophy in rats with spontaneously elevated blood pressure. Consistent with our results, Münch et al.[19] also found a correlation between MMP-9 and myocardial fibrosis in female HCM patients.

The main limitation of our study is the limited number of patients. Additionally, the visual evaluation of the existence of LGE without using software may be considered another limitation. It should be noted that not all molecules in circulation reflect changes in collagen metabolism at the cardiac level, as collagen is the most abundant protein in the body. Another potential limitation is that we did not evaluate the cardiac tissue concentration of MMPs in our study. Further research with a larger cohort should analyze a broad panel or marker cassette for validation.

In conclusion, the degree of interventricular septum thickness is an important indicator of HCM. Similar to the findings of our study, previous studies have shown that there is a positive correlation between the degree of interventricular septal thickness and the extent of myocardial fibrosis in HCM patients. Specifically, HCM patients with greater degrees of interventricular septal thickness tend to have more extensive myocardial fibrosis. This relationship highlights the importance of monitoring both interventricular septal thickness and the presence of myocardial fibrosis in HCM patients, as both parameters can provide important information for risk stratification and management of the disease.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, writing the article: S.S.; Design: Ö.Ç.; Control/supervision: A.R.D.; Data collection/processing: H.K.; Analysis/interpretation: M.A.; Literature rewiew: S.T.K.; Critical rewiews: A.R.D.; References and fundings: M.C.; Materials: Y.Ö.

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Changes in hand grip strength and associated factors after transradial coronary intervention: A longitudinal study

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ABSTRACT

Objectives: This study aims to evaluate hand grip strength following transradial coronary procedures and to identify main factors influencing these changes.

Patients and methods: Between December 2023 and March 2024, a total of 123 patients (92 males, 31 females; mean age: 63.0±9.2 years; range, 39 to 84 years) with stable angina pectoris who were scheduled for elective percutaneous transradial coronary intervention were included. Hand grip measurements were repeated one day after the transradial procedure and six months later. At six months of follow-up, the patients were divided into two groups based on the change in hand grip strength: those whose hand grip strength remained unchanged (n=84, Group 1) and those whose hand grip strength decreased (n=39, Group 2). The results were compared between the groups.

Results: At the end of the follow-up, 31.7% of the 123 patients had reduced hand grip strength. Radial artery occlusion (RAO) occurred in 8.9% of patients and was significantly associated with reduced grip strength at six months (p=0.013). Active smokers also showed a persistent reduction in hand grip strength at six months (p=0.003). Independent predictors of reduced grip strength included RAO (p=0.038), current smoking (p<0.001), and prolonged hemostasis band removal time (p=0.008).

Conclusion: Radial artery occlusion, current smoking, and prolonged hemostasis band removal time were identified as significant factors associated with the reduction in hand grip strength following the transradial approach. Recognizing these risk factors may help clinicians develop strategies to prevent hand function loss and support recovery more effectively.

Keywords: Hand function, hand grip strength, radial artery occlusion, transradial coronary intervention.

In recent years, the use of the transradial approach for percutaneous coronary procedures has been recommended due to the reduced risk of vascular complications and increased patient comfort.[1] However, the most common complication of the transradial approach is radial artery occlusion (RAO), with incidence rates ranging from 5 to 38%.[2-5] Although RAO is often considered a reversible complication following percutaneous transradial procedures, several previous reports have indicated that RAO may not be a minor side effect.[6] In addition, some patients with radial occlusion developed symptoms,[7] which can potentially lead to restricted hand function.

Hand grip strength can be easily and quantitatively measured using a hand dynamometer, with the Jamar hand dynamometer considered the gold standard for such assessments.[8,9] It is routinely used to assess neurological, muscular and skeletal disorders and to evaluate functional recovery following hand rehabilitation. While a previous study used hand dynamometry to assess short-term changes in hand grip strength in patients undergoing transradial percutaneous coronary procedures, focusing on post-procedural RAO-positive (+) and RAO-negative (–) groups,[10] no study has evaluated other factors that influence changes in hand grip strength yet.

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In the present study, we aimed to evaluate the factors which could influence changes in hand grip strength following transradial percutaneous coronary procedures.

PATIENTS AND METHODS

This single-center, longitudinal study was conducted at Bülent Ecevit University, Faculty of Medicine, Department of Cardiology between December 2023 and March 2024. We evaluated patients diagnosed with stable angina pectoris who were scheduled for elective percutaneous transradial coronary intervention. Exclusion criteria were as follows: hemodynamic instability, acute coronary syndromes, hemodialysis, or arteriovenous fistula, a sheath size other than 6-F, uncontrolled hypertension or diabetes, severe left ventricular dysfunction, contrast allergy, previous radial artery interventions, or musculoskeletal/neurological disorders that could potentially affect hand grip strength measurements. Of 140 patients who were initially found to be eligible, 123 (92 males, 31 females; mean age: 63.0±9.2 years; range, 39 to 84 years) who met the inclusion criteria were recruited. A written informed consent was obtained from each patient. The study protocol was approved by the Bülent Ecevit University Faculty of Medicine Ethics Committee (date: 04.09.2024, no: 2024/15). The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were assessed on the morning of the procedure for radial and ulnar artery patency using the reverse Barbeau test (RBT), hand grip strength, thumb, and forefinger pinch strength. Hand grip measurements were repeated one day after the transradial procedure and six months later. At six months of follow-up, the patients were divided into two groups based on the change in hand grip strength: those whose hand grip strength remained unchanged (n=84, Group 1) and those whose hand grip strength decreased (n=39, Group 2). The results were compared between the groups.

Reverse Barbeau test

The RBT uses a pulse oximeter to display the plethysmographic waveform through a sensor placed on the thumb of the tested hand. Initially, both the radial and ulnar arteries are compressed simultaneously until the plethysmographic waveform disappears. The pressure on the radial artery is, then, released and the waveform is assessed. Four waveform patterns are identified: (A) no change in shape or amplitude (indicating no dumping), (B) slight dumping, (C) temporary loss of the waveform followed by its return within 2 min, and (D) permanent loss of the waveform. Type A, B and C waveforms are indicative of radial artery patency, D pattern demonstrates occlusion.[11]

Assessment of radial artery occlusion

The RAO was initially assessed in all patients using the RBT. In those presenting with pattern D, RAO was further confirmed by Doppler ultrasound with a multifrequency linear probe (L12-3, Philips, The Netherlands) performed the day after the transradial procedure and at six months of follow-up.

Transradial coronary catheterization procedure

Radial artery access was obtained using a 6-F radial sheath (Radifocus™, Terumo Europe N.V., Leuven, Belgium) following local anesthesia with 0.5 mL of 2% xylocaine under the routine procedure. Right or left radial access was left to the operator's discretion. For diagnostic angiography, 5,000 IU of heparin was administered, while a total dose of 100 IU/kg for percutaneous coronary intervention was used. Activated clotting time (ACT) was not measured during diagnostic coronary angiographies, but ACT values were tested in all patients undergoing percutaneous coronary interventions. In all radial procedures, 100 µg of glyceryl trinitrate were administered intra-arterially at the start of the procedure as an antispasmodic agent. After the procedures, the radial sheaths were immediately removed, and a compression device (TR Band™, Terumo Europe N.V., Leuven, Belgium) was applied with minimal compression necessary to prevent bleeding. Deflation of the compression device was initiated 15 min after removing the radial sheath and placing the compression device. Hemostasis time was defined as the time from TR Band™ application to device removal.

Hand grip strength assessment

Hand grip strength was measured using a Jamar hand dynamometer (Sammons Preston, Bolingbrook, IL, USA) following the well-established Southampton protocol based on the recommendations of the American Society of Hand Therapists (ASHT).[12] All measurements were performed on the radial procedure arm by a physical medicine and rehabilitation specialist, starting prior to the radial

Figure 1. Position of the patient during the hand grip test.

procedure. The patient was seated comfortably in a standardized chair with fixed legs, back support, and armrests. The forearm rested on the chair's armrest with the wrist in a neutral position and the thumb facing upwards. The patient was instructed to squeeze the dynamometer as long and tightly as possible while the examiner encouraged maximum effort (Figure 1). Three attempts were made in each session, and the highest score was used for statistical analysis. The same procedure was repeated one day after the procedure and again at six months of follow-up.

