ISSUE
1
YEAR:2023 VOLUME:4

ARCHIVES OF
CURRENT MEDICAL
RESEARCH

ARCHIVES OF CURRENT MEDICAL RESEARCH

https://dergipark.org.tr/tr/pub/acmr

ARCHIVES OF CURRENT MEDICAL RESEARCH (ACMR)

Volume: 4

Number: 1

January 2023

Publishing Language
English

E-ISSN
2717-9788

Type of Publication
Peer Reviewed Academic Journal

Publishing Period
Three Times a Year (January, May, September)

Journal Name
Archives of Current Medical Research
Arch Curr Med Res

Owner
14th March Medical Association

General Publication Director
Mehmet Ali Tokgöz

Management Location - Content Advisor
Alban Tanıtım Ltd. Şti.
Tunalı Hilmi Cad. Büklüm Sokak No: 45/3
Kavaklıdere/Ankara Tel: 0.312 430 13 15
E-mail: info@acmronline.org
editor@albantanitim.com.tr

Graphic Design
Alban Tanıtım Ltd. Şti.

Proofreading
S. Bahar Alban

Prepress
Alban Tanıtım Ltd. Şti.

ARCHIVES OF CURRENT MEDICAL RESEARCH

Archives of Current Medical Research is an international refereed journal. Authors bear responsibility for the content of their published articles.

EDITORIAL TEAM

TABLE OF CONTENTS

01

ORIGINAL ARTICLE

Antimalarial activity of amodiaquine-moxifloxacin in parasitized mice

Elias Adikwu, Igono Simeon Ajeka, Confidence Ogechi Nworgu

07

ORIGINAL ARTICLE

Effectiveness of Anakinra Therapy on COVID-19 Patients in ICU

Elmas Uysal, Işıl Özkoçak Turan, Handan Ankaralı

13

ORIGINAL ARTICLE

Telemedicine Usage of Physicians and Views on Telemedicine

Muhammed Mustafa Uzan, Umut Gök Balcı

19

ORIGINAL ARTICLE

A new prognostic factor in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan: Hemoglobin, albumin, lymphocytes and platelets (HALP) score

Mustafa Korkmaz, Melek Karakurt Eryılmaz, Mehmet Zahid Koçak, Aykut Demirkıran, Murat Araz, Mustafa Karaağaç, Mehmet Artaç

TABLE OF CONTENTS

24

ORIGINAL ARTICLE

The importance of linear measurements made using panoramic radiography in pre-implant site assessment: actual vs. measured

Raif Alan, Ahmet Afşin Erbeyoğlu

31

ORIGINAL ARTICLE

Chronic kidney disease observational cohort study and assessment of baseline characteristics and their relationship with diabetes status and kidney function

Sümeyra Koyuncu, Koray Uludağ, Tamer Arıkan, Ali İhsan Günal

40

ORIGINAL ARTICLE

Clinicopathological evaluation of parasitic infections in appendectomy specimens

Murat Kartal, Tolga Kalaycı, Yaşar Çöpelci, Ali Kurt

47

ORIGINAL ARTICLE

Trends in Emergency Department Visits, and Hospital Admissions Pre- and During Covid 19 Pandemic

Savaş Sezik, Onur Hakoğlu, Oktay Okuş, Omay Sorgun

58

CASE REPORT

Fibrin Membrane Induced Pupillary Block Glaucoma Treated With Nd:YAG Laser After Uncomplicated Cataract Surgery

Fatma Sümer

ARCHIVES OF
CURRENT MEDICAL
RESEARCH

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):1-6

Received: 06 July 2022
Revised: 12 December 2022
Acccepted: 7 January 2023
DOI: 10.47482/acmr.1140050

ORIGINAL ARTICLE

Antimalarial activity of amodiaquine-moxifloxacin in parasitized mice

Elias Adikwu[1] **Igono Simeon Ajeka**[2] **Confidence Ogechi Nworgu**[2]

1 Niger Delta University, Faculty of Pharmacy, Department of Pharmacology/Toxicology, Bayelsa State, Nigeria
2 Ignatus Ajuru University of Education, Faculty of Natural and Applied Sciences, Department of Biology, Rivers State, Nigeria

Abstract

Background: The search for new partner drugs to increase the therapeutic activities of the existing antimalarial drugs is important because of decreased Plasmodium susceptibility. Amodiaquine (AQ) is an antimalarial drug. Moxifloxacin (MX) is a fluoroquinolone antibiotic with promising antiplasmodial activity. This study evaluated the benefit of MX as a partner drug with AQ for malaria treatment in Plasmodium berghei-infected mice.

Methods: Adult Swiss albino mice (28-35g) of both sexes, randomly grouped and inoculated with Plasmodium berghei were used. Plasmodium berghei were used. The mice were treated orally with AQ (10 mg/kg/day), MX (6 mg/kg/day) and AQ-MX, respectively using the curative, prophylactic and suppressive protocols. Chloroquine (CQ) (10 mg/kg/day) was used as the positive control. Blood samples were collected and assessed for percentage parasitemia and hematological indices. Liver samples were assessed for histological changes. Mean survival time (MST) was observed in the treated mice.

Results: The curative, prophylactic and suppressive tests showed that AQ-MX decreased percentage parasitemia with difference observed at $p<0.05$ when compared to AQ or MX. In the curative test, AQ, MX and AQ-MX produced 65.62 %, 62.03% and 85.31% parasitemia inhibitions, respectively whereas CQ produced 83.72 % parasitemia inhibition. AQ-MX prolonged MST with difference observed at $p<0.05$ in the curative, prophylactic and suppressive tests when compared to AQ or MX. The restored hematological indices caused by AQ-MX were characterized by significantly increased hemoglobin, red blood cells, and packed cell volume and significantly decreased white blood cells at $p<0.05$ when compared to AQ or MX. AQ-MX eradicates liver merozoites.

Conclusions: MX may be an effective partner drug with AQ for malaria treatment.

Keywords: Amodiaquine, Moxifloxacin, Antimalarial, Plasmodium, Mice.

Cite this article as: *Adikwu E, Ajeka IS, Nworgu CO. Antimalarial activity of amodiaquine-moxifloxacin in parasitized mice. Arch Curr Med Res. 2023;4(1):1-6*

Corresponding Author:
Elias Adikwu, Niger Delta University, Faculty of Pharmacy,
Department of Pharmacology/Toxicology, Bayelsa State, Nigeria
E-Mail: adikwuelias@gmail.com

INTRODUCTION

Malaria persists in tropical and sub-tropical regions of the world despite concerted global effort that dates back to the world health organization (WHO) global malaria eradication programme in 1950s and 1960s (1). The underprivileged rural populations consisting of young children and pregnant women are disproportionately affected by malaria. The cornerstone of malaria control efforts for the past decades has been to provide antimalarial commodities (2) toward the prevention and eradication of malaria (3).

One of the challenges in the treatment of malaria especially in the tropics is the emergence of resistant to most antimalarial drugs (4,5). Combination therapies especially artemisinin combination therapies (ACTs), which combine artemisinins with partner drugs were introduced to overcome the incidence of *Plasmodium* resistance. ACTs have produced remarkable success against *Plasmodium* resistance however, there is gradual emergence of *Plasmodium* resistance to ACTs (4,5). The de novo emergence of resistance can be prevented by the continual exploration of new antimalarial drug combinations. New combinations can delay or slow the emergence and spread of resistance by eliminating resistant mutants except those that carry two different mutations (6-8).

Amodiaquine (AQ) is an orally active 4 aminoquinoline derivative with antimalarial and anti-inflammatory properties similar to chloroquine (9). It is used for the treatment of malaria including uncomplicated *Plasmodium falciparum* malaria (10). AQ has been used with good outcomes as a partner drug with artesunate, sulfadoxine and pyrimethamine to reduce the risk of resistance (10, 11). Moxifloxacin (MX) belongs to the fluroquinoline family, it is a broad spectrum antibiotic that is active against gram positive and gram negative bacteria (12, 13). In bacteria, it inhibits DNA gyrase and topoisomerase IV (14). MX has been associated with antiplasmodial activity against Plasmodium falciparum strains with the suggestion that it may serve as a viable partner drug with artemisinins and other antimalarial drugs (15).This study assessed whether MX could be a viable partner drug with AQ in *Plasmodium berghei* (*P. berghei*)-infected mice.

MATERIALS AND METHODS

Animals, drugs and parasites

Ninety Swiss albino mice of both sexes (28-35 g) used for this study were sourced from the animal husbandry of the Department of Pharmacology, Faculty of Basic Clinical Sciences, University of Port Harcourt, Rivers State. The mice were housed in cages and acclimated for 2 weeks with access to food pellets and water freely. The mice were handled according to the guide on animal handling by European council and the Parliament.

This study was approved by Research Ethics Committee of the Department of Pharmacology/Toxicology, Faculty of Pharmacy, Niger Delta University, Bayelsa State (Approval date: 10.01.2022, Approval number: NDU/PHARM/PCO/AEC/082)

Dose selection

Chloroquine (CQ) (10mg/kg) (16), MX (6 mg/kg) (17) and AQ (10 mg/kg) (18) were used for the study.

Parasite inoculation

Donor mice infected with CQ-sensitive strain of *P. berghei* (NK65) used were obtained from Nigerian Institute of Medical Research, Yaba, Lagos. Stock inoculation containing 1×10^7 *P. berghei* infected erythrocytes in 0.2 mL was prepared by diluting portion of the blood infected with *P. berghei* with 0.9% normal saline. Erythrocytes containing 1×10^7 *P. berghei* was inoculated into each mouse through intraperitoneal (ip) route.

Determination of antiplasmodial activity

Determination of curative antiplasmodial activity

The method described by Ryley and Peters (1970) (19) was used. Thirty adult Swiss albino mice randomized into 6 groups containing 5 mice per group were used. The mice were parasitized with 1×10^7 *P. berghei* (i.p) except for the normal control. After 3 days, the mice were treated per oral (p.o) with AQ (10mg/kg), MX (6mg/kg) and AQ-MX daily for 4 days. The parasitized and normal controls were treated with normal saline (0.2 mL), whereas the positive (Standard) control was treated with CQ (10 mg/kg) daily for 4 days. On day 8, blood samples were collected from the tail and thin blood films were produced on microscope slides. The films were fixed with 10% Giemsa stain for 30 min and examined under oil immersion ×100 magnification. The number of parasitized red blood cells (RBCs) were counted against the total number of RBCs in a field. Percentage parasitemia and inhibitions were calculated as shown below.

$$\% \text{ Parasitemia} = \frac{\text{Number of parasitized red blood cells (RBCs)}}{\text{Total number of RBCs count}} \times 100\%$$

$$\% \text{ Inhibition} = \frac{(\% \text{ Parasitemia of negative control} - \% \text{ Parasitemia of treated group}) \times 100}{\% \text{ Parasitemia of negative control}}$$

Determination of suppressive antiplasmodial activity

The method described by Knight and Peters (1980) (20) was used. Thirty adult Swiss albino mice were randomly divided into 6 groups of 5 mice per group and parasitized with 1×10^7 *P. berghei* ip for 3 h. Thereafter, the mice were treated per oral (p.o) with AQ (10mg/kg), MX (6mg/kg) and AQ-MX daily for 4 days. The parasitized and normal controls were treated with normal saline (0.2 mL), while the positive (Standard) control was treated with CQ (10 mg/kg) daily for 4 days. On day 5, blood samples were collected from the tail and thin films were prepared on slides. Percentage parasitemia and inhibitions were calculated as shown above.

Determination of prophylactic antiplasmodial activity

The method described by Peters (1975) (21) was used for prophylactic test. Thirty adult Swiss albino mice randomized into 6 groups containing 5 mice per group were used. The mice were treated per oral (p.o) with AQ (10mg/kg), MX (6mg/kg) and AQ-MX daily for 4 days. The parasitized and normal controls were treated with normal saline (0.2 mL) while the positive (Standard) control was treated with CQ (10 mg/kg) daily for 4 days. On day 5, except for the normal control the mice were inoculated with 1×10^7 *P. berghei* ip and treatment continued for 4 days. Thereafter, blood samples were collected from the tail and percentage parasitemia and inhibitions were determined as stated above

Determination of mean survival time

The mice in the control and the treated groups were observed for mortality and expressed in days. Mortality expressed as mean survival time (MST) was calculated as shown below.

$$\text{MST} = \frac{\text{Sum of survival time of all mice in a group (Days)}}{\text{Total number of mice in that group}}$$

2.4.5 Evaluation of hematological parameters

Blood samples from the mice in the curative study were collected and assessed for packed cell volume (PCV), red blood cells (RBCs), hemoglobin (HB) and white blood cells (WBCs) using an auto analyzer.

Statistical analysis

Data expressed as mean ± standard error of mean (SEM). Differences between groups were determined using one-way analysis of variance (ANOVA) followed by Tukey's *post-hoc* test. Significance was considered at $P< 0.05$.

RESULTS

Curative antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*

Treatment with AQ-MX decreased percentage parasitemia significantly at $p<0.05$ when compared to individual doses of AQ and MX. AQ, MX and AQ-MX showed parasitemia inhibitions of 65.62%, 62.03%, and 85.31%, respectively, while CQ produced 83.72% parasitemia inhibition **(Table1).** Treatment with AQ-MX significantly prolonged MST when compared to AQ or MX with significance observed at $p<0.05$ **(Table 1).**

Table 1. Curative antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*.

Treatment	% Parasitemia	% Inhibition	MST(Days)
PC	31.26±1.23a	0.0	9.05±0.97 a
CQ	5.09±0.11b	83.72	27.6±3.10 b
AQ	10.75±0.15c	65.62	21.1±3.22 c
MX	11.86±0.88c	62.03	20.4±2.12 c
AQ-MX	4.59±0.02b	85.31	30.8±4.07 b

PC: Parasitized control, CQ: Chloroquine (Positive control), AQ: Amodiaquine, MX: Moxifloxacin, AQ-MX: Amodiaquine-Moxifloxacin. Values with difference superscripts down the column significantly differ at p<0.05 (ANOVA: Analysis of variance)

Suppressive antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*

AQ-MX decreased percentage parasitemia with significant difference observed at p<0.05 when compared to AQ or MX. The parasitemia inhibitions produced by AQ, MX and AQ-MX represent 72.40%, 70.63%, and 94.38%, respectively, while CQ produced 93.80% parasitemia inhibition **(Table 2).** AQ-MX prolonged MST significantly (p<0.05) when compared to individual doses of AQ and MX **(Table 2)**

Table 2. Suppressive antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*

Treatment	% Parasitemia	% Inhibition	MST(Days)
PC	27.86±2.10 a	0.00	9.23±0.13a
CQ	1.72±0.20 b	93.80	30.26±3.17b
AQ	7.69±0.16 c	72.40	28.73±3.40c
MX	8.18±0.63 c	70.63	25.13±3.66c
AQ-MX	1.58±0.04 b	94.38	33.08±7.03b

PC: Parasitized control, CQ: Chloroquine (Positive control), AQ: Amodiaquine, MX; Moxifloxacin, AQ-MX: Amodiaquine-Moxifloxacin. MST: Mean survival time, Values with difference superscripts down the column significantly differ at p<0.05 (ANOVA: Analysis of variance)

Prophylactic antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*.

Treatment with AQ-MX decreased percentage parasitemia with significance at p<0.05 when compared to individual doses of AQ and MX **(Table 3).** AQ, MX, and AQ-MX produced 75.22%, 75.27% and 97.76% parasitemia inhibitions while CQ produced 96.25% parasitemia inhibition **(Table 3).** AQ-MX significantly (p<0.05) prolonged MST when compared to individual doses of AQ and MX **(Table 3).**

Table 3: Prophylactic antiplasmodial effect of amodiaquine-moxifloxacin on mice infected with *Plasmodium berghei*

Treatment	% Parasitemia	% Inhibition	MST(Days)
PC	22.25±0.68 a	0.0	9.61±0.16 a
CQ	0.83±0.20 b	96.25	34.15±3.01b
AQ	5.51±0.01 c	75.22	29.86±3.00c
MX	6.17±0.77 c	72.27	27.54±3.21c
AQ-MX	0.50±0.01 d	97.76	38.71±5.10b

PC: Parasitized control, CQ: Chloroquine (Positive control), AQ: Amodiaquine, MX; Moxifloxacin, AQ-MX: Amodaiquine-Moxifloxacin. MST: Mean survival time, Values with difference superscripts down the column significantly differ at p<0.05 (ANOVA: Analysis of variance)

Effect of amodiaquine-moxifloxacin on hematological indices on mice infected with *Plasmodium berghei*.

RBCs, PCV and HB were significantly (p<0.05) increased whereas WBCs were significantly (p<0.05) decreased in *P. berghei*-infected mice when compared to the normal control **(Table 4).** However, treatment with AQ-MX significantly increased RBCs, PCV and HB and significantly decreased WBCs when compared to individual doses of AQ and MX at p<0.05 **(Table 4).**

Table 4: Effect of amodiaquine-moxifloxacin on hematological indices of mice infected with *Plasmodium berghei*

Treatment	RBCs (x106)	WBCs (cells/L)	PCV (%)	HB (g/dL)
NC	6.85±0.02 a	4.76±0.40 a	58.54±5.18a	15.64±0.38 a
PC	2.00±0.46 b	12.94±0.11b	20.56±3.10 b	6.36±0.26 b
CQ	5.67±0.73 c	5.35±0.30 c	49.61±6.35c	14.27±0.41c
AQ	3.36±0.17 d	8.77±0.36 d	34.74±4.98d	10.50±0.47d
MX	3.10±0.21 d	9.63±0.52 d	31.17±3.85d	10.01±0.12d
AQ-MX	5.94±0.56 c	5.00±0.30 c	52.03±5.13 c	14.95±1.33c

NC: Normal control, PC: Parasitized control, CQ: Chloroquine (Positive control), AQ: Amodiaquine, MX: Moxifloxacin, AQ-MX: Amodiaquine-Moxifloxacin RBCs: Red blood cells, WBCs: White blood cells, PCV: Packed cell volume, HB: Hemoglobin, Values with difference superscripts down the column significantly differ at p<0.05 (ANOVA: Analysis of variance)

DISCUSSION

Malaria has caused notable health and economic challenges in the world especially in sub-Saharan Africa and South East Asia (22). Based on WHO report, in 2012, 207 million malaria cases and 627,000 malaria related deaths occurred in the world (23). In the treatment of malaria, combination therapy remains a good approach, because it enhances the possibility of sustained efficacy in the advent of parasite resistance to one agent (24). However, emerging *Plasmodium* resistance to some currently used antimalarial drugs warrants the search for new partner drugs, which can be achieved through drug repurposing. Drug repositioning or the screening of existing drugs for new uses, affords an attractive, alternate and valid paradigm for drug discovery (25). This study explored whether MX can be repurposed as a partner drug with AQ for the treatment of malaria. The malaria parasites that cause infection in humans are not able to invade non-primate

animals, therefore rodent malaria parasites are usually employed for the *in-vivo* assessment of antimalarial drug candidates (26). *P. berghei*, a rodent malaria parasite was used, because it has been used for the screening of many conventional antimalarial drugs (19). This study selected the *in- vivo* malaria model, because it allows pro-drug effect and the immune function in controlling malaria infection (27). Also, it allows for parasites life cycle stages to be clearly observed on smears due to non-adherence with endothelial cells (28). A 4-day curative test for established infections and a 4- day suppressive test for early infections were used (29). In this study, curative, suppressive, prophylactic antiplasmodial assessments of AQ-MX showed reductions in percentage parasitemia levels. The prevention of malaria-related mortality is one of the most essential goals of malaria treatment (30, 31), therefore an antimalarial drug candidate is expected to prevent malaria–related mortality (32). In this study, AQ-MX reduced mortality in the treated mice as shown by prolonged MST. Malaria infection is a common cause of anemia, which has been associated with death especially among children. One of the essentials of malaria treatment is the prevention of malaria-related anemia (33, 34). AQ-MX conspicuously prevent anemia in the treated mice, which was characterized by increased RBCs, HB and PCV levels. One of the challenges in malaria treatment is the liver stage of malaria infection. It is imperative for an antimalarial candidate drug to be effective against liver stage of malaria infection (35). This study, observed merozoites, and central vein congestion in *P. berghei* -infected mice. Udongkang *et al.* reported similar findings in *P. berghei*-infected mice (36). However, treatment with AQ-MX decreased liver merozoites and restored liver histology. Interestingly, AQ-MX produced antiplasmodial effect similar to CQ the standard drug used for this study. The current study observed that the antiplasmodial effect of AQ-MX was additive. The mechanism of action by which MX inhibits *Plasmodium* parasites in not clear. However, studies suggested that it produces antiplasmodial activity by targeting the gyrase of parasites, which is an enzyme essential for apicoplast DNA replication (37, 38).

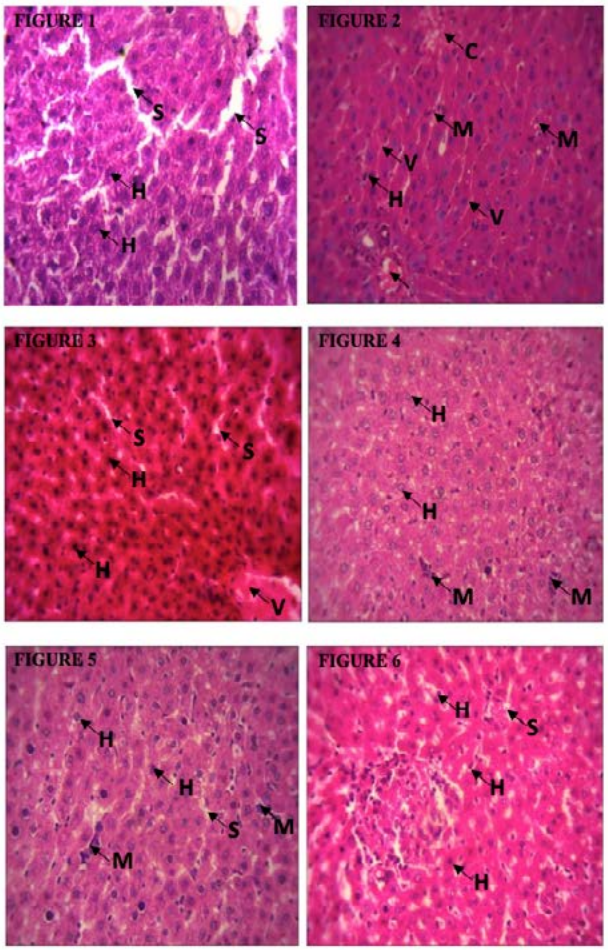


Figure 1 (Control), Figure 2 (Parasitized control), Figure 3 (Standard control), Figure 4 (Amodaiquine [10 mg/kg]-treated mice), Figure 5 (Moxifloxacin [6mg/kg] -treated mice), Figure 6 (Amodiaquine-Moxifloxacin). H: Hepatocytes, C: Congested central vein, V: Sinusoidal congestion, M: Merozoites, S: Sinusoids, A: Hepatic artery.

MX seems effective as a partner drug with AQ, therefore AQ-MX may be used for the treatment of malaria.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by Research Ethics Committee of the Department of Pharmacology/Toxicology, Faculty of Pharmacy, Niger Delta University, Bayelsa State (Approval date: 10.01.2022, Approval number: NDU/PHARM/PCO/AEC/082)

REFERENCES

1. World Health Organization. Twenty-third World Health Assembly: part I: resolutions and decisions: annexes. 1970. Available at https://apps.who.int/iris/handle/10665/85824 Accessed September 20, 2022
2. Taylor C, Florey L, Ye Y. Equity trends in ownership of insecticide-treated nets in 19 sub-Saharan African countries. Bull World Health Organ. 2017;95(5):322-332.
3. World Health Organization. Global technical strategy for malaria 2016-2030, 2021 update. 2021. Available at https://www.who.int/publications/i/item/9789240031357 Accessed September 22, 2022
4. World Health Organization. WHO Guidelines for malaria. Available at https://www.who.int/publications/i/item/guidelines-for-malaria Accessed September 22, 2022
5. Menard D, Dondorp AR. Antimalarial drug resistance: A threat to malaria elimination. Cold spring Herb Pers Med, 2017; 7(7): a025619.
6. White NJ. Antimalarial drug resistance. J Clin Invest. 2004, 113(8):1084-1092.
7. Smith DL, Klein EY, McKenzie FE, Laxminarayan R. Prospective strategies to delay the evolution of anti-malarial drug resistance: weighing the uncertainty. Malar J. 2010 Jul 23;9:217.
8. Fairhurst RM, Dondrp AM. Artemisinin resistance plasmodium falciparum malaria. Microb Spect 2016; 4-13.
9. World Health Organization. WHO Guidelines for malaria. Available at https://l24.im/zhyqJ62 Accessed September 22, 2022
10. Nair A, Abrahamsson B, Barends DM, Groot DW, Kopp S, Polli JE, Shah VP, Dressman JB. Biowaiver monographs for immediate-release solid oral dosage forms: primaquine phosphate. J Pharm Sci. 2012 Mar;101(3):936-45.
11. World Health Organization. Seasonal malaria chemoprevention with sulfadoxine-pyrithamine plus amodiaquine in children. A field guide. Available at https://apps.who.int/iris/bitstream/handle/10665/85726/9789241504737_eng.pdf Accessed September 22, 2022
12. Al Omari MM, Jaafari DS, Al-Sou'od KA, Badwan AA. Moxifloxacin hydrochloride. Profiles Drug Subst Excip Relat Methodol. 2014;39:299-431.
13. World Health Organization. Moxifloxacin tablets. Available at https://apps.who.int/iris/bitstream/handle/10665/330895/DI331-10-42-eng.pdf Accessed September 23, 2022
14. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolines. Micro Mol Biol Rev. 1998; 61(3),377-92.
15. Yadav K, Shivahare R, Shaham SH, Joshi P, Sharma A, Tripathi R. Repurposing of existing therapeutics to combat drug-resistant malaria. Biomed Pharmacother. 2021 Apr;136:111275.
16. Somsak V, Damkaew A, Onrak P. Antimalarial Activity of Kaempferol and Its Combination with Chloroquine in *Plasmodium berghei* Infection in Mice. J. Path. 2018;1-7.
17. Gaillard T, Madamet M, Tsombeng FF, Dormoi J, Pradines B. Antibiotics in malaria therapy: Which antibiotics except tetracyclines and macrolides may be used against malaria? Malar. J. 2016; 15: 1–10.
18. Yavo W, Faye B, Kuete T, Djohan V, Oga SA, Kassi RR et al. Multicentric assessment of the efficacy and tolerability of dihydroartemisinin-piperaquine compared to artemether-lumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in sub-Saharan Africa. Malar J. 2011 Jul 20;10:198.
19. Ryley J, Peters W. The antimalarial activity of some quinolone esters. Ann of Trop Med & Parasit , 1970; 84:209–222.
20. Knight D, Peters W. The antimalarial activity of N-benzyloxydihydrotriazines. Annals of Trop Med and Parasit. 1980; 74(4):393-404.
21. Peters W. The value of drug-resistant strains of *Plasmodium berghei* in screening for blood schizontocidal activity. Ann of Trop Med parasit 1975; 69(2): 155–171
22. Bahekar S, Kale R. Herbal plants used for the treatment of malaria – a Literature review. J Pharmacog and Phytochem. 2013; 8192: 141-146.
23. Birru, E.M., Geta, M, Gurmu, A.E. Antiplasmodial activity of *Indigofera spicata* root extract against *Plasmodium berghei* infection in mice. Malar J. 2017; **16,** 198; 1-7
24. Olasehinde GI, Ojurongbe O, Adeyeba AO, Fagade OE, Valecha N, Ayanda IO et al. In vitro studies on the sensitivity pattern of Plasmodium falciparum to anti-malarial drugs and local herbal extracts. Malar J. 2014 Feb 20;13:63.
25. Matthews H, Usman-Idris M, Khan F, Read M, Nirmalan N. Drug repositioning as a route to anti-malarial drug discovery: preliminary investigation of the in vitro anti-malarial efficacy of emetine dihydrochloride hydrate. Malar J. 2013 Oct 9;12:359.
26. Kalra B, Chawla S, Gupta P, Valecha N. Screening of antimalarial drugs: an overview. Indian J Pharmacol. 2006; 38 (1) 5–1.
27. Waakoab PJ, Gumedeb B, Smithb P, Folbb PI. The *in vitro* and *in vivo* antimalarial activity of *Cardiospermum halicacabum* and *Momordica foetida*," J Ethnopharmacol, 2005; 99 (1)137–143.
28. Huang BW, Kim E, and Charles C. Mouse models of uncomplicated and fatal malaria. Bio-Protocol, 2015; 5, (13); 1514
29. Adikwu E , Ajeka IS , Nworgu CO. Antiplamodial effect of sulfadoxine/pyrimethamine/clindamycin: A study in parasitized mice Bull Biotechnol 2022; 3(2):32-38
30. DuPlessis LH, Govender K, Denti P, Wiesner L. *In vivo* efficacy and bioavailability of lumefantrine: Evaluating the application of Pheroid technology. Euro J Pharm and Biopharm. 2015; 97:68-77.
31. Anosa GN, Udegbunam RI, Okoro JO, Okoroafor ON. *In vivo* antimalarial activities of *Enantia polycarpa* stem bark against *Plasmodium berghei* in mice. J of Ethnopharm 2014; 153(2):531-4.
32. Georgewill UO, Ebong NO, Adikwu E. Antiplasmodial activity of desloratadine-dihydroartemisinin-piperaquine on *Plasmodium berghei*-infected mice Journal of Applied Biol & Biotech 2021; 9 (2) 69-73
33. Saxena R, Bhatia A, Midha K, Debnath M, Kaur P. Malaria: A Cause of Anemia and Its Effect on Pregnancy. World J Anemia 2017; 1(2):51-62.
34. Chinchilla M, Guerrero O, Abarca G, Barrios M, Castro O. An in vivo model to study the anti-malaria capacity of plant extracts. Rev Biol Trop. 1998; 46:1–7.
35. Adikwu E, Ajeka IS. Artemether/lumefantrine/clindamycin eradicates blood and liver stages of *Plasmodium berghei* infection in mice. J Analy and Pharm Res. 2021; 10 (6):240–244.
36. Udonkang MA, Eluwa BK, Enun, PC, Inyang-EtohIJ. Inyang I. Studies on antimalarial activity and liver histopathological changes of artocarpus altilis on plasmodium berghei-infected mice. RJLBPCS 2018; 4(3): 106-114.
37. Dubar F, Wintjens R, Martins-Duarte ES, Vommaro RC, Souza Wet al. Ester prodrugs of ciprofloxacin as DNA-gyrase inhibitors: synthesis, antiparasitic evaluation and docking studies. Med Chem Commun. 2021; **2**:430–435.
38. Tang Girwood SC, Nenornas E, Shapiro TA. Targeting the gyrase of *Plasmodium falciparum* with topoisomerase poisons. Biochem Pharmacol. 2015; **95**:227–237.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):7-12

