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ORIGINAL ARTICLES

- ***Impact of Using Automated Blood Culture System on the Isolation Success of Causative Agents of Parapneumonic Effusions***
  Özgür Batum et al.
- ***Ocular Findings and Multimodal Imaging Characteristics of Retinitis Pigmentosa Patients***
  Semra Tiryaki Demir et al.
- ***Assessment of the Functional Health Status of Hypertension Patients in Family Medicine***
  Ogün Akbaş and Özge Tuncer
- ***Deep Neck Space Infection: Clinical Outcomes of Patients Treated in a Tertiary Care Center***
  Kerem Sami Kaya et al.
- ***A study of HIV Knowledge and Stigma Among Health Care Workers from Istanbul-Turkey***
  Osman Sağsöz et al.

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Contents

ORIGINAL ARTICLES

1 **Impact of Using Automated Blood Culture System on the Isolation Success of Causative Agents of Parapneumonic Effusions**
Otomatize Kan Kültür Sistemi Kullanımının Parapnömonik Efüzyonlara Neden Olan Ajanların İzolasyon Başarısına Etkisi
Özgür Batum, Güneş Şenol, Funda Çoşkun, Ayriz Tuba Gündüz, Sinem Ermin, Ufuk Yılmaz; İzmir, Turkey

6 **Ocular Findings and Multimodal Imaging Characteristics of Retinitis Pigmentosa Patients**
Retinitis Pigmentosa Hastalarının Oküler Bulguları ve Multimodal Görüntüleme Özellikleri
Semra Tiryaki Demir, Dilek Güven, Hakan Kaçar, Saniye Üke Uzun, Murat Karapapak; İstanbul, Şanlıurfa, Turkey

13 **Assessment of the Functional Health Status of Hypertension Patients in Family Medicine**
Aile Hekimliğinde Hipertansiyon Hastalarının İşlevsel Sağlık Durumunun Değerlendirilmesi
Ogün Akbaş, Özge Tuncer; İzmir, Turkey

20 **Deep Neck Space Infection: Clinical Outcomes of Patients Treated in a Tertiary Care Center**
Derin Boyun Enfeksiyonları: Üçüncü Basamak Bir Hastanede Takip Edilen Hastaların Klinik Sonuçları
Kerem Sami Kaya, İbrahim Yağcı, Uğur Doğan, Nurullah Seyhun, Suat Turgut; İstanbul, Turkey

27 **A Study of HIV Knowledge and Stigma Among Health Care Workers from Istanbul-Turkey**
İstanbul-Türkiye'den Sağlık Çalışanlarında HIV Bilgisi ve Stigması Üzerine Bir Çalışma
Osman Sağsöz, Sevgi Duman, Güzin Zeren Öztürk, Seçil Arıca; Düzce, İstanbul, Turkey

37 **Effects of Smoking on Acute Hypobaric Hypoxia Tolerance**
Sigara Kullanımının Akut Hipobarik Hipoksi Toleransı Üzerine Etkisi
Erdinç Ercan, Menduh Şavaş İlbasmış, Cantürk Taşçı; Ankara, Eskişehir, Turkey

43 **Analysis of Severe and Critical COVID-19 Patients Treated With Favipiravir: A Retrospective Cohort Study**
Favipiravir ile Tedavi Edilen Ağır ve Kritik COVİD-19 Hastalarının Analizi: Bir Retrospektif Kohort Çalışma
Bengü Şaylan, Tayfun Çalışkan; İstanbul, Turkey

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Impact of Using Automated Blood Culture System on the Isolation Success of Causative Agents of Parapneumonic Effusions

Otomatize Kan Kültür Sistemi Kullanımının Parapnömonik Efüzyonlara Neden Olan Ajanların İzolasyon Başarısına Etkisi

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ABSTRACT

Background: Complicated parapneumonic pleural effusion causes high morbidity and mortality. Identification of the etiological agent is the key element for appropriate treatment. The aim of this study is to investigate whether getting the higher isolation rate of causative bacterial agent is possible by additional bedside blood culture method for parapneumonic effusion samples.

Materials and Methods: Parapneumonic effusion samples taken from patients with pneumonia between January 2015 and January 2018 were studied in the referral hospital for thoracic diseases in Turkey. Samples were processed by both standard and bedside BacT/Alert blood culture method. Isolation and identification of bacterial agents were done by standard microbiological methods. The descriptive statistics were applied.

Results: Fifty one patients with pneumonia accompanied by parapneumonic effusion, who met the inclusion criteria, were included in the study. Bacterial agents were isolated by standard microbiological method in 3 (5.9%) patients and in 11 (21.5%) patients by blood culture bottle at the bedside method.

Conclusion: The bedside blood culture bottle method has been found more sensitive than the standard culture method for the detection of bacterial pathogens in parapneumonic effusions.

Keywords: Parapneumonic pleural effusion, bedside blood culture method, empyema, bacterial etiology of pleural effusion

ÖZ

Amaç: Komplike parapnömonik plevral efüzyon, yüksek morbidite ve mortaliteye neden olur. Etiyolojik ajanın tanımlanması, uygun tedavi için anahtar unsurdur. Bu çalışmanın amacı, parapnömonik efüzyon örnekleri için ek yatak başı kan kültürü yöntemi ile etken bakteriyel ajanın daha yüksek izolasyon oranının sağlanıp sağlanamayacağını araştırmaktır.

Gereç ve Yöntemler: Ocak 2015-Ocak 2018 tarihleri arasında pnömoni hastalarından alınan parapnömonik efüzyon örnekleri referans bir göğüs hastalıkları hastanesinde çalışıldı. Örnekler hem standart hem de hasta başı BacT/Alert kan kültürü yöntemiyle işlendi. Bakteriyel ajanların izolasyonu ve tanımlanması standart mikrobiyolojik yöntemlerle yapıldı. Tanımlayıcı istatistikler uygulandı.

Bulgular: Dahil edilme kriterlerini karşılayan parapnömonik efüzyonun eşlik ettiği pnömonili 51 hasta çalışmaya dahil edildi. Bakteriyel ajanlar standart mikrobiyolojik yöntemle 3 (%5,9) hastada, 11 (%21,5) hastada ise kan kültürü şişesiyle yatak başı yöntemiyle izole edildi.

Sonuç: Yatak başı kan kültürü şişesi yöntemi, parapnömonik efüzyonlarda bakteriyel patojenlerin saptanmasında standart kültür yönteminden daha duyarlı bulunmuştur.

Anahtar Kelimeler: Parapnömonik plevral efüzyon, yatak başı kan kültürü yöntemi, ampiyem, plevral efüzyonun bakteriyel etiyolojisi

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Introduction

Parapneumonic pleural effusion (PPE) is defined as pleural effusion (PE) associated with lung infections such as pneumonia, a pulmonary abscess, or infected bronchiectasis (1). Although most PPEs can be resolved with antibiotic treatment alone, some PPEs are refractory to antibiotic treatment and require surgical drainage (33%) (2). In cases with prolonged PE, pleural fibrosis (14%), prolonged hospital stay (mean 12-15 days and >1 month in 25% of cases) and high mortality rates (10-20%) were expected (3,4).

Approximately, PPEs occur in 20-60% of community acquired pneumonia (CAP) cases in Turkey. Among these cases, 5% PPE goes on with empyema. Mortality rate increases 6-7 fold higher in complicated cases compared to pneumonias non-complicated PPE (5). In the United States, over 1 million PPEs were reported annually (6,7,8). Early intervention by proper antibiotics is the main point of the management of PPEs. Identification of etiological bacteria and tailored antibiotherapy according to the agent are key elements for the treatment of pneumonia and PPEs (8). However, the inability of patient to expectorate sputum or obtaine good quality sputum sample reduces the sensitivity and specificity of sputum cultures (9). The rate of etiologic agent isolation in pneumonias is not more than 40-50% even in obtaining adequate sputum samples (9,10). Blood cultures are only positive in approximately 11-12% of pneumonia cases (2,7,11,12). With the existence of PPE, this might be the only material which the agent could be isolated from.

A positive PPE culture is diagnostic, but limitation in standard culture of pleural has already been known. They are negative in more than 50% by conventional bacteriological methods (7,9,11). Empiric treatment is essential but local epidemiological prevalence data are crucial for the selection of empiric antibiotic. Isolation of causative pathogen from PPE gives an opportunity to the modification of treatment. So, microbiological identification is recommended (9,10). Some additional techniques may be beneficial for increasing the sensitivity of culture for PPE (2,11).

The use of blood culture bottles in automated microbial detection systems for the culture of sterile body fluids other than blood gives benefits compared to the use of solid media or conventional broth cultures (13). We aimed to investigate if the higher and faster isolation rate was possible via different or additional culture method for PPE samples in this study.

Material and Methods

Study Population and Clinical Setting

The study was designed as a prospective cohort study. Patients with parapneumonic effusion between January 2015 and January 2018 were included in the study. Patients with antibiotic use during the week prior to hospitalization and with other diseases such as heart failure, renal failure, and cancer that caused pleural effusions other than infection were excluded from this study.

Pneumonia and accompanied PE are defined as follows:

- High fever, chills, shaking, cough, flank pain, different colored sputum, and elevated white blood cell
- PE which accompanies with new infiltrates pointing to pneumonia on chest X-ray or chest computed tomography, or
- Pneumonia cannot be distinguished radiologically due to atelectasis caused by pleural effusion, but PE is considered infectious according to clinical and laboratory findings.

Ten to twenty mL of pleural fluid was obtained by thoracentesis using aseptic technique in cases considered to have PPE. Biochemical (pH, glucose, lactate dehydrogenase, total protein, albumin, adenosine deaminase), microbiological and cytological analyses were performed for all samples. For microbiological analysis, 5 mL of pleural fluid specimen was sent to microbiology laboratory for standard processing of cultivation by conventional method and 5 mL pleural specimen was injected into BacT/Alert (Biomerieux, France) aerobic and anaerobic blood culture bottles at the bedside. Bacteriological identification was performed with the BDPhoenix™ (Becton, Dickenson and Company, USA) automated identification and susceptibility testing system.

Statistical Analysis

The descriptive statistics were applied using the IBM SPSS Modeler statistical data analysis program. Gender, age, biochemical parameters, presence of pneumonia symptoms, and number and type of growing isolates were expressed as number and percentage. Results of two culture methods were compared, and the difference between them was assessed by the Chi-square test. A p value of <0.05 was considered as statistically significant.

İzmir Dr. Suat Seren Chest Diseases and Surgery Research Hospital review board approved this study (08 dec 2014, no: 390), waiving the requirement for obtaining individual patient consent.

Results

Fifty one patients with pneumonia accompanied by PPE were included in the study. Demographical, clinical, laboratory and radiological features were given in Table 1.

Comparative microbiological results of two culture methods for PPE samples were given in Table 2. Any bacterial agent was isolated by conventional microbiological method in 3 (5.9%) patients while by blood culture bottle at the bedside method in 11 (21.5%) patients. The isolated microorganisms are shown in Figure 1. All isolates (*Pseudomonas aeruginosa, Streptococcus constellatus and Nocardia* ap.) which were grown by standard method were also obtained from blood culture bottles. Statistical difference was significant (p<0.0001)

Discussion

In this study, it was conducted to determine whether the microbiological culture methods made any difference and served any additional benefit for the isolation of infectious agents in parapneumonic patients.

Table 1. Demographical, clinical, laboratory and radiological features of the patients

Age	62 (17-86) years
Gender	37 (72.5%) male; 14 (27.5%) female
Fever	17 (33.3%)
Cough	23 (43.1%)
Radiological parenchymal infiltration	43 (84.3%)
Pleural pH	7.28±0.40
Pleural glucose	101.37±66.09 mg/dL
Pleural LDH	1990.96±6285.15 U/L
Pleural protein	4.08±1.30 g/dL
Pleural albumin	2.20±0.80 g/dL
LDH: Lactate dehydrogenase	

Rate of isolation and identification of bacterial agent were found approximately four fold higher at the blood culture medium compared to standard culture method (5.9% vs. 21.5%) in our study. Similar results of some studies to our study support the use of additional bed side blood culture bottles in routine care for patients with suspected pleural infection. Menzies et al. (13) reported in 2011 that the addition of blood culture bottle culture to standard culture increased the proportion of identifiable pathogens by 20.8% to 58.5%. This is consistent with a previous study, in which using blood culture bottles increased culture positivity from 44% to 64% (14). Charoentunyarak et al. (15) indicated the advantages of blood culture bottle method and found culture positivity at the rate of 14% and 24% in standard method and blood culture method in 2015, respectively.

She et al. (16) studied blood culture bottles for culturing sterile body fluids other than blood in 2018. They reported that different blood culture systems gave close results to each other. Duration time of culture positivity was shorter and isolation rate was higher than the standard culture (16).

Delays of sample transportation to the culture laboratory and tardiness in the laboratory process might also be

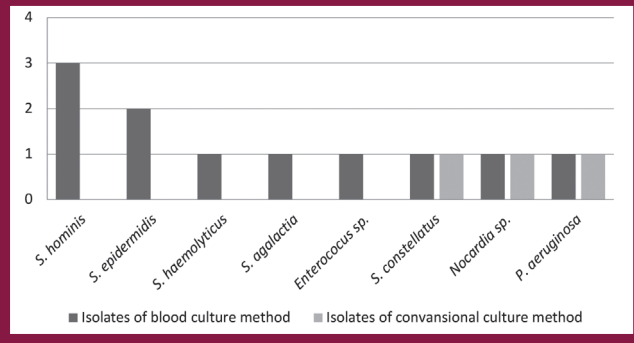

Figure 1. Isolated microorganisms in pleural samples

Table 2. Comparative microbiological results of two culture methods for PPE samples

	Patient number	Numbers of isolates from blood culture bottles	Numbers of isolates from classic culture method
Staphylococcus hominis	24, 41, 51	3	0
Streptococcus epidermidis	8, 33	2	0
Staphylococcus haemolyticus	47	1	0
Streptococcus agalactia	23	1	0
Enterococcus ssp.	10	1	0
*Streptococcus constellatus**	16	1	1
Nocardia spp.*	30	1	1
*Pseudomonas aeruginosa**	44	1	1
*Obtained from same specimens in both methods, PPE: Parapneumonic pleural effusion			

considered as factors for the differentiation of growing rate between standard and bedside blood culture systems (17). Better bacterial culture yield for pleural effusions using blood culture bottles may be achieved due to using some enrichment supplements in the medium, while the standard culture bottles do not have such supplements and less time for sample putting into the culture medium (18).

However, some previous studies recommend to be selective for pleural cultures. They state that pleural cultures give minimal additional benefit for antibiotic selection; therefore, they question the necessity of performing pleural cultures in every case (7,19,20).

PPE is expected to occur as a result of spreading of the bacteria presented in the lung parenchyma. The bacterial etiology of all PPEs is assumed to be same as that of pneumonia. For that reason, parapneumonic liquid cultures may help the identification of causative microorganism of pneumonia in case patient could not expectorate adequate sputum or lack of identification from sputum samples. In some circumstances, microorganisms identified from complicated PPE and empyema thoracis may differ from those giving rise to community acquired pneumonia. In a review of 14 studies with a total of 1383 patients with empyema, only 70% of agents were the same with pneumonia agent and the others were due to other microorganisms (21). Clinicians should be aware of that the bacteriology of CPE/ET might be different from those common pathogens of CAP, and that antibiotics recommended by treatment of CAP guidelines may not be adequate in this condition (22,23). Therefore, selecting antibiotic for treating pleural infection based solely the on the etiology of pneumonia may not be the best choice (2,24). This may explain the occasional failure of treatment in some patients treated according to CAP guidelines. Therefore, culture of pleural samples would be beneficial for appropriate antibiotic selection. Fulguera et al. (25) reported that the presence of non-complicated PPE had only mild prognostic consequences; however, the development of complicated PPE had characterized significant baseline differences and microbiological particularities (25). Menzies et al. (13) indicated that bed side blood culture bottle method identified additional clinically important co-infecting bacteria in 2/53 (3.8%) cases in their study (13).

Another important issue of our study was shorter isolation time for the recovery of nocardia species in bottle cultures than standard culture method. Nocardia was isolated in one case in our study. Pyopneumothorax is an unusual and rare presentation of pulmonary nocardiosis but once identified, treatment should be initiated immediately (2,26). We thought that using blood culture bottles for cultivating might provide additional benefits in the presence of slow-growing microorganisms like nocardia species.

One of the other beneficial point of using additional blood culture bottles was identifying non-pneumococcal *streptococci* and coagulase negative *staphylococci* better than standard culture. This finding emphasizes the importance of employing both standard and blood culture bottle culture strategies in parallel (13).

Our study had some limitations. The main limitation was that there was a small size of the study population in our study. Another concern might be that some microorganisms might be thought to be contaminant. However, it would be expected to emerge in standard cultures if there was contamination in the samples. Thus, bacteria yielded in cultures were considered as pathogens. Besides, *Streptococcus pneumoniae* is usually the most common pathogen causing community-acquired pneumonia but was not found in this study. This may also be explained by the high rate of previous antibiotic use (79.1%).

Conclusion

According to our results, the bedside blood culture bottle method was found to be more efficient than the standard culture to isolate bacterial pathogens from pleural fluid. Bedside blood bottle culture has valuable contribution to the diagnosis of pleural infection. These results indicate that adding bedside pleural fluid inoculation into blood culture bottles to standard laboratory culture should be included in routine examinations when pleural infection is considered.

Ethics

Ethics Committee Approval: İzmir Dr. Suat Seren Chest Diseases and Surgery Research Hospital review board approved this study (08 dec 2014, no: 390).

Informed Consent: Waiving the requirement for obtaining individual patient consent.

Peer-review: Internally peer-reviewed.

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Ocular Findings and Multimodal Imaging Characteristics of Retinitis Pigmentosa Patients

Retinitis Pigmentosa Hastalarının Oküler Bulguları ve Multimodal Görüntüleme Özellikleri

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ABSTRACT

Background: To investigate the ocular findings and multimodal imaging characteristics of retinitis pigmentosa (RP) patients.

Materials and Methods: Patients who were followed up in our clinic for RP were evaluated retrospectively between June 2014 and July 2017. Ophthalmological examination included best corrected visual acuity (BCVA), biomicroscopy, fundoscopy, and axial length (AL) measurements. Optical coherence tomography (OCT) and fundus autofluorescence (FAF) imaging properties of macular region were examined in detail.

Results: In the study, 865 eyes of 446 RP patients were evaluated. In biomicroscopic examination, cataract surgery was performed in 23.6% of the eyes, and 29.1% of the eyes had posterior subcapsular cataract. In fundus examination, end-stage RP was detected in 67.4% of the eyes and severe macular atrophy in 9.8% of the eyes. The mean AL was 23±1.8 mm, the mean central macular thickness (CMT) was 136.6±87.1 um, and the mean subfoveal choroidal thickness (SCT) was 178.3±89.1 um. There was a positive correlation between BCVA and CMT, SCT, external limiting membrane and ellipsoid zone line integrity ($p<0.001$). Inner limiting membrane thickening and/or epiretinal membrane 47.7%, intraretinal hyperreflective foci 43.1%, micropseudocyst 15.8% and cystoid macular edema 6.5% were among the most commonly seen macular abnormalities detected in OCT. There was presence of a hyper-autofluorescent (AF) ring in 28.4%, abnormal hyper-AF patterns at the macula in 45.3%. There was a positive correlation between external limiting membrane-ellipsoid zone line integrity and the hyper-AF ring ($p<0.001$).

Conclusion: Screening RP patients using OCT, FAF and biometry findings may be useful both for documenting of the disease and for selecting candidates for innovative treatment modalities like retinal prosthesis, stem cell therapy.

Keywords: Fundus autofluorescence, optical biometry, optical coherence tomography, retinal dystrophy

ÖZ

Amaç: Retinitis pigmentosa (RP) hastalarının oküler bulgularını ve multimodal görüntüleme özelliklerini araştırmak.

Gereç ve Yöntemler: Kliniğimizde RP nedeniyle takip edilen hastalar Haziran 2014 ve Temmuz 2017 tarihleri arasında retrospektif olarak değerlendirildi. Oftalmolojik muayenede en iyi düzeltilmiş görme keskinliği (EİDGK), biyomikroskopi, fundoskopi, aksiyel uzunluk (AL) ölçümleri yapıldı. Maküla bölgesinin optik koherens tomografi (OKT) ve fundus otofloresans (FOF) görüntüleme özellikleri ayrıntılı olarak incelendi.