The primary endpoint of the study was the change in hand grip strength from baseline (pre-procedure) to six months post-procedure, measured with a hand dynamometer. The secondary endpoint was the detection of RAO during follow-up.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 26.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were expressed in number and frequency. The normality of the distribution of parameters was assessed using the Kolmogorov-Smirnov test. The Pearson chi-square test or Fisher exact test was used to analyze categorical variables. Comparisons were made using Student t-test or Mann-Whitney U-test. Baseline, post-procedural, and follow-up hand grip strength values were analyzed according to RAO and smoking status using the Wilcoxon test (Figure 2). Univariate and multivariate logistic regression analyses were conducted to identify

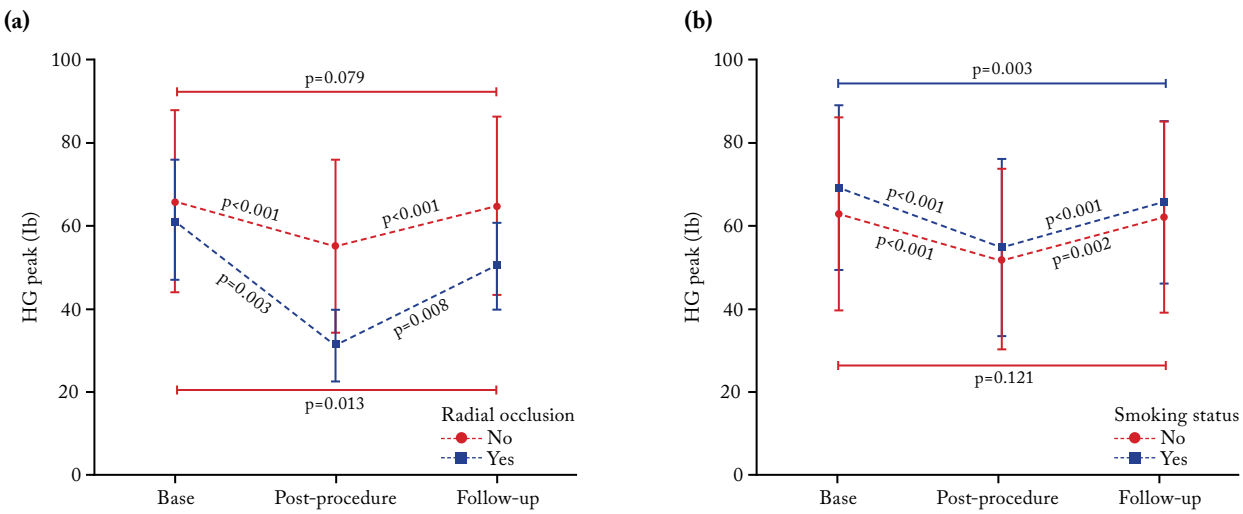

Figure 2. **(a)** Comparison of maximum hand grip strength values at baseline, post-procedure, and six-month follow-up in patients with RAO and those without. **(b)** Comparison of maximum hand grip strength values at baseline, post-procedure, and six-month follow-up in current smoker and non-smoker patient groups.

HG: Hand grip test; lb: Pound-force; RAO: Radial artery occlusion.

predictors of decreased hand grip strength. Variables with a p value of <0.1 in the univariate analysis were included in the multivariate model to identify independent predictors. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

Of the 123 patients included in the analysis, 84 (68.3%) showed no change in hand grip strength six months after the procedure compared to baseline (Group 1), while 39 (31.7%) experienced a decrease in hand grip strength (Group 2). The mean follow-up was 187±14.3 days and 184.1±14.7 days, respectively (p=0.310).

Clinical and procedural characteristics of the two groups are shown in Tables 1 and 2. Group 2 patients were predominantly male (89.7%) and had a significantly higher smoking rate (82.1%) compared

Table 1
Baseline characteristics and smoking habits in relation to changes in hand grip strength at 6-month follow-up

	Group 1 (n=84)			Group 2 (n=39)			
Variables	n	%	Mean±SD	n	%	Mean±SD	p
Age (year)			63.4±9.3			62.1±9.0	0.445
Sex							0.009
Male	57	67.9		35	89.7		
Body mass index (kg/m^2)			28.7±4.9			29.0±4.2	0.509
Systolic blood pressure (mmHg)			139.0±19.9			135.7±20.6	0.392
Diastolic blood pressure (mmHg)			83.9±10.3			84.1±11.4	0.895
Heart rate (bpm)			77.7±13.5			74.9±13.2	0.294
Current smoker	28	33.3		32	82.1		<0.001
Diabetes mellitus	44	52.4		17	43.6		0.364
Hypertension	50	59.5		24	61.5		0.832
Chronic kidney disease	16	19.0		3	7.7		0.105
Thyroid disease	10	11.9		3	7.7		0.479
Dyslipidemia	44	52.4		18	46.2		0.520
Peripheral artery disease	8	9.5		5	12.8		0.580
Previous PTCA	17	20.2		12	30.8		0.200
Previous CABG	13	15.5		7	17.9		0.729
Medications							
Acetylsalicylic acid	65	77.4		30	76.9		0.955
P2Y12 inhibitor	19	22.6		11	28.2		0.502
Oral anticoagulant	10	11.9		4	10.3		0.789
ACEi/ARB	43	51.2		25	64.1		0.180
SGLT2i	34	40.5		14	35.9		0.628
Mineralocorticoid receptor antagonist	9	10.7		2	5.1		0.312
Diuretic	38	45.2		12	30.8		0.128
Calcium channel blocker	26	31.0		12	30.8		0.984
Beta blocker	39	46.4		15	38.5		0.407
Oral nitrate	16	19.0		6	15.4		0.622
Statin	38	45.2		13	33.3		0.212

SD: Standard deviation; bpm: Beats per minute; PTCA: Percutaneous transluminal coronary angioplasty; CABG: Coronary artery bypass grafting; ACEi/ARB: Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; SGLT2i: Sodium-glucose co-transporter 2 inhibitor.

Table 2
Comparison of procedural characteristics between groups with and without changes in hand grip strength

	Group 1 (n=84)					Group 2 (n=39)					
Variables	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Diagnostic CAG	67	79.8				34	87.2				0.318
PTCA	32	38.1				22	56.4				0.057
Normal coronary arteries	16	19.0				0	0				-
Non-obstructive CAD	36	42.9				14	35.9				0.465
Quantity of opaque material (mL)				75.0	47.0-120.0				98.0	52.0-160.0	0.038
Radial sheath duration (min)				22.0	14.0-37.0				37.0	14.0-55.0	0.027
Fluoroscopy times (min)				17.0	7.6-24.5				21.0	11.0-41.0	0.016
Number of catheters used				2	2-3				3	2-3	0.009
Hemostasis band inflation volume (mL)			15.5±1.3					15.6±1.3			0.875
Hemostasis band removal time (min)			151.5±23.2					171.7±26.6			<0.001
Heparin dose (IU)				5,000	5,000-8,875				9,500	5,000-10,000	0.003
Intra-arterial SBP (mmHg)			126.1±24.8					123.5±22.6			0.567
Intra-arterial DBP (mmHg)			77.5±16.9					76.9±13.3			0.835
Heart rate (bpm)			83.0±14.8					80.5±15.0			0.377
Barbeau test D pattern	2	2.4				9	23.1				<0.001
Radial artery occlusion	2	2.4				9	23.1				<0.001

SD: Standard deviation; CAG: Coronary angiography; PTCA: Percutaneous transluminal coronary angioplasty; CAD: Coronary artery disease; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; bpm: Beats per minute.

to Group 1. There was no significant difference between the two groups in terms of body mass index (BMI), diabetes mellitus, hypertension, peripheral arterial disease or medication use (p>0.05 for all) (Table 1).

Patients with decreased handgrip strength had longer radial sheath duration (p=0.027), a higher number of catheters used (p=0.009), and longer hemostasis band removal time (p<0.001) compared to those without changes in handgrip strength. No significant differences were observed in intraoperative blood pressure or heart rate between the groups (Table 2).

Effect of radial artery occlusion and smoking status on hand grip strength

Radial artery occlusion occurred in 8.9% of patients (n=11) during follow-up. Patients were divided into two groups according to RAO status: RAO (–) and RAO (+). At baseline, hand grip strength was similar between the two groups (Table 3). However, the RAO (+) group experienced a significant decrease in grip strength immediately after the intervention (p=0.003), which persisted at six months of follow-up (p=0.013). In contrast, the RAO(-) group also showed a temporary decrease in hand grip strength after the procedure, but values recovered by the six-month follow-up (p=0.079) (Figure 2).

Similarly, current smokers showed a significant reduction in hand grip strength post-procedure (p<0.001), which was still evident at six months (p=0.003). Non-smokers also experienced an initial decrease in grip strength, but their values returned to baseline by the six-month follow-up (p=0.121) (Figure 2).

Independent predictors of decreased hand grip strength

Logistic regression analysis identified RAO, current smoking, and hemostasis band removal time as independent predictors of decreased hand grip strength after transradial intervention (p<0.001; p=0.008; and p=0.038, respectively) (Table 4).

Table 3
Comparison of hand grip strength at baseline, post-procedure and six months by RAO status

	RAO (–) (n=112)		RAO (+) (n=11)		
	Median	Min-Max	Median	Min-Max	*p*
Hand grip test (peak values)					
Baseline	62.5	50.0-80.0	64.0	52.0-75.0	0.756
Post-procedure	54.0	40.0-70.0	30.0	25.0-38.0	<0.001
Six-month follow-up	60.0	50.0-80.0	52.0	44.0-58.5	0.027

RAO: Radial artery occlusion.

Table 4
Predictors of decrease in hand grip test after transradial intervention

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*	OR	95% CI	*p*
Age (year)	0.984	0.944-1.025	0.442			
Sex						
Female	4.145	1.337-12.847	0.014			
Current smoker (Ref. no)	9.143	3.589-23.294	<0.001	6.041	2.233-16.342	<0.001
Hemostasis band removal time (min)	1.034	1.016-1.051	<0.001	1.026	1.007-1.045	0.008
Heparin dose (IU)	1.000	1.000-1.002	0.005			
Radial sheath duration	3.094	1.402-6.827	0.005			
RAO (Ref. no)	12.300	2.513-60.209	0.002	5.781	1.003-30.292	0.038

RAO: Radial artery occlusion; Ref: reference; R^2=0.397.

DISCUSSION

In the present study, we evaluated the factors which could influence changes in hand grip strength following transradial percutaneous coronary procedures. The main finding of our study is that RAO, current smoking and prolonged hemostasis band removal time were independent predictors of reduced hand grip strength after transradial coronary interventions. Furthermore, in all patients, regardless of radial artery patency or RAO, the transradial procedure was associated with a significant reduction in hand grip strength on the day after the procedure. However, by the sixth month of follow-up, this decrease disappeared in RAO (–) patients, whereas it remained significant in patients with RAO (+).

