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ABOUT JOURNAL

Koşuyolu Heart Journal is a peer-reviewed, open access e-journal that has been published three times a year in April, August and December. This is the scientific journal of the Health Sciences University Kartal Koşuyolu High Specialization Training and Research Hospital, (namely in Turkish, Sağlık Bilimleri Üniversitesi, Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye).

The aim of the Koşuyolu Heart Journal; is to present advances in the field of cardiology, cardiovascular surgery, congenital cardiac surgery and cardiovascular anesthesia to the readers. Koşuyolu Heart Journal publishes research articles, reviews, original case reports and images, letters and critiques on cardiovascular medicine. The target reader population are the doctors specialized to the cardiovascular medicine. As an open access journal, all content is freely available.

Koşuyolu Heart Journal currently has an acceptance rate of 58%. The average time between submission and final decision is 40 days and the average time between acceptance and final printed publication is 13 weeks. However, provisional copy of submissions are published online within 1 month after acceptance.

Journal History :

- Koşuyolu Heart Journal, ISSN 1300-8706, 1990 - 2007.
- Koşuyolu Kalp Dergisi, ISSN 1300-8706, 2009 - 2014.
- Koşuyolu Heart Journal, ISSN 2149-2972, eISSN 2149-2980, 2015-2021.
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Submission Process: The manuscripts should be submitted via online.The journal do not charge any article submission or processing charges.

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EDITORIAL POLICIES

Aims and Scope

Koşuyolu Heart Journal aims to present advances in the field of cardiology, cardiovascular surgery, congenital heart surgery, and cardiovascular anesthesia to the readers. In order to achieve this goal, Koşuyolu Heart Journal publishes research articles (for the clinical or laboratory studies), reviews (by invitation only), case reports, original images, original techniques for cardiovascular surgery or cardiovascular interventions and letters/critiques on cardiovascular medicine. Koşuyolu Heart Journal publishes, after double blinded peer review, the articles for the target reader population consisting of cardiologists, cardiovascular surgeons and cardiac anesthesiologists. The articles should be submitted in English, while the title and abstract should be written in both English and Turkish. Editorial and publication process of Koşuyolu Heart Journal are congruent with the standards of ICMJE, WAME, and COPE. Koşuyolu Heart Journal is an open access journal.

Originality of Manuscript

The corresponding author must certify that their article is original, has not been published previously, and is not under consideration for publication by another journal. The corresponding author should affirm originality of the work in the Article Submission Form. If the work has been presented previously at a meeting as an oral or poster presentation, corresponding author must state the name, date and place of the meeting at the Title Page.

Autorship

An individual who has made substantial intellectual contributions to the article should be an author. Each author must have a role in all of the following areas:

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2. Writing article or revising it substantially.
3. Final approval of the submitted version.

Other contributors who perform technical support, identify patients for study, translate the texts, supply materials, provide funding have not been qualified as author. These contributions may be acknowledged in the manuscript. Author roles are stated at Article Submission Form.

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The Koşuyolu Heart Journal accepts the Declaration of Helsinki Principles as the policy of the Journal. Therefore, all studies concerning human subjects must be approved by the Institutional Review Board. All study subjects should be informed and written consent should be obtained. The editor may ask for a copy of the approval document.

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3. If all work submitted for publication is to constitute a conflict of interest, and if relevant, should be indicated.
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INSTRUCTIONS for AUTHORS

Scope of the Journal

The Koşuyolu Heart Journal is published three times a year (april, august, and december). The journal accepts articles in English language. However, the articles have the titles and abstracts written in English and Turkish language. Terms written in another language should be indicated within quotation marks in articles.

All manuscripts submitted for publication should comply with Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced and updated by the International Committee of Medical Journals Editors (http://www.icmje.org/).

The Koşuyolu Heart Journal accepts the Declaration of Helsinki Principles (http:// www.wma.net/en/30publications/10policies/b3/index.html) as the policy of the Journal. Therefore, all manuscripts concerning human subjects must contain a statement in the Materials and Methods section, indicating that the study was approved by the Institutional Review Board. All study subjects should be informed and written consent should be obtained and this should be declared in the Materials and Methods section. All manuscripts dealing with animal subjects must contain a statement indicating that the study was performed according to The Guide for the Care and Use of Laboratory Animals (https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals) with the approval of the Institutional Review Board, in the Materials and Methods section. The Editor may ask for a copy of the approval document. The journals editorial and publication process are also congruent with COPE (https://publicationethics.org/guidance/Guidelines) standards.

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Style and Format: The manuscript text should be written in Times New Roman font, 12 point-type, double-spaced with 2 cm margins on the left and right sides. The article should be prepared with Microsoft Words. The pages should be numbered starting with the title page. Page numbers should appear at the bottom right corner of every page. The main text file should not contain any information regarding author names and affiliations.

Symbols, Units, and Abbreviations: In general, the Journal follows the conventions of Scientific Style and Format, The CSE Manual for Authors, Editors, and Publishers, Council of Science Editors, Reston, VA, USA (7th ed.). Please use SI units. Abbreviations should be internationally accepted and should be defined accordingly in the text in parenthesis when first mentioned and used in the text. The abbreviated form should be used all throughout the article.

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Keywords: There should be two to five key words complying with the Index Medicus Medical Subject Headings (MeSH) and Türkiye Bilim Terimleri for Turkish. Refer to https://meshb.nlm.nih.gov/search and https://www.bilimterimleri.com for English and Turkish key words, respectively.

Original Investigations are clinical or experimental research articles. They should include; Turkish title, Turkish structured abstract (limited to 300 words structured as Giriş, Hastalar ve Yöntem, Bulgular and Sonuç), Turkish key words and English title, English structured abstract (limited to 300 words structured as Introduction, Materials (or Patients) and Methods, Results and Conclusion), English key words. The other sections of the manuscript should include Introduction, Materials (or Patients) and Methods, Results, Discussion, Acknowledgement (if required) and References. All sections of the manuscripts should start on a new page. Research articles are not referred to exceed 5000 words and 40 references.

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Case Reports should include Turkish title, Turkish abstract, Turkish key words, English title, English abstract, English key words, Introduction, Case presentation, Discussion and References. Introduction and Discussion sections of the Case reports should be short and concise and the abstract should be prepared as one paragraph. Structured abstract is not required. Case reports should not exceed 1500 words and the number of references should not exceed 20.

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Letter to the Editor: Readers are encouraged to write about any topic that relates to cardiology, cardiovascular surgery, and cardiovascular anesthesiology and may include discussions on material previously printed in the Journal. Letter to the Editor should be short and concise limited to 1000 words and 5 references. Abstract is not required.

Tables and Figures: Tables, figures, graphics and pictures should be numbered with Arabic numbers in order of reference in the text. Localization of tables, figures, graphics and pictures should be indicated.

Each table should be prepared with double spacing on a separate page. Tables should have a brief title. Authors should place explanatory matter in footnotes not in the heading. Explanations should be made for all nonstandard abbreviations in footnotes. The following symbols should be used for abbreviations in sequence: *,

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Figures should be either professionally drawn or photographed, and these items should be submitted as photographic-quality digital images. Figures should be submitted in a format that will produce high-quality image (for example, JPEG or GIF). Authors should control the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. Information on staining and microscopic images, the magnification ratio.

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Legends for figures, graphics and pictures should be typed starting on a separate page, double spaced, indicating the corresponding illustrations with numbers. When symbols, arrows, numbers or letters are used to identify parts of illustrations, define each one clearly under the illustration. If quoted parts, tables, figures, graphics, pictures etc exist in the manuscript, the authors should obtain written permission from the author and copyright holder and indicate this.

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Example: Suárez De Lezo J, Medina A, Pan M, Romero M, Segura J, Pavlovic D, et al. Transcatheter occlusion of complex atrial septal defects. Catheter Cardiovasc Interv 2000;51:33-41.

If the reference is a journal supplement;

Author(s)' surname and initial(s) of the first name. Title of the article. Title of the manuscript abbreviated according to Index Medicus (http://www.ncbi.nlm.nih. gov/sites/entrez/query.fcgi?db=nlmcatalog). Year;Volume(Suppl Supplement number):First and last page number.

Example: Parsonnet V, Lean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation 1989;79(Suppl 1):S3-S12.

If the reference is a book;

Author(s)' surname and initial(s) of the first name. Title of the book. Edition number. City of publication, Country: Publisher, Year of Publication: Page numbers.

Example: Borrow K, Braunwald E. Heart Disease. 1st ed. Philadelphia, PA, USA: WB Saunders, 1988:976.

If the reference is a book chapter;

Surname and initial(s) of the first name of the author(s) of the chapter.Title of the chapter. In: Surname and initial(s) of the first name(s) of the editor(s) (ed) or (eds). Title of the book. Edition number. City of publication, Country: Publisher,

Year of publication: First and last page numbers of the chapter.

Example: Nguyen A, Imoto E, Eklof BGH. Pulmonary embolism. In: Barros DSa AAB, Chant ADB (eds). Emergency Vascular and Endovascular Surgical Practice. 2nd ed. London, UK: Hodder Arnold, 2005:251-60.

If the reference is an article presented in a meeting;

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Publisher; Year. Page numbers.

Example: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O (eds). MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. North-Holland; 1992. p. 1561-5.

If the reference is an online journal;

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Example: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis 1995;1(1). Available from: http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed date: 25.12.1999.

If the reference is a website;

Name of the web site. Access date. Available from: address of the web site.

Example: World Health Organization (WHO). Access date: 9 July 2008. Available from: http://www.who.int

If the reference is a thesis;

Author's surname and initial of the first name. Title of the thesis (Thesis). Name of the university (or educational hospital, institution, etc), City, Country, Year.

Example: Kalender M. The effect of using internal mammarian artery graft on coronary bypass morbidity and mortality in octogenarian. (Thesis). Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, İstanbul, Türkiye, 2011.

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The Impact of Serum Interleukin-4, Interleukin-10, Interleukin-17a, and Interleukin-22 Levels on the Development of Sporadic Ascending Aortic Aneurysms

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ABSTRACT

Introduction: Aortic aneurysms are chronic diseases associated with inflammatory/immunological mechanisms. Interleukins (ILs) with pro-inflammatory and anti-inflammatory activities are shown to be related to the development of aortic damage. In this context, this study aims to evaluate the serum IL-4, IL-10, IL-17A, and IL-22 in patients with sporadic thoracic ascending aortic aneurysms.

Patients and Methods: The population of this prospective study consisted of all consecutive patients with sporadic ascending aortic aneurysms who underwent thoracic aortic aneurysm repair between November 2019 and September 2022. In the end, 29 patients (the patient group) and 19 healthy voluntary participants without aortic pathology (the control group) were included in the study. The study's primary outcome was the differences in serum IL levels between the groups.

Results: The patient group was significantly older than the control group (p= 0.042). Significantly higher neutrophil-to-lymphocyte ratio (NLR) values were detected in the patient group (p= 0.031). The median IL-10 (p= 0.001), IL-17A (p< 0.001), and IL-4 (p< 0.001) levels were significantly lower in the patient group than in the control group. There were no significant correlations between serum IL levels and the aneurysm diameter (p> 0.05). On the other hand, there were moderate correlations between IL-10 and IL-17A (r= 0.409, p= 0.038), IL-10 and IL-22 (r= 0.464, p= 0.017), and IL-17A and IL-4 (r= 0.496, p= 0.006). NLR ≥1.95 was found to be an independent risk factor for sporadic ascending aortic aneurysms [Odds Ratio (OR)= 4.53, 95% confidence interval (CI)= 1.12-21.17, p= 0.040].

Conclusion: IL-10, IL-17A, and IL-4 were significantly lower in patients with sporadic ascending aortic aneurysms larger than 55 mm. NLR was an independent risk factor for sporadic ascending aortic aneurysms. The diameter of the aneurysm was not correlated with ILs. There were positive correlations between IL-10, IL-17A, and IL-4 levels.

Key Words: Ascending aorta; inflammation; interleukins

Serum İnterlökin-4, İnterlökin-10, İnterlökin-17a ve İnterlökin-22 Düzeylerinin Sporadik Asendan Aort Anevrizmalarinin Gelişimine Etkisi

ÖZET

Giriş: Aort anevrizmaları inflamatuvar/immünolojik mekanizmalarla ilişkili kronik hastalıklardır. Proinflamatuvar ve antiinflamatuvar aktivitelere sahip interlökinlerin (IL) aort hasarı gelişimiyle ilişkili olduğu gösterilmiştir. Bu bağlamda, bu çalışmanın amacı sporadik torasik asendan aort anevrizması olan hastalarda serum IL-4, IL-10, IL-17A ve IL-22 düzeylerinin değerlendirilmesidir.

Hastalar ve Yöntem: Bu prospektif çalışmanın popülasyonu, Kasım 2019 ile Eylül 2022 arasında torasik asendan aort anevrizması onarımı yapılan, cerrahi tedavisi yapılan ardışık hastaları içermiştir. Çalışmaya 29 hasta (hasta grubu) ve aort patolojisi olmayan 19 sağlıklı gönüllü (kontrol grubu) dahil edildi. Çalışmanın birincil sonlanımı, gruplar arasındaki serum IL seviyelerindeki farklılıklar olarak belirlendi.

Bulgular: Hasta grubundaki hastalar, kontrol grubuna göre anlamlı olarak daha yaşlıydı (p= 0.042). Ortanca IL-10 (p= 0.001), IL-17A (p< 0.001) ve IL-4 (p< 0.001) düzeyleri çalışma grubunda kontrol grubuna göre anlamlı olarak daha düşüktü. Serum IL düzeyleri ile anevrizma çapı arasında anlamlı bir ilişki yoktu (p> 0.05). IL-10 ile IL-17A (r= 0.409, p= 0.038), IL-10 ile IL-22 (r= 0.464, p= 0.017) ve IL-17A ile IL-4 (r= 0.496, p= 0.006) arasında orta düzeyde korelasyon tespit edildi. Nötrofil-lenfosit oranı (NLO) değerleri hasta grubundaki hastalarda daha yüksekti (p= 0.031). NLO değerinin ≥1.95 olması sporadik asendan aort anevrizmaları için bağımsız bir risk faktörü olarak bulundu [Odds Ratio (OR)= 4.53, %95 güven aralığı (CI)= 1.12-21.17, p= 0.040].

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Sonuç: IL-10, IL-17A ve IL-4, 55 mm'den büyük sporadik asendan aort anevrizması olan hastalarda anlamlı olarak daha düşüktü. NLO değeri, sporadik asendan çıkan aort anevrizmaları için bağımsız bir risk faktörü olarak bulundu. Anevrizma çapı ile IL düzeyleri arasında bir korelasyon yoktu. IL-10, IL-17A ve IL-4 seviyeleri arasında pozitif korelasyonlar tespit edildi.

Anahtar Kelimeler: Asendan aorta; inflamasyon; interlökinler

INTRODUCTION

The aorta can be subject to aortic dilatation/aneurysm, which, if left untreated, may cause aortic rupture and aortic dissection in the context of several diseases[1,2]. Giant cell arteritis, immunoglobulin (Ig) G4-related pathologies, Kawasaki disease, and Marfan syndrome are specific diseases that may lead to the development of aortic dilatations and aneurysms[1-6]. However, atherosclerotic pathogenesis-related sporadic aortic aneurysms constitute the most frequent etiology. Although several risk factors, including smoking, arterial hypertension, and male gender, have been defined as risk factors, aortic aneurysm is a chronic inflammatory disease[7-9]. The mechanisms that weaken the immune response might be beneficial in preventing the extent of aortic damage[8]. Nevertheless, the relationship between inflammatory/immunological mechanisms and aortic injury remains controversial[1,7,9].

Interleukins (ILs) are biologically active small peptides with different mechanisms of action, either pro- or anti-inflammatory, or immunomodulatory properties[6,8]. IL-1α, IL-1β, IL-4, IL-6, IL-10, IL-17A, IL-19, IL-22, and IL-32 are the ILs that promote, halt, or suppress the inflammatory processes[1,6-8,10-14]. It has been speculated that several ILs might potentially play a role in developing aortic aneurysms. The potentially beneficial effects of genetic and pharmacological inhibition of ILs on the progression of aortic dilatation have been studied in the literature[6]. However, some of these studies have failed to demonstrate any prominent relationship between these ILs and aortic aneurysm formation in animal and human studies, whereas others reported controversial results[15]. On the other hand, the relationship between ILs and arterial aneurysms has been demonstrated in animal studies. In contrast, the relevant human studies were contradictory and could not reveal any positive potential effect of ILs[1]. In addition, most of the experimental and clinical studies were related to the inflammatory changes in abdominal aortic aneurysms. Only a few were about non-familial thoracic ascending aneurysms[16,17], necessitating further studies to be conducted in order to clarify the regulatory function of the ILs with pro-inflammatory activity and the effect of the anti-inflammatory treatment strategies based on ILs[18].

This study was carried out to evaluate the serum levels of ILs, i.e., IL-4, IL-10, IL-17A, and IL-22, in patients with non-familial thoracic ascending aortic aneurysms in comparison with healthy control subjects, considering the limited number of studies about the impact of ILs with anti-inflammatory and pro-inflammatory properties on the development of the thoracic aneurysms.

PATIENTS and METHODS

Study Design

The population of this prospective study consisted of all consecutive patients with sporadic ascending aortic aneurysms who underwent thoracic aortic aneurysm repair between November 2019 and September 2022. The study protocol was approved by the local ethics committee (Approval date, Number: 08.05.2022 & E-10420511-050-14513). The study was carried out in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Population and Sample

Among the consecutive patients who underwent thoracic aortic aneurysm repair, the ones with non-familial sporadic thoracic aortic aneurysms diagnosed using transthoracic echocardiography (ECHO), computed tomography (CT), or magnetic resonance imaging (MRI), and an aortic diameter larger than 55 mm, which indicated surgical repair, were included in the study[19]. On the other hand, patients with familial and syndromic forms and autoimmune connective tissue disorders associated with aortic dilatation/aneurysm, active cancer, and an aortic diameter ≤55 mm were excluded from the study. In the end, 29 patients with sporadic ascending aortic aneurysms who underwent surgical repair were included in the patient group. The median diameters of the tubular ascending aorta at 2 cm above the sinotubular junction and the level of sinuses of Valsalva in the patient group were 51.0 mm (range 37.0-62.0) and 42.0 mm (range 32.0-60.0), respectively[20].

In addition, 19 healthy voluntary participants without a dilatation/aneurysm of the thoracic ascending aorta were included in the control group. The median diameter of the tubular ascending aorta in the control group was 32.4 mm (range 27.3-36.2).

Interventions

Transthoracic ECHO and CT&MRI were performed in all patients and healthy control subjects by an echocardiographer with at least 12 years of ECHO experience and a radiologist with 30 years of CT&MRI experience, respectively. Fasting

blood samples were taken from the patients in the last 48 hours before the surgical treatment for laboratory investigations. The serum samples were stored for immunological parameters per standard procedures at -80 °C until analysis. The IL measurements described in the literature used the techniques described in the literature[5,9]. The LEGENDplex™ Custom Human T Helper Cytokine Panel (version 2, ID: 741028, BioLegend, USA) was used to quantify the ILs simultaneously.

Variables

Demographic characteristics (age, gender, weight, and height) and laboratory characteristics [hemoglobin, neutrophil-to-lymphocyte ratio (NLR), creatinine, glycated hemoglobin (HbA1c), high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, e-glomerular filtration rate (eGFR), and C-reactive protein (CRP)] were prospectively determined during the last admission before the surgical treatment and recorded into a predesigned worksheet. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters (kg/m^2). The patients' diameters were determined during the last ECHO examination and recorded for the ascending aorta (in cm) and the sinus of Valsalva, along with the ejection fraction (%). The ILs investigated within the scope of the study were IL-4, IL-10, IL-17A, and IL-22.

Statistical Analysis

The descriptive statistics obtained from the collected data were expressed as mean ± standard deviation values in the case of continuous variables with normal distribution, as median with minimum-maximum values in the case of continuous variables without normal distribution, and as numbers and percentages in the case of categorical variables. The Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to analyze the normal distribution characteristics of the numerical variables.

Pearson's Chi-squared and Fisher's exact tests were used to compare the differences between categorical variables in 2 x 2 tables.

The Mann-Whitney U test was used to compare two independent groups where numerical variables had no normal distribution.

Spearman's rho correlation coefficients were calculated to analyze the relationships between numerical variables without normal distribution.

Univariate and multivariate logistic regression analyses determined the independent risk factors for sporadic thoracic aortic aneurysm development. Statistically significant and clinically essential factors in the univariate analysis were included in the multivariate analysis.

The receiver operating characteristic (ROC) analysis using the DeLong method with the Youden index was used to determine the optimal cut-off values of NLR, IL-10, IL-17A, and IL-4 in predicting sporadic thoracic aortic aneurysm development. The area under the curve (AUC) values and the corresponding 95% confidence interval (CI) values were calculated.

Jamovi project 2.3.24.0 (Jamovi, version 2.3.24.0, 2023, retrieved from https://www.jamovi.org) and JASP 0.17.1 (Jeffreys' Amazing Statistics Program, version 0.17.1, 2023, retrieved from https://jasp-stats.org) software packages were used in the statistical analyses. The probability (p) statistics of ≤0.05 indicated statistical significance.

RESULTS

The patient group was significantly older than the control group (p= 0.042). There was no significant difference between the groups in gender and BMI values (p> 0.05) (Table 1).

Table 1. Comparison of the study and control groups in terms of demographic characteristics and clinical/laboratory findings

	Patient Group (n= 29)	Control Group (n= 19)	p
Age (year) #	62.0 (20.0-76.0)	45.0 (19.0-81.0)	**0.042***
Sex ##			
Female	8 (27.6)	10 (52.6)	0.148**
Male	21 (72.4)	9 (47.4)	
Body mass index (kg/m^2) #	27.0 (20.5-41.5)	26.0 (24.0-32.0)	0.315*
Obesity (≥30 kg/m^2), yes ##	9 (31.0)	3 (15.8)	0.316**

##: n (%), #: median (min-max)
*: Mann-Whitney U test.
**: Pearson Chi-square/Fisher's exact test.

Table 2. Laboratory parameters of the groups

	Patient group (n= 29)	Control group (n= 19)	p*
Hemoglobin, (g/dL) #	14.2 (9.9-16.1)	14.3 (10.9-17.3)	0.555
HbA1c (%) #	5.6 (5.0-6.9)	5.5 (5.3-6.3)	0.345
HDL (mg/dL) #	45.0 (30.0-119.0)	61.0 (38.0-89.0)	**0.010**
LDL (mg/dL) #	120.0 (40.0-168.0)	132.0 (61.0-195.0)	0.129
Triglycerides (mg/dL) #	112.0 (54.0-337.0)	76.0 (42.0-223.0)	0.054
CRP (mg/dL) #	0.3 (0.0-9.7)	0.1 (0.0-1.3)	**0.004**
Creatinine (mg/dL) #	0.9 (0.4-1.6)	0.8 (0.6-1.3)	0.916
eGFR (ml/min/1.73 m^2) #	95.4 (40.9-121.0)	88.0 (65.0-127.0)	0.712
Neutrophil/lymphocyte ratio#	2.2 (1.2-5.0)	1.8 (0.9-3.2)	**0.031**
Serum interleukin levels			
IL-10 (pg/mL) #	1.7 (1.5-2.1)	2.0 (1.6-3.8)	**0.001**
IL-17A (pg/mL) #	0.1 (0.1-0.2)	0.2 (0.1-0.3)	**<0.001**
IL-4 (pg/mL) #	1.7 (1.4-3.5)	2.2 (1.7-7.8)	**<0.001**
IL-22 (pg/mL) #	2.2 (1.4-4.7)	2.5 (1.5-6.3)	0.092

#: Median (min-max)
*: Mann-Whitney U test.
HbA1c: Glycosylated hemoglobin, HDL: High density lipoprotein, LDL: Low density lipoprotein, CRP: C-reactive protein, eGFR: Estimated glomerular filtration rate, IL: Interleukin.

The median ejection fraction was higher, yet not significantly, in the control group than in the patient group (62.0% vs. 60.0%) (p= 0.121).

The distribution of the laboratory characteristics by the groups is shown in Table 2. The groups had significant differences in HDL and CRP levels and NLR values. The median HDL values were higher in the patient group (61.0 mg/dL) than in the control group (45.0 mg/dL) (p= 0.010). For the patient group, the median CRP values were measured at 0.3 mg/d, whereas 0.1 mg/dL in the control group (p= 0.004). The patient group had significantly higher NLR values than the control group (for median NLR, 2.2 vs. 1.8) (p= 0.031) (Table 2).