Received: 12 June 2022
Revised: 27 September 2022
Acccepted: 12 October 2022
DOI: 10.47482/acmr.1129700

ORIGINAL ARTICLE

Effectiveness of Anakinra Therapy on COVID-19 Patients in ICU

Elmas Uysal[1] **Işıl Özkoçak Turan**[1] **Handan Ankaralı**[2]

1 Ankara City Hospital, Department of Intensive Care, Ankara, Turkey
2 İstanbul Medeniyet University, Faculty of Medicine, Department of Biostatistics and Medical Informatics, İstanbul, Turkey

Abstract

Background: There is no consensus on effective treatments for COVID-19 disease yet. Our aims are to observe the clinical and laboratory results of anakinra treatment on intensive care patients and to contribute to the literature on its usefulness.

Methods: The characteristics of the patients receiving Anakinra treatment in the COVID ICU of xx were retrospectively reviewed. The patient's laboratory values and the corticosteroid doses (high dose(≥250 mg), low-dose (<250 mg)) and they received in addition to Anakinra treatment were also evaluated. Patients taking other corticosteroid derivatives were excluded from the study. Furthermore, the data of the patient group who did not receive Anakinra but received high-dose methylprednisolone (MP) treatment were compared with the present patient data and evaluated in terms of treatment effectiveness. And also patients receiving Anakinra+high dose MPZ and Anakinra+low-dose MPZ were compared.

Results: The patient group that receiving Anakinra+high-dose MPZ has significantly higher mortality rate (P=0.038) and significantly longer MV and hospitalization days in the intensive care unit (p=0.001, p=0.004). As the mean hospitalization days were longer in group receiving Anakinra + low-dose (<250mg) MPZ than the group receiving Anakinra + high-dose steroids (p=0.018), there was no significant difference in terms of MV time and mortality rates.

Conclusions: In our study, the patients who received Anakinra treatment had a longer hospitalization day and MV period, and the higher mortality rate was attributed to this patient group that had a more severe course. It was observed that the use of anakinra treatment after low-dose and high-dose MPZ treatment did not cause a significant difference in mortality rates.

Keywords: Anakinra Treatment, COVID-19 Disease, Cytokine Storm.

Cite this article as: *Uysal E, Turan Özkoçak I, Ankaralı H. Effectiveness of Anakinra Therapy on COVID-19 Patients in ICU. Arch Curr Med Res. 2023;4(1):7-12*

Corresponding Author:
Elmas Uysal, Ankara City Hospital, Department of Intensive Care, Ankara, Turkey
E-Mail: dr.elmas90@gmail.com

INTRODUCTION

COVID-19 disease causes a serious pandemic all over the world. As the pandemic grows, the pathophysiology of the disease becomes clearer and new treatment regimens are put on the agenda. It has been reported that COVID-19 disease is associated with both immunodeficiency and hyperinflammation, and hyperinflammation manifests itself with a cytokine storm (1). Although Tocilizumab treatment was used in 2020 when the disease first appeared, its use has gradually decreased, considering that the current treatment may prolong the period of immunosuppression and increase the risk of secondary infection in later periods (2). Due to the side effects of tocilizumab treatment, Anakinra treatment, which has a short duration of action and provides IL-1 blockade, has come to the fore.

Anakinra, as an IL-1 receptor antagonist, is one of the treatments used in rheumatoid arthritis, cryopyrin-associated periodic syndrome (CAPS) and Still disease (3). In 6 studies, it has been suggested that Anakinra treatment can have a beneficial role especially for selected patients with COVID-19 who have moderate or severe pneumonia accompanied by increased inflammatory marker levels (4).

In a study conducted in 21 patients receiving anakinra treatment; despite the significant decrease in fever, white blood cell count, ferritin, procalcitonin, creatinine and bilirubin values compared to the group that did not receive treatment, no difference was observed in terms of mechanical ventilation time or length of stay in the intensive care unit (5). In another study conducted in Italy, patients were divided into 3 groups: high-dose Anakinra (5 mg/kg twice daily, 29 patients), low-dose Anakinra (100 mg twice daily, 7 patients) and patients receiving standard therapy (16 patients). When the group receiving high-dose Anakinra and the group receiving standard treatment were compared, it was found that the respiratory functions of the patients receiving Anakinra treatment were improved and the 21-day life expectancy was significantly higher (p=0.009) (6).

Studies on the effectiveness of Anakinra treatment are continuing. For example; in SAVE-MORE double-blind studies, twenty-eight-day mortality decreased (hazard ratio = 0.45, P = 0.045), and the hospital stay was shorter (7). In this study, we aimed to investigate the significance of clinical and laboratory findings of the research between patients who received Anakinra treatment and those who did not receive Anakinra treatment, but who received high-dose MP (methylprednisolone).

MATERIALS AND METHODS

Study Sample

254 COVID-19 patients followed up in Ankara City Hospital COVID Intensive Care Unit between 01.03.2020-01.03.2021 were included in the study. 24 patients were excluded from the study due to insufficient data. 30 patients were excluded from the study due to length of stay less than 3 days. 6 patients were excluded due to pregnancy. 114 patients were excluded due to not receiving MP (Figure-1). The remaining 80 patients were evaluated.

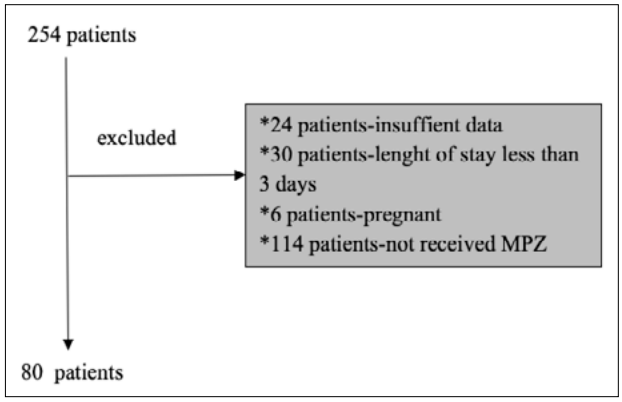


Figure-1: Study design

Study design

80 patients' data were recorded by examining patients files and charts. All treatments, the number of days in the intensive care unit, the days after the symptom onset (symptom duration), mechanical ventilation days, mortality rates, and secondary infection data were recorded. Symptom durations of the patients were recorded in two groups as shorter and longer than 7 days. At the same time, C-reactive protein (CRP), interleukin-6 (IL-6), lymphocyte count, AST, ALT, LDH, D-dimer, procalcitonin, ferritin and fibrinogen values were also recorded as helpful parameters in the diagnosis of macrophage activation syndrome. In addition, "cytokine storm score" (SFS) was calculated according to the laboratory values of the patients in our study. Based on IL-6 ≥40 pg/ml and/or two of the following as criteria: CRP ≥100 mg/L, D-dimer ≥1000 ng/ml, ferritin ≥500 ng/ml and lactate dehydrogenase ≥300 U/L , each criterion was evaluated as 1 point. (8).

Firstly; the patients were divided into 2 groups as Anakinra + high-dose MP (≥250 mg) and received only high-dose MP. Secondly; the patients were divided into

Anakinra + low-dose MP (<250 mg) and Anakinra + high-dose MP (≥250 mg), and the above-mentioned data were compared between these groups.

Anakinra doses were determined in collaboration with the Rheumatology Clinic. A cytokine storm that was both laboratory and clinically unresponsive to MP, including increased oxygen demand and tachypne, was the indication for treatment. Accordingly, doses were started at 600 mg/day (200 mg 3x1 for the first 3 days, then 100 mg 4x1 for 3 days, then 100 mg 3x1 for 3 days, then 100 mg 2x1 for 3 days, completed in 9 days in total) or 400 mg/day (reducing by 100mg every 3 days, completed in 9 days in total). Only 6 patients received 600 mg of Anakinra and it was thought that it would not be statistically significant.

Secondary infection rates were positive consultation results from Infectious Diseases Clinic mentioned in the patients' record. As the aim of our study was not to determine the infection rate of the patients, we found this information sufficient.

Ethics committee approval

Ethical committee approval was obtained for the study from Ankara City Hospital Ethical Committee (Approval date: 25.08.2021, Approval number: E1-21-1961)

Statistical Analyze

The compatibility of numerical features of the normal distribution was examined via Shapiro-Wilks test. The independent samples t-test was used to compare various groups in terms of normally distributed features, and the Mann-Whitney U test was used to compare various groups in terms of non-normally distributed features. Categorical features and intergroup relations were analyzed using the Pearson chi-square test. Statistical significance level was accepted as P <0.05 and SPSS (ver. 25) program was used for calculations.

RESULTS

80 patients diagnosed with COVID19 pneumonia in Ankara City Hospital Intensive Care Clinic were included in the study. 40 patients who received anakinra treatment and 40 patients who did not receive anakinra treatment were compared in terms of demographic data, numerical characteristics and mortality rates (Table-1). All patients receiving anakinra had previously received MP therapy. In addition, the group receiving Anakinra was divided into 2 groups as 10 patients with low-dose (<250 mg) MP and those who received high-dose (≥250 mg) MP.

Table-1: Comparison of demographic and numerical characteristics of patients who received and did not receive anakinra

	Patients receiving anakinra (n=40)	Patients not receiving Anakinra (Receiving high-dose MP (≥250 mg) (n=40)
Age (Year)	58±12	61±13
Sex(Male)	30 (%75)	28 (%70)
APACHE score	7.8±3.7	8.1±5.5
SOFA score	3.6±1.3	4.1±2.8
Day of hospitalization	17±9.8	11±5
Day of intubation	7.2±8	2.9±4.3
Rate of intubation	27 (%67.5)	17 (%42.5)
The rate of discharge	16(%40)	26 (%60)
Diabetes mellitus (n=20)	11(%27.5)	9(%22.5)
Hypertension (n=34)	20 (%50)	14 (%35)
Coronary artery disease (n=15)	10 (%25)	5(%12.5)
Chronic pulmonary disease (n=5)	1(%2.5)	4(%10)
Chronic renal disease (n=5)	2(%5)	3(%7.5)
Neurological disease (n=6)	4(%10)	2 (%5)
Malignancy (n=6)	4(%10)	2(%5)
Ferritin (μg/L)	1244±900	780±581
C-reactive protein (g/L)	119±61	146±78
IL-6 (pg/mL)	58±95	87±165
D-dimer (mg/L)	3.7±7.6	2.3±2.8
LDH (U/L)	585±194	557±293
Lymphocyte counts(10^9/L)	0.5±0.2	0.6±0.2
Procalcitonin (μg/L)	0.4±0.6	1.01±2.3

The duration of symptoms of the patients included in the study were noted. It was divided into two as <7 days and >7 days. There was no statistically significant difference

in terms of length of stay in the intensive care unit, mechanical ventilation days, and mortality between those who received anakinra and those with symptom duration >7 or <7 (P=0.293, p=0.293, p=0.182).

Hospitalization characteristics of patients who received Anakinra+ high/low-dose MPZ and only high-dose MPZ treatments are given in Table-1. Ferritin levels were significantly higher in the Anakinra treatment group (p=0.01). IL-6 value was higher in the other group (p=0.01). There was no significant difference between the two groups in CRP, procalcitonin, D-dimer and LDH values (p=0,09, p=0,4, p=0,96, p=0,2). When cytokine storm score was calculated with all values, no significant difference was observed (p=0.7).

When the patients receiving Anakinra+high-dose MPZ were compared with the patient group receiving only high-dose MPZ, the mortality rate was significantly higher (p=0,038) and the days of mechanical ventilation and hospitalization in the intensive care unit were significantly longer (p=0.001, p=0.004) in patients receiving Anakinra. However, the secondary infection rates has no significant difference (P=0.484) (Table-2), IL-6 and AST values were significantly higher of that patients received high-dose MPZ (p=0.01, p=0.01).

Table-2: Comparison of mortality, intensive care unit stay, MV days and secondary infection rates of patients who received Anakinra + high-dose MPZ and those who received only high-dose MPZ

	Patients receiving anakinra+high dose MPZ (n=30)	Patients not taking anakinra (Those who take high-dose MPZ (≥250 mg) (n=40)	p value
Day of hospitalization in ICU	18.6±9.9	11.4±5.6	0.001
Day of mechanical ventilation	8.23±8.6	2.9±4.3	0.004
Exitus rate	18 (%60)	14 (%35)	0.038
Secondary infection rate	19 (%63.3)	22 (%55)	0.48

The group receiving Anakinra + high-dose steroids and the group receiving Anakinra + low-dose steroids were compared, the average hospitalization day was significantly longer in the group receiving Anakinra + high-dose steroids (p=0.018), while the mean duration of mechanical ventilation was longer in the group receiving Anakinra + low-dose steroids. There was no significant difference in mortality rates between these groups (p=1.0) (Table-3).

Table-3 : Comparison of mortality, intensive care unit stay, MV day rates of patients receiving Anakinra + high-dose MPZ and those receiving Anakinra + low-dose MPZ

	Patients receiving anakinra + high-dose MPZ (n=30)	Patients receiving anakinra + low dose (<250 mg) MPZ (n=10)	p value
Day of hospitalization in ICU	18.6±9.9	12.1±5.8	0.018
Mechanical ventilation day	8.23±8.6	4.4±4.9	0.193
Exitus rate	12 (%40)	4 (%40)	1.0

DISCUSSION

In this study, we evaluated the characteristics of patients who received Anakinra treatment, which acts on IL-1 blockade in the case of cytokine storm in COVID-19 disease, and the differences between the group who received high-dose steroids and did not receive Anakinra. And also patients receiving Anakinra+high dose MPZ and Anakinra+low-dose MPZ were compared.

Studies on anakinra treatment in intensive care are very limited. The first case report about the treatment; A 47-year-old female patient who could not use glucocorticoid therapy due to neuropsychiatric complaints. In this patient, clinical and laboratory stabilization was detected on the 10th day after the use of 100 mg s.c. Anakinra every 6 hours. On the 19th day, it was observed that there was no oxygen support (9). In other studies, it was stated that IL-6 and IL-1 blockade treatments reduced the rate of mechanical ventilation and were safe for inpatients who were followed up with severe COVID-19 pneumonia. In

a case series of 9 patients; it was observed that 8 patients went into a fever-free period within 3 days. They showed clinical and laboratory improvement. It was observed that CRP values started to decrease on the 5th day, and at the same time, it completely returned to normal on the 11th day in 5/8 patients. The regression of CT findings were noticed on the 5th-8th days (10).

In a study conducted in Italy,120 patients diagnosed with COVID-19 were examined. 65 patients were evaluated for hyperinflammation (Ferritin 1000 ng/ml, CRP 10 mg/dl) and respiratory failure, and then treated with pulse methylprednisolone (1 mg/kg, tapering to 14 days) and Anakinra (200 mg 3x1 for the first 3 days, then 100 mg 3x1, completed in 14 days). The 28-day mortality rate was found to be significantly lower in the treated group, p=0.005). There was no significant difference between the two groups in terms of infection rate and laboratory changes (11). In our study, there was no significant difference in the secondary infection rates between the patient groups who received and did not receive Anakinra.

Although, in a study conducted by Cavalli and his colleagues, the survival time without mechanical ventilation was 72% in the Anakinra group (5 mg/kg, 2 times a day) and 50% in the other group, there was no significant difference (p=0.15) (6). In another study comparing the patient group who received 52 Anakinra treatment (2x100 mg, 3 days, followed by 1x100 mg for 7 days) and the two groups who received 44 standard treatments (oral steroids were not given, but it as stated that some patients received 500 mg MPZ), the mortality rate and intubated patients number in the Anakinra group was found to be significantly less (12). Patients with saturation 93% or 3% oxygen therapy loss and saturation less than 93% under oxygen therapy greater than 6 lt/min were used as criteria in this study. It was observed that the mortality rate was higher in the patient group receiving Anakinra + high-dose MPZ, the duration of mechanical ventilation and the length of stay in the intensive care unit were longer. However, this may be due to the fact that the patients in our study were on high flow oxygen therapy and were in a more severe patient group.

In a SAVE-MORE double-blind randomized controlled trial enrolled 594 patients with suPAR (soluble urokinase plasminogen activator receptor) ≥6 ng ml^{-1}, as an indicator of progressive respiratory failure. In this study, shorter hospital stays and a lower mortality rate were found in the group that received anakinra treatment as a secondary endpoint. (7). In another study, it was suggested that respiratory failure could be prevented and pro/anti-inflammatory balance could be achieved compared to Anakinra treatment given according to suPAR level (13).

A total of 128 patients were analyzed in a single-center study. 63 of these patients were given early rescue therapy (30 of them Anakinra only (3x100 mg, 3 days, tapering off)), 33 of them Anakinra + steroid (1-2 mg/kg/day, tapering off) and 44 of the remaining 65 patients were given standard treatment. While being followed up with treatment, late rescue therapy (Anakinra/Tocilizumab) was started in 22. Indications for early treatment are (1) positive CT or PCR result with severe COVID-19 involvement, (2) PaO2/FiO2<300 and CRP or ferritin value is more than 3 times the normal range, (3) lymphocyte value is 1000/mm3 and D-dimer or LDH value is 3 times the normal value. Results showed that early rescue treatments reduced the mortality rate by 74% (p=0.04). There was no significant difference between delayed rescue treatment and standard treatment (14). In our study, as criteria, IL-6 ≥40 pg/ml and/or two of the following: CRP ≥100 mg/L, D-dimer ≥1000 ng/ml, ferritin ≥500 ng/ml and lactate dehydrogenase ≥300 U/L based on each criterion, 1 point was evaluated. Those with a score of ≥2 were considered to be in cytokine storm. Those with a score of <2 were given treatment according to their clinical status. After the patients received MPZ treatment, Anakinra treatment was given if there was no clinical improvement. When all patients were evaluated, there was no significant difference in terms of length of stay in the intensive care unit, mechanical ventilation days and mortality between those who received Anakinra and those with >7 or <7 symptom duration.

In a meta-analysis of 6 studies, it has been suggested that Anakinra treatment can have a beneficial role especially for selected patients with COVID-19 who have moderate or severe pneumonia accompanied by increased inflammatory marker levels (4).

As a result; it is found that the patients who received Anakinra treatment had a longer hospitalization day and mechanical ventilation period, and the higher mortality rate was attributed to the fact that this patient group had more severe course in our study. It is observed that the administration of anakinra treatment after low-dose and

high-dose MPZ treatment did not cause a significant difference in mortality rates. In addition, adequate data on the time of administration of Anakinra treatment could not be provided. The limitations of the study are the small number of patients and its retrospective nature. Therefore, more comprehensive, randomized, and controlled studies are needed.

Conflict of interest

The authors have no conflicts of interest to declare and no funding.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by Ankara City Hospital Ethical Committee (Approval date: 25.08.2021, Approval number: E1-21-1961)

REFERENCES

1. Jamilloux Y, Henry T, Belot A, Viel S, Fauter M, El Jammal T et al. Should we stimulate or suppress immune responses in COVID-19? Cytokine and anti-cytokine interventions. Autoimmun Rev. 2020;19(7):102567.
2. Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J et al. IL-6 Inhibition in Critically Ill COVID-19 Patients Is Associated With Increased Secondary Infections. Front Med (Lausanne). 2020;7:583897.
3. Bachove I, Chang C. Anakinra and related drugs targeting interleukin-1 in the treatment of cryopyrin-associated periodic syndromes. Open Access Rheumatol. 2014;6:15-25.
4. Kyriakoulis KG, Kollias A, Poulakou G, Kyriakoulis IG, Trontzas IP, Charpidou A et al. The Effect of Anakinra in Hospitalized Patients with COVID-19: An Updated Systematic Review and Meta-Analysis. J Clin Med. 2021;10(19):4462.
5. Kooistra EJ, Waalders NJB, Grondman I, Janssen NAF, de Nooijer AH, Netea MG et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. Crit Care. 2020;24(1):688.
6. Cavalli G, De Luca G, Campochiaro C, Della-Torre E, Ripa M, Canetti D et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. Lancet Rheumatol. 2020;2(6):e325-e331.
7. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nat Med. 2021;27(10):1752-1760.
8. López-Zúñiga MA, Moral AM, Ocaña-Granados A, et al. High-Dose Corticocorticosteroid Pulse Therapy increases the survival rate in COVID-19 patients at risk of cytokine storm. lancet (unpublished data).
9. González-García A, García-Sánchez I, Lopes V, Moreno-Arrones OM, Tortosa-Cabañas M, Elías-Sáenz I et al. Successful treatment of severe COVID-19 with subcutaneous anakinra as a sole treatment. Rheumatology (Oxford). 2020;59(8):2171-2173.
10. Aouba A, Baldolli A, Geffray L, Verdon R, Bergot E, Martin-Silva N et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. Ann Rheum Dis. 2020;79(10):1381-1382.
11. Bozzi G, Mangioni D, Minoia F, Aliberti S, Grasselli G, Barbetta L et al. Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: An observational cohort study. J Allergy Clin Immunol. 2021;147(2):561-566.e4.
12. Huet T, Beaussier H, Voisin O, Jouveshomme S, Dauriat G, Lazareth I et al. Anakinra for severe forms of COVID-19: a cohort study. Lancet Rheumatol. 2020;2(7):e393-e400.
13. Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N et al. An open label trial of anakinra to prevent respiratory failure in COVID-19. Elife. 2021;10:e66125.
14. Pontali E, Volpi S, Signori A, Antonucci G, Castellaneta M, Buzzi D et al. Efficacy of early anti-inflammatory treatment with high doses of intravenous anakinra with or without glucocorticoids in patients with severe COVID-19 pneumonia. J Allergy Clin Immunol. 2021;147(4):1217-1225.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):13-18

Received: 01 May 2022
Revised: 26 May 2022
Acccepted: 30 June 2022
DOI: 10.47482/acmr.1111796

ORIGINAL ARTICLE

Telemedicine Usage of Physicians and Views on Telemedicine

Muhammed Mustafa Uzan[1] **Umut Gök Balcı**[1]

1 Tepecik Training and Research Hospital, Department of Family Medicine, İzmir, Turkey

Abstract

Background: With the Covid-19 pandemic, those who care about working online from home office, computer and / or phone. it is aimed to pay attention to the use of telemedicine in the field of health and the attitudes of specialist physicians.

Methods: 85 specialist physicians participated in our research. The collected selection analysis was performed with the SPSS 22.0 program.

Results: Physicians working in internal sciences constituted 76.47% (n=65) of the study group. Among the matched branches, 24% (n=16) of clinical sciences consisted of pediatricians and their sub-branch physicians. 84.70% (n=72) of the physicians participating in the study did not perform video examination with telemedicine. Since it was only reviewed with telemedicine during working hours; 90.58% (n=77) of our study group stated that patients with at least 29 and below can be treated. During both face-to-face and telemedicine visual examinations, 83.52% (n=71) of our study group stated that a maximum of 9 patients could be treated by telemedicine. 85.88% of our study (percussion, palpation, auscultation) thought that telemedicine might be insufficient in evaluating the inspection user physical examination components. As for what precautions should be taken before telemedicine applications are popularized by the public, 83% of our physicians were supporters of the insurance company that wanted to intervene in helping the malpractice police. It should be considered as 76.47% (n=65) of our study group.

Conclusions: It is thought that telemedicine will facilitate the work of specialist physicians. However, more studies and data are needed before it can be used.

Keywords: Telemedicine, Pandemic, Physical Examination.

