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Discussion

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CONTENTS

EDITORIAL

PREFACE

With the philosophy that success is dependent on continuity and stability, we take pride in sharing another issue of our magazine with you on this journey. Each new year opens new doors for the medical community. With every scientific advancement, we aim to make our mark through our magazine. Your valuable contributions of scientific studies and writings will elevate our magazine to even greater heights in the academic arena. Hoping that this issue of our magazine, with its rich content penned with different perspectives, interesting topics, and current approaches, will contribute to all our readers, I wish you enjoyable readings.

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ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J) **April 2024;11(1):1-9**

ARAŞTIMA MAKALES/ RESEARCH ARTICLE **DOI:** 10.56941/odutip.1371403

Are ECG findings overlooked in Lyme disease, which is the cause of AV complete block?

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Abstract

Objective: Lyme disease-associated carditis and conduction disturbances are well known, but there is insufficient data in the literature on the effects of Lyme disease on global electrocardiography (ECG) morphology. This study aims to evaluate the effects of Lyme disease on ECG morphology.

Method: The study included 48 consecutive patients who were hospitalised in our centre with a diagnosis of AV complete block between 01 January 2020 and 01 August 2023. Patients were divided into two groups as Lyme positive (Group 1) and negative (Group 2). Afterwards, demographic and laboratory data of the patients were recorded. All ECG data including ventricular rate, atrial rate, QRS duration, P wave dispersion (Pd), QTc dispersion (QTcd), and fragmented QRS were analysed from routine electrocardiograms obtained using standard extremity and chest leads at 25 mm/s and 10 mm/mV. The data obtained were compared between the groups.

Results: The mean age was 72.5(51.7-82.2) in group 1 and 74(68-79.7) in group 2, respectively. There was no significant difference between them (P= 0.593). In the study population, the ratio of males and females was similar between the groups. In ECG evaluation of the study population, no significant difference was found between atrial rate, ventricular rate, QRS duration, QTc duration and frequency of fragmented QRS ($p<0.05$). QTcd and Pd were significantly higher in Lyme + (Group 1). (75(56-84.5) vs 52(45-64.5), p=0.002; 58(50-62) vs 42.5(39-45.5), $p<0.001$, respectively).

Conclusion: When the results of our study are evaluated; Lyme disease causes an increase in Pd and QTcd in addition to affecting the AV node as known in the literature. These findings suggest that cardiac involvement of Lyme disease affects the cardiac conduction system more than thought.

Key Words: Lyme disease, Electrocardiography, AV complete block

AV tam blok nedeni olan Lyme hastalığında EKG bulguları gözden kaçıyor mu?

Özet

Amaç: Lyme hastalığına bağlı kardit ve ileti bozuklukları iyi bilinmektedir ancak Lyme hastalığının global elektrokardiyografi (EKG) morfolojisi üzerine etkileri konusunda literatürde yeterli veri bulunmamaktadır. Bu çalışma Lyme hastalığının EKG morfolojisi üzerindeki etkilerini değerlendirmeyi amaçlamaktadır.

Yöntem: Çalışmaya 01 Ocak 2020 ile 01 Ağustos 2023 tarihleri arasında AV tam blok tanısıyla merkezimizde yatan 48 ardışık hasta dahil edildi. Hastalar Lyme pozitif (Grup 1) ve negatif (Grup 2) olmak üzere iki gruba ayrıldı. Daha sonra hastaların demografik ve laboratuvar verileri kaydedildi. Ventriküler hız, atriyal hız, QRS süresi, P dalga dispersiyonu (Pd), QTc dispersiyonu (QTcd) ve fragmente QRS dahil tüm EKG verileri, 25 mm/s ve 10 mm/s hızlarında standart ekstremite ve göğüs derivasyonları kullanılarak elde edilen rutin elektrokardiyogramlardan analiz edildi. Elde edilen veriler gruplar arasında karşılaştırıldı.