The median IL-10 levels were significantly lower in the patient group than in the control group (1.7 pg/mL vs 2.0 pg/mL) (p= 0.001). The patient group had significantly lower median values of IL-17A (0.1 pg/mL vs. 0.2 pg/mL, p< 0.001) and IL-4 (1.7 pg/mL vs. 2.2 pg/mL, p< 0.001) than the control group. On the other hand, there was no significant difference between the groups in IL-22 levels (2.2 pg/mL vs. 2.5 pg/mL9. p= 0.292).

In predicting the development of sporadic ascending thoracic aneurysms, the ROC curve analysis revealed that optimal cut-off values of NLR, IL-10, IL-17A, and IL-4 were >1.95 (65.52% for sensitivity, 78.95% for specificity), ≤1.99 pg/mL (96.15% for sensitivity, 52.63% for specificity), ≤0.16 pg/mL (86.21% for sensitivity, 89.47% for specificity), and ≤1.92 pg/mL (79.31% for sensitivity, 88.24% for specificity), respectively (Table 3) (Figure 1). IL-17A had the highest AUC

Table 3. The receiver operating characteristics (ROC) curve analysis of the demographic and interleukin levels in predicting development of sporadic ascending aortic aneurysms

	AUC	Sensitivity	Specificity	Cut off	95% CI	p
Neutrophil/lymphocyte ratio	0.686	65.52	78.95	>1.95	0.536-0.812	**0.018**
IL-10 (pg/mL)	0.803	96.15	52.63	≤1.99	0.657-0.906	**<0.001**
IL-17A (pg/mL)	0.885	86.21	89.47	≤0.16	0.760-0.959	**<0.001**
IL-4 (pg/mL)	0.862	79.31	88.24	≤1.92	0.728-0.946	**<0.001**

AUC: Ara under the curve, CI: Confidence interval, IL: interleukin.

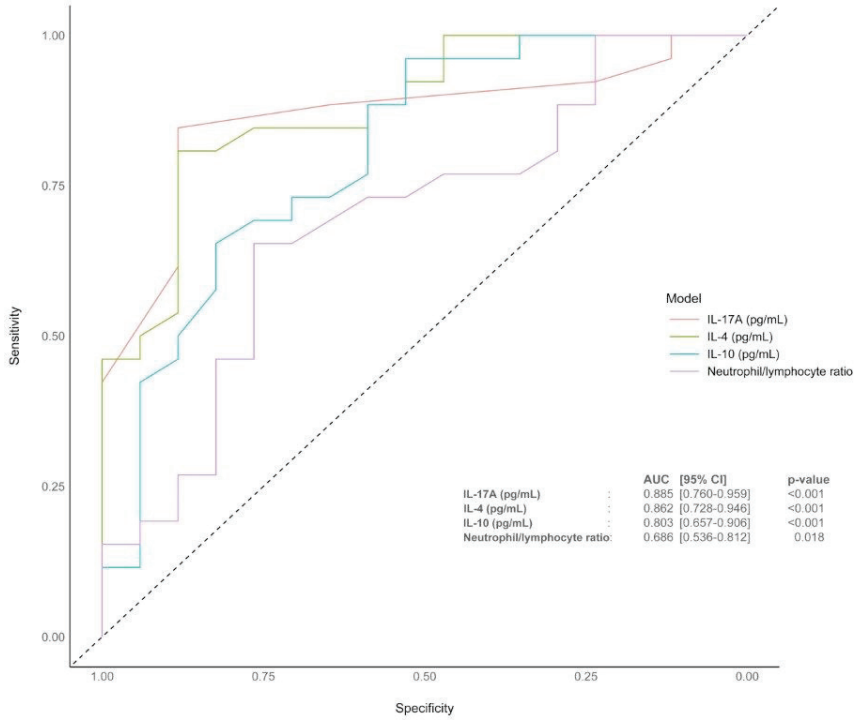

Figure 1. The receiver operating characteristics (ROC) curve analysis of ILs in predicting the development of sporadic ascending aortic aneurysms.

value (AUC= 0.085, 95% CI= 0.760-0.959, p< 0.001). IL/17A values of ≤0.16 pg/mL predicted sporadic ascending aortic aneurysms with 86.21% sensitivity and 89.47% specificity.

The results of the univariate and multivariate regression analyses on the predictive powers of the variables in predicting the development of sporadic ascending aortic aneurysms are shown in Table 4. Based on the multivariate analysis, there was

Table 4. Univariate and multivariate regression analysis in predicting the development of sporadic ascending aortic aneurysms

	Univariate		Multivariate	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Age (year)	1.05 (1.01-1.10)	**0.034**	1.04 (0.96-1.13)	0.294
Sex				
Male vs. Female	2.92 (0.88-10.19)	0.084	--	--
Obesity				
≥30 vs. <30	2.40 (0.60-12.18)	0.241	--	--
Neutrophil/lymphocyte				
>1.95 vs. ≤1.95	7.12 (2.00-30.60)	**0.004**	2.48 (0.30-20.82)	0.403
IL-10 (pg/mL)				
>1.99 vs. ≤1.99	27.78 (4.43-548.29)	**0.003**	9.46 (0.37-244.59)	0.176
IL-17A (pg/mL)				
>0.16 vs. ≤0.16	53.12 (10.54-436.53)	**<0.001**	3.70 (0.25-53.87)	0.338
IL-4 (pg/mL)				
>1.92 vs. ≤1.92	28.75 (6.09-219.07)	**<0.001**	14.67 (0.70-305.23)	0.083

OR: Odds ratio, CI: Confidence interval, IL: Interleukin.

no independent risk factor in predicting the development of sporadic ascending aortic aneurysms.

There was no significant correlation between ILs and the aneurysm diameter (p> 0.05). Nevertheless, there were moderate correlations between IL-10 and IL-17A (r= 0.409, p= 0.038), IL-10 and IL-22 (r= 0.464, p= 0.017), and IL-17A and IL-4 (r= 0.496, p= 0.006) levels.

DISCUSSION

The study indicated that serum IL-10, IL-17A, and IL-4 levels were significantly lower in patients with sporadic ascending aortic aneurysms larger than 55 mm. Even though IL-22 did not significantly differ between the patient and control groups, the significant correlations between IL-10, IL-17A, and IL-4 might indicate a compensatory anti-inflammatory status.

Previous studies reported that aortic injury, either aneurysms and/or dissection, usually lead to altered expressions and changed epigenetic regulations of several ILs, including IL-4, IL-6, IL-17, and IL-10[5,10,16,17,21-24]. Nevertheless, there were notable, controversial findings related to the IL families and their increased or decreased levels in various clinical presentations of aortic aneurysms[21,23]. We also detected that the number of studies focusing on sporadic aortic aneurysms was limited.

Malm et al. detected significantly higher IL-10 levels in patients with abdominal aortic aneurysms than in healthy control subjects[19]. Other studies reported conflicting outcomes on the plasma and tissue extract levels of IL-10[25,26]. Besides, some studies reported lower levels of anti-inflammatory ILs, including IL-10, in patients with ruptured aortic aneurysms[27]. As in this study, Liao et al. detected significantly lower IL6, IL10, and IL17A levels in patients with abdominal aortic aneurysms[28]. They also showed that IL10 was significantly correlated with aneurysm development and growth rate in the positive direction[28]. In sum, the exact role of IL-10, as an anti-inflammatory cytokine, in human aortic aneurysmatic pathologies remains obscure. Furthermore, the positive correlations found between some of the ILs analyzed in the study might suggest complex relationships between pro-inflammatory and anti-inflammatory cytokines. Counter relations between anti-inflammatory and pro-inflammatory ILs and the potentially compensatory roles of some of the ILs might lead to such controversies.

The impact of pro-inflammatory ILs, such as IL-6, IL-22, and IL-17-A, on developing aortic aneurysms has been investigated. Elevated serum levels of pro-inflammatory cytokines have been associated with aortic aneurysms[29,30]. Dawson et al. found elevated IL-6 levels within the aorta of the patients with abdominal and thoracic aortic aneurysms who underwent endovascular aneurysm repair[29]. In one experimental animal model, the authors reported a critical role of IL-17 in promoting inflammation during abdominal aortic aneurysm formation[30]. Ye et al. showed significantly higher levels of IL-22 and IL-6 in patients with acute thoracic aortic dissection than those without dissection[31]. They concluded that IL-22 might be a prognostic factor for the acute presentation of thoracic aortic aneurysms. The findings of this study contradicted the previously drawn conclusions. We found lower levels of IL-17A in patients with sporadic ascending aortic aneurysms. Besides, there were no significant differences in IL-22 levels between the patient and control groups. The compensatory mechanisms between anti-inflammatory and pro-inflammatory ILs might be essential during the development of aortic aneurysms.

The impact of ILs on aneurysm size, morphology, and growth rates has been addressed in the literature. Ahmad et al. found no significant relationship between IL-1α and the features of infrarenal abdominal aortic aneurysms[9]. Liao et al. found a weak and negative correlation between IL10 levels and maximal aortic diameters and a positive correlation between IL-17A levels and the maximal cross-sectional area of the aneurysms of 476 aortic aneurysm patients[28]. In comparison, no significant correlation was found in this study between the ILs, i.e., IL-4, IL-10, IL-17-A, and IL-22, and the diameter of the ascending thoracic aneurysms. Further large-scale studies are needed to establish the potential benefits of ILs in monitoring disease activity.

Despite the challenges in obtaining reliable data from animal models for human studies evaluating aortic aneurysms, several experimental studies that aimed to enhance anti-inflammatory and dampen pro-inflammatory pathways have been performed. In one of these studies, Adam et al. reported a reduction in the rates of aortic dissection when they transfected an IL-10 transcribing nonimmunogenic minicircle vector in a mouse model[8]. They speculated that the augmentation of systemic IL-10 expression and corresponding plasma levels led to significant reductions in the aneurysm size. IL-19, IL-32, and IL-38 were other ILs studied experimentally featuring the suppression of abdominal aortic aneurysm formation[13-15]. IL-6 infusion animal models featuring the initiation of macrophage accumulation and aortic dilatation and IL-1α disruption leading to more giant aneurysms were also performed[6,11]. IL-22 is another cytokine that reportedly increased in patients with aortic dissection[31]. In parallel, Wang et al. demonstrated the inhibition of aortic dissection via IL-22 deficiency in an experimental abdominal aortic aneurysm model[12]. In contrast, the findings of this study did not support

the impact of IL-22 on aneurysm formation. Nevertheless, future studies may reveal the potential benefits of these molecules in preventing aortic aneurysms and prolonging the time between diagnosis and the need for interventions.

The small sample size was the primary limitation of this study. On the other hand, it was essential to include only the patients with sporadic ascending thoracic aneurysms larger than 55 mm in the study to ensure the homogeneity of the sample. The age differences between the groups might be a confounding factor impacting the IL levels.

In conclusion, it was determined that the serum IL-10, IL-17A, and IL-4 levels were decreased in patients with sporadic ascending thoracic aortic aneurysms larger than 55 mm. The reduced levels of these ILs might be associated with the development of aortic aneurysms in the thoracic part of the aorta. The cytokine correlations indicate a compensatory mechanism associated with aortic aneurysm formation. Future studies are needed to further analyze the cause-and-effect relationships in the context of the development of sporadic thoracic ascending aortic aneurysms.

Ethics Committee Approval: The study protocol was approved by the local ethics committee (Approval date, Number: 08.05.2022 & E-10420511-050-14513). The study was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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REFERENCES

1. Jud P, Verheyen N, Stradner MH, Dejaco C, Szolar D, Thonhofer R, et al. Association of immunological parameters with aortic dilatation in giant cell arteritis: A cross-sectional study. Rheumatol Int 2023;43(3):477-85. https://doi.org/10.1007/s00296-022-05186-1
2. Scola L, Di Maggio FM, Vaccarino L, Bova M, Forte GI, Pisano C, et al. Role of TGF-β pathway polymorphisms in sporadic thoracic aortic aneurysm: rs900 TGF-β2 is a marker of differential gender susceptibility. Mediators Inflamm 2014;2014:165758. https://doi.org/10.1155/2014/165758
3. Lim WW, Dong J, Ng B, Widjaja AA, Xie C, Su L, et al. Inhibition of IL11 signaling reduces aortic pathology in murine marfan syndrome. Circ Res 2022;130(5):728-40. https://doi.org/10.1161/CIRCRESAHA.121.320381
4. Fujita D, Preiss L, Aizawa K, Asch F, Eagle K, Suzuki T; GenTAC registry investigators. Circulating interleukin-6 (IL-6) levels are associated with aortic dimensions in genetic aortic conditions. PLoS One 2019;14(3):e0214084. https://doi.org/10.1371/journal.pone.0214084
5. Kasashima S, Kawashima A, Zen Y, Ozaki S, Kasashima F, Endo M, et al. Upregulated interleukins (IL-6, IL-10, and IL-13) in immunoglobulin G4-related aortic aneurysm patients. J Vasc Surg 2018;67(4):1248-62. https://doi.org/10.1016/j.jvs.2016.12.140
6. Salmon M, Hawkins RB, Dahl J, Scott E, Johnston WF, Ailawadi G. Genetic and pharmacological disruption of interleukin-1α leads to augmented murine aortic aneurysm. Ann Vasc Surg 2022;85:358-70. https://doi.org/10.1016/j.avsg.2022.05.024
7. Wortmann M, Peters AS, Erhart P, Körfer D, Böckler D, Dihlmann S. Inflammasomes in the pathophysiology of aortic disease. Cells 2021;15:10(9):2433. https://doi.org/10.3390/cells10092433
8. Adam M, Kooreman NG, Jagger A, Wagenhäuser MU, Mehrkens D, Wang Y, et al. Systemic upregulation of IL-10 (Interleukin-10) using a nonimmunogenic vector reduces growth and rate of dissecting abdominal aortica aneurysm. Arterioscler Thromb Vasc Biol 2018;38(8):1796-805. https://doi.org/10.1161/ATVBAHA.117.310672
9. Ahmad M, Kuravi S, Hodson J, Rainger GE, Nash GB, Vohra RK, et al. The relationship between serum interleukin-1α and asymptomatic infrarenal abdominal aortic aneurysm size, morphology, and growth rates. Eur J Vasc Endovasc Surg 2018;56(1):130-5. https://doi.org/10.1016/j.ejvs.2018.01.015
10. Batra R, Suh MK, Carson JS, Dale MA, Meisinger TM, Fitzgerald M, et al. IL-1β (Interleukin-1β) and TNF-α (Tumor Necrosis Factor-α) impact abdominal aortic aneurysm formation by differential effects on macrophage polarization. Arterioscler Thromb Vasc Biol 2018;38(2):457-63. https://doi.org/10.1161/ATVBAHA.117.310333
11. Akerman AW, Stroud RE, Barrs RW, Grespin RT, McDonald LT, LaRue RAC, et al. Elevated wall tension initiates interleukin-6 expression and abdominal aortic dilation. Ann Vasc Surg 2018;46:193-204. https://doi.org/10.1016/j.avsg.2017.10.001
12. Wang Y, Li J, Xu Y, Liao S, Song J, Xu Z, et al. Interleukin-22 deficiency reduces angiotensin II-induced aortic dissection and abdominal aortic aneurysm in ApoE-/- Mice. Oxid Med Cell Longev 2022;2022:7555492. https://doi.org/10.1155/2022/7555492
13. Tanaka H, Xu B, Xuan H, Ge Y, Wang Y, Li Y, et al. Recombinant interleukin-19 suppresses the formation and progression of experimental abdominal aortic aneurysms. J Am Heart Assoc 2021;10(17):e022207. https://doi.org/10.1161/JAHA.121.022207
14. Bengts S, Shamoun L, Kunath A, Appelgren D, Welander M, Björck M, et al. Altered IL-32 signaling in abdominal aortic aneurysm. J Vasc Res 2020;57(4):236-44. https://doi.org/10.1159/000507667
15. Kurose S, Matsubara Y, Yoshino S, Yoshiya K, Morisaki K, Furuyama T, et al. Interleukin-38 suppresses abdominal aortic aneurysm formation in mice by regulating macrophages in an IL1RL2-p38 pathway-dependent manner. Physiol Rep 2023;11(2):e15581. https://doi.org/10.14814/phy2.15581
16. Zhang L, Liao MF, Tian L, Zou SL, Lu QS, Bao JM, et al. Overexpression of interleukin-1β and interferon-γ in type I thoracic aortic dissections and ascending thoracic aortic aneurysms: Possible correlation with matrix metalloproteinase-9 expression and apoptosis of aortic media cells. Eur J Cardiothorac Surg 2011;40(1):17-22. https://doi.org/10.1016/j.ejcts.2010.09.019
17. Scola L, Giarratana RM, Marinello V, Cancila V, Pisano C, Ruvolo G, et al. Polymorphisms of pro-inflammatory IL-6 and IL-1β cytokines in ascending aortic aneurysms as genetic modifiers and predictive and prognostic biomarkers. Biomolecules 2021;11(7):943. https://doi.org/10.3390/biom11070943
18. Wortmann M, Klotz R, Kalkum E, Dihlmann S, Böckler D, Peters AS. Inflammasome targeted therapy as novel treatment option for aortic aneurysms and dissections: A systematic review of the preclinical evidence. Front Cardiovasc Med 2022;20;8:805150. https://doi.org/10.3389/fcvm.2021.805150
19. Åström Malm I, De Basso R, Blomstrand P, Wågsäter D. Association of IL-10 and CRP with pulse wave velocity in patients with abdominal aortic aneurysm. J Clin Med 2022;11(5):1182. https://doi.org/10.3390/jcm11051182

20. Saura D, Dulgheru R, Caballero L, Bernard A, Kou S, Gonjilashvili N, et al. Two-dimensional transthoracic echocardiographic normal reference ranges for proximal aorta dimensions: Results from the EACVI NORRE study. Eur Heart J Cardiovasc Imaging 2017;18(2):167-79. https://doi.org/10.1093/ehjci/jew053

21. Balistreri CR. Genetic contribution in sporadic thoracic aortic aneurysm? Emerging evidence of genetic variants related to TLR-4-mediated signaling pathway as risk determinants. Vascul Pharmacol 2015;74:1-10. https://doi.org/10.1016/j.vph.2015.09.006

22. Stather PW, Sidloff DA, Dattani N, Gokani VJ, Choke E, Sayers RD, et al. Meta-analysis and meta-regression analysis of biomarkers for abdominal aortic aneurysm. Br J Surg 2014;101(11):1358-72. https://doi.org/10.1002/bjs.9593

23. Zeng T, Shi L, Ji Q, Shi Y, Huang Y, Liu Y, et al. Cytokines in aortic dissection. Clin Chim Acta 2018;486:177-82. https://doi.org/10.1016/j.cca.2018.08.005

24. Puchenkova OA, Soldatov VO, Belykh AE, Bushueva O, Piavchenko GA, Venediktov AA, et al. Cytokines in abdominal aortic aneurysm: Master regulators with clinical application. Biomark Insights 2022;17:11772719221095676. https://doi.org/10.1177/11772719221095676

25. Parry DJ, Al-Barjas HS, Chappell L, Rashid ST, Ariëns RA, Scott DJ. Markers of inflammation in men with small abdominal aortic aneurysm. J Vasc Surg 2010;52(1):145-51. https://doi.org/10.1016/j.jvs.2010.02.279

26. Wallinder J, Skagius E, Bergqvist D, Henriksson AE. Early inflammatory response in patients with ruptured abdominal aortic aneurysm. Vasc Endovascular Surg 2010;44(1):32-5. https://doi.org/10.1177/1538574409339358

27. Cheuk BL, Cheng SW. Differential secretion of prostaglandin E(2), thromboxane A(2) and interleukin-6 in intact and ruptured abdominal aortic aneurysms. Int J Mol Med 2007;20(3):391-5. https://doi.org/10.3892/ijmm.20.3.391

28. Liao M, Liu CL, Lv BJ, Zhang JY, Cheng L, Cheng X, et al. Plasma cytokine levels and risks of abdominal aortic aneurysms: A population-based prospective cohort study. Ann Med 2015;47(3):245-52. https://doi.org/10.3109/07853890.2015.1019916

29. Dawson J, Cockerill GW, Choke E, Belli AM, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. J Vasc Surg 2007;45(2):350-6. https://doi.org/10.1016/j.jvs.2006.09.049

30. Sharma AK, Lu G, Jester A, Johnston WF, Zhao Y, Hajzus VA, et al. Experimental abdominal aortic aneurysm formation is mediated by IL-17 and attenuated by mesenchymal stem cell treatment. Circulation 2012;126:S38-45. https://doi.org/10.1161/CIRCULATIONAHA.111.083451

31. Ye J, Wang M, Jiang H, Ji Q, Huang Y, Liu J, et al. Increased levels of interleukin-22 in thoracic aorta and plasma from patients with acute thoracic aortic dissection. Clin Chim Acta 2018;486:395-401. https://doi.org/10.1016/j.cca.2017.10.033

Exercising with a Surgical Mask is Safe but Decreases Performance in Both Athletic and Non-Athletic Individuals

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ABSTRACT

Introduction: Upper respiratory tract infections (URTI) are common medical problems in athletes. Many athletes with URTI continue to train at high-levels and even compete. Using a mask as an additional measure may be beneficial to prevent the spreading of infection among teammates. However, there are many concerns about the effects of mask use on exercise safety and performance. Although some studies have investigated the effects of masks on performance in healthy individuals, studies in athletes are even more limited. Thus, we aimed to evaluate the impact of surgical masks on performance and safety during a cardiorespiratory exercise test (CPET) test applied to both athletes and non-athletes.

Patients and Methods: A cross-over, non-randomized study was designed. The study was conducted in two phases. In phase 1, the CPET was performed without using a surgical mask. In phase 2, CPET was performed with a surgical mask in addition to the spiro mask 48 hours after the first test. Thirty participants aged 18-35 were included in the study. They were further divided as athletes (n= 17) and non-athletes (n= 13) subgroups.

Results: Significant decreases were observed in some parameters of submaximal exercise [VEan, BFan, VE/VO_2, VE/VCO_2 (p< 0.001)] and in maximal exercise [VEmax, BFmax, TVmax, VE/VO_2, VE/VCO_2 (p< 0.001)]. There were also significant decreases in VO_2 levels (VO_2an, VO_2max) when compared with and without a surgical mask in both submaximal and maximal exercise (p< 0.001). Additionally, $PETO_2$ decreased, and $PETCO_2$ increased in maximum exercise (p< 0.001), whereas no significant changes were detected at the submaximal level. In subgroup analysis, VEan, VEmax, VO_2an, VO_2max parameters were decreased in athletes compared to non-athletes in surgical masked tests.

Conclusion: Surgical masks for athletes and non-athletes decrease performance but have no detrimental effect on cardiorespiratory parameters. Athletes should be aware of this negative effect when high-level performance is demanded.

Key Words: Mask; oxygen consumption; exercise; athlete

Sporcu ve Sporcu Olmayan Bireylerde Maske ile Egzersiz Yapmak Güvenlidir Ancak Performansı Düşürür

ÖZET

Giriş: Üst solunum yolu enfeksiyonları (ÜSYE) sporcularda çok yaygın görülen tıbbi problemler arasında yer alır. ÜSYE geçirmekte olan sporcuların birçoğu yüksek seviyelerde antrenman yapmaya ve hatta yarışmaya devam etmektedir. Hijyen prosedürlerine ek bir önlem olarak maske kullanılması, enfeksiyonun takım içinde yayılmasını önlemek için faydalı olabilir. Ancak maske kullanımının egzersiz güvenliği ve performansı üzerindeki sonuçları hakkında çeşitli tartışmalar vardır. Her ne kadar maske kullanımının sağlıklı bireylerin egzersiz performans üzerine etkileri ile ilgili çalışmalar olsa da sporcularda yapılan çalışmalar kısıtlıdır. Bu nedenle bu çalışmada hem sporcu hem de sporcu olmayan bireylere uygulanan kardiyorespiratuvar egzersiz testi (KPET) sırasında, cerrahi maskelerin performans ve güvenlik üzerindeki etkisini değerlendirmeyi amaçladık.

Hastalar ve Yöntem: Çapraz, kontrollü bir çalışma tasarlandı. Çalışma iki fazda gerçekleştirildi. Faz 1'de KPET (kardiyopulmoner egzersiz testi) katılımcılara cerrahi maske kullanılmadan yapıldı. Faz 2'de katılımcılara ilk testten 48 saat sonra spiro maskesine cerrahi maske takılmak suretiyle KPET yapıldı. Çalışmaya 18-35 yaş arası 30 katılımcı dahil edildi. Katılımcılar sporcu (n= 17) ve sporcu olmayan (n= 13) şeklinde iki alt gruba ayrıldı.

