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Message from the Editor-in-Chief

Message from the Editor-in-Chief,

As we are leaving the second summer with the COVID-19 pandemic, the threat of variants started to create intense pressure in all areas. On the other hand, both the general and medical society, including the healthcare professionals and research individuals, are now doing better with the pandemic measures worldwide.

We very well know that a significant proportion of authors and readers of GMJ are involved not only in our fight against the COVID-19 as healthcare professionals in the frontline but also in research activities. Therefore, as we have been receiving a higher number of submissions in 2021 compared with the same period in the last year, we should more strongly thank the authors submitting articles to GMJ, as well as our referees and readers.

In the third issue of GMJ, we have highly interesting original articles, and case reports. As the journal's publishing team, we try to keep covering a wide range of articles from different disciplines.

Thank you for contributing to GMJ.

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

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Assessment of relative position of infraorbital foramen in dry adult skulls and its clinical implication

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Keywords: Infraorbital foramen, zygomatico-maxillary suture, anterior nasal spine, Le Fort type-1 osteotomy, accessory foramen

ABSTRACT

Aims: Knowledge of the location of infraorbital foramen (IOF) is important to avoid injuries to neurovascular structure which passes through it, as it may occur in surgical procedures such as rhinoplasty, Caldwell-Luc surgical procedures, tumor surgery, orbita basis reduction, malar region fractures, and Le Fort type-1 osteotomy. Hence, this foramen should be approached carefully to avoid damage.

Methods: Ninety dried skull bones of unknown sex, obtained from the clinic of anatomy, MVJ Medical College and Research Hospital, were used to study the shape, size, relation to maxillary tooth, presence of accessory foramen and distance of IOF from surface landmarks and results were analyzed statistically.

Results: The vertical and horizontal diameters of IOF were 3.29±0.82 mm and 3.77±0.85 mm on the right side, and 3.37±0.81 mm and 3.90±0.96 mm on the left side, respectively. Oval shape was more common. The distance between IOF and infraorbital margin was 6.34±1.63 mm on the right side and 6.40±1.48 mm on the left side; alveolar margin of maxilla was 27.82±4.13 mm on the right and was 28.40±3.40 mm on the left side; zygomatico-maxillary suture was 14.11±2.23 on the right side and 13.87±3.59 mm on the left side; and anterior nasal spine was 32.21±3.07 mm on the right side and 32.26±2.29 mm on the left side. Accessory foramen was seen in 7 (7.7%) skulls. The location of foramen was along 1st premolar tooth on the right side and towards the 2nd premolar tooth on the left side.

Conclusions: This study makes it possible to identify the exact position of IOF and its application in various surgical procedures.

Introduction

Infraorbital foramen (IOF) is an opening located on the anterior surface of maxilla, about 1 cm below the infraorbital margin. It transmits infraorbital nerve and infraorbital vessels. The infraorbital nerve is a continuation of maxillary nerve which runs along the floor of orbit in the infraorbital groove and canal, and appears in the face through the IOF below the origin of levator labii superioris muscle (1). The infraorbital nerve is divided into three groups of branches-the palpebral, the nasal and the superior labial. The palpebral branches supply the skin in the lower eyelid. The nasal branches supply the skin of the side of the nose and of the movable part of the nasal septum. The superior labial branches supply the skin of the anterior part of the cheek and the upper lip (2). The infraorbital artery is a branch from the third part of maxillary artery and follows the same course as that of nerve.

Even though the previous literature shows numerous studies on morphometry of IOF, the location of IOF is of great clinical importance as it is located nea r various important anatomical structures such as orbit, nose and oral cavity (3). Since it transmits the important neurovascular structures, the essential knowledge of topographical location of IOF is of utmost important to avoid the injuries to these structures. Infraorbital nerve block is the nerve of choice for surgeries involving orbital, nasal and buccal areas. This nerve can be entered through the intra oral or extra oral route. Hence accurate localizing of the IOF is of great clinical importance as once the location is determined, the needle can be advanced either through the skin

directly toward the IOF or through the mouth at the level of the incisor at alveolar buccal mucosal margin in the subsulcal plane (4). It provides excellent analgesia for the closure of simple lacerations, biopsies, scar revisions, maxillofacial procedures, as well as various endoscopic and cosmetic cutaneous procedures (5). In case of intractable and pharmacologically unresponsive trigeminal neuralgia, therapeutic infraorbital nerve blocks are commonly done. The presence of accessory IOF may complicate the anesthetization of the region (6). One of the main reason for dentist to avoid infraorbital nerve block is the fear of damage to eyeball which can be avoided by identifying the exact location of IOF in relation to anatomical palpable landmarks (7). Hence the present study was conducted with an aim to find out the incidence of variations in location, shape, dimensions and distance of the IOF from various bony landmarks on both sides of the same skull and the incidence of accessory foramen.

Methods

The present study was conducted on 90 dry skulls of unknown sex and age, which were obtained from the clinic of anatomy, MVJ Medical college and Research Hospital, Bangalore, Karnataka, and used to study the shape, size, exact position in relation to bony landmarks, presence of accessory IOF. The skulls with damaged infraorbital margin and IOF unilaterally and bilaterally were excluded from the study. All measurements were taken on bilaterally with the help of digital vernier caliper of 0.01 mm accuracy by two different people.

The following measurements were done in the present study:

1) Shape of IOF,

2) Size of IOF (vertical and horizontal diameters),

3) Location of IOF in relation to maxillary teeth,

4) Presence of accessory IOF,

5) Distance from the center of IOF to infraorbital l margin,

6) Distance from the center of IOF to zygomatico-maxillary suture,

7) Distance from the center of IOF to anterior nasal spine,

8) Distance from the center of IOF to alveolar margin of maxilla along the sagittal plane.

Statistical Analysis

The data obtained were analysed statistically using SPSS software. Mean and standard deviation were calculated for the distance of IOF from various anatomical landmarks and percentage was calculated for shape, accessory foramen and location of IOF in relation to maxillary tooth. The results were represented in the form of table and graph.

Results

1) Shape of infraorbital foramen. In the present study including morphometric analysis of IOF, on the right side, oval shape was seen in 51.1% (46 skulls) and round shape was seen in 48.8% (44 skulls). On the left side, 55.5% (50 skulls) had oval shape and 44.4% (40 skulls) had round shape. Oval shape was predominant in both sides (Figure 1).

2) Size of infraorbital foramen (vertical and horizontal diameters). The vertical diameter of IOF was 3.29±0.82 mm on the right side and 3.37±0.81 mm on the left side, and horizontal diameter of IOF was 3.77±0.85 mm on the right side and 3.90±0.96 mm on the left side.

3) Presence of accessory infraorbital foramen. Accessory IOF was present in 7 (7.7%) skulls, in which it was present bilaterally in one skull whereas unilaterally in 6 skulls (2 on right side and 4 on left side) (Figure 2).

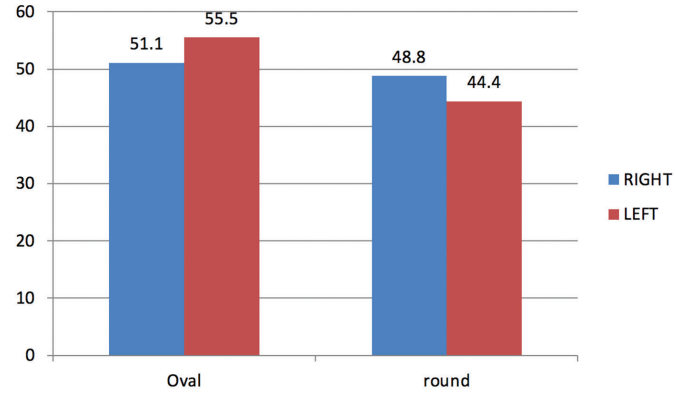

Figure 1. Bar diagram showing the shape of infraorbital foramen on the right and left sides

Figure 2. Accessory infraorbital foramen (2 accessory foramina were seen on either side of the normal infraorbital foramen-marked with red circle)

IOF: Infraorbital foramen

4) Location of infraorbital foramen in relation to maxillary teeth. On the right side, IOF was vertically oriented towards 1st premolar in 27 (30%) skulls, towards 2nd premolar in 19 (21.1) skulls, located between 1st and 2nd premolar in 14 (15.5%) skulls, between 2nd premolar and 1st molar tooth in 12 (13.3%) skulls, between canine and 1st premolar in 7 (7.7%) skulls, towards 1st molar in 5 (5.5%) skulls and towards 2nd molar tooth in 4 (4.4%) skulls. And, in 2 (2.2%) skulls, it was vertically directed towards canine tooth.

On the left side, IOF was vertically oriented towards 2nd premolar tooth in 30 (33.3%) skulls, towards 1st premolar in 25 (27.7%) skulls, between 1st premolar and 2nd premolar in 12 (13.3%) skulls, between 2nd premolar and 1st molar in 10 (11.1%) skulls, located between canine and 1st premolar in 7 (7.7%) skulls, towards 1st molar tooth in 4 (4.4%) skulls, and between 1st molar and 2nd molar in 1 (1.1%) skull. And, in 1 (1.1%) skull, the foramen was vertically directed between incisor and canine.

Hence, on the right side, in majority of skulls, IOFs were vertically oriented towards 1st premolar and on the left side, IOFs were vertically directed towards 2nd premolar tooth.

5) Distance of infraorbital foramen from anatomical landmarks (Table 1, Figure 3).

Discussion

The recent development in endoscopic surgeries has increased the importance of characteristics of facial foramens. The infraorbital nerve block which is the most common local analgesic technique used for the regional anesthesia of the face. This nerve block has got many advantages as with smaller amount of anesthetic drug, it gives better results than local infiltration. It gives anesthesia without causing any tissue distortion (2). Hence this study is an attempt to analyze the IOF in terms of its shape, size, location, presence of accessory foramens, which provides important data in giving local anesthesia in maxillofacial and plastic surgeries (7).

Table 1. Distance of infraorbital foramen from infraorbital margin, anterior nasal spine, zygomatico-maxillary suture and alveolar margin

Parameters	Right side		Left side	
	Mean (mm)	Standard deviation	Mean (mm)	Standard deviation
Infraorbital foramen-infraorbital margin	6.34	1.63	6.43	1.48
Infraorbital foramen-anterior nasal spine	32.21	3.07	32.26	3.29
Infraorbital foramen-zygomatico-maxillary suture	14.11	2.24	13.87	3.59
Infraorbital foramen-alveolar margin	27.82	4.13	28.40	3.40

In the present study, oval shape was more predominant on both right and left sides constituting 51.1% and 55.5%, respectively. Dagistan et al. (8) conducted morphometric analysis of IOF with cone computed tomography. In their study, 58% skulls showed oval shape and 42% had round shape. Singh (9) conducted a study on 110 skulls, showed 71% oval shape and 29% circular shape. Majority of studies showed oval shape as the most predominant type, followed by round shape. Some of the studies reported semilunar and triangular shapes, which was not present in our study.

The vertical diameter of IOF was 3.28±0.82 mm on the right side and 3.36±0.81 on the left side. The horizontal diameter was 3.76±0.85 mm on the right side and 3.90±0.96 mm on the left side. In a study by Singh (9), the mean vertical dimensions on the right and left sides were 3.39 mm and 3.75 mm, respectively. The mean horizontal dimensions on the two sides were 3.19 mm and 3.52 mm. The diameter of the IOF is related proportionately to that of thickness of infraorbital nerve and vessels (10).

The distances between IOF and various novel anatomical landmarks were chosen as these reference points are easily identifiable even in the presence of pathological lesions of maxillofacial regions such as fracture or edema (5). In the present study, the distance between IOF and infraorbital margin was 6.34±1.63 mm on the right side and 6.4±1.48 mm on the

Figure 3. Distance from the center of infraorbital foramen to infraorbital margin (1), anterior nasal spine (2), zygomatico-maxillary suture (3) and alveolar margin (4)

left side. This finding of our study closely relates with that of the study by Oliveira et al. (11) (right: 6.49±1.68 mm, left: 6.52±1.82 mm), Singh (9) (right: 6.12 mm and left: 6.19 mm), and Lokanayaki (12) (6.33±1.48 mm). Since the infraorbital margin is very prominent and easy to locate, it can be used as reference point by dentist while performing the nerve block anesthesia. The major limitation for dentists while taking infraorbital margin as landmark is the fear of damage to patient's eye (13).

The distance between IOF and lower end of alveolar margin of maxilla was 27.82±4.13 mm on the right side and 28.40±3.40 mm on the left side. Tewari et al. (14) conducted a study on 60 skulls of South Indian population and observed that the distance was 27.88±4.25 mm on the right side and 27.31±4.5 mm on the left side, which closely correlates with our study. Bharthi and Puranik (15) done a morphometric analysis of IOF in 100 dry skulls and the mean vertical distance from lower margin of IOF to upper alveolar margin was 28.93±4.11 mm on the right side and was 28.42 mm±4.43 mm^2 on the left side. Although it is easier to locate alveolar margin of maxilla, one of the main drawbacks in this measurement, it may resorb as a result of aging or following tooth extraction or due to any periodontal disease.

Another parameter which helps to locate the IOF is the distance between the foramen and zygomatico-maxillary suture, which was 14.11±2.23 on the right side and 13.87±3.59 mm on the left side. Raj et al. (16) conducted a study on 70 dry skulls and observed that the distance between them was 14.71±2.54 mm on the right side and was 14.83±2.36 mm on the left side. In our study, the distance between the IOF and anterior nasal spine was 32.21±3.07 mm on the right side and 32.26±2.29 mm on the left side. Nanayakkara et al. (4) conducted a study on 54 skulls of Sri Lankan skulls and the distance was 33.81±2.68 mm on the right side and 34.23±2.56 mm on the left side. In a study by Veeramuthu et al. (17) on 105 adult dry skulls, the same distance was 32.62±3.4 mm on the right side and 33.52±3.37 mm on the left side. Studies by Lopes et al. (18) and Agthong et al. (19) showed that the distance between anterior nasal spine and IOF was higher than our values, which suggests that the data from one population cannot be exchanged with other population as all these values are population specific.

In the present study, the most common location of IOF in relation to maxillary teeth was 1st premolar tooth on the right side and 2nd premolartooth on the left side. Varshney and Sharma (20) observed that the most common location was in line with the 2nd premolar tooth followed by its position between first and second premolar teeth. In a study by Aziz et al. (21), the most common location of the IOF in white, black and Hispanic skulls was in line with first premolar tooth. Varshney and Sharma (20) found that the majority of IOFs were oriented to second premolar tooth on the right side and between second premolar and first molar teeth on the left side. The literature shows extensive variations in the location of IOF in relation to maxillary teeth, which may complicate the effectiveness of nerve block during regional anesthesia (14).

Multiple IOF is the most common occurrence and the most common cause for the failure during infiltrative anesthesia for maxillofacial surgeries. The common cause for the appearance of accessory foramen is due to the branching of nerves during development. In the present study, the accessory foramen was seen in 7.7% of skulls. Berry (22) reported the frequency of occurrence of accessory foramen in different races and showed the rates as 6.7% in Indians (Punjabi), 6% in North Americans and 7.5% in Burmese. Identification of multiple such foramen is important while administering the drugs because in the presence of accessory foramen, the amount of drug may become inadequate and will not serve the purpose (18).

The main limitation of the present study is its small sample size; in the current study, we have used only 90 skulls due to the limited availability of bones, and age and sex of bones were unknown. The present study was performed in a particular center not involving multiple regions. Due to these limitations, we could not find out variations in the foramen in terms of age, sex or racial difference.

Conclusion

IOF transmits infraorbital nerve commonly used for regional anesthesia technique in nasal, oral and dental surgeries as it yields good intraoperative and postoperative results. In the present study, oval shape of foramen was more common followed by round shape. Semilunar and irregular shapes were not seen in current study. Knowledge of location of IOF is important because injuries to infraorbital nerve and vessels may occur in numerous surgical procedures of maxillofacial region. Hence this foramen should be approached carefully to avoid damage.

Ethics

Ethics Committee Approval: Since this is an osteological study which is not involving any living subject and the identity of an individual is not revealed, ethical clearance is exempted from our Institutional ethical committee.

Informed Consent: It's not necessary.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: V.KL., Design: V.KL., Data Collection or Processing: V.KL., J.N.N., Analysis or Interpretation: V.KL., Literature Search: J.N.N., Writing: V.KL., J.N.N.

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The long-term outcomes of transcanalicular diode laser-assisted endoscopic dacryocystorhinostomy in isolated nasolacrimal duct obstruction

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ABSTRACT

Aims: To evaluate the long-term surgical success of transcanalicular dacryocystorhinostomy (TCDCR) with diode-laser in the treatment of epiphora due to isolated naive nasolacrimal duct obstruction (NLDO) in adults.

Methods: This retrospective study included patients with isolated naive NLDO, who underwent diode laser-assisted TCDCR. No patients had pathology in the nasal region detected by an otorhinolaryngologist. The included patients had documented information about epiphora evaluation with lacrimal system irrigation with fluorescein dye, and annual direct imaging of osteotomy patency with nasal endoscopy. Success was defined as no postoperative epiphora, conjunctivitis or dacryocystitis, an open passage in the lacrimal system lavage, and patient satisfaction.

Results: The study included 116 patients [mean age: 49.6±11.4 years, female: 67 (57.8%)]. The success rate was 84.5% in the first year, 80.2% in the second year, and 76.7% in the third year. Following the operation, 9 (7.8%) patients had epiphora, 8 (6.9%) patients were not satisfied, and 1 (0.8%) patient developed conjunctivitis/dacryocystitis in the first year. Three (2.6%) patients had dissatisfaction and 2 (1.7%) patients had the complaints of epiphora correlated with nasolacrimal lavage obstruction in the second year. Two (1.7%) patients were dissatisfied and 2 (1.7%) patients had epiphora complaints confirmed with nasolacrimal lavage in the third year.

Conclusions: The present study showed that the treatment of epiphora due to isolated NLDO with diode laser-assisted TCDCR can provide long-term success in major outcomes in adult patients.

Introduction

The nasolacrimal duct (NLD) is a two-sided structure that carries the tear from the lacrimal sac to the nasal cavity at the level of the lower concha, located beneath the lower fold of the nasal cavity. The NLD obstruction can cause epiphora, conjunctivitis or dacryocystitis. While it usually does not cause visual impairment, it affects the quality of life due to epiphora. NLD obstruction is more common in middle-aged women than in men (1).

While medical treatment is tried primarily in acute NLD obstruction, surgical procedures come to the fore in chronic occlusions. In surgery, dacryocystorhinostomy (DCR), which is the process of creating a permanent new path between the lacrimal sac and nasal mucosa, is performed. The first externally performed DCR surgery was described by Toti et al. (2) in 1904, and today's classic external DCR technique was developed in 1971 with nasal and lacrimal mucosal flap suturing (3,4). Due to the disadvantages of external skin surgeries due to scar formation, excessive bleeding, the need for general anesthesia and the long duration of the operation, internal surgeries applied with the help of modern technology have come to the fore. Laser application for the first time in DCR surgery was started by Massaro et al. (5) with cadaver studies using Blue-Green Argon laser, and then entered clinical practice by Reifler (6) in 1993 with KTP (potassium titanyl phosphate) laser. In the following years, Excimer laser (308 NM), CO_2 laser (10600 NM), YAG laser, Nd: YAG (neodymium: yttrium, aluminum, garnet, 1064 NM) laser applications and balloon catheter dilation, silicone intubation, endonasal DCR, laser-assisted endonasal DCR procedures are also applied methods (7). Endoscopic DCR surgery with diode laser was performed for the first time by Eloy et al. (7) in 2000, and it is the most widely used laser procedure by transcanalicular method because of the most satisfying results in them. We aim to evaluate the long-term success of our transcanalicular diode laser-assisted endoscopic DCR (TCDCR) surgeries.

Methods

This retrospective study included patients with isolated naive NLDO, who underwent diode laser-assisted TCDCR. Ethical approval was obtained by the Afyonkarahisar University of Health Sciences Local Clinical Research Ethics Committee (approval number: 2018/3 2011-KAEK-2, date: 02.03.2018). The included patients had documented information about epiphora evaluation with lacrimal system irrigation with fluorescein dye, and annual direct imaging of osteotomy patency with nasal endoscopy. Whole patients had been diagnosed with isolated naive NLDO with lacrimal canal irrigation, afterward, had undergone TCDCR surgery between 2014 and 2017. The following exclusion criteria were applied: 1) The presence of any nasal pathology (intranasal synechiae, intranasal polyp, septum deviation, and concha bullosa, etc.) detected by otorhinolaryngology, 2) Having a history of having undergone any ocular or nasal surgery, 3) Having a history of smoking, 4) Having a systemic disease 5) History of any type of regular medicine use, 6) Being under 40 and over 70 years old, 7) Having bicanalicular silicone tube that cannot be intubated, and 8) Having silicone tubes that were removed before three months for any reason. Nasal endoscopy had been performed by the same otorhinolaryngology specialist physician (OKK) before the operations.

Patients' epiphora evidence, satisfaction, attack of conjunctivitis, or dacryocystitis information were taken from the patient files. According to the information obtained from these files, success was defined as no postoperative epiphora, conjunctivitis or dacryocystitis, an open passage in the lacrimal system lavage, and expression of patient's satisfaction when questioned in comparison of the preoperative and postoperative status. In the opposite situations were considered unsuccessful.

All surgeries had been performed by the same surgical team (RD, RD, OKK) under general anesthesia. After surgery, netilmicin and dexamethasone-containing eye drop (4x1), and 0.025% flunisolide nasal spray treatment had been given for three weeks (3x2), and oral amoxicillin-clavulanate 1000 mg (2x1) had been given for one week. Patients had been followed-up on the 1st day, 1st week, 1st month, 2nd month, and afterward periods in three-month and annual periods after surgery. These follow-up data were taken from their patient files. All examinations and follow-ups of the patients had been performed by the same researchers (MCS, RD, and OKK). No postoperative period complication had been observed. Silicone tubes had been removed after three months with an otorhinolaryngology specialist, by performing an endoscopic examination.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software, version 22.0 (IBM SPSS, Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation) were used in the evaluation of the data. Data were analyzed for distribution by the Shapiro-Wilk test for normality analysis. The non-parametric McNemar test was used to compare consecutive samples that did not fit the normal distribution. The evaluations were made at the 95% confidence interval, and the p values of less than 0.05 were considered statistically significant.

Results

The total number of patients evaluated was 165, and 116 patients were included in the study following exclusions. The mean age of the patients was 49.60±11.39 (30-70) years and 67 (57.8%) of the patients were female (Table 1). No complication developed intraoperatively in any patient.

The comparisons of the consecutive evaluations are shown in Table 2. The success rate for our criteria was found to be 84.5% (98 patients) in the first year, 80.2% in the second year, and 76.7% (89 patients) after the three years.

When 116 patients were evaluated for causes of unsuccess by years; in the first year (15.5%), nine patients (7.8%) had complaints of epiphora, eight patients (6.9%) had dissatisfaction, and one patient (0.8%) developed conjunctivitis/dacryocystitis attack (Figure 1). At the end of the second year (19.8%), in addition to the first year, three patients (2.6%) had dissatisfaction and two patients (1.7%) had complaints of epiphora. At the end of the third year (23.3%), in addition to the past two years, two patients (1.7%) had dissatisfaction and two patients (1.7%) had complaints of epiphora verified with nasolacrimal lavage obstruction.

Patients with obstruction in nasolacrimal canal lavage were considered to have a recurrence. The mean recurrence time in patients during the follow-ups was 16.52±6.94 months. Patients who had a recurrence and wanted to undergo surgery were re-operated with TCDCR, and most of them were found to have occlusion at the ostium level.

Table 1. Demographic characteristics of the study group

	Patients (n=116)
Age (year)	49.6±11.4
Male:female ratio	49:67
Laterality (right/left)	51/65

Table 2. The comparison of the consecutive evaluations

Total cases (n=116)	Success		p value*
	Number of patients	Rate (%)	
End of the first year	98	84.5	<0.001
End of the second year	93	80.2	<0.001 (0.063)[a]
End of the third year	89	76.7	<0.001 (0.125)[b]

*: McNemar test results of the comparison of the evaluation results immediately after surgery and at the end of each year. Immediate postoperative, no patients had complaints of epiphora or closed nasolacrimal canal lavage findings or conjunctivitis/dacryocystitis.

[a]: Comparison of the evaluation results of the first and second year-end.

[b]: Comparison of the evaluation results of the second and third year-end.

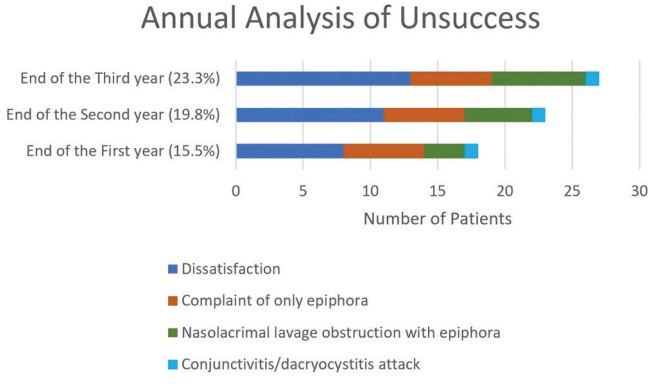

Figure 1. Annual analysis of unsuccess

Discussion

The external DCR surgery technique, which was first described in 1904 and developed in 1971, has been the gold standard treatment of chronic nasolacrimal duct obstruction for more than a hundred years (8,9). The rate of success of external DCR surgery is 85-99% and is generally above 90% (10). While the transnasal DCR surgery has a success rate of 80-85%, it has been shown that this rate is 70-90.5% in TCDCR surgeries (4,11,12). External DCR surgery results reported from Turkey has been quite satisfactory. It has been reported that approximately 90% and above anatomical and functional success have been achieved (13-15). Even good results have been reported in bilateral simultaneous surgeries (16,17). In the first studies reported with diode laser TCDCR, Eloy et al. (7) and Haefliger and Piffaretti (18) achieved 65-80% success in their series (8). Shortly after these studies, Kaynak-Hekimhan et al. (19) reported 80% success in their TCDCR study.

Despite the high success rates of external DCR surgeries, due to the disadvantages of facial skin scar formation, excessive bleeding, requiring general anesthesia, and long operation and recovery period; internal surgeries performed endoscopically have come to the fore with the contribution of modern technology (20). With these internal surgery techniques, the continuity of the pump function of the lacrimal system can be achieved by leaving the medial canthal tendon intact (21). Studies that keep TCDCR success rate equal with external DCR are also noted. In the 244-case wide series of Ajalloueyan et al. (22), success rates were found to be 92.6% in external DCR and 93.4% in TCDCR in an 18-month follow-up. In another study, the success rate was shown as 88% for TCDCR in a 36-month follow-up (12). Also, Drnovsek-Olup and Beltram (4) suggested that TCDCR surgery may be repeated in case of recurrence in obstruction of the NLD. Similarly, we had the chance to successfully re-operate in our recurrent cases. In this study, surgical success was determined in 116 patients' satisfaction and follow-up evaluation results, and an annual evaluation was made according to the information obtained from patient files. In this method, the success rate was 84.5% in the first year, 80.2% in the second year, and 76.7% in the third year. In our operations, keeping the aspirator between the concha and the mucosa, protecting the middle concha mucosa from laser or mechanical damage, not leaving the necrotized tissue caused by laser around the ostium, and placing a sponge between the concha and the rhinostomy to prevent the development of synechiae at the end of the operation may have affected our success rates (Figure 2). Similar precautions during the operation may reduce intra-nasal inflammation and reduce postoperative adhesions and protect the concha (23). Postoperative nasolacrimal lavage was performed to remove residues in the pathway. There are opinions that the tissue residues reduce the passage of the opened path (23).