Bulgular: Grup 1'de yaş ortalaması sırasıyla 72,5(51,7-82,2), grup 2'de 74(68-79,7) idi. Aralarında anlamlı bir fark yoktu (P= 0.593). Çalışma popülasyonunda gruplar arasında erkek ve kadın oranı benzerdi. Çalışma grubunun EKG değerlendirmesinde atriyal hız, ventriküler hız, QRS süresi, QTc süresi ve fragmante QRS sıklığı arasında anlamlı fark saptanmadı ($p<0,05$). QTcd ve Pd Lyme+'da (Grup 1) anlamlı derecede yüksekti. (sırasıyla 75(56-84,5) vs 52(45-64,5), p=0,002; 58(50-62) vs 42,5(39-45,5), $p<0,001$).

Sonuç: Çalışmamızın sonuçları değerlendirildiğinde; Lyme hastalığı, literatürde bilindiği gibi AV düğümünü etkilemeye ek olarak, Pd ve QTcd'de artışa neden olmaktadır. Bu bulgular Lyme hastalığının kardiyak tutulumununda, kardiyak ileti sistemini sanıldığından daha fazla etkilediğini düşündürmektedir.

Anahtar kelimeler: Lyme hastalığı, Elektrokardiyografi, AV tam blok

Suggested Citation: Bektaş O, Akkaya F. Are ECG findings overlooked in Lyme disease, which is the cause of AV complete block? ODU Med J, 2024;11(1): 1-9

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INTRODUCTION

Lyme disease is a multisystemic inflammatory disease caused by spirochetes of the genus Borrelia and occurs in temperate regions of the northern hemisphere (1). It is transmitted by ticks of the species Ixodes spp. and is the most common tick-borne zoonosis in the appropriate regions of North America, Asia and Europe (2). Generally, involves skin, joints, heart and central nervous system (1). It is the most common vector-borne infectious disease in the USA, with approximately 30,000 new cases recorded annually (3). Carditis develops in 4 to 10 % of untreated patients in the United States (4). Lyme carditis is most commonly associated with other manifestations of the disease (arthritis, erythema migrans or neurological disease), but can also occur independently (5). The spectrum of carditis is highly variable; some patients may be completely asymptomatic, while the main manifestations of Lyme carditis may be transient high-grade conduction disturbances (5).

Although Lyme disease-associated carditis and conduction disturbances are well known, there is insufficient data in the literature on the effects of Lyme disease on global electrocardiography (ECG) morphology. This study aims to evaluate the effects of Lyme disease on ECG morphology.

METHODS

The study included 48 consecutive patients who were hospitalized in our centre with a diagnosis of AV complete block between 01 January 2020 and 01 August 2023. All patients were subjected to the two-step test recommended by the American Centre for Disease Control for the serological diagnosis of Lyme disease. In the first step, antibody determination was performed by ELISA method, and in the second step, the diagnosis was confirmed by Western blot test in order to confirm the positive results. Patients were divided into two groups as Lyme positive (Group 1) and negative (Group 2). Afterwards, demographic and laboratory data of the patients were recorded. All ECG data including ventricular rate, atrial rate, QRS duration, P wave dispersion (Pd), QTc dispersion (QTcd), and fragmented QRS were analyzed from routine electrocardiograms obtained using standard extremity and chest leads at 25 mm/s and 10

mm/mV. The obtained data were compared between the groups.

P wave dispersion measurement

To determine P wave dispersion, the mean value of no less than three P wave lengths was computed for each lead. The commencement of the P wave was regarded as the initial discernible ascent from the isoelectric baseline in positive waveforms and the primary observable descent from the isoelectric baseline in negative waveforms. The return to the isoelectric line was acknowledged as the termination of the P wave. The maximum conduction time was determined by utilizing the Pmax value obtained from any derivation. The disparity between the maximum value (Pmax) and the minimum value (Pmin) was computed and designated as Pd. The measurements were conducted using manual means. The utilization of a magnifying glass and compass served to enhance the level of sensitivity. The Pd values obtained from Group 1 and Group 2 were subjected to a comparative analysis.