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Bulgular: Submaksimal egzersizin bazı parametrelerinde [VEan, BFan, VE/VO_2, VE/VCO_2 ($p< 0.001$)] ve maksimal egzersiz parametrelerinde [VEmax, BFmax, TVmax, VE/VO_2, VE/VCO_2 anlamlı düşüş gözlendi ($p< 0.001$)]. Hem submaksimal hem de maksimal egzersizde cerrahi maskeli ve maskesiz değerler karşılaştırıldığında VO_2 seviyelerinde de (VO_2an, VO_2max) anlamlı düşüş görüldü ($p< 0.001$). Ayrıca maksimum egzersizde $PETO_2$ azalıp $PETCO_2$ artarken ($p< 0.001$), submaksimal düzeyde anlamlı bir değişiklik saptanmadı. Alt grup analizinde VEan, VEmax, VO_2an, VO_2max parametreleri maskeli testlerde sporcu olmayanlara göre sporcularda azalmıştı.

Sonuç: Sporcular ve sporcu olmayanlar için cerrahi maske performansı düşürür ancak kardiyorespiratuvar parametreler üzerinde zararlı bir etkisi yoktur. Sporcular ve antrenörler, üst düzey performans talep edildiğinde bu olumsuz etkinin farkında olmalıdır.

Anahtar Kelimeler: Maske; oksijen tüketimi; egzersiz; sporcu

INTRODUCTION

Upper respiratory tract infections (URTI) are very common medical problems in athletes and cause the highest illness burden among professional football players[1,2]. It was also shown that intense exercise required for competitive sports is linked to a threefold increase in upper respiratory tract infections[3]. Illnesses not only affect the health of athletes but also impair their ability to train and compete. Prevention strategies for illnesses, in addition to injuries in sports, are critical for reducing athletes' absence from training and competitions. In the context of upper respiratory tract infections, in addition to measures like regular handwashing and maintaining distance between athletes and the team, it is crucial to control droplets when speaking, coughing, and sneezing. Obviously, preventing the spread of any upper respiratory tract infection within the team is the key factor in reducing the absence time for all athletes. However, maintaining distance between an athlete with URTI and their teammates in a team environment can be challenging due to the contact nature of some sports, travel requirements, and the natural tendency of young athletes to socialize with their teammates[4]. On the other hand, given that many athletes with URTIs continue to train at high levels and even compete, using masks could be a significant measure to prevent the transmission of the infection to teammates. A mask blocks the spread of aerosols and protects healthy athletes when speaking, sneezing, or coughing[5,6].

However, many hypotheses about the effects of using a mask during exercise have been put forward. One of these hypotheses is that respiratory air trapping and rebreathing of carbon dioxide may lead to hypercapnic hypoxia, especially during high-intensity exercise. Another is that the mask will increase the respiratory workload by creating resistance during breathing[7]. How the use of masks affects exercise performance is another question, especially in the minds of athletes. Because athletes have expressed worries about their physiologic performance while wearing a face mask, as anything that covers the mouth and/or nose can theoretically increase the resistive work of breathing[8].

To date, some studies have investigated the effects of masks on physiological and physical performance in healthy individuals. Studies in the athlete population are even more limited.

Therefore, our study aimed to examine the impact of surgical masks on maximal and submaximal exercise using the cardiopulmonary exercise test (CPET) applied to both athletic and non-athletic individuals. In this context, we primarily evaluated the following parameters: maximum oxygen consumption (VO_2max), exercise test duration, maximum heart rate (HRmax), maximum minute ventilation (VEmax), and end-tidal carbon dioxide pressure ($pETCO_2$).

PATIENTS and METHODS

General Design

A non-randomized, cross-over study was conducted in two phases. In phase 1, the CPET was performed without using a surgical mask. In phase 2, CPET was performed with a surgical mask in addition to the spiro mask 48 hours after the first test. The participants were asked not to consume caffeine and alcohol, to avoid strenuous physical activity, and to have at least 6-8 hours of night sleep before the tests.

Participants

The study included 30 participants, aged 18-35, without any health problems related to cardiopulmonary, orthopedic, or neurological systems**.** They were further divided into athletic (n= 17) and non-athletic physically active (n= 13) subgroups, according to their sport activity level. All participants underwent a detailed physical examination before enrolment in the study. The demographics of the participants were recorded.

Ethical Approval

Participants provided written informed consent prior to the study. The study was registered at ClinicalTrials.gov (NCT05282472,15.03.22).

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (File no: 2021/659).

Figure 1. Fitting of mask.

Cardiopulmonary Exercise Test (CPET)

Surgical Mask and CPET Mask Compatibility

The metabolic test device was first put on the mask (Rudolph Mask 2 way 7910) during the test. Participants were instructed to exhale forcefully, and the presence of an air leak was subsequently assessed. Following this, a 3-layer surgical mask (UNL mask, Türkiye) was applied over the original mask and secured using a CPET turbine (Figure 1).

CPET Test Protocol

The resting arterial blood pressure, heart rate, oxygen saturation (SpO_2) (EDAN Vital Sings Monitor M3A, Edan Instruments, China), and electrocardiography (ECG) measurements were performed. CPETs were carried out using the Q 5000 (Quinton 5000, USA) stress test system and the ergospirometric test system (Metalyzer 3B system, Metasoft 2.7 software, Cortex, Germany) on the Quinton 65 treadmill. O_2 and CO_2 gases were analyzed with the breath by breath method during the test, and O_2 consumption (VO_2) and CO_2 production (VCO_2) values were determined.

Bruce protocol was used and blood pressure, SpO_2 and ECG were monitored throughout the test. The test was terminated when the participants reached the maximum exercise level.

The criteria for reaching the maximum included:

1) A respiratory exchange ratio (RER) value above 1.10,

2) The age-related target heart rate reaching ± 10 beats per minute, or

3) A plateau in VO_2. Participants who met two of these three criteria were considered to have reached their maximum[9]. Active recovery was performed with a three-minute walk after the test was terminated. The highest VO_2 value analyzed within the 15-second period in the maximum phase of CPET was considered VO_2max.

Descriptive and Outcome Data

The values for heart rate (HR), target heart rate percent (HRpred%), systolic blood pressure (SBP)-diastolic blood pressure (DBP), oxygen consumption (VO_2), RER value, minute ventilation (VE), ventilation/carbon dioxide curve (VE/VCO_2 slope), ventilation/oxygen curve (VE/VO_2 slope), oxygen pulse (VO_2/HR), respiratory frequency (BF), tidal volume (TV), end-tidal oxygen pressure ($pETO_2$) and end-tidal carbon dioxide pressure ($pETCO_2$) for anaerobic threshold and maximum level were recorded during the CPET. The anaerobic threshold was calculated using the V-slope method (slope of the linear relationship between VCO_2 and VO_2)[10].

Data Analysis

Data were analyzed using SPSS 26 package software. The mean and standard deviation were calculated for the numerical data; nominal and original data were expressed as numbers and percentage distributions. The distribution of normality was tested using the Kolmogorov-Smirnov test. According to the result, the analysis of dependent groups before and after was performed with the paired sample t-test. p-value of <0.05 was considered significant. The differences between the subgroups of physically active individuals and athletes were revealed by the Linear Model Anova review.

RESULTS

A total of 30 people were included in the study. 50% (n= 15) of the participants were women, 56.7% (n= 17) were athletes. The mean ± Std age of all participants was 23.1 ± 3.5, height 174.5 ± 8.68 cm, weight 68.4 ± 10.2 kg, and BMI 22.46 ± 2.72. The demographics of the participants are given in Table 1.

There were no significant differences in the following CPET parameters; HRrest (p= 0.64), HRan (p= 0.69), HRmax (p= 0.95), HRmax/HRpred% (p= 0.84), HRrec (p= 0.96), SBPrest (p= 0.27), SBPmax (p= 0.45), SBPrec (p= 0.92), DBPrest (p= 0.10), DBPmax (p= 0.54) and DBPrec (p= 0.21), when comparing the tests with and without surgical masks in the study group (Table 2).

Table 1. Demographic features of participants

Demographic Information		n (%)	Demographic Information	Mean ± Std
Gender	Female	15 (50%)	**Age**	23.1 ± 3.5
	Male	15 (50%)	**Height**	174.5 ± 8.7
Sports Participation	Athlete	17 (56.7%)	**Weight**	68.4 ± 10.2
	Non-Athlete	13 (43.3%)	**BMI**	22.5 ± 2.7

AUC: Ara under the curve, CI: Confidence interval, IL: Interleukin.

Table 2. Results of the cardiopulmonary exercise test of volunteers with and without surgical masks

Measure	Without Mask (Mean ± Std)	With Mask (Mean ± Std)	Difference (95% CI)	Effect Size	p
VEan (L/min)	54.41 ± 18.86	46.71 ± 14.26	4.08-11.32	2.86	**<0.001**
VEmax (L/min)	101.41 ± 29.84	83.27 ± 19.93	11.90-24.38	3.37	**<0.001**
BFan (/min)	31.39 ± 8.44	28.36 ± 7.47	1.08-5.00	3.48	**<0.001**
BFmax (/min)	44.47 ± 8.66	40.78 ± 7.39	2.41-4.98	4.94	**<0.001**
TVan (L/min)	1.76 ± 0.54	1.72 ± 0.49	-0.08-0.17	0.33	0.48
TVmax (Lmin)	2.30 ± 0.58	2.07 ± 0.43	0.12-0.35	0.85	**<0.001**
VO_2an (ml/kg/min)	29.50 ± 6.55	26.27 ± 4.92	1.33-5.13	4.31	**<0.001**
VO_2max (ml/kg/min)	42.07 ± 8.84	38.03 ± 6.68	2.20-5.86	4.72	**<0.001**
RERmax	1.22 ± 0.11	1.22 ± 0.11	-0.06-0.04	-0.55	0.72
VE/VO_2an	25.25 ± 2.93	24.12 ± 2.82	0.25-2.01	7.61	**0.01**
VE/VO_2max	33.88 ± 4.89	30.98 ± 4.46	1.56-4.24	6.14	**<0.001**
VE/VCO_2an	25.76 ± 3.01	24.72 ± 2.88	0.22-1.86	7.66	**0.01**
VE/VCO_2max	27.83 ± 3.09	25.27 ± 2.79	1.83-3.29	7.31	**<0.001**
pETO_2an (mmHg)	105.90 ± 6.32	104.89 ± 4.71	-0.45-2.47	18.49	0.17
pETO_2max (mmHg)	115.55 ± 4.92	112.96 ± 5.54	1.18-4.00	20.50	**<0.001**
p$ETCO_2$an (mmHg)	42.58 ± 5.48	43.35 ± 4.44	-1.94-0.39	8.39	0.18
p$ETCO_2$max (mmHg)	39.07 ± 4.60	42.31 ± 5.15	-4.33-2.14	7.88	<0.001
CPET duration (sec)	863.23 ± 156.87	879.43 ± 167.98	-36.46-4.06	5.39	0.11
HRrest (BPM)	82.53 ± 12.97	83.57 ± 13.55	-5.48-3.41	6.20	0.64
HRan (BPM)	157.03 ± 10.31	157.53 ± 11.40	-3.00-2.00	14.45	0.69
HRmax (BPM)	191.40 ± 13.76	191.27 ± 9.19	-3.97-4.24	16.35	0.95
HRmax/HRpredic %	97.33 ± 6.83	97.13 ± 4.97	-1.85-2.25	16.07	0.84
HRrec (BPM)	127.67 ± 16.35	127.57 ± 17.81	-4.16-4.36	7.44	0.96
SBPrest (mm/Hg)	122.93 ± 13.03	120.53 ± 16.21	-2.00-6.80	7.44	0.27
SBPmax (mm/Hg)	169.43 ± 20.63	166.53 ± 18.33	-4.88-10.68	5.71	0.45
SBPrec (mm/Hg)	144.50 ± 20.97	144.83 ± 20.18	-7.49-6.82	6.08	0.92
DBPrest (mm/Hg)	68.77 ± 8.34	71.77 ± 10.10	-6.60-0.60	8.19	0.10
DBPmax (mm/Hg)	64.60 ± 10.60	66.27 ± 11.93	-7.14-3.81	8.56	0.54
DBPrec (mm/Hg)	59.37 ± 8.14	62.23 ± 11.19	-7.48-1.74	7.02	0.21

an: Anaerobic threshold, max: Maximum, VE: Minute ventilation, BF: Breath frequency, TV: Tidal volume, VO_2: Oxygen consumption, VCO_2: Carbon dioxide production, RER: Respiratory exchange ratio, pET: End tidal pressure, CPET: Cardiopulmonary exercise test, Sec: Second, HR: Heart rate, pred: Predicted, rec: Recovery, BPM: Beat per minute, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

When the ventilation parameters were evaluated; significant decreases were observed in Vean (p< 0.001), Vemax (p< 0.001), Bfan (p< 0.001), Bfmax (p< 0.001) and TVmax (p<0.001) parameters during CPET tests performed with surgical masks compared to CPET tests performed without a surgical mask (Table 2). There was no significant difference in the TVan (p= 0.48) parameter (Table 2).

The VO_2 values at both the anaerobic threshold and the maximum exercise level during the CPET tests with a surgical mask were significantly lower than those obtained during the CPET tests without a surgical mask (p< 0.001 and p< 0.001, respectively). However, no significant change was identified in the CPET duration (p= 0.11) (Table 2).

When the VE/VCO_2 slope and VE/VO_2 slope results obtained from the CPET tests with surgical masks were compared to CPET tests without surgical masks, significant decreases were detected in both the anaerobic threshold level (p= 0.01 and p= 0.01, respectively) and the maximum exercise level (p< 0.001 and p< 0.001, respectively) (Table 2).

Considering the gas pressure parameters, there was a significant decrease in $pETO_2$ at the maximum level (p< 0.001), but no significant difference was observed at the anaerobic threshold of the CPET tests (p= 0.17) when comparing tests conducted with surgical masks to those without (Table 2). The $pETCO_2$ did not show a significant change in the anaerobic threshold level (p= 0.18), in the same way as $pETO_2$. However, the $pETCO_2$ value increased significantly at the maximum exercise level (p< 0.001), unlike $pETO_2$ (Table 2).

When the subgroups were analyzed using Linear Model Anova, it was revealed that VEan (p= 0.005), VEmax (p= 0.002), VO_2an (p= 0.001), VO_2max (p= 0.001) (Figure 2) parameters were decreased significantly after the use of surgical masks in athletes compared to physically active non-athletes. Also, it was observed that the alterations in the maximal $pETCO_2$ values in the CPET tests with and without masks were not significant between the subgroups (p= 0.282).

DISCUSSION

From a physiological standpoint, the level of oxygen consumption (VO_2) results from the pulmonary, cardiovascular, and hematological systems and the aerobic ATP production capacity of the muscles. VO_2max stands as the most prominent indicator of aerobic capacity.

VO_2max measurement is accepted as the gold standard in the evaluation of the aerobic capacity of individuals, especially athletes, and these measurements are performed with CPET. These tests can be carried out for clinical purposes, not only for healthy individuals such as athletes but also for those with pathologies of respiratory and circulatory systems. In one phase of our study, a 3-layer surgical mask was used during CPET. This way, the effect of the mask on the aerobic capacity and anaerobic threshold levels of individuals was determined. In addition, other cardiopulmonary parameters monitored during the test were also evaluated.

Alterations in Maximum Exercise Level

Our results showed that surgical masks used during CPET significantly decreased VO_2max, and VEmax values, while significantly increasing $pETCO_2$max, similar to some studies in the literature (Table 2)[7]. Alkan et al. reported a decrease in VO_2max as a performance output when a surgical mask is used during maximal exercise in both young and older adult

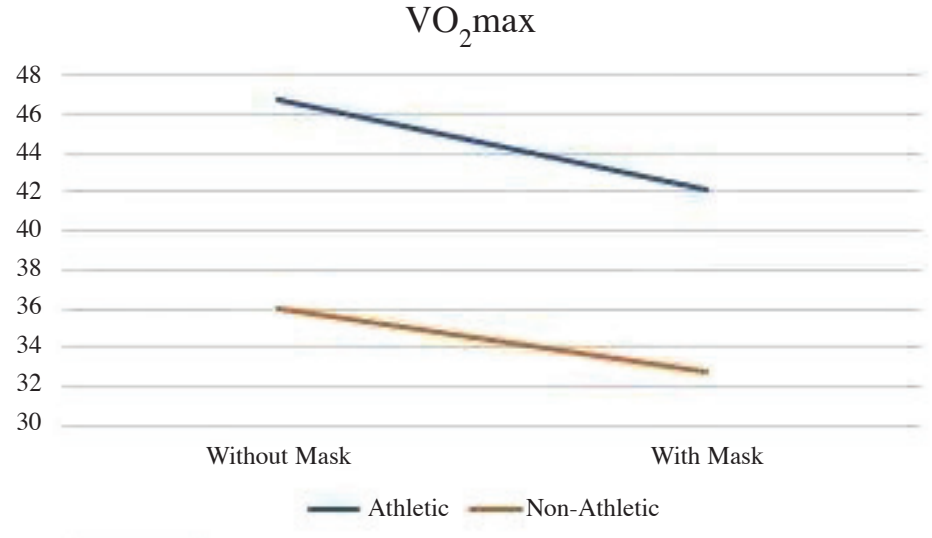

Figure 2. Maximum O_2 consumed per kg per minute (VO_2 max/kg) results of comparison of athletic and physically active non-athletic individuals; *p= 0.001.

groups[11]. Similar results were obtained in later studies, and two hypotheses were proposed. The first is the increase in airway resistance and, accordingly, the ventilatory workload due to the structure of the surgical mask. The other is that it traps a certain level of the exhaled air on the face area covered by the surgical mask, and CO_2 can be re-inspired, causing hypercapnic hypoxia[7,9]. Another study by Driver et al. reported that using cloth masks decreased VO_2max, VEmax as well as exercise duration and HRmax. Even though no direct association with the cardiovascular system has been reported in this study, due to the decrease in pulmonary function and mask discomfort, the exercise had to be terminated early[12].

Shaw et al. claimed that the spirometer mask placed separately on the surgical mask causes the surgical mask to stick to the face and eventually impairs its external permeability. They claimed that this situation might cause discomfort. Although they did not perform any ergospirometric evaluation or gas analysis, the same researchers reported that the use of surgical masks and cloth masks did not cause any significant changes in parameters such as exercise time, HRmax, SpO_2, and peak power[13].

On the other hand, Epstein et al. did not detect a significant difference in tissue oxygenation parameters, but they found a slight increase in $pETCO_2$ value. Despite this increase, they stated that the use of surgical masks during exercise remains safe[14].

In our study, unlike the previous ones, we applied a 3-layer surgical mask on the spirometer and fixed it with a CPET turbine[13,14]. We believe that this method provides the opportunity to evaluate gas exchange in conditions similar to surgical masks in daily life.

In our findings,

1) There was no statistically significant difference between CPET durations with and without a surgical mask,

2) None of the participants wished to terminate the test due to ventilation-related difficulties,

3) In terms of cardiovascular parameters, our results were in line with the studies conducted by Epstein and Shaw, which did not involve the use of a spirometry mask (Table 2).

However, the detection of a decrease in VO_2max during CPET performed with a surgical mask in our study suggests that masking individuals during maximal exercise may cause a reduction in their exercise capacity and performance. This finding distinguishes our study from the two studies above that did not directly assess aerobic capacity[13,14].

Alterations in Submaximal Exercise (Anaerobic Threshold) Level

The anaerobic threshold level is a frequently used marker for exercise prescribing, especially in endurance sports. Determination of the anaerobic threshold provides the opportunity to evaluate the metabolic response to exercise directly. It reveals the intensity of an exercise to be planned more reliably and more personalized than the calculations made on the VO_2max and HRmax percentages[15].

An exercise performed at the anaerobic threshold level is known as submaximal exercise. In a typical aerobic exercise session, activity is mostly performed at submaximal intensity. For this reason, it is crucial to know whether using a surgical mask during this type of exercise affects the anaerobic threshold level and cardiopulmonary parameters during exercise.

Many studies in the literature evaluate the effects of the mask during submaximal exercise. Lässing et al. stated that using a surgical mask during submaximal exercise, similar to maximal exercise, causes an increase in airway resistance and a decrease in maximum oxygen consumption, but no difference in endurance performance and perceived stress was observed[16]. On the other hand, Bar-on et al. stated that brisk walking with a mask for five minutes causes a significant increase in $pETCO_2$ and a slight decrease in oxygen saturation and that the situation may have clinical significance in the elderly and comorbid populations during longer exercise periods[17].

Studies evaluating the effect of surgical mask use on the anaerobic threshold and parameters during the anaerobic threshold are limited. Egger et al., by using a bicycle ergometer in their study, found that with well-trained athletes, the use of surgical masks did not change the anaerobic threshold and exercise parameters during the anaerobic threshold[18].

In our study, although changes were observed in ventilation parameters at the maximum exercise level, no significant change was found in $pETCO_2$ at the anaerobic threshold level. In line with these findings, we can say that possible re-inspiration of exhaled CO_2 during a submaximal exercise with a mask may not cause additional metabolic load.

In light of these findings, we think that submaximal exercise can be performed safely with a mask in crowded open areas such as parks and in closed areas such as gyms where the risk of URTI transmission is higher. In the medical literature thus far, we have not come across any study that reports the $pETCO_2$ value at the anaerobic threshold level during exercise with a surgical mask.

Differences Between the Sub-Groups

The results of both subgroups showed similar alterations in the evaluated parameters, but these changes were statistically significant in the athlete group.

Most of the studies we encountered in the literature were conducted with healthy and physically active volunteers[12-14]. Egger et al. suggested that the exercise test can be terminated early without complete physical exhaustion due to leg fatigue, lack of motivation, and pain intolerance in poorly trained individuals. They stated that the mask used by individuals in this population might be less deformed[18,19].

They also observed that as the duration of exercise increases in well-trained individuals, there is an increase in sweating and mouth breathing. Furthermore, individuals can achieve higher minute ventilation, which results in more water vapor retention in the surgical mask, leading to deformation of the mask. This effect may adversely affect the maximum exercise performance by causing an increase in respiratory resistance.

Based on these findings and our study results, we believe that a surgical mask has a comparable impact during exercise in individuals with varying physical activity levels, but it appears to have a more pronounced effect on the performance of athletes.

CONCLUSION

Our data has revealed that surgical masks have a detrimental impact on CPET parameters at the maximum exercise level for both athletes and physically active healthy individuals, but they can still be considered safe. In this regard, athletes and coaches should be mindful of this detrimental effect, especially in situations where peak performance is crucial, such as competitive sports and competitions. In accordance with the findings, we believe that using surgical masks during submaximal exercise does not impose an additional metabolic burden and can be considered safe. We believe that wearing masks while exercising in locations where there is a risk of transmission will have no negative consequences for physically active healthy people. In our opinion, using a surgical mask may also be safe for individuals who have chronic diseases such as diabetes, obesity, and hypertension and who exercise regularly while performing a submaximal exercise. However, further studies with relevant populations are needed to reveal the effects of surgical mask use during exercise in individuals with chronic diseases.

