Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Ann Med Res | Volume: 32 | Issue: 3 | March 2025

Original Articles

Case Reports

Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Editorial Board | Volume: 32 | Issue: 3 | March 2025

Annals of Medical Research
The Offical Journal of Inonu University Faculty of Medicine
Editorial Advisory Board | Volume: 32 | Issue: 3 | March 2025

Annals of Medical Research

The Offical Journal of Inonu University Faculty of Medicine

Table of Contents | Volume: 32 | Issue: 3 | March 2025

Original Articles

Case Reports

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Immediate effects of Mulligan mobilization and taping on pain and functional status in patients with knee osteoarthritis

Muhammet Sahin Elbasti[a,*], Songul Baglan Yentur[b]

[a] *Elazig Medical Hospital, Department of Physical Medicine and Rehabilitation, Elazig, Türkiye*
[b] *Fırat University, Faculty of Health Sciences, Department of Physiotherapy and Rehabilitation, Elazig, Türkiye*

ARTICLE INFO

Keywords:
Mobilization with movement
Mulligan mobilization
Osteoarthritis
Pain
Taping

Received: Nov 20, 2024
Accepted: Feb 11, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.11.241

Abstract

Aim: The present study aimed to examine the immediate impact of a physical therapy in combined with mobilization on pain, functional restoration, and decreasing disability in individuals with knee osteoarthritis.

Materials and Methods: Pain intensity was evaluated by Visual Analog Scale (VAS), disability by WOMAC Osteoarthritis Index, and function by functional tests. The participants of the study were randomly divided into two groups. The control group received a single session of conventional physical therapy. In contrast, the study group received 3 sets of Mulligan mobilization technique (MWM), one set made up of 10 repetitions in combination to conventional physiotherapy. In the following step, internal rotation taping was applied to the study group. Outcome measurements were repeated after the treatment.

Results: A total of 40 patients with knee osteoarthritis were included the study. No significant differences were found between the study and control groups regarding demographic characteristics ($p>0.05$). Significant changes were observed in all measured parameters within both groups ($p<0.05$). The pain evaluation showed significant changes among the groups ($p=0.002$) whereas, no significant differences were identified in functional tests or disability measures ($p>0.05$).

Conclusion: Mulligan MWM technique and internal rotation taping in addition to conventional treatment were found to be more effective in reducing pain compared to the group treated with conventional treatment alone. Adding MWM technique and taping to the routine treatment of OA may increase the success of treatment.

Introduction

Osteoarthritis (OA) is a progressive joint disorder marked by the breakdown of articular cartilage, increased density in the underlying bone (subchondral sclerosis), and alterations in the biochemical and morphological aspects of the synovial membrane and joint capsule It results in pain, joint stiffness, stiffness, stiffness in joint motion, limitation in activities of daily living and eventually disability [1]. Patients with knee OA (KOA) have symptoms such as pain, movement limitation and loss of function due to biomechanical changes. Osteoarthritis Research Society International provides pharmacologic, non-pharmacologic and surgical treatment recommendations for the treatment of osteoarthritis [2].

Physical therapy modalities are frequently used in combination with other treatment options or alone in the treatment of OA in clinical practice [3]. Mobilization methods are also used in the treatment of OA in addition to physical therapy. Manual techniques used in KOA aim to reduce pain, increase range of motion, and improve function [4]. According to Adams et al., manual therapy exerts mechanical, neurophysiological, and physiological effects on tissues. Their findings indicated immediate pain relief, activation of pain-inhibitory mechanisms, a reduction in inflammatory markers in the bloodstream, and improved joint function following joint mobilization [5]. Similarly, Moss et al. observed a rapid decrease in pain after joint mobilization in individuals with knee osteoarthritis (KOA). This pain reduction was attributed to the stimulation of mechanoreceptors and the modulation of pain perception within the cortical system [4].

Mulligan mobilization is a type of joint mobilization developed by physiotherapist Brain Mulligan in New Zealand in 1980. This method that should be applied by trained physiotherapists, and it aims to correct movement limitation in the joint and to eliminate pain and restore the

*Corresponding author:
Email address: muhammetsahinelbasti@gmail.com
(Muhammet Sahin Elbasti)

function of the joint [6]. However, there are no studies examining the effects of MWM and kinesio taping in addition to conventional physical therapy. The aim of this study was to investigate the immediate effects of MWM and kinesio taping applied in combination with a physical therapy program on pain, functionality and disability in patients with KOA.

Materials and Methods

The study received approval from the institutional review board (Fırat University Non-Interventional Clinical Research Ethics Committee, 2023/10-18) and followed the ethical guidelines outlined in the Declaration of Helsinki. Written informed consent was secured from all participants. To calculate the required sample size and ensure statistical power, the G*Power 3.1.9.4 software was employed. Using VAS mean scores reported by Kiran et al. [7], a power analysis indicated that at least 20 participants per group were needed to detect an effect size of 1.21, with an alpha level of 0.05 and a power of 0.95. Sixty-four female patients with KOA diagnosed using the American College of Rheumatology criteria, were included in this study. Eligible patients were aged 40-65 years and presented with Kellgren-Lawrence stage 1 or 2 osteoarthritis, and provided consent to participate. Exclusion criteria included pregnancy, malignancy, requirement for walking support, prior knee surgery, inflammatory arthritis, analgesic use on the day of treatment, and a history of knee trauma within the preceding six months. Pain was the primary outcome, with functional restoration and disability reduction serving as secondary outcomes.

Sixty-four female patients with KOA diagnosed using the American College of Rheumatology criteria, were included in this study. Eligible patients were aged 40-65 years and presented with Kellgren-Lawrence stage 1 or 2 osteoarthritis, and provided consent to participate. Exclusion criteria included pregnancy, malignancy, requirement for walking support, prior knee surgery, inflammatory arthritis, analgesic use on the day of treatment, and a history of knee trauma within the preceding six months. Pain was the primary outcome, with functional restoration and disability reduction serving as secondary outcomes.

Outcome measurements

Sociodemographic data, including age, height, weight, body mass index (BMI) and, current medications were recorded.

Pain assessment

Visual Analog Scale (VAS) was used to evaluate pain in functional tests before and after treatment [8].

Functional tests

Patient functional status was assessed using the pick-up, repeated sit-to-stand, socks, stair descent, stair climbing, and ten meters walk tests [9]. Patients received explanations of the tests and performed each test three times, with one-minute rest intervals between repetitions. The mean of the three scores obtained for each test was then calculated.

Disability assessment

The Western Ontario and McMaster Universities Arthritis Index (WOMAC) was utilized to assess disability. This tool consists of 24 items, categorized into three domains: pain (5 items), stiffness (2 items), and physical function (17 items) [10].

Treatment program

The patients included in the study were randomly divided into two groups using random.org. Patients in control group received combined physical therapy modalities (CPT); patients in study group received mobilization and Mulligan Concept internal rotation kinesiotaping, in addition to CPT. In the supine position, lateral, medial and rotational sliding forces were applied to the tibia, and anterior sliding force was applied to the proximal tibiofibular joint of the fibula head, to determine the sliding direction that reduced subjects pain. Three sets of 10 repetitions were performed, with 15-20 second rests between sets. After mobilization, kinesiotaping was applied using submaximal tension , adhering to the Mulligan Concept. During taping, subjects maintained 5-10 degrees of knee flexion while standing, and maximally externally rotated the hip while internally rotating the foot. The tape was then applied form the posterior aspect of the fibular head, diagonally across the anterior knee, and adhered to the posterior aspect of the medial condyle of the femur.

Hotpack (HP), TENS and ultrasound (US) were applied in CPT. Superficial heat application was applied on the knee for 30 minutes by wrapping two layers of towels on HPs. Conventional TENS with 4 electrodes for 30 minutes and Therapeutic US with 3 megahertz, 1 watt/cm2 treatment dosage for 5 minutes were applied to the knee of the patients.

Statistical analysis

All statistical analyses were performed using SPSS Version 22.0 for Windows. The normality of the data was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Based on the results, either parametric or nonparametric methods were selected for data analysis. Descriptive statistics were expressed as counts, percentages, ranges, and means ± standard deviations. Categorical variables were analyzed using the Pearson chi-square test, while continuous variables were examined using the Independent t-test and Mann-Whitney U test. For parametric comparisons, the Wilcoxon test (a nonparametric method for dependent groups) and Paired Sample tests were utilized. A p-value of less than 0.05 was considered statistically significant.

Results

Twenty-one patients did not meet inclusion criteria and three patients refused to participate. Therefore, this study was completed with 40 patients. The demographic characteristics of the patients were summarized in Table 1. There was no statistically significant difference between the demographic variables of the two groups ($p>0.05$).

When the efficacy of the treatments was analyzed, a statistically significant difference was found between all parameters evaluated for both groups ($p<0.05$) (Table 2). While

Table 1. Demographic variables in study and control groups.

Parameters	Study Group (n=20)	Control Group (n=20)	p
Age/years (Mean±SD)	51.05±4.65	50.90±5.08	0.923
Med. (Min.-Max.)	51.00 (43.00-59.00)	50.50 (41.00-59.99)	
Length/cm (Mean±SD)	159.60±6.90	160.40±5.25	0.870
Med. (Min.-Max.)	160.00 (146.00-170.00)	160.00 (150.00-172.00)	
Weight/kg (Mean±SD)	69.10±9.52	68.55±11.44 68.50	0.683
Med. (Min.-Max.)	69.00 (52.00-90.00)	(48.00-92.00)	
BMI/kg/cm^2(Mean±SD)	27.24±4.26	26.79±5.20	0.769
Med. (Min.-Max.)	26.94 (21.09-33.78)	26.28 (16.90-36.63)	

Abbreviations: cm: centimeters, kg: kilograms, BMI: Body Mass Index.

Table 2. Comparison of pain, function and disability before and after treatment of study and control groups.

Parameters	Study Group (n=20)			Control Group (n=20)		
	Before treatment	After treatment	p	Before treatment	After treatment	p
VAS (Mean±SD)	7.65±1.75	6.00±1.33	**0.001**	7.80±1.23	6.80±1.15	**0.002**
Med. (Min.-Max.)	8.00 (4.00-10.00)	6.00 (4.00-9.00)		8.00 (5.00-10.00)	7.00 (3.00-8.00)	
Picking up test (Mean±SD)	1.80±0.95	1.30±0.65	**0.008**	1.90±0.96	1.70±0.92	**0.046**
Med. (Min.-Max.)	2.00 (0.00-3.00)	1.00 (0.00-2.00)		2.00 (0.00-3.00)	2.00 (0.00-3.00)	
Repeated sit to stand test (Mean±SD)	16.50±2.81	15.45±2.94	**0.001**	16.80±4.03	16.25±4.24	**0.005**
Med. (Min.-Max.)	15.50 (13.00-24.00)	14.50 (11.00-22.00)		16.50 (10.00-25.00)	16.00 (10.00-25.0)	
Socks Test (Mean±SD)	1.95±0.68	1.15±0.58	**0.001**	1.90±0.85	1.45±1.09	**0.014**
Med. (Min.-Max.)	2.00 (1.00-3.00)	1.00 (0.00-2.00)		2.00 (0.00-3.00)	1.50 (0.00-3.00)	
Stair descent test (Mean±SD)	13.30±2.47	12.30±2.38	**0.001**	13.95±3.13	13.45±2.81	**0.014**
Med. (Min.-Max.)	14.00 (9.00-20.00)	12.00 (8.00-18.00)		14.50 (10.00-21.00)	13.50 (9.00-18.00)	
Stair climbing test (Mean±SD)	14.25±2.24	13.15±1.66	**0.001**	14.50±2.72	13.95±2.74	**0.009**
Med. (Min.-Max.)	14.00 (11.00-21.00)	14.00 (10.00-17.00)		14.00 (10.00-20.00)	14.00 (10.00-20.00)	
Ten meters walking test (Mean±SD)	14.35±2.32	13.20±2.37	**<0.001**	14.35±2.62	14.10±2.75	**0.037**
Med. (Min.-Max.)	15.00 (10.00-19.00)	13.50 (9.00-17.00)		14.50 (10.00-19.00)	14.50 (8.00-18.00)	
WOMAC-Pain (Mean±SD)	10.75±3.62	9.60±3.40	**0.002**	10.45±3.20	10.05±3.03	**0.011**
Med. (Min.-Max.)	11.50 (3.00-15.00)	11.00 (3.00-15.00)		10.00 (4.00-18.00)	10.00 (4.00-17.00)	
WOMAC- Stiffness (Mean±SD)	3.90±1.07	3.00±1.21	**0.002**	3.80±1.28	3.35±1.26	**0.024**
Med. (Min.-Max.)	4.00 (2.00-6.00)	3.00 (2.00-6.00)		4.00 (1.00-6.00)	3.00 (1.00-6.00)	
WOMAC-Function (Mean±SD)	30.10±6.71	28.85±6.50	**<0.001**	30.00±7.91	29.15±7.96	**<0.001**
Med. (Min.-Max.)	29.00 (18.00-44.00)	28.00 (17.00-43.00)		29.50 (19.00-46.00)	28.50 (18.00-46.00)	

Abbreviations: VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

there was a statistically significant difference between the groups in pain assessment (p=0.002), there was no significant difference in functional tests and disability assessment (p>0.05) (Table 3).

Discussion

Our study was designed to investigate the effects of Mulligan mobilization and taping with CPT on pain, functional status and disability in OA patients. The results of the study demonstrated that CPT and Mulligan MWM plus CPT were both effective on the parameters evaluated in these patients. In addition, it was concluded that CPT and Mulligan mobilization and taping application were more effective than CPT alone in improvement of all the evaluated parameters. However, a statistically significant difference was obtained on pain between the groups. These results indicated that Mulligan mobilization has acute effects on pain, function and disability in KOA patients and can be applied in addition to CPT.

Our results showed that the Mulligan MWM technique was found to be effective on pain, functional status, and disability. The Mulligan Concept helps to increase neuromuscular control by providing the experience of painless movement [11]. MWM application in the treatment of KOA may have reduced pain by regulating biomechanics. In additional, as a result of decreased pain, patients may gain their functions more rapidly. Furthermore, internal rotation taping may mainly contribute to the reduction of pain and improvement of function by maintaining the beneficial effects of the Mulligan MWM. A systematic review examining the effects of Mulligan mobilization in KOA patients concluded that this treatment was a promising alternative treatment method in reducing pain and improving disability [12]. Various other studies concluded that MWM technique was more effective in reducing pain than Maitland tecnique [7,13]. Bhagat et al concluded that MWM technique applied in KOA patients had acute effects on pain and balance [14]. The results of our study supported the results of the studies in the current literature.

Internal rotation taping was applied in addition to the

Table 3. Within group differences before and after the treatment.

Parameters	Before treatment			After treatment		
	Study Group (n=20)	Control Group (n=20)	p	Study Group (n=20)	Control Group (n=20)	p
VAS (Mean±SD)	7.65±1.75	7.80±1.23	0.879	6.00±1.33	6.80±1.15	**0.022**
Med. (Min.-Max.)	8.00 (4.00-10.00)	8.00 (5.00-10.00)		6.00 (4.00-9.00)	7.00 (3.00-8.00)	
Picking up test (Mean±SD)	1.80±0.95	1.90±0.96	0.711	1.30±0.65	1.70±0.92	0.080
Med. (Min.-Max.)	2.00 (0.00-3.00)	2.00 (0.00-3.00)		1.00 (0.00-2.00)	2.00 (0.00-3.00)	
Repeated sit to stand test (Mean±SD)	16.50±2.81	16.80±4.03	0.585	15.45±2.94	16.25±4.24	0.493
Med. (Min.-Max.)	15.50 (13.00-24.00)	16.50 (10.00-25.00)		14.50 (11.00-22.00)	16.00 (10.00-25.0)	
Socks Test (Mean±SD)	1.95±0.68	1.90±0.85	0.930	1.15±0.58	1.45±1.09	0.349
Med. (Min.-Max.)	2.00 (1.00-3.00)	2.00 (0.00-3.00)		1.00 (0.00-2.00)	1.50 (0.00-3.00)	
Stair descent test (Mean±SD)	13.30±2.47	13.95±3.13	0.426	12.30±2.38	13.45±2.81	0.172
Med. (Min.-Max.)	14.00 (9.00-20.00)	14.50 (10.00-21.00)		12.00 (8.00-18.00)	13.50 (9.00-18.00)	
Stair climbing test (Mean±SD)	14.25±2.24	14.50±2.72	0.753	13.15±1.66	13.95±2.74	0.385
Med. (Min.-Max.)	14.00 (11.00-21.00)	14.00 (10.00-20.00)		14.00 (10.00-17.00)	14.00 (10.00-20.00)	
Ten meters walking test (Mean±SD)	14.35±2.32	14.35±2.62	0.924	13.20±2.37	14.10±2.75	0.275
Med. (Min.-Max.)	15.00 (10.00-19.00)	14.50 (10.00-19.00)		13.50 (9.00-17.00)	14.50 (8.00-18.00)	
WOMAC-Pain (Mean±SD)	10.75±3.62	10.45±3.20	0.783	9.60±3.40	10.05±3.03	0.662
Med. (Min.-Max.)	11.50 (3.00-15.00)	10.00 (4.00-18.00)		11.00 (3.00-15.00)	10.00 (4.00-17.00)	
WOMAC- Stiffness (Mean±SD)	3.90±1.07	3.80±1.28	0.955	3.00±1.21	3.35±1.26	0.267
Med. (Min.-Max.)	4.00 (2.00-6.00)	4.00 (1.00-6.00)		3.00 (2.00-6.00)	3.00 (1.00-6.00)	
WOMAC-Function (Mean±SD)	30.10±6.71	30.00±7.91	0.966	28.85±6.50	29.15±7.96	0.897
Med. (Min.-Max.)	29.00 (18.00-44.00)	29.50 (19.00-46.00)		28.00 (17.00-43.00)	28.50 (18.00-46.00)	

Abbreviations: VAS: Visual Analog Scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

MWM technique in our study. Internal rotation of the tibia occurs with flexion in the knee joint [15]. By applying the tape in the direction of internal rotation, the procedure supports and maintains the internal rotation movement that naturally occurs during knee flexion, in accordance with the Mulligan MWM. Research indicates that this internal rotation taping technique contributes to improved knee biomechanics, further enhancing the effectiveness of the Mulligan Concept [16,17]. The results of our study demonstrated that taping with MWM was effective in the reduction of pain, and disability, and improvement in function in patients with KOA.

In the present study, we found that CPT treatment had important effects on pain, functional status and disability in KOA patients in this study. Both groups received TENS, therapeutic US and hot pack, which are frequently used in OA treatment. TENS has been widely used in KOA patients for a long time and its efficacy is well known [18]. US is safe and effective in pain reduction and function improvement in patients with KOA [19]. Hochberg et al. [20]. recommended that hot pack should be used by physiotherapists in combination with exercise. Both our study and previous research have shown that conventional physical therapy (CPT) leads to significant improvements in pain, a reduction in disability, and enhanced functional status.

There was a statistically significant improvement in pain in the study group in which MWM and taping techniques were performed. Although both techniques have comparable outcomes, MWM technique and taping seem to be superior in reducing disability and improving function in patients with KOA. The results may be more prominent in long-term applications. The biomechanical structure of the joint is restored and positional error is corrected with MWM. Painless movement is perceived and learned with repetition [11]. One of the pain mechanisms in OA is the weakening of central inhibition mechanisms and decrease in pain threshold. MWM and taping may contribute to pain desensitization due to perception of painless movement. The Mulligan MWM and taping techniques potentially contribute to pain desensitization by promoting the perception of movement without pain. As pain decreased, patients likely experienced an increase in the speed of functional movements, leading to a reduction in disability [21]. Li et al. was reported that Mulligan MWM was effective in patients with KOA as parallel to our study [12].

Our study had some limitations. The fact that we did not examine the long-term results of the methods can be seen as a limitation. In addition, the fact that we did not evaluate the proprioception of the patients can be considered as a limitation.

Conclusion

In conclusion, both CPT alone and CPT combined with Mulligan MWM and taping were effective in improving pain, disability, and function in patients with KOA. Notably, the addition of MWM and internal rotation taping to CPT demonstrated superior pain reduction compared to CPT alone. While not statistically significant, this combined approach also showed trends towards improved function and disability status. These findings suggest that incorporating MWM and taping into routine KOA treatment may enhance treatment outcomes. Future research should investigate the long-term effects of the Mulligan technique.

Ethics Committee Approval

Ethical approval was obtained for this study from the Fırat University Non-Interventional Clinical Research Ethics Committee (2023/10-18).

Conflict of Interest

The authors declare that they have no conflict of interest.

Competing Interest

Not applicable.

Funding

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

References

1. Moseng T, Vliet Vlieland TPM, Battista S, et al. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis: 2023 update. *Ann Rheum Dis.* 2024;83(6):730-40. Published 2024 May 15. doi:10.1136/ard-2023-225041.
2. Abramoff B, Caldera FE. Osteoarthritis: Pathology, Diagnosis, and Treatment Options. *Med Clin North Am.* 2020;104(2):293-311. doi:10.1016/j.mcna.2019.10.007.
3. Min Oo W, Thae Bo M. Efficacy of Physical Modalities in Knee Osteoarthritis: Recent Recommendations. *Int J Phys Med Rehabil.* 2016;4: e112. doi:10.4172/2329-9096.1000e112.
4. Moss P, Sluka K, Wright A. The initial effects of knee joint mobilization on osteoarthritic hyperalgesia. *Man Ther.* 2007;12(2):109-18. doi:10.1016/j.math.2006.02.009.
5. Adams T, Band-Entrup D, Kuhn S, et al. Physical therapy management of knee osteoarthritis in the middle-aged athlete. *Sports Med Arthrosc Rev.* 2013;21(1):2-10. doi:10.1097/JSA.0b013e318272f530.
6. Hing WA, Bigelow R, Bremner T. Mulligan's Mobilization with Movement: A Systematic Review. *Journal of Manual and Manipulative Therapy.* 2009;17(2):39E-66E. doi: 10.1179/jmt.2009.17.2.39E.
7. Kiran A, Ijaz MJ, Qamar MM, et al. Comparison of efficacy of mulligan's mobilization with movement with maitland mobilization along with conventional therapy in the patients with knee osteoarthritis: A randomized clinical trial. *Libyan Int Med Univ J.* 2018;3:26-30. doi:10.4103/LIUJ.LIUJ_12_18.
8. Goudman L, Pilitsis JG, Billet B, et al. The level of agreement between the numerical rating scale and visual analogue scale for assessing pain intensity in adults with chronic pain. *Anaesthesia.* 2024;79(2):128-38. doi:10.1111/anae.16151.
9. Moutzouri M, Koumantakis GA, Hurley M, et al. Effectiveness of a Web-Guided Self-Managed Telerehabilitation Program Enhanced with Outdoor Physical Activity on Physical Function, Physical Activity Levels and Pain in Patients with Knee Osteoarthritis: A Randomized Controlled Trial. *J Clin Med.* 2024;13(4):934. Published 2024 Feb 6. doi:10.3390/jcm13040934.
10. Tüzün EH, Eker L, Aytar A, et al. Acceptability, reliability, validity and responsiveness of the Turkish version of WOMAC osteoarthritis index. *Osteoarthritis Cartilage.* 2005;13(1):28-33. doi:10.1016/j.joca.2004.10.010.
11. Vicenzino B, Paungmali A, Teys P. Mulligan's mobilization-with-movement, positional faults and pain relief: current concepts from a critical review of literature. *Man Ther.* 2007;12(2):98-108. doi:10.1016/j.math.2006.07.012.
12. Li LL, Hu XJ, Di YH, Jiao W. Effectiveness of Maitland and Mulligan mobilization methods for adults with knee osteoarthritis: A systematic review and meta-analysis. *World J Clin Cases.* 2022;10(3):954-65. doi:10.12998/wjcc.v10.i3.954.
13. Lalnunpuii A, Sarkar B, Alam S, et al. Efficacy of mulligan mobilisation as compared to Maitland mobilisation in females with knee osteoarthritis: a double blind randomized controlled trial. *International Journal of Therapies and Rehabilitation Research.* 2017;6(2):37. doi:10.5455/ijtrr.000000241.
14. Bhagat M, Neelapala YVR, Gangavelli R. Immediate effects of Mulligan's techniques on pain and functional mobility in individuals with knee osteoarthritis: A randomized control trial. *Physiother Res Int.* 2020;25(1):e1812. doi:10.1002/pri.1812.
15. Ruiz N, Filippi GJ, Gagnière B, et al. The Comparative Role of the Anterior Cruciate Ligament and Anterolateral Structures in Controlling Passive Internal Rotation of the Knee: A Biomechanical Study. *Arthroscopy.* 2016;32(6):1053-62. doi:10.1016/j.arthro.2016.02.017.
16. Howe A, Campbell A, Ng L, et al. Effects of two different knee tape procedures on lower-limb kinematics and kinetics in recreational runners. *Scand J Med Sci Sports.* 2015;25(4):517-24. doi:10.1111/sms.12269.
17. Hendry D, Campbell A, Ng L, et al. Effect of Mulligan's and Kinesio knee taping on adolescent ballet dancers knee and hip biomechanics during landing. *Scand J Med Sci Sports.* 2015;25(6):888-96. doi:10.1111/sms.12302.
18. Mascarin NC, Vancini RL, Andrade ML, et al. Effects of kinesiotherapy, ultrasound and electrotherapy in management of bilateral knee osteoarthritis: prospective clinical trial. *BMC Musculoskelet Disord.* 2012;13:182. Published 2012 Sep 22. doi:10.1186/1471-2474-13-182.
19. Ozgönenel L, Aytekin E, Durmuşoglu G. A double-blind trial of clinical effects of therapeutic ultrasound in knee osteoarthritis. *Ultrasound Med Biol.* 2009;35(1):44-9. doi:10.1016/j.ultrasmedbio.2008.07.009.
20. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res (Hoboken).* 2012;64(4):465-74. doi:10.1002/acr.21596
21. Kim W, Vela EA. Freedom in Osteoarthritis of the Knee. *Applied Sciences.* 2022;12(2):839. https://doi.org/10.3390/app12020839.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Impact of de novo metastatic breast cancer on survival of patients: A comparative retrospective observational study

Mahmut Ucar[a,*], Mukaddes Yilmaz[a], Eda Erdis[b], Birsen Yucel[b]

[a] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Medical Oncology, Sivas, Türkiye*
[b] *Sivas Cumhuriyet University, Faculty of Medicine, Department of Radiation Oncology, Sivas, Türkiye*

ARTICLE INFO

Keywords:
Breast cancer
Metastasis
De novo
Survival analysis

Received: Oct 31, 2024
Accepted: Feb 19, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.10.230

Abstract

Aim: The aim is to compare the characteristics of de nova metastatic BC (dnMBC) and recurrent metastatic BC (rMBC).

