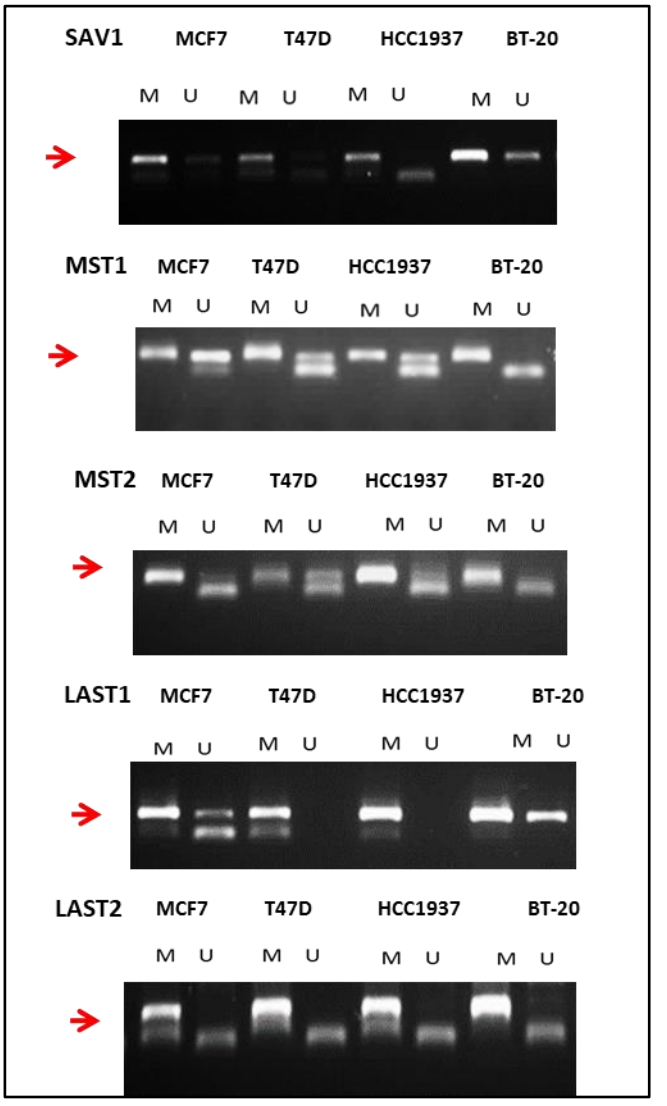
MSD
Medical Science & Discovery



hippo pathway methylated (M) and unmethylated (U) candidate genes. SAV1, MST1/2, and LATS1/2

Medical Science and Discovery (**http://www.medscidiscovery.com**) is an international open access, peer-reviewed scientific research journal that provides rapid publication of articles in all disciplines of human health, clinical and basic medical sciences such as Biophysics, Biochemistry, Histology, Physiology, Genetics, Pathology, Toxicology, Anatomical Sciences, Pharmacology, Embryology, Internal and Surgical Medicine.

The policy of top priority of MSD is to put forward and highlight medical innovations and inspiring patents.

MSD offers an exceptionally fast publication schedule including prompt peer-review by the experts in the field and immediate publication upon acceptance. The editorial board aims at reviewing the submitted articles as fast as possible and promptly including them in the forthcoming issues.

This journal is published under ethical publishing policy of international scientific Bioethics and publication rules.

MSD supports the Open Access Initiative. Abstracts and full texts (HTML and PDF format) of all articles published by MSD are freely accessible to everyone immediately upon publication.

Indexed Databases: Chemical Abstracts (CAS), Index Copernicus, Open Air, ULRICHS Database, ProQuest, Advanced Science Index, Turkish Citation Index, Research Bible, Scholar Google, NLM Catalog

Medical Science and Discovery is an international open access, peer-reviewed scientific research journal.

ISSN: 2148-6832 (Print)

E-ISSN: 2148-6832 (Online)

Category: Multi Disciplinary Health Science Journal

Abbreviated key title: Med. Sci. Discov.

Frequency: Monthly

Review System: Double Blind Peer Review

Circulation: Globally, Online, Printed

Article Processing Charge (APC): Free

Licensing: CC-BY-NC 4.0 International License Environmental

Editor-in-Chief: Assoc. Prof. Dr. Dr. Ahmad Rajabzadeh, Anatomical Department of lorestan, University of Medical Sciences, Tabriz, Iran

Established: 30.04.2014

Web address: www.medscidiscovery.com

E-mail : editor [at] medscidiscovery.com

Phone : +44 776 090 2125

Design and preparation of PDFs, Language editing, Web site design, Graphical design Services of international Journal of Medical Science and Discovery has been contracted with Lycia Press LONDON, UK (as Publisher), by the MSD Board of Directors

Publisher: Lycia Press London UK.

Address: 3rd Floor 86 - 90 Paul Street, EC2A 4NE, London, UK

Web address: www.lycians.com

Phone : +44 776 090 2125

E-mail : office [at] lycians.com

E-mail : info [at] lycians.com

Honorary Editors

We are very grateful to our honorary editors for their contribution to science

Editor in Chief

Deputy Editors

Editorial Board Members

Lycia Press Editorial Office

Medical Science and Discovery, February 2022, Vol.9, No.2

Contents

MSD

Medical Science and Discovery
ISSN: 2148-6832

Bronchoscopy Basics: Current approaches-A literature review

Naved Hasan[1]*

1 King Abdullah Medical City, Muzdalifah Road, Al Mashaer, Makkah, Saudi Arabia

*** Corresponding Author:** Naved Hasan **E-mail:** naved911@hotmail.com

ABSTRACT

Objective: This review article aims to understand the basic airway anatomy, bronchoscopy in high risk patients, premedication in bronchoscopy and performing the procedure in patients on anticoagulation. Basic bronchoscopy is the procedure done by pulmonologists, intensivists, thoracic surgery, and anesthesiologists. After a literature search from several databases, including PubMed, Google Scholar, Medline, Science Direct, Cochrane Library, Update etc., I found several categories of high-risk patients based on clinical history, Mallampati score, and 3-3-2 Rule. These include patients with pulmonary hypertension, renal failure, COPD, asthma, obesity, patients on anticoagulation. I searched the literature to find multiple expert guidelines and recommendations that suggested minimizing the risk of complications in these high-risk patients, including premedication.

Keywords: basic bronchoscopy, high risk, Mallampati score, guidelines, recommendations

INTRODUCTION

Physical Status Classification

American Society of Anesthesiologists (ASA) has classified the airway risk based on the physical status:

I- A normal healthy patient, e.g. with inguinal hernia

II- Mild systemic disease with no impact on the cardiorespiratory system. Controlled diseases, e.g. hypertension, diabetes without end-organ damage.

III- Moderately severe-COPD, bronchial asthma, lung cancer.

IV- Advanced and severe systemic disease-COPD including oxygen-dependent, advanced CHF, advanced Ca lung.

Based on the classification, numerous patients fall into groups II and IV.

Mallampati Score:

It estimates the difficulty in intubation based on the degree of visualization of soft palate, uvula, fauces, and tonsillar pillars. It is classified into 4 classes depending on the severity. Class I is the mildest and Class IV is the most severe.

Scoring has been used to predict the risk of up to 13 complications.

The most important are bronchospasm and oxygen desaturation.

Bronchospasm risk with Mallampati I-III is between 7.5-10.8. The risk peaked at 25.5 with Mallampati IV. (Respiration 2016; 92:158-165).

Oxygen desaturation risk is 36.6 in Mallampati I, and 62 in Mallampati IV.

Conscious sedation is an additional risk.

Review Article

Received 14-02-2022

Accepted 25-02-2022

Available Online: 26-02-2022

Published 28-02-2022

http://dx.doi.org/10.36472/msd.v9i2.693

3-3-2 Rule

Intubations during bronchoscopy can be difficult as it is likely to be swelling and spasm in the airways. As pulmonologists and intensivists often use fentanyl and midazolam for conscious sedation, no anesthesiologist may be present.

The 3-3-2 rule is a simple measurement to assess the likelihood of difficult intubation.

3- A measurement of 3 fingers (7 cm) between upper and lower teeth to assess good mouth opening.

3- A measurement of 3 fingers from chin to the hyoid bone. If > 3 cm, suggests distance to the posterior pharynx, which will allow easy insertion of the laryngoscope.

2- A measurement of 2 fingers from the base of the mandible to the thyroid notch will indicate the relation of the larynx to the base of the tongue.

Few have been done, but it is a quick and simple method to evaluate the patient's airway.

Bronchoscopy in pulmonary hypertension (PH)

The main issue is that we rarely know the status of pulmonary hypertension in most patients.

The majority of the experts believe that bronchoscopic inspection of the airway is a safe procedure, but TBBx is not.

An ACCP Survey was conducted in a CHEST meeting in 2001 to detect the comfort level of doing bronchoscopy in PH patients. 29% - absolute contraindication, 58%- relative contraindication, 13%- no contraindication, 40%- MPAP>40 is a contraindication. (1)

It is important to be aware of the potential predisposing conditions related to pulmonary hypertension.

Known autoimmune diseases, OHS/ sleep apnea, chronic pulmonary diseases, even COPD

Do 2D Echocardiogram, look for RVSP. If > 40-45 mm Hg, be careful and follow stringent indications. (2)

Bronchoscopy can cause bleeding, which may be minor or major. (3,4)

Minor bleeding usually stops spontaneously or requires local epinephrine or cold saline.

Major bleeding is one that may require balloon tamponade, embolization, surgical intervention, and blood transfusion.

No significant major bleeding occurs with mild to moderate pulmonary hypertension. There is, however, an increased risk of post-procedure prolonged intubation in these patients. There is no consensus in these patients and data is limited.

If PH is > 40-45, one should be very careful, especially when doing transbronchial lung biopsy (TBLBx).

Bronchoscopy in Renal Insufficiency

A study done in 2012 showed procedure-related hemorrhage most commonly occurred in patients with renal insufficiency with an unadjusted odds ratio of 2.94, adjusted odds ratio of 2.85, and $P < 0.0001$. (5)

It is recommended that if blood urea nitrogen(BUN) >30 mm/dl or serum creatinine > 2mm/dl, then desmopressin (DDAVP) should be given 30 minutes before the biopsy or needle aspiration.

Bronchoscopy in COPD

A study was published in 2017, which showed minor and major complications when bronchoscopy was done in COPD patients. (6)

Minor complications included transient desaturation, bronchospasm, epistaxis, and transient hypotension.

Major complications included respiratory failure, pneumothorax, and hemoptysis.

The most significant complication was respiratory failure, which was 4 times more common.

No cut-off for FEV1 or amount of inhaled oxygen has been shown in studies regarding when to do or not to do a bronchoscopy. It depends on individual comfort level. However, if a patient is on 6-10 liters of oxygen, one should be very careful and have all the preparations. The presence of anesthesia can also be helpful.

A study published in CHEST showed that premedication with inhaled short-acting beta-agonist is not recommended. (7)

Bronchoscopy in Bronchial Asthma

Bronchoscopy in severe asthma is usually well tolerated with proper precautions. (8,9,10)

Beta 2 agonists are recommended pre-procedure with or without anticholinergics.

No cut-off for FEV1 has been recommended.

Bronchoscopy in Obesity

A study in 2016 looked at the percentages of complications according to various indices of obesity. (11)

Early termination of the procedure is seen more in obese patients than in non-obese, 6.41 vs 2.78

There are a lot of other issues in these patients. A higher Mallampati score in obese patients has a significantly higher percentage of transient oxygen desaturation and bronchospasm.

If these patients have a triple syndrome with obesity, obstructive sleep apnea (OSA), and COPD, one should be well prepared and ideally, anesthesia should be available immediately if a need arises to intubate these patients.

Obese patients with OSA have a much higher percentage of termination of procedure as compared to obese patients without OSA. 2.5 vs 15.8, p=0.0002. They also have a higher percentage of pneumothorax 0.4 vs 5.3.

Based on the current literature, the following is recommended:

Pre-procedure assessment of hypercapnia, anticipate the difficult airway, consider CPAP during bronchoscopy, consider anesthesia support, and consider pre-emptive awake intubation.

Premedication in Bronchoscopy

Routine use of anticholinergics like atropine and glycopyrrolate is not recommended anymore. (12) They may reduce secretions but no reduction in cough, discomfort, desaturation, and procedure time. They have even been shown to be harmful and may contribute to hemodynamic instability.

Topical lidocaine may decrease the cough and the total dose of sedation. Either 1% or 2% should be used. Both have similar efficacy. A 4% concentration is not recommended as it may get absorbed and cause toxicity, including methemoglobinemia. ACCP and Thorax guidelines recommend 7mg/kg body weight to minimize the risk of complications. (13,14,15)

Nebulized lidocaine, in addition to topical lidocaine, has no benefit.

Bronchoscopy in Anticoagulated Patients (16,17,18)

Discontinue clopidogrel (Plavix) 5-7 days before the procedure, especially if a transbronchial biopsy is planned.

Aspirin should be continued.

Warfarin should be stopped 5 days prior to the procedure or based on current INR if < 1.5 and resume in 12-24 h.

LMWH should be held for 24 h (prophylactic for 12 h).

Unfractionated heparin should be held 4-6 h before the procedure.

In DOACs, stop 1-2 days before the procedure. If they have renal insufficiency with GFR < 50, then as a general principle, it should be 2-3 days. If renal failure is end-stage, it may be longer than 3 days.

CONCLUSION

Basic bronchoscopy is a safe procedure. However, in high-risk patients, several guidelines and recommendations have been proposed to minimize the complications. The majority of the patients are in ASA Class 3 or 4. MPAP > 40 is high-risk for bleeding, especially with TBBx. BUN > 30 mg/dl and creatinine > 2 mg/dl is high risk of bleeding. Consider DDAVP. No benefit of short-acting beta agonist in COPD premedication. Short-acting beta-agonist nebulization can be used in bronchial asthma. In Obese patients with BMI. 30, anesthesia support should be considered especially if they have sleep apnea. Lidocaine dose for bronchoscopy is 7 mg/kg. No benefit to adding nebulization.

Abbreviations:

COPD: Chronic Obstructive Pulmonary Disease

TBBx: Trans-bronchial Biopsy

CPAP: Continuous Positive Airway Pressure

MPAP: Mean Pulmonary Artery Pressure

BUN: Blood Urea Nitrogen

GFR: Glomerular Filtration Rate

FEV1: Forced Expiratory Volume in 1 second

DOAC: Direct Acting Oral Anticoagulants

Author Contributions: NH; Search the literature, Data collecttion, Data the analysis, manuscript Preperation, Revisions.

Acknowledgments: None

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. Wahidi MM, Rocha AT, Hollingsworth JW, Govert JA, Feller-Kopman D, Ernst A. Contraindications and safety of transbronchial lung biopsy via flexible bronchoscopy. A survey of pulmonologists and review of the literature. Respiration. 2005 May-Jun;72(3):285-95. doi: 10.1159/000085370. PMID: 15942298.

2. Diaz-Fuentes G, Bajantri B, Adrish M: Safety of Bronchoscopy in Patients with Echocardiographic Evidence of Pulmonary Hypertension. Respiration 2016;92:182-187. doi: 10.1159/000448848

3. Lashari BH, Asai M, Alswealmeen W, Hodge C, Ripley-Hager C, Patel RK. Pulmonary Hypertension and Transbronchial Lung Biopsy: Does It Increase the Risk of Hemorrhage? Cureus. 2020 Jul 9;12(7):e9084. doi: 10.7759/cureus.9084. PMID: 32789034; PMCID: PMC7417037.

4. Diaz-Guzman E, Vadi S, Minai OA, Gildea TR, Mehta AC. Safety of diagnostic bronchoscopy in patients with pulmonary hypertension. Respiration. 2009;77(3):292-7. doi: 10.1159/000197465. Epub 2009 Jan 28. PMID: 19174601.

5. Melissa H. Turkey, Renda Soylemez Wiener. Population-based estimates of transbronchial lung biopsy utilization and complications. Respir Med. 2012 Nov; 106(11): 1559-1565. DOI:https://doi.org/10.1016/j.rmed.2012.08.008

6. Bellinger, Christina R. MD*; Khan, Irtaza MD†; Chatterjee, et.al. Bronchoscopy Safety in Patients With Chronic Obstructive Lung Disease, Journal of Bronchology & Interventional Pulmonology: April 2017 - Volume 24 - Issue 2 - p 98-103. doi: 10.1097/LBR.0000000000000333

7. Stolz D, Pollak V, Chhajed PN, Gysin C, Pflimlin E, Tamm M. A randomized, placebo-controlled trial of bronchodilators for bronchoscopy in patients with COPD. Chest. 2007 Mar;131(3):765-772. doi: 10.1378/chest.06-2308. PMID: 17356091.

8. Moore WC, Evans MD, Bleecker ER, et al. Safety of investigative bronchoscopy in the Severe Asthma Research Program. J Allergy Clin Immunol. 2011;128(2):328-336.e3. doi:10.1016/j.jaci.2011.02.042

9. Van Vyve T, Chanez P, Bousquet J, Lacoste JY, Michel FB, Godard P. Safety of bronchoalveolar lavage and bronchial biopsies in patients with asthma of variable severity. Am Rev Respir Dis. 1992 Jul;146(1):116-21. doi: 10.1164/ajrccm/146.1.116. PMID: 1626794.

10. Djukanović R, Wilson JW, Lai CK, Holgate ST, Howarth PH. The safety aspects of fiberoptic bronchoscopy, bronchoalveolar lavage, and endobronchial biopsy in asthma. Am Rev Respir Dis. 1991 Apr;143(4 Pt 1):772-7. doi: 10.1164/ajrccm/143.4_Pt_1.772. PMID: 2008989.

11. Khan I, Chatterjee AB, Bellinger CR, Haponik E. Sedation for Bronchoscopy and Complications in Obese Patients. Respiration. 2016;92(3):158-65. doi: 10.1159/000448250. Epub 2016 Sep 6. PMID: 27595264.

12. Malik JA, Gupta D, Agarwal AN, Jindal SK. Anticholinergic premedication for flexible bronchoscopy: a randomized, double-blind, placebo-controlled study of atropine and glycopyrrolate. Chest. 2009 Aug;136(2):347-354. doi: 10.1378/chest.08-2924. Epub 2009 Mar 24. PMID: 19318667.

13. Webb AR, Woodhead MA, Dalton HR, Grigg JA, Millard FJ. Topical nasal anesthesia for fibreoptic bronchoscopy: patients' preference for lignocaine gel. Thorax. 1989;44(8):674-675. doi:10.1136/thx.44.8.674

14. Antoniades N, Worsnop C. Topical lidocaine through the bronchoscope reduces cough rate during bronchoscopy. Respirology. 2009 Aug;14(6):873-6. doi: 10.1111/j.1440-1843.2009.01587.x. PMID: 19703068.

15. Wahidi MM, Jain P, Jantz M, Lee P, Mackensen GB, Barbour SY, Lamb C, Silvestri GA. American College of Chest Physicians consensus statement on the use of topical anesthesia, analgesia, and sedation during flexible bronchoscopy in adult patients. Chest. 2011 Nov;140(5):1342-1350. doi: 10.1378/chest.10-3361. PMID: 22045879.

16. Ernst A, Eberhardt R, Wahidi M, Becker HD, Herth FJ. Effect of routine clopidogrel use on bleeding complications after transbronchial biopsy in humans. Chest. 2006 Mar;129(3):734-7. doi: 10.1378/chest.129.3.734. PMID: 16537875.

17. Du Rand IA, Blaikley J, Booton R, et al British Thoracic Society guideline for diagnostic flexible bronchoscopy in adults: accredited by NICE Thorax 2013;68:i1-i44.

18. Lange CM, Fichtlscherer S, Miesbach W, Zeuzem S, Albert J. The Periprocedural Management of Anticoagulation and Platelet Aggregation Inhibitors in Endoscopic Interventions. Dtsch Arztebl Int. 2016;113(8):129-135. doi:10.3238/arztebl.2016.0129

MSD

Medical Science and Discovery
ISSN: 2148-6832

The Evolution of Cholecystitis: A Global Productivity and Publication Trends: Bibliometric Analysis of Cholecystitis

Murat Baki Yıldırım[1], Murat Bulut Özkan[1]*

1 Hitit University, Faculty of Medicine, Department of Surgery, Çorum, TR

*** Corresponding Author:** Murat Bulut Özkan **E-mail:** bulutozkan@gmail.com

ABSTRACT

Objective: There is still no bibliometric study on Cholecystitis, although the literature has an increasing number of global studies. This study aims to analyse the scientific articles published on Cholecystitis between 1980 and 2020 using statistical methods.

Material and Methods: Articles on Cholecystitis published between 1980 and 2020 were downloaded using the Web of Science (WoS) database and analysed using statistical and bibliometric methods. Spearman correlation coefficient was used for correlation analyses. Non-linear (exponential model) regression analysis was used to predict the number of publications in the coming years. Keyword network visualisation maps were used to identify trend topics.

Results: A total of 5052 publications were found. 3174 (62.8%) of these publications, were articles. The top 2 countries that contributed most to the literature were the USA (788, 24.8%) and Japan (303, 9.5%). The most active top 3 institutions were Teikyo University (n=35), Washington University (35), and Seoul National University (27). The top 3 journals with the highest number of publications were Khirurgiya (n=124), American Surgeon (71), and Vestnik Khirurgii Imeni II Grekova (69). According to the average number of citations per article, the most influential journals were Annals of Surgery (Citation: 87), Radiology (61.6), and Journal of Hepato-Biliary-Pancreatic Surgery (56.9), respectively.

Conclusion: This comprehensive study on Cholecystitis, which has increased the number of articles in recent years, presented summary information of 3174 articles. Results can be said that the trend topics in cholecystitis studies in recent years are Tokyo guidelines, C-reactive protein, gallbladder drainage, emergency surgery, emergency cholecystectomy, cystic duct, choledocholithiasis, inflammation, acute cholecystitis, delayed laparoscopic cholecystectomy, and percutaneous transhepatic gallbladder drainage/aspiration. This article may be a useful resource for clinicians and scientists on global outputs of cholecystitis.

Keywords: Bibliometric analysis, Cholecystitis, cholecystectomy, gallbladder drainage, trends

Research Article

Received 07-02-2022

Accepted 17-02-2022

Available Online: 20-02-2022

Published 28-02-2022

INTRODUCTION

Acute Cholecystitis is an acute inflammatory disease of the gallbladder. It can often be attributed to gallstones; however, many associated factors including ischemia, motility disorders, direct chemical injury, infections with microorganisms, protozoa, and parasites, collagen disease, and allergic reaction (1). One of the important conditions causing abdominal pain complaints is acute Cholecystitis, accounting for 3-10% of all patients with abdominal pain. In most cases, gallstones are the cause of acute Cholecystitis. While, Cholecystolithiasis accounts for 90-95% of all causes of acute Cholecystitis, acalculous Cholecystitis accounts for the remaining 5-10% (1).

An International Consensus Meeting on the Management of Acute Cholecystitis and Cholangitis was held, and the first guideline TG07 was published in 2007 (1,2). Afterward, TG07 was revised, and Tokyo 2013 (TG13) and Tokyo 2018 (TG18) guidelines were published in order to use a common language for the diagnosis and treatment of Cholecystitis (3,5).

http://dx.doi.org/10.36472/msd.v9i2.687

The TG18/TG13 guideline defined 3 main titles of diagnostic criteria for acute Cholecystitis as follows: local signs of inflammation (Murphy's sign, Right upper quadrant mass/pain/tenderness), systemic signs of inflammation (Fever, elevated CRP, elevated WBC count), and imaging findings (3,5). The generally accepted imaging findings of acute Cholecystitis include increased gallbladder wall thickness (≥4 mm), gallbladder enlargement (long axis ≥8 cm, short axis ≥4 cm), gallstones or biliary sludge (debris), fluid accumulation around the gallbladder, and linear shadows in the adipose tissue around the gallbladder (6). One item in the local signs of inflammation and one item in the systemic signs of inflammation indicate a suspicious diagnosis, while one item in the local signs of inflammation, systemic signs of inflammation, and imaging findings indicate the definitive diagnosis (3,5).

While the mortality rate is 0-10% in patients with acute Cholecystitis, it is as high as 23-40% in patients with postoperative Cholecystitis and Cholecystitis without stones (1). Elderly patients (75 years and older) tend to have a higher mortality rate than younger patients, and the presence of a comorbid disease such as diabetes mellitus may increase the risk of death (7,8).

Bibliometric analysis is the analysis of scientific outputs using statistical methods (9). In parallel with the increasing number of publications in the literature, studies on many important medical subjects have been carried out based on statistical and bibliometric analyses, especially in recent years (9-14). Thanks to bibliometric research, researchers can dominate the literature by reading the abstract results obtained as a result of the analysis of many studies on a subject in a short time (10,11). Moreover, these studies, which were revealed using comprehensive statistical methods, also offer researchers ideas about new studies that they can design by showing past and current trends (12,13). Bibliometric studies can also demonstrate the general research trend of a subject in the world by revealing international collaborations. Thanks to bibliometric research, the most active authors, institutions, journals, and the most cited influential studies on a subject are revealed (9-14). Although the number of global studies on Cholecystitis, which has an important place among patients presenting to the emergency department, has increased in recent years, there is still no bibliometric study in the literature. The aim of this study was to analyse scientific articles published on Cholecystitis between 1980 and 2020 using statistical and bibliometric methods. As a result of the analyses, it was aimed to identify the most influential studies, authors, journals, institutions, and countries on Cholecystitis, to reveal cooperation between countries, to reveal past and current trend issues, and to summarise Cholecystitis in a holistic manner.

MATERIAL and METHODS

Web of Science (WoS) database (by Clarivate Analytics) was used for literature review. In WoS, Cholecystitis was used as the search keyword. The publication search was done only in the "title" section of the studies. All articles with Cholecystitis in the title were obtained by this search method and these articles were downloaded from the WoS database. The search process was determined as 1980-2020 (access date: 15.05.2021). Reproducibility codes for researchers to access similar documents (search findings may vary depending on different access dates): (title: (Cholecystitis) Timespan: 1980-2020. Indexes: SCI-Expanded, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI).

VOSviewer (Version 1.6.16, Leiden University's Center for Science and Technology Studies) package program was used for bibliometric network visualisations (15). The website (https://app.datawrapper.de) was used for world map drawing.

Statistical analyses were performed with the SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA, License: Hitit University) program. The normal distribution of data was tested with the Kolmogorov-Smirnov and Shapiro-Wilk tests. In order to determine whether there is an effect of economic power on world publication productivity on Cholecystitis, the Spearman correlation coefficient was calculated in accordance with the data normal distribution between the number of articles produced by world countries and some economic development indicators (Gross Domestic Product (GDP), Gross Domestic Product per capita (GDP per capita)) of world countries (data obtained from the world bank: 16). Nonlinear regression analysis (exponential model) was used to estimate the number of publications in the coming years. R2 value was used to evaluate model success in regression analysis. The statistically significant difference limit was accepted as $P<0.05$.

RESULTS

As a result of the literature review, total 5052 publications on Cholecystitis were published between 1980 and 2020 (WoS database). The distribution of publications; article (3174, 62.8%), meeting abstract (815, 16.1%), letter (372, 7.3%), editorial material (277, 5.4%), review (180, 3.5%), note (137, 2.7%), proceedings paper (131, 2.5%), and the remaining were in other publication types (discussion, correction, early access, book chapter, news item, correction addition, reprint, retraction). Bibliometric analyses were carried out with 3174 articles out of a total of 5052 publications. Of these articles, 79.8% (2534) were English, 10% (349) were Russian, 3.2% (104) were German, 2.9% (95) were French, 2.1% (67) were

Spanish, and the remaining were published in other languages (Turkish Italian, Korean, Portuguese, Hungarian, Chinese, Dutch, Icelandic, Japanese, Slovenian, and Ukrainian). The h-index of the 3174 articles was 83, with an average citation per article of 13.66 and a sum of times cited of 43362 (without self-citations: 26587).

Evolution and Future Trend of Publications

The distribution of the number of published articles by years is shown in **Figure 1** together with a line chart. The results of nonlinear exponential model regression analysis used to estimate the number of articles that can be published in 2021 and later are also shown in **Figure 1**. The compatibility of the exponential model with the data (R2=99.7) was quite successful with 99.7%. Based on the exponential model results, it was estimated that 191 (Confidence Interval%: 164-217) articles would be published in 2021 and 244 (CI%: 189-300) articles would be published in 2025 (**Figure 1**).

Active Countries on Cholecystitis

The distribution of the number of articles by world countries is shown in **Figure 2**. According to the number of articles, the first 20 countries with the highest number of articles were the USA (788, 24.8%), Japan (303, 9.5%), Russia+USSR (292, 9.2%), South Korea (142, 4.4%), Germany+German Federal Republic (142, 4.4%), UK (140, 4.4%), China (134, 4.2%), France (124, 3.9%), Turkey (115, 3.6%), Spain (105, 3.3%), Italy (94, 2.9%), India (91, 2.8%), Taiwan (90, 2.8%), Australia (70, 2.2%), Israel (70, 2.2%), Canada (54, 1.7%), Sweden (54, 1.7%), Netherlands (47, 1.4%), Greece (40, 1.2%), and Belgium (38, 1.1%).

Cluster analysis was performed among 38 countries that produced at least 5 articles from 96 countries that produced publications on Cholecystitis and had international cooperation among their authors, and 7 different clusters related to international cooperation were created based on the results of the analysis (Cluster 1: Canada, Denmark, England, Germany, Ireland, Italy, Portugal, Romania, Spain, Switzerland, Cluster 2: Argentina, New Zealand, China, Philippines, Singapore, South Korea, Thailand, Cluster 3: Brazil, Chile, Finland, Israel, Pakistan, Turkey, USA, Cluster 4: Egypt, India, Japan, Saudi Arabia, Scotland, Cluster 5: Greece, Malaysia, South Africa, Taiwan, Cluster 6: Belgium, France, Netherlands, Cluster 7: Australia, Jordan).

Correlation Analysis on Cholecystitis

There was a statistically positive and highly significant correlation between the number of articles produced by countries on Cholecystitis and GDP, and GDP per capita ($r=0.735$, $p<0.001$; $r=0.703$, p0.001).

Active Authors on Cholecystitis

The 13 most active authors who produced more than 15 articles on Cholecystitis were Yoshida M. (34), Takada T. (33), Miura F. (29), Mayumi T. (27), Pitt HA. (23), Strasberg SM. (23), Gouma DJ. (19), Itoi T. (19), Yamashita Y. (19), Fan ST. (18), Gomi H. (18), Yokoe M. (17), and Higuchi R. (16), respectively.

Active Institutions on Cholecystitis

The 20 most active universities that produced more than 15 articles on Cholecystitis were Teikyo University (35), Washington University (35), Seoul National University (27), University Ulsan (26), Harvard University (23), University Texas (23), Tokyo Womens Medical University (22), University California San Francisco (22), University of Southern California (22), Tel Aviv University (19), University Hong Kong (19), Yonsei University (19), Chinese University Hong Kong (18), International University of Health and Welfare (18), Massachusetts Gen Hospital (18), University of Occupational & Environmental Health (18), Sechenov First Moscow State Medical University (17), Toho University (17), Ogaki Municipal Hospital (16), and University Tokyo (16).

Active Journals on Cholecystitis

A total of 3174 articles on Cholecystitis were published in 787 different journals. Among these journals, the first 66 most active journals producing 10 or more articles, the total number of citations received by the journals, and the average number of citations per article are presented in **Table 1**. The citation network visualisation map for these journals is presented in **Figure 3**.

Citation Analysis on Cholecystitis

Among the 3174 articles published between 1980 and 2020, the top 20 most cited articles (articles with more than 160 citations) according to the total number of citations are presented in **Table 2**. The last column of Table 2 shows the average number of citations per year.

Co-citation Analysis on Cholecystitis

There were 25015 studies cited in the references section of all 3174 articles analysed. Among these studies, the top 8 studies that received the highest number of co-citations (more than 100 citations) were the studies of Lo et al. (1998) (Number of co-citations, NC: 185), Lai et al. (1998) (NC: 145), Hirota et al. (2007) (NC: 140), Yokoe et al. (2013) (NC: 125), Kiviluoto et al. (1998) (NC: 117), Rattner et al. (1993) (NC: 115), Gurusamy et al. (2010) (NC: 111), and Strasberg et al. (2008) (NC: 104) (2,4,17-22).

http://dx.doi.org/10.36472/msd.v9i2.687

Trend topics on Cholecystitis

In all 3174 articles published on Cholecystitis, 2497 different keywords were used. Among these keywords, 83 different keywords used in at least 8 different articles are shown in **Table 3**.

The trend visualisation network map performed to reveal trend topics among these keywords is shown in **Figure 4.a** and the keyword citation network visualisation map performed to reveal the most cited topics is shown in **Figure 4.b**.