Ethics Committee Approval: This study was approved by the İstanbul University Faculty of Medicine Ethics Committee (Decision no: E-29624016-050.99-196051, Date: 03.05.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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REFERENCES

1. Gałązka-Franta A, Jura-Szołtys E, Smółka W, Gawlik R. Upper Respiratory Tract Diseases in Athletes in Different Sports Disciplines. J Hum Kinet 2016;53:99-106. https://doi.org/10.1515/hukin-2016-0014
2. Bjørneboe J, Kristenson K, Waldén M, Bengtsson H, Ekstrand J, Hägglund M, et al. Role of illness in male professional football: Not a major contributor to time loss. Br J Sports Med 2016;50(11):699-702. https://doi.org/10.1136/bjsports-2015-095921
3. Spence L, Brown WJ, Pyne DB, Nissen MD, Sloots TP, McCormack JG, et al. Incidence, etiology, and symptomatology of upper respiratory illness in elite athletes. Med Sci Sports Exerc 2007;39(4):577-86. https://doi.org/10.1249/mss.0b013e31802e851a
4. Yao KV, Szybinski S, Varghese M, Fazekas M. Viral diseases and youth sports: How to handle common infections that sideline athletes. Pediatr Ann 2021;50(11):e454-e460. https://doi.org/10.3928/19382359-20211017-01
5. Palmer-Green D, Fuller C, Jaques R, Hunter G. The Injury/Illness Performance Project (IIPP): A novel epidemiological approach for recording the consequences of sports injuries and illnesses. J Sports Med (Hindawi Publ Corp) 2013;2013:523974. https://doi.org/10.1155/2013/523974
6. So RC, Ko J, Yuan YW, Lam JJ, Louie L. Severe Acute Respiratory Syndrome and sport: Facts and fallacies. Sports Med 2004;34(15):1023-33. https://doi.org/10.2165/00007256-200434150-00002
7. Chandrasekaran B, Fernandes S. "Exercise with facemask; Are we handling a devil's sword?" - A physiological hypothesis. Med Hypotheses 2020;144:110002. https://doi.org/10.1016/j.mehy.2020.110002
8. Lott A, Roberts T, Carter CW. Mask use for athletes: A systematic review of safety and performance outcomes. Sports Health 2022;14(5):632-647. https://doi.org/10.1177/19417381221111395
9. Metin G, Atukeren P, Alturfan AA, Gulyasar T, Kaya M, Gumustas MK. Lipid peroxidation, erythrocyte superoxide-dismutase activity and trace metals in young male footballers. Yonsei Med J 2003;44(6):979-86. https://doi.org/10.3349/ymj.2003.44.6.979
10. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985). 1986;60(6):2020-7. https://doi.org/10.1152/jappl.1986.60.6.2020
11. Alkan B, Ozalevli S, Akkoyun Sert O. Maximal exercise outcomes with a face mask: The effects of gender and age differences on cardiorespiratory responses. Ir J Med Sci 2022;191(5):2231-7. https://doi.org/10.1007/s11845-021-02861-3

12. Driver S, Reynolds M, Brown K, Vingren JL, Hill DW, Bennett M, et al. Effects of wearing a cloth face mask on performance, physiological and perceptual responses during a graded treadmill running exercise test. Br J Sports Med 2022;56(2):107-13. https://doi.org/10.1136/bjsports-2020-103758
13. Shaw K, Butcher S, Ko J, Zello GA, Chilibeck PD. Wearing of cloth or disposable surgical face masks has no effect on vigorous exercise performance in healthy ındividuals. Int J Environ Res Public Health 2020;17(21):8110. https://doi.org/10.3390/ijerph17218110
14. Epstein D, Korytny A, Isenberg Y, Marcusohn E, Zukermann R, Bishop B, et al. Return to training in the COVID-19 era: The physiological effects of face masks during exercise. Scand J Med Sci Sports 2021;31(1):70-5. https://doi.org/10.1111/sms.13832
15. Mann T, Lamberts RP, Lambert MI. Methods of prescribing relative exercise intensity: Physiological and practical considerations. Sport Med 2013;43(7):613-25. https://doi.org/10.1007/s40279-013-0045-x
16. Lässing J, Falz R, Pökel C, Fikenzer S, Laufs U, Schulze A, et al. Effects of surgical face masks on cardiopulmonary parameters during steady state exercise. Sci Rep 2020;10(1):1-9. https://doi.org/10.1038/s41598-020-78643-1
17. Bar-On O, Gendler Y, Stafler P, Levine H, Steuer G, Shmueli E, et al. Effects of wearing facemasks during brisk walks: A COVID-19 dilemma. J Am Board Fam Med 2021;34(4):798-801. https://doi.org/10.3122/jabfm.2021.04.200559
18. Egger F, Blumenauer D, Fischer P, Venhorst A, Kulenthiran S, Bewarder Y, et al. Effects of face masks on performance and cardiorespiratory response in well-trained athletes. Clin Res Cardiol 2022;111(3):264-71. https://doi.org/10.1007/s00392-021-01877-0
19. Smirmaul BP, Dantas JL, Fontes EB, Altimari LR, Okano AH, Moraes AC. Comparison of electromyography fatigue threshold in lower limb muscles in trained cyclists and untrained non-cyclists. Electromyogr Clin Neurophysiol 2010;50(3-4):149-54.

Predictive Value of the Naples Score for In-Hospital Mortality in Patients with ST-Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Introduction: ST-segment elevation myocardial infarction (STEMI) is a significant contributor to mortality. The identification of high-risk patients holds great importance for prognosis. The development of a scoring system that incorporates both inflammatory and nutritional status components can provide valuable insights into prognosis.

Patients and Methods: This is a retrospective observational study comprising 570 consecutive ST-elevation myocardial infarction patients who underwent primary coronary intervention between 2018 and 2020. Patient data were obtained from the electronic database of the hospital.

Results: The incidence of in-hospital mortality rate was 4.9%. The entire group was then divided into two groups based on the presence of in-hospital mortality: 542 patients without in-hospital mortality constituted group 1, while 28 patients with in-hospital mortality formed group 2. In the multivariate logistic regression analysis, the Naples score was identified as an independent predictor of in-hospital mortality.

Conclusion: A higher Naples score is associated with increased in-hospital mortality in patients with ST-elevation myocardial infarction who undergo primary coronary intervention.

Key Words: ST-elevation myocardial infarction; inflammation; mortality; risk scores

ST-Elevasyonlu Miyokard İnfarktüsü Nedeniyle Primer Perkütan Koroner Girişim Yapılan Hastalarda Naples Skorunun Hastane İçi Mortaliteyi Öngördürücü Değeri

ÖZET

Giriş: ST segment elevasyonlu miyokard infarktüsü mortalitenin önemli bir nedenidir. Yüksek riskli hastaları tespit etmek prognoz için çok önemlidir. İnflamasyon ve nutrisyonel durumu gösteren skorlama sistemleri prognozu öngörmede daha fazla bilgi sağlayabilir.

Hastalar ve Yöntem: 2018 ve 2020 yılları arasında, ST elevasyonlu miyokard infarktüsü nedeniyle primer perkütan girişim yapılan ardışık 570 hasta retrospektif olarak incelendi. Hasta verileri hastanenin elektronik veri tabanından elde edildi.

Bulgular: Hastane içi mortalite insidansı %4.9 idi. Tüm grup hastane içi mortalite olmasına göre ikiye ayrıldı; hastane içi mortalite olmayan 542 hasta grup 1 ve hastane içi mortalite olan 28 hasta grup 2 olarak adlandırıldı. Çok değişkenli lojistik regresyon analizinde Naples skoru hastane içi mortalitenin bağımsız öngördürücüsü olarak bulundu.

Sonuç: ST elevasyonlu miyokard infarktüsü nedeniyle primer koroner girişim yapılan hastalarda yüksek Naples skorları daha fazla hastane içi mortalite ile ilişkilidir.

Anahtar Kelimeler: ST-elevasyonlu miyokard infarktüsü; inflamasyon; mortalite; risk skorları

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a critical condition often caused by an interruption of coronary artery flow. Reperfusion therapy including percutaneous coronary intervention (PCI) should be performed as soon as possible[1]. Mortality rates after STEMI are reported as 6-14% in hospital and 12% at six months[2]. These rates may vary among different subsets of patients[3]. Identifying the high-risk patients with STEMI is of great significance in prognosis[4].

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Current scoring systems do not include inflammatory markers and nutritional status, which play a critical role in the prognosis of STEMI[5].

The Naples score (NS) is a multidimensional, comprehensive prognostic evaluation system based on serum albumin levels, serum cholesterol levels, neutrophil/lymphocyte ratio (NLR), and lymphocyte/monocyte ratio (LMR)[6]. Preoperative NS was first established as an independent prognostic factor for colorectal cancer patients by Galizia et al[6]. This score can assess both the inflammatory and nutritional status of patients. Inflammation is a well-known risk factor for atherosclerosis[7]. Low serum albumin level is also a risk factor for coronary artery disease[8]. The NS can be useful for a more comprehensive risk assessment of STEMI patients. Subsequent studies demonstrated the prognostic value of the NS in patients with STEMI[9,10].

We aimed to investigate the prognostic impact of NS at admission on in-hospital mortality among patients with STEMI who underwent PCI.

PATIENTS and METHODS

We collected data from 570 consecutive STEMI patients who underwent PCI between January 2018 and September 2020 for this retrospective observational analysis. Patients with active cancer, active autoimmune disease, active infections, and chronic renal disease requiring hemodialysis and peritoneal dialysis were excluded. This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The ethics committee of our hospital approved the study (Decision no: 2023-04-53, Date: 16.05.2023). Due to the study's retrospective nature, written informed consent from the patient was not required.

Definitions and Risk Factors

The diagnostic criteria for STEMI were as follows: typical chest pain for more than 20 minutes and ST-segment elevation in at least two contiguous leads with the following cut-off points: ≥0.2 mV in men ≥40 years old; ≥0.25 mV in men <40 years old or ≥0.15 mV in women in leads V2 to V3 and/or ≥0.1 mV in the other leads as well as posterior (V7-V9) and right derivations (V3R-V4R)[11].

Demographic and clinical parameters were recorded from the hospital database. Biochemical analyses including complete blood count, serum creatinine, serum albumin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and serum electrolyte levels were assessed. The blood samples were obtained at the time of hospital admission to the emergency service.

Hypertension was defined as a systolic blood pressure of >140 mmHg and/or diastolic blood pressure of >90 mmHg, requiring antihypertensive medication. Diabetes mellitus (DM) was defined as a fasting glucose level of ≥126 mg/dL or receiving antidiabetic therapy. Coronary angiography was performed via femoral or radial access within 90 minutes of admission for each patient.

The NS was calculated using serum albumin and serum total cholesterol levels, NLR, and LMR ratios as described in Figure 1.

Variable	Cut-off	Points	NS group
Albumin (g/L)	≥40	0	Group 0: 0 points
	<40	1	
Total cholesterol (g/dL)	>180	0	Group 1: 1 or 2 points
	≤180	1	
NLR	≤2.96	0	Group 3: 3 or 4 points
	<2.96	1	
LMR	>4.44	0	
	≤4.44	1	

Figure 1. Formulation of Naples score.
NLR: Neutrophil to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, NS: Naples score.

Statistical Analyses

Statistical analysis was conducted using the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, IBM Corp., Armonk, New York, USA). Pearson Chi-square analysis was used for categorical variables. Fitness to normal distribution was analyzed with the Kolmogorov-Smirnov test. Mann-Whitney U test was performed for variables without normal distribution and Student's t-test was used for the variables with normal distribution. Data were expressed as "mean ± standard deviation (SD)" for normal distribution and "median (25^{th}-75^{th} percentiles)" for abnormal distribution while "n (%)" for categorical variables. Univariate and multivariate logistic regression analyses were used for predicting in-hospital mortality. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 570 patients who were admitted with STEMI undergoing primary PCI were retrospectively included in this study. The incidence of in-hospital mortality rate was 4.9% (28 patients). The entire group was divided into two groups based on the presence of in-hospital mortality: group 1 consisted of 542 patients without in-hospital mortality, and group 2 included 28 patients with in-hospital mortality. The baseline demographic and clinical variables are demonstrated in Table 1. There were no differences in terms of gender, smoking status, hypertension, diabetes mellitus, peripheral arterial disease, chronic obstructive pulmonary disease, ejection fraction, and culprit vessel between groups. However, the mean age was higher in group 2 compared to group 1.

The laboratory parameters are demonstrated in Table 2. There were no significant differences in high-density cholesterol (HDL), glucose, C-reactive protein, alanine aminotransferase, hemoglobin, leukocyte, neutrophil, and thrombocyte between groups. The total cholesterol, low-density lipoprotein cholesterol (LDL), triglyceride, and lymphocyte levels were lower in group 2, while creatinine level, and NS were higher in group 2. The incidence of patients with higher (>2.96) NLR, lower (≤4.44) LMR, lower (≤180 mg/dL) total cholesterol, and lower (<4 g/dL) serum albumin were also demonstrated in group 2 compared to group 1. Additionally, the incidence of patients with NS 0 and 1 or 2 was lower in group 2 while the incidence of patients with NS three or four was higher in group 2.

Logistic regression analysis was performed, and significant variables identified in the univariate analysis were included in the multiple logistic regression analysis to predict the independent risk factors for in-hospital mortality. In the multivariate logistic regression analysis, NS was identified as an independent predictor of in-hospital mortality (Table 3).

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

	Patients without in-hospital mortality (n= 542)	Patients with in-hospital mortality (n= 28)	p
Age (years)	55.2 ± 11.2	59.8 ± 10.5	0.034
Gender (female), n (%)	104 (19.2)	7 (25.0)	0.449
Smoking, n (%)	260 (48.0)	11 (39.3)	0.370
Hypertension, n (%)	182 (33.6)	9 (32.1)	0.875
Diabetes mellitus, n (%)	111 (20.5)	5 (17.9)	0.737
Peripheral arterial disease, n (%)	19 (3.5)	0 (0)	0.378
Chronic obstructive pulmonary disease, n (%)	17 (3.1)	1 (3.6)	0.602
Ejection fraction (%)	46.8 ± 9.8	48.1 ± 1.8	0.523
Culprit vessel, n (%)			
LAD	285 (52.6)	12 (42.9)	0.550
CXA	84 (15.5)	6 (21.4)	
RCA	173 (31.9)	10 (35.7)	

LAD: Left anterior descending, CXA: Circumflex artery, RCA: Right coronary artery.

Table 2. Laboratory variables of the patients

	Patients without in-hospital mortality (n= 542)	Patients with in-hospital mortality (n= 28)	p
Total cholesterol (mg/dL)	202.2 ± 43.5	158.1 ± 25.9	<0.001
LDL cholesterol (mg/dL)	123 ± 38	85 ± 23	<0.001
HDL cholesterol (mg/dL)	39 (34-46)	43.5 (37.5-47)	0.212
Triglyceride (mg/dL)	182 (120-260)	130.5 (100-200.5)	0.018
Creatinine (mg/dL)	0.84 (0.73-1.0)	0.93 (0.80-1.13)	0.048
Glucose (mg/dL)	135 (110-194)	145 (102-212)	0.736
ALT (U/L)	20 (15-29)	18 (14-29)	0.663
C-reactive protein (mg/dL)	3.83 (1.82-8.37)	4.77 (2.28-38.61)	0.100
Hemoglobin (g/dL)	14.43 ± 1.81	14.08 ± 1.90	0.329
Leukocyte x 10^3/mm^3	11.9 (9.6-14.0)	12.1 (10.3-1.43)	0.589
Lymphocyte (10^9/L)	2.5 (1.8-3.7)	1.8 (1.5-2.6)	0.002
Neutrophil (10^9/L)	7.3 (5.5-10.0)	8.5 (6.5-10.6)	0.191
Thrombocyte x 10^3/mm^3	261 (222-318)	266.5 (234-312.5)	0.795
NAPLES score	1 (0-1)	3 (2-3)	<0.001
NLR, n (%)			
≤2.96 (0 point)	293 (54.1)	5 (17.9)	<0.001
>2.96 (1 point)	249 (45.9)	23 (82.1)	
LMR, n (%)			
>4.44 (0 point)	529 (97.6)	22 (78.6)	<0.001
≤4.44 (1 point)	13 (2.4)	6 (21.4)	
Total cholesterol, n (%)			
>180 (0 point)	379 (69.9)	5 (17.9)	<0.001
≤180 (1 point)	163 (30.1)	23 (82.1)	
Serum albumin, n (%)			
≥4 (0 point)	506 (93.4)	11 (39.3)	<0.001
<4 (1 point)	36 (6.6)	17 (60.7)	
NAPLES group, n (%)			
Group 1 (0 point)	195 (63.0)	4 (14.3)[a]	
Group 2 (1 or 2 points)	311 (57.4)	6 (21.4)[a]	<0.001
Group 3 (3 or 4 points)	36 (6.6)	18 (64.3)[b]	

[a]= Significantly lower in group 2, [b]= Significantly higher in group 2.
LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ALT: Alanine transaminase, NLR: Neutrophil to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio.

Table 3. Multivariate logistic regression analysis to predict the independent predictors of in-hospital mortality

	Odds ratio	95% CI (Lower-Upper)	p
NAPLES score	4.368	2.881-6.625	<0.001
Age	1.018	0.982-1.054	0.330
Creatinine (mg/dL)	0.791	0.335-1.872	0.594

DISCUSSION

The present study revealed that higher NS is associated with higher in-hospital mortality in STEMI patients treated with PCI. STEMI is a complex clinical scenario that requires rapid therapeutic management and early risk stratification. The identification of high-risk patients with STEMI is of great significance in guiding medical management. Inflammatory processes are believed to trigger cardiovascular disease development and final clinical events. Neutrophils drive the early inflammatory response following myocardial infarction, and a high neutrophil count is an important marker for cardiovascular mortality[12]. Lymphocytes have inflammation-suppressing properties, which leads to a lower immune response and suppressed myocardial damage[13]. Inflammatory responses induce lymphopenia due to increased lymphocyte apoptosis. Lower lymphocyte levels are associated with a higher risk of cardiovascular mortality[14]. Monocytes have a role in inflammation and the procoagulant state observed during STEMI[15]. Monocytes actively bind to platelets, forming highly thrombotic monocyte-platelet aggregates, and markers of monocyte and platelet activation involved in regulating their function are also increased in STEMI[16]. Albumin has many functions that affect the cardiovascular system besides regulating osmotic pressure in extracellular fluid. Decreased levels of albumin lead to an increase in blood viscosity and impaired endothelial dysfunction[17]. Albumin has antioxidant properties and an inverse relationship with inflammation[18]. Biccire et al.[19] demonstrated that a low level of albumin was associated with mortality in STEMI patients. Hypercholesterolemia is a well-known risk factor for the development of coronary artery disease[20]. However, some studies showed an inverse association between TC and mortality, mostly attributable to concomitant conditions such as advanced age, frailty, and poor health status[21]. However, the explanation for this paradigm remains elusive.

The NS is a useful prognostic scoring model for determining survival in various types of cancer[22]. Recent studies showed the efficacy of the NS in predicting the prognosis of STEMI patients[9,10]. All individual components of the NS have a prognostic value for the in-hospital survival of STEMI patients. Simultaneous assessment of these components might provide complementary information to predict mortality. Routine blood tests obtained from STEMI patients can contribute to identifying patients who should be followed more closely and treated more aggressively.

This study has several limitations, with the first being its retrospective and single-center design. Secondly, we did not compare our results with well-known scoring systems, such as the Global Registry of Acute Coronary Events (GRACE). Thirdly, this study involved only STEMI patients. Therefore, the results might only apply to some of the spectra of acute coronary syndrome.

CONCLUSION

The Naples score (NS), which reflects the inflammation and nutritional status of patients, can serve as a predictor of in-hospital mortality among STEMI patients treated with PCI.

Ethics Committee Approval: This study was approved by the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Ethics Committee (Decision no: 2023.04-53, Date: 16.05.2023).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - EÖ; Analysis/Interpretation - SK; Data Collection - SK; Writing - EÖ; Critical Revision - EÖ; Final Approval - EÖ; Statistical Analysis -SK; Overall Responsibility - EÖ.

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

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REFERENCES

1. Zeymer U, Ludman P, Danchin N, Kala P, Laroche C, Sadeghi M, et al. Reperfusion therapies and in-hospital outcomes for ST-elevation myocardial infarction in Europe: The ACVC-EAPCI EORP STEMI registry of the European society of cardiology. Eur Heart J 2021;42(44):4536-49.
2. Ibanez B, James S, Agewell S, Antunes MJ, Ducci CB, Byeno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
3. Fox KA, Carruthers KF, Dunbar DR, Graham C, Manning JR, De Raedt H, et al. Underestimated and under-recognized: The late consequences of acute coronary syndrome (GRACE UK-Belgian Study). Eur Heart J 2010;(22):2755-64.
4. Lin A, Devlin G, Lee M, Kerr AJ: Performance of the GRACE scores in a New Zealand acute coronary syndrome cohort. Heart 100: 1960-1966, 2014.
5. Wong BW, Meredith A, Lin D, Mc Manus BM. The biological role of inflamation in atherosclerosis. Can J Cardiol 2012;28:631-41.
6. Galizia G, Lieto E, Auricchio A, Cardella F, Mabilia A, Podzemny V, et al. Naples prognostic score, based on nutritional and inflammatory status, is an independent predictor of long-term outcome in patients undergoing surgery for colorectal cancer. Dis Colon Rectum 2017;60:1273-84.
7. Madjid M, Willerson JT. Inflammatory markers in coronary heart disease. Br Med Bull 2011;100:23-38.
8. Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: Pathogenesis and clinical significance. JPEN 2019;43:181-93.
9. Şaylık F, Çınar T, Selçuk M, Akbulut T, Hayıroğlu Mİ, Tanboğa İH. Evaluation of Naples score for long-term mortality in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Angiology 2023:33197231170982.

10. Erdoğan A, Genç Ö, Özkan E, Göksu MM, İbişoğlu E, Bilen MN, et al. Impact of Naples prognostic score at admission on in hospital and follow up outcomes among patients with ST-segment elevation myocardial infarction. Angiology 2023;74:970-80.
11. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction. J Am Coll Cardiol 2018;72:2231-64.
12. Shah AD, Denaxas S, Nicholas O, Hingorani AD, Hemingway H. Neutrophil counts and initial presentation of 12 cardiovascular diseases: A CALIBER Cohort Study. J Am Coll Cardiol 2017;69(9):1160-9.
13. Kurtul A, Yarlioglues M, Murat SN, Ergun G, Duran M, Kasapkara, H et al. Usefulness of the platelet-to-lymphocyte ratio in predicting angiographic reflow after primary percutaneous coronary intervention in patients with acute ST-segment elevation myocardial infarction. Am J Cardiol 2014;114:342-7.
14. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, et al; Intermountain Heart Collaborative Study Group. Which white cell subtypes predict increased cardiovascular risk? J Am Cardiol 2005;45:1638-43.
15. Shantsila E, Lip GY. The role of monocytes in thrombotic disorders. Insights from tissue factor, monocytes-platelet aggregates and novel mechanism. Thromb Haemost 2009;102:916-24.
16. Tapp LD, Shantsila E, Wrigley BJ, Pamukcu B, Lip GY. The CD 14++ CD+ monocyte subset and monocyte-platelet interactions in patients with ST-elevation myocardial infarction. J Thromb Haemost 2012;10:1231-41.
17. Joles JA, Willekes-Koolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. Kidney Int 1997;52(3):761-70.
18. Don BR, Kaysen G. Serum albumin: Relationship to inflammation and nutrition. Semin Dial 20114;17(6):432-7.
19. Biccire FG, Pastori D, Tanzilli A, Pignatelli P, Viceconte N, Barilla F, et al. Low serum albumin levels and in-hospital outcomes in patientswith ST segment elevation myocardial infarction. Nutr Metabol Cardiovasc Dis 2021;31:2904-11.
20. Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary artery disease continuous and graded? Findings in 356,222 primary screnees of the Multiple Risk Factor Intervention Trial (MRFIT). JAMA 1980;256:2823-8.
21. Iribarren C, Reed DM, Chen R, Yano K, Dwyer JH. Low serum cholesterol and mortality. Which is the cause and which is the effect? Circulation 1995;92:2396-403.
22. Nakagawa N, Yamada S, Sonohara F, Takami H, Hayashi M, Kanda M, et al. Clinical implications of naples prognostic score in patients with resected pancreatic cancer. Ann Surg Oncol 2020;27:887-95.

Right Mini-Thoracotomy in the Surgical Treatment of Structural Heart Diseases (SHDs): An Institutional Experience

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ABSTRACT

Introduction: Surgical treatment of structural heart diseases continues to predominantly involve median sternotomy, despite the ongoing trends favoring minimally invasive approaches that have persisted for many years. In this study, we present data on structural heart disease (SHD) surgeries conducted by our institute using a right mini-thoracotomy approach.

Patients and Methods: This single-center retrospective study included 58 patients who underwent right mini-thoracotomy procedures between February 2018 and June 1, 2023. Preoperative demographic and medical data were collected from patient files and records. Perioperative and 30-day outcome data were obtained through the national electronic record system.

Results: The average age of the participants was 39.9. Female patients accounted for 31.6% (n= 18) of the participants. The majority of surgeries in this study involved peripheral cannulation and conventional cardioplegia. Mitral valve repair and atrial septal defect closure were the most common procedures performed. Intraoperative outcomes showed favorable results, with no instances of significant bleeding, structural complications, or mortality. Regarding the postoperative 30-day outcomes, the stroke rate was 1.8% (n= 1) among the patients. There were no reported cases of transient ischemic attack (TIA), myocardial infarction (MI), and mortality. The conversion to median sternotomy occurred in 3.4% (n= 2) of the cases. Reoperation and re-exploration were required in 1.8% (n= 1) of the cases. The mean length of stay in the ICU was 1.7 days, while the mean length of ward stay was 4.2 days.

Conclusion: This study contributes to the evidence supporting the shift towards minimally invasive approaches in the surgical management of structural heart disease. The low rate of intraoperative conversion, absence of major complications, and favorable postoperative outcomes highlight the safety and feasibility of right mini-thoracotomy. Continued advancements in surgical techniques and clinical expertise are expected to further optimize patient outcomes and improve the quality of care in this field.

Key Words: Thoracotomy; MICS; MVR; mitral repair

Yapısal Kalp Hastalıklarının (YKH) Cerrahi Tedavisinde Sağ Mini-Torakotomi: Enstitü Tecrübesi

ÖZET

Giriş: Yapısal kalp hastalıklarının cerrahi tedavisi, yıllardır süregelen minimal invaziv eğilimlere rağmen halen daha çok median sternotomi ile yapılmaktadır. Bu çalışmada, enstitümüz tarafından sağ mini torakotomi ile gerçekleştirilen kalp ameliyatlarını sunuyoruz.