Cite this article as: *Uzan MM, Gök Balcı U. Telemedicine Usage of Physicians and Views on Telemedicine. Arch Curr Med Res. 2023;4(1):13-18*

Corresponding Author:
Muhammed Mustafa Uzan ,Tepecik Training and Research Hospital, Department of Family Medicine, İzmir, Turkey
E-Mail: mustafauzan65@gmail.com

INTRODUCTION

With the coronavirus pandemic (Covid-19) introduced into our lives, remote working from home or office by computer or phone has gained prominence. The success of remote working in certain areas has raised the question of whether this practice can also be successful in health.

By definition, telemedicine is the process of performing anamnesis and examination that takes place between the physician and the patient by seeing each other on any screen simultaneously with an online connection. Since physical contact with the patient is not possible, communication between the doctor and the patient should be maintained simultaneously through technological methods. Therefore, the existing infrastructure, internet network, and hospital data system should be fast and near perfect. Considering that the danger of contact with Covid-19 in health institutions is not over yet, using telemedicine may be a good option. For this reason, doctors examine patients who require green zone examination in hospitals in many countries through the telemedicine system (1).

It is stated that telemedicine was first used as a warning system based on smoke communication in an unknown epidemic (2).

In recent years, one of the most striking examples is a lung malignancy case in Antarctica in 1999. In this example, it is stated that a patient shared a mass in her chest via satellite, got diagnosed with malignancy, and the chemotherapy agents were delivered back to the patient using the airway (2).

In Turkey, this practice was first used in radiological imaging. Accordingly, images and reports were presented to an internet environment that could be accessed continuously. The "*Telemedicine and Teleradiology System Integration Guide*" prepared by the Department of System Management and Information Security was updated in July 2020 (3). The guide was specified as a system that includes imaging, teleconsultation, and teleradiology applications. Later, by logging into this system via the "*e-Nabız*" application it was made possible that the patient or physician can reach the patient's information. The system has become even more helpful with the integration of laboratory results. As a result, repeated examinations were to be prevented (4).

Departments such as Gastroenterology, General Surgery, Psychiatry, and Family Medicine of Kocaeli University Faculty of Medicine, already provide telemedicine services under the name of "web clinics" (5).

Regarding the legal aspect of telemedicine, the "*Framework for the Implementation Procedures and Principles of a TeleHealth Service*" issued in 2015 specifies the procedures and principles for medical services for aircraft and sea vehicles cruising within the Turkish Search and Rescue Area (5). In February 2021, the General Directorate of Health Information Systems of the Ministry of Health tried to create a "*dr.e.nabiz*" system and even published a user manual. (6). However, due to unknown reasons, the system was not implemented. Finally, with the "*Regulation on the Provision of Remote Health Services*" published in the official gazette on 10.02.2022, a crucial step was taken on how physicians can use this system (7). According to this regulation, health centers must get an operating permit from the Ministry of Health after fulfilling the minimum requirements.

In addition to the recent studies, in this study, telemedicine in health will be discussed to add a new aspect to the literature.

MATERIALS AND METHODS

Our study was conducted between 1.11.2021 and 31.12.2021 with the approval of Tepecik Education and Research Hospital Ethics Committee dated 15.10.2021 and numbered 2021/10-11. Our study is a descriptive, statistical study. We have included 85 specialist physicians in the study. The sample size was determined to be all available specialist physicians actively working at clinics within the attributed time. Not included were assistant physicians, emergency physicians, and preclinical physicians (biochemistry, microbiology, etc.) who do not work at clinics. Participants were asked 13 multiple-choice and 1 open-ended questions with a web-based questionnaire developed by researchers, using the remote communication method within the scope of Covid-19 measures.

The questionnaire included sociodemographic questions such as age, gender, the total period of service in the profession and specialty, as well as questions related to telemedicine. According to this, acting on assumptions, participants were asked some questions about what should be done before telemedicine is configured, the advantages or disadvantages of telemedicine in the future, and how many patients should be included in telemedicine.

SPSS 22.0 program was used to analyze the data obtained after the questions. Categorical variables were presented in tables with frequency and percentages.

RESULTS

The study group consisted of 63.52% (n=54) males and 36.48% (n=31) females.

The highest participation in the study was composed of internal medicine with 76.47% (n=65). Looking at the distribution of specialties, 24.61% (n=16) of clinical medicine consisted of the pediatric health and diseases department and its sub-branch physicians.

Looking at the total period of service in the profession, 70.58% (n=60) of the participants had worked for 14 years or less. 29.42% (n=25) of the participants had worked for 15 years or more. Sociodemographic data are given in Table 1.

Table 1. Sociodemographic Data

		n
Age		
39 and below	**70.58%**	**60**
40 and above	**29.42%**	**25**
Gender		
Female	**36.48%**	**31**
Male	**63.52%**	**54**
Department		
Internal Medicine	**76.47%**	**65**
Surgery Medicine	**23.53%**	**20**
Active Years in Profession		
14 and below	**70.58%**	**60**
15 and above	**29.42%**	**25**

84.70% (n=72) of the physicians participating in the study did not perform telemedicine video call examinations. Considering the assumption that only a video call examination will be performed with telemedicine during working hours, 90.58% (n=77) of our study group stated that a maximum of 29 patients could be examined.

Considering the assumption that the physicians will perform face-to-face and telemedicine examinations, 83.52% (n=71) of our study group stated that a maximum of 9 patients could be examined through telemedicine. 32.39% (n=23) of this rate noted that no patients could be examined.

Considering the assumption that telemedicine practices will be used by being ultimately disseminated throughout the country, 82.35% (n=70) of the study group noted that the legal ground and its comprehensive legal dimension should be addressed. Again, 85.88% (n=73) of the study group stated that telemedicine might be insufficient in evaluating other physical examination components (percussion, palpation, auscultation) other than inspection. In addition, 68.23% of the study group was worried about experiencing network and infrastructure problems.

In the study group, 88.24% (n=75) of the physicians believed that 50% or less of the target groups they provide health services for in their clinics could reach them by telemedicine using the existing internet infrastructure (Table 2).

Table 2. Telemedicine Related Data

Do You Currently Use Telemedicine?		n
Yes	15.30%	13
No	84.70%	72
What Do You Think About Telemedicine?		
I'm not interested because I think it will increase my workload.	18.82%	16
I'm not interested because it could cause malpractice.	24.70%	21
Although I am interested, I believe the physical examination of the patient should be conducted face to face.	50.59%	43
Considering the current pandemic situation, it may be possible with a certain number of appointments.	23.52%	20
If working from home can be improved, it can be a good alternative to examine patients from home with telemedicine only on certain days of the week and face-to-face in the polyclinic on other days.	27.06%	23
How Many Patients Can Be Examined with Only Telemedicine During Working Hours?		
10-19	58.82%	50
20–29	31.76%	27
30 and above	9.42%	8
How Many Patients Can Be Examined Through Telemedicine During Working Hours with Both Telemedicine and Face to Face Examination?		
0	27.06%	23
1-9	56.47%	48
10-19	11.77%	10
20 and above	4.70%	4
Is Telemedicine Applicable in Your Location?		
Yes	34.18%	29
No	65.82%	56
When You Consider Your Patients Who Apply to Your Clinic, How Many of Them Can Use Telemedicine?		
0 – 25%	60.00%	51
26 – 50%	28.24%	24
51 – 75%	9.41%	8
76 – 100%	2.35%	2
What Do You Think Will Be a Problem in Telemedicine Practices?		
It will take time to prepare documents such as e-prescription, e-report, etc.	40.00%	34
If the network of both parties is not good enough, there will be an image or sound problem.	68.24%	58
Even if there is no problem with the anamnesis, the chance of diagnosis and treatment will decrease since physical examination cannot be performed.	85.88%	73
It will not be effective unless its legal basis and legal dimension are improved.	82.35%	70

83.52% (n=73) of the physicians favored adding extra-specific articles to the malpractice policies of insurance companies about what measures should be taken before telemedicine practices are fully disseminated throughout the country. It was observed that 76.47% (n=65) of the study group were of the opinion that the infrastructure and the existing network should be accelerated (Figure 1).

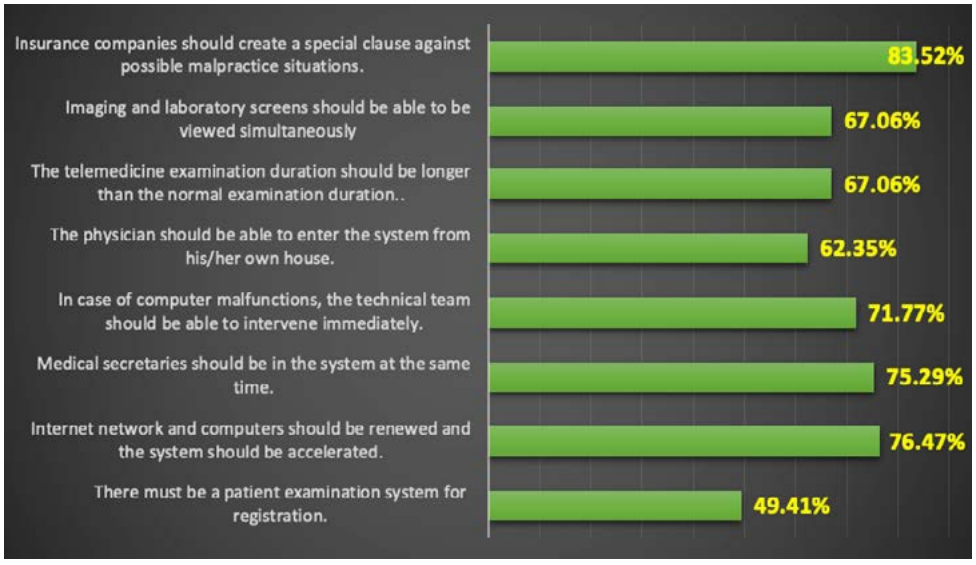


Figure 1. Measures Considered to be Taken Before Telemedicine.

Considering the benefits that telemedicine practices can provide, 85.88% (n=73) of the study group stated that patients with chronic diseases or disabilities would especially experience the ease of report renewal. 69.41% (n=59) of the study group agreed that telemedicine would be beneficial in preventing respiratory diseases such as Covid-19 (Figure 2).

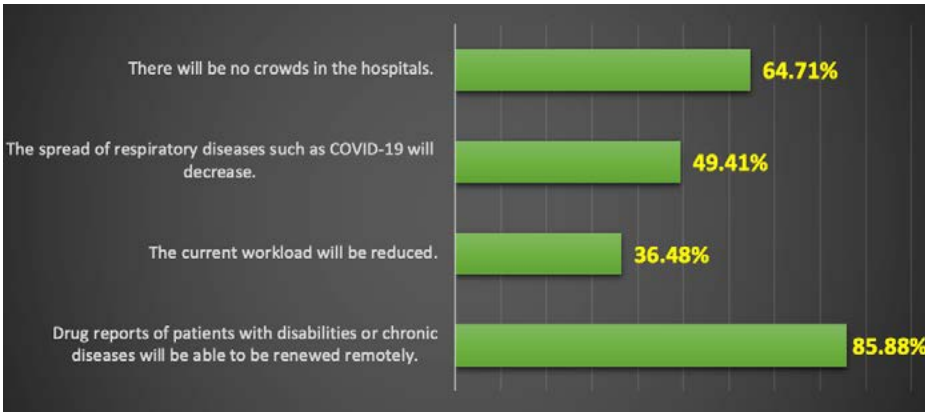


Figure 2. Advantages Telemedicine Will Bring

DISCUSSION

Considering all aspects of the literature, several studies were conducted in terms of patient satisfaction in telemedicine. However, studies on how the practice will work or what the minimum components should be are minimal.

A recent study on telemedicine, mentioning the lack of evidence in the relevant field and practice, legal gap (legal concerns), medical ethical concerns, medical prejudices, inadequacies of technical infrastructure, and server-receiver access to technology, stated that these aspects might pose an obstacle (8). In our study, too, most physicians expressed malpractice concerns and desires to strengthen the legal basis and medical malpractice insurance by increasing them. With the "*Regulation on the Provision of Remote Health Services*" published in the official gazette on 10.02.2022, we believe that the hesitations will be resolved, at least regarding which standards physicians will provide telemedicine services (7).

However, according to the studies in the literature, there are privacy concerns. In the study conducted by Gülay Y. et al. (9) on this subject, the reliability of health information on the internet is also considered a problem. It is stated that the protection of patients' medical information will be insufficient due to technical reasons (10, 11). Along with the *"Protection of Personal Data Act"* which has been frequently mentioned recently, a necessary and crucial step has been taken in this regard with the "*Regulation on the Protection and Processing of Data at the Social Security Institution"* published in the official gazette on 19.02.2022 (12).

In their study, Belazzi et al. (13) stated that telemedicine could be an effective method in increasing the patients' health, improving their precautions in primary care, and concluded that it has the potential to increase the adaptation of patients in the management of chronic diseases. Another study stated a decrease in emergency service admissions and hospitalizations of asthma and chronic obstructive respiratory disease patients thanks to telemedicine practices (14). Again, another study indicated that the practice caused a significant decrease in HbA1c levels in diabetic patients. (15).

In our study, physicians stated that they believe that disabled and chronic patients could benefit from telemedicine services at a high rate. There is a similarity with the literature in this respect. According to a recent study by Güner Y et al. (16) data were obtained on the decrease of the Covid-19 infection rate among healthcare professionals. With the decrease in the number of patients in hospitals, it may be hypothesized that Covid-19 or other respiratory diseases can be prevented.

The World Medical Association and the Standing Committee of European Doctors states that *"face-to-face interaction is gold standard communication*" and it has been noted that remote communication can only be a complementary element as long as the right technology and the requirements are provided. (17, 18). In addition, telemedicine practices may reduce face-to-face interactions with physicians and cause disease symptoms to be overlooked (5,19).

The study concluded that a complete systemic physical examination cannot be performed, and physicians may experience malpractice concerns due to insufficient pre-diagnosis. Still, telemedicine could be effective in situations that do not require a complete physical examination (report renewal, etc.). In the Covid-19 pandemic, remarkable progress has been made in the fight against Covid-19, as physicians called patients in isolation rather than video call examination (20). One of the most recent studies on this subject by Ören MM et al. stated that at least one follow-up of 1,042 patients was performed through telehealth service, and 26 physicians performed the follow-up of 860 patients for 21 days. In addition, it was determined that physicians made a total of 11,736 calls in this process (21). Obtaining these satisfactory results in video call examinations will also motivate physicians. At this point, we believe that telemedicine should be used to expand the range of health literacy.

Telemedicine will be an essential patient follow-up method, at least for internal medicine with a near-perfect infrastructure and network in the future.

In our study, physicians stated that even if anamnesis and inspection were performed face to face, palpation and auscultation stages could not be completed. However, they were of the opinion that this issue should be addressed.

It is a fact that physicians have turned to defensive medicine, especially in recent years, while practicing their profession. Integrating the minimum technological components required in the practice of medicine into telemedicine by considering costs/effectiveness will provide convenience for physicians and patients. Detailed studies on the subject are insufficient; the article was written with the available sources.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by Tepecik Education and Research Hospital Ethics Committee (Approval date: 15.10.2021 Approval number: 2021/10-11)

REFERENCES

1. Portnoy J, Waller M, Elliott T. Telemedicine in the Era of Covid-19. J Allergy Clin Immunol Pract. 2020;8(5):1489-1491.
2. Waller M, Stotler C. Telemedicine: A Primer. Curr Allergy Asthma Rep. 2018;18(10):54.
3. T.C. Sağlık Bakanlığı Sağlık Bilgi Sistemleri Genel Müdürlüğü. Ulusal Projeler Yönetim Koordinatörlüğü. Teletıp ve Teleradyoloji Sistemi Entegrasyon Kılavuzu. 2022. Available at https://www.teletip.saglik.gov.tr/docs/Telet%C4%B1pEntegrasyonK%C4%B1lavuzuV3.39.pdf Accessed October 24, 2022
4. Sungur C. Teletıp Uygulamalarında Hasta Memnuniyeti: Bir Sistematik Derleme Çalışması. Hacettepe Sağlık İdaresi Dergisi. 2020;(3):505-522
5. Dilbaz B, Kaplanoğlu M, Kaplanoğlu DK. Teletıp ve Telesağlık: Geçmiş, Bugün ve Gelecek. Eurasian Journal of Health Technology Assessment. 2020;4(1):40-56.
6. Yıldırım B, Uzan MM, Egici MT. Telemedicine/Telehealth in Preventive Medicine. Archives of Current Medical Research. 2022;3(1):1-5.
7. Resmî Gazete. T.C. Sağlık Bakanlığı. Uzaktan Sağlık Hizmetlerinin Sunumu Hakkında Yönetmelik. 2022. Available at https://www.resmigazete.gov.tr/eskiler/2022/02/20220210-2.htm Accessed October 24, 2022
8. Dağdelen S. Teletıp Uygulamaları: Bugünden Geleceğe Öngörü ve Beklentiler. In: Kutsal YG, Aslan D editors. Teletıp Yaşlılık ve Teletıp Uygulamaları. Ankara: 2021 p.127-136.
9. Yıldırım G, Karagözoğlu Ş, Yıldız E, Özbay S. Determination of Advanced Technology Usage Level of Physicians Working in Hospitals in a Province. Lokman Hekim Journal. 2022;12(1):126-135
10. Ataç A, Kurt E, Yurdakul SE. An Over View to Ethical Problems in Telemedicine Technology. Procedia – Social and Behavioral Sciences. 2013;103(26):116–121
11. İzgi C. Personal health data in the context of the concept of privacy. Turkish Journal of Bioethics. 2014;1(1):25-37
12. Resmî Gazete. Sosyal Güvenlik Kurumu Başkanlığı. Sosyal Güvenlik Kurumu Nezdindeki Verilerin Korunmasına ve İşlenmesine İlişkin Yönetmelik. 2022. Available at https://www.resmigazete.gov.tr/eskiler/2022/02/20220219-4.htm Accessed October 24, 2022
13. Bellazzi R, Arcelloni M, Ferrari P, Decata P, Elena Hernando M, García A, et al. Management of patients with diabetes through information technology: tools for monitoring and control of thepatients' metabolic behavior. Diabetes Technology & Therapeutics. 2004;6(5):567-78
14. McLean S, Nurmatov U, Liu JL, Pagliari C, Car J, Sheikh A. Telehealth Care for Chronic Obstructive Pulmonary Disease: Cochrane Review and Meta-analysis. Br J Gen Pract. 2012;62(604):e739-49.
15. Polisena J, Tran K, Cimon K, Hutton B, McGill S, Palmer K. Home Telehealth for Diabetes Management: A Systematic Review and Meta-analysis. A Journal of Pharmacology and Therapeutics. 2009;11(10):913-930
16. Güner Y, Güner KE, Çilingir D. Technological Innovations in New Type Coronavirus and Health System. Bezmialem Science. 2021;9(Supplement 1):69-73
17. World Media Association (WMA). WMA Statement on the Ethics of Telemedicine. 2007. Available at https://www.wma.net/policies-post/wma-statement-on-the-ethics-of-telemedicine/ Accessed October 24, 2022
18. Medicins Europeens European Doctors (CPME). Ethical Guidelines in Telemedicine. 1997. Available at https://www.cpme.eu/api/documents/adopted/cp-1997_033.pdf Accessed October 24, 2022
19. Kutsal YG. Teletıp. In: Kutsal YG, Aslan D editors. Teletıp Yaşlılık ve Teletıp Uygulamaları. Ankara: 2021. p. 1-16.
20. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. Temaslı Takibi, Salgın Yönetimi, Evde Hasta İzlemi ve Filyasyon. 2021 Available at https://covid19.saglik.gov.tr/Eklenti/41623/0/covid-19rehberitemaslitakibievdehastaizlemivefilyasyon-021021pdf.pdf Accessed October 24, 2022
21. Ören MM, Özgülnar N, Canbaz S, Karabey S, Önal AE, Öncül MO. An Integrated Care Model Based On Hospital and Home During The Covid-19 Pandemic: Telehealth. J Ist Faculty Med. 2022;85(1):9-14.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):19-23

Received: 17 September 2022
Revised: 4 November 2022
Acccepted: 24 November 2022
DOI: 10.47482/acmr.1175461

ORIGINAL ARTICLE

A new prognostic factor in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan: Hemoglobin, albumin, lymphocytes and platelets (HALP) score

Mustafa Korkmaz[1] **Melek Karakurt Eryılmaz**[1] **Mehmet Zahid Koçak**[1]
Aykut Demirkıran[1] **Murat Araz**[1] **Mustafa Karaağaç**[1] **Mehmet Artaç**[1]

1 Necmettin Erbakan University, Faculty of Medicine, Department of Medical Oncology, Konya, Turkey

Abstract

Background: In this study, we aimed to investigate whether hemoglobin, albumin, lymphocytes and platelets (HALP) score is a prognostic marker in bevacizumab plus irinotecan treatment in patients with recurrent glioblastoma multiforme (GBM).

Methods: Thirty-one patients were included in this study. The HALP score was calculated according to the formula: hemoglobin (g/L) x albumin (g/L) x lymphocytes (/L)/platelets (/L). The study population was divided into 2 groups (high-low) according to the HALP score. Overall survival (OS) and progression-free survival (PFS) of the two groups were compared.

Results: Median PFS and OS were 4.5 (0.9-14.9) and 8 (0.9-21.3) months, respectively. The median PFS of the low HALP score group was 1.85 (1.3-3.37) months, and of the high HALP score group was 4.96 (0.9-14.9) months (p=0.03). The OS of the high HALP score group (9.63 [7.28-11.9]) was statistically higher compared with the low HALP score group (2.26 [0.88-3.65]) (p<0.001). In multivariate Cox regression analysis, low HALP score was a significant poor prognostic factor for OS compared with high HALP score (HR: 0.063, p<0.001).

Conclusions: HALP score was determined as an independent prognostic factor for OS and PFS. Higher HALP score was associated with better OS and PFS.

Keywords: Bevacizumab, Biomarker, Glioblastoma, Prognosis.

Cite this article as: *Korkmaz M, Eryılmaz Karakurt M, Koçak MZ, Demirkıran A, Araz M, Karaağaç M, Artaç M. A prognostic factor in patients with recurrent glioblastoma multiforme treated with bevacizumab plus irinotecan: Hemoglobin, albumin, lymphocytes and platelets (HALP) score. Arch Curr Med Res. 2023;4(1):19-23*

Corresponding Author:
Mustafa Korkmaz, Necmettin Erbakan University,
Faculty of Medicine, Department of Medical Oncology,
Konya, Turkey
E-Mail: dr.musstafa@gmail.com

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. The standard treatment approach is the combination of adjuvant radiation therapy with concurrent and adjuvant temozolomide following surgery. The median overall survival (OS) is 15 months, and even with the most appropriate treatment, most patients die within two years (1, 2).

GBM is a highly vascularized tumor that requires extensive collection of blood vessels to combat hypoxia. Vascular endothelial growth factor (VEGF)-mediated inhibition of angiogenesis by bevacizumab is a therapeutic strategy for GBM at the center of several clinical studies (3). A meta-analysis of 14 clinical studies showed that bevacizumab did not improve OS, but improved radiographic response rates and progression-free survival (PFS) in GBM, either as a single agent or in combination with chemotherapy (4). And it is currently only offered as salvage therapy for treatment-resistant cases. It has been shown that radiological imaging, clinical and laboratory parameters predict bevacizumab response in recurrent GBM (5-7).

Hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been shown to be a new and potential prognostic indicator for various malignancies (8-17). This is the first study to investigate the prognostic significance of the HALP score in patients with recurrent GBM treated with bevacizumab plus irinotecan.

MATERIALS AND METHODS

In this retrospective study, all patients with a pathologically confirmed diagnosis of GBM followed in our clinic between April 2015 and July 2019 were examined. Patients who developed recurrence after adjuvant treatments and who received bevacizumab plus irinotecan in the first-line treatment were determined. Thirty-one patients whose hemoglobin, albumin, lymphocyte and platelet values could be reached at the beginning of the treatment and who received at least 3 cycles of this treatment and whose response was evaluated were included in the study. Since Isocitrate dehydrogenase mutation, 1p/19q co-deletion, O6-methylguanine-DNA methyltransferase could not be studied in our center, analysis could not be performed. This study was approved by the clinical research ethics committee of the Necmettin Erbakan University Meram Faculty of Medicine (Date: 17.07.2020 number: 2020/2749).

Albumin and hemogram levels before receiving treatment were recorded from the electronic files of the patients. The HALP score was calculated according to the formula: hemoglobin (HB) (g/L) x albumin (g/L) x lymphocytes (/L)/platelets (/L). PFS was defined as the time from the initiation of bevacizumab plus irinotecan to the first radiological progression, while OS was defined as the time from the initiation of therapy to death from any cause.

The optimal cut-off value of the HALP score was analyzed using X-tile software version 3.6.1 (Yale University, New Haven CT, USA). Kaplan-Meier method was used for survival analysis with the log-rank test used to statistical difference. A univariate Cox proportional hazards regression model was used to evaluate the prognostic value of each variable for OS. Multivariate Cox proportional hazards regression models were used to analyze independent prognostic factors. Homogenous variables in study groups according the HALP score were compared by independent samples t-test and expressed as mean ± standard deviation. Non-homogenous variables were compared by Mann-Whitney U test and expressed as median (minimum-maximum). Chi-square test or Fisher exact test was performed to comparison of categorical variables. A p value of <0.05 is considered as statistically significant. Data were analyzed by SPSS software. (SPSS 15.0; IBM Inc., Chicago, IL, USA).

RESULTS

Thirty-one patients were included the study, 5 (16%) were female and 26 (84%) were male. The mean age of all subjects was 46.3±12.2 years. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 22 (71%) patients was 1, and that of 9 (29%) patients was 2. Median follow-up time was 7.86 (0.33-21.3) months. 27 (87.1%) patients had received adjuvant temozolomide. Laboratory parameters were as follows; HB: 14.09 (11.2-18.6) g/dl, albumin 39.1 (29-49) g/L, lymphocyte 1.2 (0.2-2.70) 10^3/μL, platelet 229 (79-385) 10^9/L. Median PFS and OS were 4.5 (0.9-14.9) and 8 (0.9-21.3) months, respectively. The cut-off value for the HALP score for OS was 18 in analysis with using X-tile software (Figure 1). Those with a HALP score of 18 and below were defined as the low HALP score group, and those above 18 were defined as the high HALP

score group. Of the 31 patients, 13 had a low HALP score and 18 had a high HALP score. Age, gender, and ECOG-PS were not statistically different between the two groups (low and high HALP score group) (p=0.76, p=0.1,-p=0.12, respectively). There was no statistical difference between the histological type, residual tumor, tumor location, and surgery type low and high HALP score groups (p>0.05 for all, Table 1). The median PFS of the low HALP score group was 1.85 (1.3-3.37) months, and of the high HALP score group was 4.96 (0.9-14.9) months. This difference was statistically significant (p=0.03). The OS of the high HALP score group (9.63 [7.28-11.9]) was statistically higher compared with low HALP score group (2.26 [0.88-3.65]) (p<0.001).

