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Evaluation of Relationship of Prior Stroke History with New Stroke After Cardiac Surgery

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Abstract

Objectives: In this study, the preoperative stroke history of cardiac surgery cases was investigated. The relationships between previous stroke, vascular distribution areas related to stroke, stroke-related factors, preoperative modified rankin scale (mRs), and postoperative outcomes of patients were researched.

Materials and Methods: From 2013-2021, 3154 patients undergoing cardiac surgery were retrospectively investigated. The study included 106 patients with a preoperative stroke history brain computed tomography and diffusion magnetic resonance images taken.

Results: The preoperative stroke type distribution was 86.8% ischemic stroke, 6.6% transient ischemic stroke, 4.7% hemorrhage and 1.8% subarachnoid hemorrhage. Analysis of patients with preoperative ischemic stroke history (n: 92), indicated significant correlations between the presence of chronic atrial fibrillation (p=0.01) and mRs (p=0.02) postoperative acute ischemic stroke (AIS) development. Postoperatively, 9.4% developed AIS. The postoperative AIS distribution was 5.5% for off-pump coronary artery bypass grafting (CABG), 9.3% for on-pump CABG, and 15.3% for CABG + valve surgery. In the whole study group and the group with postoperative AIS, the proportions of the duration between previous stroke and surgery were found to be similar. For all patients in the study group, the preoperative mean mRs was 0.61, 0.92 for patients who died, and 1.0 for those who developed postoperative AIS.

Conclusion: As preoperative mRs increased, the number of patients experiencing postoperative stroke increased, and the mean mRs of patients who died postoperatively was higher. Another parameter in determining the correct time between stroke and surgery could be the preoperative mRs score.

Keywords: Stroke, prior stroke, modified rankin scale, coronary artery bypass grafting, cardiac surgery

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Introduction

Stroke occurring after cardiac surgery is a complication resulting in severe consequences. Postoperative stroke is related to long hospitalization duration and increased morbidity and mortality and hence overshadows surgical success. The incidence differs in a variety of studies, with rates of 1.2 to 6% reported after coronary artery bypass grafting (CABG) and 6.5% after CABG + valve surgery[1-8]. Stroke that develops perioperatively and postoperatively was reported to be associated with advanced age, previous stroke, carotid artery stenosis (CAS), peripheral vascular disease, cardiopulmonary bypass (CPB) duration, and postoperative atrial fibrillation (AF)[2,3,9].

There are very few data on the effect of preoperative stroke history, vascular distribution areas, and modified rankin scale (mRs) linked to stroke on the development of stroke after cardiac surgery and outcomes in patients undergoing cardiac surgery. Additionally, the data related to the timing of open-heart surgery after stroke are limited. In this study, cases operated for isolated CABG and additional cardiac reasons in addition to CABG with a preoperative stroke history were investigated. The possible relationships between previous stroke, stroke-related factors, vascular distribution areas related to stroke, preoperative mRs of patients were investigated with the perioperative/postoperative surgical and neurological/vascular data and postoperative mRs of patients developing postoperative stroke.

Materials and Methods

A total of 3154 patients were retrospectively investigated from January 2013 to June 2021 for isolated CABG and other cardiac procedures accompanying CABG, including mitral, aortic, tricuspid, and aortic surgery (on-pump CABG 2288, off-pump CABG 263, CABG + valve 562, CABG + aortic surgery 41). The study included 106 patients with preoperative stroke history, and they had preoperative brain computed tomography (CT) and brain diffusion magnetic resonance imaging (MRI) imaging taken. Cases in which a stroke attack was determined but no cranial imaging related to this stroke was available (11 patients), and cases with a postoperative stroke attack for which no cranial imaging was available (1 patient), were excluded from the study. Additionally, the study did not include patients undergoing surgery in emergency conditions nor those developing stroke after discharge. The study design is given in Figure 1.

Patients with preoperative ischemic stroke (n: 92) were additionally categorized to research the effect of: age, sex, surgery type, aortic clamping time (ACT), mortality, AF, ejection fraction (EF), preoperative mRs, stroke vascular distribution area, duration between previous stroke and surgery, and comorbid status diabetes mellitus (DM) hypertension (HT), DM+HT, body mass index (BMI), end-stage renal disease (ESRD)] on postoperative stroke development.

During admission, all patients had their general medical history taken, underwent physical and neurological examinations, had standard laboratory tests, and had a 12-derivation electrocardiogram taken. Stroke was defined as rapidly developing temporary/permanent focal neurological symptoms and the presence of symptoms of vascular origin. Patients with suspected postoperative stroke had stroke diagnosis confirmed clinically and radiologically using non-contrast CT and diffusion-weighted MRI. All data related to previous stroke and postoperative stroke attack were determined by a neurologist. Information related to patients was obtained from the hospital software system, medical records, doctor monitoring notes, and the national health system database. Written informed consent was obtained from patients for the surgical procedure. The study protocol for our retrospective study was approved by the Necmettin Erbakan University Non-Medicine and Medical Device Research Ethics Committee (approval no.: 2021/3381, date: 03.09.2021). The work has been prepared in accordance with the Declaration of Helsinki. No artificial intelligence was used in any process of the article.

The lesion site of the stroke was determined with radiological findings and the vascular distribution area of the stroke was classified as follows; A total anterior circulation infarct (TACI) is a large cortical stroke affecting the areas of the brain supplied by both the middle and anterior cerebral arteries. A partial anterior circulation infarct (PACI) is a less severe form of TACI, in which only part of the anterior circulation is compromised. A posterior circulation infarct (POCI) involves damage to the area of the brain supplied by the posterior circulation. A lacunar infarct (LACI) is a subcortical stroke that occurs secondary to small vessel disease(10). Border zones are areas that lie at the junction of two different drainage areas. Border zone infarcts (BZI) are ischemic lesions that occur in characteristic locations at the junction between two main neighboring arterial territories(11). Multiple territorial infarcts (MTI) are traditionally defined on neuroimaging as non-contiguous infarcts located in more than one cerebral circulation(12).

Patients with a preoperative stroke history, as well as those developing a postoperative stroke, had their mRs determined with the mRS. mRS is a scale commonly used to measure the degree of disability or dependence in daily activities of people with stroke or other neurological disabilities. The scale has points from 0 to 6: 0 means no symptoms; 1, no significant disability, able to perform all normal activities in spite of some symptoms; 2, mild disability, able to look after their needs without assistance but unable to complete all previous activities; 3, moderate disability, requires some help but can walk without aid; 4, moderate to severe disability, cannot meet bodily needs without aid and cannot walk; 5, severe disability, requires continuous nursing care, bedridden, incontinent; and 6, death(13).

Surgical Technique

In on-pump cases, an aortic cross-clamp was used, and cardioplegia was administered. After performing a proximal anastomosis on the heart, side clamping was applied. For all isolated CABG cases, the left anterior descending artery (LAD) was bypassed by the left internal mammary artery (LIMA). For CABG + valve cases, if the

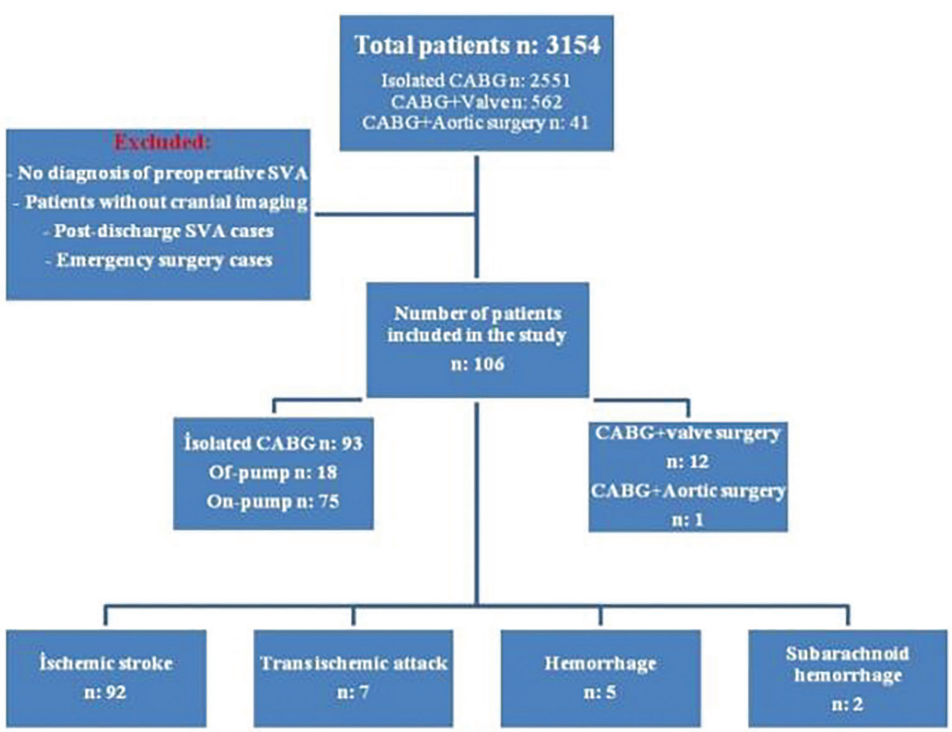

Figure 1. Study design

SVA: Cerebrovascular accident, CABG: Coronary artery bypass grafting

LAD did not require bypass, the LIMA was not used. For circumflex and right CAB, the saphenous vein was used. For off-pump CABG, side clamp wasused for proximal anastomosis of grafts apart from LIMA. Other surgeries were completed with standard CPB procedures.

Statistical Analysis

Descriptive statistics are given for all variables. Numerical variables are given as mean and standard deviation, while nominal variables are shown as frequency and percentage. The t-test was used for the analysis of numerical variables. The chi-square test and logistic regression analysis were used to analyze nominal variables. The analyses used SAS University Edition 9.4 program (SAS Institute, Cary NC), and a p-value of less than 0.05 was accepted as significant.

Results

Of patients, 75.4% were male and 24.5% were female. Mean age was 66.6 years (range: 33-86). Mean ACT was 64.2 minutes (25-181), mean BMI was 28.2 kg/m² (20.3-43), mean EF was 51.5% (25-60), preoperative mean mRs was 0.61 (0-4), mean discharge duration was 9.2 days (4-30), and mean exitus duration was 7.2 days (0-28). Of the cases, 86.7% were discharged, and 13.2% were deceased. The demographic distribution and detailed information related to surgery are given in Table 1.

The distribution of preoperative stroke type was 86.7% (n: 92), ischemic stroke, 6.6% (n: 7), transient ischemic attack (TIA), 4.7% (n: 5), intracerebral hemorrhage, and 1.8% (n: 2), subarachnoid hemorrhage Supplementary material 1. Detailed information for patients with preoperative ischemic stroke is given in Table 2. Postoperatively, 10 patients (9.4%) developed acute ischemic stroke (AIS). Detailed information about these patients is given in Table 3. Patients with preoperative TIA, hemorrhage, and subarachnoid hemorrhage did not experience any new neurological event postoperatively. Additionally, no patient was observed to newly develop TIA, hemorrhage, and subarachnoid hemorrhage postoperatively.

As a result of statistical analysis of patients with preoperative ischemic stroke history (n=92), the postoperative AIS development rate was high among those with chronic AF (p=0.01). A correlation was identified between preoperative mRs value and postoperative AIS development (p=0.02). The presence of ESRD and postoperative AIS development rate were close to significance (p=0.09). The total number of patients with preoperative mRs of 0 and 1 was 78, and 7.6% of these patients developed postoperative AIS. The total number of patients with preoperative mRs of 2, 3 and 4 was 14, and 28.5% of these patients developed postoperative AIS (Figure 2). There were no statistically significant correlations among age, sex, surgery type, EF, mortality, stroke vascular distribution area, duration between previous stroke and surgery, and comorbid status, and postoperative AIS.

Of patients with preoperative ischemic stroke history (n: 92), the duration between previous stroke and surgery was ≤1 month for 7.6%, 1-12 months for 21.7%, and >12 months for 70%. The minimum duration was 15 days, with the maximum duration 240 months. In this group, the PACI case rate was 34.7%, LACI was 32.6%, POCI was 29.3%, BZI was 3.2% and MTI was 0%.

In our study group, 10 patients developed new postoperative AIS. The preoperative neurological event in these patients was ischemic stroke. Two of the patients

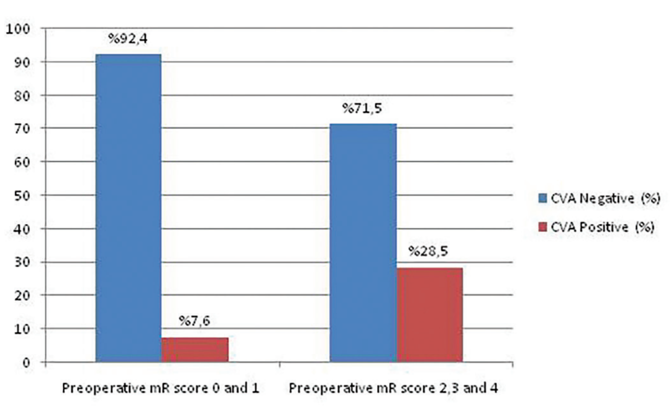

Figure 2. Distribution of patients with postoperative CVA according to preoperative mRs values

CVA: Cerebrovascular accident, mRs: Modified rankin scale

Table 1. Detailed information on demographics of patients and the surgeries performed

Patients data	Details	Numeric data
General information		
Age	<55, 55-69, ≥70	12/51/43
Gender	Male/Female	80/26
Body mass index	<25, 25-29, ≥30	27/43/36
Data on preoperative CVA		
Time between CVA and surgery	≤1 month, 1-12 month, >12 month	11/23/72
CVA type	Stroke, TIA, haemorrhage, subarachnoid	92/7/5/2
mRs	0/1/2/3/4	69/22/8/4/3
Hemisphere distribution	Right, left, bilateral, other regions	34/42/12/11
Additional preoperative data		
Diabetes mellitus	Yes/No	68/38
Hypertension	Yes/No	87/19
Diabetes + hypertension	Yes/No	61/45
Pulmonary disease	Yes/No	14/92
End-stage kidney failure	Yes/No	11/95
Peripheral artery disease	Yes/No	7/99
Carotid stent	Right/left	2/2
Malignity	Colon/Cranial/Leukaemia	1/1/1
Preoperative cardiac data		
Ejection fraction	<30, 30-49, ≥50	2/33/71
Atrial fibrillation	Chronic	8
Perioperative data		
Aorticclamp time (minute)	<50, 50-70, >70	25/37/26
Total pomp duration (minute)	<80, 80-120, >120	18/48/22
Temperature (°C)	29-31/32	8/80
The work of the heart	Spontaneous/Fibrillation	54/34
Cardioplegia type	Custodial/Cold blood	2/86
Cardioplegia path	Antegrade/Antegrade + retrograde	83/5
Autologous blood draw (unite)	0/1/2	73/12/21
Urine amount in CPB (mL)	<300/ >300	40/48
Inotropic agent requirement	Yes/No	82/24
Vasoactive medication use	Yes/No	4/102
IABP need	Yes/No	5/101
End of surgery heart rhythm	Sinus/AF/Pacemaker	94/10/2
Surgery type		
Isolated CABG	On-pump/Of-pump	75/18
CABG + valve surgery	AVR, MVR/MRA, MRA+TRA, MVR+AVR+TRA	3/7/1/1
CABG + aortic surgery	Reoperation AVR + aortic root expansion	1
Postoperative data		
Newly developed AF	In the first 24 hours/After the first 24 hours	6/5
Time to migrate postop new CVA	First 24 hours/24-72 hours/After 72 hours	1/5/4
mRs	0/1/2/3/4/5/6	63/22/9/5/5/0/2
Duration of discharge (day)	<7, 7-14, >14	50/31/11
Time of death (day)	<7, 7-14, >14	9/3/2

CVA: Cerebrovascular accident, mRs: Modified rankin scale, TIA: Trans ischemic attack, CPB: Cardio pulmonary bypass, AF: Atrial fibrillation, IABP: Intra-aortic balloon pump, AVR: Aortic valve replacement, MVR: Mitral valve replacement, MRA: Mitral ring annuloplasty, TRA: Tricuspid ring annuloplasty were female and eight were male. Mean age was 65.5 years (49-77), mean ACT was 77.3 minutes (42-181), mean EF was 51.3% (35-60), mean BMI was 28.8 kg/m^2 (23.6-43), and mean discharge duration was 17.3 days (6-27). In these patients, 90% had HT, 70% DM, 70% DM+HT, 40% chronic AF, and 30% ESRD. The mean preoperative mRs for these 10 patients was 1.0 (0-3), while the mean post-AIS postoperative mRs was 3.5 (2-6). While two patients died, eight were discharged. The duration between previous stroke and surgery was more than 12 months for 7 patients and 1, 3, and 5 months for the others. Mean postoperative AIS development time was 3.3 days (range: 2-7). The first symptom after AIS was consciousness changes in 5 patients, loss of muscle strength in 3 patients, dizziness in 1 patient and vision and balance disorders in 1 patient (Table 3).

Patients developing postoperative AIS had preoperative stroke vascular distribution of 20% PACI, 30% POCI,

Table 2. Data of patients (n: 92) with a preoperative diagnosis of ischemic stroke

	TACI (n: 0)	PACI (n: 32/34.7%)	POCI (n: 27/29.3%)	LACI (n: 30/32.6%)	WTS (n: 3/3.2%)
Age <65 (n: 31)	-	10	11	7	3
Age ≥65 (n: 61)	-	22	16	23	-/-
Gender M/F, (n: 68/24)	-	25/7	19/8	21/9	3/0
Diabetes mellitus (n: 62)	-	19	21	21	1
Hypertension (n: 76)	-	25	24	25	2
Diabetes + hypertension (n: 56)	-	17	19	19	1
Chronic AF (n: 8)	-	4	1	3	-
New AF (n: 10)	-	1	6	3	-
History of CVA time ≤1 month (n: 7)	-	1/	3	3	-
History of CVA time 1-12 month (n: 20)	-	6	6	8	-
History of CVA >12 month (n: 65)	-	25	18	19	3
EF <50% (n: 30)	-	11	11	7	1
EF ≥50% (n: 62)	-	21	16	23	2
BMI <25 (n: 23)	-	9	8	5	1
BMI 25-30 (n: 37)	-	15	10	11	1
BMI >30 (n: 32)	-	8	9	14	1
Right hemisphere involvement (n: 32)	-	11	6	14	1
Left hemisphere involvement (n: 38)	-	19	8	10	1
Bilateral involvement (n: 11)	-	2	2	6	1
Other regions involvement (cerebellum, brainstem, pons) (n: 11)	-	-	11	-	
Discharge (n: 81)	-	25	24	29	3
Death (n: 11)	-	7	3	1	-

TACI: Total anterior circulation infarct, PACI: Partial anterior circulation infarct, POCI: Posterior circulation infarct, LACI: Lacunar infarct, WTS: Watershed infarct, CVA: Cerebrovascular accident, EF: Ejection fraction, AF: Atrial fibrillation, BMI: Body mass index and 50% LACI. The new postoperative AIS vascular distribution for these 10 patients was 10% PACI, 0% LACI, 50% POCI, 20% BZI, and 20% MTI. Three of these patients had the same preoperative and postoperative vascular areas. For the other patients, the preoperative vascular areas were different from the postoperative vascular areas. Two patients had preoperative infarct, with right hemisphere localization, and it remained on the right postoperatively. The infarct hemisphere localization in other patients differed preoperatively and postoperatively. Additionally, while 1 patient had a preoperative bilateral hemisphere lesion, postoperatively, 4 patients were identified to have bilateral hemisphere lesions (Table 3).

Among all patients in the study group, 13.2% (n: 14) died postoperatively. Of these, two were patients who developed postoperative AIS. When the deceased patients are assessed in terms of preoperative stroke type, 60% (n: 3/5) had hemorrhage, 21.8% (n: 7/32) had PACI, 11.1% (n: 3/27) had POCI, and 3.3% (n: 1/30) had LACI. The mean age of deceased patients was 64.5 years (49-86); sex distribution was 14.2% women and 85.7% men. The duration between stroke and surgery for these patients was 3 months for 1 patient (7.1%), and more than 12 months for the other 13 patients (92.8%). The preoperative mean mRS for deceased patients was 0.92 (9 patients had mRS 0, 2 patients had mRS 3, and 1 patient each had mRS 1, 2, and 4). Causes of death were multiorgan failure for 42%, low cardiac output for 28%, and sepsis for 28%.

Discussion

One of the most important results of the study is that as the preoperative mRs score increased, so did the percentage of patients developing postoperative stroke, with 7.6% of patients with preoperative mRs 0 and 1,

Table 3. Detailed demographic, neurologic, and surgical-related information on patients with postoperative re-CVA

A/G	BMI	Co-morbidity	CS % right/left	AF	EF (%)	Surgery type	ACT	Heart work	Preop CVA/ month	Postop CVA/ time	Preop mRs	Postop mRs	Preop hemisp	Postop hemisp
67/M	35.2	DM, HT, ESRD	100/50	-	40	Cx2	43	SS	PACI/ 36	POCI/ 2^{th} day	0	2	Right	Right
67/M	26.3	HT	N	-	55	Cx4	59	SS	LACI/ 60	POCI/ 2^{th} day	2	4	Right	Bilateral
71/M	25.1	HT	-	Cr	60	Cx4	53	SS	LACI/ 5	WTS/ 4^{th} day	0	4	Right	Right
72/M	26.5	DM, HT	Atherosc	-	55	Cx3	42	SF	POCI/ 122	MTS/ 3^{th} day	0	2	Left	Bilateral
77/M	43	DM, HT, ESRD	-	-	45	Cx3	45	SS	LACI/ 1	MTS/ 7^{th} day	3	3	Right	Bilateral
68/M	25.6	DM, HT	Atherosc	-	55	Cx3	48	SS	LACI/ 84	POCI/ 2^{th} day	0	2	Right	Left
49/M	25.2	DM, HT, ESRD	N	Cr	35	Cx2 off pump	-	-	PACI/ 3	PACI/ 4^{th} day	3	6	Left	Right
72/M	23.6	DM, HT	-	Cr	48	Cx2+M +A*+TR	165	SS	POCI/ 24	POCI/ 2^{th} day	0	6	Bilateral	Pons
51/F	25.9	A*+M	N	Cr	60	Cx1+A**	181	SF	LACI/ 13	WTS/ 4^{th} day	0	3	Right	Bilateral
61/F	31.9	DM, HT	30/25	-	60	Cx4	60	SS	POCI/ 96	POCI/ 3^{th} day	2	3	Left cerebellar	Right cerebellar

A: Age, G: Gender, BMI: Body mass index, CS: Carotid stenosis, AF: Atrial fibrillation, EF: Ejection fraction, ACT: Aortic clamp time, CVA: Cerebrovascular accident, Preop CVA/month: Time from ex CVA to surgery, mRs: Modified Rankin scoring, Hemisp: Hemisphere, DM: Diabetes mellitus, HT: Hypertension, ESRD: End-stage renal disease, C x number: CABG and number of bypasses, SS: Spontaneous study, SF: Study in fibrillation, N: Normal, Cr: Chronic, Atherosc: Atherosclerosis, M: Mitral valve replacement, A: Aortic valve replacement, TR: Tricuspid ring annuloplasty, A**: Reoperation Aortic valve replacement + aortic root enlargement, PACI: Partial anterior circulation infarction, POCI: Posterior circulation infarction, LACI: Lacunar circulation infarction, WTS: Watershed territorial stroke, MTS: Multiple territorial stroke* and 28.5% of patients with preoperative mRs 2, 3, and 4 developing postoperative AIS. There was a statistically significant correlation between preoperative mRs score and postoperative stroke (p=0.02).