Hastalar ve Yöntem: Bu tek merkezli retrospektif çalışmaya, Şubat 2018 ile 1 Haziran 2023 tarihleri arasında sağ mini torakotomi uygulanan 58 hasta dahil edildi. Ameliyat öncesi demografik ve tıbbi veriler, hasta dosyaları ve sistem kayıtlarından toplandı. Perioperatif ve 30 günlük sonuç verileri ulusal elektronik kayıt sisteminden elde edildi.

Bulgular: Katılımcıların yaş ortalaması 39.9'du. Katılımcıların %31.6'sını (n= 18) kadın hastalar oluşturmaktaydı. Ameliyatların çoğunda periferik kanülasyon ve konvansiyonel kardiyopleji kullanıldı. Mitral kapak tamiri ve atriyal septal defektin onarımı en sık uygulanan prosedürlerdi. İntraoperatif sonuçlar, önemli kanama, yapısal komplikasyon veya ölüm vakası olmadan olumlu sonuçlar gösterdi. Postoperatif 30 günlük sonuçlara bakıldığında, hastalarda inme oranı %1.8 (n= 1) idi. Geçici iskemik atak (GİA), miyokard enfarktüsü (MI) ve ölüm vakası bildirilmedi. Vakaların %3.4'ünde (n= 2) medyan sternotomiye geçiş olduğu görüldü. Olguların %1.8'inde (n= 1) tekrar operasyon ve tekrar eksplorasyon uygulandı. Yoğun bakımda ortalama kalış süresi 1.7 gün, serviste ortalama kalış süresi ise 4.2 gündü.

Sonuç: Bu çalışma, yapısal kalp hastalığının cerrahi tedavisinde minimal invaziv yaklaşımlara geçişi destekleyen kanıtlara katkıda bulunmaktadır. Düşük intraoperatif dönüşüm oranı, majör komplikasyonların olmama-

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sı ve olumlu postoperatif sonuçlar, sağ mini torakotominin güvenliğini ve fizibilitesini vurgulamaktadır. Cerrahi teknikler ve klinik uzmanlıkta devam eden ilerlemelerin hasta sonuçlarını daha da optimize etmesi ve bu alandaki bakım kalitesini iyileştirmesi beklenmektedir.

Anahtar Kelimeler: Torakotomi; MICS; MVR; mitral onarım

INTRODUCTION

Open heart surgery initially relied predominantly on sternotomy in the early 20th century, during its experimental stages, and later during the latter part of the 20th century and the 21st century when it became widely adopted and standardized[1]. However, thoracotomy has resurfaced as a prominent approach in the past two decades and has gained widespread acceptance[1]. Particularly, mini-thoracotomy has gained popularity, initially in the repair of septal defects, and subsequently in interventions involving the mitral and tricuspid valves[2-4]. In contrast to median sternotomy, mini-thoracotomy offers advantages such as accelerated recovery and shorter hospitalization periods due to the avoidance of bone tissue incision, which facilitates quicker physical recuperation[2-6]. Additionally, mini-thoracotomy minimizes the surgical area, resulting in reduced bleeding and a decreased need for blood transfusions, thereby lowering perioperative morbidity and shortening hospital stays[2-6]. However, the diminished surgical field in mini-thoracotomy poses challenges to surgical exposure and visibility, especially in complex heart surgeries involving multiple valve repairs and procedures, casting doubt on the technical success of such operations[7,8].

The present study aims to present the perioperative and postoperative 30-day outcomes of patients with structural heart conditions who underwent right mini-thoracotomy between 2018 and 2023 at our institution, where over 2000 heart surgeries per year were performed using median sternotomy.

PATIENTS and METHODS

Study Design

This single-center retrospective study aimed to assess the feasibility and outcomes of right mini-thoracotomy heart surgery in patients with structural heart diseases. A total of 58 patients who underwent this surgical technique between February 2018 and June 1, 2023, were included in the evaluation.

Procedure

CT scan was performed on all patients in order to make preoperative anatomical evaluation and to detect possible adhesions. A 5 to 10 cm long thoracotomy was performed at the right Submammarian area through the 3rd, 4th, or 5th intercostal space according to the procedure (Figure 2). For aortic interventions, it could be also performed at the second intercostal space. A soft tissue retractor or mini-thoracotomy retractor was used to expose the surgical area. (Figure 3). The incisions were extended if adequate exploration was not obtained. Mostly direct right femoral arterial and venous cannulation was performed after ultrasonographic evaluation in addition to jugular venous cannulation with the Seldinger technique under Transesophageal Echocardiography (TEE)

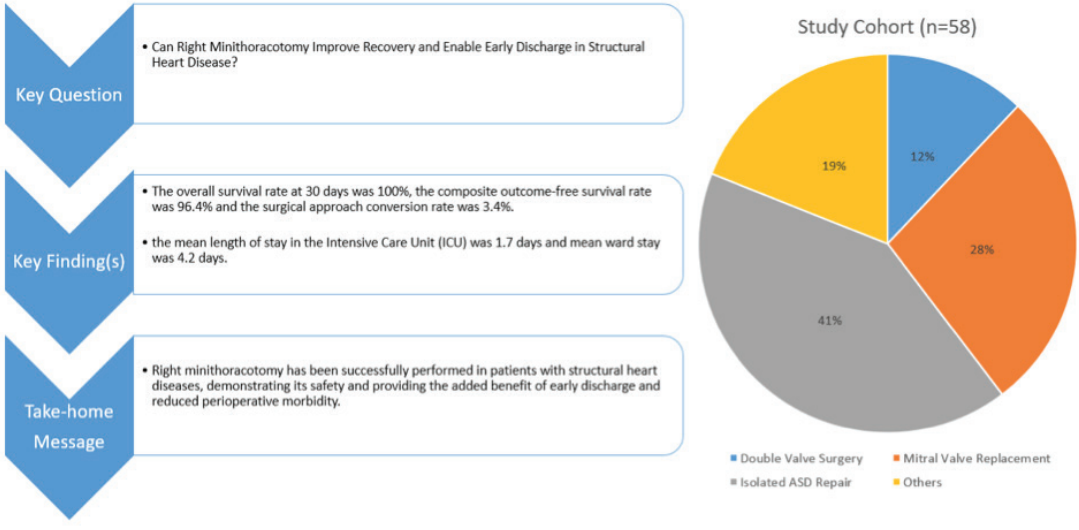

Figure 1. Central figure.

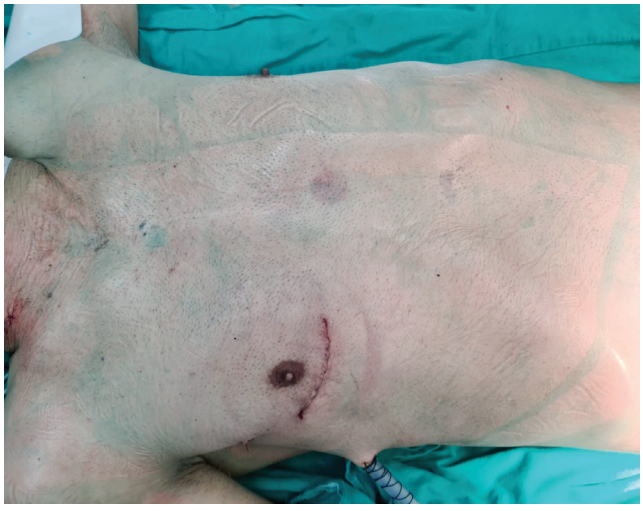

Figure 2. Right minithoracotomy incision.

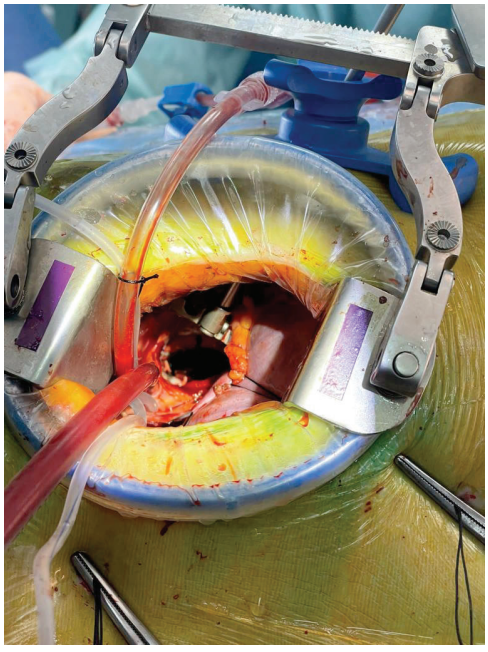

Figure 3. Operative view of mini thoracotomy during mitral valve intervention.

guidance. The pericardium was opened from the diaphragm to the aorta by securing the phrenic nerve. Direct aortic arterial and bi-caval venous cannulation were also performed for suitable patients. A cardioplegia cannula was inserted directly into the aorta. Antegrade cold blood cardioplegia was most commonly utilized. Del Nido and Custadiol solutions were also used for complex cases. The aorta was clamped with a Chit-wood clamp through a 1 cm skin incision which then would be used for chest tube insertion.

Patients and Data

The preoperative demographic and medical information of patients who underwent surgery between 2018 and 2023 were meticulously gathered from patient files and records. This task was performed by a cardiac surgery resident, closely supervised by an academic cardiac surgeon, following the approval of the ethics committee. The collection of perioperative and 30-day outcome data was facilitated through the national electronic record system, with the active involvement of both the cardiac surgery resident and the academic heart surgeon.

Statistical Analysis

In our report, for non-continuous variables, we presented percentages and counts, while for continuous variables, we reported mean values and standard deviations (SDs).

RESULTS

Patient Characteristics

Table 1 presents the preoperative demographics and medical background of 58 individuals who underwent thoracotomy. The average age of the participants was 39.9 years, with a standard deviation of 16.1. Among the participants, 31.6% (n= 18) were female. The mean body mass index (BMI) was 24.1, with a standard deviation of 5.5. Smoking was reported by 29.6% (n= 16) of the participants. In terms of comorbidities, 5.4% (n= 3) had coronary artery disease (CAD), 21.8% (n= 12) had hypertension (HT), 39.3% (n= 22) had pulmonary hypertension (PHT), 3.6% (n= 2) had peripheral artery disease (PAD), 20% (n= 11) had atrial fibrillation (AFib), 10.9% (n= 6) had chronic obstructive pulmonary disease (COPD), 10.9% (n= 6) had type 2 diabetes mellitus (T2DM), and 3.6% (n= 2) had chronic kidney disease (CKD). The left ventricular ejection fraction (LVEF) was measured to be 62.2% with a standard deviation of 7.4. The mean hemoglobin (HGB) level was 12.5 g/dL with a standard deviation of 2.0, and the mean hematocrit (HCT) was 38.6% with a standard deviation of 5.3.

Surgical Techniques and Approaches

Table 2 presents the surgical techniques and surgeries. Regarding cannulation, peripheral cannulation was the chosen method in the majority of cases, accounting for 83.4% (n= 45) of the participants, while central cannulation was used in 16.6% (n= 9) of the cases. In terms of cardioplegia techniques, the Del Nido approach was employed in 12.3% (n= 7) of the surgeries, conventional cardioplegia in 68.3% (n= 39) of the surgeries, and custadiol cardioplegia in 10.5% (n= 6) of the surgeries. Various types of surgeries were performed on the participants. Mitral valve replacement (MVR) accounted for 27.5% (n= 16) of the cases, while aortic valve replacement (AVR) and myxoma resection were performed in only 1.8% (n= 1) each. Mitral valve repair (MVR) was conducted in 22.4% (n= 13) of the cases, followed by tricuspid valve repair in 15.5% (n= 9). Atrial septal defect (ASD) closure was

Table 1. Preoperative demographics and medical history

	Thoracotomy (n= 58)	
Variable	**Mean ± SD**	**% (n)**
Age	39.9 ± 16.1	
Gender (female)		31.6 (18)
BMI	24.1 ± 5.5	
Smoking		29.6 (16)
CAD		5.4 (3)
HT		21.8 (12)
PHT		39.3 (22)
PAD		3.6 (2)
AFib		20 (11)
COPD		10.9 (6)
T2DM		10.9 (6)
CKD		3.6 (2)
LVEF (%)	62.2 ± 7.4	
HGB (g/dL)	12.5 ± 2.0	
HCT (%)	38.6 ± 5.3	

BMI: Body mass index, CAD: Coronary artery disease, HT: Hypertension, PHT: Pulmonary hypertension, PAD: Peripheral arterial disease, AFib: Atrial fibrillation, COPD: Chronic obstructive pulmonary disease, T2DM: Type 2 diabetes mellitus, CKD: Chronic kidney disease, LVEF: Left ventricular ejection fraction, HGB: Hemoglobin, HCT: Hematocrit.

Table 2. Surgical techniques and surgeries

	Thoracotomy (n= 58)	
Variable	**Mean ± SD**	**% (n)**
Cannulation		
Peripheral		83.4 (45)
Central		16.6 (9)
Cardioplegia		
Del Nido		12.3 (7)
Conventional		68.3 (39)
Custadiol		10.5 (6)
Surgery		
MVR		27.5 (16)
AVR		1.8 (1)
MVr		22.4 (13)
Tricuspid repair		15.5 (9)
ASD Closure		44.8 (26)
Complex surgery (two or more procedures)		22.4 (13)

MVR: Mitral valve replacement, AVR: Aortic valve replacement, MVr: Mitral valve repair, ASD Closure: Atrial septal defect closure.

Table 3. Intraoperative outcomes

	Thoracotomy (n= 58)	
Variable	**Mean ± SD**	**% (n)**
CPB time	138.0 ± 65.8	
AXC time	85.1 ± 54.3	
Transfusion requirement		26.3 (15)
Transfused PRBC (U)	1.1 ± 0.8	
Transfused FFP (U)	1.1 ± 0.8	
Conversion to median sternotomy		3.4 (2)
Massive bleeding		0.0 (0)
Structural complications		0.0 (0)
Mortality		0.0 (0)

CPB time: Cardiopulmonary bypass time, AXC time: Aortic cross-clamp time, Transfused PRBC (U): Transfused packed red blood cells (Units), Transfused FFP (U): Transfused fresh frozen plasma (Units).

performed in 44.8% (n= 26) of the surgeries. In addition, complex surgeries involving two or more procedures were carried out in 22.4% (n= 13) of the cases.

Intraoperative Findings

Table 3 presents the intraoperative outcomes. The mean cardiopulmonary bypass (CPB) time in this study was 138.0 minutes, with a standard deviation of 65.8. The mean aortic cross-clamp (AXC) time was 85.1 minutes, with a standard deviation of 54.3. Transfusion requirements were observed in 26.3% (n= 15) of the cases, with an average of 1.1 units of packed red blood cells (PRBC) and fresh frozen plasma (FFP) transfused. The conversion to median sternotomy was necessary in 3.4% (n= 2) of the cases. Notably, no instances of massive bleeding, structural complications, or mortality were encountered during the procedures.

Postoperative Outcomes

The postoperative outcomes at the 30-day mark are demonstrated in Table 4: 40.0% (n= 22) required transfusion, 3.5% (n= 2) experienced infection, 1.8% (n= 1) had new-onset atrial fibrillation, 15.5% (n= 9) developed acute kidney injury, and 1.8% (n= 1) suffered a stroke. There were no reported cases of TIA, myocardial infarction, and mortality. Re-exploration and reoperation occurred in 1.8% (n= 1) of the cases. The average drainage volume was 377 mL, the mean intubation time was 8.6 hours, and the mean length of stay in the ICU was 1.7 days. The length of ward stay was 4.2 days. At postoperative day one, the mean hemoglobin level was 10.6 g/dL and the mean hematocrit level was 29.4%.

DISCUSSION

In the realm of surgical interventions for structural heart diseases, the conventional approach has long involved highly invasive procedures utilizing a median sternotomy. However, with the advent of transcatheter therapies and the growing emphasis on quality of life-centered medicine, there has been a notable shift towards a minimally invasive paradigm in the surgical management of structural heart disease[7,9]. Recent advancements in valve surgery have highlighted the growing evidence supporting the benefits of mini-thoracotomy[9,10]. A comprehensive meta-analysis, encompassing 109 studies and 38.106 patients, published in 2022, revealed that mini-thoracotomy offers distinct advantages over median sternotomy, including reduced hospitalization durations and decreased blood product utilization[10].

Furthermore, the utilization of right mini-thoracotomy in atrial septal defect (ASD) repair has gained significant traction. This surgical approach, which has a longer history compared to valve surgery, has become relatively more prevalent. In a meta-analysis published in 2021, incorporating data from seven studies and 665 patients, right mini-thoracotomy demonstrated superior recovery parameters compared to median sternotomy[11]. Notably, the analysis identified significantly shorter hospitalization times, reduced intensive care unit stays, and decreased intubation durations associated with the right mini-thoracotomy technique.

In our study, a cohort of 58 patients with structural heart disease underwent open heart surgery, with a notable subset requiring complex cardiac procedures. Among these patients,

Table 4. Postoperative outcomes at 30-day

	Thoracotomy (n= 58)	
Variable	**Mean ± SD**	**% (n)**
Transfusion requirement		40.0 (22)
Infection		3.5 (2)
AKI		15.5 (9)
RRT		0.0 (0)
AFib		1.8 (1)
TIA		0.0 (0)
Stroke		1.8 (1)
MI		0.0 (0)
Surgical Re-exploration		1.8 (1)
Reoperation		1.8 (1)
Mortality		0.0 (0)
Drainage (ml)	377 ± 236	
Intubation Time (h)	8.6 ± 5.5	
Length of ICU stay (D)	1.7 ± 1.2	
Length of Ward stay (D)	4.2 ± 1.6	
Po 1 HGB (g/dL)	10.6 ± 3.2	
Po 1 HCT	29.4 ± 5.4	

AKI: Acute kidney injury, TIA: Transient ischemic attack, MI: Myocardial infarction, Drainage (ml): Drainage volume in milliliters, Intubation Time (h): Duration of intubation in hours, Length of ICU stay (D): Length of stay in the intensive care unit in days, Length of Ward stay (D): Length of stay in the general ward in days, Po 1 HGB (g/dL): Hemoglobin level at postoperative day 1 in grams per deciliter, Po 1 HCT: Hematocrit level at postoperative day 1, RRT: Renal replacement therapy.

because of strict adhesions, the need for intraoperative conversion from median sternotomy was observed in a mere 3.4% (n= 2) of cases[2-6,10]. Encouragingly, these individuals experienced successful postoperative outcomes, with no instances of morbidity or mortality. The observed conversion rate aligns closely with the existing literature, reflecting the effectiveness and feasibility of the surgical approach employed. Furthermore, our findings revealed composite outcomes, such as surgical reoperation and stroke, occurring in one patient each. In addition, one patient had postoperative new atrial fibrillation, which completely resolved on the postoperative sixth day. However, no instances of myocardial infarction (MI), acute kidney injury (AKI), mortality, structural heart defects, significant bleeding necessitating massive transfusion, or the need for renal replacement therapy (RRT) were observed in our patient cohort. These outcomes emphasize the favorable nature of the surgical interventions performed and underscore the successful management of structural heart disease in this context.

At present, our study demonstrates a composite outcome-free survival rate of 96.4% at 30 days, highlighting the overall positive prognosis for patients. Moreover, the overall survival rate of 100% further substantiates the favorable outcomes achieved. Importantly, our study cohort exhibited recovery parameters consistent with previous research, with an average hospital discharge time of less than one week[10,11]. Looking ahead, we anticipate that continued advancements in surgical and clinical expertise will further optimize and expedite the recovery process for patients undergoing open heart surgery for structural heart disease. The promising results obtained in this study underscore the potential for future refinement and improvement in patient outcomes, thereby enhancing the overall quality of care in this field.

CONCLUSION

Our study contributes to the growing body of evidence supporting the shift towards minimally invasive approaches in the surgical management of structural heart disease. By analyzing a cohort of 58 patients who underwent mini-thoracotomy, with a significant proportion requiring complex cardiac procedures, we observed a remarkably low rate of intraoperative conversion from median sternotomy (3.4%).

Importantly, these conversions did not result in any adverse events or mortality, reinforcing the safety and feasibility of the surgical approach employed. Furthermore, our findings highlight the favorable postoperative outcomes achieved in this patient population. We observed low rates of composite outcomes such as surgical reoperation and stroke, and no occurrences of myocardial infarction, acute kidney injury, mortality, structural heart defects, significant bleeding, or the need for renal replacement therapy. These findings emphasize the successful management of structural heart disease through our surgical interventions.

Ethics Committee Approval: This study was approved by the Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (Decision no: 2023/11/702, Date: 04.07.2023).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

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REFERENCES

1. Bouhout I, Morgant MC, Bouchard D. Minimally invasive heart valve surgery. Can J Cardiol 2017;33(9):1129-37. https://doi.org/10.1016/j.cjca.2017.05.014
2. Van Praet KM, Stamm C, Sündermann SH, Meyer A, Unbehaun A, Montagner M, et al. Minimally invasive surgical mitral valve repair: State of the art review. Interv Cardiol 2018;13(1):14-9. https://doi.org/10.15420/icr.2017:30:1
3. Liava'a M, Kalfa D. Surgical closure of atrial septal defects. J Thorac Dis 2018;10(Suppl 24):S2931-S9. https://doi.org/10.21037/jtd.2018.07.116
4. Wang Q, Xue X, Yang J, Yang Q, Wang P, Wang L, et al. Right minithoracotomy approach reduces hospital stay and transfusion of mitral or tricuspid valve reoperation with non-inferior efficacy: Evidence from propensity-matched study. J Thorac Dis 2018;10(8):4789-800. https://doi.org/10.21037/jtd.2018.07.53
5. Glauber M, Miceli A, Canarutto D, Lio A, Murzi M, Gilmanov D, et al. Early and long-term outcomes of minimally invasive mitral valve surgery through right minithoracotomy: A 10-year experience in 1604 patients. J Cardiothorac Surg 2015;10:181. https://doi.org/10.1186/s13019-015-0390-y
6. Nakayama T, Nakamura Y, Kanamori K, Hirano T, Kuroda M, Nishijima S, et al. Early and midterm results of minimally invasive aortic and mitral valve surgery via right mini-thoracotomy. J Card Surg 2020;35(1):35-9. https://doi.org/10.1111/jocs.14313
7. Gammie JS, Zhao Y, Peterson ED, O'Brien SM, Rankin JS, Griffith BP. J. Maxwell Chamberlain Memorial Paper for adult cardiac surgery. Less-invasive mitral valve operations: Trends and outcomes from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2010;90(5):1401-8,10. https://doi.org/10.1016/j.athoracsur.2010.05.055
8. Semsroth S, Gothe RM, Raith YR, de Brabandere K, Hanspeter E, Kilo J, et al. Comparison of two minimally invasive techniques and median sternotomy in aortic valve replacement. Ann Thorac Surg 2017;104(3):877-83. https://doi.org/10.1016/j.athoracsur.2017.01.095
9. Lamelas J, Nguyen TC. Minimally invasive valve surgery: When less is more. Semin Thorac Cardiovasc Surg 2015;27(1):49-56. https://doi.org/10.1053/j.semtcvs.2015.02.011
10. Eqbal AJ, Gupta S, Basha A, Qiu Y, Wu N, Rega F, et al. Minimally invasive mitral valve surgery versus conventional sternotomy mitral valve surgery: A systematic review and meta-analysis of 119 studies. J Card Surg 2022;37(5):1319-27. https://doi.org/10.1111/jocs.16314
11. Lei YQ, Liu JF, Xie WP, Hong ZN, Chen Q, Cao H. Anterolateral minithoracotomy versus median sternotomy for the surgical treatment of atrial septal defects: A meta-analysis and systematic review. J Cardiothorac Surg 2021;16(1):266. https://doi.org/10.1186/s13019-021-01648-y

Utility of TAPSE/sPAP Ratio in Acute Pulmonary Embolism as Valuable Prognostic Marker as PESI Score

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ABSTRACT

Introduction: The pulmonary embolism severity index (PESI) score is used to determine the risk of mortality and severity of complications in acute pulmonary embolism (APE). Tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure (TAPSE/sPAP) ratio has been recently shown to predict poor 30-day clinical outcome in APE. We aimed to analyze the prognostic value of the TAPSE/sPAP ratio for prediction of 30-day adverse clinical outcomes in APE patients, similar to PESI score.

Patients and Methods: This study enrolled 203 retrospectively evaluated patients (female 108, mean age= 57.4 ± 15.5 years) with the diagnosis of APE between 2010 and 2020. All patients underwent transthoracic echocardiography before specific APE treatment. Primary endpoints were 30-day mortality, thrombolytic therapy requirement, mechanical ventilation requirement, mental status deterioration, and persistent hypotension (systolic blood pressure <90 mmHg). The study population was divided into two groups according to the TAPSE/sPAP ratio= 114 patients in group 1 with a low TAPSE/sPAP ratio (<0.494) and 89 patients in group 2 with a high TAPSE/sPAP ratio (>0.494).