Previous studies such as the Hand Grip Test After Transradial Percutaneous Coronary Procedures (HANGAR) and Coronary Arteriography with Radial Access in Coronary Acute Disease and its Relation with Handgrip Strength and Radial Artery Permeability (CARHANG) trials measured the loss of hand grip strength after transradial intervention.[10,13] However, these studies did not identify factors that predict loss of hand grip strength. The Effects of Transradial Percutaneous Coronary Intervention on Upper Extremity Function (ARCUS) interim report, involving a sample of 191 patients, also demonstrated upper extremity dysfunction following transradial intervention, but relied on questionnaire-based scales.[14] In contrast, our study utilized a hand dynamometer to objectively measure hand grip strength and employed the RBT to assess hand ischemia before the procedure, one day after, and at six months of follow-up.

Radial artery occlusion is the most common complication after transradial percutaneous coronary intervention.[3,5,15] Although RAO is asymptomatic in most cases,[15] significant cases of hand ischemia have been reported. To illustrate, Rhyne and Mann[4] described a case requiring radial artery angioplasty to correct hand ischemia, while another report documented acute hand ischemia in a patient with Raynaud's disease complicated by thrombosis.[16] Additionally, a previous study found that patients with an abnormal Allen test after 30 min of radial occlusion exhibited elevated thumb capillary lactate levels, indicating ischemia.[17] Chronic hand ischemia, even in the absence of overt clinical symptoms, cannot be ruled out as a contributing factor to reduced hand grip strength. In line with this, our study suggests that RAO-related ischemia may play a significant role in the observed decrease in hand grip strength after transradial interventions.

In the current study, hand grip strength decreased in 39 patients, only nine of whom had RAO. Among patients without RAO, current smoking emerged as a potential factor contributing to grip strength reduction. Notably, 82.1% of patients with reduced grip strength were smokers. Smoking, a well-established modifiable risk factor for cardiovascular disease and atherosclerosis, is associated with impaired endothelium-dependent arterial dilation, reflecting endothelial dysfunction.[18-20] Heiss et al.[21] demonstrated that active smokers undergoing transradial coronary catheterization experienced more pronounced endothelial dysfunction due to mechanical irritation from the catheter, along with a slower recovery compared to non-smokers. These findings also align with our results, suggesting that active smoking may impair vascular and functional recovery, thereby contributing to the reduction in hand grip strength observed in patients without RAO.

Sheath removal after transradial catheterization typically involves external compression, achieved through either a simple bandage or specialized hemostatic devices at the insertion site. However, prolonged compression, regardless of the method used, is associated with complications such as deep vein thrombosis or chronic regional pain syndrome and significantly increases the risk of RAO.[22,23] In our study, prolonged hemostasis band removal time was identified as an independent predictor of decreased hand grip strength, suggesting that extended compression durations may adversely affect hand function recovery. While the exact mechanism remains unclear, it is hypothesized to be of vascular origin, with prolonged blood flow interruption potentially leading to stasis and local thrombus formation.[3] There was no significant difference in the inflation volume of the hemostatic band between the groups with and without reduced hand grip strength, likely as the inflation volume was adjusted to achieve bleeding control rather than using a fixed amount. However, radial sheath duration was longer and the number of catheters used was higher in patients with reduced grip strength.

Decreased hand grip strength has been suggested as a potential predictor of future disability, morbidity and mortality, with significant systemic implications.[24] The Prospective Urban Rural Epidemiologic (PURE) study also showed an association between reduced hand grip strength and both cardiovascular and non-cardiovascular mortality, as well as the development of cardiometabolic disease.[25] These findings suggest that it may be useful to identify patients at risk of clinically significant reduction in hand grip strength after transradial coronary angiography. Patients with low baseline hand grip strength, active smoking, or a predisposition to RAO may require closer monitoring. To preserve post-procedural hand function, strategies such as minimizing procedure duration, reducing the number of catheters used, and deflating the hemostasis band as early as possible can be considered.

Nonetheless, this study has several limitations: First, it reflects the experience of a single center with a relatively limited number of patients, which may preclude the generalizability of the findings to broader populations. In addition, the small number of patients with RAO limits our ability to explore whether specific subgroups might have different patterns of hand grip strength recovery. There is potential for selection bias, as we included only elective patients with stable angina, excluding those with more severe coronary conditions or acute presentations. This may have influenced the outcomes, particularly in terms of hand function recovery. Another limitation is the absence of a standardized pain scale, which could have provided valuable insight into the relationship between procedural discomfort, post-procedural upper extremity pain, and recovery of hand function.

In conclusion, our study results highlight the significant impact of RAO, active smoking and procedural characteristics, particularly prolonged hemostasis band removal time, on the reduction of hand grip strength after transradial coronary intervention. Recognizing these risk factors may help clinicians develop strategies to prevent hand function loss and support recovery more effectively. Further well-designed, multi-center, large-scale, long-term studies are needed to draw more definite conclusions on this subject.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Mitral valve replacement one month after coronary artery bypass grafting: Two unexpected cases in a row

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ABSTRACT

Redo cardiac surgery in patients with cardiac operations is a burden for both the patients and surgeons. Difficulties in exploration and further myocardial damage in recurrent operations are the main issues. Patients with recent operations pose another high-risk group. Herein, we presented two patients, a 67-year-old male and a 45-year-old male, who required mitral valve replacement surgery four weeks after surgical coronary revascularization due to pulmonary edema. The first patient had poor left ventricular functions and was operated on with beating heart surgery with cardiopulmonary bypass via mini anterior thoracotomy. The other patient was operated on with a conventional method.

Keywords: Cardiac surgical procedures, reoperation.

Reoperations in cardiac surgery have always been a challenge and have been included as a major risk factor in EuroSCORE II, which is the most commonly employed risk stratification method in cardiac surgery.[1] Not only do fibrous adhesions, exploration, and cannulation issues make it difficult, but a second intervention on the heart also increases the risk. Furthermore, a second intervention on the heart increases the risk.[2] Reoperation within short intervals is more problematic and places additional burden on the surgeon.

In patients with ischemic mitral regurgitation (IMR), simultaneous mitral valve intervention during coronary revascularization still remains controversial. Residual mitral regurgitation remains higher in unintervened patients. However, the left ventricular end systolic volume index and two-year mortality are insignificantly different.[3] Progression may be unpredictable, and redo interventions may be necessary.

Herein, we presented two patients who required mitral valve replacement (MVR) surgery four weeks after surgical coronary revascularization.

CASE REPORT

Case 1- A 67-year-old male patient was admitted with signs and symptoms of pulmonary edema. The patient had bilateral pleural effusion and underwent bilateral Pleurocan catheter (Pleuracan, B. Braun Group, Melsungen, Germany) placement. The medical history revealed a five-vessel bypass surgery in another center four weeks before admission. The procedure was performed as salvage surgery due to cardiac arrest. Preoperative echocardiography documented moderate to severe IMR, but since it was a salvage surgery, mitral pathology was ignored.

Following pulmonary edema treatment, echocardiography revealed poor left ventricular functions (ejection fraction [EF] of 30 to 35%), severe IMR, and a pulmonary artery pressure of 70 mmHg. Beating heart MVR via right anterolateral thoracotomy on the fifth intercostal space was performed. Normothermic cardiopulmonary bypass CPB (36 to 37°C) was established following femoral arterial and femoral and right internal jugular venous cannulation with a flow rate of 2.2 L/min/m^2.

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The mean arterial pressure was maintained between 65 and 80 mmHg. The aorta was not cross-clamped, no cardioplegia was used during the procedure, and the heart was allowed to beat. The patient was kept in Trendelenburg position throughout the procedure while the aortic root was vented to prevent any possible air embolism. The adequacy of the myocardial perfusion was confirmed by ECG monitorization. Standard left atriotomy incision was made. Both leaflets were fibrotic, and the annulus was severely dilated. The leaflets were left in place. The mitral valve was replaced with a 29-mm Carpentier-Edwards pericardial bioprosthesis (Baxter Healthcare Corp., Edwards Division, Santa Ana, California, USA). De-airing maneuvers were performed prior to the cessation of CPB. The CPB time was 120 min. The patient was weaned from CPB with intra-aortic balloon counterpulsation and milrinone support. He was kept intubated for four days for low cardiac output, and the balloon was withdrawn at the end of six days. The patient was followed in the intensive care unit for 11 days and was discharged on the 28th postoperative day with an EF of 30% and pulmonary artery pressure of 35 mmHg. A written informed consent was obtained from the patient.

Case 2- A 45-year-old male patient was admitted with signs and symptoms of pulmonary edema. The patient's medical history revealed a two-vessel bypass surgery three weeks before admission in another center. The patient also had sternal dehiscence and open superficial sternal wound infection being treated with vacuum-assisted closure therapy. The patient was on broad spectrum antibiotics for 10 days. Preoperative echocardiography in our hospital documented severe IMR. Prior to first operation in the outer center, moderate to severe IMR was reported, and the surgeon there ignored it and did not intervene mitral valve. Left ventricular functions were normal, and the pulmonary artery pressure was 40 mmHg. Blood and tissue culture results were negative. The median sternotomy approach was preferred, with simultaneous debridement of all necrotic and infected tissues. Mitral valve replacement (31-mm SJM mechanical prosthesis; St. Jude Medical Inc., St. Paul, Minnesota, USA) was performed under cardioplegic arrest. The patient was weaned from CPB with norepinephrine. Fibrotic tissue adhesions caused difficulties during surgery. The sternum was repaired. The patient was extubated 8 h postoperatively and was kept in the intensive care unit for two days. The patient was discharged on the seventh postoperative day. A written informed consent was obtained from the patient.

