E-ISSN 2148-9211

CVSI

CARDIOVASCULAR SURGERY *and* INTERVENTIONS

Official Electronic Journal of the Turkish Society of Cardiovascular Surgery

Turkish Society of Cardiovascular Surgery 1988

Volume: 11 / Number: 1 / March 2024

E-ISSN 2148-9211

CARDIOVASCULAR SURGERY AND INTERVENTIONS

Volume 11 - Number 1 - March 2024

Cardiovascular Surgery and Interventions is the official and periodical journal of the Turkish Society of Cardiovascular Surgery.
It is published three times a year.

The Cardiovascular Surgery and Interventions is indexed in the following database:
TÜBİTAK, ULAKBİM (Turkish Medical Abstracts), Google Scholar, Advanced Sciences Index, Directory of Research Journals Indexing, International Institute of Organized Research (I2OR), International Innovative Journal Impact Factor (IIJIF), Citefactor, ResearchBib, Asos Index, Scientific Indexing Services, J-Gate, Root Indexing, Eurasian Scientific Journal Index, Infobase, Index Copernicus International, SOBIAD, Türkiye Citation Index and TurkMedline

Türk Kalp ve Damar Cerrahisi Derneği adına Sahibi ve Sorumlu Yazı İşleri Müdürü
Levent Yılık

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Publisher / Yayıncı
Bayçınar Tıbbi Yayıncılık ve Reklam Hiz. Tic. Ltd. Şti.
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Yayıncı Sertifika No: 52284

Type of publication: Periodical
Publication date: March 25, 2024

The control of conformity with the journal standards and the typesetting of the articles in this journal, the control of the English abstracts and references and the preparation of the journal for publishing were performed by Bayçınar Medical Publishing.

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ORIGINAL ARTICLES

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Cardiovasc Surg Int 2024;11(1):1-9
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1535
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

A meta-analysis of beating versus arrested heart isolated tricuspid valve surgery

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Received: May 01, 2023 ***Accepted:*** October 27, 2023 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This meta-analysis aimed to compare postoperative outcomes of isolated tricuspid valve surgery with the beating heart and arrested heart techniques.

Materials and methods: A meta-analysis of published studies reporting the comparison of early and late follow-up of isolated tricuspid valve surgery with beating heart and arrested heart techniques was conducted. An analysis of the studies was also performed for each postoperative outcome, observed mortality, and reintervention.

Results: A total of 459 articles were identified. After the removal of duplicate and irrelevant studies and the exclusion of studies due to combined procedures, study design, and the lack of relevant outcomes, five retrospective observational studies with 566 patients were included for meta-analysis. The beating heart technique was used in 303 patients, whereas 263 underwent the arrested heart technique for isolated tricuspid valve surgery. Patients who underwent beating heart surgery had a higher EuroSCORE (European System for Cardiac Operative Risk Evaluation) II (mean difference=6.02, 95% confidence interval [CI]: 2.87-9.16, p=0.0002). No significant differences were observed in in-hospital mortality (odds ratio [OR]=0.96, 95% CI: 0.53-1.73, p=0.88) and permanent pacemaker implantation rate (OR=0.84, 95% CI: 0.49-1.46, p=0.54). Previous cardiac surgery (OR=2.87, 95% CI: 2.03-4.04, p<0.0001) was significantly higher, and infective endocarditis (OR=0.4, 95% CI: 0.26-0.60, p<0.0001) was significantly less in the beating heart group.

Conclusion: Isolated tricuspid valve surgery using the beating heart and arrested heart technique can be performed with no significant difference in postoperative morbidities and mortality. The beating heart technique may be used in more complex patients.

Keywords: Arrested heart, beating heart, surgery, tricuspid valve.

Isolated tricuspid valve surgery (TVS) is the gold standard treatment for patients with right heart failure and symptoms due to tricuspid valve disease.[1-3] Isolated TVS has high operative mortality compared to not only other isolated valve surgeries but also combined valve surgery involving the tricuspid valve.[4,5] Recently, Zack et al.[6] reported an in-hospital mortality rate of 8.8% for isolated TVS despite optimal medical treatment and increase in surgical volume. The authors noted that optimal surgical timing and patient selection is of utmost importance to have better outcomes.

Isolated TVS can be performed with a beating heart (BH) or arrested heart (AH) technique under cardiopulmonary bypass. Although both techniques have been used widely, there is no consensus on the superiority of one technique to the other.[7-12] Russo et al.[11] reported that the 30-day mortality rate was 6.2% *vs.* 5.0% in the AH and BH groups. They also stated that the BH technique was associated with increased long-term survival and freedom from reoperation compared to the standard AH technique. However, Flagiello et al.[10] reported that the BH technique showed comparable outcomes to the AH technique for isolated TV surgery despite a higher risk profile. Surgical advantages of the AH approach include bloodless surgical field and better leaflet exposure during repair or replacement procedures.

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Citation:
Duman ZM, Bayram M, Yaşar E, Timur B, Reyhancan A, Azboy D, et al. A meta-analysis of beating versus arrested heart isolated tricuspid valve surgery. Cardiovasc Surg Int 2024;11(1):1-9. doi: 10.5606/e-cvsi.2024.1535.

Alternatively, the BH technique decreases the incidence of complications related to aortic clamping, such as myocardial injury and cerebrovascular events. The effect of the suture bites on cardiac rhythm can be simultaneously monitored.

In the literature, there are few retrospective observational studies published, and to date, the advantages of the BH technique have yet to be demonstrated.[7-11] No randomized clinical trial comparing BH and AH approaches have been reported. This study aimed to reveal, through a systematic review with meta-analysis of all published comparative studies, whether the BH technique decreases postoperative mortality, rates of reexploration, permanent pacemaker implantation, or reintervention, compared to the AH technique during isolated TVS.

MATERIALS AND METHODS

Literature search strategy

An electronic search was performed using the PubMed database (United States National Library of Medicine), Scopus (Elsevier), Ovid Medline, EMBASE (Excerpta Medica Database), Cochrane Database of Systematic Reviews, and ULAKBIM (Turkish National Academic Network and Information Center) database until February 2022. The study was performed in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) criteria and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).[13,14] To have the most effective search results, the terms "beating heart," "arrested heart," or "tricuspid valve" and "surgery" were used as keywords to find publications conducted in humans. In addition, the reference list of all selected articles was checked to identify potentially relevant articles. Duplicate articles were removed. All results were independently screened for data accuracy. In case of data differences, the relevant data were reexamined.

Study design and selection criteria

Eligible studies for this systematic review and meta-analysis included comparative observational studies that included patients who underwent isolated TVS. Cohort series that did not compare the results of isolated TVS in the BH and AH groups were excluded. Abstracts, case reports, small case series (<20 patients), letters to the editor, conference presentations, editorials, and how to articles were excluded. Review articles were excluded to avoid duplication of results and potential for publication bias. Table 1 shows the characteristics of included studies.

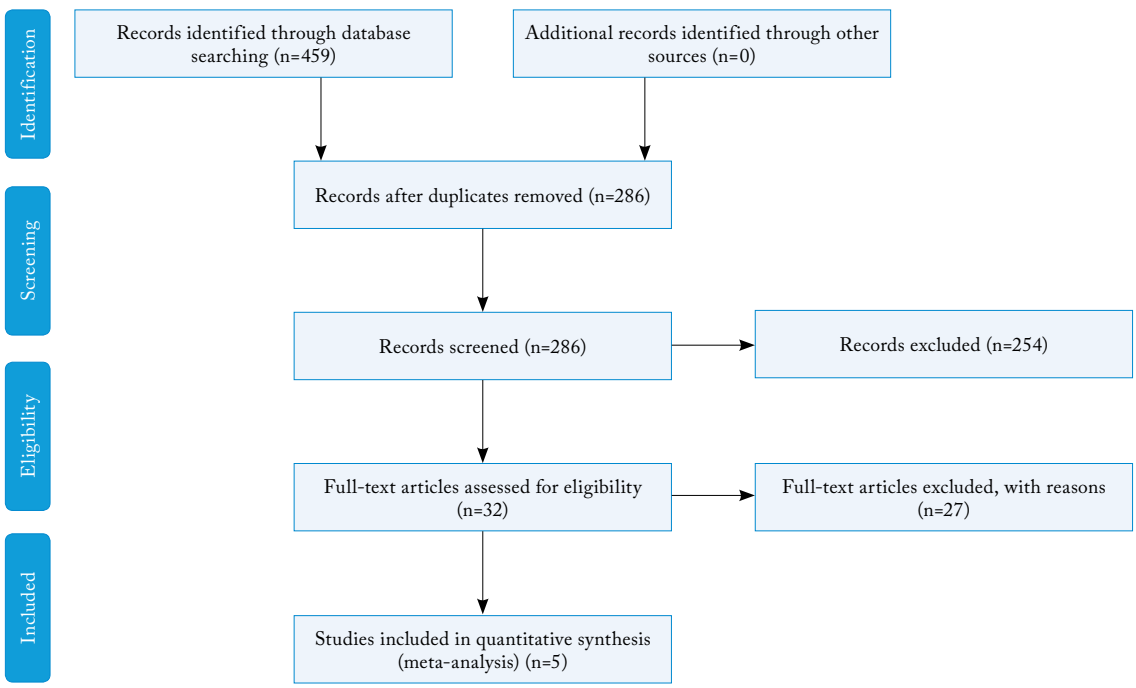

Figure 1. Flowchart of the study.

Data extraction

All data was taken from the main texts, tables, and figures of the relevant studies. Two investigators reviewed the studies and assessed the details of each article, including demographics, interventions, and outcomes. Authors of included trials were contacted when necessary to clarify data and identify multiple publications. The authors of the study reached a consensus by a discussion of the results. The senior investigator reviewed the final outcomes.

Endpoints

The primary outcome was defined as hospital mortality, which was defined as mortality occurring within 30 days after the operation. The secondary outcome was early postoperative outcomes, including re-exploration and permanent pacemaker implantation. The late secondary outcome was the need for tricuspid valve reintervention.

Statistical analysis

The statistical analyses were performed with R version 4.0.3 (The R Foundation for Statistical Computing, Vienna, Austria). Outcomes were analyzed as dichotomous variables. For dichotomous variables, the odds ratio (OR) was calculated with a 95% confidence interval (CI) for proportions. The weighted mean difference (MD) was calculated with 95% CI for means. Heterogeneity was examined using Cochran's Q test, as well as the I^2 statistic.[15,16] Recognizing that the Q-test is often underpowered to detect statistically significant heterogeneity, particularly when there are few trials in the analysis, the relatively conservative threshold of a p-value <0.10 was chosen to suggest statistically significant heterogeneity across trials. In addition to the Q statistic, the I^2 was calculated to quantify the degree of heterogeneity across trials that could not be attributable to chance alone. As the I^2 indicates the proportion of variability between trials that cannot be attributable to chance alone, it provides an improved measure of heterogeneity between trials and is not limited by power.[15,16] Forest plots were created for primary and secondary outcomes. A funnel plot was also used to examine publication bias in the primary outcome. A p-value <0.05 was considered statistically significant.

RESULTS

Description of the selected studies

Figure 1 demonstrates the search results. No randomized clinical trial or meta-analysis was found.

Table 1
Characteristics of the included studies

Study	Study type	Beating heart	Arrested heart	Follow-up			Hospital mortality	Re-exploration	Permanent pacemaker implantation	Reintervention
		n	n	Mean±SD	Median	Min-Max				
Pfannmüller et al.[7]	ROS	63	42	32.0±32.6 months			Yes	Yes	Yes	Yes
				BHG: 4.2±4.0 years						
Baraki et al.[8]	ROS	48	44	AHG: 5.4±4.3 years			Yes	Yes	Yes	Yes
Atılgan et al.[9]	ROS	16	13		N/A		Yes	Yes	No	No
Russo et al.[11]	ROS	129	129		21	1-131 months	Yes	Yes	Yes	Yes
Flagiello et al.[10]	ROS	47	35	51.2±37.1 months			Yes	Yes	Yes	No

SD: Standard deviation; AHG: Arrested heart group; BHG: Beating heart group; N/A: Not available; ROS: Retrospective observational study.

Table 2
Preoperative and operative data

	Estimate			
	MD	OR	95% CI	*p*
Preoperative data				
Age (year)[7-11]	3.78		1.24-6.3	0.0035*
Ejection fraction (%)[7,9,10]	–0.51		–3.05-2.02	0.6930
EuroSCORE II[7-9]	6.02		2.87-9.16	0.0002*
NYHA Class II-IV[8-11]		1.30	0.9-1.91	0.1610
Infective endocarditis[7,8,10,11]		0.4	0.26-0.60	<0.0001
History of previous cardiac surgery[7-11]		2.87	2.03-4.04	<0.0001*
Operative data				
Valve replacement[7-11]		1.10	0.77-1.57	0.6011
Valve repair[7-11]		0.9	0.64-1.30	0.6011
Thoracotomy incision[7-11]		2.15	1.4-3.3	0.0004*

MD: Mean difference; OR: Odds ratio; CI: Confidence interval; NYHA: New York Heart Association; * p-value <0.05 was considered statistically significant.

A total of 459 articles were identified. After removing duplicate and irrelevant studies, 32 full-text articles were reviewed for eligibility. On further examination of these retrieved studies, 27 were subsequently excluded due to combined procedures, study design, and the lack of relevant outcomes reported, such as 30-day mortality. Of the remaining studies, only five studies including 566 patients were used for meta-analysis.[7-11] All five studies included in the meta-analysis were retrospective observational studies. Table 1 summarizes the characteristics of the included studies.

Perioperative characteristics

Table 2 reveals the demographic and operative data of included studies. Patients who underwent BH isolated TVS were significantly older (MD=3.78, 95% CI: 1.24-6.3, p=0.0035) and had a significantly higher EuroSCORE (European System for Cardiac Operative Risk Evaluation) II (MD=6.02, 95% CI: 2.87-9.16, p=0.0002). In the BH group, history of previous cardiac surgery (OR=2.87, 95% CI: 2.03-4.04, p<0.0001) was significantly higher and the incidence of infective endocarditis (OR=0.4, 95% CI: 0.26-0.60, p<0.0001) was significantly decreased in comparison

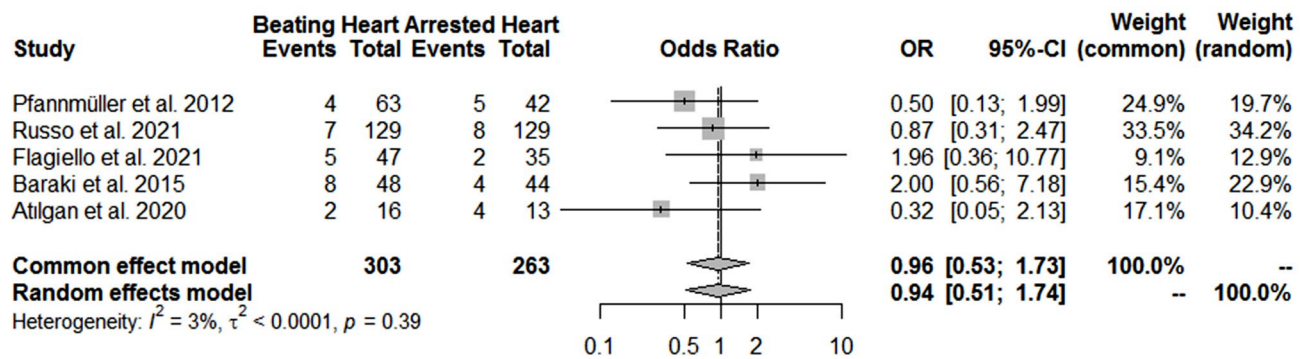

Figure 2. Forest plots for in-hospital mortality.
OR: Odds ratio; CI: Confidence interval.

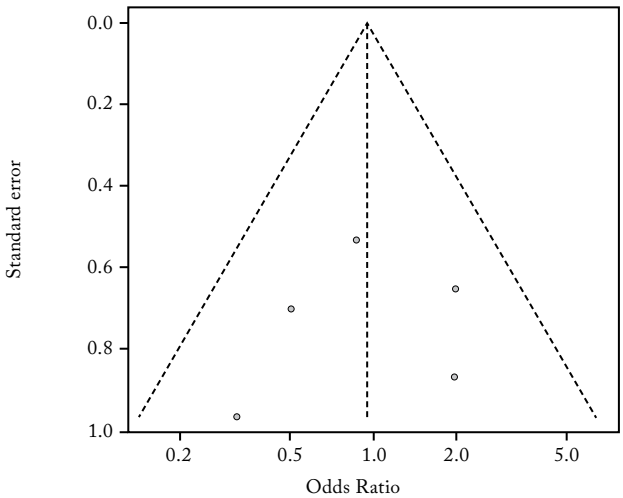

Figure 3. Funnel plot for in-hospital mortality.

to the AH group. Thoracotomy incision (OR=2.15, 95% CI: 1.4-3.3, p=0.0004) was used more in the BH group, and sternotomy was more common in the AH group.

There were no significant differences for the New York Heart Association functional Class III-IV symptoms and tricuspid valve replacement or tricuspid valve repair procedures between the BH and AH groups (p>0.05).

Primary outcome

In-hospital death occurred in 26 of 303 patients in the BH group and 23 of 263 patients in the AH group in the five studies included in the analysis. Overall, the analysis showed that the risk of hospital mortality was similar in both groups (OR=0.96, 95% CI: 0.53-1.73, p=0.88). Forest plots and funnel plots for in-hospital mortality are shown in Figures 2 and 3, respectively.

Secondary outcomes

A total of 42 patients undergoing isolated TVS required reexploration. No statistically significant difference was found in the need for reexploration in the BH and AH groups (OR=0.89, 95% CI: 0.48-1.67, p=0.72). Figure 4 displays the forest plot for postoperative reexploration.

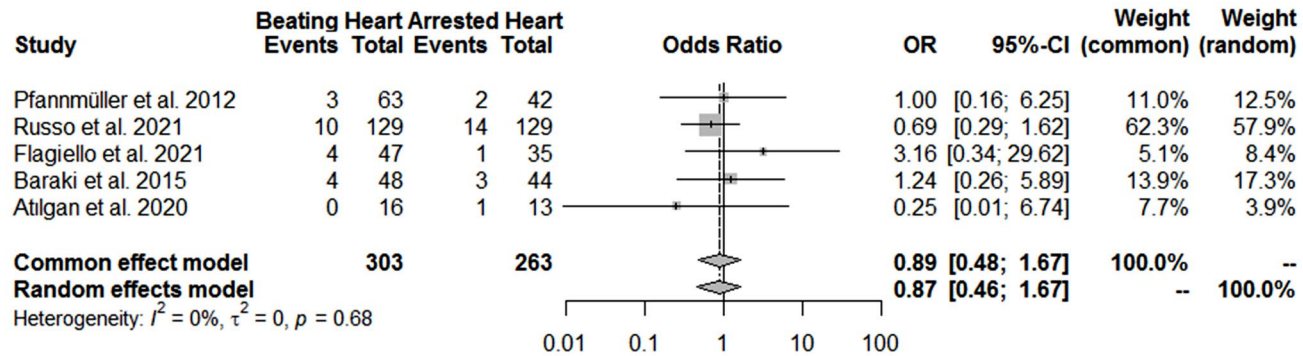

Figure 4. Forest plots for reexploration.
OR: Odds ratio; CI: Confidence interval.

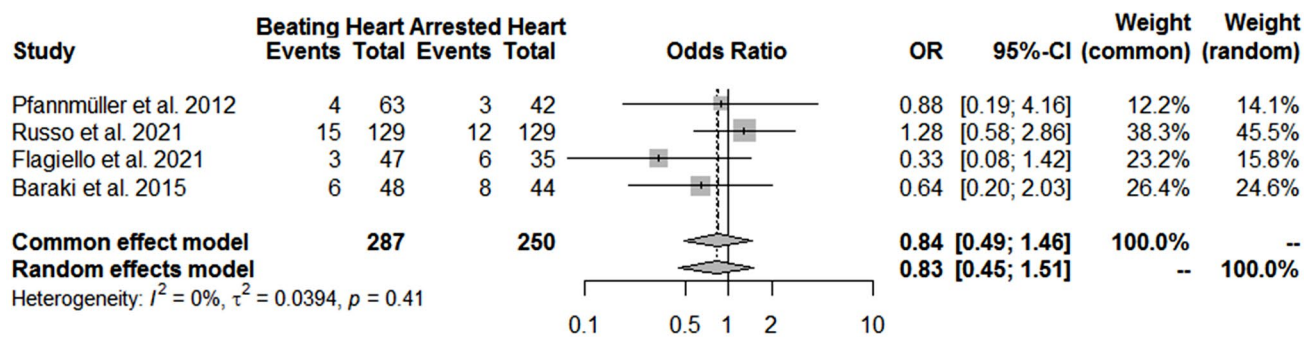

Figure 5. Forest plots for pacemaker implantation.
OR: Odds ratio; CI: Confidence interval.

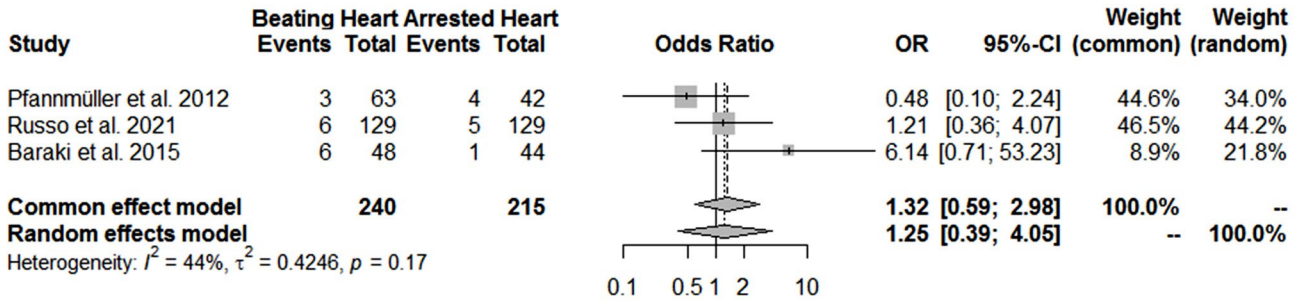

Figure 6. Forest plot for tricuspid valve reintervention.
OR: Odds ratio; CI: Confidence interval.

Four studies collected postoperative permanent pacemaker implantation data.[7,8,10,11] Permanent pacemakers were implanted in 28 of 287 patients in the BH group and in 29 of 250 patients in the AH group. The risk of permanent pacemaker implantation in the postoperative period was similar in both groups, as shown in Figure 5 (OR=0.84, 95% CI: 0.49-1.46, p=0.54).

There were three studies that collected data on patients requiring tricuspid reoperation at long-term follow-up.[7,8,11] Tricuspid valve reoperation was required in 25 of 455 patients. No statistically significant difference was found in the need for reoperation in the BH and AH groups (OR=1.32, 95% CI: 0.59-2.98, p=0.50). Figure 6 shows the forest plot for tricuspid valve reoperation.

DISCUSSION

No previous meta-analysis has studied the effect of the BH versus AH technique for isolated TVS in randomized or nonrandomized trials. A few retrospective observational studies have reported the outcomes of the comparison of the two techniques for isolated TVS.[7-11] The study by Russo et al.[11] suggested that the BH technique was associated with significant benefits in terms of long-term survival and reintervention. However, early mortality and postoperative outcomes were comparable in all published studies.[7-11] Isolated TVS remains challenging due to high mortality rate. In the articles included in this meta-analysis, the operative mortality of isolated tricuspid surgery ranged from 5.8 to 20.7%.[9,11]

Previously published studies on TVS techniques have mostly focused on tricuspid valve replacement or tricuspid valve repair.[17,18] Although the BH and AH techniques for right-sided cardiac surgery have been described for a long time, there are few studies in the literature comparing the BH technique with the AH technique in isolated TVS.[19,20] The first article was published by Pfannmüller et al.[7] in 2012. However, the number of patients included was limited, as in all subsequent articles. We performed this meta-analysis due to the limited number of available studies. To the best of our knowledge, this is the first meta-analysis to examine the postoperative outcomes of BH and AH techniques in TVS.

The main findings of this study were that there was no difference between the postoperative results of BH and AH techniques in isolated TVS. The mortality of tricuspid valve repair is lower than that of tricuspid valve replacement.[17] Since the replacement and repair patients were homogeneously distributed in the meta-analysis groups, it is not expected to affect the mortality analysis. In this analysis, we think that the BH technique was mostly used in more complex patients since EuroSCORE II, the most widely used risk scale in cardiac surgery, was higher in the BH patients. The preoperative clinical condition of isolated TVS patients is one of the most important factors in terms of postoperative mortality, as well as in patients undergoing acute aortic dissection surgery.[21] Therefore, the hospital mortality results of this meta-analysis should be carefully considered so as not to reach a definitive conclusion.