Results: The incidence of in-hospital mortality (4.4 vs. 0%, p= 0.045], 30-day mortality [n= 8 (7.0%); 0 (0%), p= 0.009] and primary adverse outcomes (35.1 vs. 0%, p< 0.001) were higher in group 1. The TAPSE/sPAP ratio was negatively correlated with PESI (r= -0.716, p< 0.001). In multivariate logistic regression analyses revealed that the TAPSE/sPAP ratio [OR= 0.001, 95C% CI= 0.000-0.476, p= 0.028] was an independent predictor of 30-day mortality in APE.

Conclusion: The present study showed that the TAPSE/sPAP ratio may be used in clinical practice for the prediction of short-term adverse outcome risk estimation in APE patients, similar to PESI score.

Key Words: Acute pulmonary embolism; echocardiography; hypotension; death; single center

Akut Pulmoner Emboli Hastalarında TAPSE/sPAP Oranının PESI Skoru Kadar Değerli Prognostik Bir Belirteç Olarak Kullanımı

ÖZET

Giriş: Akut pulmoner emboli (APE) kliniğinde hastane içi ve ilk ay mortalite ve morbidite öngördürücü olarak "pulmonary embolism severity index (PESI)" skoru kullanılmaktadır. Triküspid annüler düzlem sistolik hareketi/sistolik pulmoner arter basıncı (TAPSE/sPAP) oranının, APE'de son çalışmalarda 30 günlük kötü klinik sonlanım ile ilişkili olabileceği gösterilmiştir. Bu çalışmada TAPSE/sPAP oranının APE hastalarında PESI skoruna benzer şekilde mortalite ve morbidite öngördürücüsü olarak kullanılabilirliğinin araştırılması amaçlanmıştır.

Hastalar ve Yöntem: Bu çalışmaya 2010-2020 yılları arasında, tek merkezli, retrospektif (203 hasta, ortalama yaş= 57.4 ± 15.5 yıl) ve yeni tanı APE hastası alınmıştır. Daha önceden APE teşhis ve tedavisi alan hastalar çalışma dışı bırakılmıştır. Transtorasik ekokardiyografik değerlendirmeleri spesifik APE tedavisi başlamadan önce yapılmıştır. Çalışmanın primer sonlanım noktası 30 günlük mortalite, trombolitik tedavi ihtiyacı, sebat eden hipotansiyon (sistolik arteryel kan basıncı <90 mmhg), mekanik ventilatör ihtiyacı ve bozulmuş mental durum olarak belirlenmiştir. Hastalar TAPSE/sPAP oranına göre düşük TAPSE/sPAP oranı (<0.494) olan grup 1 (114 hasta) ve yüksek TAPSE/sPAP oranı (>0.494) ile grup 2 (89 hasta) olmak üzere iki gruba ayrılmıştır.

Bulgular: Hastane içi mortalite (4.4'e karşı %0, p= 0.045), 30 günlük mortalite (7'ye karşı %0, p= 0.009) ve birincil yan sonuçlar (35.1'e karşı %0, p< 0.001) grup 1'de daha yüksekti. TAPSE/sPAP oranı, PESI ile negatif korelasyon gösterdi (r= -0.716, p< 0.001). Çok değişkenli lojistik regresyon analizlerinde, TAPSE/sPAP oranının [OR= 0.001, 95C% CI= 0.000-0.476, p= 0.028] APE'de 30 günlük mortalitenin bağımsız bir belirleyicisi olduğu ortaya çıktı.

Sonuç: Bu çalışmada APE hastalarında TAPSE/sPAP oranının PESI skoruna benzer şekilde erken dönemde olumsuz klinik sonlanımları öngörmede kısa ve hızlı bir parametre olarak kullanılabileceği gösterilmiştir.

Anahtar Kelimeler: Akut pulmoner emboli; ekokardiyografi; hipotansiyon; ölüm; tek merkez

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INTRODUCTION

Acute pulmonary embolism (APE) caused by venous thromboembolism is the most common cardiovascular disease in the world after acute coronary syndrome and stroke[1]. In APE, the increase in the right ventricular (RV) afterload and RV dysfunction secondary to obstruction in the pulmonary vascular bed is the main cause of in-hospital and 30-day mortality[2]. Cardiogenic shock or hemodynamic instability at first admission is associated with increased mortality in APE patients[3]. However, not all APE patients are hemodynamically unstable at hospital admission. Therefore, in addition to early diagnosis, it is important to evaluate the short-term mortality risk in APE patients. Calculation of the pulmonary embolism severity index (PESI) score[4] to evaluate the mortality risk of APE patients at admission is recommended in the latest pulmonary embolism diagnosis and treatment guideline by the European Society of Cardiology[5]. Transthoracic echocardiography (TTE) in APE has become an indispensable diagnostic method in both early diagnosis and risk assessment[6,7]. Some TTE findings and criteria have been associated with an increased risk of mortality in APE[8]. Despite all these studies, no single echocardiographic parameter has been found to be fully effective in assessing the risk of mortality in APE patients. Tricuspid annular plane systolic excursion (TAPSE) shows longitudinal systolic contraction of the RV[9]. TAPSE is used as a prognostic tool in the course of many cardiac diseases. systolic pulmonary arterial pressure (sPAP) constitutes the afterload of RV. TAPSE/sPAP ratio, a new echocardiographic index, has become a parameter that included RV function and RV afterload, and thus provides information about RV performance. An increase in the ratio, approaching 1, indicates a favorable RV condition, whereas a decrease to less than 0.5 is associated with a poor prognosis in various cardiac diseases[10,11]. Recently, Lyhne et al. have reported that the TAPSE/sPAP ratio may be a short-term predictor of mortality in APE patients[12]. The goal of this study was to compare the PESI score, which shows the short-term mortality risk, and the TAPSE/sPAP ratio in APE patients.

PATIENTS and METHODS

This retrospective study was conducted in accordance with the principles of the Helsinki Declaration and approved by the local institutional ethics committee. Written informed consent was obtained from each patient. Clinical outcomes were analyzed in 203 patients with APE who were admitted or referred to our tertiary hospital between January 2010 and August 2020. Patients with a contraindication to thrombolytic therapy, onset of symptoms of >14 days, systemic arterial systolic blood pressure of <90 or >200 mmHg, end-stage liver disorder, severe thrombocytopenia (platelet count <50.000/mm^3), age <18, cardiogenic shock, poor image quality, chronic thromboembolic pulmonary hypertension patients, recurrent pulmonary embolism, moderate to severe aortic and mitral valve diseases, a history of cardiac surgery, advanced-stage heart failure, and congenital heart disease history were excluded from the study. Patients were also excluded if they had undergone thrombus-reducing therapy (e.g., thrombolysis) or received extracorporeal membrane oxygenation (ECMO) before undergoing echocardiography.

The flow chart for patient selection is summarized in Figure 1. The PESI score of the patients in this study was calculated based on the vital signs, clinical characteristics, and background information recorded at the time of their admission to the emergency service, prior to receiving treatment.

The echocardiographic parameters of the patients include the procedures performed in the first 24 hours after the diagnosis of APE and before specific treatment was started. The primary endpoints of the study are in-hospital and 30-day mortality, persistent hypotension (systolic blood pressure <90 mmHg lasting more than 10 minutes), thrombolytic therapy requirement, as well as mental status disorder due to coma and hypoperfusion (coma, stupor, and need for mechanical ventilator). Following discharge, patients were scheduled for a one-month outpatient clinic follow-up. In cases where patients did not attend this initial one-month check-up, they were contacted by phone to inquire about their health status, and if applicable, to ascertain the date of death. The study population was divided into two groups according to the TAPSE/sPAP ratio= 114 patients in group 1 with a low TAPSE/sPAP ratio (<0.494) and 89 patients in group 2 with a high TAPSE/sPAP ratio (>0.494).

Echocardiography

Transthoracic echocardiography (TTE) was performed within two hours of admission to the hospital.

The sPAP was calculated from the tricuspid regurgitation (TR) jet velocity in accordance with the modified Bernoulli equation without any degree of pulmonary valve stenosis and the right atrial pressure was estimated as 10, 15, and 18 mmHg for mild, moderate, and severe right atrial enlargement, respectively[13,14]. Tricuspid annular plane systolic excursion (TAPSE) was acquired by placing an M-mode cursor through the lateral tricuspid annulus and measuring the amount of longitudinal motion of the annulus at peak systole in the standard apical four-chamber view. In all patients, the right ventricular end-diastolic diameters were measured using the apical four-chamber view, and left ventricular end-diastolic diameters (LVEDD) were measured with M-mode

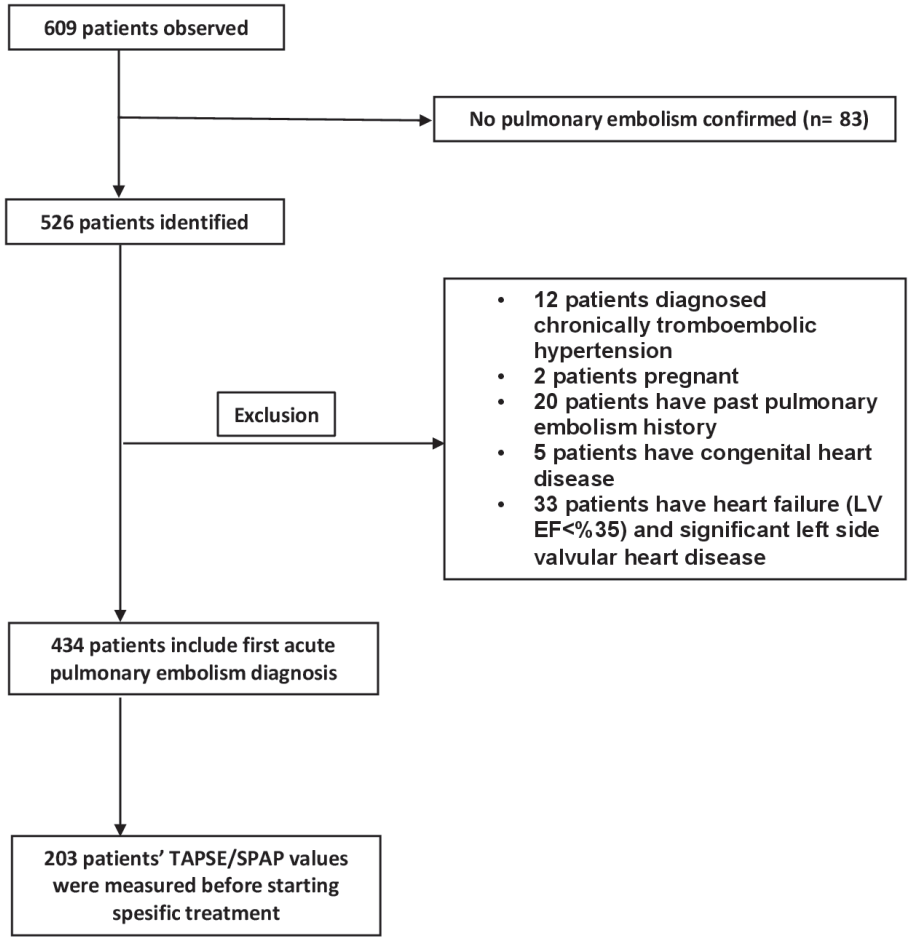

Figure 1. Flow chart of patient selection.

LVEF: Left ventricular ejection fraction, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure.

echocardiography on the parasternal long-axis view. Left ventricle ejection fraction (LVEF) was calculated by using biplane Simpson's method[15]. The interpretation of the echocardiographic findings was carried out by a cardiologist who was blinded to the patients' treatment assignments. A dichotomous value of 40 mm Hg for sPAP was used to define pulmonary hypertension.

RV enlargement was defined as a right-to-left ventricular ratio (RV/LV) of ≥0.9[13,14].

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). The data were expressed as n (%) for categorical variables. The Pearson Chi-square and Fisher's exact tests were performed for categorical variables. After normal distribution was analyzed with the Kolmogorov-Smirnov test, the data were expressed as median (25^{th} and 75^{th} percentiles) for variables without a normal distribution and mean ± SD for variables with normal distribution. Student's t-test was used for comparing quantitative variables with normal distribution while the Mann-Whitney U test was used for comparing quantitative variables without normal distribution. Univariate and multivariate logistic regression analyses were used to determine the independent predictors of 30-day mortality and primary composite endpoints. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal TAPSE/sPAP ratio value that could predict mortality and primary composite outcomes with the highest sensitivity and specificity.

Simple linear regression analysis was used to determine the relation between the TAPSE/sPAP ratio and PESI score. Additionally, Spearman correlation analysis was used to predict the correlation between the TAPSE/sPAP ratio and other clinical variables. A p-value of <0.05 was considered statistically significant.

Table 1. Baseline clinical and demographical variables of the study population

Parameters	All patients (n= 203)	TAPSE/sPAP <0.494 (n= 114)	TAPSE/sPAP >0.494 (n= 89)	p value
Age	57.4 ± 15.5	60.77 ± 14.92	53.18 ± 15.39	**<0.001**
Gender (women), n (%)	108 (53.2)	68 (59.6)	40 (44.9)	**0.037**
Height (cm)	165 (160-174)	165 (160-170)	168 (160-175)	**0.028**
Weight (kg)	80 (72-90)	80 (70-90)	80 (75-90)	0.533
BMI (kg/m^2)	29.21 (26.12-32.59)	29.36 (26.30-33.20)	29.14 (26.12-31.60)	0.410
CRP	29.95 (11.9-63.75)	21.1 (11.0-42.8)	36.8 (13.6-75.0)	**0.025**
Hs-Troponin I (positive or negative)	90 (49.2)	69 (67.6)	21 (25.9)	**<0.001**
Hs-Troponin I Level	15 (6.9-90)	39 (10-106)	10 (1-23)	**<0.001**
Hb	13.1 (11.7-14.4)	13.1 (11.6-14.4)	13.2 (12.2-14.3)	0.930
Htc	39.43 ± 5.46	39.8 ± 5.8	39.0 ± 5.0	0.295
WBC	9.76 (8.02-11.83)	9.9 (8.1-11.8)	9.6 (8.0-11.7)	0.523
PLT	233 (199-290)	232 (185-282)	239 (210-304)	0.113
RDW	13.4 (12.5-14.7)	13.9 (13.0-15.7)	12.9 (12.4-13.8)	**<0.001**
Neut	6.5 (5.1-8.49)	6.93 (5.25-8.66)	6.34 (4.95-8.09)	0.195
Lym	2.03 (1.47-2.71)	2.00 (1.45-2.67)	2.13 (1.60-2.75)	0.275
NLR	3.22 (2.25-4.98)	3.5 (2.3-5.2)	3.0 (2.1-4.4)	0.141
ALT	21 (14-36)	22 (15-45)	17 (13-30)	**0.024**
AST	23 (16-35)	24 (17-39)	22 (15-32)	0.051
Creatinine	0.89 (0.72-1.10)	0.9 (0.8-1.1)	0.8 (0.7-1.0)	**0.024**
Urea	15 (12-21)	17 (13-24)	14 (11-19)	**0.005**
INR	1.1 (1.03-1.19)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	0.450
Systolic BP	124 (110-140)	120 (95-135)	130 (120-140)	**<0.001**
Diastolic BP	75 (67-83)	70.5 (60-80)	80 (70-87)	**0.004**
Hypotension	17 (8.4)	17 (14.9)	0 (0)	**<0.001**
Heart rate	96 (80-110)	103 (87-114)	89 (78-100)	**<0.001**
Pulse O_2 saturation	94 (88-96)	89 (87-94)	96 (94-97)	**<0.001**
Respiratory rate	22 (20-24)	23 (21-26)	21 (20-23)	**<0.001**
Body fever	36.3 (36.1-36.6)	36.3 (36.1-36.5)	36.4 (36.1-36.6)	**0.021**
Altered mental status	7 (3.4)	7 (6.1)	0 (0)	**0.016**
DVT	82 (40.4)	49 (43.0)	33 (37.1)	0.395
Smoking status	38 (18.7)	20 (17.5)	18 (20.2)	0.627
DM	47 (23.2)	34 (29.8)	13 (14.6)	**0.011**
HTN	92 (45.3)	54 (47.4)	38 (42.7)	0.507
CRF	18 (8.9)	10 (8.8)	8 (9.0)	0.957
CAD	32 (15.8)	18 (15.8)	14 (15.7)	0.991
CHF	20 (9.9)	18 (15.8)	2 (2.2)	**0.001**
COAD	23 (11.3)	16 (14.0)	7 (7.9)	0.169
History of cancer	10 (4.9)	6 (5.3)	4 (4.5)	0.535
Immobilization	25 (12.3)	13 (11.4)	12 (13.5)	0.655
Recent surgery history	14 (6.9)	6 (5.3)	8 (9.0)	0.299
Thrombolytic therapy	30 (14.8)	30 (26.3)	0 (0)	**<0.001**
Anticoagulant therapy category	163 (80.3)	84 (73.7)	79 (88.8)	**0.007**
Subgroup				
Warfarin	176 (86.7)	102 (89.5)	74 (83.1)	
NOAC	17 (8.4)	7 (6.1)	10 (11.2)	0.465
LMWH	10 (4.9)	5 (4.4)	5 (5.6)	

BMI: Body mass index, CRP: C-reactive protein, Hb: Hemoglobin, Htc: Hematocrit, WBC: White blood cell, PLT: Platelets, MPV: Mean platelet volume, RDW: Red cell distribution width, Neut: Neutrophil, Lym: Lymphocytes, NLR: Neutrophil lymphocytes ration, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BP: Blood pressure, DVT: Deep vein thrombosis, DM: Diabetes mellitus, HTN: Hypertension, CRF: Chronic renal failure, CAD: Coronary artery disease, CHF: Chronic heart failure, COAD: Chronic obstructive airway disease, NOAC: Novel oral anticoagulants, LMWH: Low-molecular-weight heparin.

Table 2. Echocardiographic variables and clinical outcomes of the study population

Parameters	All patients (n= 203)	TAPSE/sPAP <0.494 (n= 114)	TAPSE/sPAP >0.494 (n= 89)	p value
TAPSE	19 (16-22)	17 (14-20)	21 (19-24)	**<0.001**
sPAP	40 (30-60)	56 (45-65)	30 (30-35)	**<0.001**
TR				
0	8 (3.9)	1 (0.9)	7 (7.9)[a]	
1	87 (42.9)	16 (14.0)	71 (79.8)[a]	**<0.001**
2	33 (16.3)	26 (22.8)	7 (7.9)[b]	
3	51 (25.1)	48 (42.1)	3 (3.4)[b]	
4	24 (11.8)	23 (20.2)	1 (1.1)[b]	
RV diameter	38 (33-42)	41 (37-45)	34 (29-38)	**<0.001**
LV ED diameter	45 (41-48)	44 (40-46)	46 (43-50)	**<0.001**
RV/LV ratio	0.83 (0.72-0.97)	0.93 (0.83-1.07)	0.74 (0.63-0.82)	**<0.001**
LVEF	60 (60-65)	60 (60-60)	60 (60-65)	**0.013**
LVDD				
None	95 (46.8)	53 (46.8)	42 (47.2)	
Grade 1	100 (49.3)	57 (50.0)	43 (48.3)	0.921
Grade 2	8 (3.9)	4 (3.5)	4 (4.5)	
MR				
0	116 (57.1)	61 (53.5)	55 (61.8)	
1	72 (35.5)	41 (36.0)	31 (34.8)	0.053
2	13 (6.4)	10 (8.8)	3 (3.4)	
3	2 (1.0)	2 (1.8)	0 (0)	
RA diameter	40 (34-45)	44 (38-50)	35 (31-40)	**<0.001**
PESI score	87 (64-109)	107 (90-118)	65 (50-75)	**<0.001**
PESI group				
1	55 (27.1)	10 (8.8)	45 (50.6)[a]	
2	42 (20.7)	12 (10.5)	30 (33.7)[a]	
3	42 (20.7)	30 (26.3)	12 (13.5)[b]	**<0.001**
4	42 (20.7)	40 (35.1)	2 (2.2)[b]	
5	22 (10.8)	22 (19.3)	0 (0)[b]	
In-hospital mortality	5 (2.5)	5 (4.4)	0 (0)	**0.045**
30-day mortality	8 (3.9)	8 (7.0)	0 (0)	**0.009**
Primary outcomes	40 (19.7)	40 (35.1)	0 (0)	**<0.001**
TAPSE/sPAP	0.454 (0.290-0.666)	0.312 (0.220-0.391)	0.700 (0.600-0.829)	**<0.001**

[a]= Significantly higher than group 1, [b]= Significantly lower than group 1.

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, TR: Tricuspid regurgitation, RV: Right ventricle, LV ED: Left ventricle and diastolic diameter, LVEF: Left ventricular ejection fraction, LVDD; Left ventricular diastolic dysfunction, MR: Mitral regurgitation, RA: Right atrium, PESI: Pulmonary embolism severity index.

RESULTS

The baseline clinical and demographic variables of the study population are given in Table 1.

ROC curve analysis was conducted to determine the optimal TAPSE/sPAP ratio cut-off value to indicate 30-day mortality. The highest combined sensitivity and specificity values crossed the curve at 0.494 (sensitivity= 100.0%; specificity= 45.6%) for 30-day mortality. The area under the curve was 0.763 (95% CI= 0.628-0.899; p= 0.012). The study population was divided into two groups according to the TAPSE/sPAP ratio. The mean age (60.77 ± 14.92 vs. 53.18 ± 15.39 years, p< 0.001), troponin [39 (10-106); 10 (1-23), p< 0.001], RDW [13.9 (13.0-15.7) vs. 12.9% (12.4-13.8), p< 0.001], ALT [22 (15-45) vs. 17 U/L (13-30), p= 0.024], creatinine [0.9 (0.8-1.1) vs. 0.8 mg/dL (0.7-1.0), p= 0.024], urea [17 (13-24) vs. 14 mg/dL (11-19), p= 0.005] heart rate [103 (87-114) vs. 89 bpm (78-100), p< 0.001] were lower in

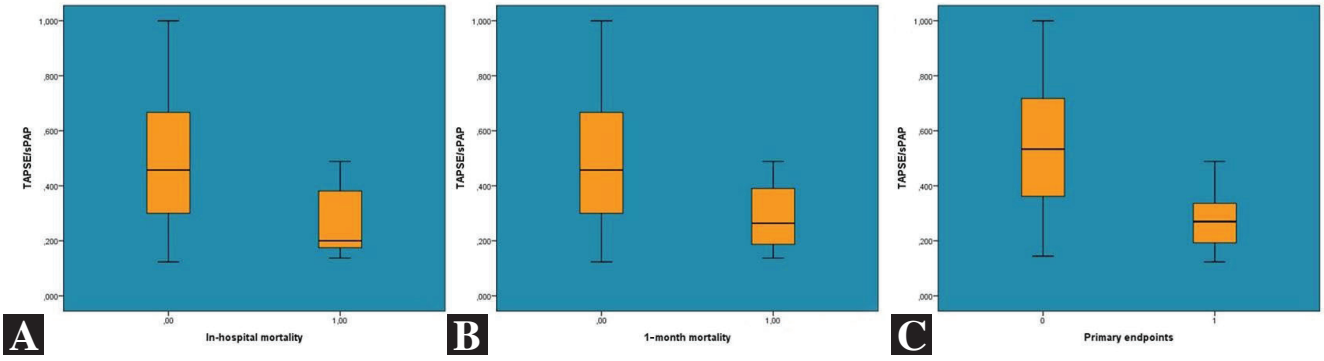

Figure 2. The TAPSE/sPAP ratios for patients with and without in-hospital mortality **(A)**, 30-day mortality **(B)** and primary endpoints **(C)**.

group 2 than group 1. CRP level [21.1 (11.0-42.8) vs. 36.8 mg/L (13.6-75.0), p= 0.025], systolic blood pressure [120 (95-135) vs. 130 mmHg (120-140), p= 0.001], diastolic blood pressure [70.5 (60-80) vs. 80 mmHg (70-87), p= 0.004], oxygen saturation [89 (87-94) vs. 96% (94-97), p< 0.001], fever [36.3 (36.1-36.5) vs. 36.4 (36.1-36.6) 0, p= 0.021] were higher in group 2. The incidence of hypotension [17 (14.9%) vs. 0, p< 0.001], mental disorder [7 (6.1%) vs. 0, p= 0.016], diabetes mellitus (DM) [34 (29.8%) vs. 13 (14.6%), p= 0.011], heart failure (HF) [18 (15.8%) vs. 2 (2.2%), p= 0.001], thrombolytic therapy [30 (26.3%) vs. 0, p< 0.001] were lower in group 2 while anticoagulant therapy [84 (73.7%) vs. 79 (88.8%), p= 0.007] was higher in group 2.