The effect of a previous stroke on mRs may extend far beyond the acute phase. In spite of rehabilitation and supportive treatment after stroke, neurological dysfunction continues for many people. Just as post-stroke mRs may be affected by situations like the clinical significance of the stroke, age, comorbidities, lesion site and volume, it may be affected by control of stroke-related risk factors and rehabilitative practices. Studies showed that patients with worse mRs had more serious risks, including death, even after accompanying cardiovascular problems were under control[14]. The results of our study support these data. Of the patients who died postoperatively, the preoperative mean mRS was higher than that of the whole patient group (mean mRS for all patients 0.61, mean mRS for exitus patients 0.92). Additionally, a change in mRs by a single point was reported to cause significant outcomes in terms of survival duration, not just in terms of patient independence[14].

Patients with postoperative AIS in the study group had a mean preoperative mRS of 1.0, and a mean mRS of 3.5 after postoperative AIS, indicating moderately severe disability. Deterioration in mRs disability increases the risk of postoperative complications including death. Additionally, patients with a history of stroke and affected by mRs should have their cerebrovascular reserve assessed for the risk of possible new postoperative stroke. It is clear that the poor preoperative mRs of patients considered to have low cerebrovascular reserve will have negative effects on neurological function postoperatively following another stroke. All these situations reveal the importance of knowing the preoperative mRs. The addition of the mRs scale to the EuroSCORE rating system, used for cardiac risk scoring, may be more beneficial for determining surgical risk, (at the moment evaluation is just neurological dysfunction present/absent).

The literature does not provide a satisfactory answer about when surgery should be performed after stroke. A study by Bottle et al.[15] reported that the time interval between previous stroke and surgery did not increase postoperative stroke, mortality, and hospitalization duration. Rorick and Furlan[16] stated that patients with a recent stroke (<3 months) have a higher probability of increased stroke-related lesions in the postoperative period, however, patients with a history of stroke (>3 months) had a higher probability of lesions associated with a new stroke. Matthews et al.[17] classified stroke history as "recent (stroke within 2 weeks before surgery), intermediate (greater than 2 weeks but less than 6 weeks before), and remote (greater than 6 weeks before)" and stated that the timing of cardiac surgery after stroke did not appear to affect postoperative stroke or mortality. Additionally, they reported that mortality associated with stroke was higher, if new postoperative stroke occurred in these patients. The results of our study did not identify associations between the interval between previous stroke and surgery, postoperative AIS, stroke vascular area, mRs, mortality, and hospitalization duration. In the whole study group, as well as in the patient group with postoperative AIS, the proportions for durations between previous stroke and surgery were similar. The percentage of patients with less than 1 month between the previous stroke and surgery was nearly 10%, while for 70%, the duration was more than 12 months.

On a different point, studies to date provide inadequate data about whether the etiology of previous stroke plays a role. For example, stroke in patients with infective endocarditis may be linked to septic embolization, different in nature from stroke in patients with atherosclerotic vascular and coronary artery disease. At this point, the etiopathogenesis in patients with a history of stroke becomes especially important. For this reason, we think the accurate duration between stroke and surgery should be revealed by adequate documentation of preoperative variables, including details related to stroke history (etiopathogenesis of previous stroke, severity, localization and volume of stroke, and available cerebrovascular reserve). It is important to note that within 30 to 90 days after discharge due to a previous stroke, 2/3 of patients experience significant changes in mRs scores (1/3 worsen, 1/3 improve, and 1/3 do not change)[18]. This data indicate that mRs in the nearly three-month period after stroke may negatively affect postoperative outcomes. Considering our data related to preoperative mRs, we think another parameter to determine the accurate duration between stroke and surgery may be the preoperative mRs score of patients.

One of the notable results of the study is that among those with preoperative ischemic stroke history (n: 92), 32% had LACI, while among patients with postoperative AIS (n: 10), 50% had LACI. None of the postoperative AIS patients had new LACI identified, with this group having 50% POCI, 20% BZI, 20% MTI, and 10% PACI. Occlusion or blockage of the small penetrating arteries causes small infarcts called lacunar strokes. Posterior circulation strokes account for approximately 20-25% of all strokes. It is stated that approximately 24% of POCI are associated with cardiac-origin emboli, while 32-35% are associated with atherosclerotic large vessel disease. BZI may be better explained by invoking a combination of two often interrelated processes: hypoperfusion and embolization. Hypoperfusion, or decreased blood flow, is likely to impede the clearance (washout) of emboli. Because perfusion is most likely to beimpaired in border zone regions, clearance of emboli will be most impaired in these regions withleast blood flow. Additionally, stenotic disease of the internal carotid artery causes both embolization and decreased perfusion. Similarly, cardiac disease is often associated with microembolization from the heart and aorta, with periods of diminished systemic and brain perfusion. Isolated cortical BZI may be embolic in nature and are less frequently associated with hemodynamic compromise. Micro emboli from the heart or atherosclerotic plaques in major arteries may preferentially propagate to cortical border zones, which have lower perfusion than other areas of the vasculature and thus limited ability to wash out these emboli[19,20].

When the literature information is assessed with the results of our study, the relationship between hypoperfusion and/or embolization as possible pathophysiological mechanisms of postoperative stroke is confirmed. In our previous study, a nearly 77.5% rate of postoperative POCI, BZI, and MTI were identified[21]. All this data indicate, that, especially for patients with a stroke history, assessment of cerebrovascular reserve in terms of the probable pathophysiological mechanisms mentioned, due to possible postoperative stroke risk, will provide serious positive contributions to decisions related to the form, type, and duration of the operation to be performed.

In our clinic, patients without any complications were discharged on the 5th postoperative day, while the mean discharge time for patients in the study group was found to be 9.2 days. In addition, in another study we conducted previously, the mean hospital stay for patients who underwent postoperative AIS was found to be 16 days[21]. In the literature, similar to our results, it has been reported that the postoperative hospital stay is prolonged in patients with a history of preoperative stroke who underwent cardiac surgery, and the probability of recurrence of stroke increases[7,15], reaching rates of 7.8%-12.4%[21,16].

It has been reported that hypotension is a potential risk factor for perioperative stroke in patients undergoing CPB and may also be an important intraoperative therapeutic hemodynamic target to reduce the incidence of stroke[6]. In addition, keeping arterial pressure high during CPB in patients with CAS may be a strategy to prevent cerebral hypoperfusion. It has been reported that as CAS rates increase in patients undergoing cardiac surgery, the incidence of stroke increases (CAS 2.1% in the 0-29% group, 2.5% in the 30-49% group, 4.5% in the 50-69% group, and 11.1% in the 70-99% group)[2]. During aortic clamping, blood flow is non-pulsatile and arterial blood pressure values are below normal physiological limits. Intracranial vascular stenosis or the presence of CAS and prolonged ACT may increase the likelihood of stroke.

Study Limitations

There are some limitations to this single-center retrospective study. Firstly, the relatively small sample size may limit the strength and clarity of significant correlation results. Secondly, there was a lack of extracranial vascular imaging for all patients developing postoperative AIS, and the carotid artery reserves were not known. Thirdly, this study included patients undergoing surgery for isolated CABG and other cardiac causes accompanying CABG. It is not possible for the findings to encompass all cardiac surgeries.

Conclusion

As preoperative mRs score increased, the number of patients experiencing postoperative stroke increased and the mean mRs of patients who died postoperatively was higher. Our study shows that another parameter that can be used to determine the correct duration between stroke and surgery is the preoperative mRs score.

Ethics

Ethics Committee Approval: The study protocol for our retrospective study was approved by the Necmettin Erbakan University Non-Medicine and Medical Device Research Ethics Committee (approval no.: 2021/3381, date: 03.09.2021). The work has been prepared in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from patients for the surgical procedure.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Işık M, Concept: Işık M, Kozak HH, Design: Işık M, Kozak HH, Data Collection and/or Processing: Işık M, Kozak HH, Analysis and/or Interpretation: Işık M, Kozak HH, Literature Search: Işık M, Kozak HH, Writing: Işık M, Kozak HH.

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Supplement Material 1. Data on patients (n: 14) with a diagnosis of CVA other than preoperative ischemic stroke

	Haemorrhage (n: 5)	Subarachnoid (n: 2)	TIA (n: 7)
Age <65 (n: 5)	2	1	2
Age ≥65 (n: 9)	3	1	5
Gender (F/M, n: 12/2)	5/-	2/-	5/2
DM (n: 6)	1	1	4
HT (n: 11)	3	2	6
DM+HT (n: 5)	-	1	4
Chronic atrial fibrillation (n: 0)	-	-	-
New atrial fibrillation (n: 1)	1	-	-
History of CVA time ≤1 month (n: 4)	-	-	4
History of CVA time 1-12 month (n: 3)	-	-	3
History of CVA >12 month (n: 7)	5	2	-
EF <%50 (n: 5)	2	-	3
EF ≥%50 (n: 9)	3	2	4
BMI <25 (n: 4)	2	1	1
BMI 25-30 (n: 6)	3	-	3
BMI >30 (n: 4)	-	1	3
Isolated CABG	5	2	7
CABG + Valve	-	-	-
Right hemisphere involvement (n: 2)	2	-	-
Left hemisphere involvement (n: 4)	3	1	-
Bilateral hemisphere involvement (n: 1)	-	1	-
Discharge (n: 11)	2	2	7
Death (n: 3)	3	-	-

TIA: Trans ischemic attack, DM: Diabetes mellitus, HT: Hypertension, CVA: Cerebrovascular accident, EF: Ejection fraction, BMI: Body mass index

Research Article

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Iron Deficiency Anemia and Mortality Rate in Heart Failure with Reduced Ejection Fraction

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Abstract

Objectives: Anemia is a common condition in heart failure (HF) patients and is associated with poor functional capacity and increased mortality and morbidity rates. However, the effect of different types of anemia on HF has not been adequately investigated in the literature In this study, we tried to determine the rate of iron deficiency anemia (IDA) and non-IDA of anemia of chronic disease (ACD) in HF patients followed in our clinic and discuss its effect on mortality.

Materials and Methods: Heart failure patients with reduced ejection fraction (HFrEF) who were admitted to the cardiology outpatient clinic between January 2021 and June 2021 were included in this study. Laboratory parameters, demographic characteristics, and clinical and echocardiographic data of the patients were examined retrospectively.

Results: A total of 521 patients were included in our study. The average age of the patients was 67±13 years. 70.6% of the patients are men. Mortality was observed to be statistically higher in the combination of HFrEF and IDA, than in the non-iron deficiency ACD groups. Cardiovascular and non-cardiovascular comorbidities were reported more frequently in the non-iron deficiency ACD group and were more particularly common in the chronic kidney disease ACD group. Statistical differences were observed in levels of serum iron metabolism parameters between IDA and ACD. Mortality rates among HFrEF patients with anemia during the total follow-up period were found to be higher than those in patients without anemia, as reported in the literature.

Conclusion: Mortality was observed to be quite high during the follow-up period in patients diagnosed with HFrEF and accompanied by ACD or IDA. The negative effects of IDA on mortality and prognosis in HF patients are well known. There are many causes of anemia in HF, although current studies and guidelines focus more on iron deficiency and IDA. In our study, iron deficiency without anemia in HF patients was shown to be an independent predictive factor for mortality.

Keywords: Heart failure, iron deficiency anemia, non-iron deficiency anemia, anemia of chronic disease, mortality

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Introduction

As a clinical syndrome accompanied by comorbid conditions, heart failure (HF) is a chronic disease that develops when the heart muscle cannot send enough blood and oxygen the body needs[1]. HF, which affects approximately 26 million people globally and approximately 2 million people in our country, is a common healthcare issue. Its frequency is increasing both globally and in our country, with novel treatment modalities that reduce mortality rates[2]. The survival rates of individuals diagnosed with HF are lower than those of bowel cancer, prostate cancer, and breast cancer. The rate of at least one hospitalization for individuals who are living with HF is 83%, and 50% of these patients are monitored in intensive care units[2]. HF is accompanied by many comorbidities [e.g., coronary artery disease, hypertension (HT), diabetes mellitus, chronic kidney disease (CKD), and anemia], these aggravate the course of the disease[3]. Iron deficiency anemia (IDA) is a common comorbidity in patients with heart failure patients with reduced ejection fraction (HFrEF) and heart failure patients with preserved ejection fraction (HFpEF) and has been shown to be associated with increased mortality and morbidity rates[4]. The prevalence of anemia is around 17% in newly diagnosed chronic heart failure (CHF) patients, 30% in clinically stable CHF patients, and 50% in hospitalized CHF patients[5]. This means that the rate of iron deficiency (ID) is significantly higher than the rate of anemia, whether considering anemia alone or in conjunction with ID[6]. This means that mortality rates are higher in patients with ID. Significant benefits have recently emerged in clinical outcomes with intravenous (IV) iron treatment administered to HF patients who have ID. Improvements include quality of life, New York Heart Association class, 6-minute walking distance, peak oxygen consumption, and reduced HF hospitalization. These benefits have brought to the clinical agenda the importance of treating ID, which was considered a treatment target for the first time in the 2016 European Society of Cardiology (ESC) HF guideline. A limited number of studies in the literature examine HF patients regarding ID and IDA[7]. Examining IDA in patients with HF and determining the factors affecting are essential for clinical practices and the prognosis of patients. In light of this information, this study aims to examine ID, IDA, and other anemia conditions in low ejection fraction HF and to investigate their effects on mortality.

Materials and Methods

The study was conducted retrospectively at Erzurum City Hospital Clinic of Cardiology, which serves the Eastern Anatolian Region, with one faculty member and nine specialist doctors. In this study, 521 patients who applied to the City Hospital Clinic of Cardiology in the six months between January 2021 and June 2021 and met the inclusion criteria were included. These patients were screened retrospectively. Patients over the age of 18 who were diagnosed with HF and had hemogram, biochemistry, ferritin, iron, iron-binding capacity, and transthoracic echocardiography (TTE) data in the hospital system were included in the study. Among patients diagnosed with anemia, patients diagnosed with cancer, patients with hematological malignancies such as lymphoma-leukemia, patients with acute bleeding conditions (such as gastrointestinal bleeding), end-stage solid organ diseases (such as liver cirrhosis), and patients receiving dialysis treatment were excluded from the study. In this study, the anemia group defined outside IDA includes anemias not accompanied by ID, seen in chronic diseases, and other than the pathologies mentioned above. Additionally, those who did not have hemogram data, biochemistry data, ferritin, iron, iron-binding capacity, and TTE data were not included in the study. As determined by the World Health Organization and ESC HF guideline 2021, the hemoglobin (HGB) value for anemia was defined as less than 12 g/dL for women and less than 13 g/dL for men. IDA was defined as a serum Ferritin level <100 μg/L or transferrin saturation (TSAT) <20% if the Ferritin level was between 100-299 μg/L. TSAT was calculated using the following formula: serum iron (mg/dL)×100 / total iron-binding capacity (mg/dL)[8]. The disease histories of the patients were recorded using the data in the hospital system. CKD: a known patient with CKD from medical records within six months prior to enrollment or when the estimated glomerular filtration rate (GFR) is <60 mL/min./1.73 m^2 by the CKD epidemiology collaboration formula using serum creatinine level[9]. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Local Ethics Committee of Erzurum Regional Training and Research Hospital (approval no: 16.05.2022/06-49, date: 16.05.2022).

Statistical Analysis

The data were analyzed with the IBM SPSS V23. Compliance with normal distribution was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Pearson chi-square test and Yates's correction test were used to compare the categorical data according to the groups. The Mann-Whitney U test was used to compare the non-normally distributed data according to binary groups. The results of the analyses were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data and as frequency and percentage for categorical data. The significance level was set at p<0.05.

Results

A total of 521 patients were included in this retrospective study. The average age of the patients was 67±13.70.6% were men. Particularly, patients in the IDA group were older than the mean age of the whole population (71.18±11.9). No statistically significant differences were detected between sex distributions according to anemia and IDA status (p=0.118). Comorbidities and mortality rates of the patients are shown in Table 1. Accordingly, statistical significance was observed in comparing mortality in patients with anemia due to ID *versus* anemia of chronic disease (ACD). Echocardiographically, the ejection fraction was observed to be lower in IDA (31.8±8.2).

Statistical analysis of the shaped elements and biochemical parameters of blood, according to whether or not ACD is present, is given in Table 2. Accordingly, statistically significant differences were detected between the hg (HGB, (10^9/L), mean corpuscular volume, neutrophil (10^9/L), lymphocyte (10^9/L), C-reactive protein, glucose, creatinine, albumin, triglyceride, high density lipoprotein, total cholesterol, and calcium values. (p<0.001) In Table 3, where patients with and without IDA are compared, iron metabolism parameters and

Table 1. The demographic characteristics of patients

	n=521 (%)	ACD (+) n=148 (%)	IDA (+) n=220 (%)	ID (+) n=41 (%)	p-value
ECHO (EF: %)	32.57±8.11	33±7.7	31.8±8.2	32.7±7.5	<0.001
Age (Mean ± SD)	67.32±13.37	68.68±13.04	71.18±11.9	70.23±12.2	<0.001
Female n (%)	153 (29.4)	46 (31.1)	60 (27.3)	13 (31.7)	0.118
CAD n (%)	139 (26.7)	51 (34.4)	59 (26.8)	18 (43.9)	0.16
AF n (%)	86 (16.5)	47 (31.7)	50 (22.7)	10 (24.3)	0.45
HT n (%)	339 (65.1)	99 (66.9)	151 (68.6)	12 (29.2)	0.33
DM n (%)	132 (25.3)	53 (35.8)	54 (24.5)	9 (21.9)	0.22
CVE n (%)	111 (21.3)	49 (33.1)	52 (23.6)	4 (9.7)	0.36
Mortality n (%)	117 (22.5)	23 (15.5)	65 (29.5)	15 (36.5)	0.02
CKD	95 (18.2)	47(31.7)	48 (21.8)	8 (19.5)	0.04

ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, ID: Iron deficiency, ECHO: Echocardiography, EF: Ejection fraction, CAD: Coronary artery disease, AF: Atrial fibrillation, HT: Hypertension, DM: Diabetes mellitus, CVE: Cerebrovascular event, CKD: Chronic kidney disease erythrocyte volume are compared, as expected, and found to be statistically significant in the IDA group. No significant differences were observed in other blood parameters. In evaluating patients without anemia in terms of ID, 41 (26.7%) had ID. In univariate and multivariate regression analyses, age, echocardiography, IDA, ID, and HGB were determined to be significant predictors of mortality in HFrEF (Table 4).

Discussion

HF is a clinical syndrome affecting millions of people on a global scale, accompanied by typical signs and symptoms developing as a result of structural and/or functional disorders of the heart[10]. The incidence of CHF is approximately 3/1000 person-years for all age groups in Europe. In adults, it is approximately 5/1000 person-years[11]. Since studies are generally evaluated on known/

Table 2. The comparison of the blood parameters according to ACD status

	ACD + (n=148)	ACD - (n=373)	
	+, Mean ± SD	-, Mean ± SD	p-value
TSAT SAT	23.53±22.9	34.02±34.77	0.148
Iron (mg/dL)	58.32±38.17	60.56±45.54	0.988
FeBC (mg/dL)	28593.96±85233.65	41034.48±115537.12	0.056
Ferritin (mg/dL)	160.4±205.52	228.96±342.29	0.918
WBC(10^9/L)	8.36±3.55	8.35±3.21	0.780
HBG (10^9/L)	10.78±1.41	14.92±1.49	**<0.001**
PLT (10^9/L)	249.13±81.25	256.95±110.33	0.814
MCV (fL)	78.6±7.9	83.8±9.45	**<0.001**
MCH (pg)	24,6±2.83	29,8±1.45	**<0.001**
PDW (10^9/L)	12.7±2.2	13±2.67	0.420
Neutrophil (10^9/L)	6.06±3.64	7.33±6.42	**0.013**
Lymphocyte (10^9/L)	2.56±3.84	2±4.53	**<0.001**
Monocyte (10^9/L)	0.84±0.3	0.89±0.65	0.748
Glucose (mg/dL)	54±72.58	145.75±77.05161	**0.005**
Creatine (mg/dL)	1.72±1.33	1.12±0.48	**<0.001**
Albumin (g/L)	34.36±10.53	36.89±13.05	**<0.001**
Sodium (mmol/L)	139.78±3.88	139.68±5.88	0.205
Potassium (mmol/L)	4.4±0.56	4.5±0.77	0.340
Uric acid (mg/dL)	6.68±2.44	7.15±2.95	0.245
Triglyceride (mg/dL)	166.82±97.9	133.29±55.09	**0.010**
HDL (mg/dL)	26.74±2518.07	36.3±11.99	**0.005**
LDL (mg/dL)	158.17±69.58	148.16±68.14	0.392
Cholesterol (mg/dL)	171.43±46.2	153.2±45.64	**0.007**
Calcium (mg/dL)	9.31±0.72	8.81±0.79	**<0.001**
Magnesium (mg/dL)	1.95±0.3	1.89±0.4	0.052
VITB12 (pg/mL)	406.82±285.64	595.28±538.11	0.124

Mann-Whitney U-test, ACD: Anemia of chronic disease, TSAT SAT: Transferrin saturation, FeBC: Iron binding capacity, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PDW: Platelet distribution width, HDL: High density lipoprotein, LDL: Low density lipoprotein, VITB12 : Vitamin B12

Table 3. The comparison of the blood parameters according to IDA status

	IDA (n=220)	non- IDA (n=301)	p-value
	+, Mean ± SD	-, Mean ± SD	
TSAT SAT	16.77±15.47	45.7±34.21	**<0.001**
Iron (mg/dL)	50.22±32.82	76.6±47.64	**<0.001**
FeBC (mg/dL)	39150.62±101116.47	12600.19±59826.7	**<0.001**
Ferritin (mg/dL)	67.55±70.09	342.42±324.54	**<0.001**
WBC (10^9/L)	8.82±3.55	8.26±3.81	**0.036**
HBG (10^9/L)	10.78±2.44	13.68±2.37	**<0.001**
PLT (10^9/L)	242.04±82.9	251.5±89.37	0.335
MCV (fL)	67.62±7.73	84.85±6.25	**<0.001**
MCH (pg)	21,7±3,4	30,6±1,47	**<0.001**
PDW (10^9/L)	13.01±2.71	12.73±2.23	0.781
Neutrophil (10^9/L)	6.9±3.51	6.54±5.84	**0.027**
Lymphocyte (10^9/L)	2.08±2.03	2.75±5.69	0.614
Monocyte (10^9/L)	0.85±0.38	0.88±0.5	0.424
Glucose (mg/dL)	159.82±79.38	149.3±78.91	0.121
Creatine (mg/dL)	1.4±1.13	1.25±0.68	0.339
Albumin (g/L)	36.22±11.35	37.49±11.25	0.104
Sodium (mmol/L)	140.33±5.09	139.64±4.21	0.194
Potassium (mmol/L)	4.49±0.63	4.43±0.64	0.385
Uric acid (mg/dL)	7.1±2.82	6.76±2.5	0.238
Triglyceride (mg/dL)	175.65±101.92	147.06±75.12	**0.018**
HDL (mg/dL)	36.57±11.2	41.26±11.78	**0.003**
LDL (mg/dL)	162.48±67.9	151.9±64.13	0.269
Cholesterol (mg/dL)	159.5±49.56	169.45±46.97	0.106
Calcium (mg/dL)	9.03±0.88	9.24±0.69	0.050
Magnesium (mg/dL)	1.95±0.36	1.93±0.33	0.647
VITB12 (pg/mL)	506.57±450.32	422.07±306.34	0.405