Table 1. 66 most active journals with more than 10 articles on cholecystitis

Journals	RC	C	AC	Journals	RC	C	AC
Khirurgiya	124	77	0.6	Journal of Clinical Ultrasound	17	282	16.6
American Surgeon	71	1450	20.4	Scandinavian Journal Of Gastroenterology	17	296	17.4
Vestnik Khirurgii Imeni II Grekova	69	7	0.1	Surgery Today	17	241	14.2
Surgical Endoscopy and Other Interventional Techniques	65	1793	27.6	Zentralblatt Fur Chirurgie	17	41	2.4
American Journal of Surgery	62	2428	39.2	Journal of Surgical Case Reports	16	11	0.7
American Journal of Roentgenology	52	1893	36.4	Medicine	16	72	4.5
Hepato-Gastroenterology	49	764	15.6	Acta Chirurgica Belgica	15	79	5.3
Journal of Hepato-Biliary-Pancreatic Sciences	48	2057	42.9	Clinical Radiology	15	198	13.2
Vrachebnoe Delo	47	10	0.2	Digestive Surgery	15	146	9.7
World Journal of Surgery	38	1214	31.9	HPB	15	262	17.5
Journal of Gastrointestinal Surgery	36	688	19.1	Abdominal Imaging	14	234	16.7
Surgical Laparoscopy Endoscopy & Percutaneous Techniques	35	478	13.7	ANZ Journal of Surgery	14	170	12.1
Klinicheskaya Meditsina	34	2	0.1	Revista Espanola De Las Enfermedades Del Aparato Digestivo	14	10	0.7
World Journal of Gastroenterology	32	514	16.1	Surgical Endoscopy-Ultrasound and Interventional Techniques	13	469	36.1
British Journal of Surgery	31	1647	53.1	Internal Medicine	13	47	3.6
Clinical Nuclear Medicine	30	202	6.7	Acta Chirurgica Scandinavica	12	142	11.8
Sovetskaya Meditsina	30	10	0.3	Australian and New Zealand Journal of Surgery	12	101	8.4
Terapevticheskii Arkhiv	30	7	0.2	BMC Gastroenterology	12	134	11.2
Radiology	29	1786	61.6	Clinical Imaging	12	100	8.3
American Journal of Gastroenterology	25	504	20.2	Endoscopy	12	454	37.8
Gastrointestinal Endoscopy	24	625	26.0	Gastrointestinal Radiology	12	202	16.8
Cureus	23	20	0.9	Southern Medical Journal	12	159	13.3
Annals of Surgery	22	1915	87.0	Surgery Gynecology & Obstetrics	12	383	31.9
Archives of Surgery	22	1093	49.7	American Journal of Emergency Medicine	11	112	10.2
Revista Espanola de Enfermedades Digestivas	22	48	2.2	Journal de Chirurgie	11	29	2.6
International Surgery	22	218	9.9	Journal of Laparoendoscopic & Advanced Surgical Techniques	11	63	5.7
Chirurg	21	121	5.8	Journal of the American College of Surgeons	11	477	43.4
Journal of Surgical Research	21	280	13.3	International Journal of Surgery	11	229	20.8
Surgery	21	763	36.3	Asian Journal of Endoscopic Surgery	10	24	2.4
Digestive Diseases and Sciences	18	330	18.3	Journal of Clinical Gastroenterology	10	285	28.5
Journal of Evolution of Medical and Dental Sciences-JEMDS	18	1	0.1	Journal of Nuclear Medicine	10	273	27.3
Journal of Hepato-Biliary-Pancreatic Surgery	18	1025	56.9	Journal of Trauma and Acute Care Surgery	10	143	14.3
International Journal of Surgery Case Reports	18	26	1.4	Pakistan Journal of Medical & Health Sciences	10	3	0.3

RC: Record Count, C: Number of Citation, AC: Average Citation Per Document

http://dx.doi.org/10.36472/msd.v9i2.687

Table 2. Top 20 most cited articles according to total citations on cholecystitis

Journals	RC	C	AC	Journals	RC	C	AC
Khirurgiya	124	77	0.6	Journal of Clinical Ultrasound	17	282	16.6
American Surgeon	71	1450	20.4	Scandinavian Journal Of Gastroenterology	17	296	17.4
Vestnik Khirurgii Imeni II Grekova	69	7	0.1	Surgery Today	17	241	14.2
Surgical Endoscopy and Other Interventional Techniques	65	1793	27.6	Zentralblatt Fur Chirurgie	17	41	2.4
American Journal of Surgery	62	2428	39.2	Journal of Surgical Case Reports	16	11	0.7
American Journal of Roentgenology	52	1893	36.4	Medicine	16	72	4.5
Hepato-Gastroenterology	49	764	15.6	Acta Chirurgica Belgica	15	79	5.3
Journal of Hepato-Biliary-Pancreatic Sciences	48	2057	42.9	Clinical Radiology	15	198	13.2
Vrachebnoe Delo	47	10	0.2	Digestive Surgery	15	146	9.7
World Journal of Surgery	38	1214	31.9	HPB	15	262	17.5
Journal of Gastrointestinal Surgery	36	688	19.1	Abdominal Imaging	14	234	16.7
Surgical Laparoscopy Endoscopy & Percutaneous Techniques	35	478	13.7	ANZ Journal of Surgery	14	170	12.1
Klinicheskaya Meditsina	34	2	0.1	Revista Espanola De Las Enfermedades Del Aparato Digestivo	14	10	0.7
World Journal of Gastroenterology	32	514	16.1	Surgical Endoscopy-Ultrasound and Interventional Techniques	13	469	36.1
British Journal of Surgery	31	1647	53.1	Internal Medicine	13	47	3.6
Clinical Nuclear Medicine	30	202	6.7	Acta Chirurgica Scandinavica	12	142	11.8
Sovetskaya Meditsina	30	10	0.3	Australian and New Zealand Journal of Surgery	12	101	8.4
Terapevticheskii Arkhiv	30	7	0.2	BMC Gastroenterology	12	134	11.2
Radiology	29	1786	61.6	Clinical Imaging	12	100	8.3
American Journal of Gastroenterology	25	504	20.2	Endoscopy	12	454	37.8
Gastrointestinal Endoscopy	24	625	26.0	Gastrointestinal Radiology	12	202	16.8
Cureus	23	20	0.9	Southern Medical Journal	12	159	13.3
Annals of Surgery	22	1915	87.0	Surgery Gynecology & Obstetrics	12	383	31.9
Archives of Surgery	22	1093	49.7	American Journal of Emergency Medicine	11	112	10.2
Revista Espanola de Enfermedades Digestivas	22	48	2.2	Journal de Chirurgie	11	29	2.6
International Surgery	22	218	9.9	Journal of Laparoendoscopic & Advanced Surgical Techniques	11	63	5.7
Chirurg	21	121	5.8	Journal of the American College of Surgeons	11	477	43.4
Journal of Surgical Research	21	280	13.3	International Journal of Surgery	11	229	20.8
Surgery	21	763	36.3	Asian Journal of Endoscopic Surgery	10	24	2.4
Digestive Diseases and Sciences	18	330	18.3	Journal of Clinical Gastroenterology	10	285	28.5
Journal of Evolution of Medical and Dental Sciences-JEMDS	18	1	0.1	Journal of Nuclear Medicine	10	273	27.3
Journal of Hepato-Biliary-Pancreatic Surgery	18	1025	56.9	Journal of Trauma and Acute Care Surgery	10	143	14.3
International Journal of Surgery Case Reports	18	26	1.4	Pakistan Journal of Medical & Health Sciences	10	3	0.3

RC: Record Count, C: Number of Citation, AC: Average Citation Per Document

http://dx.doi.org/10.36472/msd.v9i2.687

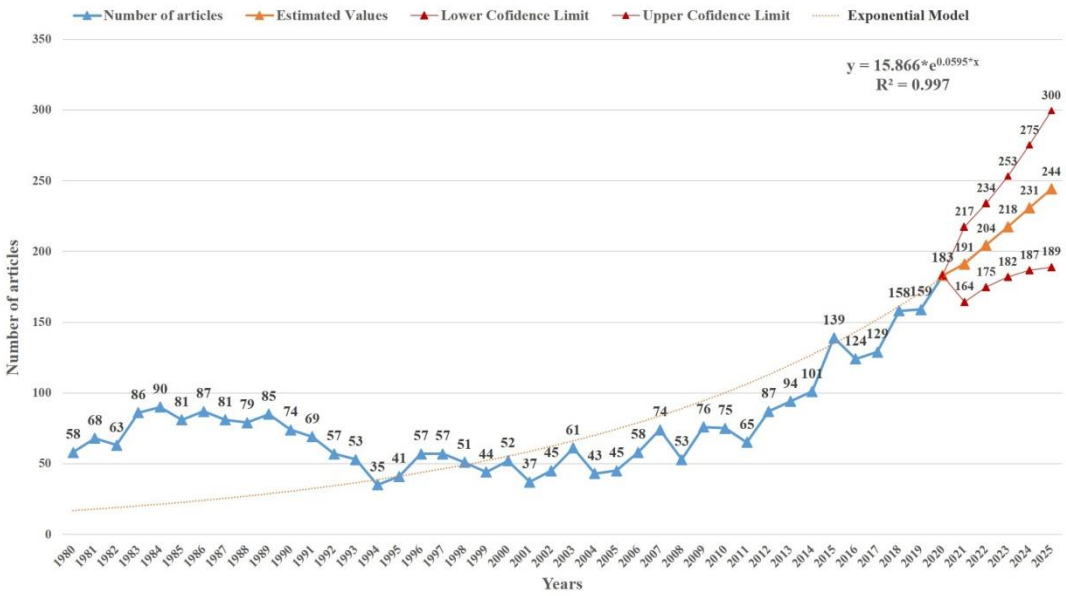


Figure 1: Number of articles published on Cholecystitis by years and estimation of the number of articles that can be published in the future with the exponential model

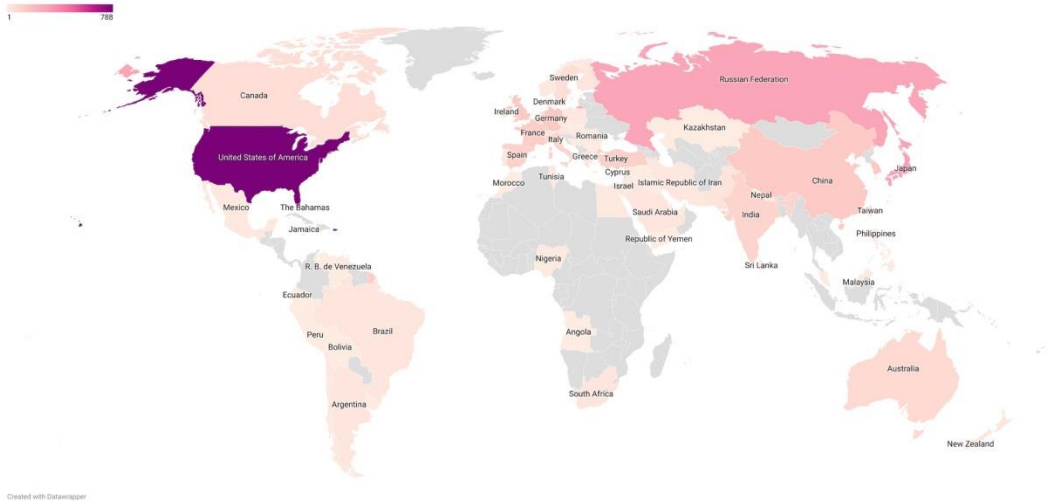


Figure 2: World map for the distribution of articles by country on Cholecystitis. Footnote: In the indicator given at the top left of the figure (article productivity increases from light to dark)

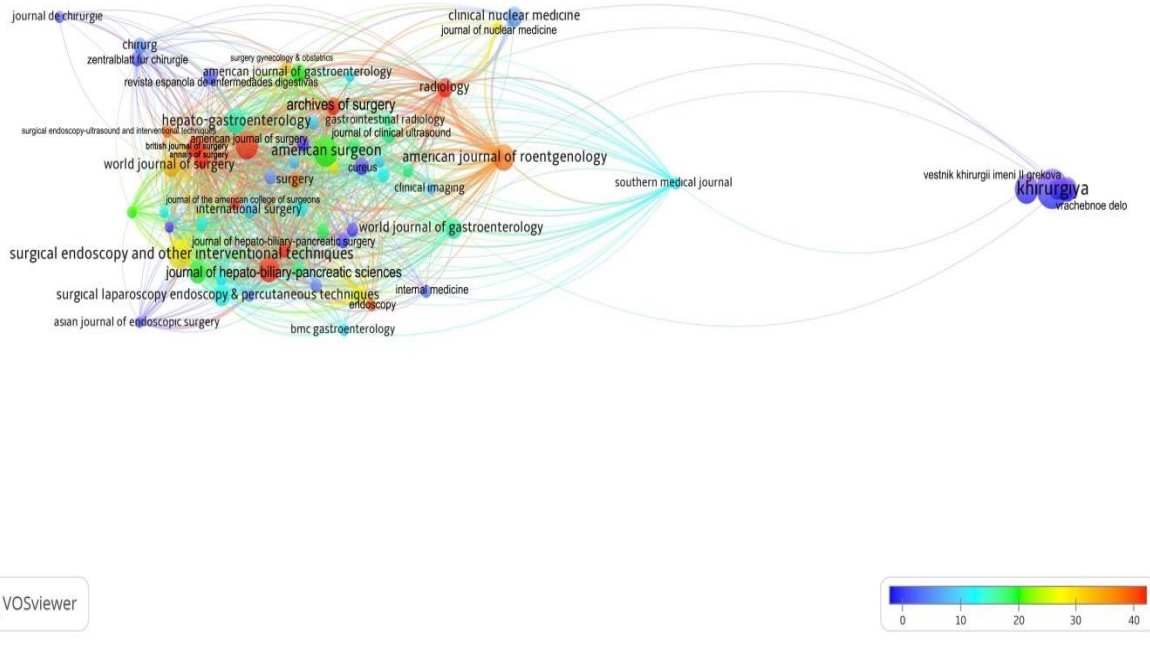


Figure 3: Network svisualisation map for citation analysis of active journals on Cholecystitis.

http://dx.doi.org/10.36472/msd.v9i2.687

Table 3. The most frequently used keywords on cholecystitis

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
Acute cholecystitis	591	Elderly	23	Eosinophilic cholecystitis	10
Cholecystitis	430	Early laparoscopic cholecystectomy	22	Epstein-barr virus	10
Laparoscopic cholecystectomy	237	Acute calculous cholecystitis	21	Hemorrhagic cholecystitis	10
Cholecystectomy	201	Diagnosis	20	Open cholecystectomy	10
Gallbladder	169	Case report	18	Percutaneous drainage	10
Acalculous cholecystitis	97	Choledocholithiasis	18	Subtotal cholecystectomy	10
Laparoscopy	76	Guidelines	18	Abdominal pain	9
Xanthogranulomatous cholecystitis	66	Gallbladder carcinoma	17	Appendicitis	9
Percutaneous cholecystostomy	61	Gallbladder drainage	17	Cholecystitis, acute	9
Cholecystostomy	58	Surgery	17	Endoscopic transpapillary gallbladder drainage	9
Acute acalculous cholecystitis	54	CT	15	Liver abscess	9
Cholelithiasis	54	Delayed cholecystectomy	15	Pancreatitis	9
Gallstone (s)	50	Hemobilia	15	Pseudoaneurysm	9
Ultrasound	47	Drainage	14	Risk factors	9
Chronic cholecystitis	43	Morbidity	14	Timing	9
Gangrenous cholecystitis	35	Mortality	14	Carcinoma	8
Complications	34	Endoscopic retrograde cholangiopancreatography	12	Child	8
Ultrasonography	31	Pregnancy	12	Cholecystolithiasis	8
Emphysematous cholecystitis	30	Acalculous	11	Clostridium perfringens	8
Outcome (s)	30	Acute cholangitis	11	Cystic duct	8
Conversion	29	Bile duct injury	11	Emergency cholecystectomy	8
Tokyo guidelines	27	Cholangitis	11	Gallbladder neoplasms	8
Acute	25	Delayed laparoscopic cholecystectomy	11	Gallstone disease	8
Laparoscopic	25	Gallbladder perforation	11	Inflammation	8
Computed tomography	24	Prognosis	11	Percutaneous	8
Gallbladder cancer	24	Cholescintigraphy	10	Percutaneous transhepatic gallbladder aspiration	8
Percutaneous transhepatic gallbladder drainage	24	C-reactive protein	10	Sonography	8
Early cholecystectomy	23	Emergency surgery	10		

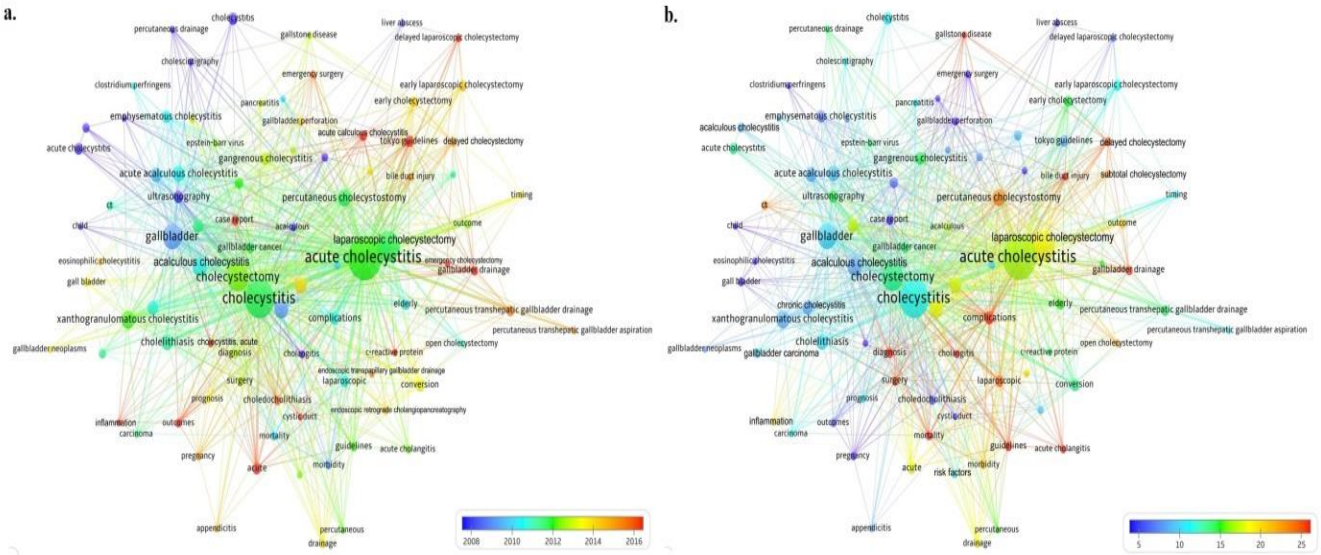


Figure 4: a. Network visualization map for trends on Cholecystitis. Footnote: Indicator shows current publications from blue to red (blue-green-yellow-red). The size of the circle indicates the size of the number of articles published on that topic.
b. Network visualization map of the most frequently cited topics on Cholecystitis. Footnote: The number of citations from blue to red increases. The size of the circle indicates the size of the number of articles published on that topic.

DISCUSSION

Our results demonstrated that 0-100 articles on Cholecystitis were initially produced between 1980 and 2013, and the average number of articles published between these years was 63. The number of articles published in 2014 exceeded 100, and there has been a remarkable increase in the number of articles in recent years, and 183 articles were published in 2020. The average number of articles published between 2014 and 2020 was 142. In recent years, there has been an increase in the number of articles with an exponential trend. The evaluation of the nonlinear regression analysis results showed that the number of articles will continue with an increasing exponential trend.

The analysis of the publication distribution of the world countries revealed that 16 of the most active 20 countries in the production of articles on Cholecystitis were developed countries, while the other 4 (Russia, China, Turkey, India) were developing countries. However, although these four countries were developing countries, they had large economies. The results of the correlation analysis in our study showed that the highly significant correlation between article productivity and economic development indicators shows that the economic development level of countries is effective in the productivity of publications on Cholecystitis. Bibliometric studies on many different medical subjects in the literature have shown that economic power is effective in publication productivity (12,14). The evaluation of the density map created according to the total cooperation score between the countries revealed that the countries with the most intensive cooperation were Japan, South Korea, Taiwan, Singapore, Argentina, Greece, and New Zealand, respectively. The analysis of the co-authorship cooperation of countries on Cholecystitis showed that cooperation based on geographical countries did not have a significant effect on article production.

The journals that published the highest number of articles on Cholecystitis were determined as Khirurgiya, American Surgeon, Vestnik Khirurgii Imeni II Grekova, Surgical Endoscopy and Other Interventional Techniques, American Journal of Surgery, American Journal of Roentgenology, Hepato-Gastroenterology, Journal of Hepato-Biliary-Pancreatic Sciences, Vrachebnoe Delo, and World Journal of Surgery, respectively. We can recommend that authors who want to publish on Cholecystitis first consider these journals. The evaluation of the citation analyses of the journals revealed the most influential journals according to the average number of citations per article they published were Annals of Surgery, Radiology, Journal of Hepato-Biliary-Pancreatic Surgery, British Journal of Surgery, Archives of Surgery, Journal of the American College of Surgeons, Journal of Hepato-Biliary-Pancreatic Sciences, American Journal of Surgery, Endoscopy, American Journal of Roentgenology, Surgery, and Surgical Endoscopy-Ultrasound and Interventional Techniques, respectively. We can recommend that researchers who want their articles to be cited more should consider these journals first.

The evaluation of the analysed articles by the total number of citations they received revealed that the most cited study was published in Gastroenterology by Fox et al. (1998) titled “Hepatic Helicobacter species identified in bile and gallbladder tissue from Chileans with chronic cholecystitis” (23). The second most influential study was the study of Lo, CM. et al. (1998) published in Annals of Surgery with the title of “Prospective randomised study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis” (17). The third most influential study was the study of Kiviluoto, T. et al. (1998) published in the Lancet with the title of “Randomised trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis” (19). The fourth and fifth most influential studies were the studies of Lai, et al. (1998) and Hirota, et al. (2007) (18, 2). The evaluation of the studies according to the average number of citations per year showed that the most influential first article was the study of Yokoe, M. et al. (2018) published in the Journal of Hepato-Biliary-Pancreatic Sciences with the title of “Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos)” (5). The second most influential article was the study of Okamoto et al. (2018) published in the Journal of Hepato-Biliary-Pancreatic Sciences with the title of “Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis” (24). The third most influential study was the study of Yokoe et al. (2013) published in the Journal of Hepato-Biliary-Pancreatic Sciences with the title of “TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos)” (4). The fourth most influential study was the study of Guttet al. (2013) published in Annals of Surgery with the title of “Acute Cholecystitis Early Versus Delayed Cholecystectomy, A Multicenter Randomized Trial (ACDC Study, NCT00447304)” (25). According to the co-citation numbers of all analysed articles, the studies of Lo et al. (1998), Lai et al. (1998), Hirota et al. (2007), Yokoe et al. (2013), Kiviluoto et al. (1998), Rattner et al. (1993), Gurusamy et al. (2010), Strasberg et al. were determined to be the most influential studies (2,4,17-22). We can recommend that clinicians and researchers interested in this subject read these publications first.

The evaluation of the keyword analysis results showed that the subjects of Cholecystitis formed clusters in 9 different colours as a result of the cluster analysis. The most cited keywords were guidelines, complications, diagnosis, cholangitis, acute cholangitis, mortality, gallbladder drainage, Bile duct injury, surgery, CT,

delayed cholecystectomy, subtotal cholecystectomy, gallstone disease, percutaneous Cholecystostomy, and open cholecystectomy. The results of the analysis conducted to determine the trend topics revealed that the keywords studied in recent years were Tokyo guidelines, C-reactive protein, gallbladder drainage, acute calculous Cholecystitis, emergency surgery, emergency cholecystectomy, cystic duct, choledocholithiasis, inflammation, acute Cholecystitis, delayed laparoscopic cholecystectomy, percutaneous transhepatic gallbladder drainage, and percutaneous transhepatic gallbladder aspiration. Based on the results of the trend subject analysis, it can be speculated that non-invasive methods have come to the fore more in recent years. We believe that this may be due to the fact that surgeons avoid surgery and head towards percutaneous methods, especially due to the COVID-19 pandemic after 2020.

As a result of the literature review on Cholecystitis, we could not find any bibliometric study. It can be said that our comprehensive study on this subject is the first bibliometric research. In the study, we used only the WoS database for literature review, which can be a limitation in our study. We did not use the Pubmed and Scopus indexes in our study since citation and co-citation analyses cannot be performed in the Pubmed database. The Scopus database also includes studies with low impact levels. The WoS database indexes articles published in more influential journals compared to other databases (12,14). In recent years, WoS has been more widely preferred for bibliometric analyses (9-14).

CONCLUSION

This comprehensive bibliometric study on Cholecystitis, which has an increasing trend in the number of articles in recent years, shared summary information of 3174 articles published between 1980 and 2020. It can be said that the trend topics in cholecystitis studies conducted in recent years are Tokyo guidelines, C-reactive protein, gallbladder drainage, acute calculous Cholecystitis, emergency surgery, emergency cholecystectomy, cystic duct, choledocholithiasis, inflammation, acute Cholecystitis, delayed laparoscopic cholecystectomy, percutaneous transhepatic gallbladder drainage, and percutaneous transhepatic gallbladder aspiration. This article may be a useful resource for clinicians and scientists on global outputs of Cholecystitis.

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by **MBY, MBÖ**

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. Kimura Y, Takada T, Kawarada Y, et al. Definitions, pathophysiology, and epidemiology of acute cholangitis and Cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14(1):15-26.

2. Hirota, M., Takada, T., Kawarada, Y., Nimura, Y., Miura, F., Hirata, K., et al. (2007). Diagnostic criteria and severity assessment of acute Cholecystitis: Tokyo Guidelines. Journal of hepato-biliary-pancreatic surgery, 14(1), 78-82.

3. Takada T, Strasberg SM, Solomkin JS, Gomi H, Yoshida M, Mayumi T, et al. TG13: Updated Tokyo Guidelines for the management of acute cholangitis and Cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:1–7.

4. Yokoe, M., Takada, T., Strasberg, S. M., Solomkin, J. S., Mayumi, T., Gomi, H., et al. (2013). TG13 diagnostic criteria and severity grading of acute Cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences, 20(1), 35-46.

5. Yokoe, M., Hata, J., Takada, T., Strasberg, S. M., Asbun, H. J., Wakabayashi, G., et al. (2018). Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute Cholecystitis (with videos). Journal of Hepato-biliary-pancreatic Sciences, 25(1), 41-54.

6. Fuks D, Mouly C, Robert B, Hajji H, Yzet T, Regimbeau J-M. Acute Cholecystitis: preoperative CT can help the surgeon consider conversion from laparoscopic to open cholecystectomy. Radiology. 2012; 263: 128– 38.

7. Hafif A, Gutman M, Kaplan O, Winkler E, Rozin RR, Skornick Y. The management of acute Cholecystitis in elderly patients. Am Surg. 1991; 57(10):648-52.

8. Ransohoff DF, Miller GL, Forsythe SB, Hermann RE. Outcome of acute Cholecystitis in patients with diabetes mellitus. Ann Intern Med. 1987; 106(6):829-32.

9. Doğan, G., Karaca, O. A bibliometric analysis of the field of anesthesia during 2009–2018: A bibliometric analysis of anesthesia. Brazilian Journal of Anesthesiology. 2020:70 (2);140-152.

10. Doğan, G., İpek, H. (2020). The evolution of hypospadias publications: A bibliometric approach. Revista internacional de andrologia.

11. Muslu Ü, Demir E. Development of Rhinoplasty: Yesterday and Today. Medical Science 2019;23:294-301

12. Golpinar, M., Demir, E. (2020). Global research output of the cerebellum: Yesterday, today, and tomorrow. Journal of the Anatomical Society of India, 69(3), 155.

13. Yildirim, E., Demir, E. (2019). Comparative bibliometric analysis of fertility preservation. Annals of Medical Research, 26(8), 1622-8.

14. Demir, E., Akmeşe, Ö. F., Erbay, H., Taylan-Özkan, A., Mumcuoğlu, K. Y. (2020). Bibliometric analysis of publications on house dust mites during 1980–2018. Allergologia et immunopathologia, 48(4), 374-383.

15. Van Eck NJ. Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. Scientometrics, 2010;84(2):523–538.

16. The World Bank (2020). Website https://data.worldbank.org/indicator/NY.GDP.MKTP.CD [accessed 1 Ekim 2020]

17. Lo CM, Liu CL, Fan ST, Lai EC, Wong J. Prospective srandomised study of early versus delayed laparoscopic cholecystectomy for acute Cholecystitis. Ann Surg. 1998;227(4):461-7.

18. P. B. S. Lai, K. H. Kwong, K. L. Leung et al., "Randomised trial of early versus delayed laparoscopic cholecystectomy for acute cholecystitis," British Journal of Surgery, vol. 85, no. 6, pp. 764–767, 1998.

19. Kiviluoto T, Sirén J, Luukkonen P, Kivilaakso E. Randomised trial of laparoscopic versus open cholecystectomy for acute and gangrenous Cholecystitis. Lancet. 1998;351(9099):321-5.

20. Rattner DW, Ferguson C, Warshaw AL. Factors associated with successful laparoscopic cholecystectomy for acute Cholecystitis. Ann Surg. 1993;217(3):233-6.

21. Gurusamy K, Samraj K, Gluud C, Wilson E, Davidson BR. Meta-analysis of srandomised controlled trials on the safety and effectiveness of early versus delayed laparoscopic cholecystectomy for acute Cholecystitis. Br J Surg. 2010;97(2):141-50.

22. Strasberg SM. Clinical practice. Acute calculous Cholecystitis. N Engl J Med. 2008;358(26):2804-11.

23. Fox, J. G., Dewhirst, F. E., Shen, Z., Feng, Y., Taylor, N. S., Paster, B. J., ... & Roa, I. (1998). Hepatic Helicobacter species identified in bile and gallbladder tissue from Chileans with chronic Cholecystitis. Gastroenterology, 114(4), 755-763.

24. Okamoto, K., Suzuki, K., Takada, T., Strasberg, S. M., Asbun, H. J., Endo, I., et al. (2018). Tokyo Guidelines 2018: flowchart for the management of acute Cholecystitis. Journal of Hepato-biliary-pancreatic Sciences, 25(1), 55-72.

25. Gutt, C. N., Encke, J., Köninger, J., Harnoss, J. C., Weigand, K., Kipfmüller, K., et al. (2013). Acute Cholecystitis: early versus delayed cholecystectomy, a multicenter srandomised trial (ACDC study, NCT00447304). Annals of surgery, 258(3), 385-393.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Improved clinical outcome after PK-Guided Personalised Prophylaxis with my-PKFIT® in patients with hemophilia A without inhibitors

Emine Türkkan[1]*, Gül Nihal Özdemir[2], Öykü Arslan[3], Serap Karaman[4], Zeynep Karakaş[4], Ayşegül Ünüvar[4]

1 Prof Dr Cemil Taşçıoğlu City Hospital, Department of Pediatrics, Istanbul, TR
2 Istinye University, Liv Hospital, Department of Pediatric Hematology-Oncology , Istanbul, TR
3 Çam ve Sakura City Hospital, Department of Hematology, Istanbul, TR
4 İstanbul University, İstanbul Faculty of Medicine, Department of Pediatric Hematology-Oncology, Istanbul, TR

*** Corresponding Author:** Emine Türkkan **E-mail:** turkkanemine92@gmail.com

ABSTRACT

Objective: Prophylaxis is the gold standard in patients with severe hemophilia. In recent years, personalisation of prophylaxis treatment according to pharmacokinetic properties has been used in treatment. In this study, personalisation treatment experience based on the pharmacokinetic dosing tool my-PKfit results in pediatric and adult patients from three centers is shared.

Material and Methods: myPKfit (www1.mypkfit.com) was used to evaluate pharmacokinetic parameters in hemophilia A patients receiving recombinant Factor VIII (Takeda Advate ®) prophylaxis. 75 samples in 34 patients (3 samples in 7 patients, 2 samples in 27 patients) were analysed for pharmacokinetic evaluation. Age, weight and baseline FVIII level of the patients were recorded. Pharmacokinetic curves were obtained after entering sampling times, factor dose and sample results. The annual bleeding rate (ABR) of the patients were evaluated before and after the changes made after the pharmacokinetic evaluation.

Results: The median age of 34 patients with severe hemophilia A without inhibitors was 12.3±8.7 (1.5-37) years, and the mean weight was 40.0±22.0 (10-83) kg. All patients had a baseline FVIII level of less than or equal to 2 IU/dl. All patients were receiving primary or secondary/tertiary prophylaxis. The mean half-life of the factors of the patients was 9.6±1.4 (7.0-13.4) hours, and the mean time reached below 1 IU/dl was 48.9±11.2 (16.0-77.0) hours. Prophylactic factor therapy was changed in 17 patients after mypk-fit, dose increased in 9 patients, the frequency increased in 6 patients, and both dose and frequency increased in 2 patients. With a mean follow-up period of 23.7 +16 (2-49) months, in 17 patients whose prophylaxis regimen was changed after the PK evaluation by myPkyfit, ABR was found to be significantly lower in the post-change period, compared to the last one year before the change of regimen (2.94 + 2.19 and 0.58 + 1.00 respectively) P: 0.028.

Discussion: A pharmacokinetic study by the Bayesian method is an increasingly used method for personalised prophylaxis regimen. We believe that myPKfit is beneficial in providing effective and appropriate prophylaxis.

Key words: Pharmacokinetic, myPKfit, hemophilia, prophylaxis

Research Article

Received 16-01-2022

Accepted 14-02-2022

Available Online: 16-02-2022

Published 28-02-2022

INTRODUCTION

In individuals with severe hemophilia, recurrent bleeding episodes in joints causes chronic arthropathy, pain and loss of function. No matter how effective is the treatment after bleeding, bleeding episodes can cause synovial damage to the joint and lead to permanent joint sequelae in long-term. Prophylaxis is the gold standard in the treatment of adults and children with hemophilia (1). Prophylactic treatment is based on the almost absence of joint problems in patients with mild disease and the rare occurrence of permanent joint damage in patients with moderate clinical course. In the 1950s, the concept of prevention of bleeding in hemophilia was first introduced by Nillsson et al. in Sweden and prophylaxis has been widely applied afterwards first in children and then in adults (2).

http://dx.doi.org/10.36472/msd.v9i2.674

The World Federation of Hemophilia (WFH) and the World Health Organization recommend prophylaxis as the "first-line" treatment for the prevention of hemophilic arthropathy in patients with severe hemophilia (3,4). World Federation of Hemophilia Guideline has classified prophylactic therapy in the hemophilia treatment as primary, secondary or tertiary according to the time of initiation of treatment. Currently, it has been shown that the most effective and safe treatment for patients is primary prophylaxis (5). However, there is no single formula on which treatment regimen is most suitable for which patient. Different centers have different approaches regarding the age, dose and frequency of prophylaxis (6). In recent years, there have been publications that "prophylaxis can be individualised" in line with different characteristics such as the patient's age, clinical bleeding characteristics, pharmacokinetic studies, target joint status, activity, lifestyle, and also the availability of the factor. (7-10).

myPKFiT® is a web-based application developed by Baxalta (Shire) (now part of Takeda) as a PK and dose calculator for Advate®. This device helps customise dosage with only 2 blood samples compared to 11 with standard PK sampling (11,12). In this study, we evaluated whether PK-specific prophylaxis is an effective option to reduce bleeding rates in children and adults with severe hemophilia A (HA) without inhibitors.

MATERIAL and METHODS

Thirty-four severe HA (FVIII <2 IU/dl) patients without inhibitors were included from three centers in Istanbul, Turkey. All patients were receiving prophylaxis with Advate®. The mean age of the patients was 12.3±8.7 years (1.5-37). Seventeen patients were on primary prophylaxis, 17 were on secondary/tertiary prophylaxis. myPKfit (www1.mypkfit.com) was used to evaluate pharmacokinetic parameters in patients with hemophilia A receiving Takeda Advate® prophylaxis. No patient had a previous pharmacokinetic study. Age, body weight, baseline FVIII levels, infused FVIII dose, infusion time were collected and loaded onto the myPKFiT medical device. After entering the date and time of collection and the FVIII level (IU) for each sample, the tool estimated the PK profile for each patient.

The target minimum FVIII trough level was chosen as 1 IU/dl because the time spent with FVIII is below 1 IU/dl as shown to be associated with an increased risk of bleeding in patients. After entering the target trough levels, the myPKFiT dosage calculation simulator provided a weekly chart with individual dosing. The suggested individual dosing was discussed with the patient and/or family to plan a new prophylactic regimen.

Annual bleeding rate (ABR) was obtained before and after adjustments according to mypk-fit using patients' clinical data. A total of 75 samples were analysed in 34 patients (3 samples in 7 patients, two samples in 27 patients) for pharmacokinetic evaluation.

Statistical Analyses: Data were calculated as median and interquartile range (25-75 percent) for continuous variables and as percentages for frequency and discrete variables. Comparison of clinical outcomes was made with the Wilcoxon rank test for paired samples, and changes in FVIII consumption were analysed using the student's t test. Significance level was determined as $P < .05$.