Bulgular: Çalışmada 446 RP hastasının 865 gözü değerlendirildi. Biyomikroskopik muayenede; gözlerin %23,6'sına katarakt ameliyatı yapılmıştı, %29,1'inde arka subkapsüler katarakt mevcuttu. Fundus muayenesinde; gözlerin %67,4'ünde son dönem RP ve % 9,8'inde ciddi maküler atrofi saptandı. Ortalama AL değeri 23±1,8 mm, ortalama merkezi maküla kalınlığı (MMK) 136,6±87,1 um, ortalama subfoveal koroid kalınlığı (SKK) 178,3±89,1 um idi. EİDGK ile MMK, SKK, external limitan membran ve elipsoid zon hattı

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ÖZ

bütünlüğü arasında anlamlı pozitif korelasyon mevcuttu (p<0,001). OKT'de saptanan en sık görülen makula patolojileri sırasıyla; iç limitan membran kalınlaşması ve/veya epiretinal membran %47,7, retina içinde hiperreflektif odaklar, %43,1, mikropseudokist %15,8 ve kistoid maküla ödemi %6,5 idi. FOF görüntülemede; gözlerin %28,4'ünde hiper-otofloresan halka, %45,3'ünde makulada anormal hiper otofloresans paternler mevcuttu. External limitan membran ve elipsoid zon hattı bütünlüğü ile hiper-otofloresan halka varlığı arasında pozitif korelasyon saptandı (p<0,001).

Sonuç: RP hastalarının OKT, FOF ve biyometri bulguları kullanılarak taranması, hem hastalığın belgelenmesi hem de retina protezi, kök hücre tedavisi gibi yenilikçi tedavi modaliteleri için adayların belirlenmesinde faydalı olabilir.

Anahtar Kelimeler: Fundus otofloresans, optik biyometri, optik koherens tomografi, retina distrofisi

Introduction

Retinitis pigmentosa (RP) encompasses a group of inherited retinal dystrophies characterized by primary degeneration of rod and cone photoreceptors and is a leading cause of visual disability, affecting more than 1.5 million patients worldwide (1).

Morphological and functional assessment of photoreceptors in the macula can be useful in estimating residual retinal function in RP patients. Optical coherence tomography (OCT) is a well-established method of examining retinal and choroidal architecture in situ. It allows the evaluation of retinal and choroidal changes of RP at presentation and during the follow-up period (2,3,4). Fundus autofluorescence (FAF) results from the accumulation of lipofuscin in retinal pigment epithelium (RPE) cells and has been used to investigate RPE and retinal function. Several FAF patterns have been observed in patients with RP (2).

In this study, the clinical and multimodal imaging findings of 446 RP patients were evaluated by using biometry, OCT and FAF. Therefore, we aimed to report our findings to contribute to the literature in terms of presenting quantitative data in Turkey.

Material and Methods

Patient charts and medical records were reviewed retrospectively between June 2014 and July 2017. Non-syndromic RP cases were evaluated. This study was approved by the local human research ethics committee, in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants.

Age, gender, past cataract or other ophthalmic surgeries and presence of additional eye disease were recorded in the patients' personal histories. Parental consanguinity was recorded in the family history. Genetic analysis was not performed in terms of hereditary transmission.

Eye position in primary gaze, presence of strabismus and nystagmus, best corrected visual acuity (BCVA), biomicroscopy and fundus were evaluated. The BCVA was recorded using the Snellen chart. Tropicamide 1% eye drops were used for pupil dilatation and lens clarity was assessed by biomicroscopy. The state of the lens was grouped as clear lens, pseudophakia, posterior subcapsular cataract (PSC), nuclear-nucleocortical cataract and aphakic.

The degree of retinopathy was assessed with fundoscopy and classified as early stage (bone spicule-like pigment changes in the equatorial region, macula and optical disc unaffected), late stage (widespread chorioretinal atrophy, loss of foveal reflex in the macula, waxy pallor of the disc), severe macular atrophy, sectorial RP and RP sine pigmento. Optical biometry (AL-Scan, Nidek Co., Aichi, Japan) was used for measuring axial length (AL).

A high resolution spectral-domain OCT (3D-OCT 2.000, Topcon Corp., Tokyo, Japan) device was used for detailed evaluation of the macula area and FAF imaging. The "6 mm 3D mode and 9 mm line mode" technique was used for macula imaging, the "9 mm line mode" enhanced depth imaging technique was used for subfoveal choroid imaging. The values of central macula thickness (CMT) and subfoveal choroidal thickness (SCT) were recorded between 12.00 and 14.00 o'clock in the afternoon. The CMT was measured from the foveola, so that the inner border would be the inner limiting membrane (ILM) and the outer border would be the RPE. The SCT was measured manually at 500 microns interval from the fovea, so that the inner border would be the RPE and the outer border would be the sclera (5). SCT less than 250 microns was evaluated as choroidal thinning. The presence of choroidal symmetry between both eyes was also recorded.

The macular area was examined in 3 groups with OCT as outer retinal, intraretinal and vitreomacular interface abnormalities. Outer retina abnormalities were evaluated in detail as loss of external limiting membrane (ELM) line integrity and loss of ellipsoid zone (EZ) line integrity. The loss of EZ and ELM line integrity was classified as total loss and partial loss (partially preserved in subfoveal area). Intraretinal abnormalities were evaluated in detail as micropseudocyst (MPC), cystoid macular edema (CME), subretinal fluid and presence of intraretinal hyperreflective foci (HF). Vitreomacular interface abnormalities were evaluated in

detail as ILM thickening (ILMT), epiretinal membrane (ERM), combination of ILMT and ERM, presence of vitreous bands, full thickness macular hole (FTMH) and lamellar macular hole (LMH).

FAF imaging was evaluated under the headings of FAF symmetry between both eyes, presence of hyper-AF ring, abnormal hyper-AF patterns at the macula with irregular distribution, absence of AF and decreased AF at the periphery (5). In case of media opacities, nystagmus, low patient cooperation FAF, OCT or biometry were not evaluated.

Statistical Analysis

SPSS 22.0 for Windows software was used for statistical analysis. Descriptive statistics were given as number and percentage for categorical variables and as mean, standard deviation, minimum, maximum, and median for numerical variables. When the numerical variables met the conditions of the normal distribution, the Student's t-test was used to compare the two independent groups and the Mann-Whitney U test was used when the normal distribution conditions were not met. Since the relationships between numerical variables did not meet the condition of a parametric test, they were analyzed using the Spearman Correlation Analysis. Statistical significance level of alpha was accepted as $p<0.05$.

Results

Demographic Findings: Eight hundred seventy-five eyes of 446 RP patients were evaluated. The mean age was 43.5±14.9 (6.5-82) years, 173 patients were (38.8%) female, 273 patients (61.2%) were male. The parental consanguinity rate was 56.4%. According to the expression of the patients, the mean age of nyctalopia was 15.8±12.3 years, the mean age of onset of central vision loss was 22.8±12.6 years, and the mean age of severe central blindness was 34.6±15 years.

Additional Eye Diseases: There was no additional ocular pathology in 639 eyes (71.6%). The most common additional eye diseases were myopia in 134 eyes (15%), glaucoma in 45 eyes (5%), hypermetropia in 26 eyes (2.9%) and corneal opacity in 15 eyes (1.6%). Nystagmus was seen in 88 (23.4%), orthophoria in 212 (57%), exotropia in 148 (39.8%), esotropia in 7 (1.9%) and vertical strabismus in 5 (1.3%) of the patients. As the BCVA decreased, the frequency of strabismus and nystagmus was found to be significantly higher ($p<0.001$).

Best Corrected Visual Acuity: Categories and corresponding percentages were: no light perception in 56 (6.4%), only light perception in 257 (29.4%), seeing hand movements in 254 (29%), counting fingers at 1 meter at 10/100 in 127 (14.5%) and ≥10/100 in 181 (20.7%) of the eyes.

Fundus Findings: Fundus examination revealed early-stage RP in 139 (16.4%), end-stage RP in 570 (67.4%), severe macular atrophy in 83 (9.8%), RP sine pigmento in 13 (1.5%) and sectorial RP in 2 (0.2%) of the eyes.

Lens Findings: Two hundred eleven (23.6%) eyes were pseudophakic and 14 eyes (1.6%) were aphakic. Biomicroscopic examination revealed clear lens in 326 (37.7%), PSC in 252 (29.1%) and senile nuclear-nucleocortical cataract in 69 (8%) of the eyes. The BCVA of the eyes with PSC and nuclear cataract were less than eyes with clear lens and pseudophakic ($p<0.001$). The mean CMT was 134.2±92 um in eyes that had undergone cataract surgery and 136.4±76 um in the others ($p=0.194$).

Axial Length: The mean AL was 23±1.8 (17-42.2) mm. There was no difference in AL between right and left eyes ($p=0.082$). There was no correlation between AL and age, CMT and SCT (p values of 0.085, 0.669, 0.073, respectively).

Macula OCT Imaging Findings: The macular area could be evaluated in 633 of the eyes (79.4%) with OCT. The distribution of OCT imaging findings of patients with RP is shown in Table 1. Macula OCT images of some of our cases are shown in Figure 1. The mean CMT was 136.6±87.1 (2-839) um. There was no significant difference in CMT between right and left eyes ($p=0.626$). There was a significant negative correlation between age and CMT ($p<0.001$), and no difference between gender and CMT ($p=0.559$).

Table 1. Distribution of optical coherence tomography imaging findings of patients with retinitis pigmentosa

	Optical coherence tomography imaging findings	Eyes (n) %
ILMT	186	28.2
ERM	108	16.3
ILMT and ERM	21	3.2
Vitreous bands	16	2.4
MPC	100	15.8
CME	41	6.5
Subretinal fluid	11	1.7
LMH	10	1.5
FTMH	6	0.9
Intraretinal HF	290	43.1
Total loss of ELM line integrity	402	60.4
Partial loss of ELM line integrity	224	33.7
Total loss of EZ line integrity	396	58.2
Partial loss of EZ line integrity	235	34.4

ILMT: Inner limiting membrane thickening, ERM: Epiretinal membrane, MPC: Micropseudocyst, CME: Cystoid macular edema, LMH: Lamellar macular hole, FTMH: Full thickness macular hole, HF: Hyperreflective foci, ELM: External limiting membrane, EZ: Ellipsoid zone

There was a positive correlation between BCVA and CMT, ELM and EZ line integrity (p<0.001). Vitreomacular interface anomalies were seen more often in patients who underwent cataract surgeries, had less BCVA and were elderly (p values of <0.001, 0.006, <0.001, respectively). A significant positive correlation was found between CMT and subretinal fluid, vitreomacular interface anomalies, and CME (p values of 0.012, <0.001, <0.001, respectively). There was a significant positive correlation between CMT and ELM and EZ line integrity (p<0.001) and a significant negative correlation between the CMT and intraretinal HF (p<0.001).

Choroidal OCT Imaging Findings: The mean SCT was 178.3±89.1 (2-441) µm. SCT thinning was observed in 521 (77.4%) of the eyes. Choroid findings were asymmetry between two eyes in 39 (12.3%) of patients. As patients were older, SCT thinning was greater (p<0.001). There was a significant positive correlation between BCVA and SCT (p<0.001). The mean SCT was 132.5±93 µm in eyes with no light perception, 157±88 µm in eyes with only light perception, 169.3±95 µm in eyes with seeing hand movements, 191.2±85 µm in eyes with counting fingers at 1 meter at 10/100 and 214.0±71 um in eyes with ⩾10/100. There was a significant positive correlation between SCT and CMT (p<0.001).

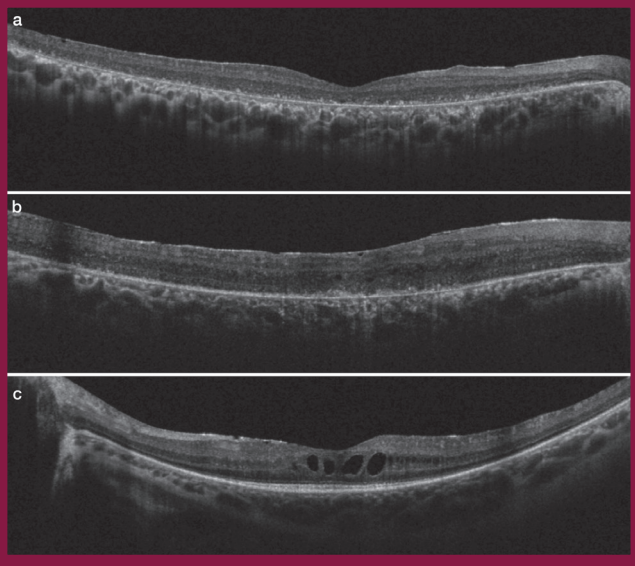

Figure 1. a-c. Macula OCT image patterns of our patients with retinitis pigmentosa. The OCT image shows intraretinal hyperreflective foci, epiretinal membrane and total loss of ellipsoid zone (EZ) and external limiting membrane (ELM) line integrity (a). The OCT image shows intraretinal hyperreflective foci, micropseudocyst, epiretinal membrane and total loss of EZ and ELM line integrity (b). The OCT image shows cystoid macular edema, inner limiting membrane thickening and partial loss of EZ and ELM line integrity (c)

Fundus Autofluorescence Imaging Findings: The distribution of FAF imaging findings of patients with RP is shown in Table 2. FAF images of some of our cases are shown in Figure 2. FAF findings of asymmetry between the two eyes were detected in 44 (15%) of the patients. There was a significant negative correlation between BCVA and loss of AF (p<0.001).

The CMT was 148.7±62 µm in eyes with hyper-AF ring and 129.1±92 µm in eyes without hyper-AF ring (p<0.001). The CMT was 115.4±87 µm in eyes with the absence of AF, 150.9±83 µm in the others (p<0.001). The CMT was 130.5±74 um in eyes with abnormal hyper-AF patterns at the macula and 139.7±97 µm in the others (p=0.254). The SCT was 209±81 µm in eyes with hyper-AF ring and 170.2±88 µm in eyes without hyper-AF ring (p<0.001). The SCT was 166±90 µm in eyes with the absence of AF and 189.9±87 µm in the

Table 2. Distribution of fundus autofluorescence imaging findings of retinitis pigmentosa patients

Fundus autofluorescence imaging findings	Eyes (n) %
Presence of hyper-AF ring	169 28.4
Abnormal hyper-AF patterns at the macula	271 45.3
Absence of AF	268 44.4
Decreased AF at the periphery	486 81.2

AF: Autofluorescence

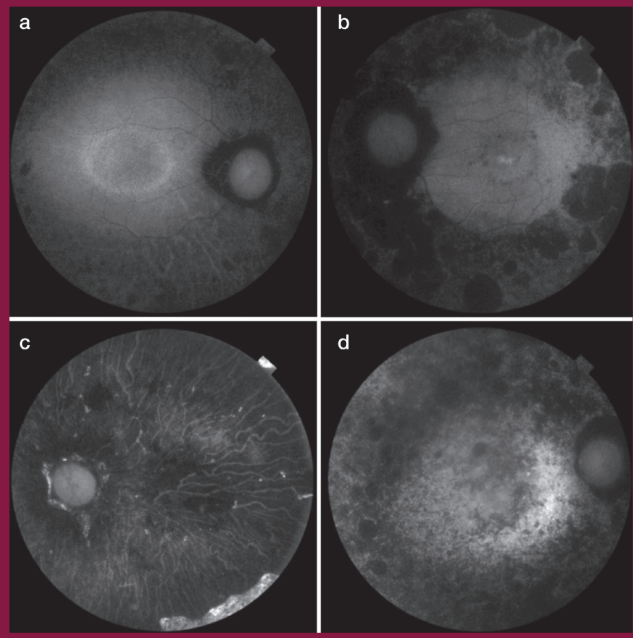

Figure 2. a-d. Fundus autofluorescence image patterns of our patients with retinitis pigmentosa. Hyper-autofluorescence (AF) ring (a). Decreased AF at the periphery (b). Absence of AF (c). Abnormal hyper-AF pattern at the macula (d)

others (p=0.002). The SCT was 187.6±85 um in eyes with abnormal hyper-AF patterns at the macula and 176.1±90 um in the others (p=0.079). We found a strong correlation between ELM-EZ line integrity and hyper-AF ring or the absence of AF (p<0.001).

Discussion

To the best of our knowledge, our study includes the ocular findings and multimodal imaging characteristics of the largest number of patients with RP were examined in Turkey. OCT and FAF imaging features of the macula region and the presence of cataract were examined in detail.

The incidence of cataracts (especially PSC) in RP is higher than in the normal population. This condition is thought to develop secondary to inflammation (6). In the study of Lee et al. (7) the incidence of PSC was 25.8%. In our study, 23.6% of the eyes had cataract surgery and 29.1% of the eyes had PSC, although the mean age was 43 years. The VA of the eyes with clear lens and pseudophakic was higher than eyes with PSC and nuclear cataract. Therefore, we think that cataract surgery should be performed in patients with RP who have decreased visual acuity due to cataracts.

It has been shown that histopathologic changes in the macula area in RP can be visualized by OCT. These changes revealed by OCT have provided insights into the pathology of RP as well as for predicting the prognosis of RP (8). Several OCT studies have been published on RP patients to determine whether there is a significant correlation between retinal microstructure and visual function (9,10,11). In our study, the CMT (136.6±87) was significantly thinner because most of our patients were end-stage RP. As the VA decreased, thinning of the CMT was greater. The EZ line integrity in patients with RP disappeared partially in the early stage and completely in the advanced stage (12). Tamaki et al. (11) reported that CMT and the presence of the EZ line could serve as objective signs for better VA in RP. In our study, deterioration in ELM line integrity was seen in 94.1% and deterioration of EZ line integrity in 92.6% of the eyes. Like other studies, we found a strong correlation between ELM-EZ line integrity and VA or CMT. We think that the presence of the ELM-EZ line integrity is associated with better VA and CMT in RP patients.

Patients with RP may develop CME due to breakdown of the blood-retinal barrier, failure (or dysfunction) of the pumping mechanism in the RPE, Müller cell oedema and dysfunction, antiretinal antibodies or vitreous traction (13). Previous studies have reported CME at the rates from 5.5% to 38% in RP patients (14,15,16,17). In our study, we detected CME in 6.5% and MPC in 15.8% of eyes. No correlation was found between VA and CME or MPC.

Kuroda et al. (12) evaluated intraretinal HF in the OCT of patients with RP. They reported that HF represented macrophages, migrating RPE cells or extracellular lipoproteins. In our study, HF was detected in 43.1% of the eyes. We found that as the CMT decreased, the ratio of HF presence increased. Therefore, we think that the presence of HF is a very important OCT finding in patients with RP during the progress of the disease.

It was reported that RP patients have a degenerative vitreous, including collapse of vitreous gel, and posterior vitreous detachment may cause macular complications related to the vitreoretinal interface (18). In the study of Testa et al. (15), ERM in 15.6%, LMH in 1% and FTMH in 0.6% were detected in patients with RP. Triolo et al. (19) found ILMT in 67%, ERM in 27.3%, ILMT and/or ERM in 94.3% and FTMH in 4.5% of 176 eyes. In our study, we detected ILMT in 28.2%, ERM in 16.3%, a combination of ILMT and ERM in 3.2%, vitreous bands in 2.4%, LMH in 1.5% and FTMH in 0.9% of 875 eyes. The incidence of vitreomacular interface abnormalities varies among studies. We think that this is due to reasons such as ethnic origin, environmental risk factors, age and having undergone ocular surgery. We also found that vitreomacular interface abnormalities were seen more often in patients who had lower VA, in the elderly and in eyes that underwent cataract surgeries.

Recent studies have evaluated changes in choroidal thickness in patients with RP (4,20,21). Dhoot et al. (4) reported that SCT was significantly reduced in patients with RP, but this did not correlate with VA or CMT. Egawa et al. (20) detected significant correlations between choroidal structures and VA and retinal structures. In our study, thinning of the SCT was found in 77.4% of the eyes. When patients were older, thinning of the SCT was greater. We found significant correlations between SCT and VA or CMT, but this did not correlate with AL.

FAF results from the accumulation of lipofuscin in RPE cells. Lipofuscin is a by-product of the degradation of photoreceptor outer segments. Hyper-AF indicates abnormal metabolism in RPE cells, a high turnover of photoreceptor outer segments, disrupted phagocytosis, or an intrinsic defect in the ability of the RPE to recycle phagosomes. Hypo-AF indicates RPE atrophy and loss of photoreceptors (22). Murakami et al. (5) reported hyper-AF ring in 59%, and abnormal central AF in 18%, and the absence of both patterns was detected in 24% of patients with RP. The hyper-AF ring is considered to represent the border between functional and dysfunctional retina (22). Lima et al. (23) reported that the diameter of the hyper-AF ring was significantly correlated with the length of the EZ line in patients with RP. In our study, we found hyper-AF ring in 28.4%, abnormal hyper-AF patterns at the macula in 45.3%, the absence of AF in 44.4% and decreased AF at the periphery in 81.2% of the eyes. We think that the rate of the presence of hyper-AF ring is less

in our study than in the other studies because the majority of our cases were end-stage RP patients (77.2%). We think that hyper-AF ring disappears as the disease progresses, and also remaining macular RPE cells filled with lipofuscin pigment are developing abnormal hyper-AF patterns at the macula. We also found a strong positive correlation between ELM-EZ line integrity and hyper-AF ring, but a strong positive correlation between ELM-EZ line integrity and the absence of AF. While the CMT and SCT were thicker in eyes with the presence of hyper-AF ring, CMT and SCT were thinner in eyes with the absence of AF. VA is significantly lower in eyes with the absence of AF. Therefore, we think that FAF images should be evaluated together with OCT at presentation and during the follow-up period in patients with RP.