Mann-Whitney U test, Mean ± SD TSAT SAT: Transferrin saturation, FeBC: Iron binding capacity, WBC: White blood cell , HGB: Hemoglobin , PLT: Platelet , MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PDW: Platelet distribution width, HDL: High density lipoprotein, LDL: Low density lipoprotein, VITB12: Vitamin B12, IDA: Iron deficiency anemia

Table 4. Relationship between univariate and multivariate regression analysis and mortality

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p-value
Age	1.050	1.030-1.070	**<0.001**	1.051	1.028-1.074	**<0.001**
ECHO-EF	0.95	0,920-0,980	**<0.001**	0.965	0.936-0.994	**0.018**
ACD	0.584	0.357-0.957	0.03	0.632	0.363-1.100	0.63
IDA	1.535	1.015-2.322	**0.04**	2.067	1.237-3.453	**0.006**
ID	1.410	1.002-1.830	**<0.001**	1.386	0.943-1.945	**<0.001**
HGB (g/dL)	0.810	0.739-0.887	**<0.001**	0.818	0.737-0.907	**<0.001**

OR: Odds ratio, CI: Confidence interval, ECHO-EF: Echocardiography-ejection fraction, ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, ID: Iron deficieny, HGB: Hemoglobin diagnosed CHF cases, the actual prevalence is probably higher[12]. Prevalence is estimated to be 1% among individuals under 55, and over 10% among those aged 70 and over[13]. With the development of treatment methods and the elucidation of the pathophysiology of the disease, significant improvements have been observed in prognosis and mortality. Still, hospitalization and mortality rates are quite high. Indeed, in the olmsted county cohort, post-diagnosis 1-year and 5-year mortality rates for all HF patients between 2000 and 2010 were 20% and 53%, respectively[14]. Study cohorts combining the Framingham Heart Study and Cardiovascular Health Study reported a 67% mortality rate at 5-year follow-up after diagnosis[15]. Our study supports existing studies, finding the mortality rate of patients with HF was found to be 22%. CHF patients are hospitalized on average once a year after initial diagnosis[16]. In another cohort, the average hospitalization rate from 2000 to 2010 was 1.3 per person-year. Interestingly, the majority of hospitalizations (63%) were for non-cardiovascular reasons[14]. In another study, age-adjusted first hospitalization rates increased by 28% for all-cause and CHF admissions, and 42% for non-cardiovascular admissions[17]. The risk of hospitalization due to HF is 1.5 times higher in patients with diabetes. AF, increased body mass index, glycated HGB, and low GFR are strong predictors of hospitalizations for CHF[18]. Due to a growing population, aging, and comorbidities, the number of hospital admissions for CHF is expected to increase by up to 50% over the next 25 years[19]. The severe nature of the disease, characterized by frequent hospitalizations and high mortality rates, with brings a great economic burden to countries and requires effective measures to tackle the factors that precipitate HF[20]. Anemia is one of the most common conditions resulting from these predisposing factors. Studies report that ACD and IDA are common in all types of HF, triggering decompensation and increasing mortality and morbidity[21]. Our study supports existing studies and finds IDA and ACD to be factors contributing to mortality in HF patients.The prevalence of anemia is around 17% in newly diagnosed CHF patients, 30% in clinically stable CHF patients, and 50% in hospitalized CHF patients[22]. In a meta-analysis that examined 34 studies covering approximately 153.180 patients, it was reported that the frequency of anemia in cases with HF was 37.2%[17]. However, this rate varies widely between 14 to 61% in different studies[23-24]. In our study, IDA was observed at 42.2% and ACD at 28.4% in patients with HF. A significant difference is observed between anemia and CHF regarding the development levels of countries, along with a negative relationship is observed[25]. In anemia, the decrease in HGB concentration lowers the oxygen-carrying capacity in the blood. As the anemia deepens, the compensatory capacity of the heart and skeletal muscle is exceeded and exercise intolerance develops. This process progresses faster in CHF[26]. Anemia is associated with poor prognosis in patients with HF[27]. Chronic anemia is an independent risk factor for mortality in patients with CHF. Although ID is a common cause of chronic anemia, other etiologies include CKD, inflammatory processes, and unexplained causes[28]. Although a specific cause cannot be found in most HF patients with anemia, it is recommended to perform the necessary tests to elucidate the etiology of anemia (hidden blood loss; iron, B12, and folate deficiency; blood dyscrasias)[10]. In our study, the effect of different types of anemia on CHF-related deaths was investigated, and mortality was found to be statistically significant in IDA patients compared to the ACD group. In comparing chronic cardiac and non-cardiac comorbidities associated with anemias in the IDA and ACD groups, comorbidities including chronic renal failure were more prevalent in chronic anemias, and statistical significance was observed. In another study conducted on a population of 90 people, an increase in uric acid levels was found to be correlated with HF mortality and was statistically significant. In our study, uric acid levels were not statistically significant[29]. Additionally, CKD was observed to be more prevalent in the ACD group. Although there are not enough data in the literature directly comparing the mortality of both groups in CHF patients, there are increased mortality rates in anemic patients with CHF[30]. In our study, ACD was observed at a rate of 28.4%

and IDA at 42.2%. Silverberg et al.[31] study found that the rate of chronic anemia due to all causes was 56%.31. In another study conducted by Tanner H[24], this rate was reported to be 15%. The reason for this low rate was due to a younger population being included in the study[24]. The average age of the patients was 54 in this study and was 67 in our study. In a prospective observational series of 546 cases, ID was detected in 32% of non-anemic cases[32]. Similarly, in our study, ID was observed in 41 (26.7%) patients without anemia. These results show that ID is present in a significant portion of HF cases without anemia. Our study supports studies in the literature. Although no statistically significant difference was detected between genders, it was determined that anemia and ID were more common in male CHF patients. Both groups ACD and IDA showed a statistically significant increase in mortality ($p<0.001$). CKD and HF frequently coexist. They share common risk factors, such as diabetes or HT. CKD may worsen coefficient of variation function, causing HT and vascular calcification. CKD is a major independent determinant of increased mortality and morbidity in HF[18]. Our study supports the current findings that CKD is more common in the ACD group and statistically significant. Both HF and CKD are increasing in prevalence as the population ages, and both conditions have been associated with ACD[33]. Anemia, even in the absence of renal disease, has also been associated with adverse clinical outcomes. However, the impact of HF, anemia, and CKD, alone or in combination, on mortality, adverse events, and hospitalization rates remains of clinical interest[34]. Certainly, ID is a common cause of anemia. However, various factors contribute to anemia, including malnutrition (iron, folic acid, and vitamin B12 deficiencies), renal dysfunction, inflammatory diseases, and unexplained anemia[35]. There are many causes of anemia in CHF, and current studies and guidelines focus more on ID and IDA[8]. Therefore, there is a need to expand the scope of research beyond ID. A thorough investigation of the mechanisms of anemia in HF may lead to new strategies in treatment. The optimal therapeutic target for anemia in CHF is currently uncertain. It has been found that mortality increases when the HGB level is <13-14g/dL or >16-17g/dL in CHF patients[36]. Additionally, repeated IV iron administration over time can lead to iron overload, which results in heart damage[5]. Therefore, there is a need to find a suitable therapeutic target for treating anemia and optimizing the prognosis of CHF. Although there are current treatment recommendations for anemia in CHF, studies showing the nature and boundaries of this complex comorbidity are still lacking[28]. It has been shown in the literature that anemia is an important factor mortality in HFrEF patients. Our study supports existing studies, and the results are consistent with the literature obtained in both anemia groups[37]. Improvements in functional capacity in quality of life in tissue oxygenation, and reduction in myocardial ischemia are achieved with treatment[37]. Blood transfusion to symptomatic patients with deficient HGB levels (<7g/dL), IV ferric carboxymaltose infusion to patients with ID with or without anemia, and treatment principles for other etiological factors must be planned by healthcare centers for HF patients[8]. Although preliminary studies showed a beneficial effect of erythropoietin (EPO) therapy on cardiac efficiency and in HF, more recent studies have not confirmed this positive impact of EPO, alluding to its side effect profile. Physical exercise significantly increases hemoglobhın levels and the response of anemia to treatment. In malnourished patients and chronic inflammatory processes, low levels of anabolic hormones, such as testosterone and insulin-like growth factor-1, contribute to the development of chronic anemia. In addition, exercise acts as a regulatory mechanism of chronic anemia and its cardiovascular consequences in patients with HF[38].

Study Limitations

The limitations of our study are that it was conducted in a single center and that patients with mid-range EF and HFpEF were not included.

Conclusion

In conclusion, initiating anemia tests and appropriate treatment modalities from primary health care institutions will benefit the prognosis of patients by correcting anemia. This study provides data that will contribute to the literature on the effects of ACD and IDA on mortality in HFrEF. Clarification of etiological factors is of vital importance in managing anemia in CHF, improving quality of life, and reducing the risk of hospitalization and death.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Local Ethics Committee of Erzurum Regional Training and Research Hospital (approval no: 16.05.2022/06-49, date: 16.05.2022).

Informed Consent: These patients were screened retrospectively.

Footnotes

Authorship Contributions

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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Southwestern Türkiye's Aortic Aneurysm Overview: Surgical Outcomes and Epidemiological Insights from Denizli and Neighboring City Referrals

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Abstract

Objectives: Aortic aneurysms are significant health risks, particularly in regions with limited specialized care. Despite advancements in imaging and surgical techniques, disparities in healthcare access influence outcomes. This study evaluates epidemiological trends, procedural outcomes, and referral dynamics, aiming to improve care strategies for aortic aneurysm patients.

Materials and Methods: This retrospective study analyzed data from 699 patients treated for aortic aneurysms between 2010 and 2023 at a single referral cardiovascular center in Southwestern Türkiye. The dataset included information on patient demographics, referral sources, birthplace of patients, aneurysm classifications, procedural details, length of hospitalization, and mortality outcomes. Statistical analyses were performed to identify significant predictors of clinical outcomes, with a significance threshold of $p<0.05$.

Results: The cohort was predominantly male (79.26%) with a mean age of 61.89 years. Ascending aortic graft replacements (42.21%) were the most common procedures, followed by abdominal (25.32%) and thoracic (13.45%) repairs. The overall mortality rate was 18.60%, with higher rates in Afyonkarahisar (23.53%) and Burdur (21.43%). Denizli accounted for 56.51% of referrals, underscoring its central role in regional care.

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Abstract

Conclusion: High-volume centers like Denizli play a crucial role in managing complex vascular cases. Addressing healthcare disparities through improved referral systems and early detection strategies is essential for enhancing outcomes across Southwestern Türkiye.

Keywords: Aortic aneurysm, surgical outcomes, Southwestern Türkiye, referral patterns, vascular surgery, epidemiology

Introduction

Aortic aneurysms are a major global health problem, characterized by the abnormal dilation of the aorta, often remaining asymptomatic until rupture, dissection occurs, or significant compression of adjacent tissues, leading to high rates of morbidity and mortality[1,2]. Despite advances in diagnostic imaging and surgical techniques, the management of aortic aneurysms remains complex, especially in areas with limited access to specialized treatment centers and a coordinated healthcare system[3]. The world-wide prevalence of aneurysms is approximately 2% to 5% in adults, with a significantly higher incidence in men and elderly populations[4,5]. Ascending aortic aneurysms and abdominal aortic aneurysms are commonly encountered, while thoracic aortic aneurysms tend to present with more acute symptoms, necessitating urgent interventions[6-8]. Aortic aneurysms present unique epidemiological health care challenges in Türkiye. This is especially true in the southwestern region, including Denizli and surrounding cities. Denizli serves as the main referral centre. It welcomes patients from a variety of urban and rural areas. This dynamic of centralized health care highlights the importance of understanding population patterns. Forwarding route and outcomes of procedures to optimize care delivery[9,10]. Studies from developed countries highlight the role of high-volume centers in improving patient outcomes. However, such information from Türkiye and other developing regions remains limited[11]. Addressing this knowledge gap is critical to designing region-specific strategies that address inequalities in health care and outcomes[12,13].

Materials and Methods

This retrospective, observational study aimed to evaluate the epidemiological characteristics, surgical outcomes, and referral patterns for aortic aneurysms in Southwestern Türkiye. The study focused on patients treated at a tertiary care center in Denizli, which serves as a central referral hub for surrounding cities. The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval no.: E-60116787-020-636206, date: 08.01.2025) ensuring adherence to the principles outlined in the Declaration of Helsinki.

Study Population: The study population comprised 699 patients diagnosed and treated for aortic aneurysms between January 2010 and December 2023. These patients were referred to Denizli from Denizli city itself and surrounding cities, including Aydın, Muğla, Manisa, Afyonkarahisar, Uşak, Kütahya, Burdur, Antalya, Isparta, and İzmir, as well as smaller neighboring regions. Data were collected from hospital electronic medical records and included age, gender, city of birth and residence. Type and location of the aneurysm, and procedure type. Length of hospital stay, mortality (in-hospital or within 30 days post-surgery), and procedural success rates. Cities with fewer than 2% of total patient referrals were grouped under "other cities" to streamline the analysis.

Procedural Types: Procedural types were classified into three main categories to ensure uniformity.

Ascending Aortic Operations: This category included ascending aortic graft replacements, hemiarch replacements, combined aortic and coronary artery procedures, and valve-sparing techniques.

Aortic Operations: This group comprised abdominal aortic aneurysm for elective aneurysm repair or rupture.

Thoracic Aortic Operations: These procedures involved thoracic aortic aneurysm repairs using endovascular approach.

The Preoperative Assessment: Including transthoracic or transesophageal echocardiography, computed tomography angiography, or magnetic resonance angiography, to provide comprehensive anatomical and functional data essential for guiding procedural planning.

The Primary Outcome Measures Included: Mortality rates, which are defined as deaths occurring during the hospitalization or within 30 days post-surgery.

Length of Hospital Stay: Calculated from the day of admission to the day of discharge or mortality day.

Geographical Analysis: Patients were stratified based on their city of referral, with an emphasis on understanding the distribution of cases and outcomes across the region. Denizli, as the central hub, accounted for the highest referral volume. Procedural trends were analyzed to assess the variability in outcomes across cities and identify areas for targeted healthcare interventions.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp, Armonk, NY), with a significance threshold set at $p<0.05$. Quantitative and qualitative data were analyzed using descriptive and inferential statistical methods. Continuous variables were presented as mean ± standard deviation and analyzed using t-test or analysis of variance for group comparisons.

Categorical Variables: Expressed as counts and percentages, with chi-square or Fisher's exact test used for intergroup comparisons.

Results

The study cohort comprised 699 patients, with a notable male predominance (n=554, 79.26%) compared to females (n=145, 20.74%). The mean age of the patients was 61.89 years, ranging from 29 to 95 years. The mean duration of hospitalization was 13.26 days, with a minimum stay of 0 days (observed in patients who succumbed intraoperatively or on the first postoperative day) and a maximum stay of 152 days (Table 1). The overall mortality rate was 18.60% (n=130). Male patients accounted for 103 of these deaths (79.23%), while females represented 27 deaths (20.77%). The most common procedure was ascending aortic graft replacement (n=295, 42.21%), followed by abdominal aortic aneurysm graft replacement (n=177, 25.32%). Thoracic aortic aneurysm endovascular graft implantation was performed in 94 cases (13.45%). Complex procedures included ascending aortic graft replacement with hemiarch replacement (n=77, 11.02%) and ascending aortic graft replacement with aortic valve replacement (n=52, 7.44%). A small number of patients (n=4, 0.57%) required ascending aortic graft replacement with the coronary artery implantation, underscoring the ability to manage highly intricate cases (Table 1). The majority of patients referred to Denizli originated from Denizli, accounting for 395 cases (56.51%). Other significant contributors included Aydın with 97 patients (13.88%) and Muğla with 78 patients (11.16%). Together, these three cities represent over 81% of the total referrals. Cities such as Manisa (26 patients, 3.72%) and Uşak (21 patients, 3.00%) made smaller yet notable contributions. Additionally, Afyonkarahisar and Burdur each accounted for a minor proportion of cases. The "other cities" category, which encompasses all cities contributing less than 2% of the total cases, collectively accounted for 77 patients (11.01%). Cities in this category include Antalya, İzmir, İstanbul, Konya, Kütahya, Mersin, Isparta, Adana, Bursa, Sakarya, Niğde, Balıkesir, Hatay, Malatya, and international locations like Bulgaria (Bar Chart 1). The distribution of birth cities offers valuable epidemiological insights into the patient population treated for aortic aneurysms in Southwestern Türkiye. Based on the patients' place of birth, Denizli emerged as the predominant contributor, accounting for 295 patients (42.21%). Other significant contributions were observed from Aydın (77 patients, 11.02%), Muğla (52 patients, 7.44%), and Manisa (29 patients, 4.15%). Afyonkarahisar

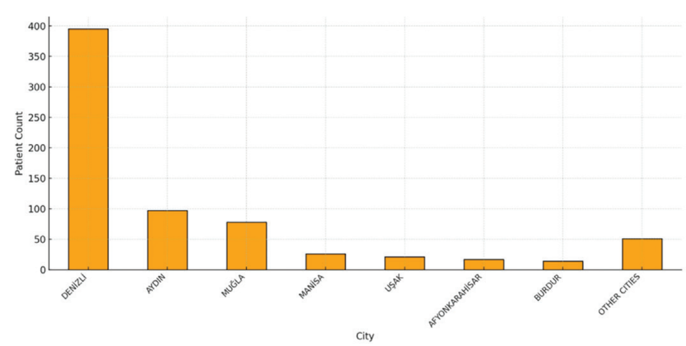
Table 1. Demographics, clinical characteristics, and surgical outcomes of patients treated for aortic aneurysms in southwestern Türkiye

Parameter	Count/Value	Percentage
Sex Male	(554) male patients	79.26%
Female	female patients	20.74%
Age Age (average) year	(61.89) years	
Age (minimum) year	(29) years	
Age (maximum) year	(95) years	
Hospitalization Hospitalization duration (average) day	(13.26) days	
Hospitalization duration (minimum) day	(0) days	
Mortality Hospitalization duration (maximum) day	(152) days	
Mortality	(130) patients died	18.60%
Male-mortality	(103) male died	79.23%
Female-mortality	(27) female died	20.77%
Procedures Ascending aortic graft replacement	(295) operations	42.21%
Ascending aortic graft replacement and hemiarch replacement	(77) operations	11.02%
Ascending aortic graft replacement and AVR	(52) operations	7.44%
Ascending aortic graft replacement and coronary artery implantation	(4) operations	0.57%
Toracic aortic aneurysm endovascular graft implantaion	(94) operations	13.45%
Abdominal aortic aneurysm graft replacement	(177) operations	25.32%

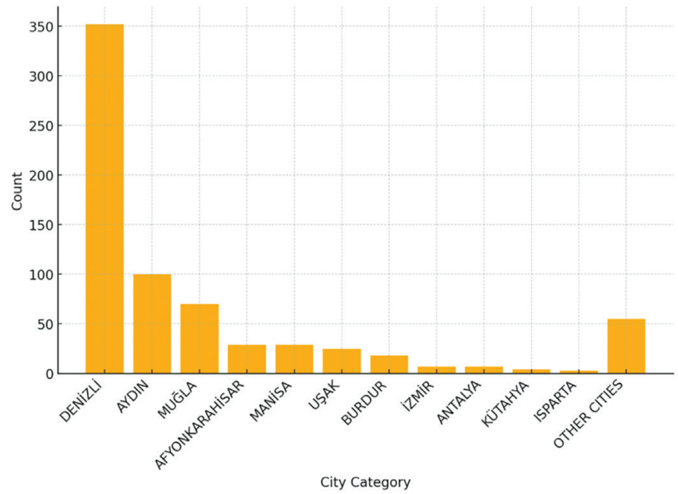
AVR: Aortic valve replacement

and Manisa each contributed 29 patients (4.15%). In contrast, İzmir (20 patients, 2.86%) and Antalya (15 patients, 2.14%) had relatively lower representation. The "other cities" category included 156 patients (22.31%), who were either visiting or tourists in these cities, including Adana.

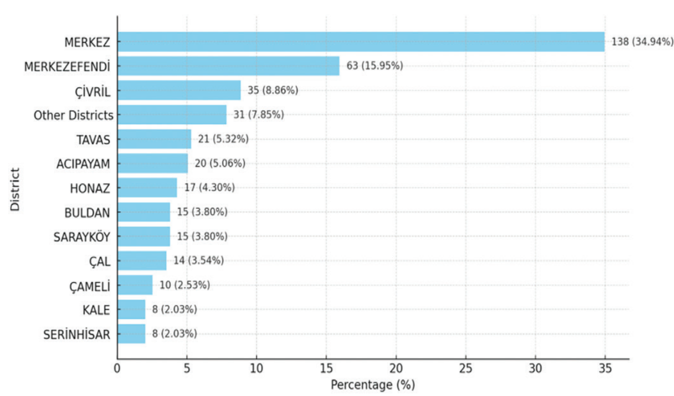
Patient Distribution by Districts in Denizli*:* The analysis of patient distribution by districts in Denizli provides significant insights into the regional referral patterns for aortic aneurysm management. The Bar Chart 2 highlights the percentage contributions of various districts, with districts contributing less than 2% grouped under "Other Districts." The central districts of Merkez and Merkezefendi accounted for the largest proportions of patients, with 34.94% (138 patients) and 15.95% (63 patients), respectively. Several peripheral districts also made notable contributions. Çivril represented 8.86% (35 patients), followed by Tavas (5.32%), Acıpayam (5.06%), and Honaz (4.30%). The "Other Districts" category collectively contributed 7.85% (31 patients) to the total patient population (Bar Chart 3). This group included



Bar Chart 1. City-wise distribution of patients transferred to Denizli for aortic aneurysm management

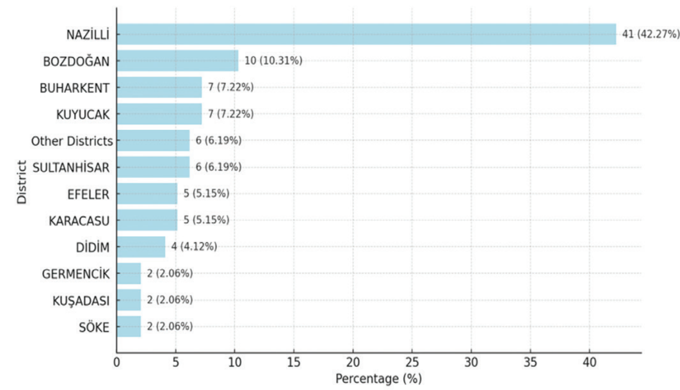


Bar Chart 2. Distribution of patients by birth cities transferred to Denizli for aortic aneurysm management

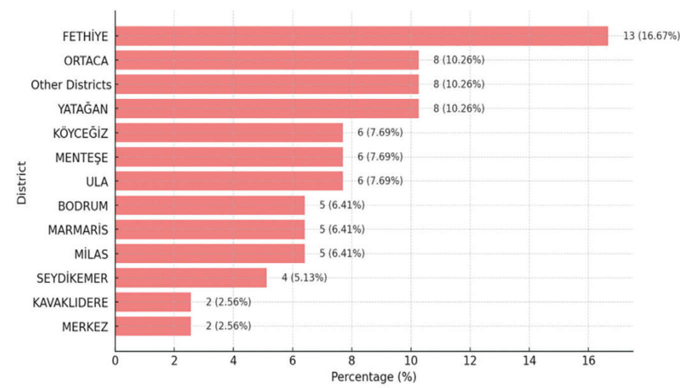


Bar Chart 3. Patient distribution by districts in Denizli: counts and percentages ordered by patient numbers

smaller districts such as Güney, Babadağ, Çardak, Bozkurt, Bekilli, Baklan, Kale, Serinhisar, Çameli, and Acıpayam. In terms of patient distribution by districts in Aydın, Nazilli emerged as the dominant contributor, accounting for 41 patients (42.27%). Bozdoğan contributed 10 patients (10.31%), while Buharkent and Kuyucak each accounted for 7 patients (7.22%). Sultanhisar followed closely with 6 patients (6.19%). Efeler and Karacasu, each contributed 5 patients (5.15%), while Didim accounted for 4 patients (4.12%). The "Other Districts" collectively



Bar Chart 4. Patient distribution by districts in Aydın: referrals to denizli for aortic aneurysm management



Bar Chart 5. Patient distribution by districts in Muğla: referrals to denizli for aortic aneurysm management

accounted for 6 patients (6.19%), including Germencik, Kuşadası, and Söke (Bar Chart 4).