The echocardiographic variables and adverse clinical events are demonstrated in Table 2. TAPSE [17 (14-20) vs. 21 mm (19-24), p< 0.001], LVEDD [44 (40-46) vs. 46 mm (43-50), p< 0.001], LVEF [60 (60-60) vs. 60% (60-65), p= 0.013] were higher in group 2 compared to group 1. sPAP [56 (45-65) vs. 30 mmHg (30-35), p< 0.001], RV diameter [41 (37-45) vs. 34 (29-38) mm, p< 0.001], RV/LV ratio [0.93 (0.83-1.07) vs. 0.74 (0.63-0.82), p< 0.001], RA diameter [44 (38-50) vs. 35 (31-40) mm, p< 0.001], PESI score [107 (90-118) vs. 65 (50-75), p< 0.001] were higher in group 1. The incidence of in-hospital mortality [5 (4.4 vs. 0%, p= 0.045], 30-day mortality [8 (7.0%) vs. 0, p= 0.009] and primary adverse outcomes [40 (35.1 vs. 0%, p< 0.001] were higher in group 1. Additionally, the incidence of moderate to severe TR was higher in group 1.

Patients with in-hospital mortality had a higher PESI score [87 (64-108) vs. 119 (108-152), p= 0.006] and a lower TAPSE/sPAP ratio [0.457 (0.300-0.667) vs. 0.200 (0.175-0.381), p= 0.031] compared to those without mortality (Figure 2A). Patients with 30-day mortality also had a higher PESI score [86 (63-108) vs. 117 (108-139), p= 0.003] and a lower TAPSE/sPAP ratio [0.457 (0.300-0.667) vs. 0.264 (0.188-0.390), p= 0.012] (Figure 2B) compared to those without mortality. Furthermore, patients who met the primary endpoints had a higher PESI score [75 (59-98) vs. 125 (114-145), p< 0.001] and a lower TAPSE/sPAP ratio [0.533 (0.361-0.720) vs. 0.270 (0.193-0.336), p< 0.001] (Figure 2C) compared to those without mortality (Table 3). Patients with higher PESI scores exhibited lower TAPSE/sPAP ratios, with values of 0.667 (0.514-0.800) for low PESI scores, 0.433 (0.356-0.533) for intermediate PESI scores, and 0.264 (0.200-0.336) for high PESI scores, respectively (p< 0.001) (Table 4).

The correlation between the TAPSE/sPAP ratio and clinical variables is demonstrated in Table 5. The TAPSE/sPAP ratio was negatively correlated with PESI (r= -0.716, p< 0.001) (Figure 3), troponin (r= -0.490, p< 0.001), RDW (r= -0.307, p< 0.001), urea (r= -0.266, p< 0.001), heart rate (r= -0.355, p< 0.001), respiratory rate (r= -0.253, p< 0.001), RV diameter (r= -0.540, p< 0.001), RV/LV ratio (r= -0.590, p< 0.001),

176 RA diameter (r= -0.558, p< 0.001) and age (r= -0.298, p< 0.001). The TAPSE/sPAP ratio was positively correlated with systolic blood pressure (r= 0.275, p= 0.001), diastolic blood pressure (r= 0.227, p< 0.001), 178 saturation O_2 (r= 0.638, p< 0.001), fewer (r= 0.158, p= 0.024), LVEDD (r= 0.325, p< 0.001) and LV EF (r= 0.230, p= 0.001).

The multivariate logistic regression analyses revealed that the TAPSE/sPAP ratio [OR= 0.001, 95% CI= 0.000-0.476, p= 0.028] was an independent predictor of 30-day mortality in APE.

The TAPSE/sPAP ratio [OR= 0.009, 95% CI= 0.000-0.972, p= 0.049], PESI score [OR= 1.090, 95% CI= 1.050-1.132, p< 0.001], and HT [OR= 4.864, 95% CI= 1.381-17.138, p= 0.014] were also independent predictors of primary composite outcomes (Table 6). In simple linear regression analysis the TAPSE/sPAP ratio was found to be associated with the PESI score with (adjusted R^2= 0.425, ANOVA p< 0.001) statistical significance (PESI= -96.20 × TAPSE/sPAP + 134.992) (Figure 3). ROC curve analysis was conducted to determine the optimal TAPSE, sPAP, and TAPSE/sPAP ratio cut-off values to

Table 3. Comparison of TAPSE/sPAP ratio and PESI score in patients with and without adverse clinical events

Parameters	All patients (n= 203)	In-hospital mortality - (n= 198)	In-hospital mortality + (n= 5)	p value
TAPSE	19 (16-22)	19 (16-22)	14 (11-16)	0.051
sPAP	40 (30-60)	40 (30-60)	45 (45-80)	0.088
TAPSE/sPAP	0.454 (0.290-0.666)	0.457 (0.300-0.667)	0.200 (0.175-0.381)	**0.031**
PESI	87 (64-109)	87 (64-108)	119 (108-152)	**0.006**
		1-month mortality – (n= 195)	**1-month mortality + (n= 8)**	**p**
TAPSE	19 (16-22)	19 (16-22)	15 (12-19)	**0.040**
sPAP	40 (30-60)	40 (30-60)	53 (45-70)	**0.036**
TAPSE/sPAP	0.454 (0.290-0.666)	0.457 (0.300-0.667)	0.264 (0.188-0.390)	**0.012**
PESI	87 (64-109)	86 (63-108)	117 (108-139)	**0.003**
		Primary composite endpoints – (n= 163)	**Primary composite endpoints + (n= 40)**	**p**
TAPSE	19 (16-22)	20 (17-22)	15 (12-19)	**<0.001**
sPAP	40 (30-60)	35 (30-55)	60 (50-70)	**<0.001**
TAPSE/sPAP	0.454 (0.290-0.666)	0.533 (0.361-0.720)	0.270 (0.193-0.336)	**<0.001**
PESI	87 (64-109)	75 (59-98)	125 (114-145)	**<0.001**

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, PESI: Pulmonary embolism severity index.

Table 4. The association between TAPSE/sPAP ratio and PESI score

Parameters	PESI low (1-2) (n= 97)	PESI intermediate (3) (n= 42)	PESI high (4-5) (n= 64)	p value
TAPSE	20 (18-23)	19 (17-21)	16 (13-19)[a,b]	<0.001
sPAP	30 (30-37)	45 (35-55)[c]	60 (50-74)[c,d]	<0.001
TAPSE/sPAP	0.667 (0.514-0.800)	0.433 (0.356-0.533)[a]	0.264 (0.200-0.336)[a,b]	<0.001

[a]= Significantly lower than group 1, [b]= Significantly lower than group 2, [c]= Significantly higher than group 1, [d]= Significantly higher than group 2.
TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, PESI: Pulmonary embolism severity index.

indicate 30-day mortality and primary adverse outcomes. In the 30-day mortality analyses, the highest combined sensitivity and specificity values crossed the curve at 14.5 (sensitivity= 50.0%; specificity= 83.6%) for TAPSE. The area under the curve was 0.714 (95% CI= 0.530-0.898; p= 0.040). The highest combined sensitivity and specificity values crossed the curve at 41 (sensitivity= 100.0%; specificity= 54.4%) for sPAP. The area under the curve was 0.717 (95% CI= 0.597-0.837; p= 0.038). The highest combined sensitivity and specificity values crossed the curve at 0.494 (sensitivity= 100.0%; specificity= 45.6%) for TAPSE/sPAP ratio (Figure 4A) The area under the curve was 0.763 (95% CI= 0.628-0.899; p= 0.012). In the primary outcomes analyses, the highest combined sensitivity and specificity values crossed the curve at 15.5 (sensitivity= 52.2%; specificity= 85.9%) for TAPSE. The area under the curve was 0.749 (95% CI= 0.660-0.838; p< 0.01). The highest combined sensitivity and specificity values crossed the curve at 49 (sensitivity= 85.0%; specificity= 71.8%) for sPAP. The area under the curve was 0.811 (95% CI= 0.752-0.870; p< 0.001). The highest combined sensitivity and specificity values crossed the curve at 0.387 (sensitivity= 92.5%; specificity= 70.6%) for the TAPSE/sPAP ratio (Figure 4B). The area under the curve was 0.855 (95% CI= 0.804-0.907; p< 0.001).

DISCUSSION

In our study, it was demonstrated that impaired TAPSE/sPAP ratio was a strong predictor of in-hospital and 30-day mortality in acute pulmonary embolism. Additionally, it was associated with adverse cardiovascular outcomes. We also revealed that the TAPSE/sPAP ratio was negatively correlated with the PESI score. To the best of our knowledge, this is the first study to compare the correlation of TAPSE/sPAP ratio with PESI score in patients with APE.

Table 5. The correlation between TAPSE/sPAP ratio and clinical variables

Parameters	Correlation coefficient	p value
PESI	-0.716	**<0.001**
Hs-Troponin I	-0.490	**<0.001**
RDW	-0.307	**<0.001**
Urea	-0.266	**<0.001**
Systolic BP	0.275	**0.001**
Diastolic BP	0.227	**<0.001**
Heart rate	-0.355	**<0.001**
Pulse O_2 saturation	0.638	**<0.001**
Respiratory rate	-0.253	**<0.001**
Fever	0.158	**0.024**
RV diameter	-0.540	**<0.001**
LV ED diameter	0.325	**<0.001**
RV/LV ratio	-0.590	**<0.001**
LV EF	0.230	**0.001**
RA diameter	-0.558	**<0.001**
Age	-0.298	**<0.001**

RCW: Red cell distribution width, TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, LV: Left ventricle, RV: Right ventricle, LV ED: Left ventricle and diastolic diameter, LVEF: Left ventricular ejection fraction, RA: Right atrium, PESI: Pulmonary embolism severity index, BP: Blood pressure.

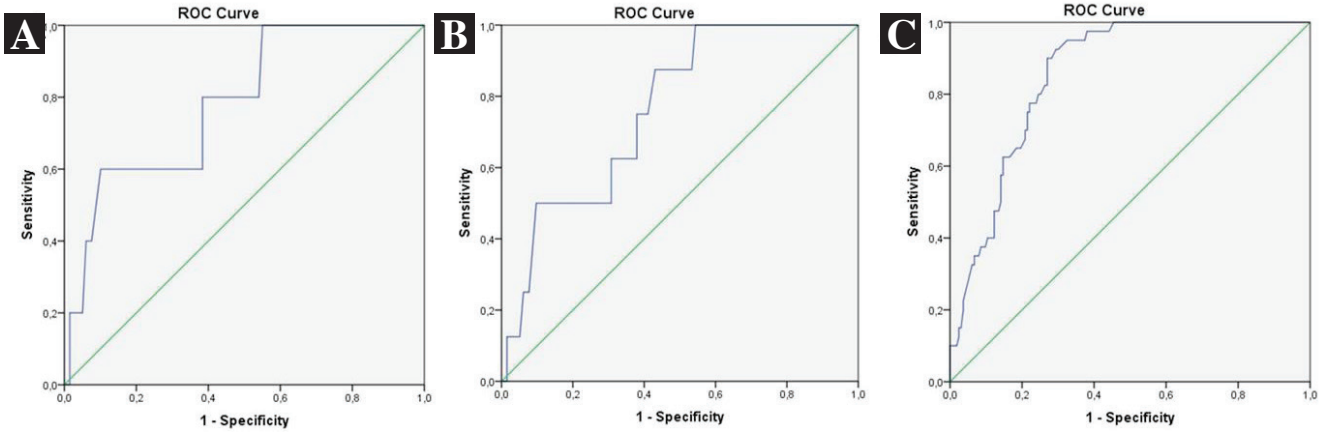

Figure 3. The correlation between TAPSE/sPAP ratio and PESI score.

While mortality is around 30% in patients with APE who are not properly diagnosed and treated, this rate ranges between 2% and 8% with early diagnosis and successful treatment[16]. For this reason, prognostic determination and choosing the right treatment for APE patients is a very important step. The RV function is of great importance in the prognostic evaluation of APE. The RV dysfunction detected in APE patients not only provides information on hypotension, cardiorespiratory deterioration and mortality that may develop, but also provides useful information on treatment selection[17,18]. TAPSE is an echocardiographic parameter that provides simple and rapid results in demonstrating right ventricular function. Previous studies have shown that TAPSE can be a physiological indicator of right ventricular systolic functions and is a method that can be used to evaluate right ventricular systolic function[19-21]. However, TAPSE alone provides only a longitudinal measurement and is insufficient to show global function[4]. Another parameter that determines the prognostic value of pulmonary embolism is pulmonary artery pressure[22]. The RV, normally working against a low afterload, causes physical occlusion of the pulmonary arteries, hypoxic vasoconstriction, and pulmonary artery vasoconstriction leading to increased resistance in the pulmonary vascular bed with RV afterload. As a result, increased pulmonary artery pressure makes it difficult for the RV to cope with this pressure load, and RV function is further impaired[23]. The TAPSE/sPAP

Table 6. Multivariate analysis giving information about independent predictors of 30-day mortality and primary composite endpoints

Parameters	Multivariate analysis		
	Odds ratio	**95% CI**	**p value**
TAPSE/sPAP	0.001	0.000-0.476	0.028
DM	1.628	0.260-10.193	0.603
HTN	1.211	0.221-6.625	0.826
WBC	1.038	0.914-1.179	0.567
Creatinine	4.202	0.737-23.971	0.106
Primary composite endpoints	**Odds ratio**	**95% CI**	**p**
Chronic renal failure	1.975	0.261-14.927	0.509
TAPSE/sPAP	0.009	0.000-0.972	0.049
PESI score	1.090	1.050-1.132	<0.001
Smoking	2.478	0.621-9.886	0.199
DM	2.076	0.480-8.984	0.329
HTN	4.864	1.381-17.138	0.014

TAPSE: Tricuspid annular plane systolic excursion, sPAP: Systolic pulmonary arterial pressure, DM: Diabetes mellitus, HTN: Hypertension, WBC: White blood cell, PESI: Pulmonary embolism severity index.

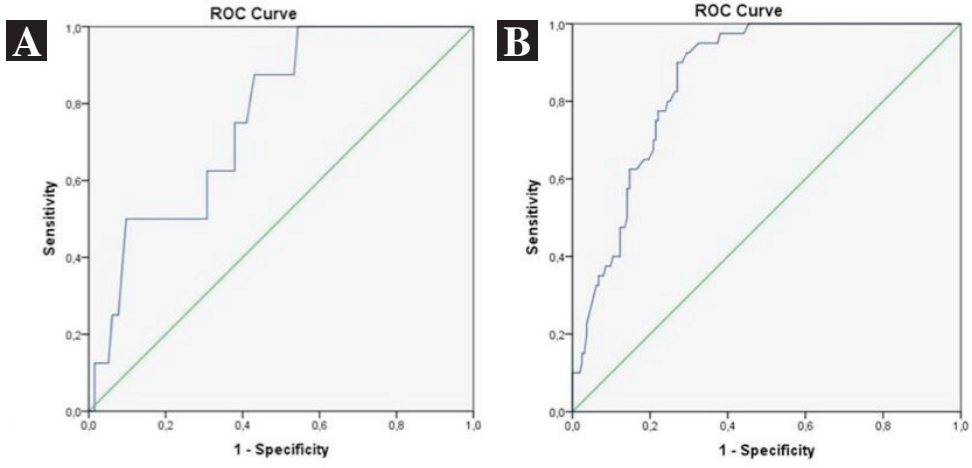

Figure 4. Receiver-operating characteristic curve indicating the discriminative ability of the TAPSE/sPAP ratio for 30-day mortality **(A)** and primary endpoints **(B)**.

ratio, calculated by these two important echocardiographic markers, provides valuable information about the global function of the RV[10,24].

The normal range for TAPSE/sPAP is typically between 0.8 and 1.8, and while these values may vary with age, they do not vary with gender[24]. Similarly, we did not see a difference between sexes in a disease state. A high ratio means the RV is functioning well given the afterload. The ratio will decrease as sPAP increases, when RV function estimated by TAPSE declines, or both[19,24,25].

The TAPSE/sPAP ratio has been associated with short-term outcomes in patients with APE in previous studies. In the study conducted by Lyhne et al., the TAPSE/sPAP ratio in low-risk APE patients was found to be 0.47 in patients with a primary endpoint of seven-day mortality and the need for invaluable treatment[12]. As a result of the data in this study, while TAPSE and TAPSE/sPAP ratio were predictive in seven-day mortality, sPAP alone was not significant. Interestingly, considering the 30-day mortality results of these patients, only the TAPSE/sPAP ratio was associated with this outcome[12]. As a result of the ROC curve analysis we conducted in our study, the predictive value of the

TAPSE/sPAP ratio in APE patients was found to be 0.494. As such, it appears to be consistent with previous studies. In the present study, a low TAPSE/PASP ratio was found to be associated with in-hospital mortality, 30-day mortality, and primary outcomes that include hypotension, and thrombolytic treatment requirement. Besides these poor outcomes, the

TAPSE/PASP ratio also had a relationship with traditional parameters of determining the right heart such as RV diameter, RV/LV ratio, tricuspid regurgitation, right atrium diameter.

Although there are many parameters that determine the prognosis in patients with pulmonary embolism, the PESI score is the most commonly used tool as recommended by the guidelines[5]. This scoring, which was put into clinical practice more than 15 years ago, is used in two different ways as the traditional PESI, which includes 11 clinical variables[4], and the simplified PESI, calculated with six criteria[26]. The PESI score, which is classified into five different groups, is considered an important predictor of 30-day mortality in APE patients. Mortality predictions ranging from 1% to 10% can be made among these five groups[4,26]. Despite all these broad usage and recommendations, the PESI scoremay not be sufficient in terms of hemodynamic evaluation. It is especially weak in evaluating the right ventricular dysfunction caused by APE. For this reason, transthoracic echocardiographic evaluations have been routinely used in APE patients in recent years as they are easy to access, inexpensive and simple methods that can be applied at the bedside, and studies have shown that this evaluation has successful predictive effects[26]. In a study by Burgos et al., TAPSE and sPAP measurements added to the PESI score were found to be a better predictor of mortality than the PESI score alone in patients with APE[27]. Although not as strong as the PESI score, TAPSE and sPAP values separately gave predictive results in terms of one-month mortality. On the other hand, they revealed that the TAPSE/sPAP ratio can be an alternative assessment to PESI. Indeed, in the correlation analysis in our study, a strong negative correlation was found between the TAPSE/sPAP ratio and the PESI score ($r= -0.716$, $p< 0.001$). In addition, the TAPSE/sPAP ratio was determined as an independent predictor of 1- month mortality in patients with acute pulmonary embolism in multivariate analysis [OR= 0.001, 95% CI= 0.000-0.476, p= 0.028].

Another data supporting the results we obtained in our study is that PESI score parameters are correlated with the TAPSE/sPAP ratio even when evaluated separately. As a matter of fact, PESI score criteria such as age, high heart rate, low oxygen saturation, fever, hypotension, and mental status disorder were found to be significantly associated with a low TAPSE/sPAP ratio. The TAPSE/sPAP ratio was found to be as predictive as the PESI score in primary composite outcomes including hypotension, shock, mental status impairment, mechanical ventilator requirement, thrombolytic requirement, and death. As such, our results seem to be compatible with the study by Lyhne et al[12].

Limitations of the study

The main limitations of the study are that it is single-centered and retrospective, and the number of patients is relatively low. Furthermore, the fact that the echocardiographically measured TAPSE measurement is only an indicator of RV longitudinal systolic functions and not RV global functions is considered a limitation. Furthermore, it's important to note that the measured systolic pulmonary arterial pressures are calculated based on the tricuspid regurgitation (TR) jet using the modified Bernoulli's formula, and these pressures are not measured invasively, which are among the significant limitations of the study. The fact that the echoparameters measured in the pre-treatment echocardiographic evaluation at the first admission, which can sometimes end in shock or cardiac arrest, such as APE, cannot be performed by more than one person and reproducibly, also creates significant limitations.

CONCLUSION

We found that the TAPSE/sPAP ratio is an important indicator in determining the prognosis of patients with acute pulmonary embolism. However, we determined a strong negative correlation between the PESI score and the TAPSE/sPAP ratio used in line with the guidelines in APE prognosis.

Therefore, the TAPSE/sPAP ratio may be used as an alternative tool in determining the prognosis of APE patients as it is easily accessible, affordable, and effective.

Ethics Committee Approval: This study was approved by the İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Clinical Research Ethics Committee (Decision no: 10678112-514.10-03, Date: 11.02.2021).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - AYÇ, SK, EGG, AKK; Analysis/Interpretation - SK; Data Collection - AG, RG; Writing - AYÇ, RG; Critical Revision - ME, MY, FU; Final Approval - AYÇ, AKK; Statistical Analysis -SK; Overall Responsibility - AYÇ.

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REFERENCES

1. Raskob GE, Angchaisuksiri P, Blanco AN, Buller H, Gallus A, Hunt BJ, et al. Thrombosis: A major contributor to global disease burden. Arterioscler Thromb Vasc Biol 2014;34(11):2363-71. https://doi.org/10.1161/ATVBAHA.114.304488
2. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: The pivotal role of pulmonary vasoconstriction. Cardiovasc Res 2000;48(1):23-33. https://doi.org/10.1016/S0008-6363(00)00168-1

3. Kasper W, Konstantinides S, Geibel A, Olschewski M, Heinrich F, Grosser KD, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: Results of a multicenter registry. J Am Coll Cardiol 1997;30(5):1165-71. https://doi.org/10.1016/S0735-1097(97)00319-7
4. Aujesky D, Obrosky DS, Stone RA, Auble TE, Perrier A, Cornuz J, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172(8):1041-6. https://doi.org/10.1164/rccm.200506-862OC
5. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603.
6. Wolde M, Söhne M, Quak E, Mac Gillavry MR, Büller HR. Prognostic value of echocardiographically assessed right ventricular dysfunction in patients with pulmonary embolism. Arch Intern Med 2004;164(15):1685-9.
7. Kjaergaard J, Schaadt BK, Lund JO, Hassager C. Prognostic importance of quantitative echocardiographic evaluation in patients suspected of first non-massive pulmonary embolism. Eur J Echocardiogr 2009;10(1):89-95. https://doi.org/10.1080/14399776.2009.10780992
8. López-Candales A, Edelman K, Candales MD. Right ventricular apical contractility in acute pulmonary embolism: The McConnell sign revisited. Echocardiography 2010;27(6):614-20. https://doi.org/10.1111/j.1540-8175.2009.01103.x
9. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107(3):526-31. https://doi.org/10.1016/0002-8703(84)90095-4
10. Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, et al. RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: Stratification of clinical phenotypes and outcomes. JACC Cardiovasc Imaging 2017;10(10 Pt B):1211-21.
11. Guazzi M, Bandera F, Pelissero G, Castelvecchio S, Menicanti L, Ghio S, et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: An index of right ventricular contractile function and prognosis. Am J Physiol Heart Circ Physiol 2013;305(9):H1373-81.
12. Lyhne MD, Kabrhel C, Giordano N, Andersen A, Nielsen-Kudsk JE, Zheng H, et al. The echocardiographic ratio tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure predicts short-term adverse outcomes in acute pulmonary embolism. Eur Heart J Cardiovasc Imaging 2021;22(3):285-94.
13. Feigenbaum H, Armstrong W, Ryan T. Hemodynamics. In: Feigenbaum's Echocardiography. Philadelphia: Lippincott Williams &Wilkins 2005:231.
14. Vonk Noordegraaf A, Chin KM, Haddad F, Hassoun PM, Hemnes AR, Hopkins SR, et al. Pathophysiology of the right ventricle and of the pulmonary circulation in pulmonary hypertension: An update. Eur Respir J 2019;53:1801900. https://doi.org/10.1183/13993003.01900-2018
15. Galderisi M, Cosyns B, Edvardsen T, Cardim N, Delgado V, Di Salvo G, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: An expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2017;18:1301-10.
16. Martin KA, Molsberry R, Cuttica MJ, Desai KR, Schimmel DR, Khan SS. Time trends in pulmonary embolism mortality rates in the United States, 1999 to 2018. J Am Heart Assoc 2020;9(17):e016784. https://doi.org/10.1161/JAHA.120.016784
17. Rydman R, Söderberg M, Larsen F, Caidahl K, Alam M. Echocardiographic evaluation of right ventricular function in patients with acute pulmonary embolism: A study using tricuspid annular motion. Echocardiography 2010;27(3):286-93. https://doi.org/10.1111/j.1540-8175.2009.01015.x
18. Bryce YC, Perez-Johnston R, Bryce EB, Homayoon B, Santos-Martin EG. Pathophysiology of right ventricular failure in acute pulmonary embolism and chronic thromboembolic pulmonary hypertension: A pictorial essay for the interventional radiologist. Insights Imaging 2019;10(1):18.
19. Lahham S, Fox JC, Thompson M, Nakornchai T, Alruwaili B, Doman G, et al. Tricuspid annular plane of systolic excursion to prognosticate acute pulmonary symptomatic embolism (TAPSEPAPSE study). J Ultrasound Med 2019;38(3):695-702. https://doi.org/10.1002/jum.14753
20. Alerhand S, Hickey SM. Tricuspid annular plane systolic excursion (TAPSE) for risk stratification and prognostication of patients with pulmonary embolism. J Emerg Med 2020;58(3):449-56. https://doi.org/10.1016/j.jemermed.2019.09.017
21. Lobo J, Sobradillo P, Obieta-Fresnedo I, Rivas A, Valle R, Navarro C, et al. TAPSE as a prognostic factor in hemodinamically stable pulmonary embolism. Eur Respiratory Soc 2011.
22. Liu YY, Li XC, Duan Z, Yuan YD. Correlation between the embolism area and pulmonary arterial systolic pressure as an indicator of pulmonary arterial hypertension in patients with acute pulmonary thromboembolism. Eur Rev Med Pharmacol Sci 2014;18(17):2551-5.
23. Mortensen CS, Kramer A, Schultz J, Lyhne MD, Nielsen-Kudsk JE, Andersen A. Impact of preload on right ventricular hemodynamics in acute pulmonary embolism. Crit Care Med 2020;48(12):e1306-e12.
24. Tello K, Wan J, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular-arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imaging 2019;12(9):e009047.
25. Jiménez D, Aujesky D, Moores L, Gómez V, Lobo JL, Uresandi F, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170(15):1383-9. https://doi.org/10.1001/archinternmed.2010.199
26. Dabbouseh NM, Patel JJ, Bergl PA. Role of echocardiography in managing acute pulmonary embolism. Heart 2019;105(23):1785-92. https://doi.org/10.1136/heartjnl-2019-314776
27. Burgos LM, Scatularo CE, Cigalini IM, Jauregui JC, Bernal MI, Bonorino JM, et al. The addition of echocardiographic parameters to PESI risk score improves mortality prediction in patients with acute pulmonary embolism: PESI-Echo score. Eur Heart J Acute Cardiovasc Care 2021;10(3):250-7. https://doi.org/10.1093/ehjacc/zuaa007

What Happens to Mild-to-Moderate Chronic Ischemic Mitral Regurgitation Following Isolated Coronary Artery Bypass Surgery?