A permanent pacemaker may be required after isolated TVS.[22] In TVS performed with the BH technique, the theoretical effect of sutures passed through the annulus of the tricuspid valve on the

heart rhythm can be directly monitored. It is expected that severe heart blocks will not be encountered by taking precautions when the stitch disruption of the rhythm is noticed. However, according to the results of the meta-analysis, we can say that this advantage of the BH technique has no effect on the reduction of permanent pacemaker implantation in the early postoperative period.

Freedom from reoperation after TVS demonstrates the success of the surgical technique and is reported in most series on the tricuspid valve.[23] Saran et al.[24] showed that tricuspid valve replacement increased the need for reoperation in the long term compared to repair. In the BH technique, placement of annular sutures is challenging due to the movement of the heart and may increase ring and valve dehiscence. Such situations may cause the need for reoperation for the tricuspid valve in the long-term follow-up. However, in this meta-analysis, there was no difference between the need for reoperation in the long-term follow-up of patients who had TVS with the BH technique and the AH technique.

As demonstrated in our meta-analysis, the preoperative demographic data of patients operated with the BH and with AH techniques were different. The main reason for this might be that all five studies included in the analysis were retrospective, and the choice of AH and BH technique might be biased according to patient characteristics. It was found that patients who underwent TVS with the BH technique were older and had a higher EuroSCORE II. However, the New York Heart Association functional classification of both patient groups was similar. The BH technique was preferred more in patients with a history of previous cardiac surgery. In the AH technique, an aortic cross clamp must be placed. The BH technique may have been preferred in most patients with a history of previous cardiac surgery to avoid the removal of periaortic mediastinal adhesions and to prevent possible aortic injuries. Tricuspid valve surgeries can be performed with right mini-thoracotomy or sternotomy.[25,26] Right mini-thoracotomy was preferred more in the BH technique than in the AH technique. Furthermore, right mini-thoracotomy may have been preferred in isolated TVS in cardiac reoperations to reduce sternal reentry injuries.[27,28]

Beating heart surgery was preferred less in patients operated for tricuspid valve infective endocarditis. The leaflets are mobile, and it is more difficult to examine the ventricular faces of the leaflets in the BH technique. The most common cause of tricuspid valve endocarditis is intravenous drug use.[29] Other causes include cardiac implantable electronic devices, long-term central venous access catheters, and congenital heart disease.[30,31] Slaughter et al.[32] reported that postoperative mortality in tricuspid valve infective endocarditis was 2% in repair patients, 3% in replacement patients, and 16% in valvectomy patients.

There are some limitations to this study. This study is based on a low level of evidence from five observational studies (one adjusted and four unadjusted). A single study provided 45.6% of the patients included in the analysis. This can be associated with a potential selection bias related to the type of surgical approach, such as repair or replacement, as well as the techniques used during those procedures. The data showed that the BH technique was mostly used in more complex patients. Publication bias, which is the common limitation of all meta-analyses, is probably valid for this meta-analysis. This study was performed to make a current data analysis and to have a conclusion for clinicians and future studies.

In conclusion, isolated TVS with beating and AH techniques are associated with similar postoperative outcomes. From available data, the BH technique generally tends to be used in more complex patients.

Ethics Committee Approval: Since this is a meta-analysis study, there is no ethics committee requirement. The data used in the study are publicly available. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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

Author Contributions: Concept/design: Z.M.D.; Data analysis/interpretation: Z.M.D., M.B., E.Y., D.A., S.Ş.; Drafting article: Z.M.D., B.T.; Critical revision of article: B.O., Approval of article: B.O.; Statistics and data collection: Z.M.D., E.Y., A.R., D.A., S.Ş.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):10-17
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1572
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Clinical significance of CONUT score in atrial fibrillation patients aged 65 and over

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Received: November 13, 2023 ***Accepted:*** December 18, 2023 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: The aim of this study was to examine the clinical importance of malnutrition in patients with non-valvular atrial fibrillation (AF) aged 65 and over who were receiving anticoagulant treatment and to distinguish the differences between direct oral anticoagulants (DOACs) and warfarin therapy.

Patients and methods: Between January 2016 and December 2020, a total of 423 AF patients (183 males, 240 females; mean age: 73.4±5.8 years; range, 65 to 89 years) were retrospectively analyzed. The patients were divided into two groups according to the Controlling Nutritional Status (CONUT) score: ≥5 (n=92) and <5 (n=331). All patients were followed for at least two years from the first presentation.

Results: Major bleeding and mortality were found to be higher in the CONUT score ≥5 group (8.7% *vs.* 3.0%, p=0.017 and 18.5% *vs.* 10.0%, p=0.025, respectively). While there was higher major bleeding and mortality in CONUT ≥5 patients using warfarin, there was no significant difference in the DOAC group (warfarin p=0.009, DOAC p=0.337 and warfarin p=0.046, DOAC p=0.171, respectively). In the receiver operating characteristic analysis, a cut-off value of 3.5 of the CONUT score predicted both mortality and major bleeding (area under the curve [AUC]: 0.781, p<0.001 and AUC: 0.733, p=0.001, respectively).

Conclusion: According to the CONUT score, a higher rate of major bleeding and mortality was found in AF patients aged 65 and over with moderate-severe malnutrition. Based on these findings, the use of DOAC may be more reliable in this patient group.

Keywords: Atrial fibrillation, major bleeding, malnutrition, mortality.

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population.[1] Its incidence increases with age, occurring in 4% of patients aged 65 years and over.[2] Serious complications such as heart failure, stroke and death may occur due to AF.[3,4] Older patients are more susceptible to nutritional deficiencies due to comorbidities and diseases.[5] Nutritional deficiencies have been studied in heart failure, malignancies, and chronic kidney disease and have been associated with mortality.[6,7] However, this has not been adequately studied in patients with AF. Screening middle-aged and elderly AF patients for nutritional deficiencies could be useful in developing individualized treatment modalities to improve patient prognosis.

The Controlling Nutritional Status (CONUT) score is an objective method that can be easily calculated from patients' laboratory data, such as albumin, total cholesterol and lymphocyte count, and indicates nutritional status.[8] Previous studies have shown that the CONUT score is useful for predicting prognosis in patients with coronary artery disease, heart failure, and transcatheter aortic valve implantation.[9-11] In a study conducted including patients hospitalized due to novel coronavirus disease 2019 (COVID-19), it was found that the CONUT score predicted in-hospital mortality.[12] In another study, malnutrition as assessed by the CONUT score was found to have a remarkable correlation with the incidence of bleeding and stroke in individuals with AF aged 80 years and older.[13]

In the present study, our primary objective was to investigate the effect of the CONUT score on clinical outcomes in patients with AF aged 65 years and older. Our secondary objective was to evaluate variations in anticoagulant selection.

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Citation:
Kılıç R, Kaya AF. Clinical significance of CONUT score in atrial fibrillation patients aged 65 and over. Cardiovasc Surg Int 2024;11(1):10-17. doi: 10.5606/e-cvsi.2024.1572.

PATIENTS AND METHODS

Patient population

This two-center, retrospective study was conducted at Çermik State Hospital and Muş State Hospital, Department of Cardiology between January 2016 and December 2020. A total of 423 patients (183 males, 240 females; mean age: 73.4±5.8 years; range, 65 to 89 years) aged 65 and over with AF were included. The diagnosis of AF was made by 12-lead electrocardiography or 24-h rhythm Holter monitoring. Patients with valvular AF, malignancy, serious infection, not using anticoagulants, and whose CONUT score could not be calculated were excluded from the study.

Medical history, demographic data, medications, laboratory and echocardiographic results of each patient were collected retrospectively from the hospital electronic clinical information system. The patients' CHADS-VASC and HAS-BLED scores were calculated. All patients were using anticoagulant medication. In patients receiving vitamin K antagonists (VKAs), time in therapeutic range (TTR) was defined as the time during which the patients' international normalized ratio (INR) value was between 2 and 3. The TTR was calculated according to the Rosendaal method.[14] Patients with TTR >65% were considered to be receiving appropriate doses of warfarin. Patients with TTR <65% were excluded from the study. In patients receiving direct oral anticoagulants (DOACs), dose adjustment was adjusted according to the guideline recommendation.[15]

Evaluation of nutritional status

In our study, we used the CONUT score to assess nutritional status.[8] The CONUT score is calculated from serum albumin, total cholesterol and lymphocyte count (Table 1). According to the CONUT score, patients are categorized into four groups: normal (0-1), mild (2-4), moderate (5-8) and severe (9-12). In our study, patients were divided into two categories: normal-mild (0-4) and moderate-severe (≥5).

Follow-up

The primary outcome measures were ischemic stroke, major bleeding, and all-cause mortality. Ischemic strokes were characterized as clinical situations in which there was a sudden onset of neurological deficits that lasted at least 24 h, and this diagnosis was confirmed by computed tomography or magnetic resonance imaging. Major bleeding was determined according to the definition of the International Society on Thrombosis and Hemostasis (ISTH).[16] The records were reviewed over a period of at least two years from the first admission to the hospital for AF.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were expressed in number and frequency. The Kolmogorov-Smirnov test was utilized to assess the normality of the distribution for continuous variables. The Student t-test was applied for normally distributed variables, while the Mann-Whitney U test was employed for variables that did not follow a normal distribution. Categorical variables were compared using the chi-square test. Receiver operating characteristic (ROC) analysis was used to test the capacity of the CONUT score to predict mortality and major bleeding, as well as to determine a cut-off value based on the sum of the

Table 1
CONUT scoring system

	Normal	Mild	Moderate	Severe
Serum albumin (g/mL)	≥3.5	3.00-3.49	2.50-2.99	<2.5
Score	0	2	4	6
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3
Lymphocytes (counts/mL)	≥1,600	1,200-1,599	800-1,199	<800
Score	0	1	2	3

CONUT: Controlling nutritional status; Normal: 0-1; Mild: 2-4; Moderate: 5-8; Severe: 9-12.

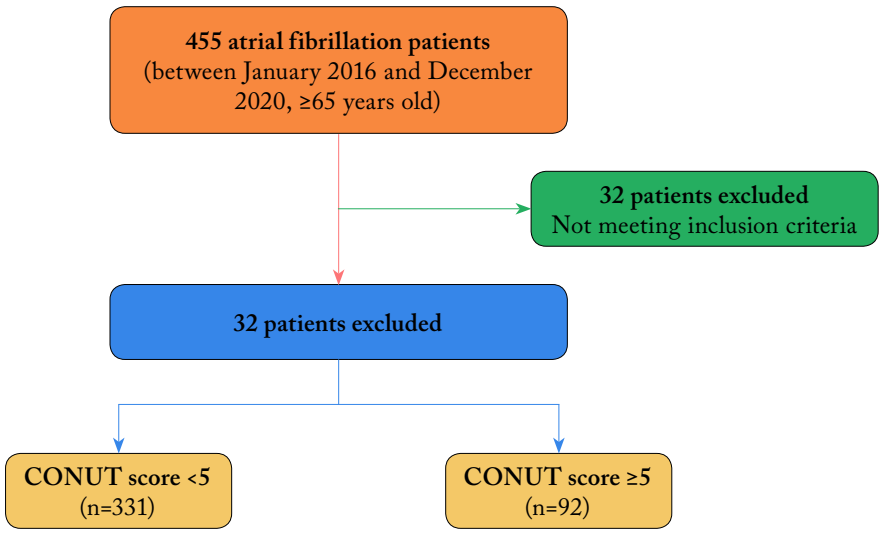

Figure 1. Study flowchart.
CONUT: Controlling nutritional status.

highest sensitivity and specificity. A *p* value of <0.05 was considered statistically significant.

RESULTS

There were 331 patients in the group with a CONUT score <5 and 92 patients in the group with a CONUT score of ≥5 (Figure 1). A statistically significant difference was found between the groups with respect to age and body mass index (BMI) (75.3±6.1 *vs.* 72.8±5.6 years, p<0.001 and 24.2±3.2 *vs.* 26.9±3.2 kg/m^2, p<0.001, respectively). The HAS-BLED and CHADS-VASC scores were similar in both groups. While creatinine was lower in the group with CONUT <5, there was no significant difference between other blood parameters (1.05 [0.84-1.57] *vs.* 0.95 [0.72-1.20], p<0.004). Additional comorbidities such as cardiomyopathy, chronic obstructive pulmonary disease, chronic renal failure, hypertension, and diabetes mellitus were present at a similar rate in each group. There was no significant difference in the choice of anticoagulant of the patients. There was a significant difference between the patient groups in terms of major bleeding and mortality (8.7% *vs.* 3.0%, p=0.017 and 18.5% *vs.* 10.0%, p=0.025, respectively). As a result, a higher rate of major bleeding and mortality was found in the group with a CONUT score of ≥5. On the other hand, the groups were similar in terms of ischemic cerebrovascular disease/transient ischemic attack (CVD/TIA) (10.3 *vs.* 12.0%, p=0.643). The essential demographic characteristics of the patient cohort are outlined in Table 2.

The CONUT score was also evaluated in the DOAC and warfarin subgroups. Accordingly, major bleeding and mortality were significantly higher in patients with CONUT ≥5 in the warfarin subgroup, but no significant difference was found in the DOAC group (warfarin p=0.009, DOAC p=0.337 and warfarin p=0.046, DOAC p=0.171, respectively). In addition, there was no significant difference in terms of ischemic CVD/TIA in both subgroups according to the CONUT classification (warfarin p=0.223, DOAC p=0.760, respectively) (Figure 2).

Based on the ROC analysis, a cut-off value of 3.5 of the CONUT score predicted mortality with 72% sensitivity and 75% specificity (area under the curve [AUC]: 0.781, 95% confidence interval [CI]: 0.729-0.832, p<0.001) (Figure 3a). Similarly, in the ROC analysis, using this cut-off value, the CONUT score predicted major bleeding with 72% sensitivity and 71% specificity (AUC: 0.733, 95% CI: 0.635-0.831, p=0.001) (Figure 3b).

DISCUSSION

In the present study, we examined the effect of nutritional status, calculated using the CONUT score, on the clinical presentation of patients with AF aged 65 years and older taking oral anticoagulants. Patients with a CONUT score of ≥5 and classified

Table 2

Baseline demographic characteristics of patients

	CONUT score ≥5 (n=92)					CONUT score <5 (n=331)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			75.3±6.1					72.8±5.6			<0.001
Sex											
Female	53	57.6				187	56.5				0.849
Body mass index (kg/m^2)			24.2±3.2					26.9±3.2			<0.001
Heart rate (min)			85.2±16.4					86.9±18.1			0.416
Systolic blood pressure (mmHg)			129±16					128±17			0.717
Diastolic blood pressure (mmHg)			78.1±12.9					78.6±12.0			0.743
Ischemic CMP	32	34.8				96	29				0.286
COPD	17	18.5				77	23.3				0.329
GFR (mL/min)				59	29-73				59	38-72	0.388
BUN (mg/dL)				34	22-52				32	21-44	0.200
C reatinine (mg/dL)				1.05	0.84-1.57				0.95	0.72-1.20	0.004
Chronic renal failure	53	57.6				170	51.4				0.288
Hypertension	65	70.7				236	71.3				0.904
Diabetes mellitus	21	22.8				77	23.3				0.930
Ejection fraction				50	35-58				54	40-60	0.168
HAS-BLED score			1.83±0.84					1.88±0.94			0.647
CHA_2DS_2-VASC score			3.93±1.41					3.79±1.48			0.420
Warfarin	28	30.4				121	36.6				0.277
DOAC	64	69.6				210	63.4				0.277
CONUT score			6.34±1.17					2.35±0.98			<0.001
Ischemic CVD/TIA											
All	11	12.0				34	10.3				0.643
DOAC	5	7.8				19	9				0.760
Warfarin	6	21.4				15	12.5				0.223
Major bleeding											
All	8	8.7				10	3.0				**0.017**
DOAC	3	4.7				5	2.4				0.337
Warfarin	5	17.9				5	4.1				**0.009**
Mortality	17	18.5				33	10.0				**0.025**

CONUT: Controlling nutritional status; CMP: Cardiomyopathy; COPD: Chronic Obstructive Pulmonary Disease; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen; DOAC: Direct oral anti coagulant; CVD/ TIA: Cerebrovascular disease/transient ischemic attack.

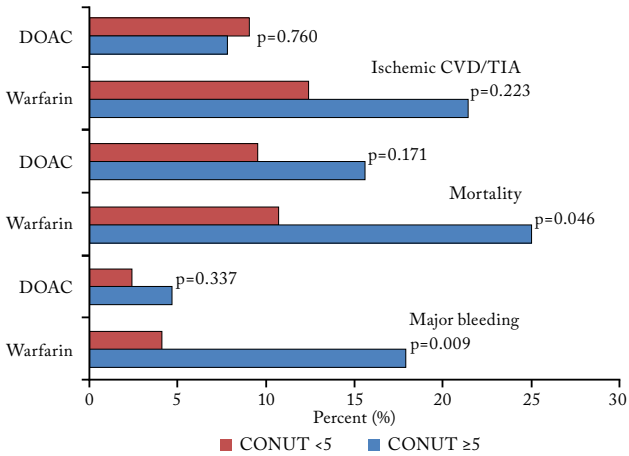

Figure 2. Evaluation of CONUT score in DOAC and warfarin subgroups.

CONUT: Controlling nutritional status; DOAC: Direct oral anticoagulants.

as moderate-severe malnutrition had a higher rate of major bleeding and mortality, and no significant difference was found in terms of ischemic stroke. While there was no significant difference in mortality and major bleeding according to nutritional status in patients taking DOAC, a higher rate of major bleeding and mortality was found in patients with moderate-to-severe malnutrition in the warfarin group.

Elderly individuals, particularly those with cardiovascular disease, often suffer from malnutrition. Based on previous research, it has been found that approximately 60 to 90% of malnourished elderly people are below a healthy weight.[17] Around 60 to 70% of elderly people who are considered frail are malnourished.[18] Malnutrition is not only a consequence of chronic diseases, but can also contribute to the progression of these diseases. Previous studies have demonstrated a link between malnutrition and unfavorable outcomes in patients with coronary artery disease or heart failure.[19,20] However, there are few studies investigating both the incidence and predictive significance of malnutrition in patients with AF.[21,22]

The BMI is a commonly used measure for evaluating nutritional status. However, its use is limited, particularly in patients with AF. This is because 21 to 68% of patients with AF have also heart failure.[23] In individuals with heart failure, the retention of sodium and water in the body can lead to weight gain, which can affect the accuracy of BMI as a measure. In addition, BMI is unable to

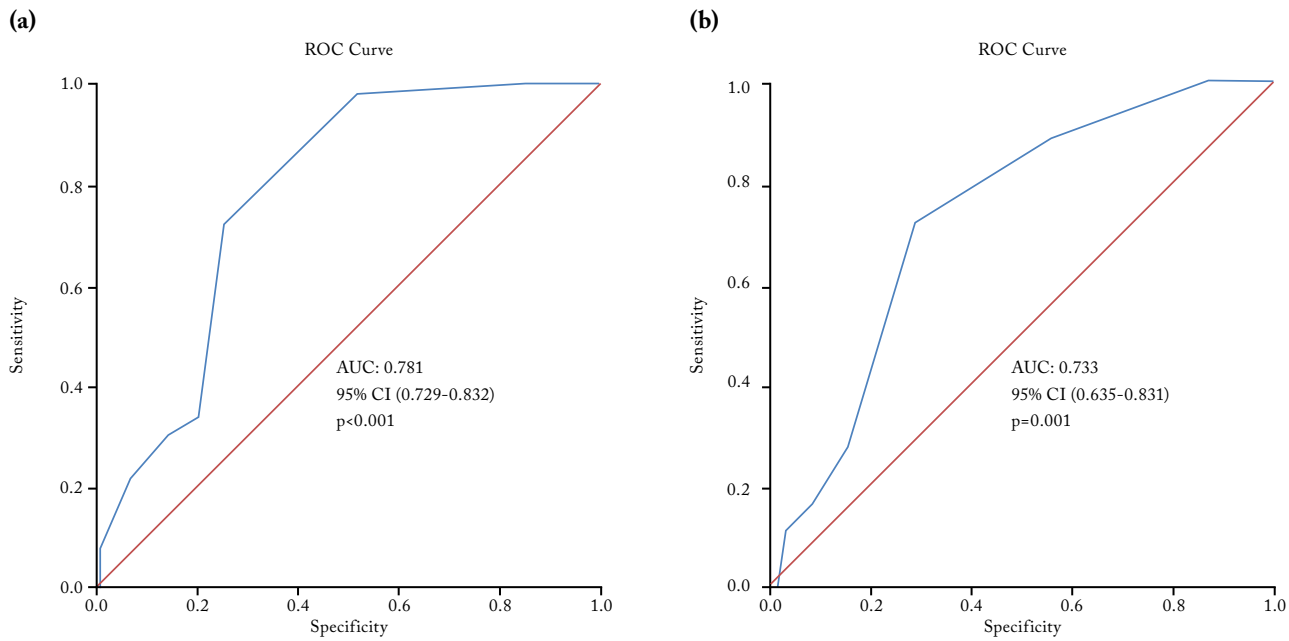

Figure 3. **(a)** ROC curve analysis of CONUT score on mortality in atrial fibrillation patients. **(b)** ROC curve analysis of CONUT score on major bleeding in atrial fibrillation patients.

ROC: Receiver operating characteristic; CONUT: Controlling nutritional status.

differentiate between muscle, fat and bone mass, and individuals with similar BMI values may have different metabolic profiles. The CONUT score is determined by measuring serum albumin, total cholesterol, and lymphocyte count. It serves as a comprehensive score that reflects the patient's frailty.

In our study, patients with a CONUT score of ≥5 were found to have a higher rate of major bleeding and mortality in the patient group receiving warfarin. However, no significant difference was observed between the groups in patients using DOAC. Polypharmacy often increases with age, as the prevalence of multiple health conditions or comorbidities increases. This situation increases the interaction of warfarin with other medications and, thus, it necessitates more frequent INR monitoring. Reduced muscle strength due to malnutrition limits physical activity and reduces hospital admissions.[24] This prevents regular follow-up and is one reason for the increase in the rate of major bleeding. Albumin level, one of the parameters in the CONUT score, is an important indicator reflecting nutritional status in clinical practice.[25] In addition, albumin levels also affect the efficacy of warfarin anticoagulation. Warfarin is completely absorbed after oral administration and subsequently binds to albumin in plasma to a high degree. The portion that remains unbound to albumin, about 1 to 10%, suppresses the synthesis of vitamin K-dependent coagulation factors in the hepatocytes, which leads to an anticoagulant effect. Previous studies have indicated increased anticoagulation and a higher risk of bleeding in individuals with low serum albumin levels receiving warfarin therapy.[26,27] These factors may explain the higher incidence of major bleeding and higher mortality in malnourished elderly AF patients taking warfarin in our study.

The assessment of malnutrition in patients with AF and the implementation of early interventions, particularly in patients with moderate to severe malnutrition, could have a significant impact on patient outcomes. Some studies have shown that the use of oral nutritional supplements and nutritional counseling can improve clinical outcomes in individuals with malnutrition.[28,29] The identification of malnutrition as an isolated risk factor for morbidity and mortality in elderly individuals with AF is important as malnutrition is a risk factor that can potentially be addressed and modified. Therefore, it is of great importance to develop a multidisciplinary team approach to reduce the negative effects of malnutrition in elderly patients with AF treated with anticoagulants. The recommendations of clinical nutritionists can play a crucial role in the development of a monitoring strategy. Incorporating oral nutritional supplementation can prove to be a valuable resource in preventing weight loss, enhancing nutritional health, and lowering complications in elderly AF patients suffering from malnutrition.

Nonetheless, there are some limitations to this study. The study was carried out in a retrospective manner at two centers, and the study sample size was relatively limited. In addition, we evaluated nutritional status exclusively at the moment of the initial hospital admission and did not explore any fluctuations or changes in nutritional status over the course of time. Therefore, it is not definitively established whether patients who had malnutrition at the beginning can maintain the same nutritional status, when they undergo clinical events. Finally, we only used the CONUT score to determine nutritional status. Therefore, we were not able to make a comparison with other nutritional scores with proven prognostic value.

In conclusion, the CONUT score is a critical measure used to evaluate the nutritional status of patients with AF. In our study, major bleeding and mortality rates increased, particularly in AF patients aged 65 and over who used anticoagulants and experienced moderate to severe malnutrition. We believe that the use of DOACs would be more appropriate in this patient group.