The patient distribution by districts in Muğla is as follows: Fethiye stands out as the largest contributor, accounting for 13 patients (16.67%) of the total referrals from Muğla. The second-largest contributor was Ortaca, with 8 patients (10.26%), sharing its contribution level with the group categorized as "Other Districts", which also contributed 8 patients (10.26%) collectively, including Yatağan, Köyceğiz, and Menteşe. Additionally, Bodrum, Marmaris, and Milas each contributed 5 patients (6.41%). Seydikemer followed with 4 patients (5.13%), while smaller districts such as Kavaklıdere and Merkez each referred 2 patients (2.56%) (Bar chart 5). The analysis

Table 2. City-wise mortality analysis of patients referred for aortic aneurysm management in Southwestern Türkiye

City	Patients number	Mortality (number of deaths)	Mortality rate (%) for each city
Afyonkarahisar	17	4	23.53%
Antalya	5	0	0%
Aydın	97	18	18.56%
Burdur	14	3	21.43%
Denizli	395	81	20.51%
Isparta	2	0	0%
Kütahya	3	0	0%
Manisa	26	4	15.38%
Muğla	78	13	16.67%
Other cities	36	5	13.89%
Uşak	21	2	9.52%
İzmir	5	0	0%

of mortality across city categories provides critical insights into the regional outcomes of aortic aneurysm management. Table 2 summarizes the total number of patients, total mortalities, and calculated mortality rates (%) for each city category. Denizli had the largest number of patients (395) and the highest total mortality (n=81, 20.51%). Afyonkarahisar recorded a mortality rate of 23.53% (4 deaths out of 17 patients), the highest among the analyzed cities. Aydın had a notable mortality rate of 18.56%, (18 deaths among 97 patients). Burdur recorded a mortality rate of 21.43% (3 deaths out of 14 patients). Muğla had a moderate mortality rate of 16.67% (13 deaths among 78 patients). Manisa reported a mortality rate of 15.38% (4 deaths out of 26 patients). Uşak recorded a low mortality rate of 9.52% (2 deaths among 21 patients). Patients grouped under "other cities" had a mortality rate of 13.89% (5 deaths among 36 patients). No mortality in Antalya, Isparta, Kütahya, and İzmir (Table 2).

The Analysis Categorizes Patients by Three Main Procedure Types: Ascending aortic operations, abdominal operations, and thoracic aortic operations; and highlights city-level contributions to the referral network centered in Denizli.

Denizli exhibited the highest patient volume across all procedure types. Ascending aortic operations were the most frequent, with 150 patients (65% male, 35% female) and an average age of 60.5 years. Thoracic and abdominal operations followed, with 55 patients (68% male) and 80 patients (70% male), respectively. Aydın had 45 ascending aortic operations (60% male), while Muğla reported 35 similar procedures (62.9% male). Both cities displayed consistent gender distributions and slightly younger average ages, with ascending aortic operations at 59.2 years in Aydın and 58.3 years in Muğla. Manisa performed 20 ascending aortic operations, while Uşak and Afyonkarahisar contributed 18 and 22 cases, respectively. These cities demonstrated comparable gender distributions and demographic trends, with average ages ranging from 58.5 to 61.2 years.

Mortality Rates Varied Significantly by City and Procedure Type: Denizli showed mortality rates of 20.0%

Table 3. Demographic and mortality analysis by procedure type and city for aortic aneurysm management in Southwestern Türkiye

City	Procedure type	Total patients number for each procedure	Male patients (%)	Female patients (%)	Total mortality	Mortality rate (%) of the procedure	Average age (years)	Median age (years)
Denizli	Ascending aortic operations	150	65%	35%	30	20%	60.5	61
	Abdominal operations	80	70%	30%	15	18.75%	67.3	66
	Thoracic aortic operations	55	68%	32%	12	21.82%	62.8	63
Aydın	Ascending aortic operations	45	60%	40%	8	17.78%	59.2	58
	Abdominal operations	30	66.7%	33.3%	6	20%	66.1	65
	Thoracic aortic operations	22	63.6%	36.4%	5	22.73%	61.4	62
Muğla	Ascending aortic operations	35	62.9%	37.1%	6	17.14%	58.3	59
	Abdominal operations	25	64%	36%	4	16%	65.5	64
	Thoracic aortic operations	20	60%	40%	3	15%	62.7	61
Manisa	Ascending aortic operations	20	70%	30%	4	20%	61.2	62
	Abdominal operations	15	66.7%	33.3%	3	20%	64.8	64
	Thoracic aortic operations	12	66.7%	33.3%	2	16.67%	63.5	62
Uşak	Ascending aortic operations	18	66.7%	33.3%	3	16.67%	60.7	60
	Abdominal operations	10	70%	30%	2	20%	66.9	66
	Thoracic aortic operations	8	62.5%	37.5%	1	12.5%	63.1	63
Afyonkarahisar	Ascending aortic operations	22	63.6%	36.4%	4	18.18%	58.5	58
	Abdominal operations	14	64.3%	35.7%	3	21.43%	64.3	64
	Thoracic aortic operations	10	60%	40%	2	20%	61.9	

for ascending aortic operations, 18.75% for abdominal operations, and 21.82% for thoracic operations. Aydın exhibited slightly lower mortality rates for ascending aortic operations (17.78%), and higher rates for thoracic operations (22.73%). Muğla had mortality rates of 17.14% for ascending aortic operations and 15.0% for thoracic operations. Abdominal operations had a comparable mortality rate of 16.0%. Manisa reported a mortality rate of 20.0% across all three operation types. Uşak showed a slightly lower mortality rate for thoracic operations (12.5%) but higher rates for abdominal operations (20.0%). Afyonkarahisar had mortality rates of 18.18% for ascending aortic operations and 21.43% for abdominal operations (Table 3).

Discussion

The study offers valuable insights into the demographic and clinical characteristics of patients with aortic aneurysms in Southwestern Türkiye, particularly those referred to Denizli for advanced management. Male patients represented 79.26% of the cohort, consistent with global data, which attributes the gender disparity to hormonal and lifestyle factors such as smoking and hypertension[14,15]. However, a notable finding was the higher mortality rate among female patients (20.77%) despite their lower representation, suggesting potential delays in diagnosis or a more aggressive disease course in women[16].

The average age of the patients was 61.89 years, with a wide age range reflecting diverse etiologies[17,18]. Hospitalization durations varied widely, averaging 13.26 days, and were influenced by the complexity of the procedure and patient-specific factors. Endovascular techniques were associated with shorter recovery times but were underutilized in this cohort, representing only 13.45% of interventions[19,20]. This low adoption rate highlights potential resource limitations, anatomical constraints, and the inability to perform such an approach in urgent cases that restrict the use of endovascular approaches[21-23]. There were various causes of mortality concerning aortic aneurysms in the southwestern region of Türkiye; some were related to late referrals, which were notably more prevalent in rural areas. Moreover, deaths were associated with much more complex surgical interventions, for instance, thoracic aorta replacements and some combined procedures. Other factors were increasing age, presence of serious comorbidities such as hypertension and diabetes, and, strikingly, greater mortality amongst women than men. Intraoperative deaths were often due to bleeding and cardiac arrest, while postoperative deaths resulted from sepsis, respiratory failure, and cerebral infarction.

The overall mortality rate of 18.60% aligns with global averages for complex aortic surgeries, though regional disparities were evident. Cities like Afyonkarahisar (23.53%) and Burdur (21.43%) reported higher mortality rates, likely due to delayed referrals and limited preoperative care. Conversely, cities such as Manisa (15.38%) and Uşak (9.52%) exhibited lower mortality rates, suggesting better coordination and efficient healthcare networks. Denizli itself had a mortality rate of 20.51%, higher than the average, reflecting the complexity of cases referred to its tertiary care centers[24,25]. Regional contributions to Denizli's caseload varied significantly. Central districts within Denizli, such as Merkez (34.94%) and Merkezefendi (15.95%), contributed the highest numbers of referrals, likely due to their proximity to healthcare facilities. Peripheral districts like Çivril (8.86%) and Tavas (5.32%) also played a significant role, emphasizing the inclusivity of the referral system. Neighboring cities such as Aydın (13.88%) and Muğla (11.16%) demonstrated the collaborative nature of the region's healthcare network, while international referrals further highlighted Denizli's reputation for advanced cardiovascular care. Surgical outcomes varied across procedures and regions. Ascending aortic operations were the most commonly performed procedure (42.21% of all procedures) and showed a male predominance (65%) with an average patient age of 60.5 years. Abdominal aortic aneurysm surgeries had higher mortality rates, particularly in older populations (average age: 64.3-67.3

years), reflecting the increased risks associated with these procedures. Thoracic aortic operations reported the highest mortality rates, especially in Denizli (21.82%) and Aydın (22.73%), due to the complexity of the surgeries and the comorbidities of the patients[14,26]. Key challenges identified include disparities in referral rates and surgical outcomes across regions. For example, lower referral rates from coastal cities like İzmir and Antalya suggest that patients may prefer local facilities for treatment rather than seeking care in Denizli.

Study Limitations

Incomplete records, lack of detailed data on comorbidities and procedures, and challenges in isolating outcome factors due to healthcare variations. Its focus on short-term outcomes excludes long-term survival and quality of life; and broad grouping of smaller districts may underrepresent their healthcare needs. Disparities in access to advanced techniques and unexplored gender-specific outcomes further limit the findings. Future research should adopt prospective designs with broader coverage and detailed data to address these gaps effectively.

Conclusion

Denizli emerged as the central hub for specialized care, supported by significant contributions from neighboring cities like Aydın, Muğla, and Afyonkarahisar. Geographic disparities in patient distribution and outcomes highlight the need for improved regional healthcare networks. The high prevalence in central and densely populated districts emphasizes the importance of targeted screening and resource allocation. Variations in mortality rates by city and procedure type underscore the critical need for early diagnosis, efficient referral systems, and equitable access to advanced surgical techniques.

Ethics

Ethics Committee Approval: The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval no.: E-60116787-020-636206, date: 08.01.2025) ensuring adherence to the principles outlined in the Declaration of Helsinki.

Informed Consent: This retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Alsalaldeh M, Gökşin İ, Concept: Alsalaldeh M, Design: Alsalaldeh M, Data Collection and/or Processing: Alsalaldeh M, Analysis and or Interpretation: Alsalaldeh M, Gökşin İ, Literature Search: Alsalaldeh M, Gökşin İ, Writing: Alsalaldeh M, Gökşin İ.

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The Role of Patch Repair in Aortic Arch Reconstruction: Enhancing Outcomes and Preserving Growth Potential in Pediatric Patients

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Abstract

Objectives: Aortic arch abnormalities are frequently observed in neonates and may be associated with other congenital cardiac anomalies. Various surgical approaches exist for the repair of these abnormalities. This study aimed to review the outcomes of aortic arch surgery in neonates and infants.

Materials and Methods: We retrospectively analyzed patients who underwent aortic arch reconstruction with or without intracardiac anomalies between 2017 and 2022. The subjects were categorized into two groups based on the arch reconstruction technique employed: group 1 underwent patch aortoplasty via sternotomy, whereas group 2 underwent arch reconstruction without a patch via thoracotomy. Demographic information, morbidity rates, and mortality statistics were extracted from the departmental database for the analysis.

Results: This study enrolled 37 patients (25 males and 12 females). Twenty-nine patients were assigned to group 1, while eight patients were allocated to group 2. No significant differences were observed in the preoperative variables between the two groups. The overall median age and weight were 11 days (range: 2-270) and 3.1 kg (range: 1.4-5.6), respectively. Nine patients had a weight <2.5 kg. Twenty-eight patients underwent concomitant cardiac procedures. The 30-day mortality rate was 10.8% (n=4), with all deceased patients belonging to STAT Mortality Category 4 (n=31). No mortality was observed in the patients with isolated hypoplastic aortic arch or concomitant ventricular septal defect repair.

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Abstract

At a median follow-up of 27 months, three patients in group 2 developed restenosis and underwent surgical correction. In group 1, restenosis was observed in only one patient, who was treated with balloon angioplasty. The incidence of recurrent arch obstruction was significantly higher in group 2 ($p=0.02$).

Conclusion: Aortic arch repair with patch through sternotomy represents a safe and efficacious approach, offering potential for intervention in intracardiac anomalies. The implementation of a patch facilitates tension-free anastomosis and optimal arch geometry, while demonstrating an acceptable rate of restenosis.

Keywords: Aorta, cardiovascular surgery, congenital heart defects

Introduction

Coarctation of the aorta (CoA) is a well-documented congenital anomaly that accounts for 6-8% of all congenital anomalies[1]. Up to 81% of patients with aortic coarctation may have a hypoplastic aortic arch (HAA), and the presence of HAA has a significant effect on the development of recoarctation after surgical repair[2]. It may be observed in conjunction with intracardiac anomalies of varying severity, ranging from a simple ventricular septal defect (VSD) to hypoplastic left heart syndrome[3,4].

The optimal surgical management of CoA with HAA remains a subject of debate. Initial surgical repair and incomplete relief of obstruction have a significant impact on coarctation recurrence, both in the intermediate and long term[5]. Commonly employed techniques for surgical repair include patch aortoplasty, direct anastomosis, sliding aortoplasty, and Extended End-to-End Anastomosis (EEEA).

Furthermore, the management of patients with intracardiac anomalies remains unclear. Although some authors have advocated staged repair, there are a increasing number of reports describing favorable outcomes of the single-stage approach[6,7].

The objective of this study was to evaluate the short- and mid-term outcomes of surgical treatment of HAA and to assess the influence of surgical techniques and the accompanying anomalies on mortality and restenosis.

Materials and Methods

This study was approved by the local institutional Ethical Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2019/12-17, date: 23.11.2011). All the procedures were conducted in accordance with the principles of the Declaration of Helsinki.

The study cohort comprised all patients who underwent aortic arch repair with or without treatment of associated intracardiac anomalies by the same surgeon at Medicana Bursa Hospital and University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital between October 2017 and February 2022. Patients with Hypoplastic Left Heart Syndrome, unstable clinical conditions or isolated discrete CoA were excluded from this study.

Definitions

The aortic segment between the brachiocephalic artery and left common carotid artery was defined as the proximal arch, whereas the segment between the left common carotid artery and left subclavian artery was defined as the distal arch. Arch hypoplasia was defined as (a) a diameter < 1 mm/kg $+ 1$, or (b) a diameter $\leq 50\%$ of the diameter of the ascending aorta. Recurrent arch obstruction was defined as an invasive gradient exceeding 20 mmHg across the repair site.

During follow-up, either percutaneous or surgical intervention of the aortic arch was considered reintervention. Early mortality was defined as death occurring within 30 days after surgery.

Surgical Technique

In group 1, dissection and mobilization of the ascending aorta, arch, and brachiocephalic vessels were performed prior to the initiation of cardiopulmonary bypass (CPB). The patients were cooled to 32 °C. Following division of the ductus arteriosus, the descending aorta was extensively mobilized (Figure 1a). The heart was arrested with del-Nido cardioplegia. Branches of the arch and descending aorta were clamped and antegrade cerebral perfusion (ACP) was initiated. ACP was established either through the graft anastomosed to the innominate artery or by advancing the aortic cannula to the innominate artery, followed by aortic arch reconstruction. All ductal and coarctation tissues were excised. An incision was made along the undersurface of the arch and extended proximal to the innominate artery. To allow for a wide anastomosis, a small incision was made on the inner surface of the descending aorta. Subsequently, the lateral aspect of the descending aorta was sutured to the lateral aspect of the arch (Figure 1b). An ellipse-shaped porcine pericardium was used at the inner curvature to augment the arch (Figure 1c, Figure 1d). In group 2, a left posterolateral thoracotomy was performed. The thoracic cavity was entered through the third intercostal space. Dissection of the aortic arch, left subclavian artery, left carotid artery, and thoracic aorta was conducted. After administration of 100 U/kg heparin, the vessels were clamped. Resection of the coarctation and EEEA was performed.

Demographic and clinical data were collected retrospectively. Echocardiographic measurements were obtained from the outpatient clinic records.

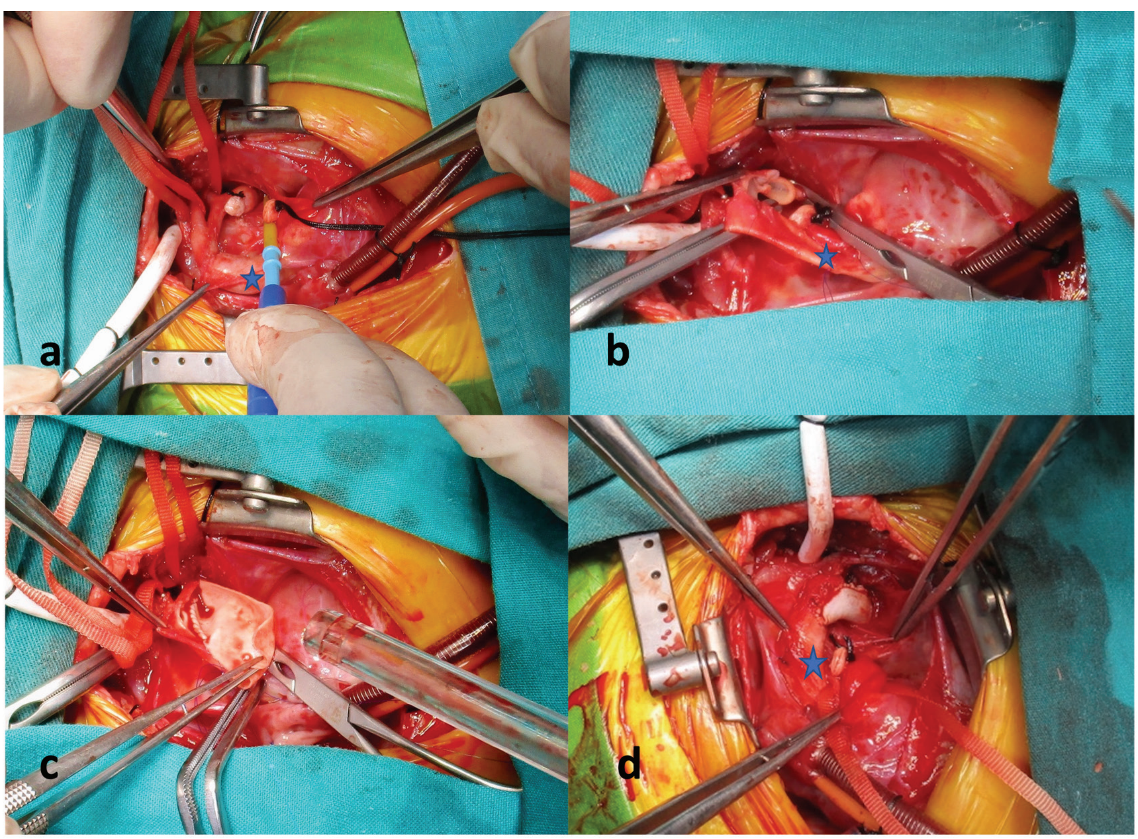

Figure 1. A, B, C, D) Surgical technique

Statistical Analysis

Data were analyzed using IBM SPSS Statistics Version 21 (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as the mean ± standard deviation. Non-normally distributed variables were presented as medians (Q1 and Q3). Categorical data were compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared using Student's t-test or the Mann-Whitney U test. Survival and freedom from reintervention are presented using Kaplan-Meier survival curves. A Cox regression model was used for univariate analysis. Statistical significance was set at $p<0.05$.