DISCUSSION

Not intervening IMR simultaneous with coronary revascularization has no effect on mortality, but in this case, further interventions for progressing IMR may be required in time. Intervened patients had higher rates of freedom from at least moderate IMR and redo intervention at even 15 years (38% *vs.* 89%).[3] Moreover, intervened patients had significantly more reduction in lower left ventricular end diastolic diameter, higher EF, lower NYHA (New York Heart Association) functional class, and lower rates of rehospitalization.

In echocardiographic examination of patients with IMR, while quantifying effective regurgitant orifice area (EROA) and regurgitant volume, lower thresholds may be accepted to define severe regurgitation. In patients with low cardiac functions, the total forward left ventricular stroke volume is lower, and this may lead to a lower estimated regurgitant volume (<60 mL/beat). Therefore, calculation of regurgitant fraction could account for lower flows and has shown prognostic implications. Moreover, the crescentic shape of the regurgitant orifice, characteristic of IMR may lead to underestimation of the vena contracta width and of the EROA. An EROA >30 mm^2 by two-demensional proximal isovelocity surface area likely corresponds to severe IMR.[4]

In the two cases we presented, the situation was likely different. In the first patient, since the patient was operated on as salvage surgery, the primary aim was to keep the patient alive. Therefore, the decision not to intervene with the mitral valve had a rationale. In the second patient, we believe that echocardiographic examination prior to CABG underestimated IMR. Therefore, in both patients, the reason for reintervention was not the progression of IMR. The challenge for the first case was low EF, in addition to the recent cardiac operation. Therefore, we preferred beating heart MVR via mini right anterior thoracotomy. It has been documented that beating heart mitral valve surgery in low cardiac function patients improves outcomes.[5] Global myocardial ischemia and reperfusion injury are avoided, and difficulty in weaning from CPB may be lessened.[5] Moreover,

less invasive nature of the method we employed eased postoperative recovery.

In the second case, since the patient had sternal dehiscence and superficial open wound infection, the most rational approach would be resternotomy, debridement of infected tissues, and repair of the sternum. The criticism could be the risk of infective endocarditis with the sternotomy approach due to inoculation from infected tissues. However, the tissue and blood culture tests were negative, and the patient was on antibiotherapy for two weeks prior to surgery.

Since both patients had severe symptomatic IMR according to the guideline-determined echocardiographic results, surgery was indicated in both patients based on the decision of the heart team. When discussing the advantages and disadvantages of repair in these patients, it is prudent to state that replacement in both cases represents definitive therapy, taking into consideration that both patients had their second heart surgery with CPB within one month. Furthermore, avoiding repair may reduce the likelihood of reintervention.

In conclusion, we believe that redo cardiac surgery in patients with recent cardiac operations is a burden for both the patients and surgeons. The best way is avoidance by meticulously performing preoperative imaging modalities, particularly echocardiographic examinations. Moreover, the decision to intervene in IMR should be cautiously made based on guideline suggestions. If such interventions are needed, we believe that beating heart mitral valve surgery in low cardiac function patients may be the best solution to improving outcomes.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control/supervision, data collection/processing, analysis/interpretation, literature review, writing article, critical review, references, materials: A.B.D., H.A.G.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Dislodgement of the stent from its balloon due to entanglement in the previously implanted stent and retriaval of both stent with snaring: An interesting complication case

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ABSTRACT

Although stent dislodgement is a rare complication in interventional cardiology, its incidence has increased with the number of percutaneous coronary interventions. Stent dislodgement is a risk-laden complication concerning morbidity and mortality, and the management of embolized material can involve various techniques, including the snare technique, balloon retrieval with a small balloon, twirling/wire entrapment technique, and surgical methods. This case report highlighted a 65-year-old male patient who underwent coronary angiography for a diagnosis of non-ST elevation myocardial infarction. During the procedure, stent dislodgement occurred at the ostial left anterior descending artery/left main coronary artery distal region. The dislodged stents were successfully retrieved using the snare technique. The report emphasized techniques that can be utilized for the retrieval of embolized material in cases of stent dislodgement.

Keywords: Percutaneous coronary intervention, snare technique, stent dislodgement.

Stent dislodgement is a rare complication in interventional cardiology, but its frequency has increased with the growing number of percutaneous coronary interventions (PCIs). Material embolization during PCI can lead to significant morbidity and mortality risks. The incidence of stent embolization has been reported to be approximately 0.3 to 1.2%.[1]

With device and technical advances, percutaneous cardiovascular interventions have been increasingly used as an alternative to surgery for cardiac complications.[2] Various methods can be employed to retrieve the embolized material in the event of stent dislodgement during PCI. Dislodgement stents can be retrieved using techniques such as the snare technique, balloon retrieval with a small balloon, twirling/wire entrapment technique, and surgical methods.[2,3] While there is no gold standard method, a versatile approach should be attempted. In this case report, we emphasized the successful retrieval of dislodged stents using the snare technique in the ostial left anterior descending artery (LAD)/left main coronary artery (LMCA) distal region and discussed techniques for managing embolized material in cases of stent dislodgement.

CASE REPORT

A 65-year-old male patient with comorbid hypertension and diabetes mellitus was admitted to the emergency department with chest pain. The electrocardiogram showed sinus rhythm and a high-sensitivity troponin I of 53.4 ng/L. Bedside echocardiography revealed a left ventricular ejection fraction of 50%. The patient was then taken to the coronary angiography (CAG) lab with a preliminary diagnosis of non-ST elevation myocardial infarction. A 6F sheath was placed in the right femoral artery, and JL4 and JR4 diagnostic catheters were used. Coronary angiography revealed normal LMCA, 40% lesion in the LAD ostial segment, 90% lesion in the D2 ostial segment, 90% lesion in the LAD beyond D3, 90%

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thrombus-containing lesion in the internal mammary artery (IMA) ostial segment, 40% lesion in the circumflex artery mid segment, and a dominant right coronary artery with plaque (Figure 1a). As an initial strategy, it was planned to first stent the culprit IMA lesion, then evaluate the mid-LAD lesion, and place a stent if necessary. A written informed consent was obtained from the patient. Subsequently, a 6F EBU (extra backup) 3.5-cm guiding catheter was positioned in the LMCA. The IMA and LAD lesions were crossed using a floppy guidewire (Figure 1b). After IMA predilatation with a 2.0×15 mm percutaneous transluminal coronary angioplasty balloon, a 2.75×18 mm drug-eluting stent (DES) was not able to cross the IMA lesion, so a 2.5×18 mm DES was implanted (Figure 1c). At the stage when pushing force was applied to advance the stent into the IMA, the LAD wire accidentally dislodged from the LAD into the aortic root. Therefore, the LAD wire was reinsterted after IMA stenting. Afterward, an attempt was made to advance the 2.75×18 mm DES to the middle LAD lesion. However, the stent could not pass through the proximal LAD segment. A 2.5×18 mm DES, which was tried later, encountered resistance in the same region and could not be advanced to the middle LAD as well. As a result of careful evaluation to understand the reason, it was thought that there might be a possible interaction with the stent placed proximal to the IMA. Therefore, an attempt was made to slowly withdraw the stent, which was tried to be advanced to the middle LAD. However, during the process, the stent dislodged from the baloon and became stuck in that segment (Figures 1d, e).

The lost stent was captured from the distal LMCA/ostial LAD using a 2-mm microsnare. During retrieval, the stent fell from the catheter tip into the ascending aorta/left sinus of valsalva. On follow-up imaging, the stent was observed to be immobile. Attempts to retrieve it with a snare were unsuccessful (Figure 1f). The patient was transferred to coronary intensive care with stable hemodynamics. Intravenous tirofiban infusion was started. The case was presented to the cardiology and cardiovascular surgery joint council.

Following the decision to attempt retrieval with a snare during the consultation, the patient was brought back to the CAG laboratory. A 6F EBU