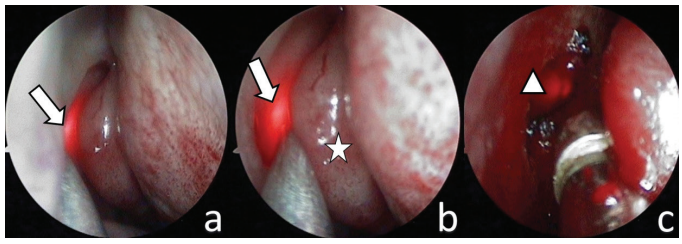

Figure 2. Transcanalicular diode laser-assisted endoscopic dacryocystorhinostomy, a: Appearance the fiberoptic probe light (arrow), b: Gently deviating the concha (star) from the probe light (arrow) with Frazier suction aspirator tube, c: Providing ostium (arrow-head) patency by laser treatment, and tissue residues cleaning with Blakesley nasal forceps

TCDCR surgeries can be performed under local and general anesthesia (24). In operations performed with local anesthesia, patients feel pain and manipulations during the operation, and this makes the operation difficult. Therefore, general anesthesia is usually used in these surgeries. In this study, whole patients had undergone TCDCR surgery under general anesthesia without any complication in terms of general anesthesia.

The main strengths of this study are the regular follow-up of patients in patient files, organization of patient files by the same physicians, and successful completion of surgeries under general anesthesia without complications with the same surgical team.

The limitations of the study are the retrospective design, exclusion of patients with nasal pathology from the study, giving personal and subjective answers in terms of patient satisfaction, and exclusion of patients without bicanalicular silicone tube intubation from the study. The inclusion of only patients with isolated and NLDO may have affected the study results. Therefore, when the study groups specified in the limitations are added to the study, the results of the study may change, and prospective researches are needed.

Conclusion

In conclusion, this study has showed that laser-assisted endoscopic TCDCR can be used for long-term outcomes of treatment in epiphora in adults due to isolated nasolacrimal duct obstruction. Further studies are needed.

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Ethics

Ethics Committee Approval: Ethical approval was obtained by the Afyonkarahisar University of Health Sciences Local Clinical Research Ethics Committee (approval number: 2018/3 2011-KAEK-2, date: 02.03.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.C.S., O.K.K., R.D., M.A.E., E.Ç., K.Y., G.F.Y., R.D., Concept: M.C.S., O.K.K., R.D., M.A.E., E.Ç., K.Y., G.F.Y., R.D., Design: M.C.S., O.K.K., R.D., M.A.E., E.Ç., K.Y., G.F.Y., R.D., Data Collection or Processing: M.C.S., M.A.E., R.D., Analysis or Interpretation: M.C.S., M.A.E., R.D., Literature Search: M.C.S., M.A.E., R.D., Writing: M.C.S., O.K.K., R.D., M.A.E., E.Ç., K.Y., G.F.Y., R.D.

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Factors predicting recurrence in non-muscle invasive bladder cancers

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Keywords: Bladder cancer, carcinoma *in situ*, survival, urothelial cancer, tumor recurrence

ABSTRACT

Aims: We aimed to assess patients with non-muscle invasive bladder cancer (NMIBC) to find out the factors affecting recurrence after initial treatment.

Methods: In this retrospective cohort study, we investigated patients who underwent transurethral bladder tumor resection (TURB) between January 2014 and April 2020. Patients' age, gender, initial symptoms, time from the initial symptoms to hospital admission, history of systemic diseases, smoking history, pathological features, intra-vesical treatment records and information about recurrence were recorded. Recurrence was considered as any tumor development other than the aforementioned residual tumor.

Results: A total of 103 patients (mean±SD age: 68.5±9.1 years; 93 men and 10 women) were evaluated. The mean diameter of the tumors was 3±1.6 cm. Following the initial TURB and/or re-TURB, 28 (27.1%) patients underwent induction chemotherapy or BCG therapy. Residual tumor was detected in 35 (34%) patients who were either detected within the first three months following the TURB, without receiving any intravesical therapy, or in re-TURB performed for the purpose of resection of the residual visible bulky lesions following an incomplete initial resection. Eleven patients (10.6%) recurred within a median of 18 months of follow-up. The median recurrence-free survival was 25 months (95% confidence interval (CI): 16.5-33.4). The presence of carcinoma *in situ* (CIS) [Hazard ratio (HR): 3.00, 95% CI: 1.2-7.6, p=0.03], female gender (HR: 2.38, 95% CI: 1.03-5.4, p=0.03) and age >70 years (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) were significantly associated with recurrence.

Conclusions: The present study showed that the presence of CIS, female gender, and age >70 years were independently associated with the recurrence of NMIBC.

Introduction

Bladder cancer is the 7th most common cancer among men and 11th among women in the world. The annual incidence of bladder cancer is 9/100,000 in males and 2.2/100,000 in females (1). Every year, 110,500 new cases in men and 70,000 new cases in women are diagnosed (2). Approximately 75% of the cases are non-muscle-invasive bladder cancer (NMIBC) at diagnosis (2). As an imaging method, ultrasonography is used with high sensitivity and specificity, and cystoscopy is still the gold standard (3,4). Owing to the high incidence of the disease and thereby of NMIBC, a precise algorithm is needed in diagnosis, treatment and follow-up of this disease. Up to 50-70% of NMIBC subsequently recur mostly within two years following the initial interventions and 10-20% of them progress to muscle invasive bladder cancer (MIBC) (5). In order to prevent the recurrence and progression, patients are followed up at short intervals of cystoscopy and administered adjuvant intravesical chemotherapy or immunotherapy when necessary (6). Intra vesical chemotherapy/immunotherapy applications reduce recurrence and progression but cause some local and systemic side effects (7). Prediction of tumor recurrence is crucial in the follow-up period of this disease. Factors including

age, tumor grade, tumor number, tumor size, presence of carcinoma *in situ* (CIS), hematuria, and intravesical therapy have been investigated for being predictors of recurrence in NMIBC in a number of studies (8-10). However, a number of possible relapse-related factors are not investigated well and are still equivocal in their link to recurrence.

In this study, we aimed to assess a six-year follow-up and treatment outcomes of patients diagnosed with NMIBC. We also examined the potential factors associated with recurrence following initial treatment.

Methods

This retrospective study was performed at Nevsehir State Hospital. Hospital records of patients who underwent transurethral bladder tumor resection (TURB) surgery between January 2014 and April 2020 were evaluated. The main inclusion criterion was the pathological diagnosis of urothelial carcinoma or transitional cell carcinoma. Patients with benign pathologies, adenocarcinoma, paraganglioma, and signed ring cell carcinoma were excluded. Since all subjects were operated in the same unit, all surgeries were performed with a 24 Fr endoscopy using bipolar energy. Recorded variables were age, gender, smoking, complaints on admission, physical findings on admission, the time between the initial complaints and hospitalization, comorbid diseases, pathology reports of the first and recurrent disease, intravesical treatment, recurrence or progression data, and disease-related oncological and functional endpoints. NMIBC was defined as papillary tumors confined to the mucosa and invading the lamina propria, and flat, high grade tumors confined to the mucosa, named as CIS (Tis). Tumor recurrence was defined as immediate failure of intravesical treatment or tumor growth at the 3th month surveillance cystoscopy in patients who did not receive induction intravesical treatment. If tumor recurrence was detected within the first three months following the first surgery, these recurrences were evaluated as residual tumors and completion surgeries were named as re-TURB. The study was approved by the Nevsehir Haci Bektas University Institutional Review Board.

Ethical issues of this study were approved by the Nevsehir Haci Bektas University Local Ethics Committee (protocol number: E.683, date: 18.06.2020).

All procedures performed in our study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Statistical Analysis

Statistical Package for the Social Sciences (15.0, Chicago, IL, USA) was used for statistical analysis. Statistical evaluation results were reported as mean±standard deviation (minimum-maximum values) or median-interquartile range (IQR) according to the normal distribution of variables. The distribution of continuous variables was evaluated by the Shapiro-Wilk test. The Student's t-test, Wilcoxon rank test and the Mann-Whitney U test were used to compare the data as appropriate. Cut-off values, sensitivity and specificity of baseline tumor size in the prediction of disease recurrence were calculated using receiver operating curves (ROC) analysis. The Kaplan-Meier survival curves were computed to display disease-specific survival. Factors associated with survival were investigated by the Cox regression analysis. $p<0.05$ was considered statistically significant in all analyses.

Results

Between January 2014 and May 2020, 150 patients underwent TURB surgery at Nevsehir State Hospital. Of these patients, 103 were included in the current analysis. The mean age of the patients was 68.5±9.1 years. The mean diameter of the tumors was 3±1.6 cm. The initial symptoms were hematuria in 93 (90.2%) patients, dysuria in four (3.88%) patients, nocturia in two (1.94%) patients, flank pain in one (0.97%) patient, incontinence in one (0.97%) patient, and lower urinary tract symptoms in two (1.94%) patients. Clinical and pathological features of the first TUR and re-TUR of the patients (if performed) are summarized in Table 1. The median follow-up time was 18 (IQR: 9-35) months.

After the first TURB or re-TURB, 28 (27.1%) patients underwent induction chemotherapy or Bacillus Calmette-Guérin (BCG) therapy. Tumor recurrence was detected in 35 (34%) of the patients within the first three months in re-TURB surgery. The characteristics of residual tumors in the first three months are summarized in Table 2.

Patients with muscle invasive cancer (pT2) or more advanced cancer detected in follow-up surveys within the first three months following the initial TURB without intravesical induction therapy or TURB before the intravesical induction treatment were excluded from further recurrence analyses. Subsequent surveys revealed recurrence in 11 (10.67%) patients. All recurrences were in non-invasive (pTa) stage with 10 (9.7%) low grade types and 1 (0.97%) high grade type. The median number of recurrences within 18 months was 2 (IQR: 1-3). The recurrence-free survival rate at 12 months was 69.4% and the median recurrence-free survival time was 25 months [95% confidence interval (CI): 16.5-33.4]. The initial tumor size in patients with vs. without subsequent recurrence was similar (mean/median 3.3±1.7/3 vs. 2.8±1.4/3, $p=0.11$).

Tumor size was greater than 3 cm in 53 (51.45%) patients. ROC analysis showed that initial cut-off tumor size of 3.75 cm might be a predictor of recurrence, being the best cut-off size with the highest diagnostic accuracy on ROC table (sensitivity: 70.2%, specificity: 39.3%; area under curve: 0.573). However, the

Table 1. Demographic, clinical and pathological features at diagnosis and initial interventions (n=103)

Age* (mean±SD) (year)	**68.5±9.1**
Gender	
Male, n (%)	93 (90.3)
Female, n (%)	10 (9.7)
Median duration time of symptom (IQR) (day)	14 (7-20)
Comorbidities (overall), n (%)	81 (78.6)
Diabetes mellitus, n (%)	26 (21.31)
Hypertension, n (%)	41 (33.60)
Coronary artery disease, n (%)	30 (24.59)
Asthma, n (%)	12 (9.83)
Others, n (%)	13 (10.65)
Tumor grade**	
Low grade, n (%)	73 (70.9)
High grade, n (%)	30 (29.1)
Tumor stage**	
pTa, n (%)	78 (75.7)
pT1, n (%)	25 (24.3)
CIS**	
Yes, n (%)	9 (8.7)
No, n (%)	94 (91.3)
Early intravesical chemotherapy	
Present, n (%)	20 (19.4)
Absent, n (%)	83 (80.6)

*Age at the time of diagnosis.
**Pathological features including tumor stage, tumor grade and presence of CIS are noted based on the higher occurrence if there was a pathologic upgrading in TURBs performed within the first three months in those who did not receive any intravesical induction therapy or before the intravesical therapy following one or more course of TURBs until the visible bulky lesions are all resected.
CIS: Carcinoma *in situ*, IQR: Interquartile range, TURB: Transurethral bladder tumor resection, SD: Standard deviation

Table 2. Patient characteristics and tumor features of residual tumors in the first three months (n=35)

Age (mean±SD) (year)	**70±9.8**
Gender	
Male, n (%)	30 (85.7)
Female, n (%)	5 (14.3)
Tumor grade	
Low grade, n (%)	18 (51)
High grade, n (%)	17 (49)
Tumor stage	
pTa, n (%)	21 (60)
pT1, n (%)	7 (20)
pT2, n (%)	6 (17.1)
pT4a, n (%)	1 (2.9)
Presence of CIS	
Yes, n (%)	3 (8.5)
No, n (%)	32 (91.5)

CIS: Carcinoma *in situ*, SD: Standard deviation

initial tumor size was not associated with recurrence (p=0.78). Similarly, the pathological stage and grade had also no association with recurrence (p=0.47 and p=0.45, respectively). On the other hand, CIS and female gender were significantly associated with the tumor recurrence. The presence of CIS (HR: 3.00, 95% CI: 1.2-7.6, p=0.03), female gender [Hazard ratio (HR): 2.38, 95% CI: 1.03-5.4, p=0.03] and age >70 years (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) were significantly associated with recurrence.

However, the time from initial symptom to hospital admission (HR: 1.28, 95% CI: 0.7-2.28, p=0.39) and the presence of comorbidities (HR: 1.49, 95% CI: 0.74-2.96, p=0.24) did not increase overall recurrence. Age >70 years at the diagnosis (HR: 1.87, 95% CI: 1.02-3.41, p=0.03) was significantly associated with disease recurrence. Survival plots in Figures 1-3 and Table 3 show the changes in survival outcomes in different subgroups.

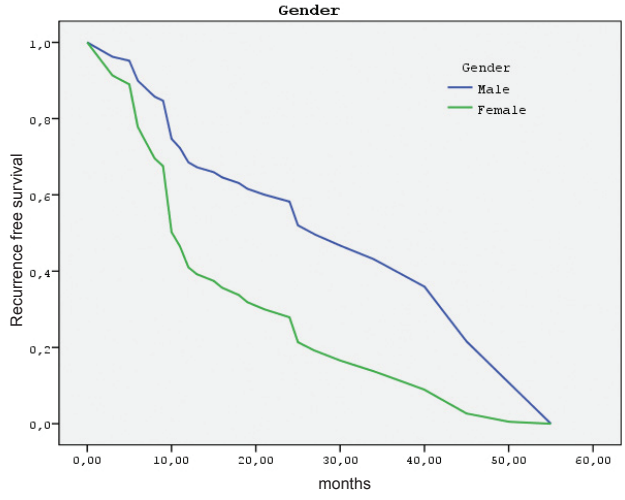

Figure 1. Recurrence-free survival according to gender

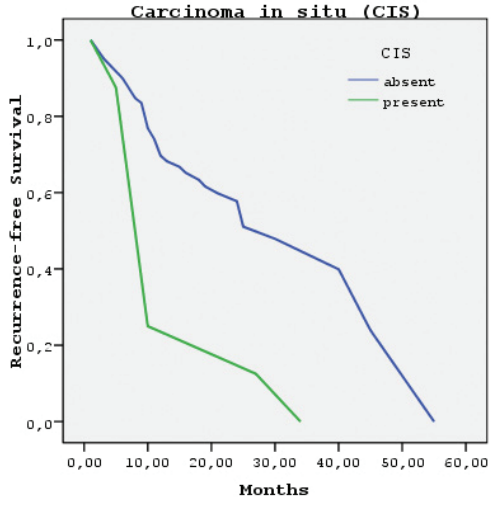

Figure 2. Recurrence-free survival according to carcinoma *in situ* presence

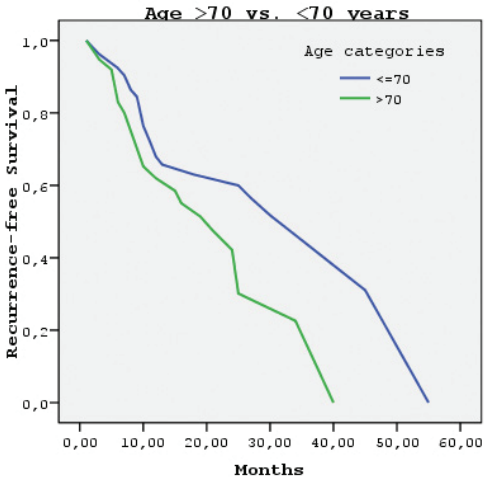

Figure 3. Recurrence-free survival according to age

Intravesical induction chemotherapy or BCG administration following initial and complementary TURB showed a weak/borderline association with disease recurrence (HR: 1.67, 95% CI: 0.9-3.1, p=0.09). This factor was not studied in Ta vs. T1 tumors and HG vs. LG tumors owing to the limited number of patients. Interestingly, history of smoking tended to show a slightly longer recurrence-free survival, which was not statistically significant (p=0.07).

Discussion

It is important to detect and treat NMIBC recurrences early and predict patients who will progress (11). The European Guidelines on Non-Muscle-invasive Urothelial Carcinoma of the Bladder 2017 suggest surveillance cystoscopy and if necessary, intravesical treatments according to the risk classification (6). In addition, re-TURB is recommended two or six weeks after the first TURB in medium and high-risk tumors (11). Clinical and pathological features can be used to predict recurrence and progression. Several factors that may affect recurrence and progression have been proposed so far and some nomograms have been developed (12).

Previous research has indicated age, tumor grade, number of tumors, tumor size and the number of past recurrences as the risk factors for the new recurrence in NMIBC (9). However, we did not observe any association of these variables with recurrence except for age. In another study, tumor grade and the presence of CIS component were identified as the predictors of recurrence (8). Our study confirms the value of CIS component on the same outcome, but we did not observe any association with baseline tumor grade and subsequent recurrences. Kim et al. (10) showed that age, macroscopic hematuria, presence of upper urinary tract tumor, higher tumor stage and tumor grade, presence of CIS, greater tumor size and tumor number, and intravesical treatment were associated with tumor recurrence. We found similar results in terms of age and the presence of CIS. Although many factors have been previously evaluated in this regard, number of previous recurrences, greater number of tumors, and tumor size come forward (13). Sylvester et al. (12) established a risk calculation system for the European Organisation for Research and Treatment of Cancer, consisting of 6 factors including tumor number, tumor size, time of tumor recurrence, tumour stage, tumor grade, and presence of CIS.

Female gender has previously been reported as a risk factor for shortening T1G3 bladder tumor recurrence time (14). The Club Urologico Español De Tratamiento Oncológico study also reported that men had a longer recurrence period than women. Similarly, in our study, female sex showed a direct correlation with recurrence rates. Mungan et al. (15) reported females had a worse prognosis in bladder tumor than males, but the clinicopathologic explanation of this phenomenon has not been made so far.

Luján et al. (9) reported higher age as a negative risk factor for recurrence-free survival while Gontero et al. (16) reported that solely age was a risk factor for recurrence in T1G3 tumors. In our study, age over 70 years was associated with shorter recurrence-free survival.

Many authors have indicated a link between smoking, bladder tumor and higher recurrence. Ucpinar et al. (17) demonstrated rapid tumor recurrence in patients with a smoking history. Soria et al. (18) also showed that smoking increased bladder tumor incidence and recurrence. Recurrences were more frequent in patients who continued smoking after the diagnosis of bladder cancer in another study (19). Interestingly, we observed less recurrence in patients who smoked, with a borderline significance (p=0.07). Nevertheless, the overall number of patients with recurrence was low.

Based on our data, it is crucial to closely monitor females, patients who are over the age of 70 years and patients with an initial diagnosis of CIS. Classification of risk can be done using various nomograms other than the previously mentioned risk factors that are associated with tumor recurrence. Accordingly, alongside CIS, which is a widely-published and known indicator of cancer recurrence, factors such as age and female gender can also be identified as leading to a poor prognosis in clinical practice. Moreover, intravesical induction chemotherapy or immunotherapy treatment may prevent tumor recurrence and even progression in this group of patients, even if they have been classified as low risk and not in need of adjuvant therapy following TURB in current clinical practice.

Our study has some limitations. The most prominent one is its being a retrospective cohort study. Another one is its being conducted on a relatively small number of patients. Owing to this, we could not study the subgroup analysis of intravesical chemotherapy and BCG. Studies with larger populations are needed to confirm these results.

Table 3. Factors evaluated for possible association with tumor recurrence and recurrence-free survival (n=96)

The duration from initial symptoms to hospital admission	Longer than 14 days	Shorter than 14 days	HR	p
Tumor-free survival at 12 months, (%)	66.1	72.4		
Median recurrence-free survival	25 mo (95% CI: 7-42.9)	25 mo (95% CI: 16.6-33.3)	1.28	0.39
Initial tumor size	Greater than 3.75 cm	Smaller than 3.75 cm		
Tumor-free survival at 12 months, (%)	70.3	69		
Median recurrence-free survival	25 mo (95% CI: 19.4-29.1)	25 mo (95% CI: 22.4-33.2)	1.09	0.51
Initial tumor stage	pTa	pT1		
Tumor-free survival at 12 months, (%)	71	63.9		
Median recurrence-free survival	27 mo (95% CI: 19.9-34)	25 mo (95% CI: 4.1-45.8)	1.26	0.47
Initial tumor grade	Low grade	High grade		
Tumor-free survival at 12 months, (%)	70.3	67.1		
Median recurrence-free survival	30 mo (95% CI: 17.3-42.6)	25 mo (95% CI: 2.4-47.5)	1.25	0.45
CIS	Present	Absent		
Tumor-free survival at 12 months, (%)	25	74.1		
Median recurrence-free survival	10 mo (95% CI: 7.6-12.4)	30 mo (95% CI: 18-41.9)	3	0.03
Gender	Male	Female		
Tumor-free survival at 12 months, (%)	72.3	45		
Median recurrence-free survival	30 mo (95% CI: 18.7-41.2)	10 mo (95% CI: 9-10.9)	2.38	0.03
Age	≤70	>70		
Tumor-free survival at 12 months, (%)	72.3	65.2		
Median recurrence-free survival	45 mo (95% CI: 27.7-62.2)	21 mo (95% CI: 10-31.9)	1.87	0.03
History of smoking	Yes	No		
Tumor-free survival at 12 months, (%)	70.9	50		
Median recurrence-free survival	27 mo (95% CI: 16.2-37.7)	10 mo (95% CI: 7.6-12.4)	3	0.07
Other systemic diseases	Yes	No		
Tumor-free survival at 12 months, (%)	72.6	58.1		
Median recurrence-free survival	27 mo (95% CI: 16.9-37)	18 mo (95% CI: 6.5-29.4)	1.49	0.24
Intravesical induction therapy	Yes	No		
Tumor-free survival at 12 months, (%)	61.5	72.8		
Median recurrence-free survival	16 mo (95% CI: 3-32.8)	40 mo (95% CI: 18.4-61.5)	1.67	0.09

HR: Hazard ratio, CI: Confidence interval, mo: Months, CIS: Carcinoma *in situ*, SD: Standard deviation

Conclusion

In conclusion, the current study showed that risk of recurrence in NMIBC is not low. Women, patients older than 70 years, and those with CIS might be candidates of a more aggressive adjuvant treatment and surveillance protocols following the initial TURB.

Ethics

Ethics Committee Approval: This study was approved by the Nevsehir Haci Bektas University Local Ethics Committee (protocol number: E.683, date: 18.06.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.O., M.C.T., R.A., Concept: S.O., H.K., M.C.T., R.A., Design: S.O., Data Collection or Processing: S.O., Analysis or Interpretation: S.O., H.K., M.C.T., R.A., Literature Search: S.O., M.C.T., R.A., Writing: S.O., H.K., M.C.T.

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The role of complete blood count parameters in distinguishing complicated and uncomplicated appendicitis

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ABSTRACT

Aims: Acute appendicitis is a prevalent disease. In recent years, conservative treatment of acute uncomplicated appendicitis has been popular but complicated disease requires surgery. This study was conducted to search whether white blood cell (WBC) count, mean platelet volume (MPV), red blood cell distribution width (RDW), and neutrophil-to-lymphocyte ratio (NLR) might be useful to distinguish complicated and uncomplicated appendicitis.

Methods: In this single-center retrospective study, we evaluated patients who underwent open appendectomy between January 2013 and December 2015. Then, the subjects were divided into two groups according to surgical exploration and pathological examination: complicated appendicitis and uncomplicated appendicitis. Complicated cases were classified into 3 subgroups: 1) appendix perforation, 2) plastron appendicitis, and 3) necrosis of appendix. WBC, MPV, RDW, and NLR values were compared in all groups.

Results: A total of 1,219 patients were analyzed. Complicated appendicitis was more common in male patients (n=71, 9.6%). The median WBC ($16.1x10^9$/L) and NLR (7.9 n/μL) were significantly higher in complicated appendicitis compared to uncomplicated disease ($p<0.001$, for both). The cut-off value for WBC and NLR to distinguish a complicated disease was $14.6x10^9$/L and 6.2 n/μL, respectively. MPV and RDW were not useful.

Conclusions: WBC and NLR may be helpful in distinguishing between complicated and uncomplicated appendiceal disease. However, we observe no significant differences in RDW and MPV levels in patients with complicated appendicitis.

Introduction

Acute appendicitis (AA) is a prevalent disease that can be life-threating if left untreated. There have been advances in imaging techniques recently, which facilitated the hand of physicians, but they are not widely available and require expertise to interpret. This makes diagnosis of appendicitis challenging for physicians working in rural regions. Complete blood count (CBC) is still the first line of test for a patient with abdominal pain in emergency departments (1). It is an easy and quick test to evaluate hematologic parameters which can be changed due to infection, hemorrhage and genetic disorders.

Systemic inflammatory response is generally associated with white blood cell (WBC) count (2). However, WBC has no role in differentiating simple and complicated appendiceal disease. In addition to WBC count, there are several other markers that can be used as a sign of inflammatory conditions. For instance, neutrophil-to-lymphocyte ratio (NLR) is an indicator of subclinical inflammation (3). Also, red blood cell distribution width (RDW) has been reported to be in relation to infection (4). Furthermore, platelets play a crucial role in inflammation and their size can change as a result of inflammatory conditions. Therefore, mean platelet volume (MPV), which is a measurement of the average size of platelet in the blood, may have diagnostic potential in various diseases (5,6).

In this study, we aimed to identify whether there was a relationship between the severity of AA and WBC, NLR, RDW, and MPV at the time of presentation to the emergency department.

Methods

This retrospective study was conducted at Kayseri City Hospital after obtaining approval from Erciyes University Scientific Research Ethics Committee (2017/599).

Database was searched retrospectively for patients with discharge diagnosis of AA, who underwent open appendectomy between January 2013 and December 2015, using keywords "acute appendicitis". The initial search delivered 1,926 patients. Records lacking pathological examination reports, preoperative laboratory evaluation, clinical and demographic parameters were excluded. Also, patients younger than 18 years of age, having hematologic disease and diagnosed with incidental appendiceal malignancy were left out of the study. In total, 1,219 records which fulfilled all the criteria were included in the study. The following variables were extracted for each patient: age, gender, admission CBC, surgical findings and pathological examination report.

The subjects were divided into two groups according to surgical exploration and pathological examination results, as complicated appendicitis and uncomplicated appendicitis. Complicated cases involved 3 subgroups: 1) appendix perforation 2) plastron appendicitis 3) necrosis of appendix. The study population was also evaluated in terms of how age affected CBC parameters. They were divided into additional two groups according to age over 65 years and under. WBC, NLR, RDW and MPV values were assessed among the groups.