Results

Thirty-seven patients (12 females, 25 males) were included in this study. In group 1, 29 patients underwent surgery via sternotomy with CPB. In group 2, eight patients underwent surgery via thoracotomy. No significant differences were observed in the preoperative variables between the two groups (Table 1). The overall median age at surgery was 11 days [interquartile range (IQR): 2.4-3.3]. The majority of patients were neonates (≤28 days; n=29; 78%), and the remaining seven (22%) were infants. The median weight at surgery was 3.1 kg (IQR: 2.4-3.3). Ten patients were under 2.5 kg. Seventeen (46%) patients required preoperative ventilatory support and 10 (27%) patients received prostaglandin E (PGE) infusion. Six patients presented with genetic abnormalities; the diagnoses included trisomy 21 (n=3), trisomy 18, Emmanuel syndrome, and DiGeorge syndrome. Only nine patients (24%) exhibited an isolated HAA. Twenty-eight patients underwent concurrent cardiac procedures, of whom 15 had VSD closures (Table 2). Five patients underwent univentricular palliative repair. There was no statistically significant difference between the two groups with respect to early postoperative variables. The median length of intensive care unit stay was nine days in both groups (Table 3). The 30-day mortality rate was 10.8% (4/37). Low cardiac output syndrome, cerebral hemorrhage, sepsis, and acute renal failure were identified as the causes of mortality. There was one case of late mortality. The patient with HAA and truncus arteriosus died 60 days after arch reconstruction and PA banding. The cause of death was determined to be sepsis. Twenty-nine patients were classified into STAT Mortality Category 4 (Figure 2). All deceased patients belonged to category 4 and underwent complex cardiac surgery. Five patients underwent concomitant univentricular palliation. Mortality was not observed in the patients with isolated arch hypoplasia, or with concomitant VSD closure. During the follow-up period, three patients (3/8) in group 2 developed restenosis and necessitated reoperation. In group 1, restenosis was observed in only one patient (1/29), who subsequently underwent balloon angioplasty. The

Table 1. Demographic data of patients

	Total n=37	Group 1 n=29	Group 2 n=8	p-value
Age at surgery, d Median (quartiles: Q1-Q3)	11 (6-26)	10 (6-26)	14.5 (7.5-26.5)	0.59
Weight, kg Median (quartiles: Q1-Q3)	3.1 (2.4-3.3)	3.2 (2.7-3.3)	2.6 (1.97-3.35)	0.18
Sex, Male/Female	25/12	19/10	6/2	0.48
PGE1 (%)	10 (27%)	8 (27.6%)	2 (25%)	0.63
Ventilatory support, %	17 (45.9%)	13 (44.8%)	4 (50%)	0.55
Low weight (<2.5 kg)	10 (27%)	6 (20.7%)	4 (50%)	0.11
Single ventricle	5/32 (13.5%)	5/24 (17.2%)	-	0.27

PGE: Prostaglandin

difference was statistically significant. Figure 3 illustrates the freedom from reintervention throughout the follow-up period. No aneurysms or bronchial compressions occurred during the follow-up period. Junctional ectopic tachycardia, managed through medical intervention, was observed in four (12%) patients in group 1. One patient

Table 2. Concomitant cardiac procedures

	n	%
VSD repair	15	40.5
Atrial septectomy + pulmonary artery banding	3	8.1
ASD repair	2	5.4
Pulmonary artery banding	2	5.4
Arterial switch operation + VSD repair	2	5.4
Damus kaye stansel procedure	1	2.7
Subaortic membrane resection	1	2.7
Aortopulmonary window repair	1	2.7
AVSD repair	1	2.7

ASD: Atrial septal defect, AVSD: Atrioventricular septal defect, VSD: Ventricular septal defect

Table 3. Postoperative details

	Total n=37	Group 1 n=29	Group 2 n=8	p-value
ICU LOS, d Median (quartiles: Q1-Q3)	9 (5.5-16)	9 (6-14)	8.5 (5-22.5)	0.63
Complex procedure, %	12 (32.4%)	10 (34.5%)	2 (25%)	0.48
Arrythmia requiring medical treatment	4 (10.8%)	4 (13.8%)	-	0.55
Early mortality, %	4 (10.8%)	3 (10.3%)	1 (12.5%)	0.56
Re-Intervention, %	4 (10.8%)	1 (3.9%)	3 (42.9%)	0.023
Follow-up (month) median (quartiles: Q1-Q3)	27 (14-43)	21 (14-40)	37.5 (10.75-54.25)	0.24

ICU: Intensive care unit, LOS: Length of stay

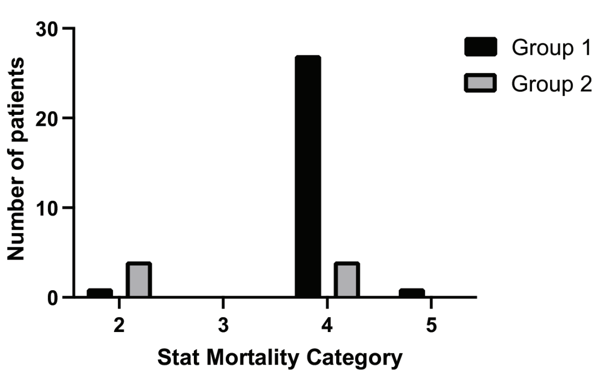

Figure 2. Stat mortality category

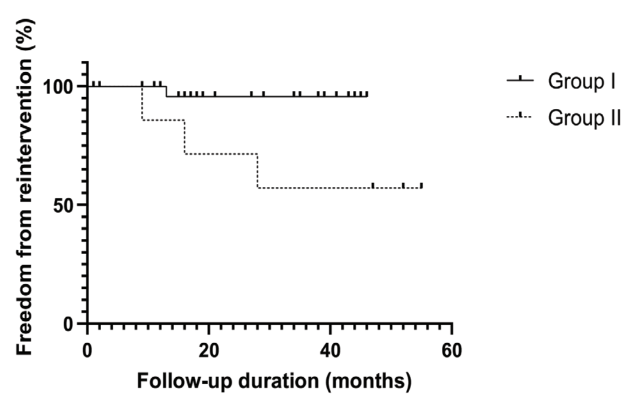

Figure 3. Freedom from reintervention

required a permanent pacemaker. Only one patient exhibited vocal cord dysfunction, and hoarseness was observed; the hoarseness subsequently resolved during the follow-up. Arch reconstruction without patch was identified as a risk factor for restenosis and reintervention ($p<0.05$). Preoperative ventilation, PGE1 infusion, or low birth weight (<2500 g) was not found to be risk factors for mortality or restenosis. Univariate analysis revealed that concomitant univentricular palliation was a significant predictor of mortality ($p=0.005$). However, this association was not significant in multivariate analysis after adjusting for other variables ($p=0.11$). Patients requiring univentricular palliation often represent a subgroup with a higher surgical complexity, which could explain the initial association with mortality.

Discussion

This retrospective study demonstrated that aortic arch reconstruction with patch through median sternotomy is an efficacious surgical technique that enables the addressing of all sites of the arch, facilitates tension-free anastomosis, and allows intervention in combined cardiac lesions.

Various surgical techniques have been employed to address aortic arch reconstruction. However, the best method for managing CoA associated with HAA remains controversial. One prevalent theory suggests that enhancing the HAA is unnecessary, as hypoplasia or residual arch obstruction is believed to resolve naturally after resection and EEEA[8]. Nevertheless, incomplete resolution of arch obstruction may increase the likelihood of recurrent obstruction. Studies have shown that recurrent coarctation rates after EEEA range from 2% to 31%[9,10]. Rakhra et al.[11] found that patients who underwent arch repair via thoracotomy had a lower 10-year freedom from recurrent arch obstruction (61%) than those who underwent arch repair via sternotomy (92%). In our cohort, the incidence of restenosis was significantly lower in patients who underwent arch reconstruction via sternotomy with patch augmentation (1/29), which aligns with the findings of Rakhra et al.[11]. This supports the hypothesis that the sternotomy approach offers better long-term patency, possibly due to improved exposure and more precise arch geometry during reconstruction.

Although EEEA via thoracotomy might be perceived as less invasive, it has several drawbacks. These include limited operating space and restricted aortic clamp time. Furthermore, clamping the proximal aortic arch during anastomosis may impair cerebral blood flow, and achieving complete relief of arch obstruction can be difficult. Studies with long-term follow-up have shown that the arch tends to remain relatively small[12]. Furthermore, residual aortic arch obstruction has been identified as a risk factor for post-repair hypertension[13]. In contrast, the midline sternotomy approach overcomes these challenges by providing safe and sufficient exposure.

Various surgical techniques, including aortic arch advancement, end-to-side anastomosis, and patch augmentation, have been described via median sternotomy[7]. Our preferred approach is the patch augmentation via sternotomy with CPB. The entire isthmic region and ductal tissue can be resected safely and easily to reduce the risk of recoarctation. The use of a patch for the inner curve of the arch following partial anastomosis of the aortic tissue ensures tension-free reconstruction of the arch and a favorable geometry. Consequently, arch obstruction is effectively resolved, even in severely HAA, and the arch retains its growth potential.

One of the important issues that has been overlooked is the type of aortic arch. Three types of aortic arches have been identified: gothic, crenel, and normal[14]. Gothic arch is characterized by acute angulation between the ascending and descending aorta and suggesting increasing the hypertension risk[1,14]. End-to-end or end-to-side anastomosis results in a more gothic arch shape post-surgery, increasing the risk of hypertension[14]. Furthermore, end-to-side anastomosis or sliding aortoplasty techniques, which preclude the use of patch material, are hypothesized to optimize the growth potential of the arch. However, direct anastomosis may induce excessive tension between the two aortic ends, potentially resulting in bronchial compression. Roussin et al.[15] observed higher rates of restenosis and bronchial compression in the native tissue repair group compared to the patch aortoplasty group. We observed no bronchial compression and a low restenosis rate during follow-up in the sternotomy group, as patch repair provided favorable geometry of the arch, tension-free reconstruction. Additionally, there were no aneurysms, although such cases have been described after patchplasty[16]. Concerns about the potential risks of CPB and ACP in neonatal cardiac surgery are often raised. However, this study supports the safety of these techniques when they are performed under controlled conditions. Only one patient experienced neurological complications. These findings are consistent with contemporary literature, which suggests that modern CPB and ACP protocols, when carefully managed, pose minimal risks and provide critical benefits, including improved exposure and the ability to address concomitant cardiac defects[9,17].

Although some surgeons have expressed concerns about performing single-stage repair for cardiac and aortic arch abnormalities, this method has gained prevalence following successful reports[10,11]. Our experience supports these reports, as the single-stage approach enabled us to successfully address both arch and intracardiac anomalies, resulting in promising short-term and long-term results.

Study Limitations

However, it is important to acknowledge the limitations of our study, including the small sample size, particularly in the EEEA group, which may have affected statistical power. The retrospective and non-randomized design restricts the ability to establish causality and introduces potential bias. Furthermore, follow-up evaluations relied primarily on echocardiographic measurements, which may have underestimated subtle cases of restenosis. Additionally, the use of multiple definitions of HAA in the study might have introduced variability, underscoring the need for standardized diagnostic criteria in future research[18].

Conclusion

In conclusion, patch aortoplasty via sternotomy is a reliable and effective technique for aortic arch reconstruction, particularly in neonates with complex cardiac anomalies. This approach offers superior outcomes in terms of restenosis, geometric optimization, and mortality while providing the flexibility needed for long-term success. Future prospective studies with standardized protocols and advanced imaging follow-up are essential to validate these findings and further refine the surgical strategies in this high-risk population.

Ethics

Ethics Committee Approval: This study was approved by the local institutional Ethical Committee of University of Health Sciences Türkiye, Bursa Yüksek İhtisas Training and Research Hospital (approval no: 2011-KAEK-25 2019/12-17, date: 23.11.2011). All the procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Seçici S, Öncü SB, Concept: Seçici S, Design: Seçici S, Data Collection and/or Processing: Seçici S, Öncü SB, Analysis and/or Interpretation: Seçici S, Öncü SB, Literature Search: Seçici S, Writing: Seçici S, Öncü SB.

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Mortality Risk Assessment Using PRECISE-DAPT and DAPT Scores in Acute Coronary Syndrome: A Comparative Analysis

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Abstract

Objectives: This study aimed to compare the data on mortality of the clinical scoring system that predicts the risk of ischemia-bleeding under dual therapy.

Materials and Methods: The records of the patients were retrospectively examined through the hospital information system and archival records. The prepared case data registration form and the Morisky Medication Adherence scale drug compliance scale were filled out. With these data, the patients' predicting bleeding complications in Patients Undergoing Stent Implantation and Subsequent dual antiplatelet therapy (PRECISE-DAPT) and DAPT scores were calculated.

Results: A total of 260 patients were included in the study. The PRECISE-DAPT and DAPT scores were calculated for the patients with acute coronary syndrome. A total of 62 patients (23.8%), exhibited a PRECISE-DAPT score of ≥25. The number of patients with a DAPT score ≥2 was found to be 193 (74.2%). In terms of mortality, patients with PRECISE-DAPT ≥25 and those with PRECISE-DAPT <25 were compared with another group (score should be specified here), and mortality was significantly higher in the high-score group [p=0.001 odds ratio: 6.94 confidence interval: (3.53-13.62)]. Patients were divided into 4 groups based on PRECISE-DAPT and DAPT scores and compared with each other (PRECISE-

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DAPT <25 and DAPT ≥2, PRECISE-DAPT ≥25 and DAPT ≥2, PRECISE-DAPT <25 and DAPT <2, PRECISE-DAPT ≥25 and DAPT <2). Patients with a high PRECISE-DAPT score had a significantly higher mortality rate compared to those with a lower DAPT score (p<0.001).

Conclusion: In our study, we discovered that the bleeding risk score was insufficient for predicting bleeding events, but it could identify high-risk patients in terms of mortality.

Keywords: PRECISE-DAPT, bleeding score, dual antiplatelet therapy, coronary artery disease

Introduction

Percutaneous stent implantation is becoming more common for the treatment of acute coronary syndrome (ACS). The guidelines strongly recommend the initiation of dual antiplatelet therapy (DAPT) following stent implantation[1,2]. The optimal duration for initiating DAPT remains a subject of ongoing debate, as a definitive consensus has yet to be reached.

In DAPT, clopidogrel, ticagrelor, and prasugrel may be included in addition to aspirin[3]. Studies have demonstrated that the use of dual antiplatelet combinations leads to a reduction in major ischemic events among individuals with ACS[3]. The diversification of the agents used in conjunction with aspirin, the advancement of stent technology, and the development of less thrombogenic stents have resulted in divergent outcomes in studies examining the duration of dual therapy. Researchers have developed risk scoring systems to evaluate the dual therapy duration of patients with stents, based on the available data, which has yielded varying results[4]. The ischemia-bleeding balance is the basis of these scoring systems, which analyze the patient's individual and procedural conditions. A risk score for ischemic events was developed in the DAPT study for this purpose by evaluating 9 parameters. Prolonging DAPT in patients with a DAPT score <2 did not result in a reduction in ischemic outcomes, but did result in a significant increase in moderate/severe bleeding events[4]. The predicting bleeding complications in Patients Undergoing Stent Implantation and Subsequent (PRECISE)-DAPT score is another DAPT scoring system. This scoring system is a risk score developed for bleeding events. Extensive DAPT in patients with a high risk of bleeding based on the PRECISE-DAPT score (PRECISE-DAPT ≥25) did not provide a significant benefit in ischemic outcomes, but significantly increased the bleeding burden [number needed to harm (NNH): 38][5]. In contrast, extended DAPT has been shown to reduce the risk of myocardial infarction (MI), stent thrombosis, stroke, and target vessel revascularization in patients without a high risk of bleeding (PRECISE-DAPT score <25). For patients at high risk of bleeding, limiting the duration of DAPT to less than 12 months may reduce the risk of excessive bleeding. In contrast, extended dual therapy may be considered a favorable option for patients who exhibit good tolerance to standard therapy and do not possess a high risk of bleeding[1,5]. This study aimed to evaluate the relationship between PRECISE-DAPT, DAPT scores and bleeding and mortality in patients who were admitted with a diagnosis of ACS and had a stent implanted while on DAPT.

Materials and Methods

Study Sample

Patients with ACS who presented to the Dokuz Eylül University Medical Faculty Hospital Department of Cardiology (cardiology service and coronary intensive care) between January 1, 2013, and July 1, 2014, had their records reviewed retrospectively using the hospital information system and archive records. Of the 948 patients screened, those under the age of 18, those with bleeding-prone disease and laboratory findings, those who decided to have a coronary artery bypass graft (CABG) operation after ACS, those who had not been implanted with a stent, those who used anticoagulants, and those with a malignancy diagnosis, were excluded, leaving 260 patients eligible for the study. The patients were contacted using the phone numbers they had registered on the system. Patients' duration of dual therapy, histories of recurrent MI and coronary angiography (CAG), bleeding histories during or after dual therapy, and drug compliance were all thoroughly investigated. The case data registration form and the Morisky Medication Adherence scale (MORISKY) drug compliance scale were telephone contact with the patients. Approval was obtained from the Dokuz Eylül University Non-interventional Research Ethics Committee (approval no.: 2019/04-23, date: 20.02.2019).

Obtaining Patient Information

The patients were contacted by phone; a case data record form with questions and answers was completed. Patients' bleeding histories, duration of dual therapy, history of recurrent MI and CAG, bleeding history during or after DAPT, and drug compliance were all thoroughly questioned. The laboratory results, echocardiography and CAG reports, and the patients' disease histories were retrieved from the recorded information in the system. With these data, the patients' PRECISE-DAPT and DAPT scores were calculated.

The DAPT score consists of nine parameters. Age, congestive heart failure/low left ventricular ejection fraction (EF), vein graft stenting, MI at admission, previous MI or percutaneous coronary intervention (PCI), diabetes, a stent diameter of 3 mm, smoking, and paclitaxel-eluting stent. These are all factors included in the DAPT score. A DAPT score of ≥2 is considered elevated, and there is a moderate increase in bleeding events with prolonged dual therapy. Prolonging dual therapy in patients with a low DAPT risk score (score <2) did not result in a reduction in ischemic outcomes, but did result in a significant increase in moderate/severe bleeding events. PRECISE-DAPT is a scoring system consisting of five parameters (age, CrCl, hemoglobin levels, white blood cell count, and history of previous spontaneous bleeding) to predict out-of-hospital bleeding in patients who are undergoing dual therapy. Extensive dual therapy in patients with a high risk of bleeding based on the PRECISE-DAPT score (PRECISE-DAPT 25) did not provide a significant benefit in ischemic outcomes, but significantly increased the bleeding burden (NNH: 38)[5]. In contrast, extended dual therapy has been shown to reduce the risk of MI, precise stent thrombosis, stroke, and target vessel revascularization in patients without a high risk of bleeding (number needed to treat = 65) (PRECISE-DAPT score <25).

In addition, the MORISKY drug compliance scale and a questionnaire form were filled out to evaluate each patient's drug compliance. The case data registration form was filled out based on the patients' responses to the questions.

Bleeding Classifications Based on Standard Bleeding Definitions

The patients were questioned about bleeding that necessitated their applying to a healthcare institution and for treatment, bleeding that resulted in death, bleeding from intracranial or other important anatomical organs, bleeding that resulted in a decrease in hemoglobin of 3-5 mg/dL or higher, and bleeding that necessitated a blood transfusion. In light of this information, bleedings were classified according to the Bleeding Academic Research Consortium (BARC), thrombolysis in MI (TIMI), and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) bleeding classifications[6-8].

Patients who could be contacted via phone were asked if they had experienced bleeding. The bleeding focus in the patients, who answered yes, was questioned. The concerns were whether they contacted the doctor in the event of bleeding, what recommendations were made by the doctors, whether the drug was discontinued, and whether blood transfusions were administered to hospitalized patients.

Determination of Drug Compliance

Patients, who were contacted by phone, were asked about their adherence to medications using the Morisky Clinical Drug Compliance scale, which consisted of 8 questions. According to the responses received, the patients' scores were calculated and the patients' degree of compliance was determined based on their scores. Patients with a score of 8 were considered to have high drug compliance, those with a score of 6 were considered to have moderate compliance, and those with a score of 5 or lower were considered to have low drug compliance.

Statistical Analysis

Statistical analysis was performed using the SPSS 24.0 program. The normal distribution of continuous variables was examined. Those with a normal distribution were evaluated using the t-test, and those without were evaluated using the Mann-Whitney U test. Those with more than two variables and a normal distribution were assessed using the ANOVA test, while those without were evaluated using the Kruskal-Wallis test. For categorical variables, the chi-square test, such as the Pearson's chi-square test and Fisher's exact test, was applied. The Kaplan-Meier survival curves of different groups were evaluated, and these groups were compared with the log-rank test. The significant results from the chi-square tests were subjected to a statistical analysis using binary logistic regression. A p-value of <0.05 was considered significant.

Results

The study included 260 patients with ACS who underwent stent implantation at the Clinic of Cardiology, Dokuz Eylul University Medical Faculty Hospital. Of the patients, 211 (81.2%) were male, and the mean age was 60.06±12.71 years. Based on the patients' medical histories, hypertension was found in 149 (57.3%), diabetes mellitus (DM) in 78 (30%), coronary artery disease (CAD) in 56 (21.5%), cerebrovascular accident (CVA) in 9 (3.5%), peripheral artery disease (PAD) in 5 (1%), and heart failure in 4 (1.5%). When the smoking histories of the patients were evaluated, it was found that 70 patients (26.9%) were non-smokers. Smokers were divided into three subgroups as in the DAPT score. There were 121 (46.5%) active smokers, 21 (8.1%) had quit smoking within two years, and 48 (18.5%) had quit smoking more than two years previously. The mean scores of PRECISE-DAPT and DAPT were calculated as 17.84±11.14 and 2.21±1.31, respectively. Table 1 displays the patients' baseline clinical, demographic, and biochemical parameters.

When the patients' admission clinic, peri-procedural angiographic, and procedural characteristics were evaluated, 153 (58.8%) were hospitalized with ST-elevation MI (STEMI), 93 (35.8%) with non-STEMI, and 14 (5.4%) with unstable angina pectoris. These patients had an average EF value of 50% (40-60 interquartile range), with 35 (13.9%) having an EF of below 40%. The target vessel for 114 (43.9%) patients was the left anterior descending artery, the circumflex for 51 (19.6%), the right coronary artery for 81 (31.2%) , and the saphenous vein graft for 14 (5.4%). The complex PCI rate was determined to be 7.3% (19 patients), and multi-vessel intervention was performed on 16.6% (44 patients) patients. Data from patients' angiographic features are shown in Table 1.

In our study, 259 (99.6%) of the 260 patients received aspirin, 254 (97.7%) received clopidogrel, 5 (1.9%) received ticagrelor, 1 (0.4%) received prasugrel, 236 (90.8%) received angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 241 (92.7%) received beta-blockers, 256 (98.5%) received statins, and 240 (92.3%) received proton pump inhibitors (PPIs). The mean duration of DAPT use was 17.61±16.72 months. The drugs prescribed to patients at discharge, as well as the duration of DAPT, are displayed in Table 2.

Bleeding occurred in 35 (13.59%) of the 260 patients enrolled in the study. Of these, 4 (11.4%) were hematuria, 13 (37.1%) were melena, 1 (2.9%) was hemoptysis, and 9 (25.7%) were other types of bleeding. 20 patients (57.1%) sought treatment at the hospital because of these bleedings. The medication for 21 (60%) of the bleeding patients was not changed; the drug was discontinued in 13 (37.1%),

Table 1. Demographic characteristics of patients, comorbid diseases, laboratory-clinical characteristics and applied procedures

Age (years) (mean ± SD)		60.12 (12.71)
Sex	Male-n (%)	211 (81.2)
	Female-n (%)	49 (18.8)
BMI (kg/m^2) (mean ± SD)		27.81 (13.6)
Hypertension		57.3
Diabetes, %		30
Cerebrovascular event, %		3.5
Coronary artery disease, %		21.5
Peripheral arterial disease, %		1.9
Smoking, %	Active smokers	46.5
	Those who had quit within the previous 2 years	8.1
	Those who had quit more than 2 years previously	18.5
	Non-smokers	26.9
History of bleeding %		5
PRECISE-DAPT score (mean ± SD)		17.84 (11.14)
DAPT score (± SD)		2.21 (1.31)
WBC (u/mcL)		11.715 (6.800)
Hb (g/dL)		13.69 (1.83)
Hb <11 g/dL		24 (9.2)
Creatinine (mg/dL)		0.86 (0.75-1.04)
GFR mL/minimum		95.37 (29.13)
GFR<60 mL/minimum		28 (10.8)
Clinic of application	STEMI-n (%)	153 (58.8)
	Non-STEMI-n (%)	93 (35.8)
	UAP-n (%)	14 (5.4)
Ejection fraction % - (IQR)		50 (40-60)
EF <40%, n (%)		35 (13.9)
Target vessel, n (%)	LAD	114 (43.8)
	Cx	51 (19.6)
	RCA	81 (31.2)
	Saphenous vein graft	14 (5.4)
Complex PCI-number (%)		19 (7.3)
Number of stents (mean number per individual)		1.39 (0.66)
Number-type of stent %	MVI	48/260 (18.5)
	First generation stent	12/260 (4.6)
	Second generation stent	176/260 (67.7)
	Dissolvable stent	1/260 (0.4)
	MVI and the first generation	3/260 (1.2)
	MVI and the second generation	17/260 (6.5)
	First and second generation	3/260 (1.2)
Total number of stents implanted		361
Multi-vessel interference		44/264 (16.6)
Total stent length - minimum		27.98 (15.8)

Mean ± standard deviation or median [interquartile range]; categorized variables, n (%), SD: Standard deviation, UAP: Unstable angina pectoris, STEMI: ST-elevated myocardial infarction, NSTEMI: Non-ST elevated myocardial infarction, PCI: Percutaneous intervention, LAD: Left anterior descending artery, Cx: Circumflex artery, RCA: Right coronary artery, EF: Ejection fraction, BMI: Body mass index, WBC: White blood cells, Hb: Hemoglobin, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy, GFR: Glomerular filtration rate, MVI: Multivessel intervention

Table 2. Drugs prescribed for patients at the time of discharge and the duration of use for dual antiplatelet therapy

Aspirin, n (%)		259/260 (99.6)
Clopidogrel, n (%)		254/260 (97.7)
Ticagrelor, n (%)		5/260 (1.9)
Prasugrel, n (%)		1/260 (0.4)
ACE Inh/ARB, n (%)		236/260 (90.08)
Beta-blocker, n (%)		241/260 (92.7)
Statin, n (%)		256/260 (98.5)
PPI, n (%)		240/260 (92.3)
Duration of use for dual therapy, month		17.61±16.72
Non-receiver, n%		5 (1.9)
Receiver	<1 month, n (%)	6 (2.3)
	1-3 months, n (%)	5 (1.9)
	3-6 months, n (%)	5 (1.9)
	6-12 months, n (%)	177 (68.1)
	12-24 months, n (%)	25 (9.6)
	24-36 months, n (%)	8 (3.1)
	>36 months, n (%)	29 (11.2)

PPI: Proton pump inhibitor, ACE: Angiotensin-converting enzyme inhibitör, ARB: Angiotensin II receptor blocker

and a drug vacation was initiated in 1 (2.9%). According to the TIMI classification, 28 (80%) of these bleeding were minimal, 5 (14.3%) minor, and 2 (5.7%) major. According to the GUSTO classification, 28 (80%) of the patients had minimal bleeding, 5 (14.3%) minor bleeding, and 2 (5.7%) major bleeding. According to the BARC classification, there were 15 (42.9%) type 1, 13 (37.1%) type 2.5 (14.3%) type 3A, and 2 (5.7%) type 3D bleeding events. Furthermore, 15 (42.8%) of 35 bleeding events occurred while patients were receiving dual therapy.