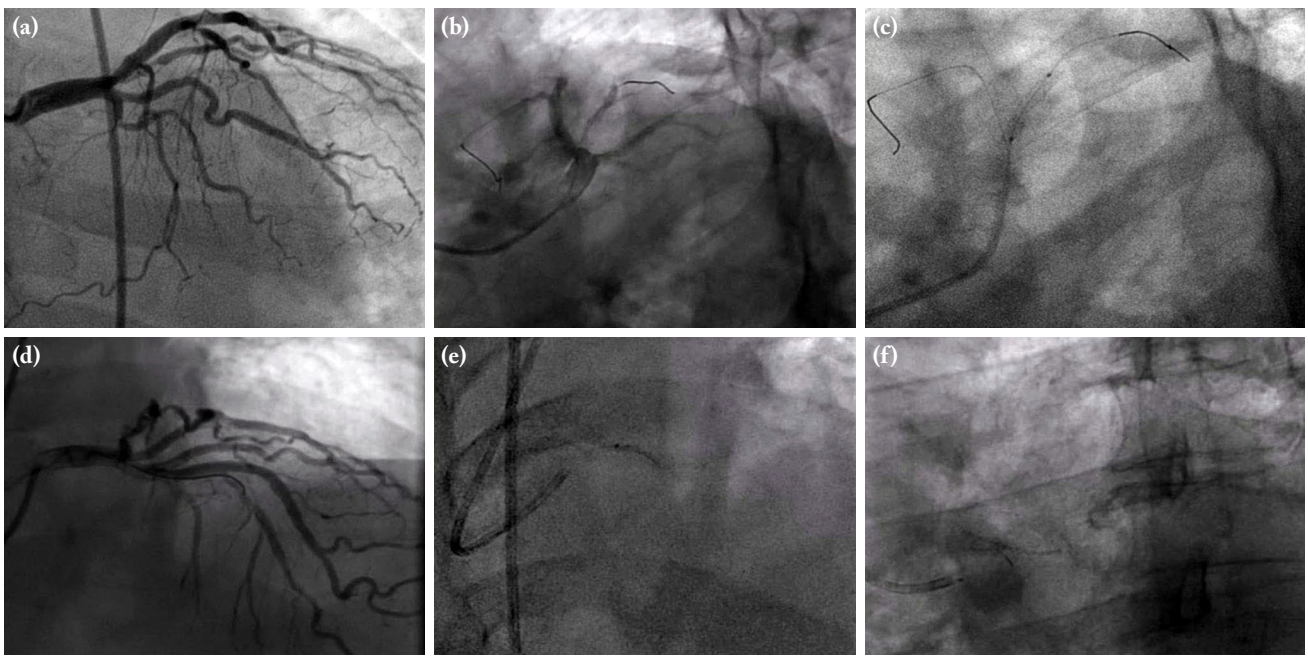

Figure 1. **(a)** Presence of IMA ostial and LAD lesions in CAG. **(b)** Internal mammary artery and LAD lesions crossed using a floppy guidewire. **(c)** After predilatation with a 2.0×15 mm percutaneous transluminal coronary angioplasty balloon, a 2.5×18 mm DES was implanted in the IMA ostial lesion. **(d)** A 2.5×18 mm DES could not be advanced through the LAD lesion. **(e)** During retrieval, the stent was observed to have dislodged at the distal LMCA/proximal LAD. **(f)** The stent was attempted to be retrieved from the distal LMCA using a snare.

IMA: Internal mammary artery; LAD: Left anterior descending; CAG: Coronary angiography; DES: Drug-eluting stent; LMCA: Left main coronary artery.

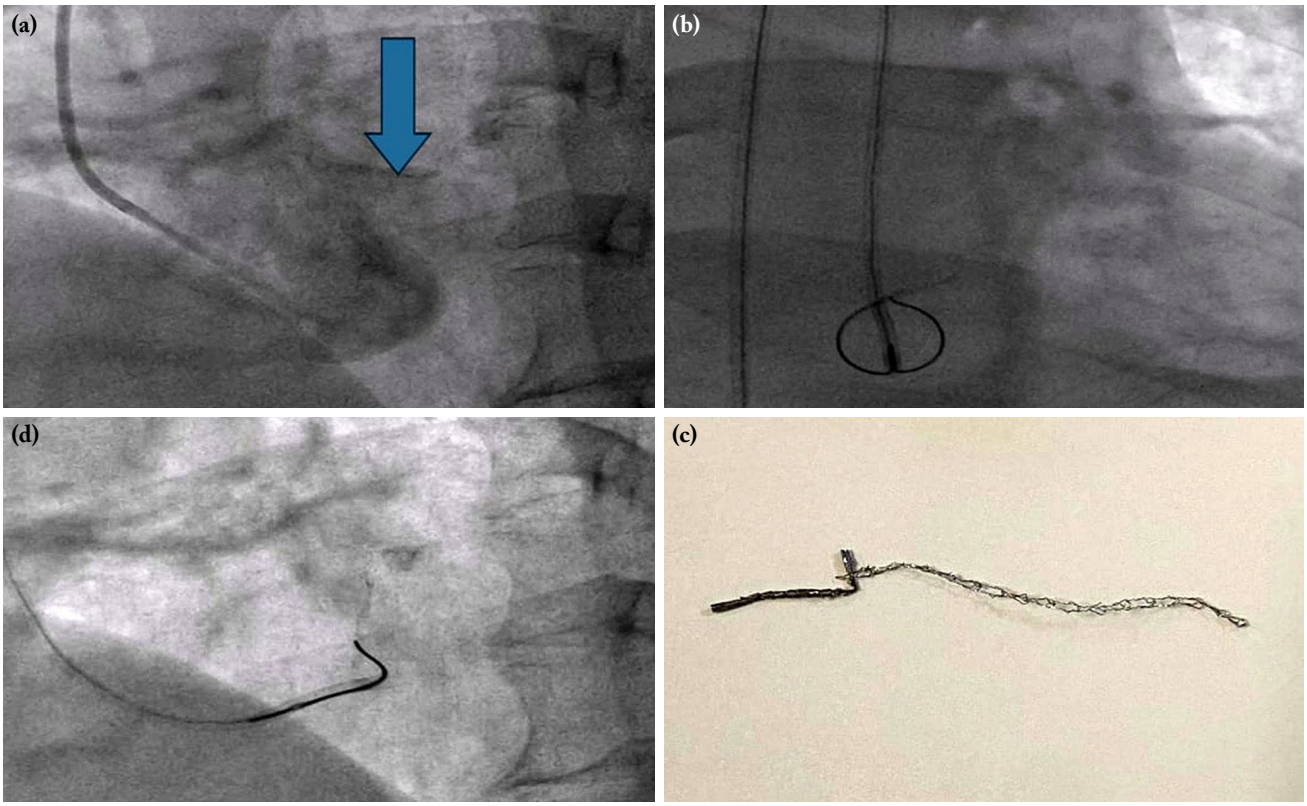

Figure 2. **(a)** On follow-up imaging, the stent was observed to be immobile in the ascending aorta (the lost stent is indicated by the arrow). **(b)** The lost stent was captured with a snare. **(c)** The lost stent was pulled into the guiding catheter using the snare. **(d)** Postprocedure material.

3.5-cm guiding catheter was positioned in the LMCA. The stent, which had remained stable at the LMCA ostium and was directed towards the aortic root, was captured with a snare (Figures 2a, b). During the retrieval attempt, unexpected resistance was encountered. The stent was extracted using the snare through the guiding catheter (Figure 2c). It was observed that the stent had an extended portion at the tip of the snare, indicating that the stent included a part of the IMA stent. It was determined that the stent intended for the LAD had passed through the citrated segments of the IMA stent ostial region, which prevented its advancement and led to dislodgement. During the retrieval attempt, it was noted that the IMA stent had also extended and then retracted (Figure 2d). It was thought that the guidewire passed through the protruding part of the IMA stent struts during the rewiring stage for the LAD lesion after IMA stent placement, therefore LAD stent advancement was blocked by IMA stent struts. The procedure was then continued with LAD PCI. The procedure was completed with TIMI 3 flow. The patient was discharged in good health after four days.

DISCUSSION

Material embolization during coronary angioplasty procedures, although rare, significantly increases morbidity and mortality. The incidence of stent dislodgement has been estimated at approximately 1.2%.[1] When stent dislodgement occurs, the primary objective is to employ maneuvers that minimize harm to the patient and prevent the stent from embolizing, particularly to the cerebrovascular system.[1,3] Various techniques are available for retrieving embolized material, and the choice of technique may depend on the diversity of equipment in the catheterization laboratory, the patient's clinical condition, and the operator's clinical experience.

Factors increasing the risk of stent dislodgement include coronary tortuosity and calcification, attempting to advance the stent without adequate vessel preparation, direct stenting, using a small guiding catheter (e.g., 5F catheter), advancing a stent through a previously deployed stent, and continuing to forcefully retract the stent into the guiding catheter despite resistance.

In our case, during rewiring, the LAD wire passed through the struts of the IMA stent. Therefore, the LAD stent could not be advanced, and during the retraction of the LAD stent, the IMA stent was dislodged along with it.

In cases where other treatment methods fail, the technique of crushing the lost stent against the vessel wall can be performed using another stent. However, this technique increases the metal burden and should be applied with caution.[4] If the wire position on the stent is lost or the stent cannot be retrieved, this technique may serve as an alternative.[4,5]

The small balloon technique involves advancing a small balloon towards the stent when the wire position is preserved, inflating the balloon distal to the stent, and withdrawing the lost stent along with the balloon.[6,7] If the balloon has partially advanced through the stent, inflating it in the proximal midsection of the lost stent and withdrawing the system can be attempted.[4]

A variety of snares are used in both coronary and peripheral circulation. Snare loops are typically made of nitinol and are advanced into a microcatheter to be positioned around the lost material before being withdrawn into the catheter. The Amplatz Goose Neck snare (Medtronic, Inc., Minneapolis, MN, USA) features a single loop and is commonly used in daily practice.[4] If a snare is not available in the catheterization laboratory, an exchange wire of similar length (0.014 inches) and a smaller diagnostic catheter can be used to retrieve the lost material by removing and reintroducing the catheter from the distal end.[8,9]

When intervening in the LAD or circumflex coronary arteries, it is important to treat the distal coronary lesion first. Otherwise, stent protrusion will cause difficulties when stenting is required in the other vessel, and this may cause stent dislodgement. Stent dislodgement may also cause coronary flow restriction, and when the stent is removed, there may be damage to the vascular endothelium. A previous study indicated that no reflow may occur when postdilatation is performed; therefore, it may be more logical to implant the stent to the stenosis area rather than the balloon.[10,11] It is important to note that each case of stent dislodgement is unique, and different techniques or combinations of techniques may need to be employed.