Statistical Analysis

Statistical analysis was performed on Statistical Package for the Social Sciences (SPSS) 23.0 software package (SPSS, Inc., Chicago, Illinois). Categorical data were expressed as number (percentage) and continuous data as median interquartile range (IQR) 25^{th}-75^{th} percentile. For statistical comparison between the groups, the chi-square test for categorical data and the Mann-Whitney U test for continuous data were used. Also, receiver operating characteristics (ROC) analysis was used to investigate the status of CBC parameters in diagnosis of complicated appendicitis. Statistical significance was accepted at 0.05.

Results

A total of 1,219 patients who underwent open appendectomy were included in the analysis. While the majority of the patients were male (60.5%), the median age was 30 (IQR: 22-42) years. While 1,108 (90.9%) patients had uncomplicated appendicitis, 79 (6.5%) had perforated, 11 (0.9%) had necrotic and 21 (1.7%) had plastron appendicitis, which were confirmed with pathological examination. Whilst patients with plastron appendicitis were older, subjects having necrosis of the appendix were the youngest among the groups (p<0.001). The male patients presented with slightly higher rates of perforation and the female patients had slightly higher rates of appendix necrosis. The median appendix length was 6.5 mm (IQR: 5-8) according to the pathological examination.

When all of the patients with AA were evaluated, the median value of WBC was 13.5×10^9/L. However, patients older than 65 years of age had mildly lower WBC counts but the difference between those and younger patients was not statistically significant (p=0.115). On the other hand, the patients presenting with necrosis of the appendix had the highest WBC counts and there was statistically significant difference among the groups in terms of WBC (p<0.001). In addition, uncomplicated appendicitis cases had the lowest WBC counts (median $13.4x10^9$/L).

The median MPV value was 13.3 fL (IQR: 10.2-14.7) when all of the patients were evaluated. Including patients older than 65 years of age and younger (p=0.071), there was not statistically significant difference when MPV values were compared among the groups (p=0.060). However, MPV values of the patients with plastron appendicitis or appendix necrosis were slightly lower than uncomplicated group and patients with appendix perforation. When the RDW values were compared, there was also not statistically significant difference among the groups (p=0.129).

In addition to WBC, MPV and RDW, NLR was also evaluated. For patients <65 and ≥65, there was no significant difference in terms of NLR values (p=0.182), but NLR was significantly different between complicated and uncomplicated cases (p<0.001). The highest NLR values were observed in patients with necrosis of appendicitis (median, 9.8 n/μL). The uncomplicated cases had the lowest median NLR value (median, 5.1 n/μL) among the groups (Table 1).

Diagnostic potential of CBC parameters was evaluated by the ROC analysis. WBC and NLR values were found to be meaningful in discriminating complicated disease from uncomplicated (p<0.001). For WBC, the cut-off value for the diagnosis of complicated appendicitis was $14.6x10^9$/L with sensitivity of 64.1% and, for NLR, it was 6.2 n/μL with a sensitivity of 60.3%. The area under the ROC curve was 0.687 for WBC and 0.670 for NLR. WBC was a more accurate predictor of complicated appendicitis (Figure 1, Table 2).

Discussion

The study results indicated that while majority of the patients were male, patients tended to present with appendix perforation with increasing age. From the CBC parameters, only WBC and NLR were found to be associated with disease severity. The highest WBC and NLR were observed in patients with appendix necrosis, followed by perforation and plastron disease. Higher WBC values than 14.6×10^9/L were indicative of complicated disease with a sensitivity of 64.1%. For NLR, the cut-off for complicated disease was 6.2 n/μL with a sensitivity of 60.3%. MPV and RDW were not informative of appendiceal disease. In this study, CBC had limited role in distinguishing complicated appendicitis from uncomplicated.

Table 1. Comparison of clinical, pathological and biochemical parameters of patients with acute appendicitis

Values		p value
Age, years, mean (range)	30 (22-42)	
Uncomplicated	29 (22-41)[a]	
Perforated	31 (20-44)[b]	**<0.001**
Plastron	43 (37-61)[c]	
Necrosis	20 (18-25)[d]	
Gender, n (%)		
Male	738 (60.5)	
Uncomplicated	667 (90.4)	
Perforated	52 (7)	
Plastron	13 (1.8)	
Necrosis	6 (0.8)	-
Female	481 (39.5)	
Uncomplicated	441 (91.6)	
Perforated	27 (5.6)	
Plastron	8 (1.7)	
Necrosis	5 (1)	
Appendix length, mm	6.5 (5-8)	-
WBC, 10^9/L	13.5 (11-16)	
<65	13.5 (11.1-16.1)	0.115
≥65	13 (9.9-15.1)	
Uncomplicated	13.4 (10.9-15.7)[a]	
Perforated	16.1 (13.3-20)[b]	**<0.001**
Plastron	15.1 (12.6-16.6)[c]	
Necrosis	25.2 (23.3-26.3)[d]	
MPV, fL	13.3 (10.2-14.7)	
<65	13.3 (10.2-14.6)	0.071
≥65	14 (10.8-15.5)	
Uncomplicated	13.3 (10.5-14.7)[a]	
Perforated	13.5 (12-14.9)[a]	0.060
Plastron	11.6 (8-13.5)[a]	
Necrosis	12.9 (12-14.9)[a]	
RDW, %	8.9 (7.8-25.6)	
<65	8.9 (7.8-30)	0.945
≥65	9 (7.4-26)	
Uncomplicated	8.9 (7.7-12.4)[a]	
Perforated	9 (7.8-11.1)[a]	0.129
Plastron	11 (7.9-45)[a]	
Necrosis	10.4 (9.8-42)[a]	
NLR, n/μL	5.3 (3.4-8.7)	
<65	5.3 (3.4-8.6)	0.182
≥65	5.2 (3.6-12.1)	
Uncomplicated	5.1 (3.3-8.3)[a]	
Perforated	8.4 (5.3-12.7)[b]	**<0.001**
Plastron	6 (4.1-10.8)[c]	
Necrosis	9.8 (4.4-16.4)[d]	

[a, b]p≤0.05
WBC: White blood cell count, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red blood cell distribution width

The definition of complicated appendicitis is usually used for appendicitis with signs of perforation, phlegmon or abscess (7). According to the study by Perez and Allen (7), complicated appendicitis mostly occurs in males. In our study, the percentage

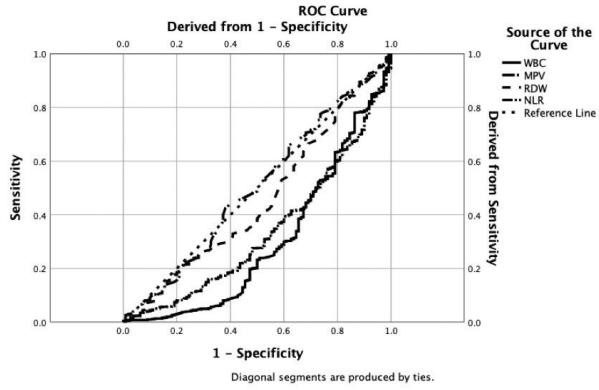

Figure 1. Graphical representation of the receiver operating characteristic curve
ROC: Receiver operating characteristics, WBC: White blood cell, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red blood cell distribution width

Table 2. Results of receiver operating characteristic and optimal cut-off values to predict complicated appendicitis

Variable	Cut-off value	Area under curve	p value	95% confidence interval	
				Lower bound	Upper bound
WBC, 10^9/L	14.6	0.687	**<0.001**	0.618	0.755
MPV, fL	-	0.547	0.765	0.483	0.611
RDW, %	-	0.510	0.163	0.444	0.576
NLR, n/μL	6.2	0.670	**<0.001**	0.608	0.732

WBC: White blood cell, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, RDW: Red blood cell distribution width

of complication in males was 9.6% while it was 8.3% in females. We also observed that subjects with either plastron or perforation were significantly older than patients with uncomplicated appendicitis. However, cases with appendix necrosis were significantly younger than uncomplicated cases. It is hard to find a similar result in the literature because complicated cases were mostly evaluated as a whole. In their study, Eddama et al. (8) reported that patients with complicated appendicitis were significantly older than patients with uncomplicated appendicitis, but they did not perform subgroup analysis similar to this study. The results of this study regarding necrosis may be interpreted as younger patients tend to delay hospital submission, the appendiceal disease may progress.

It would be ideal if appendiceal disease had a unique marker. In this regard, multiple studies have looked at varied markers. However, there is no general consensus that would have been reached declaring one marker as the gold standard. WBC remains the most common marker used in AA diagnosis. According to this study results, WBC values were significantly different among the groups. The highest values were observed in cases with necrosis followed by appendix perforation and

plastron disease. In the systematic review by Acharya et al. (9), the pooled sensitivity of WBC count was 0.79 and the specificity was 0.55. For the diagnosis of perforated appendicitis, the sensitivity was 0.70 and the specificity was 0.49. In this work up, in patients older than 65 years of age, relatively low levels of WBC count were observed. However, in 83.5% of the patients, WBC count was higher than then the upper limit of normal, which is $10x10^9$/L for the institution. In the elderly, low levels of WBC should not dissuade physicians from AA suspicion. However, there are also conflicting papers in the literature. For instance, Tind et al. (10) concluded that leucocyte counts did not influence clinical decision-making. We believe, when combined with anamnesis and physical examination, elevated levels of WBC are highly accurate in AA diagnosis. The cut-off value for WBC in diagnosis of complicated appendicitis was $14.6x10^9$/L. The sensitivity was 64.1%, which is acceptable considering not only perforation but also plastron and necrotic appendiceal disease was included in the complicated group.

To increase the accuracy of AA diagnosis, researchers have used many laboratory parameters. One of them is MPV because platelets play a crucial role in inflammation and biomarkers such as MPV are in relation to platelet morphology. In the study of Daldal and Dagmura (11), they found elevated MPV values in patients with appendix diameter of <6 mm. Considering the that the median diameter of appendix was 6.5 mm in our study, we could not find significant difference among the groups in relation to MPV. Bozkurt et al. (12) and Dinc et al. (13) also suggested that there was an association between AA and MPV. In the work of Tanrikulu et al. (14), they found significantly lower levels of MPV in patients with AA than healthy subjects, but reported sensitivity was 45% and specificity 89.2%. However, WBC was 76.2% sensitive and 90.5% specific in diagnosis of AA. It seems MPV has limited role in AA diagnosis.

It has been reported in the recent years that high RDW values could be a new prognostic indicator that may reflect an underlying inflammatory condition (15). Additionally, it has been reported to be related to outcome in cases of infection, especially sepsis (3). However, in this work-up, we could not demonstrate significant difference among the groups in terms of RDW. In a study by Boshnak et al. (1), they also indicated that RDW was not useful in AA diagnosis.

In the study by Daldal and Dagmura (11), they also reported that NLR was an important parameter if appendix diameter was >6 mm. In this study, we found similar results to their study. NLR was significantly different between complicated and uncomplicated cases. In their meta-analysis, Hajibandeh et al. (3) observed similar findings for NLR. They reported that NLR of 8.8 n/μL was cut-off for complicated appendicitis (sensitivity 76.92%, specificity 100%). However, we only observed higher values in patients with appendix necrosis. Our results for plastron disease and appendix perforation did not consist with their results. Also, we found the cut-off for complicated appendicitis as 6.2 n/μL, which was relatively lower than that Hajibandeh et al. (3) reported.

However, there are limitations to this study. First, due to retrospective nature of the study, there were not clear data about comorbidities on the database. Therefore, impact of comorbidities could not be evaluated among the groups. But also, considering that the subjects were relatively young, significant impact of comorbidities is not expected. Furthermore, it is within possibility that some patients may have been admitted to other hospitals earlier and delay in submission might have affected laboratory parameters.

Conclusion

In conclusion, determining the severity of appendicitis is considered important because a complicated disease can require a longer hospitalization period. In the light of the literature and present results, WBC may be the most important parameter in the diagnosis of AA. NLR also seems to be increased in patients with complicated appendicitis. This study did not find any difference in the level of RDW and MPV in patients with complicated appendicitis.

Ethics

Ethics Committee Approval: This study was performed after obtaining approval from Erciyes University Scientific Research Ethics Committee (numbered: 2017/599).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.S., U.A., Concept: T.S., U.A., Design: T.S., U.A., Data Collection or Processing: T.S., U.A., Analysis or Interpretation: T.S., U.A., Literature Search: T.S., U.A., Writing: T.S., U.A.

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Factors affecting the caregiver burden following traumatic brain injury

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ABSTRACT

Aims: This study aimed to investigate the factors that had an effect on the burden of the caregivers of moderate to severe traumatic brain injury (TBI) patients.

Methods: Between December 2018 and June 2019, patients with moderate to severe TBI and their caregivers were included in the study. Caregivers were assessed with the Zarit Burden Interview and short form-36 health survey scale, and patients were assessed with the Disability Rating Scale and Functional Independence Measure.

Results: The study included 58 patients [age, median (min-max): 45 (21.0-60.0), female 72.4%]. A negative correlation was found between the caregiver's age, unemployment status and comorbidities with the caregiver burden (p=0.007, p=0.073, p=0.168 respectively). A positive correlation was found between the caregivers who were the members of the family and the caregiver burden (p=0.001). In univariate and multivariate regression analysis, the caregiver's age was found to be independent predictors of the increased burden of care (p=0.007, p=0.016), and being a member of the family was found to be independent predictors of the decreased burden of care (p=0.001, p=0.048).

Conclusions: This study demonstrates the effects of the caregiver's age and relationship with the patient on caregiver burden.

Introduction

Traumatic brain injury (TBI) is one of the most common causes of death and disability with a wide spectrum of symptoms that range from mild to severe in children and adults (1). TBI can cause many medical, physical, cognitive, behavioral, emotional, social, and economic difficulties. It has a profound effect on the lives of patients and their families (2). Thus, continuity of patient care is of great importance for the patient, the patient's family, and the health care system during both the acute and chronic periods of patients with TBI.

Caregivers play an essential role in the care of patients with TBI. Caregiver burden refers to the physical, psychosocial, and financial hardships that can occur during the course of providing care (3). As the severity of symptoms and disability of the patient increase, the workload, and, consequently, caregiver depression can also increase (4).

Manskow et al. (1) investigated factors affecting caregiver burden after TBI. They found that communication problems, patient's functional status, and feeling alone were the strongest determinants of caregiver burden. In another study, Qadeer et al. (5) reported that insufficient attention to caregivers resulted in psychological and health complaints. They suggested that caregivers should be educated about medications, management, and health maintenance before discharge.

Factors affecting caregiver burden of patients with chronic diseases like multiple sclerosis, stroke, Parkinson's disease have been investigated in many studies but to our knowledge, this is the first study evaluating the caregiver's burden following TBI in Turkey (6-8). In this study, we aimed to investigate the factors affecting the burden of the caregivers of patients with TBI in a province of Turkey.

Methods

Study Design

This cross-sectional single-center study included 58 patients and their caregivers who were hospitalized in a Physical Medicine and Rehabilitation Clinic from December 2018 to June 2019. The study was approved by the University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital Local Institutional Ethics Committee (approve date: 17.12.2018, approval number: 57/05). Before the study, all patients' caregivers were informed about the study. Written consent was obtained for the study. All procedures were conducted according to the Helsinki Declaration of 2004.

Participants

The caregiver inclusion criteria were as follows: Age over 18 years and status as the primary caregiver (i.e., living with the patient), being able to read and comprehend the written informed consent form in Turkish.

Exclusion criteria included the inability to give informed consent and refuse to participate in the study.

The patient inclusion criteria were as follows: Age over 18 years, having moderate or severe subacute or chronic period TBI.

The patient exclusion criteria included a previous history of neuropsychiatric disorders due to alcoholism, drug abuse (patient and caregiver), having progressive (multiple sclerosis, amyotrophic lateral sclerosis, etc.) or non-progressive (cerebrovascular disease, cerebral palsy, etc.) neurological disease.

Demographic and Disease Characteristics

Age, gender, educational status, marital status, occupational status, comorbidity, occupation, number of other persons cared for, and general health (GH) status of each caregiver were recorded. GH status of the caregivers was assessed with the short form-36 (SF-36) health survey. It has eight domains scored from 0 to 100, divided across physical and psychological domains: physical functioning, role physical, bodily pain, GH, vitality, social functioning, role emotional, and mental health (MH) (9). SF-36 results can be aggregated into two summary measures, the physical component summary (PCS) and the mental component summary (MCS). The PCS and MCS scores were used in this study. The Turkish language validation of the SF-36 was previously accomplished (10).

Caregiver burden was assessed using the Zarit Burden Interview (ZBI), one of the most commonly used instruments to evaluate the physical, psychological, and social consequences of caring activities. The ZBI was developed by Zarit et al. (11) in 1980. It consists of 22 items rated on a 5-point Likert scale that ranges from 0 (never) to 4 (nearly always) with the sum of scores ranging between 0 and 88. The ZBI reflects caregiver burden, with higher scores being associated with increased burden. A validity study for ZBI was previously completed (12).

For each patient, the age, sex, educational status, presence of additional injuries, duration of coma, hospitalization, homestay, and total trauma (in days), as well as the presence of tracheostomy and/or gastrostomy, mechanical ventilation, spasticity, and presence of bowel and/or bladder dysfunction, Disability Rating Scale (DRS), and Functional Independence Measure (FIM) scores, were recorded. The DRS was previously developed and tested in patients with moderate and severe TBI, particularly during rehabilitation. It can track an individual from the stage of coma to rehabilitation in the community and classifies recovery according to three categories: impairment, disability, and handicap (13). The lowest score is 0, which represents no disability. The highest score is 29, which represents the extreme vegetative state. The DRS total score was used in this study to represent the level of functioning of the patient with TBI.

FIM is widely used and accepted as an assessment of the functional status of patients with neurologic disorders (14). It is composed of 18 items divided into 6 parts. The highest score 126 indicates total independence in functional activities. The Turkish versions of the FIM were validated previously (15). Each item is scored from 1 to 7 (1 point indicates complete dependence, 7 points indicates complete independence).

Statistical Analysis

Data analyses were made using the Statistical Package for the Social Sciences 22.0 for Windows. The continuous variables were evaluated with the Kolmogorov-Smirnov test as to whether or not they were different from a normal distribution. Descriptive statistics were shown as mean±standard deviation and median (minimum-maximum) for continuous variables and frequencies and percentages (%) for categorical variables.

Point biserial (categorical) and Spearman's correlation tests were used to establish the relationship between the caregiver burden scale scores and demographic and disease variables. The univariate logistic regression analysis for significant correlations (age, working state as unemployment, presence of comorbidity, and being a member of the informal caregiver) and multivariate regression analysis were performed. The statistical significance level was set at $p<0.05$.

Results

The median caregiver age was 46.0 years (range: 21.0-60.0). Forty-two (72.4%) of the caregivers were female, while 16 (27.6%) were male. The median patient age was 30.0 (18.0-64.0) years. Fourteen (24.1%) patients were female and 44 (75.9%) were male. Twenty-seven (44.8%) patients and their caregivers had the same gender. The characteristics of the caregivers and patients are presented in Table 1 and Table 2.

The patients' mean DRS score was 15.4±7.8. The median FIM score was 32.0 (range: 18.0-115.0). The median MH score of the caregivers according to the SF-36 scale was 35.1 (range: 4.5-77.5), and the median physical health score was 46.6 (27.7-95.5). ZBI severity was mild in 9 (15.5%), mild to moderate in 8 (13.8%), moderate to severe in 28 (48.3%), and severe in 13 patients (22.4%).

Correlation results between caregivers' caregiver burden scale scores and caregiver and patient characteristics are presented in Table 3 and Table 4, respectively.

We found a significant correlation between caregiver burden and caregiver's age, employment status, relationship with the patient (formal, informal caregiver), and comorbidity ($r=0.306$, $p=0.019$, $r=0.280$, $p=0.033$, $r=-0.578$, $p=0.021$ and $r=0.251$, $p=0.048$, respectively). We found a significant positive correlation between the age of the caregiver and working status of unemployment and comorbidity of the caregiver. Also, we found a significant negative correlation between caregiver burden and informal caregivers.

We did not find a significant correlation between demographics and disease characteristics of the patients and caregiver burden scores ($p>0.05$).

In univariate and multivariate regression analyses, the caregiver's age was found to be independent predictor of the increased burden of care ($p=0.007$, $p=0.016$), and being a member of the family was found to be independent predictor of the decreased burden of care ($p=0.001$, $p=0.048$) (Table 5, Table 6).

Discussion

Mortality rates related to TBIs have decreased dramatically with advances in intensive care services, but morbidity has increased (5). TBI affects the family and patient both socioeconomically and psychologically because their lives change markedly. Family *caregivers* play critical roles in the plan of care for patients with chronic diseases (16). In addition to the care itself, increasing economic problems and the physical and emotional demands of long-term care can result in adverse impacts on caregivers. We examined the effects of the following variables on caregiver burden: the patient's comorbidities, intensive care period, spasticity, presence of a tracheostomy or gastrostomy, speech or swallowing disorder, and bladder or bowel dysfunction.

The current study found that the strongest predictors for a high burden were related to the burden on the caregiver and associated with the caregiver's age and relationship with the

Table 1. Characteristics of caregivers

	n=58 Mean±SD, median (min-max), n (%)
Age (years)	45 (21.0-60.0)
Sex	
Female	42 (72.4)
Male	16 (27.6)
Educational status	
Illiterate	0
Literate	4 (6.9)
Primary school	21 (36.2)
Secondary school	28 (48.3)
High school	5 (8.6)
University or higher	0
Marital status	
Married	56 (96.6)
Single	2 (3.4)
Divorced	0
Working state	
Employment	30 (51.7)
Unemployment	28 (48.3)
Presence of comorbidity	52 (89.7)
Number of people living together	3.00 (1.0-5.0)
SF-36	
MH	35.12 (4.5-77.5)
Physical health	46.62 (27.75-95.50)
Domains	
Physical functioning	77.50 (0.0-100.0)
RP	40.00 (0.0-100.0)
BP	53.00 (20.0-100.0)
GH	52.00 (40.0-86.0)
V	45.00 (10.0-87.0)
SF	37.00 (0.0-100.0)
RE	30.0 (0.0-100.0)
MH	48.00 (0.0-72.0)
Zarit Caregiver Burden Scale	45.00 (25.0-83.0)

SD: Standard deviation, min-max: Minimum-maximum, SF-36: Short form-36, RP: Role physical, BP: Bodily pain, GH: General health, V: Vitality, SF: Social functioning, RE: Role emotional, MH: Mental health

Table 2. Demographic features and disease characteristics of the patients

Characteristics	n=58 Mean±SD, median (min-max), n (%)
Age (years)	30.00 (18.0-64.0)
Sex	
Female	14 (24.1)
Male	44 (75.9)
Educational status	
Illiterate	0
Literate	0
Primary school	25 (43.1)
Secondary school	18 (31)
High school	10 (17.3)
University or higher	5 (8.6)
Premorbid comorbidity	10 (17.3)
Hypertension	9 (90)
Diabetes mellitus	3 (30)
Coma time (day)	4.00 (1.0-5.0)
Time after trauma (day)	269.72±31.67
Hospital stay (day)	144.58±14.29
Homestay (day)	95.72±2.37
Concomitant injury	42 (72.4)
The presence of tracheostomy	33 (56.9)
The presence of gastrostomy	35 (60.3)
The presence of mechanical ventilation	0
The presence of swallowing disorder	34 (58.6)
The presence of speech disorder	44 (75.9)
Bladder dysfunction	45 (77.6)
Bowel dysfunction	44 (75.9)
Spasticity	39 (67.2)
DRS (0-29)	15.48±7.87
FIM	
Motor	24.00 (12.0-80.0)
Cognitive	10.50 (4.0-35.0)
Total score	32.0 (18.0-115.0)

DRS: Disability Rating Scale, FIM: Functional Independent Measurement, SD: Standard deviation, min-max: Minimum-maximum

patient. The caregivers experienced moderate levels of burden, which is consistent with many studies that have investigated the caregiver burden related to patients with TBI (17).

In the current study, it was determined that unemployed caregivers had a higher care burden. Like our study, researchers (18) found that employment reduced the burden on the caregiver. Financial difficulties resulting from their unemployed status could negatively affect these caregivers' burdens. It has been suggested that caregivers have to be provided financial support to prevent an increase in caregiver burden due to low income (19).

Table 3. Correlation results of caregiver characteristics and caregiver burden

	r	p
Age (years)	**0.306°**	**0.019**
Sex	-0.189*	0.155
Educational status	0.194*	0.145
Marital status	0.237*	0.073
Working state (unemployment)	**0.280***	**0.033**
Relationship with patient (family member)	**-0.578***	**0.021**
Comorbidity	0.251*	**0.048**
Number of people living together	0.115°	0.388
SF-36		
MH	0.160°	0.249
Physical health	-0.211°	0.127
Domains		
Physical functioning	-0.181	0.196
RP	-0.134	0.338
Pain	-0.258	0.060
GH	0.037	0.491
V	-0.024	0.865
SF	-0.201	0.150
RE	0.029	0.834
MH	0.201	0.149

*: Point biserial correlation test, °: Spearman's correlation test, r: Correlation coefficient, SF-36: Short form-36, RP: Role physical, GH: General health, V: Vitality, SF: Social functioning, RE: Role emotional, MH: Mental health

In the current study, the factor related to the burden was the age of the caregiver. It was observed that the older age of the caregivers increased the caregiver burden. Similar to the current study, Nabors et al. (20) found that the burden of care was higher for older caregivers than for younger caregivers. They explained this with the fact that younger caregivers had fewer needs. Davis et al. (21) suggested that caregivers' preinjury medical and psychiatric histories were both risk factors for caregiver distress. They indicated caregivers who were at risk of developing distress and caregiver burden should be evaluated to prevent distress in the post-acute period.

A substantial part of the care for patients may require long-term and be provided by informal caregivers such as spouses or parents (22). In our study, another factor related to burden was the caregivers' relationship with the patient. We found being family members reduced the caregiver burden. Similarly, Marks et al. (23) reported that caregivers could acquire satisfaction from helping their family members.