RESULTS

Thirty-four patients with severe HA who received regular prophylactic factor therapy (with Takeda Advate ®) from three hemophilia centers in Istanbul, Turkey were included in the study. The mean age of the patients was 12.3±8.7 (1.5-37) years, and mean body weight was 40.0±22.0 (10-83) kg (**table 1**). The prophylaxis doses of the patients were 50.08±13.26 (22-86) units per week, the prophylaxis frequency was every 78.82±23.45 (48-144) hour (between 1-3 per week), and the mean ABR at baseline 2.20+1.88 (10-0) (**table 2**).

A total of 75 blood samples were taken from 34 patients. Mean baseline factor levels were 0.95±1.41 (0-8) IU. The pharmacokinetic profiles of patients were calculated by myPKfit with basal, 4th and 24th hour factor levels and the mean factor VIII dose recommended by the program is 92.88±30.51 (61.5-181.8) unit/kg per week and mean factor prophylaxis frequency was every 50.11±6.90 (48-72) hour (**table 2**, **figure 1,2,3**). The mean half-life of the factors of the patients was 9.6±1.4 (7.0-13.4) hours, and the mean time reached below 1 IU/dl was 48.9±11.2 (16.0-77.0) hours (**table1**).

A change in dose or frequency was recommended in 30 patients in the myPKfit program and no change was recommended in the current prophylactic dose or frequency in 4 patients. Evaluating the clinical status, bleeding frequency and treatment compliance of the patients, the prophylaxis program was changed in 17 of the 30 patients by discussing with patient and/or family. It was determined that frequency increased in 6 patients, frequency and dose increased in 2 patients, only dose increased in 9 patients.

The current prophylaxis program was continued although an increase in frequency was recommended by myPKfit program in 13 patients according to the choice of the treating physician and the patient/family. It was determined that the annual bleeding frequency was low in 10 of these 13 patients, the patient or his parents did not accept the increase in the frequency of prophylaxis in 2 of them,

http://dx.doi.org/10.36472/msd.v9i2.674

and the same prophylaxis regimen was continued in one patient due to vascular access problem. With a mean follow-up period of 23.7 +16 (2-49) months, in 17 patients whose prophylaxis regimen was changed after the PK evaluation by myPkyfit, ABR was found to be significantly lower in the post-change period, compared to the last 1 year before the change of regimen (2.94 + 2.19 and 0.58 + 1.00 respectively) P: 0.028.

Table 1. Demographic characteristics of hemophilia A patients undergoing pharmacokinetic evaluation

Age (years) (Mean ± SS)	12.3±8.7 (1.5-37)
Age to start prophylaxis (years) (Mean ± SS)	4.15±4.48 (0-19)
Annual bleeding rate (Mean ± SS)	2,20±1,88 (10-0)
Target joint development %	23.5
Body weight (kg) (Mean ± SS)	40.0±22.0 (10-83)
Basal FVIII level (IU/dl), (Mean ± SS)	0.95±1.41 (0-8)
Faktör VIII half-life (hour), (Mean ± SS)	9.6±1.4 (7.0-13.4)
The mean time reached below 1 IU/dl (Mean ± SS)	48.9±11.2 (16.0-77.0)

Table-2: Treatment schedule of patients before and after pharmacokinetic evaluation (with myPKfit)

	Before PK evaluation	Recommended by myPKfit	After PK evaluation
Frequency of Prophylaxis Mean ± SS (hours)	78.82±23.45 (48-144)	50.11±6.90 (48-72)	66.35±17.78 (48-144)
Prophylaxis dose Mean ± SS (IU/kg/week)	50.08±13.26 (22-86)	92.88±30.51 (61.5-181.8)	56.56±19.00 (22.00-93.75)

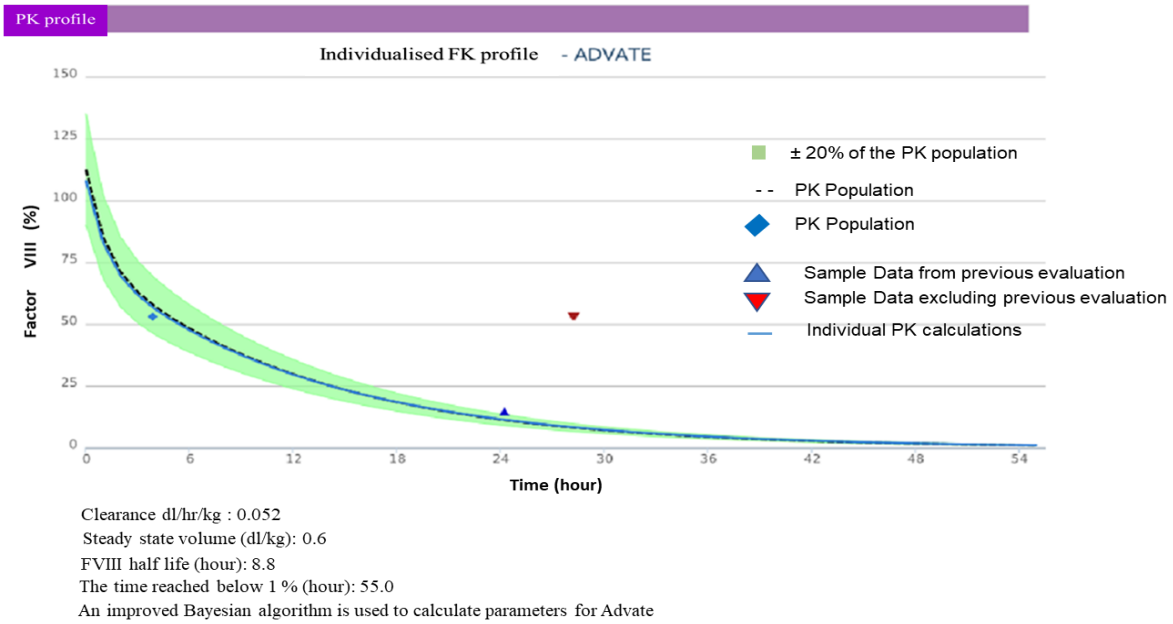


Figure 1: individualised FK profile

1.Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Dose (IU)	500 IU		500 IU		500 IU		500 IU
Dose (IU/kg)	43,5 IU/kg		43,5 IU/kg		43,5 IU/kg		43,5 IU/kg
Targeted Trough Value Above Baseline Level	1,4 %		1,5 %		1,5 %		1,5 %
Time Above Factor VIII % 10	23 hours		23 hours		23 hours		23 hours
Time Below Factor VIII % 5	16 hours		16 hours		16 hours		16 hours
2.Week							
Dose (IU)		500 IU		500 IU		500 IU	
Dose (IU/kg)		43,5 IU/kg		43,5 IU/kg		43,5 IU/kg	
Targeted Trough Value Above Baseline Level		1,5 %		1,5 %		1,5 %	
Time Above Factor VIII % 10		23 hours		23 hours		23 hours	
Time Below Factor VIII % 5		16 hours		16 hours		16 hours	

Figure 2: Individualised FK profile, dose adjustments

http://dx.doi.org/10.36472/msd.v9i2.674

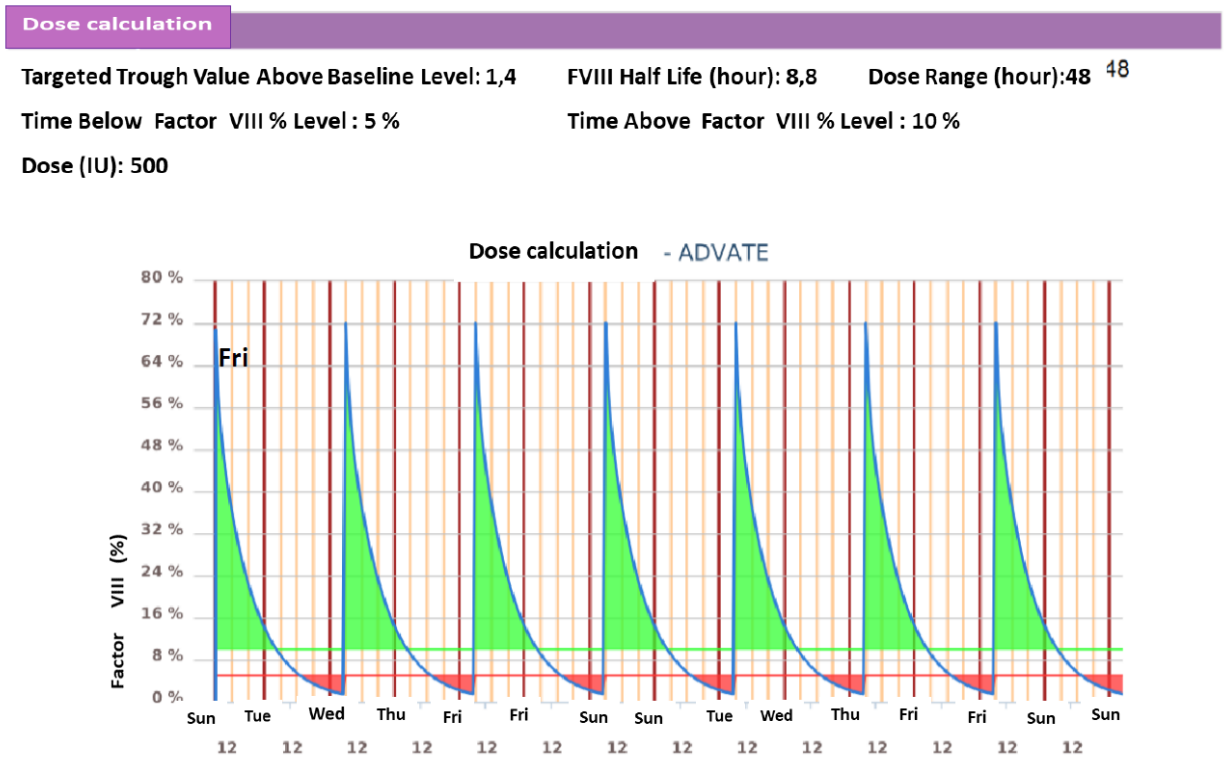


Figure 3: Shema of suggested weekly prophylaxis by myPKFiT® of one of the patients

DISCUSSION

Due to inter-patient variability, the standard dosing of prophylaxis based on body weight may result in over- or under-dosing in prophylaxis haemophilia therapy. Pharmacokinetic study using the Bayesian method is an increasingly popular method for individualisation of treatment in hemophilia (13). The Bayesian approach not only reduces the need for many samples for PK study, but also minimises interindividual variability by including variables such as age, weight, and von Willebrand factor levels in a multivariate model of the patient population. Generally, only two samples are required at 4 to 48 hours after infusion for FVIII products with standard half-life, and even single samples have been evaluated.

myPKFiT and Web-Accessible Population Pharmacokinetics Service-Hemophilia (WAPPS-Hemo) are web-based population-based applications developed to help physicians personalise and optimise their replacement therapy in hemophilia (14). myPKFiT was originally developed for use only with Octocog alfa (Advate, Takeda Pharma), but more recently it has also been used for the pegylated form of this molecule (rurioctocog alfa pegol, Adynovi, Takeda Pharma). WAPPS-Hemo can be used for all available factor concentrate products. Estimated dosing and frequency of administration are provided to achieve specific target levels for each. Implementation of individual pharmacokinetic (PK)-based adaptation may improve treatment guideline adherence and thus clinical outcomes.

Apart from the PK profile, other factors such as bleeding phenotype, musculoskeletal system status are also important in personalising the treatment. The objective and clear information provided by myPKFiT® is useful for discussing the treatment regimen between the healthcare team and the patient or their parents and making changes as needed. In our study, we showed that PK-guided prophylaxis using myPKFiT® resulted in individually improved clinical outcome and optimised FVIII consumption in a study population with a choice of 1 IU/dl trough level. As a result of the PK data obtained with myPKFiT®, half of the patients required modification (frequency and/or dose increase) in the treatment in our study. After this change, a significant reduction in ABR was observed, with an overall beneficial effect on clinical outcomes. The results of our study are consistent with those previously reported. Castellano et al. recruited 36 patients in their study in 3 centers in Spain. (15). Patients' ABR and annual joint bleeding rate were significantly reduced after pharmacokinetic dosing. Adjustment had an impact on most patients' individual FVIII consumption: the annual amount was reduced in 18 cases and increased in 14 cases. In our study, modifications significantly increased total FVIII consumption. A possible cause may be that most patients received insufficient dose and frequency of prophylaxis. A total of 27 patients with severe hemophilia A without inhibitors were included in the study by Alverez et al. (12). A change in prophylaxis was made after a PK

study using mypkfit in 10 patients. The use of mypfit has increased in their center after the study. Our study also increased the number of PK studies in patients treated at our centres, thus providing an objective tool for the recommended adaptation of prophylaxis. We have observed that the graphs obtained by mypk-fit are helpful, especially when discussing prophylaxis regimens with families and patients. In our series, we thought that good clinical outcomes were also associated with better patient compliance. As previously suggested, the graphical output of myPKFiT® is a useful tool for educating patients and their families in the hematology clinic. These data can be used to promote adherence to treatment (16). In this context, resources can help facilitate communication, and our experience of using these tools and applications is that the graphics produced by myPKFiT® are very helpful.

Standard pharmacokinetic (PK) assessments for people with hemophilia A are challenging, requiring a 72 hour washout and 5 to 11 blood samples. With myPKFiT®, PK parameters can be obtained with a small number of blood samples to adapt prophylaxis regimens as suggested by previous studies and the user manual (17,18). Blanchette et al. compared PK parameters in people with severe hemophilia A receiving Advate® obtained with a conventional washout, 6-sampling time-point PK protocol and a protocol without wash, only single clinic visit and 2 samples (19). A total of 39 inhibitor-negative males (factor VIII activity [FVIII:C] <2%) were enrolled in PK study. As a result, it has been shown that the two methods give similar results. In our study, only two blood samples were sufficient in the majority of patients.

We did not perform a pharmacoeconomic evaluation in this study, but other authors have reported a cost reduction associated with PK evaluation. Pasca et al. performed PK evaluations of 14 patients. (20). The weekly infusion frequency was decreased in three severe patients, increased in four patients, and remained the same in the other five patients. It was shown that the annual concentrate consumption decreased in 81.8% of the patients. A subsequent economic evaluation of each of the twelve patients with severe hemophilia A included in this analysis comparing standard and PK-guided prophylaxis showed that an optimised treatment could result in an average annual savings of €20.525 (-%15,8). The main goal of hemophilia treatment is to combine efficacy, safety, improvement in quality of life and cost savings. Cost savings are especially important in developing and middle-developed countries. WHEN pharmacoeconomic calculations are made, it is necessary to consider not only the amount of factor use, but also other factors such as absence from work or school due to bleeding or joint problems, surgical and/or arthroscopic interventions, hospitalisation and hospital visits. Many additional costs will be reduced by effective prophylaxis and reduction of bleeding. For these reasons, we consider our results to be even more important.

Our results may reflect real life experience as they are demonstrated by clinical experiences in three different large tertiary hospitals in Istanbul. Despite the small number of patients and only 1 year follow-up, we believe that this information is useful. Long follow-up clinical results will provide more information on this subject.

CONCLUSION

PK-guided dosing allows physicians to evaluate the FVIII half-life and clearance in patients with severe hemophilia without inhibitors and modify prescribed Advate® prophylaxis to ensure a good patient care. Requirement of only two samples to estimate pharmacokinetic parameters makes it easy to use in routine clinical practice with little inconvenience for patients and caregivers. Our results suggest that pharmacokinetic prophylaxis may be an effective option for reducing bleeding rates for children and adults in severe HA without inhibitor. In addition, we observed that giving the graphical printout to the patients and showing the pharmacokinetic results improved adherence to treatment. Further studies on pharmacoeconomic evaluation based on these results may guide us on factor consumption, especially in countries with limited resources.

Author Contributions: ET, GNÖ, ÖA, SK, ZK, AÜ: Project design, Patient examinations, Data analyses **ET:** Manuscript preparation, revisions.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Cemil Tasçıoğlu City Hospital approved the study.

REFERENCES

1. Nilsson I, Berntrop E, Lofqvist T, Pettersson H. Twenty-five years experience of prophylactic treatment in severe hemophilia A and B. J Intern Med. 1992;232:25-32.

2. Nilsson IM, Hedner U, Ahlberg A. Haemophilia prophylaxis in Sweden. Acta Paediatr Scand. 1976;65:129–135.

3. Stoffman J, Andersson NG, Branchford B, Batt K, D'Oiron R, Escuriola Ettingshausen C, et al. Common themes and challenges in hemophilia care: a multinational perspective. Hematology. 2019;24(1):39-48.

4. Skinner MW. WFH--the cornerstone of global development: 45 years of progress. Haemophilia. 2008;14 Suppl 3:1-9.

5. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007;357:535–544.

6. Oldenburg J. Optimal treatment strategies for hemophilia : achievements and limitations of current prophylactic regimens. Blood. 2015;125(13):2038–45.

7. Ar MC, Vaide I, Berntorp E. Methods for individualising factor VIII dosing in prophylaxis. Eur J Haematol Suppl. 2014;76:16–20.

8. Petrini P, Valentino LA, Gringeri A, Re WM, Ewenstein B. Individualizing prophylaxis in hemophilia: a review. Expert Rev Hematol. 2015;8(2):237-46.

9. Ar MC, Baslar Z, Soysal T. Personalized prophylaxis in people with hemophilia A: challenges and achievements. Expert Rev Hematol. 2016;9(12):1203-1208.

10. Hart DP, Kessler CM, Aledort L. Re-personalization and stratification of hemophilia care in an evolving treatment landscape. Hematology. 2019;24(1):737-741.

11. Reiniger A, Spotts G, Low-Baselli A et al. Optimizing prophylaxis: development of an advate PK calculator and dosing medical device based on a bayesian population PK model [Abstract OR07]. Haemophilia. 2014;20:15.

12. Álvarez-Román MT, Fernandez-Bello I, de la Corte-Rodríguez H, Hernández-Moreno AL, Martín-Salces M, Butta-Coll N, et al. Experience of tailoring prophylaxis using factor VIII pharmacokinetic parameters estimated with myPKFiT® in patients with severe haemophilia A without inhibitors. Haemophilia. 2017;23(1):50-54.

13. Nagao A, Yeung CHT, Germini F, Suzuki T. Clinical outcomes in hemophilia A patients undergoing tailoring of prophylaxis based on population-based pharmacokinetic dosing. Thromb Res. 2019;173:79-84.

14. Arvanitakis A, Berntorp E, Astermark J. A comparison of MyPKFiT and WAPPS-Hemo as dosing tools for optimizing prophylaxis in patients with severe haemophilia A treated with Octocog alfa. Haemophilia. 2021;27(3):417-424.

15. Mingot-Castellano ME, Parra R, Núñez R, Martorell M. Improvement in clinical outcomes and replacement factor VIII use in patients with haemophilia A after factor VIII pharmacokinetic-guided prophylaxis based on Bayesian models with myPKFiT®. Haemophilia. 2018;24(5):338-343.

16. Lock J, de Bekker-Grob EW, Urhan G, Peters M, Meijer K, Brons P, et al. Facilitating the implementation of pharmacokinetic-guided dosing of prophylaxis in haemophilia care by discrete choice experiment. Haemophilia 2016; 22: e1–10.

17. Björkman S. Limited blood sampling for pharmacokinetic dose tailoring of FVIII in the prophylactic treatment of hemophilia A. Haemophilia. 2010;16(4):597-605.

18. Inc B. MyPKFiT User Manual, DHF-000951 Revision 4.0. 2020. 2020. https://fr-prd-hema.mypkfit.com/documents/DHF000951_MYPKFIT3_HCP_USER_MANUAL_en_GB.pdf. Accessed October 2020.

19. Blanchette VS, Zunino L, Grassmann V, Barnes C, Carcao MD, Curtin J, Jackson S, Khoo L, Komrska V, Lillicrap D, Morfini M, Romanova G, Stephens D, Zapotocka E, Rand ML, Blatny J. A Practical, One-Clinic Visit Protocol for Pharmacokinetic Profile Generation with the ADVATE myPKFiT Dosing Tool in Severe Hemophilia A Subjects. Thromb Haemost. 2021;121(10):1326-1336.

20. Pasca S, Zanon E. Savings without changing: How to use the MyPKfit® device to improve treatment strategies in a cohort of patients with haemophilia A. Thromb Res. 2019;183:1-3.

Medical Science and Discovery
ISSN: 2148-6832

Can galectin-3 be used to predict the severity of vasoocclusive crisis in patients with sickle cell anaemia?

Mahmut Bakir Koyuncu[1]*, Hakan Basir[2], Berkan Karadurmus[2], Selma Unal[3], Anil Tombak[4], Eyup Naci Tiftik[4]

1 Department of Hematology, Adana City Research and Training Hospital, Adana, TR
2 Department of Internal Medicine, Faculty of Medicine, Mersin University, Mersin, TR
3 Department of Pediatric Hematology, Faculty of Medicine, Mersin University, Mersin, TR
4 Department of Hematology, Faculty of Medicine, Mersin University, Mersin, TR

*** Corresponding Author:** Mahmut Bakir Koyuncu **E-mail:** mahmutbakirkoyuncu@gmail.com

ABSTRACT

Objective: The number of markers showing the severity of the disease and the number of drugs that can be used in the treatment is very low in vasoocclusive crises seen in patients with sickle cell anemia. This study aims to evaluate the levels and changes of serum galectin-3 levels, which are known to have many roles in the body, during a painful crisis.

Material and Methods: In addition to the 0th and 48th hour galectin-3 levels in patients hospitalized for a painful crisis, galectin-3 measurements were also performed in stable patients with sickle cell anemia and healthy individuals.

Results: Galectin-3 levels were statistically significantly different in patient groups (p=0.001). It was observed that galectin-3 levels at the 48th hour were markedly higher than at the 0th hour in patients with painful crises. It was found that galectin-3 levels at both 0th and 48th hours were correlated with the duration of hospitalization due to painful crisis and the period of intravenous opioid use.

Conclusion: Galectin-3 levels, which are elevated during the painful crisis in patients with sickle cell anemia, are associated with the severity of the painful crisis

Keywords: sickle cell disease, vasoocclusive crisis, galectin-3

INTRODUCTION

Sickle cell anaemia is characterized by chronic hemolytic anaemia and recurrent painful crises. The most common reason for hospitalization in these patients is painful vasoocclusive crises.

The frequency and severity of painful crises vary among patients. Apart from pain treatment, the number of drugs used in vasoocclusive crises is very limited today (1).

The pathophysiology of vasoocclusive crises is quite complex. It is believed that clinical symptoms occur with endothelial activation, increased adhesion of erythrocytes and leukocytes to endothelial cells, and increased oxidative stress conditions causing vascular occlusion (2).

Galectin-3, which is known to have a role in many places such as cell adhesion, activation, chemotaxis, growth and differentiation, and resistance to oxidative stress, is a molecule belonging to the galectin family (3).

Due to these features of galectin-3, which may have a role in the pathophysiology of vasoocclusive crisis, its use as a marker showing the clinical course of these patients and as a treatment target may be on the agenda.

The objective of this study is to examine the levels and changes of serum galectin-3 during the painful crisis in patients with sickle cell anaemia, and to evaluate whether or not these levels and changes are related to the severity of the painful crisis.

Research Article

Received 17-01-2022

Accepted 08-02-2022

Available Online: 16-02-2022

Published 28-02-2022

http://dx.doi.org/10.36472/msd.v9i2.675

MATERIAL AND METHODS

Patients aged 18 years and older hospitalized in Mersin University Hematology and Pediatric Hematology clinics and Adana City Training and Research Hospital Hematology clinic between February 2021 and June 2021 due to vasoocclusive crisis were included in the study. For the sickle cell anaemia control group, stable patients with sickle cell anaemia who applied to the outpatient clinic in the same centers were included. For the healthy control group, healthy individuals who applied to the haematology outpatient clinic in the same centers were included.

For measurement of galectin-3, blood samples were collected twice from patients hospitalized with vasoocclusive crisis, immediately before the start of opioid infusion therapy (hour 0) and at 48 hours of infusion. A blood sample was collected once for the sickle cell anaemia control group and once for the healthy control group. The collected blood samples were centrifuged, and then the serum samples obtained were kept at -80 0C until the study was completed, and galectin-3 levels were studied in the samples at the end of the study. Galectin-3 measurements were made with ELISA kits, and results are shown in ng/mL.

Routine hemogram values, HbS and HbF percentages in haemoglobin electrophoresis, ferritin levels, number of days of hospitalization, and intravenous opioid days of patients hospitalized for the painful crisis were recorded.

Patients under 18 and whose vasoocclusive crisis duration was less than 48 hours were excluded from the study.

A signed informed form was obtained from all patients and healthy volunteers participating in the study. This study was approved by Mersin University Clinical Research Ethics Committee (2021/13).

Statistical Method: NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analysis.

Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used to evaluate study data.

The conformity of the quantitative data to the normal distribution was tested with the Kolmogorov-Smirnov, Shapiro-Wilk test, and graphical evaluations. The Student's t-test was used to compare normally distributed quantitative data between two groups, and the Mann Whitney U test was used for two-group comparisons of non-normally distributed quantitative data. Pearson Chi-Square test was used to compare qualitative data. In evaluating the relations between the variables, Pearson Correlation Analysis was used for normally distributed variables, and Spearman's Correlation Analysis was used for non-normally distributed variables. Significance was evaluated at the $p<0.05$ level at least.

RESULTS

The distribution of the descriptive characteristics of the patients included in the study is given in Table-1. Galectin-3 levels were statistically significantly different in patient groups (p=0.001). According to the results of the pairwise comparisons made to determine the difference, the Galectin-3 value of the individuals in Group 1 was significantly higher than the subjects in Group 2 and the control group (p=0.001). Likewise, the Galectin-3 levels of Group 2 individuals were significantly higher than those in the control group (p=0.001). The Galectin-3 levels of the patient groups and control group are given in Figure-1.

When Table-2 is examined, it is observed that serum Galectin-3 levels are correlated with both the duration of the crisis and the number of days that require intravenous opioids. It is noteworthy that the correlation degrees of Galectin-3 levels at the 48th hour are stronger than galectin levels at the 0th hour.

When Table-3 is examined, it is observed that there is no statistically significant relationship between Galectin-3 values at 0th and 48th hours and Hb, HbA2, HBS, HBF and Ferritin values of the individuals participating in the research.

Table 1: Distribution of descriptive features

		Total	Group 1	Group 2	Control	
		n (%)	n (%)	n (%)	n (%)	*p*
Gender	*Female*	*61 (49,2)*	20 (16,1)	18 (14,5)	23 (18,5)	[a]***0,675***
	Male	*63 (50,8)*	20 (16,1)	23 (18,5)	20 (16,1)	
Age (years)	*Mean±Sd*	*32,82±10,95*	30,37±9,77	33,92±9,69	34,04±12,84	[b]***0,214***
Galectin-3 levels (ng/mL)	*Median (Min-Max)*	*11,9 (6,4-25,7)*	19,6 (12,1-25,7)	11,9 (6,7-18,9)	8,4 (6,4-13,1)	

A Pearson Chi-Square Test b Kruskal Wallis Test
Group 1: Patients with sickle cell anemia hospitalized with a painful crisis
Group 2: Patients with sickle cell anemia without painful crisis
Control: Healthy adult patients participating in the study

http://dx.doi.org/10.36472/msd.v9i2.675

Table 2: Evaluations of the duration of the painful crisis and the number of days of intravenous opioid

	Crisis Period		Number of Iv opioid Days	
	r	*p*	*r*	*p*
Age (years)	-0,096	[d]*0,558*	-0,029	[d]*0,861*
Galectin-3 at 0th hour	0,442	[d]*0,007***	0,509	[d]*0,001***
Galectin-3 at 48th hour	0,828	[d]*0,001***	0,896	[d]*0,001***
Hb	0,014	[d]*0,930*	0,017	[d]*0,916*
HbA2	0,090	[d]*0,581*	0,047	[d]*0,774*
HBS	0,030	[c]*0,856*	0,084	[c]*0,608*
HBF	0,156	[c]*0,336*	0,179	[c]*0,269*
Hematocrit	0,049	[c]*0,763*	0,031	[c]*0,848*
Platelet	0,119	[c]*0,463*	0,142	[c]*0,381*
Leukocyte Count	0,200	[d]*0,217*	0,241	[d]*0,135*

Table 3: Relationship between serum Galectin 3 levels and some laboratory parameters in the patient group with painful crisis

	Galectin3 at 0th hour		Galectin3 at 48th hour	
	r	*p*	*r*	*p*
Hb	-0,058	[d]*0,609*	0,024	[d]*0,885*
HbA2	0,034	[d]*0,765*	-0,083	[d]*0,610*
HBS	-0,086	[c]*0,444*	0,124	[c]*0,445*
HBF	0,106	[c]*0,346*	0,136	[c]*0,401*
Ferritin	0,046	[c]*0,682*	0,362	[c]*0,022**

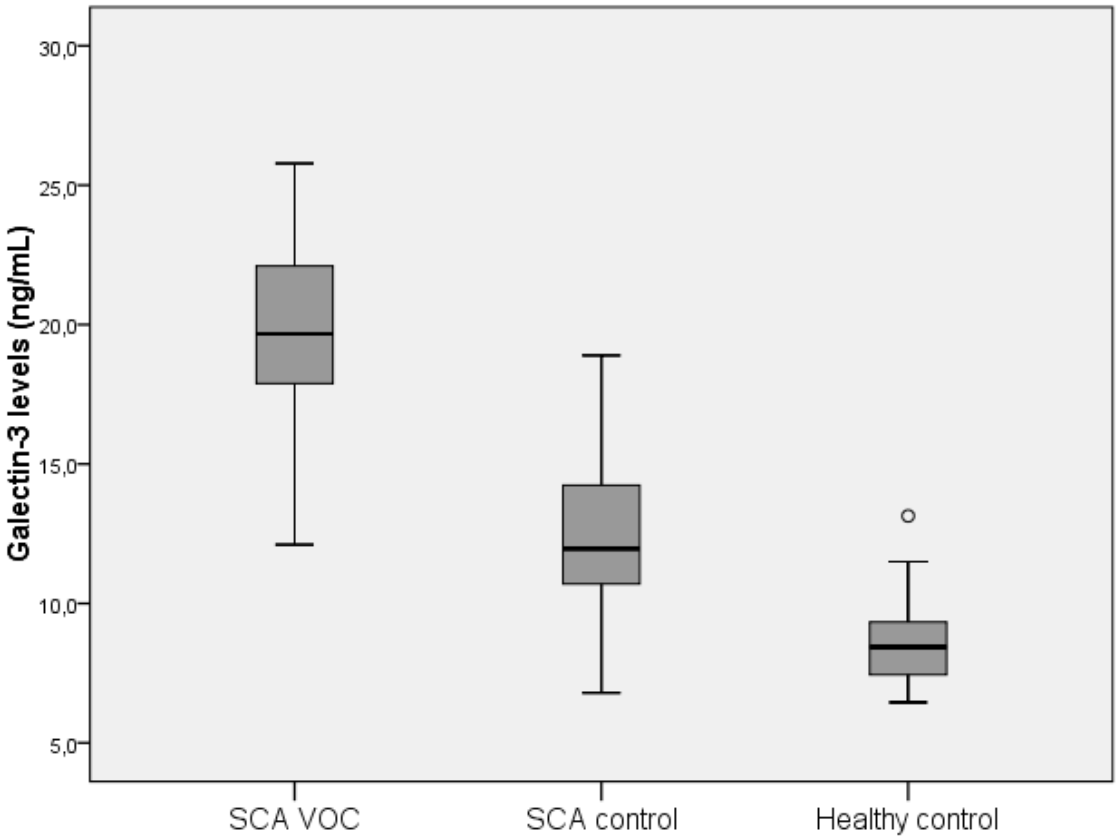


Figure 1: Galectin-3 levels. **SCA:** Sickle cell anaemia, **VOC:** Vasoocclusive crisis

DISCUSSION

This prospective and controlled study demonstrates that galectin-3 levels are higher in patients with painful crises than stable patients with sickle cell anaemia and healthy individuals. Moreover, it was determined that Galectin-3 levels continued to increase in the 48th hour of the painful crisis and were better correlated with the duration of the painful crisis and the duration of an intravenous opioid requirement compared to the 0th-hour measurements.

Sickle cell anaemia is the most common hemoglobinopathy globally and presents with severe organ damage with advancing age and recurrent transfusions (4). These patients mostly apply to the emergency department with a painful crisis and suffer from severe pain (5). There are many ongoing studies to reduce the duration and severity of the painful crisis in hospitalized patients. However, an ideal molecule has not been found yet (6). Hydroxyurea therapy has been used for a long time to increase HbF levels in these patients. Still, despite using hydroxyurea, there are many patients who are admitted to the hospital with severe painful crises.

Two molecules with proven effectiveness in preventing painful crises in recent years stand out. The first of these, L-glutamine, has been shown to reduce the frequency of painful crises. It is believed that this molecule acts by reducing oxidative stress in erythrocytes (7). Crizanlizumab, which has recently been approved by the FDA and acts by inhibiting P-selectin, is another molecule. It has been found that this molecule also reduces the frequency of painful crises in patients with sickle cell anaemia and does this independently of hemolysis (8). Despite the current developments in this regard, the need for biomarkers that will enable the prediction of the severity of the painful crisis as well as the search for molecules that reduce the frequency and severity of painful crises continues.

Galectin-3 is involved in various biological processes such as cellular adhesion, activation, chemotaxis, growth and differentiation, resistance to oxygen and nitrogen radicals, damage and apoptosis (9). In many disease groups, especially malignant diseases, chronic inflammatory diseases and diseases with fibrosis, Galectin-3 levels were studied. It has been shown by Aksan et al. that Galectin-3 levels are high in patients with coronary atherosclerosis and can be used in risk classification. (10). It has been observed that Galectin-3 may have a role in the pathogenesis of pulmonary hypertension in mouse models and it is predicted that it can be used for treatment in the future (11). Studies are showing that Galectin-3 can be used for diagnostic and prognostic purposes in patients with gastric cancer (12). It has been stated that this marker is also increased in peripheral arterial disease, and that it also correlates with oxidative stress markers and inflammation markers (13). It has been shown by Jiang et al. that Galectin-3 is associated with poor prognosis in patients with primary hepatocellular cancer (14). Moreover, Galectin-3 has been shown to have a role in the metastases of some cancers and it has been stated that Galectin-3 inhibitors can be used to reduce metastasis in metastatic cancer patients (15). Many ongoing phase studies are investigating the use of Galectin-3 inhibitors in fibrosis and metastatic cancers.

Although few in number, there are also studies in the literature on the role of Galectin-3 levels in the development of pulmonary hypertension and pulmonary fibrosis in patients with sickle cell anaemia (9, 16). However, no study examining the relationship between Galectin-3 and painful crisis in these patients was found in the literature review. In this respect, what makes this study important is that it is the first to show the relationship between Galectin-3 level and the severity of painful crisis in patients with sickle cell anaemia.