Sujirakul et al. (24) followed patients with RP by multimodal imaging for 2 years. They demonstrated an asymmetric structural progression rate between the two eyes. In our study, asymmetry was also observed between the two eyes of the same patient in terms of choroidal and FAF findings. For this reason, we have evaluated both eyes of our patients separately. We think that this should be taken into consideration in subsequent studies.

Study Limitations

The limitation of this study was the lack of genetic testing for a hereditary transition pattern and electrophysiologic testing. The different patterns we detected in OCT and FAF imaging may be specific to some particular gene defects.

Conclusion

This is the largest report on clinical and multimodal imaging characteristics of RP in Turkey. In countries with high consanguineous marriages, like Turkey, it is thought that the frequency of seeing issues with time will increase. OCT, FAF and biometry should be used in the examination and follow-up of patients with RP. We believe that this study will provide a database for describing the patients who can benefit from innovative treatment strategies such as retinal prosthesis and stem cell therapy.

Ethics

Ethics Committee Approval: This study was approved by the local human research ethics committee, in accordance with the Declaration of Helsinki (number: 1129, date: 24/11/2015).

Informed Consent: Written informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.G., S.T.D., H.K., M.K., S.Ü.U., Concept: D.G., S.T.D., Design: D.G., S.T.D., H.K., S.Ü.U., M.K., Data Collection or Processing: H.K., M.K., S.Ü.U., Analysis or Interpretation: D.G., S.T.D., Literature Search: H.K., M.K., S.Ü.U., Writing: S.T.D., D.G.

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

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Assessment of the Functional Health Status of Hypertension Patients in Family Medicine

Aile Hekimliğinde Hipertansiyon Hastalarının İşlevsel Sağlık Durumunun Değerlendirilmesi

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ABSTRACT

Background: In this study, it was aimed to evaluate the functional health status of hypertensive patients and to determine the factors affecting their functional health status.

Materials and Methods: This is a single-center, cross-sectional, descriptive survey study. It was carried out in İzmir Provincial Health Directorate Bayraklı No.15, İsmet Akman Family Health Center between 01/06/2019 and 01/09/2019. The study included 322 non-pregnant volunteers without communication problem (aged>18 years), who had a diagnosis of hypertension for at least a year based on sample size estimation of unknown population at error level of 0.05 and confidence interval of 0.95, and the frequency of hypertension was taken as 30% on average. All participants completed a 21-item questionnaire about sociodemographic and hypertension characteristics. In addition, all participants were asked to complete Turkish version of Dartmouth COOP/WONCA functional status charts. Descriptive statistics are presented as count, percentage, mean and standard deviation. The Kolmogorov-Smirnov test, Fisher's coefficient of skewness, t-test and Kruskal-Wallis test were used in the statistical analysis.

Results: The mean age was 63.10±11.63 years (min 21-max 95 years) in the study population and majority of participants (66.5%) were female. Of the participants, 35.7% were obese and 44.7% had a comorbid disease. When the average blood pressure values were assessed, it was found that blood pressure was high-normal in 20.5%, there was stage 2 hypertension in 20.2%, and regular drug use was seen in 94.7% of participants. Of the participants, 60.6% had uncontrolled blood pressure. In the evaluation of the responses to the COOP/WONCA functional status scales, the highest functional disability was found in the physical health domain with the mean score of 3.49±1.07 while lowest functional limitation was found in the social activities domain with the mean score of 1.77±0.98.

Conclusion: Hypertension and factors causing hypertension negatively affect the functional health status of individuals and lead to a decreased quality of life. Achievement of treatment goals in hypertension including ensuring blood pressure regulation and adoption of life style changes led improved quality of life through positive effects on functional health status.

Keywords: Hypertension, Dartmouth COOP/WONCA, functional health status, quality of life

ÖZ

Amaç: Bu araştırmada, hipertansiyon hastalarının işlevsel sağlık durumlarının değerlendirilmesi ve işlevsel sağlık durumuna etki eden faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Araştırma tek merkezli, kesitsel, tanımlayıcı bir anket çalışmasıdır. İzmir İl Sağlık Müdürlüğü Bayraklı 15 No'lu İsmet Akman Aile Sağlığı Merkezinde 01/06/2019 ile 01/09/2019 tarihleri arasında yapılmıştır. Araştırmaya evreni belli olmayan örneklem hesabı ile hipertansiyon sıklığı ortalama %30 olarak alınarak 0,05 yanılgı, 0,95 güven aralığında gönüllü, iletişim sorunu olmayan, 18 yaşından büyük, gebe olmayan ve en az 1 yıldır hipertansiyon tanısına sahip 322 kişi dahil edilmiştir. Katılımcılara sosyo-demografik ve hipertansiyon hastalığına ilişkin verilerin değerlendirildiği 21 soruluk anket uygulanmış ve sonrasında katılımcılar tarafından Dartmouth COOP/WONCA işlevsel durum ölçeğinin Türkçe çevirisi cevaplanmıştır. Verilerin istatistiksel değerlendirmesinde sayı, yüzde, ortalama, standart sapma, Kolmogorov-Smirnov ve Fisher'in çarpıklık katsayısı, t-testi ve Kruskal-Wallis testi kullanılmıştır.

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ÖZ

Bulgular: Katılımcıların yaş ortalaması 63,10±11,62 (min 21-max 95 yaş) olup, yarısından fazlası (%66,5) kadın ve %35,7'si obezdi. Hastaların %44,7'sinde hipertansiyon dışı ek bir hastalık vardı. Katılımcıların ortalama tansiyon değerlerine bakıldığında grubun %20,5'i yüksek normal, %20,2'si evre 2 hipertansiyon değerlerine sahipti ve %94,7'si ilaçlarını düzenli almaktaydı. %60,6 oranında katılımcının kan basıncı kontrol altında değildi. COOP/WONCA işlevsel durum ölçeklerine verilen cevapların değerlendirilmesinde en fazla işlevsel kısıtlılık 3,49±1,07 ortalama puan ile bedensel sağlık alanında, en az işlevsel kısıtlılık ise 1,77±0,98 ortalama ile sosyal faaliyetler alanında saptanmıştır.

Sonuç: Hipertansiyon ve hipertansiyona neden olan faktörler bireylerin işlevsel sağlık durumlarını olumsuz yönde etkileyerek yaşam kalitelerinin azalmasına neden olmaktadır. Hipertansiyon hastalığının tedavi hedefi olan kan basıncı regülasyonunun sağlanması ve gerekli yaşam tarzı değişikliklerinin uygulanması işlevsel sağlık durumunu olumlu yönde etkileyerek yaşam kalitesinin artmasına neden olmaktadır.

Anahtar Kelimeler: Hipertansiyon, Dartmouth COOP/WONCA, işlevsel sağlık durumu, yaşam kalitesi

Introduction

The World Health Organization (WHO) suggests that hypertension is the leading risk factor for mortality globally (1). In 2017, the hypertension caused 10.44 million deaths from all age groups regardless of gender worldwide. In 2015, WHO reported that there were 1.13 billion patients with hypertension worldwide (2). The hypertension prevalence ranges from 30% to 45% across the world. Hypertension becomes more common with advancing age with prevalence reaching up to 60% in individuals aged >60 years (3). In 2017 TEKHARF study, hypertension prevalence was found as 36.4% in rural areas and 31.7% in urban areas with overall prevalence of 33.7% in Turkey. In the study, it was estimated that there were 14.3 million patients with hypertension (8 million women and 6.3 men) in Turkey (4). The hypertension is defined as systolic blood pressure ⩾140 mmHg and/or diastolic blood pressure ⩾90 mmHg measured in office after resting in more than one occasion (5). The hypertension is a chronic systemic disorder that is characterized by increased risk for major complications such as stroke and coronary heart disease. The hypertension is a global health issue due to its high prevalence and life-threatening complications in uncontrolled cases.

The quality of life (QOL) consists of several components including satisfaction, individual wellbeing, happiness, functional sufficiency, social wellbeing and economic self-sufficiency (6). The WHO QOL Work Group (WHO QOL) defines QOL as "individual's perception of their position in life in the context of culture and value systems in which they live and in relation to goals, expectations, standards and concerns" (7). Functional health status (FHS) is the major component of health-related QOL.

FHS, in other words, functional status is defined as individual's ability of adaption to his/her environment in a certain time period, which can be measured in subjective and objective manner. In general, one of the methods to assess the outcomes of health-related procedures is to measure ability to perform daily life activities. It is particularly difficult to measure QOL and wellness since they are highly abstract and range in a wide spectrum. In fact, functionality, a major component of health and quality of life, is a measurable concept of health (8).

The tools for the measurement of health-related QOL are classified as general scales and specific scales. The health profiles classified under general scales can be used in several health conditions and disorders. They can be applied to any population or any disease or health condition. They include Dartmouth COOP/WONCA Functional Health Charts, Sickness Impact Profile, World Health Organization Health-related QOL (WHOQOL), Nottingham Health Profile, Short Form-36 (SF-36, Medical Outcome Study 36-items Short Health Survey), Duke Health Profile and Quality of Well-being Scale among others.

In this study, it was aimed to assess FHS and potential confounders on FHS in patients with hypertension by using COOP/WONCA functional health assessment parameters. It will be guiding to determine the effects of daily activities, functional limitations and factors involved in the management of patients with hypertension, which is a common health problem in the community. Early interventions including medical therapy, lifestyle changes and long-term social support will aid to reduce complications and mortality at long-term.

Material and Methods

This is a single-center, cross-sectional, descriptive survey. In this study, FHS was assessed in patients with hypertension using Dartmouth COOP/WONCA Functional Health Charts. The study was approved by Ethics Committee on Clinical Research of İzmir Bozyaka Training and Research Hospital, Health Sciences University (approval: 22/05/2019-8). The survey was conducted at Health Directorate of İzmir Province Bayraklı İsmet Akman Family Health Center No 15 between 01.06.2019 and 01.09.2019. The study included 322 non-

pregnant patients aged >18 years without communication problems, who had diagnosis of hypertension for at least one year, based on sample size estimation of unknown population at error level of 0.05 and confidence interval of 0.95. All participants gave written informed consent.

Participants completed a 21-item questionnaire about sociodemographic characteristics (age, gender, marital status, education level etc.), disease characteristics (duration of hypertension, frequency of blood pressure measurements, number of medications, comorbid conditions, treatment compliance) and habits (alcohol consumption, smoking status, dietary habits, physical exercises). Before questionnaire, blood pressure measurement was performed by researcher and body mass index was calculated by quantification of weight and height in all participants. After completion of questionnaire, all participants completed Turkish version of 8-item Dartmouth COOP/WONCA Functional Health Chart, which assesses physical fitness, feelings, change in health, overall health, QOL and pain. Dartmouth charts were first developed under the leadership of Dartmouth Medicine School and Dartmouth-Hitchcock Medical Center in 1977 (9). It is also known as Primary Care Cooperative Information Project (COOP) (10). The COOP charts were revised for use in general medicine worldwide by Classification Committee involving primary care physicians, which was endorsed by WONCA (10). The charts include physical health status, emotions, daily activities, social activities, health transformation and overall health sub-domains while QOL and pain sub-domains can be added optionally. It is a patient-based assessment tool (11). COOP/WONCA charts assess FHS of individuals within prior 2 weeks. Each chart involves one item of COOP scale. Each chart includes a question on FHS and 5 answers (rated from 1 to 5). For each answer, there are simple figures representing emotions in addition to rating for use of illiterate individuals. Answer in each chart is assessed individually with higher scores indicating worse functional health status. Turkish validity and reliability study was performed by Çalışkan and Uzuner (12).

Statistical Analysis

Data were analyzed using SPSS version 21.0 (Statistical Package for Social Sciences). Descriptive data were presented as frequency, percent and mean ± standard deviation. Normal distribution was assessed using the Kolmogorv-Smirnov test and Fisher's coefficient of skewness which revealed skewed distribution for COOP/WONCA Functional Health Chart scores and sociodemographic characteristics. As COOP/WONCA Functional Health Charts were rated as +3.5 according to central limit theorem, which was smaller than +3, parametric t-test was used. Non-parametric Kruskal-Wallis test was used to assess the mean COOP/WONCA Functional Health Chart scores according to occupation and education level. For all tests, a p value <0.05 was considered as statistically significant.

Results

Table 1 presents sociodemographic characteristics of participants. We questioned disease duration and medications in 322 patients with hypertension and hypertension was classified according to the 2018 european society of hypertension/european society of cardiology (ESC/ESH) Guidelines for Management of Arterial Hypertension. Table 2 presents hypertension-related characteristics. We calculated the average blood pressure values measured from either right or left arm according to gender. The maximum blood pressure was 220/100 mmHg among female participants and 220/130 mmHg among male participants. It was found that the mean systolic and diastolic blood pressure values were higher in female participants than in male participants.

Of the participants, 35.1% were attending regular exercises; 91.9% did not consume alcohol; 24.8% were smokers; and 38.5% had no dietary regimen adapted. Table 3 presents the distribution of answers to COOP/WONCA Functional Health Charts. When answers to COOP/WONCA Functional Health Charts were assessed, it was found that 39.1% of participants responded as "light" to item "During past 2 weeks, what was the hardest physical activity you could do for at least 2 minutes". The highest functional limitation (mean score: 3.49±1.07) was detected in physical health. When physical health status was compared with sociodemographic data, it was found that the female participants ($p<0.001$), those aged ⩾60 years ($p<0.001$), single participants ($p<0.001$), those not attending regular exercises ($p=0.04$), housewives and those with education level below primary school ($p<0.001$) had milder physical activity and experienced limitations in physical health.

Of the participants, 48.4% responded as "moderate" to item "During the past 2 weeks, how much have you been bothered by emotional problems such as feeling anxious, depressed, irritable or downhearted and blue". The mean score was 2.89±1.04 with moderate limitation in feelings. In our study, it was seen that individuals without comorbid disorders experienced significantly higher limitation ($p=0.03$).

Of the participants, 27.6% responded as "no difficulty at all" to item "During the past 2 weeks, how much difficulty have you had doing your usual activities or tasks, both inside and outside the house because of your physical and emotional health". The mean score was 2.37±1.09 and partial limitation was detected in daily activities. It was found that female participants, those aged >60 years, single participants ($p<0.001$), non-smokers ($p=0.02$), those not consuming alcohol

Table 1. Distribution of participants according to their sociodemographic characteristics

Demographic characteristics		n	%
Gender	Female	215	66.5
	Male	107	33.5
Age (years)	<40	4	1.3
	40-49	33	10.3
	50-59	82	25.3
	60-69	98	30.3
	70-79	82	25.6
	≥80	235	7.2
BMI	Underweight	6	1.9
	Normal	76	23.6
	Overweight	114	35.4
	Obese	115	35.7
	Morbid obese	11	3.4
Marital status	Married	251	78.0
	Single	71	22.0
Occupation	Housewives	178	55.3
	Retired	106	32.9
	Unemployed	5	1.6
	Active employee	33	10.2
Monthly income	<Minimum wage	37	11.5
	Minimum wage	159	49.4
	Minimum wage- 3000 TL	92	28.6
	>3000 TL	34	10.5
Education level	Illiterate	62	19.3
	Literate	28	8.7
	Primary school	166	51.6
	Secondary school	26	8.0
	High school	31	9.6
	≥Undergraduate	9	2.8
Family	Single	65	20.2
	Elementary family (partner plus children)	250	77.6
	Extended family (elementary family plus parents)	7	2.2
Social insurance	None	29	9.0
	SGK	279	86.7
	Private insurance	14	4.3
Comorbid disease	Yes	144	44.7
	No	178	55.3
Total		322	100.0

BMI: Body mass index, SGK: Social security institution

(p<0.001), those with average blood pressure of ≥140 mmHg (p=0.04), those not attending regular exercises (p<0.001), housewives and those with education level below primary school (p<0.001) experienced significantly higher limitation in daily activities.

One half of the participants responded as "not at all" to item "During the past 2 weeks, has your physical and emotional health limited your social activities with family, friends, neighbors or groups?". The mean score was 1.77±0.98 while the lowest mean score was detected in social functionality. It was found that there was significantly higher limitation in elder individuals (p=0.01), those with elevated blood pressure, single participants not attending regular exercises (p<0.001),

Table 2. Distribution of hypertension-related characteristics in participants

Characteristics		n	%
Hypertension classification	Optimal	18	5.6
	Normal	43	13.3
	High-normal	66	20.5
	Grade 1	63	19.6
	Grade 2	65	20.2
	Grade 3	30	9.3
	Isolated systolic	37	11.5
Duration of hypertension diagnosis	1-5 years	140	43.5
	6-9 year	67	20.8
	≥10 years	115	35.7
Regular medication	Yes	305	94.7
	No	17	5.3
Antihypertensive agent	1	234	72.7
	2	76	23.6
	3	8	2.5
	>3	4	1.2
Duration of antihypertensive medication	1-5 years	140	43.5
	6-9 years	67	20.8
	≥10 years	115	35.7
Drugs other than antihypertensive agents	Yes	175	54.3
	No	147	45.7
Frequency of blood pressure measurement	Daily	38	11.8
	Weekly	116	36.0
	Monthly	104	32.3
	Never	64	19.9
Frequency of presentation to healthcare facility for blood pressure measurement	3 months	109	33.9
	6 months	76	23.6
	1 years	66	20.5
	>1 year	71	22.0
Total		322	100.0

Table 3. Distribution of answers to COOP/WONCA functional health charts in participants

		n	%
Physical health	Very heavy	19	5.9
	Heavy	35	10.9
	Moderate	90	28.0
	Light	126	39.1
	Very light	52	16.1
Feelings	Not at all	37	11.5
	Slightly	57	17.7
	Moderately	156	48.4
	Quite a bit	47	14.6
	Extremely	25	7.8
Daily activities	No difficulty at all	89	27.6
	A little bit difficulty	84	26.1
	Some difficulty	93	28.9
	Much difficulty	52	16.2
	Could not do	4	1.2
Social activities	Not at all	169	52.5
	Slightly	85	26.4
	Moderately	46	14.3
	Quite a bit	17	5.3
	Extremely	5	1.5
Change in health	Much better	16	5.0
	A little better	73	22.6
	About same	197	61.2
	A little worse	35	10.9
	Much worse	1	0.3
Overall health	Excellent	10	3.1
	Very good	39	12.1
	Good	176	54.7
	Fair	84	26.1
	Poor	13	4.0
Quality of life	Very well: could hardly be better	6	1.9
	Pretty good	92	28.7
	Good and bad parts about equal	196	61.0
	Pretty bad	24	7.5
	Very bad: could hardly be worse	3	0.9
Pain	No pain	64	19.9
	Very mild pain	50	15.6
	Mild pain	85	26.5
	Moderate pain	96	29.9
	Severe pain	27	8.1
Total		322	100.0

housewives (p=0.02) and those with education level below primary school (p=0.01).

For the item "How would you rate your overall health now compared to 2 weeks ago", the mean score was found as 2.79±0.71 and 61.2% of participants gave almost the same answer. It was found that the participants not consuming alcohol (p=0.03) and those without comorbid disease (p=0.01) had significantly higher limitation compared to remaining participants.

The mean score was 3.16±0.80 for the item "During the past 2 weeks, how would you rate your health in general?". It was the parameter which showed second highest score in the charts. Of the participants, 54.7% responded as "good" while one-third responded as "fair" or "poor". It was found that general health status was defined as poorer by female participants (p=0.03), elder individuals (p<0.001), those not consuming and not attending regular exercises (p=0.01) and those with education level below primary school (p<0.001).

Of the participants, 61.0% responded as "good and bad parts about equal" to item "How have things been going for you during the past 2 weeks". The mean score was found as 2.77±0.64 and moderate limitation was detected in quality of life. Female participants (p=0.06), elder individuals (p=0.01), those with high blood pressure and not consuming alcohol (p<0.001), those not attending regular exercises (p=0.02) and housewives (p<0.001) rated their quality life as poorer.

Of the participants, 19.9% responded as "no pain to item During the past 2 weeks, how much bodily pain have you generally had", while 29.9% as moderate pain and 8.1% as "severe pain". The mean score was 2.91±1.25 while more than one-half of patients reported mild or moderate pain. It was found that elder female participants (p<0.001), single participants (p=0.01), non-smokers (p=0.01), those not-consuming alcohol (p<0.001), housewives and those with education level below primary school (p<0.001) experienced pain-related limitation.