Ethics Committee Approval: The study protocol was approved by the Mardin Artuklu University Ethics Committee (date: 06.11.2023, no: 2023/11-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Idea/concept, design, control/supervision, data collection and/or processing, analysis and/or interpretation, literature review, writing the article, critical review, references and fundings, materials: R.K.; Design, control/supervision, data collection and/or processing, literature review, critical review, references and fundings, materials: A.F.K.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):18-25
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1568
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Clinical predictors of fragmented QRS and abnormal QRS-T angle in type 2 diabetic patients without known cardiovascular diseases

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Received: October 21, 2023 ***Accepted:*** January 06, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aims to investigate the association of clinical and glycemic parameters with fragmented QRS (fQRS) and frontal plane QRS-T (fQRS-T) angle in type 2 diabetes mellitus (DM) patients without a known cardiovascular disease (CVD).

Patients and methods: Between September 2020 and September 2021, a total of 414 consecutive type 2 DM patients (209 males, 205 females; mean age: 44.7±6.1 years; range, 33 to 61 years) without established CVD were included in this prospective study. The patients were divided into two groups according to presence or absence of fQRS on electrocardiography (ECG). Clinical and glycemic parameters of patients were compared based on fQRS, fQRS-T angle, and disease duration of DM.

Results: The frequency of fQRS on ECG was 22.9%. The glycated hemoglobin (HbA1c) levels were higher, and DM duration was longer in patients with fQRS compared to those without fQRS and in patients with fQRS-T angle >90° compared to patients with fQRS-T angle ≤90°. The frequency of fQRS and mean fQRS-T angle were significantly higher in patients with DM duration ≥10 years compared to those with DM duration <10 years. Multivariate analysis revealed that HbA1c and DM duration were independent predictors of both presence of fQRS on ECG ($p<0.001$ for both) and fQRS-T angle >90° ($p<0.001$ for both).

Conclusion: The fQRS and fQRS-T angle may predict hyperglycemic status and subclinical cardiovascular involvement in type 2 DM patients without known CVDs.

Keywords: Diabetes mellitus, diabetic cardiomyopathy, electrocardiography, fragmented QRS, frontal plane QRS-T angle.

Diabetes mellitus (DM) is a major risk factor for cardiovascular diseases (CVDs), and atherosclerotic CVD is the leading cause of morbidity and mortality in diabetic patients.[1] Besides its role in the accelerated and exaggerated atherosclerosis in the coronary arteries, DM has also direct toxic effects to the myocardium that may cause myocardial fibrosis and diabetic cardiomyopathy.[2,3] Therefore, early detection and accurate management of subclinical abnormalities in the cardiac structure and functions is essential for adequate prevention of established CVDs in diabetic patients.[4] Electrocardiography (ECG) has a crucial role in the diagnosis and monitoring of diabetic cardiomyopathy, and several ECG alterations can be seen in diabetic patients even when cardiac involvement is clinically not yet evident.[5,6] Moreover, ECG alterations may independently predict future cardiovascular events in patients with DM.[7,8] However, no ECG changes have been reported to be specific to diabetic cardiomyopathy yet, and little is still known regarding the association of clinical and glycemic parameters with ECG alterations in diabetic patients without known CVDs.

Fragmented QRS (fQRS) and increased frontal plane QRS-T (fQRS-T) angle are ECG signs of myocardial fibrosis and damage and are independent predictors of adverse cardiovascular events in a wide variety of patients with and without CVDs.[9-16] More importantly, the presence of fQRS on ECG and increased fQRS-T angle, particularly an angle >90°, seem to be associated with subclinical myocardial damage and predict adverse cardiovascular events independently in diabetic patients.[17-19] However, the

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Citation:
Eyüboğlu M, Çelik A. Clinical predictors of fragmented QRS and abnormal QRS-T angle in type 2 diabetic patients without known cardiovascular diseases. Cardiovasc Surg Int 2024;11(1):18-25. doi: 10.5606/e-cvsi.2024.1568.

association of glycemic parameters with these ECG abnormalities in patients with DM has not been well established yet.

In the present study, we aimed to investigate the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle in diabetic patients without known CVDs and to identify the predictors of fQRS and increased fQRS-T angle in patients with type 2 DM in the absence of CVD.

PATIENTS AND METHODS

Study population

This prospective study was conducted at Gaziosmanpaşa University School of Medicine, Department of Cardiology between September 2020 and September 2021. A total of 453 consecutive patients with known diagnosis of type 2 DM and without established CVD were screened. Among these, 39 patients were excluded due to presence of complete or incomplete bundle branch block on ECG. Finally, the remaining 414 patients (209 males, 205 females; mean age: 44.7±6.1 years; range, 33 to 61 years) were included in the study. The patients were divided into two groups according to presence or absence of fQRS on ECG. Also, patient characteristics were compared based on fQRS-T angle and DM duration, and the association of clinical and glycemic parameters with fQRS and fQRS-T angle was investigated. Clinical and demographic characteristics of patients were recorded at baseline. Diabetes duration was defined based on the patients' medical records. Biochemical analyses were performed using venous blood samples obtained after an overnight fasting. Echocardiography was performed to all participants to assess the cardiac functions. Hypertension was defined as systolic blood pressure levels of ≥140 mmHg and/or diastolic blood pressure levels of ≥90 mmHg and/or known treatment with antihypertensive medications. Diabetes mellitus was defined as at least two fasting plasma glucose levels of ≥126 mg/dL, or 2-h plasma glucose levels of ≥200 mg/dL, or glycated hemoglobin (HbA1c) levels of ≥6.5% or known treatment with antidiabetic drugs.[20] Smoking was defined as the regular use of cigarettes.

ECG, fQRS, and fQRS-T angle

A standard 12-lead surface ECG (Nihon Kohden, Tokyo, Japan) using a 0.16 to 100 Hz filter range, 25 mm/s speed, and 10 mm/mV amplitude was obtained from all patients. The fQRS was defined as presence of various morphologies in the original QRS complex (<120 ms) which included an additional R wave (R') or notching in the nadir of the S wave, or >1 R' (fragmentation) in two contiguous leads, corresponding to a major coronary artery territory.[21] The fQRS was reported according to its localization on ECG as: fQRS in anterior leads (V1 to V5), inferior leads (DII, DIII, and aVF) and lateral leads (V6, DI and aVL). The fQRS-T angle, which describes the angular difference between depolarization and repolarization vectors, was calculated as absolute difference between QRS axis and T wave axis obtained from automated ECG reports. If the angle exceeded 180°, it was calculated by subtracting from 360°.[12,22] All ECGs were analyzed by two experienced independent cardiologists who were totally blinded to the study protocol. In case of disagreement regarding the presence of fQRS, the final decision was achieved by mutual agreement. Figure 1 demonstrates an example of fQRS and measurement of fQRS-T angle from a 12-lead surface ECG.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. The normality distribution of continuous variables was tested using the Kolmogorov-Smirnov or Shapiro Wilk tests. Continuous variables were compared using the independent samples Student t-test and categorical data were compared using chi-square test or Fisher exact test. The Spearman or Pearson correlation coefficients were used to investigate the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle. Multivariate logistic regression analysis was performed to identify the independent predictors of fQRS and increased fQRS-T angle. All variables with a p value of <0.1 in the univariate analysis were included in the model. A p value of <0.05 was considered statistically significant.

RESULTS

The mean DM duration was 4.7±3.3 years and the frequency of fQRS on ECG was 22.9%. The patients with fQRS were older, had significantly higher fasting glucose and HbA1c values, and duration of DM was significantly longer compared to those without fQRS.

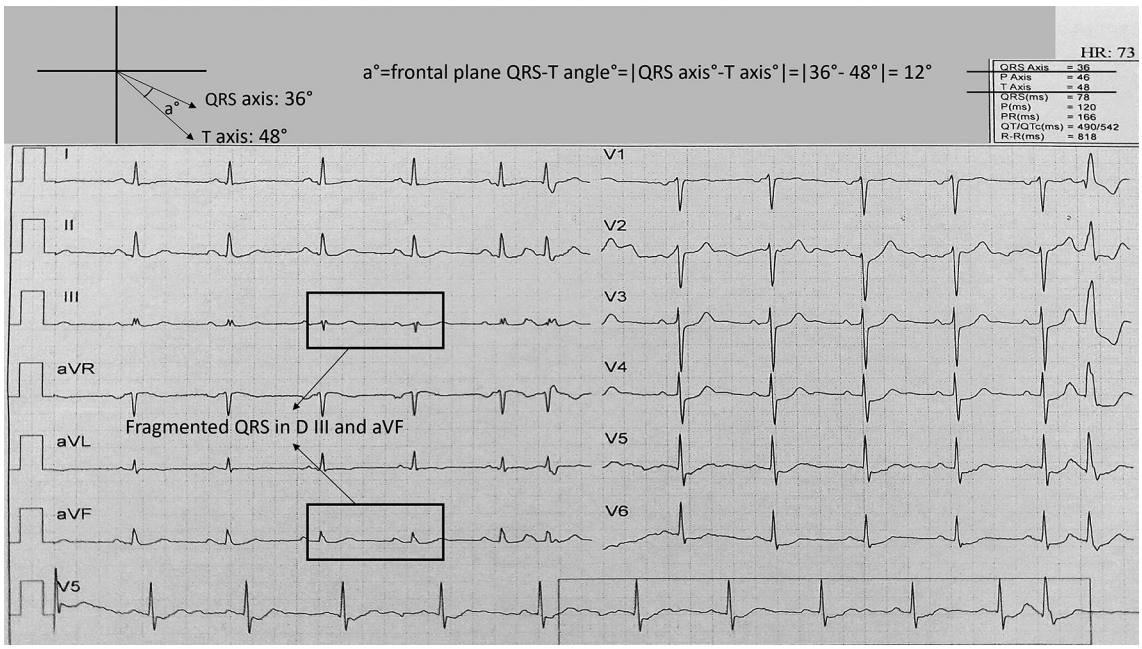

Figure 1. An example of fQRS and measurement of frontal plane QRS-T angle from a 12-lead surface electrocardiography.

Table 1
Clinical characteristics of patients with and without fragmented QRS

Variables	fQRS (n=95)			No fQRS (n=319)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (year)			46.5±6.4			44.2±5.9	0.001
Sex Male	49	51.6		160	50.2		0.808
Body mass index (kg/m^2)			28.1±2.24			27.8±2.04	0.239
Hypertension	39	41.1		128	40.1		0.872
Smoking	27	28.4		96	30.1		0.754
Fasting glucose (mg/dL)			148±20.7			144±11.5	0.019
HbA1c (%)			7.29±0.80			6.90±0.38	<0.001
Diabetes duration (year)			6.86±3.94			4.11±2.85	<0.001
fQRS-T angle (°)			62.39±39.49			53.47±28.90	0.016
Creatinine (mg/dL)			1.04±0.27			0.98±0.30	0.086
Aspartate aminotransferase (U/L)			21.37±6.82			20.80±5.93	0.431
Thyroid-stimulating hormone (μIU/mL)			2.60±0.65			2.48±0.49	0.058
Hemoglobin (g/dL)			12.75±1.10			12.65±1.15	0.482
White blood cell count (×10^3/μL)			7.79±1.24			7.53±1.06	0.053
Platelet count (×10^3/μL)			262.63±59.16			272.97±56.21	0.121
Triglyceride (mg/dL)			144.56±52.61			140.91±43.84	0.499
LDL-cholesterol (mg/dL)			117.37±30.32			115.82±22.85	0.593
HDL-cholesterol (mg/dL)			41.68±6.14			42.20±4.59	0.370

fQRS: Fragmented QRS; SD: Standard deviation; HbA1c: Hemoglobin A1c; fQRS-T angle: Frontal plane QRS-T angle; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 1 demonstrates the clinical characteristics of patients with and without fQRS.

The mean fQRS-T angle was 55.5°±31.8°, and while 62 (15%) patients had fQRS-T angle >90°, 352 (85%) patients had fQRS-T angle ≤90°. The patients with fQRS-T angle >90° were older, had worse renal functions, and had higher frequency of male gender, hypertension and fQRS compared to those with fQRS-T angle ≤90°. The HbA1c levels were significantly higher and DM duration was also significantly longer in patients with fQRS-T angle >90° compared to patients with fQRS-T angle ≤90°. Table 2 shows the clinical characteristics of patients according to fQRS-T angle.

Additionally, DM duration was ≥10 years in 57 (13.8%) patients. The patients with DM duration ≥10 years were older and had significantly higher HbA1c values. The frequency of fQRS and mean fQRS-T angle were also significantly higher in patients with DM duration ≥10 years compared to those with DM duration <10 years. Table 3 shows the clinical characteristics of patients according to DM duration. The correlation analyses revealed that there was a strong positive correlation between fQRS-T angle and DM duration (r=0.783, p<0.001), a moderate positive correlation between fQRS-T angle and HbA1c (r=0.646, p<0.001), a low positive correlation between fQRS and HbA1c (r=0.472, p<0.001), and a moderate positive correlation between fQRS and DM duration (r=0.558, p<0.001).

The multivariate analysis demonstrated that HbA1c (odds ratio [OR]: 1.136, 95% confidence

Table 2
Comparison of clinical characteristics of patients according to frontal plane QRS-T angle

	fQRS-T angle (>90°) (n=62)			fQRS-T angle (≤90°) (n=352)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.6±5.7			43.3±5.0	<0.001
Sex							0.036
Male	36	58.1		173	49.1		
Body mass index (kg/m^2)			29.3±1.51			27.6±2.08	<0.001
Hypertension	30	48.4		137	38.9		0.022
Smoking	22	35.5		101	28.7		0.118
fQRS	30	48.4		65	18.5		<0.001
Localization of fQRS							0.227
Anterior	11	36.7		18	27.7		
Inferior	11	36.7		36	55.4		
Lateral	8	26.6		11	16.9		
Fasting glucose (mg/dL)			145±16.0			145±13.9	0.968
HbA1c (%)			7.90±0.55			6.78±0.33	<0.001
Diabetes duration (year)			10.68±3.01			3.69±2.04	<0.001
Creatinine (mg/dL)			1.41±0.28			0.92±0.23	<0.001
Aspartate aminotransferase (U/L)			21.06±4.84			20.90±6.34	0.854
Thyroid-stimulating hormone (μIU/mL)			2.25±0.43			2.55±0.54	0.042
Hemoglobin (g/dL)			12.21±0.91			12.76±1.16	0.016
White blood cell count (×10^3/μL)			7.53±0.99			7.60±1.31	0.622
Platelet count (×10^3/μL)			205.32±66.80			282.10±46.50	0.006
Triglyceride (mg/dL)			138.18±59.31			142.51±41.94	0.371
LDL-cholesterol (mg/dL)			120.81±24.01			115.36±24.80	0.110
HDL-cholesterol (mg/dL)			41.94±6.52			42.11±4.28	0.486

fQRS: Fragmented QRS; SD: Standard deviation; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 3
Clinical characteristics of patients according to diabetes duration

	Duration ≥10 years (n=57)			Duration <10 years (n=357)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.7±5.8			43.5±5.1	<0.001
Sex							
Male	31	54.4		178	49.8		0.271
Body mass index (kg/m^2)			29.2±1.35			27.6±2.11	<0.001
Hypertension	29	50.9		138	38.7		0.008
Smoking	19	33.3		104	29.1		0.356
fQRS-T angle (°)			112±20.4			47±22.9	<0.001
fQRS	25	43.9		70	19.6		<0.001
Localization of fQRS							0.124
Anterior	10	40.0		19	27.1		
Inferior	8	32.0		39	55.7		
Lateral	7	28.0		12	17.1		
Fasting glucose (mg/dL)			145±16.2			145±13.8	0.855
HbA1c (%)			7.86±0.57			6.80±0.37	<0.001
Creatinine (mg/dL)			1.43±0.26			0.93±0.24	<0.001
Aspartate aminotransferase (U/L)			20.86±4.44			20.94±6.37	0.923
Thyroid-stimulating hormone (μIU/mL)			2.24±0.46			2.57±0.56	0.028
Hemoglobin (g/dL)			12.32±0.88			12.73±1.03	0.044
White blood cell count (×10^3/μL)			7.49±0.92			7.62±1.16	0.562
Platelet count (×10^3/μL)			245.43±56.72			274.46±61.36	0.088
Triglyceride (mg/dL)			140.26±47.61			142.21±51.67	0.613
LDL-cholesterol (mg/dL)			121.22±22.46			116.16±28.44	0.362
HDL-cholesterol (mg/dL)			40.86±5.37			42.31±4.81	0.058

SD: Standard deviation; fQRS: Fragmented QRS; HbA1c: Hemoglobin A1c; LDL: Low-density lipoprotein; HDL: High-density lipoprotein.

Table 4
Independent predictors fragmented QRS and frontal plane QRS-T angle >90° in multivariate analysis

	OR	95% CI	*p*
Fragmented QRS			
HbA1c	1.136	1.054-1.918	<0.001
Diabetes duration	1.201	1.176-2.132	<0.001
Frontal plane QRS-T angle >90°			
Creatinine	1.447	1.157-1.985	<0.001
Age	1.572	1.168-2.241	<0.001
HbA1c	1.772	1.314-2.612	<0.001
Diabetes duration	2.463	1.854-3.217	<0.001

OR: Odds ratio; CI: Confidence interval; HbA1c: Hemoglobin A1c.

interval [CI]: 1.054-1.918, p<0.001) and DM duration (OR: 1.201, 95% CI: 1.176-2.132, p<0.001) were the independent predictors of fQRS on ECG, and creatinine level (OR: 1.447, 95% CI: 1.157-1.985, p<0.001), age (OR: 1.572, 95% CI: 1.168-2.241, p<0.001), HbA1c (OR: 1.772, 95% CI: 1.314-2.612, p<0.001) and DM duration (OR: 2.463, 95% CI: 1.854-3.217, p<0.001) were the independent predictors of fQRS-T angle >90°. Table 4 shows the independent predictors fQRS and fQRS-T angle >90° in the multivariate analysis.

DISCUSSION

The main finding of the present study was that HbA1c and DM duration were significantly associated with the presence of fQRS on ECG and increased fQRS-T angle in DM patients, even in the absence of clinically evident CVDs. These results suggest that both ECG parameters may be useful to demonstrate and monitor the subclinical myocardial damage in DM patients without established CVDs.

Diabetes mellitus causes significant changes in the physiological properties of the myocardium that leads myocardial fibrosis and diabetic cardiomyopathy,[2,3] and CVD is the major cause of mortality in patients with type 2 DM.[1,23] Of note, ECG has a crucial role in the monitoring of diabetic cardiomyopathy and ECG alterations detected in the clinical follow-up of DM patients are associated with both clinical and subclinical myocardial involvement, and significantly predict adverse cardiovascular events.[5-8] However, little is known regarding the relationship of clinical and glycemic parameters with fQRS and fQRS-T angle in asymptomatic patients with type 2 DM. The fQRS is a depolarization abnormality that is an ECG sign of myocardial fibrosis and damage and is an independent predictor of future cardiovascular events in a wide variety of patients with and without CVD.[9-11,24-26] More importantly, fQRS is significantly associated with subclinical myocardial fibrosis, deteriorated cardiac functions, and adverse events in DM patients even in the absence of apparent CVD.[17,18,27,28] Additionally, as a sign of ventricular repolarization heterogeneity, increased fQRS-T angle is a predictor of abnormal cardiac functions and is associated with adverse cardiovascular events independent of underlying cardiovascular status.[12,13] Moreover, increased fQRS-T angle is significantly associated with diabetic cardiomyopathy and adverse cardiovascular events in DM patients.[19] In this context, both ECG parameters seem to be useful in the monitoring of diabetic cardiomyopathy and to demonstrate the early-stage myocardial fibrosis and damage before the emergence of manifest CVD in patients with DM.

The HbA1c level is a sign of mean blood glucose concentrations over the preceding three months, considered as a cardiovascular risk factor and is significantly associated with cardiovascular complications and adverse cardiovascular events in patients with DM.[1,8] More importantly, hyperglycemia and HbA1c is the leading cause of ECG abnormalities in patients with DM.[5,8] However, little is known regarding the relationship of HbA1c with fQRS and fQRS-T angle in DM patients without known CVD. The results of our study demonstrated that HbA1c was an independent predictor of fQRS on ECG and increased fQRS-T angle and we found a significant positive correlation between HbA1c levels and both ECG parameters. Therefore, our results suggest that fQRS and fQRS-T angle may be useful ECG findings to demonstrate the hyperglycemia related subclinical myocardial damage in the early phase of diabetic cardiomyopathy before the occurrence of clinically evident CVD. Additionally, DM duration is usually considered as a cardiovascular risk factor and is significantly associated with diabetic cardiomyopathy and future cardiovascular events in asymptomatic patients with type 2 DM independent of coexisting risk factors.[8,29] Nevertheless, the impact of DM duration on ECG parameters has not been well described yet. In the present study, we demonstrated that prolonged DM duration was the most powerful predictor of presence of fQRS on ECG and increased fQRS-T angle in DM patients without known CVD. In this context, both ECG parameters may be considered as the ECG signs of prolonged DM duration related subclinical diabetic cardiomyopathy. Hence, fQRS and fQRS-T angle may have a significant association with prolonged hyperglycemia and DM duration and may be useful in the monitoring of subclinical diabetic cardiomyopathy.

Nonetheless, there are some limitations in this study. The main limitation was the lack of data regarding the clinical events. However, this study was not a follow-up study and the association of both ECG parameters with cardiovascular events is well described in previous studies. Also, the clinical importance of our findings needs to be investigated in further

studies to demonstrate whether effective treatment of DM leads disappearance of fQRS or narrowing in the fQRS-T angle. Finally, the absence of confirmation of subclinical myocardial fibrosis with cardiac magnetic resonance imaging is another limitation.

In conclusion, type 2 DM confers a significant increase in the risk of CVD and CVD is the leading cause of mortality in DM patients. The ECG has an important role in the monitoring of diabetic cardiomyopathy and demonstrating the cardiovascular involvement in patients with type 2 DM. Our study results demonstrated that glycemic parameters HbA1c and DM duration were significantly associated with fQRS and increased fQRS-T angle in type 2 DM patients without manifest CVDs. Therefore, both ECG parameters may be useful in the monitoring glycemic status and cardiovascular involvement in type 2 DM patients without known CVDs.

Ethics Committee Approval: The study protocol was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (date: 25.06.2020, no: 20-KAEK-151). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Idea/concept, data collection and/or processing, writing the article: M.E.; Design, control/supervision, analysis and/or interpretation, literature review, critical review: M.E., A.Ç.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):26-32
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1606
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Experiences with extracorporeal membrane oxygenation in severe COVID-19 infection: A single-center retrospective study

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Received: January 24, 2024 ***Accepted:*** March 11, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aimed to share our experiences using extracorporeal membrane oxygenation (ECMO) for severe coronavirus disease 2019 (COVID-19) to explain the mechanisms of disease and death related to COVID-19 and improve ECMO supportive treatment.

Patients and methods: This retrospective study was conducted with 26 COVID-19 patients (10 males, 16 females; mean age: 34.4±11.5 years; range, 12 to 59 years) who received ECMO support between January 1, 2021, and December 31, 2021. A multidisciplinary team closely followed patients with COVID-19 who required ECMO support. The data were carefully recorded, and their effects on ECMO follow-up and the results obtained were examined.

Results: Only 34.6% of the patients were able to come off ECMO support, and the mortality rate during ECMO support was 80.8%. However, the mortality rate for weaned patients decreased significantly over the last six months.

Conclusion: Overall, our findings suggest that ECMO intervention should be done early for better treatment outcomes, and mild sedation in ECMO follow-up for COVID-19 patients is linked to lower mortality rates.

Keywords: Conscious sedation, COVID-19, ECMO, respiratory distress syndromes.

Coronavirus disease 2019 (COVID-19) is a pandemic with a high mortality rate, particularly among patients who require mechanical ventilation. Much is still unknown about this virus, such as its natural history, long-term complications, virus persistence, or prognosis in different patient subgroups.[1] Extracorporeal membrane oxygenation (ECMO) may be appropriate for patients with severe heart and lung failure due to COVID-19, resistance to mechanical ventilation, and other optimal medical treatments.[2] The mortality rate is higher in patients on ECMO support due to the progression of COVID-19 to acute respiratory distress syndrome (ARDS).[3,4] Available data on using ECMO in these patients are limited, and earlier results are discouraging.[5]

In this study, we shared our experiences using ECMO for severe COVID-19 in a pandemic hospital. We believe that, with similar studies, the mechanisms of disease and death related to COVID-19 can be better understood, and ECMO-supportive treatment can be applied more healthily in patients.