In the current study, gender, educational status, marital status, the severity of the patient's injury, and the patient's comorbidities were all found to have no significant impact on caregiver burden. Our findings could be relevant to the disease

Table 4. Correlation results of patient characteristics and caregiver burden

Characteristics	r	p
Age (years)	-0.003°	0.983
Sex	-0.145*	0.228
Educational status	-0.064*	0.712
Premorbid comorbidity		
Hypertension	0.022*	0.168
Diabetes mellitus	0.138*	0.255
Coma time (day)	0.014°	0.927
Time after trauma (day)	0.242°	0.078
Hospital stay (day)	-0.041°	0.777
Homestay (day)	0.294°	0.038
Concomitant injury	0.115*	0.409
The presence of tracheostomy	0.035*	0.810
The presence of gastrostomy	0.063*	0.359
The presence of mechanical ventilation	0.128*	0.058
The presence of swallowing disorder	-0.043*	0.779
The presence of speech disorder	0.120*	0.478
Bladder dysfunction	0.031*	0.818
Bowel dysfunction	0.103*	0.442
Spasticity	-0.210*	0.167
DRS (0-29)	0.019°	0.890
FIM		
Motor	-0.049°	0.713
Cognitive	-0.037°	0.795
Total score	-0.047°	0.736

DRS: Disability Rating Scale, FIM: Functional Independent Measurement, *: Point biserial correlation test, °: Spearman's correlation test, r: Correlation coefficient

Table 5. Univariate regression analysis between Zarit Burden Interview mild severity parameters (as dependent variable) and caregiver characteristics

	B	SE	95% CI (lower-upper) for B	p
Age	0.552	0.208	0.136-0.968	**0.007**
Having a comorbidity	1.217	0.712	0.933-5.412	0.168
Unemployment	4.885	2.675	0.467-10.237	0.073
Being an informal caregiver	1.381	0.380	0.618-2.143	**0.001**

p=p-values of univariate logistic regression analysis.
B: Regression coefficients (B), CI: Coefficient interval, SE: Standard error

features of the patients who participated in the study. A review that focused on factors affecting the caregiver burden of TBI patients reported more caregiver burden for spouses and

Table 6. Multivariate regression analysis between Zarit Burden Interview mild severity parameters (as dependent variable) and caregiver's age and being an informal caregiver

	B	SE	95% CI (lower-upper) for B	p
Age	0.848	0.327	0.175-1.521	**0.016**
Being an informal caregiver	6.517	3.142	0.034-12.996	**0.048**

p=p-values of multivariate logistic regression analysis.
B: Regression coefficients (B), CI: Coefficient interval, SE: Standard error

women than for parents and men. They reported that 48.8% of TBI patients reported divorce or separation from their spouse, and 6.10% of still married individuals reported having problems in their marriage. Also, they have reported that providing social support has a positive effect on the caregiver burden. Similar to our study, in this review, the severity of the injury was found to have no significant impact on the caregiver burden (5).

Patients and caregivers need long-term professional follow-up to alleviate the caregiver burden (1,24). A study showed that telephone-based problem-solving interventions improved the well-being of TBI caregivers. They found that the caregivers who received telephone-based problem-solving interventions felt better and were able to care for themselves and reported using more active coping skills (25). Also clinicians should focus on providing caregiver education including managing stress, coping, and problem-solving strategies. It is important to take care of the needs of caregivers and to ensure them with sufficient social, economic, physical, and psychological support (26).

The strength of the current study is that we used validated assessment tools. Also, caregivers were evaluated not only with the ZBI but also with the health survey scale. Limitations of our study are that it did not assess the level of social support provided to caregivers and it included a small sample size of participants from a single center. Another limitation is our lack of information about the premorbid properties that could affect the caregiver's ability to cope with the situation. In future studies, a larger sample from different regions of our country will better identify the factors affecting caregiver burden.

Conclusion

Caregivers play a very important role in the subacute-chronic period rehabilitation after moderate to severe TBI. This study highlights the factors that affect the burden by primary caregivers of adults with moderate to severe TBI. This study provides important information about the burden of care, particularly by demonstrating that a caregiver's age and relationship to the patient contribute to the level of caregiver burden.

Understanding the relevant factors that affect caregiver burden may help identify and take early interventions for caregivers who are at a risk for high burden. Since post-TBI care

involves a very long process, meeting the needs of caregivers and supporting them both psychologically and financially are important to reduce the caregiver's burden and to improve the quality of life of the patient.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital Local Institutional Ethics Committee (approval date: 17.12.2018, approval number: 57/05).

Informed Consent: All patients' caregivers were informed about the study

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.T., Design: N.T., E.U., A.Ç. Data Collection or Processing: N.T., E.U., Analysis or Interpretation: E.U., Literature Search: N.T., E.U., A.Ç. Writing: N.T.

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Long-term results of patients treated with bronchoscopic lung volume reduction

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ABSTRACT

Aims: Surgical and bronchoscopic treatments are tried to reduce hyperinflation together with medical treatments in patients with chronic obstructive pulmonary disease (COPD) and emphysema. Therefore, bronchoscopic lung volume reduction (BLVR) procedures can improve the success of treatment and quality of life of patients.

Methods: We investigated the efficacy and safety of BLVR treatment retrospectively. Demographic characteristics, modified Medical Research Council (mMRC) and COPD assessment test (CAT) questionnaires, 6-minute walking distance (6-MWD) and all pulmonary function tests of the patients, who were treated with BLVR, were examined. The values before the procedure and the values at the third and sixth months after the procedure were analyzed statistically.

Results: Twenty-five patients were examined (one was female). Six patients (59±10.4 years, forced expiratory volume in 1 s (FEV1) 21.7±5.7% pred) were bronchoscopically treated with coils, with a median of 9.33 (range 8-11) coils per procedure. Nineteen patients (65.8±6 years, FEV1 26.9±9% pred) were treated with valves, with a median 3.52 (range 3-4) valves per patient. At 3 and 6 months, respectively, ΔCAT was −4.8±6 and −7.5±7.2 points, Δ6-MWD was +103.4±139 m and +160.8±149 m [endobronchial valve (EBV)], ΔFEV1 was +0.15±0.3 L and +0.21±0.3 L, ΔFVC was +0.44±0.7 L and +0.5±0.7 L, (all $p<0.05$), and ΔRV (residual volume) was −0.52±1.1 L and 0.32±1.5 L ($p>0.05$).

Conclusions: In our study, BLVR (EBV and coil) treatments were used in patients with severe to very severe emphysema in COPD, in appropriate indications and in selected cases, and statistically significant well-being was observed in spirometric parameters in the first six months after the procedure.

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with persistent respiratory symptoms due to airway and/or alveolar abnormalities and is associated with a more or less emphysema phenotype (1), which is the dominant pathological feature of COPD. It is observed with damage and progressive condition in the terminal bronchioles and distal airways (2). Loss of lung elastic recoil results in airflow obstruction, leading to gas compression and increased lung volumes (3,4). Among the current standard treatment options for COPD, the most important ones are smoking cessation and pharmacological treatments. In addition, there is respiratory rehabilitation applied in specialized centers (1). Despite optimal pharmacological treatment in COPD patients with a predominant emphysema phenotype, pharmacological treatments are insufficient and medical treatment does not prevent the progression of the disease in these patients (5,6).

Since 2002, several bronchoscopic interventions have been evaluated in clinical trials. The aim is to reduce hyperinflation and thus improve respiratory mechanics (7). Many clinical studies have shown positive effects on patients. After bronchoscopic interventions, a decrease in symptoms due to residual volume reduction is observed and an increase in quality of life is observed (6). Bronchoscopic interventions for lung volume reduction basically include reversible and irreversible blocking techniques. The choice of the different bronchoscopic lung volume reduction (BLVR) techniques depends on expert bronchoscopists. The distribution of emphysema is important in this decision, and the

evaluation of collateral ventilation determines the success of the procedure. However, positive results are obtained with the appropriate technique for the appropriate patient.

In our study, we aimed to examine the changes in the symptoms of patients who were applied BLVR treatment, and to examine the changes in spirometry, lung volumes and diffusion lung capacity of carbon monoxide (DLCO) test in respiratory function tests.

Methods

Study Design

The clinical records of patients were retrospectively reviewed between October 2017 and October 2019. Patients with severe to very severe emphysema, who underwent endobronchial valve (EBV) and lung volume reduction coil (LVRC) placement, were included.

NETT study criteria were accepted for inclusion criteria and exclusion criteria in this study. Inclusion criteria were as follows: Being >18 years of age, having CT scan showing heterogeneous emphysema (criteria for EBV only), GOLD Stage 3 or 4, post-bronchodilator forced expiratory volume first second (FEV1) <50% of predicted, residual volume (RV) >150% of predicted, total lung capacity (TLC) >100% of predicted, DLCO >20% of predicted, 6-minutes walking distance test (6-MWD) <500 meters, systolic pulmonary artery pressure <50 mmHg on echocardiography, using optimal bronchodilator therapy, at least 6 weeks of pulmonary rehabilitation and having stopped smoking for >8 weeks prior to the study. Exclusion criteria included having with pregnancy or lactation status, active lung cancer, history of frequent respiratory tract infections, giant bullae in the lungs, clinically significant bronchiectasis, history of lung volume reduction surgery, transplantation or lobectomy history and having collateral ventilation (criteria for EBV only).

Demographic characteristics of patients, including age, gender, height, weight, body mass index (BMI), duration of illness, comorbidity, smoking history, drugs used, and first and second visits, were recorded using the data preparation form.

COPD assessment tests (CAT) and modified Medical Research Council (mMRC) dyspnea scoring were used to assess dyspnea. mMRC is a scale system with scores between 0 and 4. With a few simple questions asked to patients, the patient with the least symptoms is given a low score, and the patient with the most symptoms is given a high score. CAT score, on the other hand, is a scoring used for the evaluation of patients with COPD, which is formed by adding scores between 0 and 5 given to 8 different questions. 0 is the score obtained by the patients with the lowest symptoms and 40 by the patients with the most symptoms (8).

The results of the 6-MWD applied in the pulmonary rehabilitation unit were examined (9). BODE index, consisting of BMI, airway obstruction, dyspnea, and exercise capacity, were calculated.

Measurements were made with a COSMED, MINISIPIR brand spirometer, which can measure within the volume limits of 15 seconds, volumes up to 20 L, the total resistance of all parts in the range of 0.02-20 L/s. For FRC, RV and TLC measurements, a multi-term nitrogen washout test with a VMAX brand device (cardiopulmonary exercise testing ergo spirometer device) was used. The most commonly used method in DLCO measurement is the single breath CO method. Gas concentrations are measured at the beginning and at the end of 10 seconds.

The third month after the procedure was the first endpoint and the sixth month was the second endpoint. Baseline tests and post-procedure tests were compared.

Procedure

All patients were hospitalized before the procedure. Patients with dyspnea after procedure were given systemic steroids against foreign body reaction. All patients were admitted to hospital for a period of 3 to 5 days. A posteroanterior chest X-ray was routinely obtained following the procedure.

Endobronchial Valve

The EBV procedures were done using a flexible bronchoscope (BF-1TQ180 Olympus, Tokyo, Japan) with a working channel of 2.8 mm. The procedure was under conscious sedation with intravenous midazolam. High resolution computerized tomography (HRCT) with thin slice imaging and quantitative lung perfusion scintigraphy were used to choose the target lobe. Chartis collateral ventilation system (Pulmonx, Redwood City, CA, USA) was used to detect collateral ventilation (Zephyr Tm EBV, Pulmonx Inc., Redwood, CA, USA).

Lung Volume Reduction Coil

LVRC procedures were performed under general anesthesia. HRCT with thin slice and quantitative lung perfusion scintigraphy were used to choose the target lobe. Following the patient's intubation, the coils (Coil, PneumRx Inc. Mountain View, California, USA) were placed into the subsegmental airway with fluoroscopy guidance.

Statistical Analysis

Our study includes a retrospective analysis of patients who underwent BLVR therapy. Statistical Package for the Social Sciences (SPSS) for Mac version 22.00 (SPSS Inc., Chicago, IL., USA) package program was used for the statistical analysis of the data obtained at the end of the study. Data were given as mean and standard deviation (SD). Continuous variables were expressed as mean±SD, and categorical variables as numbers and percentages (%). Whether continuous variables fit the normal distribution or not was evaluated using the Kolmogorov-Smirnov test. For the comparison of groups, the chi-square test

Table 1. Demographics and baseline characteristics

	EBV (n=19)	LVRC (n=6)	Total (n=25)
Variable	**Mean±SD**	**Mean±SD**	**Mean±SD**
Age, year	65.8±6.0	59.0±10.4	64.1±7.7
BMI	21.9±5.0	24.6±4.3	22.6±4.9
Smoking, pack/year	52.3±15.6	50.8±41.4	51.9±23.5
First diagnosis, year	10.2±3.9	8.3±4.5	9.7±4.0
Pulmonary function			
FVC, L	2.23±0.60	2.27±0.69	2.24±0.61
FVC, % pred	63.3±16.8	58.5±17.5	62.1±16.7
FEV1, L	0.74±0.23	0.66±0.15	0.72±0.21
FEV1, % pred	27.0±8.1	21.6±5.7	25.7±7.9
FEV1/ FVC	34.1±10.5	29.8±3.5	33.1±9.4
TLC, L	6.88±0.93	6.17±2.06	6.72±1.24
TLC, % pred	112.1±18.0	94.4±30.9	108.3±21.9
RV, L	4.57±0.98	3.78±1.34	4.40±1.08
RV, % pred	193.1±44.5	159.4±52.4	185.8±47.3
RV/TLC, % pred	66.5±7.79	61.0±6.2	65.3±7.7
VC, L	2.31±0.53	2.38±0.86	2.33±0.59
VC, % pred	62.7±11.9	59.4±21.5	61.9±13.9
DLCO, % pred	35.7±12.1	37.4±7.7	36.1±11.1
Arterial blood gas			
pH	7.43±0.38	7.39±0.33	7.42±0.39
pCO_2, mmHg	3685±5.88	41.26±6.26	37.77±6.10
pO_2, mmHg	64.15±16.14	70.42±12.05	65.45±15.36
sO_2, %	90.03±8.32	94.04±1.53	90.86±7.58
FCOHb	1.81±0.83	1.72±0.31	1.79±0.75
HCO_3	24.16±3.22	24.62±2.15	24.25±2.99
PAPs, mmHg	23.6±7.7	27.0±6.7	24.3±7.5
mMRC, point	3.63±0.49	3.66±0.52	3.64±0.49
CAT, point	26.26±7.03	24.66±4.27	25.88±6.43
BODE, point	8.11±1.37	7.83±1.33	8.04±1.33
6-MWD, m	182.5±122.3	219.1±124.2	191.3±121.2

BMI: Body mass index, FVC: Forced vital capasity, FEV1: Forced expiratory volume first second, TLC: Total lung capacity, RV: Residual volume, VC: Vital capacity, DLCO: Diffusing capacity for carbon monoxide, pCO_2: Partial pressure of carbon dioxide, pO_2: Partial pressure of oxygen, sO_2: Oxygen saturation, FCOHb: Carboxyhemoglobin, HCO_3: Level of bicarbonate, PAPs: Systolic pulmonary arterial pressure, mMRC: modified Medical Research Council, CAT: COPD assessment test, 6-MWD: 6-minute walk distance

was used for discrete variables, and for continuous variables (such as FEV1, DLCO, mMRC, and age) the Wilcoxon paired two-sample test or paired samples t-test was used according to the presence of normal distribution. Statistical significance was taken as $p<0.05$.

Table 2. Details of procedures

	Endobronchial valve (n=19)	Endobronchial coil (n=6)
Target lobe, patient head		
Right upper lobe, n (%)	14 (73)	2 (33)
Right upper + left upper lobe n (%)	0	3 (50)
Right upper + middle lobe n (%)	1 (5.3)	0
Right lower lobe n (%)	1 (5.3)	0
Left upper lobe n (%)	2 (10.6)	1 (17)
Left lower lobe n (%)	1 (5.3)	0
Number of valves/coils, per patient	3.52	14
4.0 / 100 mm n (%)	36 (54)	59 (70)
4.0 LP / 125 mm n (%)	3 (4)	25 (30)
5.5 n (%)	28 (42)	-
Total	67 (100)	84 (100)
Hospital stay after operation, days	4.5±2.6 (2-13)	3.5±1.2 (3-6)

Results

A total of 28 patients were identified, 3 patients were excluded due to exclusion criteria. EBV was performed in 19 patients and LVRC was performed in 6 patients. One procedure was performed for 19 valve patients and a second procedure was performed for 3 of 6 coil patients, and a total of 28 procedures were performed.

Twenty-four patients were male and one was female. The mean age of all patients was 64.1±7.7 (48-80) years. Twenty-three patients had a smoking history, and the average of all patients was calculated as 51.9±23.5 packs/year. Two patients had biomass exposure. The demographic and clinical characteristics of EBV and LVRC groups before the treatment were similar. The average of the tests performed before the procedure is given in Table 1.

A total of 67 valves were used, and the average per patient was 3.52. And total of 84 coils were used, the number of coils used was 9.33 per procedure and an average of 14 per patient. The right upper lobe was frequently used. Details of procedure are given in Table 2.

While there were no comorbid diseases in 10 patients in their anamnesis and medical records taken before the treatment, cardiac arrhythmia was seen in 5 patients, hypertensive heart disease in 4 patients, coronary/peripheral artery disease in 4 patients, diabetes mellitus in 1 patient, and mild systolic heart failure in 2 patients. Two patients had second degree heart valve failure, 2 patients had hypothyroidism, and 1 patient used drugs for depression.

While bronchospasm was observed most frequently in patients (n=11), hemoptysis was observed following the LVRC

Table 3. Adverse events at the 6th month

	(0-30 days)	(31-180 days)
Bronchospasm, n (%)	11 (44)	0
Hemoptysis, n (%)	1 (4)	0
Pneumothorax, n (%)	1 (4)	0
Pneumonia, n (%)	2 (8)	2 (8)
COPD exacerbation, n (%)	4 (16)	2 (8)
Subcutaneous emphysema, n (%)	1 (4)	0
Valve migration, n (%)	1 (4)	0
Death, n (%)	0 (0)	1 (4)

COPD: Chronic obstructive pulmonary disease

procedure in 1 patient and pneumothorax and subcutaneous emphysema following EBV procedure in another patient. One patient died on the second month following EBV therapy secondary to COPD exacerbation (Table 3).

The mMRC dyspnea scores, CAT scores, BODE index and 6-MWD data recorded in the third and sixth months after the procedure were statistically significant. Forced vital capacity (FVC) and vital capacity (VC) measurements of all patients were statistically significant at the 3rd and 6th months after the procedure ($p<0.05$).

The mean FEV1 value at the 3rd month of the patients who underwent EBV was 0.88±0.3 L (p=0.041), and the mean FEV1 value at the 6th month after the procedure was 0.92±0.4 L (p=0.102). FEV1 value change was 0.14±0.25 L at the 3rd month and 0.18±0.3 L at the 6th month. The mean FEV1 value at the 3rd month of the patients who underwent LVRC was 0.81±0.2 L (p=0.003), and the mean FEV1 value at the 6th month after the procedure was 0.92±0.2 L (p=0.104). When the FEV1 percentages were examined one by one, according to the basal values, the increase in FEV1 of 12% was observed in all 6 patients. The mean FEV1 value of all patients was 0.86±0.3 L (p=0.005) at the 3rd month after the procedure, and the mean FEV1 value of all patients was 0.92±0.4 L (p=0.035) at the 6th month after the procedure. The mean FEV1 value change of all patients was 0.15±0.3 L at the 3rd month and 0.21±0.3 L at the 6th month. After the procedure, an increase was observed in 17 (68%) of the patients in our study, compared to the previous FEV1 value. A total of 14 patients (56%) had an average increase of 12% in FEV1.

The mean RV percentage was 169.2±37.6% (p=0.058) at the 3rd month of the patients who underwent EBV, and the mean RV percentage at the 6th month after the procedure was 179.6±72.1% (p=0.365). The mean RV value of patients who underwent EBV decreased by 0.75±0.9 L (p=0.066) at the 3rd month and by 0.5±1.4 L (p=0.442) at the 6th month compared to the baseline. The mean RV percentage at the 3rd month of the patients who underwent LVRC was 169.6±49.2% (p=0.681), and

Table 4. Outcomes at the 3rd month

	EBV		LVRC	
	Δ	p value	Δ	p value
FVC, % pred	-5.9±18.5	0.203	-27.2±18.8	0.001
FEV1, % pred	-4.9±9.6	0.044	-5.6±6.9	0.016
TLC, % pred	10.7±19.7	0.126	-20.6±27.8	0.109
RV, % pred	32.9±41.7	0.058	-10.2±50.7	0.681
VC, % pred	-5.9±16.6	0.108	-37.6±15.2	0.012
DLCO, % pred	-1.7±16.6	0.678	-19.8±16.9	0.147
mMRC, point	0.8±0.7	0.010	0.8±0.45	0.033
CAT, point	4.5±6.2	0.018	4.8±5.5	0.033
BODE, point	1.8±1.4	0.026	2±1.4	0.089
6-MWD, m	-107.5±121.4	0.082	-106.2±126.3	0.091

*FVC: Forced vital capasity, FEV1: Forced expiratory volume first second, TLC: Total lung capacity, RV: Residual volume, VC: Vital capacity, DLCO: Diffusing capacity for carbon monoxide, mMRC: Modified Medical Research Council, CAT: COPD assessment test, 6-MWD: 6-minute walk distance, LVRC: Lung volume reduction coil

Tablo 5. Outcomes at the 6th month

	EBV		LVRC	
	Δ	p value	Δ	p value
FVC, % pred	-8.8±18.3	0.065	-24.2±19	0.030
FEV1, % pred	-5.3±11	0.086	-8.6±7.8	0.133
TLC, % pred	5.7±20.8	0.454	-11.2±26.9	0.556
RV, % pred	23.5±56.9	0.365	-18.3±73.5	0.687
VC, % pred	-8.3±16.2	0.085	-11.6±16.4	0.195
DLCO, % pred	-9.7±20.2	0.300	-3.1±11.3	0.205
mMRC, point	1.2±0.75	0.005	1.5±1	0.383
CAT, point	6.7±7.45	0.011	9.3±5.5	0.115
BODE, point	1.9±1.65	0.009	1.7±2	0.369
6-MWD, m	-171.2±134	0.021	-172.7±111.5	0.034

*FVC: Forced vital capasity, FEV1: Forced expiratory volume first second, TLC: Total lung capacity, RV: Residual volume, VC: Vital capacity, DLCO: Diffusing capacity for carbon monoxide, mMRC: Modified Medical Research Council, CAT: COPD assessment test, 6-MWD: 6-minute walk distance, LVRC: Lung volume reduction coil

the mean RV percentage at the 6th month after the procedure was 177.7±94.6% (p=0.687). The mean RV value of patients who underwent LVRC increased by 0.07±1.15 L (p=0.898) at the 3rd month and by -0.11±1.45 L (p=0.735) at the 6th month compared to the baseline. Third-and sixth-month test changes of all patients are given in Table 4 and 5.

Discussion

Cessation of smoking and traditional medical treatments have been shown to be effective in COPD at first, but the effectiveness of these treatment modalities in preventing exercise dyspnea is limited (10). In the GOLD 2017 report, it is atated that “in selected patients with heterogeneous or

homogeneous emphysema and significant hyperinflation despite optimized medical care, surgical or BLVR methods (eg. EBV one-way valves or coils) may be considered" (11).

In this study, the short-term effectiveness and safety of BLVR procedures in patients with emphysema who received optimal medical therapy were evaluated. Improvements were observed in the exercise capacity, quality of life and pulmonary function parameters of the patients after the procedure. The mMRC dyspnea scores, CAT scores, BODE index and 6-MWD data recorded at the 3rd and 6th months after the procedure were statistically significant. FEV1, FVC and VC measurements of patients were statistically significant at the third and sixth months after the procedure ($p<0.05$). When we look at the literature, in many studies, FEV1 value and percentage increase together with the decrease in RV values and percentages are used to evaluate the effectiveness of BLVR. Meta-analyses compiled from these studies frequently include the change in these values of patients (2,4,12).

While the mean baseline FEV1% values of the patients in previous BLVR studies ranged between 26% and 33.4%, the FEV1% values in the RENEW and REVOLENS studies were the closest values to our study with 26% and 26.3% (12-14). The mean increases in FEV1 of our patients who underwent EBV was 180 mL and it was observed to be more than 100 mL, which is the minimal significant value. Davey et al. (6) reported an increase in FEV1 of 60 mL and 8.7% in the 6-month follow-up in the EBV series of 25 patients. And, Klooster et al. (15) reported that there was 147 mL increase in the EBV group with 40 patients. In the prospective multicenter randomized controlled TRANSFORM study published in 2017, the highest mean value was recorded as 230 mL and a significant increase in FEV1 (12%) was observed in 66% of the patients ($p<0.001$) (16). Valipour et al. (17) in a prospective study of 93 patients, in which 43 patients undergoing EBV were compared with standard treatment, showed an increase of 120 mL and a FEV1% improvement of 3.5% versus 13.7% in their 6-month follow-up compared to the control group ($p=0.002$), and it was noted that 14 patients (42%) who underwent the procedure had an increase of 100 mL and over 12%. When compared to this study, it was observed that 56% of our patients had an increase of 12% and 100 mL.

Decrease in RV is accepted as one of the first endpoints with the increase of FEV1 in BLVR studies. Although the change in the mean RV values of our patients who underwent EBV was more than 350 mL, which was considered significant change with 500 mL at the end of the 6th month, it was not statistically significant. When looking at other EBV studies in 2016 and beyond; Valipour et al. (17) found a reduction in mean RV of 480 mL (n=43), Klooster et al. (15) 672 mL (n=40), Kemp et al. (16) 670 mL (n=65). It is observed that our EBV patients are close to these values with the continuation of 750 mL at the 3rd month and 500 mL at the 6th month. As a long-term follow-up for 60 months, Fiorelli et al. (18) gave a reduction rate of approximately 39% from 247% to 207% in EBV patients in their article in 2017, but the most important change in this study is 0-3 months (it was 41%) and then small changes were observed in ±0-3% values. This suggests that the most important change occurred in the first 3 months. In our study, the most important change occurred in the first 3 months.

In our patients who underwent LVRC, the mean increases in FVC at the 3rd and 6th months were statistically significant and the change was greater while the basal FVC% values were lower than those who underwent EBV. Similarly, the VC% change was statistically significant at the end of the 3rd month.

In the 6-MWT values in which the exercise capacity of the patients was measured, an average increase of more than 100 m was observed in the patients who underwent EBV and LVRC at the 3rd month, but statistically $p>0.05$ was not considered significant. The increase in exercise capacity continued at the 6th month and was statistically significant. In a meta-analysis of 140 patients who underwent LVRC in 2015, Slebos et al. (19) reported an increase of 44.1 m ($p<0.001$) in the mean 6-MWT distance at the 6th month. In the review by Gülşen (2), in which BLVR treatments were evaluated in 2018, they reported an increase of 40.8 m (9.3-91 m) in EBV and 47 m (14.6-84 m) in LVRC procedures. Similarly, in the systematic meta-analysis published in 2019 by Rustagi et al. (4), 39.8 m (18-61 m) increase in EBV and 33.5 m (5.8-61.1 m) increase in LVRC were reported. Usually, 3-6-12-month follow-up is reported in all studies. In a single study that can be considered as a long-term follow-up, the mean change in a series of 33 patients after 5 years of follow-up was reported as +91 m (18). In our patients, the highest values in 6-MWT values were usually observed at the 3rd month, and in 5 patients (20%), walking distance continued to increase at the 6th month.

In our study, mMRC dyspnea scoring was used to evaluate shortness of breath in patients with COPD. The change in mMRC dyspnea score of the patients was considered significant in both groups. In the GOLD guideline, it is absolutely recommended to use mMRC and/or CAT scores for symptom scoring, and they are used to evaluate the severity of the disease (1). The CAT is a more detailed evaluation questionnaire than mMRC that examines different symptoms together. The changes in mean CAT scores of the patients in both groups were statistically significant. Similarly, in the REACH study, the mean change in CAT scores of 107 people in the 6th month was found to be statistically significant ($p=0.017$) (19,20). Similarly, an average decrease of 2 points was recorded in the BeLieVeR study (6). It is known that CAT score is highly correlated with quality of life. The BODE index was developed for the evaluation of mortality risk in COPD, and it was also used for hospitalization and evaluation of response to treatment. Significant improvements

were observed in the mean BODE index change in the EBV group in our patients. It was observed that significant results including dyspnea scale (mMRC) and exercise capacity (6-MWT) were also reflected in the change in BODE index.