Materials and Methods: The study included female patients diagnosed with histologically dnMBC and rMBC who received treatment at a tertiary care center from 2010 to 2019. Medical records were utilized to collect information regarding the patients' tumors, alongside clinical and demographic characteristics. Each patient's overall survival (OS) was determined starting from the moment they were diagnosed with MBC. The patients with dnMBC and rMBC were compared statistically based on their clinical and sociodemographic features.

Results: Out of the 322 patients, 213 (66.1%) had rMBC, and 109 (33.9%) had dnMBC. Patients with dnMBC were older ($p<0.001$), and had a worse Eastern Cooperative Oncology Group Performance Score ($p<0.001$), a higher number of postmenopausal patients ($p<0.001$). Multicentricity/multifocality ($p=0.017$), human epidermal growth factor receptor 2 positivity ($p=0.010$), T-stage, N-stage ($p<0.001$), and tumor marker levels ($p<0.05$) showed significant differences between the groups. However, neither the median OS (29.0 months vs 21.0 months, respectively; $p=0.152$) nor the metastatic spread patterns ($p>0.05$) differed significantly between the groups.

Conclusion: There was no difference in OS. Clinic subtype, tumor grade, and treatment modalities may confuse the survival outcomes in BC patients.

Introduction

Breast cancer (BC) ranks among the most commonly diagnosed cancers globally [1, 2]. In addition, the incidence of BC progressively rises [3]. Early-stage BC mortality rates have decreased, distant disease-free survival rates have increased [4] and metastatic BC (MBC)-related survival trends have improved in recent years [5].

MBC diagnosis is established either at the time of or shortly after BC diagnosis (de novo MBC [dnMBC]) or at the time of recurrence in non-metastatic cancer (recurrent MBC [rMBC]) [6-8]. Patients with dnMBC represent 5%-15% of all BC cases, while 20%-30% of early BC patients develop rMBC following standard treatment [1, 6].There is no study to date on the probable survival differences between dnMBC and rMBC patient populations [4]. Previous studies have suggested that dnMBC and rMBC patients represent two distinct populations with diverse histological and molecular profiles, e.g., metastatic site, demographic characteristics, e.g., age at metastatic diagnosis and socioeconomic status, and clinical risks, e.g., intrinsic BC subtypes, all of which likely influence prognosis [1, 4, 6]. Survival outcomes of rMBC patients are generally worse than those of dnMBC patients yet are known to vary depending on patient- and tumor-related features [4, 9]. Large-scale studies including diverse populations are essential to clarify the influence of the type of metastasis on BC prognosis.

The objective of this investigation was to analyze the clinicopathological traits of patients suffering from dnMBC and rMBC, as well as to identify the risk factors that impact their survival outcomes.

Materials and Methods

Study design and patients selection

It was carried out as a comparative retrospective observational analysis. The study protocol received approval from the local ethics committee (Sivas Republic University, ethical committee for non-invasive clinical research, approval

*Corresponding author:
Email address: dr.mahmutucar@gmail.com (Mahmut Ucar)

on November 16, 2023, decision no: 2023-11/12). The research was conducted following the ethical principles in the Declaration of Helsinki. Because of the retrospective design of the study and the patients' anonymity, written informed consent could not be obtained.

The study included female patients aged 18 and older with histologically confirmed dnMBC and rMBC, treated at the Oncology Center of Cumhuriyet University in Sivas, Turkey, from 2010 to 2019. Patients with non-metastatic disease, bilateral BC, other malignancies, local recurrence limited to regional lymph nodes and/or chest wall, and incomplete demographic, clinical, and tumor data were excluded from the study. Overall, 322 MBC patients took part in the study.

For BC staging, the 7th AJCC guideline was followed, and stage IV disease was grouped as dnMBC and rMBC [10]. Distant metastasis found at admission or within three months of the diagnosis is classified as dnMBC [7, 8]. Metastatic disease identified more than three months after the diagnosis is classified as rMBC [6].

Data collection

Patients' sociodemographic, i.e., age, body mass index (BMI), menopausal status, and familial BC history, the Eastern Cooperative Oncology Group (ECOG) performance status, tumor markers at the time of metastatic BC dignosis, tumor characteristics, i.e., side, size, T and N staging, histological type and grade, human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), estrogen receptor (ER) positivity, Ki-67 value, location and type of organ metastasis, and treatment details were gathered from the medical records accessible in the hospital's information system.

Positive nuclear immunohistochemical staining of at least 1% of the tumor cells was considered to indicate ER and PR positivity [1]. Patients with strong HER2 (+3) staining on immunohistochemical staining were considered HER2-positive. The preparations of patients with moderate (+2) staining were checked for HER2-positivity by fluorescence in situ hybridization. ER, PR, and HER2 positivity were used to identify the intrinsic BC subtypes. The luminal-A subtype was identified in patients with low Ki-67, ER and PR positive, and HER2 negative, while the luminal-B subtype was defined as patients who were HER2 negative ER or PR positive but high Ki-67. Furthermore, patients with HER2 and ER and/or PR positive were classified as having the luminal-B HER2 subtype. Only HER2 positive cases were included in the HER2 positive subtype. The triple-negative subtype was defined as patients who were negative for ER, PR, and HER2 [6].

Imaging and/or pathology results supported the diagnosis of metastatic disease based on clinical signs of metastases associated with the affected organ or system. We categorized BC cases as oligo- ($\leq$5) or polymetastatic (>6) based on the number of metastases [11]. The metastases were also categorized according to their site, i.e., bones, lung/pleura, liver, distant lymph node, and central nervous system, e.g., parenchymal brain metastasis and/or leptomeningeal metastasis [1].

Treatments

In line with the standard treatment approaches for MBC, patients with luminal BC subtypes were started on systemic treatment along with chemotherapy as well as hormonal treatment, provided that there was no visceral crisis, patients with HER2 positivity were started on anti-HER2 treatment along with chemotherapy, and patients with triple-negative BC subtype were started on chemotherapy.

Statistical analysis

For the statistical analysis of collected data, we employed the JASP 0.17.3 software (Jeffreys' Amazing Statistics Program, version 0.17.3, 2023, available at https://jasp-stats.org), Jamovi project 2.3.28 (Jamovi, version 2.3.28, 2023, available at https://www.jamovi.org), and SPSS version 23 (IBM Corp., Armonk, New York, USA). When α=0.05, β=0.10, 1-β=0.98, it was decided to include 322 individuals, and the power of the test was determined as 0.98844. In the G Power program (version 3.1.9.7), the power of the study was calculated by selecting effect size=0.5. For continuous variables that conformed to a normal distribution, the descriptive statistics derived from the data were expressed as mean ± standard deviation (SD) values. For continuous variables that deviated from normal distribution, they were represented as medians along with minimum and maximum values. Categorical variables were presented as numbers (n) and percentage values (%). The normal distribution properties of continuous variables were assessed using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. Fisher's Exact Test was applied when the expected count of cells in 2x2 tables was less than five; Pearson's chi-square test was utilized when the expected count of cells in 2x2 tables was five or more; and the Fisher-Freeman-Halton test was employed when the expected count of cells in RxC tables was less than five. These tests were used to compare the differences in categorical variables across groups. In the chi-square test, a Bonferroni adjustment was applied to identify the variable that influenced the multiple counts of cells in tables such as 2x3 and 2x4. The Mann-Whitney U test and independent samples t-test were used to compare two independent groups based on continuous data.

Each patient's overall survival (OS) was determined starting from the moment they were diagnosed with metastatic BC. As a result, OS denoted the interval between the diagnosis of MBC and the date of death or the most recent follow-up [12]. The survival curves were plotted using the Kaplan-Meier survival method. Using the log-rank test, we evaluated the groups' differences in survival outcomes.

Statistical significance was defined as probability (p) statistics of < 0.05.

Results

Between 2010 and 2019, 1198 patients were admitted to Sivas Cumhuriyet University Oncology Center with breast carcinoma and 322 (27%) had metastatic disease. Of the 322 patients included in the study, 109 (33.9%) had dnMBC, and 213 (66.1%) had rMBC. The median metastasis development time in the rMBC group was 37.0 (range:

Table 1. Sociodemographic and clinical characteristics of the study groups.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
Age †	57.0 [18.0 – 83.0]	47.0 [25.0 – 77.0]	<0.001**
Age groups ‡			
<65 years	80 (73.4)	188 (88.3)	0.001*
≥65 years	29 (26.6)	25 (11.7)	
BMI (kg/m^2) †	29.2 ± 5.9	29.9 ± 5.5	0.456***
Menopause status ‡			
Pre	34 (31.2)	112 (52.6)	<0.001*
Post	75 (68.8)	101 (47.4)	
Family history of breast cancer ‡	20 (18.3)	41 (19.2)	0.964*
ECOG Performance status ‡			
0[a]	28 (25.7)	111 (52.1)	
1	45 (41.3)	73 (34.3)	<0.001*
2 or more[a]	36 (33.0)	29 (13.6)	
Comorbidities ‡			
Hypertension	31 (28.4)	53 (24.9)	0.580*
Diabetes mellitus	18 (16.5)	31 (14.6)	0.765*
Coronary artery disease	7 (6.4)	14 (6.6)	0.999*

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, BMI: body mass index, ECOG: the Eastern Cooperative Oncology Group. *. Pearson Chi-Square test. **. Mann-Whitney U test. ***. Independent Samples T-Test. [a]: variables that make a difference between groups after bonferroni adjustment.

4-218) months. In approximately two-thirds (67.0%) of the rMBC patients, metastasis was diagnosed 24 months or later after the initial BC diagnosis. Table 1 shows the comparison of sociodemographic and clinical characteristics of the groups. There were statistically significant differences between the groups in terms of age, menopausal status and performance status (<0.05 for all cases). Table 2 shows how the study groups' tumoral features were distributed at the time of the initial BC diagnosis. Multicentricity/multifocality, HER2 positive, T-stage tumor, and N-stage tumor rates showed significant variations across the groups (p<0.05 for all cases). There were significant differences between the groups in CEA and CA 15-3 levels and in the rates of patients with high and normal CEA and CA 15-3 levels (Table 3). There was no significant difference between the groups in the characteristics of metastatic disease, i.e., site and number of metastases (p>0.05) (Table 4). In this study, median follow-up was 22 (1-186) months. Median OS was 31.0 months in the dnMBC group and 25.0 months in the rMBC group (Figure 1). Kaplan-Meier survival analysis using the Log-Rank test revealed no significant difference in OS between the groups (p=0.393).

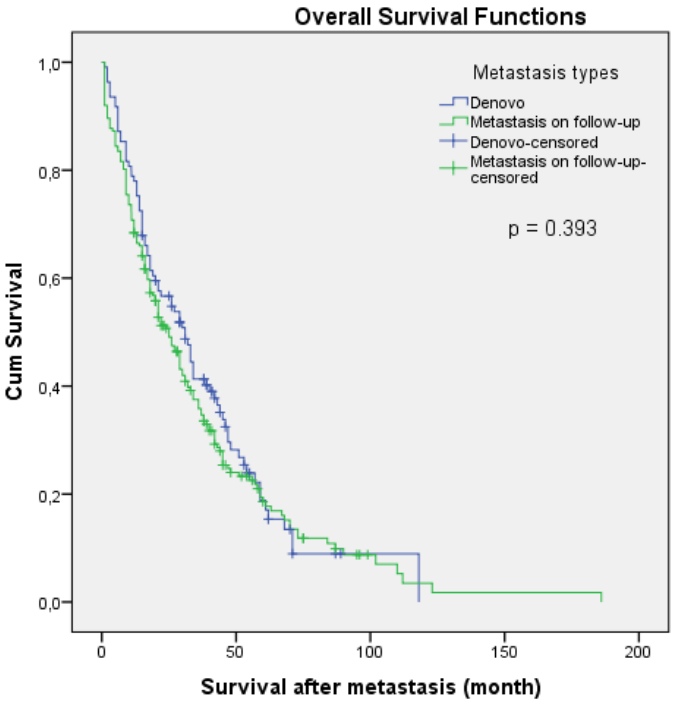

Figure 1. Kaplan-Meier Analysis of Overall Survival after Metastasis in Group dnMBC and Group rMBC.

Discussion

Our findings indicated significant differences in demographic and clinical characteristics, such as age, menopausal status, and ECOG performance status, between BC patients with dnMBC and rMBC. Accordingly, older, postmenopausal patients with higher ECOG performance status were more likely to have dnMBC than rMBC. Tumors with higher T and N stages and elevated tumor markers were significantly associated with dnMBC. Yet, no significant difference was found between the patients with dnMBC and rMBC in terms of survival outcomes. There are similar studies in the literatüre. the observations of our clinic in this regard will be discussed.

There is some controversy about the definition of dnMBC. BC patients who develop metastasis within three months

Table 2. Tumoral characteristics of the patients at the diagnosis of breast cancer in Groups dnMBC and rMBC.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
Side ‡			
Right	61 (56.0)	95 (44.6)	0.070*
Left	48 (44.0)	118 (55.4)	
Tumor diameter (cm) †	3.0 [0.0 – 52.0]	3.3 [0.0 – 85.0]	0.939**
Multi-centricity/focality ‡	17 (34.0)	35 (17.5)	**0.017***
Histology grades ‡			
1	22 (20.2)	42 (19.7)	
2	54 (49.5)	101 (47.4)	0.893*
3	33 (30.3)	70 (32.9)	
Histopathology ‡			
Ductal	97 (89.0)	170 (79.8)	
Lobular	3 (2.8)	11 (5.2)	0.227*
Mixed	6 (5.5)	17 (8.0)	
Others	3 (2.8)	15 (7.0)	
ER status ‡, *Positive*	77 (70.6)	138 (64.8)	0.352*
PR status ‡, *Positive*	62 (56.9)	124 (58.2)	0.912*
HER2 status ‡, *Positive*	48 (44.0)	60 (28.8)	**0.010***
HER2 IHC results ‡			
0 and 1[a]	49 (45.0)	130 (61.0)	
2	22 (20.2)	38 (17.8)	**0.012***
3[a]	38 (34.9)	45 (21.1)	
Ki-67 (%) †	30.0 [0.0 – 90.0]	29.0 [0.0 – 100.0]	0.338**
Molecular subtypes ‡			
Luminal A	22 (20.2)	48 (23.1)	
Luminal B HER2 negative	25 (22.9)	56 (26.9)	
Luminal B HER2 positive	31 (28.4)	41 (19.7)	0.077*
HER2 positive	17 (15.6)	19 (9.1)	
Triple negative	14 (12.8)	44 (21.2)	
Lymphovascular invasion ‡	33 (62.3)	123 (65.4)	0.793*
Perineural invasion ‡	18 (47.4)	85 (51.8)	0.752*
T stage ‡			
T1	15 (13.8)	29 (13.6)	
T2[a]	25 (22.9)	123 (57.7)	
T3	14 (12.8)	39 (18.3)	**<0.001***
T4	17 (15.6)	20 (9.4)	
TX[a]	38 (34.9)	2 (0.9)	
T staging groups ‡			
T1-3	54 (76.1)	191 (90.5)	**0.004***
T4	17 (23.9)	20 (9.5)	
N stage ‡			
N0[a]	4 (3.7)	41 (19.2)	
N1[a]	7 (6.4)	38 (17.8)	
N2[a]	17 (15.6)	77 (36.2)	**<0.001***
N3	38 (34.9)	55 (25.8)	
NX[a]	43 (39.4)	2 (0.9)	
N staging groups ‡			
N0	4 (6.1)	41 (19.4)	**0.017***
N 1-3	62 (93.9)	170 (80.6)	

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, ER: estrogen receptor, PR: progesterone receptor, HER2: human epidermal growth factor receptor 2, IHC: immunohistochemical. *. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test. **. Mann-Whitney U test. [a]: variables that make a difference between groups after bonferroni adjustment.

Table 3. Laboratory investigations of the patients at the diagnosis of metastasis.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values
CEA (ng/dL) †	3.8 [0.4 – 921.3]	1.9 [0.2 – 1444.0]	**<0.001****
CA 15-3 (U/mL) †	28.2 [2.1 – 2894.6]	22.5 [0.9 – 600.0]	**0.017****
CEA groups ‡			
Normal (<2.5 ng/mL)	58 (61.7)	146 (79.8)	**0.002***
High (≥2.5 ng/mL)	36 (38.3)	37 (20.2)	
CA 15-3 groups ‡			
Normal (<30 U/mL)	43 (44.8)	109 (58.0)	**0.047***
High (≥30 U/mL)	53 (55.2)	79 (42.0)	

†: median [min-max], ‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer, CEA: carcinoembryonic antigen. *. Pearson Chi-Square, Fisher's Exact or Fisher Freeman Halton test. **. Mann-Whitney U test.

Table 4. Clinical findings associated with the metastatic disease.

	Group dnMBC (n=109)	Group rMBC (n=213)	p-values*
Site of metastasis ‡			
Distant lymph node	19 (17.4)	35 (16.4)	0.945
Bone	78 (71.6)	149 (70.0)	0.865
Liver	34 (31.2)	68 (31.9)	0.994
Lung/pleura	33 (30.3)	77 (36.2)	0.354
Central nervous system	31 (28.4)	64 (30.0)	0.865
Skin	5 (4.6)	15 (7.0)	0.535
Grouping for metastatic sites ‡			
Non-visceral	34 (31.2)	63 (29.6)	
Visceral	21 (19.3)	48 (22.5)	0.793
Both	54 (49.5)	102 (47.9)	
Oligometastasis ‡	18 (16.5)	19 (8.9)	0.066
Number of metastatic sites ‡			
1	40 (36.7)	84 (39.4)	
2	49 (45.0)	73 (34.3)	0.120
3	20 (18.3)	56 (26.3)	
Overall survival			
The 2-year (%)	57	51	
The 5-year (%)	17	19	0.393
Median (month±SE†)	31±4.37	25±2.47	

‡: n (%). dnMBC: de novo metastatic breast cancer, rMBC: recurrent metastatic breast cancer. *. Pearson Chi-Square test. †: SE: standard error.

after the initial diagnosis are generally considered to have dnMBC [3,7,8,13]. In contrast, several authors considered only patients with confirmed distant metastatic BC at the time of diagnosis [14] or within 120 days of initial diagnosis [6,15] to have dnMBC, whereas others characterized dnMBC by the development of metastases before or shortly after the identification of a primary breast tumor and did not specify the interval [12,16-18]. Yamamura et al. [19] characterized rMBC by the development of distant metastasis after the removal of the primary BC following standard adjuvant treatment, excluding locoregional recurrences. De Maar et al. [20] excluded the patients with distant metastasis within three months of the primary diagnosis from their sample. The incidence or prevalence of dnMBC among all breast or metastatic BC patients reported in the literature varies significantly, ranging between 8.8% and 71.9%, due to differences in the definition of dnMBC and patient populations [1,6,8,12,13,14,16-18]. Gilbert et al. [9] reported that 71.9% of BC patients were diagnosed with MBC within the first four months after the initial diagnosis. The rate of patients with dnMBC in this study was 33.9%, comparable to the patient populations in previously published studies. In contrast, in a study conducted in Turkey, Dogan et al. [7] reported that almost half (47.7%) of their patients had dnMBC. In the said study, although metastasis within three months after the initial diagnosis was defined as dnMBC, as in our study, the rates of patients with DnMBC were higher than in our study. The differences between the studies in the prevalence of dnMBC or rMBC may be attributed to the

varying diagnostic imaging capacities of the institutions in visualizing MBC.

Previous studies reported significant differences between the patients with dnMBC and rMBC in demographic and clinical characteristics, including different patterns of metastatic spread. In a large cohort study conducted in France, Marshall et al. [12] reported that dnMBC patients were significantly older than rMBC patients, and there were significantly more postmenopausal patients in dnMBC patients than in rMBC patients, as in this study. Similarly, another study reported that the dnMBC patients were significantly older than rMBC patients [6,7,20]. Triple-negative tumors and high grades were reportedly related to rMBC [12]. Several studies found no significant difference between dnMBC and rMBC patients [9,15,19]. In our study, no significant difference was found between dnMBC and rMBC patients in molecular subtypes, histological grades, and metastatic spread patterns. In our study, no significant difference was found between dnMBC and rMBC patients in terms of molecular subtypes, histologic grades and metastatic spread patterns. However, it was also observed that they did not have exactly the same clinicopathologic features. Patients with dnMBC exhibited older median age, more patients with postmenopause, worse performance status, more multi-centricity/focality, more advanced T and N stages, more HER2-positivity, and higher tumor markers than rMBC. In contrast, rMBC had more triple negative disease. The higher rate of HER2-positivity in the dnMBC group compared to the rMBC group, as in McKenzie's [14] and de Maar's studies [20], might be associated with improved survival outcomes secondary to anti-HER2 medications [13].

Although several authors speculated that dnMBC and rMBC are distinct patterns of MBC based on the differences in clinicopathological characteristics and survival [3,13,20], it is generally accepted that better survival outcomes in dnMBC are associated with higher HER-2-positivity rates [7,13]. Hence, the discrepancies between the studies may be attributed to the heterogeneity in clinical and tumoral characteristics of MBC.

The survival outcomes in metastasic BC vary depending on whether it is dnMBC or rMBC [4,9]. It has been speculated that the patients with rMBC may be followed up better than those with dnMBC, given the higher possibility of diagnosing metastasis at an earlier stage [9,12]. In contrast, several studies reported that dnMBC patients had better prognosis after metastasis development than rMBC patients [2,6-8,12,14-16,19,21]. Better prognosis in patients with dnMBC compared to patients with rMBC may be due to having treatment-naive oligometastatic BC featuring only bone metastasis, higher rates of hormone positivity, lower rates of resistance to the first systemic palliative therapy, and the use of more aggressive first-line treatment [9,15-18]. The improvement in prognosis is reportedly more pronounced if MFS is less than 24 months [18]. Although there were more patients with oligo-and bone metastasis in the dnMBC group than in the rMBC group, we did not detect a significant difference in prognosis between the groups.

Others speculated that dnMBC diagnosis is associated with adverse tumor features [14]. In a systematic review [4], Lord et al. stated that population-level improvements have been observed in the OS of dnMBC patients since 1995. In parallel, we found that the OS of the patients with dnMBC was more prolonged, albeit not significantly, compared to those with rMBC. Several other studies have found similar findings regarding the OS of dnMBC and rMBC patients [17,18] as in this study. These results suggest that de novo type metastasis is not an independent prognostic factor of OS in MBC patients [7]. Studies with larger sample sizes may be needed to offset the variations in population characteristics, study periods, and follow-up durations when assessing the prognostic differences between dnMBC and rMBC.

Limitations

The fact that the study featured real-life practice patterns from a tertiary center over ten years is its primary strength. The study did have many drawbacks, though, the main one being that it was retrospective in nature. Secondly, the fact that the impact of treatment characteristics, such as the treatment duration and patient compliance, has not been addressed may be considered another limitation of the study.

Conclusion

Patients with dnMBC exhibited older median age, more patients with posmenopause, worse performance status, more multi-centricity/focality, more advanced T and N stages, more HER2-positivity, and higher tumor markers than rMBC. In contrast, rMBC had more triple negative disease. However, no significant difference in OS was detected between dnMBC and rMBC patients.

Acknowledgments

We sincerely thank our colleagues from the Medical and Radiation Oncology Departments at Sivas Cumhuriyet University for their constant support and collaboration.

Ethics Committee Approval

The present study was conducted in accordance with the principles of the Declaration of Helsinki. On November 16, 2023, the Ethics Committee of Sivas Cumhuriyet University granted approval (decision no: 2023-11/12).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Funding

This is a self-funded study.

Authors' Contributions

MU: Conception, Design, Writing- Original draft preparation; MY: Data collection, Writing- Original draft preparation, Analysis and interpretation; EE: Conception, Materials, Data collection; BY: Writing- Reviewing and Editing, Supervision, Critical Review.