BARC3 bleeding, considered major bleeding, occurred in 7 patients, representing 2.8% of all patients included in the study and 20% of patients with bleeding. When we examined the bleeding events in these patients, we observed that a total of 4 individuals (11.4%) experienced bleeding while receiving DAPT, whereas 3 individuals (8.5%) experienced bleeding while receiving single antiplatelet therapy. One (2.8%) of the patients who had bleeding under dual therapy had a hemorrhagic CVA, which resulted in death. The remaining 3 (8.5%) patients were admitted to the hospital with gastrointestinal (GI) system bleeding and required at least two units of erythrocyte suspension. Two of the three (8.5%) patients, who experienced bleeding while undergoing single antiplatelet therapy, were admitted to the hospital with GI bleeding and required at least two units of erythrocyte replacement, while the remaining patient, accounting for (2.8%) experienced a hemorrhagic CVA. Two (5.6%) of the patients who experienced bleeding while on single antiplatelet therapy received aspirin, and one (2.8%) received clopidogrel. Of the 7 (20%) patients who had BARC 3 major bleeding, 4 (11.4%) died due to various causes. Of the patients who died while receiving dual therapy, 1 (2.8%) died due to hemorrhagic CVA, while the other 2 (5.6%) patients died due to causes unrelated to bleeding. The patient, who died while taking clopidogrel, had GI bleeding and was diagnosed with gastric carcinoma via endoscopic examination; this patient succumbed to sepsis in the subsequent period. Data on bleeding rates in patients are shown in detail in Table 3.

The study recorded a mortality rate of 18.8% (n=49) among 260 patients. Of these deaths, 27 (55.1%) were due to cardiovascular causes. The mean time to death after index ACS was 34±21 months. While 10 deaths (20.4%)

occurred within the first year, 39 (79.6%) occurred after one year (Table 3). When the baseline clinical and demographic characteristics of patients who died and those who did not were compared, it was discovered that the patients who died were older, and had more co-morbid diseases. No statistically significant difference was found among bleeding history, MORISKY drug compliance scale score, and mortality (p=0.68, p=0.11, respectively). The mortality data of the patients are shown in Table 4.

Table 3. Patients' bleeding and mortality data

Bleeding, n (%)		**35/260 (13.5)**
	Hematuria - n (%)	4 (11.4)
Type of bleeding, n (%)	Melena - n (%)	13 (37.1)
	Epistaxis - n (%)	8 (22.9)
	Hemoptysis - n (%)	1 (2.9)
	Other - n (%)	9 (25.7)
Application to the hospital due to bleeding, n (%)		20/35 (57.1)
Bleeding management, n (%)	No drug changes	21 (60.0)
	Drug vacation	1 (2.9)
	Drug discontinuation	13 (37.1)
Bleeding under double antiplatelet, n (%)		15/35 (42.8)
TIMI, n (%)	Minimal	28 (80)
	Minor	5 (14.3)
	Major	2 (5.7)
GUSTO	Mild	28 (80)
	Moderate	5 (14.3)
	Severe	2 (5.7)
	Type 1	15 (42.9)
	Type 2	13 (37.1)
BARC	Type 3A	5 (14.3)
	Type 3B	0 (0)
	Type 3C	2 (5.7)
	Type 4	0 (0)
	Type 5	0 (0)
Mortality, n (%)		49 (18.8)
Death due to cardiovascular causes, n (%)		27 (55.1)
Cardiovascular death due to following causes	ME	7 (25.9)
	CTF	6 (22.2)
	Stroke	2 (7.4)
	Sudden cardiac death	8 (29.6)
	Arrhythmia/other	4 (14.8)
Oncological causes, n (%)		11 (22.4)
Other reasons, n (%)		11 (22.4)
Time passed until mortality, month		34 (21)
Death within a year, n (%)		10 (20.4)
Death after one year, n (%)		39 (79.6)

TIMI: Thrombolysis in myocardial infarction, BARC: Bleeding academic research consortium, GUSTO: Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries, CTF: Common terminology criteria for adverse events

In our investigation, patients were categorized into four groups: the first group with PRECISE-DAPT <25 and DAPT ≥2, the second group with PRECISE-DAPT ≥25 and DAPT ≥2, the third group with PRECISE-DAPT <25 and DAPT <2, and the fourth group with PRECISE-DAPT ≥25 and DAPT <2. These groups were subjected to analysis using the Kaplan-Meier survival analysis method to assess the correlation between mortality and PRECISE-DAPT and DAPT scores (Figure 1).

The analysis performed using the Kaplan-Meier method revealed that the PRECISE-DAPT score significantly increased mortality regardless of the DAPT score ($p<0.001$). The mean PRECISE-DAPT and DAPT scores of the 260 patients included in the study were calculated as 17.84±11.14 and 2.21±1.31, respectively. There were 62 (23.8%) patients with a PRECISE-DAPT score of 25, indicating a high risk for bleeding. There were

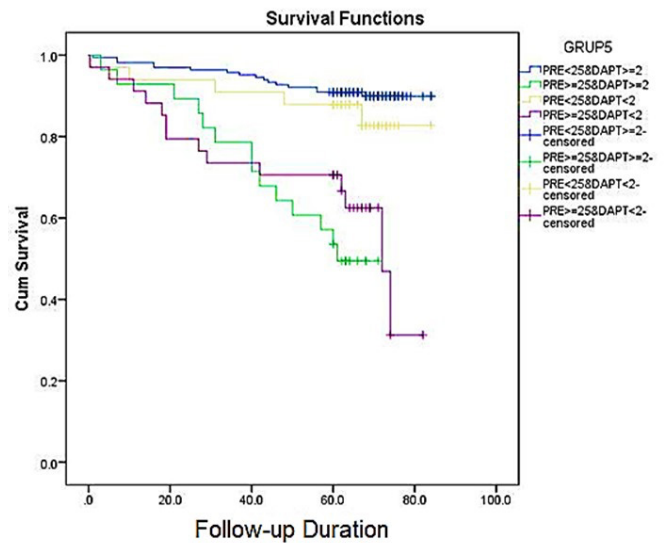

Figure 1. Kaplan-Meier survival analysis (based on PRECISE-DAPT and DAPT scores) log-rank p-value <0.001

BARC: Bleeding academic research consortium, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

Table 4. Comparison of demographic characteristics, examination and score data between patients who died and those who survived

	Survived (n=211)	Died (n=49)	p-value
Age, (mean ± SD)	57.16±11.24	72.86±10.71	<0.001
Female, n (%)	16.6	28.6	0.053
Hypertension, %	55.5	65.3	0.209
Diabetes mellitus, %	25.6	49.0	0.001
Cerebrovascular event, %	1.9	10.2	0.004
Coronary artery disease, %	17.5	38.8	0.001
Peripheral arterial disease, %	0.9	6.1	0.018
Smoker, %	51.2	26.5	0.002
History of bleeding, %	4.7	6.1	0.68
Congestive heart failure, %	0	8.2	0.001
Creatinine, median (IQR)	0.85 (0.74-1.01)	0.94 (0.80-1.33)	0.002
GFR, mean ± SD	99.46±26.78	77.76±32.40	<0.001
WBC, median (IQR)	10800 (8500-13800)	10000 (7900-12300)	0.081
Hb, median (IQR)	14.30 (12.80-15.20)	12.40 (11.20-13.70)	<0.001
EF, median (IQR)	50 (45-60)	50 (35-55)	0.008
BMI, median (IQR)	26.79 (24.67-29.71)	25.39 (22.03-28.57)	0.031
PRECISE-DAPT ≥25	34/62 (54.8%)	28/62 (45.2%)	<0.001
PRECISE-DAPT <25	177/198 (89.4%)	21/198 (10.6%)	
DAPT ≥2	163 (84.5%)	30 (15.5%)	
DAPT <2	48 (71.6%)	19 (28.4%)	0.021

SD: Standard deviation, EF: Ejection fraction, BMI: Body mass index, WBC: White blood cells, Hb: Hemoglobin, IQR: Interquartile range, GFR: Glomerular filtration rate, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

193 (74.2%) patients with a DAPT score of 2 or higher, indicating a high risk of ischemia. The mean age was 71.25±1.30 in the DAPT <2 group, while it was 56±0.79 in the DAPT ≥2 group (p<0.001).

When patients with PRECISE-DAPT scores greater than 25 were compared to patients with PRECISE-DAPT scores of less than 25, it was found that mortality was significantly higher in the group with higher scores [odds ratio (OR): 6.94, 95% confidence interval (CI): 3.53-13.62, p<0.001)] (Table 4). When patients with a DAPT score of 2 were compared to patients with a DAPT score of less than 2, mortality was significantly higher in the group with a low DAPT score [p=0.021 or 0.465 (0.241-0.898)]. When the DAPT score was compared to deaths from cardiovascular causes, no significant effect on cardiovascular mortality was found (p=0.38).

The Morisky clinical drug compliance scale was also used to evaluate patients' drug compliance. The MORISKY drug compliance scale was evaluated in 252 out of the 260 patients, with instances of missing data observed in 8 patients. It was discovered that 101 (38.8%) of these patients were highly drug-compliant.

In our research, we also evaluated the association between sex and mortality, bleeding, and scoring. When females' and males' mortality rates were compared, no significant difference was found (p=0.053); however, females' mortality rate was found to be numerically higher (28.6% vs. 16.6%) (Table 4). While there was no significant difference between the two groups in terms of PRECISE-DAPT and DAPT scores (p=0.21 and p=0.051; respectively), females had higher PRECISE-DAPT scores (30.6% vs. 22.3% PRECISE-DAPT 25) and males had higher DAPT scores (76.8% vs. 63.3%).

The relationship between patients with and without a history of CAD and mortality was compared in our study, and mortality was observed to be significantly higher in the CAD group (OR: 2.97, 95% CI: 1.5-5.8, p=0.001). An examination of the relationship between PAD and mortality revealed that mortality was significantly higher in the group with a PAD history (OR: 6.81, 95% CI: 1.10-41.95, p=0.04). Patients with a history of CVA had significantly higher mortality than patients without a history of CVA (OR: 5.88, 95% CI: 1.51-22.78, p=0.04). When the relationship between diabetes and mortality was evaluated, mortality was discovered to be significantly higher in the DM group compared to that in the non-DM group (OR: 2.79, 95% CI: 1.47-5.29, p=0.001) (Table 5). Considering these findings, individuals aged ≥75 years face a 14.5-fold increase in mortality; a history of PAD corresponds to an 8.5-fold rise; experiencing BARC3 bleeding is associated with an 8.5-fold elevation; glomerular filtration rate <60 mL/min/1.73m^2 leads to a 5-fold surge; a history of CVA results in a 5-fold increase; and having diabetes is linked to a 3.5-fold increase.

In terms of bleeding, no significant difference was found when the group with a high PRECISE-DAPT score was compared to the group with a low score in all bleeding events (p=0.56) (Table 6). Since there was no statistically significant relationship between PRECISE-DAPT scoring and all bleeding events, the relationship between major bleeding (BARC3) and PRECISE-DAPT score was investigated. No statistically significant difference was observed between these two groups (p=0.23) (Table 6). Bleeding history, which is also one of the parameters of the PRECISE-DAPT score, along with all bleeding events that occurred,, were compared in our study. In patients with a previous history of bleeding, no significant difference was observed in all bleeding events (p=0.526) (Table 6). BARC3 bleeding events with a history of bleeding were compared in our study. No significant difference was observed in BARC3 bleeding events occurring in patients with a previous bleeding history (p=0.538). Patients with bleeding were compared to those without bleeding in terms of mortality. When the relationship between the patients with bleeding and mortality was evaluated, no significant difference was found in terms of mortality (p=0.689) (Table 4). Since all bleeding events were found to be unrelated to mortality, the relationship between major and minor bleeding and mortality was evaluated separately.

Since all bleeding events did not have a significant relationship with mortality, BARC1 bleeding (those that did not even necessitate hospitalization) was excluded, and the mortality relationship was evaluated with patients who had BARC2 or BARC3 bleeding. The presence of BARC2 or BARC3 bleeding was found to have no effect on mortality (p=0.18) (Table 5). The correlation between BARC2 bleeding and mortality was evaluated, revealing that it did not significantly affect mortality (p=1). The association with mortality was studied in patients with BARC3 bleeding, later classified as major bleeding. Mortality was found to be significantly increased in patients with BARC3 bleeding (OR: 6.16, 95% CI: 1.33-28.49, p=0.025) (Table 5).

Based on the duration of dual therapy, patients were divided into two groups in our study: those who had

Table 5. Relationship between risk factors and mortality

Subgroup		Survived (number of events/total)	Died (number of events/total)	p-value
Age	<75	193/224 (88.4%)	26/224 (11.6%)	<0.001
	≥75	13/36 (36.1%)	23/36 (63.9%)	
GFR	<60 mL/min/1.73m²	12/28 (42.9%)	16/28 (57.1%)	<0.001
	≥60 mL/min/1.73m²	199/232 (85.8%)	33/232 (14.2%)	
Hb	<11g/dL	10/24 (41.7%)	14/24 (58.3%)	0.003
	≥11g/dL	197/236 (83.5%)	39/236 (16.5%)	
History of bleeding	Yes	10/13 (76.9%)	3/14 (23.7%)	0.52
	No	201/247 (84.4%)	46/247 (16.6%)	
DM	Yes	54/78 (69.2%)	24/78 (30.8%)	0.001
	No	201/247 (84.4%)	25/182 (13.7%)	
History of CAD	Yes	37/56 (66.1%)	19/56 (33.9%)	0.001
	No	174/204 (85.3%)	30/204 (14.7%)	
History of PAD	Yes	2/5 (40%)	3/5 (60%)	0.04
	No	209/255 (82%)	46/255 (18%)	
History of CVE	Yes	4/9 (44.4%)	5/9 (55.6%)	0.04
	No	207/251(82.5%)	44/251 (17.5%)	
Repetitive ME	Yes	48/59 (81.4%)	11/59 (18.6%)	0.96
	No	163/201 (81.1%)	38/201 (18.9%)	
Ejection fraction	<%40	21/35 (60%)	14/35 (40%)	<0.001
	≥40%	187/216 (86.6%)	29/216 (13.4%)	
BARC2	Yes	11/13 (85.6%)	2/13 (15.4%)	1
	No	200/247 (81%)	47/247 (19%)	
BARC2 or BARC3	Yes	14/20 (70%)	6/20 (30%)	0.18
	No	197/240 (82.1%)	43/240 (17.9%)	
BARC3	Yes	3/7 (42.9%)	4/7 (57.1%)	0.025
	No	208/253 (82.2%)	45/253 (17.8%)	
Drug compliance	Yes (8 points)	122/151 (80.8%)	29/151 (19.2%)	0.123
	No (<8 points)	89/101 (63.4%)	12/101 (11.9%)	
DT duration	<12 months	167/198 (84.3%)	44/62 (71%)	0.019
	≥12 months	31/198 (15.7%)	18/62 (29%)	

GFR: Glomerular filtration rate, Hb: Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding Academic Research Consortium, DT: Duration of dual therapy received dual therapy for 12 months or less and those who had received 12 months or more of therapy. Patients receiving short-term (≤12 months) and long-term (>12 months) dual therapy were compared. When the short-term dual therapy group was compared to the long-term dual therapy group, mortality was found to be significantly higher in the long-term group (OR: 2.20, 95% CI: 1.12-4.30, p=0.019) (Table 7). In our study, a subgroup analysis of increased total mortality was performed after dividing the long-term dual therapy group into two groups based on causes of mortality (cardiac and non-cardiac). When deaths from cardiac and non-cardiac causes were compared between the long-term and short-term dual therapy groups, no significant difference was observed (p=0.51). In order to investigate why long-term dual therapy increased all-cause mortality, the two groups' baseline clinical characteristics and laboratory findings were compared. There were more smokers in the short-term dual therapy group compared to the other group (49.5% vs. 37.1%) (p=0.008). The history of CAD was found to be more common (18.2% vs. 32.3%) in the long-term dual therapy group (p=0.019). However, no significant difference was observed in other basal characteristics (Table 6).

Since the mortality rate in the group receiving long-term dual therapy was significantly higher, the two groups were compared in terms of PRECISE-DAPT score, but there was no significant difference among them (p=0.44)

Table 6. Comparison of patients with low and high PRECISE-DAPT scores

	PRECISE-DAPT <25 (n=198)	PRECISE-DAPT ≥25 (n=62)	p-value
Age (year)	56.52±10.86	71.63±11.31	<0.001
Female, %	17.2	24.2	0.21
HT, %	54.0	67.7	0.57
DM, %	28.3	35.5	0.28
CVE, %	3.0	4.8	0.49
CAD, %	18.2	32.3	0.019
PAD, %	1.5	3.2	0.39
Smoker, %	52.5	27.4	0.001
History of bleeding, %	1.5	16.1	<0.001
CTF	1	3.2	0.21
Creatinine, median (IQR)	0.82 (0.73-0.96)	1.10 (0.89-1.38)	<0.001
GFR, mean ± SD	102.49±24.9	72.62±30.15	<0.001
WBC, median (IQR)	10500 (8300-13350)	11450 (8800-15250)	0.10
Hb, median (IQR)	14.2 (12.9-15.1)	12.5 (10.77-14.40)	<0.001
EF, median (IQR)	50 (45-60)	50 (40-55)	0.008
BMI, median (IQR)	26.80 (24.71-29.75)	25.71 (23.18-28.85)	0.024
Morisky, median (IQR)	8 (5-8)	8 (6.75-8)	0.11
No bleeding	170 (85.9%)	55 (88.7%)	0.56
Bleeding	28 (14.1%)	7 (11.3%)	
No BARC3	194 (98.0%)	59 (95.2%)	0.56
BARC3	4 (2.0%)	3 (4.8%)	
Dual therapy ≤12 months	153 (77.3%)	45 (72.6%)	0.44
Dual therapy >12 months	45 (22.7%)	17 (27.4%)	

SD: Standard deviation, GFR: Glomerular filtration rate, Hb : Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding Academic Research Consortium, DT: Duration of dual therapy, HT: Hypertension, CTF: Common terminology criteria for adverse events, IQR: Interquartile range, BMI: Body mass index, EF: Ejection fraction, PRECISE-DAPT: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy

Table 7. Comparison of patients receiving short and long dual therapy

	DT duration ≤12 months (n=198)	DT duration >12 months (n=62)	p-value
Age (year)	59.44±12.55	62.27±13.06	0.12
Female, n (%)	35/198 (17.7)	14/62 (22.6)	0.38
HT, %	54.5	66.1	0.10
DM, %	29.3	32.3	0.65
CVE, %	3.0	4.8	0.49
CAD, %	18.2	32.3	0.019
PAD, %	1.5	3.2	0.39
Smoker, %	49.5	37.1	0.008
History of bleeding, %	4.5	6.5	0.54
CTF	1	3.2	0.21
Creatinine, median (IQR)	0.86 (0.75-1.03)	0.86 (0.73-1.06)	0.82
GFR, mean ± SD	96.50±29.51	91.76±27.80	0.26
WBC, median (IQR)	10750 (8500-14125)	10300 (7975-12800)	0.072
Hb, median (IQR)	14.1 (12.67-15.1)	13.6 (12.0-14.55)	0.06
EF, median (IQR)	50 (40-50)	50 (45-60)	0.72
BMI, median (IQR)	26.80 (24.71-29.75)	25.71 (23.18-28.85)	0.25
Morisky	8 (5-8)	8 (6-8)	0.44
No bleeding	180 (90.9%)	45 (72.6%)	<0.001
Bleeding	18 (9.1%)	17 (27.4%)	
No BARC3	195 (77.1%)	58 (22.9%)	0.056
BARC3	3 (42.9%)	4 (57.1%)	

GFR : Glomerular filtration rate, Hb: Hemoglobin, DM: Diabetes mellitus, CAD: Coronary artery disease, PAD: Peripheral artery disease, CVE: Cerebrovascular event, BARC: Bleeding academic research consortium, DT: Duration of dual therapy, HT: Hypertension, CTF: Common terminology criteria for adverse events, IQR: Interquartile range, EF: Ejection fraction, BARC: Bleeding academic research consortium

(Table 6). Following that, the group that received long-term dual therapy was divided into two groups (12-36 months and >36 months). These two groups were compared, and no significant difference was observed between them (p=0.055). In fact, mortality was found to be numerically higher in the 12-36 month group (39.4% vs. 17.2%).

In our study, long-term and short-term dual therapies were compared in terms of bleeding occurrence. Bleeding episodes were found to be significantly higher in the long-term use group (OR: 3.77, 95% CI: 1.80-7.9, p<0.001). After it was discovered that long-term dual therapy increased bleeding significantly, the two groups were compared to investigate the effect of long-term dual therapy on major bleeding. Although the number of BARC3 bleedings was higher in the group receiving long-term dual therapy, it did not reach statistical significance (OR: 4.48; 95% CI: 0.975-20.607, p=0.056) (Table 7).

Discussion

The positive effects of clopidogrel administration in addition to aspirin therapy in patients with stent placement and a diagnosis of ACS in the CURE study have brought DAPT to the literature(9). Aside from aspirin therapy, different molecules have been developed and tested in the process of DAPT. Ticagrelor was compared to clopidogrel in dual therapy in the Platelet Inhibition and Patient Outcomes study, and it was found that it reduced death, MI, and stroke without increasing major bleeding(10). It was found in another study that it reduced ischemic events without increasing major bleeding in patients who were started on prasugrel alongside aspirin(11).