The secondary goal of BLVR treatments is to evaluate their safety. In the first 6 months of follow-up, 1 patient died. When we look at the literature, Davey et al. (6) reported a mortality rate of 8% after 6 months of follow-up in their series of 25 cases. On the other hand, in the study of Herth et al. (21) which included 111 patients, the mortality rate was 5.4% at the end of the 12th month. Considering the mortality rates in LVRC studies, Deslée et al. (13) reported 8% in their 50-case study in 2016, and Sciurba et al. (14) reported 6.5% mortality in the 12-month follow-up of 158 cases (13). In the continuation study evaluating the long-term results of the STELVIO study, which is another study evaluating the effectiveness of EBV, it was reported that mortality was observed in only 2 patients after 12 months of 64 patients who did not have collateral ventilation (15).

In a study conducted in our country, Tanrıverdi et al. (22) observed that mortality was observed in a total of 7 patients in their 12-month follow-up study in which complications of a total of 66 patients (37 patients EBV, 29 patients LVRC) who underwent EBV or LVRC were evaluated. The researchers reported that 4 of these patients who underwent EBV and 3 who underwent LVRC died. And the annual mortality rate was 10.6%. The main issue highlighted in this study was that all patients with mortality had at least one additional disease and the mortality rate was higher in the presence of more than one additional disease, especially in the LVRC group. Although one case in our study had pneumothorax and another patient had hemoptysis, no mortality was observed in the perioperative and postoperative acute period. In an article in which studies published between 2010 and 2017 were compiled, it was reported that COPD exacerbation, followed by pneumonia and pneumothorax, was observed most commonly in those who underwent EBV and LVRC. Among the data on complications in published studies, COPD exacerbation rates are 9.3-64.0%, pneumonia rates are 0-11.7%, pneumothorax rates are 4.2-29.2%, and valve migration and replacement rates are between 1.5% and 20% (2). While the COPD exacerbation rates of our patients were similar to these studies, our rate of pneumonia was higher. However, in some of our patients who developed pneumonia, the observation of pneumonia not in the target lung lobe, where BLVR was applied, but in another lung area does not suggest this situation as a procedure-related complication.

One of the limitations of our study is that it was designed as a single center and retrospective study. Since the data of the patients for the first year and later were not available, they could not be used in the study. Lack of long-term results and the low number of cases can be considered as the limitations of our study. For all these reasons, we think that our findings should be supported by larger series and prospective studies.

Conclusion

When we look at the results of our patients, we can evaluate that BLVR methods are successful in reducing symptoms, with significant improvements in mMRC dyspnea score, CAT score, and BODE index after the procedure, although the number of our patients were few. Significant improvements in pulmonary function test parameters and effort capacity of our patients with treatment in study population, low perioperative and early postoperative complications suggest that the procedure is effective and safe. Although EBV or LVRC treatments for BLVR are advantageous compared to surgical methods in terms of both mortality and morbidity, it should be kept in mind that LVRS or lung transplantation may be required in selected cases. In addition, long-term follow-up data of the patients will reveal the true effectiveness of BLVR treatments.

Ethics

Ethics Committee Approval: The study was approved by Universty of Health Sciences Turkey, Gülhane Training and Research Hospital, Non-interventional Research Ethics Committee (date: 12.11.2019, approvel number: 19/355).

Informed Consent: Written informed consent form was obtained from each participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.T., D.D., Concept: A.Ç., C.T., D.D., Design: A.Ç., C.T., D.D., Data Collection or Processing: A.Ç., C.T., D.D., Analysis or Interpretation: C.T., D.D., Literature Search: A.Ç., D.D., Writing: A.Ç., C.T., D.D.

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Role of tumor necrosis factor-α, interleukin-1β, interleukin-6 in liver inflammation in chronic hepatitis B and chronic hepatitis C

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Keywords: Chronic hepatitis B, chronic hepatitis C, IL-1β, IL-6, TNF-α

ABSTRACT

Aims: Cytokines play important roles in the immunopathogenesis of chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infections. The aim of this study was to examine the changes in serum levels of interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α cytokines in patients with CHB and CHC, and the relationship of these cytokines with chronic inflammation, disease progression and fibrosis.

Methods: We prospectively enrolled patients with CHB and CHC and control subjects from August 2016 to August 2018. Liver biopsy samples were obtained as a part of the routine care. Serum levels of IL-6, IL-1β, and TNF-α were determined by the enzyme-linked immunosorbent assay method.

Results: The final sample included 90 patients with CHB (age, mean±SD: 42.6±11.8) 40 patients with CHC (age, mean±SD: 45.1±13.6) and 50 controls (age, mean±SD: 39±15.0). IL-1β, TNF-α and IL-6 serum levels were statistically significantly higher in patients with CHB and CHC than in the control group [IL-1β (ng/mL): 133.7±37.0, 125.92±12.7, 85.7±9.8; TNF-α (ng/mL): 307.9±68.9, 286.0±43.2, 72.0±14.01; IL-6 (ng/mL): 50.6±10.1, 55.07±9.79, 8.85±7.07, respectively, p=0.001]. TNF-α level was statistically significantly higher in patients with significant fibrosis (320.5±36.9) than those with mild fibrosis (257.3±21.6) (p=0.04). Alpha-fetoprotein level was statistically significantly higher in CHC patients than CHB and control groups.

Conclusions: This study showed increased levels of IL-1β, IL-6 and TNF-α in CHB and CHC patients. TNF-α level further increased in patients with documented liver fibrosis.

Introduction

Hepatitis B (HBV) and hepatitis C (HCV) viruses are important health problems because they cause serious consequences such as chronic hepatitis, cirrhosis, fulminant hepatitis, and hepatocellular carcinoma (HCC) (1). Chronic liver disease occurs as a result of the relationship between a progressive wound healing process and inflammatory response (2). The mechanism of persistent and progressive HBV infection is not clear yet, and it is thought that host immune and genetic factors may play an important role (3).

Cytokines play a fundamental role in the immunopathogenesis of HBV infection and may affect the susceptibility to HBV infection and the natural course of the infection (4). HCV infection stimulates the production of inflammatory cytokines and chemokines, resulting in hepatic inflammation and chronic hepatitis (5). Many cytokines that affect the progression of liver disease and play an important role in the fibrotic process have been reported. Cytokines can reduce viral replication and control the host immune response. Accordingly, it can be said that the serum level of cytokines affects the outcome of the disease (6).

Interleukin (IL)-1β is one of the powerful proinflammatory cytokines, a multifactorial inflammatory cytokine that has a central role in host defense and is an important immune response regulator (5). High IL-6 level may reflect more active hepatic necroinflammation. Therefore, it is a sensitive index for disease severity and progression (7).

Tumor necrosis factor (TNF)-α is a pro-inflammatory and antiviral cytokine secreted by macrophages and cytotoxic T lymphocytes in the liver, regulating immune reaction, cell growth and apoptosis. Therefore, TNF-α expression is considered to be an important molecular link between liver inflammation, steatosis, and fibrosis (8).

The aim of this study was to examine the changes in serum levels of IL-1β, IL-6 and TNF-α cytokines in patients with chronic hepatitis B (CHB) and chronic hepatitis C (CHC), and the relationship between these cytokines with chronic inflammation, disease progression and fibrosis.

Methods

Patients and Controls

In this prospective clinical research study, a total of 90 CHB patients, 40 CHC patients, and a 50 controls without a history of hepatitis B surface antigen (HBsAg), anti-HCV and anti-human immunodeficiency virus (HIV) negative, acute and chronic hepatitis and any chronic disease, who came to the unit of infectious diseases between august 2016 and august 2018, were included. When the study started, CHB and CHC patients had not taken any medication.

Patients with a co-infection of hepatitis A and HCV, HIV patients who could not undergo liver biopsy, patients with positive autoimmune serology, and patients with HCC and cirrhosis were excluded from the study. The diagnosis of CHB and CHC was made according to the criteria of the European Association for the Study of the Liver (with laboratory and pathological evaluation) (9).

Data Collection

All of the CHB and CHC patients underwent liver biopsy. Liver biopsy specimens were scored using the Ishak histological scoring system (fibrosis was evaluated out of 6). CHB and CHC cases were divided into two groups as prominent fibrosis (stage 3-4) and mild fibrosis (stage 1-2) (since there were no stages 5 and 6).

As a part of routine patient analysis, the standard blood tests that were performed included HBsAg, HBV viral load (HBV DNA), HCV viral load (HCV RNA) serum alanine aminotransferase and aspartate aminotransferase, gamma glutamyl transferase, and alpha-fetoprotein (AFP) levels. Liver biopsy was performed as a part of routine clinical assessment (in HBV DNA >2000 IU/mL and HCV RNA positive cases).

Determination of Serum Levels of IL-1β, IL-6, TNF-α

Approximately 5 cc of blood was drawn from the peripheral venous blood from the patients and separated into ethylenediamine tetraacetic acid-containing tubes. Within 40 minutes after collection, the obtained blood samples were centrifuged for 10 minutes at 3500 rpm. Serums were stored at -80 ºC in a deep freezer. Serums were brought to room temperature and melted in weekdays. Serum IL-6, IL-1β, and TNF-α levels were determined by the enzyme-linked immunosorbent assay method (R&D Systems, Minneapolis, MN, USA). Test results are expressed in ng/mL.

The study protocol was in accordance with the Helsinki Declaration of ethics and the study was approved by the Firat University Clinical Research Ethics Committee (Code: 14.12.2017/05). Patients' informed consent was obtained with the form.

Statistical Analysis

Data analysis procedures were carried out using Statistical Package for the Social Sciences 22.0 (Chicago, USA) package statistics software. The Kolmogorov-Smirnov and Shapiro-Wilk normality analyses were performed to determine the conformity of continuous variables to normal distribution. Student's t-tests were used in the analysis of continuous variables conforming to normal distribution. The "chi-square test" was used in the analysis of categorical data. Numerical data were expressed as mean±standard deviation, and categorical data as %. One-way ANOVA (Tukey, Bonferroni) test was used for multiple comparisons. $P<0.05$ value was considered significant in statistical comparisons.

Results

The final sample included 90 patients with CHB, 40 patients with CHC and 50 controls. Overall, 49 of CHB cases were female while 41 were male (age range: 42.6±11.8). There were 15 female and 25 male (age range 45.12±13.6) cases of CHC, while the control group consisted of 30 female and 20 male cases (age range: 39±15.04). There was no statistically significant difference between CHB, CHC and control groups in terms of age, gender and biochemical parameters ($p>0.05$). The demographic characteristics of CHB and CHC patients and the control group are shown in Table 1.

IL-1β, TNF-α and IL-6 serum levels were higher in CHB and CHC cases than in the control group and this was statistically significant [IL-1β (ng/mL): 133.7±37.0, 125.92±12.7, 85.7±9.8; TNF-α (ng/mL): 307.9±68.9, 286.0±43.2, 72.0±14.01; IL-6 (ng/mL): 50.6±10.1, 55.07±9.79, 8.85±7.07, respectively] ($p=0.01$). However, there was no significant difference between CHB and CHC cases in terms of the levels of these cytokines ($p=0.22$, $p=0.20$, $p=0.10$, respectively). Serum IL-1β, TNF-α and IL-6 levels and p values of CHB, CHC cases and control group are shown in Table 2.

Table 1. Demographic characteristics of chronic hepatitis B, chronic hepatitis C cases and control group, average values of laboratory tests

	CHB (n=90)	CHC (n=40)	Control (n=50)	p value
Age	42.6±11.8	45.1±13.6	39±15.0	0.24
Gender (female/male)	49/41	15/25	30/20	0.27
AST (IU/mL)	28.4±18.0	25.0±11.7	21±7.76	0.23
ALT (IU/mL)	40.7±41.3	27.4±19.0	23.7±14.8	0.32
GGT (IU/mL)	22.8±19.9	30.3±24.9	21.9±13.1	0.32
AFP (µg/L)	2.19±1.09	4.03±2.94	2.15±1.03	0.04
Total bilirubin	0.53±0.33	0.63±0.35	0.43±0.25	0.13
PTZ	11.6±0.84	11.7±1.03	11.1±1.36	0.18
PLT (x10^3/µL)	274±95.8	301±10	231±23.6	0.12
HBV DNA (10^3 IU/mL)	85189±372100			
HCV RNA (10^3 IU/mL)		5602.7±2947.5		

Data were expressed as mean±standard deviation. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, AFP: Alpha fetoprotein, PTZ: Prothrombin time, PLT: Platelet, HBV: Hepatitis B virus, HCV: Hepatitis C virus

Table 2. Serum cytokine levels and p values of chronic hepatitis B, chronic hepatitis C cases and control group

	CHB (n=90)	CHC (n=40)	Control (n=50)	p1	p2
IL-1β (ng/mL)	133.7±37.0	125.92±12.7	85.7±9.8	0.01	0.22
TNF-α (ng/mL)	307.9±68.9	286.0±43.2	72.0±14.01	0.01	0.20
IL-6 (ng/mL)	50.6±10.1	55.07±9.79	8.85±7.07	0.01	0.10

Data were expressed as mean±standard deviation. p1: p values between CHB, CHC and control group; p2: CHB-CHC p value.
CHB: Chronic hepatitis B, CHC: Chronic hepatitis C, IL: Interleukin, TNF: Tumor necrosis factor

In CHC and CHB cases, there was no statistically significant difference in serum levels of IL-1β and IL-6 cytokines between patients with significant fibrosis and mild fibrosis (IL-1β: p=0.44, p=0.49; IL-6: p=0.50, p=0.38, respectively). However, TNF-α (ng/mL) level of patients with CHC with significant fibrosis (320.5±36.9) was significantly higher than that with mild fibrosis (257.3±21.6) (p=0.04). Serum TNF-α levels of CHB cases were higher in those with significant fibrosis than those with mild fibrosis. However, this was not statistically significant (p>0.05). IL-1β, TNF-α and IL-6 serum levels and p values according to the fibrosis scores are shown in Table 3.

AFP (µg/L) levels of patients with CHC (4.03±2.94) were statistically significantly higher than those of the patients with CHB (2.19±1.09) (p=0.01) and control groups (2.15±1.03 µg/L) (p=0.01).

Discussion

Despite advances in medicine and technology, morbidity and mortality rates of CHB and CHC are high, especially in developing countries (10). In recent studies, it has been reported that the increase in proinflammatory cytokines such as IL-1β, TNF-α, and IL-8 may be effective in the development of tumors and chronic inflammatory diseases (11,12). In chronic viral hepatitis cases, increased cytokine levels cause inflammation in the liver (1). Therefore, measuring cytokine levels provides useful information about the activity and prognosis of the disease (13).

In a study conducted on patients with CHC, it was reported that the increase in IL-1β activity caused the development of fibrosis and inflammation to be more severe. In addition, it is stated that IL-1β plays a role in the pathogenesis of chronic hepatitis by reducing interferon-induced antiviral activity (1). It has been suggested that IL-1β mediates immune responses by inducing other proinflammatory genes. There are several studies documenting increased serum IL-1β levels in CHB cases (14). Watashi et al. (15) have shown that IL-1 can protect against HBV infection.

It has been suggested that the high production of IL-1β can help increase the production of other cytokines such as IL-2, IL-6 and TNF-α and trigger complex immunological processes to eradicate the virus (16). In this study, in accordance with the studies, IL-1β serum levels were statistically significantly higher in CHB and CHC than in the control group (p=0.01). This may indicate that IL-1β may be effective in the pathogenesis of CHB and CHC.

IL-6 is a multifunctional cytokine, important in inflammation, cell differentiation and tumor development (11,17). Levels of IL-6 have been shown to be significantly higher in CHB patients than in healthy humans and are expressed at significantly higher levels in those with severe liver disease (12,18). Again, a number of studies have shown that serum levels of IL-6 are increased in patients infected with HBV and are significantly higher in patients with severe acute infection than in patients with chronic active infection (2).

Table 3. Interleukin (IL)-1β, tumor necrosis factor-α and IL-6 serum levels and p values according to the fibrosis scores

	CHB (n=90)			CHC (n=40)		
	Mild fibrosis (stage 1-2)	Significant fibrosis (stage 3-4)	p value	Mild fibrosis (stage 1-2)	Significant fibrosis (stage 3-4)	p value
IL-1β	121.7±13.0	124.4±7.69	0.44	130.5±14.3	69.6±81.9	0.49
TNF-α	302.3±68.9	317.3±24.2	0.46	257.3±21.6	320.5±36.9	0.04
IL-6	54.0±12.9	51.2±4.69	0.50	57.7±6.65	48±5.65	0.38

Data were expressed as mean±standard deviation. CHB: Chronic hepatitis B, CHC: Chronic hepatitis C

It has been reported that IL-6 levels are high in autoimmune and chronic inflammatory diseases, and therefore IL-6 can be a good marker for disease progression associated with HBV. Various studies have shown that IL-6 can suppress HBV replication and inhibit HBV entry (6). Kuo et al. (19) demonstrated that IL-6 suppresses HBV proliferation in the HBV replication cell line. Hösel et al. (20) showed that IL-6 participates in the inhibition of HBV replication in hepatocytes, provides early control of the virus, and limits the adaptive immune response.

Many studies have shown that serum IL-6 levels increase in the progression of HBV disease. It has been reported that IL-6, the main immunomodulatory cytokine, plays an important role in CHB pathology and that increased levels of IL-6 are an index of increasing disease severity (21). In another study, it was stated that serum IL-6 levels were increased in HCV-infected patients compared to healthy controls (22). In this study, in accordance with the studies, IL-6 serum levels were higher in cases with CHB and CHC than in the control group and this was statistically significant (p=0.01).

Produced in the liver and many organs, TNF-α plays an important role in all types of viral hepatitis and participates in the regeneration of liver cells in CHC. Serum concentration increases significantly in chronic hepatitis (9). In many studies conducted with CHC patients, TNF-α concentration values were found to be significantly higher than in healthy individuals (23). Neuman et al. (24) found that serum TNF-α values were significantly higher in patients with CHB than in patients with CHB and in patients with CHB than in the control group.

Recent publications have observed high levels of TNF-a in the serum of HCV-infected patients. It has been reported that the increase in TNF-a levels may also cause an increase in other proinflammatory cytokines such as IL-6 in HCV infection (25). TNF-α levels increase in serum and liver tissues of patients with CHB and CHC infection (9). Some studies have found significant relationships between serum TNF-α levels and hepatic inflammation (4).

In this study, in accordance with the studies, serum levels of TNF-α were significantly higher in cases with CHB and CHC than in the control group (p=0.01). In addition, TNF-α was significantly higher in patients with CHC than those with significant fibrosis and those with mild fibrosis.

AFP is a marker used to predict HCC development not only in patients with cirrhosis but also in HCV-infected chronic hepatitis patients (26). In this study, the AFP levels of the patients with CHB were statistically significantly higher than in the patients with CHB (p=0.01) and the control group (p=0.01) (12).

The study has some limitations. There was no patient group with fibrosis 5 and 6 and HCC. The study had a small sample size, especially a few cases with KHC.

Conclusion

In conclusion, we found higher IL-1β, IL-6 and TNF-α levels in patients with CHB and CHC compared to healthy individuals. The findings suggest that these cytokines may play a role in chronicity and hepatic inflammation and immunosuppression, and may also affect the progression of CHB and CHC. Besides, circulating TNF-α level can be used for early detection of fibrosis and determining prognosis in cases with CHC. Nevertheless, these findings need to be explored in larger studies.

Ethics

Ethics Committee Approval: The study protocol was in accordance with the Helsinki Declaration of ethics and the study was approved by the Firat University Clinical Research Ethics Committee with the decision dated 14.12.2017 and numbered 05.

Informed Consent: Patients' informed consent was obtained with the form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ş., Design: A.Ş., N.Ö.A., Data Collection or Processing: A.Ş., Ö.A.S, N.Ö.A., Analysis or Interpretation: A.Ş., Ö.A.S, N.Ö.A, Literature Search: A.Ş., Writing: A.Ş.

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Hematological indices in congenital male hypogonadism and the effects of testosterone replacement therapy: a retrospective study

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ABSTRACT

Aims: Mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are surrogate markers of adverse cardiovascular (CV) outcomes. The aim of this study was to investigate the platelet count, MPV level, PLR, NLR, and the effect of testosterone replacement therapy (TRT) on these parameters in patients with congenital hypogonadotropic hypogonadism (CHH).

Methods: Young male patients with CHH and healthy controls were recruited from the outpatient setting. Blood pressures, height, weight, waist circumference (WC), and blood tests including triglyceride (TG) level, insulin, homeostatic model assessment-insulin resistance (HOMA-IR), PLR, and NLR were calculated between CHH patients and controls and following TRT.

Results: Sixty-six patients with CHH (mean age: 21.5±2.0 years) and 67 healthy controls (mean age: 21.9±1.3 years) were included in the study. CHH patients had higher platelet count (262.9±50.7 vs 232.1±49.2, p=0.001), MPV level (8.63±0.87 vs 8.16±0.92, p=0.004), PLR (114.01±25.68 vs 100.59±25.49, p=0.003), WC (86.8±9.1 vs 83.7±7.9, p=0.04), TG (96.0 vs 80.0, p=0.02), insulin (9.41 vs 6.92, p<0.001), and HOMA-IR (1.95 vs 1.47, p<0.001) than healthy controls. NLR was similar in both groups. After TRT, CHH patients showed significant elevations in body mass index, WC, total testosterone, and HOMA-IR and reduction in high density lipoprotein cholesterol level; however, platelet count, MPV, PLR, and NLR indices remained unchanged. Total testosterone level was also correlated with platelet count, MPV, and PLR.

Conclusions: This study showed higher platelet count and surrogate markers of CV risk such as MPV and PLR in patients with CHH. However, short time TRT did not show any effect on these indices.

Introduction

Patients with hypogonadism present with clinical findings of low testosterone levels such as low libido, loss of energy, depression, and muscle atrophy. In addition to fertility defects, the prevalence of type 2 diabetes, hypertension, and dyslipidemia is increased in patients with hypogonadism (1,2). Recent studies have also showed a relationship between low testosterone level and atherosclerosis, coronary artery disease, or cardiovascular (CV) events (3,4). Inflammation and thrombosis have important roles in the pathogenesis of atherosclerosis and CV diseases (CVD) (5). Testosterone deficiency is associated with metabolic profiles that are known to be associated with atherosclerosis such as high glucose, low

density lipoprotein cholesterol (LDL-Chol) and pro-inflammatory cytokine levels and low high density lipoprotein cholesterol (HDL-Chol) and anti-inflammatory cytokine levels (6). However, the mechanism of increased atherosclerosis and CVD risk in patients with hypogonadism is still unknown.

The hematological indices, mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and neutrophil-to-lymphocyte ratio (NLR) are surrogate markers of adverse CV outcomes. MPV is a new CV risk factor, which is considered to be a simple marker of platelet size and activation (7). Metabolically and enzymatically more active larger platelets have higher thrombotic potential. Elevated MPV level is reported in coronary artery disease and in many other diseases such as hypertension, diabetes and hypercholesterolemia (8,9). Platelets have a critical role in emerging of atherosclerosis. There is an association between elevated blood platelet counts and CVD. Also, previous studies reported an association between lymphopenia and CVD. The ratio of the platelet to lymphocyte count, PLR is a prognostic marker in different types of CVD (10-12). Similarly, NLR is also a novel marker of inflammation, and is reported to be associated with adverse cardiac outcomes (11,13).

All of these hematological indices are inexpensive, easy to obtain, and widely available markers of adverse cardiac outcomes. However, there are limited data about the levels of these parameters in patients with congenital hypogonadism. It is also unknown whether the testosterone replacement therapy (TRT) affects these hematological parameters. Therefore, in this retrospective study, we aimed to investigate the platelet count, MPV level, PLR, and NLR in patients with hypogonadism and also study the effect of TRT on these indices.

Methods

Study Design and Patient Selection

This retrospective analysis was performed using the database of an endocrinology unit of a tertiary hospital. Male patients with the diagnosis of congenital hypogonadotropic hypogonadism (CHH), who were 18 years old or over and never received TRT or human chorionic gonadotropin, were identified and included in the analyses. Patients under 18 years old or who had pituitary mass lesions in magnetic resonance imaging or had laboratory values consistent with panhypopituitarism or who had any other chronic metabolic disorder and/or organ dysfunction were excluded. The stage of pubertal development (Tanner's stage), serum level of total testosterone, follicle stimulating hormone (FSH) and luteinizing hormone (LH) were obtained from the database. The subjects in the control group were selected from the previous studies performed on this database (14,15). Control subjects did not have chronic disorders and were not taking any drug treatment. Also, none of the patients or control subjects had any signs of infection or had a history of any medication known to influence platelet function at least 2 weeks (e.g., acetylsalicylate, antiepileptics, or heparin) before study initiation. The Local Ethical Committee of University of Health Sciences Turkey Gülhane Faculty of Medicine approved the study (code: 16.06.2016, 50687569-1491-440-16/1648-1562).

Definitions

The methods for the assessment of anthropometric and laboratory variables in the database were as follows; height, weight, and waist circumference (WC) were measured while wearing underwear. After exhalation, WC was measured from the line on the iliac crest parallel to the ground. Body mass index (BMI) was computed as the ratio of weight to the square of height (kg/m^2). Arterial blood pressures were measured two times by a mercury column sphygmomanometer with appropriate-size cuff after a resting period of at least 5 min. The average of the measurements was recorded as the systolic and diastolic blood pressures of the patients and controls. The anthropometric measurements and laboratory values at three and/or six-month follow-up of treatment were retrieved from the database.

The venous blood samples of the patient and control groups were collected between 08:00 and 09:00 h after an overnight fasting and were stored at -80 °C after centrifugation for 15 min. Complete blood count was obtained using the Olympus AU-2700 autoanalyzer (GmbH). Fasting plasma glucose, total cholesterol, triglyceride (TG), and HDL-Chol level were measured by the enzymatic colorimetric method, and serum basal insulin, total testosterone, FSH and LH level were measured by the chemiluminescence method. LDL-Chol level was calculated with the Friedewald formula. For the enzymatic calorimetric analyses Olympus AU-2700 autoanalyzer (Hamburg, Germany), and chemiluminence analyses UniCel DxI 800 Access Immunoassay System (Miami, FL, USA) was used. Insulin sensitivity was calculated by the homeostatic model assessment-insulin resistance (HOMA-IR) using the following formula: HOMA-IR=[insulin (mU/mL) × glucose (mg/dL)] / 405.

Testosterone Replacement Therapy

Patients who received TRT (injectable or transdermal) for at least six months were included in the analyses. The injectable regimen was an oil-based injectable blend of four esterized testosterone compounds (™Sustanon 250 mg; testosterone Propionate of 30 mg, testosterone phenylpropionate and testosterone isocaproate of 60 mg, and testosterone decanoate of 100 mg) injected once every 21 days. The transdermal regimen was a once daily testosterone gel formula (testogel 50 mg gel). Laboratory tests in the database were performed using the blood samples collected before the first testosterone administration as the baseline metabolic parameters.