References

1. Zhang N, Xiang Y, Shao Q, Wu J, Liu Y, Long H, Tao D, Zeng X. Different risk and prognostic factors for liver metastasis of breast cancer patients with de novo and relapsed distant metastasis in a Chinese population. *Front Oncol.* 2023 Apr 14;13:1102853. doi: 10.3389/fonc.2023.1102853.
2. Cheng HF, Tsai YF, Huang CC, Lien PJ, Wang YL, Hsu CY, Chen YJ, Liu CY, Chao TC, Lin YS, Feng CJ, Chiu JH, Chau GY, Tseng LM. Clinical outcomes and metastatic behavior between de novo versus recurrent HER2-positive metastatic breast cancer: A 17-year single-institution cohort study at Taipei Veterans General Hospital. *J Chin Med Assoc.* 2022 Jan 1;85(1):88-94. doi: 10.1097/JCMA.0000000000000622.
3. Seltzer S, Corrigan M, O'Reilly S. The clinicomolecular landscape of de novo versus relapsed stage IV metastatic breast cancer. *Exp Mol Pathol.* 2020 Jun;114:104404. doi: 10.1016/j.yexmp.2020.104404.
4. Lord SJ, Bahlmann K, O'Connell DL, Kiely BE, Daniels B, Pearson SA, Beith J, Bulsara MK, Houssami N. De novo and recurrent metastatic breast cancer - A systematic review of population-level changes in survival since 1995. *EClinicalMedicine.* 2022 Jan 29;44:101282. doi: 10.1016/j.eclinm.2022.101282.
5. Lao C, Kuper-Hommel M, Elwood M, Campbell I, Edwards M, Lawrenson R. Characteristics and survival of de novo and recurrent metastatic breast cancer in New Zealand. *Breast Cancer.* 2021 Mar;28(2):387-397. doi: 10.1007/s12282-020-01171-3.
6. Dogan I, Aksoy S, Cakar B, Basaran G, Ercelep O, Molinas Mandel N, Korkmaz T, Gokmen E, Sener C, Aydiner A, Saip P, Eralp Y. Demographic and Clinical Features of Patients with Metastatic Breast Cancer: A Retrospective Multicenter Registry Study of the Turkish Oncology Group. *Cancers (Basel).* 2023 Mar 8;15(6):1667. doi: 10.3390/cancers15061667.
7. File DM, Pascual T, Deal AM, Wheless A, Perou CM, Claire Dees E, Carey LA. Clinical subtype, treatment response, and survival in De Novo and recurrent metastatic breast cancer. *Breast Cancer Res Treat.* 2022 Nov;196(1):153-162. doi: 10.1007/s10549-022-06700-6.
8. Gilbert A, Williams C, Azuero A, Burkard ME, Kenzik K, Garrett-Mayer E, Meersman S, Rocque G. Utilizing Data Visualization to Identify Survival and Treatment Differences Between Women With De Novo and Recurrent Metastatic Breast Cancer. *Clin Breast Cancer.* 2021 Aug;21(4):292-301. doi: 10.1016/j.clbc.2020.11.009.
9. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol.* 2010 Jun;17(6):1471-4. doi: 10.1245/s10434-010-0985-4.
10. Sinn HP, Kreipe H. A Brief Overview of the WHO Classification of Breast Tumors, 4th Edition, Focusing on Issues and Updates from the 3rd edition. *Breast Care (Basel).* 2013 May;8(2):149-54. doi: 10.1159/000350774.
11. Genestie C, Zafrani B, Asselain B, Fourquet A, Rozan S, Validire P, Vincent-Salomon A, Sastre-Garau X. Comparison of the prognostic value of Scarff-Bloom-Richardson and Nottingham histological grades in a series of 825 cases of breast cancer: major importance of the mitotic count as a component of both grading systems. *Anticancer Res.* 1998 Jan-Feb;18(1B):571-6.
12. Rastogi S, Gulia S, Bajpai J, Ghosh J, Gupta S. Oligometastatic breast cancer: A mini review. *Indian J Med Paediatr Oncol.* 2014 Jul;35(3):203-6. doi: 10.4103/0971-5851.142035.
13. Marshall EM, Bertaut A, Desmoulins I, Darut-Jouve A, Ponnelle T, Poillot ML, Beltjens F, Arveux P. Prognostic Factors of Survival among Women with Metastatic Breast Cancer and Impact of Primary or Secondary Nature of Disease on Survival: A French Population-Based Study. *Breast J.* 2017 Mar;23(2):138-145. doi: 10.1111/tbj.12717.
14. Tripathy D, Brufsky A, Cobleigh M, Jahanzeb M, Kaufman PA, Mason G, O'Shaughnessy J, Rugo HS, Swain SM, Yardley DA, Chu L, Li H, Antao V, Hurvitz SA. De Novo Versus Recurrent HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from the SystHERs Registry. *Oncologist.* 2020 Feb;25(2):e214-e222. doi: 10.1634/theoncologist.2019-0446.
15. McKenzie HS, Maishman T, Simmonds P, Durcan L; POSH Steering Group; Eccles D, Copson E. Survival and disease characteristics of de novo versus recurrent metastatic breast cancer in a cohort of young patients. *Br J Cancer.* 2020 May;122(11):1618-1629. doi: 10.1038/s41416-020-0784-z.
16. Malmgren JA, Mayer M, Atwood MK, Kaplan HG. Differential presentation and survival of de novo and recurrent metastatic breast cancer over time: 1990-2010. *Breast Cancer Res Treat.* 2018 Jan;167(2):579-590. doi: 10.1007/s10549-017-4529-5.
17. Weiner CM, Mathewos A, Addissie A, Ayele W, Aynalem A, Wondemagegnehu T, Wienke A, Jemal A, Zerche P, Thomssen C, Seidler A, Kantelhardt EJ. Characteristics and follow-up of metastatic breast cancer in Ethiopia: A cohort study of 573 women. *Breast.* 2018 Dec;42:23-30. doi: 10.1016/j.breast.2018.08.095.
18. Valachis A, Carlqvist P, Ma Y, Szilcz M, Freilich J, Vertuani S, Holm B, Lindman H. Overall survival of patients with metastatic breast cancer in Sweden: a nationwide study. *Br J Cancer.* 2022 Sep;127(4):720-725. doi: 10.1038/s41416-022-01845-z.
19. Barcenas CH, Song J, Murthy RK, Raghavendra AS, Li Y, Hsu L, Carlson RW, Tripathy D, Hortobagyi GN. Prognostic Model for De Novo and Recurrent Metastatic Breast Cancer. *JCO Clin Cancer Inform.* 2021;5:789-804. doi: 10.1200/CCI.21.00020.
20. Yamamura J, Kamigaki S, Fujita J, Osato H, Komoike Y. The Difference in Prognostic Outcomes Between De Novo Stage IV and Recurrent Metastatic Patients with Hormone Receptor-positive, HER2-negative Breast Cancer. *In Vivo.* 2018 Mar-Apr;32(2):353-358. doi: 10.21873/invivo.11245.
21. de Maar JS, Luyendijk M, Suelmann BBM, van der Kruijssen DEW, Elias SG, Siesling S, van der Wall E. Comparison between de novo and metachronous metastatic breast cancer: the presence of a primary tumour is not the only difference-a Dutch population-based study from 2008 to 2018. *Breast Cancer Res Treat.* 2023 Apr;198(2):253-264. doi: 10.1007/s10549-022-06837-4.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Strategies for expanding the lung donor pool and increasing the number of transplants in Turkey

Sevinc Citak[a,*], Mesut Metin[b], Ayse Nigar Halis[c], Ertan Saribas[c], Murat Ersin Cardak[a], Mustafa Vayvada[a], Ahmet Erdal Tasci[a]

[a] *Kosuyolu High Specialization Education and Research Hospital, Department of Thoracic Surgery, Istanbul, Türkiye*
[b] *Kocaeli University, Faculty of Medicine, Department of Thoracic Surgery, Kocaeli, Türkiye*
[c] *Kosuyolu High Specialization Education and Research Hospital, Department of Pulmonology, Istanbul, Türkiye*

ARTICLE INFO

Keywords:
End-stage lung diseases
Lung donor
Lung transplantation
Deceased donor organ transplantation

Received: Jan 17, 2025
Accepted: Feb 24, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2025.01.021

Abstract

Aim: Lung transplantation is the treatment of choice in end-stage lung diseases. However, the shortage of organ donors is a significant challenge. This study analyzes lung donor characteristics and evaluates strategies to expand the donor pool in Turkey.

Materials and Methods: Data from 136 cadaveric lung donors offered to our clinic between 2021 and 2023 were examinedincluding donor characteristics such as age, medical history, cause of death, and laboratory results. The donors were divided into two groups: accepted versusrejected.

Results: This study evaluated 136 out of 959 deceased donors in Turkey, representing 14.1% of all deceased donors between 2021 and 2023. Fifty-three deceased donors were offered to the lung transplant clinic in 2021, 44 in 2022, and 39 in 2023. Among these, 25 donors were accepted for transplantation, and 111 were rejected .The mean age of the donors was 37.5 years. The patients in the rejected group were significantly older than the patients in theaccepted group. The most common cause of death of the deceased donors was intracranial hemorrhage. Significant differences were observed between the groups in terms of PaO_2/FiO_2 ratios were lower than 300 mm-Hg in the majority of the patients in the rejected group. Furthermore, patients in the rejected group had a higher prevalence of hypertension and a history of smoking in the rejected group.Microbial growth was observed in 22.42% of total donors, with a higher rate in the accepted group. Transoesophageal echocardiography (TOE) or transthoracic echocardiography (TTE) was used for cardiac evaluation of donor.

Conclusion: The decline in donor availability and lung transplants in Turkey highlights the need for expanding donor criteria, including marginal donorsAdditionally, increasing public awareness and strengthening healthcare infrastructure are crucial to improving deceased donor organ donation rates and solid organ transplantation rates in Turkey.

Introduction

Lung transplantation is universally recognized as a life-saving therapeutic intervention and the gold standard treatment for patients with end-stage lung diseases [1]. The limited availability of deceased organ donors significantly restricts access to lung transplantation and leads to elevated waiting-list mortality rates, posing a critical challenge both globally and in Turkey. Increasing the number of available donors has therefore emerged as a paramount priority in the field of lung transplantation. The COVID-19 pandemic, which emerged globally in early 2020, disrupted organ donation and transplantation processes, significantly reducing donation rates in Turkey [2, 3]. This decline, driven by resource diversion, quarantine measures, and shifts in public perception, exacerbated challenges for patients on the waiting list for lung lung transplantation.

In the post-pandemic period, various strategies have been tried to increase organ donation rates. Donor characteristics areidentified as a critical factor in improving donor availability and promoting organ donation [4-6]. Analyzing these characteristics provides insights into barriers to organ donation and supports the development of targeted solutions to optimize donor profiles. Key factors influencing organ donation include donor age, cause of death, medical history, and organ viability. Additionally, socialawareness, supportive health policies, and educational programs play an essential role in promoting organ donation rates.

*Corresponding author:
Email address: sevinccitak@gmail.com (Sevinc Citak)

On of the main objectives is to promote awareness for organ donation in a society.

This study aims toexplore the initiatives undertaken in Turkey to increase organ donations for lung transplantation, with a particular focus on identifying donor characteristics and analyzing their impact on donation rates. Additionally, the study aims toaddress the current challenges in organ donation, propose potential solutions, and discuss future strategic directions.

Materials and Methods

Study design and primary outcome variables

This retrospective study evaluates the demographic, medical, and laboratory characteristics of deceased donorlung donationsto identify factors influencing donor selection and transplant eligibility. The primary outcome variable is the successful acceptance of donors for lung transplantation. The study variables include demographic characteristics, donor medical history, and laboratory results.

Deceased donor lung donationsoffered to our Lung Transplant Clinic between January 2021 and December 2023 were analyzed. Data were collected from the form provided by the Turkish Donor and Organ Tracking System (TDIS). The demographic details of the donors, such as gender, age, height, weight, blood type, and causes of death (including suicide, gunshot wound, poisoning, intracranial hemorrhage, drowning, and traumatic intracranial hemorrhage), were examined. In addition, hospitalization status, hospital admission information, hospital type (state hospital, private hospital, university hospital, or research and training hospital), and the results of their most recent tests of the deceased donors were analyzed. The medical history of the donors, including conditions like congenital heart disease, hypertension, diabetes mellitus, neurological disorders, and malignancy, were also evaluated.Furthermore, microbial culture tests (trachea, blood, urine), antibiotic use, WBC count, C-reactive protein (CRP), and procalcitonin levels were also evaluated. Transoesophageal echocardiography (TOE) or transthoracic echocardiography (TTE) results were reviewed, and the differences between donors with an ejection fraction (EF) <55 and those with EF ≥ 55 were analyzed. Additionally, findings on the CT scan were examined for any pathological findings. Demographic differences between accepted and rejected donors were investigated. The donor evaluation process and acceptance criteria were carried out as outlined in our previous [5].

The annual organ donation and lung transplantation numbers were obtained from the official website of the Public Awareness Platform for Transplantation, Dialysis and Follow-up Systems of the Ministry of Health of the Republic of Turkey. The numbers of donors presented to our lung transplantation clinic were compiled annually from our internal TDİS (Transplantation and Donor Service) [6].

Sample size calculation

The sample size was determined based on prior studies evaluating lung donor characteristics and acceptance criteria. The study includes all lung donors presented to our center between January 2021 and December 2023, meeting predefined inclusion criteria.

Sampling method

A non-probability consecutive sampling approach was used, including all available lung donors during the study period without any random selection.

Statistical analysis

Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables (e.g., gender, cause of death, smoking status) were summarized as frequencies and percentages.Continuous variables (e.g., age, PaO_2/FiO_2 ratio) were presented as means and standard deviations (for normally distributed data) or medians and interquartile ranges (for non-normally distributed data).Chi-square test was used to compare categorical data, and independent samples t-test or Mann-Whitney U test was used for continuous data depending on the normality assumption (Shapiro-Wilk test). Logistic regression analysis was conducted to identify predictors of donor acceptance.

Results

A total of 136 donors were evaluated in the study, accounting for 14.1% of all deceased donors (136/959) in Turkey. Among these, 53 out of 305 (17.3%) donors in 2021, 44 out of 349 (13.4%) in 2022, and 39 out of 305 (12.7%) in 2023 were offered to our lung transplant clinic (Table 1).

The study comprised 111 rejected donors and 25 accepted donors. The mean age was 37.5 years (range: 10–63 years. The patients in the rejected group weresignificantly older (40 years, range: 10–63) than thepatients in the accepted group (30 years, range: 15–51). Male donors donated 66.67% of the organs in the rejected group and 48% of the organs in the accepted group. There were no significant differences in height or weight of the donors between the groups.

The most common cause of death was intracranial hemorrhage (ICH), accounting for 79 out of 136 cases (58.09%). In the rejected group, 63 out of 111 deaths (56.76%) were due to ICH, with 16 out of 25 deaths (23.42%) resulting from traumatic ICH. In the accepted group, 64% of deaths (16 patients) were attributed to ICH, while 24% (6 patients) were caused by drowning. Other causes included gunshot wounds, which accounted for 15 patients (11.03%) overall, with 12 patients (10.81%) in the rejected group and 3 patients (12%) in the accepted group. The PaO_2/FiO_2 ratio <300 mmHg was observed in 35.29% of total donors, significantly higher in the rejected group (41.44%) than in the accepted group (8%) ($p = 0.001$).

Donors were referred from state hospitals (25%), private hospitals (18.38%), university hospitals (15.44%), and education and research hospitals (ERH, 41.18%). The accepted group had a lower proportion of ERH donors (12%) compared to the rejected group (38.74%).

In terms of medical history, 75% of donors had no comorbidities. Hypertension was the most common comorbidity(12.5% total, 14.41% in rejected, 4% in accepted). Smoking history was more prevalent in the rejected group (37.84% vs. 24%). Positive microbial culture

Table 1. Trends in deceased donors, lung transplants, and transplant activities at our clinic.

Years	Number of deceased donors in Türkiye	Number of lung transplants in Türkiye	Offered donor (%)*	Number of performed lung transplants in our clinic (%)**
2017	554	42	101 (18.1%)	26 (25.7%)
2018	598	43	145 (24.2%)	25 (17.2%)
2019	619	33	129 (20.8%)	16 (12.4%)
2021	305	21	44 (17.3%)	10 (22.7%)
2022	289	11	47 (15.2%)	5 (10.6%)
2023	305	15	45 (12.7%)	7 (15.5%)

* Indicates the percentage of the offered donor to the deceased donor in Turkey. ** Indicates the usage percentage of the "Offered Donor".

tests were detected in 22.42% of donors. It washigher in the accepted group (32% vs. 22.79% in rejected).

Pathological findings in CT scans were seen in 22.06% of donors. TOE/TTE was not performed in 5.88% of the deceased donors, and EF <55% was detected in 7.35% of all donors, with a higher proportion in accepted donors (12% vs. 6.31% in rejected, p = 0.035).

Complete demographic data and comparison of the clinical and demographic characteristics of the patients weresummarizedin Table 2.

Discussion

According to data obtained from the Turkish Transplantation, Dialysis, and Follow-up Systems Public Awareness Platform, a significant decline in the number of deceased donors was observed in Turkeybetween 2021 and 2023. The number of deceased donors decreased from 554 in 2017 to 305 in 2023. Consequently, the total number of lung transplants in Turkey decreased from 33 in 2019 to 10 in 2023. A similar decline has been observed at Koşuyolu High Specialization Training and Research Hospital, where the number of transplants decreased from 26 in 2017 to 7 in 2023. In 2023, lung donors accounted for 12.7% of all donors, compared to over 20% before the pandemic. In the organ donation system, organs such as the heart, kidneys, and liver are offered individually, which may have led donors to refrain from donating lungs due to concerns about the impact of the pandemic on lung organs [7].

There are several studiessuggesting that donors with a partial oxygen pressure (PaO_2) level below 300 mmHg can still be accepted for lung donation. According to the results of thesestudies, PaO_2 levels did not affect graft survival. This finding indicates that the use of donors with lower PaO_2 levels could substantially increase the donor pool, potentially reducing the number of patients waiting for transplants and saving more lives. Although, it is undeniable that PaO_2 is an important criterion in donor evaluation, its importance is not as critical as previously believed, especially in comparison to other evaluation criteria [8]. For instance, factors such as the overall donor health, lung function, age, history of smoking , and evaluation of the function of other organ systems may have a more decisive impact on transplant success. Therefore, rather than viewing PaO_2 levels as an insurmountable barrier, considering them as part of a broader evaluation process may help expand the potential donor pool and offer more opportunities to patients. There has been longstanding hesitancy regarding the use of lungs from donors aged 65 and above, largely due to concerns about the physiological aging process in the lungs. This includes decreased elasticity which results in reduced functional capacity and exercise tolerance, as well as increased residual volume. The aging lung is also more susceptible to infections due to altered immunologic homeostasis and impaired mucociliary clearance. Additionally, older lungs may have a higher risk of previous damage from infections or noxious agents, resuting inthe fibrotic scarring. Especially smoking accelerates this process through telomere reductionand oxidative stress-induced DNA damage. Recent studies have demonstrated the feasibility of using lungs from older donors with proper screening. Donors with a smoking history below 20 pack-years without severe chronic lung disease could still be eligible for transplantation according tointernational donor acceptance trends [9]. We believe that healthy lungs from older donors could also be used in our country. Evaluating this potential could reduce the number of patients waiting for transplants and save more lives. Careful selection and appropriate evaluation of older donorswill be an important step toward improving lung transplant success.

Smoking is a significant problem jeopardizing the lung health in our country. However, the view that lungs from donors with a history of smoking should be rejected has been questioned in recent studies. Successful outcomes have been achieved in both our clinic and worldwide in donors with a smoking history of more than 20 pack-years. Lungs from smokers are generally associated with a modest risk of postoperative lung/graft dysfunction (PGD) but have not been shown to increase recipient mortality. This finding suggests that using lungs from smokers is a safe option and may significantly expand the donor pool [10]. The presence of positive microbial cultures is nota reason for rejecting a lung graft. What is critical is the antibiotic resistance profile of the microorganism. There is very limited information in the literature regarding the transmission of microorganisms from the donor to the recipient and the subsequent development of pneumonia after transplantation. Few studies available suggest that microbial transmission from lung donors to recipients does not lead to pneumonia [11]. Studies on the potential safety of using lung allografts from MDR (multidrug-resistant) bacteria-infected donors, with appropriate prophylaxis, indicate that this could expand treatment options for patients with advanced lung disease awaiting transplantation. However, caution should be exercised in the case of donor lungs infected with MDR Klebsiella pneumoniae, which is associated with high mortality. In addition Stenotrophomonas

Table 2. Demographic data of donors.

	Total (n= 136)	Rejected (n= 111)	Accepted (n= 25)	p value
Gender (male), n (%)	86	74 (66.67%)	12 (48%)	0.080
Age, years	37.0 (10-63)	40 (10-63)	30(15-51)	**0.017**
Height, cm	170 (140-190)	170 (140-190)	170 (155-182)	0.880
Weight, kg	75 (40-97)	75 (40-97)	70 (45-82)	0.063
Blood type n (%)				
0	47 (34.56%)	42 (37.84%)	5 (20%)	
A	64 (47.06%)	49 (44.14%)	15 (60%)	
B	17 (12.5%)	13 (11.71%)	4 (16%)	
AB	8 (5.88%)	7 (6.31%)	1 (4%)	
Cause of death n (%)				0.951
Suicide (Hanging)	3 (2.21%)	3 (2.70%)	-	
Gunshot wound	15 (11.03%)	12 (10.81%)	3 (12%)	
Intoxication	4 (2.94%)	4 (3.60%)	-	
ICH	79 (58.09%)	63 (56.76%)	16 (64%)	
Drowning In Water	3 (2.21%)	3 (2.70%)	-	
Traumatic ICH	32 (23.53%)	26 (23.42%)	6 (24%)	
Apnea test				
Not performed n (%)	31 (22.79%)	27 (24.32%)	4 (16%)	
Performed n (%)	105 (77.21%)	84 (75.68%)	21 (84%)	
Hospital admission	354 (46-381)	310 (46-667)	523 (186-681)	
Last test result	351 (40-686)	319 (47-569)	461 (40-686)	
PaO_2/FiO_2 ratio <300 mmHg, n	48 (35.29%)	46 (41.44%)	2 (8%)	**0.001**
Hospital status n (%)				0.514
State hospital	34 (25%)	30 (27.03%)	4 (16%)	
Private	25 (18.38%)	20 (18.02%)	5 (20%)	
University	21 (15.44%)	18 (16.22%)	3 (12%)	
ERH	56 (41.18%)	43 (38.74%)	13 (12%)	
Background n (%)				
No features	102 (75%)	81 (73.00%)	21 (84%)	
HT	17 (12.5%)	16 (14.41%)	1 (4%)	
Neurological	8 (5.88%)	5 (4.50%)	3 (12%)	
CHD	5 (3.68%)	5 (4.50%)	-	
DM	5 (3.68%)	4 (3.60%)	1 (4%)	
Malignancy	1 (0.74%)	1 (0.90%)	-	
Cardiac arrest n (%)				0.874
Yes	31 (22.79%)	25 (22.52%)	6 (24%)	
No	105 (77.21%)	86 (77.48%)	19 (76%)	
Smoking history n (%)				0.191
Yes	48 (35.29%)	42 (37.84%)	6 (24%)	
No	88 (64.71%)	69 (62.16%)	19 (76%)	
Intubation Duration	5 (1-21)	5 (1-21)	5 (1-12)	0.680
Microbial Reproduction				
No, n (%)	103 (75.74%)	86 (77.48%)	17 (68%)	0.318
Yes, n (%)	33 (24.26%)	25 (22.42%)	8 (32%)	
Trachea	19 (13.97%)	16 (14.41%)	3 (12%)	0.522
Blood	11 (8.08%)	8 (7.2%)	3 (12%)	0.327
Urine	5 (3.6%)	3 (2.7%)	2 (8%)	0.228
Antibiotic, n (%)				
Yes	116 (85.29%)	97 (87.39%)	19 (%76)	0.129
No	20 (14.71%)	14 (12.61%)	6 (%24)	
WBC (10^3/ µl)				
Hospital admission	17.3 (3.3-71)	17.6 (3.3-71)	15 (4.5-34.2)	0.098
Last test result	16.8 (2.68-45.3)	15.7 (2.68-36.7)	21.2 (4.9-45.3)	0.124

	Total (n= 136)	Rejected (n= 111)	Accepted (n= 25)	p value
CRP (mg/L)				
Hospital admission	6.2 (0.02-318)	6.3 (0.02-318.0)	3.41 (0.2-96.0)	0.175
Last test result	80.5 (0.33-422)	74.7 (0.33-422)	81 (8.2-34.3)	0.682
Procalcitonin				
No, n (%)	26 (19.12%)	23 (20.72%)	3 (12%)	0.272
Yes, n (%)	110 (80.88%)	88 (79.28%)	22 (88%)	0.751
Median	0.67 (0.01-72)	1.18 (0.01-72	0.67 (0.04-12.1)	
TOE/ TTE, n (%)				
Not performed	8 (5.88%)	7 (6.31%)	1 (4%)	
EF < 55	10 (7.35%)	7 (6.31%)	3 (12%)	0.281
EF ≥ 55	118 (86.76%)	97 (87.39%)	21 (84%)	
TOE/TTE (pathological finding), n (%)				
Not performed	8 (5.8%)	7 (6.31%)	1 (4%)	
Yes	14 (10.2%)	8 (8.11%)	6 (24%)	0.035
No	114 (83.8%)	96 (18.92%)	18 (72%)	
Pathological findings in CT, n (%)				
Yes	30 (22.06%)	21 (18.92%)	9 (36%)	0.063
No	106 (77.94%)	90 (81.08%)	16 (64%)	

ICH; intracranial hemorrhage, PaO_2; Partial pressure of oxygen; FiO_2; Fraction of inspired oxygen, ERH; education and research hospital, CHD; coronary heart disease, HT; hypertension, DM; diabetes mellitus, WBC; white blood cell, CRP; C-reactive protein, EF; ejection fraction, CT; computerized tomography, TOE: transoesophageal echocardiography, TTE: transthoracic echocardiography.

maltophiliais linked to the development of chronic lung allograft dysfunction (CLAD) in the recipients in the long term [11].

The duration of mechanical ventilation has been proven to increase lung damage. Prolonged mechanical ventilation can lead to barotrauma, volutrauma, and oxygen toxicity in the lungs, which can impair lung function. However, studies have shown that lung transplantation (LTx) from donors on mechanical ventilation for longer than 5 days yields outcomes comparable to those from donors on mechanical ventilation for shorter periods. These findings suggest that, under appropriatemanagement and careful selection, donors on prolonged mechanical ventilation could be utilized as a viable strategy to expand the donor pool for LTx [12]. In this context, the duration of mechanical ventilation is not the sole determining factor of lung damage. The condition of the lungs depends on a variety of factors, including the overall health of the donor, lung function, disease history, age, and other potential risk factors. Therefore, instead of automatically excluding donors with prolonged mechanical ventilation, a careful selection and evaluation process could allow the use of their lungs, leading to successful transplant outcomes. While prolonged mechanical ventilation increases the risk of lung damage, with appropriate prophylaxis and monitoring, these risks can be minimized, making the lungs from these donors a valuable resource for patients in need.