PATIENTS AND METHODS

In this retrospective study, 26 patients (10 males, 16 females; mean age: 34.4±11.5 years; range, 12 to 59 years) hospitalized in the intensive care unit of the Sancaktepe Sehit Prof. Dr. İlhan Varank Education and Research Hospital due to COVID-19 infection between January 1, 2021, and December 31, 2021 were evaluated. Patients with COVID-19 who required ECMO support during

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Citation:
Durmaz A, Özen Y, Özbek İC, Adıyeke E, Kerimoğlu S, Uğur M. Experiences with extracorporeal membrane oxygenation in severe COVID-19 infection: A single-center retrospective study. Cardiovasc Surg Int 2024;11(1):26-32. doi:10.5606/e-cvsi.2024.1606.

the follow-up period were included in the study. Patient demographics, clinical information, and laboratory findings were obtained from the medical records.

Indications for ECMO for patients whose hypoxic respiratory failure persisted despite adequate ventilation therapy were determined following the Extracorporeal Life Support Organization (ELSO) Guidelines on ARDS as severe hypercapnia (pH <7.2 and $PaCO_2$ (partial pressure of carbon dioxide) >80 in 6 h), prolonged ventilation (>7 days), and refractory cardiogenic shock (determined as Murray score >3 or one organ failure in COVID-19 patients with or without comorbidity).

The patients were closely followed during ECMO support in the intensive care unit by a multidisciplinary team of cardiovascular surgeons, intensivists, and perfusion specialists. The ventilator values, time required for intensive care, need for mechanical ventilation afterward, and treatment protocols received during this process before ECMO support for ARDS were recorded. The treatments and doses administered to the patients with underlying diseases were evaluated during ECMO support. Data on ECMO-related complications and their etiologies were examined to evaluate complications associated with ECMO support.

During this process, different levels of sedation were applied to patients, and their alertness levels were recorded. A reanimation and anesthesiology specialist prepared the sedation protocol using ECMO support. The Richmond Agitation Sedation Scale (RASS) was used in the follow-up of patients to evaluate the level of sedation in detail and allow drug titration. We applied light (RASS +1/–1), moderate (RASS –2/–3), and deep (RASS –4/–5) sedation according to the RASS. It was evaluated whether the data obtained varied among the patients in whom ECMO support could be safely terminated.

Statistical analysis

All statistical analyses were performed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to test the normality of the data distribution. Continuous variables were expressed as mean ± standard deviation (SD) and median (25^{th}-75^{th} percentiles), and categorical variables were expressed as frequency (percentage). Nonnormally distributed continuous variables were compared between the groups using the Mann-Whitney U test. Categorical variables were compared between the groups using Fisher exact chi-square test and Yates' chi-square test. Statistical significance was defined as a two-sided p-value <0.05.

RESULTS

The patients' mean body mass index was 27.38±2.71. All the patients had severe ARDS that

Table 1
Mean times and values in patient follow-up

	First 6 months			Last 6 months			
	Median	25^{th}-75^{th} percentile	Min-Max	Median	25^{th}-75^{th} percentile	Min-Max	*p*
Time from onset of symptoms to admission to intensive care unit (days)	6	3-8	1-14	9	6-10	2-20	0.830
Time from admission to intensive care unit to intubation (days)	1	0-1	0-3	1	0-5	0-37	0.778
Duration of mechanical ventilator support (days)	14	10-28	9-79	24	5-38	1-100	0.778
Time from intubation to ECMO support (days)	6	1-20	0-24	2	0-7	0-30	0.254
Duration of stay in the intensive care unit	16	11-48	9-66	24	8-38	2-100	0.778
Average values before ECMO support							
pO_2 (mmHg)	49.6	46.7-53.8	34-128	46.1	37.4-73.6	30.2-88.1	0.231
pCO_2 (mmHg)	49.6	46.7-53.8	34-128	42	35.2-61	23-116	0.461
FiO_2 (%)	100	100-100	100-100	1000	100-100	100-100	0.692

ECMO: Extracorporeal membrane oxygenation; pO_2: Partial pressure of oxygen; pCO_2: Partial pressure of carbon dioxide; FiO_2: Fractional inspired oxygen.

progressed rapidly during the follow-up period. All adult patients were healthy before the COVID-19 diagnosis. Known coronary artery disease and smoking rates were 3.8%. Two of the three patients in the pediatric age group had different syndromes, such as hemolytic uremic syndrome and Kawasaki syndrome.

The median time from the onset of all patients' symptoms to the time they needed intensive care was 8.62 days. Support with ECMO was required with a median of 4.27 days after intubation (Table 1). While venovenous ECMO support was performed in 76.9% of the patients, venoarterial ECMO (VA-ECMO) support was provided in 23.1% due to septic conditions. Femorojugular access was performed in 84.6% of the patients. Distal perfusion was achieved in all patients receiving VA-ECMO support. The median intubation duration was 17.5 days. Tracheostomy was required in 34.6% of the patients. Although ECMO support was initiated under sedation, almost 19.2% of the patients were awake during ECMO. The median length of stay of the patients in the intensive care unit was 22.50 days, and the hospitalization period was 35.27 days (Table 1).

All patients were administered appropriate antibiotics according to the recommendations of the Department of Infectious Diseases, and additional antiviral treatment was administered to 73.1%. Various complications developed due to the length of intensive care unit stay. The infection progressed to sepsis in 92.3% of the patients, and multiple organ failure developed in 26.9%. All the complications are presented in Table 2.

Table 2
Rates of ECMO supportive therapy

	n	%
Rates pertaining to the application		
Venovenous ECMO	20	76.9
Venoarteriel ECMO	6	23.1
Femoro-jugular access	22	84.6
Femoro-femoral access	4	15.4
Distal perfusion	6	100
Awake ECMO	5	19.2
Need for tracheostomy	9	34.6
Applied medical treatments:		
Antibiotic therapy	26	100
Antiviral therapy	19	73.1
Steroid therapy	24	92.3
Inotrope support	25	96.2
Vasopressor therapy	21	80.8
Renal replacement therapy	4	15.4
Plasmapheresis	7	26.9
Heparin (Anticoagulant therapy)	8	30.8
Bivalirudin (Anticoagulant therapy)	18	69.2
Antiplatelet therapy	3	11.5
Complications and outcome of ECMO support		
Sepsis	24	92.3
Multiple organ failure	7	26.9
Renal failure	3	11.5
Major bleeding	5	19.2
Ischemic CVD	1	3.8
Pneumothorax	9	34.6
Pulmonary hemorrhage and hemothorax	4	15.4
Weaning	9	34.6
Mortality	21	80.8

ECMO: Extracorporeal membrane oxygenation; CVD: Cerebrovascular disease.

It was observed that in the first six months after ECMO support treatment was started, weaning could be performed in three out of seven patients, but all of the patients died. Weaning was performed in six of the 19 patients over the next six months, and five survived. No statistically significant difference was observed between the mortality and weaning rates (p=0.342 and p=0.661, respectively). However, a statistically significant 83.3% of patients who underwent weaning in the last six months survived.

DISCUSSION

Coronavirus disease 2019 is a highly contagious disease that infects millions of people worldwide.[6] Symptoms in COVID-19 patients are variable and can progress from mild to severe symptoms that can result in ARDS, multiple organ failure, or death.[7] A practical and specific treatment for COVID-19 has yet to be proven. According to the World Health Organization, COVID-19 management mainly focuses on infection prevention, case detection and monitoring, and supportive care.

The World Health Organization and Centers for Disease Control and Prevention have published recommendations regarding ECMO support in patients with severe or critical respiratory failure and cardiac involvement who do not respond to conventional therapy.[8] Extracorporeal membrane oxygenation is a form of extracorporeal life support that temporarily compensates for deficient lungs or a failing heart by oxygenating the blood while minimizing iatrogenic ventilator-induced lung injury.[9]

Poor outcomes in patients undergoing ECMO during the COVID-19 pandemic include old age, low PaO_2 (arterial oxygen partial pressure)/FiO_2 (fractional inspired oxygen) ratio, immunocompromised status, comorbidities, and need for VA-ECMO.[9] Decisions on ECMO support should also consider these factors and the patient's condition.[10] In our study, only one patient had coronary artery disease. One patient had a history of smoking but no chronic obstructive pulmonary disease diagnosis. Our patients were mainly young, with a mean age of 34.4±11.5 years. No statistically significant correlation was found between the patient's age, other diseases, smoking history, prolonged intensive care follow-up, and the need for ECMO support.

ECMO therapy can be organized into two basic methods: venovenous ECMO and VA-ECMO. For ARDS, such as COVID-19, and its respiratory complications, the predominantly used ECMO mode is venovenous.[4,11] However, pulmonary complications, such as ARDS, and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection may also cause cardiovascular damage. In this case, VA-ECMO mode was used. The rate of cardiorespiratory combined ECMO support (VA or venoarteriovenous ECMO) among COVID-19 patients was <10%, and these patients were found to have poor prognosis.[12] In our study, only 11.53% of the patients required VA-ECMO, and 66.6% survived. Three of these patients were in the pediatric age group and received VA-ECMO support for multisystem inflammatory syndrome.

It is thought that there is a relationship between the early initiation of ECMO treatment and survival. It is not recommended after lung damage due to advanced mechanical ventilation support and after end-organ dysfunction has started.[13] However, in the first and last six months, no significant statistical difference existed between the start of the patient's symptoms and the timing of intensive care unit hospitalization, intubation, or the beginning of ECMO support and treatment (p=0.083, p=0.778, and p=0.254, respectively). In addition, there were no significant statistical differences in the first and last six months' levels of pO_2 (partial pressure of oxygen), pCO_2 (partial pressure of carbon dioxide), and FiO_2 values obtained before ECMO support. (p=0.231, p=0.461, and p=0.692, respectively).

Weaning could be performed in only 42.92% of the patients who were in the first six months of follow-up, but none survived among these patients. In the last six months of follow-up, weaning was performed in 31.6% of the patients; 83.3% of these patients achieved weaning, and the mortality rate was 16.6%. While there was no significant statistical difference between the mortality rates in the first and last six months, it was observed that mortality between weaning decreased, particularly in the previous six months (p=0.002).

Patients with COVID-19 may require more sedation than critically ill patients due to their younger age, higher respiratory pathologies, increased clearance from other drugs, and intense inflammatory responses.[14] Sedatives and neuromuscular blocking drugs eliminate asynchronies that occur with mechanical ventilation.[15] There are more detailed studies on the effects of sedative agents on oxygen

and energy consumption;[16] however, these studies are few and contradictory.[17,18] Murphy et al.[19] showed that critical respiratory events in the postanesthesia care unit are closely related to the high incidence of severe residual blockade. In this study, most patients were curarized (80.76%). Patients (19.23%) who did not experience tachypnea, deep hypercarbia, or hypoxia during the intensive care follow-up and whose hemodynamics were more stable than others were not curarized during their follow-up.

The sedation follow-up of the patients was performed using the RASS since it shows the sedation levels in detail and allows the titration to be made more easily in drug treatment.[20] Propofol, remifentanil, midazolam, remifentanil, and dexmedetomidine with or without remifentanil were alternately administered as sedation agents. Short-acting sedation agents were preferred and stopped once daily, and the state of consciousness was evaluated and monitored neurologically. The mean RASS of the patients who were followed up for the first six months was −4.6±0.467, and for the patients who were followed up in the last six months, it was −4.0±1.76. In the previous six months, the patients who underwent weaning from ECMO and survived were not curarized, and four of them were followed by RASS -1 and one with −3 (mean: −1.4±0.89). This difference was statistically significant ($p<0.001$).

The use of ECMO is associated with significant risks, such as bleeding, infection, need for frequent transfusions, stroke, and embolisms of small blood clots or air bubbles.[21] Major bleeding, pulmonary hemorrhage, and hemothorax were detected in 19.2% and 15.4% of the patients, respectively. Multiple organ failure, renal failure, ischemic cerebrovascular events, and pneumothorax were also observed. Sepsis was detected at a high rate (92.3%). This finding was interpreted to be primarily due to ARDS and pneumonia. Only one patient required circuit replacement due to issues with ECMO return.

The European chapter of the ELSO determined the in-hospital mortality rate to be 44% in the first 1,531 COVID-19 patients who received ECMO support.[22-23] However, this rate might be slightly higher than what is known since long-term survival information about patients is unavailable. Another study by Lebreton et al.[24] reported that 46% of the patients were alive 90 days after ECMO onset. The ELSO reported independent mortality factors, such as temporary circulatory support (VA-ECMO support), advanced age, low PaO_2/FiO_2 ratio, acute kidney injury, chronic respiratory failure, immunosuppressed conditions, and a history of cardiac arrest before ECMO.[12] In this study, cardiopulmonary failure was the leading cause of death (73.1%), followed by multiple organ failure (23.1%) and neurological pathologies (3.8%). Only 34.6% of patients were weaned off ECMO. The mortality rate during ECMO support was 80.8%. Of the patients, 42.9% were weaned in the first six months, and 31.6% were weaned in the next six months. In patients who were weaned in the first six months, mortality was 100%, while this rate remained at 16% in the last six months. The mortality ratio of weaning patients was statistically significant ($p<0.001$). Based on our team's increasing experience, we believe that mild sedation was applied to the departure of patients diagnosed with ARDS associated with COVID-19.

There are some limitations to this study. The limited number of patients and retrospective nature of the study make it impossible to evaluate other factors affecting the results and conduct further examinations. The results would be more meaningful if the study had progressed with more patients and instant observations.

In conclusion, venovenous ECMO support remains a salvage treatment for patients with COVID-19 who have refractory hypoxemia despite mechanical ventilation therapy. However, based on these criteria, early intervention is vital for a successful treatment. In light of this retrospective examination, mild sedation during ECMO follow-up in patients with COVID-19 is associated with more positive results. However, more data are needed to finalize this situation and to examine its causes.

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences, Sancaktepe Şehit Prof. Dr. Ilhan Varank Training and Research Hospital Scientific research Ethics Comitee (date: 08.09.2021, no: 2021-188). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Conseptualsation and writing: A.D.; Conceptualisation: Y.Ö.; Data Curation: İ.C.Ö., S.K.; Methodology: E.A.; Methodology and writing: M.U.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):33-41
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1609
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Our clinical experience in the management of COVID-19-related arterial thrombosis with acute limb ischemia

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Received: January 30, 2024 ***Accepted:*** February 15, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aimed to report our clinical experience regarding the surgical management and perioperative treatment strategy of patients who presented to our clinic or were consulted with coronavirus disease 2019 (COVID-19)-associated acute limb ischemia (ALI).

Patients and methods: This retrospective observational single-center study was conducted with 40 patients (26 males, 14 females; mean age: 67.2±16.9 years; range, 26 to 92 years) between January 2020 and April 2021. All the patients diagnosed with mild to severe COVID-19 infection and presenting with ALI were managed and included in the study. The primary outcomes of the study were freedom from reocclusion, freedom from amputation, ALI-related early- to late-term survival, absence of early reocclusion (<30 days), forefoot ischemia, major amputation, and death <24 h after the operation. Secondary outcomes were postoperative complications.

Results: There was a significant relationship between early mortality and main femoral artery involvement (p=0.046). There was also a significant relationship between early mortality and the COVID-19 polymerase chain reaction test (p=0.013). Early mortality was observed in 100% of those who were intubated. Age and median fibrinogen levels of the group with late mortality were significantly higher than the group without late mortality (p=0.014 and p=0.021, respectively). The median fibrinogen levels of those with amputation were found to be significantly higher than those without amputation (p=0.048). Eleven (27.5%) patients included in the study died in the early period, whereas five (12.5%) died in the late period. Amputation was performed in three (7.5%) patients, and complications developed in seven (17.5%) patients.

Conclusion: According to the results of this study, surgical intervention for ALI might be difficult and more challenging than anticipated in patients with COVID-19 due to the hypercoagulable state. Cardiovascular surgeons and physicians should be aware of the benefits of extended pre- and postoperative anticoagulant administration.

Keywords: Acute limb ischemia, arterial thrombosis, COVID-19, embolectomy, thrombectomy.

It has been reported that a coronavirus disease 2019 (COVID-19) infection predisposes to arterial and venous thrombosis, resulting in morbidity and mortality.[1] Due to the nature of the disease, an increase in thromboembolic events has been reported in many cases as a result of the disruption of the coagulation cascade.[2,3]

Acute limb ischemia (ALI) has a symptom duration of less than two weeks and is characterized by a sudden decrease in arterial perfusion of the limb, requiring urgent evaluation and treatment and posing a potential threat to the survival of the limb.[4] In a systematic review of five cohort studies, the incidence of ALI in patients with mildly symptomatic COVID-19 was reported to be 0.4 to 0.9%, compared to 2.5% in critically ill patients (58% of all arterial thrombosis).[5,6]

The pathophysiology of COVID-19-associated ALI is not fully understood. Coagulopathy, hyperinflammation, and endothelial damage are the main factors that lead to micro- and macrovascular thrombosis.[6] Numerous case reports have been published regarding COVID-19-related ALI in patients without known peripheral artery disease and even in young patients without comorbidities or atherosclerosis.[7,8] In particular, some patients may

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Citation:
Özen A, Yiğit G, Yıldırım A, Gül EB, Yılmaz M, İşcan HZ. Our clinical experience in the management of COVID-19-related arterial thrombosis with acute limb ischemia. Cardiovasc Surg Int 2024;11(1):33-41. doi: 10.5606/e-cvsi.2024.1609.

present with ALI as the first sign of a COVID-19 infection.[5] It is crucial to develop treatment strategies based on guidelines and clinical experience to prevent ALI-related morbidity and mortality. Hence, this study aimed to report our clinical experience regarding the surgical management and perioperative treatment strategy of patients who presented to our clinic or were consulted with COVID-19-associated ALI.

PATIENTS AND METHODS

This retrospective observational single-center study was conducted at the Ankara City Hospital between January 2020 and April 2021. A total of 40 patients (26 males, 14 females; mean age: 67.2±16.9 years; range, 26 to 92 years) were included in the study. All the patients diagnosed with mild to severe COVID-19 infection and presenting with ALI were managed and included in the study. Patients younger than 18 years of age, patients with an unconfirmed diagnosis of COVID-19, and pregnant women were excluded. All interventions for aneurysmal disease and carotid artery disease were also excluded.

Tests and methods used in the diagnosis of COVID-19 were positive real-time reverse transcription-polymerase chain reaction (PCR), serology (anti-severe acute respiratory syndrome coronavirus 2 antibodies), and high-resolution chest computed tomography. Blood parameters that could potentially affect the prognosis during hospitalization were collected from patient records and automation systems (e.g., white blood cell count, fibrinogen, and interleukin [IL]-2).

Clinical examination of the vascular system, pulse examination, computed tomography angiography (CTA), and color Doppler ultrasonography evaluations were performed for all patients. In cases where blood flow to the acute extremity was disrupted, with cessation of arterial flow or lack of flow during the color Doppler ultrasonography examination, CTA examination was performed as a further examination. More information was obtained about the extent of the occluded arterial segment, collaterals, and target vessels using CTA. All patients received low-molecular-weight heparin (LMWH) during their hospital stay and for one month after discharge unless they had active bleeding or a high-risk profile for major bleeding. If the D-dimer level was <1000 ng/mL, prophylactic doses of LMWH were administered, and if the D-dimer level was ≥1000 ng/mL or there were additional venous or arterial thromboembolic event risk factors, therapeutic doses were administered. Subsequently, their treatment with oral anticoagulant (warfarin) was adjusted to keep INR (international normalized ratio) levels effective.

Operative procedure

All procedures were performed in the hybrid room, paying attention to appropriate sterilization and wearing personal protective equipment. Most patients with ALI underwent surgical thromboembolectomy using a Fogarty catheter of appropriate diameter and under local anesthesia and appropriate intravenous sedation. Critically ill patients who had been intubated in intensive care units due to COVID-19-related pneumonia were operated on-site under general anesthesia. All patients were given 100 mg/kg of unfractionated heparin and prophylactic antibiotic therapy before arteriotomy. In patients with acute lower extremity occlusion, a standard longitudinal groin incision was made to visualize the common femoral, superficial, and deep femoral arteries. Acute limb ischemia in the upper extremities was managed with a slightly oblique S-shaped incision that visualized the brachial artery. However, in some patients with forearm ALI, the incision was appropriately widened so that selective embolectomy could be performed on the radial or ulnar arteries. All the patients with ALI underwent thromboembolectomy using an appropriately sized Fogarty catheter according to the site of the occlusion, with subsequent revascularization (Figures 1-4).

Outcome measures and follow-up

The primary outcomes of the study were freedom from reocclusion, freedom from amputation, ALI-related early- to late-term survival, absence of early reocclusion (<30 days), forefoot ischemia, major amputation, and death <24 h postoperatively. Secondary outcomes were postoperative complications. All patients received a standardized antithrombotic regimen postoperatively, along with hourly clinical examinations and appropriate blood tests every 8 h. If the hemoglobin was below 8 g/dL, a transfusion of packed red blood cells was administered. A specialist pulmonologist and anesthesiologist frequently examined all the patients throughout the admission course to adjust the type, dose, and interval of antibiotics and antiretroviral treatment. At discharge, every postoperative patient was placed on enoxaparin sodium injections for at-home use at a therapeutic

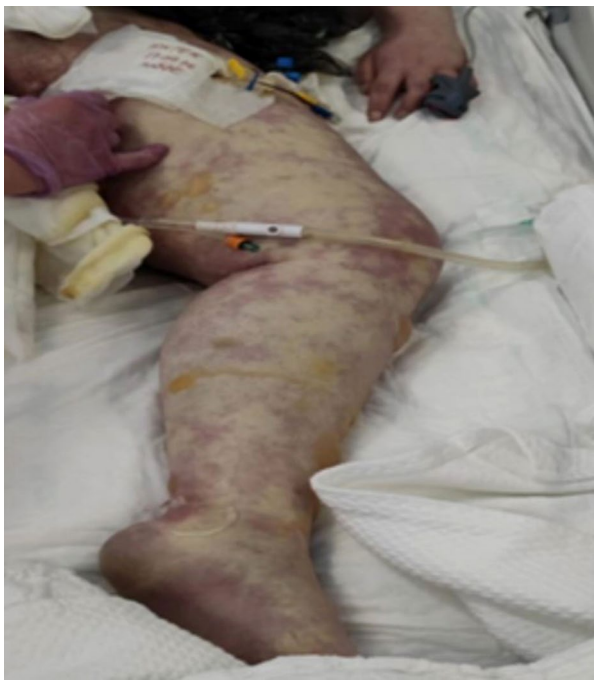

Figure 1. Clinical appearance of lower extremity ALI in a hospitalized patient with COVID-19 (Patient 1).

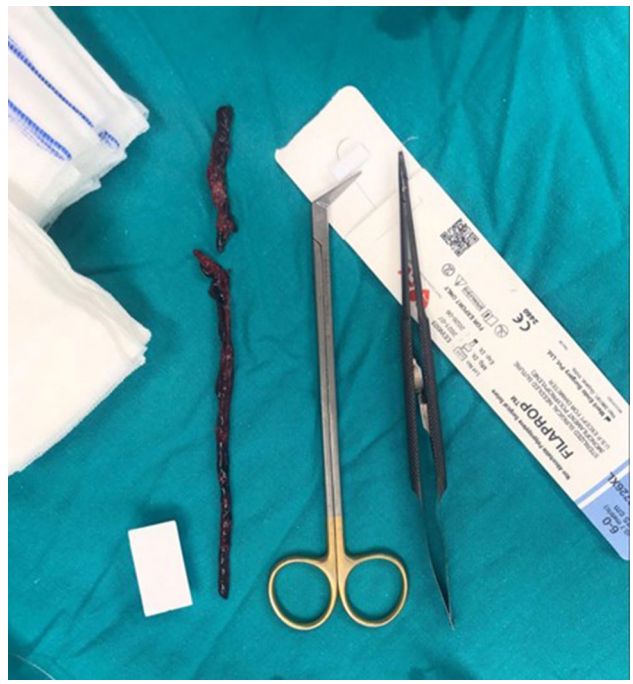

Figure 2. Thrombus material obtained during the surgical thrombectomy procedure performed on Patient 1.

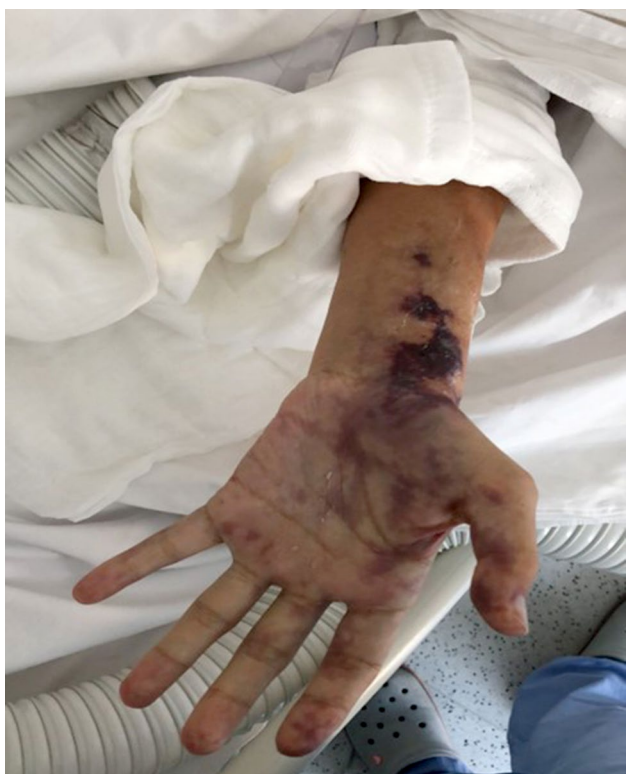

Figure 3. Clinical appearance of upper extremity ALI in a hospitalized patient with COVID-19 (Patient 2).