Table 1. The demographic and metabolic parameters of the patients with congenital hypogonadotrophic hypogonadism and the healthy control subjects

Variables	Healthy controls (n=67)	Patients (n=66)	Patients after treatment (n=66)	p1*	p2*
Age, (yr), mean±SD	21.9±1.3	21.5±2.0	-	0.24	-
BMI, (kg/m²), mean±SD	23.9±2.6	23.2±2.6	24.6±2.9	0.11	**<0.001**
WC, (cm), mean±SD	83.7±7.9	86.8±9.1	89.1±8.9	**0.04**	**0.001**
FBG, (mg/dL), mean±SD	85.2±12.6	85.4±7.3	86.5±7.3	0.94	0.51
TG, (mg/dL), mean±SD	80.0 (55.0-109.0)	96.0 (65.2-132.5)	95.5 (72.0-136.0)	**0.02**	0.54
HDL-Chol, (mg/dL), mean±SD	47.3±8.4	46.7±9.7	40.7±9.3	0.71	**<0.001**
LDL-Chol, (mg/dL), mean±SD	94.3±23.2	89.9±21.9	87.0±20.3	0.29	0.22
FSH, (mIU/mL), mean±SD	3.1±2.38	0.74±0.61	0.81±1.30	**<0.001**	0.58
LH, (mIU/mL), mean±SD	4.3±1.58	0.43±0.54	0.57±0.93	**<0.001**	0.05
T.Testosterone, (ng/dL), mean±SD	517.0±120.1	28.5±18.5	230.2±206.4	**<0.001**	**<0.001**
Insulin, (µU/mL)[a] median (min.-max.)	6.92 (5.09-8.74)	9.41 (6.83-14.39)	11.6 (6.8-14.9)	**<0.001**	0.53
HOMA-IR[a], median (min.-max.)	1.47 (0.95-1.93)	1.95 (1.47-2.88)	2.36 (1.41-3.30)	**<0.001**	**0.03**
Platelet count, x10³, cells/µL, mean±SD	232.1±49.2	262.9±50.7	257.2±52.2	**0.001**	0.39
MPV, (fL), mean±SD	8.16±0.92	8.63±0.87	8.79±0.91	**0.004**	0.14
PLR, mean±SD	100.59±25.49	114.01±25.68	110.86±37.44	**0.003**	0.45
NLR, mean±SD	1.57±0.79	1.57±0.53	1.54±0.66	0.96	0.61

Data were expressed as mean±standard deviation or median (minimum-maximum).*Pearson's correlation (p1: between healthy controls and patients; p2: between before and after testosterone replacement).
BMI: Body mass index, WC: Waist circumference, FBG: Fasting blood glucose, TG: Triglyceride, HDL-Chol: High-density lipoprotein cholesterol, LDL-Chol: Low-density lipoprotein cholesterol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, T. Testosterone: Total testosterone, HOMA-IR: Homeostatic model assessment for insulin resistance, MPV: Mean platelet volume, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio, yr: Year

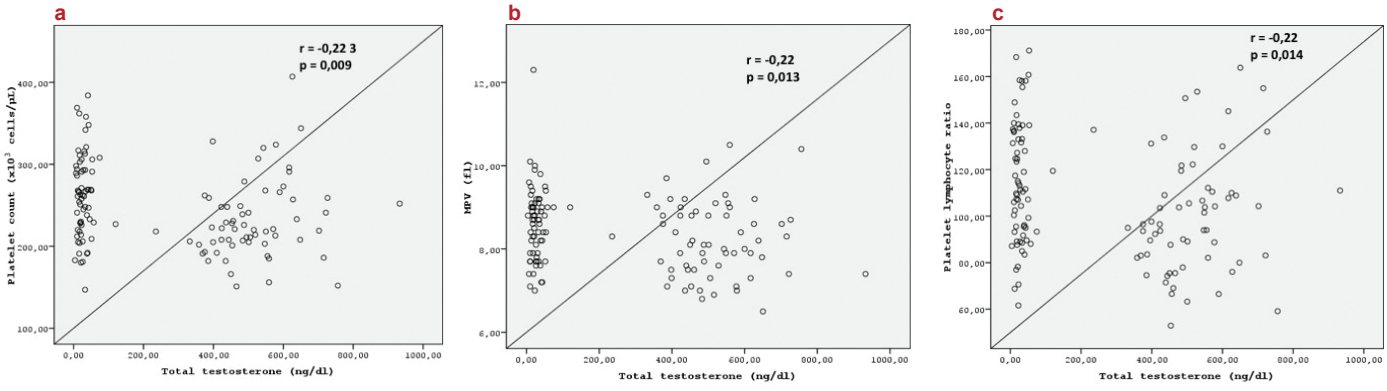

Figure 1. Scatter plot diagrams of correlation between total testosterone and platelet count (a), mean platelet volume (b) and platelet-to-lymphocyte ratio (c)

Statistical Analysis

The statistical analyses were performed by Statistical Package for the Social Sciences version 18.0 (Chicago, IL, USA). Results were expressed as mean±standard deviation or median (minimum-maximum). The Kolmogorov-Smirnov test was used for normality assessments, and the Levene's test was used to evaluate the equality of variance. While the Student's t-test and Mann-Whitney U test were used for inter-group differences as appropriate, paired samples t-test was used for intra-group changes at two time points. Relationships among MPV level, PLR, NLR, and clinical and biochemical parameters were evaluated by the Pearson correlation coefficient. Stepwise multiple regression analysis was performed to test whether MPV level, PLR, and NLR were independently associated with the total testosterone level. Differences were considered significant at $p<0.05$.

Results

A total of 66 treatment-naïve young male patients with CHH (mean age: 21.5±2.0 years) and a group of 67 healthy male subjects matched for age and BMI (mean age: 21.9±1.3 years) were included. The demographic and biochemical characteristics

Table 2. The correlation analysis between platelet count, mean platelet volume levels, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio and clinical and biochemical parameters

Variables	Platelet count		MPV		PLR		NLR	
	r*	p*	r*	p*	r*	p*	r*	p*
WC (cm)	0.02	0.85	**0.21**	**0.02**	-0.13	0.13	-0.05	0.58
BMI (kg/m²)	-0.07	0.46	0.10	0.23	**-0.21**	**0.02**	-0.14	0.12
HDL-Chol (mg/dL)	0.06	0.51	-0.03	0.73	0.07	0.40	-0.06	0.49
Triglyceride (mg/dL)	0.05	0.60	-0.002	0.98	-0.07	0.43	0.04	0.67
Insulin (µU/mL)	0.11	0.21	**-0.18**	**0.04**	0.06	0.54	-0.01	0.91
HOMA-IR	0.12	0.18	-0.18	0.055	0.05	0.57	-0.02	0.86
FSH (mIU/mL)	-0.15	0.10	**-0.29**	**0.001**	**-0.24**	**0.008**	-0.09	0.32
LH (mIU/mL)	**-0.21**	**0.02**	**-0.30**	**0.001**	**-0.24**	**0.008**	0.04	0.63
Total testosterone (ng/dL)	**-0.23**	**0.009**	**-0.22**	**0.013**	**-0.22**	**0.014**	0.01	0.87

*Pearson's correlation.
WC: Waist circumference, BMI: Body mass index, HDL-Chol: High-density lipoprotein cholesterol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, HOMA-IR: Homeostatic model assessment for insulin resistance, MPV: Mean platelet volume, PLR: Platelet-to-lymphocyte ratio, NLR: Neutrophil-to-lymphocyte ratio

of the patients and control subjects were shown in Table 1. WC (p=0.04), TG (p=0.02), insulin (p<0.001), HOMA-IR (p<0.001), platelet count (p=0.001), MPV (p=0.004), and PLR (p=0.003) were significantly higher, and FSH, LH, and total testosterone (p<0.001) level were significantly lower in patients with CHH than in healthy controls.

After 5.9±2.1 months of follow-up with TRT, CHH patients had significantly elevated BMI, WC, total testosterone, and HOMA-IR (p<0.001, p=0.001, p<0.001, and p=0.03, respectively) and decreased HDL-Chol level (p<0.001); however, changes in platelet count, MPV level, PLR, and NLR were not significant.

Among the CHH patients, platelet count correlated negatively with LH (r=-0.21, p=0.02) and total testosterone level (r=-0.23, p=0.009) (Figure 1a). MPV level positively correlated with WC (r=0.21, p=0.019) and negatively correlated with insulin (r=-0.18, p=0.04), FSH (r=-0.29, p=0.01), LH (r=-0.30, p=0.01) and total testosterone level (r=-0.22, p=0.013) (Figure 1b). PLR negatively correlated with LH (r=-0.24, p=0.008), FSH (r=-0.24, p=0.008), BMI (r=-0.21, p=0.02), and total testosterone level (r=-0.22, p=0.014) (Figure 1c) (Table 2).

Discussion

The results of the present study showed that platelet count, MPV level, and PLR were significantly higher in treatment naïve young patients with CHH. There was also a significant association between these parameters and total testosterone level. In addition, there was no effect of TRT on the platelet count, MPV level, PLR, and NLR. These results may reflect platelet activation in patients with hypogonadism.

The risk of CVD is increased in patients with hypogonadism (16). Patients with type 2 diabetes, metabolic syndrome, and CVD also have low testosterone level (17,18). Therefore, it seems that there is a mutual link between hypogonadism and cardiometabolic diseases. Furthermore, several physiological factors including aging (19), obesity (20), and commonly used medications (21) may also confound the relationship between hypogonadism and cardiometabolic diseases. For this reason, we enrolled the young treatment naïve patients with CHH, who did not have other chronic diseases. In a previous study, we have reported that these patients have metabolic derangements such as visceral obesity and dyslipidemias at a very young age (15,22). Similarly, in the present study, higher WC, TG, and HOMA-IR level in patients with CHH indicated the metabolic derangements in these patients and supported our previous results. However, the precise mechanism of this increased CV risk in patients with hypogonadism remains unclear.

Platelets have a crucial role in the emergence of atherosclerosis. It is reported that there is an association between higher platelet count and adverse outcomes (23). MPV is a simple marker of platelet size and reactivity (24) and its increased level is considered to be a CV risk factor (7,25). Larger platelets are metabolically more active than smaller ones and have higher thrombotic potential. Larger platelets contain more granules and higher thromboxane A2 level and also express more glycoprotein 1b and 2b/3a receptors. Increased MPV levels are reported in different types of CVD. MPV level is increased in patients with coronary artery disease (7) and are also reported to be associated with the severity of atherosclerosis. Shah et al. (26) also showed that MPV was strongly and independently associated with the presence and severity of diabetes. In addition, several studies have showed that MPV level is increased in all subtypes of ischemic stroke (7). In our study, we also found increased platelet count and MPV level in patients with CHH. In addition, there was also negative correlation between total testosterone level and platelet count and MPV level. These findings imply that patients with CHH are susceptible to increased platelet activation even at a young

age. Our results are consistent with the study of Carlioglu et al. (27) that showed elevated MPV level in patients with idiopathic hypogonadotropic hypogonadism. We also showed increased platelet count and metabolic derangements such as increased WC, TG, and HOMA-IR level.

PLR is also considered a new marker of CV risk. Elevated PLR indicates a state of activated hemostasis that leads to adverse CV events (10,11). Similar to platelets, white blood cells also play an important role in the pathogenesis of CVD. It is showed that higher neutrophil counts were related to increased atherosclerosis severity in coronary artery disease. NLR, a new inflammatory biomarker for CVD, is associated with severity and prognosis of CVD (28). This is the first study to evaluate PLR and NLR in patients with CHH. We found that PLR was elevated in patients with CHH, whereas NLR was not different between patients with CHH and the healthy controls. When PLR is considered to be a CV risk marker, these results may indicate that platelets, but not neutrophils, may play a crucial role in the pathogenesis of increased CV risk in patients with hypogonadism.

TRT is an emerging treatment option for the metabolic abnormalities in patients with hypogonadism. However, there are controversial data and growing skepticism about the effect of TRT on the improvement of the patient's cardiometabolic risk. Some studies report that TRT improves metabolic parameters (29,30), whereas other studies report increased CV events in patients with hypogonadism under TRT (31,32). However, so far there has been no randomized placebo-controlled prospective study which has investigated the long-term CV effects of TRT in patients with hypogonadism. Therefore, measuring the surrogate marker of CV risk is an alternate way to evaluate the CV effects of TRT in patients with hypogonadism. In the present study, we found no effect of TRT on the whole blood count indices such as platelet count, MPV level, PLR, or NLR, which are surrogate markers of CV risk. This study showed that patients with CHH had worse platelet functions than healthy controls. However, approximately six months of TRT do not improve poor platelet function in patients with CHH. Moreover, TRT led to poor metabolic control such as increased BMI, WC, and HOMA-IR level and decreased HDL-Chol level. TRT may ignite pubertal growth in these young patients, which is not seen in elderly hypogonadal patients of etiologies. This may partly explain the rapid increase in BMI and WC and poor metabolic control. Therefore, our results do not support the studies showing that TRT improves CV outcomes (29,30). The short time of TRT or the retrospective nature of our study may be the reason of these conflicting results.

This study may have both limitations and strengths. First, the retrospective design of the study does not allow a causal relationship. Also, the specific population of young treatment naïve patients included in the analyses may not adequately represent all hypogonadism patients. In addition, the small sample size and relatively short duration of follow-up precludes further mechanistic comments. On the other hand, the study population is unique for the fact that it is very uncommon to identify untreated CHH patients until adult age. The homogeneous study population of young male patients, and the lack of confounding factors such as chronic metabolic disorders and concomitant medications can be counted among the strengths of this study.

Conclusion

The results of the present study showed that the platelet count and surrogate markers of CV risk such as MPV level and PLR were significantly increased in patients with CHH. Moreover, the short time TRT in young treatment naïve patients with CHH showed no effect on the platelet count and size. Future prospective, randomized controlled studies are warranted to clarify the role of platelet functions in the pathogenesis of increased CV risk in patients with hypogonadism.

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Ethics

Ethics Committee Approval: The Local Ethical Committee of University of Health Sciences Turkey Gülhane Faculty of Medicine approved the study (date: 16.06.2016, approval date: 50687569-1491-440-16/1648-1562).

Informed Consent: Retrospective study.

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Authorship Contributions

Design: C.H., O.A., A.S., Data Collection or Processing: İ.D., O.D., C.M., Analysis or Interpretation: İ.D., C.H., A.A., Literature Search: İ.D., O.A., C.M., A.A., Writing: İ.D., C.H., A.S.

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Lactate kinetics in intensive care unit admissions due to diabetic ketoacidosis

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ABSTRACT

Aims: We conducted this study to investigate the clinical significance of lactate kinetics in patients admitted to the intensive care unit (ICU) for diabetic ketoacidosis (DKA).

Methods: This retrospective study was conducted between November 1, 2016, and December 31, 2020. Serial lactate measurements (at the hospital admission, ICU admission, and in 24 hours periods until 48 hours of ICU stay) of the patients admitted to our ICU with a diagnosis of DKA were recorded.

Results: Forty patients were included in the study (mean age: 50.6±19.4 years, female 60%). Eighty-five percent (n=34) of patients had increased (>2 mmol/L) blood lactate levels on admission. There was no significant difference between the low (lactate <4 mmol/L) and high-lactate (lactate ≥4 mmol/L) groups in mortality (p=0.195), ICU stay (p=0.966) and hospital length of stay (LOS) (p=0.274). However, the group with less than 40% decrease in lactate level from hospital admission to ICU had significantly higher Acute Physiology and Chronic Health Assessment II score [24 (12-46) vs. 18 (2-27), p=0.007], longer ICU stay [5 (1-40) vs. 3 (2-8) days, p=0.032], and higher mortality rate [6 (26.1) vs. 0 (0.0), p=0.030]. Additionally, non-survivors (n=6) had significantly higher lactate levels at hospital admission [3.0 (1.3-15.0) vs. 5.1 (3.9-13.5) mmol/L, p=0.017], and ICU admission [2.3 (0.6-9.4) vs. 5.0 (2.4-16.0) mmol/L, p=0.010] than survivors.

Conclusions: Although the ICU LOS and mortality did not differ between initial high and low-lactate groups in the present study, the lactate kinetics, especially in the early treatment period, can guide referral to the ICU level of care and determine the DKA patients at higher risk of death.

Introduction

Diabetic ketoacidosis (DKA) is primarily characterized by hyperglycemia, ketonemia, and acidosis with an increased anion gap. The number of cases with DKA has been increasing in the last two decades (1,2). The mortality rate of DKA varies across the world due to psychosocial and economic diversities; mainly, it has been reported as less than 1% (3,4). Although the risk of death is low, intensive care units (ICU) are still the places where these patients are primarily treated, and the prolongation of the ICU stays leads to an increase in hospital costs and ICU overcrowding. In addition, there are no specific criteria for determining whether the patients with DKA should be treated in the ICU or not.

Increased blood lactate concentration, a significant prognostic predictor for many clinical conditions in critically ill patients, is also typical in patients with DKA (5). This may occur due to impaired glucose metabolism with hypoperfusion and poorly understood mechanisms such as the glyoxal pathway and alternative energy substrate in DKA. In addition, there are still controversies regarding the role of increased lactate levels in the course of DKA. Unfortunately, there are insufficient data to suggest that the lactate kinetics in DKA patients may help evaluate treatment response over time and ICU outcomes (6).

This study investigated the clinical significance of lactate kinetics in patients admitted to ICU for DKA.

Methods

Study Population

This retrospective study included patients with DKA hospitalized in the medical ICU between November 01, 2016 and December 31, 2020. The study was approved by the Gülhane Faculty of Medicine, Local Ethics Committee (number: 2020/504, date: 16.06.2016) and performed following the Helsinki Declaration. Patients who had (1) plasma glucose level greater than 250 mg/dL, (2) presence of ketone in serum (3 mmol/L) or urine (≥2+), and (3) plasma bicarbonate level less than or equal to 18 mEq/L and/or blood pH less than or equal to 7.30 were included. Patients under 18 years of age and those found to have other causes of lactic acidosis, such as convulsions, use of linezolid or antiretroviral agents, were excluded.

Data Collection

Demographic characteristics (age, sex), history and type of diabetes mellitus (DM) (type 1 or 2), precipitants for DKA, history of metformin use, comorbidities, and Acute Physiology and Chronic Health Assessment (APACHE) II scores which calculated in the first day of ICU admission were recorded. Systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure at the ICU admission were obtained. Additionally, arterial blood gas analysis results (pH, lactate, HCO_3 levels), plasma glucose and other laboratory data at hospital admission, hemoglobin A1c (HbA1c) (glycosylated hemoglobin) levels measured during the hospital stay or in the last three months before hospital admission were obtained. Hospital length of stay (LOS), ICU LOS, and in-hospital mortality were recorded.

Patients were grouped into two as low (lactate <4.0 mmol/L) and high-lactate (lactate ≥4.0 mmol/L) on admission. Additionally, the serial measurements of lactate levels in 24 hours periods until 48 hours of ICU stay, or ICU discharge, whichever came first, were recorded. Laboratory data including plasma glucose, pH, bicarbonate, sodium, and osmolality measured simultaneously with lactate screening (at hospital admission, ICU admission, 24^{th} hr, 48^{th} hr of ICU stay) were obtained.

As there are no published data on the optimal ratio of decrease in lactate levels to predict response to treatment and/or prognosis in patients with DKA, and the magnitude of lactate reduction following treatment is highly variable in different patient populations (7), we defined a 40% decrease in lactate levels as the threshold in the early treatment period (between hospital and ICU admissions) for prognosis prediction. Thus, the patients were grouped into two by 40% or higher decrease in lactate levels from hospital admission to ICU admission. Two previous studies strengthen the feasibility of this approach. Walker et al. (8) suggested a cut-off level of 36% in lactate clearance in the first 6 hours of treatment for mortality prediction in severe sepsis and septic shock patients who were referred to ICU from the emergency department (ED). In another study, Hernandez et al. (9) reported a >50% decrease in lactate levels in the first 6 hours of resuscitation in patients with septic shock. The time (hours) between these two analyses was recorded. The two groups were compared for mortality, APACHE II score, ICU, and hospital LOS.

Statistical Analysis

Distribution normality for continuous variables was determined by the Shapiro-Wilk test, skewness and kurtosis coefficients, and histogram graphics. The mean (standard deviation) was used to represent parametric continuous variables, and the median (minimum-maximum) was used to represent nonparametric continuous variables. Categorical variables were expressed as numbers (percentage distributions). Independent samples t-test was used to compare parametric variables, and the Mann-Whitney U test was used to compare nonparametric variables. The chi-square test or Fisher's exact test was used for the comparison of categorical variables. Correlations were tested using the Spearman correlation analysis. $P<0.05$ was considered statistically significant. The data analysis was performed using the IBM Statistical Package for Social Sciences statistics 25.0 (IBM.Corp., Armonk, NY, 2017).

Results

There were 43 patients with the diagnosis of DKA. After excluding three patients due to missing data, the study population included 40 patients. The mean age of patients was 50.6±19.4 (19-81) years, and 24 (60%) patients were female. While 15 (37.5%) patients had type 1 DM, 25 (62.5%) patients had type 2 DM. The poor compliance with the treatment (n=25, 62.5%) was identified as the most common precipitating factor, followed by infections (n=10, 25%), newly diagnosed DM (n=1, 2.5%) and other causes (n=4, 10%). Two patients had chronic kidney disease that did not require renal replacement therapy, and three patients had advanced stage malignancy without hepatic involvement. Eighteen patients had been prescribed oral metformin before admission. The median ICU and hospital LOS were 4.0 (1.0-40.0) and 9.0 (2.0-77.0) days, respectively. The overall mortality rate was 15% (n=6).

Eighty-five percent (n=34) of patients have increased lactate levels (>2 mmol/L) on admission. High lactate levels (lactate ≥4 mmol/L) were observed in 16 (40%) of patients. The comparison of demographic, clinical, and laboratory data of low-lactate and high-lactate groups are presented in Table 1. There was no significant difference between the two groups in terms of age, gender, APACHE II score, type of DM, metformin use, blood pressures at ICU admission, duration of DM, glucose, pH, bicarbonate, sodium, urea, creatinine, leukocyte count, hemoglobin, platelet, C-reactive protein, procalcitonin, aspartate

Table 1. Comparison of the diabetic ketoacidosis patients according to lactate levels at hospital admission

Variables	Low-lactate <4.0 mmol/L n=24 (60.0%)	High-lactate ≥4 mmol/L n=16 (40.0%)	p value
Age, years, median (min.-max.)	51.5 (19-81)	53 (19-80)	0.413ᵞ
Gender, female, n (%)	16 (66.7)	8 (50.0)	0.469ᵅ
Type of DM, n (%)			0.739ᵅ
Type 1	10 (41.7)	5 (31.3)	
Type 2	14 (58.3)	11 (68.8)	
Metformin use, n (%)	11 (45.8)	7 (43.8)	1.000ᵅ
APACHE II, median (min.-max.)	18.0 (2-46)	22.5 (12-41)	0.078ᵞ
Blood pressures, mmHg			
Systolic, mean±SD	121.2±17.1	120.7±24.0	0.939ᵝ
Diastolic, median (min.-max.)	66.5 (32.0-79.0)	68.5 (45.0-89.0)	0.171ᵞ
Mean, mean±SD	84.3±10.8	87.1±13.3	0.467ᵝ
HbA1c ¶, %, mean±SD	12.5±2.4	10.6±1.5	**0.029ᵝ***
Duration of DM§, years, median (min.-max.)	10.0 (0.0-39.0)	8.0 (2.0-45.0)	0.510ᵞ
pH, mean±SD	7.10±0.1	7.12±0.1	0.658ᵝ
Glucose level, mg/dL, median (min.-max.)	563.0 (159.0-1378.0)	397.0 (161.0-837.0)	0.050ᵞ
Bicarbonate, mEq/L, median (min.-max.)	5.7 (2.1-21.9)	9.7 (2.4-32.3)	0.136ᵞ
Sodium, mmol/L, mean±SD	130.0±7.8	133.9±4.6	0.091ᵝ
Osmolality, mOsm/kg, median (min.-max.)	300.7 (263.1-352.7)	304.6 (287.7-349.6)	0.890ᵞ
Hemoglobin, g/dL, mean±SD	13.3±2.2	12.8±2.7	0.582ᵝ
WBC, x10^3/mm^3, mean±SD	16.0±6.7	16.9±6.3	0.657ᵝ
Platelet, x10^3/mm^3, median (min.-max.)	296.0 (47.0-652.0)	335.5 (181.0-559.0)	0.194ᵞ
Urea, mg/dL, median (min.-max.)	53.5 (21.0-240.0)	48.5 (31.0-216.0)	0.720γ
Creatinine, mg/dL, median (min.-max.)	1.15 (0.73-6.40)	1.42 (0.64-13.0)	0.782γ
Albumin, g/dL, mean±SD	3.34±0.66	3.45±0.70	0.637ᵝ
AST, U/L, median (min.-max.)	20.5 (5.0-119.0)	26.5 (8.0-407.0)	0.240ᵞ
ALT, U/L, median (min.-max.)	14.0 (4-43)	21.5 (0-309)	**0.047ᵞ***
Bilirubin (total), mg/dL, median (min.-max.)	0.51 (0.10-4.30)	0.49 (0.10-3.90)	0.841ᵞ
CRP, mg/L, median (min.-max.)	56.63 (0.44-421.80)	30.78 (2.50-190.00)	0.773ᵞ
Procalcitonin, ng/mL, median (min.-max.)	0.70 (0.01-16.35)	1.34 (0.02-249.00)	0.256ᵞ
ICU LOS, days, median (min.-max.)	4.0 (1.0-22.0)	3.5 (2.0-40.0)	0.966ᵞ
Hospital LOS, days, median (min.-max.)	9.0 (2.0-43.0)	7.5 (2.0-77.0)	0.274ᵞ
In hospital mortality, n (%)	2 (8.3)	4 (25.0)	0.195ᵈ

ᵅChi-square test, ᵝIndependent samples t-test, ᵞMann-Whitney U test, ᵈFischer's Exact test, *=p<0.05, ¶A total of 28 patients (18 in low lactate group 10 in high lactate group) with available HbA1c levels included in the analysis.
§A total of 26 patients (16 in low lactate group, 10 in low lactate group) with available DM history included in the analysis.
DM: Diabetes mellitus, APACHE II: Acute Physiology and Chronic Health Evaluation II, WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, CRP: C-reactive protein, ICU: Intensive care unit, LOS: Length of stay, min.-max.: Minimum-maximum, SD: Standard deviation

aminotransferase, total bilirubin levels, serum osmolality, ICU and hospital LOS or mortality. However, the patients in high-lactate group had significantly lower HbA1c (12.5±2.4 vs. 10.6±1.5%, p=0.029) and higher alanine aminotransferase levels [14.0 (4.0-43.0) vs. 21.5 (0.0-309.0) U/L, p=0.047] than patients in low-lactate group.

The serial change of lactate levels of the survivors (n=34) and non-survivors (n=6) over time is presented in Figure 1. The median lactate levels were [3.0 (1.3-15.0) vs. 5.1 (3.9-13.5) mmol/L, p=0.017] in survivors and in non-survivors on admission, [2.3 (0.6-9.4) vs. 5.0 (2.4-16.0) mmol/L, p=0.010] at ICU admission, [1.3 (0.3-3.5) vs. 1.4 (0.9-11.8) mmol/L, p=0.425] at the 24th hour of the ICU stay, and [1.3 (0.5-4.7) vs. 1.6 (0.7-5.4) mmol/L, p=0.370] at the 48th hour of the ICU stay, respectively.