Conclusion

The decline in deceased donor numbers and lung transplants in Turkey emphasizes the urgent need to expand the donor pool. Strategies such as including marginal donors, evaluating lungs from older donors, and considering donors with a smoking history should be implemented based on international best practices. Public awareness campaigns, educational programs, and policy-driven incentive structures should be prioritized to increase organ donation rates. In addition to expanding donor criteria, social awareness and public engagement play a crucial role in increasing donation rates. Countries with high organ donation rates have implemented nationwide awareness campaigns and incentive-based donation programs. Future efforts in Turkey should prioritize similar initiatives to encourage organ donation. Additionally, refining donor evaluation protocols by incorporating broader clinical and laboratory parameters can help maximize the use of available donors.Evidence suggests that lower PaO_2 levels, older donor age, smoking history, and prolonged mechanical ventilation should not be viewed as absolute barriers but rather as modifiable factors within a comprehensive evaluation process. With careful selection criteria, appropriate prophylaxis, and monitoring, risks associated with microbial infections and other complications can be effectively managed, enhancing transplant success rates. By broadening donor criteria and enhancing social awareness, more patients in critical need can receive life-saving lung transplants, ultimately improving transplant accessibility and patient outcomes in Turkey.

Acknowledgments

None.

Data Availability

All data generated or analyzed during this study are included in this published article. However, if requested, we can share the requested data of all our cases with the editor and the relevant reviewers.

Ethics Committee Approval

The study protocol was approved by the Ethical Committee of Clinical Research of Kartal Kosuyolu High Specialization Education & Research Hospital (No: 2024/20/963). This study was conducted according to the Helsinki principles, patients signed informed consent for participation, and nothing invasive of patients' privacy was done.

Consents to Participate

The study was a human organ/tissue transplant study, as it involved deceaded donors. We confirm that organs/tissues were not taken from prisoners. Each organ/tissue was taken from volunteer donors. And when these donors became brain dead, Written informed consent was also obtained from their first-degree relatives. And also, written informed consent was obtained for publication of this original article and all accompanying images from all patients who underwent transplantation and from whom that tissue/organ was taken.

Consent for Publication

Not applicable.

Author Contributions

SC, ES, ANH, MM, AET, MEC collected the data and drafted the manuscript. SC, MV edited the manuscript, participated in the study design and coordination. All authors read and approved the final manuscript.

Competing Interests

The authors declare that they have no competing interests.

Funding

None.

References

1. Yusen RD, Christie JD, Edwards LB, et al. International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report--2013; focus theme: age. *J Heart Lung Transplant.* 2013;32(10):965-78. DOI: 10.1016/j.healun.2013.08.007.
2. Angelico R, Trapani S, Manzia TM, et al. The COVID-19 outbreak in Italy: initial implications for organ transplantation programs. *Am J Transplant.* 2020;20(7):1780-84. DOI: 10.1111/ajt.15904.
3. Uysal Yazıcı M, Torun EG. Effect of coronavirus pandemic on organ donation and transplantation in Turkey. *Turk J Med Sci.* 2021;51(5):2792-94. DOI: 10.3906/sag-2105-188.
4. Sahin MF, Beyoglu MA, Turkkan S, et al. Donor Lung Evaluation and Lung Transplantation in the COVID-19 Era. *Exp Clin Transplant.* 2022;20(9):842-48. DOI: 10.6002/ect.2020.0567.
5. Vayvada M, Taşçı AE. Donor selection for lung transplant in Turkey: Is it necessary to wait for an ideal donor? *Turk Gogus Kalp Damar Cerrahisi Derg.* 2021;29(3):339-46. DOI: 10.5606/tgkdc.dergisi.2021.19953.
6. https://organkds.saglik.gov.tr/dss/Default.aspx.
7. Putzer G, Gasteiger L, Mathis S, et al. Solid Organ Donation and Transplantation Activity in the Eurotransplant Area During the First Year of COVID-19. *Transplantation.* 2022 Jul 1;106(7):1450-1454. DOI: 10.1097/TP.0000000000004158.
8. Zafar F, Khan MS, Heinle JS, et al. Does donor arterial partial pressure of oxygen affect outcomes after lung transplantation? A review of more than 12,000 lung transplants. *J Thorac Cardiovasc Surg.* 2012;143(4):919-25. DOI: 10.1016/j.jtcvs.2012.01.044.
9. Darie AM, Levvey BJ, Shingles HV, et al. Impact of donor age ≥65 years on graft survival in large lung transplant cohorts. *J Heart Lung Transplant.* 2024; 12:S1053-2498(24)01942-9. DOI: 10.1016/j.healun.2024.11.002.
10. Diamond JM, Cantu E, Calfee CS, et al. The Impact of Donor Smoking on Primary Graft Dysfunction and Mortality after Lung Transplantation. *Am J Respir Crit Care Med.* 2024;209(1):91-100. DOI: 10.1164/rccm.202303-0358OC.
11. Abdulqawi R, Saleh RA, Alameer RM, et al. Donor respiratory multidrug-resistant bacteria and lung transplantation outcomes. *J Infect.* 2024;88(2):139-48. DOI: 10.1016/j.jinf.2023.12.013.
12. Sugimoto S, Kurosaki T, Otani Set al. Feasibility of lung transplantation from donors mechanically ventilated for prolonged periods. *Surg Today.* 2019;49(3):254-60. DOI: 10.1007/s00595-018-1730-z.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

The relationship between annual lung function decline and serum bilirubin levels in chronic obstructive pulmonary disease

Sinem Berik Safci[a,*], Ozlem Ercen Diken[a], Sibel Kara[a], Meliha Kus[a]

[a] *Adana Education and Research Hospital, Department of Pulmonology, Adana, Türkiye*

ARTICLE INFO

Keywords:
Total bilirubin
Lung function test
COPD

Received: Sep 29, 2024
Accepted: Feb 26, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.09.195

Abstract

Aim: To study the relationship between the level of bilirubin in the serum and the annual decline in lung function in chronic obstructive pulmonary disease (COPD).

Materials and Methods: The medical records of 1,574 patients diagnosed with COPD were reviewed in this retrospective study. In total, 126 eligible patients were included. Data from the initial visits and lung function tests performed at the end of the first year, along with serum direct bilirubin and total bilirubin (TB) measurements, were obtained from the electronic system and analyzed. Pearson correlation was used to determine the association between two continuous parameters.

Results: Negative correlation was found between the annual changes in the first second of forced expiration (FEV_1) percentage, FEV_1 ml, predicted forced vital capacity (FVC) percentage, FVC ml, and predicted forced expiratory flow $(FEF)_{25–75\%}$ percentage and the mean TB values and it was statistically significant (r: -0.202, -0.342, -0.236, -0.287, and -0.136, respectively). However, TB values did not have a significant relationship with the change in the FEV_1/FVC ratio.

Conclusion: The progression speed of COPD may vary among different patients. An elevated serum TB concentration within physiological limits could be considered a parameter that may slow the progression of COPD.

Introduction

COPD is a lung disease characterised by chronic respiratory symptoms such as dyspnoea, cough, production of sputum and/or exacerbations due to disorders in the airways and/or alveoli, typically leading to progressive and persistent airflow obstruction [1]. COPD's high global prevalence, combined with its significant morbidity and mortality rates, imposes a substantial healthcare burden [2].

A critical part in the pathophysiology and progressive nature of COPD is played by chronic inflammation and oxidative stress induced by environmental and endogenous factors [3]. Mediators released by increased macrophages, lymphocytes, and neutrophils in the airways, like tumor necrosis factor-alpha, chemokine ligand 8, chemokine ligand 2, interleukin-1, interleukin-6 and matrix metalloproteinases, are considered responsible for chronic inflammation [4].

Bilirubin is a potent endogenous antioxidant and anti-inflammatory agent, released during the breakdown of the heme molecule and counteracts oxidative damage and helps control oxidative stress by neutralizing free radicals associated with lipid peroxidation [5]. Researchs have shown that elevated levels of bilirubin within physiological limits are correlated with a lower incidence of COPD diagnosis, fewer exacerbations, slower lung function decline, and lower mortality rates [6-8].

The aim of this study was to estimate the association between serum bilirubin levels and annual decline in lung function in COPD.

Materials and Methods

Study subjects

The medical records of patients diagnosed with COPD who applied to the Chest Diseases Clinic of Adana City Training and Research Hospital between January 1, 2022 and January 1, 2023 were reviewed after obtaining ethics committee approval (Adana City Training and Research Hospital Clinical Research Ethics Committee, approval number: 3264). Patient data, including age, gender, smoking history (pack-years), comorbidities, and serum levels of total bilirubin (TB), direct bilirubin (DB), albumin, aspartate

*Corresponding author:
Email address: sinemberik@hotmail.com (Sinem Berik Safci)

aminotransferase, alanine aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase, were collected from the initial visit and the first-year follow-up. In addition, post-bronchodilator values obtained from pulmonary function tests, namely forced expiratory volume in the FEV_1 (predicted percentage and ml), FVC (predicted percentage and ml), FEV_1/FVC ratio, and $FEF_{25–75\%}$ (predicted percentage), were transferred to a computer environment.

The inclusion criteria were a diagnosis of COPD with a post-bronchodilator FEV1/FVC ratio $<$ 70% on spirometric testing, $\geq$ 18 years old, and a smoking history of $\geq$20 pack-years. The exclusion criteria were the presence of comorbidities that could elevate bilirubin levels, such as hemolytic and hepatobiliary disorders, malignancy or Gilbert's syndrome; TB levels exceeding 1.75 mg/dL in females or 2.34 mg/dL in males; inability to access first-year follow-up data; continued active smoking; failure to receive regular treatment; ongoing exposure to environmental risk factors; and a $<$20 pack-years of smoking in background. Figure 1 presents the patient flowchart.

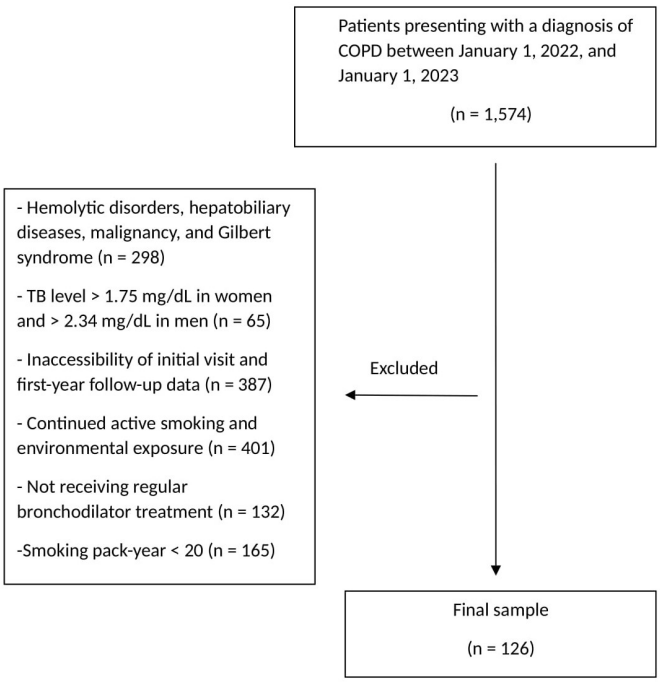

Figure 1. Patient flowchart.

Lung function test

Pre- and post-bronchodilator lung function tests were conducted using the CareFusion spirometer (SentrySuite version 2.19.7, Germany 234 GmbH, Leibnizstraße). Post-bronchodilator measurements were taken 20 minutes after administering 400 µg of salbutamol sulfate aerosol. Testing adhered to maneuver and quality standards set by the European Respiratory Society [9]. Post-bronchodilator values were used in analysis.

The severity of airflow limitation in patients with a FEV_1/FVC ratio $<$ 70% (post-bronchodilator) was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as follows:

- Stage 1: predicted $FEV_1 \geq 80\%$
- Stage 2: predicted $FEV_1 = 50–80\%$
- Stage 3: predicted $FEV_1 = 30–50\%$
- Stage 4: predicted $FEV_1 \leq 30\%$

Bilirubin measurement

Venous blood samples were collected after an eight-hour fasting period as part of routine practice. Samples were centrifuged at 3,000 rpm at 4 °C, and bilirubin levels were measured using the vanadate oxidase method in the central laboratory.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for the IBM SPSS Statistics for Windows, Version 20.0 (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was utilized to evaluate the data distribution's normality. Data that followed a normal distribution were expressed as mean ± standard deviation values, Pearson correlation analysis was employed to assess the degree of linear association between two continuous variables. We calculated the sample size using the G-power programme. For the correlation model, the confidence interval was 95% and a standart deviation of 0.5, the effect size was 0.3. Statistical significance was defined as a p-value of less than 0.05.

Results

Of the 126 patients included in the study, 83.3% (n = 105) were male and 16.7% (n = 21) were female, with a mean age of 63.9 years (±8.49, range: 41–85). The mean body mass index was 28.9 (±6.5, range: 21–33), the mean smoking history was 35.5 pack-years (±14.5, range: 20–80), and the mean time since smoking cessation was 6.5 years (±4.5, range: 2–13).

When classified according to the severity of airflow limitation, 25 patients were in stage 1, 32 were in stage 2, 39 were in stage 3, and 30 were in stage 4. The mean baseline spirometric values were as follows: FEV_1/FVC ratio, 57.8% (±11.5); predicted FEV_1 percentage, 54.6% (±18.6); FEV_1 mL, 1,601.4 (±654.9); predicted FVC percentage, 71.3% (±17.4); FVC ml, 2,653 (±941.7); and predicted $FEF_{25–75\%}$ percentage, 53.2% (±15.8).

A significant positive correlation was observed between initial visit TB levels and baseline FEV_1/FVC, predicted FEV_1 percentage, and FEV_1 ml (r = -0.416, -0.346, and -0.284, respectively). However, no significant correlation was found between TB levels and predicted FVC percentage, FVC ml, or predicted $FEF_{25-75\%}$ percentage. A significant positive correlation was also observed between initial visit DB levels and baseline FEV_1/FVC (r = -0.335), although no significant relationship was found with predicted FEV_1 percentage, FEV_1 ml, predicted FVC percentage, FVC ml, or predicted $FEF_{25–75\%}$ percentage (Table 1).

At the first-year follow-up, a significant negative correlation was detected between mean TB levels and the annual changes in predicted FEV_1 percentage, FEV_1 ml, predicted FVC percentage, FVC ml, and predicted $FEF_{25–75\%}$

Table 1. Relationship between baseline pulmonary function test parameters and baseline bilirubin concentrations.

		FEV_1/FVC	Predicted FEV_1 %	FEV_1 ml	Predicted FVC %	FVC ml	Predicted $FEF_{25–75\%}$
Total bilirubin (mg/dl)	r	0.416	0.346	0.284	0.114	0.106	0.214
	p	**0.01**	**0.04**	**0.03**	0.40	0.43	0.09
Direct bilirubin (mg/dl)	r	0.335	0.146	0.200	0.018	0.042	0.132
	p	**0.02**	0.32	0.17	0.90	0.78	0.09

FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, FEF: forced expiratory flow, r: correlation coefficient. Statistically significant at p<0.05.

Table 2. Relationship between changes in pulmonary function test parameters and bilirubin levels.

		FEV_1/FVC	Predicted FEV_1 %	FEV_1 ml	Predicted FVC %	FVC ml	Predicted $FEF_{25–75\%}$
Total bilirubin (mg/dl)	r	-0.230	-0.202	-0.347	-0.236	-0.287	-0.136
	p	0.88	**0.04**	**0.009**	**0.04**	**0.03**	**0.04**
Direct bilirubin (mg/dl)	r	-0.024	-0.234	-0.076	-0.129	-0.082	-0.213
	p	0.87	0.55	0.08	0.06	0.87	0.09

FEV_1: forced expiratory volume in the first second, FVC: forced vital capacity, FEF: forced expiratory flow, r: correlation coefficient. Statistically significant at p<0.05.

percentage (r = -0.202, -0.342, -0.236, -0.287, and -0.136, respectively), but there was no significant relationship between TB and the change in the FEV_1/FVC ratio. Furthermore, no significant correlation was found between the mean DB levels and the annual changes in FEV_1/FVC, predicted FEV_1 percentage, FEV_1 ml, predicted FVC percentage, FVC ml, or predicted $FEF_{25–75\%}$ percentage (Table 2).

Discussion

This study showed that as mean annual serum TB levels increased, the rate of annual decline in lung function decreased. In COPD, increased inflammation and oxidative stress arise from exogenous sources, such as smoking, or endogenous production. These oxidative products cause damage to DNA, lipids, and proteins [10]. Harijith et al. reported that nicotinamide adenine dinucleotide phosphate oxidase contributed to lung remodeling [11]. Other studies have shown that lipid peroxidation in human lungs leads to cellular membrane component damage, impairing cell structure and permeability [12] and that higher levels of lipid peroxidation products are found in the sputum of patients with COPD [13]. As a result, the remodeling of airways leads to airway obstruction and irreversible limitations detected in pulmonary function tests.

The degradation of heme to biliverdin by hem oxygenase is the first step in the biochemical production of bilirubin [14]. Biliverdin is then converted into bilirubin by biliverdin reductase [15]. Heme oxygenase-1, an inducible isoform, is upregulated by oxidative stress and hypoxia and is produced by type 2 pneumocytes and alveolar macrophages [16, 17]. Increased intracellular biliverdin/bilirubin redox couple protects the vascular endothelium against reactive oxygen and nitrogen [18]. In a COPD rat model study, exogenous bilirubin administration was shown to reduce lung inflammation, suppress regional oxidative lipid damage, and mitigate smoking-induced pulmonary emphysema [19]. A systematic review of 13 observational studies concluded that benign increases in serum bilirubin reduced mortality and had positive effects on lung capacity and COPD prognosis [20].

Apperley et al. and Dai et al. reported a negative correlation between annual FEV_1 decline and total bilirubin concentrations [6, 21]. Consistent with the literature, our study revealed that as the annual mean TB levels in patients with COPD decreased, there was an increase in FEV_1 loss (in both predicted percentage and milliliters) during pulmonary function tests. This finding suggests that physiological levels of serum TB may slow remodeling through its antioxidant effects and help prevent functional decline.

In contrast to expectations, another study found no significant relationship between TB and the FEV_1/FVC ratio in patients with COPD [21]. In our study, while a positive correlation was detected between baseline FEV_1/FVC values and TB, there was no relationship between mean TB and annual FEV_1/FVC changes, which is consistent with the literature.

Our results also demonstrated a relationship between baseline FEV_1 values and mean serum TB levels. Supporting our findings, Leem et al. found that higher bilirubin concentrations were associated with higher FEV_1, longer six-minute walking test distances, and better quality of life [22]. These results suggest that an increase in TB concentrations may limit remodeling from the early stages through its anti-inflammatory and antioxidant effects, thus preventing loss of lung capacity.

In this study, while no significant relationship was found between TB and baseline $FEF_{25–75\%}$, there was a correlation between the annual change in $FEF_{25–75\%}$ and mean serum TB levels. Similarly, Curjuric et al. reported a significant relationship between serum bilirubin levels and FEV_1/FVC and $FEF_{25–75\%}$ in non-smokers [23]. $FEF_{25–75\%}$ is used in pulmonary function tests as a parameter representing small airway diseases. Due to the anti-inflammatory effects of TB, particularly at the alveolar and bronchiolar levels, it may limit the decline in

$FEF_{25–75\%}$.

Limitations

First, we did not have data on patients' pulmonary function tests or lung capacity before COPD, making it difficult to comment on the impact of TB on the onset of the disease. Second, we did not exclude genetic factors that may facilitate the progression of the disease and loss of lung capacity in patients with COPD. To address these limitations, there is a need for long-term prospective studies with larger patient groups that exclude modifying factors.

Conclusion

COPD is an airway disease characterized by irreversible airway obstruction and progressive loss of lung capacity. Patients' illness progressions differ from one another. Higher serum TB concentrations within physiological limits can be considered one of the parameters that slows the progression of COPD.

Ethics Committee Approval

The research was approved by the Clinical Research Ethics Committee of Adana City Training and Research Hospital on 28 March 2024 with the approvel number 3264. Throughout the trial, researchers ensured the confidentiality of patient data and adhered to the ethical principles of clinical research as outlined in the Declaration of Helsinki. Due to the retrospective nature of the study, the ethical committee waived the need for informed consent.

Consent for Publication

All co-authors have seen and approved the contents of the manuscript. We confirm that this manuscript is our own original work and is not currently under consideration by any other publication. Data available on consent due to privacy/ethical restrictions.

Competing Interests

The authors certify that they have no conflicting interests with regard to this study or its publication.

Data Availability

We agree to keep records for at least 5 years. All data generated in the study will be made available to the corresponding author upon reasonable request.

Author Contributions

Concept: SBS, OED, acquisition of subjects and/or data: OED,MA, analysis and interpretation of data: SBS, SK, MA and preparation of study: SBS, SK, MA

References

1. Venkatesan P. GOLD COPD report: 2024 update. *Lancet Respir Med.* 2024 Jan;12(1):15-16. doi: 10.1016/S2213-2600(23)00461-7. Epub 2023 Dec 4. PMID: 38061380.
2. Blasi F, Chalmers JD, Aliberti S. COPD and bronchiectasis: phenotype, endotype or co-morbidity? *COPD.* 2014 Dec;11(6):603-4. doi: 10.3109/15412555.2014.974744. PMID: 25384083.
3. van Eeden SF, Hogg JC. Chronic obstructive pulmonary disease: do regional differences in tissue inflammation matter? *Respiration.* 2011;81(5):359-61. doi: 10.1159/000323869. Epub 2011 Feb 18. PMID: 21335946.
4. Barnes PJ. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.* 2016 Jul;138(1):16-27. doi: 10.1016/j.jaci.2016.05.011. Epub 2016 May 27. PMID: 27373322.
5. Lapenna D, Ciofani G, Pierdomenico SD, et al. Association of serum bilirubin with oxidant damage of human atherosclerotic plaques and the severity of atherosclerosis. *Clin Exp Med.* 2018 Feb;18(1):119-124. doi: 10.1007/s10238-017-0470-5. Epub 2017 Sep 25. PMID: 28948382.
6. Apperley S, Park HY, Holmes DT, et al. Serum Bilirubin and Disease Progression in Mild COPD. *Chest.* 2015 Jul;148(1):169-175. doi: 10.1378/chest.14-2150. PMID: 25539285; PMCID: PMC4493872.
7. Brown KE, Sin DD, Voelker H, et al. COPD Clinical Research Network. Serum bilirubin and the risk of chronic obstructive pulmonary disease exacerbations. *Respir Res.* 2017 Oct 24;18(1):179. doi: 10.1186/s12931-017-0664-0. PMID: 29065885; PMCID: PMC5655988.
8. Leem AY, Kim HY, Kim YS, et al. Association of serum bilirubin level with lung function decline: a Korean community-based cohort study. *Respir Res.* 2018 May 23;19(1):99. doi: 10.1186/s12931-018-0814-z. PMID: 29792214; PMCID: PMC5966910.
9. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26(2):319–338. doi: 10.1183/09031936.05.00034805.
10. van Eeden SF, Sin DD. Oxidative stress in chronic obstructive pulmonary disease: a lung and systemic process. *Can Respir J.* 2013 Jan-Feb;20(1):27-9. doi: 10.1155/2013/509130. PMID: 23457671; PMCID: PMC3628643.
11. Harijith A, Natarajan V, Fu P. The Role of Nicotinamide Adenine Dinucleotide Phosphate Oxidases in Lung Architecture Remodeling. *Antioxidants (Basel).* 2017 Dec 19;6(4):104. doi: 10.3390/antiox6040104. PMID: 29257052; PMCID: PMC5745514.
12. Repine JE, Bast A, Lankhorst I. Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group. *Am J Respir Crit Care Med.* 1997 Aug;156(2 Pt 1):341-57. doi: 10.1164/ajrccm.156.2.9611013. PMID: 9279209.
13. Nowak D, Kasielski M, Antczak A, et al. Increased content of thiobarbituric acid-reactive substances and hydrogen peroxide in the expired breath condensate of patients with stable chronic obstructive pulmonary disease: no significant effect of cigarette smoking. *Respir Med.* 1999 Jun;93(6):389-96. doi: 10.1053/rmed.1999.0574. PMID: 10464820.
14. Tomaro ML, Batlle AM. Bilirubin: its role in cytoprotection against oxidative stress. *Int J Biochem Cell Biol.* 2002 Mar;34(3):216-20. doi: 10.1016/s1357-2725(01)00130-3. PMID: 11849989.
15. Noriega GO, Balestrasse KB, Batlle A, Tomaro ML. Heme oxygenase exerts a protective role against oxidative stress in soybean leaves. *Biochem Biophys Res Commun.* 2004 Oct 22;323(3):1003-8. doi: 10.1016/j.bbrc.2004.08.199. PMID: 15381099.
16. Carter EP, Garat C, Imamura M. Continual emerging roles of HO-1: protection against airway inflammation. *Am J Physiol Lung Cell Mol Physiol.* 2004 Jul;287(1):L24-5. doi: 10.1152/ajplung.00097.2004. PMID: 15187007.
17. Fredenburgh LE, Perrella MA, Mitsialis SA. The role of heme oxygenase-1 in pulmonary disease. *Am J Respir Cell Mol Biol.* 2007 Feb;36(2):158-65. doi: 10.1165/rcmb.2006-0331TR. Epub 2006 Sep 15. PMID: 16980551; PMCID: PMC2176110.
18. Ziberna L, Martelanc M, Franko M, Passamonti S. Bilirubin is an Endogenous Antioxidant in Human Vascular Endothelial Cells. *Sci Rep.* 2016 Jul 6;6:29240. doi: 10.1038/srep29240. PMID: 27381978; PMCID: PMC4933905.
19. Wei J, Zhao H, Fan G, Li J. Bilirubin treatment suppresses pulmonary inflammation in a rat model of smoke-induced emphysema. *Biochem Biophys Res Commun.* 2015 Sep 18;465(2):180-7. doi: 10.1016/j.bbrc.2015.07.133. Epub 2015 Jul 30. PMID: 26232645.