Figure 4. Thrombus material obtained during the surgical thrombectomy procedure performed on patient 2.

dose or 20 mg of oral rivaroxaban. Patients were followed up at one, three, six, and 12 months and annually thereafter. During the follow-up period, the patients underwent CTA, as well as detailed clinical examinations. Patients requiring reoperation were admitted to the clinic for treatment.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and frequency for categorical variables. Chi-square analysis was used to determine whether there was a relationship between dependent variables (early mortality, late mortality, amputation, and complications) and categorical variables. The Pearson chi-square test result was taken into account if the rate of eyes with an expected frequency of <5 did not exceed 20%. The Mann-Whitney U test was used to determine whether there was a difference between the yes or no categories of dependent variables in terms of numerical variables since parametric test assumptions were not provided. Since a nonparametric test was used, the median (25^{th} percentile-75^{th} percentile or min-max) was used as the descriptor. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline characteristics of the study population are summarized in Table 1. Diabetes mellitus was present in 32.5%, and hypertension was present in 42.5% of the patients. Hyperlipidemia was present in 22.5%, chronic obstructive pulmonary disease in 10%, atrial fibrillation in 20%, coronary artery disease in 27.5%, and chronic kidney disease in 13.9%. Clinical characteristics of the study population is summarized in Table 2. Common femoral artery involvement was present in 37.5%, superficial femoral artery in 50%, and brachial artery in 12.5% of the patients. More than one extremity was involved in 12.5%, and 87.5% of the patients had single extremity involvement.

When the factors affecting early mortality were analyzed, significant differences were found in terms of arterial involvement, COVID-19 PCR test, dyspnea, and intubation compared to other patients. There was a relationship between early mortality and main femoral artery involvement (p=0.046). Accordingly, the early mortality rate in the superficial femoral artery group (6.7%) was lower than in the main femoral artery group (45%). There was also a strong relationship between early mortality and the COVID-19 PCR test (p=0.013). Furthermore, there was a relationship between early mortality and dyspnea (p=0.022).

Table 1
Baseline characteristics of the study population (n=40)

Variables	n	%	Mean±SD
Age (year)			67.2±16.9
Sex			
Male	26	65	
Female	14	35	
Diabetes mellitus	13	32.5	
Atrial fibrillation	8	20	
Family history	2	5	
Congestive heart failure	3	7.5	
Hypertension	17	42.5	
Hyperlipidemia	9	22.5	
Coronary artery disease	11	27.5	
Chronic obstructive pulmonary disease	4	10	
Chronic renal failure	10	25	

SD: Standard deviation.

Table 2
Clinical characteristics of the study population (n=40)

Variables	n	%
Arterial involvement		
Common femoral artery	15	37.5
Superficial femoral artery	20	50
Brachial artery	5	12.5
Extremity involvement		
Single extremity	35	87.5
More than one	5	12.5
COVID-19 PCR test		
Positive	20	50
Negative	20	50
COVID-19 CT signs		
Positive	39	97.5
Negative	1	2.5
Arrhythmia		
Positive	32	75
Negative	8	25
Fever		
Yes	7	17.5
No	33	82.5
Dyspnea		
Yes	21	52.5
No	19	47.5
Intubation		
Yes	8	25
No	32	75

COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction; CT: Computed tomography.

There was also a significant relationship between early mortality and intubation (p<0.001). Early mortality was observed in 100% of those who were intubated, while it was observed in 9.38% of those who were not intubated. Statistical analysis of other factors associated with early mortality is given in Table 3. Median values for white blood cell count, neutrophil count, C-reactive protein, procalcitonin (PRC), IL-6, lactate dehydrogenase, and ferritin of the group with early mortality were higher than the group without early mortality (p<0.05).

There was a relationship between late mortality and dyspnea (p=0.049). Statistical analysis of other factors associated with late mortality is given in Table 4. Age and median fibrinogen levels of the group with late mortality were higher than the group without late mortality (p=0.014 and p=0.021, respectively). The median fibrinogen levels of those with amputation were found to be higher than those without amputation (p=0.048). However, since the overall number of amputations was low (n=3), the power of this result was low. The median platelet levels of those with complications were found to be lower than those without complications (p=0.004).

The mortalities occurring in the first six months of the follow-up were accepted as early mortality, and the mortalities observed later than six months were

Table 3
Statistical analysis of other factors associated with early mortality

	Early mortality						
	No (n=29)			Yes (n=11)			
	Median	25th-75th percentile	Min-Max	Median	25th-75th percentile	Min-Max	*p*
Age (year)	69	56-83	37-92	64	61-73	26-91	0.353
WBC	10670	8480-14800	5960-151300	17700	14150-26600	10400-28900	0.001
NEU	6600	4860-11900	5.92-16900	14500	9600-25800	22.47-27200	0.006
PLT	297	243-341	122-465	223	119-309	54-550	0.196
Fibrinogen	4.01	2.88-4.6	1.87-6.06	3.26	2.3-5.12	1.22-6.47	0.530
CRP	0.04	0.01-0.1	0.001-0.35	0.142	0.096-0.157	0.038-0.2	0.002
D-Dimer	5.01	2-7.22	0.4-35.2	7.6	1.6-10.2	0.7-12.4	0.516
PRC	0.1	0.04-0.2	0.02-45.92	3.11	0.2-7.62	0.11-58.3	0.002
IL-6	22.4	18-31.2	2.93-83.3	44.2	26.2-103	20.1-176	0.023
CK	151	47.65-500	20-6000	192	61-1998	40-34653	0.437
LDH	306	264-429	180-1043	855	686-1174	301-2591	<0.001
Ferritin	440	107.9-582.2	4-4957.3	825	782-6014	233-15052	0.001

WBC: White blood cell count; NEU: Neutrophil count; PLT: Platelet count; CRP: C-reactive protein; PRC: Procalcitonin; IL-6: Interleukin-6; CK: Creatin kinase; LDH: Lactate dehydrogenase.

Table 4
Statistical analysis of other factors associated with late mortality

	Late mortality						
	No (n=35)			Yes (n=5)			
	Median	25th-75th percentile	Min-Max	Median	25th-75th percentile	Min-Max	*p*
Age (year)	66	54-82	26-91	84	75-84	73-92	**0.014**
WBC	13790	8600-17700	5960-151300	11620	10670-14280	6950-14890	0.524
NEU	9000	4860-13250	5.92-27200	8700	4910-13280	9.02-13520	0.874
PLT	297	220-342	54-550	243	151-249	148-286	0.170
Fibrinogen	3.6	2.52-4.6	1.22-6.47	5.04	4.3-5.7	4.03-6.06	0.021
CRP	0.042	0.01-0.142	0.001-0.35	0.13	0.13-0.14	0.02-0.295	0.228
D-Dimer	5.805	1.83-10.2	0.4-35.2	5.01	3.8-5.25	0.64-9.47	0.554
PRC	0.13	0.04-0.64	0.02-58.3	2.1	0.14-2.93	0.07-45.92	0.170
IL-6	26.3	21-48.5	2.93-176	21.1	17-24.3	15-30.8	0.170
CK	192	47.65-772	20-34653	151	135-366	100-1332	0.781
LDH	323	283-810	180-2591	398	296-446	264-1043	0.968
Ferritin	522	250-873	4-15052	173.4	32.4-439	20.2-4957.3	0.157

WBC: White blood cell count; NEU: Neutrophil count; PLT: Platelet count; CRP: C-reactive protein; PRC: Procalcitonin; IL-6: Interleukin-6; CK: Creatin kinase; LDH: Lactate dehydrogenase.

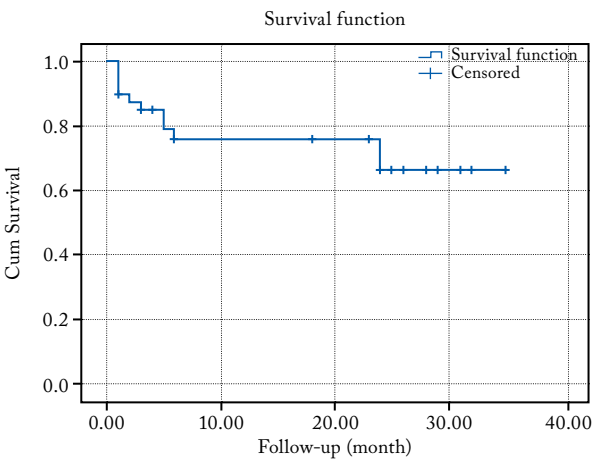

Figure 5. Kaplan-Meier survival curve for early mortality.

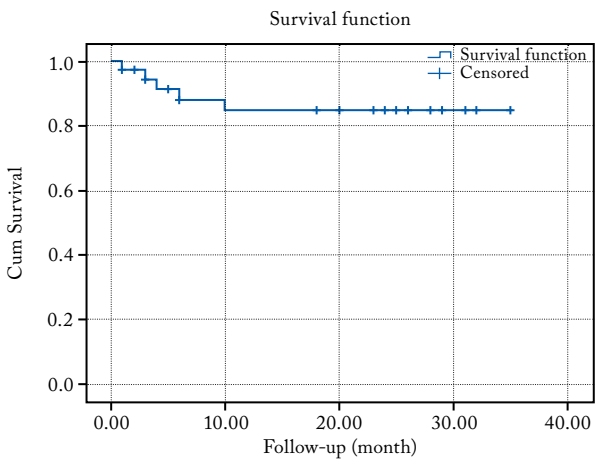

Figure 6. Kaplan-Meier survival curve for late mortality.

accepted as late mortalities. Eleven (27.5%) patients included in the study died in the early period, whereas five (12.5%) died in the late period. Amputation was performed in three (7.5%) patients, and complications developed in seven (17.5%) patients. Five of the patients developed myocardial infarction. The other two patients required revision due to bleeding and hematoma. Early and late Kaplan-Meier survival curves are given in Figures 5 and 6.

DISCUSSION

Acute limb ischemia is characterized by a sudden decrease in blood perfusion that endangers the

viability of the limb.[9] Although hypercoagulability conditions are rare causes for ALI, the incidence of thromboembolic complications can be observed up to 40%, particularly in cases with a COVID-19 infection.[10] In addition, critically ill patients have an even higher risk of both venous and arterial thromboembolism, which is associated with high mortality.[11] As we found in the present study, ALI was associated with an early mortality rate of 27.5% and late mortality rate of 12.5%, although the reported mortality in non-COVID-19 populations with ALI ranges from 5 to 9% in the literature.[12] In parallel with our current finding, comparative studies have also shown that the incidence of thrombotic events, such as stroke, is higher in COVID patients compared to others.[13]

Another important point to focus on is whether the incidence of ALI as a result of COVID-19 varies by age, sex, comorbid factors, and ethnicity. In the current study, most of our patients admitted with ALI and COVID-19 were male, and patients generally had additional comorbidities, such as hypertension, diabetes mellitus, and coronary artery disease. Other studies in the literature also reported cases with similar sex and age distribution and comorbidities.[6] However, ALI has been reported to occur in patients suffering from COVID-19 without known peripheral arterial disease, even in young patients without comorbidity or previous significant atherosclerosis.[8,14] Although these new reports associated with ALI are available, more efforts are needed to understand the COVID-19 disease due to the lack of large population-based studies that can confirm this observation.

The pathophysiology and phenotype of ALI in COVID-19 are still the subject of research. Severe acute respiratory syndrome coronavirus 2, like other members of the coronavirus family, causes isolated respiratory tract infection. However, in some patients, inappropriate triggering of the immune system may cause the release of cytokines and chemokines, leading to multiple organ failure.[15] Factors causing ischemia in COVID-19 patients can be considered endothelial damage, coagulopathy and hypercoagulability conditions, hyperimmune reaction, and platelet aggregation. Although myocardial damage and arrhythmia caused by COVID-19 infection can lead to thromboembolic events, the virus can also directly cause vascular endothelial damage.[16] In addition, complement activation also causes endothelial cell damage, leading to cell death and the release of thrombogenic basement membrane. It was reported that more than 70% of patients died from COVID-19-related disseminated intravascular coagulation.[17]

High D-dimer levels, fibrinogen degradation products, and prolonged thromboplastin and prothrombin times in COVID-19 cases have been associated with higher in-hospital mortality and the need for mechanical ventilation.[18] High levels of D-dimer may have predictive value for the occurrence of arterial thromboembolic events in COVID-19 patients. Monitoring the values of D-dimer and fibrin breakdown products can help the clinician with the early diagnosis of severe cases of COVID-19-related thromboembolism.[19] In our study, the levels of fibrinogen, D-dimer, and other laboratory markers at the time of diagnosis of ALI were examined in all patients. In addition, the effects of preoperative laboratory markers on early and late mortality in the study were investigated. There was no association of D-dimer levels with early and late mortality. However, white blood cell count, neutrophil count, C-reactive protein, PRC, IL-6, lactate dehydrogenase, and median ferritin levels of the group with early mortality were significantly higher than the group without early mortality. Fibrinogen median levels of the group with late mortality were also significantly higher than the group without late mortality. Due to the small number of patients, the relevant data may not be meaningful. However, an optimal cut-off level and its prognostic value in COVID-19-related ALI cases are still unknown. In addition, a certain cut-off value related to markers may be determined by prospective studies with a large number of patients in terms of their effects on mortality.

Essentially, COVID-19 patients who develop an upper or lower limb injury usually have a large clot burden, which is an anatomically more common disease and is accompanied by higher amputation rates.[20] Therefore, it is recommended to perform complete imaging with CTA from the aortic arch to the upper and lower extremities in such patients. Detection of other thromboembolic events, such as pulmonary thromboembolism, cardiac thrombus, and aortic thrombus, using whole-body CTA scan is of great benefit to the clinician. After a detailed CTA evaluation, the recommendations in the guidelines should be applied in the initial management of ALI patients. These include adequate analgesia, intravenous rehydration,

oxygen therapy, and intravenous heparin administration.[8,21] Therapeutic anticoagulation with intravenous unfractionated heparin should be provided following the diagnosis of ALI, unless there are significant contraindications, such as active severe bleeding or recent surgery within 48 h. There is no published study that shows the superiority of a particular anticoagulant.

As an initial strategy, all patients in the current study were given LMWH during their hospital stay and for one month after discharge if they did not have active bleeding or a high-risk profile for major bleeding. Rivaroxaban treatment as oral anticoagulation after the procedure was preferred in long-term follow-up.

The choice of endovascular or surgical methods after initial treatment may vary depending on the experience of the clinician and the clinic. In patients admitted with ALI, treatment should not be postponed regardless of the severity of COVID-19, and treatment should be applied urgently according to current guidelines.[4] Endovascular procedures such as catheter-mediated thrombolysis and mechanical thrombectomy may be preferred in selected patients. Although reported in some publications, systemic thrombolysis is not recommended as the initial treatment of ALI in severe COVID-19 patients due to a lack of supporting evidence.[22] In patients with a demarcation line and motor loss, the decision on the timing of major amputation should be made according to the severity of COVID-19 symptoms. In our clinical experience and the patient's preference, surgical methods are preferred for the management of COVID-19-related ALI cases. Open surgical treatment using thromboembolectomy remains the most common revascularization technique in many countries and centers.[7] We perform surgical embolectomy using appropriate brachial, femoral, and popliteal incisions. In contrast, intra-arterial locoregional thrombolysis using alteplase can be considered an adjunct to thromboembolectomy, particularly in patients with residual distal thrombus and foot ischemia. Regional anesthesia may be preferred instead of general anesthesia to avoid any airway manipulation in COVID-19 cases.[23] Although there is no scientific evidence to support this theory, we performed our local anesthesia procedures under sedation whenever possible in our clinical practice. In addition, a total complication rate of almost 17.5% and an amputation rate of 7.5% were present in our study, and the majority of these were major amputations. In comparison to clinical series previously reported in the literature, successful revascularization in COVID-19 patients in our study was disappointingly low.[24] Medical follow-up in selected comorbid patients may be superior to surgery in patients with COVID-19-associated ALI. It is difficult to make a definite comment on this issue. It would be more accurate to develop patient-based treatment strategies, and wider publications may surely shed light on what should be done.

Although COVID-19, which had a high mortality rate during the pandemic period, appears to have decreased, its effects still continue, albeit low, and should be taken into consideration. Additionally, the effects on long-term vascular pathologies are still a matter of research.

There are some limitations to this study. This study was a single-center retrospective study with a small sample size. Randomized controlled studies of larger populations are needed to assess its general applicability and management strategy.

In conclusion, the choice of patient-based endovascular or surgical methods to be applied after appropriate anticoagulation in COVID-19, where high thrombotic events are observed, is crucial in terms of reducing morbidity and mortality rates. In cases of ALI associated with this disease, the chances of successful revascularization are relatively less. In some selected comorbid patients, medical follow-up may be superior to surgery. Development of patient-based treatment strategies for the treatment of COVID-19-associated ALI is essential.

Ethics Committee Approval: The study protocol was approved by the Ankara Bilkent City Hospital Ethics Committee (date: 19.04.2021, no: E1-21-1747). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Idea/concept: A.Ö., G.Y.; Design: A.Ö., M.Y.; Control/supervision, critical review, references and fundings: H.Z.İ.; Data collection and/or processing, materials: A.Y., E.B.G.; Analysis and/or interpretation: G.Y., M.Y.; Literature review: A.Ö., G.Y., A.Y., E.B.G.; Writing the article: A.Ö., G.Y., A.Y.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):42-51
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1635
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Short-term preoperative intravenous iron replacement: Impact on surgical outcomes in cardiovascular disease

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Received: March 02, 2024 ***Accepted:*** March 08, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aimed to compare surgical outcomes between patients scheduled for cardiovascular surgery diagnosed with anemia according to the World Health Organization criteria who received intravenous iron replacement and those who were not anemic.

Patients and methods: This retrospective study analyzed patients who underwent cardiovascular surgery between February 2021 and January 2024. Patients with preoperative anemia treated with intravenous iron replacement were compared with nonanemic patients. Data on demographics, preoperative conditions, surgical details, and postoperative outcomes were analyzed.

Results: Of the 193 patients (142 males, 51 females; mean age: 62±10 years; range, 27 to 82 years) analyzed, 173 survived, and 20 did not. Surviving patients were younger and had a lower body mass index. Comorbidities such as congestive heart failure and a history of cerebrovascular events were associated with mortality. Laboratory results showed significant differences in hemoglobin levels and iron binding capacity between survivors and nonsurvivors. The study found no significant differences in surgical procedures or reoperation rates between the groups. However, nonsurvivors had more postoperative complications. Multivariate analysis identified cardiopulmonary bypass time and new-onset acute renal failure as independent risk factors for 30-day mortality. Anemic patients treated with intravenous iron replacement had comparable perioperative outcomes to nonanemic patients, including similar lengths of intensive care unit and hospital stays and mortality rates.

Conclusion: Treatment of preoperative anemia with intravenous iron replacement in patients undergoing cardiovascular surgery resulted in outcomes comparable to those of nonanemic patients. This suggests that short-term intravenous iron replacement may be an effective strategy to improve surgical readiness and outcomes in anemic patients.

Keywords: Anemia, intravenous iron replacement, mortality, open heart surgery.

Cardiovascular diseases are the primary cause of death globally. Surgical procedures used to treat these diseases have become increasingly advanced, but mortality rates persist. Anemia detected in the preoperative period is a significant risk factor for mortality. Many publications have identified it as a critical factor in determining survival.[1-4] Managing preoperative anemia is crucial.[5] A thorough preoperative assessment of transfusion risk, particularly for low-risk patients who often undergo elective surgery, could improve their transfusion risk profile and reduce surgery-related morbidity and mortality.[6] While transfusion is a quick and easy method, it carries the risk of infection and additional volume, which is a significant concern in patients with heart failure. Therefore, short-term preoperative intravenous (IV) iron treatments are increasingly being emphasized as a safer alternative.

In the preoperative period, patients who received IV iron replacement (IVIR) have shown positive effects on important perioperative outcomes of open heart surgery, according to some publications.[7,8] Most studies use other treatments along with IVIR, and they typically focus on outcomes related to the amount of red blood cell (RBC) transfusions during the perioperative period. However, there are few studies that have compared the data of anemic

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Citation:
Köseoğlu FD, Daylan A, Rahman ÖF, Cansu D, Metehan EO, Bozok Ş. Short-term preoperative intravenous iron replacement: Impact on surgical outcomes in cardiovascular disease. Cardiovasc Surg Int 2024;11(1):42-51. doi: 10.5606/e-cvsi.2024.1635.

patients receiving IVIR with nonanemic patients, particularly with respect to key surgical outcomes, and that have been conducted in a single center with patients undergoing standard surgical procedures. Hence, this study aimed to compare surgical outcomes between patients scheduled for cardiovascular surgery diagnosed with anemia according to World Health Organization (WHO) criteria who received IVIR and those who were not anemic.

PATIENTS AND METHODS

In this retrospective study, all consecutive patients who underwent open heart surgery at the cardiovascular surgery clinic of the Izmir Bakırçay University Hospital between February 2021 and January 2024 were included. Preoperative preparations, perioperative follow-ups, and surgeries were performed by the same surgical team. All patients were evaluated within the patient blood management protocol applied in the department, and IVIR was administered to patients identified as anemic according to the WHO definition.[9,10] Anemic patients who received IVIR were compared with those who did not have anemia.

The study collected data from the patient records in the hospital information system. The data on the patients' demographic characteristics, treatment history, preoperative data, surgical procedure details, postoperative complications, length of hospital stay, and several factors related to mortality were collected. The severity of heart disease was assessed using the New York Heart Association (NYHA) functional class and Canadian Cardiovascular Society angina grade. EuroSCORE II was calculated for the prediction of the risk of mortality. We excluded patients with incomplete data, those who had not received IVIR despite being anemic, and those who received RBC suspension prior to surgery (Figure 1).

The primary endpoint was 30-day mortality between the anemic and nonanemic groups. Secondary endpoints were the duration of cardiopulmonary bypass (CPB) and aortic cross-clamp, ICU length of stay, hospital length of stay, and in-hospital mortality. Additionally, several features including demographic characteristics, pre-operative measures, surgical procedure, post-operative complications, and survival measures were analyzed between survivors and nonsurvivors.

Statistical analysis

The data collected were analyzed using IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Categorical variables were presented as frequencies and proportions, while continuous variables were expressed as mean ± standard deviation (SD) (min-max) and medians (interquartile range), depending on the distribution of the data. Comparisons for continuous data were made using the independent samples t-test or the Mann-Whitney U test, depending on whether the data were parametric. The chi-square test was used to compare categorical variables. Variables that were found to be significant in the univariate analysis underwent multivariate analysis using logistic regression. A p-value <0.05 was considered statistically significant.

RESULTS

The study analyzed the outcomes of 193 patients (142 males, 51 females; mean age: 62±10 years; range, 27 to 82 years), of whom 173 (89.6%) survived, and 20 (10.4%) did not. The data are summarized in Table 1. Age was a significant factor, with surviving patients being younger than those who died. Lower body mass index was associated with worse outcomes. Congestive heart failure and a history of cerebrovascular events were significantly

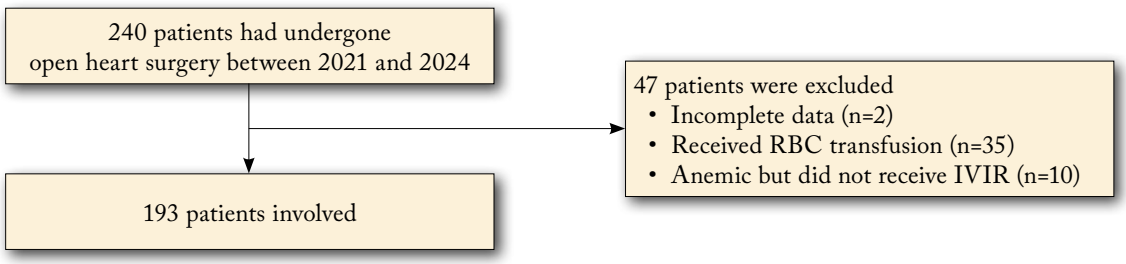

Figure 1. Flowchart on the selection of the patients.
RBC: Red blood cell; IVIR: Intravenous iron replacement.