As for the limitations of the study, first of all, we can say that the number of patients was relatively small. Second, although we did examine the relationship between the number of days of intravenous opiod and Galectin-3 levels; since patients were not evaluated daily with pain scores, the relationship with the degree of daily pain was not examined. Third, in patients with sickle cell anaemia who were discharged after a painful crisis attack, Galectin-3 levels could not be examined when they were stable. If they had been examined, we guess we could have found more precise results.

CONCLUSION

In conclusion, in patients with sickle cell anaemia, Galectin-3 may be one of the indicators of disease severity during the painful crisis. Phase studies of Galectin-3 inhibitors are ongoing for many diseases, and the use of these drugs in patients with sickle cell anaemia in painful crisis may also be considered in the light of future studies involving more patients.

Author Contributions: MBK, HB, BK, SU, AT, ENT: wrote the manuscript and obtained the patient consent. **MBK:** critically reviewed and edited the report. All authors read and approved the final manuscript.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Cemil Tasçıoğlu City Hospital approved the study.

REFERENCES

1. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. Lancet. 2017;390(10091):311-23.
2. Zhang D, Xu C, Manwani D, Frenette PS. Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology. Blood. 2016;127(7):801-9.
3. Dong R, Zhang M, Hu Q, Zheng S, Soh A, Zheng Y, et al. Galectin-3 as a novel biomarker for disease diagnosis and a target for therapy (Review). Int J Mol Med. 2018;41(2):599-614.
4. Mburu J, Odame I. Sickle cell disease: Reducing the global disease burden. Int J Lab Hematol. 2019;41 Suppl 1:82-8.
5. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. Jama. 2014;312(10):1033-48.
6. Biemond BJ, Tombak A, Kilinc Y, Al-Khabori M, Abboud M, Nafea M, et al. Sevuparin for the treatment of acute pain crisis in patients with sickle cell disease: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Haematol. 2021;8(5):e334-e43.
7. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226-35.
8. Ataga KI, Kutlar A, Kanter J, Liles D, Cancado R, Friedrisch J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-39.
9. Mendonça Belmont TF, do Ó KP, Soares da Silva A, de Melo Vilar K, Silva Medeiros F, Silva Vasconcelos LR, et al. Single Nucleotide Polymorphisms at +191 and +292 of Galectin-3 Gene (LGALS3) Related to Lower GAL-3 Serum Levels Are Associated with Frequent Respiratory Tract Infection and Vaso-Occlusive Crisis in Children with Sickle Cell Anemia. PLoS One. 2016;11(9):e0162297.
10. Aksan G, Gedikli Ö, Keskin K, Nar G, İnci S, Yıldız SS, et al. Is galectin-3 a biomarker, a player-or both-in the presence of coronary atherosclerosis? J Investig Med. 2016;64(3):764-70.
11. Barman SA, Li X, Haigh S, Kondrikov D, Mahboubi K, Bordan Z, et al. Galectin-3 is expressed in vascular smooth muscle cells and promotes pulmonary hypertension through changes in proliferation, apoptosis, and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2019;316(5):L784-l97.
12. Cheng D, Liang B, Li Y. Serum galectin-3 as a potential marker for gastric cancer. Med Sci Monit. 2015;21:755-60.
13. Fort-Gallifa I, Hernández-Aguilera A, García-Heredia A, Cabré N, Luciano-Mateo F, Simó JM, et al. Galectin-3 in Peripheral Artery Disease. Relationships with Markers of Oxidative Stress and Inflammation. Int J Mol Sci. 2017;18(5).
14. Jiang SS, Weng DS, Wang QJ, Pan K, Zhang YJ, Li YQ, et al. Galectin-3 is associated with a poor prognosis in primary hepatocellular carcinoma. J Transl Med. 2014;12:273.
15. Wu KL, Huang EY, Yeh WL, Hsiao CC, Kuo CM. Synergistic interaction between galectin-3 and carcinoembryonic antigen promotes colorectal cancer metastasis. Oncotarget. 2017;8(37):61935-43.
16. Lee I, Anea C, Kumar S, Falls G, Oseghale A, Brittain J. Galectin-3 Is a Mediator of Pulmonary Fibrosis in Sickle Cell Disease: Novel Roles for Hemolysis and Acute Chest Syndrome. Blood. 2016;128(22):2480-.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Clinical results of PRP application for Gonartrosis; Comparison of one or two week interval application achievements.

Abbas Tokyay[1]*, Necip Güven[1], Sezai Özkan[1], Tülin Türközü[1]

1 Yüzüncü Yıl University School of Medicine, Department of Orthopedics and Traumatology,Van, TR

*** Corresponding Author:** Abbas Tokyay **E-mail:** dr.abbas_tokyay@hotmail.com

ABSTRACT

Objective: Intra-articular platelet-rich plasma PRP (platelet-rich plasma) treatment can be applied at an early stage of Gonarthrosis in addition to medical treatment. There is no consensus in the literature regarding the dose interval of PRP. Our aim in this study is to compare the short-term clinical results of three doses of PRP administered at one and two-week intervals in the treatment of early-stage Gonarthrosis.

Material and Methods: Three doses of PRP were applied to one knee of the patients at intervals of one week and to the other knee at intervals of two weeks. All patients were clinically evaluated with McMaster Universities Arthritis Index (WOMAC) and Visual Analogue Scale (VAS) before the PRP application and at the 1st, 3rd and 6th months after the application.

Results: The mean age of 61 (40 female, 21 male) patients included in this study was 56.75 years and the mean BMI (Body Mass Index) was determined as 25.45±3.15 kg/m2. In the clinical evaluation at the end of the 1st, 3rd, and 6th months after PRP, there was no significant difference between the one-week interval and two-week application. However, it was observed that PRP application provided statistically significant improvement in WOMAC and VAS scores in both applications ($p<0.05$).

Conclusion: According to the findings we obtained in our study, it has been determined that there was no difference between applying three doses of PRP at one- or two-weeks intervals.

Keywords: Platelet-Rich Plasma, PRP, Knee Osteoarthritis, Intra-articular Injection

INTRODUCTION

Knee osteoarthritis (Gonarthrosis) is a common due to the increased elderly population and prevalence of obesity. In various epidemiological studies that were conducted all around the world, it was determined that the symptomatic Gonarthrosis was present in 10-30% of individuals over the age of 65 years (1,2). Gonarthrosis is generally evaluated with Kellgren Lawrence (K-L) radiographic grading scale (3).

Although there are many current treatment methods for Gonarthrosis, the majority of treatments other than surgical treatment are palliative and the aim is to reduce pain and improve the quality of life (3,4). Palliative treatment includes lifestyle modifications such as losing weight and exercise. On the other hand, analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections are used as medical treatment. Hyaluronic acid (HA), corticosteroid, PRP and autologous mesenchymal stem cells are the most applied treatment modalities as intra-articular injections (5,6).

The use of PRP, which is obtained by centrifugation of whole blood and contains a higher concentration of platelets and growth factors than whole blood, has recently become widespread(1,7). Indications of PRP, ideal PRP preparation, dosage, number of doses and dose intervals are frequently discussed in the literature in order to obtain safe and effective applications of PRP in the treatment of early-stage Gonarthrosis (8,9). Although there is not a complete consensus in the literature about application intervals; several studies are present the literature reporting a dose interval of one- to four- weeks (10,11).

Research Article

Received 21-01-2022

Accepted 08-02-2022

Available Online: 17-02-2022

Published 28-02-2022

Our aim in this study is to evaluate the clinical results of 3 doses of PRP, which we applied as a medical treatment option in our clinic in the treatment of early stage Gonarthrosis, at intervals of one and two weeks, according to WOMAC and VAS indexes, and to compare the short-term results of both applications.

MATERIAL and METHODS

Patients who applied to our clinic between 01.04.2021 and 15.06.2021 due to knee pain were evaluated. Patients with a BMI of 20-32kg/m2 and between the ages of 45-75 with bilateral knee stage 2-3 Gonarthrosis according to the American College of Rheumatology (12) clinically and the Kellgreen Lawrence classification(13) radiologically, were included in the study. A total number of 70 patients, who met the inclusion criteria, were included in this prospective randomized study. Nine patients, who did not attend their regular follow-ups and whose treatment was not completed were excluded from the study. The evaluation was performed on the remaining 61 patients and 122 knees. The study was started after the approval of the local ethics committee of our hospital. Three doses of PRP were applied to one knee at one-week intervals and to the other knee at two-week intervals of the patients who were included in this study with bilateral Gonarthrosis. In order to standardize the PRP application, three doses of PRP were applied to the right knee with one-week interval in the first 35 patients, and three doses of PRP were applied to the left knee with two-week intervals for the remaining 35 patients according to their order of admission to the hospital. All patients were clinically evaluated according to VOMAX and VAS scales before the PRP application and at the 1st, 3rd, and 6th months after the PRP application. Patients who had undergone knee surgery due to a history of Gonarthrosis or previous trauma, patients who had undergone intra-knee injection or arthroscopy in the last 6 months, those with immunosuppression and a history of malignancy, and those with arthrosis in one knee were excluded from the study.

Preparation of PRP

For the preparation of PRP, 10 ml of blood was collected using a vacuum system from the antecubital vein in a sterile way into the tubes, including sodium citrate. The blood sample was centrifuged at room temperature for 5 minutes at 3000 rpm and two layers were formed. The plasma in the upper layer was separated by pipetting method and then it was re-centrifuged at 3000 rpm for 10 minutes. The upper layer was discarded from the reconstituted two layers, and 4-6 ml of platelet-rich PRP was obtained from the lower layer.

Route of administration

PRP, prepared in the same way, was used in all patients to achieve standardization. Administration was performed by the same orthopedist from the same localization with the standard injection tip (21-gauge needle). After the patient is seated on the stretcher, the feet were hung down and the knee joint was flexed to approximately 90 degrees. Under sterile conditions, an appropriate dose of PRP was administered into the knee by entering the upper part of the tibial plateau (from the lateral portal) from the lateral side of the patella and patellar tendon junction. After covering the injection site with a sterile sponge, the knee was flexed and extended two or three times to distribute the PRP in the knee. No local anesthetic drug was used before PRP application. It was recommended not to use NSAIDs, not to exercise and long walk outside of daily routine activities, and not to use stairs if possible before the administration of the second dose.

Results of the measurement

All patients were interviewed by an experienced orthopedist using the Turkish version of the WOMAC and VAS questionnaires (21). VOMAC index consists of 24 questions, including five questions for pain, two questions for stiffness, and 17 questions for physical function. Each question was scored from zero (not at all) to four (extreme). The overall WOMAC score ranges from 0 to 96, with higher scores indicating worse results. For VAS index, using a ruler, the patient was asked to mark the place of pain on the ruler as zero (no pain) and ten (worst possible pain).Six months later, the VAS and VOMAC scores of both knees were compared.

Statistical Analysis

Statistical package program SPSS 23.0 was used for the analysis of data. The normal distribution of the data was determined by the Kolmogorov-Smirnov test. Paired sample t-test was used to evaluate the difference between repeated measurements of numerical data. Data were given as Mean±Standard deviation. $p<0.05$ was considered as a statistically significant difference.

RESULTS

The mean age of 61 (40 female, 21 male) patients included in the study was 56.75±7.58 and the mean BMI was 25.45±3.15 kg/m2. The VOMAC and VAS indices of all patients before PRP application and at the 1st, 3rd, and 6th months after PRP application are shown in **Table-1** and **Table-2**.The VOMAC scale of patients to whom PRP was applied at one-week and two-week intervals before and after the application is shown in **Figure-1** and **Figure-2**.

http://dx.doi.org/10.36472/msd.v9i2.681

There was no significant difference in terms of VOMAC and VAS indices between applications performed at one-week intervals and two-week intervals. In the clinical evaluation, it was observed that the total VOMAC and VAS scores of PRP applied at intervals of one and two weeks decreased from the first month, and this decrease was statistically significant($p<0.05$).

A statistically significant decrease in total VOMAC and VAS indices was detected at the end of six months in both application groups after treatment ($p<0.05$). This results show that PRP is effective on the clinical improvement. Superficial skin rash was developed in three of our patients, but it was not interpreted as an infection and completely healed within 2-3 days.

Table 1. PRP, which was applied with one-week intervals

VOMAC	Before PRP	1st month	3rd month	6th month
Pain (0-20)	10.3±1.52[a]	9.7±1.08[b]	5.45±1.19[c]	4.55±0.82[d]
Stiffness(0-8)	3,35±1.18[a]	3.0±1.07[b]	2.15±0.74[c]	2±0.72[c]
Function(0-68)	44.2±4.7[a]	43.1±4.29[b]	31.7±3.75[c]	29.1±3.75[d]
Total (0-96)	57.9±5.42[a]	55.8±5.06[b]	39.3±4.11[c]	35.6±3.36[d]
VAS(0-10)	5.55±1.09[a]	4.85±0.87[b]	2.45±0.61[c]	1.91±0.64[d]

Values with different letters in the same line are statistically significantly different $p<0.05$

Table 2. PRP, which was applied with two-week intervals

VOMAC	Before PRP	1st month	3rd month	6th month
Pain (0-20)	10.5±1.35[a]	9.5±0.88[b]	5.35±1.22[c]	4.7±0.81[d]
Stiffness (0-8)	3.4±1.18[a]	3.15±1.18[a]	2.0±0.85[b]	1.9±0.96[b]
Function (0-68)	44.0±4.42[a]	41.2±4.54[b]	31.5±3.95[c]	28.2±2.63[d]
Total (0-96)	57.8±4.91[a]	53.9±5.04[b]	38.9±4.14[c]	34.8±2.92[d]
VAS(0-10)	5.25±1.01[a]	4.85±1.04[b]	2.8±0.83[c]	2.05±0.61[d]

Values with different letters in the same line are statistically significantly different $p<0.05$

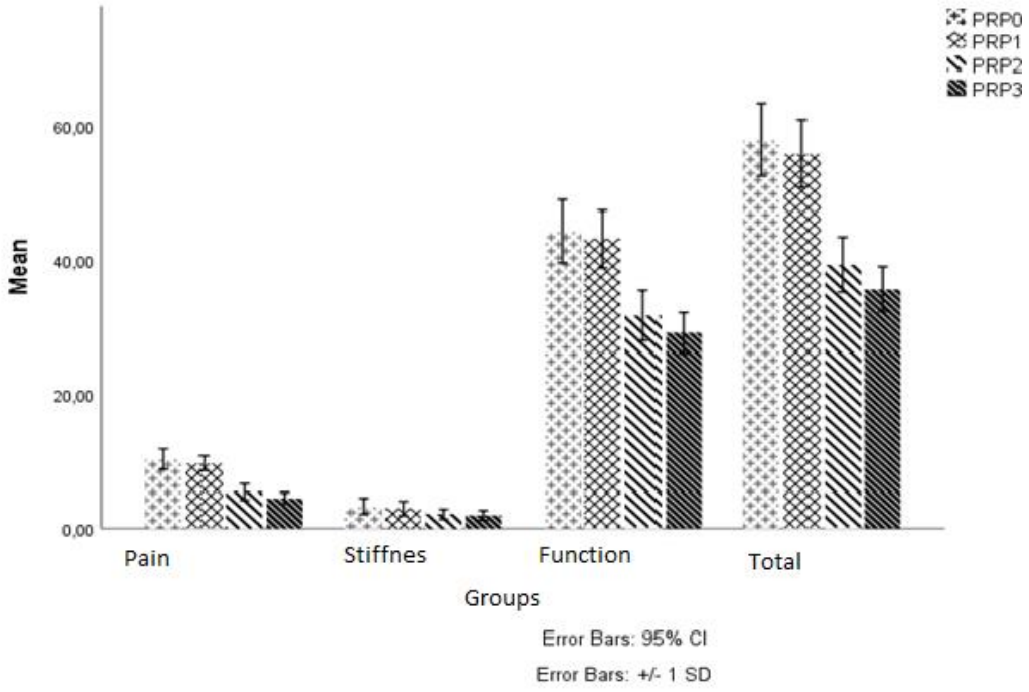


Figure 1: After PRP applied at one-week intervals; pain, stiffness, function, and total VOMAC scale distribution are shown. Error bar shows the SD. (PRP 0; before PRP administration, PRP 1; 1st month after administration, PRP 2; 3rd month after administration, PRP 3; 6th month after administration)

http://dx.doi.org/10.36472/msd.v9i2.681

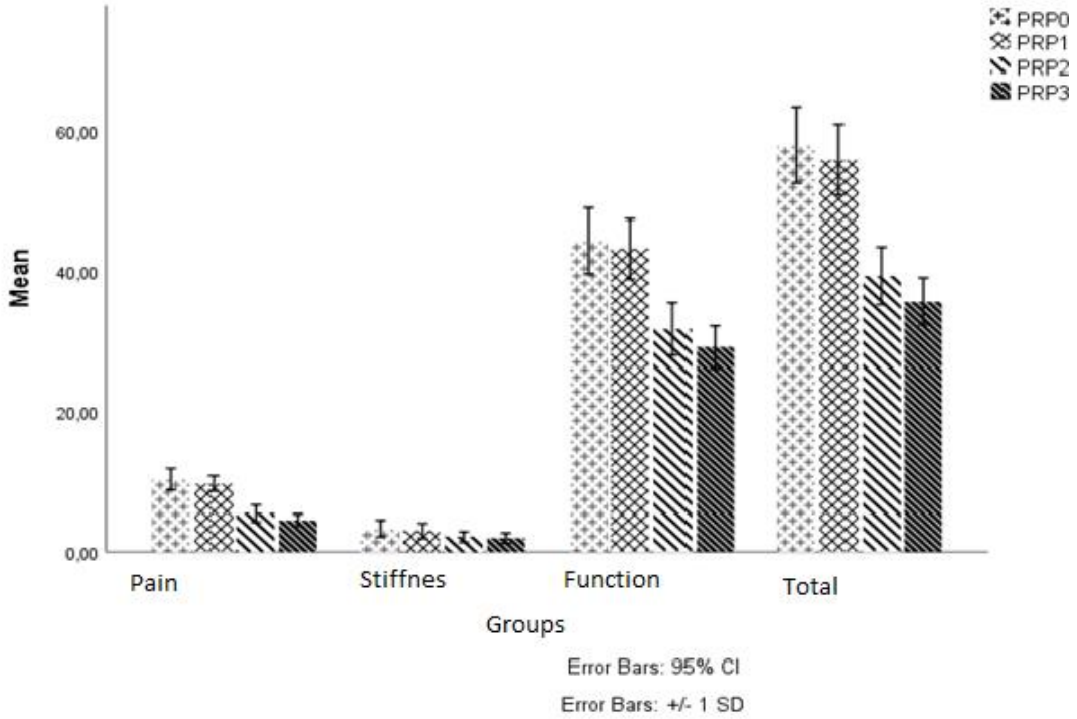


Figure 2: After PRP is applied at two-week intervals; pain, stiffness, function, and total VOMAC scale distribution are shown. Error bar shows the SD. (PRP 0; before PRP administration, PRP 1; 1st month after administration, PRP 2; 3rd month after administration, PRP 3; 6th month after administration)

DISCUSSION

When the demographic characteristics of the patients were evaluated, a similarity was found in the literature in terms of age, gender, and BMI (9,14). Gonarthrosis is seen in women in old age and especially in those with high BMI. In our study, the number of women was found to be higher, and their BMI was high.

Despite its common clinical applications, no consensus is present in the literature about the preparation, application method, number of doses and dose intervals of PRP. Nowadays, PRP is commonly applied in early stage Gonarthrosis that does not need surgery or in patients whose general condition is not suitable for surgical interventions. The results of these treatments are frequently discussed in the literature (15-19). When the dose intervals of PRP were compared in our study, there was no significant difference between the clinical results of three doses of PRP performed at one-week and two-week intervals. In both applications, clinically significant decreases were detected in VOMAC and VAS scores after six months of follow-up. As a result of our study, it was seen that PRP applied at intervals of one and two weeks as dose intervals were effective and successful in both applications. There are studies reporting that the ethnicity of the individual influences the platelet function during PRP administration (20). Considering this characteristic of PRP, this activity difference was tried to be eliminated by applying PRP to different knees of the same individual. Thus, specificity was achieved in our study with PRP applied in the same way on the same person.

PRP can be prepared as a result of one or two times of centrifugation (21, 22). It is known that the patient's age, comorbid diseases, the amount of blood taken at the beginning and the preparation technique are effective on the platelet concentration in the PRP (22). The PRP used in our study was obtained in the same standards by centrifuging twice with the help of our technician using the device in our center.

There are studies about the administration of a single dose or multiple doses of PRP in the literature (23-25). Clinical results were found to be more successful with multiple doses (21). In animal studies, the curative effect of PRP on synovial and cartilage tissue was found to be more effective with multiple doses (17). Based on such studies in literature and our clinical experiences, we applied three doses of PRP to all our patients.

Different recommendations are present in literature about the method of administration and the position of patient. Method of administration includes injection directly into the joint and administration via collagen membrane (22, 26).

Patient positions include administration to suprapatellar region at supine position of patient and full extension of knee or administration from the lateral portal of the knee in the sitting position with the knee flexed at 90 degrees (9,14).

Our routine practice in our study was administration of PRP in sitting position with the knee flexed, from the lateral portal directly into the joint, and no membrane was used.

Considering the mechanism of action of PRP, platelets, especially growth factors, cytokines and chemokines secreted from alpha granules, stimulate chondrocyte and chondrogenic structures and increase chondrocyte cartilaginous matrix secretion after intraarticular administration (27). Although this situation increases cartilage regeneration, the lack of vascular and nerve structure of the cartilage limits this regeneration (28). Although the duration of the PRP effect is not clear in literature, studies have shown that the duration of this effect may vary between 6 months and 2 years (21,26,29). In our study, the results of PRP in the first six months were evaluated based on the most effective time in the literature and various suggestions are present in the literature regarding the administration interval for PRP. However, there is still no consensus about this subject. Generally, this interval ranges from one week to four weeks (10,11). Some studies have reported that it is sufficient to repeat it once a year (21,30). We think that the evaluation of the clinical results of the same PRP at different time intervals with VOMAC and VAS scores for the same patient will provide more objective results. After this evaluation, no significant difference was found between clinical results in terms of dose intervals in our study.

There are also some limitations of our study. These limitations include; the low number of our patients, relatively short patient follow-up times, and lack of radiological evaluation.

CONCLUSION

In our study, no clinically significant difference was found between three doses of PRP which was administered at one- or two-week intervals in early-stage Gonarthrosis. However, it was determined that there was a significant clinical improvement in the knees for both administration intervals compared to pre-PRP values.

Author Contributions: AT, NG, SÖ, TT: Project design, Patient examinations, Data analyses **AT:** Manuscript preparation, revisions.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. O'Neill TW, Felson DT. Mechanisms of Osteoarthritis (OA) Pain. Curr Osteoporos Rep. 2018;16:611-16.
2. Wang-Saegusa A, Cugat R, Ares O, Seijas R, Cuscó X, Garcia-Balletbó M. Infiltration of plasma rich in growth factors for osteoarthritis of the knee short-term effects on function and quality of life. Arch Orthop Trauma Surg. 2011;131:311-17.
3. Murray I, Benke M, Mandelbaum B. Management of knee articular cartilage injuries in athletes: chondro protection, chondro facilitation, and resurfacing. Knee Surg Sports Traumatol Arthrosc. 2015;24:1617–26.
4. Kellgren JH, Lawrence J. The epidemiology of chronic rheumatism. In: Atlas of Standard Radiographs of Arthritis, Volume II. Oxford, UK: Black wellScientific; 1963.
5. Cole BJ, Karas V, Hussey K, Pilz K, Fortier LA. Hyaluronic Acid Versus Platelet-Rich Plasma: A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis. Am J Sports Med. 2017;45:339-46.
6. Wang P, Yang L, Li H, et al. Effects of whole-body vibration training with quadriceps strengthening exercise on function in gand gait parameters in patients with medial compartment knee osteoarthritis: a randomised controlled preliminary study. Physiotherapy. 2016;102:86–92.
7. Paoloni J, De Vos RJ, Hamilton B, Murrell GA, Orchard J. Platelet-rich plasma treatment for ligament and tendon injuries. Clin J Sport Med 2011;21:37-45.
8. Dório M, Pereira RMR, Luz AGB, Deveza LA, de Oliveira RM, Fuller R. Efficacy of platelet-rich plasma and plasma for symptomatic treatment of knee osteoarthritis: a double-blinded placebo-controlled randomized clinical trial. BMC Musculoskelet Disord. 2021 24;22:822.
9. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2030;41:356-64.
10. Zhang W, Robertson J, Jones A, Dieppe P, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis. 2008;67:1716–23.
11. Huang PH, Wang CJ, Chou WY, Wang JW, Ko JY. Short-term clinical results of intra-articular PRP injections for early osteoarthritis of the knee. Int J Surg. 2017;42:117-22.
12. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum. 2000;43:1905-15.
13. Petersson IF, Boegård T, Saxne T, Silman AJ, Svensson B. Radiographic osteoarthritis of the knee classified by the Ahlbäck and Kellgren& Lawrence systems for the tibio femoral joint in people aged 35-54 years with chronic knee pain. Ann Rheum Dis. 1997;56:493-96.
14. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single- and double-dose of platelet-rich plasma versus hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. World J Orthop. 2019;10:310-26.

15. Smith PA. Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 2016;44:884-91.

16. Cole BJ, Karas V, Hussey K, Merkow DB, Pilz K, Fortier LA. Hyaluronic acid versus platelet-rich plasma: a prospective, double-blind randomized controlled trial comparing clinical out comes and effects on intra-articular biology for the treatment of knee osteoarthritis. Am J Sports Med. 2017;45:339-46.

17. Chouhan DK, Dhillon MS, Patel S, Bansal T, Bhatia A, Kanwat H. Multiple Platelet-Rich Plasma Injections Versus Single Platelet-Rich Plasma Injection in Early Osteoarthritis of the Knee: An Experimental Study in a Guinea Pig Model of Early Knee Osteoarthritis. Am J Sports Med. 2019;47:2300-2307.

18. Cole BJ, Karas V, Fortier LA. Hyaluronic Acid Versus Platelet-rich Plasma: Response. Am J Sports Med. 2017;45:NP21-NP22.

19. Campbell KA, Saltzman BM, Mascarenhas R, et al. Does Intra-articular Platelet-Rich Plasma Injection Provide Clinically Superior Outcomes Compared With Other Therapies in the Treatment of Knee Osteoarthritis? A Systematic Review of Overlapping Meta-analyses. Arthroscopy. 2015;31:2213-21.

20. Taniguchi Y, Yoshioka T, Kanamori A, Aoto K, Sugaya H, Yamazaki M. Intra-articular platelet-rich plasma (PRP) injections for treating knee pain associated with osteoarthritis of the knee in the Japanese population: a phase I and II a clinical trial. Nagoya J MedSci. 2018 ;80:39-51.

21. Gobbi A, Lad D, Karnatzikos G. Theeffects of repeated intra-articular PRP injections on clinical outcomes of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2015;23:2170-77.

22. Shahid M, Kundra R. Platelet-rich plasma (PRP) for knee disorders. EFORT Open Rev. 2017;2:28-34.

23. Almasry SM, Soliman HM, El-Tarhouny SA, Algaidi SA, Ragab EM. Platelet rich plasma enhances the immunohistochemical expression of platelet derived growth factor and vascular endothelial growth factor in the synovium of the meniscectomized rat models of osteoarthritis. Ann Anat. 2015;197:38-49

24. Kazemi D, Fakhrjou A. Leukocyte and Platelet Rich Plasma (L-PRP) Versus Leukocyte and Platelet Rich Fibrin (L-PRF) For Articular Cartilage Repair of the Knee: A Comparative Evaluation in an Animal Model. Iran Red Crescent Med J. 2015;17:e19594.

25. Liu J, Song W, Yuan T, Xu Z, Jia W, Zhang C. A comparison between platelet-rich plasma (PRP) and hyaluronate acid on the healing of cartilage defects. PLoS One. 2014;9:e97293.

26. Dhillon MS, Patel S, Bansal T. Improvising PRP for use in osteoarthritis knee- upcoming trends and futuristic view. J Clin Orthop Trauma. 2019;10:32-35.

27. Cook CS, Smith PA. Clinical Update: Why PRP Should Be Your First Choice for Injection Therapy in Treating Osteoarthritis of the Knee. Curr Rev Musculoskelet Med. 2018;11:583-92.

28. Filardo G, Kon E, Buda R, et al. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2011;19:528e535.

29. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. 2017;12:16.

30. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy. 2016 ;32:495-505.

Medical Science and Discovery
ISSN: 2148-6832

The effects of computer-based cognitive training program on reaction times of patients with early stage Alzheimer's disease and traumatic brain injury

Büşra Sümeyye Arıca Polat[1]*, Ayşe Cağlar Sarılar[2]

1 Gulhane Training and Research Hospital, Department of Neurology, Ankara, TR
2 Erciyes University, School of Medicine, Department of Neurology, Kayseri, TR

*** Corresponding Author:** Busra S. Arica Polat **E-mail:** busrarica@yahoo.com

ABSTRACT

Objective: Computer-Based Cognitive Training Programs (CBCT) are considered to be effective both in reducing cognitive deficits in the process of Alzheimer's disease (AD) and the treatment of cognitive dysfunction in patients with traumatic brain injury (TBI). This research aimed to investigate the effects of this program on reaction times of AD and TBI patients and to evaluate its applicability for patients with various levels of cognitive dysfunction.

Material and Methods: The data of patients with early-stage Possible AD or TBI who had at least 20 sessions of the CBCT program because of cognitive dysfunctions were evaluated retrospectively. The age, gender, educational status, marital status, systemic diseases, family history for dementia, and disease duration of the patients were recorded. NoroSOFT® Cognitive Training Program was applied to all participants three days a week for eight weeks. The patients' total scores, total accuracy percentages, and total levels as well as the reaction times of all patients in the first and last session of their performance, were determined at the end of the program.

Results: In this study, the data of 31 patients [17 Traumatic Brain Injury (54.8%), 14 Early-Stage Alzheimer's disease (45.2%)] who completed the CBCT Program were analyzed. The mean age of Alzheimer's patients was 73.28±4.89 years, and the mean age of TBI patients was 30.94 ± 12.24 years. The reaction times at the end of the program were significantly better in both groups than before (in TBI;14.55±7.32 sec, 7.23±3.07 sec $p<0.01$ / in AD; 13.43±6.90 sec, 9.48±3.55 sec $p<0.01$). Total memory scores were found to be significantly better in patients with TBI than in patients with AD (1404.64±435.87 points, 932.47±503.06 points $p=0.01$, respectively) at the end of the program. There was no drop-out of the patients and no side effects were reported during the program.

Conclusion: CBCT programs are easily applicable and sustainable interventions in the patients with TBI and early-stage AD. Cognitive exercises may improve patients' reaction times and should be considered in routine treatment protocols.

Keywords: Computer-based cognitive training, reaction time, traumatic brain injury, early-stage Alzheimer's disease, applicability

Research Article

Received 26-01-2022

Accepted 14-02-2022

Available Online: 18-02-2022

Published 28-02-2022

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting all cognitive domains, especially memory (1). It is estimated that the number of Alzheimer's patients will be 115.4 million in 2050 in the world (2). In "Early-stage AD" which is the initial stage of AD, the functionality of patients is relatively preserved despite difficulties in more than one cognitive area, and they can live independently (3). It is already known that the effect of acetylcholinesterase inhibitors and memantine usage in the treatment is limited. For this reason, non-pharmacological methods have been applied to patients recently in addition to pharmacological treatment (4). Traumatic Brain Injury (TBI) is defined as the structural and physiological deterioration of the brain functions caused by an external force. After this deterioration, decreased level of consciousness or complete loss of consciousness, inability to remember events before or after the injury, mental status changes, neurological deficits, or intracranial lesions can be experienced (5).

http://dx.doi.org/10.36472/msd.v9i2.683

It is a critical healthcare issue as it mostly affects young adults and causes advanced functional limitations in survivors (6). A multidisciplinary approach is recommended in the management of TBI. Cognitive interventions targeting memory, attention, executive, and visuospatial functions, therapies for regaining behavior, mood and insight, sleep therapy, and vestibular rehabilitation are very important in the rehabilitation process in addition to physical rehabilitation (for gait, balance and mobility) (7).

Cognitive training is considered to be effective both in reducing cognitive deficits in the AD process and the treatment of cognitive dysfunction in TBI patients (8, 9). Cognitive training is defined as systematic, functionally focused therapeutic activities based on the understanding and evaluation of the brain-behavioral deficiencies of patients (10). It is already known that Computer-Based Cognitive Training Programs (CBCT), whose difficulty level increases gradually according to patients' performance, are the most beneficial intervention in this field (11).

It was shown that the exercises in these programs can result in improvement in memory, executive functions, naming, attention, social cognition, and information processing speed skills in both diseases (12, 13). Also, the easy implementation of CBCT programs has an important advantage for patients and their caregivers and healthcare professionals who deal with these groups (14).

The purpose of the present study was to investigate the effects of the Computer-Based Cognitive Training Program on reaction times of patients with early-stage Alzheimer's disease and traumatic brain injury. It was also aimed to evaluate the applicability of this program for patients with various levels of cognitive dysfunction.

MATERIAL and METHODS

Patients

The data of patients who presented to the neurology clinic between January 2018 and December 2021 and who had at least 20 sessions of the CBCT program because of cognitive dysfunctions were evaluated retrospectively. The study included fourteen Alzheimer's patients who met the diagnostic criteria of "Possible AD" according to the latest diagnostic guideline (15). Seventeen TBI patients who had an open, closed, or penetrating head injury and therefore received physical rehabilitation treatment and whose cognitive deficits were detected after neuropsychological evaluation. Alzheimer's patients were in the mild dementia stage (CDR:1) according to the Clinical Dementia Rating Scale (CDR) (16). TBI patients were selected among mild/moderate patients who had lesions and brain damage that were detected in brain imaging (17). Those who did not complete the CBCT Program, had insufficient data in their medical record, had severe systemic diseases that could affect cognitive functions, and were still receiving cancer treatment were excluded from the study. The age, gender, educational status, marital status, systemic diseases, family history for dementia, and disease duration (according to symptom onset) of the patients were recorded.

Ethics committee approval was obtained for the study and necessary consents were obtained from the relatives of the patients that their data could be used for scientific purposes. The study was conducted in line with the principles of the Declaration of Helsinki 2008.

NoroSOFT® Cognitive Training Program

NoroSOFT® Cognitive Training Program was applied to all participants in sitting positions. This program includes Turkish exercises prepared in line with Turkish culture and can be applied online on the web, which improves memory, attention, concentration, executive functions, visual-spatial perception, and conceptualization skills. The percentage of accuracy and reaction times of the answers given are determined by the scores in the five cognitive sub-domains mentioned above. As the total daily score (determined from the answers and reaction times) increases, the exercises become more difficult. A total of ten exercises, two from each of these five cognitive domains, were applied to the patients in each session, which lasted approximately 25-30 minutes (3 days a week, a total of 8 weeks). The patients' total scores, total accuracy percentages, and total levels were determined in these five areas at the end of the program.