20. MacDonald DM, Kunisaki KM, Wilt TJ, Baldomero AK. Serum bilirubin and chronic obstructive pulmonary disease (COPD): a systematic review. *BMC Pulm Med.* 2021 Jan 20;21(1):33. doi: 10.1186/s12890-021-01395-9. PMID: 33472602; PMCID: PMC7816373.
21. Dai C, Wu F, Wang Z, et al The association between small airway dysfunction and aging: a cross-sectional analysis from the ECOPD cohort. *Respir Res.* 2022 Sep 4;23(1):229. doi: 10.1186/s12931-022-02148-w. PMID: 36058907; PMCID: PMC9441095.
22. Leem AY, Park B, Kim YS, Chang J, Won S, Jung JY. Longitudinal decline in lung function: a community-based cohort study in Korea. *Sci Rep.* 2019 Sep 20;9(1):13614. doi: 10.1038/s41598-019-49598-9. PMID: 31541126; PMCID: PMC6754397.
23. Curjuric I, Zemp E, Dratva J, et al; SAPALDIA team. Determinants of change in airway reactivity over 11 years in the SAPALDIA population study. *Eur Respir J.* 2011 Mar;37(3):492-500. doi: 10.1183/09031936.00188609. Epub 2010 Jun 7. PMID: 20530037.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Effects of combining nicardipine and remifentanil on surgical visual field and hemodynamic parameters in functional endoscopic sinus surgery

Oya Olcay Ozdes[a,*], Erol Karaaslan[b], Ahmet Selim Ozkan[b], Yeliz Tunc Ozer[c], Nurcin Gulhas[b]

[a] *Battalgazi State Hospital , Department of Anesthesiology and Reanimation, Malatya, Türkiye*
[b] *Inonu University, Faculty of Medicine, Department of Anesthesiology and Reanimation, Malatya, Türkiye*
[c] *Diyarbakır Oral and Dental Health Hospital, Department of Anesthesiology and Reanimation, Diyarbakır, Türkiye*

ARTICLE INFO

Keywords:
Controlled hypotension
Nicardipine/Remifentanil combination
Surgical visualfield

Received: Nov 27, 2024
Accepted: Feb 26, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.11.250

Abstract

Aim: This study examined the impact of using a Nicardipine/Remifentanil combination inducing controlled hypotension (CH) in Functional Endoscopic Sinus Surgery (FESS). The goal was to minimize bleeding and enhance the visibility of the endoscopic field. The study focused on surgical field visibility, asccess, its hemodynamic consequences, and the impact on postoperative paraöeters such as nausea, vomiting, and pain.

Materials and Methods: Our study included 73 patients whose age ranging between 18 and 65 years. The patients were randomly assigned to two groups. Group R (Remifentanil) (n=36) patients, and Group RN (Remifentanil/Nicardipine combination) (n=37) patients. Following intubation, In Group R, patients were administered an intravenous (IV) infusion of Remifentanil at a rate of 0.05–2.0 µg/kg/min, while Group RN received Remifentanil at 0.025–1 µg/kg/min, Nicardipine at 0.5–3.5 µg/kg/min. Target mean arterial pressure (MAP) was set at 50–65 mmHg. After the surgical procedure began, bleeding volume, suction requirements, and surgical field visibility were assessed at 15-minute intervals using the Boezaart scale. Duration of stay in the Post-Anesthesia Care Unit (PACU), incidence of nausea, vomiting, and pain assessment with the Numeric Rating Scale (NRS) were evaluated.

Results: PACU length of stay was considerably shorter in Group RN compared to Group R (p=0.003). Pain scoring was greater in Group R (p=0.001). Nausea and vomiting scores were less in group RN (p=0.037). SAP and MAP were considerably lower in group RN (p=0.018 and p=0.023). HR values şin all time intervals were greater in group RN (p= <0.001). Boezaart score was lower in group RN during in all intervals (p= <0.001).

Conclusion: The Remifentanil/Nicardipine combination provides better surgical field access and visibility byb inducing controlled hypotension (CH) in FESS. This combination is preferable over Remifentanil alone. It effectively maintains CH and shows greater success in reducing postoperative pain, nausea, and vomiting scores.

Introduction

Functional endoscopic sinus surgery (FESS) is a procedure used to cure conditions that cause obstruction in the sinuses by hindering drainage [1]. The most common indication for FESS is chronic rhino-sinusitis. Other indications for FESS include nasal polyposis, cerebrospinal fluid leak, fungal infections, foreign bodies, mucoceles, periorbital abscesses, orbital decompression, post-traumatic evaluations, dacryocystorhinostomy, epistaxis, and resection of various tumors [2].

One of the most common issues during this surgery is bleeding [3]. Disruption of the endoscopic view due to hemorrhage can lead to additional complications because the sinuses are anatomically close to structures like the skull base and orbital cavity [4]. Even minimal bleeding can threaten the successful completion of the surgery, increase the risk of complications, and prolong the surgical duration [5].

One method used to reduce hemorrhage under general anesthesia is controlled hypotension (CH), which consists of intentionally reducing the blood pressure of the patients below the baseline levels. Diverse pharmacological substances are utilized to induce controlled hypotension, ei-

*Corresponding author:
Email address: oya.ozdes@inonu.edu.tr (Oya Olcay Ozdes)

ther individually or in combination.

The primary objective of this study was to evaluate the impact of controlled hypotension induced by remifentanil alone versus a remifentanil/nicardipine combination on visibility and accessibility of the endoscopic surgical field and hemodynamic stability. The secondary objective was to assess their effects on postoperative nausea, vomiting, and pain.

Materials and Methods

Protocol

Our study was conducted in the operating room of the Otorhinolaryngology Department at our institution. The study was approved by the institutional review board (protocol code 2023/05) and adhered strictly to the principles of the Declaration of Helsinki. Written and verbal informed consent was obtained preoperatively. Supervised by the Department of Anesthesia and Reanimation in accordance with operating room standards, the study was primarily conducted by two anesthesiologists. The otolaryngologists confirmed the findings and changes in the intraoperative surgical field.

Inclusion criteria

Patients between the ages of 18 and 65 years, categorized as American Society of Anesthesiologists (ASA) I-II, and scheduled for FESS without any additional procedures in the same session were included in the present study for analyses.

Exclusion criteria

Patients were excluded if their records were incomplete, informed consent was not obtained, they were under 18 or over 65 years old, or had a body mass index >30 kg/m^2, ASA score of 3 or higher, pregnancy, diabetes, significant hepatic or renal insufficiency, cerebral and/or aortic or mitral stenosis, or cardiac insufficiency. Additionally, patients with a history of chronic medication use were reviewed, and those taking cimetidine were also excluded.

Randomization and blinding

In total, 73 patients enrolled in our study and were randomly divided into two groups: Group R (Remifentanil) with 36 patients and Group RN (Remifentanil/Nicardipine combination) with 37 patients. To prevent selection bias, the assignment of drugs to the groups was not based on any specific order (e.g., remifentanil was not consistently given to the first 35 patients). Instead, drugs were administered randomly until a sufficient number of patients were enrolled, and the groups were formed by chance. This randomization process was performed using MedCalc statistical software, version 16 (medcalc.com.tr) for Windows. Each morning, the drugs were prepared by an anesthesia technician who was unaware of the group assignments. Similarly, the anesthesia and patient management were carried out by another anesthesiologist who had no knowledge of the group allocations. The anesthesiologist who managed the anesthesia and administered the medication was different from the anesthesiologist who managed the study. Additionally, the surgeon performing the endoscopic sinus surgery was not informed about which drug was administered. Based on this setup, our study was designed to be both randomized and double-blind.

Preoperative procedures

In the patients included in the study, vascular access was routinely provided with a 20 G intravenous (IV) line inserted in the ante-cubital vein. Premedication was administered with 0.05 mg/kg midazolam 30 minutes before surgery. ECG, noninvasive blood pressure monitoring, SpO_2, and $EtCO_2$ surveillance were performed on all patients admitted to the operating room.

Anesthesia management

All patients were preoxygenated for 3 minutes. Anesthesia induction was performed by intravenous infusion of propofol 2 mg/kg iv, fentanyl 1-2 µg/kg iv, rocuronium 0.5 mg/kg. Once the patients were unconscious and jaw relaxation was adequately established, endotracheal intubation was performed by the anesthesiologist who was blinded to the study group. The cuff of the intubation tubes was inflated to no more than 25 cm H_2O. The patient's head was elevated approximately 15-30 degrees by adjusting their position appropriately. Sevoflurane was administered at 1 MAC in a 50% O_2/air mixture to sustain anesthesia. Intraoperatively, respiratory rate and ventilation were maintained to provide a tidal volume of 6-8 mL/kg and an $EtCO_2$ value of 35-45 mm Hg in both groups. Following intubation in Group R: Remifentanil: 0.05-2.0 µg/kg/min, Group RN: Remifentanil 0.025-1 µg/kg/min, Nicardipine: 0.5-3.5 µg/kg/min iv infusion was started. In both groups, the goal MAP was set at 50-65 mmHg and drug dosages were raised till the goal MAP was reached. A HR below 45 beats/min for more than 120 seconds was considered as bradycardia and remifentanil dose was decreased. If the response was not adequate, atropine 0.5 mg IV was administered. When the mean arterial pressure (MAP) exceeded 65 mm Hg for more than 5 minutes, nicardipine and remifentanil infusions were titrated and increased in both groups. Upon completion of the surgical procedure, neuromuscular blockade was reversed using intravenous injection of atropine at a dose of 0.02 mg/kg and neostigmine at a dose of 0.04 mg/kg. Patients who responded to stimulation by opening their eyes, exhibited regular spontaneous breathing with a respiratory rate of 12–20 breaths per minute, and maintained oxygen saturation levels above 95% were extubated and transferred to the recovery room. Those who achieved a Modified Aldrete score of 9 were subsequently moved to the otolaryngology unit. In the recovery room, trained technicians monitored the patient and recorded the data.

Outcome measures

SAP, DAP, MAP, HR values were recorded every fifteen minutes at T0; before induction, T8; during extubation, T9; at 10 minutes in the post-anesthesia care unit (PACU). $EtCO_2$ values were recorded every fifteen minutes after induction until extubation.

The amount of bleeding, need for assistance with suction, and surgical field visibility were evaluated every fifteen

minutes by a surgeon blinded to the study group. The evaluation of the surgical site was performed by using a 6-point scale (Boezaart scale) with the lowest bleeding score being zero and the highest score being 5 (Table 1) [6].

Table 1. Boezaart Scale [6].

Score	Bleeding	Definition
0 points	No bleeding	
1 points	Minimal Bleeding	Aspiration is not necessary.
2 points	Bleeding Less	Occasional aspiration required, surgical field open.
3 points	Bleeding Less	Aspiration is necessary, the need for aspiration in the surgicalfield happens again after a few seconds.
4 points	Moderate Bleeding	Frequentaspirationrequired, bleedingimmediately after aspiratorremoval, surgicalfield not open.
5 points	Severe Bleeding	Continuousaspiration is necessary. Surgery is not possibledue to severe loss of vision in the surgicalfield.

Time of anesthesia, time to reach the target MAP, duration of operation, extubation time, recovery time, PACU stay, total fluid given, pain and episodes of nausea/vomiting were recorded. A comparison was conducted across the two groups.

Anesthesia time; the time from induction of anesthesia until extubation, whereas surgical time is measured from the initial surgical incision to the conclusion of the procedure. Extubation time was described as the time from the completion of operation and discontinuation of anesthetic drugs until extubation, and verbal response (recovery) time was defined as response to basic verbal instruction given after extubation. Duration of stay in the PACU was described as the time from when the patient was taken to the recovery room until the patient was sent to the relevant service.

Pain scores were evaluated 10 minutes after arrival in the PACU. Pain was assessed by a blinded anesthesiologist according to a numerical rating scale (NRS) (0-10 rating (0-1: mild, 2-4: moderate, 5-7: medium, 8-10: severe). (NRS) $\geq$5 cases were given 15 mg/kg i.v. paracetamol as a rescue analgesic and pain control was achieved.

In the PACU, nausea and vomiting were evaluated using a 4-point scale (0 = no nausea, 1 = moderate nausea, 2 = severe nausea, 3 = retching/vomiting). Patients with severe nausea were treated with ondansetron 50 µg/kg IV as an antiemetic.

In this study, we examined the demographic data of the patients, general symptoms such as nausea and vomiting as well as pain, the duration of anesthesia, surgery, recovery, and the stay in the PACU. We also analyzed the time it took to reach MAP and compared the values of SAP, DAP, MAP, HR, SpO_2, and $EtCO_2$ between the groups, considering their distribution across defined intervals. Additionally, we evaluated the distribution of Boezaart scoring between the groups according to these time intervals.

Statistical analysis

One of the primary outcome measures of this thesis research is the PACU Length of Stay (minutes) variable. According to the findings of the experimental power analysis, with a type I error (α) of 0.05, a total sample size of 73, an effect size of 0.87789, and a two-tailed alternative hypothesis (H1), the observed statistical power (1-β) for the independent two-sample t-test is calculated as 0.99.

All analyses were conducted using IBM SPSS Statistics 26.0 for Windows (New York, USA). The Shapiro-Wilk test, histogram distribution, and skewness-kurtosis parameters were applied for normality analysis. Descriptive statistics were presented as mean $\pm$ standard deviation for normally distributed variables, median (min-max) for non-normally distributed variables, and frequency and percentage for nominal variables. In statistical analyses, categorical comparisons were made using Yates' corrected chi-square test. For quantitative variables, an independent samples t-test was used for comparisons between two independent groups. For analyses involving repeated measurements over time, the General Linear Model - Repeated Measures Analysis (Greenhouse-Geisser Test) was used. For dependent quantitative variables in multiple comparisons, the Bonferroni corrected dependent samples t-test was used for repeated measures analysis of variance. In the applied statistical analyses, $p < 0.05$ was considered statistically significant.

Results

Of the 73 patients who underwent functional endoscopic sinus surgery, 65 were operated for chronic sinusitis. The remaining 6 patients were operated for dacryocystorhinostomy and 2 for cerebrospinal fluid leakage.

When the demographic information of the groups was compared, no significant difference was observed between gender, body mass index, and ASA values (Table 2). Mean age was significantly different among groups (p=0.026). No significant difference between the time to reach the target MAP, mean surgical time, time under anesthesia,

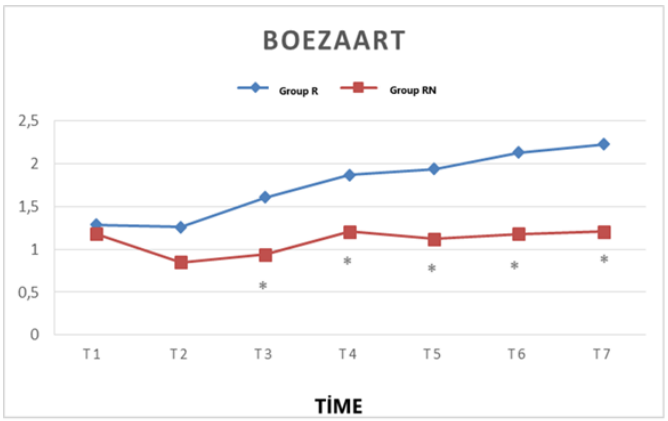

Figure 1. Distribution of Boezaart scoring between the groups in defined intervals.

extubation, and recovery times. PACU stay was considerably shorter in Group RN than Group R (p=0.003). No difference in the total amount of fluid infusion among the groups.

There was a significant difference in the distribution of SAP (p=0.018) and MAP (p=0.023) values in both groups in all intervals, while no difference was detected in the DAP value. SAP and MAP showed a lower course in Group RN (Table 3 and Table 4). There was no difference in the distribution of HR in the two groups in all intervals and it was greater in Group RN (p= <0.001) (Table 5). As a result of the analysis conducted to examine the interaction between interval measurements and the study groups, SAP, MAP, and HR were comparable among the independent variables analyzed. This indicated that there was no interaction between time measurements and groups. The distribution of SpO_2 and $EtCO_2$ values did not significantly change among the groups in any interval.

The Boezaart scores were significantly lower in the Group RN (p= <0.001) (Figure 1). The NRS for evaluation of the intensity of pain was lower in the Group RN (p=0.001).

Table 2. Demographic data, clinical, and operative chartacteristics of the study groups.

Variables	Group R	Group RN	p
Age (year)	41.53 ± 13.94	34.38 ± 11.29	**0.026***
Tall (cm)	169.28 ± 10.58	170.24 ± 9.33	0.618*
Weight (kg)	72.53 ± 14.61	68.54 ± 13.09	0.291*
BMI (kg/m^2)	25.42 ± 5.92	23.48 ± 3.45	0.111*
Gender n(%)			
Male	19 (52.8)	16 (43.2)	0.415**
Female	17 (47.2)	21 (56.8)	
ASA			
1	15 (41.7)	18 (48.6)	0.549**
2	21 (58.3)	19 (51.4)	
Anesthesia Duration (minutes)	141.33 ± 47.12	157.81 ± 48.47	0.108*
Surgical Duration (minutes)	124.28 ± 46.53	142.30 ± 47.61	0.077*
ExtubationTime (minutes)	8.72 ± 3.20	8.38 ± 3.65	0.575*
Recovery Time (minutes)	14.47 ± 4.57	14.57 ± 5.06	0.942*
PACU Duration of Stay (minutes)	17.64 ± 9.44	11.78 ± 0.03	**0.003***
Time to reach MAP (minutes)	28.14 ± 17.53	25.19 ± 12.38	0.595*
Total Fluid Infusion (ml)	1148.61 ± 348.77	1129.73 ± 349.49	0.977*
Remifentanil Infusion Dose (mcg)	710.01 ± 597.24	360.55 ± 240.94	**0.023***
Nicardipine Infusion Dose (mg)	-	2.79 ± 2.57	-

BMI: Body Mass Index; ASA: American Society of Anesthesiologists; MAP: mean arterial pressure; PACU:Postanesthetic Care Unit; *: Independent sample t-test; **: Chi-square test with Yates' correction.

Table 3. Comparison of SAP between groups in defined intervals.

	SAP		
	Group R (Mean ± SD)	Group RN (Mean ± SD)	p
Time			**0.018** *
T0	134.84 ± 16.44	123.12 ± 15.69	**0.003** *
T1	112.35 ± 16.68	104.79 ± 11.78	**0.015** *
T2	97.81 ± 14.34	99.88 ± 16.98 6	0.922
T3	91.65 ± 19.54	90.64 ± 17.20	0.634
T4	89.87 ± 14.80	87.73 ± 10.29	0.724
T5	87.39 ± 12.54	86.45 ± 8.12	0.852
T6	89.06 ± 11.61	87.76 ± 8.96	0.787
T7	90.16 ± 10.88	87.24 ± 9.09	0.248
T8	112.13 ± 13.09	113.42 ± 11.88	0.434
T9	130.35 ± 27.80	116.12 ± 20.3	**0.032** *

SD: Standard deviation; SAP:systolic arterial pressure; Pre-induction (T0), 15 minutes after induction (T1), 30 minutes after induction (T2), 45 minutes after induction (T3), 60 minutes after induction (T4), 75 minutes after induction (T5), 90 minutes after induction (T6), 105 minutes after induction (T7), during extubation (T8), 10 min in PACU (T9). *Meaningful difference among the groups (p<0.05).

Table 4. Distribution of MAP value between groups in defined intervals.

	MAP		
	Group R (Mean ± SD)	Group RN (Mean ± SD)	p
Time			**0.023** *
T0	104.87 ± 13.52	93.61 ± 12.28	**<0.001** *
T1	87.42 ± 16.14	78.15 ± 0.77	**0.002** *
T2	74.84 ± 11.68	74.45 ± 13.28	0.525
T3	70.87 ± 12.35	63.76 ± 9.58	**0.011** *
T4	67.16 ± 13.98	62.18 ± 9.58	0.100
T5	65.97 ± 12.12	62.39 ± 8.36	0.126
T6	67.35 ± 11.31	62.85 ± 7.13	0.083
T7	68.00 ± 8.89	62.42 ± 6.45	**0.005** *
T8	82.94 ± 14.53	85.03 ± 12.31	0.398
T9	105.19 ± 24.70	91.45 ± 18.55	**0.012** *

SD: Standard deviation; MAP: Mean arterial pressure; Pre-induction (T0), 15 minutes after induction (T1) ,30 minutes after induction (T2), 45 minutes after induction (T3), 60 minutes after induction (T4), 75 minutes after induction (T5), 90 minutes after induction (T6), 105 minutes after induction (T7), during extubation (T8), 10 min in PACU (T9). *Meaningful difference among the groups (p<0.05).

The episodes of nausea and vomiting are lower and less intense in the Group RN (p=0.037).

Discussion

In our study, SAP and MAP were significantly lower in Group RN, while HR was statistically significantly lower in Group R. Bradycardia occurred in 3 cases in Group R, whereas no bradycardia developed in Group RN. The MAP was maintained between 50-65 mm Hg in both groups to ensure appropriate surgical conditions without endangering patients in terms of end-organ ischemia, but a more stable success was observed in Group RN. The time to reach MAP did not indicate a statistically notable difference among the groups.

Table 5. Distribution of HR values between groups in defined intervals.

	HR		
	Group R (Mean ± SD)	Group RN (Mean ± SD)	p
Time			**<0.001** *
T0	104.87 ± 13.52	93.61 ± 12.28	0.757
T1	87.42 ± 16.14	78.15 ± 0.77	0.131
T2	74.84 ± 11.68	74.45 ± 13.28	0.268
T3	70.87 ± 12.35	63.76 ± 9.58	**<0.001** *
T4	67.16 ± 13.98	62.18 ± 9.58	**<0.001**
T5	65.97 ± 12.12	62.39 ± 8.36	**<0.001** *
T6	67.35 ± 11.31	62.85 ± 7.13	**<0.001**
T7	68.00 ± 8.89	62.42 ± 6.45	**<0.001** *
T8	82.94 ± 14.53	85.03 ± 12.31	**<0.001** *
T9	105.19 ± 24.70	91.45 ± 18.55	0.812

SD: Standard deviation; HR: HeartRate; Pre-induction (T0), 15 minutes after induction (T1) , 30 minutes after induction (T2) , 45 minutes after induction (T3), 60 minutes after induction (T4), 75 minutes after induction (T5), 90 minutes after induction (T6), 105 minutes after induction (T7) , during extubation (T8), 10 min in PACU (T9). *Meaningful difference among the groups (p<0.05).

Remifentanil is a powerful opioid with extremely short-acting properties. These attributes enable precise and rapid titration, making it highly suitable for managing various surgical procedures. However, in patients receiving remifentanil intraoperatively, there is a need for increased opioid consumption, which is associated with bradycardia, hypotension, and secondary hyperalgesia [7]. Nicardipine, a dihydropyridine class calcium channel antagonist, is an arteriolar smooth muscle-specific vasodilator with no notable effect on cardiac conduction and cardiac contractility. Its quick onset and termination of action allow for fast titration and regulation of blood pressure. Due to these favorable characteristics, it has been successfully used in the management of intraoperative hypertension [8,9].

A randomized controlled study by Shin et al. [10] compared the dynamics of heart rate variability during deliberate hypotension with nicardipine, remifentanil, and dexmedetomidine.

In the nicardipine group, there were significant increases above 100/min at certain time intervals, which may cause problems in patients with cardiovascular illnesses or reduced cardiac output. In the study by Won et al. [11] comparing the effects of nicardipine and remifentanil in thyroidectomy cases undergoing controlled hypotension (CH), heart rate was found to be significantly greater in the nicardipine group than in the remifentanil group. In a study using nicardipine as a controlled hypotension (CH) agent during spine surgery in twenty-four pediatric patients, tachycardia exceeding 100 beats per minute was observed in 6 patients and was managed with esmolol [12]. In our study, consistent with the literature, HR was higher in the remifentanil-nicardipine combination group compared to the remifentanil group. However, HR was not evaluated as tachycardia at any time point. This may be because, in our study, nicardipine, which was administered at high infusion doses such as a 100 mcg bolus or 5-10 mcg/kg/min in previous studies, was combined with remifentanil and titrated at a lower dose range of 0.5-3.5 mcg/kg/min.

Although not statistically significant, bradycardia occurred in 3 cases in Group R and none in Group RN. Therefore, we believe that the combination of nicardipine and remifentanil may be an advantageous alternative because it provides a good surgical field of view and protects against bradycardia caused by remifentanil due to the opposite effects of these two drugs on heart rate.

The Beozaart hemorrhage score was markedly lower in the RN group, which had lower MAP values and higher HR values throughout all time periods. When evaluating the results of our study alongside the literature, it is crucial to consider other parameters that may affect bleeding besides MAP and HR, such as the extent of the lesion and surgical conditions, and to observe the effects of anesthesia and controlled hypotension techniques on the quality of the surgical field accordingly.