In conclusion, stent dislodgement is a rare complication in interventional cardiology, but its frequency has increased with the growing number of PCIs. The embolized material can be retrieved using techniques such as the snare technique, balloon retrieval with a small balloon, twirling/wire entrapment technique, and surgical methods. While there is no gold standard method, a versatile approach should be attempted. If stent dislodgement occurs while intervening in more than one coronary artery, and resistance is encountered when retracting the dislodged stent with the snare method, it should be considered that the dislodged stent may be attached to the ostial segment or to a proximally located stent implanted for another coronary artery.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Cardiovascular Surgery and Interventions

Case Report Open Access

A rare and unruptured but potentially life-threatening presentation of a huge cardiac hydatic cyst

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ABSTRACT

Hydatid cyst is a parasitic infectious disease caused by *Echinococcus granulosus*, commonly involving cysts in the liver and lungs. Cardiac hydatid cysts are rare but can lead to severe, life-threatening complications. This case report presents the surgical treatment of an unruptured, but potentially life-threatening multivesicular hydatid cyst occupying a large area within the left ventricular cavity.

Keywords: Anaphylactic reaction, cardiac, cystic echinococcosis.

Hydatid cyst is a common parasitic infection endemic to regions with widespread livestock farming, including Türkiye.[1] While hydatid cyst disease is most frequently observed in the liver and lungs, *Echinococcus* parasites can infiltrate neighboring organs or spread to distant ones via hematogenous and lymphatic routes. Liver involvement constitutes 65% of cases, lung involvement constitutes 25%.[1,2] Cardiac involvement occurs in <2% of cases.[1,2] The distribution of echinococcosis within the heart depends on the blood flow to specific regions of the heart. Coronary circulation is the primary route through which parasitic larvae reach the heart, pulmonary veins have also been implicated. Due to its rich coronary blood flow, the left ventricular wall is the most common site of cardiac involvement, followed by the right ventricle, pericardium, atria, and interventricular septum.[2]

Medical treatment of cardiac cysts can reduce their dissemination during and after surgery. However, it may not prevent cyst rupture or the development of life-threatening complications. Therefore, the treatment of cardiac cysts is primarily surgical, accompanied by pre- and postoperative medical therapy to prevent recurrence.[1]

In this article, we present a rare and unruptured, but potentially life-threatening case of a huge cardiac hydatic cyst.

CASE REPORT

A 44-year-old male patient presented to the emergency department with complaints of swelling in the eyelids, hands, and lips, along with shortness of breath, chest pain, and palpitations. His medical history included surgery for a liver hydatid cyst 11 years prior. No abnormality such as ischemia or conduction disorder was detected on electrocardiography. The chest radiography demonstrated a normal cardiac image. Due to the potential recurrence of the hydatid cyst and the risk of rupture leading to an anaphylactic reaction, the patient was referred to the Department of Dermatology. Medical treatment for anaphylactic reaction was initiated. Following symptomatic improvement, transthoracic echocardiography (TTE), contrast-enhanced thoracic computed tomography (CT), and contrast-enhanced magnetic resonance imaging (MRI) were promptly performed. The patient was referred to our clinic with a preliminary diagnosis of cardiac hydatid cyst.

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Transthoracic echocardiography showed that the left ventricle ejection fraction was 60%. Aortic and mitral valve structure and function were normal. Transthoracic echocardiography revealed a well-defined hypoechoic cystic structure, measuring 63×52 mm (Figure 1a), occupying a large portion of the left ventricular cavity, with daughter cysts observed within the anterolateral wall of the left ventricle's apical segment. Thoracic CT confirmed the presence of a cardiac hydatid cyst (Figure 1b). Thoracic MRI identified a well-demarcated 67×51 mm cystic hyperintense structure with septations and daughter vesicles in the apicolateral region of the left ventricle (Figure 1c, d). To assess the potential dissemination of the cyst, cranial and abdominal MRI scans were also performed, but no pathology indicative of hydatid cysts was detected. Laboratory tests revealed elevated high-sensitivity troponin I (1.96 µg/L), procalcitonin (2.85 ng/mL), and eosinophilia (1.03 K/uL). The hydatid cyst indirect hemagglutination test was positive at 1/640. Albendazole 400 mg twice a day was started five days before the surgical treatment. After discharge, a three-month course of medical therapy and follow-up by the Department of Infectious Diseases and Clinical Microbiology were planned.

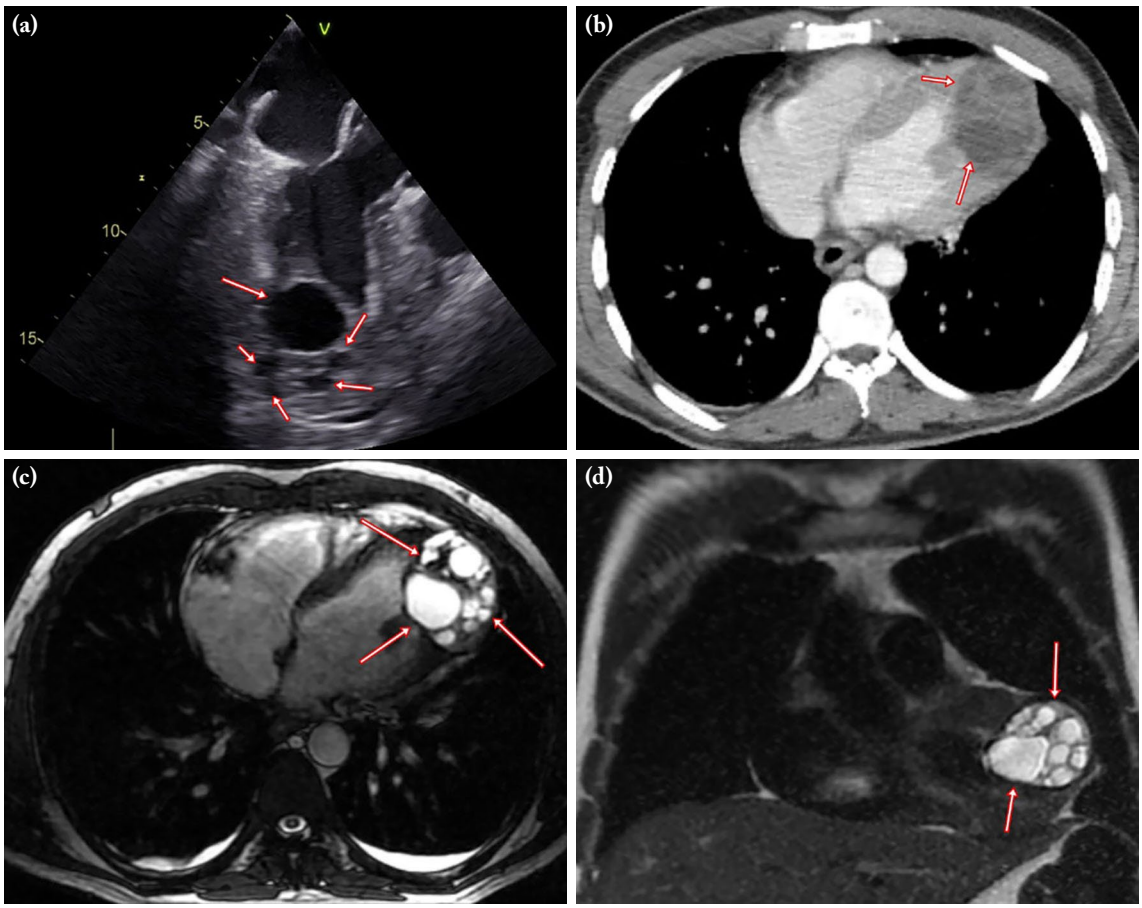

Figure 1. Transesophageal echocardiographic appearance and radiological images of cardiac hydatid cyst **(a)** Intraoperative transesophageal echocardiographic view demonstrating a large mass occupying the left ventricle cavity. Different sized "daughter cysts" may be seen within the larger cyst (red arrow), **(b)** Hypodense cyst view in the left ventricle on computed tomograph axial section (red arrow), **(c)** Hyperintense daughter cysts and septation appearance in the left ventricle on axial FIESTA magnetic resonance imaging (red arrow), **(d)** On magnetic resonance imaging, hydatid cysts appear as a high signal intensity on the coronal T2-weighted images (red arrow).

FIESTA: Fast Imaging Employing Steady-state Acquisition.