In patients with or without %40 or more decrease in lactate levels, there was no significant difference in time from hospital admission to ICU admissions (2.25 vs 3.22 hours, p=0.556). However, the group with less than 40% decrease in lactate levels

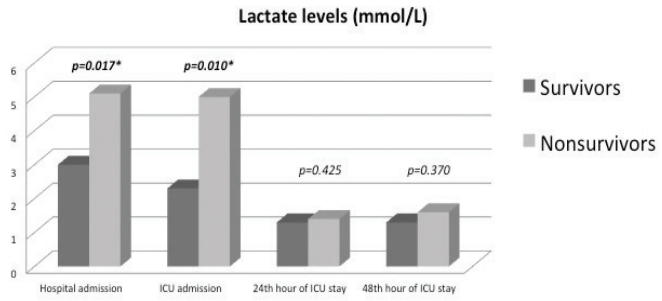

Figure 1. The serial change of lactate levels of survivors and non-survivors over time
ICU: Intensive care unit

Table 2. Comparison of the diabetic ketoacidosis patients according to decrease of lactate levels by ≥40% from hospital admission to intensive care unit admission

	Total n=40	Decrease in lactate <40% n=23 (57.5%)	Decrease in lactate ≥40% n=17 (42.5%)	p value
Time between hospital and ICU admission, hours, median (min.-max.)	2.82 (0.47-76.37)	2.25 (0.47-39.87)	3.22 (0.60-76.37)	0.556[α]
APACHE II, median (min.-max.)	18 (2-46)	24 (12-46)	18 (2-27)	**0.007[α],***
ICU LOS, days, median (min.-max.)	4 (1-40)	5 (1-40)	3 (2-8)	**0.032[α],***
Hospital LOS, days, median (min.-max.)	9 (2-77)	11 (2-43)	8 (2-77)	0.329[α]
In hospital mortality, n (%)	6 (15)	6 (26.1)	0 (0.0)	**0.030[β],***

[α]Mann-Whitney U test, [β]Fischer's Exact test, *=p<0.05.
ICU: Intensive care unit, APACHE II: Acute Physiology and Chronic Health Evaluation II, LOS: Length of stay, min.-max.: Minimum-maximum

had significantly higher APACHE II score [24 (12-46) vs 18 (2-27), p=0.007], longer ICU stay [5 (1-40) vs 3 (2-8) p=0.032], and higher mortality rate [26.1 (6) vs 0 (0.0), p=0.030] (Table 2).

In correlation analysis, low to moderate significant correlations were found between the initial lactate level and APACHE II score (r=0.336, p=0.034) and HbA1c level (r=-0.493, p=0.008). However, there was no correlation between the initial lactate level and ICU LOS (p=0.211), hospital LOS (p=0.603), systolic, diastolic and mean arterial blood pressures (p=0.758, p=0.659 and p=0.268, respectively), glucose (p=0.090), pH (p=0.838), bicarbonate (p=0.456), osmolality (p=0.844), and other laboratory tests (not shown).

Discussion

We hypothesized in the present study that serial changes in lactate level might be more informative than a single admission level in DKA patients. In parallel with previous data (5), there was no difference in mortality and ICU LOS between the on admission high and low-lactate groups in our study. However, it was shown that there was no death among patients who showed more than 40% decrease in lactate level within the median 3.22 hours before the ICU admission. It was also observed that these patients stayed for a shorter period in the ICU than the patients who could not achieve this decrease. Therefore, it can be thought that decreasing lactate levels in DKA patients, especially in the ED, may help predict the prognosis and decide on the unit (ICU, ED, or general medical ward) where the patient will be managed.

DKA is a common complication of DM, and it constitutes up to 28% of diabetes-related hospital admissions (10). Many DKA patients are still being treated in ICUs. The main reasons for this preference are the presence of varying degrees of metabolic acidosis, frequent monitoring requirements for blood gas, vital signs, urine output, and serum electrolyte level, and the necessity of intravenous insulin infusion (10-12). However, overcrowding of ICU beds and increased hospital costs must be considered when selecting the ICU level of care to treat these patients. In a study by Marinac and Mesa (13), DKA patients were retrospectively grouped in five severity grades using diastolic blood pressure and some laboratory data (serum bicarbonate, osmolality, anion gap, and base excess). According to their scoring system, the authors reported that more than one-third of all DKA admissions to the ICU were not appropriate in this cohort.

Additionally, previous studies showed that these patients, especially with non-severe DKA, could be safely managed in non-ICU settings such as ED and general medical wards (14-16). Nevertheless, the exact criteria for deciding which patient with DKA should be admitted to the ICU have not been fully established yet. The lactate kinetics in the early period of DKA treatment may help this decision.

The inadequate tissue perfusion due to volume depletion was considered the leading cause of elevated lactate levels in DKA patients. Consequently, relative hypoxemia causes an increase in lactate levels by stimulating anaerobic glycolysis (17,18). However, there was no difference in blood pressures between initial high and low-lactate groups in the current study. As explained above, it is thought that tissue hypoxia may not be the only mechanism responsible for elevated lactate levels in DKA patients. Previously, Cox et al. (5) reported a positive correlation between serum lactate and glucose levels in patients with DKA. This finding may indicate a relationship between lactate levels and altered glucose metabolism. On the contrary,

no correlation was found between initial lactate and glucose levels in the current study, and even a negative correlation was found between HbA1c and lactate levels.

The reason for the increase in intra-erythrocyte glucose during DKA is that erythrocytes do not need insulin for glucose uptake. The increased intra-erythrocyte glucose is converted first to pyruvate and then to L-lactate through aerobic glycolysis. The remaining amount of glucose is first transformed into methylglyoxal and then to D-lactate with the glyoxalase system. This system also allows the formation of D-lactate in plasma during DKA (19-21). Lu et al. (21) reported that D-lactate levels increased significantly with increased methylglyoxal production during DKA and that high D-lactate levels were significantly correlated with a rising anion gap and decreased bicarbonate levels and thus were associated with DKA severity. The lactate formed during DKA can be used for gluconeogenesis and can be directed to other tissues as an alternative energy substrate due to cellular glucose deficiency. This can be attributed to another mechanism that stimulates the activity of muscle Na+/K+ pumps via the increased catecholamine production due to stress and insulin deficiency in DKA (22,23). As a result, lactate, which increases as an alternative energy substrate for tissues during DKA, can be expected to decrease after the administration of insulin infusion. Therefore, it can be thought that the decrease in lactate level with the initiation of treatment in DKA patients is not only due to rehydration but also due to the decrease in the need for energy substrate with the initiated insulin infusion. The serial measurements of lactate levels may thus be more informative than a single measurement in DKA patients. A systematic review by Vincent et al. (7) on lactate kinetics in critically ill patients suggested that assessing lactate kinetics at 1-2 hour intervals may be more predictive for mortality than baseline values. This recommendation may also be helpful for DKA patients.

The mortality rate in adult DKA patients varies across the world. In the US and UK, the mortality rate has been reported to be less than 1% (24,25). However, in low-income countries, the in-hospital mortality rate has been reported to be as high as 30% (26,27). Mortality in adult DKA patients is more likely to result from underlying comorbid diseases, cardiopulmonary complications, or metabolic disorders (hypokalemia/hypoglycemia), which occur during therapy (28). In our study, the overall mortality rate is higher than previously reported. This may be related to the older age of the study population [30% (n=12) of patients were 65 years of age or older], had a high APACHE II score (20.7±9.10), and had high HbA1c (11.87±2.32) levels indicating long term bad metabolic status.

Additionally, in terms of comorbidities, three patients had advanced stage malignancy without hepatic involvement. Furthermore, a quarter of patients had an infection as a precipitating factor. In a study by Azevedo et al. (12), the in-hospital mortality rate was 4% in cases admitted to the ICU due to DKA, while it was reported as 9% in severe DKA cases. Another study by Pasquel et al. (29) revealed that lower bicarbonate levels on admission were significantly related to increased mortality rates. Similarly, in our study, 28 patients had bicarbonate levels less than 10 mEq/L, which could be considered severe DKA. The higher mortality rate observed in our study can be explained by poor comorbid conditions, long-term inadequate medical care, and a high rate of infections.

This study has some limitations. The first is its retrospective design, which may contribute to the results due to other undocumented factors it hides. The lactate metabolism may differ significantly in type 2 DM patients because of more frequent liver involvement than in type 1 DM patients. Evaluation of these two different types of diabetes together may have affected our results. Since our entire study population consisted of critically ill patients and a standard treatment protocol was used independent of diabetes type, we included both types of DM patients in our analyses. In addition, none of the patients included in our study had known chronic liver disease or concomitant fulminant liver failure. The other potential limitation of this study is that the total number of included patients remains small. Additionally, in this study, plasma L-lactate and D-lactate levels were not studied separately. While L-lactate is a marker of tissue hypoxia, D-lactate is a marker of metabolic disarrangements. Therefore, our assessment of the possible pathophysiological mechanisms of changes in lactate kinetics has been limited.

Conclusion

Although the ICU LOS and overall mortality did not differ between initial high and low-lactate groups, the lactate kinetics, especially in the early treatment period, can guide referral to ICU and determine the DKA patients at higher risk of death. Our results could be confirmed with further studies, including higher numbers of patients to test DKA lactate kinetics.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey Gülhane Faculty of Medicine, Local Ethics Committee (number: 2020/504, date: 16.06.2016) and performed following the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: G.T., M.Y., H.Ş., İ.S.G., Data Collection or Processing: G.T., S.Y., H.S., Analysis or Interpretation: G.T., H.Ş., İ.S.G., M.Y., Literature Search: G.T., S.Y., H.Ş., H.S., S.T., Writing: G.T., M.Y., L.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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Assessment of association between ankle-brachial pressure index and pulse wave velocity in patients with isolated hypertension according to gender

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Keywords: ankle-brachial pressure index, arterial stiffness, isolated hypertension, pulse wave velocity

ABSTRACT

Aims: Endothelial dysfunction and atherosclerosis are well-known risk factors for cardiovascular diseases in hypertension (HT). This study investigated the relationship between ankle-brachial pressure index (ABPI) and pulse wave velocity (PWV) in patients with isolated HT (IHT) and the difference according to gender.

Methods: This single-center, cross-sectional, and observational study was carried out between November 2014 and May 2015 in the outpatient clinic of the Department of Internal Medicine of Gülhane Military Medical Academy.

Results: The study included 90 patients with IHT (mean±SD age: 57.25±14.5 years, 63.3% female). No statistically significant difference was detected in ABPI (1.1±0.1 vs. 1.1±0.2, p=0.342) and PWV (10.9±2 vs. 10.5±1.9, p=0.341) measurements between male and female patients. In both sexes, SBP and DBP values correlated with CAP (Female: r=0.935, p<0.001; r=0.637, p<0.001, respectively. Male: r=0.944, p<0.001; r=0.749, p<0.001, respectively). SBP values correlated with ABPI among female patients (r=-0.277, p=0.037) but not among male patients. DBP did not correlate with ABPI in both sexes. No correlation was found between CAP and PWV in both sexes.

Conclusions: ABPI and PWV values may not be alternative to each other in patients with IHT.

Introduction

Hypertension (HT) is a chronic disease that threatens public health due to its complications and has an increasing prevalence (1). The prevalence of HT in the adult population is 30.3%, while it is 28.4% in males and 32.3% in females in Turkey (2). High blood pressure (BP) is a potent risk factor for the development of cardiovascular diseases (CVDs) (3,4). HT is a primary factor for CVD, which is the leading cause of the death. The 50-75% of strokes and 45-55% of both myocardial infarction and also congestive heart failure detected in the population were caused by HT.

HT leads to the development of endothelial dysfunction (ED) and atherosclerosis that play a crucial role in the pathogenesis of the damage of target organs (5). It has shown that ED is a precursor of atherosclerosis, which may occur prior to atherosclerosis in the presence of increased risk factors (6,7). ED is the first step for the atherosclerotic process that leads to plaque formation. Also, ED induces the growth and rupture of

the formed plaque and triggers thrombogenic events (8). A study conducted with young patients with coronary artery disease (CAD) showed that ED was seen not only in atherosclerotic vessels, but also in non-atherosclerotic vessels (9). It is thought that ED may indicate the tendency for the development of atherosclerosis. Also, the presence of ED may be a bad prognostic indicator in CVDs (10). To evaluate the presence of atherosclerosis and the potential stiffness of the vessel wall, Ankle-Brachial Pressure Index (ABPI) and pulse wave velocity (PWV) can be used as non-invasive methods.

Measurement of ABPI is an inexpensive and easy-to-implement method. It can be calculated by dividing the ankle systolic pressure value by the simultaneously measured brachial systolic pressure value. Regularly, the systolic pressure measured in the ankle is equal to or greater than the systolic pressure measured in the arm. Therefore, the normal ABPI value is equal to or greater than 1, but, due to technical differences in measurements and acceptable mild vascular stenosis, the values above 0.90 are considered as normal (11). Lower levels of ABPI (<0.90) can predict CVDs and atherosclerosis. Additionally, an ABPI value equal to or lower than 0.90 has 90% sensitivity and 98% specificity for peripheral artery disease (PAD) (12). Whereas, a low ABPI value can be used for confirmation of PAD, and also, it may indicate the presence of PAD in asymptomatic patients (13). Low levels of ABPI may be an indicator for poor prognosis in long-term risk assessment in patients with PAD. A 3- to 6-fold increased risk of death due to CVD is associated with low ABPI values. On the other hand, high ABPI (>1.4) has also been found to be associated with an increased mortality rate (14).

In the assessment of arterial stiffness, various parameters have been defined. Because of the difficulty in the application of catheter-based interventional measurements, noninvasive methods have been developed. Measurement of PWV by using an arterial tonometer is a frequently used noninvasive method for determining arterial stiffness. Left ventricle contracts provide the strength to push the blood through the ascending aorta, which creates a pressure wave on the arterial vessels of the whole body. The spreading speed of this wave is PWV, which is an indicator for arterial stiffness (15). As arterial stiffness increases, PWV spreading through the arterial system also increases (16,17). The higher the PWV, the weaker the arterial expansion ability (distensibility) (15). According to the 2013 criteria of the European Society of Cardiology and the European Society of HT (ESC/ESH), the threshold value of PWV is determined as 10 m/s (18). The increase in PWV leads to an early reflection and a faster access of the pulse wave to the periphery vessels. The attainment of the reflected wave to the heart removes from diastole to systole with time. Consequently, a rise in arterial stiffness causes an increased pressure at the aortic root, also named central aortic pressure (CAP), in late systole, decreased pressure in diastole, and an increase in mean arterial pressure (19). Measurement of ABPI and PWV can predict the presence of aggravated atherosclerosis and arterial stiffness, and may aware physicians of increased CVD risk in patients with HT.

This study aimed to evaluate the relationship between ABPI and PWV values in male and female patients with HT, the role of these parameters to get precautions for CVD and providing contributions to the follow-up and treatment of CVD.

Methods

Study Design and Patient Selection

This was a single-center, cross-sectional, and observational study that was carried out between November 2014 and May 2015 in the outpatient clinic of the Department of Internal Medicine of Gülhane Military Medical Academy, Ankara, Turkey. A total of 90 patients who were followed up with isolated HT (IHT) according to the recommendations of the 2013 ESC/ESH guidelines were included in the study (18). Written informed consents were obtained from all participants.

HT was defined as a systolic BP (SBP) equal to and greater than 140 mmHg and a diastolic BP (DBP) equal to and greater than 90 mmHg, or elevated BP that increases the risk of damage in the target organs such as the heart, brain, kidney, and retina. Participants' age, gender, smoking status, comorbid diseases, and medications were recorded. Biochemical parameters including renal function tests, transaminase levels, serum lipid profile, and blood glucose levels, and complete blood count levels which were evaluated within three months were recorded in the patients' follow-up forms. Body mass index (BMI) calculated by dividing weight by height squared (kg/m^2) was recorded for each participant. Patients who had malignancies, diabetes mellitus (DM), hyperlipidemia, PAD, CAD, and thyroid disease, who were under 18 years old, and who did not approve to participate in the study were excluded from the study.

Measurement of ABPI

ABPI measurement was made by a trained physician with a hand-held Doppler probe (Hadeco, Japan) and calibrated standard sphygmomanometers with a 12 cm cuff width (ERKA, D-83646, Germany) in an isolated room. The patients rested for at least 5 minutes before the measurement. ABPI measurement was performed while the patient was lying in the supine position with a cuff wrapped around just above both arms and ankles, beginning from the right arm. Consequtive measurements were taken from the right leg, the left leg and the left arm. The hand-held Doppler device placed on the brachial artery, the anterior tibial artery, and the posterior tibial artery determined SBP. While deflating the cuff slowly, the first pulse detected from the Doppler was noted as BP. The highest value of right and left brachial pressure was noted as the value of the upper extremity. The procedure was repeated for both right and left anterior and

posterior tibialis arteries and the highest value was accepted as the ankle pressure. ABPI was calculated for both right and left by dividing the lower extremity value by the upper extremity value. The lowest value from the right and left extremity was accepted as the ABPI value of the patient.

Measurement of PWV

PWV measurement was performed by The TensioMed (Budapest, Hungary) brand arteriography, in an isolated room after a rest for at least 5 minutes in the supine position. Smoking and caffeinated beverages were stopped within 30 minutes before measurement. The distance between the jugular notch and the symphysis pubis was measured and recorded in the device in centimeters. After the pressure was measured with the arteriography device, the cuff was inflated at least 35 mmHg above the systolic pressure value detected simultaneously. During the measurement (for 8-20 seconds), the blood flow cessation was provided by the complete brachial artery occlusion. The signals obtained were transferred to the computer and analyzed to receive SBP, DBP, central aortic (or aortic) pressure 'CAP', and PWV values automatically by the device.

Statistical Analysis

Statistical analyses were performed using IBM Statistical Package for the Social Sciences for Windows version 21.0 package program (Armonk, NY: IBM). Numerical variables were summarized with mean±standard deviation or median (minimum-maximum) values, and categorical variables with numbers and percentages. Whether numerical variables showed normal distribution or not was examined using the Kolmogorov-Smirnov test. Similarity of group variances was investigated by the Levene test. Difference between the two groups in terms of numerical variables (if any) was investigated using the t-test in independent groups if the parametric test assumptions were met, and with the Mann-Whitney U test if not. Whether there was a difference between the groups in terms of categorical variables was examined using the chi-square test. The relationship between numerical variables was evaluated with the Pearson correlation coefficient. Level of statistical significance was accepted as $p<0.05$.

Results

A total of 90 patients with IHT, including 33 (36.7%) male and 57 (63.3%) female, were included in the current study. The mean age of the patients was 57.3±14.5 years. According to the 2013 ESC/ESH guideline, 5 (5.6%) patients had optimal BP, 9 (10%) had normal BP, 12 (13.3%) had high-normal BP, 38 (42.2%) had stage 1 HT, 15 (16.7%) had stage 2 HT, and 11 (12.2%) had stage 3 HT. There was no significant difference between male and female patient groups in terms of HT stages ($p>0.05$). Female patients had higher BMI and waist circumference than male patients ($p<0.001$ and $p=0.002$, respectively), whereas male patients were taller than female patients ($p<0.001$). The smoking rate was higher among males than females ($p=0.002$). Forty-seven (82.5%) female patients and 27 (81.8%) male patients were receiving treatment for HT ($p>0.05$). There was no difference between male and female patients in terms of the number of antihypertensive drugs used ($p>0.05$) (Table 1).

The mean value of PWV was 10.9±2 m/s in male patients and 10.5±1.9 m/s in female patients ($p=0.341$). The mean ABPI value was 1.1±0.1 in male patients and 1.1±0.2 in female patients ($p=0.342$). Normal ABPI values were present in 60 (66.7%) patients, whereas 10 (11.1%) patients had low values, 19 (21.1%) patients had borderline ABPI values, one (1.1%) patient had high ABPI value (Table 2). In female patients, as BP increased, CAP increased and ABPI values decreased ($p=<0.001$ and $p=0.003$, respectively). In male patients, as arterial BP increased, CAP increased ($p=<0.001$). There was no relationship between arterial BP and PWV values in male or female patients (Table 3).

A positively significant correlation was present between CAP and values of SBP and DBP in female and male patients. On the other hand, a significant negative correlation was present between ABPI and SBP values in female patients. There was no relationship between ABPI and PWV values in male and female patients (Table 4).

Discussion

Determination of arterial stiffness and atherosclerosis with non-invasive methods in patients with increased risk for CVD is inexpensive and these methods are easily applicable methods that help physicians in follow-up and treatment course of CVDs. The current study evaluated arterial stiffness and atherosclerosis by non-invasive methods and showed that, because of the relationship between ABPI and SBP, these patients should be assessed for PAD cautiously. Additionally, according to the findings of the current study, PWV and ABPI cannot be used instead of each other.

ED may appear as an important risk factor for CVD in the early stages of atherosclerosis. Detection of ED at early stages may provide early diagnosis, effective treatment, and follow-up for CVD. Therefore, recent studies tried to reveal parameters that recognize CVD earlier by assessing arterial stiffness. To investigate the relationship between the risk of CVD and arterial stiffness parameters, 2,232 participants were assessed in the Framingham Heart Study, which showed higher PWV values were related to an increased risk for CVD (20). According to the study performed by Scuteri with 4,000 participants who were followed-up for 9.4 years, the increase of BP with age did not directly influence PWV, besides, gender and the other factors that lead to arterial stiffness might affect SBP, PWV and pulse pressure (21). In the current study, though it was not statistically

Table 1. Demographic and clinical characteristics of the study groups

		Female (n=57)	Male (n=33)	p
Age*		58.6±14.2	55.9±16.6	0.417[a]
Height (cm)*		159.1±6.7	171.8±7.5	<0.001[a]
Weight (kg)*		82±13.7	81.5±14.1	0.865[a]
BMI (kg/m²)*		32.4±5.6	27.5±4.3	<0.001[a]
Waist circumference (cm)*		109.1±11	101.2±11.5	0.002[a]
SBP (mmHg)*		148.5±22.5	151.6±24.9	0.543[a]
DBP (mmHg)*		87.7±10.4	88.4±12.9	0.813[a]
Mean AP (mmHg)*		108.5±13.7	109.5±16.1	0.769[a]
Smoking	Yes, n (%)	9 (15.8)	16 (48.5)	0.002[b]
	No, n (%)	48 (84.2)	17 (51.5)	
Receiving treatment	Yes, n (%)	47 (82.5)	27 (81.8)	1.000[b]
	No, n (%)	10 (17.5)	6 (18.2)	
Number of antihypertensive drugs**		1 (0-3)	2 (0-5)	0.275[b]
Leucocyte (/mm³)*		6904.7±1494.7	7452.1±1960.8	0.140[a]
Hemoglobin (g/dL)*		13.3±1.4	15.3±1.6	<0.001[a]
Thrombocyte (x1000/mm³)*		277.3±66.8	245.8±61.4	0.029[a]
Creatinine (mg/dL)*		0.9±0.2	1.1±0.3	<0.001[a]
Sedimentation (mm/h)*		22.3±13.2	13.9±12.2	0.005[a]

[a]t test in independent groups, [b]Mann-Whitney U test, *: Mean±SD **: Median (minimum-maximum).
BMI: Body mass index, AP: Arterial pressure, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation

Table 2. Comparison of arterial stiffness parameters according to gender

		Female (n=57)	Male (n=33)	p
PWV (m/s) *		10.9±2	10.5±1.9	0.341[a]
CAP (mmHg) *		145.3±21.2	148.1±29.1	0.642[a]
ABPI *	Total*	1.1±0.1	1.1±0.2	0.342[a]
	Low, ≤0.90, n (%)	7 (12.3)	3 (9.1)	0.477[b]
	Intermediate, 0.91-0.99, n (%)	13 (22.8)	6 (18.2)	
	Normal, 1.00-1.40, n (%)	37 (64.9)	23 (69.7)	
	High, ≥1.41, n (%)	-	1 (3)	

[a]t test in independent groups, [b]Chi-square test, *: Mean±SD.
PWV: Pulse wave velocity, CAP: Central aortic pressure, ABPI: Ankle-Brachial Pressure Index, SD: Standard deviation

significant, an increase in PWV was found with increasing SBP similar to the study performed by Scuteri et al. (21). However, increased systolic and DBP were strongly associated with increased CAP.

In CVD, increased CAP due to the early return of the reflected wave in late systole develops additional load on the ventricle, and consequently causes a decrease in ejection fraction, a rise in the requirement of myocardial oxygen, and increase in mortality (22). Totaro et al. (23) investigated 430 normotensive participants and showed that 16% of the participants had high CAP levels and increased risk for target organ damage. There was a relationship between high central BP and early cardiovascular dysfunction. Similarly, a meta-analysis of 11 studies with a total of 5,488 cases presented by Vlachopoulos et al. (24) found out that an increase of 10 mmHg in CAP was associated with mortality related to CVD. In this respect, as recommended by guidelines in new-onset HT, in addition to the measurement of PWV, measuring CAP associated with BP levels may be crucial in the treatment and follow-up of patients with HT.

HT, DM, hyperlipidemia, smoking and aging are risk factors associated with both atherosclerosis and PAD (25). Most of the patients with PAD have risk factors for CVD. Ness et al. (26) demonstrated that HT was an independent risk factor for PAD. Albuquerque et al. (27) found out that patients with HT, who had low ABPI levels but without clinical complaints associated with PAD, had increased risk for left ventricular hypertrophy and CVD. High also low ABPI levels in patients with HT were found to be related to death and CVD (28). When participants without HT were followed-up for 47 months, the development of HT was found to be related to normal or high ABPI levels at the beginning (29). Similar to the literature, the current study showed a relationship between BP and ABPI levels in female patients. CVD risk factors, such as HT, that pose a risk for atherosclerosis and PAD may play a role in long-term morbidity and mortality rates. Physicians should be aware of applying

Table 3. Comparison of hypertension stages and arterial stiffness parameters according to gender

Female	Optimal	Normal	High normal	Stage 1 HT	Stage 2 HT	Stage 3 HT	p
PWV* (m/s)	10.3 (9.0-11.9)	11.1 (8.8-12.7)	10.5 (6.9-14.6)	10.8 (8.3-14.5)	10.6 (8.5-14)	10.1 (8.3-16)	0.890
CAP* (mmHg)	115.3 (108.6-119.4)	119.2 (112.4-133.3)	127.4 (122-141.8)	147.0 (126.1-159)	156.5 (143.9-178.5)	194.4 (178.7-219.5)	<0.001
ABPI*	1.0 (1.0-1.08)	1.0 (0.87-1.12)	1.0 (0.85-1.29)	1.1 (0.86-1.25)	1.0 (0.91-1.26)	0.9 (0.81-0.95)	0.003
Male	**Optimal**	**Normal**	**High normal**	**Stage 1 HT**	**Stage 2 HT**	**Stage 3 HT**	**p**
PWV* (m/s)	9.4 (8.1-10.7)	9.5 (7.4-11.8)	8.8 (8.3-13.5)	10.4 (7-15.3)	10.1 (9.7-11.1)	11.8 (8.5-13.4)	0.695
CAP* (mmHg)	106.6 (102.7-110.5)	118.5 (108.5-122.0)	131 (123.8-138.0)	143.7 (119.7-156.4)	167.5 (154-185.8)	190 (155.3-212.1)	<0.001
ABPI*	1.1 (1-1.28)	1.1 (0.96-1.23)	1.1 (0.99-1.63)	1.1 (0.9-1.19)	1.1 (0.85-1.18)	1.0 (0.85-1.28)	0.889

Kruskal-Wallis test, *: Median (minimum-maximum).
PWV: Pulse wave velocity, CAP: Central aortic pressure, ABPI: Ankle-Brachial Pressure Index, HT: Hypertension

Table 4. The relationship between central aortic pressure and Ankle-Brachial Pressure Index values between systolic and diastolic blood pressures and arterial stiffness parameters according to gender

	CAP			
	Female		Male	
	r	p	r	p
SBP (mmHg)	0.935	<0.001	0.944	<0.001
DBP (mmHg)	0.637	<0.001	0.749	<0.001
	ABPI			
PWV (m/s)	-0.071	0.600	-0.229	0.199
CAP (mmHg)	-0.204	0.128	-0.116	0.522
SBP (mmHg)	-0.277	0.037	-0.154	0.393
DBP (mmHg)	-0.154	0.253	-0.061	0.734

Pearson correlation coefficient.
SBP: Systolic blood pressure, DBP: Diastolic blood pressure, PWV: Pulse wave velocity, CAP: Central aortic pressure, ABPI: Ankle-Brachial Pressure Index

protective measures and should treat CVD risk factors. There are limited data in the literature regarding the comparison of arterial stiffness and ABPI measurements. A recent study presented that ABPI values were associated with PWV in nondiabetic patients with PAD (30). Patients without CVD at baseline were followed up for 8.5 years by Zi et al. (31). At the end of the follow-up time, significant increases in vascular stiffness and PWV were recognized in patients with low ABPI levels at baseline. In a study, which evaluated arterial stiffness and ABPI values in patients without PAD, no statistically significant relationship between PWV and ABPI was found (32). In our study, to exclude the effect of gender-related factors, such as hormonal status and muscle mass, levels of PWV and ABPI were evaluated in male and female patients. Similar to the study performed by Rabkin et al. (32), the current study found no relationship between ABPI values and PWV in female and male patients with HT and without PAD.