In a study by HJ Ahn et al. [13] comparing surgical conditions during propofol/remifentanil or sevoflurane/remifentanil anesthesia in FESS, heart rate and intraoperative blood loss were found to be lower with intravenous anesthesia than with balanced anesthesia, provided the patients had no cardiovascular illness and MAP was maintained within the same limit. Unlike previous studies, the size of the preoperative lesion was taken into account in this study, and patients were further classified according to the extent of the preoperative lesion using the Lund-Mackay score determined by computed tomography. We combined remifentanil with other agents. However, the best result we achieved was the hypotension induced by titrating the dose of the remifentanil-nicardipine combination, which resulted in low Boezaart scores. Although the primary aim of this combination was to reduce bleeding and clear the field of vision, it also provided hemodynamic advantages compared to other combinations. According to these studies, surgical conditions and indications seem to be more standardized in our cases. FESS is performed in a very limited area and the comorbidities of the patients are similar. In other words, there are no large lesions such as tumors. Therefore, it can be said that the hemorrhage score checked at certain intervals is a reliable evaluation [14].

While there was no notable difference between the two groups in terms of anesthesia, surgery, and recovery times, the length of stay in the PACU was significantly shorter in Group RN. NRS pain scores and nausea and vomiting scores in the PACU were significantly lower in Group RN. In a study comparing the clinical efficacy of remifentanil, nicardipine, and the remifentanil-nicardipine combination for controlled hypotension (CH) during arthroscopic shoulder surgery, no significant difference was found between the duration of anesthesia, operation time, and PACU stay [15]. In a randomized controlled study comparing the effect of remifentanil and nicardipine on surgical pleth index during thyroidectomy, anesthesia and recovery times were reported to be comparable among the study groups [11]. In our study, the markedly shorter length of stay in the PACU in Group RN was due to the need for rescue analgesics or antiemetics. The NRS pain score evaluated in the PACU was statistically significantly lower in Group RN, while the nausea/vomiting scores were statistically signif-

icantly greater in Group R.

In a study by Kim JY et al. [15] comparing the use of nicardipine, remifentanil, and nicardipine plus remifentanil for controlled hypotension (CH) in arthroscopic shoulder surgery cases, visual analog pain scores were evaluated in the PACU, and pain scores in Group R were found to be higher, confirming our study. In addition, in this study, although the need for antiemetics in the PACU in Group RN was found to be lower than in the other groups, the result was not notable. Although studies have shown that acute opioid tolerance develops at remifentanil infusion rates above 0.25 µg/kg/min, with reduced pain, pressure, cold or mechanical thresholds, a wider range of hyperalgesia, and an increase in postoperative opioid requirements at infusion rates exceeding 0.2 µg/kg/min, it is difficult to determine the optimal remifentanil dose range. Another study evaluated strategies such as gradual opioid reduction, opioid rotation, detoxification, multimodal analgesia, and the combination of adjuvants to mitigate or prevent opioid-induced hyperalgesia [16]. In our study, we concluded that the combination of remifentanil and nicardipine may be clinically advantageous in terms of preventing remifentanil-induced hyperalgesia.

Research has demonstrated that opioid-free anesthesia protocols reduce post-surgical opioid consumption and are associated with a lower risk of post-surgical nausea and vomiting [17-19]. In our study, postoperative nausea and vomiting values were notably greater in Group R compared to Group RN, consistent with the literature. In Group RN, the remifentanil infusion dose was halved to avoid these opioid-related side effects.

Conclusion

Although remifentanil is a widely used agent for controlled hypotension (CH), undesirable effects such as bradycardia, postoperative nausea/vomiting, and hyperalgesia—which increase with the consumption of excess doses alone—may significantly limit its use. The search for alternative drugs or drug combinations to overcome these limitations is ongoing. In this study, the combination of nicardipine and remifentanil was more successful in maintaining stable CH, preventing bradycardia, reducing bleeding, and improving endoscopic surgical field visibility in FESS cases. Additionally, postoperative nausea, vomiting, and pain scores were lower in the nicardipine/remifentanil group, suggesting that this combination may be an advantageous alternative in many ways. Further studies on drug combinations are needed to find the ideal controlled hypotension agents that will provide the desired level of surgical field clarity with minimal side effects.

Ethics Committee Approval

Ethical approval was obtained for this study from the Malatya Clinical Research Ethics Committee (Decision no: 2023/05).

References

1. Mackay IS. Endoscopic sinus surgery. *Ann Acad Med Singapore.* 1991 Sep;20(5):690–5. PMID: 1781657.
2. Maran AG. Endoscopic sinus surgery. *Eur Arch Otorhinolaryngol.* 1994;251(6):309–18. https://doi.org/10.1007/BF00171536.
3. Baradaranfar MH, Dadgarnia MH, Mahmoudi H, Behniafard N, Atighechi S, Zand V, et al. The Effect of Topical TranexamicAcid on Bleeding Reduction during Functional Endoscopic Sinus Surgery. *Iran J Otorhinolaryngol.* 2017 Mar;29(91):69–74. PMID: 28393053.
4. Brunner JP, Levy JM, Ada ML, Tipirneni KE, Barham HP, Oakley GM, et al. Total intravenous anesthesia improves intraoperative visualization during surgery for high-grade chronicrhinosinusitis: a double-blindrandomized controlled trial. *Int Forum AllergyRhinol.* 2018 Oct;8(10):1114–22. https://doi.org/10.1002/alr.22173.
5. Parvizi A, Haddadi S, Faghih Habibi A, Nemati S, Akhtar N, Ramezani H. Dexmedetomidine Efficacy in Quality of Surgical Field During Endoscopic Sinus Surgery. *Iran J Otorhinolaryngol.* 2019 Sep;31(106):281–8. PMID: 31598495.
6. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodiumnitroprusside- and esmolol-induced controlled hypotension for functional endoscopic sinus surgery. *Can Anesth.* 1995 May;42(5 Pt 1):373–6. https://doi.org/10.1007/BF03015479.
7. Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia.* 2019;74(6):793–800. https://doi.org/10.1111/anae.14657.
8. Lambert CR, Hill JA, Nichols WW, Feldman RL, Pepine CJ. Coronary and systemic hemodynamic effects of nicardipine. *Am J Cardiol.* 1985 Mar 1;55(6):652–6. https://doi.org/10.1016/0002-9149(85)90130-4.
9. Frishman WH. New therapeuticmodalities in hypertension: focus on a new calcium antagonist-nicardipine. *J ClinPharmacol.* 1989 Jun;29(6):481–7. https://doi.org/10.1002/j.1552-4604.1989.tb03368.x.
10. Shin S, Lee JW, Kim SH, Jung YS, Oh YJ. Heart rate variability dynamics during controlled hypotension with nicardipine, remifentanil and dexmedetomidine. *Acta Anaesthesiol Scand.* 2014 Feb;58(2):168–76. https://doi.org/10.1111/aas.12233.
11. Won YJ, Lim BG, Yeo GE, Lee MK, Lee DK, Kim H, et al. The effect of nicardipine on the surgical pleth index during thyroidectomy under general anesthesia: A prospective double-blind randomized controlled trial. *Medicine (Baltimore).* 2017 Feb;96(6):e6154. https://doi.org/10.1097/md.0000000000006154.
12. Tobias JD, Hersey S, Mencio GA, Green NE. Nicardipine for Controlled Hypotension During Spinal Surgery. *J Pediatr Orthop.* 1996 Jun;16(3):370. https://doi.org/10.1097/00004694-199605000-00015.
13. Ahn HJ, Chung SK, Dhong HJ, Kim HY, Ahn JH, Lee SM, et al. Comparison of surgical conditions during propofol or sevoflurane anaesthesia for endoscopic sinus surgery. *Br J Anaesth.* 2008 Jan 1;100(1):50–4. https://doi.org/10.1093/bja/aem304.
14. Wormald PJ, vanRenen G, Perks J, Jones JA, Langton-Hewer CD. The effect of the total intravenous anesthesia compared with inhalational anesthesia on the surgical field during endoscopic sinus surgery. *Am J Rhinol.* 2005 Sep-Oct;19(5):514-20. PMID: 16270608.
15. Kim JY, Song SH, Cho JH, Cho HR. Comparison of clinical efficacy among remifentanil, nicardipine, and remifentanil plus nicardipine continuous infusion for hypotensive anesthesia during arthroscopic shoulder surgery. *J OrthopSurg Hong Kong.* 2017;25(2):2309499017716251. https://doi.org/10.1177/2309499017716251.
16. Yu EHY, Tran DHD, Lam SW, Irwin MG. Remifentanil tolerance and hyperalgesia: short-termgain, long-termpain? *Anaesthesia.* 2016;71(11):1347–62. https://doi.org/10.1111/anae.13602.
17. Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. *J ClinAnesth.* 2006 Feb;18(1):24–8. https://doi.org/10.1016/j.jclinane.2005.05.009.
18. Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanil in postoperative pain control after spinal surgery: a randomized controlled study. *BMC Anesthesiol.* 2015;15:21. https://doi.org/10.1186/s12871-015-0004-1.
19. Ziemann-Gimmel P, Goldfarb AA, Koppman J, Marema RT. Opioid-free total intravenous anaesthesia reduces postoperative nausea and vomiting in bariatric surgery beyond triple prophylaxis. *Br J Anaesth.* 2014 May;112(5):906–11. https://doi.org/10.1093/bja/aet551.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Association between serum vitamin D levels and prostate cancer: A cross-sectional analysis

Ahmet Yuce[a,*], Erdal Benli[a], Ahmet Anil Acet[a], Abdullah Cirakoglu[a], Mevlut Keles[a], Ayhan Arslan[a]

[a] *Ordu University, Faculty of Medicine, Department of Urology, Ordu, Türkiye*

ARTICLE INFO

Keywords:
Prostate cancer
Vitamin D
Inflammation
Marker

Received: Nov 01, 2024
Accepted: Mar 04, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.11.233

Abstract

Aim: This study aims to examine whether inflammatory parameters such as vitamin D, CRP, and sedimentation measured in the serum of patients diagnosed with prostate cancer are different from those of their healthy peers.

Materials and Methods: The results of 163 patients who applied to Ordu University Urology Clinic with a diagnosis of prostate cancer between December 2019 and December 2023 and 140 healthy men who applied for other reasons in the same period were examined. Vitamin D levels and inflammatory markers such as CRP and ESR were compared between groups.

Results: The age distribution of patients in the prostate cancer and control group was 66.9±8.6 and 61.8±7.6 years, respectively. The vitamin D levels were identified as 17.25 [9.18] (5.27 – 55) µg/L and 20.74 [7.98] (6.94 – 51.01) in the prostate cancer and control group, respectively (p=0.001). Additionally, inflammatory markers like CRP and ESR were identified to be high in the prostate cancer group (p<0.001).

Conclusion: The vitamin D levels measured in patients with prostate cancer diagnosis were reduced compared to the control group and inflammatory markers were found to be increased. There is insufficient evidence in the literature on vitamin D and cancer. Disruption of the oxidant-antioxidant balance due to the inflammatory microenvironment may lead to a decrease in compounds such as vitamin D and predisposition to prostate cancer.

Introduction

Prostate cancer (PCa) is the second most frequently diagnosed cancer in men worldwide [1]. 15–25% of men newly diagnosed with cancer are diagnosed with PCa [2]. The exact cause of this disease, other than age, genetic, and racial characteristics, is not fully known. PSA, discovered in the 1980s, and MRI, which has recently become available in the diagnosis of the disease, have revolutionized the diagnosis of the disease despite some shortcomings. However, the expected decrease in the mortality rate of PCa has not occurred and PCa-related mortality rates continue to increase [3]. As life expectancy increases worldwide, more men are expected to reach older in the coming days. The American Cancer Society reported that there will be 240 thousand new cases annually worldwide, and approximately 34 thousand newly diagnosed patients will die due to cancer [4]. In conclusion, PCa remains an important public health issue. For this reason, today, there is a great effort to reveal the causes responsible for the development of the disease or to detect some pathology that occurs during the development of the disease early. This is especially important in terms of monitoring risky patients and giving them recommendations for cancer prevention. Although the exact etiology of prostate cancer is unknown, important clues are accumulating on this subject. Significant evidence can be found in the literature indicating the involvement of an inflammatory process in the development or progression of the disease [5]. The most important evidence appears to come from pathological examination reports. In radical prostatectomy reports, there are often inflammatory findings accompanying cancer. The fact that this disease occurs especially in aging men indicates that a chronic process is effective. Some behaviors and habits that begin early in life, or the deficiency or excess of certain substances in the body, may contribute to this process. For example, the results of a previous study we conducted showed that a person's sexual behavior and the number of partners are associated with cancer, and inflammatory parameters are increased in cancer patients [6].

*Corresponding author:
Email address: ahmetyuce7@gmail.com (Ahmet Yuce)

One of the substances that attracts the most attention in recent studies is vitamin D. Vitamin D plays an important role in many essential cell functions in the human body, especially calcium and bone metabolism. In addition, it has been suggested that it may be associated with the development of some cancers, including PCa [7]. Studies have reported that vitamin D may be involved in the cancer development process through intracellular and extracellular pathways. Studies on this subject have reported that it may inhibit cancer development through its anti-angiogenesis, anti-inflammatory effects, and the immune system [8]. There are also study results to the contrary. For example, in the study conducted by Kim MH et al. in 2022, PCa patients had lower vitamin D levels, but no statistically significant difference was found [2]. Voutilainen et al. also confirmed the result of this study [9]. As a result, today, the relationship between vitamin D and PCa has not been clearly established. For this reason, no recommendations are made regarding vitamin D in the EAU or AUA guidelines, and studies on this subject are ongoing.

This study aims to examine whether inflammatory parameters such as vitamin D, CRP, and sedimentation measured in the serum of patients diagnosed with prostate cancer are different from those of their healthy peers.

Materials and Methods

Study design and patients

This study was conducted at Ordu University Faculty of Medicine Urology Clinic. Permission for the study was obtained from the local ethics committee (No: 2023/278). Between December 2019 and December 2023, 163 patients with elevated PSA and diagnosed with prostate cancer as a result of prostate biopsy and 140 healthy people who applied for other reasons in the same period were included in the study. Study data were recorded prospectively by an expert in this field. The serum samples of the patients were taken in the morning at the first admission, after a 10-hour fast. In patients with a PSA value of ≥4 ng/mL, the elevation in PSA values was confirmed 2 - 4 weeks after benign causes were excluded. Patients with a PSA value of ≥4 ng/mL were subjected to a 12-quadrant systemic biopsy under transrectal ultrasound guidance after necessary information and written consent. Male patients with serum total PSA value <2.5 ng/mL were recorded for the control group.

Male patients diagnosed with prostate cancer, not receiving vitamin D or calcium treatment, and without any known bone disease were included in the study. Patients for whom pathology results could not be obtained, patients whose pathology results did not clearly indicate malignancy such as PIN, ASAP, prostatitis, patients with a known bone disease, those taking vitamin D externally, or those using medications that could affect vitamin D metabolism were excluded from the study. Demographic characteristics of the patients, such as age, BMI, and comorbidities, were recorded. In addition, accessible data such as serum total PSA, vitamin D, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), which could be determined at the time of admission to the clinic, were recorded.

Statistical analysis

The SPSS 20.0 package (Statistical Package for the Social Sciences, Version 20.0 SPSS Inc. Illinois, USA) was used to analyze the data. For the simplest within-group and between-group comparisons, approximately n=220 (110+110) was needed at alpha=0.05 and the effect size was determined for statistical power of 0.95 (Sample size was obtained using GPower 3.1 software). Arithmetic mean ± standard deviation, median (1st Quarter-3rd Quarter), minimum and maximum values were used to summarize numerical data, and numbers and percentages were used to summarize categorical data. The suitability of the data for normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogrorov-Smirnov/Shapiro-Wilk tests). Relationships between categorical data were evaluated with the Chi-square test. To evaluate the relationship between numerical data determined to be not normally distributed and categorical data, the Mann-Whitney U test was used if the categorical data was in two categories. Correlation between values was done using Spearman's rank correlation coefficient. Situations with $p<0.05$ were considered statistically significant.

Results

A total of 303 patients, 163 diagnosed with prostate cancer and 140 patients as the control group, were enrolled in this study. The mean age (mean ± Std) of prostate cancer patients was 66.92±8.67 years, and the control group was 61.8±7.68 years ($p<0.001$). The BMI distribution of the groups was 27.27±12.89 and 27.73±6.56, respectively ($p<0.001$) (Table 1). Laboratory parameters are shown as mean ± Std for normal distribution and median [IQR] (min–max) for non-normal distribution. The PSA value was 9.09 [67.76] (4.12 – 706.7) ng/mL in the PCa group and 0.895 [1.04] (0.13 – 2.49) ng/mL in the control group ($p<0.001$). The median values of the groups in terms of

Table 1. PCa and Control Group characteristics and serum values.

	Groups		
	PCa Group	Control Group	p
Age[a]	66.92±8.67	61.80±7.68	<0.001***
BMI[a]	27.27±12.89	27.73±6.56	<0.001***
PSA (ng/mL)[b]	9.09 [67.76]	0.895 [1.04]	<0.001***
Testosterone (ng/dL)[b]	4.79 [2.59]	5.865 [3.17]	0.012*
Sedimentation (min)[b]	19.7 [19]	16.2 [11.25]	<0.001***
CRP (mg/L)[b]	0.27 [0.48]	0.135 [0.24]	<0.001***
Calcium (mg/dL)[b]	9.5 [0.7]	9.6 [0.8]	0.024*

[a]: mean ± SD, [b]: median [IQR]. *:<0.05, ***:<0.001

Table 2. Vitamin D Mann-Whitney U Test with groups.

Groups	n	Median	Mean Rank	u	p
PCa	163	17.25	164.14	8.321	0.001*
Control	140	20.74	131.53		

The median value of serum 25-Hydroxy Vitamin D level was 20.74 µg/L in the control group and 17.25 µg/L in the PCa group (p=0.001). *:<0.05, ***:<0.001.

Table 3. PSA Level and Vitamin D Level Spearman Correlation test.

Groups	n	r	p
Vitamin D Level PSA Level	303	-0.166	0.005*

According to the results to determine the relationship between the patients' serum 25-Hydroxy Vitamin D levels and serum total PSA levels, there is a negative linear relationship between 25-Hydroxy Vitamin D levels and serum total PSA levels (r = -0.166, p = 0.005).

r-value	Linear Relationship Size
Up to 0.30	Small (weak correlation)
Between 0.30 -0.70	Moderate (moderate correlation)
Greater than 0.70	Large (strong correlation)

*:<0.05, ***:<0.001.

total testosterone were determined as 4.79 [2.59] (0.23 – 10.47) ng/dL in PCa patients and 5.865 [3.17] (1.53 – 13.9) ng/dL in the control group (p = 0.012). The distribution of calcium value according to groups was determined as 9.5 [0.7] (5.5 – 10.6) mg/dL and 9.6 [0.8] (8.8 – 11.9) mg/dL for the PCa and control groups, respectively (p = 0.024) (Table 1).

When the groups were compared in terms of inflammatory markers measured in serum, the sedimentation rate was 19.7 [19] (1 – 78) min and 16.2 [11.25] (1 – 49) min for the prostate cancer and control groups, respectively (p<0.001). Likewise, the distribution of the groups for CRP was determined as 0.27 [0.48] (0.00 – 21) mg/L and 0.135 [0.24] (0.00 – 3.78) mg/L, respectively (p<0.001) (Table 1).

The median value of serum 25-Hydroxy Vitamin D level was 20.74 [7.98] (6.94 – 51.01) µg/L in the control group and 17.25 [9.18] (5.27 – 55) µg/L in the PCa group (p=0.001) (Table 2). A negative linear relationship exists between the groups' vitamin D levels and serum total PSA levels (r = -166, p = 0.005) (Table 3).

Discussion

Despite advances in the diagnosis and surgical treatment of prostate cancer, the expected improvements in morbidity and mortality have not occurred. Today, many patients and their families continue to be affected by this disease. There are intense efforts to identify the factors that cause the onset and development of this disease or to detect the markers that appear in the early stages of the disease. This issue is important in terms of preventing the disease and making recommendations to patients at risk. This study was designed by retrospectively examining prospectively recorded data to investigate the relationship between vitamin D and inflammatory parameters and prostate cancer. As a result of the study, it was determined that the vitamin D value measured in the serum of patients diagnosed with PCa was decreased compared to their healthy peers. In addition, the increase in CRP and sedimentation values measured in serum detected the presence of an inflammatory background in cancer patients. When these results are evaluated together, it appears that there may be a relationship between vitamin D and cancer. The reason for the decrease in vitamin D in prostate cancer patients may be its use as an antioxidant substance consumed in the inflammatory environment. It is thought that there is an increased inflammatory response in cancer patients, in which the oxidant-antioxidant balance is disrupted in favor of the oxidant and vitamin D decreases in this environment.

The number of men reaching older ages is increasing in developed countries. This means more men are diagnosed with prostate cancer [10]. In our study, the average age of the cancer group was 66.92 years, and the age of the cancer patients was approximately five years older than the control group. This cancer remains a significant public health problem affecting all societies. There is a great effort to prevent this disease in developed countries. Studies have provided important evidence, such as age, genetics, and racial characteristics related to PCa, but the exact cause of the disease has not been understood [11]. Today, diagnosis and surgical techniques have recorded the greatest successes regarding this disease. There is no recommendation to be given, especially to patients at risk for PCa, and the guidelines are silent on this issue.

A careful review of the literature reveals an important relationship between PCa and a chronic inflammatory process. The fact that the prostate is open to the outside world through the urethra makes it a particularly vulnerable target for infectious agents. For example, a sexually transmitted microorganism can settle in the prostate tissue and initiate a chronic inflammatory process. In a study on this subject, Cohen and his colleagues demonstrated the presence of P. Acne in the pathological specimens of prostate cancer patients. Additionally, the presence of significant inflammation along with cancer has been reported in patients carrying this agent [12]. The results of a previous study we conducted also support these data. In this study, we found that there is a relationship between sexual behaviors and prostate cancer. It has been shown that inflammatory parameters such as CRP and NLR measured in the serum of patients with PCa are increased compared to the control group [6]. There may be many reasons for the development of cancer in a chronic inflammatory environment. For example, the oxidative environment resulting from the arrival of many immune system cells, such as macrophages and lymphocytes, in this environment and the secretion of many pro-inflammatory substances, such as cytokines, may be the reason for this. This oxidative environment is unsuitable for normal cell physiology, resulting in cell death and apoptosis. Cell proliferation increases to replace destroyed cells. This accelerated cell regeneration may cause some cells to get out of control and gain immortality [13]. Additionally, oxidative stress resulting from this inflammatory process may initiate or affect the oncogenic process by causing DNA damage [14]. Studies have shown that inflammatory cells such as macrophages accompany cancerous tissue in cancers seen in humans and rats [15]. It has been shown that PSA values decrease in some PCa patients using acetylsalicylic acid and NSAID [16]. The results of this study presented also support these data. Compared to the control group, inflammatory markers such as CRP and ESR measured in the serum of prostate cancer patients were

observed to increase. When these results and the data in the literature are considered together, it is understood that an inflammatory environment is effective in the development of PCa. There are other cancers that develop on a chronic inflammatory basis, such as thyroid cancer, cervical cancer, and urothelial cancer. Some authors even thought that cancer could be prevented by eliminating this inflammatory environment. NSAIDs have been used to reduce the incidence of cancer [17]. In conclusion, there is serious evidence showing that there is a close relationship between an inflammatory environment that occurs for various reasons and the development of many cancers, such as prostate cancer.

Vitamin D, which plays an important role in many cellular functions such as calcium and bone metabolism, has recently been extensively studied in the literature, especially regarding cancer. Its association with many cancers, such as breast, colon, rectum, stomach, and esophagus, has been reported [18]. Likewise, its relationship with prostate cancer was also examined. One of the first studies on this subject examined the effect of vitamin D on normal, benign, and cancerous prostate cell cultures. As a result of the study, it was reported that vitamin D irreversibly inhibited epithelial cells and that the prostate cell inhibition effect of vitamin D could be used for treatment purposes [19]. Although the relationship between vitamin D and cancer has not been definitively established, significant evidence exists on this subject. This effect is thought to occur through many different pathways, such as cell differentiation inhibition, apoptosis induction, cellular proliferation, and angiogenesis [20]. What most studies have in common is its inhibitory effect on the inflammatory process. In a study on this subject, Gupta reported that vitamin D is effective in prostate cancer by inhibiting some pathways that play a role in inflammation, such as the production of inflammatory cytokines and inhibition of nuclear factor κB (NF-κB) signaling [21]. Selective COX-2 inhibitor NSAIDs, such as celecoxib, have been shown to suppress PCa in the TRAMP PCa model [22]. In another study, Kim et al. showed in a multivariate analysis that the incidence of clinically significant prostate cancer was significantly increased in people with low vitamin D levels [2]. The effect of vitamin D on some precancerous lesions known for prostate cancer was also examined. In an interesting study on this subject, the effect of vitamin D on PIN, considered a precancerous lesion, was examined. In this experimental model, vitamin D slowed or prevented the progression of PIN to cancer [23]. Some studies examined the effect of vitamin D on PSA in patients diagnosed with cancer. In one of these studies, Campbell et al. started vitamin D in patients with PCa who were followed up with active surveillance. Compared to the baseline, as the vitamin D levels of the patients increased, their PSA values decreased [24]. Our study found a negative relationship between vitamin D value and PSA. This decrease is significant, considering the importance of PSA in the follow-up and prognosis of cancer patients.

There are also some studies reporting that there is no relationship between vitamin D and prostate cancer. In a study on this subject, Voutilainen et al. examined the relationship between vitamin D and lung and prostate cancer. As a result of the study, they did not find any relationship [9]. However, there are not enough studies in the literature to support these results. This may be related to the shortcomings of the studies.