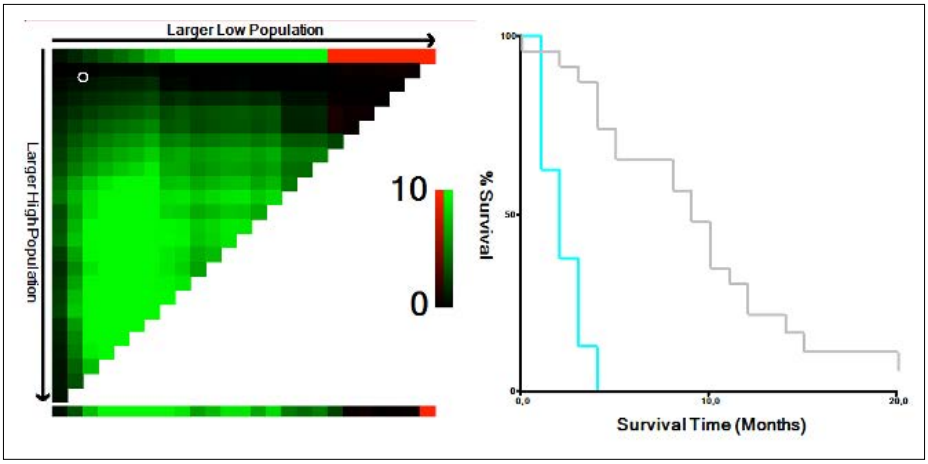


Figure 1: Cut- off values for the HALP score (hemoglobin, albumin, lymphocyte, and platelet) by X-tile software version 3.6.1.

Table 1: Demographic and clinical characteristics of the patients according to the HALP score. (HALP: hemoglobin, albumin, lymphocyte, and platelet)

≤18		The HALP score		
		>18	p	
Age (years) (mean ± st.d.)		47.5±12.7	45.9±12.2	0.76
Gender (n)	Female	4 (12.9)	1 (3.2)	0.01
	Male	4 (12.9)	22 (71)	
ECOG-PS (n)	1	4 (12.9)	18 (28.1)	0.12
	2	4 (12.9)	5 (16.1)	
Histological type (n)	GBM	6 (19.4)	20 (64.5)	0.42
	Secondary GBM	2 (6.5)	3 (9.7)	
Residual tumor (n)	No	2 (6.5)	11 (35.5)	0.41
	Yes	6 (19.4)	12 (38.7)	
Adjuvant temozolomide (n)	No	2 (6.5)	2 (6.5)	0.26
	Yes	6 (19.4)	21 (67.7)	
Progression free survival (month) (median[min-max])		1.85 (1.3-3.37)	4.96(0.9-14.9)	**0.03**

ECOG-PS: The Eastern Cooperative Oncology Group Performance Status. GBM: Glioblastoma multiforme.

Univariate analysis showed that HALP Score (≤18 vs >18), residual tumor (no vs. yes), and ECOG-PS (1 vs. 2) were important prognostic factors (Table 2). HALP Score was a significant prognostic factor; patients with low HALP score had a poorer prognosis than high HALP score (≤ 18 vs. >18; HR: 0.063, 95% CI: 0.016-0.249, p<0.001). The multivariate analysis showed that HALP score (p=0.003), and residual tumor (p=0.029) were significant prognostic factors. In multivariate Cox regression analysis, low HALP score was a significant poor prognostic factor for OS compared with high HALP score (≤ 18 vs. >18; HR: 0.063, 95% CI: 0.016-0.249, *p*<0.001) (Table 2).

Table 2: Univariate and multivariate analyses of overall survival in patients with brain tumor.

	Univariate analyses			Multivariate analyses		
Variable	HR	95% CI	p	HR	95% CI	p
HALP Score (≤18 / >18)	0.063	0.016-0.249	**<0.001**	0.077	0.015-0.408	**0.003**
Residual tumor (No/Yes)	3.445	1.449-8.192	**0.015**	2.69	0.222-3.646	**0.029**
Gender (F/M)	0.414	0.151-1.164	0.08	0.89	0.222-3.646	0.88
ECOG-PS (1/ 2)	3.07	1.230-7.680	**0.016**	2.14	0.841-5.492	0.11

F: female; M: male; HALP – hemoglobin, albumin, lymphocyte, and platelet; HR – hazard ratio; CI – confidence interval.

DISCUSSION

We found that the HALP score at the beginning of treatment in recurrent GBM patients treated with bevacizumab plus irinotecan is an independent prognostic factor for PFS and OS. PFS and OS were significantly shorter for patients in the low HALP score group than those in the high HALP score group.

As known, while hemoglobin and albumin levels are associated with the nutrition status of the body, lymphocytes and platelets are related to the immune system. The HALP score has been usually used to predict the prognosis of some types of cancers by using the character of showing the two main roles (inflammation and nutrition status) in the prognosis of cancer (16). Chen et al. firstly described this HALP score to predict the prognosis of gastric cancer. In 1332 patients with gastric cancer who underwent gastrectomy, the preoperative HALP ≥ 56.8 group had a significantly better prognosis than the HALP < 56.8 group (8). Also, the prognostic effectiveness of the HALP score has been investigated in, esophageal squamous cell cancer (9), pancreatic cancer (10), colorectal cancer (11), renal cell carcinoma (12), bladder cancer (13), prostate cancer (14, 15), and small cell lung cancer (16, 17). Low HALP score was associated with worse survival outcomes in all studied cancers. However, the optimum cut-off value was different in each study, so it is very important to define the optimal cut-off value of HALP score.

Bevacizumab, a humanized monoclonal IgG1 antibody, acts to bind to human VEGF and inhibit its activity (18). The objective response rate achieved with the combination of bevacizumab plus irinotecan in recurrent GBM is 38%, and the median PFS and OS are 5.6 and 9.2 months, respectively (19). Predictive factors of bevacizumab response in recurrent GBM have been investigated in several studies. In these studies, it has been shown that the development of hypertension and proteinuria, high eosinophil and lymphocyte levels, and low C-reactive protein (CRP)- to albumin ratio (CAR) and platelet to lymphocyte ratio (PLR) values due to bevacizumab treatment are predictive for better survival (6, 7, 20).

Inflammatory factors have been recognized as an important contributing factor to the complexity and lethality of GBM. Therefore, many studies are carried out considering that inflammatory factors may be prognostic factors for cancers, and the search continues. Previous studies have reported that tumor necrosis factor alpha and CRP are noticeably higher in patients with glioblastoma compared to healthy controls. However, the relationship between inflammatory factors and glioma risk or prognosis is controversial. There are positive and negative studies on this (21). A recent study showed that elevations

in all inflammatory markers were associated with poor OS in those using bevacizumab in recurrent GBM, but only elevated CAR and PLR were reported to be an independent predictive factor. The prognostic significance of the increase in neutrophil to lymphocyte ratio has not been demonstrated in this study (20).

This is the first study to show that the HALP score predicts the response to bevacizumab plus irinotecan treatment in patients with recurrent GBM. This score will be useful because it can be easily calculated with routine blood tests, is cheap and objective. If these results are confirmed by studies involving large patients group, they can be used in routine practice.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the Necmettin Erbakan University School of Medicine Ethical Committee (Approval date: 17.07.2020, Approval Number: 2020/2749).

REFERENCES

1- Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-96.

2- Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459-66.

3- Hundsberger T, Reardon DA, Wen PY. Angiogenesis inhibitors in tackling recurrent glioblastoma. Expert Rev Anticancer Ther. 2017;17(6):507-515.

4- Kaka N, Hafazalla K, Samawi H, Simpkin A, Perry J, Sahgal A et al. Progression-Free but No Overall Survival Benefit for Adult Patients with Bevacizumab Therapy for the Treatment of Newly Diagnosed Glioblastoma: A Systematic Review and Meta-Analysis. Cancers (Basel). 2019;11(11):1723.

5- Kickingereder P, Wiestler B, Burth S, Wick A, Nowosielski M, Heiland S et al. Relative cerebral blood volume is a potential predictive imaging biomarker of bevacizumab efficacy in recurrent glioblastoma. Neuro Oncol. 2015;17(8):1139-47.

6- Carvalho B, Lopes RG, Linhares P, Costa A, Caeiro C, Fernandes AC et al. Hypertension and proteinuria as clinical biomarkers of response to bevacizumab in glioblastoma patients. J Neurooncol. 2020;147(1):109-116.

7- Vaios EJ, Winter SF, Muzikansky A, Nahed BV, Dietrich J. Eosinophil and lymphocyte counts predict bevacizumab response and survival in recurrent glioblastoma. Neurooncol Adv. 2020;2(1):vdaa031.

8- Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. Oncotarget. 2015;6(38):41370-82.

9- Hu SJ, Zhao XK, Song X, Lei LL, Han WL, Xu RH et al. Preoperative maximal voluntary ventilation, hemoglobin, albumin, lymphocytes and platelets predict postoperative survival in esophageal squamous cell carcinoma. World J Gastroenterol. 2021;27(4):321-335.

10- Xu SS, Li S, Xu HX, Li H, Wu CT, Wang WQ et al. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. World J Gastroenterol. 2020;26(8):828-838.

11- Jiang H, Li H, Li A, Tang E, Xu D, Chen Y et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. Oncotarget. 2016;7(44):72076-72083.

12- Peng D, Zhang CJ, Tang Q, Zhang L, Yang KW, Yu XT et al. Prognostic significance of the combination of preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in patients with renal cell carcinoma after nephrectomy. BMC Urol. 2018;18(1):20.

13- Peng D, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS et al. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. Sci Rep. 2018;8(1):794

14- Guo Y, Shi D, Zhang J, Mao S, Wang L, Zhang W et al. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score is a Novel Significant Prognostic Factor for Patients with Metastatic Prostate Cancer Undergoing Cytoreductive Radical Prostatectomy. J Cancer. 2019;10(1):81-91.

15- Kaya C, Caliskan S, Sungur M, Aydın C. HALP score and albumin levels in men with prostate cancer and benign prostate hyperplasia. Int J Clin Pract. 2021;75(3):e13766.

16- Shen XB, Zhang YX, Wang W, Pan YY. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score in Patients with Small Cell Lung Cancer Before First-Line Treatment with Etoposide and Progression-Free Survival. Med Sci Monit. 2019;25:5630-5639.

17- Yang N, Han X, Yu J, Shu W, Qiu F, Han J. Hemoglobin, albumin, lymphocyte, and platelet score and neutrophil-to-lymphocyte ratio are novel significant prognostic factors for patients with small-cell lung cancer undergoing chemotherapy. J Cancer Res Ther. 2020;16(5):1134-1139.

18- Ghiaseddin A, Peters KB. Use of bevacizumab in recurrent glioblastoma. CNS Oncol. 2015;4(3):157-69.

19- Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733-40.

20- Besiroglu M, Shbair AT, Yasin AI, Topcu A, Turk HM, Demir T. Systemic Inflammatory Markers for Prediction of Bevacizumab Benefit in Glioblastoma Multiforme. J Coll Physicians Surg Pak. 2021;31(1):39-44.

21- Feng Y, Wang J, Tan D, Cheng P, Wu A. Relationship between circulating inflammatory factors and glioma risk and prognosis: A meta-analysis. Cancer Med. 2019;8(17):7454-7468.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):24-30

Received: 12 September 2022
Revised: 24 November 2022
Accepted: 30 November 2022
DOI: 10.47482/acmr.1174345

ORIGINAL ARTICLE

The importance of linear measurements made using panoramic radiography in pre-implant site assessment: actual vs. measured

Raif Alan[1] **Ahmet Afşin Erbeyoğlu**[2]

1 Çanakkale Onsekiz Mart University, Faculty of Dentistry, Department of Periodontology, Çanakkale, Turkey.
2 Private Practice, Division of Periodontics, İstanbul, Turkey.

Abstract

Background: In order to reduce post-operative failure and ensure successful rehabilitation, patients scheduled for dental implant treatment are often evaluated pre-operatively using radiographic images in addition to clinical examination. This study aimed to investigate the reliability of digital panoramic radiography in the pre-implant site assessment.

Methods: Panoramic images of 150 patients with a total of 396 implants placed in the maxilla (n=165) and mandible (n=231), were examined in the study. Radiographic measurements (vertical and horizontal) were recorded on the computer using the automatic calibration tab for each radiograph and compared with the actual implant dimensions. Moreover, the effects of location, gender, and change in dimensions on magnification rate (MR) were also investigated. The measurements were made by two experienced observers.

Results: Panoramic vertical measurements were significantly higher in both the maxilla and mandible compared to the actual implant lengths ($p<0.05$), with excellent inter-observer agreement values ($r=0.969$). MR of horizontal measurements showed significant differences just in the premolar and molar regions ($p<0.05$). MR exhibited negative correlation with increases in the implant length and diameter.

Conclusions: When attempting to use panoramic radiographs for pre-implant site assessment, the MRs should be considered along with a good clinical examination and experience.

Keywords: Dental Implants, Dimensional Measurement Accuracy, Image Processing, Panoramic Radiography.

Cite this article as: *Alan R, Erbeyoğlu AA. The importance of linear measurements made using panoramic radiography in pre-implant site assessment: actual vs. measured. Arch Curr Med Res. 2023;4(1):24-30*

Corresponding Author:
Raif Alan, Çanakkale Onsekiz Mart University, Faculty of Dentistry, Department of Periodontology, Çanakkale, Turkey.
E-Mail: drraifalan17@gmail.com

INTRODUCTION

Prior to dental implant surgery, evaluation of the height of the residual alveolar bone in the region where the dental implants will be inserted, the position of the base of the nose and maxillary sinus, the position of the mandibular canal, the determination of lesions in the bones and the distance to the adjacent dental roots are prerequisites (1). The presence of a restricted bone volume and weak bone quality may result in early implant failure and less predictable bone apposition. A comprehensive radiographic evaluation is crucial to evaluate these factors and to inform patients about dental implants for successful rehabilitation. The purpose of the pre-operative radiographic assessment is to detect pathological lesions, determine critical structures in potential implant sites and the guidance of the implants. Bone quantity and quality will affect the selection of implants by number, diameter, length, and type (2).

In recent years, the frequency of Computed Tomography (CT) and Cone Beam Computed Tomography (CBCT) usage has increased for pre-implantation evaluation. CT and CBCT techniques allow the anatomical osseous structures to be displayed in three planes in accordance with the dimensions and show the best image quality without distortion (3-5). However, if there are metal components, CT may produce artifact lines. In addition, another disadvantage of CT is that the patient has to stand still for a relatively long-time during imaging (6,7).

Panoramic radiographs are often used as a radiographic method for the preparation of pre-implant evaluation and treatment protocols (1). Panoramic radiographs are fast, inexpensive and their radiation dose is low in comparison to CTs and other equivalent/similar techniques (6,7). On the other hand, unpredictable distortion of structures, low level of repeatability (2) and uneven magnification of parts (8) are the main disadvantages of panoramic radiography.

Due to the widespread use and sometimes first choice method, it becomes a question of whether panoramic radiographs are reliable due to these disadvantages. The aim of this study is to examine the reliability of panoramic radiography in the pre-implant region evaluation by considering the dimensions of the dental implants placed.

MATERIALS AND METHODS

This retrospective study was approved by the ethics committee of the Faculty of Dentistry at Necmettin Erbakan University (Date 08.2018, Decision Number 2018/02) and conducted in the Department of Periodontology, Faculty of Dentistry, Necmettin Erbakan University. The sample group was gathered from the panoramic radiographic images (pre-op. and postop.) of 150 patients with implants placed in the edentulous areas. A total of 396 implants from 7 different implant systems were placed in the edentulous areas.

Panoramic images were obtained with Morita Veraviewepocs 3D Digital Panoramic X-Ray Device (J. Morita Corp, Kyoto, Japan). Dental implant application areas were divided into four groups; anterior, canine, premolar and molar regions. Radiographic measurements (vertical and horizontal) were recorded on the computer using the automatic calibration tab for each radiograph and compared with the actual implant dimensions. To determine the radiographic linear measurements of surgically placed implants, the distance corresponding to the length and diameter of implant recommended by the dental implant manufacturers was measured. Moreover, the magnification rate (MR) was calculated for each implant as follows: (radiological implant dimensions/actual implant dimensions)x100 (1). In addition, the effects of gender, implant sites (anterior, canine, premolar or molar region), locations (maxilla or mandible), increase in length and diameter on MR were also investigated. Dental implant application and radiographic analysis were performed by two experienced physicians.

The data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, USA) for Windows. All data were first analyzed descriptively and presented as mean, SD, min and max values. Kruskal-Wallis and Mann-Whitney U test were used to compare the mean values. Correlation between observers was analyzed using Pearson correlation coefficient. The significance level was set at $p<0.05$.

RESULTS

Of the 396 implants, 165 and 231 implants were placed in the maxilla and mandible, respectively. The distribution of the actual length and diameters of implants analyzed according to their placement areas were presented in Figure 1.

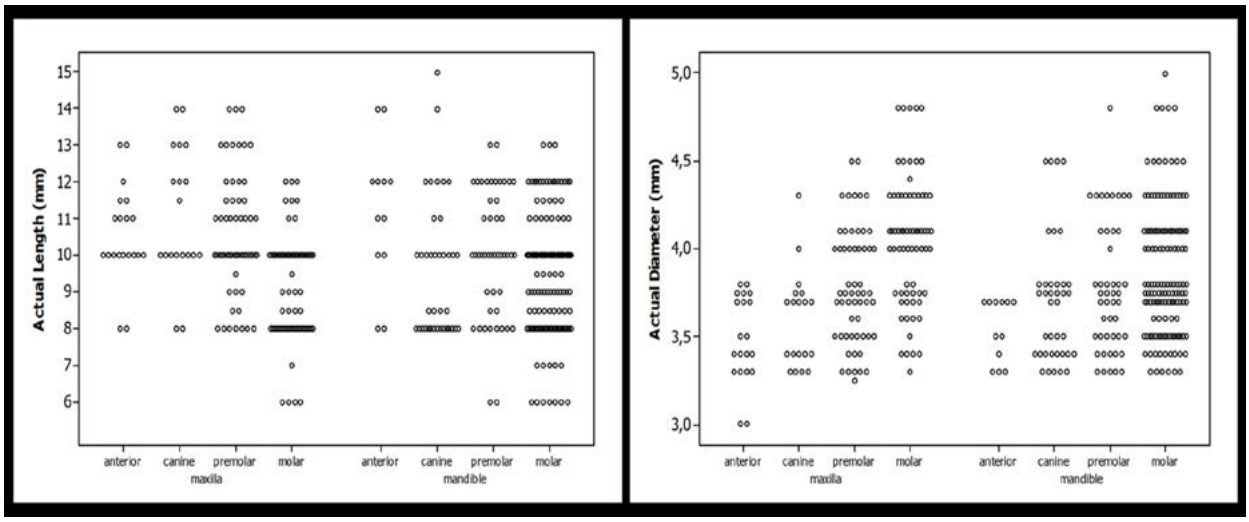


Figure 1. Distribution of actual implant dimensions according to their placement areas.

An evaluation with respect to the locations showed that inter-observer reliability was good and the correlation coefficient for vertical measurements was 0.969. The radiographic vertical measurements were significantly high in both maxilla and mandible, compared with the known implant lengths ($p<0.05$). On the other hand, significant differences between observers were found according to horizontal measurements in both maxilla and mandible although excellent inter-observer agreement values were obtained in vertical measurements (Table 1).

Table 1. Comparison of the radiographic and actual implant dimensions.

	Maxilla (*n*=165)								
	Length					**Diameter**			
	Mean	SD	Min	Max		Mean	SD	Min	Max
Actual	10.03	1.72	6.00	14.00		3.84	0.39	3.00	4.80
Obs-1	10.42[a]	1.66	7.25	14.90		3.86	0.53	2.55	5.45
Obs-2	10.51[a]	1.66	7.00	14.80		3.73[ab]	0.50	2.60	5.00
p-value	0.006				**p-value**	0.024			
	Mandible (*n*=231)								
	Length					**Diameter**			
	Mean	SD	Min	Max		Mean	SD	Min	Max
Actual	9.70	1.76	6.00	15.00		3.81	0.37	3.30	5.00
Obs-1	10.20[a]	1.78	5.45	15.00		4.02[a]	0.49	2.85	5.80
Obs-2	10.31[a]	1.76	6.10	14.80		3.89[b]	0.50	2.90	5.80
p-value	<0.001				**p-value**	<0.001			

These notations must be deleted because the actual p-values were indicated in the table.

[a]statistically significant difference according to actual measures

[b]statistically significant difference according to Obs-1

Comparison of the total MRs of the length and diameter according to the location (maxilla or mandible), and the anterior, canine, premolar, and molar regions for both observers were presented in Table 2. There were significant differences between MR of horizontal measurements just in the premolar and molar regions ($p<0.05$).

Table 2. Comparison of the MRs of the length and diameter according to the regions.

	Maxilla (*n*=165)								
	MR_{Length} mean±SD					$MR_{Diameter}$ mean±SD			
	anterior	canine	premolar	molar		anterior	canine	premolar	molar
Obs-1	0.99±0.06	1.01±0.04	1.04±0.04	1.07±0.06		1.00±0.15	1.02±0.14	0.99±0.09	1.02±0.10
Obs-2	1.01±0.04	1.04±0.05	1.05±0.04	1.08±0.07		0.97±0.13	1.00±0.10	0.96±0.08	0.98±0.09
p-value	*0.279*	*0.075*	*0.339*	*0.711*		*0.279*	*0.430*	0.040	0.015
	Mandible (*n*=231)								
	MR_{Length} mean±SD					$MR_{Diameter}$ mean±SD			
	anterior	canine	premolar	molar		anterior	canine	premolar	molar
Obs-1	1.02±0.07	1.06±0.04	1.04±0.05	1.06±0.04		1.14±0.17	1.13±0.11	1.07±0.11	1.03±0.09
Obs-2	1.06±0.07	1.07±0.04	1.06±0.04	1.07±0.05		1.06±0.14	1.09±0.13	1.04±0.10	1.00±0.09
p-value	*0.119*	*0.063*	*0.067*	*0.413*		*0.165*	*0.104*	*0.063*	0.001

These notations must be deleted because the actual p-values were indicated in the table.

MR= Magnification Ratio

The effects of an increase in length and diameter of the implant on MRs for both observers were presented in Figure 2. MR exhibited negative correlation with increasing in the implant length and diameter. Increase in length and diameter of the implant decrease MRs for both observers.

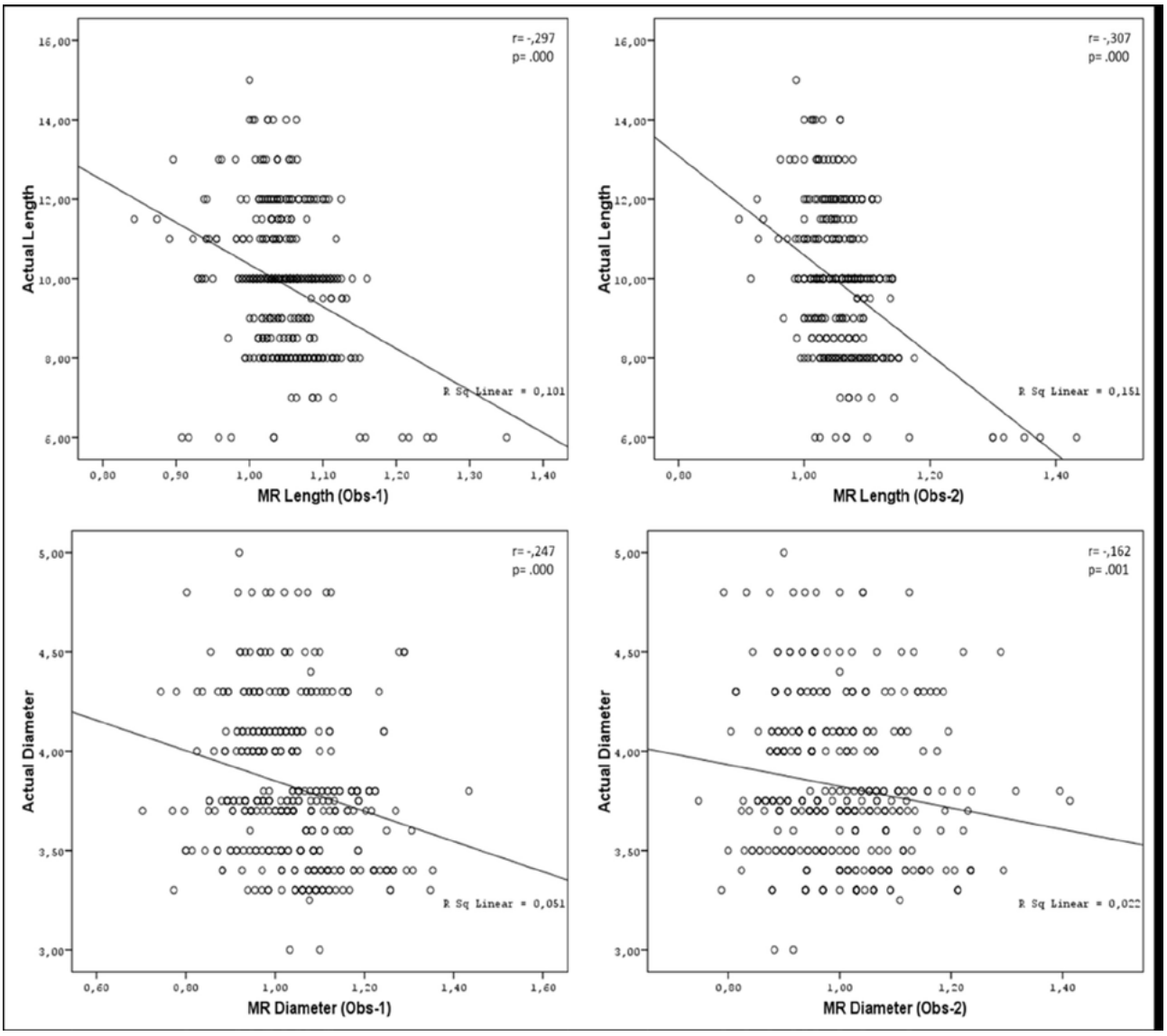


Figure 2. The effects of an increase in length and diameter of the implant on MRs.

In 150 patients whose radiographic images were analyzed, there were 80 female and 70 male patients with a mean age of 48.70±13.28 and 54.14±11.96, respectively. There was significant difference in the magnification of diameter for the implant in regard to gender for both observers. Based on this, the average MRs of the diameter was higher in females than those in males for both observers ($p<0.001$) (Table 3).

Table 3. Comparison of the MRs of the implant dimensions according to gender.

	MR_{Length}									
	Female					Male				
	Mean	SD	Min	Max		Mean	SD	Min	Max	
Obs-1	1.06	0.05	0.84	1.35		1.04	0.05	0.89	1.25	0.007
Obs-2	1.06	0.05	0.90	1.32		1.06	0.06	0.93	1.43	*0.396*
	$MR_{Diameter}$									
	Female					Male				
	Mean	SD	Min	Max		Mean	SD	Min	Max	
Obs-1	1.07	0.11	0.80	1.43		1.01	0.11	0.70	1.29	<0.001
Obs-2	1.02	0.10	0.79	1.41		0.98	0.10	0.75	1.40	<0.001

These notations must be deleted because the actual p-values were indicated in the table.

MR= Magnification Ratio

DISCUSSION

Appropriate treatment planning is an essential step in implant treatment, and radiographic evaluation of the recipient area for an appropriately sized implant selection is an indispensable part of this procedure (9). Digital panoramic radiographs are a valuable aid in implant dentistry for helping preoperative diagnosis and treatment planning. In most cases, these radiographs, together with appropriate clinical examination, may be sufficient to determine the size and location of the implants if distortion is taken into account (10).