Also, the reaction times of all patients in the first and last session of their performance in the CBCT program were recorded in seconds.

Statistical Analysis: The SPSS 21.0 (Statistical Package for Social Sciences, Chicago, IL, USA) was used for statistical analysis. Descriptive statistics were expressed as mean ± standard deviation for continuous and discrete numerical variables, and the number of cases and percentage (%) for the nominal variables. The comparison of data that were expressed as percentages was compared with the Fisher Freeman Halton Test and the Chi-Square Test, and the continuous variables were compared with the Mann-Whitney U-Test. $p< 0.05$ values were considered statistically significant.

RESULTS

In this study, the data of 31 patients [17 Traumatic Brain Injury (54.8%), 14 Early-Stage Alzheimer's disease (45.2%)] who completed the CBCT Program were analyzed. The mean age of Alzheimer's patients was 73.28 ± 4.89 years, and the mean age of TBI

http://dx.doi.org/10.36472/msd.v9i2.683

patients was 30.94 ± 12.24 years. All AD patients were receiving Donepezil 10 mg/day for treatment. Those who had a diagnosis of TBI did not use any medical treatment for cognitive dysfunction. The demographic characteristics of the patients are summarized in Table 1.

The mean reaction time of TBI patients in the first session when they started the CBCT Program was 14.55±7.32 sec, and 13.43±6.90 sec for AD patients. The reaction time in the last session of the approximately eight-week program was 7.23±3.07 sec in those with TBI, and 9.48±3.55 sec in AD patients. The reaction times at the end of the program were significantly better in both groups than before ($p<0.01$, $p<0.01$).

The total exercise scores, accuracy percentages, and the total levels reached by the patients in the five sub-domains obtained at the end of the CBCT program are given in Table 2. Total memory scores were significantly better in patients with TBI than in patients with AD (1404.64±435.87 points, 932.47±503.06 points $p=0.01$, respectively) at the end of the program. It was also found that the reaction time in the last sessions of TBI patients was faster than AD, although not statistically significant (7.23±3.07 sec, 9.48±3.55 sec; $p=0.06$). No significant differences were detected between the two groups in terms of percentage of total accuracy, total level achieved, total attention and concentration, executive functions, visuospatial perception, and conceptualization scores.

There was no drop-out of the patients during the program. Also, no side effects were reported.

DISCUSSION

The results of the present study showed that the eight-week CBCT program improved the information processing speeds of both early-stage Alzheimer's patients and patients with Traumatic Brain Injury. However, the total memory scores of TBI's were found to be higher than those with AD at the end of the program. Also, it was stated in subjective feedback that this program was easily applicable and sustainable by the patients, and no negative effects were observed during the program.

Recently, in diseases such as TBI and AD causing cognitive damage, it is considered that cognitive training practices can reduce and/or improve the progression of cognitive deficits as well as medical treatments (8, 13). It is already known that especially CBCT programs are more effective than traditional paper-pencil methods and occupational therapy applications (11, 13). It was found that these programs stimulate residual cognitive skills in TBI patients resulting in improvement in many cognitive areas, especially memory and attention (18). Similarly, it was also speculated that rehabilitation of posttraumatic memory, attention, and executive functions may provide positive effects in improving symptoms (17, 19). Because of these positive effects, CBCT programs are recommended in the clinical management of patients with TBI (20). As in TBI, moderate positive effects of such exercises on cognition were demonstrated in early-stage AD as well (11).

Table 1. Demographic characteristics of the patients diagnosed with TBI and AD

	TBI	AD
Gender, Male, n (%)	10 (58.8)	12 (85.7)
Age, Years (Mean±SD)	30.94±12.24	73.28±4.89
Marital status, Married, n (%)	4 (23.5)	11 (78.6)
Presence of systemic disease, n (%)	1 (5.9)	12 (85.7)
Family history of dementia, n (%)	1 (5.9)	5 (35.7)
Education duration, years (Mean±SD)	10.88±3.10	7.78±2.75
Disease duration, years (Mean±SD)	2.11±2.06	1.53±0.84

TBI: Traumatic brain injury; AD: Alzheimer disease; SD: Standard deviation

Table 2. Scores of patients after the CBCT program and reaction times of the first and last session

	TBI	AD	p
Total accuracy percentage (Mean±SD)	77.17±7.10	75.28±6.83	0.45
Total level (Mean±SD)	4.88±2.86	6.21±1.88	0.14
Total memory score (Mean±SD)	1404.64±435.87	932.47±503.06	**0.01***
Total attention and concentration score (Mean±SD)	1285.05±916.66	1532.85±585.48	0.38
Total executive function score (Mean±SD)	788.64±507.22	761.21±325.80	0.28
Total visual-spatial perception score (Mean±SD)	904.41±632.19	1080.64±529.22	0.41
Total conceptualization score (Mean±SD)	520.05±324.18	639.21±283.51	0.29
First reaction time (Mean±SD)	14.55±7.32	13.43±6.90	0.66
Last reaction time (Mean±SD)	7.23±3.07	9.48±3.55	0.06

CBCT: Computer-based cognitive training; TBI: Traumatic brain injury; AD: Alzheimer's disease; SD: Standard deviation; *p value < 0.05

http://dx.doi.org/10.36472/msd.v9i2.683

It was suggested that these practices may provide some positive effects in improving the learning and short-term memory performance of patients with mild cognitive impairment and/or dementia (21). In the present study, it was shown that cognitive function scores improved in TBI patients and early-stage AD patients after the CBCT program, in line with previous studies. Total memory scores of patients with TBI were better than those with AD at the end of the CBCT program. This may be because of the static lesions in TBI patients and the absence of a degenerative process. Also, the younger age of TBI patients and the lower incidence of comorbidities that may affect cognitive functions may explain this difference.

It was found in the present study that there was a significant improvement in the reaction time, in other words information processing speed, of the patients in both groups at the end of the program which was consistent with previous studies. In a randomized controlled study conducted with fifty early-stage AD patients, it was shown that a 15-week CBCT program increased the information processing speed of the treated patients when compared to the controls in each session lasting approximately one hour and applied twice a week (22). Similarly, a meta-analysis of 12 studies speculated that these exercises might be a valid complementary treatment method especially for age-related reaction times (12). The effects of CBCT programs on reaction times of TBI's are similar to those of AD. In a review conducted by Sigmundsdottir L. et al., it was argued that Computer-Based Cognitive Training has moderate to strong evidence in improving the reaction times of patients in TBI (23). In the present study, the reaction times of TBI patients were found to be better than those with AD at the end of the program, although no statistically significant differences were detected. Large-scale randomized studies are needed to demonstrate whether there is a difference in reaction times in these two diseases.

It was found that these programs are easily applicable and sustainable for patients who have degenerative and posttraumatic cognitive impairment (11, 24). The clinical usefulness of these ergonomically designed programs was confirmed by the increased performance of all patients in the functions investigated (25). The results of the present study were compatible with other studies. All of the patients completed the eight-week CBCT program successfully, and there was no drop-out. Also, with subjective feedback from the patients, it was learned that the motivation of the patients was high during the program and no side effects were observed.

Cognitive training creates changes in the structure of synapses and increases neurogenesis (26).

It is considered that cognitive exercises can improve cognition in both AD and TBI patients providing preliminary evidence for neuroplasticity (8, 27).

The present study had some limitations. Since it has a retrospective design, it was not possible to reach the neuropsychological evaluations of the patients before and after the program from the file data. Also, the number of patients analyzed in the study was relatively small. Therefore the benefit of moderate to severe TBI patients from this program could not be analyzed.

CONCLUSION

Computer-Based Cognitive Training programs are easily applicable and sustainable applications in traumatic brain injury and early-stage Alzheimer's patients. Cognitive exercises improve patients'reaction times and must be included in routine treatment protocols. Randomized controlled large-scale studies are required to more clearly demonstrate the cognitive and behavioral effects of such programs on people with both degenerative and posttraumatic cognitive impairment.

Author Contributions: BSAP, ACS: Research concept and design, collection and/or assembly of data, data analysis and interpretation, writing the article, critical revision of the article,final approval of article**.**

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. Clare L, Woods RT. Cognitive training and cognitive rehabilitation for people with early-stage Alzheimer's disease: a review. Neuropsychol Rehab 2004;14(4): 385-401.

2. Fiest KM, Roberts JI, Maxwell CJ, Hogan DB, Smith EE, Frolkis A, et al. The prevalence and incidence of dementia due to Alzheimer's disease: a systematic review and meta-analysis. Can J Neurol Sci 2016;43(1):51-82.

3. Panegyres P, Berry R, Burchell J. Early dementia screening. Diagnostics. 2016;6(1):6.

4. Olazarán J, Muiz R, Reisberg B, Casanova J, del Ser T, Cruz-Jentoft AJ, et al. Benefits of cognitive-motor intervention in MCI and mild to moderate Alzheimer disease. Neurology 2004;63(12):2348-2353.

5. McMilla A, Baer G, Beattie A, Carson A, Edwards M, Evans J, et al. Brain injury rehabilitation in adults: a national clinical guideline [Internet]. Edinburgh: SIGN guidelines, 2013. http://www.sign.ac.uk.

6. Dikmen SS, Machamer JE, Powell JM, Temkin NR. Outcome 3 to 5 years after moderate to sever traumatic brain injury. Arch Phys Med Rehabil 2003;84:1449-1457.

7. Lee SY, Amatya B, Judson R, Truesdale M, Reinhardt JD, Uddin T, et al. Clinical practice guidelines for rehabilitation in traumatic brain injury: a critical appraisal. Brain Inj 2019;33(10):1263-1271.

8. Choi J, Twamley EW. Cognitive rehabilitation therapies for Alzheimer's disease: a review of methods to improve treatment engagement and self-efficacy. Neuropsychol Rev 2013;23(1):48-62.

9. Spreij LA, Visser-Meily JM, van Heugten CM, Nijboer TC. Novel insights into the rehabilitation of memory post acquired brain injury: A systematic review. Frontiers in Human Neuroscience 2014;8:993.

10. Cicerone KD, Langenbahn DM, Braden C, Malec JF, Kalmar K, Fraas M, et al. Evidence-based cognitive rehabilitation: Updated review of the literature from 2003 through 2008. Arch of Physical Medicine and Rehabil 2011;92:519-530.

11. García-Casal JA, Loizeau A, Csipke E, Franco-Martín M, Perea-Bartolomé MV, Orrell M. Computer-based cognitive interventions for people living with dementia: a systematic literature review and meta-analysis. Aging & Mental Health. 2017;21(5):454–467.

12. Shao YK, Mang J, Li PL, Wang J, Deng T, Xu ZX. Computer-based cognitive programs for improvement of memory, processing speed and executive function during age-related cognitive decline: a meta-analysis. PLoS One. 2015;10(6): e0130831.

13. De Luca R, Calabrò RS, Gervasi G, De Salvo S, Bonanno L, Corallo F, et al. Is computer-assisted training effective in improving rehabilitative outcomes after brain injury? A case-control hospital-based study. Disability and Health Journal 2014;7:356-360.

14. Lebowitz MS, Dams-O'Connor K, Cantor JB. Feasibility of computerized brain plasticity-based cognitive training after traumatic brain injury. J Rehabil Res Dev. 2012;49(10):1547-1556.

15. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 2011;7(3):263–269.

16. Morris JC. Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9:1:173-176.

17. The Management of Concussion-mild Traumatic Brain Injury, Working Group. VA/DoD clinical practice guideline for the management of concussion-mild traumatic brain injury [Internet]. 2016. https://www.healthquality.va.gov/guidelines/Rehab/mtbi/mTBICPGFullCPG50821816.pdf

18. Cho HY, Kim KT, Jung JH. Effects of computer assisted cognitive rehabilitation on brain wave, memory and attention of stroke patients: A randomized control trial. Journal of Physical Therapy Science 2015;27:1029-1032.

19. Wheeler S, Acord-Vira A. Occupational therapy practice guidelines for adults with traumatic brain injury. 1st. Lieberman D, Arbesman M, editors. Bethesda: AOTA Press; 2016;1-47.

20. Department of Labor and Employment. Traumatic brain injury medical treatment guidelines. State of Colorado: Department of Labor and Employment, Division of Workers' Compensation; 2013.

21. Klimova B, Maresova P. Computer-Based Training Programs for Older People with Mild Cognitive Impairment and/or Dementia. Front Hum Neurosci. 2017;11:262.

22. Nousia A, Siokas V, Aretouli E, Messinis L, Aloizou AM, Martzoukou M, et al. Beneficial Effect of Multidomain Cognitive Training on the Neuropsychological Performance of Patients with Early-Stage Alzheimer's Disease. Neural Plast 2018;11:2845176.

23. Sigmundsdottir L, Longley WA, Tate RL. Computerized cognitive training in acquired brain injury: A systematic review of outcomes using the International Classification of Functioning (ICF). Neuropsychol Rehabil 2016;11:1-69.

24. Yoo C, Yong MH, Chung J, Yang Y. Effect of computerized cognitive rehabilitation program on cognitive function and activities of living in stroke patients. Journal of Physical Therapy Science 2015;27:2487-2489.

25. Fernández E, Bringas ML, Salazar S, Rodríguez D, García ME, Torres M. Clinical impact of RehaCom software for cognitive rehabilitation of patients with acquired brain injury. MEDICC Review 2012;14:32-35.

26. Verhelst H, Giraldo D, Vander Linden C, Vingerhoets G, Jeurissen B, Caeyenberghs K. Cognitive Training in Young Patients With Traumatic Brain Injury: A Fixel-Based Analysis. Neurorehabil Neural Repair 2019;33(10):813-824.

27. Voelbel GT, Lindsey HM, Mercuri G, Bushnik T, Rath J. The effects of neuroplasticity-based auditory information processing remediation in adults with chronic traumatic brain injury. NeuroRehabilitation 2021;49(2):267-278.

Medical Science and Discovery
ISSN: 2148-6832

Is it possible to predict the development of anaphylaxis before oral food challenge tests administered to evaluate tolerance in IgE-mediated food allergy in children?

Serdar Al[1]*, Suna Asilsoy[1], Dilek Tezcan[1], Özge Atay[1], Özge Kangallı[1], Gizem Atakul[1], Seda Şirin Köse[2], Nevin Uzuner[1], Özkan Karaman[1]

1 Dept of Pediatric Allergy and Clinical Immunology, Dokuz Eylul University Faculty of Medicine, Izmir, TR
2 Dept of Pediatric Allergy and Clinical Immunology, Dr. Sami Ulus Child Disease Training and Research Hospital, Ankara, TR

*** Corresponding Author:** Serdar Al **E-mail:** drserdaral@gmail.com

ABSTRACT

Objective: Life-threatening anaphylaxis may occur in IgE-mediated food allergy. Oral Food Challenge (OFC) is the gold standard in demonstrating tolerance and diagnosing food allergy; however, these tests may cause anaphylaxis. Predicting the risk of developing anaphylaxis before performing OFC is valuable information in evaluating tolerance as in diagnosis. The present study aims to evaluate the effectiveness of the tests used in clinical practice in predicting the risk of anaphylaxis during OFC in IgE-mediated food allergy. To our knowledge, this is the first study evaluating skin prick tests in the prediction of anaphylaxis.

Material and Methods: In this descriptive cross-sectional study, the history, demographic, clinical and laboratory data of the patients, followed up with the diagnosis of IgE-mediated food allergy, on whom OFC was performed, were evaluated retrospectively.

Results: Of the 254 patients who underwent OFC, 133 were followed up with a diagnosis of IgE-mediated food allergy. The mean age was 21 months (12-120), and anaphylaxis occurred in nine (6.7%) of them during OFC. According to the frequency, the food responsible for IgE-mediated food allergy was determined as milk, egg and egg-milk combination. Age during the challenge and total IgE levels were higher in the group that experienced OFC-related anaphylaxis. The tests that could best determine the risk of anaphylaxis before the challenge was the skin prick test (SPT) and prick to prick (PTP) test for milk. Milk SPT and PTP test at the time of initial diagnosis and determination of milk sIgE and egg white sIgE before challenge were found to predict the risk of anaphylaxis. The negative predictive value was over 95% in tests that gave significant results for milk. There was no statistically significant finding associated with other allergenic foods.

Conclusion: In evaluating tolerance development, performing sIgE, SPT and/or PTP tests for milk before OFC is useful in predicting anaphylaxis. Studies with larger numbers of cases are needed to assess the risk of anaphylaxis caused by other foods.

Keywords: Food challenge in children, allergy in childhood, skin prick test, prick to prick test, specific IgE, anaphylaxis during provocation

Research Article

Received 26-01-2022

Accepted 14-02-2022

Available Online: 18-02-2022

Published 28-02-2022

INTRODUCTION

Food allergy is defined as an unexpected immunological response that develops after exposure (usually ingestion) to food and can be repeated after encountering the same food (1). Food allergy is a severe public health problem that affects society, especially children, with no known radical cure despite the risk of severe allergic reaction and even death, increasing in prevalence in our country and throughout the world (2). Although the prevalence varies according to countries, it was determined as 0.6-12% according to survey-based studies and 0.3-7.7% according to food allergy clinical practise (3). Food-related immunological reactions are classified as immunoglobulin E (IgE)-mediated, non-IgE and mixed type reactions (4).

http://dx.doi.org/10.36472/msd.v9i2.684

IgE-mediated food allergies are reactions that typically begin within minutes to two hours after ingestion. Rash, urticaria-angioedema, pruritus, erythema, contact urticaria, vomiting, nausea, abdominal pain, nasal congestion, nasal itching, sneezing, hoarseness, wheezing, stridor, cough, respiratory distress, hypotension, somnolence, incontinence, convulsion, syncope and anaphylaxis with multi-organ involvement may occur (5,6). The food that causes IgE-mediated food allergy varies according to the nutritional habits of the population. The most common food-allergy type in our country is the allergies emerging after cow's milk and eggs (7,8). Milk and egg allergy in children is a common cause of anaphylactic reactions. Milk is also one of the most common causes of fatal food-borne anaphylactic reactions (9,10). The diagnosis of IgE-mediated food allergy is made by skin prick test (SPT), prick-to-prick test (PTP) or demonstration of IgE sensitivity via food-specific IgE and oral food challenge test (OFC) (11).

OFC is the gold standard in the demonstration of tolerance and in diagnosing food allergy. Restarting the responsible food that is thought to be allergic or starting the responsible food that is not consumed may cause the development of anaphylaxis in a patient with IgE-mediated food allergy. Generally, the recommended time to evaluate the tolerance to the responsible food is 12-18 months after the last reaction. Predicting whether a patient will experience anaphylaxis before oral food challenge in the evaluation of the tolerance as well as during diagnosis is valuable information from the point of deciding in which case OFC should or should not be performed. Yanagida et al. evaluated the relationship between anaphylaxis risk and sIgE during OFC (12). To our knowledge, there is not any research in the literature evaluating the risk of anaphylaxis with sIgE/total IgE, SPT and PTP during OFC. To our knowledge, this is the first study in the literature to evaluate the sIgE, sIgE/total IgE, SPT and PTP tests to predict the risk of anaphylaxis before OFC. This study aims to investigate whether it is possible to predict anaphylaxis that may develop during OFC to evaluate the development of tolerance in IgE-mediated food allergy and to determine which test is more valuable in showing the reaction that may develop.

MATERIAL and METHODS

Patients who were followed up with the diagnosis of IgE-mediated food allergy and evaluated via OFC concerning tolerance development in the Pediatric Allergy and Clinical Immunology Department of Dokuz Eylul University Faculty of Medicine (DEU) between January 2016 and December 2020 were retrospectively included in the present study.

In our clinic, the diagnosis of food allergy is made utilizing history, examination findings, laboratory tests, and the elimination-provocation method. Furthermore, provocation tests are performed to evaluate the development of tolerance.

Gender, clinical findings, age of the first symptom, history of the atopic disease diagnosed by a physician in the family, allergen foods, presence of additional allergic disease, inhaled allergen sensitivity, reactions with food intake during the challenge test, allergic food-specific IgE levels, skin prick test, prick to prick test. Total IgE levels were obtained from the polyclinic files of the cases followed up due to food allergy and evaluated, and the factors that could help the prediction of the development of anaphylaxis during OFC were assessed. Those with the values of ≥0.35 kU/L for specific IgE and presence of an induration ≥3 mm wider than the negative control for skin prick test and prick to prick tests were considered positive. If the eosinophil count was greater than 500 per microliter of blood, it was considered eosinophilia. In the food challenge test, low-intermediate and full dose incremental food challenge protocols were applied (12). Tolerance was determined via a negative OFC test result according to PRACTALL (13). Data were checked by two independent researchers. This study was approved by the DEU non-interventional studies ethics committee (Approval no: 2020/12-45). Informed consent was obtained from all parents of the children enrolled in the study.

Statistics: The data were evaluated in the IBM SPSS Statistics 22.0 (IBM Corp. Armonk, New York, USA) statistical package program. Descriptive statistics were given as the number of units (n), percent (%), mean±standard deviation ($\bar{x}$±sd), median values, and minimum-maximum values. Numerical variables were evaluated with the normality test. Comparisons between groups were made with two independent samples t-test for normally distributed variables and Mann-Whitney U analysis for non-normally distributed variables. Logistic regression analysis was used as multivariate analysis to calculate odds ratios (ORs) and 95% confidence intervals (95% CI). Values pertaining to laboratory parameters that allow making a diagnostic decision in predicting anaphylaxis were analyzed using Receiver Operating Characteristics (ROC) curve analysis in anaphylaxis cases during OFC. The sensitivity, specificity ratios and areas under the curves (AUC) for these cut-off points were calculated in the presence of significant cut-off points. Chi-square, Yates correction (continuity correction) and Fisher's exact tests were used to assessing whether the categorical variables were dependent or not. A p-value of <0.05 was considered statistically significant.

http://dx.doi.org/10.36472/msd.v9i2.684

RESULTS

Between January 2016 and December 2020, 254 patients underwent oral challenge tests with food. Of these, 133 were IgE-mediated food allergy patients to whom OFC was applied to assess food tolerance. Seventy-nine (59.4%) of them were male and the time of OFC for the evaluation of tolerance development was 21 months (12-120).

For the patients, the time to apply to the physician with the first complaint and/or findings was seven months (2-60 months) on average, while 62 (72.9%) of them had a cesarean section, 92 (86.8%) had a delivery at term, and the mean birth weight was 3300 g (1400-4400).

Eight (6.9%) had a family history of consanguineous marriages, and 86 (65.6%) had atopic disease diagnosed by a physician. Among the first-degree family members, 43 (32.8%) of them had a history of asthma, 36 (27.5%) had allergic rhinitis (AR), 19 (14.5%) had atopic dermatitis, 20 (15.3%) had a food allergy and five (3.8%) drug allergy. Except for food allergy, 84 (63.3%) cases had one or more additional atopic diseases. There was a history of atopic dermatitis in 59 (44.4%) of them, had recurrent wheezing/asthma in 31 (23.3%), AR in 10 (7.5%) and drug allergy in four (3%). Concomitant diseases were present in three (2.2%) cases (esophageal atresia and diaphragmatic hernia in one, Di-George syndrome in another and G6PD deficiency in the other).

Sixteen (12%) of the patients had a history of food-related anaphylaxis in the past. The clinical findings associated with food allergy in patients are summarized in **Table 1**.

When the distribution of food that causes food allergies was considered, a combination of milk and egg was the most common, followed by egg and milk. The distribution of allergic food is shown in **Figure 1**. Except for the combination of milk and egg, multiple food allergies were detected in 26 patients. Of these, 12 (46%) had an allergy to tree nuts, nine (34.6%) had a wheat allergy, and other cases had allergies to pulses, potatoes, kiwi, soy and chicken meat.

The median value of the eosinophil count of the patients was 500/mm3 (0-4200), 72 (55.4%) of them had eosinophilia, and the total IgE level was 84 (2-2422) IU/mL. In 36 (27%) cases, two or more OFCs were performed 47 times in total, with the same food gradually or with different foods. In 52 (39%) of the cases, OFC was made with baked food containing milk and/or egg protein, in 48 (36%) of them with boiled eggs, in 19 (14.3%) with fermented milk products, in 18 (23.5%) with pasteurized milk, in two (1.5%) with tree nuts, in two pieces (1.5%) of bread, in one of the cases with potato and one with semolina.

During these tests, reactions developed in 24 (18%) of the cases. While skin findings were observed in 21 (87.5%) cases, upper and/or lower respiratory tract findings were observed in 12 (50%) cases, GIS findings in seven (29.2%), while cardiovascular, neurological and other systemic symptoms were not detected in any of the patients. The reactions in nine (6.5%) cases were evaluated as anaphylaxis. 14 (10.5%) of the patients were administered medication for the developed reaction. Adrenaline injection was administered to seven (5.3%) of the patients, anti-histaminic to 12 (9%) of them, bronchodilator to five (3.8%), and systemic steroid to two (5%). None of the patients needed a second dose of adrenaline and fluid resuscitation. 122 (91.7%) of the patients were started on the tested food during OFC.

There was no difference between patients who had anaphylaxis and those who did not, concerning gender, birth history (term-preterm, normal-cesarean section, birth weight), atopic disease diagnosed by a doctor in the family, and the presence of atopic disease in addition to food allergy.

The nutritional sIGE, SPT, and PTP values of the patients were compared at the time of diagnosis and before OFC. It was detected that history of food-related anaphylaxis, age during the challenge, total IgE, milk sIgE, SPT, PTP at diagnosis, milk sIgE, SPT and PTP before the challenge, and egg sIgE, milk sIgE/total IgE differed between the group that experienced and the group that did not experience anaphylaxis during oral challenge test. A comparison of test results is shown in **Table 2**. ROC curves and cut-off points are shown in **Table 3**.

Cut-off points of tests were evaluated for anaphylaxis. The tests which had the best area under the curve in the ROC curves, that is, the tests which could determine the risk of anaphylaxis best, were SPT (AUC: 0.937-p: 0.001) and PTP (AUC: 0.928-p: 0.001), which were performed for milk before provocation.

Besides these, milk sIgE (AUC:0.760, cut-off:4.6 IU/mL, p:0.01), SPT (AUC:0.879, cut-off:4.5 mm, $p<0.001$), PTP (AUC:0.862, cut-off: 9.5 mm, $p<0.001$) during diagnosis and milk sIgE, the ratio of sIgE/total IgE before provocation had power to predict the risk of anaphylaxis ($p<0.05$). The negative predictive value of the tests that gave significant results for milk was over 95%. Although sIgE measurement for egg before provocation was significant, it predicted that moderate anaphylaxis might develop. The characteristics of children with anaphylaxis are shown in **Table 4**.

http://dx.doi.org/10.36472/msd.v9i2.684

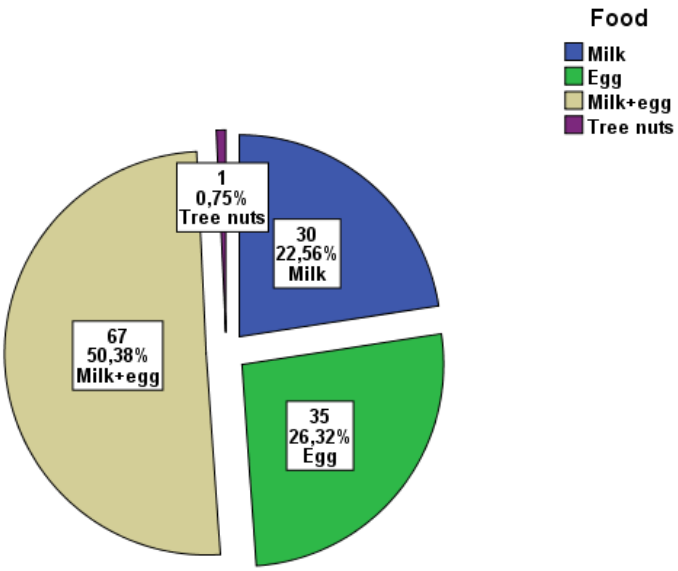


Figure 1: Distribution of food that causes food allergies

Table 1: Classification of clinical conditions seen in patients with food allergy

	Number	%
Rash-erythema	59	44.3
Atopic dermatitis*	54	40.6
Urticaria-angioedema*	22	16.5
Anaphylaxis	13	9.8
GIS findings	13	9.8
AR*	2	1.5

Patients other than those with anaphylaxis may have more than one clinical finding. (*) three cases had a history of food-related anaphylaxis

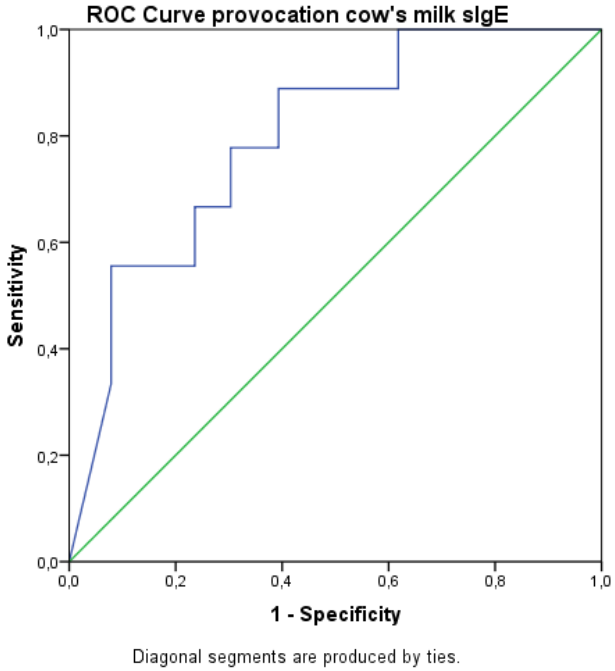
Table 2: Comparison of anaphylaxis-related test results

Variable°	Anaphylaxis via OFC (+) (n=9)	Anaphylaxis (-)(n=124)	p*
Age during challenge	47(12-96)	20 (12-60)	**0.006**
Total IgE (IU/mL)	173(73-800)	76.6(6-2000)	**0.013**
Eosinophil (cell/uL)	700(200-4000)	400(0-2300)	0.590
Anaphylaxis in history	5/9(55.5%)	11/124(0.8%)	**0.001**
Tests performed during diagnosis.			
sIgE milk	5(1-100)	1.020(0-100)	**0.007**
Milk sIgE/total IgE	0.065(0-0.200)	0.13(0-3.32)	0.189
Egg white sIgE	1.68 (0-17)	3.53 (0-100)	0.344
Egg white sIgE/total IgE	0.007(0-0.080)	0.37(0-1.97)	0.115
Egg yolk sIgE	0 (0-3)	0 (0-20)	0.771
Egg yolk sIgE/total IgE	0(0-0.03)	0(0-0.24)	0.615
SPT milk (mm)	7(5-9)	0(0-8)	**<0.001**
PTP milk (mm)	9(5-13)	0(0-14)	**<0.001**
Tests performed before the oral food challenge.			
sIgE milk	77.8(1.6-100)	0.48(0-100)	**0.003**
Milk sIgE/total IgE	0.075(0-1.080)	0.12(0-0.60)	**0.048**
Egg white sIgE	0.72 (0-18.40)	1.63(0-100)	**0.028**
Egg white sIgE/total IgE	0.008(0-0.080)	0.007(0-0.880)	0.921
Egg yolk sIgE	0 (0-3)	0(0-8)	0.417
Egg yolk sIgE/total IgE	0(0-0.01)	0.001(0-0.580)	0.357
SPT milk (mm)	5.5 (3-9)	0(0-7)	**<0.001**
PTP milk (mm)	9(5-13)	0(0-8)	**<0.001**

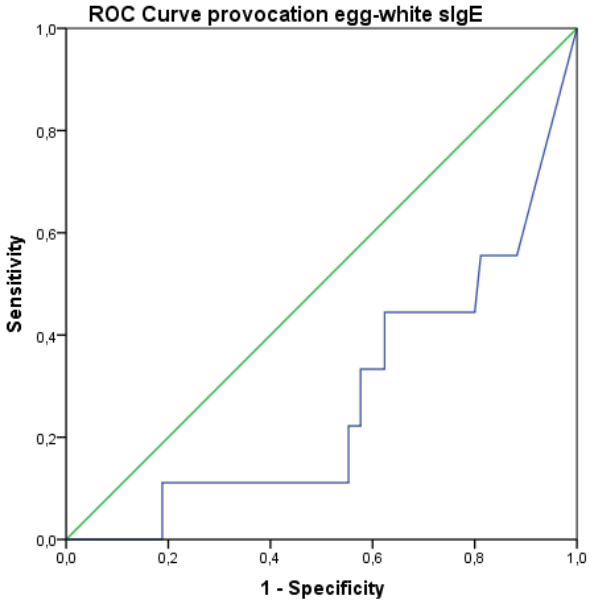
*The significance data of the results which were determined as P<0.05 are demonstrated with bold numbers. * The variables are given as median (min-max).

http://dx.doi.org/10.36472/msd.v9i2.684

Table 3: ROC curves regarding anaphylaxis and cut-off points

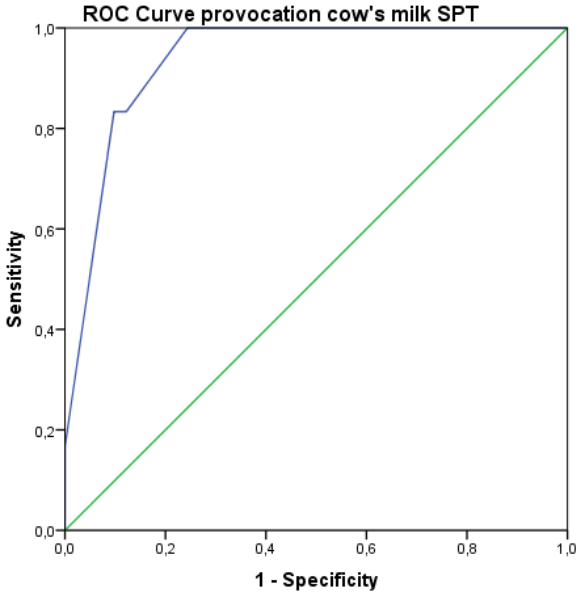


Risk factor	AUC (95%)	Cut-off (IU/mL)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk sIgE	0.797 (0.661-0.934)	3.81	0.003	66.7	69.7	18.2	95.4



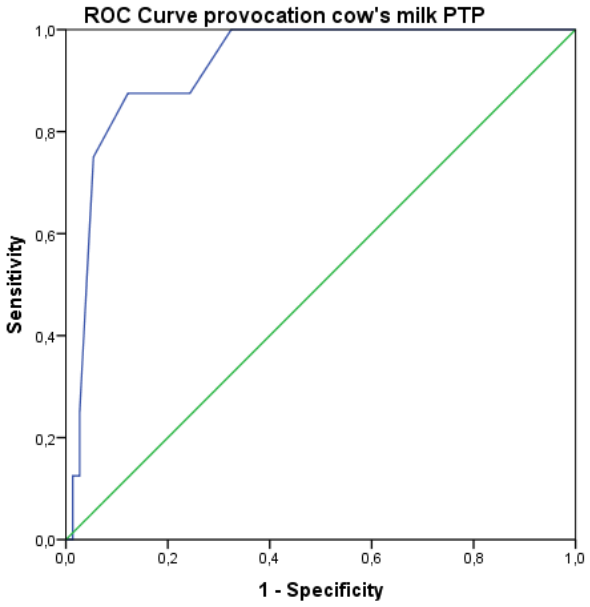
Risk factor	AUC (95%)	Cut-off (IU/mL)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation sIgE egg white	0.276 (0.105-0.448)	1.51	0.028	33.3	37.6	5.4	84.2

http://dx.doi.org/10.36472/msd.v9i2.684



Diagonal segments are produced by ties.