There is confusion about vitamin D in the literature, and there may be many reasons for this. Especially the retrospective planning of the studies and the lack of data on inflammatory parameters feed this problem. Our study provides important information to the literature in this field by prospectively recording the data and including inflammatory parameters such as CRP and ESR. As a result of the study, it was shown that the vitamin D value measured in the serum of prostate cancer patients decreased compared to the control group, and inflammatory markers such as CRP and ESR increased. In conclusion, vitamin D seems to be related to cancer with its anti-inflammatory effect on the immune system [25]. The increased inflammatory environment in patients with prostate cancer may cause the oxidant-antioxidant balance to deteriorate and antioxidant compounds to decrease. It is known that some antioxidant compounds are reduced in the increased inflammatory environment in patients with PCa [26]. Vitamin D may also be an anti-inflammatory or antioxidant substance consumed in this environment.

Limitations

The study has some problems, such as not being double-blind and reflecting the results of a single center. According to our study results, although a correlation with vitamin D was found, it was found to be quite weak. For this reason, randomized and multicenter studies are needed on this subject. However, there are features that make the study strong, such as its prospective design and the study of inflammatory parameters, unlike many previous studies. We think it will shed light on the confusion about vitamin D in the literature.

Conclusion

There are major efforts to discover various markers that occur during the development of prostate cancer. These studies are very important in terms of recommendations or treatments for patients. In our study results, it was determined that vitamin D levels decreased compared to the control group. In addition, the presence of an inflammatory environment in prostate cancer patients was demonstrated by CRP and ESR measured in serum. When the study results are evaluated together, vitamin D may be reduced as a protector against cancer development and as an antioxidant substance in the inflammatory environment created by cancer cells. As a result, it was determined that low vitamin D level may be a risk factor for prostate cancer. We think that risky people should be followed up early and the deficiency should be replaced.

Ethics Committee Approval

This study was conducted at Ordu University Faculty of Medicine Urology Clinic. Permission for the study was obtained from the local ethics committee (No: 2023/278).

References

1. Al-Ghazawi M, Salameh H, Amo-Afful S, et al. An In-Depth Look Into the Epidemiological and Etiological Aspects of Prostate Cancer: A Literature Review. *Cureus.* 2023;15(11):e48252. DOI: 10.7759/cureus.48252.
2. Kim MH, Yoo S, Choo MS, et al. The role of the serum 25-OH vitamin D level on detecting prostate cancer in men with elevated prostate-specific antigen levels. *Sci Rep.* 2022;12(1):14089. DOI: 10.1038/s41598-022-17563-8.
3. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. *CA Cancer J Clin.* 2024;74(1):12-49. DOI: 10.3322/caac.21820.
4. Creighton CJ, Zhang F, Zhang Y, et al. Comparative and integrative analysis of transcriptomic and epigenomic-wide DNA methylation changes in African American prostate cancer. *Epigenetics.* 2023;18(1):2180585. DOI: 10.1080/15592294.2023.2180585.
5. Benli E, Cirakoglu A, Ayyıldız SN, Yüce A. Comparison of serum uric acid levels between prostate cancer patients and a control group. *Cent European J Urol.* 2018;71(2):242-47. DOI: 10.5173/ceju.2018.1619.
6. Benli E, Yuce A, Cirakoglu A, et al. Comparison of Sexual Behavior and Inflammatory Parameters in Prostate Cancer Patients with Control Group: Prospective Controlled Study. *Urol J.* 2021;19(2):101-05. DOI: 10.22037/uj.v18i.6464.
7. Stroomberg HV, Vojdeman FJ, Madsen CM, et al. Vitamin D levels and the risk of prostate cancer and prostate cancer mortality. *Acta Oncol.* 2021;60(3):316-22. DOI: 10.1080/0284186X.2020.1837391.
8. Wang L, Wang C, Wang J, et al. Longitudinal, observational study on associations between postoperative nutritional vitamin D supplementation and clinical outcomes in esophageal cancer patients undergoing esophagectomy. *Sci Rep.* 2016;6:38962. DOI: 10.1038/srep38962.
9. Voutilainen A, Virtanen JK, Hantunen S, et al. Multiplicative, additive, and interactive associations of 25-hydroxyvitamin D with lung and prostate cancer. *Int J Vitam Nutr Res.* 2024;94(2):133-42. DOI: 10.1024/0300-9831/a000780.
10. Schwartz SM. Epidemiology of Cancer. Clin Chem. 2024;70(1):140-49. DOI: 10.1093/clinchem/hvad202.
11. Cui H, Zhang W, Zhang L, et al. Risk factors for prostate cancer: An umbrella review of prospective observational studies and mendelian randomization analyses. *PLoS Med.* 2024;21(3):e1004362. DOI: 10.1371/journal.pmed.1004362.
12. Cohen RJ, Shannon BA, McNeal JE, et al. Propionibacterium acnes associated with inflammation in radical prostatectomy specimens: a possible link to cancer evolution? *J Urol.* 2005;173(6):1969-74. DOI: 10.1097/01.ju.0000158161.15277.78.
13. Ge M, Papagiannakopoulos T, Bar-Peled L. Reductive stress in cancer: coming out of the shadows. *Trends Cancer.* 2024;10(2):103-12. DOI: 10.1016/j.trecan.2023.10.002.
14. Iqbal MJ, Kabeer A, Abbas Z, et al. Interplay of oxidative stress, cellular communication and signaling pathways in cancer. *Cell Commun Signal.* 2024;22(1):7. DOI: 10.1186/s12964-023-01398-5.
15. Rasheed RA, Sadek AS, Khattab RT, et al. Diacerein provokes apoptosis, improves redox balance, and downregulates PCNA and TNF-α in a rat model of testosterone-induced benign prostatic hyperplasia: A new non-invasive approach. *PLoS One.* 2023;18(11):e0293682. DOI: 10.1371/journal.pone.0293682.
16. Fowke JH, Motley SS, Smith JA Jr, et al. Association of nonsteroidal anti-inflammatory drugs, prostate specific antigen and prostate volume. *J Urol.* 2009;181(5):2064-70. DOI: 10.1016/j.juro.2009.01.031.
17. Kolawole OR, Kashfi K. NSAIDs and Cancer Resolution: New Paradigms beyond Cyclooxygenase. *Int J Mol Sci.* 2022;23(3):1432. DOI: 10.3390/ijms23031432.
18. Sobhi P, Bahrami M, Mahdizadeh F, et al. Vitamin D and potential effects on cancers: a review. *Mol Biol Rep.* 2024;51:190. DOI: 10.1007/s11033-023-09111-y.
19. Erzurumlu Y, Aydogdu E, Dogan HK, et al. 1,25(OH)2 D3 induced vitamin D receptor signaling negatively regulates endoplasmic reticulum-associated degradation (ERAD) and androgen receptor signaling in human prostate cancer cells. *Cell Signal.* 2023;103:110577. DOI: 10.1016/j.cellsig.2022.110577.
20. Hendrickson WK, Flavin R, Kasperzyk JL, et al. Vitamin D receptor protein expression in tumor tissue and prostate cancer progression. J Clin Oncol. 2011;29(17):2378-85. DOI: 10.1200/JCO.2010.30.9880.
21. Gupta S. Prostate cancer chemoprevention: current status and future prospects. *Toxicol Appl Pharmacol.* 2007;224(3):369-76. DOI: 10.1016/j.taap.2006.11.008.
22. Kido LA, Montico F, Sauce R, et al. Anti-inflammatory therapies in TRAMP mice: delay in PCa progression. *Endocr Relat Cancer.* 2016;23(4):235-50. DOI: 10.1530/ERC-15-0540.
23. Abu El Maaty MA, Grelet E, Keime C, et al. Single-cell analyses unravel cell type-specific responses to a vitamin D analog in prostatic precancerous lesions. *Sci Adv.* 2021;7(31):eabg5982. DOI: 10.1126/sciadv.abg5982.
24. Campbell RA, Li J, Malone L, Levy DA. Correlative Analysis of Vitamin D and Omega-3 Fatty Acid Intake in Men on Active Surveillance for Prostate Cancer. *Urology.* 2021;155:110-16. DOI: 10.1016/j.urology.2021.04.050.
25. Ao T, Kikuta J, Ishii M. The Effects of Vitamin D on Immune System and Inflammatory Diseases. *Biomolecules.* 2021;11(11):1624. DOI: 10.3390/biom11111624.
26. Jiang J, Chen B, Tang B, Wei Q. Selenium in Prostate Cancer: Prevention, Progression, and Treatment. *Pharmaceuticals (Basel).* 2023;16(9):1250. DOI: 10.3390/ph16091250.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Disruption of kinesthesia and position sense in the ankle joint is an independent predictor of falls in elderly patients undergoing hemodialysis

Nihal Sumeyye Ulutas[a], Recep Bentli[b], Ilhami Berber[b], Ozkan Ulutas[b,*]

[a] *Malatya Turgut Ozal University, Faculty of Medicine, Department of Anatomy, Malatya, Türkiye*
[b] *Inonu University, Faculty of Medicine, Department of Internal Medicine, Malatya, Türkiye*

ARTICLE INFO

Keywords:
Kinesthetic position sense
Falls
Hemodialysis
Elderly

Received: Dec 22, 2023
Accepted: Mar 04, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2023.12.342

Abstract

Aim: Patients receiving HD are more prone to accidental falls than elderly individuals not undergoing HD, leading to higher morbidity and mortality in this group. In this study, we hypothesized that senior HD patients with a history of falls may have impaired ankle kinesthetic position sense.

Materials and Methods: This study included 63 hemodialysis patients aged 65 and older. Baseline Timed Up and Go (TUG) test durations and ankle joint inclinometric deviation measurements were assessed in all participants, who were then monitored for fall events over a 12-month period. Patients who experienced one or more falls were classified as the faller group, while the rest were categorized as the non-faller group. Demographic data, laboratory values, TUG test durations, and ankle joint inclinometric deviations were compared between the two groups.

Results: Among the 63 patients, 25 (39.7%) were classified as fallers. The mean inclinometric deviation for the entire study population was 4.1±1.9 degrees. Notably, patients in the faller group had a significantly higher deviation (5.5±1.9) compared to those in the non-faller group (3.1±1.2, p=0.000). Age, serum albumin levels, TUG test duration, inclinometric deviation of patients have been included in the logistic regression analysis. Of these parameters, only inclinometric deviation (OR=2.627, p=0.003) was determined as an independent predictor of falls.

Conclusion: Falls are prevalent among elderly hemodialysis patients, and impairment of ankle kinesthetic position sense is evident in those who have experienced falls.

Introduction

As the number of elderly patients undergoing hemodialysis (HD) in recent years continues to rise, the number of the geriatric complaints experienced by these patients also increases. Patients maintained on HD have numerous functional and cognitive problems leading to frailty of these patients and, consequently, causing increase in mortality, hospital admissions and dialysis-related complications. A major issue that arises with aging involves accidental falls [1]. The aging process contributes to gait and balance impairments, diminished postural reflexes, neurosensory disorders, neurological and cardiovascular comorbidities, osteoarthritis, and reduced muscle strength [2]. In hemodialysis patients, the risk of falling is heightened due to dialysis-related factors, underlying causes of end-stage renal failure, and declining kidney function [3]. Compared to elderly individuals not on hemodialysis, HD patients experience a higher incidence of accidental falls, leading to increased morbidity and mortality in this population [4].

Functional mobility was assessed through the Timed Up and Go (TUG) test. Kinesthesia and position sense are components of proprioception and consciously or unconsciously effective on balance, as it senses lower extremity movements and the position of the joints [5]. In normal ambulation, ankle dorsiflexion is about 10 degrees and sensed by proprioceptors [6]. In this study, we investigated whether basal TUG test durations and ankle joint inclinometric deviation representing disruption in proprioceptive sensation differ in fallers and non-fallers.

Materials and Methods

This study aims to reveal that ankle kinesthetic position sense may be impaired in hemodialysis patients older than 65 years. Based on a theoretical power analysis conducted

*Corresponding author:
Email address: drozkanulutas@yahoo.com (Ozkan Ulutas)

using the G*Power 3.1 program, a minimum sample size of 50 patients (25 per group) was required to detect a significant difference between the two groups using an independent two-sample t-test. This calculation was performed with a Type I error rate (alpha) of 0.05, a test power (1-beta) of 0.80, an effect size of 0.81 (large effect), an alternative hypothesis (H1) assuming a two-tailed distribution, and a group allocation ratio of 1:1 [7]. All patients aged 65 years or older undergoing outpatient hemodialysis at Malatya Education and Research Hospital were eligible for inclusion in the study. Patients were excluded if they were unable or unwilling to provide informed consent. Additionally, individuals with amputations or those using a wheelchair were not included.

Sixty-three patients on hemodialysis aged 65 or more included to the present study. Approval for the ethics of the study was granted by the Malatya Regional Research Ethics Board (File No. 2018/162).

Medical history, cause of ESKD, and laboratory values were obtained from electronic computer records. Patients' TUG test and ankle joint inclinometric measurements were performed at the beginning of the study and noted. TUG tests and inclinometric measurements were done before the HD session. Fall is defined as, unintentionally coming to rest on the ground, floor, or other lower level [8]. All patients were questioned for falling events every Mondays and Tuesdays during the study period. Those who fell at least once during the study period were considered as fallers. Laboratory values, inclinometric deviations and TUG test durations of fallers and non-fallers were compared.

Kinesthesia and position sense of the ankle was measured using a simple digital inclinometer instrument on the dominant side. While the patients were in supine position, and their eyes were closed, their ankles were brought to 10 degrees of dorsiflexion by the help of study nurse. Afterwards, the patients were asked to come back to the starting point, and actively return to the set angle 3 times without help [5] (Figure 1). All patient attempts were recorded, and the deviation of the error angle from the set angle was used as the outcome measure. The test result was determined as the average of three recorded values.

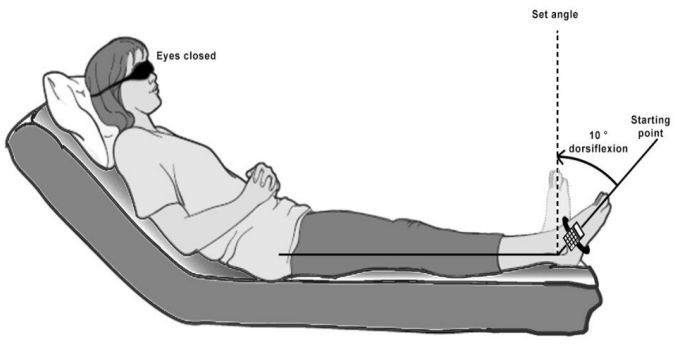

Figure 1. Inclinometric measurement of ankles.

In the TUG test, participants were instructed to rise from a chair, walk 3 meters, and return to a seated position. The completion time was recorded, with scores below 10 seconds considered normal. Patients scoring between 10–15 seconds were classified as having 'slowed mobility,' while those exceeding 15 seconds were categorized as having 'impaired mobility' [9].

Descriptive data were presented as mean and standard deviation (SD) or median and quartiles for continuous variables, as appropriate, and as frequency for ordinal or nominal data. The normality of continuous variables was assessed using the Shapiro-Wilk test. Group differences were analyzed using either the Mann–Whitney U test or Student's t-test, depending on the distribution of the data. A logistic regression analysis was performed to determine the independent predictors of falls. All probability values were reported two tailed and p value <0.05 was considered statistically signifcant. Analyses were performed using IBM SPSS software (ver. 23.0; SPSS Inc., Chicago, IL, USA).

Results

Of the 63 patients included in the present study, 49.2% were male. Etiology of kidney disease was diabetes mellitus (DM) in 22 (34.9%), hypertension (HT) in 20 (31.7%), glomerulonephritis (GN) in 7 (11.1%), and other causes (polycystic kidney disease, amyloidosis, renovascular diseases, kidney stones, and postrenal diseases) in 6 (9.5%) of the patients. Renal disease was of unknown origin in 8 (12.7%) of the patients. Among 63 patients, 25 (39.7%) patients were fallers. Median predialysis medical treatment duration was 2 (0-240) months, and median HD therapy duration was 26 (3-217) months. Mean hemoglobin (Hg) concentration was 11.1±1.5 g/dL, mean creatinin (cre) level was 5.3±1.8 mg/dL, mean 25-Hydroxyvitamin D level was 19.8±16.1 ng/mL, and mean parathormone (PTH) level was 421.3±401.1 pg/mL in study population. Mean hemoglobin, creatinine, 25-Hydroxyvitamin D, and PTH levels were similar among fallers and non-fallers. Both faller (11, 10-14.3) and non-fallers (10.7, 9-12) had slowed mobility according to TUG times, However, fallers had significantly longer ($p=0.018$) test durations .

The mean age of the study population was 73.9±7.5 years, with a significantly higher mean age of 76.8±7.2 years in the faller group ($p=0.003$). Serum albumin concentration was notably lower in the faller group, averaging 3.3±0.4 g/dL ($p=0.018$). The mean inclinometric deviation for the overall study population was 4.1±1.9 degrees, which was significantly greater in the faller group (5.5±1.9 degrees) compared to the non-faller group (3.1±1.2 degrees, $p<0.001$) (Table 1).

In the univariate analysis, age, serum albumin levels, TUG test duration, and p values of patients' inclinometric deviation were lower than 0.05 and were included in the logistic regression analysis. Inclinometric deviation was obtained as an independent significant risk factor in both univariate and multivariate analyses. Although age, albumin and TUG duration were significant in the univariate analysis, they were not significant in the multivariate analysis. According to the univariate analysis, when the Inclinometric deviation value increases, the risk of falling increases by 3.17 times (OR = 3.167, $p<0.001$). On the other hand, according to the multivariate analysis, even when other variables (age, albumin, TUG duration, etc.) are controlled, the risk of falling increases by 2.63 times in individuals with high Inclinometric deviation (OR = 2.627, $p=0.003$). Therefore, as the Inclinometric deviation value increases

Table 1. Baseline characteristics of study population.

	Study population (n=63)	Fallers (n=25) (39.7%)	Non-Fallers (n=38) (60.3%)	P value
Age (years)	73.9±7.5	76.8±7.2	72±7.1	**0.003***
Sex (% of males)	31(49.2%)	11 (44%)	20 (52.6%)	0.680
Etiology				
DM	22 (34.9%)	10 (40%)	12 (31.6%)	
HT	20 (31.7%)	6 (24%)	14 (36.8%)	
GN	7 (11.1%)	3 (12%)	4 (10.5%)	0.813
Others	6 (9.5%)	2 (8%)	4 (10.5%)	
Unknown	8 (12.7%)	4 (16%)	4 (10.5%)	
Median duration of RRT in months (range)	26 (3-217)	23 (12-217)	36 (3-203)	0.246
Number of antihypertensive medication (range)	0 (0-2)	0 (0-2)	0 (0-2)	0.706
Mean creatinin level (mg/dL)	5.3±1.8	5.4±1.6	5.3±1.9	0.908
Hemoglobin (g/dL)	11.1±1.5	11.1±1	11±1.7	0.752
Albumin (g/dL)	3.4±0.4	3.3±0.4	3.5±0.3	**0.018***
25-Hydroxyvitamin D (ng/mL)	19.8±16.1	19±16.8	20.3±15.9	0.373
PTH (pg/mL)	421.3±401.1	413±398.7	426±388.8	0.385
Median TUG test time (sn)	10.8 (9-14.3)	10.7 (9-12)	11(10-14.3)	**0.018***
Inclinometric deviation (degree)	4.1±1.9	5.5±1.9	3.1±1.2	**<0.001***
Number of falls (range)	0 (0-10)	1 (1-10)	0 (0-0)	**<0.001***
Number of falls with fracture (range)	0 (0-2)	0 (0-2)	0 (0-0)	**<0.001***

DM: Diabetes Mellitus, HT: Hypertension, GN: Glomerulonephritis, PTH: Parathormone, TUG: Timed up and go test, RRT: Renal replacement therapy, NS: Not significant *: Statistically significant.

Table 2. Independent predictors of falls.

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.096 (1.016-1.183)	**0.003***	1.103 (0.993-1.225)	0.066
Albumin	0.162 (0.034-0.772)	**0.022***	0.110 (0.007-1.691)	0.113
TUG duration	2.364 (1.211-4.616)	**0.012***	2.195 (0.839-5.747)	0.109
Inclinometric deviation	3.167 (1.730-5.799)	**<0.001***	2.627 (1.382-4.993)	**0.003***

TUG: Timed up and go test, OR: Odds ratio, CI: Confidence Interval, *: Statistically significant.

in individuals who have fallen, the risk of falling increases significantly (Table 2).

Discussion

This study shows that in elderly HD patients, the frequency of falls is high, TUG test durations are longer, and increased inclinometric deviation of the ankle is an independent determinant of the risk of falling. This study is the first study, that demonstrates proprioceptive sensory loss in HD patients with simple inclinometric measurements and shows that inclinometric deviation increases more in falling patients and is an independent determinant of the risk of falling.

Among many geriatric problems, falls are associated with severe morbidity and mortality in elderly patients who undergo hemodialysis and who do not. In addition to the difficulties of aging, many additional risk factors trigger falls in hemodialysis patients. Neuropathies related to diabetes mellitus (DM), uremia or atherosclerosis in patients on HD are common. In addition to neuropathies, muscle and bone pain, muscle atrophies due to immobility, rapid electrolyte and hemodynamic changes due to HD session, and disruptions in the leukomotor system appear as additional risks in HD patients [10-11-12]. A retrospective study conducted by Cook and Jassal reported that while 27% of senior HD patients fell during the last one year, an additional another 16% fell during the previous year [13]. Roberts at al. demonstrated that, with a rate of 1.76 falls/patient year, 38% of HD patients fell within the one year period [14]. This rate was 1.60 falls/patient year in the study reported by Cook et al. [15]. In correlation with such prior studies, in the present study 39.7% of patients were fallers.

The dynamic balance and functional mobility of the pa-

tients included in the present study were assesed by means of TUG test. TUG test durations were significantly longer in fallers, and both fallers and non-fallers demonstrated slowed mobility. Zanotto et al. reported that falls were associated with longer duration of TUG tests and also showed that longer duration of TUG tests were independent predictors of falls in HD patients [16]. Nevertheless, TUG test durations were not independent predictors of falls in the logistic regression analyses of the present study.

Proprioception is defined as the perception of position and movement of the joints and the application of force in space [17-18]. Proprioceptive receptors and mechanoreceptors located on tendons, ligaments and joint capsules, percive the signals that are transmitted to central nervous system (CNS) via afferent sensory pathways and that ultimately culminate in the formation of proprioception. Signals from proprioceptive receptors and mechanoreceptors are integrated and processed in the CNS, and a response is sent to relevant tissues [19]. Maintaining balance, controlling body posture, and ensuring the stability of the body during static and dynamic activities are the main tasks of proprioception. If proprioception fails to function adequately, risk of falling increases [20]. The role of proprioception in falling is a topic that is mentioned very little in geriatric patient groups. Moreover, the role of proprioception in falling has never been studied in geriatric patients also receiving HD. Basic inclinometric deviation measurements of the ankle are indicative of proprioceptive sensation.

In the present study, inclinometric deviation of ankles was significantly higher in the falling group ($p<0.001$). In the logistic regression analysis, which included the patients' age, TUG test durations, ankle inclinometric deviation measurements, as well as albumin levels, high ankle inclinometric deviation appeared as the independent determinant of the falls (OR=2,627, p=0.003). The data obtained by the present study shows proprioceptive sensation is more impaired in fallers. There are many reasons for falls in HD patients. HD patients are prone to neuropathy due to etiological reasons and uremia-related causes. Diabetic polyneuropathy and uremic polyneuropathy are common in dialysis patients. In the present study, the number of patients diagnosed with diabetic nephropathy was 22 (34.9%). A comparison of the number of falls reported by patients diagnosed with diabetic nephropathy and the number of falls documented for patients suffering from nephropathy of other etiological causes, there was no significant difference in terms of the number of falls. Uremic polyneuropathy is a frequent finding and is demonstrated in more than 60% of chronic kidney disease patients [21]. Although the cause of uremic polyneuropathy is unknown, it is thought to be caused by thiamine, zinc and biotin deficiencies, or by the toxicity of middle molecular weight uremic toxins that are more difficult to remove by hemodialysis [22]. Uremic polyneuropathy is a distal symmetrical sensorymotor neuropathy. The afferent pathway of proprioception is also transmitted to CNS via sensory nerves. Proprioception pathways may be more affected in the falling group of HD patients. Although there are no studies showing receptor activities in HD patients, it is possible to hypothesize that mechanoreceptor and proprioceptive receptor activities in falling HD patients may be more impaired. We also do not know whether there are changes in the proprioceptive interpretation of the CNS in uremic patients.

Small study population is a limitation of our study. Performing EMG of patients would be helpful to demonstrate whether there were basal neuropathies. Comparing the patients with healthy controls would show the effect of uremia on proprioceptive sensation more clearly.

The present study also has some strengths. Firstly, it is important to note that this is the first study examining the relationship between proprioception and falls in hemodialysis patients. Additionally, the fact that all inclinometric measurements were made by the same study nurse is also of great significance. Finally, that both TUG tests and inclinometric measurements were performed 3 times and averages were accepted as test results adds to the strengths of the present study.

In summary, falls are common in elderly hemodialysis patients, and disruption of ankle proprioception is evident in HD patients who fell. Exercise programs for increasing the proprioceptive inflow may be beneficial to prevent subsequent falls.

Conflict of Interest

The authors declare that they have no conflicts of interest that are directly relevant to the content of this article.

Ethics Committee Approval

This study was conducted on human participants. The study was approved by the Malatya Regional Research Ethics Board, Malatya, Turkey. File number: 2018/162.

Informed Consent

Informed consent was obtained from all participants included in the study.

Explanation

The English in this document has been checked by at least two professional editors, both native speakers of English.