Table 1
Characteristics of the patients

	Total						Survivors group						Nonsurvivors group						
	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	*p*
Demographics																			
Age (year)			62±10		27-82				61±10		27-82				69±7		58-82		0.002*
Sex																			0.879**
Male	142						127						15						
Female	51						46						5						
Body mass index (kg/m²)				26.6		24.6-29.7				26.8		25.0-29.7				25.1		23.3-28.0	**0.039†**
Body surface area (m²)			1.9±0.2		1.3-2.5				1.9±0.2		1.4-2.5				1.8±0.2		1.3-2.3		0.356*
Active smoker	55	28.5					50	28.9					5	25.0					0.714**
Comorbidites																			
Hyperlipidemia	153	79.4					138	79.8					15	75.0					0.618**
Hypertension	138	71.5					124	71.7					14	70.0					0.875**
Chronic kidney disease	95	49.2					82	47.4					13	65.0					0.136**
Diabetes mellitus	81	42.0					74	42.8					7	35.0					0.505**
Congestive heart failure	45	23.3					36	20.8					9	45.0					0.015**
Atrial fibrillation	23	11.9					20	11.6					3	15.0					0.875**
History of serebrovascular event	23	11.9					20	11.6					3	15.0					0.012**
Carotis artery disease	22	11.4					19	11.0					3	15.0					0.405**
History of rheumatic heart disease	15	7.8					14	8.1					1	5.0					0.523**
Peripheral artery disease	10	5.2					8	4.6					2	10.0					0.277**
Chronic obstructive pulmonary disease	9	4.7					6	3.5					3	15.0					0.054**
Chronic liver disease	1	0.5					1	0.6					0	0					0.896**
New York Heart Association Functional Classes																			0.077**
I	104	53.9					98	56.6					6	30.0					
II	58	30.1					29	28.3					9	45.0					
III	31	16.1					26	15.0					5	25.0					
IV	0	0					0	0					0	0					
Canadian Cardiovascular Society Angina Grade (of 136 patients)																			**0.021****
I	36	26.5					34	27.6					2	15.4					
II	74	54.4					69	56.1					5	38.5					
III	22	16.2					16	13.0					6	46.2					
IV	4	2.9					4	3.3					0	0					
Hematological medications																			
Acetylsalicylic acid	123	63.7					112	64.7					11	55.0					0.391**
P2Y12 inhibitors	62	32.1					56	32.4					6	30.0					0.830**
Low molecular weight heparin	19	9.8					18	10.4					1	5.0					0.387**
Direct oral anticoagulants	12	6.2					10	5.8					2	10.0					0.359**
Warfarin	7	3.6					7	4.0					0	0					0.459**

Table 1
Continued

	Total						Survivors group						Nonsurvivors group						
	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	*p*
Preoperative measures																			
Selected laboratory results																			
Hemoglobin (g/dL)				13.4		11.5-14.3				13.6		11.78-14.4				12.5		11.1-13.3	**0.044**†
Hematocrit (%)				40.3		35.0-43.3				40.9		35.6-43.4				37.0		34.1-40.0	**0.056**†
Platelet count (×10^3/mm^3)			256±82		103-591				257±83		103-591				249±81		119-376		0.684*
International normalized ratio				1.03		0.96-1.10				1.02		0.96-1.10				1.05		0.97-1.14	0.224†
Alanine aminotransferase				17		12-24				18		12-25				13		7-19	**0.019**†
Creatinine (mg/dL)				0.93		0.76-1.10				0.92		0.76-1.10				1.00		0.82-1.12	0.288†
Glomerular filtration rate (mL/min)			95±40		10-229				98±40		10-229				73±31		12-125		**0.008***
Calcium (mg/dL)			9.1±0.5		7.7-10.5				9.2±0.4		7.7-10.5				8.7±0.5		7.8-9.8		**<0.001***
Potassium (mg/dL)			4.3±0.4		3.3-5.8				4.3±0.4		3.3-5.8				4.4±0.6		3.5-5.7		0.525*
Serum iron			73±32		13-174				73±32		13-174				73±25		33-104		0.958*
Ferritin				108		59-191				108		58-191				108		68-204	0.628†
Iron binding capacity				225		184-288				228		189-304				187		160-206	**0.003**†
Transferrin saturation				25.2		17.6-34.0				25.0		17.5-33.5				30.7		17.6-39.6	0.229†
Folic acid				7.9		5.1-10.0				7.9		5.2-10.1				7.4		4.0-9.2	0.162†
Vitamin B12				367		262-532				369		264-554				357		254-478	0.602†
Left ventricular ejection fraction (%)			53±9		25-70				53±9		25-70				50±10		25-65		0.164*
Anemia	67	34.7					57	32.9					10	50.0					0.129**
Thrombocytopenia	11	5.7					8	4.6					3	15.0					0.092**
Hypofibrinogenemia	66	34.2					57	32.9					9	45.0					0.282**
History of balloon angioplasty	26	13.5					25	14.5					1	5.0					0.212**
<2 weeks	7	26.9					7	28.0					0	0					
2-4 weeks	6	23.1					6	24.0					0	0					
>4 weeks	13	50.0					12	48.0					1	100					
History of coronary stents	40	20.7					35	20.2					5	25.0					0.618**
<3 months	16	40.0					15	42.9					1	20.0					
3-6 months	4	10.0					3	8.6					1	20.0					
>6 months	20	50.0					17	48.6					3	60.0					
Bleeding risk																			**0.006****
Low	108	56.0					102	59.0					6	30.0					
Intermediate	77	39.9					66	38.2					11	55.0					
High	8	4.1					5	2.9					3	15.0					
Preoperative measures																			
Thrombosis risk																			0.481**
Low	19	9.8					18	10.4					1	5.0					
Intermediate	4	2.1					3	1.7					1	5.0					
High	170	88.1					152	87.9					18	90.0					
EuroSCORE II				1.30		0.87-2.90				1.21		0.83-2.55				2.75		1.30-6.56	**0.002**†
CHA_2DS_2-VASc score (of 23 patients)				2		2-4				2		2-3				4		3-Nd	0.090†
Shock	1	0.5					0	0					1	5.0					0.104**
Preoperative medication																			
Anticoagulant bridge	16	8.3					15	8.7					1	5.0					0.487**
Antithrombotic bridge	16	8.3					15	8.7					1	5.0					0.487**
Antifibrinolytic	132	68.4					123	71.1					9	45.0					**0.017****
Intravenous iron supplementation	67	34.7					57	32.9					10	50.0					0.129**

Table 1
Continued

	Total						Survivors group						Nonsurvivors group						
	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	*p*
Surgical procedure																			
Operation type																			0.375**
Coronary artery bypass graft surgery	122	63.2					112	64.7					10	50.0					
Valvular surgery	26	13.5					23	13.3					3	15.0					
Combined surgery	45	23.3					38	22.0					7	35.0					
Redo operation	3	1.6					3	1.7					0	0					0.719**
Operation timing																			**0.005****
Emergent	11	5.7					7	4.0					4	20.0					
Early	23	11.9					19	11.0					4	20.0					
Elective	159	82.4					147	85.0					12	60.0					
Off-pump procedure	9	4.7					9	5.2					0	0					0.365**
Minimal invasive extra-corporeal circulation	35/184	19.0					31/164	18.9					4/20	20.0					0.553**
Cardiopulmonary bypass time (min)			124±48		28-365				120±43		28-255				156±72		61-365		**0.002***
Aortic cross-clamp duration (min)			83±32		20-179				83±33		20-179				87±30		42-178		0.603*
Lowest body temperature (°C)			30.4±1.6		26.0-35.0				30.5±1.6		26.0-35.0				29.7±2.1		26.0-32.0		**0.044***
Postoperative complications																			
Arrhythmia	60	31.1					46	36.6					14	70.0					**<0.001****
Atrial fibrillation	47	24.4					39	22.5					12	60.0					
Ventricular fibrillation	12	6.2					5	2.9					7	35.0					
Ventricular tachycardia	7	3.6					3	1.7					4	20.0					
Atrioventricular block	5	2.6					1	0.6					4	20.0					
Low cardiac output state	53	27.5					40	23.1					13	65.0					**<0.001****
Intra-aortic balloon pump	19	9.8					8	4.6					8	40.0					**<0.001****
Myocardial infarction	5	2.6					2	1.2					3	15.0					**0.008****
Reexploration	7	3.6					2	1.2					5	25.0					**<0.001****
Late tamponade	4	2.1					3	1.7					1	5.0					0.357**
Erythrocyte replacement (units)				2		1-4				2		0-3				7		3-11	**<0.001**†
Acute renal failure	69	35.8					56	32.3					13	65.0					**<0.001****
Respiratory complications																			**0.002****
Pneumonia	19	9.8					12	6.9					7	35.0					
Pulmonary edema	18	9.3					14	8.1					4	20.0					
Adult respiratory distress syndrome	13	6.7					10	5.8					3	15.0					
Atelectasis	9	4.7					9	5.2					0	0					
TRALI	4	2.1					3	1.7					1	5.0					
Pulmonary thromboembolism	2	1.0					0	0					2	10.0					
Others	9	4.7					6	3.5					3	15.0					

Table 1
Continued

	Total						Survivors group						Nonsurvivors group						
	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	n	%	Mean±SD	Median	Min-Max	IQR	*p*
Surgical procedure																			
Surgical site infections	13	6.8					12	7.0					1	5.0					0.238**
Superficial	2	1.0					2	1.2					0	0					0.803**
Mediastinitis																			
Gastrointestinal system complications	4	2.1					2	1.2					2	10.0					0.054**
Serebrovascular event	5	2.6					0	0					5	25.0					<0.001**
Disseminated intravascular coagulation	11	5.7					5	2.9					6	30.0					<0.001**
Survival measures																			
Intensive care unit stay (days)				3		2-4				3		2-4				4		1-13	0.166†
Mechanical ventilation duration (h)				9		6-14				9		6-13				18		13-82	**<0.001†**
Hospital stay (days)				7		6-11				7		6-10				6		1-18	0.504†
In-hospital mortality	18	9.3					-	-					-	-					
30-day mortality	20	10.4					-	-					-	-					

SD: Standard deviation; IQR: Interquartile range; EuroSCORE: The European System for Cardiac Operative Risk Evaluation; VAS: Visual Analog Scale; TRALI: Transfusion-related acute lung injury; * Independent samples t test; ** Chi-squared test; † Mann-Whitney U test; Nd: Not defined.

associated with mortality. In this study, it was found that common comorbidities, such as hyperlipidemia, hypertension, chronic kidney disease, and diabetes mellitus, did not have a significant impact on mortality. Although there was no significant difference in the distribution of NYHA functional classes, there was a significant difference in the Canadian Cardiovascular Society Angina Grade. With respect to medication, there were no significant differences observed in the use of acetylsalicylic acid, P2Y12 inhibitors, low-molecular-weight heparin, direct oral anticoagulants, or warfarin between survivors and nonsurvivors.

Nonsurvivors had lower hemoglobin levels, and there was a significant difference in iron binding capacity between the two groups. The presence of WHO-defined anemia was not different between survivors and nonsurvivors, which may be related to sex-related cut-offs. Nonsurvivors had lower alanine aminotransferase levels and reduced glomerular filtration rates.

Periprocedural data

Although specific cardiovascular risk scores, such as EuroSCORE (European System for Cardiac Operative Risk Evaluation) II, showed a significant divergence indicating a higher predicted risk in nonsurvivors, other clinical and procedural history factors, such as a history of balloon angioplasty or coronary stents, did not show a statistical difference in distribution between survivors and nonsurvivors. When considering bleeding and thrombotic risks, a significantly higher proportion of nonsurvivors were classified into higher bleeding risk categories.

No significant differences were found in the types of surgery performed or in the rates of reoperation between survivors and nonsurvivors when analyzing surgical procedures. However, the timing of surgery emerged as a significant factor. Emergent and early surgery had a higher percentage of nonsurvivors compared to elective surgery. In terms of the technical aspects of surgery, nonsurvivors had a significantly longer CPB time. However, there were no significant differences between the groups in terms of the duration of aortic cross-clamping or the use of off-pump or minimally invasive extracorporeal circulation.

When analyzing postoperative complications, it was found that nonsurvivors experienced significantly more arrhythmias, including atrial fibrillation,

ventricular fibrillation, ventricular tachycardia, and atrioventricular block. Nonsurvivors also had higher rates of low cardiac output, requiring intra-aortic balloon pump support. Nonsurvivors had significantly higher rates of myocardial infarction and reexploration for bleeding or tamponade. The difference in RBC transfusion between survivors and nonsurvivors highlights the impact of anemia and the need for blood transfusions on mortality. The median RBC transfusion in the survivors and nonsurvivors groups was 2 and 7 units, respectively (p<0.001). Additionally, nonsurvivors experienced significantly more acute renal failure and respiratory complications, such as pneumonia, pulmonary edema, and adult respiratory distress syndrome.

Survival analysis

The survival analysis showed no significant difference in the median length of stay in the intensive care unit (ICU) between survivors and nonsurvivors. However, the duration of mechanical ventilation was significantly longer in nonsurvivors. It is worth noting that the median length of hospital stay did not differ significantly between the survivors and nonsurvivors groups. The rates of in-hospital and 30-day mortality provide a direct measure of short-term outcomes after cardiovascular surgery, with rates of 9.3% and 10.4%, respectively. The multivariate analysis revealed that CPB time (hazard ratio=1.019, 95% confidence interval [CI]: 1.006-1.033, p=0.004) and the development of newly onset acute renal failure (hazard ratio=36.8, 95% CI: 4.7-284.9, p=0.001) were two independent risk factors for 30-day mortality.

Main endpoints

When comparing anemic patients who received IVIR to those without anemia, significant differences were observed in the NYHA functional class (p=0.001) and the prevalence of congestive heart failure. Anemic patients had higher NYHA classes and a higher prevalence of congestive heart failure (37.3% in anemic patients *vs.* 15.9% in nonanemic patients, p=0.001). Furthermore, it was discovered that anemic patients have a higher preoperative bleeding risk score (p=0.001). The difference in EuroSCORE II scores between anemic and nonanemic patients (median score: 1.79 *vs.* 1.15; p=0.003) emphasizes the higher risk profile of anemic patients. It is worth noting that there was a slightly higher incidence of emergent cases in nonanemic patients (%7.1 *vs.* %3.0 p=0.040). There were no significant differences in the duration of CPB and aortic cross-clamp, ICU length of stay, hospital length of stay, in-hospital mortality, and 30-day mortality between the anemic and nonanemic groups.

DISCUSSION

Several studies have demonstrated that patients with anemia experience worse outcomes after cardiovascular surgery.[11-16] This phenomenon may be due not only to characteristics inherent to anemia itself but also to the fact that anemia is often associated with other comorbidities, suggesting that it may reflect the underlying frailty of the patient.[17] In a meta-analysis that included 35 studies with a total of 159,025 patients, preoperative anemia was associated with an increased risk of death (odds ratio=2.5, 95% CI: 2.2-2.9, p<0.001).[18] Meta-regression analysis revealed that lower hemoglobin levels and studies with a lower proportion of male patients were associated with an increased risk of mortality. Additionally, preoperative anemia was linked to longer hospital stays and an increase in postoperative complications.

Given the significant role of anemia as a factor, the importance of its correction and management prior to surgery has often been studied. Several publications discuss managing anemic patients before surgery, particularly with regard to IVIR therapy. Cladellas et al.[7] conducted a study to assess the effects of treating anemia with recombinant human erythropoietin and iron prior to cardiac surgery on postoperative outcomes and RBC transfusion needs. The study compared a group of 75 patients who received recombinant human erythropoietin at a dose of 500 IU/kg/day for four weeks and a fifth dose 48 h prior to surgery, along with IV iron sucrose supplementation, with an observation group of 59 untreated patients. After adjusting for confounding variables, the study found that the combined therapy was independently associated with reduced postoperative morbidity and in-hospital mortality. Specifically, the intervention reduced postoperative renal failure, decreased the rate of RBC transfusion from 93% in the observation cohort to 67%, and shortened hospital stays.

In their study, Spahn et al.[8] investigated the impact of immediate preoperative combination treatment on reducing perioperative RBC transfusions and improving outcomes in patients with anemia or isolated iron deficiency who were scheduled for elective cardiac surgery. The study involved 505 patients

who were randomly assigned to receive either a placebo or a combination treatment comprising IV ferric carboxymaltose, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid on the day before surgery. The primary outcome was the number of RBC transfusions during the first seven days after surgery. The combination treatment led to a significant reduction in the median number of RBC transfusions required during the first seven days. Similar reductions were observed on the postoperative Day 90. Additionally, patients in the treatment group exhibited higher hemoglobin concentrations, reticulocyte counts, and reticulocyte hemoglobin content during the first seven days.

Another study by Evans et al.[19] aimed to evaluate the effectiveness of preoperative IV iron administration in anemic patients undergoing cardiac surgery. Out of the 447 patients analyzed, 75 (17%) were anemic and received IV iron treatment, while 72 (16%) were anemic but did not receive any treatment. The aim of the treatment was to achieve a hemoglobin level of ≥130 g/L on the day of surgery. The anemic patients who were successfully treated showed a mean increase in hemoglobin of 17 g/L and received significantly fewer blood transfusions than the untreated anemic patients. The study concluded that anemic patients who were successfully treated required less blood perioperatively. More than half of these patients did not require any transfusion at all.

Klein et al.[20] conducted a prospective multicenter study to investigate the feasibility and effectiveness of introducing a preoperative IV iron service as a national initiative in cardiac surgery. The primary feasibility outcome was to determine if the clinics could be established, while the primary effectiveness outcome was the change in hemoglobin concentration between intervention and surgery. The study found that out of 11 hospitals, seven successfully established iron clinics and recruited 228 patients. Patients with anemia who received IV iron showed a significant increase in hemoglobin concentration from baseline to preoperative, with a mean increase of 8.4 g/L ($p<0.001$). However, despite the increase in hemoglobin, the study was unable to demonstrate an effect on transfusion rates or patient outcomes, possibly due to the small sample size.

Another study by Kong et al.[21] aimed to determine an effective treatment for preoperative anemia associated with iron deficiency in elective cardiac surgery patients. The study was a single-center, open-label, randomized trial involving 156 participants. It compared the effectiveness of IV ferric derisomaltose and subcutaneous darbepoetin (intervention group) to oral ferrous sulfate (control group) in patients with low preoperative hemoglobin levels and iron deficiency. The study's main results indicate that the intervention group had significantly lower odds of requiring RBC transfusion compared to the control group. Additionally, there was a significant increase in hemoglobin levels from randomization to surgery in the intervention group.

Shokri and Ali[22] assessed the impact of preoperative IV iron infusion on hemoglobin levels, blood transfusion needs, and the occurrence of postoperative adverse events in patients undergoing coronary artery bypass grafting. The randomized study enrolled 80 patients aged 52 to 67 years who were assigned to receive either IV ferric carboxymaltose (iron group) or saline (placebo group) seven days before surgery. The study revealed that iron therapy was linked to a lower incidence of anemia four weeks after discharge, significantly higher Hb levels preoperatively, postoperatively, and four weeks after discharge, and shorter hospital and ICU stays. Additionally, iron therapy led to a decreased requirement for packed RBCs after the operation. The study concluded that the treatment is associated with higher postoperative hemoglobin levels, shorter hospital and ICU stays, and reduced perioperative RBC transfusion requirements.

Jafari et al.[23] conducted a study to assess the effectiveness of IV iron sucrose and erythropoietin in reducing transfusion requirements for patients with preoperative iron deficiency anemia undergoing on-pump coronary artery bypass grafting surgery. The study was an open-label, randomized clinical trial that enrolled 114 patients who were divided into two groups: intervention (iron plus erythropoietin) and control. The intervention group received a 200 mg IV dose of iron sucrose and a 100 IU/kg bolus of erythropoietin one to two days prior to surgery. The results showed a significant reduction in the number of RBC units transfused per patient in the intervention group compared to the control group. Additionally, the intervention group exhibited a noteworthy rise in ferritin levels on the seventh postoperative day and experienced shorter stays in both the ICU and hospital. No adverse events were reported in either group.

After evaluating all presented studies, it is observed that administering IVIR to anemic patients before cardiovascular surgery results in positive outcomes for the examined endpoints. However, some publications report contrary results. A recent meta-analysis on the impact of anemia on outcomes after cardiac surgery also conducted a secondary analysis of seven studies involving 1,012 patients and found that short-term preoperative treatments for anemia did not significantly reduce mortality.[18] Similarly, Quarterman et al.[24] presented a retrospective observational review from January 2017 to December 2019. The study evaluated the effectiveness of preoperative IV iron in treating patients with iron deficiency anemia scheduled for elective cardiac surgery. Among the 190 patients who received IV iron, there was a median increase in hemoglobin of 8.0 g/L. However, patients who received IV iron had a significantly higher incidence of transfusion (60%) compared to the nonanemic cohort (22%). Additionally, the treated group had significantly higher rates of new need for renal replacement therapy and stroke, but there was no significant difference in in-hospital mortality.

The present study indicates that patients with anemia who received IVIR prior to cardiovascular surgery had perioperative outcomes comparable to those of nonanemic patients. This includes similar lengths of ICU and hospital stays, as well as in-hospital and 30-day mortality rates. This is consistent with most published literature. These findings suggest that IVIR is a viable strategy to improve the surgical readiness of anemic patients and to bring their outcomes in line with those of their nonanemic counterparts. However, the precise mechanisms by which IV iron influences surgical outcomes, particularly through potential effects on cellular functions, remain to be fully understood.

It is important to note that this study has several limitations. These limitations include its retrospective and observational nature, patient selection based on specific criteria, lack of comparative data with nonsupplemented anemic patients, and exclusion of nonanemic patients who were indicated for iron supplementation. Due to its observational nature, this study cannot establish a cause-and-effect relationship regarding the mechanism of action of iron supplementation.

In conclusion, perioperative outcomes for anemic patients who received IVIR did not differ from patients without anemia. Nonetheless, nonsurvivors had lower preoperative hemoglobin levels, suggesting that more severe anemia may be associated with poorer outcomes. The findings suggest that short-term IVIR may positively impact immediate surgical outcomes, although it is important to consider that many factors influence the complex process of cardiovascular surgery. In addition to correcting hemoglobin levels, further investigation is needed to determine the potential impact of IVIR on cellular function and overall patient recovery and outcomes.

Ethics Committee Approval: The study protocol was approved by the Izmir Bakırçay University Ethics Committee (date: 21.02.2024, no: 210224/1467). The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Concept, design, analysis, literature review, writing the article: F.D.K., A.D.; Control, supervision: Ş.B.; Data collection: F.D.K., A.D., Ö.F.R., D.C., E.O.M.; Materials: F.D.K., A.D., Ö.F.R., D.C., E.O.M.; Critical review: Ş.B.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):52-57
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1613
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Comparison of short-term outcomes of patients with embolism-protected and unprotected carotid artery stenting

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Received: February 05, 2024 ***Accepted:*** March 03, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aimed to evaluate the effect of using or not using a protective device on clinical outcomes in patients undergoing carotid artery stenting.

Patients and methods: A total of 80 patients (53 males, 27 females; mean age: 68.1±9.1 years; range, 47 to 93 years) with symptomatic severe carotid artery stenosis or asymptomatic severe carotid artery stenosis were included in the prospective study between March 2016 and August 2018. The patients were divided into two groups: those who used an embolism protection device (n=60) and those who did not (n=20).

Results: In terms of primary endpoints, rates of ischemic stroke (5% *vs.* 5%, p=1.00) and transient ischemic attack (5% *vs.* 0%, p=0.56) were found to be similar between the protected and unprotected groups after carotid artery stenting. While total embolism numbers (2.11±2.62 *vs.* 1.26±2.19, p=0.072) and infarct sizes (8.80±4.5 mm *vs.* 9.00±5.05 mm, p=0.97) were similar between the protected and unprotected groups, the presence of silent microemboli was higher in the unprotected group (40% *vs.* 15%, p=0.02).

Conclusion: Although embolism protection devices do not reduce the risk of clinically significant embolism, they significantly reduce the risk of silent microemboli.

Keywords: Carotid artery stenting, embolism protection, microemboli.