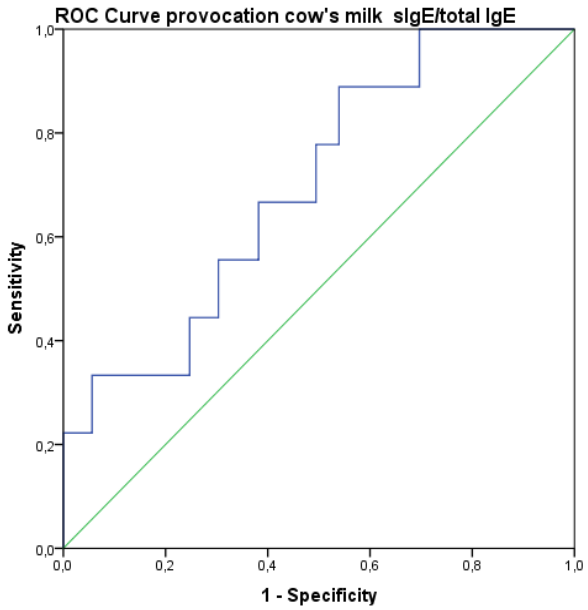
Risk factor	AUC (95%)	Cut-off (mm)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation SPT milk	0.937 (0.864-1.000)	3.5	0.001	83.3	87.8	50	97.3



Diagonal segments are produced by ties.

Risk factor	AUC (95%)	Cut-off (mm)	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk PTP	0.928 (0.857-1.000)	7.5	0.001	87.7	87.8	34	99

http://dx.doi.org/10.36472/msd.v9i2.684



Risk factor	AUC (95%)	Cut-off	p	Sensitivity %	Specificity %	PPV %	NPV %
Provocation Milk sIgE/total IgE	0.698 (0.532-0.864)	0.0425	0.048	65.7	61.8	11	99

Table 4: Characteristics of children experiencing anaphylaxis

No	Diagnosis age (month)	Age during OFC (month)	Gender M/F	Sensitization	Food that causes anaphylaxis	Additional atopy	Familial atopy	Adrenaline	Anaphylaxis during OFC
Individuals with a history of anaphylaxis, experiencing anaphylaxis during OFC									
1	5	96	K	Milk+egg	Formula	Asthma	+	+	+
2	24	120	E	Milk+egg+wheat	Wheat	Asthma and AR	-	+	+
3	15	75	K	Milk	Fermented milk	Asthma	+	+	+
4	10	58	K	Milk+egg + pistachio nut	Baked milk	Asthma	+	+	+
5	7	96	E	Milk	Milk	-	+	+	+
Those with no history of anaphylaxis but experienced anaphylaxis during OFC									
6	7	60	E	Milk+egg	Baked milk	-	-	-	+
7	6	12	E	Milk+egg	Baked milk	Asthma	+	+	+
8	15	17	E	Milk+egg	Milk	-	+	-	+
9	6	36	E	Milk	Fermented milk	-	+	+	+

DISCUSSION

There is a risk of anaphylaxis during challenge tests performed to evaluate food tolerance, as in provocations for diagnostic purposes. It is important to predict the risk of anaphylaxis before this test, performed in the evaluation of tolerance as in diagnosis. For this aim, we searched for markers that predict the risk of anaphylaxis during the oral challenge test performed to assess tolerance in our study. Anaphylaxis developed during OFC in 6.7% of our patients. In our patients who had anaphylaxis during OFC, while the tests that can best determine the risk of anaphylaxis were SPT and PTP performed before provocation for milk; milk sIgE, SPT, PTP during diagnosis, and sIgE, sIgE/total IgE ratio before provocation, were also found to be able to predict the risk of anaphylaxis.

The factors causing food allergies may differ according to the nutritional habits of the societies (14).

In studies conducted in Europe and our country, milk and egg seem to be the most common cause of IgE-mediated food allergy (15,16). In our country, the most common cause of anaphylaxis in infants is milk (17). In our study, while the most common cause of IgE-mediated food allergy was milk and egg, also milk was the most common cause of anaphylaxis in the OFCs performed to evaluate tolerance. Generally, the male gender is a risk factor for allergic diseases. There is also data showing that food allergies are more common in boys (18). Similarly, boys were more common in our study group (F:M=1:1.46).

In the literature, up to 88% of the groups with food allergies had additional allergic diseases (19). Especially for IgE-mediated food allergies, allergic diseases are common in close family members, such as parents and siblings (20,21). In most of our cases (65.6%), a history of allergic disease has existed in the family members. We think this will contribute to the early detection of children with risk factors.

In our findings, rash, erythema and atopic dermatitis were the most common findings of IgE-mediated food allergy. It has been reported that IgE-mediated food allergy can be seen up to 40% in patients with atopic dermatitis (22). In our patients with atopic dermatitis, erythema and rash frequently developed within the first two hours after exposure to food. Anaphylaxis developed in one patient.

In recent studies, the findings suggest that the application of gradual OFC may contribute to the development of earlier full tolerance and improvement of prognosis (12,23). It has been shown that 70% of children who have milk and egg allergies can tolerate baked milk and eggs (24,25). Cooking is a method that transforms cow's milk and eggs into a less allergenic form (25). In our cases, OFC was performed mostly with baked food containing milk and/or eggs, including gradually increasing doses of protein.

Our patients who experienced anaphylaxis were older, because we performed OFCs later, in the children with a history of anaphylaxis in the last year or those with severe anaphylaxis. Total IgE levels were higher in children who had anaphylaxis. We suggest that this is related to high allergic inflammatory activities. In our cases, milk was at the forefront as the cause of anaphylaxis.

PTP and SPTs are good indicators to rule out IgE-mediated food allergy (26). In a study conducted in Japan, the findings showed that high sIgE levels for food were associated with the risk of anaphylaxis (27). In another study, PPVs and NPVs were reported at levels similar to those in our study for SPT (9).

In Kwan et al.'s study, all of the individuals with a result of <8 mm, and 60% of those with a result of 8-14 mm in PTP tests, which was made with baked muffin slurry containing milk, tolerated OFC made with baked muffins containing milk without any problems (28). In our study, the induration diameter of <3.5 mm in SPT and the induration diameter of <7.5 mm in the pre-OFC PTP test were the best predictive test criteria for anaphylaxis, with an NPV of 99%. NPV was over 95% in general, in sIgE and skin tests performed for milk as the cause of anaphylaxis. In egg allergy, no significant result could be determined except for egg white sIgE. Four patients without a history of anaphylaxis experienced anaphylaxis during OFC performed to evaluate food tolerance.

In IgE-mediated food allergy, anaphylaxis may develop when food is reintroduced after elimination, even if patients without a history of anaphylaxis. Thus, we recommend that tests that will enable the evaluation of risky situations, especially SPT and PTP tests, to also be performed before OFC.

The retrospective nature of our study and the low number of patients who had anaphylaxis during OFC were important limitations. The patients were evaluated using basal tests in the allergy clinic, and further evaluations, such as molecular diagnostic tests, could not be performed.

CONCLUSION

IgE-mediated food allergy is a clinical problem with an increasing prevalence. Appropriate diagnosis, treatment and follow-up should be dealt with by allergists. Milk and eggs are the most common responsible food in our country. Even if the first reaction is not anaphylaxis in patients which the responsible food has been eliminated due to food allergy, challenge tests to evaluate tolerance should be performed in centers specialized in anaphylaxis management. The tests that can best determine the risk of anaphylaxis before OFC in our patients were determined as DPT and PTP for pre-challenge milk. A personalized approach (e.g., baked product and fermented product) should be used to prepare the product to be selected for the provocation after evaluating the patient with the tests performed before the provocation (SPT, PTP, sIgE, sIgE/total IgE).

Author Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Serdar Al, Gizem Atakul, Özge Atay, Özge Kangallı, Seda Şirin Köse, Dilek Tezer, Suna Asilsoy, Nevin Uzuner and Özkan Karaman. The first draft of the manuscript was written by Serdar Al, Suna Asilsoy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. Approval was granted by the Ethics Committee of Dokuz Eylul University Non-Interventional Studies Ethics Committee (Approval no: 2020/12-45). Informed consent was obtained from all parents of the children enrolled in the study.

REFERENCES

1. Boyce JA, Jones SM, Rock L, Sampson HA, Cooper SF, Boyce S, et al. Guidelines for the Diagnosis and Management of Food Allergy in the United States: Report of the NIAID-Sponsored Expert Panel. J Allergy Clin Immunol [Internet]. 2010 Dec [cited 2021 Sep 17];126(6):S1–58. Available from: /pmc/articles/PMC4241964/

2. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JKH, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013;6(1):1–12.

3. Akçay A. Global Prevalence of Food Allergies. In: Güler N, editor. Türkiye Klinikleri PEDIATRIC IMMUNOLOGY AND ALLERGIC DISEASES - SPECIAL TOPICS FOOD ALLERGY IN CHILDREN. 1.Edition. Ankara: Türkiye Klinikleri; 2021. p. 29–34.

4. Muraro A, Roberts G. Food Allergy and Anaphylaxis Guidelines. Eur Acad Allergy Clin Immunol [Internet]. 2014;294. Available from: http://www.eaaci.org/foodallergyandanaphylaxisguidelines/Food Allergy - web version.pdf (Último acceso 23 noviembre 2018).

5. Longo G, Berti I, Burks AW, Krauss B, Barbi E. IgE-mediated food allergy in children. Lancet. 2013 Nov 16;382(9905):1656–64.

6. Pajno GB, Fernandez-Rivas M, Arasi S, Roberts G, Akdis CA, Alvaro-Lozano M, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy Eur J Allergy Clin Immunol. 2018;73(4):799–815.

7. Sirin Kose S, Asilsoy S, Uzuner N, Karaman O, Anal O. Outcomes of Baked Milk and Egg Challenge in Cow's Milk and Hen's Egg Allergy: Can Tolerance Be Predicted with Allergen-Specific IgE and Prick-to-Prick Test? Int Arch Allergy Immunol [Internet]. 2019 Nov 1 [cited 2021 Sep 6];180(4):264–73. Available from: https://www.karger.com/Article/FullText/502957

8. Akarsu A, Ocak M, Köken G, Şahiner ÜM, Soyer Ö, Şekerel BE. Ige mediated food allergy in turkey: different spectrum, similar outcome. Turk J Pediatr [Internet]. 2021;63(4):554. Available from: http://www.turkishjournalpediatrics.org/doi.php?doi=10.24953/turkjped.2021.04.002

9. Cianferoni A, Muraro A. Food-Induced Anaphylaxis. Immunol Allergy Clin North Am [Internet]. 2012 Feb [cited 2021 Sep 19];32(1):165–95. Available from: /pmc/articles/PMC3440177/

10. Bock SA, Muñoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. J Allergy Clin Immunol [Internet]. 2001 Jan;107(1):191–3. Available from: https://linkinghub.elsevier.com/retrieve/pii/S009167490114683X

11. Foong R-X, Dantzer JA, Wood RA, Santos AF. Improving Diagnostic Accuracy in Food Allergy. J Allergy Clin Immunol Pract [Internet]. 2021 Jan;9(1):71–80. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219820310862

12. Yanagida N, Minoura T, Kitaoka S, Ebisawa M. A three-level stepwise oral food challenge for egg, milk, and wheat allergy. J Allergy Clin Immunol Pract [Internet]. 2018;6(2):658-660.e10. Available from: https://doi.org/10.1016/j.jaip.2017.06.029

13. Sampson HA, Wijk RG van, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology–European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol [Internet]. 2012 Dec 1 [cited 2021 Sep 19];130(6):1260–74. Available from: http://www.jacionline.org/article/S0091674912016636/fulltext

14. Tang R, Wang Z-X, Ji C-M, Leung PSC, Woo E, Chang C, et al. Regional Differences in Food Allergies. 2016; Available from: https://doi.org/10.1007/s12016-018-8725-9

15. Kahveci M, Koken G, Şahiner ÜM, Soyer Ö, Şekerel BE. Immunoglobulin E-Mediated Food Allergies Differ in East Mediterranean Children Aged 0–2 Years. Int Arch Allergy Immunol [Internet]. 2020 May 1 [cited 2021 Jan 21];181(5):365–74. Available from: https://www.karger.com/Article/FullText/505996

16. Lyons SA, Clausen M, Knulst AC, Ballmer-Weber BK, Fernandez-Rivas M, Barreales L, et al. Prevalence of Food Sensitization and Food Allergy in Children Across Europe. J Allergy Clin Immunol Pract. 2020 Sep 1;8(8):2736-2746.e9.

17. Kahveci M, Akarsu A, Koken G, Sahiner UM, Soyer O, Sekerel BE. Food-induced anaphylaxis in infants, as compared to toddlers and preschool children in Turkey. Pediatr Allergy Immunol. 2020;31(8):954–61.

18. Pyrhönen K, Hiltunen L, Kaila M, Näyhä S, Läärä E. Heredity of food allergies in an unselected child population: An epidemiological survey from Finland. Pediatr Allergy Immunol [Internet]. 2011 Feb 1 [cited 2021 Sep 21];22(1pt2):e124–32. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1399-3038.2010.01095.x

19. Sampson HA, Sicherer SH; Concomitant Allergic Diseases in Persons with Peanut and Tree Nut Allergy in a Population Based Survey. In: Journal of Allergy and Clinical Immunology. 2011. p. AB187.

20. Koplin JJ, Allen KJ, Gurrin LC, Peters RL, Lowe AJ, Tang MLK, et al. The Impact of Family History of Allergy on Risk of Food Allergy: A Population-Based Study of Infants. Int J Environ Res Public Health [Internet]. 2013 Oct 25 [cited 2021 Sep 22];10(11):5364. Available from: /pmc/articles/PMC3863850/

21. Yuenyongviwat A, Koosakulchai V, Treepaiboon Y, Jessadapakorn W, Sangsupawanich P. Risk factors of food sensitization in young children with atopic dermatitis. Asian Pacific J Allergy Immunol [Internet]. 2021 [cited 2021 Sep 22]; Available from: https://apjai-journal.org/wp-content/uploads/2021/01/AP-250820-0946.pdf

22. Eigenmann A, Sicherer S, Borkowski T, Cohen B, Sampson H. Prevalence of IgE-mediated food allergy among children with atopic dermatitis. Pediatrics [Internet]. 1998 [cited 2021 Sep 22];101(3). Available from: https://pubmed.ncbi.nlm.nih.gov/9481027/

23. Cox AL, Nowak-Wegrzyn A. Innovation in Food Challenge Tests for Food Allergy. Curr Allergy Asthma Rep [Internet]. 2018 Dec 30 [cited 2021 Sep 22];18(12):74. Available from: https://link.springer.com/article/10.1007/s11882-018-0825-3

24. Lemon-Mulé H, Sampson HA, Sicherer SH, Shreffler WG, Noone S, Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. J Allergy Clin Immunol [Internet]. 2008 Nov;122(5):977-983.e1. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0091674908016680

25. Leonard SA, Caubet J-C, Kim JS, Groetch M, Nowak-Węgrzyn A. Baked Milk- and Egg-Containing Diet in the Management of Milk and Egg Allergy. J Allergy Clin Immunol Pract [Internet]. 2015 Jan;3(1):13–23. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213219814004188

26. Nowak-Węgrzyn A, Burks AW, Sampson HA. Reactions to Foods. In: Middleton's Allergy [Internet]. Elsevier; 2014. p. 1310–39. Available from: https://linkinghub.elsevier.com/retrieve/pii/B9780323085939000826

27. Yanagida N, Sato S, Takahashi K, Nagakura K, Asaumi T, Ogura K, et al. Increasing specific immunoglobulin E levels correlate with the risk of anaphylaxis during an oral food challenge. Pediatr Allergy Immunol [Internet]. 2018 Jun 1 [cited 2021 Sep 27];29(4):417–24. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/pai.12896

28. Kwan A, Asper M, Lavi S, Lavine E, Hummel D, Upton JE. Prospective evaluation of testing with baked milk to predict safe ingestion of baked milk in unheated milk-allergic children. Allergy, Asthma Clin Immunol [Internet]. 2016 Dec 24 [cited 2021 Sep 27];12(1):54. Available from: /pmc/articles/PMC5078900/

MSD

Medical Science and Discovery
ISSN: 2148-6832

Use of neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) as biomarkers in the differential diagnosis of malignant solitary pulmonary nodules

Murat Kuru[1], Tamer Altinok[1]

1 Department of Thoracic Surgery, Necmettin Erbakan University, Medical Faculty of Meram, Konya, TR

*** Corresponding Author:** Murat Kuru **E-mail:** surgeonblack@hotmail.com

ABSTRACT

Objective: Histopathological diagnosis of atypical lung nodules is often not possible in the preoperative period. This study evaluates the diagnostic value of neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) as biomarkers in the differentiation of undiagnosed lung nodules.

Material and Methods: The study includes 91 patients (21 females, 70 males, mean age: 59.35 ± 11.85, age interval 20-81) operated on for lung nodules between September 2010 and September 2020. Age, gender, type of operation performed, histopathological type of the tumor, nodule size, SUVmax values measured on PET-CT, preoperative neutrophil/lymphocyte, and lymphocyte/monocyte ratios were analyzed retrospectively. These values were compared in patients with primary lung cancer (Group 1) and patients with secondary lung cancer, that is, patients with lung metastases from other organs (Group 2).

Results: NLR was statistically significantly higher in group 2 patients (N: 37)(3.38 ± 2.03). There was no statistically significant difference between the two groups in terms of LMR.

Conclusion: For lung nodules with unknown histopathological diagnosis, NLR values lower than 1.69 in preoperative complete blood count suggest primary lung cancer, and values above 2.92 suggest metastasis from other organs to the lung.

Keywords: Neutrophil/lymphocyte ratio; Lymphocyte/monocyte ratio; Biomarker; Pulmonary nodule; Malignant

INTRODUCTION

Solitary pulmonary nodules are lesions which located in the lung parenchyma and are smaller than 3 cm in diameter on radiological evaluation. In order for lesions in the lung parenchyma to be called solitary pulmonary nodules (SPN), these lesions should not be accompanied by atelectasis, lymphadenopathy, and pleurisy (1). Until proven otherwise, a nodule detected in the lung should be considered malignant and the examinations should be arranged accordingly. There has been a significant increase in the number of nodules detected in the lung, especially with the frequent use of thoracic computed tomography (CT). Although the characteristic features of the nodule on thorax CT inform us about the possibility of malignancy, this information is often insufficient. Identification and characterization of lung nodules are common in radiology (2). FDG uptake in Positron Emission Tomography (PET-CT) imaging provides information about the probability of malignancy in the nodule. Despite all examinations, the gold standard in diagnosis is tissue biopsy sampling. Unfortunately, a biopsy is not always possible due to the atypical location of the nodule. Many studies in recent years have suggested that systemic inflammation seen in malignancy patients may be associated with tumor burden, metastasis, invasion, and progression. One study showed that patients with malignancy may have neutrophilia and/or lymphopenia in peripheral blood evaluation (3). Considered more useful than neutrophil and lymphocyte counts, the neutrophil/lymphocyte ratio (NLR) is a newly developed marker for inflammation, and its elevation appears to be associated with a poor prognosis.

Research Article

Received 20-01-2022

Accepted 10-02-2022

Available Online: 21-02-2022

Published 28-02-2022

A routine hemogram test is an evaluation that can be applied to almost all patients after hospitalization, as it is inexpensive, minimally invasive, and provides predictions about many diseases. Recently, hemogram-derived neutrophil/lymphocyte ratios started to be used to determine the prognosis in patients followed for lung cancer (4).

The lymphocyte/monocyte ratio (LMR) is under investigation as another biomarker in patients followed up for lung cancer. Most of the research on LMR focuses on lung cancer prognosis. A meta-analysis of 20 studies showed that low pre-treatment LMR negatively affected overall survival and disease-free survival (5). However, to the best of our knowledge, there are no studies in the literature on the diagnostic role of NLR and LMR in the non-invasive histopathological evaluation of lung cancer and the preoperative differentiation of undiagnosed nodules as primary lung tumors or lung metastases from other organs.

In this study, we planned to calculate the neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) in the preoperative complete blood test of patients with lung nodules and compare these ratios with the histopathology of the postoperative resected nodule. Accordingly, we aimed to evaluate the effectiveness of NLR and LMR as biomarkers in differentiating the nodule as a primary lung tumor or lung metastasis from other organs.

MATERIAL and METHODS

This study includes 91 patients (21 females, 70 males, mean age 59.35 ± 11.85, age interval 20-81) operated on between September 2010 and September 2020 for thorax computed tomography (CT) detected lesions smaller than 3 cm in the lung parenchyma that were not associated with atelectasis, lymphadenopathy or pleurisy. Patients were assessed retrospectively in terms of age, gender, type of operation performed, histopathological type of the tumor, size of the lung nodule, postoperative histopathological diagnosis, preoperative neutrophil, lymphocyte, monocyte counts, and ratios. All patients underwent preoperative complete blood count as well as thorax CT and PET-CT. The nodules were evaluated by a radiologist. All nodules in our study were solid. The patients were examined in 2 groups according to the histopathological diagnosis of the excised nodule. The nodules were evaluated as primary lung cancer in group 1 patients (N=54) and secondary lung cancer in group 2 (N=37), i.e., metastasis from other organs to the lung. In patients operated on for suspected lung metastasis, the primary tumor was under control. The neutrophil, lymphocyte, monocyte counts and the ratio of these values to each other were calculated in the preoperative complete blood count of the patients in both groups. All hematological evaluations were performed in the same laboratory. Histopathological comparison of the resected lung nodules of the patients was performed with these ratios. NLR was obtained by dividing the number of neutrophils detected in the complete blood count in the preoperative period by the number of lymphocytes, and the LMR by dividing the lymphocyte number by the number of monocytes. The results were analyzed with statistical analysis programs, and the correlation between the hemogram-derived ratios and the postoperative histopathological type was evaluated. Preoperative lung function tests and arterial blood gas analysis were performed for all patients.

The study aimed to assess the clinical effectiveness of NLR and LMR in differentiating lung nodules as a primary lung tumor or lung metastasis from other organs.

The primary outcome of this study was to predict the histopathology of the nodule in patients who could not be biopsied.

Ethics committee approval was obtained for the study protocol. Informed consent for the operation was obtained from each patient in the study. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Inclusion Criteria: Patients over the age of 18 with a lesion smaller than 3 cm in the lung parenchyma on thorax computed tomography (CT) were included in our study.

Exclusion Criteria: Patients with lung nodules larger than 3 cm and with atelectasis and pleurisy were not included in the study.

Statistical Analysis: Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk NY, USA) for Windows. Descriptive data were expressed as mean ± standard deviation (SD), median (min-max), number, and frequency. Variable distributions and conformity to normal distribution analyzes were checked with the Kolmogorov-Smirnov test. The Student's t-test was used for comparison between groups. The correlation between variables was evaluated using Pearson Correlation Analysis. ROC (Receiver Operating Characteristic) analysis was performed for cut-off values. P<.05 was accepted as the threshlold for statistical significance.

RESULTS

Group 1 patients (N: 54) consisted of 47 males, 7 females with a mean age of 62.7 (9.6) (range 23-81), and group 2 patients (N: 37) consisted of 23 males, 14 females, with a mean age of 54.4 (13.2) (between 20-73) (**Table 1**).

http://dx.doi.org/10.36472/msd.v9i2.679

Table 1: Patients' Characteristics

	Group 1 (N:54)	Group 2 (N:37)	P Value
Age(years)	62.7±9.6	54.4±13.2	(p=0.001)
Gender			(p=0.005)
Male	47	23	
Female	7	14	
NLR	2.19 ± 0.95	3.38 ± 2.03	(p=0.001)
LMR	4.51 ± 2.01	3.76 ± 2.57	(p=0.12)
Size of the Nodule(mm)	20.05±7.4	15.02±5.79	(p=0.001)
SUVmax values	8.24±4.28	5.35±2.64	(p<0.001)
Wbc(10^3/ml)	7.43±2.65	6.89±1.87	(p=0.082)
Neutrophil(10^3/ml)	4.55±2	4.51±1.52	(p=0.11)
Lymphocyte(10^3/ml)	2.17±0.65	1.65±0.73	(p=0.063)
Monocyte(10^3/ml)	0.63±0.79	0.52±0.23	(p=0.094)

NLR: neutrophil/lymphocyte ratio, LMR: lymphocyte/monocyte ratio, Wbc: white blood cell

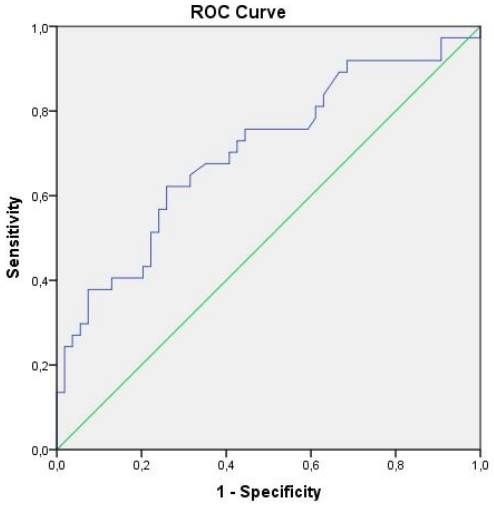


Figure 1: ROC(Receiver operating characteristic) analysis for NLR. AUC: 0.704, p=0.001, CI:0.592-0.815

Table 2: Cut-off values for NLR

	Cut-off	Sensitivity	Specificity	Youden's Index
Optimal	2.21	67.6	60.3	0.269
Max sensitivity	1.69	91.9	31.5	0.234
Max specificity	2.92	56.8	80.04	0.372

NLR: Neutrophil/lymphocyte ratio

The mean age in group 1 was higher than group 2 and this value is statistically significant.(p=0.001) The mean NLR was 2.19 (0.95) in group 1 and 3.38 (2.03) in group 2. There was a statistically significant difference in NLR values between the two groups, and the NLR was higher in group 2. For NLR, ROC analysis revealed AUC: 0.704, P= .001, CI: 0.592-0.815 (**Figure 1**).

Sensitivity and specificity analysis were performed for NLR at 3 different cut-off values. Cut-off was calculated as 1.69 (sensitivity 91.9%, specificity 31.5%), 2.92 (sensitivity 56.8%, specificity 80.04%), 2.21 (sensitivity 67.6%, specificity 60.3%) (**Table 2**).

The LMR was 4.51 (2.01) in group 1 and 3.76 (2.57) in group 2 (P=.12). There was no significant difference between the two groups. Although the neutrophil, lymphocyte, and monocyte counts were high in the first group, it was not statistically significant.

Nodule size is significantly different between two groups (p=0.001) and SUVmax is significantly different between two groups (p<0.001)

In group 1 patients, a moderately strong, significant, and positive correlation was observed between nodule size and SUVmax values (r=0.48, P=.001). There was no such relationship in Group 2.

DISCUSSION

Inflammation may occur intensely in cases such as tumor development, invasion, and metastasis. Although there are many articles on the relationship between lung cancer and NLR and LMR, these have generally focused on the prognosis of patients with lung cancer (4,5,6). Neutrophils have an important role in angiogenesis during tumorigenesis (7). Lymphocytes, on the other hand, have tumor growth-reducing effects in the body (8). Since most lung nodules are similar on thoracic CT imaging, radiological differentiation is difficult. Genetic analyzes and tumor marker evaluations are both expensive and incapable of distinguishing nodules. However, complete blood count to be used for preoperative NLR and LMR assessment is an easily accessible and inexpensive method.

This study reveals that high NLR values on the hemogram of a patient with a lung nodule may indicate lung metastasis of other organ malignancies. At the beginning of our study, we hypothesized that LMR would also be significant. Our study also concludes that LMR cannot be an effective marker for differentiating primary lung cancer and lung metastasis of other organ malignancies.

There was no significant difference between the two groups included in the study in terms of leukocyte, neutrophil, lymphocyte, and monocyte values. The NLR provides more information in detecting systemic inflammation than the evaluation of neutrophil and lymphocyte counts alone. These results show that systemic inflammation is more common in patients with metastasis (9,10). In accordance with the literature, since NLR was higher in the group operated on due to metastasis in our study, it is thought that systemic inflammation was higher as well. Although the primary tumor was under control, the high NLR detected in the group with metastasis may indicate that the effects of the primary tumor continued. In another study, the NLR was shown to be higher in patients with lung cancer compared to the normal population (11). High NLR values indicate that malignancies may be widespread throughout the body. A study conducted on patients with ovarian cancer reported that NLR values were higher in advanced-stage (Stage 3-4) patients than in early-stage (Stage 1-2) patients (12).

It is known that patients with a previous history of extrapulmonary malignancy are more likely to develop a new malignancy. Therefore, a lung nodule detected on the thorax CT of a patient with a malignancy history causes difficulties in diagnosis. In cases with atypical nodule localization, where histopathological examination cannot be performed, NLR to be calculated in hemogram test may be useful as a marker in preoperative diagnosis along with radiological nodule evaluation. NLR values <1.69 predict the histopathological result to be a lung-derived malignancy with a sensitivity of 91.9% and a specificity of 31.5%. Cut-off values of NLR less than 1.69 support primary lung cancer with much higher selectivity. On the other hand, in cases with an NLR above 2.92, it would be appropriate to interpret it as the metastasis of a previously detected malignancy with 56.8% sensitivity and 80.04% specificity. Although histopathological evaluation is the gold standard in the assessment of nodules, we believe that NLR will make a significant contribution to the diagnosis since hemogram evaluation is routinely performed for each patient.

While the immune system regulates tumor growth and metastasis, monocytes support tumor formation and metastasis (13). Multivariate analyzes in studies conducted for LMR in the literature show that LMR is an independent prognostic factor in NSCLC (14). Although our research determined higher LMR in group 1 patients than group 2 (4.51/3.76), the difference was not statistically significant to support its use as a biomarker in differentiating lung nodules as primary/metastatic. Studies with more patients may be beneficial to demonstrate the correlation between LMR and nodule histopathology.

A study comparing PET-CT-derived SUVmax values and nodule size determined that the SUVmax values of lung nodules larger than 1 cm, centrally located, and with irregular borders were significantly higher (15). Similarly, our study revealed a moderately strong, significant, and positive correlation between nodule size and SUVmax values in Group 1 patients. The lack of significant difference in SUVmax values between the two groups may be attributed to the relatively lower accuracy of PET-CT for solitary pulmonary nodules smaller than 3 cm.

CONCLUSION

Despite the limitations of our study, we think that NLR evaluation as a biomarker on hemogram, which is an inexpensive and easily accessible method, will be beneficial in the preoperative diagnosis of patients and prevent unnecessary large resections. We can also conclude that LMR should not be used as a marker in this evaluation. We think that studies with a larger number of patients on this subject will support our study.

Author Contributions: MK, TA: Project design, Patient examinations, Data analyses **MK:** Manuscript preparation, revisions.

Acknowledgments: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive

and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. The Ethics Committee of the Necmettin Erbakan University Hospital approved the study.

REFERENCES

1. Kartaloğlu Z. Approach to solitary pulmonary nodules. Turkish J Thorac Cardiovasc Surg.2008;16(4):274-283.
2. Vlahos I, Stefanidis K, Sheard S, Nair A, Sayer C, Moser J. Lung cancer screening: nodule identification and characterization. Transl Lung Cancer Res. 2018;7(3):288-303
3. Kumar R, Geuna E, Michalarea V, Guardascione M, Naumann U, Lorente D et al. The neutrophil-lymphocyte ratio and its utilisation for the management of cancer patients in early clinical trials. Br J Cancer 2015;112:1157-65.
4. Yu Y, Qian L, Cui J. Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: A meta-analysis of 7,219 patients. Mol Clin Oncol 2017;7(3):498-506.
5. Wang Y, Huang D, Xu W.Y., Wang Y.W, Che G.W. Small Cell Lung Cancer: A Meta-Analysis. Oncol Res Treat 2019;42:523-30.
6. Sanchez-Salcedo P, de-Torres JP, Martinez-Urbistondo D, Gonzalez-Gutierrez J, Berto J, Campo A et al. The neutrophil to lymphocyte and platelet to lymphocyte ratios as biomarkers for lung cancer development. Lung Cancer. 2016;97:28–34.
7. Van Egmond M, Bakema JE. Neutrophils as effector cells for antibody-based immunotherapy of cancer. Semin Cancer Biol. 2013;23:190–9.
8. Pan YC, Jia ZF, Cao DH, Wu YH, Jiang J, Wen SM et al. Preoperative lymphocyte-to-monocyte ratio (LMR) could independently predict overall survival of resectable gastric cancer patients. Medicine. 2018;97:e13896.
9. Zheng SH, Huang JL, Chen M, Wang BL, Ou QS, Huang SY. Diagnosis value of preoperative inflammatory markers in patients with glioma: a multicenter cohort study. J Neurosurg 2017;3:1-10. DOI: 10.3171/2017.3.JNS161648
10. Baran O, Kemerdere R, Korkmaz TS, Kayhan A, Tanrıverdi T. Can preoperative neutrophil to lymphocyte, lymphocyte to monocyte or platelet ratios differentiate glioblastoma from brain metastasis?. Medicine 2019;98:50(e18306)
11. Kemal Y, Yücel I, Ekiz K, Demirag G, Yilmaz B, Teker F et al. Elevated Serum Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios Could be Useful in Lung Cancer Diagnosis. Asian Pac J Cancer Prev. 2015;15(6):2651-4.
12. Wu Y, Qin Y, Qin J, Zhang X, Lin F. Diagnostic value of derived neutrophil-to-lymphocyte ratio in patients with ovarian cancer. J Clin Lab Anal 2019;33;e22833.
13. Hanna RN, Cekic C, Sag D, Tacke R, Thomas GD, Nowyhed H et al. Patrolling Monocytes Control Tumor Metastasis to the Lung. Science. 2015;11(20):350;985-990. DOI: 10.1126/science.aac9407
14. Hu P, Shen H, Wang G, Zhang P, Liu Q, Du J. Prognostic significance of systemic inflammation-based lymphocyte-monocyte ratio in patients with lung cancer: based on a large cohort study. PloS One.2014;9(9):e108062.
15. Yilmaz F, Tastekin G. Sensitivity of (18)F-FDG PET in evaluation of solitary pulmonary nodules. Int J Clin Exp Med. 2015; 8(1):45-51.