Distortion is one of the limitations of panoramic radiographs and occurs when the degree of magnification changes in vertical and horizontal planes (11). Image magnification can be affected by different factors such as patient position, jaw shape and size, mandibular angulation, implant type, gender, and anatomical area in the jaw (12,13). In addition, based on the results of this study, it is believed that the probability of the MR increasing is related to the decrease in the measured distance.

Choi et al. (12) evaluated the effects of gender on magnification and concluded that the horizontal magnification was significantly higher in females. However, gender did not affect vertical magnification. In addition, in another study, the authors found that there was no significant difference in vertical and horizontal magnifications of implants by gender (1). On the contrary, in the present study, higher horizontal MR was detected in females for both observers. These differences are thought to confirm the view that the jaw structure (shape, size) is effective on MR.

Kim et al. (1) found that vertical and horizontal MR differ significantly depending on the anatomical location and stated that the maxilla tends to be slightly more distorted when compared to the mandible. Similarly, in this study, a significant difference was observed in the premolar region in addition to the molar region in the maxilla in terms of horizontal MR. On the other hand, it has been reported that digital panoramic radiography can accurately determine the length of the preoperative implant in the premolar and molar mandibular segments (14). As mentioned earlier, these differences may occur depending on the patient's position, jaw shape/size, and mandibular angulation (12,13). To reduce positional errors, the calibration using the correct bite block and guide beam lines can be beneficial (13).

The vertical size should be carefully evaluated and an adequate margin of safety should be established, especially when the treatment site is close to vital structures such as the inferior alveolar canal and the maxillary sinus (10). Vazquez et al. (14) have confirmed that vertical measurements have acceptable accuracy and

repeatability, and if a software-based calibrated measuring instrument is used, digital panoramic radiography can be safely used to determine the preoperative length of the implant in the premolar and molar mandibular segments. In this study, higher vertical and horizontal radiographic measurements were found in both jaws compared to the actual implant size. In addition, although there was no difference between observers in vertical measurements, a difference was observed in horizontal measurements. On the contrary, another study reported no difference between the actual diameter in both the mandible and the maxilla and radiographic measurements (10). This discrepancy may be a problem in the clinic. The choice of the length and diameter of the implant is primarily determined by the volume of the alveolar crest, the position of the adjacent teeth and the location of the vital anatomical structures. This is based on the principle that the implant body should ideally be encircled by a sufficient bone quantity. It is sensible to assume that an attentive radiographic evaluation and excellent implant size selection reduce the risk of injury and associated complications of vital anatomical structures (9). Since jaw size and shape, mandibular angulation, and patient position, which are not evaluated in this study and can therefore be considered as limitations, may affect the magnification (12,13), further studies including these factors are recommended to overcome these limitations.

In conclusion, MRs of panoramic radiographs and the factors affecting these MRs should be taken into account during the pre-implant site assessment. Thus, the chance of success in implant placement can be increased. Therefore, the clinician is expected to be successful in estimating appropriate implant sizes with experience in radiographic measurements (reading calibration skills). This reduces the risk of unexpected events and any injuries or complications during and after the procedure.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the ethics committee of the Faculty of Dentistry at Necmettin Erbakan University. (Date 08.2018, Decision Number 2018/02).

REFERENCES

1. Kim YK, Park JY, Kim SG, Kim JS, Kim JD. Magnification rate of digital panoramic radiographs and its effectiveness for pre-operative assessment of dental implants. Dentomaxillofac Radiol. 2011;40(2):76-83.
2. Siu AS, Chu FC, Li TK, Chow T, Deng F. Imaging modalities for preoperative assessment in dental implant therapy: an overview. Hong Kong Dent J. 2010;7:23-30.
3. Mengel R, Candir M, Shiratori K, Flores-de-Jacoby L. Digital volume tomography in the diagnosis of periodontal defects: an in vitro study on native pig and human mandibles. J Periodontol. 2005;76(5):665-73.
4. Mengel R, Kruse B, Flores-de-Jacoby L. Digital volume tomography in the diagnosis of peri-implant defects: an in vitro study on native pig mandibles. J Periodontol. 2006;77(7):1234-41.
5. Tohnak S, Mehnert AJ, Mahoney M, Crozier S. Synthesizing dental radiographs for human identification. J Dent Res. 2007;86(11):1057-62.
6. Cho YS. Diagnostic value of dental CT (DentaScan) in dental implant. Chungbuk Med J. 1998;8:11-9.
7. Nagarajan A, Perumalsamy R, Thyagarajan R, Namasivayam A. Diagnostic imaging for dental implant therapy. J Clin Imaging Sci. 2014;27:4(Suppl 2):4.
8. Ogawa K, Langlais RP, McDavid WD, Noujeim M, Seki K, Okano T, et al. Development of a new dental panoramic radiographic system based on a tomosynthesis method. Dentomaxillofac Radiol. 2010;39(1):47-53.
9. Schropp L, Stavropoulos A, Gotfredsen E, Wenzel A. Comparison of panoramic and conventional cross-sectional tomography for preoperative selection of implant size. Clin Oral Implants Res. 2011;22(4):424-9.
10. Kayal RA. Distortion of digital panoramic radiographs used for implant site assessment. J Orthod Sci. 2016;5(4):117-20.
11. McDavid WD, Dove SB, Welander U, Tronje G. Dimensional reproduction in direct digital rotational panoramic radiography. Oral Surg Oral Med Oral Pathol. 1993;75(4):523-7.
12. Choi YG, Kim YK, Eckert SE, Shim CH. Cross-sectional study of the factors that influence radiographic magnification of implant diameter and length. Int J Oral Maxillofac Implants. 2004;19(4):594-6.
13. Park JB. The evaluation of digital panoramic radiographs taken for implant dentistry in the daily practice. Med Oral Patol Oral Cir Bucal. 2010;15(4):e663-6.
14. Vazquez L, Nizamaldin Y, Combescure C, Nedir R, Bischof M, Dohan Ehrenfest DM, et al. Accuracy of vertical height measurements on direct digital panoramic radiographs using posterior mandibular implants and metal balls as reference objects. Dentomaxillofac Radiol. 2013;42(2):20110429.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):31-39

Received: 09 July 2022
Revised: 10 November 2022
Acccepted: 08 December 2022
DOI: 10.47482/acmr.1142775

ORIGINAL ARTICLE

Chronic kidney disease observational cohort study and assessment of baseline characteristics and their relationship with diabetes status and kidney function

Sümeyra Koyuncu[1] **Koray Uludağ**[1] **Tamer Arıkan**[1] **Ali İhsan Günal**[1]

1 Kayseri City Training and Research Hospital, Department of Internal Medicine, Division of Nephrology, Kayseri, Turkey

Abstract

Background: Chronic kidney disease (CKD) may result in end-stage renal disease (ESRD) and undesirable outcomes such as death and dialysis. We carried out an observational cohort study to ascertain risk factors for renal outcomes and all-cause mortality in patients with CKD.

We aimed to conduct a historical cohort study to determine the risk factors affecting renal outcomes, all-cause mortality, and comorbid burden in patients with CKD living in the Central Anatolian region of Turkey.

Methods: A single-center, retrospective, observational cohort study was conducted at the outpatient Nephrology Clinic of Health Sciences University, Kayseri Medical Faculty, from January 1, 2010, to December 31, 2020. We designed the study in patients with stage 3-4 renal failure. Age 18 to 70 years and eGFR 15 to 59 mL/min/1.73 m2 were inclusion criteria. Baseline demographic and laboratory data were documented.

Results: One thousand seventy-three patients with CKD were enrolled in the study. Mean (SD) age was 55.87 (8.83) years, and 53.2% were men. %45.9 and %84.4 had diabetes mellitus and hypertension, respectively. The mean body mass index was 26.73 (3.95) kg/m2. Mean eGFR was 34.14 (10.45) mL/min/1.73 m2 using chronic kidney disease epidemiology collaboration. Median (p25-p75) urinary protein-creatinine ratio was 48.80 [22.40, 89.00] mg/mmol. Older patients had a lower eGFR, and the male gender was more common in stage 3 patients. Stage 4 patients had lower hemoglobin and serum calcium levels. Also, low eGFR was associated with high uric acid levels.

Conclusions: This study, along with future analysis may elucidate the natural history and clinical consequences of CKD. Controllable factors could be understood, and CKD progression and adverse outcomes may be prevented in this way.

Keywords: Chronic Kidney Disease, Diabetes, Hypertension.

Cite this article as: *Koyuncu S, Uludağ K, Arıkan T, Günal Aİ. Chronic kidney disease observational cohort study and assessment of baseline characteristics and their relationship with diabetes status and kidney function. Arch Curr Med Res. 2023;4(1):31-39*

Corresponding Author:
Sumeyra Koyuncu, Kayseri City Training and Research Hospital, Department of Internal Medicine, Division of Nephrology, Kayseri, Turkey
E-Mail: sumeyraozberk@hotmail.com

INTRODUCTION

The incidence of end-stage renal disease (ESRD) has increased worldwide during the past three decades (1). Subjects with ESRD have substantial risks of various complications, such as cardiovascular disease (CVD), bone mineral disorders, infectious diseases, and malignancies (2). On the other hand, the prevalence of chronic kidney disease (CKD) is approximately 10–15% in the adult population living in countries that come from diverse traditions and different backgrounds. CKD may progress to ESRD requiring renal replacement therapy, have a negative impact on quality of life, and have important cost implications for the healthcare system (3). Also, progression rates vary widely in patient subgroups, some progressing rapidly, while others may be relatively stable in kidney function over time (4). Because CKD can be progressive and is associated with adverse consequences, prevention of progression may necessitate early intervention in the clinical ground. Although a decrease in renal function and the presence of proteinuria would have invaluable prognostic significance, the current knowledge, individually from Turkey, regarding the predictors of the progress of CKD is scarce in the literature (5). Especially appropriate care and surveillance in a nephrology clinic could help in minimizing complications and optimizing prognosis in CKD patients (6).

CKD is associated with hypertension, diabetes, proteinuria, obesity, and cardiovascular events, which increase as GFR declines. Also, some studies reported that patients with CKD had a higher death risk than those with ESRD (7,8). Besides traditional risk factors, proteinuria and anemia might play a role in developing CVD in CKD (9,10). In population studies, CVD significantly jeopardizes patients with CKD, increasing their risk with decreasing renal function.[11] However, the number of cohorts is not enough to estimate prognostic consequences precisely in the CKD population. The prevalence of CVD in CKD ranges from 26.8% to 39.1% in various studies (10-12). High cardiovascular mortality results from arteriosclerosis with increased arterial stiffness in CKD patients (13). Patients should be recognized, traced congruously, and treated suitably to overcome challenges for healthcare systems globally. Although significant results were obtained in identifying individuals with CKD from community studies, relatively little has been documented about the features of CKD patients receiving nephrological management.

We conducted a historical cohort study aiming to identify risk factors affecting renal outcomes, all-cause mortality, and comorbid burden in patients with CKD who live in the central Anatolian region of Turkey. We define the baseline demographic and laboratory features of patients forming the cohort, stratified by initial GFR levels and diabetes status in this paper.

MATERIALS AND METHODS

The study design was a single-center, retrospective, observational cohort of individuals observed until death, loss to follow-up, or ESRD. They consisted of recently referred or prevalent patients. It was carried out at the outpatient Nephrology Clinic of Health Sciences University, Kayseri Medical Faculty, from January 1, 2010, to December 31, 2020. Approval was obtained from the Kayseri City Hospital Ethics Committee (Date 09.09.2021, Decision Number 473). The research has attempted to evaluate particularly individuals receiving nephrology care to overcome heterogeneity in management and identify unique risks.

Consecutive patients were included throughout the enrollment period between January 2010 and December 2018. Laboratory databases and medical records were implemented for the enrollment of patients. The inclusion criteria were: 1) age 18–70 years and 2) eGFR 10–59 mL/min/1.73 m^2. Exclusion criteria were: 1) polycystic kidney disease, 2) liver cirrhosis, 3) existing malignancy or chemotherapy over the previous two years, 4) prior organ transplantation or treatment with chronic dialysis, 5) pregnancy, 6) heart failure (New York Heart Association [NYHA] class 3-4), 7) solitary kidney, 8) immunosuppressive treatment, 9) active infection/inflammatory disorders. A total of 14347 patients were screened for eligibility. The number of excluded patients was thirteen thousand and two hundred seventy-four, arising from lack of information regarding their previous medical records (n=5481), eGFR > 59 mL/min/1.73 m^2 (n=4238), age > 70 years (n =3316), or the existence of exclusion criteria (n = 239), resulting in a final cohort of 1073 subjects.

The endpoints were CKD progression as measured with a decline in eGFR and all-cause death. The MDRD and CKD-EPI creatinine equation were used to calculate the eGFR regularly. A composite renal event was attributed to a reduction in eGFR of more than 50% from baseline, a doubling of serum creatinine, or the onset of ESRD. Registrations about events were screened throughout the study period from medical records. Information on the time of death and the precise reasons for dying were gathered.

Baseline assessment includes demographic data, family and medical history, pre-existing comorbidities, medications, blood pressure, and body mass index (BMI). Laboratory data were documented and maintained regularly for assessment of serum creatinine, whole blood count, and other biochemical parameters such as lipid profile, uric acid, HbA1c, high-sensitivity C-reactive protein (CRP), calcium, phosphorus, intact parathyroid hormone (PTH), serum albumin, urine protein, and urine creatinine. After a 5-minute waiting, the arterial tension is checked using a sphygmomanometer in the outpatient department. If there were systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg, or drug use, it was accepted as a hypertension diagnosis. Diabetes was described as fasting glucose >126 mg/dl, random glucose > 200 mg/dl, or antidiabetic use. Dyslipidemia was defined as total serum cholesterol > 200 mg/dL, or triglycerides > 150 mg/dL, or high-density lipoprotein (HDL) cholesterol < 40 mg/dL in men or < 48 mg/dL in females, or low-density lipoprotein (LDL) cholesterol > 100 mg/dL, or lipid-lowering drug use.

Baseline values were reported as means (SD) or medians (p25-p75) for continuous variables, whereas categorical variables were represented as numbers and percentages. Baseline characteristics were compared across groups using t-tests or chi-square testing, as appropriate. If the continuous variable's distribution did not correspond to the normal distribution, the Kruskal-Wallis rank-sum test was employed. The percentages of missing values for variables were as follows: BMI (2.9), CRP (2.3), HA1c (5.1), and BP (17.8). Other variables having less than 2% missingness were albumin, phosphorus, uric acid, urine protein-creatinine ratio (UPCR), and PTH. The chained equations method using the MICE package in R was applied for imputing missing data values. A two-sided P value less than 0.05 was considered significant.

RESULTS

Baseline demographic and clinical characteristics were evaluated in one thousand seventy-three patients with CKD. Mean (standard deviation [SD]) age was 55.87 (8.83) years, and 53.2% were men. The proportion of diabetes mellitus (DM) was %45.9, and %84.4 of subjects had a diagnosis of hypertension. Mean systolic and diastolic BPs were measured as 135.09 (24.50) and 81.18 (12.61) mmHg, respectively. The BMI was calculated to be 26.73 (3.95) kg/m^2. 18.9% of the total cohort had a history of coronary artery disease (CAD). Congestive heart failure (CHF) was noted in ninety-seven patients. 5.1% and 6.7% of the subjects had peripheral vascular disease (PAD) and cerebrovascular disease (CeVD), respectively. Mean eGFRs were 32.99 (10.03) and 34.14 (10.45) mL/min/1.73 m^2 using MDRD formula and chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation, respectively. Mean hemoglobin and median [25%-75% percentiles] CRP levels were 12.41 (2.02) g/dl and 3.20 [1.50, 6.40] mg/L, respectively. The mean calcium, phosphorus, and the median intact PTH level were 9.31 (0.64), 4.46 (0.95) mg/dl, and 129.30 [72.00, 214.20] μg/L. Serum albumin level was 4.09 (0.50) g/dL, and serum uric acid level was 7.39 (1.65) mg/dl. Median UPCR was 48.80 [22.40, 89.00] mg/mmol. Plasma lipid levels were given entirely in Table 1. The proportion of patients taking an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker was 57.5%. The percentage of patients on vitamin D supplementation and phosphate binders were 24.6% and 16.5%, respectively. 62.8%, 45.7%, and 38% of subjects were using diuretics, Ca channel blockers, and B-Blockers, respectively. 32.6% of patients were under dyslipidemia treatment with lipid-lowering drugs (Table 1).

Table 1. Baseline characteristics of the cohort by CKD stage

	Overall	Stage 3	Stage 4	p-value
n	1073	688	385	
Age, years	55.87 (8.83)	54.87 (8.86)	57.65 (8.50)	<0.001
Male, n (%)	571 (53.2)	441 (64.1)	130 (33.8)	<0.001
BMI, kg/m^2	26.73 (3.95)	26.91 (4.04)	26.43 (3.77)	0.055
Diabetes mellitus, n (%)	492 (45.9)	311 (45.2)	181 (47.0)	0.612
Hypertension, n (%)	906 (84.4)	588 (85.5)	318 (82.6)	0.248
Systolic blood pressure, mmHg	135.09 (24.50)	134.11 (24.10)	136.85 (25.13)	0.079
Diastolic blood pressure, mmHg	81.18 (12.61)	80.75 (12.59)	81.96 (12.63)	0.133
Coronary artery disease, n (%)	203 (18.9)	132 (19.2)	71 (18.4)	0.828
Congestive heart failure, n (%)	97 (9.0)	63 (9.2)	34 (8.8)	0.946
Cerebrovascular disease, n (%)	72 (6.7)	41 (6.0)	31 (8.1)	0.235
Peripheral vascular disease, n (%)	55 (5.1)	40 (5.8)	15 (3.9)	0.222
Serum creatinine, mg/dl	2.01 (0.49)	1.75 (0.29)	2.47 (0.42)	<0.001
eGFR (MDRD), ml/min/1.73 m^2	32.99 (10.03)	38.14 (7.60)	23.79 (6.70)	<0.001
eGFR (CKD-EPI), ml/min/1.73 m^2	34.14 (10.45)	40.11 (7.93)	23.47 (3.83)	<0.001
White blood cell, X10^3/μL	8.24 (1.84)	8.24 (1.84)	8.25 (1.84)	0.928
Hemoglobin, g/dl	12.41 (2.02)	12.63 (1.97)	12.01 (2.03)	<0.001
CRP, mg/L	3.20 [1.50, 6.40]	3.35 [1.50, 6.40]	3.00 [1.50, 6.30]	0.530
Calcium, mg/dl	9.31 (0.64)	9.34 (0.63)	9.25 (0.66)	0.026
Phosphorus, mg/dL	4.46 (0.95)	4.42 (0.95)	4.52 (0.95)	0.081
PTH, μg/L	129.30 [72.00, 214.20]	123.55 [70.50, 213.85]	140.60 [73.10, 215.10]	0.137
Serum albumin, g/dl	4.09 (0.50)	4.09 (0.50)	4.09 (0.51)	0.988
UPCR, mg/mmol	48.80 [22.40, 89.00]	46.45 [21.48, 88.32]	54.20 [24.50, 93.70]	0.223
Uric acid, mg/dl	7.39 (1.65)	7.28 (1.61)	7.58 (1.69)	0.004
Total cholesterol, mg/dl	209.79 (34.21)	207.38 (34.25)	214.09 (33.76)	0.002
LDL, mg/dl	117.87 (30.47)	116.57 (30.73)	120.18 (29.91)	0.063
HDL, mg/dl	49.08 (10.53)	49.62 (10.63)	48.12 (10.29)	0.025
Triglyceride, mg/dl	194.86 [132.22, 273.95]	187.92 [124.98, 263.79]	206.87 [144.64, 285.88]	0.002
HbA1c, %	6.91 (1.74)	6.92 (1.77)	6.88 (1.68)	0.734
ACEI/ARB, n (%)	617 (57.5)	375 (54.5)	242 (62.9)	0.010
Diuretic use	674 (62.8)	426 (61.9)	248 (64.4)	0.456
CCB, n (%)	490 (45.7)	312 (45.3)	178 (46.2)	0.830
Beta blocker, n (%)	408 (38.0)	264 (38.4)	144 (37.4)	0.804
Lipid-lowering drug, n (%)	350 (32.6)	238 (34.6)	112 (29.1)	0.076
Antiplatelet agent, n (%)	380 (35.4)	241 (35.0)	139 (36.1)	0.774
Phosphorus-lowering drug, n (%)	177 (16.5)	106 (15.4)	71 (18.4)	0.231
Uric acid-lowering drug, n (%)	562 (52.4)	340 (49.4)	222 (57.7)	0.011
Vitamin D use, n (%)	264 (24.6)	166 (24.1)	98 (25.5)	0.682

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index eGFR, estimated GFR; PTH, intact parathyroid hormone; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL high-density lipoprotein; MDRD, Modification of Diet in Renal Disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD, chronic kidney disease; UPCR, urinary protein-creatinine ratio; CCB, calcium channel blocker.

The proportions of subjects with stage 3-4 CKD were 64% and 36%, respectively. The baseline features were summarized by CKD stages in Table 1. Patients with a lower eGFR were older than those with a higher eGFR, and the male gender predominated among stage 3 patients. Stage 3 patients were more likely to have a higher BMI, but the difference was marginal for statistical significance. Prevalence of DM and hypertension were not significantly different between CKD Stage 3 and 4 patients. Also, stage 3 and 4 CKD patients had no noteworthy diversities in the frequency of cardiovascular diseases such as CAD, CHF, CeVD, and PAD.

The hemoglobin levels were lower in stage 4 patients compared to stage 3 patients. Serum calcium decreased, and serum phosphate and PTH increased with decreasing eGFR, although the last two did not reach statistical significance. Uric acid levels increased in proportion to eGFR decline. High-density lipoprotein (HDL) cholesterol levels were higher in stage 3 patients, while higher total cholesterol and triglycerides were seen in stage 4 patients. More patients were taking RAS inhibitors and uric acid-lowering drugs in stage 4 CKD. The percentage of patients using other agents was similar in terms of statistical significance between the two groups.

There were also some disparities between individuals with and without diabetes (Table 2). Diabetic patients were more likely to be male, hypertensive, tended to have a higher BMI, systolic BP, and diastolic BP than non-diabetics. Patients with diabetes were slightly older than those without diabetes, but the trend did not achieve statistical significance. CAD, CHF, CeVD, and PAD were more common in diabetic patients. They also had high serum albumin, uric acid, and UPCR levels as compared with non-diabetic patients. While HDL levels were lower in patients with diabetes, LDL levels were higher than in those without diabetes. ACEI/ARB, diuretic, and other anti-hypertensive agent use were frequent in diabetic patients. This patient group was using anti-hyperlipidemic, uric acid-lowering drugs, and antiplatelet agents more commonly than those without diabetes.

DISCUSSION

The study was conducted in the CKD population at stages 3-4 living in the central Anatolian region. It may give critical health data regarding initial comorbid conditions, CKD course, varied sequelae, including bone-mineral problems, anemia, and cardiovascular issues. Different laboratory and clinical indicators would also be obtained concerning potential risks for negative consequences through this study. The nephrologists were treating subjects, thereby providing better patient care. Furthermore, the study's longitudinal design could give data-driven models capable of identifying patients at high risk for CKD progression and clarifying numerous associations for clinical practice and cardiovascular disease consequences. In this paper, we provide the beginning features of the cohort and highlight the main disparities comparing stage 3 and 4 CKD patients. We also analyzed differences between patients with and without diabetes. The goal of our study was to create a similar cohort for the other studies carried out in the past, most of which looked at risk variables for CKD progression and the development of cardiovascular illnesses. The data retrieved from the study could supplement and expand the information obtained from prior research (14-18).

When the baseline characteristics of the patients were compared to those of the CRIC study, our patients were younger and had higher creatinine levels. The proportion of male patients in our study was similar to that of the CRIC research, but it was less than in Asian cohort studies (2,19). Diabetes was found in 45.9 percent of our subjects, comparable to that of CRIC participants. On the other hand, the CKD-JAC study had superior glycemic control in diabetics than the CRIC study, while the mean A1C was 8.5%, relatively poorer in our cohort. We can attribute this situation to the diet incompatibility of our patients to a large extent. In addition, non-compliance with treatment may be another factor. The vast majority of the individuals (84.4%) had hypertension diagnoses in our study. Data from the National Health and Nutrition Examination Survey indicated that the hypertension prevalence was 29.0% during 2015–2016 in the US (20). 34.2 million people have diabetes (10.5% of the US population) according

Table 2. Baseline demographic and clinical characteristics of the cohort according to diabetes status

	No	Yes	p-value
n	581	492	
Age, years	55.43 (8.78)	56.38 (8.87)	0.077
Male, n (%)	280 (48.2)	291 (59.1)	<0.001
BMI, kg/m^2	26.38 (3.85)	27.16 (4.02)	0.001
Hypertension, n (%)	478 (82.3)	428 (87.0)	0.041
Systolic blood pressure, mmHg	127.84 (22.20)	143.66 (24.35)	<0.001
Diastolic blood pressure, mmHg	76.19 (10.96)	87.08 (11.88)	<0.001
Coronary artery disease, n (%)	93 (16.0)	110 (22.4)	0.010
Congestive heart failure, n (%)	33 (5.7)	64 (13.0)	<0.001
Cerebrovascular disease, n (%)	26 (4.5)	46 (9.3)	0.002
Peripheral vascular disease, n (%)	22 (3.8)	33 (6.7)	0.043
Serum creatinine, mg/dl	1.98 (0.48)	2.04 (0.50)	0.074
eGFR (MDRD), ml/min/1.73 m^2	33.10 (10.08)	32.86 (9.98)	0.693
eGFR (CKD-EPI), ml/min/1.73 m^2	34.18 (10.44)	34.08 (10.48)	0.873
White blood cell, X10^3/μL	8.17 (1.83)	8.32 (1.85)	0.170
Hemoglobin, g/dl	12.42 (2.09)	12.40 (1.93)	0.896
CRP, mg/L	3.00 [1.30, 6.30]	3.55 [1.60, 6.50]	0.073
Calcium, mg/dl	9.29 (0.63)	9.33 (0.65)	0.241
Phosphorus, mg/dL	4.45 (0.96)	4.46 (0.95)	0.863
PTH, μg/L	134.60 [75.00, 210.70]	123.20 [68.15, 216.95]	0.423
Serum albumin, g/dl	4.06 (0.50)	4.13 (0.51)	0.012
UPCR, mg/mmol	44.60 [18.30, 83.00]	54.85 [26.92, 99.00]	<0.001
Uric acid, mg/dl	7.23 (1.61)	7.58 (1.67)	<0.001
Total cholesterol, mg/dl	206.67 (33.10)	213.47 (35.15)	0.001
LDL, mg/dl	114.95 (30.00)	121.31 (30.70)	0.001
HDL, mg/dl	50.00 (10.52)	48.00 (10.46)	0.002
Triglyceride, mg/dl	194.17 [130.14, 270.83]	198.04 [134.00, 276.33]	0.233
HbA1c, %	5.52 (0.38)	8.54 (1.23)	<0.001
ACEI/ARB, n (%)	297 (51.1)	320 (65.0)	<0.001
Diuretic use	341 (58.7)	333 (67.7)	0.003
CCB, n (%)	225 (38.7)	265 (53.9)	<0.001
Beta blocker, n (%)	199 (34.3)	209 (42.5)	0.007
Lipid-lowering drug, n (%)	169 (29.1)	181 (36.8)	0.009
Antiplatelet agent, n (%)	174 (29.9)	206 (41.9)	<0.001
Phosphorus-lowering drug, n (%)	87 (15.0)	90 (18.3)	0.169
Uric acid-lowering drug, n (%)	277 (47.7)	285 (57.9)	0.001
Vitamin D use, n (%)	140 (24.1)	124 (25.2)	0.728

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index eGFR, estimated GFR; PTH, intact parathyroid hormone; CRP, C-reactive protein; LDL, low-density lipoprotein; HDL high-density lipoprotein; MDRD, Modification of Diet in Renal Disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD, chronic kidney disease; UPCR, urinary protein-creatinine ratio; CCB, calcium channel blocker

to the National Diabetes Statistics Report (21). As one would expect, these two diagnoses were more common in CKD patients than described in the reports.