Today, clopidogrel, ticagrelor, and prasugrel are initiated in addition to aspirin in DAPT. Although the guidelines strongly recommend starting dual therapy, it is unclear how long it should be used. In studies testing DAPT, different results were observed as a result of developing stent technologies and newly released molecules in terms of the balance between bleeding and ischemia. The researchers developed scoring systems to determine the duration of dual treatment, considering that the patient-based approach will be more effective than general recommendations. The DAPT score evaluates ischemic events that may develop during dual therapy. In this scoring, it is recommended that dual therapy be given for longer than 12 months in patients with a DAPT score of ≥2 to prevent ischemic events[4]. In the study of Costa et al.[5], it was predicted that bleeding events would increase with the lengthening of the dual therapy period, and the PRECISE-DAPT score, which calculates bleeding risk, was developed in this regard. According to this scoring system, which considers factors such as age, creatinine clearance, hemoglobin, white blood cell count, and previous bleeding, patients with a score of 25 or higher have a high risk of bleeding with no significant benefit in terms of ischemia. These scoring systems were subsequently tested in numerous studies. Wester et al.[12] discovered that the PRECISE-DAPT score predicted moderate major bleeding in patients who underwent PCI after MI in their study. The predictive capacity of the score was deemed ineffective, in anticipating major bleeding in individuals with low scores, as this was influenced by factors such as advanced age, low body weight, anemia, and cancer. Similarly, Dannenberg et al.[13] found the PRECISE-DAPT score to be moderately sensitive in predicting bleeding in an analysis of 994 patients who underwent PCI. When all bleeding events were evaluated in our study, no significant difference was observed between patients with high and low PRECISE-DAPT scores (p=0.56). In terms of major bleeding (BARC3), the results were comparable, with no statistically significant difference (p=0.23) observed. The intense use of PPI in our study, the exclusion of patients who underwent CABG and medical treatment, and the fact that there were fewer and more isolated patients all point to the score having an effect on the success of predicting bleeding. When other studies were combined, it was discovered that the score was affected by variable conditions and was not always effective in predicting bleeding risk.

Mortality independent of bleeding was observed to be significantly higher in patients with PRECISE-DAPT ≥25 compared to those with PRECISE-DAPT <25; the group with high scores showed significantly higher mortality (p<0.001). This significant difference indicates that patients who are at high risk of bleeding are also at high risk of mortality. Many studies have shown that mortality increases independently in patients with bleeding events[14,15]. This suggests that the PRECISE-DAPT score is a successful scoring system in selecting high-risk patients. The increase in mortality, independent of bleeding, in our study indicates that patients with high scores are at high risk. Furthermore, in 2019, the Academic Research Consortium published a consensus report on the definition of high bleeding risk in PCI patients[16]. According to this publication, none of the scores, including the PRECISE-DAPT score, are accurate enough to predict bleeding or identify patients at high risk of bleeding. A more reliable scoring system for predicting bleeding in dual therapy should be developed.

The DAPT score is another score that can be used to evaluate mortality during dual therapy. Kwok et al.[17] investigated the relationship between DAPT score and mortality in their study. In this study, which included 243440 patients, who underwent PCI were divided into two groups: those with DAPT scores of 2 and above and those with DAPT scores below 2, and 1- and 3-year mortality rates were compared. It was found that the 1-year and 3-year mortality rates were statistically significantly lower in patients with a DAPT score of ≥2 compared to patients with a DAPT score of <2.17 similarly, in our study, patients with higher DAPT scores had lower mortality (lower DAPT score, higher mortality).

The number of studies in which PRECISE-DAPT and DAPT scores were evaluated concurrently during dual therapy in PCI patients is limited. Boudreau et al.[18] designed a study in which PRECISE-DAPT and DAPT scores were analyzed together. In this study, we aimed to evaluate how well PRECISE-DAPT (predicting bleeding complications in patients receiving stent placement followed by double antiplatelet therapy) and DAPT scores agreed on treatment recommendations and how well they predicted ischemic and bleeding complications. Patients receiving 12 months of dual therapy were divided into two groups based on their PRECISE-DAPT score: extended (>25) and shortened (≤25), and similarly, based on their DAPT score: extended (>2) and shortened (≤2). The PRECISE-DAPT and DAPT score recommendations were found to be compatible in 56.7% of the patients after 1 year. No difference was observed in composite major adverse cardiovascular and cerebrovascular events between patients with high or low PRECISE-DAPT or DAPT scores. Patients with high PRECISE-DAPT scores had a significantly higher 1-year increase in all-cause mortality rate and bleeding events than those with low scores. No difference was found in mortality or bleeding rates between patients with high DAPT scores and those with low DAPT scores. According to the study results, PRECISE-DAPT and DAPT scores frequently result in inconsistent DAPT duration recommendations[18]. Similarly, in our study, patients were divided into four groups based on their scores (PRECISE-DAPT 25 and DAPT 2). Using the Kaplan-Meier survival analysis method, these groups were compared in terms of mortality, and patients with a high PRECISE-DAPT score were found to have a higher mortality independent of other factors (p<0.001).

Prolonged use of dual therapy may result in fewer ischemic events but more bleeding events[4,19]. It is recommended to extend and personalize dual therapy based on the individual characteristics of the patient and the stent procedure, due to the risk of bleeding. Prolonging dual therapy reduces ischemic outcomes significantly; however, it increases major bleeding significantly[4,19]. Therefore, when deciding on the duration of dual therapy, evaluating the risk of ischemia and bleeding and tailoring the treatment to the individual are recommended. Many studies and meta-analyses have been conducted to date comparing the short-term dual therapy regimen to the long-term dual therapy regimen[20,21]. According to the results of these studies and meta-analyses, short dual therapy was not inferior to standard or extended dual therapy, and the regimen of short dual therapy resulted in less bleeding[21].

Study Limitations

Taking into account the constraints of these investigations the limitations include an inadequate number of patients, events occurring infrequently compared to the anticipated frequency of events, and the exclusion of many patients (such as those with ACS), leading to the incorporation of low-risk patient populations. In comparison to these investigations, the DAPT study involved 11,648 patients to compare extended dual therapy with standard therapy, and it was discovered that the group that continued thienopyridine treatment for more than 1 year had a 53% reduction in MI and a 71% relative risk reduction in stent thrombosis. However, despite this benefit, it was observed that all-cause mortality increased significantly in the extended dual treatment group (p=0.05)[4]. In our study, patients who received short-term (≤12 months) and long-term (>12 months) dual therapy were compared in terms of mortality and bleeding events. In the DAPT study, deaths were found to be significantly higher in the long-term dual therapy group compared to the short-term dual therapy group (p=0.019).

In our study, due to the high mortality rates in the long dual therapy group, the groups were evaluated in terms of bleeding risk, using the PRECISE-DAPT score. In terms of PRECISE-DAPT score, there was no significant difference between the two groups (PRECISE-DAPT <25 vs. ≥25) (p=0.44). When we compared the baseline demographic characteristics of long-term dual therapy and short-term therapy, we found that a higher history of

CAD was observed in the long-term dual therapy group (p=0.019), with no other significant differences.

The literature contains contradictory results regarding the use of long-term DAPT and mortality. The DAPT study's results revealed that patients receiving long-term dual therapy had high all-cause mortality rates. In a subgroup analysis of deaths in the DAPT study, it was discovered that death from non-cardiovascular causes in the long-term dual group was responsible for this difference[22]. When non-cardiovascular causes were investigated, the results of the subgroup analysis revealed that these deaths were not caused by bleeding. This difference has been explained by cancer-related deaths. It has been stated that this may have happened by chance. More studies are needed to better understand the relationship between extended dual therapy and mortality.

Bleeding rates were found to be significantly higher in the group receiving long dual therapy (OR: 3.77, 95% CI: 1.80-7.90, p<0.001). After it was discovered that long-term dual therapy increased bleeding events significantly, the two groups were compared to investigate the effect on major bleeding. Although the number of BARC3 bleedings was higher in the group receiving long-term dual therapy, it did not reach statistical significance (OR: 4.48, 95% CI: 0.975-20.607, p=0.056). Many studies in the literature support the idea that the prolonged dual therapy regimen is associated with an elevated risk of bleeding[4]. The insignificant relationship between long-term dual therapy and major bleeding in our study could be attributed to the small number of patients who experienced major bleeding.

Conclusion

In our study, we found that the PRECISE-DAPT and DAPT scores, which are scoring systems that calculate the ischemia-bleeding balance to determine the duration of DAPT, did not have a significant relationship with the bleeding events that occurred. Additionally, the mortality of the patient group with a high PRECISE-DAPT score was higher, regardless of the DAPT score. PRECISE-DAPT score was found to be a predictor of mortality independently of DAPT score.

Ethics

Ethics Committee Approval: Approval was obtained from the Dokuz Eylül University Non-interventional Research Ethics Committee (approval no.: 2019/04-23, date: 20.02.2019).

Informed Consent: The records of the patients were retrospectively examined through the hospital information system and archival records.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N, Concept: Alak Ç, Özpelit E, Çırgamış D, Design: Alak Ç, Data Collection and/or Processing: Alak Ç, Analysis and/or Interpretation: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N, Literature Search: Alak Ç, Writing: Alak Ç, Özpelit E, Çırgamış D, Abusharekh M, Barış N.

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The Predictive Value of Inflammatory Indices in Complications Following Lead Extraction: A Retrospective Analysis

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Abstract

Objectives: Lead extraction is a critical procedure for managing complications in patients with cardiovascular implantable electronic devices. The potential predictive value of inflammatory indices, such as the systemic immune-inflammation index (SII), pan-immune-inflammation value (PIV), and prognostic nutritional index (PNI), in determining procedural outcomes remains unclear. This study aimed to evaluate the relationship between complications following lead extraction and inflammatory indices in patients undergoing the procedure, with a particular focus on those treated for infectious versus non-infectious causes.

Materials and Methods: This retrospective, single-center study analyzed patients who underwent lead extraction between 2019 and 2020. Complications, including hematoma, pericardial effusion, and sudden cardiac death, were assessed. Multivariate logistic regression identified predictors of adverse outcomes, and ROC curve analysis evaluated the predictive value of SII, PIV, and PNI.

Results: Among the 234 patients included (mean age 62, 81% male), complications occurred in 25.6% (n=60), with mortality recorded in 3.8%. Hematoma and pericardial effusion were observed in 12% and 14.5% of patients, respectively. ROC analysis revealed no significant association between the inflammatory indices (SII, PIV, PNI) and complications. Multivariate logistic regression identified diabetes mellitus (DM) as a significant independent predictor of complications ($p<0.05$). No differences in outcomes were noted between infectious and non-infectious lead extraction subgroups.

Conclusion: While inflammatory indices showed limited predictive utility, DM emerged as a critical risk factor for complications following lead extraction. Comprehensive preprocedural risk stratification, with attention to metabolic

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conditions such as diabetes, is essential to improving procedural outcomes. Further studies are needed to refine predictive models incorporating both systemic and procedure-specific variables.

Keywords: Antiarrhythmics, cardiology, heart, heart failure

Introduction

Cardiovascular implantable electronic devices (CIEDs) such as pacemakers, implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices play crucial roles in the management of various cardiac conditions. These devices form a vital component of contemporary therapeutic strategies addressing arrhythmias, heart failure (HF), and conduction disorders to improve survival and quality of life among affected patients(1). Previous studies have shown that using CIEDs is associated with improved survival, reduced hospitalisation and improved quality of life in patients with various heart conditions(2). The expanded utilization of CIEDs has inevitably led to an increase in the incidence of complications(3). Challenges such as electrode malfunction, infection, and inappropriate shocks remain for patients with CIEDs. Ongoing advancements in device technology are targeted at mitigating these challenges, thereby enhancing patient outcomes(4).

The relationship between inflammatory conditions and CIEDs is clinically significant, as the presence of inflammation can affect both device performance and patient outcomes(5). Inflammatory conditions, such as systemic autoimmune diseases or localized infections, can lead to complications such as device-related infections or increased thromboembolic risk(5,6). In particular, patients with conditions such as rheumatoid arthritis or vasculitis may experience an exaggerated immune response to foreign devices, such as pacemakers or ICDs. This immune reaction can manifest as fibrosis or granuloma formation around the device leads, which may impair the functionality of the device, lead to increased resistance in electrical conduction, or necessitate device replacement(7). These risks highlight the need for careful management of inflammatory conditions in patients using intracardiac devices, with close monitoring for signs of infection and potential device malfunction. Monitoring inflammatory indexes in patients with signs of device erosion or lead exposure is crucial for early detection and management, which often necessitates prompt lead extraction, antibiotic therapy, or device revision to prevent severe complications. Understanding the role of inflammation in lead extraction can help guide clinical decision-making and improve patient outcomes through timely intervention. Lead extraction has become increasingly significant in the follow-up of CIED patients. Although technical facilities have reduced the risk of complications during lead extraction, the success of the procedure is still significantly affected by individual comorbidities(8). In this study, patients who developed complications following lead extraction were analyzed to evaluate the relationship between these complications and inflammatory indices that have gained prominence in the cardiovascular field in recent years.

Materials and Methods

This was a single-center, retrospective study conducted in our hospital between 2019 and 2020. Data from all the patients who underwent lead extraction for any reason were retrospectively reviewed. Cardiac rupture during the procedure, sudden cardiac death, postprocedural hematoma, and pericardial effusion were defined as cardiac complications. The baseline demographic and laboratory values of patients with and without complications were compared. Patients who developed mechanical complications during intracardiac device implantation, those with malignancy, those on oral anticoagulant therapy, and those with a history of pericardial effusion were excluded from the study.

The predictive value of the inflammatory indices was evaluated in patients who underwent lead extraction due to infection, and in those who underwent the procedure for non-infectious reasons. To account for potential fluctuations in inflammatory status, preoperative blood samples drawn within 24 hours prior to the procedure were used to calculate the inflammatory indices. Manual extraction, which included traction with locking stylets or standard instruments without additional mechanical support, was preferred for recently implanted leads (<1 year). However, detailed procedural variables, such as lead dwell time, lead type, extraction technique, and operator expertise, were not available, which may constrain the interpretation of results.

The systemic immune-inflammation index (SII) was determined using the formula, platelet count × neutrophil-to-lymphocyte ratio × 10^9/L[9]. The prognostic nutritional index (PNI) was calculated as 10 × serum albumin value (g/dL) + 0.005 × peripheral lymphocyte count (per mm^3)[10]. The pan-immune-inflammation value (PIV) was calculated using the formula: neutrophil count (10^9/L) × platelet count (10^9/L) × monocyte count (10^9/L) / lymphocyte count (10^9/L)[11].

Cardiac rupture was defined as rupture of the tricuspid valve, right atrium, or right ventricle, identified during or immediately after lead extraction. Sudden cardiac death was defined as a rapid, unforeseen fatal event of cardiovascular origin, occurring with a loss of consciousness within one hour after the onset of symptoms. Hematoma was defined as a localized area of bleeding that developed post-procedure at the site of lead extraction. Pericardial effusion was defined as the accumulation of fluid in the pericardial space following lead extraction, in patients without a history of pericardial effusion.

This study was approved by the Scientific and Ethical Review Board for Medical Research No. 1 (TABED) under the chairmanship of the Ethics Committee (approval no.: 1-24-11, date: 14.02.2024).

Statistical Analysis

All data analyses were conducted using the IBM SPSS Statistics software. The study population was divided into two groups: those with complications and those without. The Kolmogorov-Smirnov test was employed to assess the normality of the distribution. Variables with a normal distribution were reported as mean ± standard deviation, while variables with a non-normal distribution were presented as median with interquartile range. Categorical variables were expressed as frequencies and percentages. For all patients who underwent lead extraction, the predictive value of complications in relation to the SII, the PIV, and PNI was analyzed using ROC curve analysis. Additionally, for patients who underwent lead extraction solely due to infection, the predictive value of the SII, PIV PNI were assessed using ROC curve analysis. Multivariate logistic regression analysis was performed to assess the independent predictors of complication development following lead extraction.

Results

The mean age of the study population was 62 years, with a percentage of males of 81%. The mean left ventricular ejection fraction was 32%. More patients were classified as New York Heart Association functional capacity II. The prevalence of diabetes mellitus (DM) was significantly higher in the group with complications (p=0.011). No significant differences in hypertension, chronic kidney disease, or HF were observed between the groups. Additionally, there were no differences in the rates of ICD, CRT, or pacemaker implantation (Table 1). Lead extraction was performed in 190 patients due to infection, and in 44 patients for non-infectious indications. The total incidence rate of adverse events was 25.6%, affecting 60 patients. Mortality was recorded in 3.8% of patients (a total of 9 patients). No cases of cardiac rupture have been reported. Hematoma occurred in 12% of the patients (29 patients), while pericardial effusion was observed in 14.5% (34 patients) (Table 2).

Table 3 presents the laboratory values of the study population. There were no significant differences between the groups in terms of laboratory values and inflammatory indices.

Table 1. Baseline demographic and clinical characteristics of the study population

Characteristic	Total (n=234)	No complication (n=174)	Complication (n=60)	p-value
Age (years)	62±14	62±14	63±12	0.904
Male, n (%)	190 (81.2)	145 (83.3)	45 (75.0)	0.180
LVEF (%), Mean ± SD	32±20	31±14	32±19	0.615
LVEDD (mm), Mean ± SD	57±11	58±11	57±13	0.325
NYHA FC (%)				0.281
Class I	81 (34.6)	65 (37.4)	16 (26.7)	
Class I-II	6 (2.6)	5 (2.9)	1 (1.7)	
Class II	124 (53.0)	85 (48.9)	39 (65.0)	
Class II-III	9 (3.8)	7 (4.0)	2 (3.3)	
Class III	14 (6.0)	12 (6.9)	2 (3.3)	
DM, n (%)	115 (49.1)	77 (44.3)	38 (63.3)	0.011 (*)
HT, n (%)	172 (73.5)	126 (72.4)	46 (76.7)	0.612
CKD, n (%)	71 (30.3)	55 (31.6)	16 (26.7)	0.518
HF, n (%)	179 (76.5)	133 (76.4)	46 (76.7)	0.562
ICD, n (%)	138 (59.0)	103 (59.2)	35 (58.3)	0.512
CRT, (%)	69 (29.5)	52 (29.9)	17 (28.3)	0.871
PM, n (%)	28 (12.0)	20 (11.5)	8 (13.3)	0.818

**P-values less than 0.05 were considered statistically significant, indicating a meaningful difference between the complication and non-complication groups. LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end-diastolic diameter, NYHA FC: New York Heart Association Functional Classification, DM: Diabetes mellitus, HT: Hypertension, CKD: Chronic kidney disease, HF: Heart failure, ICD: Implantable cardioverter-defibrillator, CRT: Cardiac resynchronization therapy, PM: Pacemaker, SD: Standard deviation*

Table 2. Indications, adverse events, and outcomes in patients undergoing lead extraction

Before extraction	
Primary prevention of SCD	180 (76.9)
Secondary prevention of SCD	26 (11.1)
ICMP	123 (52.6)
DCMP	73 (31.2)
HCMP	6 (2.6)
Infection	190 (81.2)
Non-infection	44 (18.8)
After extraction	
Total adverse event	60 (25.6)
Death	9 (3.8)
Cardiac rupture	0
Hematoma	29 (12)
Pericardial eff	34 (14.5)

SCD: Sudden cardiac death, ICMP: Ischemic cardiomyopathy, DCMP: Dilated cardiomyopathy, HCMP: Hypertrophic cardiomyopathy

In Figure 1, ROC analysis of the entire cohort did not identify a significant cut-off value for predicting complications based on the SII, the PIV, or PNI. Evaluation of the group that underwent lead extraction due to infection did not reveal a significant cut-off value for predicting complications based on the SII, the PIV, or PNI (Figure 2). Figure 3 shows that the scatter plots did not exhibit statistically significant associations. As shown in Table 4, a multivariate logistic regression analysis was conducted to evaluate the clinical parameters predicting complications following lead extraction. Among these parameters, DM has emerged as a significant independent predictor of postprocedural complications.