MSD

Medical Science and Discovery
ISSN: 2148-6832

DNA Methylation Analysis of the Hippo signalling Pathway Core Component Genes in Breast Cancer Cells

Amal Majed Alenad[1]*

1 King Saud University, College of Science, Riyadh, Saudi Arabia

*** Corresponding Author:** Amal Majed Alenad **E-mail:** aalenad@ksu.edu.sa

ABSTRACT

Objective: Breast cancer is one of the most frequent malignancies among women. According to the World Health Organization (2020), an estimated 2.3 million women were diagnosed with breast cancer, while 685,000 died worldwide. Therefore, an early diagnosis of cancer is crucial for survival. This study analyses the methylation status of the promoter regions of core component genes of the hippo pathway. The Hippo pathway is a tumor suppressor pathway as this pathway hinders cell growth and cell proliferation and motivates cell death.

Material and Methods: Methylation-sensitive PCR method was used to examine the altered methylation patterns of SAV1, LAST1/2, and MST1/2 in different breast cancer cell lines (MCF7, T47D, HCC1937, and BT-20).

Results: Interestingly, we have found that the promoter regions of the genes being studied are all hemimethylated in all cell lines used in this investigation, apart from the LAST1 gene promoter, which was hypomethylated in T47D and HCC1937 cell lines.

Conclusion: This indicates the importance of hemimethylation, as it is considered an aberrant methylation pattern. Thus, its effect on gene expression must be further considered.

Keywords: Breast Cancer; Hippo pathway; DNA methylation

INTRODUCTION

Breast cancer in female counts for 15.5% of cancer-associated mortality. The Hippo pathway is acknowledged as a tumor suppressor pathway that hinders cell growth, cell division and motivates cell death. The core gene component of the Hippo pathway resampled cascade of kinases includes Salvador homolog-1 protein (SAV1) at the top of the hippo signal pathway, the upstream mammalian STE20-like protein kinase (MST1/2) that activates a downstream large tumor suppressor (LATS1/2) kinase, leading to phosphorylation and inactivation of transcriptional cofactors YAP/TAZ (1,2,3,4). In the Hippo pathway, SAV1 directly binds to protein kinases MST1/2 and induces the kinase cascade that promotes MST1/2, LATS1/2, and YAP/TAZ phosphorylation. Then, the phosphorylated YAP and TAZ are degraded via the ubiquitin–lysosome system (4,5,6,7,8,9,10,11). YAP protein is found at the end of the Hippo signalling pathway and the most important downstream activator, it transfers between the nucleus and cytoplasm. Additionally, the activation of the Hippo pathway causes the YAP to associate with transcriptional factors and functions as a transcriptional co-activator to promote hippo target gene expression (12). The Hippo pathway has the capacity to lead to tumorigenesis. Mutations and altered expression of its core components (SAV1, MST1/2, LATS1/2) promote the migration, invasion, malignancy of cancer cells. Currently, the significance of the biological and deregulation of the Hippo pathway has attracted immense interest among researchers in the past few years. Furthermore, understanding of hippo pathway intensifies the cancer treatment process.

Toward the interest of this study, biomarker research related to cancer has shown that not only genetic mutations but also epigenetic alterations such as promoter methylation patterns potentially contributes to malignant growth and could be used in early identification too. Thus, identifying the most significant genes that can be used to detect and tailored therapies of Brest cancer is greatly needed.

Research Article

Received 09-02-2022

Accepted 20-02-2022

Available Online: 23-02-2022

Published 28-02-2022

http://dx.doi.org/10.36472/msd.v9i2.688

Particularly, altered methylation of the promoter region of the Hippo pathway, core genes. Moreover, the hippo core component genes serve a critical role in invasive breast tumor colonization or metastasis through different mechanisms (13,14). Growing evidence underlines the significance of DNA methylation as a reversible epigenetic mechanism, therefore, making it a sought-after target for anticancer treatment in breast cancer. Therefore, to understand the abnormal expression of the Hippo pathway gene component, we studied the methylation status of the promoter region of SAV1, MST1/2, LATS1/2 genes in certain breast cancer cell lines (MCF7, T47D, HCC1937, and BT-20). Methylation sensitive PCR-based technique was used in this investigation.

MATERIAL and METHODS

Cell culture

The study was conducted on four cell lines, namely, MCF7, T47D, HCC1937, and BT-20. Cells were purchased from American Type Culture Collection (ATCC) (Manassas, VA, USA). All cell culture media were obtained from ATCC, whereas supplements such as fetal bovine serum (FBS) and trypsin-EDTA were obtained from Gibco (Gaithersburg, MD, USA).

Cell lines

Cells were routinely passaged by mild trypsin-EDTA detachment and cultured in a humidified atmosphere of 95% air and 5% CO2 at 37°C.

Human breast adenocarcinoma MCF7 cells (ATCC HTB 22): Are originally mammary gland epithelial cells of breasts obtained from metastatic site pleural effusion adenocarcinoma, MDA-MB231 is ER-negative and p53 mutant while MCF-7 is ER-positive and p53 wild-type (Cailleau et al., 1974; Landers et al., 1997. Pratt and Pollak, 1993). MCF7 cells were cultured in phenol red-free DMEM supplemented with 10% FCS, 0.1 mM nonessential amino acids, 110 g/ml sodium pyruvate, and 1% glutamine.

Human breast carcinomaT-47D cells (ATCC HTB 133): Were cultured in a-MEM containing 10% FCS, 0.1 mM nonessential amino acids, 6 @Lg/m1 insulin, and 1% glutamine (GIBCO).

Human breast carcinoma BT-20 cells (ATCC HTB 19): Were established from a pleural effusion in the 1950s, and many of the most studied cell lines (e.g., MDA-MB-231) were established in the 1970s. These tumor cell lines were derived before the routine evaluation of hormone receptor expression and HER-2/Neu amplification in clinical samples.

BT-20 cells were cultured in EMEM with the omission of any added insulin.

HCC1937 cell line: This cell line was initiated from a primary ductal carcinoma on October 13, 1995. This took 11.5 months to be established. The tumor was classified as TNM Stage IIB, and grade 3 BRCA1 analysis revealed that the cell line is homozygous for the BRCA1 5382C mutation.

The lymphoblastoid cell line derived from the same patient is heterozygous for the same mutation. Besides, cells were cultured in RPMI 1640 medium (Life Technologies, Paisley, UK) with 2 mM L-glutamine adjusted to contain 1.5 g/L sodium bicarbonate, 4.5 g/L glucose, 10 mM HEPES, and 1.0 mM sodium pyruvate, 90%; fetal bovine serum, 10%.

DNA extraction

The cells were harvested by trypsinization and were transferred into 1.5ml centrifuge tubes. Genomic DNA extraction was performed using the Wizard Genomic DNA purification Kit (Promega, Madison, WI, USA). Briefly, the cells were lysed using nuclei lysis buffer, and the RNase digestion step was included at this time.

The cellular proteins are then removed by a salt precipitation step, which precipitates the proteins but leaves the high molecular weight genomic DNA in solution. Finally, genomic DNA is concentrated and desalted by isopropanol precipitation. The DNA concentration and purity (260/280) were checked using a Nano-drop spectrophotometer.

Bisulphite conversion.

Bisulphite conversion of DNA takes advantage of the bisulphited-mediated chemical conversion of unmethylated cytosine residues into uracil. Methylated cytosine residues were remain unchanged, while the sequence-specific PCR primers can distinguish unmethylated genomic regions after bisulphite conversion (Herman and Braylin 2003).

Aliquots of 2 µg of each DNA sample were subjected to Bisulphite modification using Methyl Edge Bisulphite Conversion System (Promega) following the manufacturer's instructions. Briefly, 2 µg of DNA was mixed with 130 µl of bisulphite conversion reagent.

The bisulphite conversion was performed using the following thermal cycling program: denaturation at 98°C for 8 min followed by another incubation at 54°C for 60 min. After cycling, the bisulphite-converted DNA was purified on a spin column, eluted in a volume of 20-µl, and stored at -20˚C.

http://dx.doi.org/10.36472/msd.v9i2.688

Methylation analysis.

The methylation status of the promoter regions of SAV1, MST1, MST2, LATS1, and LATS2 was analysed using methylation-specific PCR (MS-PCR). One hundred nanograms of bisulphate- treated DNA was PCR amplified in a 20-µl reaction buffer containing 10x Taq hot start master mix (New England Biolabs, Ipswich, MA). Primer sequences and reaction conditions are listed in Table 1. PCR reactions of the genes were performed using Touchdown (TD) PCR method. TD-PCR offers a simple and rapid means to optimize PCRs, increasing specificity, sensitivity, and yield without the need for lengthy optimizations and/or the redesigning of primers. TD-PCR employs an initial annealing temperature above the projected melting temperature (Tm) of the primers being used, then progressively transitions to a lower, more permissive annealing temperature throughout successive cycles. Any difference in Tm between correct and incorrect annealing will produce an exponential advantage of the two-fold per cycle (Korbie and Mattick 2008). The cycling program for TD-PCR involves two separate phases.

Phase 1 is the touchdown phase, which comprises 10 cycles with annealing temperature above Tm of the primers being used and transitions to a lower annealing temperature throughout successive cycles. Phase 2 is a generic amplification stage of 20 or 25 cycles using the final annealing temperature reached in Phase 1.

Phase 1 annealing temperature of 630C to 530C (MST2-USP {unmethylation specific primers}; SAV1-USP), 680C to 580C (MST2-MSP {methylation specific primers}, SAV1-MSP), 600C to 500C (LATS1-USP), 650C to 550C (LATS1-MSP, LATS2-MSP, LATS2-USP) for 10 cycles followed by phase 2 with an annealing temperature of 530C (MST2-USP; SAV1-USP), 580C (MST2-MSP, SAV1-MSP), 500C (LATS1-USP) and 550C (LATS1-MSP, LATS2-MSP, LATS2-USP) for 30 cycles. The extension was performed at 680C for 30 sec for all genes. PCR products were separated on 2.5% agarose gel and visualized with ethidium bromide.

RESULTS

Each experiment has been repeated three to six times to ensure reproducibility. TD-PCR products were visualized on 2.5% agarose gel. Looking at the TD-PCR of the MST1/2 genes in all Cell lines (MCF7, T47D, HCC1937, and BT-20). The gel image shows that MST1/2 genes are hemimethylated in MCF7, T47D, HCC1937, and BT-20 as PCR products were observed with both MSP and USP primers. For SAV1, the gene was also hemimethylated in MCF7, T47D, HCC1937, and BT-20 cell lines. Whereas LAST1 gene promoter was unmethylated in T47D and HCC1937 cell lines, but it was hemimethylated in MCF7 and BT-20 cell lines. Finally, the LAST2 gene promoter was hemimethylated in all study cell lines (Fig 1).

Table 1: Primers and conditions for Methylation-Specific PCR

Gene	CpG island Promoter size (bp)	transcription start	Primer	Product size (bp)	Tm (C^0)	TD-PCR Annealing Temp (C^0)
MST1	442	-70 to +50	MSP-F: GCGGGGCGGGTTTAGGAGGTTC MSP-R: CCAATAACCCCTCACCGACGC	120	67 62	58
		-73 to +52	USP-F: AACCAATAACCCCTCACCAACACAACAA USP-R: CGGGAGGGAGATTCGTCGCG	125	61 64	56
MST2	755	-18 to +81	MSP-F: CGGGAGGGAGATTCGTCGCG MSP-R: AAACCGAAACACCGACCGACCG	99	64 63	58
		-25 to +83	USP-F: TTTTAAGTGGGAGGGAGATTTGTTGTGG USP-R: AAAAACCAAAACACCAACCAACCAAACC	108	59 59	53
SAV1	909	-183 to -67	MSP-F: GATAGTCGTAGTTCGGCGGGG AC MSP-R: GCAACGCGAACCGCCG	116	61 63	58
		-187 to -56	USP-F: TGAGGATAGTTGTAGTTTGGTGGGGAT USP-R: AAAAACTCAACACAACACAAACCACCA	131	60 58	53
LATS1	473	-39 to +87	MSP-F: GAACGATTAGAGTTGCGGGCGAC MSP-R: AAC ATTTCCCGACGTCGCTTACG	126	61 61	56
		-40 to +88	USP-F: TGAATGATTAGAGTTGTGGGTGATGT USP-R: AAACATTTCCCAACATCACTTACACA	128	56 55	50
LATS2	1414	-123 to +14	MSP-F: TTCGTTCGGATTGGTATGCGGTC MSP-R: CCATCTTCCCGAAACGCTCACG	137	60 62	55
		-128 to +13	USP-F: GGTGTTTTGTTTGGATTGGTATGTGGTT USP-R: CATCTTCCCAAAACACTCACACCACA	141	58 60	55

MSP-F – Methylation-specific primer forward; USP-F – Unmethyaltion-specific forward
MSP-R – Methylation-specific primer reverse; USP-R – Unmethyaltion-specific reverse

http://dx.doi.org/10.36472/msd.v9i2.688

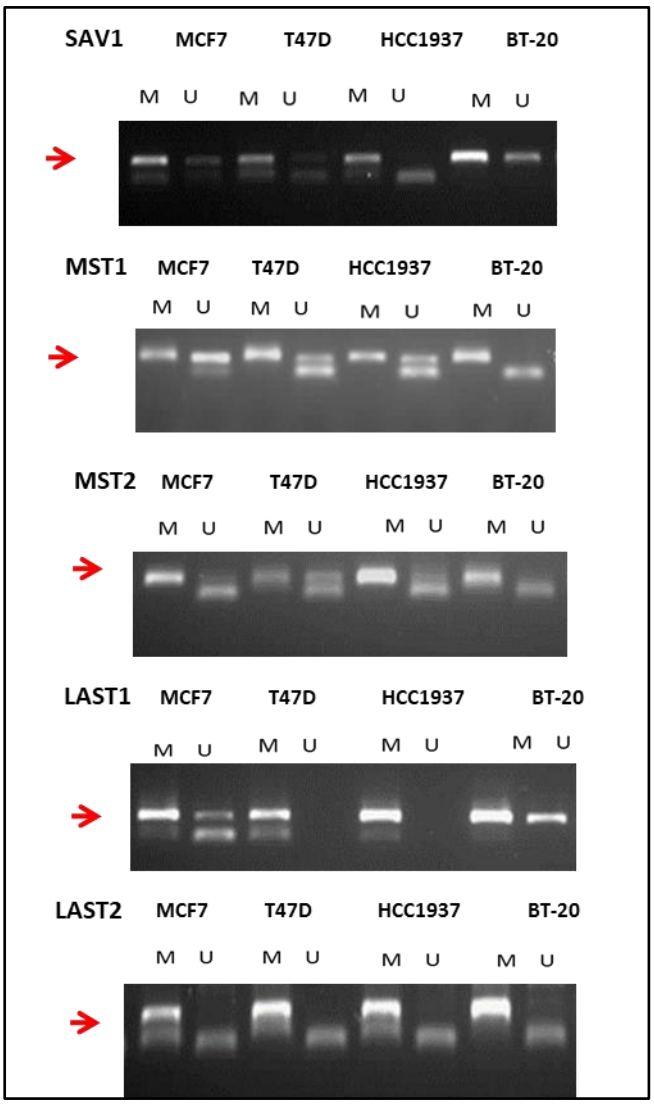


Fig 1: Gel images for hippo pathway methylated (M) and unmethylated (U) candidate genes. SAV1, MST1/2, and LATS1/2 were examined via MSP (M) and USP (U). Cell lines: MCF7, 2-T47D, 3-HCC1937, 4-BT-20. Separate MSP reactions were conducted for both methylated and unmethylated DNA sequences using primer sets specific for each reaction. The PCR products were separated by electrophoresis on 2.5% agarose gel mixed with ethidium bromide staining to visualize bands under UV light. For each run, we included positive control, which is a fully methylated DNA (EpiTect Control DNA (human); Qiagen), while nuclease-free sterile water used as a negative control.

DISCUSSION

Altered DNA methylation patterns in cancer tissues were first reported almost 40 years ago. This was accomplished when global methylation analysis by chromatographic techniques indicated a reduction of DNA methylation levels in numerous types of tumors from which the tumors originated compared to normal tissue [15,16,17]. Southern blotting techniques were then used to evaluate the hypomethylation changes for specific genes and at repetitive sequences [18,19].

It is well established that active genes in somatic cells maintain most of the CpG islands in their promoter regions unmethylated to ensure gene transcription. Furthermore, DNA methylation could prevent gene transcription by shifting transcription factor binding affinity to a gene promoter, stopping the binding of methylation-specific recognition factors to promoter or gene bodies, and condense the chromatin structure to limit the accessibility of transcription factors and/or other DNA binding proteins.

This study was devoted to studying the methylation status of the promoter regions of genes which, are recognized as the core component of the Hippo pathway that is linked to Brest cancer development and mortality rate. We have studied the methylation of SAV1, MST1/2, and LAST1/2 gene promoters in MCF7, T47D, HCC1937, and BT-20 breast cancer cell lines. SAV1 is at the front of the hippo signal pathway and is needed to activate the pathway. Remarkably, SAV1 plays a vital role in tumor suppression via hippo pathway-dependent and -independent mechanisms (20).

Moreover, recent research studies findings revealed low expression levels of MST1/2 in breast cancer and were closely associated with the poor prognosis of patients. Therefore, it was suggested that MST1 is an independent risk factor for breast cancer. However, overexpression of MST1 significantly inhibited the proliferation and migration while promoting the apoptosis of breast cancer cells. Moreover, the overexpression of MST1 significantly activated the Hippo signalling pathway (21).

With regard to LAST1 and LAST2, which are part of the hippo pathway, they were shown to participate in the regulation of human breast cell fate by direct interaction between hippo and estrogen receptor-α (ERα) signalling. The absence of LATS stabilizes ERα and the hippo effectors YAP and TAZ, which together control breast cell fate through intrinsic and paracrine mechanisms (22). Our study showed that SAV1, MST1/2, and LAST2 promoter regions were all hemimethylated in MCF7, T47D, HCC1937, and BT-20 cell lines.

This proves that linking specific DNA methylation changes with tumorigenesis in a cause-and-effect relationship has been challenging. However, Chunbo Shao et al. suggested that hemimethylated CpG dyads are intermediates in active demethylation during carcinogenesis and not just due to a failure of maintenance methylation during replicative DNA synthesis (23). Using openly available reduced representation bisulphite-sequencing (RRBS) data (GSE27003) of 7 breast cancer cell lines, namely (BT20, BT474, MCF7, MDAMB231, MDAMB468, T47D, and ZR751), Shuying Sun et al., has identified

hemimethylated sites for genes are involved or known to be involved in breast cancer (24).

Research findings were mainly obtained using statistical and bioinformatics data analysis to detect the hemimethylated sites of genes (25). Our findings, though, would be more meaningful because we investigated our genes of interest by examining the methylation status of their promoters' regions using bisulphite conversion and MSP in a wet lab. For LAST1, we observed that the promoter region was hypomethylated in both T47D and HCC1937 cell lines, whereas it was hemimethylated in MCF7 and BT-20 cell lines.

To the best of our knowledge, we are the first to show that the core component genes in the Hippo pathway about breast cancer, SAV1, MST1/2, and LAST 2 are hemimethylated in the breast cancer cell lines we studied. Thus, it is also significant to examine hemimethylated genes' expression levels and how these levels are related to the methylation and hemimethylation patterns of these genes.

Although DNA methylation controls genes by affecting gene expression, the relationship of hemimethylated patterns and gene expression in Brest cancer is not well studied yet. Some research findings suggested that it is important to study the relationship between hemimethylation patterns and gene expression in cancers.

Because, many of the previous methylation studies are conducted by assuming symmetric methylation, i.e., not considering hemimethylated (26). Therefore, identifying the hemimethylated profile for each single cell line or each breast cancer subtype is critical because some genes that contain hemimethylated CpG sites may play a role in tumor growth or suppression. Additionally, some of the hemimethylated genes associated with breast cancer are connected through biological pathways.

Lastly, these results suggest that certain genes in breast cancer cells may undergo active methylation or demethylation, which results in genome-wide hemimethylated and may indicate a transition between different stages of breast cancer. This transition may occur before tumour development. Thus, further study of hemimethylation may serve as a method to identify breast cancer in earlier stages and increase the chances of patient survival.

CONCLUSION

Because of the existence of hemimethylation, its impact on transcription must be studied in-depth. Also, it is constructive if research article states which DNA strand is analyzed after bisulfite conversion. We also suggest in the future that it would be optimal if a methylation analysis is carried out on both DNA strands separately.

The net result of some of these cancer-associated DNA hemimethylation could be abnormal modulation of transcription and even some aberrant post-transcriptional processing of transcripts and increases in DNA recombination, thereby contributing to tumor formation and progression.

Author Contributions: **AMA:** Project design, DNA extraction and analyses, **AMA:** Manuscript preparation, revisions.

Acknowledgments: I would like to thank the staff of Chair for Biomarkers of Chronic Diseases for lab assistance.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. Moroishi T, Hansen CG, Guan KL. The emerging roles of YAP and TAZ in cancer. Nat. Rev. Cancer.2015; 15(2): 73–79.
2. Donninger H, Allen,N, Henson A, Pogue J, Williams A, Gordon L, Kassler S, Dunwell T, Latif F, Clark GJ. Salvador protein is a tumor suppressor effector of RASSF1A with hippo pathway-independent functions. J. Biol. Chem. 2011; 286(21): 18483–18491.
3. Kai T, Tsukamoto Y, Hijiya N, Tokunaga A, Nakada C, Uchida T, Daa T, Iha H, Takahashi M, Nomura T, Sato F, Mimata H, Ikawa M, Seto M, Matsuura K, Moriyama M. Kidney-specific knockout of Sav1 in the mouse promotes hyperproliferation of renal tubular epithelium through suppression of the Hippo pathway. J. Pathol. 2016; 239(1): 97–108.
4. Wang L, Wang M, Hu C, Li P, Qiao Y, Xia Y, Liu L, Jiang X. Protein salvador homolog 1 acts as a tumor suppressor and is modulated by hypermethylation in pancreatic ductal adenocarcinoma. Oncotarge.2017; 8(38): 62953–62961.
5. Yim,SY, Shim JJ, Shin JH, Jeong YS, Kang SH, Kim SB, Eun YG, Lee DJ, Conner EA, Factor VM, Moore DD, Johnson RL, Thorgeirsson SS, Lee JS. Integrated genomic comparison of mouse models reveals their clinical resemblance to human liver cancer. Mol. Cancer Res. 2018;16(11): 1713–1723.
6. Jiang J, Chang W, Fu Y, Gao Y, Zhao C, Zhang X, Zhang S. SAV1, regulated by microRNA-21, suppresses tumor growth in colorectal cancer. Biochem Cell Biol.2019; 97(2): 91–99.
7. Ni L, Luo X. Structural and biochemical analyses of the core components of the hippo pathway. Methods Mol. Biol. 2019; 1893: 239–256.
8. Kim HB, Myung S J. Clinical implications of the Hippo-YAP pathway in multiple cancer contexts. BMB Rep. 2018; 51(3): 119–125.
9. Dent P, Booth L, Roberts JL, Liu J, Poklepovic A, Lalani AS, Tuveson D, Martinez J, Hancock JF. Neratinib inhibits Hippo/YAP signaling, reduces mutant K-RAS expression, and kills pancreatic and blood cancer cells. Oncogene. 2019; 38(30), 5890–5904.
10. Sun X, Ding Y, Zhan M, Li Y, Gao D, Wang G, Gao Y, Li Y, Wu S, Lu L, Liu Q, Zhou Z. Usp7 regulates Hippo pathway through deubiquitinating the transcriptional coactivator Yorkie. Nat. Commun.2019; 10(1): 411.

11. He W, You Y, Du S, Lei T, Wang H, Li X, He H, Tong R, Wang Y. Anti-neoplastic effect of mangiferin on human ovarian adenocarcinoma OVCAR8 cells via the regulation of YAP. Oncol. Lett. 2019;17(1): 1008–1018.

12. Sudol M., Shields DC, Farooq A. Structures of YAP protein domains reveal promising targets for development of new cancer drugs. Semin Cell Dev. Biol.2012; 23(7): 827–833.

13. Wei C, Wang Y, Li X. The role of Hippo signal pathway in breast cancer metastasis. Onco Targets and Therapy. 2018;11: 2185–2193.

14. Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, Minn AJ, van de Vijver MJ, Gerald WL, Foekens JA, Massagué J. Genes that mediate breast cancer metastasis to the brain. Nature. 2009; 459 (7249):1005–1009.

15. Ehrlich M, Lacey M. DNA hypomethylation and hemimethylation in cancer. Adv. Exp. Med. Biol. 2013;754: 31–56.

16. Gama-Sosa MA, Slagel, VA, Trewyn RW, Oxenhandler R, Kuo KC, Gehrke CW, Ehrlich M. The 5-methylcytosine content of DNA from human tumors. Nucleic Acids Res. 1983;11(19): 6883–6894.

17. Romanov GA, Vanyushin BF. Methylation of reiterated sequences in mammalian DNAs. Effects of the tissue type, age, malignancy and hormonal induction. Biochim. Biophys. Acta. 1981; 653(2): 204–218.

18. Feinberg AP, Vogelstein B. Hypomethylation of ras oncogenes in primary human cancers. Biochem. Biophys. Res. Commun. 1983; 111(1): 47–54.

19. Feinberg APA, Vogelstein B. Hypomethylation distinguishes genes of some human cancers from their normal counterparts. Nature. 1983; 301(5895): 89–92.

20. Zhao Z Xiang S, Qi J, We Yi, Zhang M, Yao J, Zhang T, Meng M, Wang X , Zhou Q. Correction of the tumor suppressor Salvador homolog-1 deficiency in tumors by lycorine as a new strategy in lung cancer therapy. Cell Death & Disease. 2020; 11(5):387.

21. Jin X, Zhu L, Xiao S, Cui Z, Tang J, Yu J, Xie M. MST1 inhibits the progression of breast cancer by regulating the Hippo signaling pathway and may serve as a prognostic biomarker. Molecular Medicine Reports. 2021; 23(5): 383.

22. Britschgi A, Duss S, Kim S, Couto JP, Brinkhaus H, Koren S, Silva DD, Mertz KD, Kaup D, Varga Z, Vissieres HVA, Leroy C, Roloff T, Stadler MB, Scheel CH, Miraglia LJ, Orth AP, Bonamy GMC, Reddy VA, Bentires-Alj M. The Hippo kinases LATS1 and 2 control human breast cell fate via crosstalk with ERα. Nature. 2017; 541(7638):541-545.

23. Shao C, Lacey M, Dubeau L, Ehrlich M. Hemimethylation footprints of DNA demethylation in cancer. Epigenetics. 2009; 4(3): 165-175.

24. Sun S, Lee YR, Enfield B. Hemimethylation Patterns in Breast Cancer Cell Lines. Cancer Informatics. 2019;18: 1176935119872959.

25. Sun S, Zane A, Fulton C, Philipoom J. Statistical and bioinformatic analysis of hemimethylation patterns in non-small cell lung cancer. BMC Cancer. 2021; 21(1): 268.

26. Naue J, Lee HY. Considerations for the need of recommendations for the research and publication of DNA methylation results. Forensic Sci Int Genet. 2018; 37: e12-e14.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Evaluation of the Effects of Attachment Type and Implant Number on Life Quality of Implant-Supported Mandibular Overdenture Prosthesis Patients

Beyza Ünalan Değirmenci1*, Murat Eskitaşçıoğlu1

1 Van Yüzüncü Yil University Faculty of Dentistry, Department of Prosthodontics, Van, TR

*** Corresponding Author:** Beyza Ünalan Değirmenci **E-mail:** beyzaunalan@hotmail.com

ABSTRACT

Objective: The current study aimed to evaluate the life quality of implant-assisted mandibular overdenture patients who have had additional implant applications and were rehabilitated with ball or bar attachment.

Material and Methods: 53 patients who came to Van Yüzüncü Yil University, Faculty of Dentistry, Prosthodontics Clinic for implant-supported mandibular overdenture treatment between 2019 and 2021 were included in this prospective clinical study (32 females, 30 males; mean age: 64.03; age range: 33-90). The patients were called back for the study precisely one year after prosthetic loading of their implants. Implant-supported mandibular overdenture prosthesis patients diverged into six groups: splinted two implants (bar attachment), single two implants (ball attachment), splinted three implants (bar attachment), single three implants (ball attachment), splinted four implants (bar attachment) and single four implants (ball attachment). And they asked for completing the Turkish version of the OHIP-14 questionnaire.

Results: Ball attachment was used in 45.28% of the participants, a mandibular overdenture design supported by a bar attachment was preferred in 54.72%. Kruskal-Wallis test results indicated that the number of implants had a statistically significant effect only on functional limitation and psychological disability among the seven OHIP-14 categories evaluated ($p=0.018$, $p=0.009$). Accordingly, the average functional limitation score in individuals with four implants was 4.44 ± 1.89.

Conclusion: We found that there are a positive correlation between the number of implants and the patient's life quality; however, it can be concluded that attachment type does not significantly affect the scores of the life quality.

Keywords: Dental Implants, Quality of Life, Quality Improvement

INTRODUCTION

The total loss of natural teeth and the consequent alveolar bone resorption are considered an oral health disorder (1). Although it is stated that the incidence is higher in individuals over the age of 65, it is known that it affects all age groups (2). Recent studies report the distinctions in the incidence of total edentulism by country and point out the problems that individuals experience due to this condition (3). It is a scientific fact that tooth loss triggers nutritional disorders and induces functional and sensory changes in the oral mucosa. All these changes restrict the patient's daily activities such as chewing and speaking and cause aesthetic concern in the patient hence, total edentulism was recognized as a physical disability by the World Health Organization (WHO) in 2001 (4). Kutkut et al., in a systematic review study which they evaluated the effects of total edentulism, conveyed that there was a significant decrease in the life quality of edentulous patients who were not rehabilitated (5).

Recent research highlights the importance of considering patient satisfaction and/or oral health-related life quality as an outcome variable to understand patients' needs and post-rehabilitation satisfaction and assess the impact of treatment on patients' life quality (6). Studies carried out over the past three decades, rooted in this focus, have utilized questionnaires such as the Oral Health Impact Profile (OHIP) to assess impacts (7).

Research Article

Received 11-02-2022

Accepted 23-02-2022

Available Online: 24-02-2022

Published 28-02-2022

Fueki et al. (8) and Armellini et al. (9) reported that OHIP in patients with removable partial dentures in implant-supported prosthesis patients was effective in patient-based evaluation of treatment efficacy. As it is known, the most common rehabilitation method in the treatment of total edentulism is traditional total dentures. However, high success has been achieved thanks to increased patient awareness and dental implantology. As a result, a significant increase has been achieved in today's treatment scenarios (1). However, total edentulism is more common in countries with relatively worse socio-economic conditions, so there may be a need for cheaper treatment costs (10). As proof of this finding, Dye et al. conducted a pioneering study in which individuals aged 50 and over evaluated the benefits of rehabilitation for total edentulism. In this study, he noted that the economic situation of the person played an important role in the recovery related to rehabilitation and defined the economic situation as a factor in the success of rehabilitation (11). This means that the number of implants planned in implant-assisted overdenture prostheses and the type of attachment used in its design are critical (12).

Implant-assisted mandible overdenture prostheses have a large number of attachment types available for the interforaminal region, depending on the preference of clinicians (13). Bilhan et al. reported that the most frequently preferred attachments in the market are bar, ball, magnet and locator attachments (14). Although attachment type preference today has become the hot topic of dental implantology, the research results published in this regard are quite contradictory (12). Moreover, according to the current authors, there are only two studies evaluating the effects of attachment type and the number of implants on the quality of life of implant-assisted mandibular overdenture patients. This is a significant impediment for clinicians to operate evidence-based implantology procedures. Based on this deficiency in the literature, the current study aimed to evaluate the life quality of implant-assisted mandibular overdenture patients who have had additional implant applications and rehabilitated with ball or bar attachment.

The first null hypothesis of the study is that the attachment type does not affect the quality of life of implant-assisted mandibular overdenture prosthesis patients. The secondary null hypothesis is that there will not be any distinction in the life quality of the patients depending on the number of implants.

MATERIAL and METHODS

Sixty-two patients who came to Van Yüzüncü Yil University, Faculty of Dentistry, Prosthodontics Clinic for implant-supported mandibular overdenture treatment between 2019 and 2021 were included in this prospective clinical study (32 females, 30 males; mean age: 64.03; age range: 33-90) The criteria for inclusion of the study are as follows: determination of mandible total edentulism, absence of any systemic diseases that may endanger the outcome of the implant, reading and signing written approval, having sufficient interocclusal distance and not having a history of using moving prosthesis before. However, patients with poor oral hygiene, current complaints of orofacial pain, acute oral infections and who refused to participate in follow-up check-ups were excluded from the study. All patients were provided with detailed information before the study and were requested to sign an informed consent form. The study protocol was approved by the Van Yüzüncü Yıl University Clinical Research Ethics Committee (18.12.2019/02).

The patients were called back for the study precisely one year after prosthetic loading of their implants. Implant-supported mandibular overdenture prosthesis patients diverged into six groups: splinted two implants (bar attachment), single two implants (ball attachment), splinted three implants (bar attachment), single three implants (ball attachment), splinted 4 implant (bar attachment) and single four implants (ball attachment). Experienced prosthetists carried out all clinical procedures, and all laboratory procedures were performed by the same qualified and experienced dental laboratory technicians. All prosthesis designs by the bilateral balanced occlusion scheme are cautiously developed. At the end of 1 year, the clinical examinations of the patients who were called for the control session were carried out by two experienced prosthesis faculty members. Prosthetic parameters such as retention, tissue compatibility, occlusion of the prosthesis and the condition of the stressed soft tissues were also carefully checked.

In the study, instead of the original OHIP questionnaire with 49 questions, the Turkish version of the OHIP-14 questionnaire, which offers reader convenience, includes the same seven categorical (functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap) evaluations, and has proven validity-reliability was used (15). The same five categories of answers were formed for each question: "never", "seldom", "occasionally", "quite often" and "very often". Responses were scored on a five-point scale ranging from 0 = 'never' to 4 = 'very often'. And a lower OHIP-14 score was considered to represent a higher life quality.

Statistical Analysis: The data were analyzed using IBM SPSS V23. While the conformity to the normal distribution was examined with the Shapiro-Wilk test, the Chi-square test was used to compare the categorical variables according to the groups.

http://dx.doi.org/10.36472/msd.v9i2.691

The Mann-Whitney U test was used to compare the data that was not normally distributed according to the paired groups, and the Independent Two-Sample T-test was used to compare the data that was not normally distributed. Kruskal-Wallis test was preferred in the comparison of the data that were not normally distributed according to groups of three or more, and multiple comparisons were examined with Dunn's test.

One-way analysis of variance has been used to compare the normally distributed data in groups of three or more. Analysis results were presented in mean ± standard deviation and median (minimum-maximum) for quantitative data and categorical data as frequency (percentage). The significance level was accepted as $p<0.050$.