Under general anesthesia, a median sternotomy was performed. Aortic arterial and bicaval venous cannulation were established, and a venting cannula was placed in the right upper pulmonary vein. After cross-clamping, the heart was arrested antegradely using a modified cold (10°C) del Nido solution. Cardiopulmonary bypass was performed at a flow rate of 2.2 to 2.4 L/min/m^2 under mild hypothermia (30 to 32°C). A cyst measuring approximately 6×5 cm was observed in the anterolateral wall of the left ventricle (Figure 2a). Compressors soaked in 1% povidone-iodine and 20% hypertonic saline were used to isolate the cyst from the surgical field. The cyst cavity was sterilized by injecting 20%

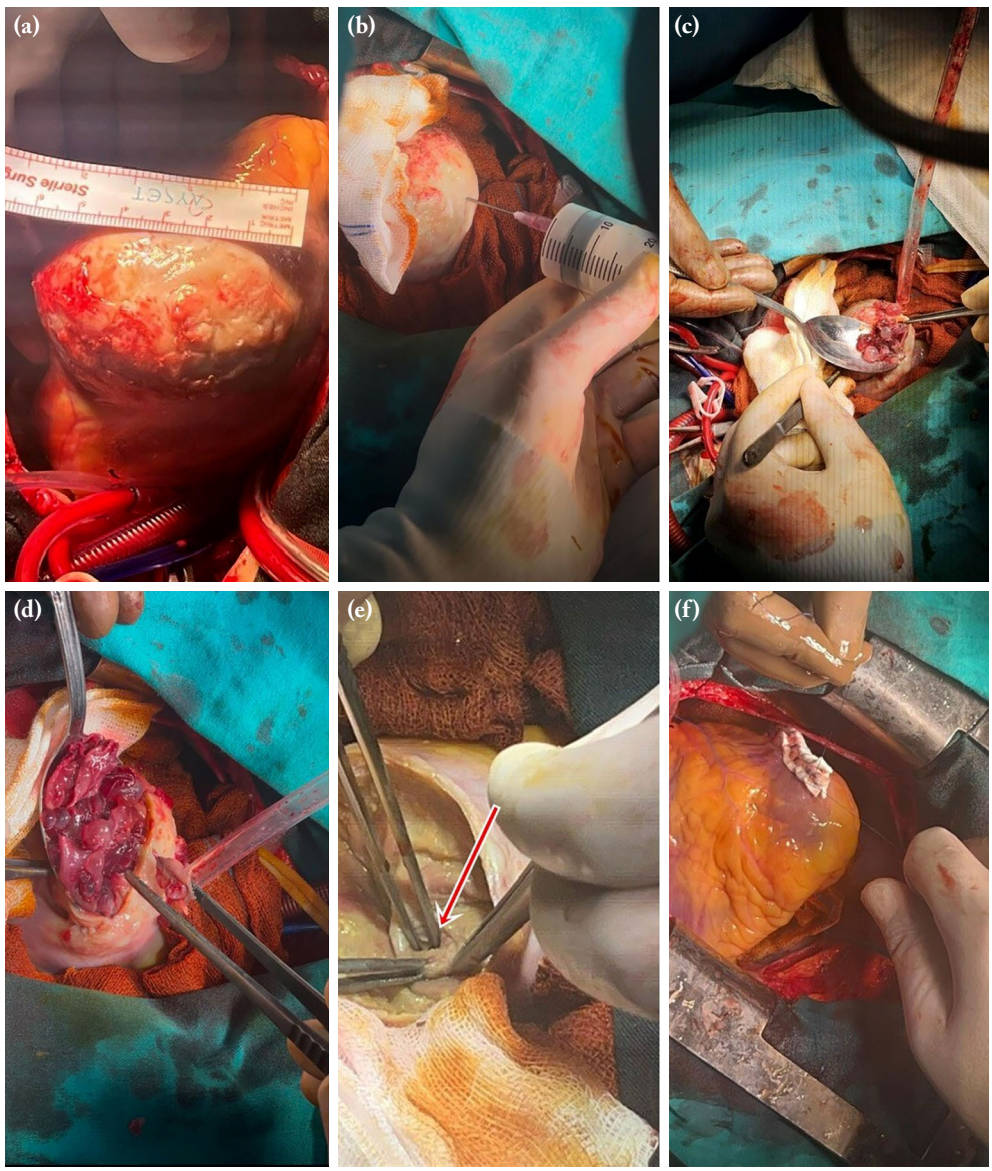

Figure 2. Surgical exploration of the giant left ventricle hydatic cyst. **(a)** Pericyst capsule of the hydatic cyst (outside view), **(b)** Intraoperative view of aspiration of cystic fluid and 20% hypertonic saline injected, **(c, d)** Intraoperative view of the left ventricular cyst showing the multiple daughter cysts and removal of cyst material, **(e)** Tunnel-shaped defect between the cyst cavity and the left ventricle (red arrow), **(f)** In the surgical view, repair of the left ventricle defect with the capitonnage similar to ventricular aneurysm repair.

hypertonic saline (Figure 2b). The pericystic layer was longitudinally opened, and the cyst contents were aspirated and evacuated.

The germinal membrane was excised, revealing numerous daughter cysts of varying sizes (Figure 2c, d). These cysts were meticulously removed without rupture. The cyst cavity was irrigated with both 1% povidone-iodine and 20% hypertonic saline. A tunnel-shaped defect of approximately 5×5 mm was identified connecting the cyst cavity with a blind end through the left ventricular septum (Figure 2e). The defect was repaired primarily with 4/0 polypropylene sutures. The cyst's free walls were resected down to healthy tissue. The left ventricular wall was closed with continuous Fontan sutures using two 4/0 polypropylene sutures, reinforced bilaterally with Teflon felt and closed linearly, similar to aneurysm repair techniques (Figure 2f). Intraoperative transesophageal echocardiogram (TEE) confirmed that there was no residual cyst structure. Histopathological examination of the excised material confirmed multivesicular hydatid cyst. The postoperative period was uneventful, and the patient was discharged on postoperative Day 7 with albendazole prescribed to prevent recurrence. At one-month of follow-up, TTE showed no cardiac abnormalities. A follow-up MRI was scheduled after three months of medical treatment. A written informed consent was obtained from the patient.

DISCUSSION

Cardiac involvement in hydatid disease caused by *Echinococcus granulosus* larvae is extremely rare, with a prevalence of less than 2%.[2] The left ventricle is the most commonly affected site in approximately 55 to 60% of cardiac cases.[3] Larvae are transported to the myocardium via the coronary arteries and the formation of cysts can take one to five years.[1] It has been reported that pulmonary veins may also play a role in the transport of larvae in the myocardium.[3] In most cases, cysts in the left ventricle are subepicardially located and rarely rupture into the pericardium, potentially leading to tamponade, pericarditis, anaphylactoid reactions, or asymptomatic presentations.[1] In our case, the patient presented to the Emergency Department years after liver hydatid cyst surgery with anaphylactoid reactions, but no cyst rupture.

Surgical excision is the primary treatment option for cardiac echinococcosis, even in asymptomatic and unruptured cases, due to potential complications. Median sternotomy is preferred for optimal visualization, although anterolateral thoracotomy can be performed in select cases.[4] Cardiopulmonary bypass and cross-clamping of the aorta is the most preferred method for excision of myocardial cysts and the most reliable method for prevention of systemic embolization. In excision of cysts located in the right heart, clamping of the pulmonary arteries is also recommended to prevent dissemination via the pulmonary artery.[5] Resection of epicardial cysts can be performed without the necessity of cardiopulmonary bypass. To prevent direct regional dissemination in the surgical field, site control should be performed with gauzes impregnated with scolicidal solutions such as 20% NaCl solution and hydrogen peroxide.[4]

Surgical techniques include cyst puncture, aspiration of its contents, resection of the germinal membrane, and cystectomy. Following excision, the cavity is irrigated with scolicidal solutions and either closed via capitonnage or left open for secondary healing, depending on its location.[4] Various complications may occur after surgery depending on the surgical techniques used. Some of these complications include atrioventricular block leading to the need for permanent pacemaker, myocardial rupture and ventricular arrhythmias due to ventricular scar which may lead to sudden death.[1] Albendazole therapy should continue postoperatively to reduce recurrence risk, as hydatid cysts have a 10% recurrence rate.[6]

In conclusion, cardiac hydatid cysts are quite rare. As demonstrated in this case presentation, cardiac hydatid cysts should be considered in the differential diagnosis of patients with unexplained cardiac symptoms. Surgery is the definitive treatment and should not be delayed, as medical treatment alone does not guarantee against life-threatening complications in the event of cyst rupture or, as in our case, even without cyst rupture. Combined surgical and medical therapy is essential to reduce recurrence and dissemination risk.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conception and design of the study: İ.K., U.A.; Literature review: U.A., K.G.; Writing the article: İ.K., S.S., U.A; Control/supervision: İ.K., F.T. All authors participated in drafting and revising the manuscript critically for important intellectual content.

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Cardiovascular Surgery and Interventions

Case Report Open Access

Unusual complication of scarf pin aspiration: Thoracic aortic penetration and surgical management

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ABSTRACT

Scarf pin aspiration is a rare but significant health concern, primarily affecting young Muslim women who wear headscarves. Herein, we present a 13-year-old female case who aspirated a metallic scarf pin, which migrated into her thoracic aorta. Despite being asymptomatic, imaging revealed the extent of the injury, necessitating open thoracic surgery for pin retrieval and aortic repair. The patient recovered fully without complications. This case highlights the critical role of advanced imaging and surgical expertise in managing such cases and underscores the need for preventive measures, including public education and safer scarf pin designs.

Keywords: Foreign body aspiration, scarf pin, thoracic aorta.

Scarf pin aspiration represents a significant health concern, particularly among young Muslim women who commonly wear headscarves. This phenomenon arises from the widespread practice of holding scarf pins in the mouth while adjusting the hijab, inadvertently increasing the risk of aspiration. Most cases are reported among adolescent and young adult females in regions such as the Middle East, South Asia, and North Africa, although reports from multicultural regions have also emerged.[1]

The sharp and metallic design of scarf pins poses a unique risk, differentiating these cases from other foreign body aspirations. Their pointed nature often leads to complications, including tissue penetration into mediastinal or vascular structures.[2] Despite the potential for life-threatening outcomes, awareness of this condition remains limited outside culturally endemic areas. Management is often challenging, requiring advanced imaging for diagnosis and complex interventions such as rigid bronchoscopy or surgical procedures for retrieval and repair.

In this article, we present a rare case who aspirated a metallic scarf pin migrating into her thoracic aorta. This report highlights the diagnostic and therapeutic challenges associated with this condition and emphasizes the need for public awareness and preventive strategies.