Discussion

In our study, the mean age was 63.10±11.62 years among participants. Of the participants, 30.3% were in the age group of 60-69 years, comprising greater proportion in the study. Of all individuals included, 81.2% were 50 years or older. The hypertension prevalence ranges from 30% to 45% across the world. Hypertension becomes more common with advancing age with prevalence reaching up to 60% in individuals aged >60 years (3). In our study, underweight participants (1.9%) were the smallest group while overweight (35.4%) and obese participants (35.7%) were the greatest group. Like our study, hypertension prevalence was found as 34.7% in overweight individuals whereas 47.1% in obese individuals in PATENT-2 study from Turkey (13). In our study, it was found that 44.7%

of participants had comorbid disease while hypertension was accompanied by diabetes mellitus in 31.3% of patients. In a study from Turkey, Akman and Akşit (14) found that diabetes mellitus was the most common comorbid disease by 41% in patients with hypertension. In our study, blood pressure was <140/90 mmHg in 39.4% while ≥140/90 mmHg in 60.6% of participants. Given that participants in our study had the diagnosis of hypertension for at least one year, the blood pressure was under control in 39.4% while there was uncontrolled blood pressure in 60.6% of participants. In the PATENT-2 study from Turkey (2012), it was found that blood pressure was under control in only 28.7% of all hypertensive individuals while it was under control in 53.9% of those receiving anti-hypertensive treatment (15). We questioned habits regarding exercises, alcohol, smoking and diet as they were risk factors for blood pressure elevation and part of life style changes recommended in the treatment of high blood pressure. It was found that, of the participants, 35.1% attended to regular exercises, 91.9% were not using alcohol, 75.2% were non-smokers, 21.1% were on DASH diet, and 40.1% had restricted salt intake. Based on our findings, it was seen that only one-fourth of participants adapted lifestyle changes recommended while majority of patients did not adapt such recommendations. In a study by Aypak et al. (16), it was found that 73% of patients were non-smokers while 43.8% had never adapted a dietary regimen, 25.6% partially adapted dietary recommendation and only 13.6% adapted a regular dietary regimen.

When the mean scores in 8-item Dartmouth COOP/WONCA chart were assessed, it was seen that there was functional limitation in all 8 sub-domains as being more prominent in physical activity and overall health. In the literature, there are many studies demonstrating that QOL was negatively affected in patients with hypertension. Although different assessment tools were used, it has been shown that hypertension has a negative effect on health-related QOL and FHS of individuals. In a study on 5,404 individuals, Bardage and Isacson (17) investigated QOL in hypertensive patients and showed that QOL was poorer and was improved by education level. In a population-based study from China, Zhang et al. (18) found that QOL was worsened by hypertension and factors leading hypertension.

In our study, it was observed that female participants with hypertension, particularly housewives, had decreased functional status in all sub-domains other than feelings. Similarly, in a study by Göçgeldi et al. (19), it was shown that QOL and satisfaction were poorer in women with hypertension when compared to men. In our study, 82.8% of participants were housewives. In previous studies, it was shown that housewives experienced more psychological problems such as anxiety, depression, anger or obsession and had less social support compared to working women (20). It is thought that orderly social life and support from family members have positive influence on QOL and functional health status. In our study, it was seen that there was limitation in almost all sub-domains of FHS by decreasing educational level in the participants. In the studies by Bardage and Isacson (17) and Li et al. (21), it was found that QOL was improved by increasing educational level. It was observed that improved awareness and health literacy about hypertension and its treatment due to increased education level had positive impact on individual's functional health status. In our study, it was found that participants not attending regular exercises experienced limitation in sub-domains of FHS including physical health, daily activities, social activities, overall health and quality of life. It is well-known that regular exercises, an important component of lifestyle changes, have a positive effect on blood pressure values in patients with hypertension (22). Physical exercises have positive influences on quality of life, body composition, muscle strength and mental status (23).

In many studies on hypertension and quality of life, it was shown that elevation in blood pressure was associated with QOL and FHS with worsened QOL by increasing blood pressure values (17,21). In our study, a positive correlation was detected between blood pressure evaluation and limitation in daily activities, social activities and QOL sub-domains of functional health status. In our study, it was found that 44.7% of participants had a comorbid disease. It was observed that diabetes mellitus was the most common comorbid chronic condition accompanying to elevated blood pressure. In some studies, it was reported that the presence of comorbid disease worsened QOL in patients with hypertension (19). In our study, it was found that FHS was better in patients without comorbid disease when compared to those with comorbid disease. FHS is defined as individual's ability of adaption to his/her environment in certain time period, which can be measured in subjective and objective manner (10). It is assessed by individual's perception and expectations about life. It can be directly affected by environmental factors. Based on our data, it was seen that majority of patients without comorbid disease were women. It is known that satisfaction and FHS are poorer in women when compared to men. It is though that the results inconsistent with literature can be associated to gender and environmental and sociocultural factors that may affect perceptions of participants in our study.

Conclusion

Our data together with literature findings show that the assessment of FHS in the management in patients with hypertension cannot only allow taking measures to improve QOL but also provide information about environmental factors, lifestyle and habits that may increase cardiovascular risk. In

patients with hypertension, achieving blood pressure control, counseling regarding lifestyle changes and patient education will positively affect functional status. The assessment of FHS by family practitioners providing individual-centered healthcare to an individual, his/her family and community can be guiding for hypertension management, follow-up, prevention of potential complications through lifestyle changes and determination of social support.

Ethics

Ethics Committee Approval: Ethics Committee on Clinical Research of İzmir Bozyaka Training and Research Hospital, University of Health Sciences Turkey (approval: 22/05/2019-8).

Informed Consent: All participants gave written informed consent.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: O.A., Ö.T., Design: O.A., Ö.T., Data Collection or Processing: O.A., Ö.T., Analysis or Interpretation: O.A., Ö.T., Literature Search: O.A., Writing: O.A.

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Deep Neck Space Infection: Clinical Outcomes of Patients Treated in a Tertiary Care Center

Derin Boyun Enfeksiyonları: Üçüncü Basamak Bir Hastanede Takip Edilen Hastaların Klinik Sonuçları

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ABSTRACT

Background: Deep neck space infection (DNSI) is a suppurative infection of the visceral cavities of the neck, which usually begins in the form of fasciitis and progresses to abscess formation. Immediate evaluation and management of deep neck space infections is imperative.

Materials and Methods: A total of 109 patients who were hospitalized and treated in our ear, nose and throat clinic with the diagnosis of DNSI were included in the study. No age or gender restrictions were made. Patient charts were analyzed retrospectively, and information about demographic characteristics of the patients, complaints at presentation and time of admission, location, antibiotics that were used in treatment, duration of hospitalization and complications were recorded.

Results: In our study, 60.6% of the patients were male and the mean age was 31 years (3.5 months-103 years). It was observed that the most frequent admissions to our clinic were in the months of April and January. The most common anatomical locations of infection and abscess were the submandibular region and level 2 in neck, respectively. The most common complaint at presentation was pain (92%), 47.7% of the patients (52) developed DNSI on the right side, and microorganism growth was reported in 52% of 48 patients whose culture results could be reached, and in 32% of these patients (8/25) *Staphylococcus* spp. and in 20% (5/25) *M. tuberculosis* growth was observed. The average age of the patients who required multiple antibiotics was found to be significantly higher.

Conclusion: Although *M. tuberculosis* is not frequently encountered as a causative microorganism in the literature, it was determined as the second most frequently encountered agent in our study and it is an important factor that should be considered. In addition, three important steps in the management of DNSI patients are; ensuring airway safety, appropriate antibiotherapy and surgical drainage. These crucial steps are very important in terms of protection from complications.

Keywords: Deep neck infection, neck abscess, tooth decay, *M. tuberculosis*

ÖZ

Amaç: Derin boyun enfeksiyonlarının (DBE) acil olarak değerlendirilmesi ve yönetimi zorunludur, çünkü tedavi edilmemesi durumunda yıkıcı sonuçlara neden olabilir. Kliniğimizde derin boyun enfeksiyonu nedeniyle tedavi edilen hastaların olası etiyolojik faktörlerinin, DBE boyun bölgelerinin, komorbid durumlarının, karşılaşılan komplikasyonlarının ve yapılan tetkik ve tedavilerinin kapsamlı bir şekilde incelenmesi amaçlandı.

Gereç ve Yöntemler: Çalışmaya derin boyun enfeksiyonu tanısı ile kulak burun boğaz servisimize yatışı yapılan ve tedavileri uygulanan 109 hasta dahil edildi. Yaş ve cinsiyet sınırlaması yapılmadı. Hasta dosyaları retrospektif olarak taranarak hastaların demografik özellikleri, başvuru şikayeti ve zamanı, sigara kullanım öyküsü, travma öyküsü, enfeksiyonun lokalizasyonu (seviye ve taraf), kullanılan antibiyotik özellikleri, hastanede yatış süresi ve gelişmişse komplikasyonlar ile ilgili bilgileri toplandı.

Bulgular: Çalışmamız da hastaların %60,6'sı erkek olup ortalama yaş 31 (3,5ay-103 yaş) olarak hesaplandı. Kliniğimize en sık başvuru yapılan ayların ise Nisan ve Ocak ayları olduğu gözlendi. Hastalarda enfeksiyonun ve apsenin en sık saptandığı anatomik

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ÖZ

lokalizasyonlar ise sırasıyla submandibuler bölge ve boyun seviye 2 idi. En sık başvuru şikayeti %92 ile ağrı olup hastaların %47,7'sinde (52) sağ tarafında derin boyun enfeksiyonu geliştiği ve kültür sonucuna erişilebilen 48 hastanın %52'sinde ise mikroorganizma üremesi raporlanmış olup bu hastaların %32'sinde (8/25) *Staphylococcus* %20'sinde (5/25) ise *M. tuberculosis* üremesi gözlendi. Çoklu antibiyotik kullanım gerekliliği olan hastaların yaş ortalamasının belirgin olarak yüksek olduğu saptandı.

Sonuç: Literatürde etken mikroorganizma olarak *M. tuberculosis* ile sık karşılaşılmasa da çalışmamızda en sık karşılaşılan ikinci etken olarak görülmüş olup dikkate alınması gereken önemli bir faktördür. Bunun yanında DBE hastalarının yönetiminde üç önemli adım; hava yolu güvenliği, uygun antibiyoterapi ve cerrahi drenajı sağlamaktır. Bu önemli adımlar komplikasyonlardan korunma açısından çok önemlidir.

Anahtar Kelimeler: Derin boyun enfeksiyonu, boyun apsesi, diş çürüğü, *M. tuberculosis*

Introduction

Deep neck space infection (DNSI) is a suppurative infection of the visceral cavities of the neck, which usually begins in the form of fasciitis and progresses to abscess formation (1). While the most common cause in adult patients is odontogenic origin, it often develops after tonsillopharyngitis in the pediatric age group (2,3). Less common causes are suppurative lymphadenitis, infection of congenital neck cysts and otologic infections (4).

There are 13 different compartments on the neck. If the primary infection originating in a region is not treated in time, the infection may spread to these compartments rapidly in accordance with the fascial plans (5). These infections, which initially start as cellulite and fasciitis, may progress to local organ damage with abscess formation and tissue necrosis in time (6). As a result, this complications such as airway obstruction, vascular pathologies (deep vein thrombosis), pleural or pericardial complications, empyema, mediastinitis, and vertebral osteomyelitis can be seen and these complications may result in serious morbidity or be fatal in patients due to sepsis or respiratory distress (7). Besides, death is often associated with mediastinal invasion or vascular complications in patients with DNSI (6,8). Therefore, a complete physical examination and appropriate treatment should be initiated promptly for the correct management of DNSI patients (2). Also, due to possible complications, comorbid conditions of patients may need to be handled in a multidisciplinary manner.

The aim of this study is to investigate the demographic characteristics of patients treated for DNSI in our clinic, to investigate the etiological causes of the disease and the anatomical spread regions, to evaluate the treatment applied and the approach to the complications encountered.

Material and Methods

Ethics committee approval for the study was obtained from the local ethics committee with the approval number of 2019/1994 and the study was conducted in accordance with the Helsinki Declaration-2008 principles. Informed consent was obtained from all patients included in the study.

This study was conducted from January 2013 to February 2020 in the otorhinolaryngology clinic of our tertiary hospital. One hundred nine patients who were hospitalized and treated with the diagnosis of DNSI were involved in the study.

No age or gender limitation was made for the patients that were included in the study. Patients who had a known malignancy in the head and neck region or who received treatment for this reason within the last 1 year, and outpatients were not included in the study. In addition, patients who were discharged due to treatment refusal were excluded from the study. All patients who met these criteria and were treated in our clinic with the diagnosis of DNSI were included in the study.

Patient data were scanned retrospectively, and information on demographic characteristics of the patients, complaints and time of admission, smoking history, trauma history, location of infection (level and side), antibiotic that were used in treatment, duration of hospitalization and complications (if developed) were collected.

In examination, patients with abscesses or those whose clinical findings were consistent with inflammation in deep tissue plans were visualized by ultrasonography (USG) and/or contrast-enhanced neck computed tomography. Also, superficial abscesses were aspirated with a needle in the clinic. Abscesses which were not superficial or could not be drained with a needle were drained under USG guidance with needle aspiration, and if the incoming material was purulent, it was sent to the microbiology laboratory for culture and antibiogram study.

All patients who were hospitalized and treated with the diagnosis of DNSI were treated with IV antibiotherapy. Empirical treatment was started with ampicillin-sulbactam at a dose of 150 mg/kg/day (maximum 4x1.5 gr), and according to the clinical response and antibiogram results of the patient, treatment was changed to multiple antibiotherapy or drug change was carried out.

Statistical Analysis

SPSS program was used for statistical analysis. Descriptive statistics were given as number and percentage for categorical variables, as mean and standard deviation for numerical variables with homogeneous distribution, and as median and minimum-maximum for numerical variables without homogeneous distribution. When numerical variables did not meet the normal distribution condition, comparisons of two independent groups were made using the Mann-Whitney U test. Statistical significance level was accepted as $p<0.05$.

Results

In our study, there were 109 patients with DNSI, who were hospitalized and treated in our clinic, and the clinical characteristics of these patients were evaluated. The average age of the patient population was 31 years (3.5 months-103 years), 60.6% of the patients were male (M/F: 66/43) (Table 1).

It was observed that 47.7% (52) of the patients developed DNSI on the right side, 35.8% (39) on the left side and 16.5% (18) developed bilateral or midline deep neck infections (Table 1). In addition, in Table 1, patient characteristics such as the presence of dental caries, smoking history, trauma history, use of multiple antibiotic treatments and whether surgical procedures were performed are also shown. The most common initial complaint of the patients was pain (92%), followed by fever and swelling in the neck (Table 2).

The most common anatomical locations for infection and abscess were the submandibular region and neck level 2, respectively (Table 3). 83% of the patients were punctured with a needle and a sample was sent for culture if there was an incoming purulent fluid. The results of 10 of the 58 patients whose samples were analyzed could not be reached through patient data forms and 23 (48%) of the 48 patients whose results were available did not have any from the samples taken. Microorganism growth was reported in 52% of 48 patients whose culture results could be reached, and *Staphylococcus* growth was observed in 32% (8/25) of these patients and *M. tuberculosis* was observed in 20% (5/25) (Table 4).

In 29 (26%) of 109 patients who received empiric treatment, multiantibiotic treatment was initiated according to clinical response and/or culture results. In addition to the empirical ampicillin-sulbactam treatment, Metronidazole (16/29) was more frequently added to the treatment, and different antibiotic preferences were made according to the culture-antibiogram results and clinical responses.

Table 1. Demographic and clinical characteristics of the patients

		n	Median	Minimum-maximum
Age		109	31	3.5 months-103 years
Hospital stay (days)		109	6	2-60
		n	**%**	
Gender	**Male**	66	60.6	
	Female	43	39.4	
Smoking	**Yes**	52	47.7	
	No	57	52.3	
Tooth decay	**Yes**	68	62.3	
	No	41	37.7	
Surgical intervention	**Yes**	22	20.2	
	No	87	79.8	
	Revision surgery	4	3.6	
Trauma history	**Yes**	5	4.6	
	No	104	95.4	
Use of antibiotics	**Single**	79	73.1	
	Multiple	29	26.9	
Tonsillectomy procedure	**Yes**	2	98.1	
	No	107	1.9	
Infection localization	**Right**	52	47.7	
	Left	39	35.8	
	Bilateral or median	18	16.5	

Four patients had to be followed up in the intensive care unit (ICU) due to their general conditions and respiratory symptoms. Tracheotomy was performed in 3 of these patients due to prolonged intubation caused by respiratory tract obstruction or general condition of the patient. In two patients, the infection advanced through the facial planes and mediastinitis developed. Surgical interventions for the neck and mediastinum were performed in both patients with the diagnosis of mediastinitis. While one patient completed his treatment and was discharged, the second patient, who was tracheotomized, died due to the progression of mediastinitis and septic shock.

Multiple antibiotic treatment was required for all patients (4 patients) treated in the intensive care unit. In addition, when all patients were evaluated, patients who required multiple antibiotics were found to have a statistically significantly longer hospitalization period ($p<0.001$) compared to other patients, and the mean age of the patients was higher ($p=0.026$) compared to that of patients using single antibiotics. Although the use of multiple antibiotics was observed more frequently in patients with dental caries, it was not statistically significant ($p=0.168$) (Table 5).

As abscess drainage under local anesthesia in clinic conditions was not thought to be sufficient, a total of 22 patients underwent abscess drainage under general anesthesia. Necrotic tissue debridement was also performed since 2 of these 22 patients also had skin necrosis. Also, surgical intervention was required for the second time after the first surgery in a total of 3 patients, one of whom underwent necrotic tissue debridement and two of whom underwent abscess drainage. Reconstruction of the open wound with free skin and drainage of regenerating abscesses were performed in these revision surgical interventions (Table 1).

When the time of admission to the hospital was evaluated monthly and seasonally, it was found that the patients were most frequently admitted to the hospital in the spring, then in the winter and autumn, respectively. It was observed that the months when admissions were mostly made were April and January (Figure 1).

Table 2. Symptom frequency

Symptom	%
Pain	92.66
Fever	74.31
Swelling	86.24
Dysphagia	40.37
Trismus	34.86

Table 3. Anatomical location where infection was detected

	N	%
Submandibular region	43	39.45
Neck level I-II	15	13.76
Buccal/premaxillary region	3	2.75
Neck level II	16	14.68
Neck level II-III-IV	9	8.26
Neck level IV	2	1.83
Neck level V	1	0.92
Retropharyngeal region	4	3.67
Parotids region	4	3.67
Parapharyngeal region	2	1.83
Undefined	10	9.17
Total	**109**	**100.0**

Table 4. Microorganisms detected in culture samples

Microorganism name	n
Staf aureus (3)	3
Staf epidermidis (3)	3
MRSA (2)	2
M.tuberculosis (5)	5
Enterobacter (2)	2
Klebsiella (2)	2
Streprococcus viridans (2)	2
Streptoccus constellatus	1
pharyngis	1
Proteus mirabilis (1)	1
Streptococcus lugdunensis (1)	1
Finegoldia magna (1)	1
Prevotella denticola (1)	1
Candida albicans (1)	-

Discussion

Dental problems, advanced age, comorbid diseases and smoking are important factors for the development of DNSI (2). In our study, 60.6% of our study consisted of men (M/F: 66/43), and the average age of the patient population was 31 years. The smoking rate of the patients in our study was

Table 5. Relationship of multiple antibiotic use with other clinical conditions

Demographic or clinical feature	p
Age of the patient	0.026*
Tooth decay	0.168
Hospital stay	0.001*
Gender	0.805
Smoking	0.943
Major surgical intervention	0.026*
Diabetes mellitus	0.490

*p<0.05

47.7% and this rate was higher than the smoking rate (30.5%) in the Turkish population reported by Özer et al. (9) (Table 1). In addition, it is stated in the literature that the average length of stay in the hospital of the patients varies between 5 and 8 days (2,10). Also in our study, the average length of stay was 6 days.

In particular, factors that adversely affect the immune system, such as diabetes mellitus, human immunodeficiency virus (HIV), alcoholism, drug addiction and being elderly with comorbid diseases, cause higher risk for DNSI complications (11). Apart from the mentioned comorbid conditions, there are studies in the literature reporting that low socio-economic status and low educational status increase the susceptibility to the development of DNSI (12,13,14). In addition, infections caused by resistant microorganisms due to the widespread use of antibiotics also increase the risk in this population (6,15). Due to the widespread and timely use of antibiotics and the easy accessibility to broad-spectrum antibiotics, the incidence of deaths and complications due to DNSI has decreased (16). However, it is still possible to encounter with severe neck infections due to delayed diagnosis or the comorbid status of the patients (5). Although the incidence is not very high, diagnosis, treatment and management of DNSI are still an important issue.

Three important steps in the correct management of DNSI were defined as ensuring airway safety, antibiotherapy and surgical drainage (2,17).