References

1. van Loon IN, Joosten H, Iyasere O, Johansson L, Hamaker ME, Brown EA. The prevalence and impact of falls in elderly dialysis patients: Frail elderly Patient Outcomes on Dialysis (FEPOD) study. *Arch Gerontol Geriatr.* 2019;83:285–291. doi:10.1016/j.archger.2019.05.015.
2. Plantinga LC, Patzer RE, Franch HA, Bowling CB. Serious Fall Injuries Before and After Initiation of Hemodialysis Among Older ESRD Patients in the United States: A Retrospective Cohort Study. *Am J Kidney Dis.* 2017;70(1):76–83. doi:10.1053/j.ajkd.2016.11.021.
3. Farragher J, Rajan T, Chiu E, et al. Equivalent Fall Risk in Elderly Patients on Hemodialysis and Peritoneal Dialysis. *Perit Dial Int.* 2016;36(1):67–70. doi:10.3747/pdi.2014.00163.
4. Farragher J, Chiu E, Ulutas O, Tomlinson G, Cook WL, Jassal SV. Accidental falls and risk of mortality among older adults on chronic peritoneal dialysis. *Clin J Am Soc Nephrol.* 2014;9(7):1248–1253. doi:10.2215/CJN.11001013.
5. Ha SY, Han JH, Sung YH. Effects of ankle strengthening exercise program on an unstable supporting surface on proprioception and balance in adults with functional ankle instability. *J Exerc Rehabil.* 2018;14(2):301–305. Published 2018 Apr 26. doi:10.12965/jer.1836082.041.

6. Weir J, Chockalingam N. Ankle joint dorsiflexion: Assessment of true values necessary for normal gait. *International Journal of Therapy and Rehabilitation.* Vol. 14, No. 2.76-82, https://doi.org/10.12968/ijtr.2007.14.2.23518.
7. Buchner A, Erdfelder E, Faul F, Lang A. G* Power 3.1 manual. Düsseldorf, Germany: Heinrich-Heine-Universitat Dusseldorf. 2017.
8. Buchner DM, Hornbrook MC, Kutner NG, et al. Development of the common data base for the FICSIT trials. *J Am Geriatr Soc.* 1993;41(3):297–308. doi:10.1111/j.1532-5415.1993.tb06708.x.
9. Botolfsen P, Helbostad JL, Moe-Nilssen R, Wall JC. Reliability and concurrent validity of the Expanded Timed Up-and-Go test in older people with impaired mobility. *Physiother Res Int.* 2008;13(2):94–106. doi:10.1002/pri.394.
10. Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int.* 2000;58(1):396–399. doi:10.1046/j.1523-1755.2000.00178.x
11. Soangra R, Lockhart TE, Lach J, Abdel-Rahman EM. Effects of hemodialysis therapy on sit-to-walk characteristics in end stage renal disease patients. *Ann Biomed Eng.* 2013;41(4):795–805. doi:10.1007/s10439-012-0701-6.
12. Erken E, Ozelsancak R, Sahin S, et al. The effect of hemodialysis on balance measurements and risk of fall. *Int Urol Nephrol.* 2016;48(10):1705–1711. doi:10.1007/s11255-016-1388-7.
13. Cook WL, Jassal SV. Prevalence of falls among seniors maintained on hemodialysis. Int Urol Nephrol. 2005;37(3):649–652. doi:10.1007/s11255-005-0396-9.
14. Roberts R, Jeffrey C, Carlisle G, Brierley E. Prospective investigation of the incidence of falls, dizziness and syncope in haemodialysis patients. *Int Urol Nephrol.* 2007;39(1):275–279. doi:10.1007/s11255-006-9088-3.
15. Cook WL, Tomlinson G, Donaldson M, et al. Falls and fall-related injuries in older dialysis patients. *Clin J Am Soc Nephrol.* 2006;1(6):1197–1204. doi:10.2215/CJN.01650506.
16. Zanotto T, Mercer TH, van der Linden ML, et al. The relative importance of frailty, physical and cardiovascular function as exercise-modifiable predictors of falls in haemodialysis patients: a prospective cohort study. *BMC Nephrol.* 2020;21(1):99. Published 2020 Mar 14. doi:10.1186/s12882-020-01759-z.
17. Westlake KP, Culham EG. Sensory-specific balance training in older adults: effect on proprioceptive reintegration and cognitive demands. Phys Ther. 2007;87(10):1274–1283. doi:10.2522/ptj.20060263.
18. Ribeiro F, Oliveira J. Aging effects on joint proprioception: the role of physical activity in proprioception preservation. Eur Rev Aging Phys Act. 2007; 4(2): 71-76. https://doi.org/10.1007/s11556-007-0026-x.
19. Myers JB, Lephart SM. The role of the sensorimotor system in the athletic shoulder. *J Athl Train.* 2000;35(3):351–363.
20. Ferlinc A, Fabiani E, Velnar T, Gradisnik L. The Importance and Role of Proprioception in the Elderly: a Short Review. Mater Sociomed. 2019;31(3):219–221. doi:10.5455/msm.2019.31.219-221.
21. Baumgaertel MW, Kraemer M, Berlit P. Neurologic complications of acute and chronic renal disease. *Handb Clin Neurol.* 2014;119:383–393. doi:10.1016/B978-0-7020-4086-3.00024-2.
22. Guolo M, Stella AM, Melito V, Parera V, Del C Batlle AM. Altered 5-aminolevulinic acid metabolism leading to pseudoporphyria in hemodialysed patients. *Int J Biochem Cell Biol.* 1996;28(3):311–317. doi:10.1016/1357-2725(95)00133-6.

Ann Med Res

Current issue list available at AnnMedRes

Annals of Medical Research

journal page: www.annalsmedres.org

Urethral stones and benign prostatic hyperplasia: Presentation of a rare case

Ahmet Alper Ozdes[a,*], Ridvan Canturk[b], Necip Pirincci[b]

[a] *Karakoçan State Hospital, Department of Urology, Elazığ, Türkiye*
[b] *Fırat University, Faculty of Medicine, Department of Urology, Elazığ, Türkiye*

ARTICLE INFO

Keywords:
Benign prostate hyperplasia
Urethra
Bladder
Stone
Surgery

Received: Dec 23, 2024
Accepted: Mar 07, 2025
Available Online: 25.03.2025

DOI:
10.5455/annalsmedres.2024.12.276

Abstract

An 86-year-old male patient presented with urinary incontinence, fever, weakness, and hematuria. Investigations revealed benign prostatic hyperplasia (BPH) with multiple bladder stones and several stones in both the anterior and posterior urethra, without causing acute urinary retention (AUR). During the same session, endoscopic urethral stone treatment, open transvesical prostatectomy, and cystolithotomy were performed. Benign prostatic hyperplasia and urethral stones can lead to acute urinary retention. However, in this case, the patient did not develop acute urinary retention despite having both benign prostatic hyperplasia and multiple urethral stones at the same time. This case demonstrates that multiple causes of urinary obstruction may coexist without resulting in AUR. It also highlights the feasibility of combining different surgical techniques in treatment. Factors such as the concomitant comorbidities, stone and prostate size and location, condition of the patient, and duration of the symptoms must be considered to establish an appropriate treatment strategy.

Introduction

Benign Prostatic Hyperplasia (BPH) is one of the most common causes of lower urinary tract symptoms in men, with its incidence increasing with age. It is diagnosed in approximately 30-40% of men during the fourth decade of life and its prevalence reaches nearly 70-80% in individuals over 80 years old [1]. BPH can lead to bladder outlet obstruction, resulting in urinary distension, bladder stones, and structural changes in the bladder and detrusor muscle, such as bladder diverticulum and detrusor instability. Bladder stones originating from BPH may migrate into the urethra, exacerbating lower urinary tract symptoms. Clinically, primary urethral stones are rarely seen, whereas secondary urethral stones are more common. Urethral stones are typically expelled with the urinary stream. However, in conditions where voiding function is impaired, such as neurogenic bladder, incomplete emptying can lead to urinary stasis. This may result in the formation of urethral stones, the accumulation of residual stone fragments in the urethra, and consequently, hinder their expulsion [2]. In this study, we present a rare case of a patient with long-standing lower urinary tract symptoms, neurogenic bladder, a large prostate volume, and multiple stones in both the bladder and urethra, but without any symptoms related to urinary retention.

Case Presentation

An 86-year-old male patient presented to our clinic with intermittent hematuria, urinary incontinence, dribbling of urine, and complaints of fever and weakness over the past three days. His medical history revealed that he suffered from Alzheimer's disease and heart failure. The patient had a 15-year history of ongoing difficulty in urination despite medical treatment. He was advised to undergo prostate surgery at another center but refused the operation. Physical examination revealed a poor general condition and a fever of 38.5 °C, while other vital signs were normal. During inspection, the bladder appeared globular and dribbling incontinence was observed. An attempt to insert a catheter in a patient with overflow incontinence was unsuccessful because there was a stone in the penile urethra.

*Corresponding author:
Email address: ahmetalperozdes@gmail.com (Ahmet Alper Ozdes)

Laboratory results showed a C-Reactive Protein (CRP) level of 175 mg/L and creatinine of 2.1 mg/dL, with urinalysis revealing abundant leukocytes. The patient was admitted after undergoing contrast-free abdominal CT and urine culture examinations. The urine culture revealed ESBL (+) E. coli growth. Imaging showed multiple stones from the urethra to the bladder. The prostate volume was 200 cm^3, and there were advanced bladder trabeculations (Figures 1-3).

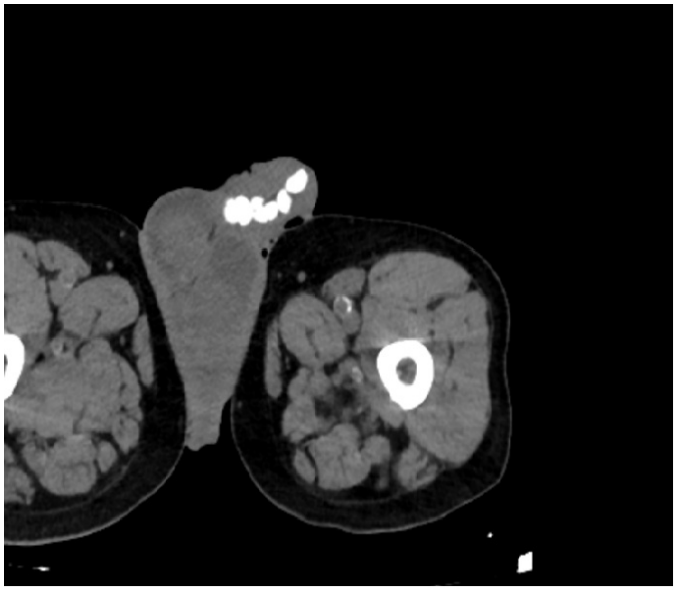

Figure 1. Stones in the anterior urethra.

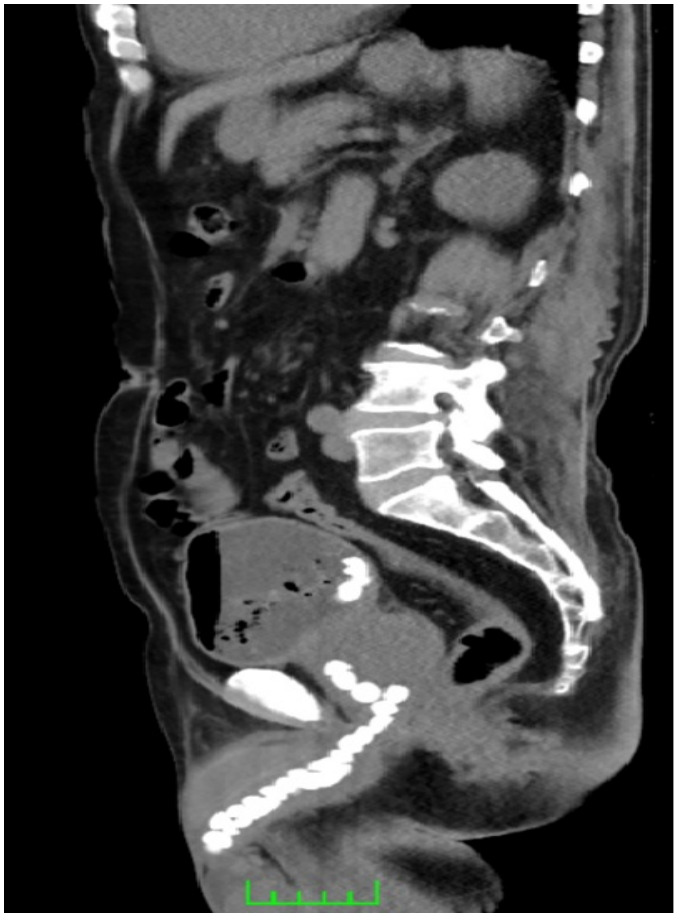

Figure 2. CT images of stones in the urethra and bladder. Abbreviations: CT: Compurterized Tomography.

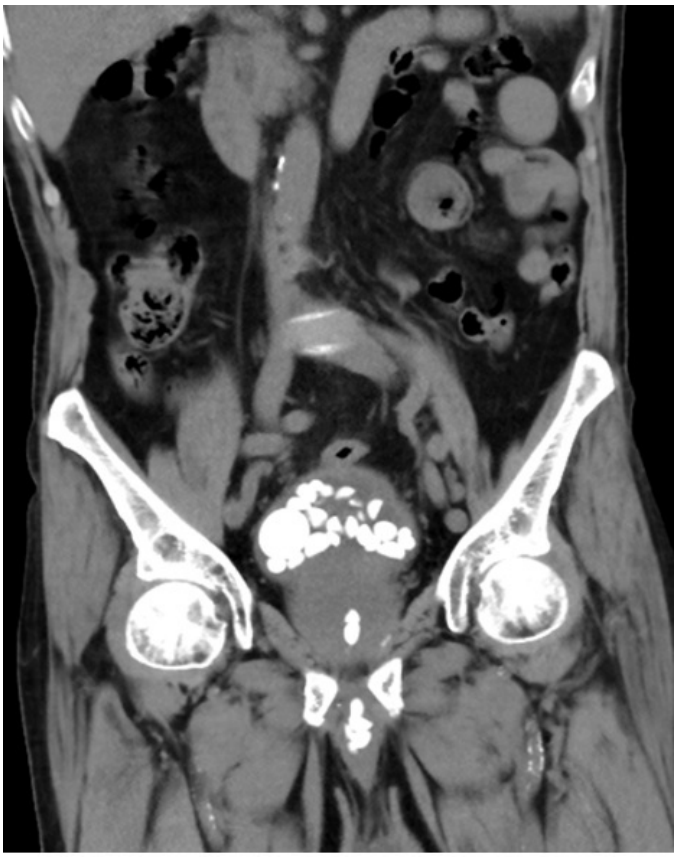

Figure 3. CT images of stones in the urethra and bladder. Abbreviations: CT: Compurterized Tomography.

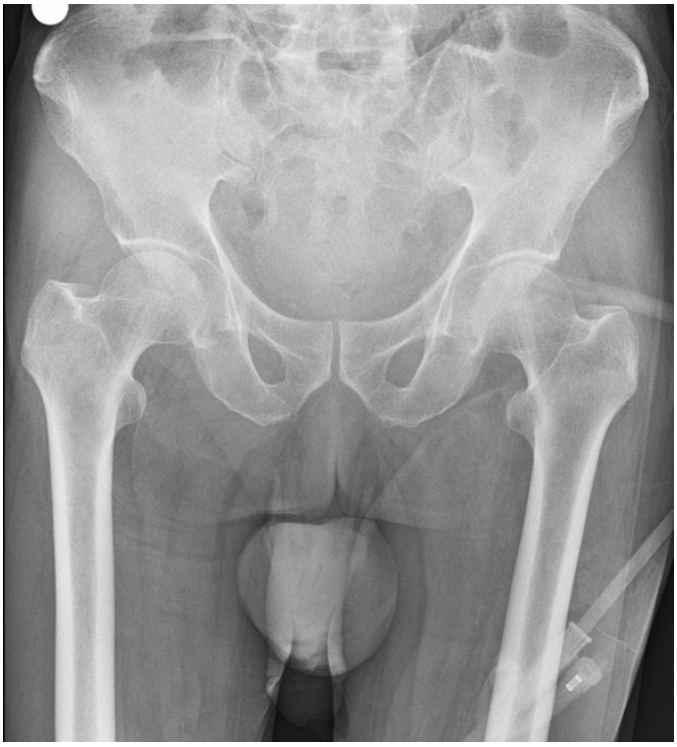

Figure 4. Post-operative imaging of the patient. No stones are observed, and the catheter balloon in the bladder is visible.

Despite the suspicion of neurogenic bladder, the presence

of hematuria, frequent urinary tract infection episodes, and multiple stones necessitated urological surgical intervention following the treatment of the infection. The patient was evaluated as high-risk for surgery during anesthesia preparations. Given the neurogenic component and comorbidities, the risks of surgery and high complication risks were explained to the patient. The patient consented to surgery, and meropenem 2x1 g IV antibiotic therapy was initiated by our infectious diseases department. The creatinine levels dropped to 1.4 mg/dL during the preoperative hospitalization period. After the urine culture results became negative, the patient was operated.

During the operation, cysto-urethroscopy was performed first, and stones from the penile urethra to the prostatic urethra were removed individually using foreign body forceps. Since the stones were appropriately sized, all were removed via cysto-urethroscopy without the need for internal urethrotomy. Subsequently, in the supine position with a transvesical approach, an open prostatectomy and cystolithotomy were performed. The removed prostate weighed 195 grams. The operation lasted 90 minutes, and no blood transfusion was needed. The patient had an uneventful postoperative course, with positive primary wound healing and no complications. Pathological examination confirmed BPH with chronic inflammation. On the 10^{th} postoperative day, imaging showed no stones (Figure 4), and the catheter was removed while monitoring the patient's ability to urinate. For the patient unable to urinate unaided, a catheter was reinserted, and urodynamic testing confirmed the diagnosis of neurogenic bladder, after which clean intermittent catheterization was initiated. During routine follow-ups at six months, it was observed that symptoms such as hematuria, burning sensation during urination, and fever did not recur. Signed consent for this case report was obtained from the patient on April 13, 2022.

Discussion

Urethral stones are among the rarest types of urinary tract stones, presenting with a wide variety of clinical symptoms. "Patients may present with acute urinary retention, weak urinary stream, frequent urination, hematuria, urethral trauma, dysuria, a sensation of a mass in the penis, and pain in the peno-rectal or perineal regions [2]. Although urethral stones can emerge as primary stones, secondary urethral stones, which result from the migration of stones from the bladder, ureters, or kidneys into the urethra, are more common. In a study conducted by Koga et al. [3] showed that 32% of patients had stones located in different parts of the urinary system.

Most urethral stones are expelled spontaneously through the urethral lumen. However, a significant proportion of stones, particularly those located in the posterior urethra, fail to pass naturally. Various etiological factors contribute to the retention of these stones, including prior endo-urological procedures, neurogenic bladder, infections, foreign bodies, and structural abnormalities of the urethra [2,4]. In our case, the multiple stones that were present in the urethra were presumed to be retained due to neurogenic bladder.

The literature emphasizes the preference for minimally invasive methods in the treatment of urethral stones. Endoscopic techniques are frequently chosen due to their ability to evaluate the urethral anatomy thoroughly [5]. However, in cases involving large stones or associated urethral diverticula, open surgical approaches remain the preferred option. Open surgery carries risks such as high infection rates, urethral strictures, delayed wound , and urinary fistulas, which is why it is generally considered a last resort [5]. In our case, the presence of multiple stones from the penile to the posterior urethra made it difficult to push the stones towards the bladder. "Nevertheless, due to the small size of the stones and the absence of other urethral pathologies (such as urethral diverticula or strictures), the stones were successfully removed individually using foreign body forceps during cysto-urethroscopy without the need for an internal urethrotomy.

Benign Prostatic Hyperplasia (BPH) is one of the most common diseases in elderly men, characterized histopathologically by an increased number of epithelial and stromal cells in the periurethral region of the prostate [6]. BPH leads to bladder outlet obstruction, resulting in lower urinary tract symptoms. As the obstruction progresses, detrusor muscle dysfunction can develop. Initially, there is hypertrophy of the detrusor muscle and thickening of the bladder wall, which leads to reduced oxygen levels in the tissue and chronic ischemia. Although contractions initially increase to compensate, over time, detrusor function weakens, and the muscle enters a decompensated state. Even after the obstruction is relieved, detrusor function may not recover if the muscle has already entered the decompensated phase [7]. In our case, it is known that the patient had been experiencing lower urinary tract symptoms for many years and did not receive appropriate treatment due to comorbidities. The clinical presentation suggested deteriorated detrusor function. Although urodynamic studies are indicated preoperatively in patients with BPH-related lower urinary tract symptoms and impaired detrusor function, the presence of hematuria and persistent urinary tract infections due to stones necessitated surgical intervention.

Complications of BPH include acute urinary retention, recurrent macroscopic hematuria, recurrent urinary tract infections, renal insufficiency, and bladder stones. According to the European Association of Urology guidelines, bladder stones are considered a complication of BPH, and surgical treatment of BPH is strongly recommended in the presence of bladder stones [8]. Surgical treatment of symptomatic BPH can be categorized into three main approaches: 1) Minimally Invasive Surgical Therapies (MIST); 2) Simple prostatectomy; and 3) Transurethral procedures.

Currently, endoscopic procedures are the first choice for small to medium-sized prostates. Transurethral resection of the prostate (TURP) is considered the gold standard treatment for BPH. However, in large prostates exceeding 100-150 ml, endoscopic procedures are less preferred due to longer operative times, difficulties in controlling bleeding, and increased complication rates (such as urethral strictures). The surgical treatment of large prostates requires traditional open surgical enucleation via suprapubic and transvesical or retropubic approaches is recom-

mended. These methods are beneficial in patients with multiple bladder stones as they allow simultaneous intervention on the stones, making open simple prostatectomy a useful technique in such cases [9]. In our case, the patient had a prostate volume of 200 ml and multiple bladder stones, making open simple prostatectomy the most suitable option.

In recent years, less invasive alternatives such as laparoscopic and robot-assisted simple prostatectomy have been developed [10,11]. These approaches offer promising results with shorter postoperative duration of catheterization, reduced length of hospital stay, and lower complication rates compared to open surgery. However, open simple prostatectomy has advantages over laparoscopic and robot-assisted techniques, including broader intervention capabilities, direct tactile feedback, ease of intervention in emergencies, and lower costs. In our case, given our extensive experience with open simple prostatectomy in our clinic, we opted for open intervention.

Conclusion

Benign Prostatic Hyperplasia (BPH) and its complications pose significant health challenges for the aging male population. When not treated promptly and adequately, patients may develop severe complications such as detrusor failure, hematuria, and urinary tract infections. In this case presentation, we demonstrate the management of a patient presenting with these symptoms through combined endoscopic urethral stone treatment, transvesical open prostatectomy, and cystolithotomy. This case is extremely rare and underscores the importance of meticulous follow-up and well-planned surgical intervention. In complex cases with multiple comorbidities, it is essential to minimize operative times and prioritize less invasive methods while remaining prepared for open surgical intervention when necessary.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Funding

None.

Author Contributions

Ahmet Alper Özdeş; writing- data collection. Rıdvan Cantürk; literature review- data collection. Necip Pirinççi; supervision.

References

1. Lim K Bin. Epidemiology of clinical benign prostatic hyperplasia. *Asian J Urol.* 2017 Jul;4(3):148–51. DOI: 10.1016/j.ajur.2017.06.004.
2. Maheshwari PN, Shah HN. In-Situ Holmium Laser Lithotripsy for Impacted Urethral Calculi. *J Endourol.* 2005 Oct;19(8):1009–11. DOI: 10.1089/end.2005.19.1009.
3. Koga S, Arakaki Y, Matsuoka M, Ohyama C. *Urethral Calculi. Br J Urol.* 1990 Mar 26;65(3):288–9. DOI: 10.1111/j.1464-410x.1990.tb14730.x.
4. Atılgan D, Kölükçü E, Fırat F, Kölükçü V. Efficacy and Safety of Holmium Laser Lithotripsy Under Local Anesthesia in the Treatment of Urethral Stones in Elderly Male Patients. *Healthcare (Basel).* 2020 Jun 1;8(2):150. DOI: 10.3390/healthcare8020150.
5. Kamal BA, Anikwe RM, Darawani H, Hashish M, Taha SA. Urethral calculi: presentation and management. *BJU Int.* 2004 Mar 20;93(4):549–52. DOI: 10.1111/j.1464-410x.2003.04660.x.
6. Aaron L, Franco OE, Hayward SW. Review of Prostate Anatomy and Embryology and the Etiology of Benign Prostatic Hyperplasia. *Urologic Clinics of North America.* 2016 Aug;43(3):279–88. DOI: 10.1016/j.ucl.2016.04.012.
7. Kahokehr AA, Gilling PJ. Recent advances in the understanding of male lower urinary tract symptoms (LUTS). *F1000Res.* 2016 Apr 21;5:715. DOI: 10.12688/f1000research.8638.1.
8. Oelke M, Bachmann A, Descazeaud A, Emberton M, Gravas S, Michel MC, et al. EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. *Eur Urol.* 2013 Jul;64(1):118–40. DOI: 10.1016/j.eururo.2013.03.004.
9. Aghamir SMK, Khatami F, Rahimi MR, Guitynavard F. Giant benign prostatic hyperplasia: A case report. *Urology Case Reports.* 2020 Jan 1;28:101051. DOI: 10.1016/j.eucr.2019.101051.
10. Guleser AS, Basaga Y, Karadag MA. Comparison of enhanced recovery after surgery protocol and conventional approach after laparoscopic transperitoneal radical prostatectomy: a retrospective analysis. *African Journal of Urology.* 2021 Dec 15;27(1):129. DOI: 10.1186/s12301-021-00233-y.
11. Chughtai B, Rojanasarot S, Neeser K, Gultyaev D, Fu S, Bhattacharyya SK, et al. A comprehensive analysis of clinical, quality of life, and cost-effectiveness outcomes of key treatment options for benign prostatic hyperplasia. *PLoS One.* 2022 Apr 15;17(4):e0266824. DOI: 10.1371/journal.pone.0266824.