Obesity is widely established to be one of the predictors for CKD progression (22). The CRIC research participants seem to be more overweight than our participants. The mean BMI was 32.1 kg/m^2 in the CRIC and 23.5 kg/m^2 in the CKD-JAC study. In comparison, it was 26.7 kg/m^2 in our cohort. In addition, we found a significant difference in overweight between diabetic and non-diabetic subjects. Ethnicity is one of the differences in baseline variables between our study and other cohort studies. Our cohort consists of Turkish individuals, whereas the CRIC cohort consisted of 45 percent white, 46 percent black, and 5 percent Hispanic people. There is little understanding of the relationship between ethnicity and CKD. More investigation is thus needed to elucidate this relationship.

CKD patients have an increased rate of developing cardiovascular disease (23). It is envisaged that our cohort study may provide explanations for this kind of issue. Diabetic patients had a higher CVD prevalence than those without diabetes in our cohort, as in the CRIC cohort. These outcomes support clinical study observations signifying the CVD load commences early in the ESRD population having diabetes in the duration of CKD (24). The total frequency of CVD (32%) seems to be higher in our cohort than in Mediterranean cohort of patients followed by nephrologists (29.7 percent).[25] In contrast to prior findings (25), our study revealed that a decreased GFR was not associated with a significant incidence of cardiovascular illness. The risk of developing CVD in patients with CKD exceeds the hazard of reaching end-stage renal disease(26). In other words, it can be interpreted as if the CVD frequency is relatively decreasing or there is no difference due to the increased mortality risk as the CKD progresses.

Mean blood pressure levels were higher than the prescribed limit(27). Similarly, other CKD cohorts previously documented unsatisfactory BP levels (28), and thus the results in our cohort underline the importance of good BP treatment in CKD as a primary intervention. CKD stage 3 and 4 patients did not have considerable variability in BP levels. While there is much disagreement, most specialists do not believe that a blood pressure target of 130/80 mmHg is a life-saving or kidney preventive measure in patients with CKD (29).

Anemia was more common and severe in CKD stage 4 individuals than in CKD stage 3 patients. As predicted, the hemoglobin levels decreased as the eGFR increased. Phosphate-lowering drug use was low in the total study population, and there was no difference between the two-stage. Therefore, it may be expected that serum phosphorus increases with decreasing eGFR. Vitamin D and the use of its analogs were also at low levels, suggesting that they should be used more commonly in treating hyperparathyroidism.

The proteinuria in our study was higher than in the CRIC study, perhaps due to the strict control of BP in the CRIC study. It was also verified in a study that rigorous blood pressure control was associated with better control of proteinuria (30). The amount of proteinuria was more prominent in stage 4 CKD than in stage 3 CKD, but it did not reach statistical significance. As expected, patients with diabetes were more likely to have higher proteinuria.

Possible biases or residual confounding might have restricted inferences about causation because of the retrospective observational design. Second, the number of young diabetics was not sufficient in this study, similar to CRIC. Third, some forms of renal diseases were underrepresented in the cohort, like glomerulonephritis. Fourth, comorbidities derived from chart review may have integral limitations in terms of accuracy. Finally, because this study exclusively covers Turkish patients, the results cannot be generalized to other ethnic groups. Also, study subjects may differ from the CKD population in the community because of patients referred to nephrology clinics.

In conclusion, this CKD cohort study would shed light on the natural history and clinical consequences of CKD in the Turkish population. In addition, controllable variables can be found through the data obtained from the study and the renal replacement needs of patients can be reduced by using them to prevent CKD development and poor outcomes.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by the Division of Nephrology, Department of Internal Medicine, Kayseri City Training and Research Hospital, Kayseri (Date 09.09.2021, Decision Number 473)

REFERENCES

1. Bikbov B, Purcell C, Levey AS, Smith M, Abdoli A, Abebe M, et al. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395(10225):709-733.
2. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic Kidney Disease Japan Cohort (CKD-JAC) study: design and methods. Hypertens Res. 2008;31(6):1101-7.
3. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.
4. Li L, Astor BC, Lewis J, Hu B, Appel LJ, Lipkowitz MS, Tet al. Longitudinal progression trajectory of GFR among patients with CKD. Am J Kidney Dis. 2012;59(4):504-12.
5. Astor BC, Matsushita K, Gansevoort RT, van der Velde M, Woodward M, Levey AS, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. Kidney Int. 2011;79(12):1331-40.
6. Rucker D, Hemmelgarn BR, Lin M, Manns BJ, Klarenbach SW, Ayyalasomayajula B, et al. Quality of care and mortality are worse in chronic kidney disease patients living in remote areas. Kidney Int. 2011;79(2):210-7.
7. Weiner DE, Krassilnikova M, Tighiouart H, Salem DN, Levey AS, Sarnak MJ. CKD classification based on estimated GFR over three years and subsequent cardiac and mortality outcomes: a cohort study. BMC Nephrol. 2009;10:26.
8. Abboud H and Henrich WL. Clinical practice. Stage IV chronic kidney disease. N Engl J Med. 2010; 362: 56-65
9. Drury PL, Ting R, Zannino D, Ehnholm C, Flack J, Whiting M, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54(1):32-43.
10. Iimori S, Naito S, Noda Y, Nishida H, Kihira H, Yui N, et al. Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study. Nephrology (Carlton). 2015;20(9):601-8.
11. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
12. Shah R, Matthews GJ, Shah RY, McLaughlin C, Chen J, Wolman M, et al. Serum Fractalkine (CX3CL1) and Cardiovascular Outcomes and Diabetes: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. Am J Kidney Dis. 2015;66(2):266-73.
13. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H, et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. J Am Soc Nephrol. 2001;12(10):2117-2124.
14. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rahman M, et al. Chronic Renal Insufficiency Cohort (CRIC) Study: baseline characteristics and associations with kidney function. Clin J Am Soc Nephrol. 2009;4(8):1302-11.
15. Imai E, Matsuo S, Makino H, Watanabe T, Akizawa T, Nitta K, et al. Chronic Kidney Disease Japan Cohort study: baseline characteristics and factors associated with causative diseases and renal function. Clin Exp Nephrol. 2010;14(6):558-70.
16. Martínez-Castelao A, Górriz JL, Portolés JM, De Alvaro F, Cases A, Luño J, et al. Baseline characteristics of patients with chronic kidney disease stage 3 and stage 4 in Spain: the MERENA observational cohort study. BMC Nephrol. 2011;12:53.
17. Titze S, Schmid M, Köttgen A, Busch M, Floege J, Wanner C, et al. Disease burden and risk profile in referred patients with moderate chronic kidney disease: composition of the German Chronic Kidney Disease (GCKD) cohort. Nephrol Dial Transplant. 2015;30(3):441-51.
18. Kang E, Han M, Kim H, Park SK, Lee J, Hyun YY, et al. Baseline General Characteristics of the Korean Chronic Kidney Disease: Report from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). J Korean Med Sci. 2017;32(2):221-230.
19. Imai E, Horio M, Iseki K, Yamagata K, Watanabe T, Hara S, et al. Prevalence of chronic kidney disease (CKD) in the Japanese general population predicted by the MDRD equation modified by a Japanese coefficient. Clin Exp Nephrol. 2007;11(2):156-163.
20. Fryar CD, Ostchega Y, Hales CM, Zhang G, Kruszon-Moran D. Hypertension Prevalence and Control Among Adults: United States, 2015-2016. NCHS Data Brief. 2017;(289):1-8.
21. National Diabetes Statistics Report, 2020, Centers for Disease Control and Prevention, Atlanta, GA:Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services, 2020.
22. Hsu CY, McCulloch CE, Iribarren C, Darbinian J, Go AS. Body mass index and risk for end-stage renal disease. Ann Intern Med. 2006;144(1):21-8.
23. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003;42(5):1050-65.
24. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345(12):861-9.

25. De Nicola L, Minutolo R, Chiodini P, Zoccali C, Castellino P, Donadio C, et al. Global approach to cardiovascular risk in chronic kidney disease: reality and opportunities for intervention. Kidney Int. 2006;69(3):538-45.

26. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-1172.

27. Levey AS, Rocco MV, Anderson S, Andreoli SP, Bailie GR, Bakris GL, et al. K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis. 2004;43(5 Suppl 1):S1-290.

28. Duru OK, Li S, Jurkovitz C, Bakris G, Brown W, Chen SC, et al. Race and sex differences in hypertension control in CKD: results from the Kidney Early Evaluation Program (KEEP). Am J Kidney Dis. 2008;51(2):192-8.

29. Agarwal R. Debate: CON Position. People with chronic kidney disease should have a blood pressure lower than 130/80 mm Hg. Am J Nephrol. 2010;32(4):374-6; discussion 377-8.

30. Appel LJ, Wright JT Jr, Greene T, Agodoa LY, Astor BC, Bakris GL, et al. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010;363(10):918-29.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):40-46

Received: 06 July 2022
Revised: 19 August 2022
Acccepted: 13 September 2022
DOI: 10.47482/acmr.1141714

ORIGINAL ARTICLE

Clinicopathological evaluation of parasitic infections in appendectomy specimens

Murat Kartal[1] **Tolga Kalaycı**[2] **Yaşar Çöpelci**[3] **Ali Kurt**[4]

1 Ataturk University Faculty of Medicine, Department of General Surgery, Erzurum, Turkey
2 Ağrı İbrahim Çeçen University Faculty of Medicine, Department of General Surgery, Ağrı, Turkey
3 University of Health Sciences, Erzurum Regional Education and Research Hospital, Department of General Surgery, Erzurum, Turkey
4 University of Health Sciences, Erzurum Regional Training and Research Hospital, Department of Pathology, Erzurum, Turkey

Abstract

Background: This study aimed to determine the incidence of parasitic infections in adult patients who underwent appendectomy and to compare the clinicopathological features of parasitic infections in appendectomy specimens.

Methods: Patients with pre-diagnosis of acute appendicitis who underwent appendectomy between January 2018 and December 2019 and reported parasitic infection in appendectomy specimens were evaluated retrospectively. Demographic data, comorbidities, clinical and radiological findings, laboratory results, surgical methods, length of hospital stay, postoperative complications, and histopathological examination reports were analysed.

Results: 939 adult patients underwent appendectomy with a pre-diagnosis of acute appendicitis. Upon detecting parasitic infection in the histopathological examination, thirty-one (3.3%) patients were included in this study. Twenty (64.5%) patients were women, and the overall mean age was 31.9 years (18-70 years). Twenty-three (74.2%) patients had Enterobius vermicularis, and 8 (25.8%) patients had Taenia saginata. On laboratory examination, the mean percentage of monocytes was only higher in the Taenia saginata group (0.80 vs 0.66; p=0.039). Both ultrasonography findings and tomography findings were similar in both groups. The morbidity rate of the study was 12.9% (n=4). There was no difference between the two groups regarding the length of hospital stay or morbidity.

Conclusions: Parasitic infections may cause symptoms mimicking acute appendicitis. It should be kept in mind that even in patients with a diagnosis of parasitic intestinal infection, symptoms may have been caused by acute appendicitis, not solely due to parasitic infection.

Keywords: Appendectomy, Enterobius Vermicularis, Taenia Saginata.

Cite this article as: *Kartal M, Kalaycı T, Çöpelci Y, Kurt A. Clinicopathological evaluation of parasitic infections in appendectomy specimens. Arch Curr Med Res. 2023;4(1):40-46*

Corresponding Author:
Tolga Kalaycı, Ağrı İbrahim Çeçen University Faculty of Medicine, Department of General Surgery, Ağrı, Turkey
E-Mail: dr.tolgakalayci@gmail.com

INTRODUCTION

Acute appendicitis (AA) is the most common cause of emergency abdominal surgery (1). Although it is mainly seen in the 7-35 age range, it can be encountered in any age group (2). Abdominal pain, anorexia, nausea/vomiting, and elevation of serum inflammatory markers are typical findings of AA. The standard gold treatment for AA is appendectomy (3). It has been reported that fecalith and lymphoid hyperplasia may predispose the development of AA by obstructing the lumen of the appendix vermiformis (AV). Vegetable/fruit seeds, tumours, and parasites are rarely included in AA aetiology (4).

Intestinal parasitic infections can be seen at all ages, especially in children. Although the prevalence varies according to geography and socioeconomic level, it has been reported at a high rate of 44.6% (5). Parasitic intestinal infections most frequently affect the colon in the gastrointestinal system, a parasitic infection of the AV is rare. Intestinal parasites can mimic AA, and the diagnosis is usually made by histopathological examination of appendectomy specimens (6). The most common parasites associated with appendicitis are *Enterobius vermicularis (EV)*, *Ascaris lumbricoides*, *Entamoeba histolytica*, *Taenia saginata* (TS) and *Schistosoma sp*. Although the role of parasites in AA aetiology has not been fully clarified, it is thought that they cause the development of AA by both occluding the lumen of the AV and creating inflammatory reactions (7).

This study aimed to determine the incidence of parasitic infection in adult patients who underwent appendectomy with a pre-diagnosis of AA and to compare the clinicopathological features of parasitic infections in appendectomy specimens.

MATERIALS AND METHODS

Patients' Selection and Searched Parameters

Patients who underwent an appendectomy in a tertiary health centre with a pre-diagnosis of AA and reported the presence of parasitic infection in appendectomy specimens were evaluated retrospectively. All adult patients who met the criteria between January 2018 and December 2019 were included in the study. All surgeries and histopathological examinations were performed at the same clinics. Incidental appendectomies, patients younger than 18, and patients whose detailed data could not be accessed were excluded from the study.

Demographic data, comorbidities, preoperative clinical and radiological findings, laboratory results, surgical methods, length of stay in hospital (LOS), complications, and histopathological examination reports were analysed hospital data management system of Sisoft (Sisoft Healthcare Information Systems, Turkey) and patient files retrospectively. Appendectomy specimens with reported parasitic infections were re-examined pathologically by a consulting pathologist. Thus, the diagnosis of parasitic infections and parasite types was re-confirmed.

Statistical Analysis

Statistical data analysis was performed using SPSS (SPSS Inc. v23.0, USA). Mean and standard deviation were used in descriptive statistics for quantitative variables, and numbers and percentages were used for qualitative variables. The normal data distribution was evaluated with the Shapiro-Wilk and Kolmogorov-Smirnov tests. If the data showed normal distribution, data were analysed with an independent samples t-test, and independent qualitative data were analysed with chi-square. If the normal distribution assumption was not met, the Mann-Whitney U test was used for independent quantitative data, and the Wilcoxon test was used for dependent quantitative data. The significance level was accepted as 0.05.

Ethical Approval and Patient Consent

Data collection and analysis for the study were initiated after the study was deemed ethically appropriate by the Ethics Committee of University of Health Sciences, Erzurum Regional Training and Research Hospital (Decision no: 2021 / 06-136, Decision date: 15.03.2021). Since it is a retrospective study, patient consent is not required.

RESULTS

Nine hundred thirty-nine adult patients underwent appendectomy with a pre-diagnosis of AA between January 2018 and December 2019. Thirty-one (3.3%) patients were included in the study upon detecting parasitic infection in their histopathological examination and meeting the other inclusion criteria. Of 31 patients, twenty (64.5%) were women, and eleven (35.5%) were men. The mean age of all patients was 31.9 years (18-70 years).

Three (9.7%) patients had at least one comorbid disease or previous surgical history. Medically treated chronic obstructive pulmonary disease (COPD) and diabetes mellitus (DM) were found as comorbidities in one patient. Two (6.4%) patients had a history of total thyroidectomy. Both patients received hormone replacement therapy and were euthyroid during the perioperative period.

Physical examination of all patients showed tenderness and defence in the right lower quadrant. On laboratory examination, the mean percentage of monocytes was only higher in the Taenia saginata group (0.80 vs 0.66; p=0.039). The mean value of other complete blood count parameters was similar in both groups. A comparison of the complete blood count parameters according to parasite type is shown in **Table 1**.

Table 1. Comparison of the complete blood count parameters according to parasite type.

Parameters (mean)	EV Group (n=23)	TS Group (n=8)	P-value
White blood cell (103/mm3)	10.35 (4.9-18.10)	13.40 (5.20-20.79)	0.46*
Red blood cell (106/mm3)	4.96 (3.90-6.41)	5.13 (3.99-5.54)	0.47*
Hemoglobin (g/dL)	13.7 (10.10-17.00)	14.8 (10.10-16.90)	0.97*
Haematocrit (%)	40.15 (30.40-52.90)	43.10 (31.80-49.00)	0.87**
Mean cell volume (fL)	82.70 (75.50-91.40)	83.00 (63.10-88.50)	0.16**
Mean corpuscular haemoglobin (pg)	28.50 (25.30-32.10)	29.31 (18.80-31.60)	0.17*
Mean corpuscular haemoglobin concentration (g/dL)	34.25 (30.60-36.10)	34.30 (29.80-35.80)	0.39**
Platelet count (10^3/mm^3)	282000 (64000-442000)	266000 (193000- 815000)	0.19**
Reticulocyte distribution width (%)	13.25 (10.80-16.00)	13.39 (12.10-18.10)	0.20*
Platelet distribution width (%)	16.30 (9.60-20.90)	16.00 (10.60-17.60)	0.41*
Mean platelet volume (fL)	8.52 (6.20-10.00)	8.96 (6.60-10.60)	0.61*
Neutrophil #	7.55 (2.60-16.90)	8.30 (2.50-18.28)	0.63**
Lymphocyte #	1.54 (0.70-4.10)	2.15 (1.14-3.90)	0.38**
Monocyte #	0.66 (0.10-1.20)	0.80 (0.30-7.50)	**0.039****
Eosinophil #	0.17 (0.01-0.42)	0.20 (0.07-0.53)	0.30**
Basophil #	0.02 (0.00-1.00)	0.11 (0.00-0.90)	0.26**

EV: Enterobius vermicularis, TS: Taenia saginata. *Independent samples t-Test, **Mann Whitney U test.

Ultrasonography (USG) examination, the first diagnostic imaging tool, was performed on all patients included in the study during emergency room admissions. 58.1% of all patients (n=18) had USG findings compatible with AA. The calculated mean diameter of the AV was 8.23 mm. Seven (22.6%) of these 18 patients also had mesenteric heterogeneity on the right upper quadrant on USG. Computed tomography (CT) was planned for only one of the patients with mesenteric heterogeneity on USG because of the suspicion of a simultaneous cecum tumour. Still, no tumoral mass was seen on the CT scan of this patient. However, an additional imaging tool was not needed in patients with other mesenteric heterogeneity. On the other hand, AV was not seen on USG in 13 (41.9%) patients. Because AV could not be seen on USG, CT was planned for these 13 patients (negative USG). Findings consistent with AA were reported in 11 (35.5%) of 14 patients who underwent CT examination. The mean diameter of the AV was reported as 9.3 mm on CT. Mesenteric heterogeneity was reported in only three patients, and in one of them, heterogeneity was said to be accompanied by abscess formation. The distribution of evaluated USG and CT parameters was similar in both groups. Clinicopathological features according to parasite type and a comparison of these features are shown in **Table 2**.

Table 2. Clinicopathological features according to the type of parasite.

	General N=31	EV Group N=23	TS Group N=8	P-value
USG findings (n=31)				
Appendix vermiformis visualisation				0.228*
· *Yes*	18 (58.1%)	15 (83.3%)	3 (16.7%)	
· *No*	13 (41.9%)	8 (61.5%)	5 (38.5%)	
Mean appendix diameter	8.23 mm	8.09 mm	8.77 mm	0.652**
Mesenteric heterogeneity				0.576*
· *Yes*	9 (29%)	7 (77.8%)	2 (22.2%	
· *No*	22 (71%)	16 (72.7%)	6 (27.3%)	
CT findings (n=14)				
Appendix vermiformis visualisation				NE
· *Yes*	11 (78.6%)	9 (81.8%)	2 (18.2%)	
· *No*	3 (21.4%)	3 (100%)	0 (0%)	
Mean appendix diameter	9.3 mm	9 mm	11 mm	0.250***
Mesenteric heterogeneity				NE
· *Yes*	3 (21.4%)	3 (100%)	0 (0%)	
· *No*	11 (78.6%)	9 (81.8%)	2 (18.2%)	
Histopathological examination				
Presence of acute inflammation				0.698*
· *Yes*	17 (54.8%)	12 (70.6%)	5 (29.4%)	
· *No*	14 (45.2%)	11 (78.6%)	3 (21.4%)	
Mean length of appendix vermiformis	70 mm	63 mm (22-100)	80 mm (55-100)	0.210***
Mean diameter of the appendix	8 mm	7.5 mm (5-20)	9 mm (5-10)	0.960***
Length of stay in hospital (day)	2.32 (1-7)	2.12 (1-7)	3 (1-6)	0.510***
Postoperative complications				1.000*
· *Yes*	4 (12.9%)	3 (75%)	1 (25%)	
· *No*	27 (87.1%)	20 (74.1%)	7 (25.9%)	

USG: ultrasonography, CT: computed tomography, NE: not evaluated. *Chi-square test, **Independent samples t-Test, ***Mann Whitney U test.

Laparoscopic appendectomy was performed in 23 (74.2%) patients, and conventional appendectomy was completed in 8 (25.8%) patients. There was no conversion from laparoscopy to conventional appendectomy or any reported perioperative complications. Perioperative drains were placed in six patients due to purulent fluid collection in the pelvic region during surgery.

The mean length of stay (LOS) was 2.3 days (ranging from one day to seven-day), and the morbidity rate of the study was 12.9% (n=4). None of the patients required intensive care follow-up, and postoperative mortality was not observed. The most prolonged LOS was seen in patients with postoperative complications.

Postoperative complications were seen in 4 (12.9%) patients, surgical site complications in 3 (9.7%) patients, and ileus in one (3.2%) patient. Patients with surgical site complications were as follows: A 70-year-old male patient with multiple comorbid diseases (COPD, DM) and presence of abscess formation on preoperative CT (Length of stay (LOS): 6 days) had left pararectal redness and port-side seropurulent fluid collection on the tenth postoperative day. A 63-years-old male with DM (LOS: 7 days) had a port-side abscess on the thirteenth postoperative day. In addition, a 22-year-old female patient with no other disease (LOS: 5 days) had a port-side seroma on the third postoperative day. All surgical site complications were treated with drainage and daily cleaning. The patient with postoperative ileus was treated with conservative treatment with nasogastric decompression. All patients with postoperative complications had a history of perioperative drain placement. There was no difference between the two groups regarding the length of hospital stay or morbidity. Additionally, a perioperative haemorrhage occurred in a 27-year-old male patient (LOS: 7 days) without any other illness.

In appendectomy specimens, twenty-three (74.2%) patients had Enterobius vermicularis, and 8 (25.8%) patients had Tenia saginata. The mean length of AV was 70 mm, and the mean AV diameter was 8 mm. Presence of lymphoid hyperplasia was reported in 11 (35.5%) patients. Histopathologically, 17 (54.8%) specimens had signs of acute inflammation, while 14 (45.2%) specimens did not have signs of inflammation consistent with AA. In specimens with acute inflammation, the lumen of the AV was occluded with parasites in thirteen specimens and fecalith in four specimens. Luminal obstruction due to lymphoid hyperplasia was not detected. Parasitic infections in appendectomy specimens were most common in May with five cases, followed by four cases each in April and June. All patients were given mebendazole or albendazole after the histopathological examination revealed parasitic infections.

DISCUSSION

Acute appendicitis (AA) is the most common cause of acute abdominal pain. Anorexia, nausea, vomiting, abdominal pain migrating to the right lower quadrant, and mild leukocytosis are frequently observed signs/symptoms and findings. In addition to the anamnesis and physical examination findings, the diagnosis of appendicitis is supported by laboratory tests and imaging methods such as USG and CT (8).

AA is commonly considered to develop due to obstruction of the AV. While faecalis or lymphoid hyperplasia is frequently found in the aetiology, foreign bodies and parasitic causes are rarely encountered (1,9). The presence of parasitic infections up to 6.4% has been shown in appendectomies (10). The most common parasite is *Enterobius vermicularis* (EV). Rarely, *Entamoeba histolytica*, *Schistosoma sp.*, *Taenia saginata* (TS), *Ascaris lumbricoides*, and *Balantidium coli* can also be detected (7). Only adult patients were included in our study, and parasitic infection was found in 31 (3.3%) of 939 appendectomy specimens. EV was identified in 23 (2.45%) specimens and TS in 8 (0.85%).

The incidence of EV identification in appendectomy specimens ranges between 0.6-3.8% (6). This rate is 2.45% in the present study, similar to the literature. Although EV is frequently encountered in the pediatric age, it can also be detected in adults. Albendazole, mebendazole, and pyrantel pamoate are used in treatment. Since the risk of transmission among family members is very high, treatment and hygienic measures should cover the whole family (11). Although it is not possible and logical to establish a direct relationship between parasitic infection and the development of appendicitis with this limited data, we believe it may inspire further studies.

Another parasite diagnosed in appendectomy specimens in the present study is TS. The definitive host for TS is

human (12). Although most carriers are asymptomatic, they may cause symptoms such as nausea and loss of appetite. Very rarely, they can cause appendicitis (13). Our study identified TS infection in 8 (0.85%) appendectomy specimens. We believe that the incidence of TS infection in 0.85% of appendectomy specimens in the adult population will be important data for further studies.

Appendix vermiformis is reported as normal in 3-25% of the histopathological examinations of appendectomy specimens (14). In a cross-sectional study examining the presence of EV infection in appendectomy specimens, it was reported that no histopathology was found in them in 77.4% of the cases (6). In our study, the presence of acute inflammation was shown in 12 (52.1%) of 23 specimens with EV. In 5 (62.5%) of 8 specimens with TS, acute inflammation was present in histopathological examination. TS, whose relationship with appendectomies is rarely reported in case of reports or as an unusual finding in extensive studies (13,15), was written in 8 patients in our research, and it was found to cause a higher rate of acute inflammation compared to EV (52.1% vs 62.5%).

In the literature, in appendectomy specimens with EV infection, the mean length of AV was 61.6 mm, and the mean diameter of AV was 5.8 mm (6). In the current study, the average size of AV was 63 mm, and the mean diameter of AV was 7.5 mm in appendectomy specimens with EV infection. In specimens with TS infection, it is seen that the mean length of AV is 80 mm, and the mean diameter is 9 mm. Our study presented larger appendix diameters than those reported in the literature. We think that the higher rates of acute inflammation found in our study than the rates reported in the literature may be effective in the occurrence of the difference in appendix diameters (16).