In recent years, the use of distal protection devices during carotid artery stenting (CAS) has been the subject of frequent discussion. In the subgroup analysis of the SPACE study, no results were found to support the use of these devices.[1] On the other hand, several studies claim that the results of procedures performed without a distal protection device are excellent.[2-5] In addition to these studies, another important data came from Oteros et al.[6] In their study, 212 high-risk symptomatic patients were stented in the carotid artery without a distal protection device. In 55% of these patients, the severity of the lesion ranged from 90 to 99%, while the severity of the lesion in the remaining patients ranged from 70 to 90%. In this nonrandomized study, the 30-day rate of stroke, death, and myocardial infarction was 1.36%. This rate ranges from 5.2 to 9.6% in large randomized studies comparing endarterectomy and carotid stenting, the majority of which used a distal protection device.[7-9] These results, contrary to expectations, raise the question of whether distal protection devices increase complication rates. Two randomized studies that screened microemboli with diffusion magnetic resonance imaging (MRI) revealed that CAS using an embolism protection device increased the frequency of microemboli in diffusion MRI.[10,11] In light of these conflicting results, this study aimed to compare the use and nonuse of a protective device in patients undergoing CAS.

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Citation:
Demir Y, Şenöz O, Eren A, Demir A. Comparison of short-term outcomes of patients with embolism-protected and unprotected carotid artery stenting. Cardiovasc Surg Int 2024;11(1):52-57. doi: 10.5606/e-cvsi.2024.1613.

PATIENTS AND METHODS

This single-center, prospective study was conducted at the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, Department of Cardiology between March 2016 and August 2018. A total of 80 patients (53 males, 27 females; mean age: 68.1±9.1 years; range, 47 to 93 years) with symptomatic severe carotid artery stenosis [angiography ≥50%, ultrasound ≥70%, or computed tomography (CT)/MRI ≥70%] or asymptomatic severe carotid artery stenosis (angiography ≥60%, ultrasound ≥70%, or CT/MRI ≥80%) were included in the study. The patients were divided into two groups: those who used an embolism protection device (n=60) and those who did not (n=20). Those who had a transient ischemic attack, those with amaurosis fugax, those who had a minor or major stroke within six months before the procedure, and those with ischemic defects on cerebral imaging were considered symptomatic. Those who had a major stroke within a week, those with intracranial tumor or arteriovenous malformation, dementia, or severe impairment as a result of stroke, and those with intracranial stenosis were excluded from the study. All patients were started on 100 mg acetylsalicylic acid and 75 mg clopidogrel at least five days before the procedure. This treatment was continued for at least one month after the procedure. Carotid angiography was performed by femoral, brachial, or radial access under local anesthesia with 5F or 6F diagnostic catheters. A Right Judkins coronary catheter or 5F Simmon catheter was used for selective visualization of each of the carotid arteries. Carotid arteries were examined from anteroposterior and lateral poses. The location of the lesion, its length, the degree of stenosis, whether there was compensation from the Willis polygon or the pial arteries, and the presence of anastomosis between the internal and external carotid arteries were evaluated with these angiographies. Open-cell stents were used in all patients. The use of an embolism protection device during the stenting procedure was recorded according to their proximal (EmboShield R; Abbott Vascular, Abbott Park, IL, USA) and distal (Mo. Ma; Medtronic, Minneapolis, MN, USA) locations. Cranial MRI was performed before the CAS procedure. This procedure was repeated after CAS to investigate the presence of new microemboli. Patients who underwent diffusion MRI up to seven days before the procedure were included in the study. Postprocedure diffusion MRI was performed between 24 and 48 h before discharge. In all imaging protocols, diffusion-weighted image sequences were taken to visualize acute and subacute ischemia or infarct. The number and size of the lesions were evaluated by the radiologist.

The CAS procedure was performed under 100 μ/kg unfractionated heparin, and additional heparin was administered when necessary, considering the activated clotting time during the procedure to be 250 to 350 sec. All stent systems, type of embolism protection devices, predilatation, postdilation, use of atropine and anchor technique, telescopic technique, and guiding catheter technique were left to the operator's preference during the CAS procedure. Hemodynamic parameters (e.g., blood pressure, pulse, conscious states, slurred speech, headache, loss of vision, and limitation of extremity movement) were closely monitored for a day in patients who were followed up under coronary intensive care conditions after the CAS procedure. If any neurological signs or symptoms were detected in the patients, their follow-up was completed by asking the opinion of a neurologist urgently.

The primary endpoint of the study was the presence of acute or subacute new ischemic or infarct areas on intrahospital diffusion MRI before discharge, stroke, transient ischemic attack, and myocardial infarction. Stroke was defined as a neurological event lasting ≥24 h. Transient ischemic attack was defined as any neurological event that lasted <24 h. Myocardial infarction was defined as the presence of two of the three criteria: specific cardiac enzymes exceeding two times the upper limit, chest pain that is typical and lasting longer than 30 min, or specific abnormalities on electrocardiography. Technical success was defined as successful stent placement in the carotid artery.

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 software (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was checked using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) and evaluated using Student's t-test. Categorical variables were presented as number and frequency and assessed using the chi-square. A p-value <0.05 was considered statistically significant.

Table 1
Baseline characteristics of the patients

Variables	Protected group (n=60) n	%	Mean±SD	Unprotected group (n=20) n	%	Mean±SD	*p*
Age (year)			67.8±9.7			69.0±7.2	0.634
Smoking	36	60		8	40		0.097
Diabetes mellitus	23	38.3		6	30		0.502
Sex							
Male	44	78.3		9	45		0.020
Coronary artery disease	39	65		12	60		0.407
Chronic renal failure	5	8.3		3	15		0.405
Hypertension	45	75		15	75		1.00
Hyperlipidemia	14	23.3		9	45		0.064
Chronic heart failure	13	21.7		1	5		0.089
Peripheral artery disease	11	18.3		3	15		1.00
Contralateral carotid stenosis	20	33.3		5	25		0.509
6 months> stroke or TIA	24	40		7	35		0.653

SD: Standard deviation; TIA: Transient ischemic attack; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

Table 2
Laboratory characteristics of the patients according to groups

Variables	Protected group (n=60) Mean±SD	Unprotected group (n=20) Mean±SD	*p*
Fasting blood glucose (mg/dL)	113.7±27.4	115.2±35.3	0.85
Urea (mg/dL)	41.7±15.5	42.1±17.2	0.95
Creatinine (mg/dL)	1.3±2.4	1.2±0.9	0.86
Sodium (mEq/L)	138.7±3.4	137.6±2.1	0.16
Potassium (mEq/L)	4.3±0.5	4.5±0.4	0.37
AST (IU/L)	19.8±11.1	19.3±9.6	0.85
ALT (IU/L)	19.4±14.1	20.2±11.7	0.83
White blood cell count ($\times 10^9$/L)	4.1±4.5	5.4±3.4	0.21
Neutrophil count ($\times 10^9$/L)	2.5±3.1	3.2±2.2	0.31
Lymphocyte count ($\times 10^9$/L)	1.1±1.3	1.5±1.1	0.07
Hemoglobin (g/dL)	17.1±2.3	13.1±2.1	0.46
Hematocrit (%)	37.4±6.6	39.4±4.9	0.22
Platelet count ($\times 10^9$/L)	127.1±139.1	189.1±126.4	0.08
LVEF (%)	57.5±5.6	56.5±6.9	0.48

SD: Standard deviation; AST: Aspartat transferaz; ALT: Alanin aminotransferaz; LVEF: Left ventricular ejection fraction; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

Table 3
Procedure-related characteristics of patients

Variables	Protected group (n=60)			Unprotected group (n=20)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Clinically asymptomatic patient	21	35		9	45		0.51
Presence of embolism/infarction before the procedure	54	90		17	85		0.786
Presence of embolism in MRI after the procedure	9	15		8	40		**0.02**
Number of embolisms in MRI after the procedure			2.11±2.62			1.26±2.19	0.072
Embolism size in MRI after the procedure (mm)			8.80±4.5			9.00±5.05	0.979
Mortality (in-hospital)	1	1.7		0	0		0.744
Myocardial infarction (in-hospital)	0	0		0	0		1.00
Intracranial hemorrhage (in-hospital)	0	0		0	0		1.00
Stroke (in-hospital)	3	5		1	5		1.00
Transient ischemic attack	3	5		0	0		0.56
Procedural site complication	5	8.3		0	0		0.32
Hyperperfusion syndrome	0	0		1	5		0.25
Hypotension during the procedure	12	20		1	5		0.167
Bradycardia/atropine during the procedure	14	23.3		0	0		**0.016**
Hypertension during the procedure	0	0		1	5		0.25

SD: Standard deviation; MRI: Magnetic resonance imaging; Group 1: Embolism protection device used; Group 2: Embolism protection device not used.

RESULTS

In the protective device group, a distal protection device was used in 55 patients, and a proximal protection device was used in five patients. Bilateral carotid stenosis was present in 25 (31.2%) of the patients. Thirty-one (38.7%) of the patients had a history of ischemic stroke or transient ischemic attack before six months. There was no significant difference in baseline characteristics between embolism-protected and unprotected groups, except for sex (Table 1). More males were present in the protected group (p=0.02). The mean left ventricular ejection fraction of the patients was 57.25±5.9%. There was no significant difference between the laboratory findings of the groups (Table 2). Thirty (37.5%) of the patients who underwent CAS were clinically asymptomatic. Sixty-one (76.2%) of the patients had infarct findings in the MRI performed before the procedure. In-hospital mortality developed in one (1.25%) patient after the procedure. Considering the primary endpoints, the rates of ischemic stroke (5% *vs.* 5%, p=1.00) and transient ischemic attack (5% *vs.* 0%, p=0.56) were found to be similar between the protected and unprotected groups after the CAS procedure. While total emboli numbers (2.11±2.62 *vs.* 1.26±2.19, p=0.072) and infarct sizes (8.80±4.5 mm *vs.* 9.00±5.05 mm, p=0.97) were similar between the protected and unprotected groups, the presence of silent microemboli was higher in the unprotected group (40% *vs.* 15%, p=0.02). Bradycardia and atropine requirement during the procedure was significantly higher in the group using a protective device (23.3% *vs.* 0%, p=0.016, Table 3).

DISCUSSION

Cerebral protection devices were started to be used with the assumption that they would prevent cerebral embolism during carotid stent placement. Case reviews compared old unprotected data with newly protected data.[11,12] However, this mostly reflects advances in technique and patient selection. New studies reveal that cerebral protection devices have no effect on death, stroke, and myocardial infarction in the first 30 days, contrary to today's general use.[13,14] In another study, it was found that the use of a protective device led to new ischemic lesions revealed by diffusion MRI after

the procedure.[14] Contrary to these studies, in the first 80 patients of the EVA-3 (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis) study, stroke was detected four times more frequently in unprotected CAS, and the study was interrupted.[15] However, this difference is unlikely to be explained by the use of a protection device since only two of the patients who did not use a filter had a stroke on the day of the procedure. In our study, although it was not statistically significant, stroke or transient ischemic attack developed in six patients in whom protection was used, while it occurred in only one case in which protection was not used.

The 2017 European Society of Cardiology guideline raised the use of protective devices to class 2A.[16] However, the studies used justified to this change are old and not multicenter, randomized studies. Two small randomized studies have shown that microemboli protection devices increase microemboli.[6-11,17] In our study, microemboli were more common in the unprotected group in postprocedure MRI (p=0.020). However, our study was not a randomized study, and the unprotected group consisted of more difficult cases where the use of filters was not possible. More ischemic foci were detected in the MRI images before the procedure in the unprotected group. However, the number of clinically significant events after the procedure was higher in the protected group. In addition, bradycardia and atropine requirement during the procedure were higher in the group using the protective device. The reason for this was thought to be the increased stimulation of the carotid bulb due to manipulation of the protection device. This is an important problem of the CAS process and adversely affects the results.

The main limitation of the study is that it was not a randomized controlled trial. Another limitation is the lack of statistical significance in the primary endpoints due to the relatively small number of patients.

In conclusion, the present study showed that cerebral protection devices used in carotid stenting did not reduce the risk of clinically reflected cerebral embolism but significantly reduced the risk of silent microemboli.

Ethics Committee Approval: The study protocol was approved by the Acibadem University Medical Research Evaluation Board (date: 31.03.2016, no: 2016-5/8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: Conception and design of the study, data collection and drafting of manuscript: Y.D., A.D.; Analysis and interpretation of data: O.Ş.; Acquisition of data and critical revision: A.E.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):58-63
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1607
www.e-cvsi.org

Cardiovascular Surgery and Interventions

Original Article Open Access

Surgery for thoracic outlet syndrome: Holding a tiger by the tail?

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Received: January 26, 2024 ***Accepted:*** March 06, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: In this study, the patients operated on for thoracic outlet syndrome were evaluated in terms of their presenting symptoms, physical examination findings, laboratory test results, complications, and the effectiveness of surgical treatment.

Patients and methods: Surgical procedures performed on 28 patients (21 females, 7 males; mean age: 32.4±11.7 years; range, 16 to 59 years) between June 2004 and March 2010 were included in the retrospective study. Demographic characteristics, occupation, complaints, time from symptom onset to surgery, postoperative follow-up data, and preoperative and postoperative ulnar nerve conduction velocity tests were recorded through careful review of medical records, operative reports, and patient interviews.

Results: Thirty-two surgical procedures were performed in total. Transaxillary surgery was performed in all cases. Electromyography examination results showed a significant improvement in nerve conduction velocity after surgery. Recurrence occurred in only three of 32 (9.4%) surgeries, and in one of these three cases, subsequent surgery was performed. According to clinical results, the success rate was 90.6%.

Conclusion: Complaints in thoracic outlet syndrome coincide with the period when physical activities are the most intense. It is observed that being a housewife has an important place in the etiology of disease in Türkiye. The optimal surgical approach through transaxillary route is valuable for the management of the disease.

Keywords: Brachial plexus, subclavian artery, subclavian vein, thoracic outlet syndrome.

Thoracic outlet syndrome (TOS) is the term that describes whole symptoms in locations including the neck, shoulder, and upper extremity that develop due to compression and irritation of the subclavian vein, subclavian artery, and brachial plexus in the thoracic outlet and costoclavicular region. The incidence of TOS is 3-80/1,000. It is generally observed in the 20 to 50 age group and in females.[1] Neurogenic or vascular symptoms develop as a result of compression of the neurovascular structures for various reasons while passing through the cervicoaxillary canal.[2] It is divided into arterial, venous, and neurological types according to the type of the leading symptoms.[1,2] A detailed history and comprehensive physical examination of the patient have an important place in the diagnosis. Provocative tests support the diagnosis. Diagnosis is reached in the light of radiological and electrophysiological examinations.[3]

Transaxillary surgery is the operative approach in which the first rib or cervical rib is excised and scalenectomy is performed. Supraclavicular and infraclavicular approaches, video-assisted thoracic surgery, robotic-assisted thoracic surgery, and posterior routes are other alternative surgical approaches.[1,4] Transaxillary intervention is widely used in the treatment of TOS, and success rates vary between 80% and 97%.[5-8] This study aimed to evaluate the effectiveness of surgical treatment of patients with TOS.

PATIENTS AND METHODS

Twenty-eight patients (21 females, 7 males; mean age: 32.4±11.7 years; range, 16 to 59 years)

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Citation:
Anbar R. Surgery for thoracic outlet syndrome: Holding a tiger by the tail?. Cardiovasc Surg Int 2024;11(1):58-63. doi: 10.5606/e-cvsi.2024.1607.

who underwent surgery with the diagnosis of TOS at the thoracic surgery clinic of the Siyami Ersek Education and Research Hospital between June 2004 and March 2010 were included in the retrospective study. The medical records, preoperative examinations [electromyography (EMG), upper extremity arterial Doppler ultrasonography, cervical computed tomography, and subclavian computed tomography angiography] and postoperative clinical follow-ups of the cases were evaluated retrospectively (Figure 1). Additionally, preoperative and postoperative clinical findings were noted to evaluate the effectiveness of the surgery. Preoperative and postoperative EMG ulnar nerve conduction velocity (UNCV) test values were recorded and compared. In our clinical approach, diagnostic criteria for TOS are provocation test positivity together with nerve compression compatible tests on EMG for neurogenic TOS and compression findings compatible with TOS on vascular Doppler for vascular TOS. Cases with complaints compatible with TOS and without any other pathological conditions that could cause these complaints were accepted as definite TOS. Cases with complaints compatible with TOS, without any other pathological conditions that could cause these complaints, and with EMG and vascular Doppler results that did not support TOS were considered as possible TOS. Patients with definite or possible TOS suspicion and whose other diseases were excluded in the differential diagnosis were first referred to the rehabilitation clinic and received physical therapy. Patients who did not receive the expected benefit from physical therapy and whose complaints affected their daily lives were operated on. The surgical technique we adopted and clinically applied in TOS was the transaxillary approach. Scalene muscle excision was performed in all patients, and the first rib was removed (Figures 2-4). If a cervical rib was detected, excision was performed.

All patients were called for follow-up at one year. Electromyography in neurogenic TOS and Doppler ultrasonography in vascular TOS were performed and compared with preoperative findings. Our criteria for improvement were the patient's statement

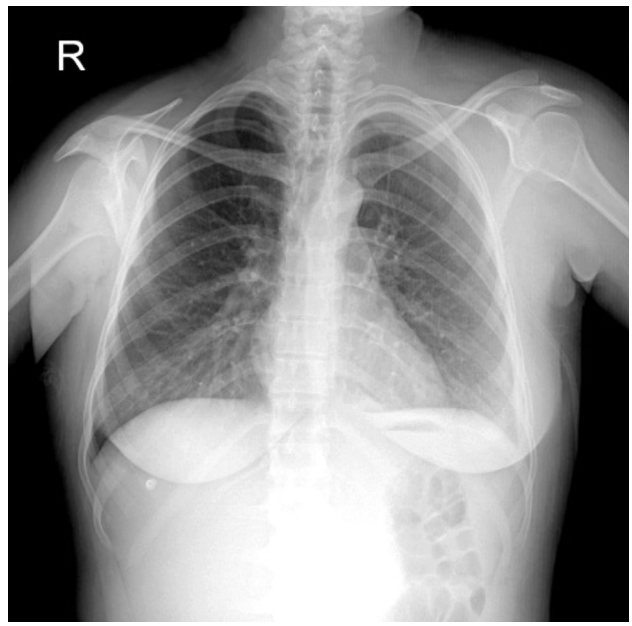

Figure 2. Postoperative chest X-ray.

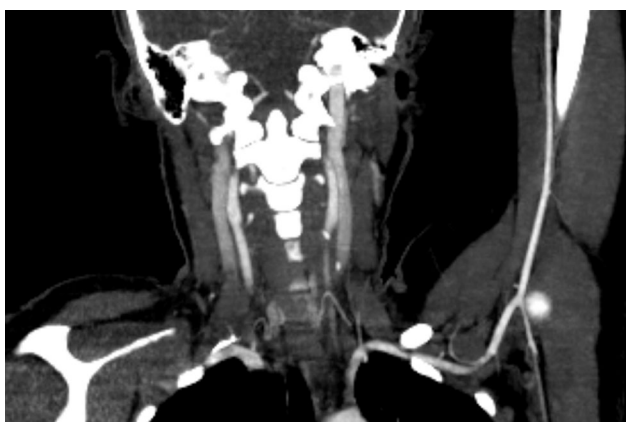

Figure 1. Computed tomography angiography shows compression of the subclavian artery between the first rib and the clavicle.

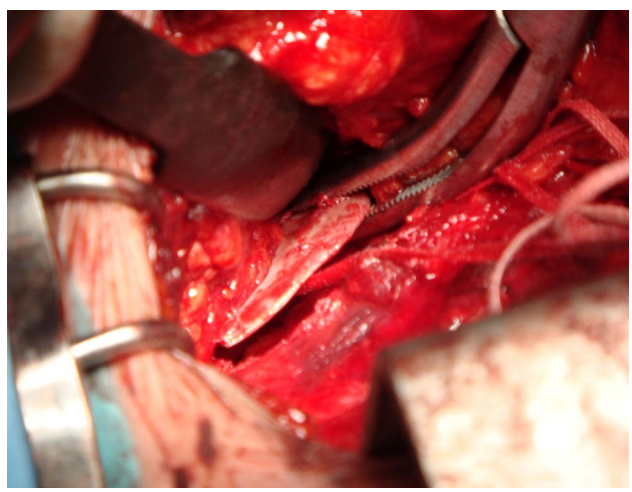

Figure 3. The first rib is disarticulated and removed.

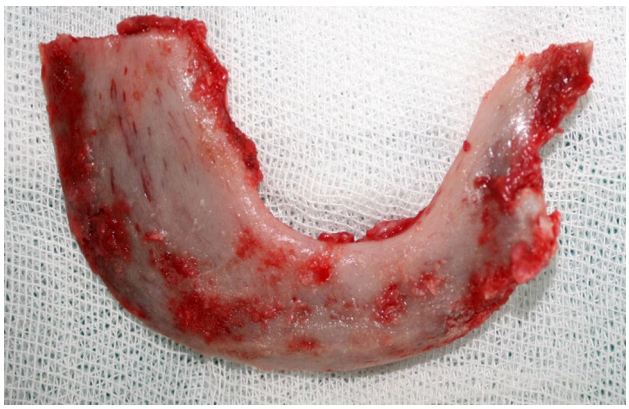

Figure 4. Removed first rib.

that their complaints had improved and did not affect their daily activities, negative provocation tests on physical examination, and improvement in EMG and Doppler findings. The patients' statements regarding improvement were categorized as those with complaints that affected their daily activities and no change. The operation was recommended for three patients with no change in complaints and whose daily activities were affected. One of these patients who accepted surgery was operated on again using the transaxillary route (Figures 3, 4). The fibrous tissue causing subclavian artery compression was removed, and the compression was resolved. Complete recovery was achieved after the operation. Two patients did not accept the operation. All patients were referred to the rehabilitation clinic postoperatively.

Statistical analysis

The NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 (NCSS, Kaysville, UT, USA) were used for data analysis. In addition to descriptive statistical methods (mean, standard deviation, and frequency), the Mann-Whitney U test was used for comparisons of quantitative data between two groups for parameters that did not show normal distribution. The chi-square test and Fisher exact chi-square test were used for the comparison of qualitative data. A p-value <0.05 was considered statistically significant.

RESULTS

Thirty-two TOS procedures were performed on 28 patients. Twenty-four (85.7%) patients were operated unilaterally. Fourteen (43.7%) operations were performed on the left side, and 18 (56.3%) were performed on the right side. One male and three female patients were operated bilaterally.

Four (12.5%) of the cases were 20 years or younger, 13 (40.6%) were between 20 and 29 years of age, six (18.8%) were between 30 and 39 years of age, six (18.8%) were between 40 and 49 years of age, and three (9.4%) were 50 years or older.

Considering the occupational distribution of female cases, 58.3% of them were housewives (Table 1). Pain in the arm was found to be the most common discomfort among the symptoms. Other symptoms and findings are given in Table 2.

The preoperative UNCV value ranged between 44.8 and 64.3 m/sec, and the postoperative UNCV value ranged between 55.3 and 70 m/sec. The mean preoperative UNCV value was 58.07±4.58 m/sec, and the postoperative UNCV value was 66.5±3.50 m/sec. Accordingly, a 16.81% increase in the UNCV value (difference in means: 9.6 m/sec) was detected.

According to clinical, radiological, and laboratory findings, neurological TOS was detected in 28 (87.5%) of the cases, while venous TOS was detected in three (9.4%), and arterial TOS was detected in one (3.1%).

The operative time ranged between 60 and 180 min, with a mean of 135.0±5.3 min. Complications were observed in six (18.7%) of 32 operations. The most common complication was pneumothorax

Table 1
Distribution of occupation (n=32)

	n	%
Housewife	14	43.8
Public servant	5	15.6
Clerk	2	6.3
Student	2	6.3
Computer operator	2	6.3
Teacher	2	6.3
Secretary	1	3.1
Accountant	1	3.1
Garment worker	1	3.1
Construction worker	1	3.1
Freelancer	1	3.1

Table 2
Distribution of symptoms and findings (n=32)

	n	%
Pain in arm	26	81.3
Numbness	20	62.5
Weakness in the arm	9	28.1
Tingle	7	21.9
Shoulder pain	5	15.6
Getting tired easily	4	12.5
Head & neck pain	3	9.4
Bruising on the arm	3	9.4
Chest pain	3	9.4
Edema in the arm	3	9.4
Feeling cold	2	6.3
Atrophy	1	3.1
Discoloration	1	3.1
Swelling in the cervical area	1	3.1

(six cases). Long thoracic nerve damage was observed in one of the six cases that developed pneumothorax. Since the pleura was open during the operation, tube thoracostomy with a hemovac drain or tube thoracostomy only was performed on the same side due to pneumothorax. Hemovac drain, tube thoracostomy, or both did not make a statistically significant difference in terms of the duration of hospitalization (Tables 3, 4).

In the postoperative follow-up, complaints persisted in three (9.4%) of 32 procedures. After the remaining 29 operations, patients stated they did not have any complaints affecting their daily activities. Physical examination and Doppler or EMG findings were found to support patient statements. According to the results obtained, the success rate was determined as 90.6%.