Our study had some limitations. To evaluate the differences between hypertensive and normotensive individuals, normotensive healthy individuals as a control group could be included in the study. To investigate the effect of treatment on arterial stiffness parameters, patients could be separated into groups according to the treatment. Further studies with larger samples in prospective design will address more accurate information about the clinical importance of ABPI and PWV.

Conclusion

In conclusion, PWV and ABI measurements, which are the noninvasive indicators of arterial stiffness and atherosclerosis related to vascular remodeling due to HT, could not be used instead of each other. Additionally, due to the relationship between BP levels and CAP and the relationship between SBP and ABPI especially in female patients, high CAP and low ABPI levels should be considered to provide the early diagnosis, effective treatment, and prevention from cardiovascular morbidity and mortality in patients with HT.

Ethics

Ethics Committee Approval: The study was approved by the Gülhane Military Medical Academy Ethics Committee (Code: 1491-585-14/1648.4-2006, date: 10.14.2014).

Informed Consent: Verbal and written informed consents were obtained from all participants.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.T., E.B., K.S., Concept: E.T., E.B., K.S., Design: E.T., E.B., K.S., Data Collection or Processing: E.T., K.S., Analysis or Interpretation: E.T., E.B., K.S., Literature Search: E.T., E.B., K.S., Writing: E.T., E.B., K.S.

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Three-dimensional imaging of hemifacial microsomia: a case report

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ABSTRACT

Craniofacial microsomia or hemifacial microsomia (HFM) is a unique congenital facial deformity causing underdevelopment of the structures derived from first and second pharyngeal arches. The maxilla, mandible, temporomandibular joint, ear, trigeminal and facial nerves are commonly affected. This article presents a case of HFM in a 17-year-old male who was reported with unilateral facial hypoplasia. The diagnosis was confirmed with routine and advanced radiological investigations. Cone beam computed tomography with 3D reconstruction played an important role in determining the diagnosis of HFM.

Introduction

The first and second branchial arches are responsible for the development of various facial structures like the maxilla, mandible, temporomandibular joint (TMJ), zygomatic bone and ear (1). The formation and development of these branchial arches is carried out by various neural crest cells and any damage to these cells can result in abnormalities of various associated facial structures (1). The unilateral underdevelopment of hard and soft tissues, characterized by a wide range of anomalies, is called hemifacial microsomia (HFM). The term HFM was coined by Carl Ferdinand von Arlt in 1881. The first case was reported in 1960s with developmental defects in aural, oral and mandibular regions (2). HFM is reported to be the second most common developmental craniofacial anomaly with an incidence between 1 in 3000 or 5600 births, after cleft lip and palate (3).

This craniofacial disorder includes the underdevelopment of various skeletal tissues (like the maxilla, mandible, temporal and zygomatic bones) and soft tissues such as the external and middle ear, leading to conductive hearing loss in patient (4). Besides the clinical presentation, radiographic investigations are required to confirm the diagnosis of HFM. Various radiographic investigations have been attempted for a long time to determine the exact diagnosis of this pathology. These include routine investigations like panoramic radiograph, lateral and posterioanterior skull view. Whereas, advanced radiographic investigations like computed tomography, cone beam computed tomography (CBCT), and magnetic resonance

imaging (MRI) are beneficial for both diagnosis and treatment plan of this pathology. This article presents a case of 17-year-old patient suffering from HFM along with clinical and radiological features highlighted.

Case Presentation

A 17-year-old male patient was reported to the department of oral medicine and radiology with a chief complaint of facial asymmetry since childhood. It was revealed from his history that the patient had facial asymmetry and difficulty in opening the mouth for past 12 years. He was having sensitivity on taking hot and cold food items. No significant medical history was reported. Family history was noncontributory. No significant changes were present on general physical examination. Extraoral examination revealed a gross facial asymmetry on the right side (Figure 1A). The lips were incompetent. Anotia and ear tags were noticed on the right side (Figure 1B). TMJ examination revealed right side deviation with no tenderness, clicking or crepitus. Mouth opening was 38 mm. On intraoral examination, high arched palate and generalized gingival inflammation was noticed. Hard tissue examination revealed dental caries with mandibular right second premolar, first molar and right and left second molars (Figures 1C, 1D). Malocclusion was observed with crowding in anterior region. Based on clinical features, the patient was provisionally diagnosed as HFM affecting the right side, with a differential diagnosis of Goldenhar syndrome. Panoramic radiograph revealed altered condylar and coronoid morphology on the right side. The condyle and ramus of mandible was also smaller on the right side than left side. The joint space was found to be less prominent on the right of TMJ. Mandibular left third molar was horizontally impacted (Figure 2A). Lateral cephalogram revealed the presence of underdeveloped mandible with a steep mandibular plane (Figure 2B). PA view of the patient showed a prominent facial asymmetry (Figure 2C).

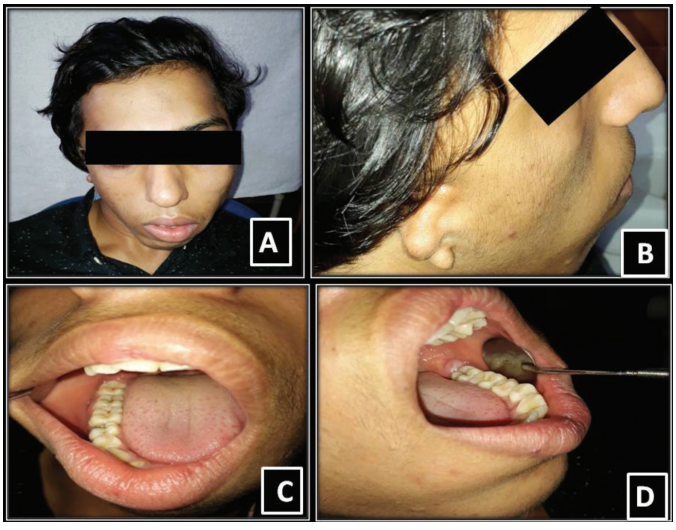

Figure 1. Extra and intraoral examination. A) Extraoral examination revealed gross facial asymmetry on the right side; B) Right ear showing features like anotia and ear tags; C) and D) Dental caries with mandibular right second premolar, first molar and right and left second molars

CBCT images were obtained at various planes. Coronal section revealed that right condyle appeared to be smaller in size than left condyle (Figure 3A). Axial section of CBCT showed morphological alterations on the right side (Figure 3B). In sagittal plane, right condyle was hypoplastic (Figure 3C, 3D). 3D reconstruction showed asymmetry of the face (Figures 4A, 4B, 4C). Underdeveloped ear pinna on the right side of face was shown (Figures 4D, 4E).

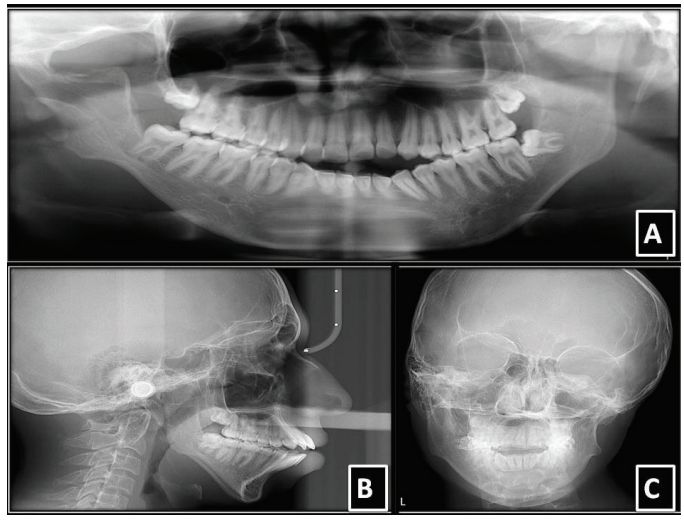

Figure 2. Radiographic examination. A) Panoramic radiograph showing hypoplastic right condyle, reduced ramal height on right side; mesioangular impaction of 38. B) Lateral cephalogram showing the presence of underdeveloped mandible with a steep mandibular plane; C) PA view showed a prominent facial asymmetry

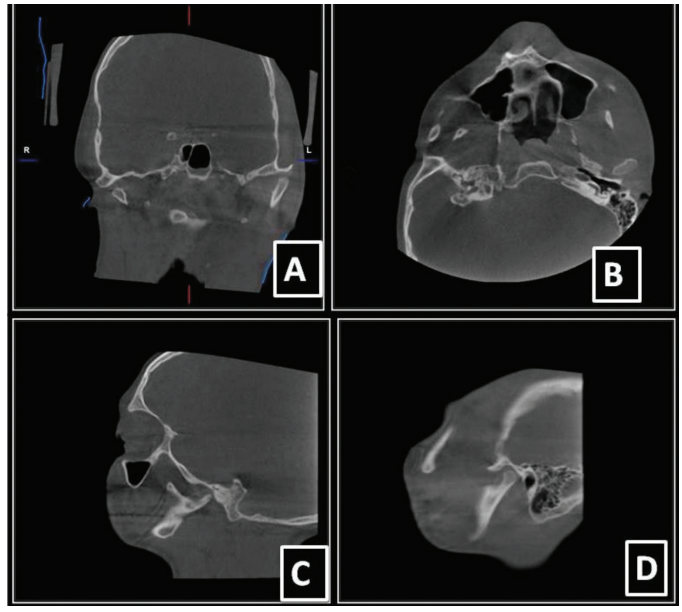

Figure 3. Cone beam computed tomography scan images. A) Coronal view showing altered condylar morphology in the right side; B) Axial view; C and D) Right sagittal view showing hypoplastic condyle compared to left sagittal view

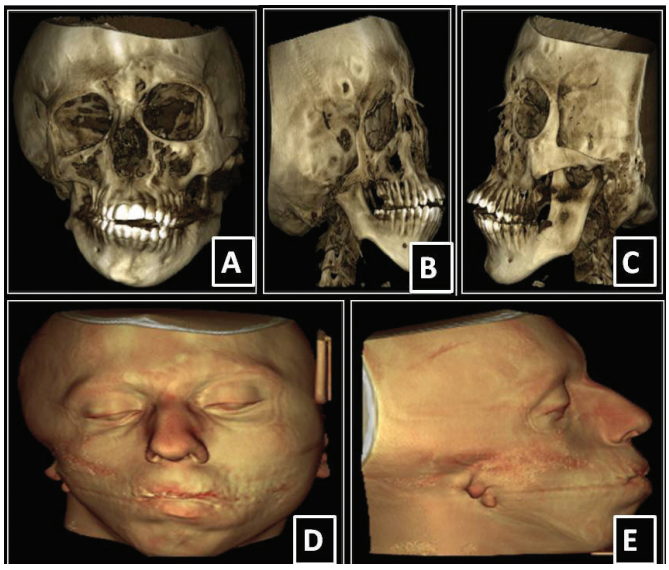

Figure 4. 3D reconstruction shows asymmetry of the face (A, B, C). Underdeveloped ear pinna on the right side of face was shown (D, E)

On the basis of clinical and radiographic findings, final diagnosis of HFM was made.

The patient was referred to an otolaryngologist for evaluation. The patient was advised oral prophylaxis and restoration of decayed teeth. The patient was also advised corrective surgery and correction of malocclusion, ear prosthesis for ear abnormalities.

Discussion

HFM is an anomaly featured by the presence of unilateral hypoplasia affecting various skeletal and soft tissues. It is found that the maxilla, mandible and ear are more commonly affected structures. The disease is characterized by the presence of underdeveloped condyle and coronoid process, short mandibular ramus, malformed ears with preauricular tags (5). The present case also showed similar features. Around 55% HFM patients were reported with extracranial anomalies affecting the kidney, lungs, heart, skeletal tissues, gastrointestinal and central nervous system.

The etiology of HFM is heterogeneous and unknown. The basis of this disease lies in the disruption of first and second branchial arches during the first 6 weeks of gestation. The disruption could be due to teratogens like retinoic acid, primidone and thalidomide, vascular anomalies and defective genes. Various laboratory studies propose that early loss of neural crest cells is responsible for HFM and its related syndromes (6).

As Meckel's cartilage is responsible for the development of the mandible and middle ear, any damage to Meckel's cartilage in HFM causes abnormality in these skeletal tissues, causing flattening of the affected side of the face (5). Hypoplastic maxillary and mandibular bones, malformed ear, lowering of eye position, and hypoplastic muscles of mastication cause chin and facial midline to appear as shifted to the affected side. Similar clinical presentation was observed in our patient.

Patients with HFM report with mild to severe ear deformities. External ear deformity might range from a flattened helical rim to a complete absence of auricle. Since middle ear ossicles are also derived from first and second branchial arches, thus they are commonly affected in HFM. Stenosis or atresia of the external auditory canal can also be observed. Thus, external and middle ear malformations can cause conductive hearing loss (7,8). The present case had no hearing loss.

Clinical findings are followed by radiographic investigations that include routine and advanced imaging techniques. Routine radiographic investigations revealed hypoplastic maxillary, mandibular and zygomatic bones. Advanced radiographic techniques like CT, CBCT, MRI etc. are required to assess the abnormality in skeletal and soft tissues by observing involved structures in various planes (9,10). CBCT is generally performed in patients of HFM, when facial asymmetry is to be corrected with orthodontic treatment and orthognathic surgery. Furthermore, for orthognathic surgeries, 3D images obtained from CBCT are proven to be very helpful (10). In the present case, we also subjected our patient to undergo CBCT investigation and 3D images were also obtained. CBCT scan showed hypoplasia of right side articular eminence, maxilla, mandibular ramus, condyle and coronoid process. External ear structures of the right side were affected.

Conclusion

HFM is a rare developmental anomaly of the maxillofacial region, which involves one side of the face. For the maintenance of esthetics and proper functioning of the orofacial structures, early treatment intervention is necessary. This can be achieved with proper diagnosis.

Ethics

Informed Consent: The consent form was filled out by a participant.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., S.S., Concept: A.B., S.H., Design: A.B., S.H., Data Collection or Processing: A.B., S.H., Analysis or Interpretation: A.B., S.S., Literature Search: S.H., G.S.B., V.A., Writing: A.B., S.H.

Conflict of Interest: No conflict of interest was declared by the authors.

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Metastatic chorioretinal abscess: an unusual complication of pyogenic liver abscess

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ABSTRACT

Liver abscesses are the most common type of visceral abscess, which accounts for around one half of all visceral abscesses. Rarely, the liver abscess can metastasize to distant organs and diabetes mellitus is an important risk factor for septic metastasis. We here present one such rare case of chorioretinal abscess in a diabetic male with pyogenic liver abscess. A 54-year-old diabetic male presented with the complaints of fever, pain abdomen and blurring lasting for one week. After detailed evaluation, he was diagnosed to have pyogenic liver abscess with chorioretinal abscess. He was treated with parenteral and topical antibiotic for eyes, strict glycemic control and ultrasound guided aspiration of liver abscess. The patient symptomatically improved and improvement in vision was also noted.

Introduction

Liver abscesses are the most common type of visceral abscess, which accounts for around one half of all visceral abscesses. In Asia, the enteric Gram-negative bacilli, particularly *Escherichia coli* and *Klebsiella pneumoniae*, are the most common organisms. Rarely, the liver abscess can metastasize to distant organs. Diabetes is an important risk factor for septic metastasis due to increased chances of bacteremia in them. Metastatic chorioretinal abscess is a rare subset of metastatic endophthalmitis.

Case Presentation

A 54-year-old diabetic man came to the outpatient department with seven-day history of fever, cough and abdominal pain. Fever was high grade, intermittent with chills and rigors. Cough was mild and non-productive. His abdominal pain was severe, was located in the right upper quadrant and increased with change of posture. He was a non-smoker and occasionally consumed alcohol. The examination revealed mild icterus and right hypochondriac tenderness. Other systemic examinations were normal. His initial blood investigations revealed leukocytosis (16,300/μL) and poorly controlled diabetes with glycated hemoglobin of 12%. There was conjugate hyper bilirubinemia with total bilirubin of 3.2 mg/dL (normal: 0.2-1.1 mg/dL) and direct bilirubin of 2.3 mg/dL (normal: 0.0-0.2 mg/dL). Liver enzymes were also elevated; alanine aminotransferase of 181 U/L (normal level: 12-38 U/L), aspartate aminotransferase of 187 U/L (normal level: 15-37 U/L), alkaline phosphatase of 110 U/L (normal level: 45-115 U/L. Renal function tests and serum electrolytes were normal. Chest X-ray (Figure 1) showed an elevated right

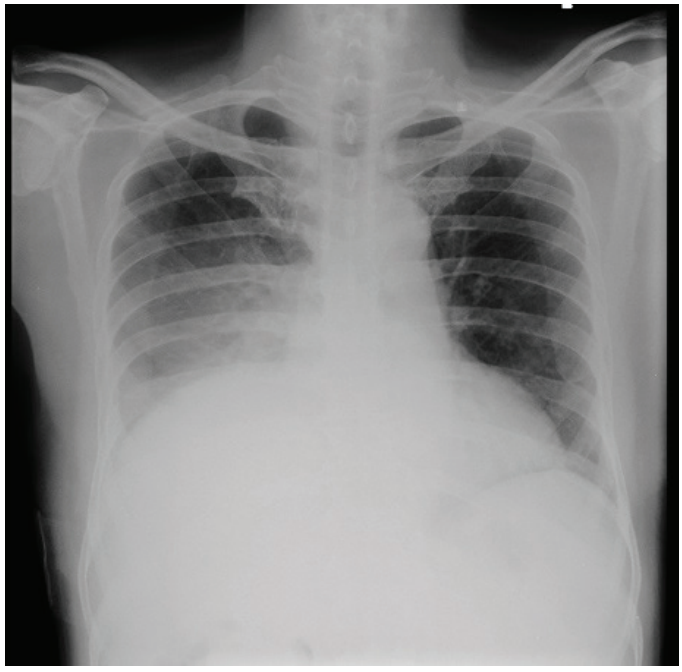

Figure 1. Frontal chest radiograph showing the elevation of right hemi-diaphragm

hemi-diaphragm with mild right sided pleural effusion. Contrast enhanced computed tomography (CECT) of the abdomen (Figure 2) revealed hypo-dense lesion with irregular walls in the liver (measuring 7.1 x 6.5 x 4.6 cm), involving segment VII and VIII with multiple air pockets within, suggestive of abscess.

The abscess was drained with a pig tail catheter, which was inserted under ultrasound guidance. Pus was sent for culture which grew multi drug resistant *Escherichia coli*. Even the blood culture grew the same organism sensitive only to amikacin and meropenem.

On day four of admission, the patient started noticing blurring of vision in his left eye. Ophthalmology evaluation showed decreased visual acuity (counting fingers at 3 meters) in the left eye. Vitreous exudates and hemorrhage could be seen on fundus examination. A yellowish circular deep choroidal lesion with retinal oedema and sheathing of the retinal blood vessels, which was noted as suggestive of chorioretinal abscess, were observed (Figure 3).

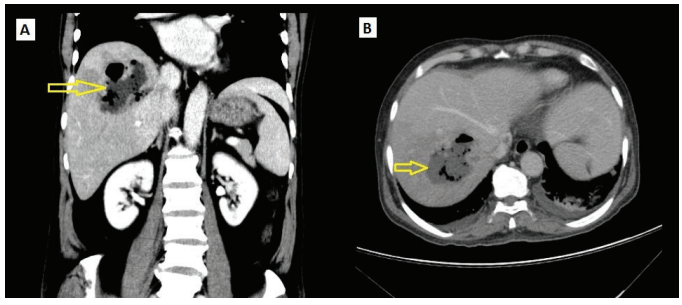

Figure 2. Contrast enhanced computed tomography abdomen (A: coronal, B: axial views) showing hypo-dense lesion with irregular walls in the liver (measuring 7.1x6.5x4.6 cm) involving segment VII and VIII with multiple air pockets within, suggestive of abscess

The patient received intravenous (amikacin and meropenem) and topical (tobramycin) antibiotics for two weeks, with which he improved symptomatically.

Liver abscesses are the most common type of visceral abscess, which account for around one half of all visceral abscesses. In Asia, the enteric Gram-negative bacilli, particularly *Escherichia coli* and *Klebsiella pneumoniae*, are the most common organisms. Whereas in the United States, Streptococci (in particular, the *Streptococcus* milleri group) were the most common pathogen of pyogenic liver abscess. Most common clinical features are fever and abdominal pain with or without other constitutional symptoms (1).

Rarely, the liver abscess can metastasize to distant organs. Diabetes is an important risk factor for septic metastasis due to increased chances of bacteremia in them. Metastatic chorioretinal abscess is a rare subset of metastatic endophthalmitis. Endophthalmitis refers to a condition characterized by inflammation of inner structures of the eyeball, which includes anterior as well as posterior segment structures. Infectious cause may be endogenous or exogenous. Endogenous/ metastatic endophthalmitis results from bacteremia secondary to an infective foci in body (2).

Clinical features include ocular pain, redness, lacrimation and photophobia. Panophthalmitis and vision loss are among

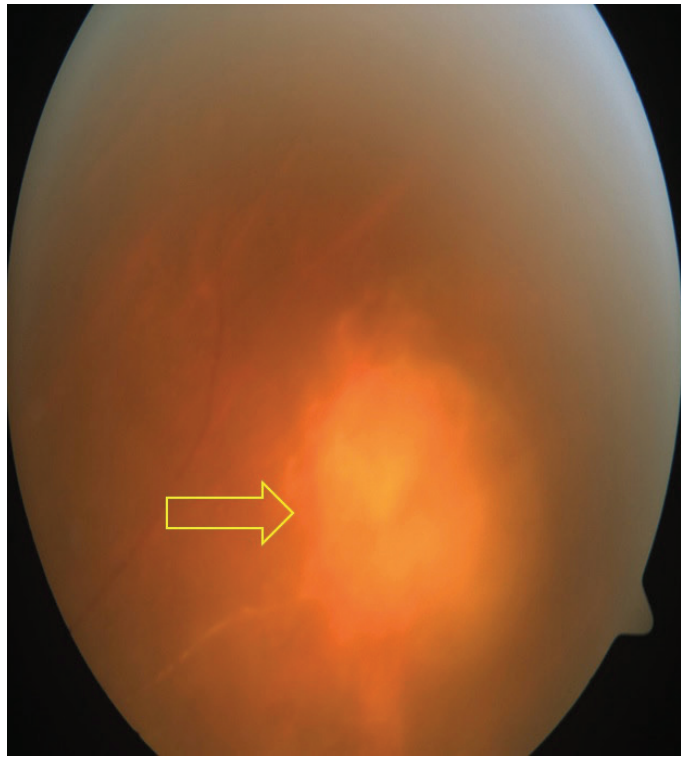

Figure 3. Fundus picture showing focus of retinitis temporally with features suggestive of chorioretinal abscess

the dreaded complications of this condition. Antibiotics are the principle mode of treatment. Usually topical antibiotics are initiated first, followed by intravitreal antibiotics. Supportive therapy like cycloplegics for pain relief and intraocular pressure lowering drugs are also used (3).

If it complicates to panophthalmitis, then there is the risk of orbital cellulitis, cavernous sinus thrombosis and meningitis. Immediate evisceration has to be performed under the cover of broad spectrum antibiotics to avoid further spread. Early eye evaluation and continued intravenous antibiotics are important treatment aspects. Any delay in intervention may result in permanent loss of vision (4,5).

Our patient had poorly controlled diabetes as a risk factor and presented with classical symptoms of liver abscess. Here the organism was *Escherichia coli* and the patient received both systemic and topical antibiotics. Intravitreal antibiotic therapy was not given as there was dramatic improvement in visual acuity within three days of the initiation of the treatment. Follow-up images taken after three weeks showed significant resolution of both liver abscess and chorioretinal abscess (Figure 4).

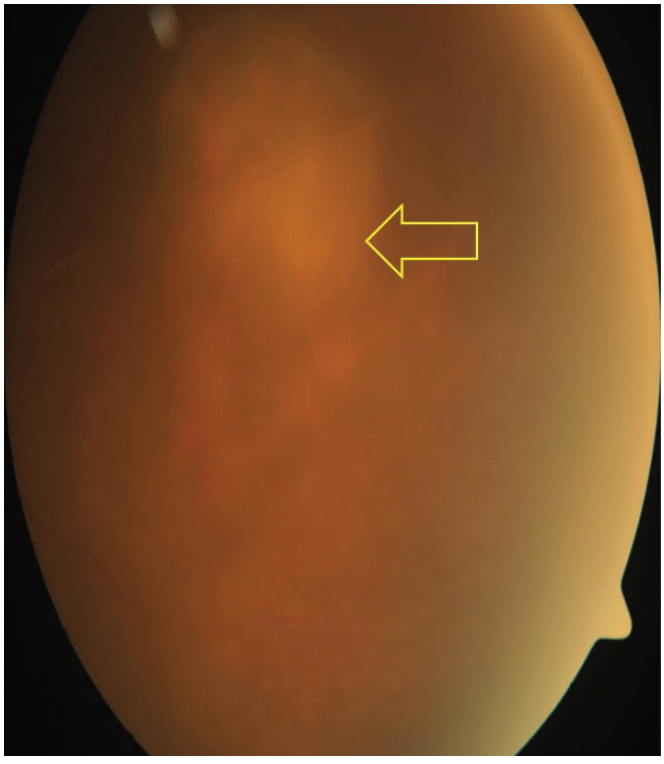

Figure 4. Fundus picture showing a more localized and resolving lesion

Conclusion

Metastatic chorioretinal abscess is an unusual complication of pyogenic liver abscess. Poorly controlled diabetes is an important risk factor. Prompt diagnosis and early systemic antibiotic therapy are cornerstone to prevent its progression to fulminant endophthalmitis and subsequent permanent blindness.

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Ethics

Informed Consent: Consent form was filled out by all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.V.A., S.B., Concept: S.M.P., R.V.A., Design: S.M.P., Data Collection or Processing: S.B., C.T.R., Analysis or Interpretation: S.M.P., Literature Search: G.K., C.T.R., Writing: G.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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