QT Dispersion Measurement

The QT interval in milliseconds was determined by measuring the distance between the commencement of the Q wave to the point where the T wave returns to the isoelectric line. In electrocardiograms (ECGs) exhibiting U waves, the nadir between the T and U waves has traditionally been regarded as the termination point of the T wave. The Bazett formula (QTc) was utilized to compute the corrected QT interval, taking into account the heart rate (QT/_R-R). The QTc interval of each derivation was determined by calculating the mean corrected QT interval of three consecutive beats. The measurement of QTc dispersion (QTcd) involved the computation of the discrepancy between the highest QTc interval (QTc maximum) and the shortest QT interval (QTc minimum). All measurements were conducted by hand. The utilization of a magnifying glass and compass served to enhance the level of sensitivity. The QTcd values obtained from Group1 and Group2 were subjected to a comparative analysis.

Statistical Analysis

The data were inputted into the SPSS (Statistical Package for Social Sciences) 22.0 statistical software program (IBM Corp., Armonk, NY, USA). The continuous variables were represented using either the mean ± standard deviation or the median with the interquartile range (median, 25th-75th percentiles), depending on the distribution of the data. The categorical variables were represented using frequency and percentage. The normality of the data was assessed using the Kolmogorov-Smirnov test and distribution graphs. The distinction between the groups was assessed using the Student's t-test (for data that followed a normal distribution) or the Mann-Whitney U test (for data that did not follow a normal distribution). The Chi-square

test was utilized to compare categorical data. The accepted level of statistical significance was determined to be $p<0.05$.

RESULTS

The study comprised a cohort of 48 individuals diagnosed with AV full block, divided into two groups: Group 1, consisting of 16 patients with Lyme disease, and Group 2, consisting of 32 patients without Lyme disease. The average age in group 1 was 72.5 years (with a range of 51.7 to 82.2 years), whereas in group 2 it was 74 years (with a range of 68 to 79.7 years). There was no statistically significant difference seen between the two groups, as shown by a p-value of 0.593. Within the research cohort, there was a comparable distribution of males and females across the various categories. There was no statistically significant disparity observed among the groups in relation to hypertension, diabetes, coronary artery disease, and smoking history ($p>0.05$). During the regular transthoracic echocardiogram, it was seen that the left ventricular ejection fractions were comparable between the two groups. The ejection fractions were measured to be 55 (with a range of 50-60) in one group and 55 (with a range of 50-55) in the other group. The statistical analysis indicated that there was no significant difference between the groups, with a p-value of 0.221. The demographic and baseline laboratory characteristics of the research population are shown in Table 1.

Table 1. Demographic information and basic blood parameters of the groups

Variables	Lyme + Group 1 (n=16)	Lyme – Group 2 (n=32)	P value
Age (years)	72.5(51.7-82.2)	74(68-79.7)	0.593
Gender (n%female)	6(37.5)	17(53.1)	0.262
HT n(%)	10(62.5)	27(84.4)	0.134
DM n(%)	4(25)	15(46.9)	0.194
Smoking n(%)	3(18.8)	8(25)	0.514
CAD n(%)	4(25)	11(34.4)	0.515
LV EF	55(50-60)	55(50-55)	0.221
Creatinine (mg/dl)	0.88±0.29	0.83±0.23	0.245
Haemoglobin (g/dl)	14.10±1,29	13,65±1,14	0.185
Haematocrit	42.30±4,18	42.39±4.25	0.321
White blood cell (10^3/mL)	8.3±2.5	8.5±2.9	0.456
Sodium (mEq/L)	138 ± 3.5	139 ± 2.4	0.395
Potassium (mEq/L)	4.3 ± 0.2	4.4 ± 0.3	0.186