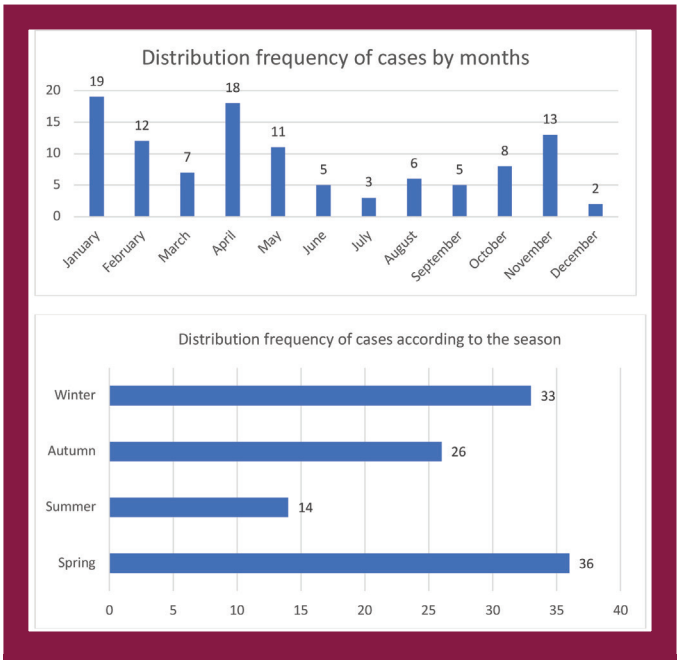

Figure 1. Frequency of the patients' application times by (a) months and (b) seasons

In the literature, it is recommended to use penicillin, gentamicin and combined antimicrobial therapies and, when necessary, metronidazole could be added to prevent anaerobic bacteria (2,4,15,17,18). In our clinic, metronidazole (16/29) was most frequently used additional treatment to ampicillin-Sulbactam treatment, and different antibiotics were added in the treatment according to the clinical response and culture-antibiogram results. However, it was determined that the hospitalization periods of the patients requiring multiple antibiotics were statistically longer ($p<0.001$) and the mean age of the patients was higher ($p=0.026$), and it was also found that no statistically significant difference was detected between dental caries and multiple antibiotic use ($p=0.168$) (Table 5).

Moreover, abscess drainage was performed under general anesthesia in all patients who were found to have deep abscess that could not be drained under USG guidance. In addition, four patients whose general conditions and respiratory symptoms worsened despite medical treatment had to be followed up in ICU conditions. Tracheotomy was required for 3 of these patients.

In a retrospective analysis with 248 diabetic patients, they had longer hospital stay than non-diabetic patients (19). In our study, while no significant difference was detected between diabetic and non-diabetic patients in terms of length of stay and use of multiple antibiotics, a statistically significant difference was found in terms of the need for hospitalization in the ICU ($p=0.048$) and the need for tracheotomy ($p=0.052$).

Prabhu and Nirmalkumar (2) stated that according to the culture results of 1034 patients, *Streptococcus viridans* sp. (19.82%) and *S. aureus* (18.66%) were the most common pathogens. However, *M. tuberculosis* was not detected in their study. Also, Sittitrai et al. (20) found that, among 223 patients, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes* were the three most frequently isolated bacteria in 31 HIV patients, while *Streptococcus pyogenes*, *Streptococcus pneumonia* and *Streptococcus viridans* were the most common pathogens in the non-HIV group (192), *M. tuberculosis* was not detected in this study, too. Besides, Martínez et al. (10) revealed that the most common isolated bacteria in 330 patients was *S. viridans* (32.1%), followed by *Streptococcus pyogenes* (22.6%). *Staphylococcus aureus* was found in 5.1% and M. tuberculosis was found in 0.7%. Agarwal et al. (16), Rana et al. (21) and Mungul and Maharaj (22) stated that *Staphylococcus aureus* was the most common pathogen detected in their studies. Also in our study, microorganism growth was reported in 52% of 48 patients whose culture results could be reached, and the most common microorganism was *Staphylococcus aureus* and it was detected in 32% (8/25) of the patients. However, unlike the literature, *M. tuberculosis* growth was observed in 20%

(5/25) of our patients (Table 4). However, it is an important limitation that 58 of the treated patients were taken for culture and only 25 of the patients had culture results.

DNSI often occurs in potential spaces of the neck such as the submandibular region, peritonsillar region, parapharyngeal or retropharyngeal space, and masticator space (6). Martínez et al. (10) reported that 65.2% of the patients had infection located in the peritonsillar region and 0.9% in the submandibular region. Buckley et al. (8) stated that infection was located in the parapharyngeal region at the rate of 60%. Moreover, Prabhu and Nirmalkumar (2) detected that, in 52% of the patients, infection was in the submandibular region, and Motahari et al. (18) revealed that infection was detected in the submandibular region in 45% of the 815 patients. Also in our study, the most common area of infection was the submandibular region with a rate of 39.45%.

Conclusion

Although *M. tuberculosis* is not frequently encountered as the causative microorganism in the literature, it was found to be the second most frequently encountered agent in our study and it is an important factor that should be considered. In addition, when the patient is admitted to the hospital, it is important to start treatment early against frequently encountered causative microorganisms and proper treatment plan management is very important in terms of protection from complications as delayed treatment of DNSI carries a serious risk of morbidity and mortality.

Ethics

Ethics Committee Approval: Ethics committee approval for the study was obtained from the local ethics committee with the approval number of 2019/1994 and the study was conducted in accordance with the Helsinki Declaration-2008 principles.

Informed Consent: Informed consent was obtained from all patients included in the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practies: K.S.K., İ.Y., U.D., N.S., S.T., Concept: K.S.K., S.T., Design: K.S.K., İ.Y., Data Collection or Processing: İ.Y., U.D., N.S., Analysis or Interpretation: K.S.K., İ.Y., U.D., N.S., Literature Search: İ.Y., U.D., S.T., Writing: K.S.K., İ.Y., U.D., N.S., S.T.

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A Study of HIV Knowledge and Stigma Among Health Care Workers from Istanbul-Turkey

İstanbul-Türkiye'den Sağlık Çalışanlarında HIV Bilgisi ve Stigması Üzerine Bir Çalışma

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ABSTRACT

Background: Human immunodeficiency virus (HIV) is a global public health problem affecting over 38 million people. While the yearly number of new cases is reducing in the world, this number is increasing in our country. Among the health care workers (HCW), stigma is an important obstacle. We aimed to assess the knowledge and attitudes related to HIV/AIDS among HCW.

Materials and Methods: The study included HCW actively working at University of Health Sciences Turkey Şişli Hamidiye Etfal Training and Research Hospital for one year or longer, who visited the hospitals exclusive health clinic for hospital personnel for any reason from July to October 2019 and agreed to participate in the study. Participants took an information form prepared by researchers in face-to-face interviews. The statistical program SPSS was used to analyze data.

Results: A total of 332 participants with the mean age of 28.5 years (min 21, max 60) were included. 52.4% (n=174) successfully identified the transmission routes and the most known route was "transmission by sexual routes" and the most mistaken route was "body fluids". 17.8% responded with "I agree" to the "all HIV (+) individuals should be quarantined" statement, 20.2% agreed that "I wouldn't let my child meet with the child of an HIV (+) parent". 9.6% agreed with "HIV (+) individuals should carry an externally visible sign" and 5.4% agreed "HIV is only seen in homosexuals". Nurses and personnel had high agreement rates with the quarantine and labeling judgments. Personnel most frequently agreed with "HIV is only seen in homosexuals". When education status and Likert-type questions about stigma were compared, there were significant differences identified for all 4 questions (p=0.000).

Conclusion: Inadequate information and prejudices of HCW may lead to serious results in terms of stigma for HIV (+) individuals. Providing information about problems encountered by these people and revealing the outcomes of stigma may ensure HCW to develop empathy and break the negative feedback cycle of stigma.

Keywords: HIV, HIV stigma, health care workers, HIV knowledge

ÖZ

Amaç: İnsan bağışıklık eksikliği virüsü (HIV) dünya üzerinde 38 milyon insanı etkileyen küresel bir halk sağlığı sorunudur. Dünya genelinde yıllık yeni olgu sayısı azalırken, ülkemizde bu sayı giderek artmaktadır. HIV ile ilgili bakım zincirinin her alanında bulunan sağlık çalışanlarında HIV stigması büyük bir problemdir. Bu nedenle çalışmamızda sağlık çalışanlarının HIV/AIDS ile ilgili bilgi ve tutumlarını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Çalışma 2019 Temmuz-Ekim ayları arasında herhangi bir nedenle Sağlık Bilimleri Üniversitesi Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi çalışan sağlığı polikliniğine gelen ve çalışmaya katılmayı kabul eden; bir yıl ve üstünde Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesinde aktif çalışan sağlık çalışanlarına yapılmıştır. Katılımcılara tarafımızdan hazırlanan bilgi formu yüz yüze sorgulama yöntemi ile uygulanmıştır. İstatistiksel analizde SPSS programı kullanılmıştır.

Bulgular: Çalışmaya toplam 332 kişi katılmış olup; yaş ortalaması 28,5 (min: 21-maks: 60) idi. Katılımcılardan bulaş yolunu bilme açısından başarılı olanların oranı %52,4 (n=174), en fazla bilinen doğru yol "cinsel yol ile bulaş" ve yanlış yol "vücut sıvıları" idi. %17,8 "Tüm HIV (+) bireyler karantinaya alınmalıdır" yargısına katılmıştır. %20,2 "Çocuğumu, ebeveyni HIV (+) olan

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ÖZ

çocukla görüştürmem", %9,6 "HIV (+) bireyler dışarıdan görülebilen işaret taşımalıdır." ve %5,4 "HIV sadece eşcinsellerde görülür" yargılarına katılmışlardır. Karantina ve işaret taşıma yargılarında hemşireler ve personeller yüksek oranda katılıyorum cevabı verirken, "HIV (+) bireyler sağlık kurumlarında çalışmamalıdır" ve "HIV (+) öğretmenin olduğu sınıfta çocuğumun eğitim almasını istemem." yargılarına doktorlar daha sık katılıyorum cevabı vermiştir. "HIV sadece eşcinsellerde görülür" yargısına ise personeller en sık katılıyorum cevabı vermiştir. Eğitim alma durumu, stigma ile ilgili Likert tipi sorularla karşılaştırıldığında, 4 soruda da anlamlı farklılık saptanmıştır (p=0,000).

Sonuç: Sağlık çalışanlarının bilgi eksikliği ve önyargıları HIV (+) bireyler için stigma açısından ciddi sonuçlar doğurabilir. Verilen eğitimlerde teknik konuların yanında bu kişilerin karşılaştıkları problemleri ortaya koyan eğitimlerin verilmesi, stigmanın sonuçlarının ortaya konması sağlık çalışanlarının empati kurmasını sağlayarak; stigmanın ortaya çıkardığı kısır döngünün kırılmasına neden olabilir.

Anahtar Kelimeler: HIV, HIV stigması, sağlık çalışanları, HIV bilgisi

Introduction

Human immunodeficiency virus (HIV) is a global public health problem affecting over 38 million people around the world. Since the first HIV case was observed in Turkey in 1985, there have been 25,809 HIV (+) people reported to be positive with confirmed tests and 1985 AIDS cases (1). While the yearly number of new cases is reducing in the world in general, this number is increasing in our country (2). A study in 2019 observed that half of the people with HIV infection were late to seek medical help (3).

One of the reasons for this delay is the fear of stigmatization due to HIV. Stigma related to HIV can be defined as negative attitudes and beliefs about people living with HIV (PLWH) and a process of devaluation (4,5). Stigma related to HIV may be expressed through a variety of routes. It may be categorized as stigma expected to be experienced when the HIV status is known, perceived stigma related to how people living with HIV should behave, internalized stigma, shame, experienced stigma and discrimination (6). Due to the fear created by stigmatization, individuals may delay getting tested for HIV (7), and experience difficulty in disclosing their seropositive status to those around them, beginning and continuing treatment and seeking medical care when they require (8,9,10). The fight against stigma and fear related to HIV have become a part of the fight against HIV. Health care workers have a big role in this fight. For this reason, in our study, we aimed to assess the knowledge and attitudes related to HIV/AIDS among health care workers.

Material and Methods

The study included health care workers (doctors, nurses and other personnel) actively working at University of Health Sciences Turkey Şişli Hamidiye Etfal Traning and Research Hospital for one year or longer, who visited the Şişli Hamidiye Etfal Training and Research Hospital exclusive health clinic for hospital personnel for any reason from July to October 2019 and agreed to participate in the study. Verbal consent was obtained from the participants. Participants took an information form prepared by the researchers in face-to-face interviews. During this period, the number of personnel working in the hospital was 2.432, with sample size calculated as 332 for 95% confidence interval.

Our study received permission from University of Health Sciences Turkey Şişli Hamidiye Etfal Training and Research Hospital ethics committee, dated 25.06.2019 and numbered 2452.

Information Form

The information form prepared by the researchers after literature screening included questions about the participants' sociodemographic information in addition to questions about general information related to HIV, transmission routes, and risk factors and 3-point Likert judgement statements to assess attitudes towards PLWH.

Participants were given points according to their status of knowing transmission routes and individuals at risk (Cronbach alpha: 0.632). According to a Cronbach alpha reliability study, this value is acceptable (11). Correct answers about at-risk individuals and risky situations were given 1 point, with wrong answers given 0 points and response points for total risk status was calculated for all participants. The median value was calculated as 7 (min 2, max 8) for those with points above 7 accepted as successful in correctly knowing risk groups, while those with points below 7 were accepted as unsuccessful in knowing risk groups.

Correct answers to questions related to transmission routes were given 1 point, with wrong answers given 0 points and knowledge of transmission route totals were calculated for all participants. The median value was 12 (min 5, max 13) with 12 points or more accepted as successfully knowing

transmission route and less than 12 points accepted as unsuccessful.

Statistical Analysis

The statistical program SPSS was used to analyze data. Parameters in the study were classified as categoric and discrete. Numerical data were given as mean and standard deviation while categorical data were given as median and percentage. T-test was used in comparisons of numerical data while the chi-square test was used in comparisons of categorical data. Statistical analyses were completed using the SPSS software with a p value of 0.05 accepted as statistically significant.

Results

The study included a total of 332 participants with the mean age of 28.5 years (min 21, max 60). The sociodemographic features of participants are given in Table 1. The number of individuals who received education related to HIV was 234. Among participants, 84.3% (n=280) stated they had encountered PLWH at least once.

Assessment of Responses to Questions About Knowledge of HIV/AIDS

When the responses about the frequency of HIV/AIDS in Turkey were analyzed, 155 people (46.7%) answered correctly. The majority of these people (72.3%; n=112) worked in clinical units, while 79.4% (n=123) had received education. The rate of correct responses to the question about the % probability of transmission after needlestick injuries was 41% (n=136).

Table 1. Sociodemographic features of participants

Variable	n (%)
Sex	
Female	242 (72.9)
Male	90 (27.1)
Occupation	
Doctor	171 (51.5)
Nurse	98 (29.5)
Personnel	63 (19)
Department	
Internal medicine	230 (69.3)
Surgical	71 (21.4)
Emergency	31 (9.3)
Training related to HIV/AIDS	
Received	234 (70.5)
Did not receive	97 (29.5)
Estimated number of PLWH known	
None	52 (15.7)
1-4	128 (38.5)
5-10	51 (15.4)
>10	101 (30.4)

HIV: Human immunodeficiency virus

Responses of participants to knowledge statements in likert scale are given in Table 2, with the association with occupation evaluated. Nurses had higher rates of "I agree" in response to the question "I think I have adequate information about HIV" compared to doctors and personnel (p=0.003). Doctors responded to the question "HIV (+) individuals should be checked for other infectious diseases" with "I agree" mostly (p=0.000). Nurses had higher rates of "I agree" in response to the statement "I know how to approach an HIV (+) patient" (p=0.000). Doctors were more likely to disagree with the false statement "there is no transmission if tests are negative in the first week after unprotected sexual relations with an HIV (+) individual" (p=0.000).

Assessment of Knowledge of HIV/AIDS Transmission Routes and Related Factors

The knowledge of transmission routes of participants is given in Table 3, with the most known routes of "transmission by sexual routes" and the most mistaken route of "body fluids." The number of people who correctly identified all routes was 94 (28.3%). All participants were given a score according to their correct answers regarding transmission routes, and those who scored equal to or greater than the calculated median value were considered successful. The percentage of individuals who successfully identified the transmission routes was 52.4% (n=174), but the rate of those who were unsuccessful was 43.1% (n=143).

Table 4 shows the relationship between knowledge of HIV transmission routes and influencing factors, and correctly identifying transmission routes was found to be related to HIV education (p=0.000). Doctors were the most successful group whereas other personnel were the least successful group (p=0.000). When success in identifying transmission routes was compared according to department, the success rate was 35.5% for those working in the emergency service, 59.2% for those in the surgical unit, and 59.1%for those in clinics, and this was statistically significant (p=0.041).

Assessment of Knowledge of HIV/AIDS risk Status and Related Factors

The participants' knowledge on risk status is given in Table 5 with the most well-known risk of "unprotected sexual relations" and least well known risk of "unprepared medical interventions." All participants were given a score according to their correct answers regarding at-risk individuals and risky situations, and those who scored equal to or greater than the calculated median value were considered successful. The percentage of successful participants in terms of identifying at-risk individuals and risky situations was 52.4% (n=174), and

Table 2. Responses of participants to knowledge statements

		Doctor	Nurse	Personnel	p
		n (%)	n (%)	n (%)	
HIV (+) individuals should be checked for other infectious diseases	I agree	158 (92.4)	84 (85.7)	45 (71.4)	0.000
	I don't know	2 (1.2)	11 (11.2)	12 (19)	
	I disagree	11 (6.4)	3 (3.1)	6 (9.5)	
I know how to approach HIV (+) patients.	I agree	100 (58.5)	70 (71.4)	29 (46)	0.000
	I don't know	33 (19.3)	19 (19.4)	26 (41.3)	
	I disagree	38 (22.2)	9 (9.2)	8 (12.7)	
If tests are negative in the first week after unprotected sexual relations with an HIV (+) individual, there is no transmission.	I agree	11 (6.4)	6 (6.1)	11 (17.5)	0.000
	I don't know	14 (8.2)	22 (22.4)	37 (58.7)	
	I disagree	146 (85.4)	70 (71.4)	15 (23.8)	
I think I have adequate information about HIV.	I agree	81 (47.4)	51 (52)	14 (22.2)	0.003
	I don't know	38 (22.2)	18 (18.4)	18 (28.6)	
	I disagree	52 (30.4)	29 (29.6)	31 (49.2)	

HIV: Human immunodeficiency virus

Table 3. Responses about HIV/AIDS transmission routes and data

Transmission Routes	% of people answering yes	% of people answering no
Through blood	96.7	3.3
Intravenous drug, substance use	74.2	25.8
Sexual relations	98.3	1.7
Body fluids (sweat, tears)	35	65
Personal belongings (clothing, towels)	8.3	91.7
In air	0.8	99.2
Skin contact (handshakes)	2.5	97.5
Domestic items (forks, knives)	9.2	90.8
Common use areas (pools, gyms)	6.7	93.3
Toilets, sinks	10	90
Insect bites	13.3	86.7
From mother to infant during birth	83.3	16.7
Organ transplants	86.7	13.3

HIV: Human immunodeficiency virus

the percentage of successful participants was 47.6% (n=158). Success rate was associated with receiving HIV education.

The association between participants' knowing risk status and influencing factors is given in Table 6. There was a significant association identified with occupation. Doctors and nurses were more successful, in that order, compared to other health personnel (p=0.000). Educational status and place of education were statistically significant (p=0.000).

Assessment of Judgement Statements About Assessment of PLWH Attitudes: (People Living with HIV)

Among participants, 17.8% responded with "I agree" to the "all HIV (+) individuals should be quarantined" statement, 23.8% agreed that HIV (+) individuals should not work in health facilities, 24.7% agreed that "I would not like my child to receive education in a class with an HIV (+) teacher", 20.2% agreed that "I would not let my child meet with the child of an HIV (+) parent". Of participants, 9.6% agreed with the judgement statement that "HIV (+) individuals should carry an externally visible sign' and 5.4% agreed that 'HIV is only seen in homosexuals".

The association of judgement statements to assess participant attitudes to PLWH with occupation is given in Table 7. Apart from the statements "the individual being HIV (+) is an obstacle to marriage", "I would not let my child meet with the child of an HIV (+) parent" and "if my child had HIV, I would support them instead of blaming them", all judgements were identified to be associated with occupation. Nurses and personnel had high agreement rates with the quarantine and labeling judgments, while doctors responded with "I agree" more often to "HIV (+) individuals should not work in health facilities" and "I would not like my child to receive education in a class with an HIV (+) teacher" statements. Personnel most frequently agreed with the judgement that "HIV is only seen in homosexuals". When education status and Likert-type questions about stigma were compared, it was found that there were significant differences identified for all 4 questions (p=0.000).