Table 3. Comparison of laboratory parameters between patients with and without complications

Parameter	Total (mean ± SD)	No complication (n=174)	Complication (n=60)	p-value
Glucose (mg/dL)	149.8±88.4	144.0±71.8	151.8±93.6	0.898
Creatinine (mg/dL)	1.2±1.0	1.2±1.1	1.1±0.6	0.237
Total protein (g/dL)	67.3±6.6	67.2±6.8	67.5±6.1	0.972
Albumin (g/dL)	40.8±5.4	41.3±4.6	39.0±6.9	0.079
Triglycerides (mg/dL)	183.2±111.9	185.2±115.8	177.4±100.4	0.926
Total cholesterol (mg/dL)	159.5±37.5	159.3±38.0	160.0±36.5	0.837
LDL (mg/dL)	90.4±28.9	89.5±29.1	93.0±28.5	0.352
HDL (mg/dL)	35.9±10.4	35.7±10.4	36.4±10.6	0.605
Hemoglobin (g/dL)	13.3±1.9	13.3±1.9	13.1±2.0	0.780
Neutrophils (/μL)	5691.1±2936.2	5836.2±3183.2	5272.8±2030.1	0.286
Lymphocytes (/μL)	1871.0±680.5	1875.5±700.2	1858.0±625.5	0.826
Platelets (10³/μL)	252.2±194.8	245.4±177.8	271.5±237.9	0.661
WBC (10³/μL)	8436.2±3302.8	8576.6±3565.6	8031.3±2367.7	0.452
CRP (mg/L)	16.7±33.9	18.5±36.5	11.6 ±24.6	0.283
Monocytes (/μL)	532.6±209.1	539.9±214.4	511.3± 192.9	0.406
PNI	50.9±9.9	51.2±8.7	50.2±12.2	0.069
SII	955.8±624.3	965.9±665.1	926.6±596.7	0.811
PIV	509.5±391.0	926.6±596.7	521.8±400.4	0.623

LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, WBC: White blood cell, CRP: *C-reactive protein, PNI: Prognostic nutritional index, SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value*

Table 4. Multivariate logistic regression analysis identifying predictors of postprocedural complications following lead extraction

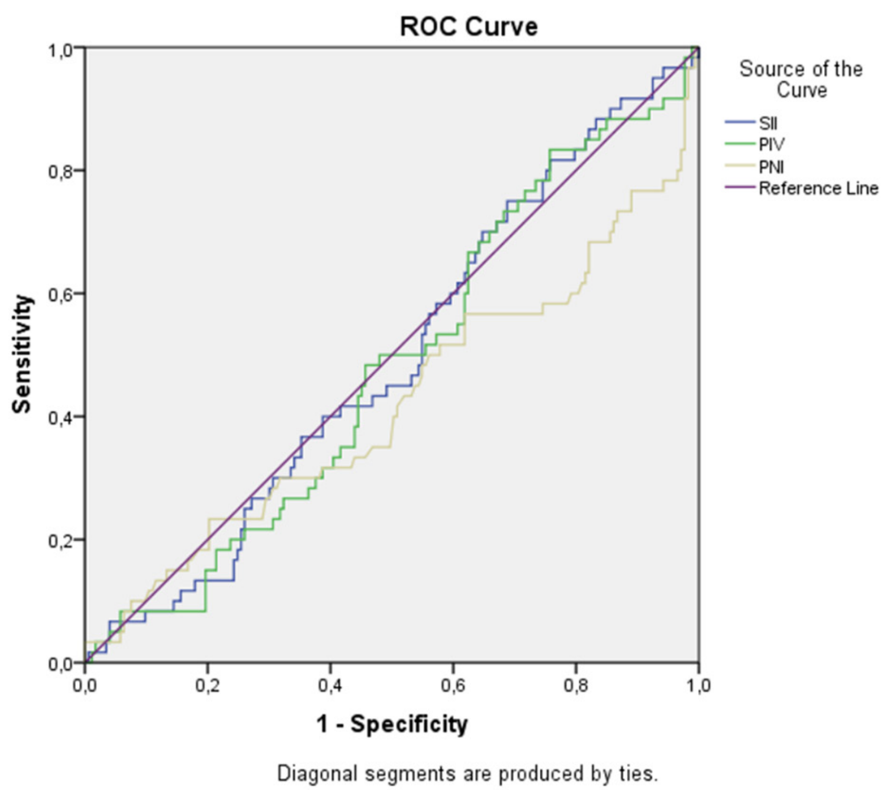
Variable	Odds ratio	95% Confidence interval for exp. (B)	p-value
Age	1.000	0.976-1.024	0.989
Male	0.649	0.307-1.372	0.258
LVEF	1.007	0.985-1.031	0.522
DM	2.396	1.235-4.647	0.010
HT	1.078	0.489-2.377	0.853
CKD	0.661	0.324-1.349	0.256

LVEF: Left ventricular ejection fraction, DM: Diabetes mellitus, HT: Hypertension, CKD: Chronic kidney disease

Discussion

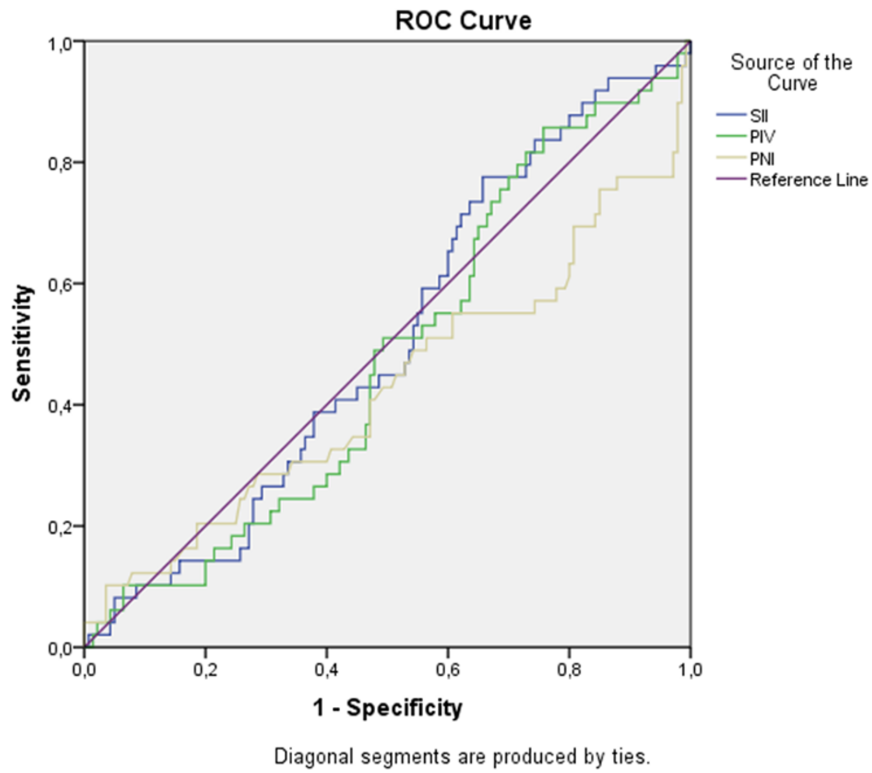
In this study, we evaluated a population of patients who underwent lead extraction and divided them into two groups based on the presence or absence of complications: complicated and uncomplicated groups. Our analysis aimed to investigate the significance of demographic parameters and inflammatory markers in predicting the development of complications after the procedure. Interestingly, no significant association was identified between the inflammatory markers and the occurrence of complications.

Inflammatory markers, including indices such as the SII, the PIV, and PNI, have been widely studied in cardiovascular research for their potential role as predictors of adverse events[12-15]. The SII, derived from platelet, neutrophil, and lymphocyte counts, has been proposed as a robust indicator of the balance between proinflammatory and anti-inflammatory processes. Elevated SII levels have been associated with worse outcomes in various cardiovascular conditions, such as HF and coronary artery disease, owing to their implication in thrombogenesis and immune dysregulation[16,17].



Test Variable	Area	Asymptotic Significance (p-value)	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)
SII	492	855	410	574
PIV	479	623	396	561
PNI	419	63	328	510
SII: Systemic Immune-Inflammation Index, PIV: Pan-Immune-Inflammation Value , PNI: Prognostic Nutritional Index,				

Figure 1. ROC curve analysis of systemic immune-inflammation index, pan-immune-inflammation value, and prognostic nutritional index for predicting post-procedural complications
SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value, PNI: Prognostic nutritional index



Test Variable	Area	Asymptotic Significance (p-value)	95% Confidence Interval (Lower Bound)	95% Confidence Interval (Upper Bound)
SII	503	942	414	593
PIV	477	636	387	568
PNI	426	125	325	528
SII: Systemic Immune-Inflammation Index, PIV: Pan-Immune-Inflammation Value , PNI: Prognostic Nutritional Index,				

Figure 2. ROC curve analysis of systemic immune-inflammation index pan-immune-inflammation value, and prognostic nutritional index for predicting complications in patients undergoing lead extraction
SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value, PNI: Prognostic nutritional index

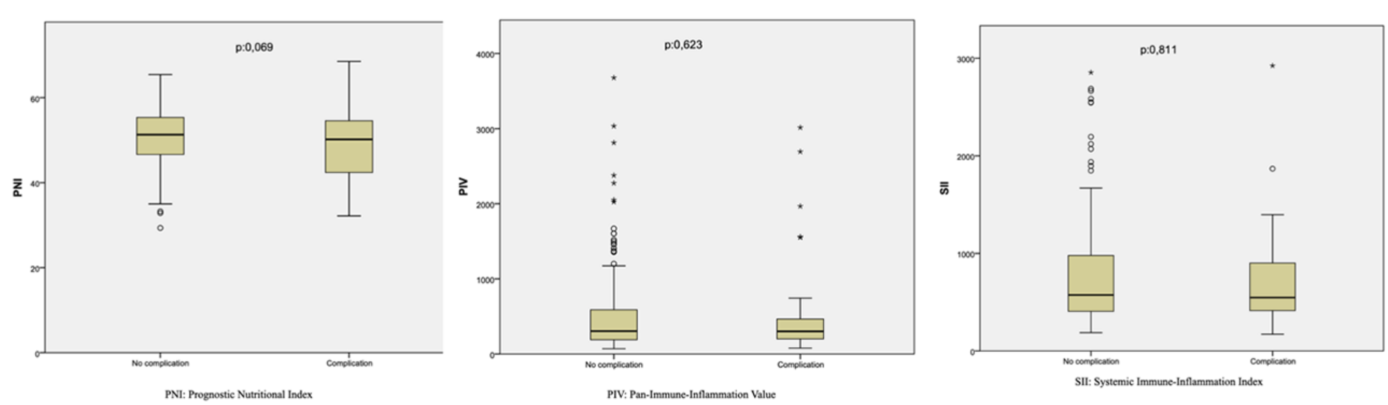


Figure 3. Boxplots comparing systemic immune-inflammation index, pan-immune-inflammation value, and prognostic nutritional index between patients with and without complications
SII: Systemic immune-inflammation index, PIV: Pan-immune-inflammation value, PNI: Prognostic nutritional index

Although there is substantial evidence supporting the role of inflammation in predicting adverse outcomes in cardiovascular conditions, most studies have focused on generalized inflammatory markers rather than establishing a specific association between the SII and complications in patients with intracardiac devices. Lead extraction, a critical procedure performed to address infections or lead malfunctions, is associated with significant risks including vascular injury, cardiac rupture, and systemic complications. Elevated levels of the SII have been linked to increased long-term mortality, which is potentially attributable to the underlying pro-inflammatory and pro-thrombotic states that these patients often exhibit(18). Oliveira et al.(19) identified predictors of mortality in patients with cardiac device-related infective endocarditis, emphasizing the role of systemic inflammation in patient outcomes. Lead extraction, a necessary procedure in cases of infection or lead malfunction, carries inherent risks including vascular injury, cardiac rupture, and systemic complications. To our knowledge, the prognostic value of the SII in predicting procedural outcomes in patients with ICED has not been investigated previously. Similarly, the PIV is a marker of inflammation and thrombosis. Higher PIV values are thought to signify a heightened inflammatory state and predisposition to adverse events, such as vascular complications and impaired tissue healing(20). Several studies have explored the relationship between PIV and the prognosis of patients with CIEDs, with a focus on its predictive value for complications, such as device-related infections, endocarditis, and long-term mortality. Elevated PIV levels have been associated with poorer outcomes in terms of infection rates, reflecting the inflammatory and immune response activation that could predispose patients to infections or delayed recovery post-procedure(21). In a cohort of patients with pacemakers and defibrillators, high PIV values correlated with an increased risk of pocket infections, a common complication following device implantation(21). Moreover, the role of PIV in predicting long-term mortality in patients treated with CIEDs has been highlighted in several retrospective analyses. Studies suggest that a higher PIV is a reflection of a systemic inflammatory state that may contribute to cardiovascular deterioration, possibly through mechanisms like endothelial dysfunction, atherosclerosis, and pro-thrombotic tendencies(22). Habib et al.(23) further highlighted predictors of mortality in patients with CIED infections, supporting the association between inflammation and adverse outcomes. On the other hand, the PNI, which incorporates serum albumin levels and lymphocyte counts, provides insight into the patient's nutritional and immunological status. Lower PNI values have been linked to poor outcomes, including increased susceptibility to infection and delayed recovery following invasive procedures(24). Despite their increasing relevance in cardiovascular research, these markers showed no significant association with complications in the current study. This lack of association suggests that the inflammatory burden captured by these indices is insufficient for predicting procedural complications in the context of lead extraction**.** Inflammatory indices, such as the SII, PIV, and PNI, did not predict complications in patients undergoing lead extraction, which may stem from several factors. First, these indices are composite markers that capture systemic inflammatory and nutritional status but may not adequately reflect localized or procedure-specific inflammatory processes. Lead extraction procedures involve mechanical disruption within the vascular and cardiac environments, potentially triggering localized inflammatory or thrombotic responses that are not directly proportional to systemic inflammatory levels. Technical and procedural factors during lead extraction can independently influence complication rates, overshadowing the impact of systemic inflammatory markers. The complexity of lead characteristics, operator experience, and procedural techniques might play pivotal roles in determining outcomes, rendering systemic inflammation indices less predictive. A recent study investigated predictors of percutaneous lead extraction complications, reinforcing the importance of procedural and technical factors in determining patient outcomes(25). We identified DM as a significant independent predictor of complication development, a finding that aligns with its well-established role in worsening cardiovascular disease outcomes. Diabetes is a multifactorial condition that affects cardiovascular health through a range of mechanisms, including chronic hyperglycaemia, systemic inflammation, and oxidative stress[26]. These processes contribute to endothelial dysfunction, reduced nitric oxide bioavailability, and prothrombotic states, all of which exacerbate cardiovascular morbidity and mortality[26,27]. Furthermore, diabetes impairs wound healing due to alterations in collagen synthesis, diminished angiogenesis, and persistent low-grade inflammation. These factors collectively increase the risk of adverse outcomes following both medical and surgical interventions in diabetic patients[26]. In our study, the chronic systemic effects of diabetes, such as microvascular and macrovascular complications, appeared to play a critical role in the development of procedural complications. Impaired microvascular circulation, coupled with a heightened inflammatory state, may predispose patients with diabetes to localized tissue injury, delayed healing, and increased susceptibility to infection, thereby elevating the risk of both immediate and long-term complications. This finding is particularly relevant to our study's primary hypothesis, which aimed to evaluate the predictors of adverse outcomes following lead extraction. Additionally, our results suggest that diabetes should be carefully considered a critical risk factor during the preprocedural assessment of patients undergoing lead extraction. The identification of diabetes as a significant predictor underscores the importance of individualized risk stratification and highlights the need for meticulous perioperative management in patients with diabetes. Moreover, the long-term consequences of lead extraction, particularly in high-risk populations, such as those with diabetes, warrant further investigation to develop targeted strategies to optimize patient outcomes and minimize procedural risks. Carlini et al.[28] investigated predictors of cardiac implantable electronic device infections and readmissions, providing further evidence on the clinical significance of diabetes in post-procedural complications.

Study Limitations

This study has several limitations. Primarily, it is a single-center retrospective analysis, which inherently restricts the generalizability of the findings. Furthermore, the relatively small sample size limits the statistical power and may impact the robustness of the conclusions drawn. The timing of biomarker assessment is critical. The indices were likely measured preoperatively and thus may not account for the acute inflammatory surge or other physiological changes occurring during or immediately after the procedure. Monitoring the real-time inflammatory responses perioperatively may provide better predictive insights.

Future research should focus on refining the utility of these biomarkers by incorporating real-time inflammatory data, exploring localized inflammatory markers, and integrating procedural variables to develop comprehensive predictive models tailored to the context of lead extraction.

Conclusion

Our findings emphasize the importance of a thorough preprocedural risk assessment, particularly in patients with diabetes, to optimize outcomes. Future studies with larger sample sizes and prospective designs may help to further elucidate the interplay between systemic inflammation, metabolic conditions, and procedural complications, ultimately contributing to the development of targeted strategies to improve patient safety in lead extraction procedures.

Ethics

Ethics Committee Approval: This study was approved by the Scientific and Ethical Review Board for Medical Research No. 1 (TABED) under the chairmanship of the Ethics Committee (approval no.: 1-24-11, date: 14.02.2024).

Informed Consent: This was a single-center, retrospective study conducted in our hospital between 2019 and 2020.

Authorship Contributions

Surgical and Medical Practices: Çakmak Karaaslan Ö, Güray Ü, Concept: Çakmak Karaaslan Ö, Özilhan MO, Güray Ü, Design: Çakmak Karaaslan Ö, Güray Ü, Data Collection and/or Processing: Çakmak Karaaslan Ö, Girgin Dirliktutan G, Kaplan Z, Analysis and or Interpretation: Çakmak Karaaslan Ö, Güray Ü, Literature Search: Çakmak Karaaslan Ö, Girgin Dirliktutan G, Kaplan Z, Özilhan MO, Güray Ü, Writing: Çakmak Karaaslan Ö, Güray Ü.

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Case Report

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Surgical Treatment of Asymptomatic Left Ventricular Pseudoaneurysm Which Occurred After A Long Period from Cardiac Surgery: Case Report

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Abstract

Left ventricular pseudo-aneurysms are rare clinical conditions that can have serious consequences if left untreated. Pseudo-aneurysms differ from true aneurysms, in that they do not contain endocardium or myocardial tissue, but only pericardium and fibrous elements. Pseudo-aneurysms often develop secondary to myocardial infarction, but can also be seen after cardiac surgery, infective endocarditis, and trauma. In this study, a case of an asymptomatic left ventricular pseudo-aneurysm that was noticed incidentally after a long period of cardiac surgery and showed rapid growth within a year was presented. Due to limited experience in left ventricular pseudo-aneurysm surgery, we wanted to share the successful surgical treatment, echocardiography, and radiological images of the case.

Keywords: Left ventricular pseudo-aneurysm, cardiac surgery, ventriculoplasty

Introduction

Left ventricular pseudoaneurysms (LVP) are rare clinical conditions that can have serious consequences due to the high risk of rupture. Pseudoaneurysms differ from true aneurysms in that they do not contain endothelium or myocardial tissue, but only pericardium and fibrous elements. LVP often develops as a result of myocardial infarction (MI), but can also occur after cardiac surgery,

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infective endocarditis, and trauma[1]. It can be clinically silent, but it can also result in hemopericardium, subsequent cardiac tamponade, and sudden death. While ventricular aneurysms are seen in 22% after MI, pseudoaneurysms have been reported to be less than 0.5%[2,3]. LVP can progress with a very high mortality rate (23-50%) in cases that are treated surgically, particularly in the early period after MI[4,5]. The best diagnostic method is contrast ventriculography[6]. In treatment, small-scale asymptomatic cases can be managed with surgical repair, percutaneous, and conservative methods[7]. In this study, we presented a case of asymptomatic LVP that was noticed incidentally and showed rapid growth within a year after a long period of cardiac surgery. Due to our limited experience in LVP surgery, we wanted to share the successful surgical treatment of the case its echocardiography, and its radiological images.

Case Presentation

The patient is a 59-year-old male who had a coronary bypass surgery 7 years ago and has hypertension and hyperlipidemia. He had no history of previous trauma or intervention. Informed consent for surgery was obtained from the patients. Since this is a case report, ethical approval is not applicable. The patient, who was under follow-up at an external center, was told that he had a small bubble (2x1.5 cm) in his heart a year ago and that it needed to be monitored. He was referred to our clinic, because of rapid growth in his measurements over the past year. The patient had no clinical complaints. The transthoracic echocardiography performed at our hospital showed an ejection fraction (EF) of 50%, no significant valve pathology, a left ventricular wall motion defect, and a pseudo-aneurysm measuring approximately 5.3x5 cm at the base of the posterior wall (Figure 1). Other laboratory parameters were within normal limits. The patient underwent cardiac computed tomography (CT) imaging, and the diagnosis of LVP was confirmed. The medications he regularly used were acetylsalicylic acid, beta blockers, and atorvastatin. In the preoperative coronary angiography, left internal mammary artery-left anterior descending, obtuse marginal artery (saphenous vein) and right coronary artery (saphenous vein) bypasses were open. As a result of the Cardiology-Cardiovascular Surgery Council, a surgical treatment decision was made. Median sternotomy was performed under general anesthesia. Aortic, bicaval venous, and sump cannulations were placed. Del Nido cardioplegia was given. An incision was made over the aneurysmal sac on the posterior wall of the left ventricle. A large quantity of organized thrombus was removed from the sac. A Teflon cardiac patch of approximately 5x3.5 cm was used to replace the aneurysm sac. Then, the aneurysm tissues were closed over the cardiac patch with the help of double-sided Teflon felt (Dor ventriculoplasty). The patient was extubated at the 6th hour postoperatively and discharged on the 7th day. In the first week follow-up echocardiography, EF was 50% and left ventricular wall motion disorder was observed. The pathology samples taken were reported as fibrin material, and left ventricular wall. The control CT and magnetic resonance angiography images showed thrombosis of the aneurysmal dilatation in the postero-lateral wall of the left ventricle (Figure 2).

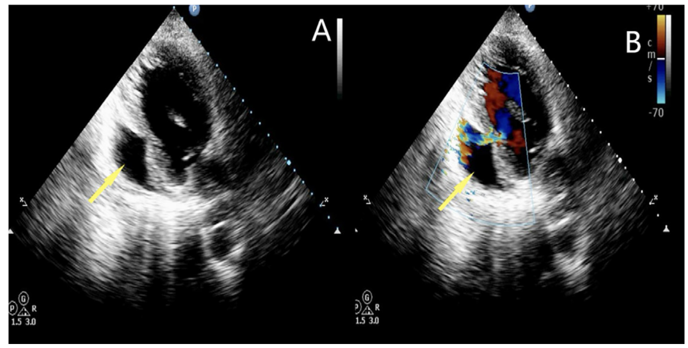

Figure 1. A, B) Preoperative echocardiographic image of left ventricular pseudoaneurysm

Discussion

LVP is important to treat, as it may be, a source of embolism, arrhythmia, rupture, and result in sudden death. In the event of free wall rupture, the in-hospital mortality rate has been reported as high as 90%[8]. Congestive heart failure, chest pain, dyspnea, and syncope are the most common presenting complaints, while 10% of patients

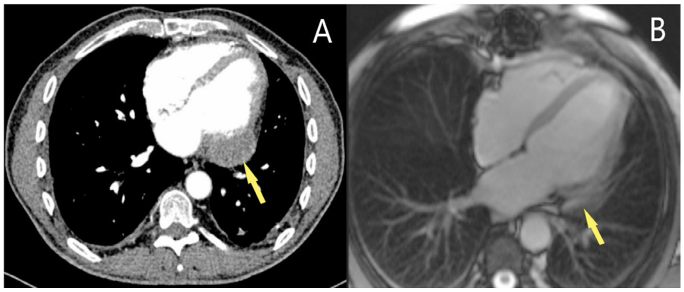

Figure 2. A, B) Postoperative CT and MRI images of a patient who underwent left ventricular pseudoaneurysm repair
CT: Computed tomography, MRI: Magnetic resonance imaging

may be asymptomatic[9]. Although there is no consensus on treatment, it has been reported that LVPs that occur within the first 3 months after MI, especially if their diameter is larger than 3 cm, require urgent surgery[2]. In chronic cases, there is no consensus because the risk of rupture decreases as the left ventricular cavity stabilizes and the high mortality of surgical treatment. Perioperative mortality has been reported to be around 10-20%[2].

In this case, although the patient was asymptomatic, a decision was made to perform surgical intervention because the LVP had shown rapid growth in the last year. In addition, the large diameter of the LVP was effective in the decision to perform surgery. Pseudo-aneurysms can also occur in the right ventricle, the left ventricle, but since the left ventricle has the largest muscle mass and is the most functionally effective part, aneurysms developing in this region attract more attention. Pseudo-aneurysms are three times more common in the inferior and posterolateral walls, as a result of occlusion of the right coronary artery or circumflex artery. In contrast, in 80-90% of cases, true aneurysms are located in the apical region or in the anterolateral wall and are a result of occlusion of the left anterior descending artery[10]. Possible conditions that may cause aneurysm during coronary artery bypass grafting (CABG) include poor myocardial protection (non-homogeneous distribution of cardioplegia), myocardial injury due to cardiac slings used to shape the heart during bypass, and aneurysm formation in the sutured areas over time. In our case, we believe that the possible causes of LVP are pseudo-aneurysm formation in areas affected by ischemia before CABG, or previous cardiac surgery. The patency of bypass grafts in coronary angiography performed before LVP repair was crucial for reaching this conclusion. In acutely developing aneurysms, the fragility of the tissue and the prevalence of acute inflammation may lead to poor surgical repair outcomes and the need for secondary intervention. Aneurysm tissue that develops on a chronic basis is more stable and, therefore, can contribute positively to surgical repair results. In conclusion, LVP surgical treatment is associated with a high mortality rate. Although the experience gained from a single case is insufficient, results may be better in slowly developing chronic cases.

Ethics

Informed Consent: Informed consent for surgery was obtained from the patients. Since this is a case report, ethical approval is not applicable.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Işık M, Görmüş N, Concept: Işık M, Görmüş N, Design: Işık M, Tutsoy F, Data Collection and/or Processing: Işık M, Tutsoy F, Tatar S, Analysis and/or Interpretation: Işık M,Tutsoy F, Tatar S, Literature Search: Işık M, Tutsoy F, Writing: Işık M, Tutsoy F.

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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