A limited number of studies report that intestinal parasitisation is frequently encountered in the spring and summer (17,18). In addition to the literature, the current study evaluates the presence of parasitic infection in appendectomy specimens histopathologically instead of using sample tests and reveals that parasitic infection is most frequently encountered in appendectomies performed in May, followed by April and June. We believe further studies should be conducted to show seasonal differences in parasitic infection incidence in appendectomy specimens.

There are also limiting factors in our study. The retrospective design of the study is the main limiting factor. The number of specimens with parasitic infections and species was insufficient to allow for detailed and further statistical analysis.

Parasitic infections may cause symptoms mimicking AA. We believe that adult patients with acute abdominal pain in endemic regions for parasitic infection should be questioned in detail about the presence of a possible parasitic disease. Considering the high rate of acute inflammation, it should be kept in mind that even in patients with a diagnosis of parasitic intestinal infection, symptoms may have been caused by AA, not solely due to parasitic infection.

Declarations

The authors received no financial support for this article's research and/or authorship. There is no conflict of interest.

Data collection and analysis for the study were initiated after the study was deemed ethically appropriate by the Ethics Committee of University of Health Sciences, Erzurum Regional Training and Research Hospital (Decision no: 2021 / 06-136, Decision date: 15.03.2021). Since our study is a retrospective study, patient consent is not required.

REFERENCES

1. Wagner M, Tubre DJ, Asensio JA. Evolution and Current Trends in the Management of Acute Appendicitis. Surg Clin North Am. 2018;98(5):1005-1023.
2. Ceresoli M, Zucchi A, Allievi N, Harbi A, Pisano M, Montori G, et al. Acute appendicitis: Epidemiology, treatment and outcomes- analysis of 16544 consecutive cases. World J Gastrointest Surg. 2016;8(10):693-699.
3. Téoule P, Laffolie J, Rolle U, Reissfelder C. Acute Appendicitis in Childhood and Adulthood. Dtsch Arztebl Int. 2020;117(45):764-774.
4. Yabanoğlu H, Aytaç HÖ, Türk E, Karagülle E, Calışkan K, Belli S, et al. Parasitic infections of the appendix as a cause of appendectomy in adult patients. Turkiye Parazitol Derg. 2014;38(1):12-6.
5. Yentur Doni N, Gürses G, Şimşek Z, Yıldız Zeyrek F. Prevalence and associated risk factors of intestinal parasites among children of farm workers in the southeastern Anatolian region of Turkey. Ann Agric Environ Med. 2015;22(3):438-42.
6. Hasan A, Nafie K, El-Sayed S, Nasr M, Abdulmohaymen A, Baheeg M, et al. Enterobius vermicularis in appendectomy specimens; Clinicopathological assessment: Cross sectional study. Ann Med Surg (Lond). 2020;60:168-172.

7. Zarbaliyev E, Celik S. Parasitic Appendicitis: A Novel Laparoscopic Approach for the Prevention of Peritoneal Contamination. Can J Infect Dis Med Microbiol. 2018;2018:3238061.

8. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020;15(1):27.

9. Tran N, Emuakhagbon VS, Baker BT, Huerta S. Re-assessing the role of the fecalith in acute appendicitis in adults: case report, case series and literature review. J Surg Case Rep. 2021;2021(1):rjaa543.

10. Charfi S, Sellami A, Affes A, Yaïch K, Mzali R, Boudawara TS. Histopathological findings in appendectomy specimens: a study of 24,697 cases. Int J Colorectal Dis. 2014;29(8):1009-12.

11. Wendt S, Trawinski H, Schubert S, Rodloff AC, Mössner J, Lübbert C. The Diagnosis and Treatment of Pinworm Infection. Dtsch Arztebl Int. 2019;116(13):213-219.

12. Flisser A, Viniegra AE, Aguilar-Vega L, Garza-Rodriguez A, Maravilla P, Avila G. Portrait of human tapeworms. J Parasitol. 2004;90(4):914-6.

13. Altun E, Avci V, Azatcam M. Parasitic infestation in appendicitis. A retrospective analysis of 660 patients and brief literature review. Saudi Med J. 2017;38(3):314-318.

14. Gelpke K, Hamminga JTH, van Bastelaar JJ, de Vos B, Bodegom ME, Heineman E, et al. Reducing the negative appendectomy rate with the laparoscopic appendicitis score; a multicenter prospective cohort and validation study. Int J Surg. 2020;79:257-264.

15. Emre A, Akbulut S, Bozdag Z, Yilmaz M, Kanlioz M, Emre R, et l. Routine histopathologic examination of appendectomy specimens: retrospective analysis of 1255 patients. Int Surg. 2013;98(4):354-62.

16. Luiz do Nascimento Junior P, Teixeira Brandt C, Petroianu A. Differences between inflamed and non inflamed appendices diagnosed as acute appendicitis. Ann Med Surg (Lond). 2021;62:135-139.

17. Soltani S, Salmanzadeh S, Soltani S, Kahvaz MS, Mobarak S, Hezarian M, et al. Prevalence of Intestinal Parasitic Infections in the Southwest of Iran: A Four-year Retrospective Study. Infect Disord Drug Targets. 2020;20(6):854-859.

18. González-Moreno O, Domingo L, Teixidor J, Gracenea M. Prevalence and associated factors of intestinal parasitisation: a cross-sectional study among outpatients with gastrointestinal symptoms in Catalonia, Spain. Parasitol Res. 2011;108(1):87-93.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):47-57

Received: 04 November 2022
Revised: 01 December 2022
Acccepted: 23 December 2022
DOI: 10.47482/acmr.1199056

ORIGINAL ARTICLE

Trends in Emergency Department Visits, and Hospital Admissions Pre- and During Covid 19 Pandemic

Savaş Sezik[1] **Onur Hakoğlu**[1] **Oktay Okuş**[2] **Omay Sorgun**[1]

1 Ödemiş State Hospital, Department of Emergency Medicine, İzmir, Turkey.
2 Ödemiş State Hospital, Department of Anesthesiology and Reanimation, İzmir, Turkey.

Abstract

Background: During the Coronavirus Disease 2019 pandemic period, the unnecessary use of the emergency department (ED) affects the motivation of health care providers leading the healthcare services to be far from being efficient, delays the care of the patients having an actual emergency situation and reduces the quality of education in teaching clinics.

Methods: Diagnoses in the visits were classified based on International Statistical Classification of Diseases and Related Health Problems, Tenth Revision categories and were analyses into subgroups based on common reasons for ED visits.

Results: While the number of ED visits in the first year of the pandemic period decreased by 26% compared to the previous year, the frequency of admissions in the circulatory system, stomach and intestinal system, nervous system, trauma, infectious disease, endocrine system, muscular system and connective tissues, gynecology and pregnancy, environmental emergencies, mental and behavioral disorders, examination and encounter for administrative purposes was higher than expected and the frequency of admission and referral was also significantly more than the expected value ($p < 0.001$).

Conclusions: In addition to the significant decrease in the number of ED visits during the pandemic, the fact that higher admission and referral frequency were observed indicating that the patients visited the emergency service in the late phases with severe clinical conditions.

Keywords: COVID-19 pandemic, Emergency Departments, ICD Codes, Patient Admission, Outpatients.

Cite this article as: *Sezik S, Hakoğlu O, Okuş O, Sorgun O. Trends in Emergency Department Visits, and Hospital Admissions Pre- and During Covid 19 Pandemic. Arch Curr Med Res. 2023;4(1):47-57*

Corresponding Author:
Savaş Sezik, Ödemiş State Hospital, Department of Emergency Medicine, İzmir, Turkey.
E-Mail: savassezik@gmail.com

INTRODUCTION

Since the start of the COVID-19 (Coronavirus Disease 2019) pandemic, the burden on emergency services has increased in Turkey and around the world. Many people who experience COVID-19 symptoms rush to the emergency department (ED) of hospitals for urgent treatment, along with individuals with other acute conditions. Throughout the pandemic so far, many factors have caused a reduction in the use of health services especially for emergencies, such as failure of patients with serious or life-threatening conditions (including those not related to COVID-19) to seek care, avoiding ED visits for elective situations, and shifting emergency care to telemedicine (1). In addition, it is estimated that more than one third of all ED visits have been non-urgent even though the strict implementation of social distancing, quarantine rules, and stay-at-home orders by the local governments due to the infection risk are notably affecting the ED visits (2, 3).

Studies have shown that there has been a fall in the number of ED visits during the pandemic even though the information on the changes in the distributions of patient visits and hospital outcomes (outpatient treatment, admission, and referral) is limited (1). The purpose of this study was to analyze the impact of the COVID-19 pandemic on ED visits and to compare the distributions of the outcomes. The first hypothesis was that there has been no significant difference in the distribution of ED visits before and during the pandemic. The second hypothesis was concerning the outcome distribution: that there has been no difference in the distribution (outpatient treatment, admission, and referral) of patients who visited the ED before the pandemic and who have visited it so far during the current pandemic. The third hypothesis was that there has been no difference in the distribution of outcomes (outpatient treatment, admission, and referral) according to ED visits before and during the pandemic.

MATERIALS AND METHODS

Study Design

The study hospital is 110 km away from the İzmir province center, has a 300-bed capacity, and serves an approximately 250,000 population. Its ED is staffed by physicians 24 hours a day, 7 days a week. The study was a retrospective, observational, and before-and-during cohort analysis approved by the Clinical Research Ethics Committee of the University of Health Sciences, İzmir Dr. Suat Seren Chest Diseases, Surgery Training and Research Hospital (Date 14.01.2022, Decision Number 2021/78-/6). It was guided by the ethical guidelines of the Declaration of Helsinki.

Study Population

All ED patient visits (including visits by children 0–17 years of age) within the period from March 15, 2019 to March 31, 2021 were examined. Data were extracted directly from a systematic query of the electronic health records as part of the health data management solution system. The first COVID-19 patient in Turkey was diagnosed on March 13, 2020. Two time-based cohorts were defined and analyzed in this study: the before pandemic term (March 15, 2019 to March 15, 2020) and the pandemic term (March 16, 2020 to March 31, 2021). The International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) was used to identify the principal diagnosis groups. See the appendix for the coding details.

The patients with more than one diagnostic coding were separated. The ICD-10 codes were determined on the basis of the main complaints of the patients. The patients who could not be grouped, whose files could not be accessed or adequately obtained, or whose files did not contain a single ICD-10 code were excluded from the study.

The outcomes of the patients diagnosed under the ICD-10 code were recorded as outpatient treatment, admission, or referral. Outpatient ED visits were the visits to the ED of the hospital by all the patients who were discharged from the ED within one day. The admission category was created for all the patients who were admitted to the relevant service and intensive care units of the hospital. The referral category was created for all the patients who were referred to a center in the province because there was no available specialist physician, service, and/or bed in the hospital.

Data Analyses

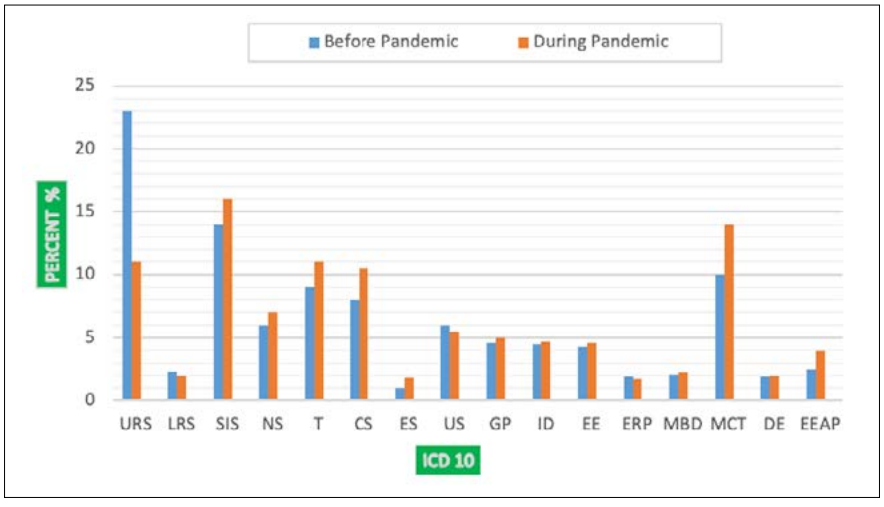
The categorical variables were compared through $\chi 2$ tests. The adjusted residuals were calculated for each cell in the cross-tabulation. In cases where the adjusted residuals were < -1.96 and > 1.96, the adjusted residuals were considered significant according to the Ho hypotheses (4). All the analyses were performed using IBM SPSS Statistics

for Windows 27.0 (IBM Corp., Armonk, NY, USA). The threshold for statistical significance was $p < 0.05$.

RESULTS

The number of ED visits was recorded as 233.078 for the pre-pandemic period and 171.859 for the pandemic period, with a 26% decrease observed in the ED visit rate during the pandemic. A total of 297.810 patients (pre-pandemic period: 191.152; pandemic period: 106.658) were included in this study. Fifty-two percent of the patients in the pre-pandemic period and 47% of those in the pandemic period were women. The mean ages of the patients in the pre-pandemic and pandemic period were 48.50 18.76 and 49.91 17.49, respectively ($p > 0.005$). The numbers of admissions and referrals were 7,113 and 6,058 in the before pandemic period, respectively, and 1,147 and 1,133 in the pandemic period. The percentages of decrease in the sub diagnosis groups were as follows: upper respiratory system (URS), 73%; lower respiratory system (LRS), 46%; stomach and intestinal system (SIS), 40%; nervous system (NS), 41%; trauma (T), 35%; circulatory system (CS), 32%; endocrine system (ES), 22%; urinary system (US), 49%; gynecology and pregnancy (GP), 33%; infectious diseases (ID), 38%; environmental emergencies (EE), 29%; ear and respiratory passage (ERP), 51%; mental and behavioral disorders (MBD), 34%; muscular system and connective tissues (MCT), 25%; diseases of the eye (DE), 23%; and examination and encounter for administrative purposes (EEAP), 7%.

The distribution of ICD-10 groups by periods (before and during pandemic) is shown in Figure 1. The frequency of ED visits in the before pandemic period was higher than expected for the URS, US, and ERP groups whereas the frequency of ED visits in the pandemic period were higher for the CS, SIS, NS, ID, ES, MCT, GP, EE, MBD, and EEAP groups. Except for the LRS group, all the groups contributed to the distribution of differences (Table 1). The comparison of the hospital outcomes by pandemic period and by independent diagnosis groups is shown in Graph 2. The frequency of outpatients in the before pandemic period and the frequency of admissions and referrals in the pandemic period were higher than expected (Table 2). The hospital outcomes (outpatient, admission, and referral) in the before pandemic and pandemic periods in the ICD-10 groups are compared in Table 3. The US, EE, ERP, DE, and EEAP groups did not contribute to the distribution of differences. When the LRS, NS, and ES groups were evaluated, it was found that the outpatient treatments under indifference in the before pandemic period and the admissions in the pandemic period were higher than expected. When the MCT, ID, GP, CS, T, SIS, and URS groups were analyses, it was observed that the outpatient treatments under indifference in the before pandemic period and the admissions and referrals in the pandemic period were higher than expected. In the MBD group, the outpatient treatments under indifference in the before pandemic period and the referrals in the pandemic period were also higher than expected.



See at Appendix for URS, SIS, NS,T, CS, ES, US, GP, ID, EE, ERP, LRS, MBD, MCT, DE, EEAP

Figure 1. Comparison of the distributions of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD 10) groups by period

Table 1. Comparison of the distributions of the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD 10) groups by period.

	Before Pandemic	During Pandemic	Total (n*)	P
URS n % Adjusted residuel	44298 23.2% 82.5	11584 10.9% -82.5	55882	<0.001
LRS n % Adjusted residuel	4795 2.5% 1.7	2569 2.4% -1.7	7364	
SIS n % Adjusted residuel	27856 14.6% -7.4	16617 15.6% 7.4	44473	
NS n % Adjusted residuel	10965 5.7% -3.6	6464 6.1% 3.6	17429	
T n % Adjusted residuel	17847 9.3% -13	11533 10.8 13	29380	
CS n % Adjusted residuel	15935 8.3% -17	10875 10.2 17	26810	
ES n % Adjusted residuel	1860 1% -9.5	1442 1.4% 9.5	3302	
US n % Adjusted residuel	11754 6.1% 6.2	5956 5.6% -6.2	17710	
GP n % Adjusted residuel	7969 4.2% -10.4	5321 5% 10.4	13290	
ID n % Adjusted residuel	8040 4.2% -5.8	4971 4.7% 5.8	13011	
EE n % Adjusted residuel	6471 3.4% -12.7	4593 4.3% 12.7	11064	
ERP n % Adjusted residuel	2586 1.4% 3.9	1264 1.2% -3.9	3850	
MBD n % Adjusted residuel	4434 2.3% -7.1	2923 2.7% 7.1	7357	
MCT n % Adjusted residuel	19194 10% -28.8	14431 13.5% 28.8	33625	
DE n % Adjusted residuel	3291 1.7% -12.2	2527 2.4% 12.2	5818	
EEAP n % Adjusted residuel	3857 2% -22.6	3588 3.4% 22.6	7445	

The threshold for statistical significance was $p < 0.05$. n: Number of patients. See at Appendix for URS, SIS, NS,T, CS, ES, US, GP, ID, EE, ERP, LRS, MBD, MCT, DE, EEAP

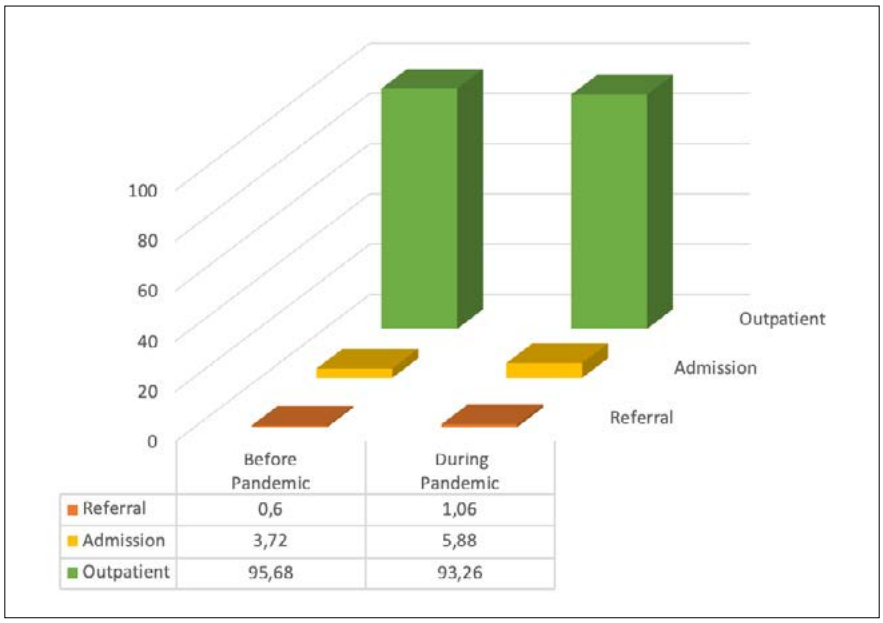


Figure 2. Comparison of hospital outcomes (outpatient, admission, referral) by period

Table 2. Comparison of hospital outcomes (outpatient, admission, referral) by period.

	Before Pandemic	*During Pandemic*	*Total (n*)*	*p*
Outpatient n % Adjusted residuel	182892 95.7% 28.6	99467 93.3% -28.6	282359	
Admission n % Adjusted residuel	7113 3.7% -24.9	6058 5.7% 24.9	13171	<0.001
Referral n % Adjusted residuel	1147 0.6% -13.9	1133 1.1% 13.9	2280	

The threshold for statistical significance was $p < 0.05$. n: Number of patients

Tablo 3. Comparison of hospital outcome (outpatient, admission, referral) by period in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD 10) groups

		Outpatient N* % Adjusted residuel	Admission N* % Adjusted residuel	Referral N* % Adjusted residuel	Total N*	P
URS	Before Pandemic	43892 99.08% 26.8	395 %0.89 -26.4	11 %0.02 -4.4	44298	<0.001
	During Pandemic	11064, 95.51% -26.8	506 %4.37 26.4	14 %0.12 4.4	11584	
LRS	Before Pandemic	4005 83.5% 2.9	681 14.2% -3.3	109 2.3% 0.6	4795	0.004
	During Pandemic	2077 80.8% -2.9	439 17.1% 3.3	53 2.1% -0.6	2569	
SIS	Before Pandemic	26000 93.3% 7	1684 6 % -6.3	172 0.6% -3.1	27856	<0.001
	During Pandemic	15213 91.6% -7	1259 7.6% 6.3	145 0.9% 3.1	16617	
NS	Before Pandemic	10305 94% 6.6	587 5.4% -6.4	73 0.7% -1.8	10965	<0.001
	During Pandemic	5903 91.3% -6.6	502 7.8% 6.4	59 0.9% 1.8	6464	
T	Before Pandemic	17213 96.4% 7.1	575 3.2% -5.7	59 0.3% -5	17847	<0.001
	During Pandemic	10926 94.7% -71.	520 4.5% 5.7	87 0.8% 5	11533	
CS	Before Pandemic	14938 93.7% 9.4	392 2.5% -6.5	605 3.8% -6.7	15935	<0.001
	During Pandemic	9858 90.6% -9.4	417 3.8% 6.5	600 5.5% 6.7	10875	
ES	Before Pandemic	1497 80.5% 5	329 17.7% -4.6	34 1.8% -1.4	1860	<0.001
	During Pandemic	1055 73.7% -5	350 24.3% 4.6	37 2.6% 1.4	1442	
US	Before Pandemic	11492 97.8% 1.5	250 2.1% -1.7	12 0.1% 0.4	11754	0.23
	During Pandemic	5801 97.4% 1.5	150 2.5% 1.7	5 0.1% -0.4	5956	

Tablo 3. (Continue) Comparison of hospital outcome (outpatient, admission, referral) by period in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD 10) groups

		Outpatient N* % Adjusted residuel	Admission N* % Adjusted residuel	Referral N* % Adjusted residuel	Total N*	P
GP	Before Pandemic	6501 81.6% 4.5	1465 18.4% -3.8	3 0% -5.7	7969	<0.001
	During Pandemic	4172 78.4% -4.5	1121 21.1% 3.8	28 0.5% 5.7	5321	
ED	Before Pandemic	7607 94.6% 8.3	398 5% -7.7	35 0.4% -2.8	8040	<0.001
	During Pandemic	4516 90.8% -8.3	414 8.3% 7.7	41 0.8% 2.8	4971	
EE	Before Pandemic	6295 97.3% 1.5	158 2.4% -1.5	18 0.3% -0.3	6471	0.29
	During Pandemic	4445 96.8% -1.5	134 2.9% 1.5	14 0.3% 0.3	4593	
ERP	Before Pandemic	2578 99.7% 1.8	8 0.3% -1.1	0 0% -2.0	2586	0.67
	During Pandemic	1255 99.3% -1.8	7 0.6% 1.1	2 0.2% 2.0	1264	
MCT	Before Pandemic	19077 99.4% 6.6	108 0.6% -5.6	9 0% -3.9	19194	<0.001
	During Pandemic	14244 98.7% -6.6	160 1.1% 5.6	27 0.2% 3.9	14431	
MBD	Before Pandemic	4418 99.6% 2.5	15 0.3% -0.7	1 0% -3.5	4434	0.002
	During Pandemic	2900 99.2% -2.5	13 0.4% 0.7	10 0.3% 3.5	2923	
DE	Before Pandemic	3288 99.9% 0.3	3 0.1% -0.3		3291	1.00
	During Pandemic	2524 99.9% -0.3	3 0.1% 0.3		2527	
EEAP	Before Pandemic	3786 98.2% 0.7	65 1.7% -0.2	6 0.2% -1.4	3857	0.38
	During Pandemic	3514 97.9% -0.7	63 1.8% 0.2	11 0.3% 1.4	3588	

The threshold for statistical significance was $p < 0.05$. N: Number of patients

See at Appendix for URS, SIS, NS, T, CS, ES, US, GP, ID, EE, ERP, LRS, MBD, MCT, DE, EEAP

DISCUSSION

The three hypotheses established in the study, which intended to evaluate the effect of the pandemic on ED visits and to compare the outcomes of ED visits, were all rejected. This was one of the few studies designed to associate the reasons for visiting the ED (classified according to the ICD-10 groups) with hospital outcomes, and significant results were found. Medical admissions fell dramatically with the spread of COVID-19 in March and April 2020. Subsequent surveys sampling patient behavior indicated fears surrounding COVID-19 as a valid reason for this avoidance and delay in seeking care, with up to 12% avoiding urgent or emergency care (5). Several studies have shown that pandemic-related infection-independent effects (myocardial infarction and ischemic stroke) have led to a massive reduction in patient visits to healthcare facilities for non-COVID-19 concerns (6). Santana et al. reported that the total number of ED visits within a month (March 2020) during the COVID-19 outbreak significantly decreased by 48% (7). In a single-center report of an urban hospital in the United States, Westgard et al. reported a 35% decline in ED visits compared with the previous year (2019) (8). In another study, the number of ED visits was found to have been reduced by 30.9% in 2020 compared to 2019 (9). Hendrikse et al. (10) ascertained a 15% decrease in the number of ED visits in 2020 compared to the previous year, and a 35% decrease in the period after the full lockdown compared to the previous period. In the study by Birkmeyer et al., which examined approximately one million medical visits, it was found that the hospital admissions decreased dramatically with the onset of the COVID-19 pandemic, and that these reductions exceeded 20% for all primary admission diagnoses (5). In this study, similar to the aforementioned studies, a 26% reduction in ED patient volumes was observed in the study hospital during the COVID-19 pandemic.

Jeffery et al., in their cross-sectional study of 24 EDs in five healthcare systems in the USA (Colorado, Connecticut, Massachusetts, New York, and North Carolina), observed a rapid decline in ED visits in March 2020 (41.5% in Colorado; 63% in New York). They reported that the rates of admission from the ED remained stable until an increase in the number of COVID-19 cases was found locally, followed by a relative increase of 22–149% in the subsequent periods (1). Giamello et al. reported a 50% decrease in the number of ED visits in Italy during the pandemic compared to the previous year, but an 11% and 21% increase in admissions depending on the time (11). In this study, as in the aforementioned studies, a decrease in the number of ED visits and an increase in the frequency of admission and referral were observed during the pandemic.

Kansagra et al. stated that the acute stroke cases declined by 39% during the pandemic (12). Bulrich et al. reported that although the number of stroke cases decreased by 20% in 2020 compared to 2019, the number of admissions did not change (13). In this study, there was an increase in the number of hospital admissions (due to the increase in the number of patients who came with more severe conditions) and a decrease of approximately 41% in the neurological diagnosis group.