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ABSTRACT

Introduction: The aim of this study was to assess the efficacy of isolated coronary artery bypass grafting (CABG) on preoperatively existing mild-to-moderate chronic ischemic mitral regurgitation.

Patients and Methods: A retrospective analysis was conducted on 30 patients who had coronary artery disease and chronic ischemic mitral regurgitation, and underwent isolated CABG at the Department of Cardiovascular Surgery, Kocaeli University, between January 2012 and February 2014. Preoperative demographic and clinical characteristics, as well as postoperative outcomes, were evaluated. The degree of IMR, left ventricular ejection fraction (LVEF), left ventricular end-systolic dimension (LVESD), left ventricular end-diastolic dimension (LVEDD), and left atrial dimension (LAD) were assessed preoperatively, and at the postoperative 12th month.

Results: There was no mortality during the early postoperative period. There were statistically similar measurements for LVEF, LVESD, LVEDD, and LAD between preoperative and postoperative periods ($p> 0.05$). However, a decrease in the degree of IMR was detected during the specified periods ($p< 0.05$).

Conclusion: Isolated CABG can be safely performed in patients with mild/moderate chronic ischemic mitral regurgitation. The efficacy of isolated CABG was demonstrated to improve the degree of mitral regurgitation in selected patients based on echocardiographic measurements.

Key Words: Mitral valve regurgitation; echocardiography; coronary artery bypass surgery

İzole Koroner Arter Bypass Cerrahisinin Ardından Hafif ve Orta Dereceli Kronik İskemik Mitral Yetersizliğine Ne Olur?

ÖZET

Giriş: Hafif/orta mitral yetersizliği (MY) olan hastalarda izole koroner arter bypass grefti (CABG) cerrahisinin etkinliğini değerlendirmek.

Hastalar ve Yöntem: Ocak 2012 ile Şubat 2014 Kocaeli Üniversitesi Kalp Damar Cerrahisi biriminde izole CABG uygulanan 30 hasta retrospektif olarak incelendi. Ameliyat öncesi demografik ve klinik özellikler ile ameliyat sonrası sonuçlar değerlendirildi. Hastaların MY derecesi, sol ventrikül ejeksiyon fraksiyonu (SVEF), sol ventrikül sistol sonu boyut (SVSSB) ve sol ventrikül diyastol sonu boyut (SVDSB), sol atriyum boyutu (SAB) ameliyat öncesi ve ameliyat sonrası 12. ayda kontrol edildi.

Bulgular: Hiçbir hastada mortalite görülmedi. Hastaların ameliyat öncesi ve ameliyat sonrası SVEF, SVSSB, SVDSB ve SAB ölçümlerinde istatiksel olarak benzerlik mevcuttu ($p> 0.05$). Ancak belirtilen periyotlarda hastaların MY derecelerinde azalma tespit edildi ($p< 0.05$).

Sonuç: Hafif/orta mitral yetmezliği bulunan hastalarda izole CABG güvenle uygulanabilir. CABG'nin etkinliği hastaların ekokardiyografik ölçümlerinde özellikle MY derecesinin azalmasıyla olumlu bir şekilde gösterilmiştir.

Anahtar Kelimeler: Mitral kapak yetersizliği; ekokardiyografi; koroner arter bypass cerrahisi

INTRODUCTION

Ischemic mitral regurgitation (IMR) is a common complication after myocardial infarction[1]. There is no consensus on the surgical treatment of patients with coronary artery disease and mild-to-moderate IMR. It was suggested in several studies that isolated coronary artery bypass grafting (CABG) surgery may reduce the degree of IMR by improving left ventricular function[2].

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Some researchers recommend mitral annuloplasty repair at the time of CABG to directly reduce the degree of IMR[3,4]. However, the addition of mitral valve repair to CABG may increase operative morbidity and mortality rates. The aim of this retrospective study was to evaluate the clinical and echocardiographic results of changes in IMR degree at postoperative one-year in patients who had mild or moderate IMR and coronary artery disease and underwent isolated CABG.

PATIENTS and METHODS

A retrospective analysis of 30 patients with mild/moderate chronic IMR was performed among 298 patients who underwent isolated CABG between January 2012 and February 2014 in the Cardiovascular Surgery Clinic of Kocaeli University Faculty of Medicine. This study was approved by Kocaeli University Clinical Ethics Committees on 30.12.2014 with KOÜKAEK: 2014/353 certificate number.

Preoperative echocardiography was performed within one week before surgery to determine the etiology and degree of IMR. Patients with mild or moderate IMR were included in the study. The exclusion criteria were determined as an absence of sinus rhythm, severe valvular stenosis, mitral valve pathologies due to prolapse, rheumatic, endocarditis, annular calcification, leaflet damage, history of reoperation, and unstable clinical conditions. Standard transthoracic echocardiography with Philips IE 33 system (S5-1 probe, 2.5-5.5 MHz; Philips Healthcare, Andover, Mass) was performed preoperatively and at postoperative 12th month. Left ventricular ejection fraction (LVEF), left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and left atrial diameter (LAD) were evaluated. IMR was assessed according to the diagnostic criteria of the European Society of Echocardiography.

Clinical data were recorded as age, sex, arterial blood pressure, arterial hypertension, dyslipidemia, diabetes, smoking, New York Heart Association (NYHA) functional class, outcome (survival or death), length of intensive care unit or hospital stay, and major complications related to the operation, including respiratory complications, neurological complications (stroke or transient ischemic attack), and low cardiac output before or after surgery.

Regarding perioperative variables, low cardiac output syndrome was defined as the need for an intra-aortic balloon pump. Transient ischemic attack (TIA) was defined as a transient neurological event with loss of neurological function during less than 24 hours. Pneumonia and atelectasis have been defined as respiratory complications. Renal complication was defined as the need for dialysis after CABG, and serum Cr >1.8 mg/dL.

Standard median sternotomy was performed under general anesthesia in all patients. After appropriate anticoagulation with 400 IU/kg heparin, cardiopulmonary bypass (CPB) was initiated by cannulation of the ascending aorta and right atrium. All patients were monitored with moderate hypothermia (28-32 °C) and myocardial protection was achieved with antegrade-retrograde combined isothermic blood cardioplegia. Mean arterial pressure was maintained between 60 and 80 mmHg during CPB.

All data were analyzed using the SPSS 20.0 package program and were expressed as mean ± standard deviation. The Chi-square test was used for categorical data analysis. The difference between preoperative and postoperative values was evaluated by the Paired-t test for numerical variables with normal distribution, and the Wilcoxon test for numerical variables without normal distribution. Values of $p< 0.05$ were considered statistically significant.

RESULTS

Patient's Data

CABG procedure was performed with cardiopulmonary bypass in 30 patients. The mean age was 62.6 ± 6.4 years. Baseline demographic data and EF values of the patients are presented in Table 1.

Operative Data

There was no mortality in any patient. The mean cardiopulmonary bypass (CPB) and aortic cross-clamp times (ACC) were 74 ± 24 minutes and 50 ± 16 minutes, respectively. One patient underwent reoperation due to bleeding at the postoperative 5th hour. In one patient, an intraaortic balloon pump was administered because of low cardiac output. Operative data of the patients are shown in Table 2.

Echocardiographic results

Echocardiography was performed in all patients preoperatively, and at 12 months postoperatively. No statistical difference was found in the LVEF, LVEDD, LVESD, and LAD measurements of the patients preoperatively, and at 12 months postoperatively ($p> 0.05$). However, a statistical difference was found in terms of the degree of MR in the preoperative and postoperative 12th-month periods ($p< 0.05$) (Table 3).

Table 1. Patient data

Patients (n= 30)	n/%	Mean ± SD	Range
Age		62.6 ± 6.4	(51-74)
Gender (Male)	21 (70%)		
BSA (m^2)		1.79 ± 0.47	(1.65-2.04)
Euro-Score		7.8 ± 3.1	(6.4-11)
Hypertension	16 (53.3%)		
COPD	3 (10%)		
Diabetes mellitus	14 (46.7%)		
Smoking	12 (40%)		
NYHA class III-IV	14 (46.6%)		
Use of SVG	30 (100%)		
LVEF	30 (100%)		
<35%	5 (16.6%)		
35-50%	21 (70%)		
>50%	4 (13.3%)		
MR (2+) (Mild to Moderate)	24 (80%)		
MR (1+) (Mild)	6 (20%)		

BSA: Body surface area, COPD: Chronic obstructive pulmonary disease, NYHA: New York heart association, SVG: Saphenous vein graft, MR: Mitral regurgitation.

Table 2. Operative data

Variables (n= 30)	n/%	Mean ± SD	Range
CPB (min)		74 ± 24	(50-98)
ACC (min)		50 ± 16	(35-66)
Mechanical Ventilation (hrs.)		10.5 ± 2.8	(7.1-18.5)
ICU stay (hrs.)		21.6 ± 5.8	(14-27)
Discharge (days)		7.6 ± 2.9	(5-10)
Drainage (mL)		320 ± 125	(250-600)
Bleeding Revision	1 (3.3%)		
LCOS	1 (3.3%)		
• IABP	1 (3.3%)		
Renal Complication	2 (6.7%)		
• Dialysis	1 (3.3%)		
• Creatinine >1.8 mg/dl	1 (3.3%)		
Neurological Complication	1 (3.3%)		
• TIA	1 (3.3%)		
Respiratory Complication	2 (6.7%)		
• Atelectasis	1 (3.3%)		
• Pneumonia	1 (3.3%)		
ECMO	0		
Mortality	0		

CPB: Cardiopulmonary bypass, ACC: Aortic cross-clamp, ICU: Intensive care unit, IABP: Intra-aortic balloon pump, ECMO: Extracorporeal membrane oxygenation, TIA: Transient ischemic attack.

Table 3. Echocardiographic results

Variable		Echocardiography (Preoperative)	Echocardiography (Postoperative one yr.)	p
Patients		**n= 30**	**n= 30**	
LVEF (%)	Mean ± SD Range	46.1 ± 5.7 (30-60)	48.1 ± 4.3 (35-60)	0.244
LVEDD (cm)	Mean ± SD Range	5.23 ± 0.65 (4.7-5.5)	5.29 ± 0.64 (4.9-5.6)	0.567
LVESD (cm)	Mean ± SD Range	3.60 ± 0.82 (3.4-4.4)	3.58 ± 0.92 (3.2-4.4)	0.897
LAD (cm)	Mean ± SD Range	4.35 ± 0.4 (4.00-4.40)	4.45 ± 0.4 (4.30-4.70)	0.077
MR	Mean ± SD	1.8 ± 0.4	1.33 ± 0.47	0.034*

LVEF: Left ventricular ejection fraction, LVEDD: Left ventricular end diastole dimension, LVESD: Left ventricular end systolic dimension, LAD: Left atrial dimension, MR: Mitral regurgitation, *: p< 0.05.

DISCUSSION

Ischemic mitral regurgitation (IMR), often referred to as functional mitral regurgitation, is mitral regurgitation that occurs as a result of myocardial ischemia or infarction. By definition, the mitral valve leaflets are structurally normal in IMR. IMR is due to the malcoaptation of the leaflets, and a consequence of acute papillary muscle dysfunction or changes in geometry with left ventricular remodeling[5,6].

Mitral valve insufficiency is a functional problem that occurs in 30% to 50% of patients with myocardial infarction (MI)[7]. Geometric remodeling of the left ventricle displaces the papillary muscles and subsequently affects the chordae tendineae, leading to valvular insufficiency. Echocardiographic evaluation of ischemic MR includes measurement of MR severity, assessment of leaflet and chordal pathology, assessment of papillary muscles, assessment of left ventricular global and regional function, left ventricular ejection fraction, left ventricular wall motion, and dimensions[8].

The majority of these patients have 1+ to 2+ mitral regurgitation, without evidence of heart failure[9-14]. Optimal management of IMR remains elusive. Although concomitant severe (3+ and 4+) IMR should be managed surgically at the time of CABG, the optimal management of mild to moderate (1+, 2+) IMR remains controversial[5].

In patients with acute post-infarction angina with 1+ or 2+ MR, urgent myocardial revascularization is indicated to relieve angina and prevent infarct spread. Thrombolysis or percutaneous coronary intervention is usually performed to prevent the progression of IMR or the development of congestive heart failure[6]. Important factors to consider when intervening for (1+), (2+) IMR include the impact of CABG alone on the progression of IMR, the impact of CABG with and without MV intervention on survival, the additional risk of MV intervention during CABG, and the decision for valve repair or replacement[5].

To assess MR levels on echocardiography, MR is classified as mild(1+), mild to moderate (2+), moderate (3+), and severe (4+). Although mitral valve repair concomitant with CABG may improve functional capacity and MR severity in advanced MR[15], the appropriate surgical approach for mild to moderate MR is still controversial. It has been reported that successful revascularization may also be favorable for mitral valve function in patients with MR, associated with a reduction in left ventricular size, increased mitral valve closure forces, improved papillary-muscle synchrony, and increased myocardial contractility[16].

In this study, we analyzed the changes in mitral valve and left ventricular structures preoperatively and one year postoperatively in patients with mild/moderate IMR who underwent isolated CABG. Due to its efficacy and safety, there are many studies aiming to evaluate the effects and outcomes of adding mitral valve intervention to CABG or performing isolated CABG. Fattouch et al. found that adding mitral valve repair to CABG was associated with efficacy, improvement in the percentage of LVEF in NYHA functional class, and reduction in the degree of mitral regurgitation, left ventricular end-diastolic and end-systolic diameters, pulmonary artery pressure and left atrial size[3].

Those who advocate the conservative approach of revascularization alone without treatment of the IMR argue that revascularization will improve regional wall motion abnormalities, and papillary muscle function, and potentially correct IMR[11,17,18].

Moreover, some data suggest that survival and long-term functional status are not improved with concomitant MV interventions[19,20]. Previous studies suggest that CABG alone improves IMR grade and functional status[11,17,18].

Kim et al. found similar five-year survival with combined mitral valve repair and revascularization compared to revascularization alone in patients with MR[21]. In addition, a 2009 meta-analysis reported no survival benefit of adding mitral valve intervention to CABG[22]. In another study, Sun et al. stated that the outcomes of patients with moderate MR are associated with LVEF and post-infarction timing, and that isolated CABG is an effective approach in patients with good LVEF and early post-infarction intervention[23].

In this retrospective analysis, 30 patients were evaluated preoperatively and at 12 months postoperatively. There was no statistically significant difference between the preoperative EF, LVEF, LVEDD, LVESD and LAD values and the postoperative 12-month values. This is a positive result in terms of complications related to prolonged cardiopulmonary bypass and aortic clamping times due to the addition of mitral valve repair to CABG. In addition, the preoperative MR grade of the patients was found to have regressed according to the 12-month postoperative examination. This suggests that the approach applied in patients with mild to moderate MR is correct.

CONCLUSION

In conclusion, our approach showed that patients with mild to moderate MR are likely to benefit from isolated CABG and is in line with similar studies. We believe that isolated CABG may improve mitral regurgitation in cases of mild to moderate MR. However, the limiting factors of this study include its single-center and retrospective nature, potentially impacting generalizability.

There are no randomized trials showing a survival benefit with mitral valve repair/replacement in IMR. The similarity of outcomes between surgical and medical treatment suggests that the pathophysiology of IMR and left ventricular remodeling needs to be better understood.

Mild (1+) IMR should be left alone, unless: (1) preoperative signs and symptoms are suggestive of periods of more severe mitral regurgitation; and (2) intraoperative TEE demonstrate anatomical findings requiring MVR (i.e., significant annular dilatation, leaflet tenting)[5]. We believe a randomized trial investigating the clinical outcomes and survival benefits of mitral valve surgery for IMR is warranted.

Ethics Committee Approval: This study was approved by the Kocaeli University Clinical Research Ethics Committee (Decision no: 25/13, Date: 30.12.2014).

Informed Consent: This is retrospective study, we could not obtain written informed consent from the participants.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - DD; Analysis/Interpretation - HT; Data Collection - SG; Writing - DD; Critical Revision - KTB; Final Approval - DD; Statistical Analysis -SG; Overall Responsibility - DD.

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REFERENCES

1. Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, et al. Heart failure and death after myocardial infarction in thecommunity: The emerging role of mitral regurgitation. Circulation 2005;111(3):295-301. https://doi.org/10.1161/01.CIR.0000151097.30779.04
2. Penicka M, Linkova H, Lang O, Fojt R, Kocka V, Vanderheyden M, et al. Predictors of improvement of unrepaired moderate ischemic mitral regurgitation in patients under going elective isolated coronary artery bypass graftsurgery. Circulation 2009;120(15):1474-81. https://doi.org/10.1161/CIRCULATIONAHA.108.842104
3. Fattouch K, Guccione F, Sampognaro R, Panzarella G, Corrado E, Navarra E, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: A randomized trial. J Thorac Cardiovasc Surg 2009;138(2):278-85. https://doi.org/10.1016/j.jtcvs.2008.11.010
4. Chan KM, Punjabi PP, Flather M, Wage R, Symmonds K, Roussin I, et al; RIME Investigators. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: Final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. Circulation 2012;126(21):2502-10. https://doi.org/10.1161/CIRCULATIONAHA.112.143818
5. Cohn LH. Cardiac surgery in the adult 4th edition, McGraw Hill Professional 2012;Ischemic Mitral Regurgitation 2012;629-47.
6. Bates ER, Califf RM, Stack RS, Aronson L, George BS, Candela RJ, et al. Thrombolys is and angioplasty in myocardial infarction (TAMI-1) trial: Influence of infarct location on arterial patency, left ventricular function and mortality. J Am Coll Cardiol 1989;13(1):12-8. https://doi.org/10.1016/0735-1097(89)90542-1
7. Mihos CG, Santana O. Mitral valve repair for ischemic mitral regurgitation: Lessons from the cardiothoracic surgical trials network randomized study. J ThoracDis 2016;8(1):E94-9.
8. Dudzinski DM, Hung J. Echocardiographic assessment of ischemic mitral regurgitation. Cardiovasc Ultrasound 2014;12:46. https://doi.org/10.1186/1476-7120-12-46
9. Hickey MS, Smith LR, Muhlbaier LH, Harrell FE Jr, Reves JG, Hinohara T, et al. Current prognosis of ischemic mitral regurgitation. Implications for future management. Circulation 1988;78(3 Pt 2):I51-9.
10. Frantz E, Weininger F, Oswald H, Fleck E. Predictors for mitral regurgitation in coronary artery disease, in Vetter HO, Hetzer R, Schmutzler H (eds). Ischemic Mitral Incompetence. Springer;New York 1991;57. https://doi.org/10.1007/978-3-662-08027-6_5
11. Balu V, Hershowitz S, Zaki Masud AR, Bhayana JN, Dean DC. Mitral regurgitation in coronary artery disease. Chest 1982;81(5):550-5. https://doi.org/10.1378/chest.81.5.550
12. Pinson CW, Cobanoglu A, Metzdorff MT, Grunkemeier GL, Kay PH, Starr A, et al. Late surgical results for ischemic mitral regurgitation. Role of wall motion score and severity of regurgitation. J Thorac Cardiovasc Surg 1984;88(5 Pt 1):663-72. https://doi.org/10.1016/S0022-5223(19)35434-0
13. Connolly MW, Gelbfish JS, Jacobowitz IJ, Rose DM, Mendelsohn A, Cappabianca PM, et al. Surgical results for mitral regurgitation from coronary artery disease. J Thorac Cardiovasc Surg 1986;91(3):379-88. https://doi.org/10.1016/S0022-5223(19)36053-2

14. Karp RB, Mills N, Edmunds LH Jr. Coronary artery bypass grafting in the presence of valvular disease. Circulation 1989;79(6 Pt 2):I182-4.

15. Varma PK, Krishna N, Jose RL, Madkaiker AN. Ischemic mitral regurgitation. AnnCardAnaesth 2017;20(4):432-9. https://doi.org/10.4103/aca.ACA_58_17

16. Meluzín J, Cerný J, Frélich M, Stetka F, Spinarová L, Popelová J, et al. Prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients with coronary artery disease and leftventricular dysfunction. Investigators of this Multicenter Study. J Am Coll Cardiol 1998;32(4):912-20. https://doi.org/10.1016/S0735-1097(98)00324-6

17. Christenson JT, Simonet F, Bloch A, Maurice J, Velebit V, Schmuziger M. Should a mild to moderate ischemic mitral valve regurgitation in patients with poor left ventricular function be repaired or not? J Heart Valve Dis 1995;4(5):484-8; discussion 8-9.

18. Tolis GA Jr, Korkolis DP, Kopf GS, Elefteriades JA. Revascularization alone (without mitral valve repair) suffices in patients with advanced ischemic cardiomyopathy and mild-to-moderate mitral regurgitation. Ann Thorac Surg 2002;74(5):1476-80; discussion 80-1. https://doi.org/10.1016/S0003-4975(02)03927-9

19. Talwalkar NG, Earle NR, Earle EA, Lawrie GM. Mitral valve repair in patients with low left ventricular ejection fractions: Early and late results. Chest 2004;126(3):709-15. https://doi.org/10.1378/chest.126.3.709

20. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol 2007;49(22):2191-201. https://doi.org/10.1016/j.jacc.2007.02.043

21. Kim YH, Czer LS, Soukiasian HJ, De Robertis M, Magliato KE, Blanche C, et al. Ischemic mitral regurgitation: Revascularization alone versus revascularization and mitral valve repair. Ann Thorac Surg 2005;79(6):1895-901. https://doi.org/10.1016/j.athoracsur.2004.11.005

22. Benedetto U, Melina G, Roscitano A, Fiorani B, Capuano F, Sclafani G, et al. Does combined mitral valve surgery improve survival when compared to revascularization alone in patients with ischemic mitral regurgitation? A meta-analysis on 2479 patients. J CardiovascMed (Hagerstown) 2009;10(2):109-14. https://doi.org/10.2459/JCM.0b013e32831c84b0

23. Sun X, Huang J, Shi M, Huang G, Pang L, Wang Y. Predictors of moderate ischemic mitral regurgitation improvement after off-pump coronary artery bypass. J Thorac CardiovascSurg 2015;149(6):1606-12. https://doi.org/10.1016/j.jtcvs.2015.02.047

26. Cilt Dizini
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26. Cilt Dizini
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2023 yılında Koşuyolu Kalp Dergisinin makalelerini değerlendirme görevini üstlenen, aşağıda isimleri yer alan değerli meslektaşlarıma teşekkür ederim.

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