RESULTS

At the end of 1 year, a total of 53 patients, 25 male and 28 female, participated in the study and the study was completed with the loss of 9 participants. It was recorded that 18 of the volunteers with a mean age of 67.78 had two implants, 16 had three implants and 19 had four implants. There was no statistical difference between the groups determined by the number of implants in terms of gender and age ($p=0.642$, $p=0.0549$) (**Table 1**).

Moreover, ball attachment was used in 45.28% of the participants, a mandibular overdenture design supported by a bar attachment was preferred in 54.72%.

The Chi-Square test results revealed that there was no significant age and gender difference between the groups according to the type of attachment used ($p=0.719$, $p= 0.859$) (**Table 2**).

Kruskal-Wallis test results indicated that the number of implants had a statistically significant effect only on functional limitation and psychological disability among the seven OHIP-14 categories evaluated ($p=0.018$, $p=0.009$). Accordingly, the average functional limitation score in individuals with four implants was 4.44 ± 1.89, and in individuals treated with two implants, this score was 6.21 ± 1.78 (**Table 3**).

There was no significant difference according to the number of implants in the categories of physical pain, psychological discomfort, physical disability, social disability and handicap ($p>0.05$). Nonetheless, while the psychological disability score treated with four implants was 2.69 ± 0.70, this score was 4.05 ± 1.87 in patients with overdentures supported by two implants is especially unusual (**Table 3**).

However, the Mann-Whitney U test revealed that ball or bar attachment preference did not have a statistical significance in the seven categorical evaluations of the patient ($p>0.05$) (**Table 4**).> Lower physical pain, psychological discomfort, physical disability, psychological and social disability scores were calculated in bar attachment patients. However, this difference was not statistically significant ($p>0.05$).

Table 1. Comparison of demographic characteristics according to the number of implants

	Implant Number			Total	Test Statistics	*P value*
	2	3	4			
Gender						
Male	9 (50)	6 (37.5)	10 (52.6)	25 (47.2)	0.886	0.642*
Female	9 (50)	10 (62.5)	9 (47.4)	28 (52.8)		
Age	67.78 ± 10.76	60.13 ± 11.38	58.63 ± 13.62	62.19 ± 12.50	3.002	0.059**
	66.00 (45.00 – 87.00)	61.50 (39.00 – 76.00)	62.00 (33.00 – 76.00)	62.00 (33.00 – 87.00)		

*Chi-Square test, **One Way ANOVA results, mean ± standard deviation, median (min-max), frequency (percentage)

Table 2. Comparison of demographic characteristics by attachment type

	Attachment Type		Total	Test Statistics	*P value*
	Ball	Bar			
Gender					
Male	11 (45.8)	14 (48.3)	25 (47.2)	0.031	0.859*
Female	13 (54.2)	15 (51.7)	28 (52.8)		
Age	61.50 ± 14.46	62.76 ± 10.84	62.19 ± 12.50	-0.362	0.719**
	63.50 (33.00 – 82.00)	62.00 (39.00 – 87.00)	62.00 (33.00 – 87.00)		

* Chi-Square test, ** Independent two-sample t-test, mean ± standart deviation, median (minimum – maximum), frequency (percentage)

Table 3. Results of OHIP categories for all groups according to implant number

Domain	Implant Number 2	3	4	Test Statistics	*P value**
Functional Limitation	6.21 ± 1.78 6.00 (2.00 – 8.00)[b]	5.63 ± 1.96 6.00 (2.00 – 8.00) [ab]	4.44 ± 1.89 4.00 (2.00 – 8.00) [a]	8.066	**0.018**
Physical Pain	5.39 ± 2.17 6.00 (2.00 – 8.00)	6.06 ± 2.02 6.50 (2.00 – 8.00)	6.89 ± 1.20 7.00 (5.00 – 8.00)	4.673	0.097
Psychological Discomfort	3.67 ± 1.68 3.00 (2.00 – 8.00)	3.75 ± 1.39 4.00 (2.00 – 6.00)	4.16 ± 1.61 4.00 (2.00 – 8.00)	1.179	0.554
Physical Disability	2.94 ± 1.89 2.00 (2.00 – 8.00)	2.25 ± 0.58 2.00 (2.00 – 4.00)	3.79 ± 2.42 2.00 (2.00 – 8.00)	3.981	0.137
Psychologic Disability	4.05 ± 1.87 3.00 (2.00 – 8.00)[b]	4.00 ± 1.50 4.00 (2.00 – 7.00) [b]	2.69 ± 0.70 3.00 (2.00 – 4.00)[a]	9.336	**0.009**
Social Disability	2.83 ± 1.38 2.00 (2.00 – 7.00)	2.25 ± 0.45 2.00 (2.00 – 3.00)	2.95 ± 1.72 2.00 (2.00 – 7.00)	1.177	0.555
Handicap	3.22 ± 1.26 3.00 (2.00 – 7.00)	3.31 ± 1.01 3.00 (2.00 – 5.00)	4.16 ± 1.46 4.00 (2.00 – 8.00)	5.676	0.059

*Kruskal Wallis test a-b: There is no difference between the number of implants with the same letter, mean ± s. deviation, median (min-max)

Table 4. Results of OHIP categories for all groups according to attachment type

Domain	Attachment Type Ball Attachment	Bar Attachment	Test Statistics	*P value**
Functional Limitation	5.33 ± 1.88 5.50 (2.00 – 8.00)	5.52 ± 2.10 6.00 (2.00 – 8.00)	323.5	0.657
Physical Pain	6.33 ± 2.10 7.00 (2.00 – 8.00)	5.97 ± 1.74 6.00 (2.00 – 8.00)	278	0.200
Psychological Discomfort	4.04 ± 1.68 4.00 (2.00 – 8.00)	3.72 ± 1.46 3.00 (2.00 – 8.00)	308.5	0.470
Physical Disability	3.25 ± 2.11 2.00 (2.00 – 8.00)	2.86 ± 1.77 2.00 (2.00 – 8.00)	289.5	0.221
Psychologic Disability	3.63 ± 1.79 3.00 (2.00 – 7.00)	3.62 ± 1.40 3.00 (2.00 – 8.00)	314.5	0.536
Social Disability	2.83 ± 1.46 2.00 (2.00 – 7.00)	2.59 ± 1.24 2.00 (2.00 – 7.00)	323	0.582
Handicap	3.54 ± 1.56 3.00 (2.00 – 8.00)	3.62 ± 1.12 4.00 (2.00 – 6.00)	299	0.364

*Mann-Whitney U testi, mean ± s. deviation, median (minimum – maximum)

DISCUSSION

Patients often have problems using traditional mandibular total dentures developed for total edentulism. An alternative option, implant-supported mandibular overdenture prostheses, promises more stabilization and retention (13). As a result of the current study originating from this focus, it was determined that there was a difference in the OHIP-14 scores of the patients due to the use of ball or bar attachments. Therefore, the first null hypothesis of the study was accepted. However, the findings revealed that patients with four implants scored lower on functional limitation and psychological disability from the seven assessment categories of OHIP-14 compared to cases rehabilitated with two implants (p=0.018, p=0.009). Therefore, the secondary null hypothesis of the research was rejected partially.

It is known that the type of attachment in implant-supported overdenture prosthesis has effects on the retention of the prosthesis, chewing efficiency, adaptation to phonation, aesthetics and ease of hygiene (16).

Research on this subject has often focused on the negative effects of magnet attachments (17). However, as emphasized by current studies, locater, ball and bar attachments are frequently preferred by dentists in overdenture prostheses. The evaluation of this situation by researchers is very important in terms of forming a guide for clinicians. In the current study, overdenture patients rehabilitated with ball and bar attachments were included to compensate for this deficiency in the literature. According to the York Consensus, implanting two implants in patients with implant-supported mandibular overdentur is a standard procedure for minimal care in the rehabilitation of edentulous patients (18). However, there are meta-analyses indicating that there is an improvement in peri-implant health parameters when the number of implants is increased to 3 and 4 (19). In the light of this information, patients who were rehabilitated with two implants, as well as patients with mandibular overdenture prosthesis supported by 3 and 4 implants, were included in our study.

Although it is assumed that the changes in the field of implantology will have an impact on the patients, there are very limited studies on the effects of the number of implants used in rehabilitation on the patients' life quality. El Syad et al. conducted a study evaluating the OHIP-14 scores of users of total dentures, fixed dentures, and bar-supported overdenture prostheses. In this study, he reported that the highest scores representing the worst quality of life were in total prosthesis patients, and there was an important decrease in OHIP-14 scores as the number of implants increased. Additionally, supporting this finding, they emphasized that the patient group with the highest life quality was fixed prosthesis users (20). Mumcu et al. also stated that the increase in the number of implants provoked a significant decrease in the OHIP-14 scores. They also discovered a similar effect in the visual analogue scale scores that they evaluated in their study. They reported that the lowest OHIP-14 score was obtained after bar supported overdenture prosthesis application, which also supports this (13). In the present study, a decrease in the OHIP-14 scores of the patients was received with the increased number of implants. This situation can be interpreted as the patients' life quality increases as the number of implants increases, which is in line with the results of all these studies. On the other hand, Swelem et al. stated that the number of implants is an effective factor in the total OHIP-14 scores, however when evaluated categorically, the effect was not detected in all seven categories. The study findings emphasized that with the increase in the number of implants, a statistically significant decrease was seen only in the scores of functional limitation, psychological discomfort, and physical disability (12). A similar study conveyed that the number of implants did not cause a significant score change in any category (21). In the current study, a significant difference in scores was obtained only in the functional limitation and psychological disability categories with the increase in the number of implants. This difference in the findings may be related to the difference that may occur in the tolerance levels of the participants depending on the age and gender difference, as well as the duration of using the prostheses of the patients who participated in the research.

A wide variety of attachment systems are available for the retention and support of overdenture prostheses; however, there is still no clear consensus on the effects of these attachments on functionality, biomechanics, clinical life and patient comfort (22). Gonçalves et al., in their systematic review study deriving from this deficiency, the clinical performances of attachment systems and their effects on patient satisfaction were evaluated, and it was noted that attachment preference did not have a substantial effect on patient satisfaction (23).

In a 10-year clinical follow-up study by Cune et al, it has been reported that patients with mandibular overdenture prosthesis designed with bar/ball attachment supported by 2 implants have equal satisfaction at the end of this process (24).

In the longitudinal prospective pioneer study conducted by Bergendal et al, it was emphasized that similar satisfaction scores were obtained in maxillary/mandibular overdenture prosthesis patients supported with different numbers of implants (2-5) and attachment types (25).

However, none of these studies directly evaluated the effects of attachment preference on patients' life quality. The patient satisfaction parameter, which has a positive correlation with the quality of life, was employed (26). Regarding this existing positive correlation, it can be stated that these findings are in parallel with the results of the current study. In the study performed by Bilhan et al., where the patients' life quality with mandibular overdenture prosthesis supported by two different attachment systems and two implants was evaluated, no significant difference was discovered in OHIP-14 scores depending on the attachment type, which is proof for this assertion (14). However, in a different study evaluating the effects of attachment type and the number of implants on the patients' life quality, it has been reported that the quality of life increases significantly and significantly eliminates psychological discomfort in mandibular overdenture prostheses designed with bar-type attachment supported by four implants of the attachment type (13). This difference in our findings may be due to the retrospective nature of the study design.

There are some main limitations of the present study. The first is that the patient group rehabilitated with conventional total dentures was not included in the study and the comparative effects of mandibular overdenture prostheses with traditional treatment procedures were not evaluated. Another limitation is that the effects of the restoration status of the maxillary arch and the implant positions used in the mandibular arch were ignored in the study.

CONCLUSION

Within the limitations of this study, a positive correlation between the number of implants and the patient's life quality has been found; however, it can be concluded that attachment type does not have a significant effect on the scores of the life quality.

Author Contributions: BÜD and **ME:** Concept, Data collection and/or processing, Analysis and/or interpretation, Literature review, **BÜD:** Writing, Revision

Acknowledgments: The authors would like to thank all the participants of this study. We also thank Dr. Naci Murat for his valuable contributions for statistical analysis.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. This study was approved by Van Yüzüncü Yil University Van Yüzüncü Yıl University Clinical Research Ethics Committee (18.12.2019/02).

REFERENCES

1. Mishra SK, Chowdhary R. Patient's oral health-related quality of life and satisfaction with implant supported overdentures -a systematic review. J Oral Biol Craniofac Res. 2019;9(4):340-6.
2. Egido Moreno S, Ayuso Montero R, Schemel Suárez M, Roca-Umbert JV, Izquierdo Gómez K, López López J. Evaluation of the quality of life and satisfaction in patients using complete dentures versus mandibular overdentures. Systematic review and meta-analysis. Clin Exp Dent Res. 2021;7(2):231-41.
3. Cardoso RG, Melo LA, Barbosa GA, Calderon PD, Germano AR, Mestriner WJ, et al. Impact of mandibular conventional denture and overdenture on quality of life and masticatory efficiency. Braz Oral Res. 2016;30(1):e102.
4. Kroll P, Hou L, Radaideh H, Sharifi N, Han PP, Mulligan R, et al. Oral Health-Related Outcomes in Edentulous Patients Treated With Mandibular Implant-Retained Dentures Versus Complete Dentures: Systematic Review With Meta-Analyses. J Oral Implantol. 2018;44(4):313-24.
5. Kutkut A, Bertoli E, Frazer R, Pinto-Sinai G, Fuentealba Hidalgo R, Studts J. A systematic review of studies comparing conventional complete denture and implant retained overdenture. J Prosthodont Res. 2018;62(1):1-9.
6. Bedi R, Gulati N, McGrath C. A study of satisfaction with dental services among adults in the United Kingdom. Br Dent J. 2005;198(7):433-7.
7. Preciado A, Del Río J, Suárez-García MJ, Montero J, Lynch CD, Castillo-Oyagüe R. Differences in impact of patient and prosthetic characteristics on oral health-related quality of life among implant-retained overdenture wearers. J Dent. 2012;40(10):857-65.
8. Fueki K, Yoshida-Kohno E, Wakabayashi N. Oral health-related quality of life in patients with non-metal clasp dentures: a randomised cross-over trial. J Oral Rehabil. 2017;44(5):405-13.
9. Armellini DB, Heydecke G, Witter DJ, Creugers NH. Effect of removable partial dentures on oral health-related quality of life in subjects with shortened dental arches: a 2-center cross-sectional study. Int J Prosthodont. 2008;21(6):524-30.
10. Petersen PE, Bourgeois D, Ogawa H, Estupinan-Day S, Ndiaye C. The global burden of oral diseases and risks to oral health. Bulletin of the World Health Organization. 2005;83:661-9.
11. Dye BA, Weatherspoon DJ, Lopez Mitnik G. Tooth loss among older adults according to poverty status in the United States from 1999 through 2004 and 2009 through 2014. J Am Dent Assoc. 2019;150(1):9-23.e3.
12. Swelem AA, Abdelnabi MH. Attachment-retained removable prostheses: Patient satisfaction and quality of life assessment. The Journal of Prosthetic Dentistry. 2021;125(4):636-44.
13. Mumcu E, Bilhan H, Geckili O. The effect of attachment type and implant number on satisfaction and quality of life of mandibular implant-retained overdenture wearers. Gerodontology. 2012;29(2):e618-23.
14. Bilhan H, Geckili O, Sulun T, Bilgin T. A quality-of-life comparison between self-aligning and ball attachment systems for 2-implant-retained mandibular overdentures. J Oral Implantol. 2011;37 Spec No:167-73.
15. Basol ME, Karaagaçlioglu L, Yilmaz B. Developing a Turkish Oral Health Impact Profile-OHIP-14-TR. Turkiye Klinikleri Dishekimligi Bilimleri Dergisi. 2014;20(2):85.
16. Al-Harbi FA. Mandibular Implant-supported Overdentures: Prosthetic Overview. Saudi J Med Med Sci. 2018;6(1):2-7.
17. Ellis JS, Burawi G, Walls A, Thomason JM. Patient satisfaction with two designs of implant supported removable overdentures; ball attachment and magnets. Clin Oral Implants Res. 2009;20(11):1293-8.
18. Thomason JM, Feine J, Exley C, Moynihan P, Müller F, Naert I, et al. Mandibular two implant-supported overdentures as the first choice standard of care for edentulous patients--the York Consensus Statement. Br Dent J. 2009;207(4):185-6.
19. Bi Y, Aldhohrah T, Mashrah MA, Su Y, Yang Z, Guo X, et al. Effects of attachment type and number of dental implants supporting mandibular overdenture on peri-implant health: A systematic review and network meta-analysis. J Prosthodont Res. 2021.
20. El Syad M, Elgamal M, Mohammed Askar O, Youssef Al-Tonbary G. Patient satisfaction and oral health-related quality of life (OHRQoL) of conventional denture, fixed prosthesis and milled bar overdenture for All-on-4 implant rehabilitation. A crossover study. Clin Oral Implants Res. 2019;30(11):1107-17.
21. Kuoppala R, Näpänkangas R, Raustia A. Quality of Life of Patients Treated With Implant-Supported Mandibular Overdentures Evaluated With the Oral Health Impact Profile (OHIP-14): a Survey of 58 Patients. J Oral Maxillofac Res. 2013;4(2):e4-e.
22. Takahashi T, Gonda T, Tomita A, Maeda Y. Effect of Attachment Type on Implant Strain in Maxillary Implant Overdentures: Comparison of Ball, Locator, and Magnet Attachments. Part 2: Palateless Dentures. Int J Oral Maxillofac Implants. 2018;33(2):357-64.
23. Gonçalves F, Campestrini VLL, Rigo-Rodrigues MA, Zanardi PR. Effect of the attachment system on the biomechanical and clinical performance of overdentures: A systematic review. J Prosthet Dent. 2020;123(4):589-94.
24. Cune M, Burgers M, van Kampen F, de Putter C, van der Bilt A. Mandibular overdentures retained by two implants: 10-year results from a crossover clinical trial comparing ball-socket and bar-clip attachments. Int J Prosthodont. 2010;23(4):310-7.
25. Bergendal T, Engquist B. Implant-supported overdentures: a longitudinal prospective study. Int J Oral Maxillofac Implants. 1998;13(2):253-62.
26. De Kok IJ, Cooper LF, Guckes AD, McGraw K, Wright RF, Barrero CJ, et al. Factors Influencing Removable Partial Denture Patient-Reported Outcomes of Quality of Life and Satisfaction: A Systematic Review. J Prosthodont. 2017;26(1):5-18.

MSD

Medical Science and Discovery
ISSN: 2148-6832

Nursing care based on Dorothy Johnson's Behavioral System Model in Coronary Artery Disease: A case report

Selva Ezgi Aşkar[1]*, Özlem Ovayolu[2]

1 Mustafa Kemal University Hospital, Department of Education, Hatay, TR
2 Gaziantep University, Faculty of Health Science, Department of Nursing, Gaziantep, TR

*** Corresponding Author:** Selva Ezgi Aşkar **E-mail:** selvaezgiaskar@gmail.com

ABSTRACT

Objective: The use of theory/model is very important in providing nursing care in standardized frameworks. One of these models in the literature is Dorothy Johnson's "Behavioural System Model".

Material and Methods: In this study, the nursing process of a 59-year-old patient who was followed up with the diagnosis of coronary artery disease and had many comorbid conditions but continued her negative behaviors towards her diseases was presented using Johnson's Behavioural System Model.

Case: In our case, first of all, a detailed medical history was taken and physical examination was performed, and conditions that disrupted the balance of the subsystems in the model were determined. Afterwards, a nursing care planthat can be implemented to provide behavioural change to restore balance was designed.

Conclusion: Since it is very important to provide behavior change in chronic diseases, it is recommended to use Johnson's Behavioural System Model in chronic disease management and to conduct studies in different chronic diseases.

Keywords: Behavioural system model, care plan, coronary artery disease, nursing

INTRODUCTION

The use of care plans prepared in line with the nursing process is very important in order to deal with the individual in a holistic and systematic way and to provide a standard nursing care [1]. Nurses have put forward some theories to show the relationship between this professional care given in line with the plan and the results obtained. These theories establish relationships between concepts. Models are defined as symbolic or physical ideas that are used to easily explain the relationship between concepts as well as thoughts. Accordingly, it is crucial to use theory/model in making nursing practices in a standard framework and eliminating deficiencies [2-4]. Implementing the nursing care process based on theory/models helps collect and analyze data and provide holistic care [3].

Nursing models such as Neuman Systems Model, Roy Adaptation Model, Orem's Self-Care Deficit Theory, Peplau's Theory of Interpersonal Relations, Pender's Health Promotion Model, Dorothy Johnson's Behavioural System Model have been used in case reports investigating the clinical use of nursing models in the literature [3]. Therefore, this study aims to provide the behavioural system model-based nursing care of a case diagnosed with coronary artery disease (CAD) and to contribute to the literature.

Dorothy Johnson's Behavioural System Model

The Behavioural System Model was first defined by Dorothy Johnson in 1980 and is based on behavioural sciences such as psychology, sociology and ethnology [4]. According to Johnson, the nurse helps the individual to facilitate behavioural functions before, during and after the illness. Nursing, on the other hand, is a professional discipline focusing on keeping the individual in balance and re-establishing the balance in case of imbalance [4,5]. Nursing interventions include protecting, supporting, and stimulating subsystems and ultimately regulating the entire system [6]. Moreover, another component of the model, the individual, is defined as the behavioural system. The behavioural system includes subsystems that affect each other and are interdependent.

Case Report Article

Received 16-01-2022

Accepted 14-02-2022

Available Online: 23-02-2022

Published 28-02-2022

http://dx.doi.org/10.36472/msd.v9i2.671

Each subsystem interacts with the environment. Disruption of any subsystem leads to the impairment of balance, thus in turn resulting in impairment of health. The nurse, on the other hand, supports the individual's attempts to maintain the balance with the Behavioural System Model with his/her roles such as education and intervention [4,6]. Johnson's Behavioural System Model consists of seven subsystems [4,6-8]:

- Affiliative subsystem; it is the basis of social events. People have warmer relationships with others.
- Dependence subsystem; people pay attention to and feel trust towards others without any expectation with the aim of getting help.
- Ingestive subsystem; it is the maintenance of the integrity of the organism by meeting the needs of the individual such as food and oxygen.
- Eliminative subsystem; it is the excretion of biological waste from the organism
- Sexual subsystem; it is development of sexual identity and supporting sexual satisfaction.
- Achievement subsystem; individuals motivate themselves and their circle in order to meet the needs and achieve the goal.
- Aggressive subsystem; individuals make attempts to defend themselves and their circle in order to preserve and maintain integrity.

Each subsystem consists of four structural elements. These elements are drive, set, choice, and action [8,9]. Furthermore, in the model, Johnson classifies nursing diagnoses as various "insufficiency, discrepancy, incompatibility, and dominance" based on the individual's problems with these diagnoses. Depending on the situation, the nurse applies interventions that are not easily observed but can be deduced. As a result, the nursing intervention is evaluated by directly observing the individual's behavior or performance. [9].

Profile of the Case with Coronary Artery Disease

A 59-year-old female patient is unemployed. She is married and has three children. She lives at home with her husband and a single son.

The patient applied to the cardiology outpatient clinic due to the complaint of chest pain. After the evaluation, it was planned to admit her to the service. She stayed at the hospital several times before and she underwent coronary angiography four times. She underwent her last coronary angiography in March 2021. Coronary angiography was planned for her during this hospitalization, as well. When she learned that she was going to undergo angiography again, she started to cry and said, “Why couldn’t I recover? Yow… same again, they will do an angiogram operation for me again.”. She has a medical history of CAD, diabetes, hypertension, and heart failure. She stated that she did not monitor her blood glucose regularly and did not check blood pressure because she felt well at home. She also has the diagnosis of breast cancer in her medical history and underwent a left mastectomy in 2017. She is not a smoker but said that she was accompanying her husband with 1-2 cigarettes while they are drinking a cup of coffee. She does not consume alcohol.

She stated that she was living at home with her husband and one child and they ate the same meal because she could not cook separately for everyone, therefore she did not follow any dietary program for her diseases, she was generally eating two meals and did not eat snacks, she was paying attention to take her drugs but she rarely forgot to take them. Her drugs were Acetylsalicylic acid 100 mg 1x1 tb, Metoprolol succinate 50 mg 1x1 tb, Ramipril/ hydrochlorothiazide 10/25 mg 1x1 tb, Amlodipine 10 mg 1x1 tb, Clopidogrel 75 mg 1x1 tb, Pantoprazole 40 mg 1x1 tb, Atorvastatin (Ator) 40 mg 1x1 tb, Atorvastatin (Colastin-L) 20 mg 1x1 tb, Letrozole 2.5 mg 1x1 tb, Pioglitazone HCl 45 mg 1x1 tb, and Empagliflozin 25 mg 1x1 tb.

She stated that she is doing her housework - albeit taking breaks periodically. She claimed that she is exhausted and (yet) looks after herself. She added that her works never end because her husband is constantly inviting guests over and doesn't help her out. Moreover, she told us that her married son always accompanies her to the hospital. She feels as though she is a burden on him, and that she has kept him away from his family. This, in turn, has upset her and caused her stress.

The patient stated that she had no problem about urination, but she did not defecate for two days since the hospital influenced her. She stated that she could not sleep at night, woke up for no reason, and often could not fall asleep for more than 30 minutes. She said that she prayed for having a comfortable sleep, had concerns about the future, felt uneasy, and sometimes very sad, and she wanted to regain her health. Her mother suffers from hypertension and heart disease and her father has diabetes, she lost her brother due to myocardial infarction and her sister due to bowel cancer, all of which underlies her fears and concerns.

The physical examination of the patient was performed by the first author and physician. In the inspection and palpation performed by the first author, it was observed that there was no edema in the body, no obvious complaint about lymphedema, and no other finding other than dryness and thickening in the skin of the feet. She suffered from tingling, burning sense, and sometimes stinging pain in her feet. Peripheral arterial pulses were taken in bilateral lower and upper extremities. The auscultation findings made by the physician were accessed from the patient file. During

http://dx.doi.org/10.36472/msd.v9i2.671

auscultation, it is recorded that respiratory sounds were normal and S1 and S2 heart sounds were heard. No additional sound or murmur was heard. Her other system examinations were assessed as normal. Among her vital signs, body temperature: 36.7°C, blood pressure: 143/79 mmHg, pulse: 73/min, respiration: 24/min, and oxygen saturation: 96%. Her laboratory findings were glucose: 191 mg/dl and HbA1C: 8.2% (high) and cholesterol levels and other laboratory findings were normal. Electrocardiography findings were at the sinus rhythm and echocardiography findings decreased with 35-40% ejection fraction (EF) and first-degree tricuspid insufficiency (TI), dilated left atrium (LA), and left ventricular hypertrophy (LVH) were noted.

The patient underwent coronary angiography as planned. Left Anterior Descending (LAD) was proximal stenosis at the rate of 70%, Circumflex (Cx) had plaque and Right Coronary Artery (RCA) was open. The patient was suggested to receive stent for LAD and medical treatment for CAD and discharge was planned.

Nursing Care of the Case According to the Behavioural System Model

The nursing process planned according to Johnson's Behavioural System Model for the patient who was diagnosed with CAD, underwent coronary angiography several times and had a comorbid condition is shown in the **table 1**.

Table 1. The nursing process planned according to Johnson's Behavioural System Model

Subsystem	Function	Diagnosis	Planning and Application
Affiliative	- Living at home with her husband and son. - Her married son does not spend time with his wife and children since he accompanies her. Her daughter-in-law did not call her throughout her last hospitalization and all of this makes her upset. - Not going outside too much, getting tired due to her diseases. - Having fear since she suffers from diseases in her family history, thinking that her own outcome would also be bad like theirs and stating that she have many sleepless nights without any reason	- Insufficiency/ Dominance	- An environment with her husband and son is created and the importance of family support and assistance is emphasized. - She is encouraged to talk to her daughter-in-law and supported in solving the problem. - It is recommended for her to make non-tiring activities and take a slow walk in the fresh air. - She is allowed to express concerns and fears. Lifestyle changes are planned to control the disease. - Non-pharmacological (breathing techniques, relaxation, etc.) methods are taught her to eliminate sleep problems. - She is allowed to express her thoughts about death.
Dependence	- Providing self-care. - Suffering from dyspnea while dealing with household chores.	- Insufficiency/ Dominance	- She is provided support for household chores. - She is trained to take breaks frequently and control breathing (breathing deeply and slowly) to conserve energy and reduce dyspnea while doing household chores.
Aggressive	- Being unable to usually finish household chores and getting tired of guests her husband always invites at home. - Stating that her husband was constantly smoking next to her even though she herself did smoke and that she was smoking one or two cigarettes with her coffee just to accompany him.	- Insufficiency/ Dominance	- She is encouraged to talk to her husband about the situations she feels uncomfortable. - A meeting with her husband is planned. He is informed about the necessity of meeting her care needs and its importance. - The relationship of smoking with chronic diseases is explained. The harms of passive smoking are indicated. Not smoking and the effects of smoking next to her are explained. If necessary, professional support is provided in this regard.
Ingestive	- Eating without any help. - Not following a specific diet for diabetes and hypertension. - Having never seen a diabetes nurse and a dietitian even though she had a history of diabetes for nine years. - Eating two meals a day and having irregular eating habits without taking any snacks. - Not knowing how to eat and not applying it.	- Insufficiency/ Dominance - Discrepancy/ incompatibility	- A meeting with the diabetes nurse is scheduled. - If necessary, a dietitian support is provided to regulate her nutrition. - The importance of monitoring blood glucose and blood pressure is emphasized. - It is questioned whether she has a personal glucometer and blood pressure monitor. If she does not have it, she will be helped to buy them. - Hypoglycemia and hyperglycemia are defined. She is informed about their symptoms. She is enabled to take measures. - She is informed about the relationship of nutrition with chronic diseases. - The importance of foot care is explained to her. - By providing an environment where family members living at home are present, it is planned to serve the meals that will be suitable for her, as well.

Eliminative	- No problem in urinating. - Being unable to defecate for two days. - Stating that the hospital environment affected her and she had related problems.	- Insufficiency/ Dominance	- Defecation is followed up. Bowel movements of the patient are checked. - She is enabled to eat fibrous foods.
Sexual	- Being married and having three children, undergoing left mastectomy and going through menopause.	- it was not assessed.	- It was not assessed.
Achievement	- Having difficulty in doing household chores. - Being unable to check blood glucose and blood pressure. - Keeping follow-up of her drugs and taking them herself. - Expressing that she could not realize her own in the hospital and thinking that she was imposing a burden to her married son. - Inability to sleep well due to worries and fears. - Saying that she still has clogged vessels in her coronary angiography. - Thinking that she cannot take her disease under control and cannot recover despite taking her drugs regularly.	- Insufficiency/ Dominance	- She is enabled to take support for household chores. - She is informed about the importance of monitoring blood glucose and blood pressure. Her knowledge on this subject is questioned and her lack of knowledge is met. - Since she provides self-care, this is maintained. Her positive behaviors are supported. - The stress associated with the concerns and fear she feels and the negative relationship of stress with her diseases are explained to her. - Stress-related coping methods are taught to her. - She is encouraged to freely express her thoughts about the future. Her concerns are eliminated.

CONCLUSION

In this study, the nursing process of a patient who was diagnosed with CAD, underwent coronary angiography several times and had a comorbid condition but continued her negative behaviors towards her diseases, was presented using Johnson's Behavioural System Model. As is known, the Behavioural System Model provides a conceptual framework in nursing practices [4]. It also reveals the situations requiring the nurse's attention during her care. The main task of the nurse is to help the individual to change his/her behavior [7]. In the present case, the medical history of her, which we considered as the behavioural system, was taken in detail, her physical examination was carried out and then conditions disrupting the balance of subsystems were detected. Afterwards, a nursing care plan, which can be implemented by the nurse, a component of the external environment, was designed to provide behavioural change to bring into balance again. There are a limited number of studies in Turkey using the Behavioural System Model. However, studies also show that the model is useful in planning an effective nursing care [6,7,10,11]. The international literature has revealed that the model has a positive effect on nursing outcomes in different studies based on the Behavioural System Model in their theoretical frameworks [5,9,12,13]. It is very important to provide behavioural change in chronic diseases. In this sense, it is suggested to use Johnson's Behavioural System Model in management of chronic diseases and to conduct studies on different chronic diseases, as well.

Author Contributions: SEA: wrote the manuscript and obtained the patient consent. **ÖO:** critically reviewed and edited the report. All authors read and approved the final manuscript.

Conflict of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. This research did not receive and a specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee.

REFERENCES

1. Kocaçal E, Aktan GG, Eşer E. Development of nursing process and care plans in historical process. Anatolian Journal of Nursing and Health Sciences. 2021;24(2):284-290.
2. Koç Z, Kızıltepe KS, Çınarlı T, Sener A. The use of theory in nursing practice, research, management and education. Koç University Journal of Education and Research in Nursing. 2017;14(1):62-72.
3. Şahin G, Buldak Cİ, Kaya V, Güvenç G, İyigün E. The examination of the graduate studies performed by using the theory and model in the nursing field at turkey: A systematic review. Koç University Journal of Education and Research in Nursing. 2020;17(2):170-9.
4. Velioğlu P. Concepts and theories in nursing. Istanbul: Academy Press; 2012.
5. Tynan A. Supporting positive lifestyle changes among patients with diabetes mellitus type 2. Nursing Senior Theses 4. 2020.
6. Evgin D, Özdil K. A theoretical approach to encouraging fathers to support breastfeeding: Johnson's behavioural system model. 6th International Congress on Women and Chıldren's Health and Education Proceedings Book. 2020;75-83.
7. Kardaş Kin Ö, Türeyen A. interpretation Dorothy Johnson's behavioural system model: COPD case report. Journal of Nursing Science. 2018;1(3):46-50.
8. Pektekin Ç. Nursing philosophy. Istanbul: Istanbul Medical publications 2013.
9. Karkhah S, Ghazanfari MJ, Norouzi M, Taheri Z. Designing a nursing care plan based on Johnson's Behavioural Model in patients with wrist joint hematoma: A case study. Research Square. 2020.

10. Erkoç A, Yürügen B. Dorothy E. Johnson's Behavioural Systems Model: Case report. 14th National İnternal Medicine Congress Proceedings Book. 2012;395-396.

11. Evgin D, Bayat M. The effect of Behavioural System Model based nursing intervention on adolescent bullying. Florence Nightingale Journal of Nursing. 2020;28(1):71-82.

12. McGuiness M. Utilizing the Behavioural System Model for adolescent depression in the school setting. 2021.

13. Runner TR, Berryman JJ, Lehrer JC. Utility of the beck depression inventory in patients with chronic kidney disease stage 4 without kidney replacement therapy. Nephrology Nursing Journal: Journal of the American Nephrology Nurses' Association. 2021;48(2):147-167.

MSD

Medical Science & Discovery

International Journal of
Medical Science and Discovery
Open Access Scientific Journal
ISSN: 2148-6832
Lycia Press LONDON U.K.
www.medscidiscovery.com

lycians

www.lycians.com