Erol et al. stated that there was a 47.1% decrease in acute myocardial infarction (AMI) admissions during the pandemic, and the hospital admission process was prolonged for ST-segment-elevation myocardial infarction (STEMI) and non-STEMI (14). Kuitunen et al. reported that the number of ED visits declined by 16% and the number of admissions, by 15%, in the 6-week timeframe before and after the lockdown while the rates of AMI and stroke remained stable (15). In our study, the ED visits decreased but the hospital admission rate in the NS group and the admission and referral rates in the CS group increased. These differences may have been related to the duration of the studies. Similar to the results of the study by Giamello et al. (11), who found a decrease in the admission rates of patients with trauma, acute coronary syndrome, heart failure, and stroke, a decrease in ED visits was observed in the trauma, acute coronary syndrome, heart failure, and stroke groups in our study. It is thought that the curfews and the fear of infection risk by the patients were the reasons for the decreases in admission rates in the aforementioned study.

In a study conducted in France, it was determined that there was a 15% decrease in trauma patients during the pandemic's lockdown period (16). Nunez et al. reported that although there were significant reductions in the ED visit and hospital admission rates due to occupational accidents, traffic accidents, and other trauma causes during the pandemic, the osteoporotic hip fracture visits remained stable (17). In our study, a 37% decrease in the

number of outpatient trauma patients and an increase in the admission and referral rates were observed. It is thought that these were due to the unprecedented level of quarantine and travel ban that the Turkish government had implemented during the pandemic, as in many other countries in the world.

Gonçalves-Pinho et al. reported that there was a 52.2% decrease in the ED admission rate due to psychiatric conditions during the pandemic (18). Capuzzi et al. reported that the number of hospital admissions was higher despite this decrease, which they found to be similar to the results of other studies (19). Our results showed a decrease in the number of ED visits and an increase in the number of referrals for admission, which are in line with the results of both the aforementioned studies. This is justified by the fact that the referral outcomes during the pandemic were higher than expected, and can also be explained by the fact that the study hospital does not have inpatient service, thus referring the patients to other institutions for admission.

Cano-Valderrama et al. found a 58.9% decrease in the ED visits of patients with acute abdomen complaints, and that the admission period was prolonged (20). Similarly, the increase in admission rate in the present study may have been due to the late patient admissions.

In another study conducted in Italy, Morello et al. reported a 66.4% decrease in ED visit rates after the first wave of the pandemic, and a 23.5% decrease in the following periods. They also reported that the rate of admissions decreased by 39.5% at the beginning of the pandemic and by 12.2% in the following periods. In their study, the oncological, metabolic, endocrine, and hematological diagnosis rates were reported as unchanged and significant reductions in other diagnoses (infectious, psychiatric, non-COVID-19 respiratory, gastrointestinal, urological, obstetrical/gynecological diseases, and trauma) in the following periods were also reported. Again, in such study, the decline in non-emergency codes was evaluated as an indicator of the inappropriate use of the ED (21). In the present study, the increases in admission and referral rates, in addition to the decreases in ED visits for all the diagnostic groups, support the perspective that the emergency service was used inappropriately. Also, Morello et al. reported that there were less differences between the diagnostic groups in the centers where the patients were referred due to service limitations. This might explain why the aforementioned findings differed from those in our study.

While Carret et al. (22) stated that the rate of inappropriate use of emergency services varies between 20% and 40%, this rate is reported as 9.6% in Singapore, 11.7% in England, and 19.6% in Italy (23–25). The inappropriate use of the ED leads to adverse consequences for patients, staff, and the health system (26). In an article published by the American College of Emergency Physicians, the situations caused by the inappropriate use of the ED were listed as follows: examination of patients and their families in areas not considered suitable for their privacy, increased mortality and morbidity, longer admission period of admitted patients, decreased patient satisfaction, decreased satisfaction of emergency service personnel, significant delay in the evaluation and treatment of emergency conditions, patients leaving before the treatment completion, and increased cost and loss of reputation of the institution (27). The fact that there were no differences between the US, EE, ERP, DE, and EEAP groups in terms of numbers of outpatient visits, admissions, and referrals without the effect of the pandemic showed that the patients in these groups used the emergency services appropriately, as opposed to the other groups. Only the decrease in hospital admissions of the T group may be considered normal due to the curfews that were imposed at certain times in Turkey.

During the COVID-19 pandemic, temporal associations between decrease in ED visits and increase in hospital admission rates were observed. These findings suggest that practitioners and public health officials should emphasize the importance of visiting the ED during the COVID-19 pandemic for serious symptoms, illnesses, and injuries that cannot be managed in other settings.

There has been a decrease in the number of ED visits during the pandemic, and late patient admission may lead to conditions with a more severe clinical course and may increase hospital admissions. Additionally, emergency services have also been used inappropriately, except for certain clinics. Healthcare authorities should consider taking the necessary precautions by paying attention to these matters during a pandemic.

Moreover, while non-emergency patients are praised for not visiting the ED, for those with conditions such as chest pain, neurological symptoms, and shortness of breath, which worsen with time, a delayed ED visit can lead to serious complications. It is important to raise patients' awareness of the acute conditions that require immediate medical attention to prevent potentially fatal situations.

Study Limitations

The present study had some limitations, including the fact that the age, sex, and other sociodemographic characteristics, and the comorbidities, of the patients who visited the ED and of those who were hospitalized were not studied. This study was a retrospective study that utilized aggregated health data from the health data management solution system. There may have been errors caused by the user physician, and the accuracy of the electronic records was not confirmed. In addition, the findings of the study cannot be generalized as the study was conducted in a single center.

Funding sources

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

Declaration of Interest

The authors have no potential conflicts of interest to declare.

This study was approved by the Attending Physician of Emergency Medicine, Division of Emergency Medicine, Odemiş State Hospital, Izmir, Turkey (Date 14.01.2022, Decision Number 2021/78-/6).

Appendix

1. Upper Respiratory System (URS): J00, J02, J03, R05, R52, R53
2. Lower Respiratory System (LRS): J18, J22, J44, J45.9
3. Stomach and Intestinal System (SIS): R10, R10.4, R11, R14, K21, K29, K30, K52, K92.2
4. Nervous System (NS): I69, R42, R55, G43.9, R51
5. Trauma (T): W01, W19, W45, V29, V49, S61, S00, S01.3, S01, S51, S41, S50, S60, S63, S90, S93, T15, Y28
6. Circulatory System (CS): I10, I20, I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I46, I48, I50.9, R00, R00.0, R00.2, R07.4
7. Endocrine System (ES): D64, D68, E10, E11
8. Urinary System (US): N22, N23, N30, N39.0
9. Gynecology and Pregnancy (GP): N94.6, O26, Z32, Z33
10. Infectious Diseases (ID): A09, K52.9, L08, R50, R50.9, Z23.5
11. Environmental Emergencies (EE): L50, W54, W55, X22, X23, X44
12. Ear and Respiratory Passage (ERP): H60, H65.0, J30.3, R04.0
13. Mental and Behavioral Disorders (MBD): F23.2, F33, F41, F41.0, F41.1, F41.2, F41.3, F41.8, F41.9
14. Muscular System and Connective Tissues (MCT): M54.4, M79, M79.7
15. Diseases of the Eye (DE): H10
16. Examination and Encounter for Administrative Purposes (EEAP): Z02

REFERENCES

1. Jeffery MM, D'Onofrio G, Paek H, Platts-Mills TF, Soares WE 3rd, Hoppe JA, et al. Trends in Emergency Department Visits and Hospital Admissions in Health Care Systems in 5 States in the First Months of the COVID-19 Pandemic in the US. JAMA Intern Med. 2020;180(10):1328-1333.
2. Uscher-Pines L, Pines J, Kellermann A, Gillen E, Mehrotra A. Emergency department visits for nonurgent conditions: systematic literature review. Am J Manag Care. 2013;19(1):47-59.
3. Durand AC, Gentile S, Devictor B, Palazzolo S, Vignally P, Gerbeaux P, et al. ED patients: how nonurgent are they? Systematic review of the emergency medicine literature. Am J Emerg Med. 2011;29(3):333-45.
4. Everitt BS. The analysis of contingency tables. 2nd ed. Chapman and Hall/CRC; 1992.
5. Birkmeyer JD, Barnato A, Birkmeyer N, Bessler R, Skinner J. The Impact Of The COVID-19 Pandemic On Hospital Admissions In The United States. Health Aff (Millwood). 2020;39(11):2010-2017.
6. Alwood S, Musso MW, Jones GN, Mosley J, Wippel B, Theriot L, et al. The impact of the COVID-19 pandemic and governor mandated stay at home order on emergency department super utilizers. Am J Emerg Med. 2021;48:114-119.
7. Santana R, Sousa JS, Soares P, Lopes S, Boto P, Rocha JV. The Demand for Hospital Emergency Services: Trends during the First Month of COVID-19 Response. Port J Public Health 2020;38:30–6.
8. Westgard BC, Morgan MW, Vazquez-Benitez G, Erickson LO, Zwank MD. An Analysis of Changes in Emergency Department Visits After a State Decleration During the Time of COVID-19. Ann Emerg Med. 2020;76(5):595-601.
9. Baugh JJ, White BA, McEvoy D, Yun BJ, Brown DFM, Raja AS, Dutta S. The cases not seen: Patterns of emergency department visits and procedures in the era of COVID-19. Am J Emer Med 2021;46:476-481.
10. Hendrikse C, Parak M, Van Hoving DJ. A descriptive analysis of the effect of the national COVID-19 lockdown on the workload and case mix of patients presenting to a district-level emergency centre in Cape Town, South Africa. S Afr Med J. 2020;110(11):113-18.
11. Giamello JD, Abram S, Bernardi S, Lauria G. The emergency department in the COVID-19 era. Who are we missing? Eur J Emerg Med. 2020;27(4):305-06.
12. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral Effect of Covid-19 on Stroke Evaluation in the United States. N Engl J Med. 2020;383(4):400-401.

13. Bres Bullrich M, Fridman S, Mandzia JL, Mai LM, Khaw A, Vargas Gonzalez JC, et al. COVID-19: Stroke Admissions, Emergency Department Visits, and Prevention Clinic Referrals. Can J Neurol Sci. 2020;47(5):693-696.

14. Erol MK, Kayıkçıoğlu M, Kılıçkap M, Güler A, Yıldırım A, Kahraman F, et al. Treatment delays and in-hospital outcomes in acute myocardial infarction during the COVID-19 pandemic: A nationwide study. Anatol J Cardiol. 2020;24(5):334-342.

15. Kuitunen I, Ponkilainen VT, Launonen AP, Reito A, Hevonkorpi TP, Paloneva J, et al. The effect of national lockdown due to COVID-19 on emergency department visits. Scand J Trauma Resusc Emerg Med. 2020;28(1):114.

16. Moyer JD, Abback PS, Hamada S, Martinez T, Werner M, James A, Traumabase®Group. Effect of 2020 containment strategies on trauma workflow in Ile-de-France region: another benefit of lockdown? Scand J Trauma Resusc Emerg Med. 2021;29(1):135.

17. Nuñez JH, Sallent A, Lakhani K, Guerra-Farfan E, Vidal N, Ekhtiari S, et al. Impact of the COVID-19 Pandemic on an Emergency Traumatology Service: Experience at a Tertiary Trauma Centre in Spain. Injury. 2020;51(7):1414-1418.

18. Gonçalves-Pinho M, Mota P, Ribeiro J, Macedo S, Freitas A. The impact of COVID-19 pandemic on psychiatric emergency department visits - a descriptive study. Psychiatr Q. 2021;92(2):621-631.

19. Capuzzi E, Di Brita C, Caldiroli A, Colmegna F, Nava R, Buoli M, et al. Psychiatric emergency care during Coronavirus 2019 (COVID 19) pandemic lockdown: results from a Department of Mental Health and Addiction of northern Italy. Psychiatry Res. 2020;293:113463.

20. Cano-Valderrama O, Morales X, Ferrigni CJ, Martín-Antona E, Turrado V, García A, et al. Reduction in emergency surgery activity during COVID-19 pandemic in three Spanish hospitals. Br J Surg. 2020;107(8):e239.

21. Morello F, Bima P, Ferreri E, Chiarlo M, Balzaretti P, Tirabassi G, et al. After the first wave and beyond lockdown: long-lasting changes in emergency department visit number, characteristics, diagnoses, and hospital admissions. Intern Emerg Med. 2021;16(6):1683-1690.

22. Carret ML, Fassa AC, Domingues MR. Inappropriate use of emergency services: a systematic review of prevalence and associated factors. Cad Saude Publica 2009;25(1):7-28.

23. Oh HC, Chow WL, Gao Y, Tiah L, Goh SH, Mohan T. Factors associated with inappropriate attendances at the emergency department of a tertiary hospital in Singapore. Singapore Med J 2020;61(2):75-80.

24. McHale P, Wood S, Hughes K, Bellis MA, Demnitz U, Wyke, S. Who uses emergency departments inappropriately and when - a national cross-sectional study using a monitoring data system. BMC Medicine 2013;11:258.

25. Bianco A, Pileggi C, Angelillo IF. Non-urgent visits to a hospital emergency department in Italy. Public Health. 2003;117(4):250-5.

26. Morley C, Unwin M, Peterson GM, Stankovich J, Kinsman L. Emergency department crowding: A systematic review of causes, consequences and solutions. PloS One 2018 30;13(8):1-42.

27. American College of Emergency Physicians. Crowding. 2019. Available at https://www. acep.org/patient-care/policy-statements/crowding/ Accessed September 25, 2021.

Archives of Current Medical Research
Arch Curr Med Res 2023;4(1):58-61

Received: 26 July 2022
Revised: 22 December 2022
Acccepted: 7 January 2023
DOI: 10.47482/acmr.1148751

CASE REPORT

Fibrin Membrane Induced Pupillary Block Glaucoma Treated With Nd:YAG Laser After Uncomplicated Cataract Surgery

Fatma Sümer[1]

1 Recep Tayyip Erdoğan University, Faculty of Medicine, Department of Ophthalmology

Abstract

Fibrin pupillary-block glaucoma is a rare complication after uneventful cataract surgery. We aimed to share our treatment approach with Nd:YAG laser fibrin membranotomy. A 68-year-old man, whom does not have any systemic comorbidity developed acute elevation of intraocular pressure with a shallow anterior chamber 7 days after uneventful cataract surgery. Right visual acuity(VA) VA was 0.1 and intraocular pressure (IOP) IOP was 48 mmHg. There was a fibrin membrane that completely closed the pupillary distance and with 360 degrees of peripheral iridocorneal touch. An Nd:YAG laser was used to create an opening in the superior margin of the membrane. Perforation of the membrane led to rapid deepening of the anterior chamber, permitting a sequential argon–Nd:YAG peripheral iridotomy to be performed at the same sitting. Although the fibrin membrane seen after uneventful cataract surgeries usually suggests that an inflammation is triggered, these results can sometimes occur even before the disease is present.

Keywords: Fibrin Membrane, Pupillary Block Glaucoma, Cataract Surgery, Nd: Yag Laser.

Cite this article as: *Sümer F. Fibrin Membrane Induced Pupillary Block Glaucoma Treated With Nd:YAG Laser After Uncomplicated Cataract Surgery. Arch Curr Med Res. 2023;4(1):58-61*

Corresponding Author:
Fatma Sümer, Recep Tayyip Erdoğan University,
Faculty of Medicine, Department of Ophthalmology
E-Mail: fatmasumer_@hotmail.com

INTRODUCTION

Complications related to cataract surgery are gradually decreasing, depending on the development of technology and techniques used. Despite all these advances in surgical technique, fibrin membrane-bound pupillary block glaucoma (PBG) is a rare complication seen after uneventful phacoemulsification cataract surgeries and can be seen rarely (1). Fibrin-derived PBG is the clinical picture with peripheral angle closure and increased intraocular pressure (IOP) due to the fact that the pupillary cavity is completely covered by the fibrin membrane (2). Severe corneal edema due to increased IOP hinders biomicroscopic examination and complicates early diagnosis. However, the presence of fibrin membrane in the pupillary space after uneventful cataract surgery suggests PBG.

We present a case of fibrin pupillary block glaucoma in a patient who was successfully treated with primary Neodyum YAG (**Ytrium Aluminyum oxide Garnet** (Nd: YAG) Nd:YAG laser.

CASE REPORT

On January 10, 2022, the patient was admitted with the complaint of low and blurred vision in the right eye. His visual acuity (VA) was 0.3 in the right eye and 1.0 in the left eye. IOP was 13 mmHg and 14 mmHg in the right and left eyes, respectively. Corneas were clear in both eyes, and the depth of the anterior chamber was normal. Nuclear cataract and pseudophakia were detected in the right and left eyes, respectively. There was no systemic comorbidity. After an uneventful phacoemulsification cataract surgery, intracapsular hydrophobic acrylic intraocular lens (IOL) (Acriva-VSY) was placed. In the examination performed on the first postoperative day, the right eye VA was 0.8 and IOP was 14 mmHg. The depth of the anterior chamber was normal, and there was a mild inflammation in the anterior chamber (1+ cell reaction), and clear cornea. In the control examination performed on the first postoperative day, it was observed that there was no leakage at the wound site. Moxifloxacin eye drop six times a day (Moxai, Abdi İbrahim) and prednisolone eye drop eight times a day (Pred Forte, Allergan) were prescribed after discharge. The patient was called for control examination after 1 week. On the control day, the patient was admitted to our hospital with sudden onset of pain, redness, and low-vision in the operated eye. His right VA was 0.1 and IOP was 48 mmHg. Congestion was observed in the conjunctiva. The depth of the anterior chamber was too decreased, despite the fact that it could not be evaluated with certainty due to an intense corneal edema. The patient was initiated 300 cc. intravenous mannitol 20%, systemic acetazolamide 4times/day, topical dorzolamide–timolol maleate 2x1 (tomec, Abdi İbrahim), and topical Brimogut (Brinzolamid, Bilim) were initiated. Although corneal edema regressed slightly after treatment, pain did not change. His right VA was 0.1 and IOP was 48 mmHg. IOP was not changed. When the corneal edema decreased, it was observed that there was a fibrin membrane that completely closed the pupillary distance and with 360 degrees of peripheral iridocorneal touch (Figure 1).

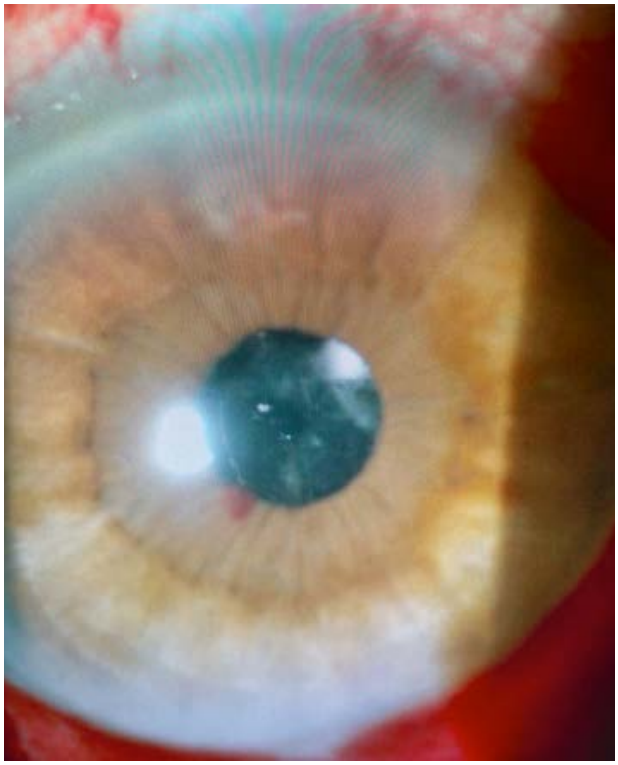


Figure 1: Fibrin membrane that completely closed the pupillary distance and with 360 degrees of peripheral iridocorneal touch.

An Nd:YAG laser was used to create an opening in the superior margin of the membrane. Perforation of the membrane led to rapid deepening of the anterior chamber, permitting a sequential argon–Nd:YAG peripheral iridotomy to be performed at the same sitting. The IOP was 26 mmHg after these procedures. In order for the pupillary opening to not close again, a 360-degree

ND:YAG laser was applied to the pupillary margin and the fibrin membrane was completely separated (Figure 2).

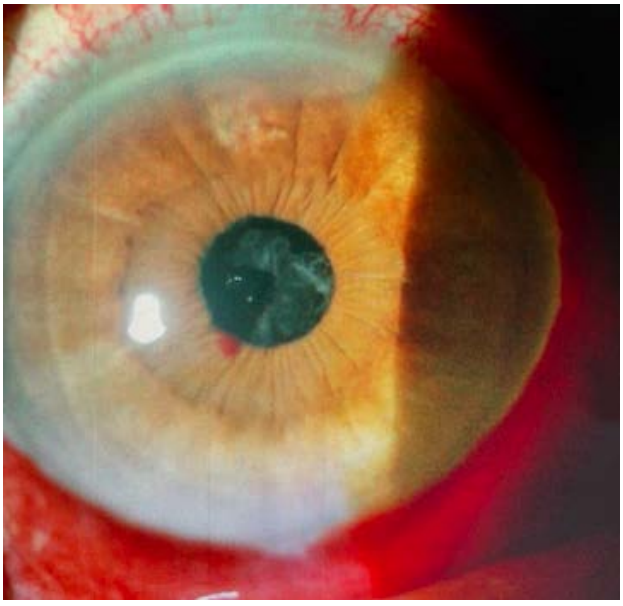


Figure 2: 360-degree ND:YAG laser was applied to the pupillary margin and the fibrin membrane was completely separated.

In the examination performed the next day, it was observed that the opening in the fibrin membrane started to close again, despite the hourly administration of 1% prednisolone acetate to the right eye. The laser iridotomy site was patent. Cyclopentalate and tropicamide (Tropamid 0.05%-Bilim) were added every 4 hours to prevent adhesion for pupil dilation. The fibrin eventually resolved without recurrence after 2 weeks of intensive topical steroid use; the IOP remained normal. VA had improved to 1.0 in the right eye and IOP was 15 mmHg, the anterior chamber remained deep and the cornea was clear (Figure 3). Fundus examination was normal. Consent was obtained from the patient before all procedures and to share this case.

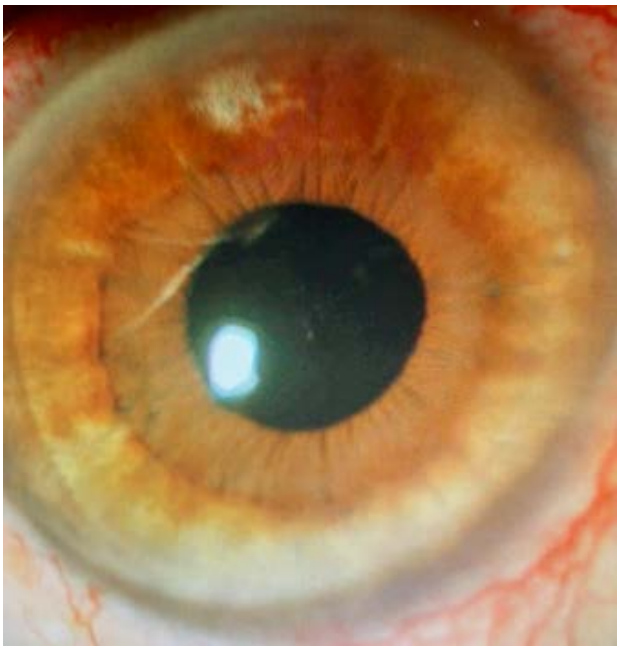


Figure 3: The fibrin eventually resolved, the anterior chamber remained deep and the cornea was clear.

DISCUSSION

The differential diagnosis for a shallow anterior chamber associated with elevated IOP after cataract surgery includes pupillary block (fibrin membrane, Soemmering's ring and posterior synechia, capsular block syndrome and malignant glaucoma) (2–6). Although fibrin membrane pupillary-block glaucoma is more common after pars plana vitrectomy, there are a few reports of fibrin membrane pupillary-block glaucoma after cataract surgery (7,8).

This case report describes how the Nd: YAG laser was used to successfully remove the fibrinous pupillary membrane that causes pupillary-block glaucoma. The development of fibrin pupillary-block glaucoma is dependent on the formation of an inflammatory membrane, which completely occludes the pupil. This results in redirection of fluid into a 'third space' cavity between the iris and intraocular lens, which leads to bowing of the iris and subsequent swallowing of the anterior chamber with resultant pupil block. The similar anatomical morphology to aqueous misdirection glaucoma may hinder early diagnosis (8).

The development of these fibrinous membranes is thought to be the outcome of an immune reaction in which the blood-aqueous barrier is broken, resulting in an increased proclivity to inflammation (9).

As a result, although the Nd:YAG laser procedure applied in our case with pupillary block glaucoma after cataract surgery eliminated the problem, it was not fully understood why this situation developed as a secondary reaction. Although we predict the most likely reason for this case as the inability of our patient to apply steroid drops regularly, other possible causes may be: secondary reaction to the viscoelastic material used or remaining intracapsular viscoelastic material.

After the successful operation in our case, the main treatment of fibrin pupillary block glaucoma, which was caused by the inability of our patient to use the drugs correctly, was performed with Nd:YAG laser. This is most likely related to the use of high-frequency topical steroids in combination with cycloplegia to minimize the inflammatory response to laser therapy, which was already exacerbated by the presence of a diagnosis of mixed connective tissue disease.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

Ethical Committee approval was not required. Informed consent was obtained from all participants

REFERENCES

1. Yoshino H, Seki M, Ueda J,Yoshino T,Fukuchi T, Abe H.Fibrin membrane pupillary-block glaucoma after uneventful cataract surgery treated with intracameral tissue plasminogen activator: a case report. *BMC Ophthalmol* 2012;12(1).
2. Khor WB, Perera S, Jap A, Ho CL,Hoh ST. Anterior segment imaging in the management of postoperative fibrin pupillary-block glaucoma. *J Cataract Refract Surg*. 2009;35(7): 1307–1312.
3. Kobayashi H, Hirose M, Kobayashi K. Ultrasound biomicroscopic analysis of pseudophakic pupillary block glaucoma induced by Soemmering's ring. Br J Ophthalmol. 2000;84(10): 1142–1146.
4. Aslanides IM, Libre PE, Silverman RH, Reinstein DZ, Lazzaro DR, Rondeau MJ,et al. High frequency ultrasound imaging in pupillary block glaucoma. Br J Ophthalmol. 1995;79(11): 972–976.
5. Theng JTS, Jap A, Chee SP. Capsular block syndrome: A case series. J Cataract Refract Surg. 2000;26(3): 462–467.
6. Halkias A, Magauran DM, Joyce M. Ciliary block (malignant) glaucoma after cataract extraction with lens implant treated with YAG laser capsulotomy and anterior hyaloidotomy. Br J Ophthalmol. 1992;76(9): 569–570.
7. Lewis H, Han D, Williams GA. Management of fibrin pupillary-block glaucoma after pars plana vitrectomy with intravitreal gas injection. Am J Ophthalmol. 1987;103(2): 180–182.
8. Khan S, Elashry M. The Nd:YAG laser as first-line treatment for fibrin pupillary-block glaucoma following uncomplicated cataract surgery. Oxf Med Case Reports. 2019;2019(1):omy113.
9. Wålinder PEK, Olivius EOP, Nordell SI, Thorburn WE. Fibrinoid reaction after extracapsular cataract extraction and relationship to exfoliation syndrome. J Cataract Refract Surg. 1989;15(5): 526–530.

ARCHIVES OF
CURRENT MEDICAL
RESEARCH

www.acmronline.org

https://dergipark.org.tr/tr/pub/acmr