CASE REPORT

A 13-year-old female patient presented asymptomatically to the clinic five days after accidentally aspirating a metallic scarf pin while adjusting her headscarf. She exhibited no respiratory distress or hemodynamic instability upon examination. Her physical findings and systemic evaluations were unremarkable, with normal hemoglobin levels and coagulation parameters. Initial imaging with a posteroanterior chest X-ray revealed a radiopaque foreign body approximately 4 cm in length, located in the left lung field (Figure 1). No signs of pneumothorax, hemothorax, or mediastinal shift were observed. Rigid bronchoscopy was attempted for retrieval but was unsuccessful, suggesting migration or deeper penetration of the pin. Computed tomography (CT) with a contrast agent confirmed that the pin

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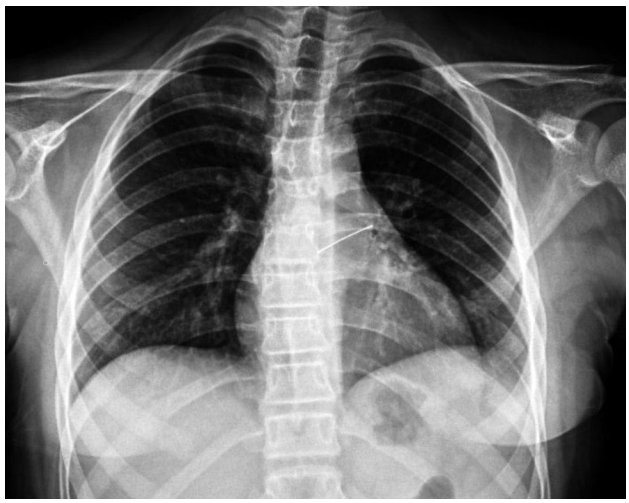

Figure 1. Posteroanterior chest X-ray showing the aspirated pin.

migrated into the left bronchus and penetrated the thoracic aorta (Figure 2).

The patient was referred for surgical intervention, and a decision was made to proceed with open thoracic surgery. A left posterolateral thoracotomy was performed through the fourth intercostal space. Lung retraction revealed periaortic tissue stiffness, likely due to minor leakage from the aorta. The injured aortic segment was identified, and heparin (100 U/kg) was administered. The proximal and distal injured segments were clamped and repaired with 2/0 monofilament non-absorbable pledgeted sutures. After a thorough search, the pin was located in the lung, with its rounded head extending into the bronchial lumen (Figure 3). Forceful traction was required for removal, and resultant bronchial and pulmonary injuries were repaired with 3/0 polypropylene sutures. Prophylactic cefazolin was administered perioperatively. The postoperative course was uneventful. A written informed consent was obtained from the parents and/or legal guardians of the patient.

DISCUSSION

Scarf pin aspiration, also known as "hijab syndrome," is a culturally driven health concern affecting young Muslim women.[3] The practice

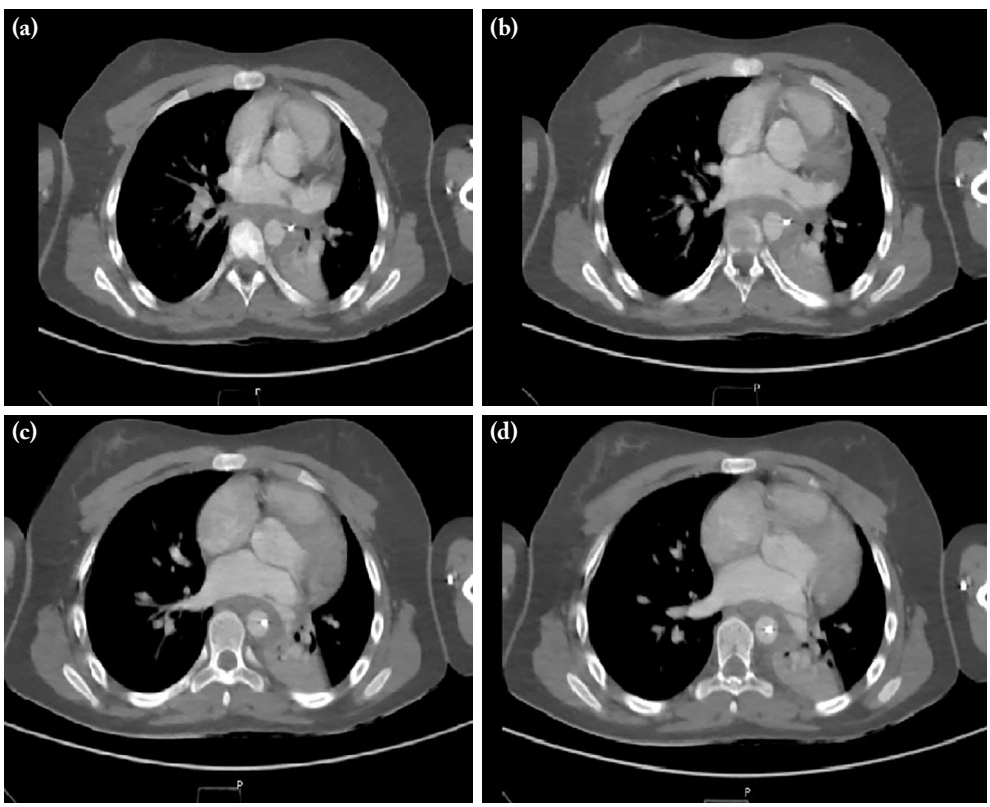

Figure 2. Computed tomography of thorax revealed the scarf pin penetrated the thoracic aorta.

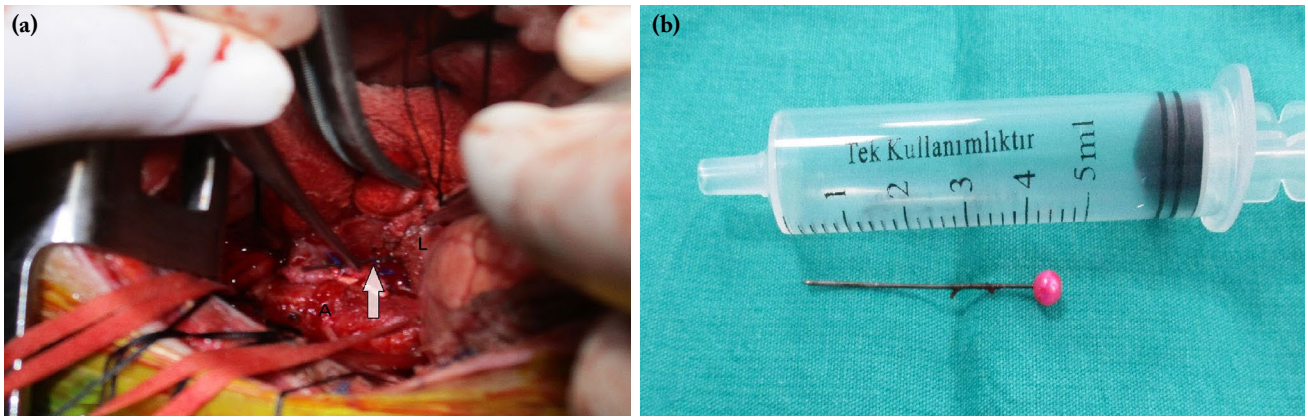

Figure 3. Extraction of the pin, **(a)** the pin was extracted via thoracotomy, **(b)** the scarf pin with its plastic head. White arrow indicates the pin.
A: Aorta; L: lung.

of holding pins in the mouth, often during scarf adjustment, predisposes individuals to accidental aspiration. This condition is most prevalent in regions with high Muslim populations, and the majority of cases involve young females, with a significant number of incidents occurring in adolescents aged 12 to 18 years.[4]

The sharp design of scarf pins increases their propensity to migrate and penetrate surrounding tissues, including vascular structures.[5] The clinical presentation varies widely, ranging from asymptomatic cases to severe complications such as pneumothorax, mediastinitis, or cardiac tamponade.[2] Advanced imaging, particularly contrast-enhanced CT, plays a critical role in identifying the location of aspirated pins and assessing associated complications. Standard chest X-rays often fail to detect pins that migrate into soft tissues or vascular structures.

Management typically involves rigid bronchoscopy, which has a high success rate for most cases of scarf pin aspiration.[1] However, surgical intervention becomes necessary in complex cases involving deep penetration or vascular injury. In a limited number of selected cases, endovascular repair or endoscopic systems have been utilized, thereby avoiding the necessity for invasive surgical procedures.[6]

This case required open thoracotomy due to the pin's migration to the left bronchus and subsequent penetration into the thoracic aorta. Minimally invasive approaches were deemed inappropriate due to the high risk of hemorrhage and the anatomical complexity.

Preventive strategies are crucial in addressing this condition. Public education campaigns should target at-risk populations, emphasizing the dangers of holding pins in the mouth and promoting safer alternatives, such as magnetic or pre-fastened scarf pins. Healthcare providers must also be trained to recognize and manage these cases effectively, particularly in high-prevalence regions.

In conclusion, scarf pin aspiration, though preventable, remains a significant health hazard in regions where headscarves are commonly worn. This case highlights the rare but severe complication of thoracic aortic penetration, underscoring the importance of advanced imaging and surgical expertise. Effective prevention strategies, including public education and the development of safer scarf pin designs, are critical in reducing incidence and associated morbidity. Increased awareness among healthcare providers is essential for early detection and management of this unique clinical entity.

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