Table 3
Length of hospital stay

	n	Mean±SD	Min-Max
All patients	32	4.06±1.27	2-8
Patients receiving hemovac drain only	26	3.92±1.32	2-8
Patients who underwent tube thoracostomy only	3	4.33±0.57	4-5
All patients with hemovac drains	29	4.03±1.32	2-8
All patients who underwent tube thoracostomy	6	4.67±0.81	4-6

SD: Standard deviation.

Table 4
Evaluation of hospital stay in patients who underwent hemovac drain placement and tube thoracostomy

	n	Mean±SD	Median	p^*
Patients with hemovac drains only				
Yes	26	3.92±1.32	3.5	0.292
No	3	4.33±0.57	4	
Patients undergoing tube thoracostomy only				
Yes	3	4.33±0.57	4	0.292
No	26	3.92±1.32	3.5	
All patients with hemovac drains				
Yes	29	4.03±1.32	4	0.418
No	3	4.33±0.58	4	
All patients undergoing tube thoracostomy				
Yes	6	4.67±0.81	5	0.070
No	26	3.92±1.32	4	

SD: Standard deviation.

DISCUSSION

Studies have shown that TOS is common in females. The male/female ratio (MFR) has been reported to be between 1/3 and 1/9 in case series.[1,4] In our study, this ratio was 1/3. The MFR is also preserved in bilaterally operated cases. In this study, the MFR was found to be compatible with the literature.

The most common period with TOS is the third decade of life, which coincides with the period when patients' physical activities are most intense.[1,9] The mean age of the patients operated on in our clinic was 36.2±11.7 years. When distribution was made according to age groups, the ratio of cases between the ages of 20 and 39 to all patients was 87.5%. The mean age of the patients in our study and the fact that the majority of the cases were between the ages of 20 and 39 are compatible with the literature.

It is accepted that TOS may develop due to excessive tension in the upper extremities and neck area, load on the neck area, shoulder muscle and scalene muscle hypertrophy due to the constant use of the upper extremities in the same position, and chronic trauma during work done with the upper extremities, depending on working conditions. Thoracic outlet syndrome findings are more common in occupational groups such as construction workers, secretaries, and computer operators, who work with repetitive movements of the upper extremity with support from the arms, compared to other occupational groups.[10] In a study conducted in Türkiye, female patients (housewives) who did not work in any job constituted 51.4% of the etiology of TOS.[11] In this study, it was determined that 43.8% of the cases were housewives.

In EMG studies, it has been shown that the UNCV value is higher in postoperative measurements compared to preoperative measurements and is above the 60 m/sec limit.[5,10] In our study, postoperative UNCV values were higher than preoperative measurements, indicating that surgical decompression eliminates nerve irritation and contributes to nerve healing in cases where the brachial plexus is affected.

In the transaxillary approach, the surgery is performed in a deep and narrow area. The reported complication rate in the transaxillary region is approximately 13 to 26%, and the incidence of pneumothorax is approximately 14%. Complications encountered after decompressive procedures for TOS include long thoracic nerve injury, pneumothorax, intercostobrachial neuropathy, and arterial and venous hemorrhages.[5,6,9] In our study, the complication rate was 18.7%, and the most common complication was pneumothorax. In cases where the pleura was opened, tube thoracostomy was performed, and in fewer patients, tube thoracostomy and hemovac drains were used. Following the end of the operation, it is recommended to apply a hemovac drain to the operation area.[6,9,12] In many studies, tube thoracostomy on the same side is recommended in case of pleural tear. There are also studies that recommend opening the pleura to prevent the development of fibrous tissue and hematoma formation in the operation area. Tube thoracostomy and opening the pleura to prevent hematoma at the operation site have also been recommended as drainage options.[7,12] According to our results, hemovac drain or tube thoracostomy did not affect hospital discharge. From this point of view, tube thoracostomy as a drainage method becomes a drainage method that can be preferred alone.

Conditions that negatively affect the quality of life of patients and complaints that are at a level that requires reoperation are considered as recurrence. Neurological findings are more evident in clinical practice. In published series, it has been reported that with appropriate patient selection and operation technique, 80 to 90% success rates are achieved with surgical treatment, and pain complaints are significantly reduced.[5-8] This rate is 97% in the case series of Urschel et al.[11] In our follow-up results, we saw that there was recurrence in three cases. While neurological findings were observed in two of these cases, vascular findings were prominent in one case. Two of our patients were directed to receive physical therapy, and one patient was operated on due to vascular findings and the symptoms affecting the quality of life. In our study, the success rate of our surgical interventions was 90.6%.

The retrospective nature and the relatively small number of patients included are among the limitations of our study. Nonetheless, although the small sample size may limit our ability to analyze and compare our data to other previously published studies, statistical power in the present study still correlates with the overall conclusions.

In conclusion, it was determined that the complaints of TOS patients coincided with the

period when physical activity was most intense, and housewifery has an important place in the etiology of TOS in Türkiye. Significant improvements were observed between the tests evaluated for TOS preoperatively and those performed postoperatively. High surgical success rate was observed in our patients who failed in conservative treatment, and transaxillary approach appears to be an effective method of treatment.

Acknowledgements: The author wishes to thank Doç. Dr. Mehmet Yıldırım, who supported in the study as thesis advisor.

Ethics Committee Approval: This thesis study was performed at Dr Siyami Ersek Education and Research Hospital, Thoracic Surgery Clinic, with the permission of the thesis jury. Approved on 23.12.2010. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Conflict of Interest: The author declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The author received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):64-69
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1595
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Cardiovascular Surgery and Interventions

Original Article Open Access

Transthoracic echocardiographic evaluation of cardiac remodeling after thoracic endovascular aortic repair

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Received: January 14, 2024 ***Accepted:*** February 20, 2024 ***Published online:*** March 25, 2024

ABSTRACT

Objectives: This study aimed to evaluate post-thoracic endovascular aortic repair (TEVAR) cardiac remodeling with transthoracic echocardiography.

Patients and methods: Thirty-two patients (27 males, 5 females; mean age: 61±12.8 years; range, 27 to 85 years) who underwent TEVAR, with an Ishimura zone 3 proximal landing zone, due to thoracic aortic aneurysm were retrospectively evaluated between January 2019 and January 2023. Pre- and postprocedural transthoracic echocardiography data of the patients were compared. Measurements of left ventricular end-diastolic diameter, left ventricular ejection fraction, interventricular septum, and ascending aorta were performed.

Results: The mean follow-up period was 23.7±8.4 months. There was a significant increase in interventricular septum measurements (p=0.041). In addition, a significant decrement was observed in the comparison of left ventricular ejection fraction values (p=0.01). There was no difference found at the pre- and post-TEVAR ascending aortic diameters or valvular regurgitation in aortic valves.

Conclusion: Despite our evaluation being conducted in a limited patient population, our findings suggest that the stiffening of the aortic structure after TEVAR has a negative impact on cardiac remodeling. Consequently, it is imperative to explore new and more flexible designs for thoracic endograft structures.

Keywords: Aorta, endovascular aneurysm repair, left ventricular remodeling, thoracic aortic aneurysm, transthoracic echocardiography.

Thoracic endovascular aortic repair (TEVAR) has become the preferred treatment method for thoracic aortic aneurysms (TAAs) for anatomically suitable patients in recent years due to its lower mortality and morbidity rates in the early- and mid-term compared to open surgical repair.[1-3]

However, for long-term follow-up, cardiac mortality is still one of the leading causes of late mortalities, maybe due to associated coronary artery disease or comorbidities. In recent years, another important factor was also argued for late mortalities and cardiovascular complications: aortic stiffness created by TEVAR endografts. Aortic stiffening is known to play a crucial role in the development and progression of cardiovascular diseases.[4,5] Moreover, the compliance of the aorta is essential in reducing the workload of the heart. Experimental studies have shown that increased aortic stiffness after TEVAR may result from the complex interaction between the aorta and the endograft.[6-8] The motionless state of the arch and proximal descending aorta in patients who underwent TEVAR may be the reason for aortic stiffness. Therefore, designing more flexible and physiological endografts may lead to better results. Afterload reduction by medical treatment may be another important issue. The aortic arch contributes significantly to arterial compliance; therefore, TEVAR may have a negative impact on compliance, increasing left ventricular afterload and myocardial

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Citation:
Hasanzade S, Mola S, Çelikten AE, Gevrek M, Karadeniz B. Transthoracic echocardiographic evaluation of cardiac remodeling after thoracic endovascular aortic repair. Cardiovasc Surg Int 2024;11(1):64-69. doi: 10.5606/e-cvsi.2024.1595.

energy requirements.[9,10] This issue needs further investigation with larger series with comparison of different endografts, different landing zones at the descending aorta, and post-TEVAR medications. Therefore, new designs or materials able to minimize their impact on pulse wave profile and aortic wall mechanical properties may be the next step.[11]

This study aimed to evaluate the echocardiographic changes after TEVAR in TAAs where the proximal landing zone was Ishimura zone 3.

PATIENTS AND METHODS

The data of 108 patients who underwent TEVAR due to TAA at the Ankara Bilkent City Hospital between January 2019 and January 2023 were retrospectively evaluated, and 32 eligible patients (27 males, 5 females; mean age: 61±12.8 years; range, 27 to 85 years) were included in the study. Patients with available pre- and post-TEVAR echocardiography and computed tomography angiography were included. All patients had proximal landing zones at Ishimura zone 3. Other proximal landing zones were excluded. Aortic dissections, prior surgical or endovascular aortic repair, and emergent cases in which transthoracic echocardiography could not be performed before the procedure were excluded from the study.

Procedural details and management strategy

Patients who underwent TEVAR procedures using the technique described in our previous article.[12] All procedures were successfully performed without complications. The endografts for all patients were placed with proximal attachment zones in Ishimura zone 3 (Figure 1). Zone 3 was thought to interfere with aortic stiffness the most as it was the starting point of a standard TEVAR procedure at the descending aorta.

In the intensive care unit following TEVAR, either intravenous beta-blockers or calcium channel blockers, administered individually or in combination, were employed as an initial therapy to bring down systolic blood pressure to less than 120 mmHg. Out of the 32 patients, around 24 (75%) individuals had a documented history of hypertension prior to the operation. Subsequently, the intravenous medications were substituted with oral antihypertensive drugs, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics, either independently or in conjunction. Medications were adjusted to maintain target systolic blood pressure at or below 120 mmHg during in-hospital monitoring and postdischarge follow-ups. Target blood pressure values were achieved at the time of patient discharge, and patients were consistently monitored at target levels during the follow-up periods. The decision on when, whether, and how to administer oral antihypertensive medications was left to the discretion of the treating physician, in accordance with prevailing guidelines and optimal clinical practices.

Study endpoints and follow-up

Transthoracic echocardiography measurements were compared before and after the procedures. Aortic valve structure (bicuspid/tricuspid), aortic regurgitation, left ventricular end-diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), interventricular septum (IVS) and ascending aortic diameter were measured. Follow-up visits were scheduled at one week and one month, and subsequently, every three months, during which medical treatments were adjusted, and patients were counseled on their lifestyle modifications.

Statistical analysis

The data were analyzed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA) and MedCalc version 15.8 (MedCalc Software bvba, Ostend, Belgium). Descriptive statistical methods (frequency, percentage, mean, standard

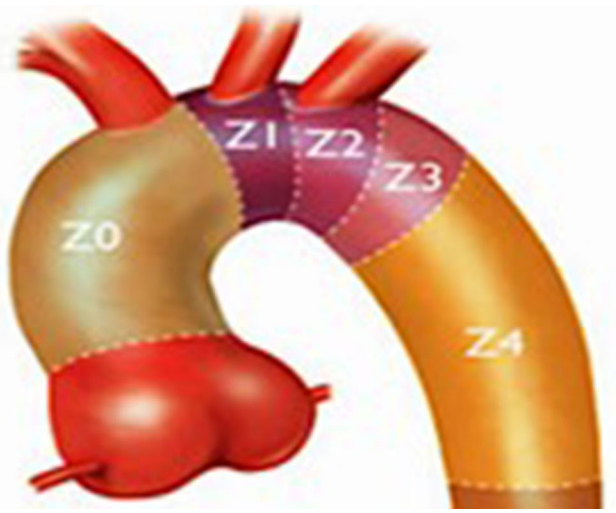

Figure 1. Ishimura zones.

Table 1
The demographic data of the patients

	n	%	Mean±SD	Median	Min-Max
Age (year)			61±12.8	62	27-85
Sex					
Female	5	15.6			
Male	27	84.4			
Comorbidities					
Diabetes mellitus	19	59.3			
Coronary artery disease	2	6,25			
Smoking	11	34.3			
Chronic obstructive pulmonary disease	3	9.3			
Hypertension	24	75			
Hyperlipidemia	18	56.25			

SD: Standard deviation.

Table 2
Comparison of preoperative and postoperative echocardiographic data

	Preoperative			Postoperative			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	*p*
Aortic regurgitation	0.91±0.86			0.81±0.74			0.184*
Ascending aorta	3.83±0.45			3.81±0.45			0.557*
Interventricular septum	1.23±0.19			1.27±0.21			0.041*
LVEDD	4.89±0.49			4.83±0.44			0.291*
LVEF		60.00	20.00-66.00		55.00	20.00-60.00	0.010‡

* Paired Samples t test; ‡ Wilcoxon Signed Ranks test; LVEDD: Left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction.

deviation, median, and min-max) were used during the evaluation of the data. The distribution of the data was evaluated through the Shapiro-Wilk test, skewness and kurtosis measures, and graphical methods (histogram, Q-Q Plot, stem and leaf, and boxplot). For the comparison of pre- and postoperative values, a paired samples t-test was applied to normally distributed data, while the Wilcoxon signed-rank test was used for nonnormally distributed data. The statistical significance level was accepted as $p<0.05$.

RESULTS

Baseline demographic and clinical characteristics of the patients are shown in Table 1. The aortic valve was bicuspid in one (3.1%) patient and tricuspid in other patients. All patients were treated with a single endograft, and zone 3 TEVAR was the proximal landing zone in all patients. A comparison of pre- and post-TEVAR echocardiography data was reported in Table 2. The mean follow-up period was 23.7±8.4 months. There was a significant increase in IVS measurements ($p=0.041$). In addition, a significant decrease was observed in the comparison of LVEF values ($p=0.01$). Ascending aortic diameter and LVEDD data, as well as valvular regurgitations at the aortic valves, were similar before and after the procedure.

DISCUSSION

The goal of the present study was to elucidate the effects of TEVAR-induced aortic stiffening on LVEF and other cardiac remodeling parameters. It is known that from the origin of the left subclavian artery, mobility and compliance decrease towards the descending aorta and infrarenal aorta. Therefore, in patients with TAA, cases in which the proximal landing zone was zone 3 were selected, and this zone

was thought to be the most influencing area for aortic stiffness as it is the closest zone to the aortic arch.

The elastic structure of the aorta plays a critical role in hemodynamic adaptation.[5] However, the elastic properties of the aorta diminish with age or the presence of risk factors, such as smoking, hypertension, hyperlipidemia, and atherosclerosis. Apart from these factors, stiffening of the aortic wall after TEVAR due to the endograft structure affects cardiac remodeling. Some studies involving animal experiments have indicated clinical conditions such as tachycardia, hypertension, and reduced coronary perfusion in the early period after TEVAR.[9] However, in our patient group, these clinical findings were not observed in the early period. No early cardiac or adverse hemodynamic events were detected in any of the patients. In a report published by Kreibich et al.,[13] the impact of TEVAR on cardiac remodeling for aortic aneurysms was investigated in a cohort of 31 patients, revealing a decline in biventricular functions. Additionally, the research highlighted a decrease in TAPSE (tricuspid annular plane systolic excursion) and LVEF within the study group. In our study, we evaluated the left ventricular functions using LVEF measurements, and similarly, we observed a statistically significant reduction in LVEF (p=0.01) during the postoperative follow-up period. Furthermore, a notable increase in IVS thickness, a parameter utilized for assessing left ventricular mass (p=0.041), was also evident. This situation may indicate a subclinical coronary perfusion reduction that manifested as an effect over time.

Sincos et al.[14] reported in a histologic and immunohistochemical study the structural deterioration of the aortic wall after implantation of an endograft, with decreased amounts of muscle and elastic fibers. Halloran et al.[15] demonstrated that collagen and elastin content relative to the luminal surface area decrease with distance from the heart. Therefore, we may conclude that TEVAR procedures pose a higher risk of arterial stiffness compared to infrarenal abdominal aortic cases. These differences likely affect the compliance and structural integrity of the aorta.

Not only the decrease of mobility of the aortic arch but the oversizing of the endograft is one of the factors influencing the arterial stiffness. In patients with blunt thoracic aortic injury, particularly those who are younger and nonatherosclerotic aortas with smaller diameters, it is recommended that oversizing should not exceed 10%, as do the type B aortic dissections. Notably, after endovascular repair, there is an observed loss of elasticity in the aortic wall regardless of the degree of oversizing. Based on the best available evidence, the current standard of 10 to 20% of oversizing, depending on the aortic pathology, appears to be safe and preferable.[16,17]

In 2018, van Bakel et al.[18] examined cardiac remodeling based on preoperative and postoperative data of eight patients who underwent TEVAR for TAAs. A significant increase in left ventricular mass index due to afterload increase was observed. In the same study, the preoperative and postoperative antihypertensive drug regimens of the patients were evaluated. Prior to TEVAR, 25 patients were receiving antihypertensive treatment, while after the procedure, antihypertensive drugs were prescribed to all 31 patients. Patients were administered dual (p=0.75) or triple (p=0.33) antihypertensive drug therapy after TEVAR. Beta-blockers and calcium channel blockers were the most commonly used medications.[18] During the follow-up, dual antihypertensive medication was initiated for treatment in our study cohort. Among those not achieving the target blood pressure range during follow-ups, triple antihypertensive therapy was prescribed for eight (25%) patients. In dual therapy, beta-blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were preferred. For patients requiring triple therapy, calcium channel blockers were added to the treatment regimen.

Reducing aortic stiffness will contribute to the long-term preservation of the left ventricle and a decrease in hypertensive-related adverse cardiac effects. With an appropriate antihypertensive treatment plan aiming to lower afterload, it is likely that the heart can be protected through this mechanism in the long term. According to our research, medical device producers ought to create more compliant endografts to mitigate the mismatch between the device and aorta. To further manage blood pressure following TEVAR, extensive antihypertensive medication is required.

There are some limitations to this study. The number of patients included in this study is relatively small, as the majority of patients who were treated at our center were excluded. Due to the retrospective design of the study, we could only compare routine measurements, such as LVEF, LVEDD, and IVS diameter, during preoperative

preparation and postoperative follow-up. However, more valuable parameters, such as left ventricular mass index, LVPWd (left ventricular posterior wall end-diastole), and TAPSE, could be investigated to assess cardiac remodeling. Since echocardiogram dates were randomly determined, we could not provide information about the change processes. However, at the end of the follow-up period, there was a statistical change in both LVEF and IVS.

In conclusion, endovascular aortic procedures increase aortic stiffness, while open surgical repair does not. Therefore, lifelong follow-up should be mandatory to evaluate the aortic disease progression or endovascular complications, as well as related cardiovascular outcomes. For more accurate results, prospective studies involving large cohorts are necessary. Despite our evaluation being conducted in a limited patient population, our findings suggest that the stiffening of the aortic structure after TEVAR has a negative impact on cardiac remodeling. Consequently, it is imperative to explore new and more flexible designs for thoracic endograft structures. Careful adjustment of medical treatment may warrant the addition of medications that reduce afterload for patients.

Ethics Committee Approval: The study protocol was approved by the Ankara Bilkent City Hospital Ethics Committee (date: 01.12.2021, no: E1-21-2184). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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Cardiovasc Surg Int 2024;11(1):70-71
http://dx.doi.org/DOI: 10.5606/e-cvsi.2024.1586
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Cardiovascular Surgery and Interventions

Interesting Image Open Access

A rare cause of bilateral isolated cruris edema: Liver neuroendocrine tumor

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Received: December 26, 2023 ***Accepted:*** January 05, 2024 ***Published online:*** March 25, 2024

In this article, we would like to highlight an interesting patient and draw attention to an important issue. Edema in the lower extremities is a common clinical condition. As it is known, there are three types of leg edema. Venous edema, lymphedema and lipoedema. Venous edema consists of an extremely low-viscosity, protein-poor interstitial fluid resulting from increased capillary permeability that cannot be accommodated by a normal lymphatic system. Lymphedema occurs as a result of increased protein-rich interstitial fluid in the skin and subcutaneous tissue resulting from lymphatic dysfunction. Lipoedema, on the other hand, is considered a form of maldistribution of fatty tissue rather than true edema.[1] Edema may develop due to many congenital and acquired causes. These causes are trauma, recurrent infections (cellulite, lymphangitis, and parasitic diseases), after surgical interventions (such as lymph node dissection in cancer patients), pelvic area cancers that cause lymph node metastasis (prostate, ovary, cervix, colorectal cancer, etc.), Klippel-Trenaunay syndrome and lymphangiosarcoma.[2] Cruris edema due to liver neuroendocrine tumor is an entity that we rarely encounter in the clinic.

On physical examination of a 51-year-old male patient who presented with bilateral isolated cruris edema, there was edema in both legs below the knees, particularly around the ankle. There were no signs of inflammation such as pain, tenderness,

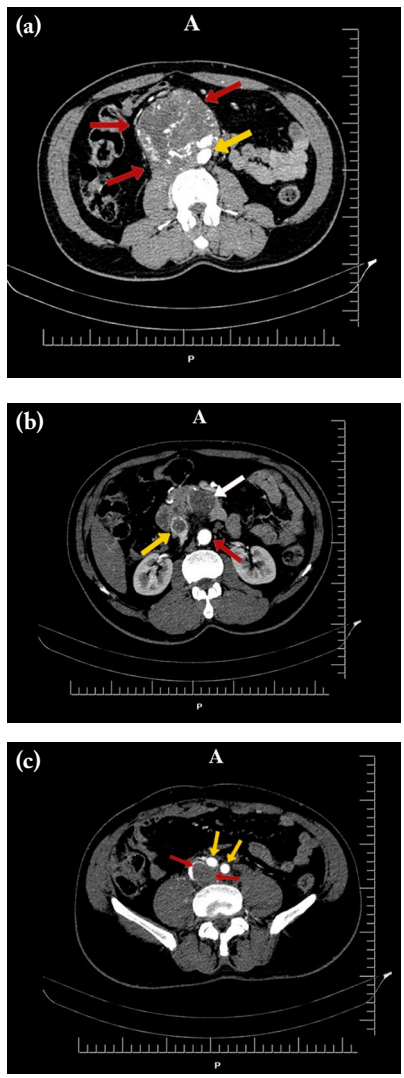

Figure 1. **(a)** A mass lesion with lobulated contours dense vascularity extending to the iliac bifurcation level, surrounding the aorta (red arrows), abdominal aorta (yellow arrow). **(b)** Thrombosed inferior vena cava (yellow arrow), abdominal aorta (red arrow), tumoral mass (white arrow), **(c)** Right and left iliac arteries (yellow arrows), Thrombosed right and left iliac veins (red arrows).

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Citation:
Alur İ. A rare cause of bilateral isolated cruris edema: Liver neuroendocrine tumor. Cardiovasc Surg Int 2024;11(1):70-71. doi: 10.5606/e-cvsi.2024.1586.

redness. Peripheral pulses were palpable. Other cardiovascular examination findings were normal. No venous thrombosis or thrombophlebitis was detected in the lower extremity venous color Doppler ultrasound (CDUS). The quantitative D-dimer level was measured as high as 2.82 ug/mL (normal range: 0 to 0.5 ug/mL). On abdominal computed tomography (CT) angiography, a mass lesion with lobulated contours measuring approximately 85×88×100 mm in size, with dense vascularity extending to the iliac bifurcation level, surrounding the aorta in the paracaval area in the retroperitoneum of the pancreatic head, but not narrowing it, was observed, and the appearance of a tumor thrombus extending from the mass into the inferior vena cava was observed (Figure 1a, b). The inferior vena cava and iliac veins appeared thrombosed (Figure 1c). Liver neuroendocrine tumor was diagnosed in the biopsy taken from the patient at an external center.

In conclusion, patients with complaints of edema in the lower extremities, no venous thrombosis detected in CDUS, and high quantitative D-dimer levels should undergo abdominal CT angiography, if their renal functions are normal. Abdominal CT angiography, or alternatively magnetic resonance angiography, is a useful examination in that it provides detailed information about both iliocaval thrombosis and surrounding organs and formations.

Patient Consent for Publication: A written informed consent was obtained from the patient.

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

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

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