Discussion

Health care workers are professionally educated health service providers and are responsible for providing accurate

Table 4. Correlations of success about HIV/AIDS transmission routes and influencing factors

		Successful	Failed	p
According to sex	**Female**	59.1%	40.9%	0.193
	Male	51.1%	48.9%	
According to department	**Emergency**	35.5%	64.5%	0.041
	Surgery	59.2%	40.8%	
	Clinic	59.1%	40.9%	
According to occupation	**Doctor**	78.9%	21.1%	0.000
	Nurse	50%	50%	
	Personnel	7.9%	92.1%	
According to training status	**Received**	66%	34%	0.000
	Did not receive	35.1%	64.9%	

HIV: Human immunodeficiency virus

Table 5. Responses about risk status for HIV/AIDS

Risk states	% of people answering yes	% of people answering no
Being a health care worker	88	12
Having unprotected sexual relations	95.2	4.8
Using intravenous medication (drugs)	88.9	11.1
Sexual relations with an HIV + individual	83.4	16.6
Be exposed to sexual assault	69.9	30.1
Having tuberculosis	18.1	81.9
Travelling in risky regions	24.1	75.9
Unprepared medical interventions	45.8	54.2

HIV: Human immunodeficiency virus

Table 6. Correlation of participant knowledge on risky situations and influencing factors

		Successful	Failed	p
According to sex	**Female**	54.1%	45.9%	0.182
	Male	47.8%	54.1%	
According to department	**Emergency**	48.6%	51.6%	0.887
	Surgery	53.5%	46.5%	
	Clinic	52.6%	47.4%	
According to occupation	**Doctor**	59.6%	40.4%	0.000
	Nurse	57.1%	42.9%	
	Personnel	25.4%	74.6%	
According to training status	**Received**	59.1%	40.9%	0.000
	Did not receive	36.1%	63.9%	

and reliable information to society about topics like diseases, preventive precautions and treatments. For this reason, in-service education in the health field is important in terms of keeping up to date.

As a result of developments in the field of HIV/AIDS, important steps have been taken in terms of early diagnosis and treatment to stop the disease for PLWH. There are studies showing that when the viral load of PLWH is at unidentifiable levels, these people are not infectious (12).

When participants were asked about transmission risk due to needlestick injuries in our study, 41% gave the correct answer. When divided according to occupation, 25% of nurses and 8% of personnel gave the correct response. Studies show that especially nurses and laboratory employees encounter contact with blood and body fluids with needlestick accidents; however, when questions about the transmission rate due to being stuck by an infected patient's needle were asked, only a very small portion gave the correct answer (13,14). Studies, similarly, showed lack of information about occupational diseases and work accidents among health personnel (15,16), and that adding these topics to educational meetings during working life and even informing individuals who attend routine check-ups in occupational health clinics with special booklets/brochures will be beneficial.

In a study on assistant doctors, most participants gave the correct answer when asked about the prevalence of HIV in Turkey (17). In our study, less than half of participants correctly knew the prevalence. The reason for this may be that the sample comprised of other health personnel along with doctors.

When previous studies were investigated, it was observed that health care workers had inadequate information about HIV transmission routes; inadequacies about questions related to transmission routes like saliva, sharing drinking glasses and fly bites were notable (18,19,20). In our study, 56.9% successfully knew information about transmission routes, with 28.3% providing all the right answers. The most commonly mistaken transmission route was 38.9% for body fluids (sweat, tears). Among those who were unsuccessful, 25.2% were doctors (n=36), 34.2% were nurses (n=49) and

40.6% were other personnel (n=58). It is considered that the reason for the wrong answers by clinicians may be due to their branches. In fact, those working in branches with high infection probability like surgery and emergency services had more information. While doctors and nurses had similar rates of success for correct answers about risk status, there was a significant difference for the points for transmission route knowledge. In the two groups, those who had received education were significantly more successful, which is parallel to the findings of studies before and after education in the literature (13,18,21). We think training of health personnel about infectious diseases during and after faculty education will reduce this deficient information.

One of the basic factors in the stigma forming against PLWH is the thought of catching HIV infection while providing health services (6). Incorrect information about

Table 7. Correlation of judgement statements about PLWH of participants with occupation

		Doctor	Nurse	Personnel	p
		n (%)	n (%)	n (%)	
I think all the people who visited hospital should be screened for HIV.	I agree	43 (25.1)	70 (71.4)	43 (68.3)	0.000
	I don't know	16 (9.4)	6 (6.1)	8 (12)	
	I disagree	112 (65.5)	22 (22.4)	12 (19)	
HIV (+) individuals' diagnosis should be shared with other health care workers when they visited health facilities.	I agree	113 (66.1)	78 (79.6)	41 (65.1)	0.007
	I don't know	12 (7)	7 (7.1)	11 (17.5)	
	I disagree	46 (26.9)	13 (13.3)	11 (17.5)	
Laboratory results of HIV (+) individuals should be told to partners/families.	I agree	61 (35.7)	50 (51)	37 (58.7)	0.000
	I don't know	21 (12.3)	17 (17.3)	13 (20.6)	
	I disagree	89 (52)	31 (31.6)	13 (20.6)	
HIV (+) individuals should be quarantined.	I agree	7 (4.1)	23 (23.5)	29 (46)	0.000
	I don't know	7 (4.1)	6 (6.1)	17 (27)	
	I disagree	157 (91.8)	69 (70.4)	17 (27)	
HIV (+) individuals should not be employed in health facilities.	I agree	37 (21.6)	21 (21.4)	21 (33.3)	0.000
	I don't know	26 (15.2)	24 (24.5)	22 (34.9)	
	I disagree	108 (63.2)	53 (54.1)	20 (31.7)	
An individual having HIV (+) is an obstacle to marriage.	I agree	42 (24.6)	23 (23.5)	15 (23.8)	0.376
	I don't know	45 (26.3)	16 (16.3)	15 (23.8)	
	I disagree	84 (49.1)	59 (60.2)	33 (52.4)	
HIV is only seen in homosexuals.	I agree	2 (1.2)	2 (2)	14 (22.2)	0.000
	I don't know	7 (4.1)	3 (3.1)	18 (28.6)	
	I disagree	162 (94.7)	93 (94.9)	31 (49.2)	
HIV (+) individuals should carry an external label identifying their diagnosis.	I agree	4 (2.3)	13 (13.3)	15 (23.8)	0.000
	I don't know	13 (7.6)	15 (15.3)	20 (31.7)	
	I disagree	154 (90.1)	70 (71.4)	28 (44.4)	
I would not let my child meet with the child of an HIV (+) parent.	I agree	27 (15.8)	22 (22.4)	18 (28.6)	0.062
	I don't know	36 (21.1)	19 (19.4)	18 (28.6)	
	I disagree	108 (63.2)	57 (58.2)	27 (42.9)	
I do not want my child to receive education in a class with an HIV (+) teacher.	I agree	42 (24.6)	19 (19.4)	21 (33.3)	0.038
	I don't know	25 (14.6)	16 (16.3)	16 (25.4)	
	I disagree	104 (60.8)	63 (64.3)	26 (41.3)	
If my child had HIV, I would be supportive and not blame them.	I agree	126 (73.7)	77 (78.6)	45 (71.4)	0.419
	I don't know	22 (12.9)	15 (15.3)	10 (15.9)	
	I disagree	23 (13.5)	6 (6.1)	8 (12.7)	

HIV: Human immunodeficiency virus, PLWH: People living with HIV

transmission routes and related rates may trigger this fear and increase the stigma. In our study, when the status of receiving education was compared with questions about stigma related to PLWH, receiving education was found to be associated with less stigma. The increase in knowledge levels with education will reduce incorrect information about transmission routes and rates and may reduce this fear and stigma.

In our study, participants responded to statements questioning stigma like "I would not let my child meet with the child of an HIV (+) parent", "I do not want my child to receive education in a class with an HIV (+) teacher", "HIV (+) individuals should be quarantined", and 'HIV (+) individuals should carry an external label identifying their diagnosis" with "I agree" at substantial rates (10-20%). A study in India found that similar statements received similar response rates (22). These rates were similar in our study. A study in Washington in America questioning stigma among health care workers in a variety of categories obtained similar results from a scale for stigma rates, as in our study (23). A similar study in Saudi Arabia found stigma rates were again similar to our study (20). This situation shows that a significant portion of health care workers have prejudice against HIV (+) individuals, even though they live in different areas of the world. The stigma related to HIV does not display cultural and geographical differences, though there are some small differences. In this situation, precautions should be taken against poor outcomes that may be involved for HIV (+) individuals.

In the study, the majority of responses to statements related to knowledge and stigma displayed significant differences identified between doctors, nurses and personnel, but it is notable that the 3 occupational groups had rates of agreement above 70% for the statement "if my child had HIV, I would be supportive and not blame them". This situation shows that observing HIV in our close surroundings may ensure empathy forms and prejudices are revised.

Fear of stigma is known to be a factor delaying early diagnosis and treatment of infection and as a result, spreading infection in terms of increasing transmission (7,8,9,10). In addition to technical topics like treatment and surveillance about HIV/AIDS infection in trainings, providing information about problems encountered by these people and revealing the outcomes of stigma may ensure health employees to develop empathy and break the negative feedback cycle of stigma Appendix (1,2).

Conclusion

Inadequate information and prejudices of health care workers, who have an important role in all areas of the care chain, related to HIV may lead to serious results in terms of stigma for HIV (+) individuals. Though this rate is low among doctors and nurses, it is high among hospital personnel. For this reason, it is essential to train all health personnel about this topic.

In addition to technical topics like treatment and surveillance about HIV/AIDS infection in trainings, providing information about problems encountered by these people and revealing the outcomes of stigma may ensure health care workers to develop empathy and break the negative feedback cycle of stigma.

Ethics

Ethics Committee Approval: Our study received permission from University of Health Sciences Turkey Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee, dated 25.06.2019 and numbered 2452.

Informed Consent: Verbal consent was obtained from the participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: O.S., S.D., G.Z.Ö., S.A., Design: O.S., S.D., G.Z.Ö., S.A., Data Collection or Processing: O.S., S.D., S.A., Analysis or Interpretation: O.S., S.D., G.Z.Ö., S.A., Literature Search: O.S., S.D., S.A., Writing: O.S., S.D., G.Z.Ö.

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Appendix 1. Human immunodeficiency
1- Age:
2- Gender:
a) Female
b) Male
3- Job definiton:
a) Doctor
b) Nurse
c) Other health personnel
4- Which department are you working?....
5- Working field?
a) Inpatient clinic
b) Outpatient clinic
c) Emergency room
5- How long have you been working? ..... month/year
6- Approximately how many HIV (+) patients have you encountered?
a) None
b) 1-4
c) 5-10
d>10
7- Have you ever received education about HIV/AIDS?
a) Yes
b) No
8- If yes, where?
a) University
b) After university
9- What do you think is prevalance of HIV/AIDS in Turkey?
a) 0-10
b) 10-20
c) 20-30
d) 30-60 60-100
11- Which ones are at risk for HIV infection?
a) Health care workers
b) Having unprotected sexual intercourse and having multiple partners
c) Intravenous drug use and joint needle usage
d) Being in a relationship with an HIV (+) individual
e) Traveling to high risk areas or living in a high risk area
f) Being exposed to sexual violence
g) Tuberculosis disease
h) Unprepared medical interventions

Appendix 1. Continued
12- How much is the possibility of HIV transmission with a needle stick injury?
a) 0.3
b) 3
c) 30
d) 0
e) 100
13- Which route/routes is HIV transmitted? (you may choose more than one)
a) Thorough blood
b) Intravenous drug use
c) Sexual relations
d) Body fluids (sweat, tears)
e) Personal belongings (clothes, towels)
f) In air
g) Skin contacts (handshakes)
h) Domestic items (forks, knives)
i) Common use areas (pool, gym)
j) Toilets, sinks
k) Insect bites
l) From mother to infant during birth
m) Organ transplant

Appendix 1. Continue			
	I agree	Neutral	I disagree
1- All HIV (+) individuals should be quarantined.			
2- I think all the people who visited hospital should be screened for HIV.			
3- HIV (+) individuals' diagnosis should be shared with other health care workers when they visited health facilities.			
4- I think I have adequate information about HIV.			
5- Individuals being HIV (+) is an obstacle to marriage.			
6- I know how to approach HIV (+) patients.			
7- I do not want my child to receive education in a class with an HIV (+) teacher.			
8- If my child had HIV, I would be supportive and not blame them.			
9- If tests are negative in the first week after unprotected sexual relations with an HIV (+) individual, there is no transmission.			
10- Laboratory results of HIV (+) individuals should be told to partners/families.			
11- HIV (+) individuals should not be employed in health facilities.			
12- HIV (+) individuals should be checked for other infectious diseases			
13- HIV (+) individuals should carry an external label identifying their diagnosis.			
14- I would not let my child meet with the child of an HIV (+) parent.			
15- HIV is only seen in homosexuals.			

ORIGINAL ARTICLE

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Effects of Smoking on Acute Hypobaric Hypoxia Tolerance

Sigara Kullanımının Akut Hipobarik Hipoksi Toleransı Üzerine Etkisi

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ABSTRACT

Background: Smoking may impair oxygen transport ability of blood and airway destructions might be seen in long term smokers. After 1-3 cigarette smoking, it leads to a rise in carboxyhemoglobin level in blood, and it has a negative effect such as taking extra 5,000-8,000 feet altitude. Thus, it is thought that smoking before or in-flight may contribute to altitude hypoxia. The objective of this study was to evaluate the effects of smoking on acute hypobaric hypoxia tolerance at 30,000 ft. simulated altitude.

Materials and Methods: This study was planned prospectively, and a standardized survey that consisted of smoking status and demographic characteristics of subjects was applied before the procedures. Aircrews are exposed to high altitude during "Hypobaric Hypoxia Training" in an altitude chamber. Pulse oximeter measurements were done to analyze oxygen saturations during different stages of the hypoxia trainings.

Results: Seventy eight male healthy aircrews were included in this study. Twenty five (32.1%) of subjects stated that they were currently smoking (4.9±2.6 years). Hypoxic pulse oximeter mean values of the Nonsmoker Group were higher than those of the Smoker Group (p>0.05). The three most frequently checked symptoms were numbness, tingling and perspiration among all participants. Flushing was the most frequent symptom in the Smoker Group while numbness was the most frequent symptom in the Nonsmoker Group. Both early and late symptoms among pilots were higher in the Smoker Group (p>0.05). More symptoms were checked among smokers during hypoxia exposure in this study(p>0.05).

Conclusion: Our results might be attributed to hypoxia sensitiveness of smokers, and the use of tobacco products by aviation personnel was considered to be disadvantage in aviation environment. Because of this, doctors who carry out aviation examinations and practise preventive medicine in aviation field should be aware of the importance of this issue. The influences of carboxyhemoglobin on hypoxia tolerance might be better observed at lower altitudes if this study would have been redone at 18,000 and 25,000 simulated altitudes.

Keywords: hypobaric hypoxia training, smoking, altitude tolerance, hypoxia tolerance

ÖZ

Amaç: Sigara kullanımı kanda oksijen transportunu bozduğu gibi uzun dönem kullanımında solunum yolu harabiyetine neden olur. Bir ile üç arasında sigara içimi kanda karboksihemoglobin seviyelerini artırır ve 5.000-8.000 ft. daha yüksek irtifada bulunuyormuş gibi negatif bir etki oluşturur. Böylece, uçuştan hemen önce veya uçuş sırasında sigara içilmesi irtifa hipoksisini arttırabilir. Bu çalışmanın amacı 30.000 ft. simüle irtifada oluşan hipobarik hipoksi toleransına sigara kullanımının etkilerinin değerlendirilmesidir.

Gereç ve Yöntemler: Prospektif planlanan bu çalışmaya başlanmadan önce kişilerin demografik özelliklerini ve sigara kullanım durumlarını sorgulayan bir anket çalışması uygulandı. İrtifa odasında icra edilen hipobarik hipoksi eğitimi sırasında havacılık personelleri yüksek irtifaya maruz kalmaktadırlar. Çalışmamızda, hipoksi eğitiminin çeşitli safhalarında kan oksijen satürasyon değişimlerinin analizi için pulse oksimetre ölçümleri yapılmış ve ölçüm sonuçları sigara kullanım durumlarına göre karşılaştırılmıştır.

Bulgular: Bu çalışmaya 78 sağlıklı erkek havacılık personeli dahil edildi. Katılımcılardan 25'i (%32,1) sigara kullandığını belirtmiştir (4,9±2,6 yıl). Sigara kullanmayanların hipoksik pulse oksimetre ortalamaları sigara kullananlara göre yüksek bulunmuştur (p>0,05). Tüm katılımcılar arasında en sık işaretlenmiş olan üç semptom uyuşma, karıncalanma ve terlemedir. Sigara kullanan grupta en sık işaretlenen semptom ateş basması iken sigara içmeyen grupta en sık işaretlenen bulgu uyuşma olmuştur. Katılımcılar arasında

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ÖZ

hem erken hem de geç hipoksi semptomları sigara içen grupta daha fazla bulunmuştur (p>0,05). Bu çalışmada hipoksi maruziyeti sırasında sigara içenler daha fazla semptom işaretlemiştir (p>0,05).

Sonuç: Bizim sonuçlarımız sigara kullananların irtifa hipoksisine daha duyarlı olduğunu düşündürmektedir. Diğer taraftan havacılık personelinde sigara kullanımı sıklığının normal popülasyona benzerlik göstermesinden ötürü sigara kullanımı havacılık ortamında dezavantaj olarak kabul edilebilir. Bu nedenle, havacılık muayenelerini gerçekleştiren ve havacılık alanında koruyucu hekimlik icra eden doktorların bu durumun öneminin farkında olması gerekmektedir. Karboksihemoglobinin hipoksi toleransına etkileri daha düşük irtifalarda daha iyi gözlemlenebilir ve bu çalışmanın 18.000 ft. ve 25.000 ft. simüle irtifalarda tekrarlanması ile istatistiksel anlamlı sonuçlar elde edilebilir.

Anahtar Kelimeler: hipobarik hipoksi eğitimi, sigara kullanımı, yüksek irtifa toleransı, hipoksi toleransı

Introduction

There are four types of hypoxia. Respiratory problems or scarcity of the oxygen impair alveolocapillary diffusion and lead to hypoxic or hypobaric hypoxia. Transport deficiencies of the oxygen or the blood to the tissues lead to Hypemic or stagnant hypoxia. When utilization of the oxygen in the cells is degraded, it is called histotoxic hypoxia. Acute hypoxia in aviation is generally caused by low partial oxygen pressure (PO_2) at high altitudes. Hypoxia impairs consciousness and psychomotor functions of the aviators and risks aviation safety.

It is thought that respiratory function impairments and airway destructions, as is seen in long term smokers or in many diseases of respiratory system, may contribute to hypoxia. Smoking before or in-flight may impair oxygen transport ability of blood. After 1-3 cigarette smoking, it leads to a rise in carboxyhemoglobin level in blood, and it has a negative effect such as taking extra 5,000-8,000 feet altitude (1,2). So, this is expected to reduce hypoxia tolerance of the aviation personnel.

The objective of this study was to evaluate the effects of smoking on acute hypobaric hypoxia tolerance at 30,000 feet simulated altitude.

Material and Methods

Research Design

This study was planned prospectively, and subjects were fully informed about the procedure and written consent was taken. Each stage of the research was carried out based on the Declaration of Helsinki, and the Committee of Clinical Research Ethics approved the study (Number: 1491-1268-11/1539, Date: 21/02/2011). A standardized survey that consisted of smoking status and demographic characteristics of subjects was applied before the procedures.

After routine medical examinations, aircrew are enrolled in the aerospace physiology trainings. One of these trainings is "Hypobaric Hypoxia Training" and in this training, aircrews are exposed to 30,000 feet altitude equivalent hypobaric environment in an altitude chamber. Ten aircrews attend hypoxia training in one session and experience hypoxia to learn counter measures. Hypobaric hypoxia training starts with 30 minutes of 100% oxygen pre-breathe for denitrogenation via tight fitted oronasal aviation mask. After denitrogenation, immediate ascend and descent to/from 5,000 feet simulated altitude procedure is performed for any possible barotrauma problem before the procedure that is called "sinus check". Unless any ear or sinus barotraumas do not occur in any of trainees, ascending continues until the 30,000 feet simulated altitude (5,000 feet/min climb rate) is reached. Inside chamber, operators breathe 100% O_2 during all phases of the training while trainees breathe 100% O_2 in all phases of the training except hypobaric hypoxia test period (Figure 1).

At the training altitude, 2 or 3 trainees take off their masks and start solving provided hypoxia test sheet while the other trainees observe the hypoxia training. The hypoxia training is terminated when the trainees become succumb or pulse oximeter value (SpO_2) decrease to 60%. Inside operator puts the trainees' oxygen mask on unless trainees recognize hypoxia and recover by themselves.

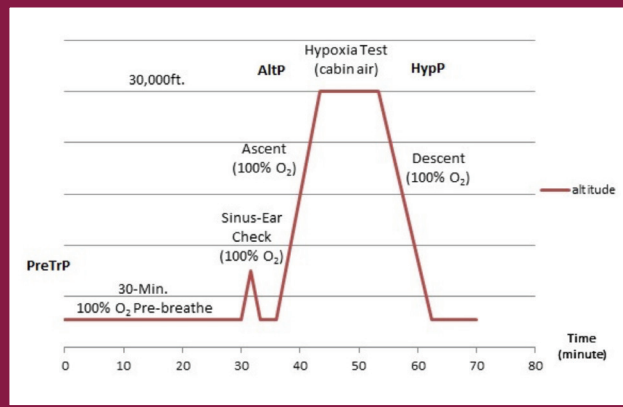


Figure 1. Hypobaric hypoxia training profile

Subjects

Aircrews who were admitted to physiological trainings were in the same medical and physical standards as they had the similar education. All subjects passed aero-medical examination and had the medical report of "fit to fly" before the physiological trainings.

Procedure

We used noninvasive pulse oximeter to analyze the blood oxygen saturation changes of the subjects during different stages of the hypoxia training. First pulse oximetry measurements (PreTrP) were performed before the training, second measurements (AltP) were performed at training altitude before taking off the oxygen masks, and last measurements (HypP) were done at training altitude after hypoxia test before mask on (Figure 1). We used point merging puzzles for hypoxia test. During the hypoxia test, subjects completed the first puzzle in approximately one minute and they checked or wrote the early symptoms that they felt at that moment below the first puzzle. Later trainees continued to the second puzzle and checked or wrote late symptoms that they felt at that moment below the second puzzle (Figure 2).

Statistical Analysis

The study data were edited in Microsoft® Excel software and Statistical analysis was performed in SPSS® data analysis software. The Kolmogorov-Smirnov normality test was used for all parameters. The Independent Samples t-test or Mann-Whitney U test was used in between-groups analyses, and the Paired t-test or the Wilcoxon t-test was used in within-group (Pre/Post exposure) analyses. The chi-square test and Fischer's Exact test were also executed for statistical significance. A value of $p<0.05$ was considered to be statistically significant.

Results

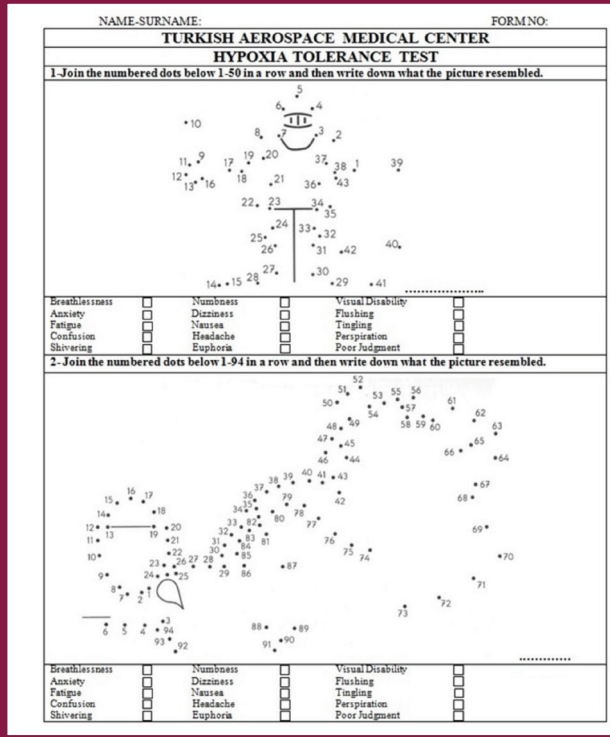
Eighty eight male aircrews were admitted to physiological trainings. A total of 10 subjects were excluded from the study because 2 trainees did not properly fill or return the questionnaire, 3 in-flight medical events (2 emesis, 1 epistaxis) led to the cancelation of hypoxia training sessions of 5 more trainees.

So, seventy eight male healthy pilot aircrews whose ages varied between 21 and 24 years (mean: 22.53±0.6) were included in this study. Their heights were ranged between 170 cm and 194 cm (mean: 178.83 cm ±5.2) and weights ranged between 56 kg and 98 kg (mean: 72.83±7.7). Body mass index values were calculated and ranged between 17.28 and 28.39 (mean: 22.75±1.9).

In this study, smoking status of the subjects was questioned and 25 (32.1%) of 78 subjects stated that they were currently smoking (4.9±2.6 years). Study results were grouped according to smoking status and presented in Table 1. During training, Hypoxic Pulse values of the Nonsmoker Group were higher than those of the Smoker Group, but it was statistically insignificant ($p>0.05$). Other results were very close in both groups ($p>0.05$) (Table 1).

All subjects completed the first puzzle that took about one minute for each subject to solve. Four subjects in Smokers' Group (SMK) and five subjects in Non-SMK could not complete the second puzzle and did not check the symptom they felt at that moment. When we analyzed these nine subjects who did not check late symptoms, three of them were in SMK and four of them were in Non-SMK who already checked early symptoms.

The three most frequently checked symptoms were numbness, tingling and perspiration among all participants. The symptoms that were widely checked by the subjects in SMK at early phase were flushing, perspiration, numbness, visual disturbances, and headache. Additionally, frequently reported symptoms in SMK participants at the late phase were numbness, dizziness, flushing and tingling. The symptoms that the Non-SMK mostly checked at the early phase were dizziness, numbness, perspiration, and tingling.


NAME-SURNAME: FORM NO:

TURKISH AEROSPACE MEDICAL CENTER

HYPOXIA TOLERANCE TEST

1-Join the numbered dots below 1-50 in a row and then write down what the picture resembled.

Breathlessness	Numbness	Visual Disability
Anxiety	Dizziness	Flushing
Fatigue	Nausea	Tingling
Confusion	Headache	Perspiration
Shivering	Euphoria	Poor Judgment

2- Join the numbered dots below 1-94 in a row and then write down what the picture resembled.

Breathlessness	Numbness	Visual Disability
Anxiety	Dizziness	Flushing
Fatigue	Nausea	Tingling
Confusion	Headache	Perspiration
Shivering	Euphoria	Poor Judgment

Figure 2. Hypoxia test sheet

Also, frequently reported symptoms in Non-SMK participants were anxiety, shivering, perspiration, numbness and tingling at the late phase. Both early and late symptoms among pilots were higher in SMK group (p>0.05). Flushing was the most frequent symptom in SMK group and numbness was the most frequent symptom in Non-SMK group (Table 2).

Discussion

Many chemicals, which are considered to be toxic and carcinogenic, are released during the combustion of tobacco. The best known of these substances are tar and carbon

Table 1. Study results according to smoking status.

Variables	n	SMK	n	Non-SMK	p
		Mean ± SD		Mean ± SD	
Age	25	22.40±0.6	53	22.58±0.6	0.19**
BMI		22.99±1.8		22.63±1.9	0.43*
Hb		14.88±1.0		14.80±0.7	0.69*
Htc		45.46±2.6		45.48±2.4	0.97*
PreTrP (SpO_2)	21	98.43±1.1	47	98.7±1.0	0.36**
AltP (SpO_2)	25	99.44±2.2	53	99.79±0.8	0.57**
HypP (SpO_2)		65.32±6.6		66.11±5.8	0.49**

SMK: Smokers' Group, Non-SMK: Non-Smokers' Group. *Independent sample t-test **Mann-Whitney U test BMI: Body mass index, hb: Hemoglobin, Htc: Hydrothermal carbonization

Table 2. Frequencies and percentage of the Hypoxia symptoms according to smoking status

S/N	HYPOXIA SYMPTOMS	SMK								NON-SMK								All
		Early			Late			Total		Early			Late			Total		Total
		Within Symptoms		SMK Pilots N=25	Within Symptoms		SMK Pilots N=21	Within Symptoms		Within Symptoms		Non SMK Pilots N=53	Within Symptoms		Non SMK Pilots N=48	Within Symptoms		Within Symptoms
		n	%	%	n	%	%	n	%	n	%	%	n	%	%	n	%	n
1	Breathlessness	0	0	0	3	5.45	14.29	3	3.85	3	5	5.66	4	4.30	8.33	5	3.94	8
2	Anxiety	1	3.23	4	4	7.27	19.05	4	5.13	4	6.67	7.55	7	7.53	14.58	8	6.30	12
3	Fatigue	2	6.45	8	4	7.27	19.05	5	6.41	2	3.33	3.77	6	6.45	12.5	7	5.51	12
4	Confused	1	3.23	4	3	5.45	14.29	4	5.13	4	6.67	7.55	5	5.38	10.42	7	5.51	11
5	Shivering	0	0	0	2	3.64	9.52	2	2.56	6	10	11.32	7	7.53	14.58	10	7.87	12
6	Numbness	3	9.68	12	7	12.73	33.33	9	11.54	7	11.67	13.21	24	25.81	50	28	22.05	37
7	Dizziness	2	6.45	8	6	10.91	28.57	8	10.26	7	11.67	13.21	5	5.38	10.42	9	7.09	17
8	Nausea	2	6.45	8	3	5.45	14.29	4	5.13	2	3.33	3.77	4	4.30	8.33	4	3.15	8
9	Headache	3	9.68	12	0	0	0	3	3.85	3	5	5.66	2	2.15	4.17	4	3.15	7
10	Euphoria	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
11	Visual Disturbances	3	9.68	12	3	5.45	14.29	6	7.69	2	3.33	3.77	5	5.38	10.42	6	4.72	12
12	Flushing	6	19.35	24	6	10.91	28.57	9	11.54	5	8.33	9.43	6	6.45	12.5	10	7.87	19
13	Tingling	2	6.45	8	6	10.91	28.57	8	10.26	7	11.67	13.21	8	8.60	16.67	13	10.24	21
14	Perspiration	4	12.9	16	5	9.09	23.81	9	11.54	7	11.67	13.21	7	7.53	14.58	12	9.45	21
15	Poor Judgment	2	6.45	8	3	5.45	14.29	4	5.13	1	1.67	1.89	3	3.23	6.25	4	3.15	8
	TOTAL	31	100	52	55	100	76.2	78	100	60	100	39.6	93	100	70.8	127	100	205
			p	0.336*			0.774**					0.336*			0.774**			

SMK: Smokers' Group, Non-SMK: Non-Smokers' Group, *, ** Chi-square test and Fisher's Exact test

monoxide. Carbon monoxide (CO) that presents in cigarettes leads to oxygen deficiency in cells in two ways. Firstly, CO has 250 times greater affinity to hemoglobin than O_2 and smoking reduces oxyhemoglobin rate while increasing carboxyhemoglobin rate in the blood. Secondly, it has directly toxic effects on the tissue cells. Even very low levels of CO pressure like 0.6 mmHg in the air can be fatal (3). Smoking may cause anemic hypoxia and aggravate hypoxia symptoms (4).

Smoking is the leading cause of many different health issues within society. The World Health Organization states that many types of cancers, heart diseases, and lung diseases have been associated with smoking. More than 7 million people die from tobacco related diseases in each year (5). In 2020, a total of 31.2% of adults (approximately 16 million) aged 15 years and older were currently smoking in Turkey. Prevalence was higher among men (47.9%) than women (15.2%). Approximately 12 million men and 4 million women smoked tobacco. (6). The use of tobacco products among aviation personnel is similar to that of the normal population (7). In addition, it was reported that smoking was also the risk factor for cardiovascular diseases in a study conducted on commercial pilots (8).

Deussing et al. (9) administered a survey to naval aviators and of the 566 aviators who completed the survey before the aviation physiology training, 112 (20%) reported experiencing hypoxia symptoms in a tactical jet aircraft and 64 aviators (57%) indicated that they were not wearing the required oxygen mask when the incident first occurred. Cable GG executed a study in "Australian All Aircraft Safety Occurrence Reports" data base for investigation of hypoxia as a factor between 1990 and 2001. During this period, 27 reports of hypoxia were filed, involving 29 aircrew. Consciousness was lost in only two cases, and one of these resulted in a fatal accident. Most incidents (85.1%) occurred in fighter or training aircraft with aircrew who used oxygen equipment routinely (10). Hypoxia has long been recognized as a significant physiological threat at altitude and flight mishaps can be attributable to hypoxia. Regarding this, "Hypoxia Familiarization Training" remains a vital component of aircrew trainings.

Yoneda et al. (11) conducted a study in 152 nonsmoking males who were divided into 2 groups as juniors and seniors. The mean age of juniors group was 26.8±0.5 years and the mean hypoxic saturation rate of them was reported as 58.4% ±0.9 (11). Our Non-SMK groups resembles the Yoneda's junior group, but all subjects of our study were younger than Yoneda's junior group (22.58±0.6 years vs. 26.8±0.5 years) and hypoxic saturation rates were higher in our study (66.11% ±5.8 vs.58.4% ±0.9).

Smoking may decrease hypoxia tolerance and may have negative effects on the safe operation of the aircraft. In this aspect, we investigated the effect of smoking (Carbon Monoxide) on the oxyhemoglobin saturation in this study. There were no statistically significant differences detected in PreTrP, AltP and HypP parameters between SMK and Non-SMK groups. All three-oxygen saturation means of Non-SMK subjects were slightly higher than those of SMK, but these differences were not statistically significant ($p>0.05$). These results may be resulted from a negative effect of Carbon Monoxide (CO) due to chronic cigarette smoking. We have also considered that the absence of statistical significance between these two groups might have been caused by the low number of the subjects and 30,000 feet very high study altitude. At these altitudes, saturation of the oxyhemoglobins known to be reduced to the level of 60% and the characteristics of unsaturated hemoglobin dissociation curve may give rise to this result.

In Deussing et al. (9) study, the three most common recorded in-flight hypoxia symptoms were tingling (54%), difficulty in concentrating (32%), and dizziness (30%). In Cable GG's study, the most common reported symptoms were cognitive impairment, dizziness/lightheadedness, paresthesia and unwellness (non-specific) (10). In Yoneda et al. (11) study, flushing and thinking impairment were the most frequently observed symptoms (more than 80%), while nausea and euphoria were the least common (less than 10%). On the other hand, in our study, we also address the subjective symptoms that may appear in hypoxic environment of aviation. Also, in this study, the three most common symptoms for all participants were numbness, tingling and perspiration and the least common reported symptom was euphoria in our study. Our results were concordant with published literature.

Yoneda et al. (11) executed another study on 590 nonsmokers and 582 smokers. The mean age of Non-SMK and SMK were 33.5±9.9 years and 33.2±9.2 years, respectively. Subjects were asked to fill out the questionnaire concerning the symptoms that they felt during hypoxia after the completion of the training. The intensity of subjective symptoms during hypoxia was placed in the rank order. The order is almost the same for both groups. Non-smokers showed significantly sensitive responses to the five symptoms of thinking impairment, visual impairment, fatigue, dyspnea, and tremor (12). The participants experience transient amnesia during altitude hypoxia but in Yoneda's 1997 study, survey was completed after full recovery from hypoxia. We considered this was a limitation for Yoneda's study. However, in our study, 2 surveys were filled out during hypoxia to exclude phenomena of the hypoxic amnesia. Flushing was the most frequent symptom in SMK group, numbness was the most frequent symptom in Non-SMK group in present study. In contrast to the Yoneda's study, more symptoms were checked among SMK subjects for both in early and late phases of hypoxia in this study. This

might be attributed to hypoxia sensitiveness of SMK subjects. We considered that this situation could be considered as a disadvantage of smokers in aviation environment.

Conclusion

In response to the efforts of many anti-smoking organizations, several states and local governments have passed ordinances to restrict smoking in many public places, putting warning labels on tobacco packaging, collecting more tobacco taxes, and banning on advertising, promotion, and sponsorship for tobacco products (13). Antismoking efforts also put in aviation sector. The ICAO approved to prohibit smoking on international commercial flights by the 1st of July 1996. Too many airlines and governments have proposed a rule that would extend the prohibition of cigarette smoking in all commercial flights (14). On the other hand, the use of tobacco products in aviation personnel is similar to that of the normal population. Because of this, doctors who carry out aviation examinations and practise preventive medicine in aviation field should be aware of the importance of this issue and well know the tobacco cessation treatment (7).

Because of the technical difficulties and standard training procedures, we performed this study at 30,000 feet altitude. We have considered that statistically significant results may have been gained if this study would have been redone at 18,000 and 25,000 simulated altitudes. In these altitudes, oxygen saturation would be higher and the influences of carboxyhemoglobin on hypoxia tolerance could be better observed.

Ethics

Ethics Committee Approval: Ethics committee approval was received from Gülhane Military Medical Academy Command (number: 1491-1268-11/1539, date: 21/02/2011).

Informed Consent: Patients gave written informed consent before the study procedures.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: E.E., M.Ş.İ., C.T., Design: E.E., M.Ş.İ., C.T., Data Collection or Processing: E.E., M.Ş.İ., C.T., Analysis or Interpretation: E.E., M.S.İ., C.T., Literature Search: E.E., M.Ş.İ., C.T., Writing: E.E., M.Ş.İ., C.T.

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Analysis of Severe and Critical COVID-19 Patients Treated With Favipiravir: A Retrospective Cohort Study

Favipiravir ile Tedavi Edilen Ağır ve Kritik COVİD-19 Hastalarının Analizi: Bir Retrospektif Kohort Çalışma

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ABSTRACT

Background: We aimed to analyze demographic characteristics, smoking status, comorbidities, laboratory parameters and other treatments before favipiravir use in severe to critically ill patients with coronavirus disease-2019 (COVID-19) who were treated with favipiravir in Turkey.

Materials and Methods: This study was conducted as a retrospective observational study in a tertiary reference hospital for COVID-19. Clinical and laboratory data of COVID-19 patients who were consecutively treated with favipiravir were evaluated. The patients were divided into two groups as survivors and non-survivors.

Results: The mean ages of the non-survivors and survivors were 67.3±13.3 and 57.3±16.4 years (p<0.0001), respectively. The smoking rate was 44.4% in non-survivor group and 9.1% in the survivor group (p=0.01). Older age [odds ratio (OR): 1.04, 95% confidence interval (CI): 1.016-1.069], smoking (OR: 5.76, 95% CI: 1.84-18.03), presence of one or more comorbidity (OR: 4.43, 95% CI: 1.79-10.91), coronary artery disease (CAD) (OR: 2.66, 95% CI: 1.06-6.72), arrhythmia (OR: 3.4, 95% CI: 1.78-9.82) and congestive heart failure (CHF) (OR: 14.4, 95% CI: 2.9-71.43) were significantly related to mortality (p<0.05). The rate of patients who were treated with lopinavir/ritonavir before favipiravir was higher in the non-survivor group (p=0.0001). Favipiravir treatment was started earlier in survivors than in non-survivors (3.1±2.2 and 4.7±3.4 days, respectively, p=0.006).

Conclusion: Older age, smoking, presence of one or more comorbidity, CAD, arrhythmia, CHF and treatment with lopinavir/ritonavir before favipiravir were associated with mortality. Favipiravir was started earlier in survivors. Oxygen saturation levels and platelet count increased, and C-reactive protein (CRP) and lactate dehydrogenase levels decreased with favipiravir treatment in survivors. Higher CRP levels were also associated with mortality.

Keywords: Favipiravir, mortality, COVID-19, comorbidity, coronavirus

ÖZ

Amaç: Türkiye'de favipiravir ile tedavi edilen ağır ve kritik koronavirüs hastalığı-2019 (COVİD-19) hastalığı olan hastaların demografik özelliklerini, sigara içme durumunu, komorbiditelerini, laboratuvar parametrelerini ve favipiravir öncesinde uygulanan tedavileri analiz etmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışma, COVİD-19 için üçüncü basamak bir referans hastanesinde retrospektif bir gözlemsel çalışma olarak gerçekleştirildi. Favipiravir ile art arda tedavi edilen COVİD-19 hastalarının klinik ve laboratuvar verileri değerlendirildi. Hastalar hayatta kalanlar ve kalmayanlar olarak iki gruba ayrıldı.

Bulgular: Hayatta kalmayanların ve hayatta kalanların yaş ortalaması sırasıyla 67,3±13,3 ve 57,3±16,4 (p<0,0001) idi. Hayatta kalmayan grupta sigara içme oranı %44,4, sağ kalan grupta ise %9,1 idi (p=0,01). İleri yaş [olasılık oranı (OO): 1,04,%95 güven aralığı (GA): 1,016-1,069], sigara içme (OO: 5,76, %95 GA: 1,84-18,03), bir veya daha fazla komorbiditenin varlığı (OO: 4,43, %95 GA: 1,79-10,91), koroner arter hastalığı (KAH) (OO: 2,66,% 95 GA: 1,06-6,72), aritmi (OO: 3,4,% 95 GA: 1,78-9,82) ve konjestif kalp yetmezliği (KKY) (OO: 14,4,% 95 GA: 2,9-71,43) anlamlı şekilde mortalite ile ilişkiliydi (p<0,05). Favipiravirden önce lopinavir/ritonavir ile tedavi edilen hastaların oranı hayatta kalmayanlar grubunda daha yüksekti (p=0,0001). Favipiravir tedavisi hayatta kalanlarda hayatta kalmayanlara göre daha erken başlanmıştı (sırasıyla 3,1±2,2 ve 4,7±3,4 gün, p=0,006).

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ÖZ

Sonuç: İleri yaş, sigara kullanımı, bir veya daha fazla komorbiditenin varlığı, KAH, aritmi, KKY ve favipiravirden önce lopinavir/ritonavir ile tedavi mortalite ile ilişkiliydi. Favipiravir hayatta kalanlarda daha erken başlandı. Hayatta kalanlarda favipiravir tedavisi ile oksijen satürasyonu seviyeleri ve trombosit sayısı arttı ve C-reaktif protein (CRP) ile laktat dehidrojenaz seviyeleri azaldı. Daha yüksek CRP seviyeleri de mortalite ile ilişkiliydi.

Anahtar Kelimeler: Favipiravir, mortalite, COVİD-19, komorbidite, koronavirüs

Introduction

Currently, there is no approved drug except remdesivir for the treatment of the coronavirus disease-2019 (COVID-19); therefore, drugs approved for other diseases such as chloroquine, hydroxychloroquine, lopinavir/ritonavir and favipiravir are used experimentally in the treatment of COVID-19. There are differences among countries in terms of treatment protocols and the availability of the drug is one of the most important factors in this regard. Favipiravir is a purine analog which inhibits RNA-dependent RNA polymerase and was approved in Japan in 2014 to treat pandemic influenza virus infections (1). Favipiravir has been used for COVID-19 treatment considering that it may be effective in Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is an RNA virus (2). Favipiravir has a broad-spectrum antiviral activity against different RNA viruses and a high barrier for resistance (3). Favipiravir is one of the potential candidates for the treatment of COVID-19 (4) and it may be a relatively safe and effective drug for COVID-19 (5). Favipiravir is frequently used for COVID-19 treatment in Turkey. This study was conducted to analyze demographic characteristics, smoking status, comorbidities, laboratory parameters and additional treatments in severe to critically ill patients with COVID-19 who were treated with favipiravir in Turkey.

Material and Methods

This is a retrospective observational study on adult inpatients (≥18 years old) diagnosed with COVID-19 pneumonia and hospitalized in Umraniye Training and Research Hospital, which is a tertiary training hospital and also a COVID-19 reference center during pandemic, in Istanbul between March 25 and April 25, 2020. The study was approved by the Ethics Commission of Umraniye Training and Research Hospital (125/April 28, 2020) the requirement of informed consent was waived by the ethics commission. The COVID-19 guidelines of the Scientific Committee of Turkish Ministry of Health recommended favipiravir or lopinavir/ritonavir for the treatment of patients with severe COVID-19 or patients who did not respond to initial treatment (6). Favipiravir was used only for the patients who had severe pneumonia with hypoxia described as oxygen saturation in room air (SpO_2) level <90% in the room air. Lopinavir/ritonavir (400/100 mg, twice a day for 10-14 days) was recommended for patients who had severe COVID-19 pneumonia that did not respond to initial treatment but did not have the hypoxia criteria described above.

The eligibility criteria for the study were: 1. Adults patients (≥18 years old) diagnosed as COVID-19 with polymerase chain reaction (PCR) positivity, 2. Those diagnosed as COVID-19 based on clinical, laboratory and radiological findings especially with computed tomography (CT) findings despite COVID-19 PCR negativity, 3. Those who used favipiravir treatment for at least 5 days, based on the treatment protocol as favipiravir 1600 mg twice a day for first day, then 600 mg twice a day for four days, and 4. Patients who had SpO_2 level <90% in the room air and had COVID-19 pneumonia findings on chest CT. Exclusion criteria for the study: 1. Those younger than 18 years old, 2. Patients with mild-to moderate disease, 3. Alanine transaminase (ALT), aspartate transaminase (AST) above 4 times higher or known chronic liver disease before treatment, 4. Human immunodeficiency viruses positive 5. SpO_2 ≥90% in room air, 6. Patients those are not eligible for favipiravir, 7. Pregnant woman. SARS-CoV-2 detection in throat-swab specimens was conducted with next-generation sequencing or real-time RT-PCR methods.

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records of the hospital. Demographic information (age, gender), smoking history, symptoms, comorbidities including coronary artery disease (CAD), arrhythmia, hypertension, congestive heart failure (CHF), diabetes, chronic obstructive pulmonary disease (COPD), and asthma, malignancy history, immunosuppression and laboratory parameters including white blood cell, neutrophil, lymphocyte, platelet, ALT, AST, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), fibrinogen, and ferritin values were obtained. Smoking status was classified as actively smoking and not smoking. Treatment location, treatment with lopinavir/ritonavir before favipiravir, time to favipiravir treatment initiation and duration of favipiravir treatment after hospitalization were also noted. We grouped patients based on their radiology scores as mild for a total score between 1 and 5, moderate for a total score of 6-10, severe for a total score of 11-15, and very severe for a total

>15 by modifying the radiological scoring system offered for radiological severity assessment for COVID-19 (7). The patients were divided into two groups as those who died and survived. Clinical characteristics and laboratory parameters were compared between the two groups and before and after favipiravir treatment.

Statistical Analysis

While analyzing the data and performing the statistics of continuous structured data, the mean and standard deviation, the minimum and maximum values of the features were used. Frequency and percentage values were used to define categorical variables. Student's t-test statistics were used to compare the means of the two groups and paired t-test statistics were used to compare the means of the two dependent groups. The chi-square (χ^2) test statistics were used to evaluate the relationship between categorical variables. The exposure ratios [odds ratio (OR)] of variables thought to be related to death were given. To reveal the risk factors associated with in-hospital death, univariable logistic regression models were used. The statistical significance level of the data was accepted as p<0.05. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistics package program were used to analyze the data.

Results

A total of 148 hospitalized, severe to critically-ill COVID-19 patients treated with favipiravir were enrolled in the study. Of the 148 patients, 53 (35.8%) were females and 95 (64.2%) were males and the mean age of the patients was 59.9±16.2 years (Table 1). Among them, 55 (37.2%) patients were admitted to intensive care unit (ICU), 41 (27.7%) of them were admitted to ICUs from the clinic and 14 (9.5%) of them directly from the emergency department. 93 of the patients were treated for COVID-19 in clinic (Table 1). The patients were divided into two groups as non-survivors (n=38) and survivors (n=110). The mean age of the non-survivor group was 67.3±13.3 years and the mean age of the survivors was 57.3±16.4 years (p<0.0001). Smoking rate was higher in the non-survivor group (44.4%) than in the survivor group (9.1%) (p=0.01). Compared to patients who survived, non-survivors were older and there was no gender difference in two groups. The most common symptoms were fever (86.5%), cough (65.5%), dyspnea (35.8%), gastrointestinal symptoms (22.3%) and myalgia (19.6 %), respectively (Table 1). There was no statistically significant difference in terms of symptoms between the non-survivors and the survivors (p>0.05).

Those with comorbid diseases were 81.6% of the non-survivor group and 50% of the survivors (p=0.001) (Table 1). Patients who died had higher rates of comorbidities including CAD (26.3% to 11.8%, p=0.03), arrhythmia (21.1% to 7.3%, p=0.03), diabetes mellitus (21.1% to 7.3%) and Congestive heart failure (CHF) (36.8% to 20.9%, p=0.0001). Hypertension (50% to 37.3%) was the most common comorbidity in two groups, but the difference between groups was not statistically significant (p=0.17). There was no statistically significant difference between the non-survivors and survivors in terms of diabetes, COPD, asthma, immunosuppression, and malignancy history (p>0.05).

The rate of patients who were treated with lopinavir/ritonavir before favipiravir was higher in the non-survivor group than in the survivor group (47.4% vs. 10%, p=0.0001). The relationship between the radiological stage of the disease and mortality was statistically significant (p=0.002). Favipiravir treatment was started 4.7±3.4 days after the hospitalization of the non-survivors and 3.1±2.2 days after the hospitalization of the survivors (p=0.006).

In the non-survivor group, neutrophil count (7.6±4.4 vs. 12.89±9.2, p<0.0001), ferritin (1274.1±1765.9 vs. 5326.46±10309.4, p=0.02), fibrinogen (647.8±160.4 vs. 576.37±222.28, p=0.03), AST (38.3±22.6 vs. 99.21±123.71, p=0.004) and direct bilirubin (0.3±0.2 vs. 0.93±1.43, p=0.01) values were significantly different before and after favipiravir treatment (Table 2). Platelet count (209.2±80.9 vs. 333.7±143.1, p<0.0001), CRP (69.5±63.9 vs. 28.6±46.3, p<0.0001), LDH (633.8±824.7 vs. 439.4±160.6, p=0.01), ALT (43.0±73 vs. 72.4±76, p<0.0001) and total bilirubin (1.2±5.0 vs. 5.1±20.5, p=0.049) values were significantly different before and after favipiravir treatment in survivors. AST, direct bilirubin, neutrophil, and ferritin values increased, and SpO_2 and fibrinogen levels decreased after treatment in non-survivors. ALT, total bilirubin, platelet, and SpO_2 values increased and CRP and LDH values decreased after treatment in survivors.

Factors affecting the mortality of COVID-19 patients were examined (Table 3). Older age (OR): 1.04, 95% [Confidence interval (CI): 1.016-1.069], smoking (OR: 5.76, 95% CI: 1.84-18.03), presence of at least one or more comorbid diseases (OR: 4.43, 1.79-10.91), CAD (OR: 2.66, 95% CI: 1.06-6.72), arrhythmia (OR: 3.4, 95% CI: 1.78-9.82) and CHF (OR: 14.4, 95% CI: 2.9-71.43) were statistically related to mortality (p<0.05). Mortality was associated with treatment with lopinavir/ritonavir (OR: 8.1, 95% CI 3.32-19.74) before favipiravir. Increased lymphocyte level (OR: 0.098, 95% CI: 0.03-0.29) and high SpO_2 (OR: 0.99, 95% CI: 0.996-1.001) were related to reduced mortality. High CRP levels (OR: 1.01, 95% CI: 1.008-1.019), radiological stage of disease (OR: 3.12, 95% CI: 1.31-7.43) and transfer to ICUs from clinic departments (OR: 34.7, 95% CI: 9.43-127.94) or directly admission to ICUs (OR: 390, 95% CI: 37.69-4035.3) were associated with increased mortality.

Discussion

Dyspnea was revealed as a risk factor for mortality in patients with COVID-19 by Leung (8); however, there was no association between none of the symptoms including dyspnea and mortality in the present study. According to the results of this study, active smoking, older age, and presence of one or more comorbidities, (particularly CAD, arrhythmia and CHF) were associated with increased

Table 1. The baseline characteristics of the patients treated with favipiravir

	Total n=148 (%)	Non-survivors n=38 (%)	Survivors n=110 (%)	p[a]
Age (Mean ± SD)	59.86±16.2	67.3±13.3	57.3±16.4	**<0.0001**
Gender				
Female	53 (35.8)	14 (36.8)	39 (35.5)	0.87
Male	95 (64.2)	24 (63.2)	71 (64.5)	
Smoking	18 (18)	8 (44.4)	10 (9.1)	**0.01**
Symptoms				
Fever	128 (86.5)	33 (86.8)	95 (86.4)	0.94
Cough	97 (65.5)	20 (52.6)	77 (70)	0.052
GIS	53 (35.8)	17 (44.7)	36 (32.7)	0.18
Diarrhea	33 (22.3)	6 (15.8)	27 (24.5)	0.26
Myalgia	29 (19.6)	5 (13.2)	24 (21.8)	0.25
Headache	12 (8.1)	2 (5.3)	10 (9.1)	0.46
Anosmia/Disguise	6 (4.1)	2 (5.3)	4 (3.6)	0.66
Comorbidities				
CAD	23 (15.5)	10 (26.3)	13 (11.8)	**0.03**
Arrhythmia	16 (10.8)	8 (21.1)	8 (7.3)	**0.02**
Hypertension	60 (40.5)	19 (50)	41 (37.3)	0.17
CHF	10 (6.8)	8 (21.1)	2 (1.8)	**<0.0001**
Diabetes	37 (25)	14 (36.8)	23 (20.9)	0.051
COPD	7 (4.7)	3 (7.9)	4 (3.6)	0.29
Asthma	6 (4.1)	2 (5.3)	4 (3.6)	0.66
Malignancy history	3 (2)	1 (2.6)	2 (1.8)	0.76
Comorbidity (≥1)	86 (58.1)	31 (81.6)	55 (50)	**0.001**
Immunosuppression	3 (2)	-	3 (2.7)	0.3
Radiological involvement				
Mild	2 (1.4)	-	2 (1.8)	**0.002**
Moderate	56 (37.8)	8 (21.1)	48 (43.6)	
Severe	71 (48)	19 (50)	52 (47.3)	
Very Severe	19 (12.8)	11 (28.9)	8 (7.3)	
Treatment Department				
Clinic	93 (62.8)	3 (7.9)	90 (81.8)	**<0.0001**
Clinic + ICU	41 (27.7)	22 (57.9)	19 (17.3)	
ICU	14 (9.5)	13 (34.2)	1 (0.9)	
Lopinavir/ritonavir before favipiravir	29 (19.6)	18 (47.4)	11 (10)	**0.0001**
Duration of hospitalization before starting favipiravir (Mean ± SD, day)	3.5±2.6	4.7±3.4	3.1±2.2	**0.006**

[a]p is significant at the level of <0.05 (chi-square test). n: Number, SD: Standard deviation, GIS: Gastrointestinal symptoms such as diarrhea, vomiting, loss of appetite, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit

Table 2. Comparison of laboratory parameters before and after favipiravir treatment

Parameter (Mean ± SD)	Non-survivors (n=38)		p[a]	Survivors (n=110)		p[a]
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
WBC (K/mm^3)	10.1±14.3	14.83±9.9	0.19	11.6±48.9	10.7±39.9	0.88
Lymphocyte (K/mm^3)	0.9±0.5	1.057±0.9	0.99	1.7±3.4	2.6±9.7	0.2
Neutrophil (K/mm^3)	7.6±4.4	12.89±9.2	**<0.0001**	5.5±5.9	4.5±2.7	0.09
Platelet (K/mm^3)	229.7±121.7	265.6±280.6	0.42	209.2±80.9	333.7±143.1	**<0.0001**
CRP (mg/L)	137.5±73.3	117.9±87.3	0.27	69.5±63.9	28.6±46.3	**<0.0001**
Ferritin (mg/L)	1274.1±1766	5326.46±103	**0.02**	1533.4±4936	2206.9±1147	0.45
D-dimer (µg/L)	3408.2±5028	6223.9±8006	0.06	1170.4±2258	1017.7±1377	0.55
LDH (U/L)	790.2±350	1048.4±829	0.06	633.8±825	439.4±161	**0.01**
ALT (IU/L)	30.6±19	63.38±68	**0.006**	43.0±73	72.4±76	**<0.0001**
AST (IU/L)	38.3±23	99.21±124	**0.004**	66.0±325	54.0±191	0.36
Total bilirubin (mg/dL)	0.7±0.5	3.004±8.8	0.11	1.2±5	5.1±20.5	**0.049**
Direct bilirubin (mg/dL)	0.3±0.2	0.933±1.43	**0.01**	0.3±0.2	0.5±1.1	0.2
SpO_2 (%)	82.95±9.35	76.39±1136	**0.003**	90.28±3.72	95.05±2.75	**<0.0001**
Fibrinogen (µmol/L)	647.8±160.4	576.37±222.3	**0.03**	612.83±17.7	605.72±193	0.75

[a]p is significant at the level of <0.05. (Paired t-test). n: Number, SD: Standard deviation, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, ALT: Alanine transaminase, AST: Aspartate transaminase, SpO_2: Oxygen saturation in room.

Table 3. The risk factors associated with mortality

Variable	OR	Lower (%95 CI)	Upper (%95 CI)	p[a]
Age	1.04	1.016	1.069	<0.05
Smoking	5.76	1.84	18.03	<0.05
Comorbidities				
CAD	2.66	1.06	6.72	<0.05
Arrhythmia	3.4	1.78	9.82	<0.05
CHF	14.4	2.9	71.43	<0.05
Comorbidity (≥1)	4.43	1.79	10.91	<0.05
Laboratory parameters				
Lymphocyte	0.098	0.03	0.29	<0.05
Radiological involvement	3.12	1.31	7.43	<0.05
SpO_2	0.75	0.67	0.836	<0.05
Treatment Department				
Clinic + ICU	34.7	9.43	127.94	<0.05
ICU	390	37.69	4035.3	<0.05
Lopinavir/ritonavir treatment before favipiravir	8.1	3.32	19.74	<0.05

[a]p is significant at the level of <0.05. CAD: Coronary artery disease, CHF: Congestive heart failure, SpO_2: Oxygen saturation in room air, ICU: Intensive care unit OR: Odds Ratio

mortality in hospitalized severe and critically ill patients with COVID-19 treated with favipiravir. In a systematic review, the prevalence of current smoking was low among patients with COVID-19 in China, when compared to the population smoking prevalence (9). Zhou et al. (10) evaluated clinical course and risk factors for mortality in 191 adult patients hospitalized with the diagnosis of COVID-19 and there was no statistically significant difference in recovered and died patients in terms of active smoking (4% and 9%, respectively, p=0.21). In a multi-center retrospective cohort study by Liu et al. (11), multivariate logistic regression analysis revealed that smoking was a risk factor for disease progression (OR: 14.285; 95% CI: 1.577-25.000; p=0.018). According to the present study results, the smoking rate was higher in non-survivors and smokers had 5.76 times more likely to die.

In the study evaluating the data of 72,314 patients diagnosed with COVID-19 in China, the case fatality rate increased with older age and comorbidity (12). Wang R. et al. (13) have concluded that older age, the presence of underlying disease, and smoking may be risk factors that cause the disease to worsen. These results are compatible with our results in this study. Although COPD was not identified as a risk factor for mortality in the present study, COPD and smoking history were associated with disease progression and poor clinical outcomes in a systematic review investigating the effect of COPD and smoking on COVID-19 severity (14).

Hypertension, diabetes, asthma, immunosuppression and malignancy history were not related to mortality according to this study. Patients with severe COVID-19 disease reported to have higher rates of cardiac comorbidities such as hypertension (58%), coronary heart disease (25%) and arrhythmia (44%) (15). Patients with older age, male sex,

chronic hypertension, and cardiovascular disease were found to be more common among non-survivors in another study (16). CAD, arrhythmia and CHF were more common in non-survivors and were significantly associated with mortality in the present study group. Although hypertension was more common in non-survivors, the difference was not statistically significant.

According to a meta-analysis, patients with severe and fatal disease had significantly increased white blood cell (WBC) count, and decreased lymphocyte and platelet counts compared to non-severe disease and survivors. Biochemical markers such as LDH, ALT, AST and total bilirubin, inflammation markers such as CRP, and ferritin, and coagulation markers such as D-dimer were also significantly elevated in patients with poor clinical outcome (17). In another study conducted to establish a prediction of disease progression, lymphocyte count, D-dimer and LDH were significantly different between patients with stable and severe disease (18). Lower lymphocyte level, decreased SpO_2, high CRP level and advanced radiological stage of disease were related to increased mortality according to the results of this study. Other laboratory parameters including D-dimer, platelet, WBC, LDH, ferritin and fibrinogen were not risk factors for mortality in contrast with literature.

Lopinavir/ritonavir treatment before favipiravir was associated with increased mortality in patients treated with favipiravir in the present study. The efficacy of lopinavir/ritonavir was investigated in COVID-19 patients in a randomized controlled study and there was no statistically significant difference in terms of clinical improvement and mortality in 28 days between the treatment group and the standard care group (19).

Favipiravir treatment started earlier in surviving patients. This finding supports the early initiation of favipiravir treatment to reduce mortality. Favipiravir treatment increased AST, direct bilirubin, neutrophil, and ferritin levels, and decreased SpO_2 and fibrinogen levels in non-survivors. In survivors, ALT, total bilirubin, platelet and SpO_2 increased, and CRP and LDH levels decreased with favipiravir treatment. Favipiravir increased the oxygenation of patients and decreased CRP and LDH levels in the present study. Mortality rate was higher in patients with increased ferritin levels.

The most important limitation of this study was that it was a retrospective observational study. It was not a clinical trial which was designed to evaluate favipiravir efficacy. This study may give direction for controlled studies in the future.

Conclusion

Older age, smoking, presence of one or more comorbidity, especially CAD, arrhythmia, and CHF, and treatment with lopinavir/ritonavir before favipiravir were associated with increased mortality in patients with severe and critical COVID-19 pneumonia treated with favipiravir. Favipiravir treatment increased SpO_2 levels and platelet count, and decreased CRP and LDH levels in survivors. Increased ferritin may be a predictor of worsening of COVID-19. Early initiation of favipiravir treatment may be beneficial. Higher CRP levels at the beginning of treatment also increased the risk of mortality.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of the Umraniye Training and Research Hospital (125/April 28, 2020).

Informed Consent: Informed consent was waived because of the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Concept: T.Ç., Design: B.Ş., Data Collection or Processing: B.Ş., Analysis or Interpretation: T.Ç., Literature Search: B.Ş., Writing: T.Ç.

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