Table 2. Comparison of ECG parameters of the groups

Variables	Lyme + Group 1 (n=16)	Lyme – Group 2 (n=32)	P value
Ventricle rate *bpm*	41(35-44,75)	44(40-45)	0.067
P wave rate *bpm*	70(60-84)	70(60-76,25)	0.78
QRS time *msec*	100(93,5-142)	110(90-139,5)	0.868
QTc interval *msec*	394(382-457,5)	389(378-442)	0.221
QTc dispersion	75(56-84,5)	52(45-64,5)	**0.002**
P dispersion	58(50-62)	42,5(39-45,5)	**<0.001**
Fragmented QRS n(%)	9(56.3)	10(31.3)	0.102

In the assessment of the study population's electrocardiogram (ECG), there was no statistically significant disparity seen in terms of atrial rate, ventricular rate, QRS duration, QTc length, and frequency of fragmented QRS. The study found that there was a statistically significant increase in QTc dispersion and P wave dispersion in individuals with Lyme disease (Group 1). The comparison between the two groups yielded the following results: 75 (56-84.5) vs 52 (45-64.5), with a p-value of 0.002; and 58 (50-62) versus 42.5 (39-45.5), with a p-value less than 0.001, respectively. The ECG parameters of the groups are presented in a comprehensive manner in Table 2.

DISCUSSION

The evaluation of the research cohort's electrocardiogram (ECG) revealed no statistically significant differences in atrial rate, ventricular rate, QRS duration, QTc interval, and frequency of fragmented QRS complexes. The research investigation revealed a statistically significant elevation in QTc dispersion and P wave dispersion among people diagnosed with Lyme disease (Group 1). The findings of the comparison between the two groups are as follows: Group A had a median value of 75 (range: 56-84.5), while Group B had a median value of 52 (range: 45-64.5), with a statistically significant p-value of 0.002. Similarly, Group A had a median value of 58 (range: 50-62), while Group B had a median value of 42.5 (range: 39-45.5), with a p-value less than 0.001, indicating a significant difference between the two groups. Table 2 provides a complete presentation of the ECG parameters for the respective groups.

Lyme disease is a zoonotic illness that is characterized by systemic manifestations and has the potential to induce acute atrioventricular (AV) blockages of varied severity. The incidence of cardiac involvement in the progression of Lyme disease is rather infrequent. In general, the prognosis of Lyme carditis is favorable (6). It is advisable to consider hospitalization for patients who exhibit a high level of clinical suspicion for Lyme disease, together with instances of syncope or the presence of second or third degree atrioventricular block (7). Around 35% of those diagnosed with Lyme carditis may experience the advancement of atrioventricular block, necessitating the temporary insertion of a cardiac pacemaker (8, 9). Nevertheless, it has been observed that individuals diagnosed with high-grade AV block often experience recovery over a span of around one week, whereas those with less severe conduction problems tend to recover within a timeframe of approximately six weeks (10, 11). Due to the notable incidence of remission, it is advised against expeditiously proceeding with the permanent installation of a cardiac pacemaker (8).

The most prevalent symptom of Lyme carditis, as determined by a research assessing patients with this condition, was identified to be temporary

atrioventricular block. The observed distribution of maximal atrioventricular block in all patients was found to be 49% for third degree, 16% for second degree, and 12% for first degree. The electrophysiological findings indicate that the engagement of the cardiac conduction system might exhibit either localized or extensive characteristics (8). Nevertheless, the findings of our study indicate that there is a resemblance in QRS shape between individuals who tested positive for Lyme disease and those who tested negative. This implies that the atrioventricular (AV) node may exhibit heightened sensitivity to Lyme illness. Although antibiotic therapy is administered, the occurrence of permanent pacemaker installation for Lyme carditis is infrequent (12, 13).

Lyme disease is often categorized into three distinct phases. The initial phase of infection in a specific area (stage 1) often manifests within a timeframe of 2 to 30 days following the bite of a tick. This stage is marked by symptoms like those of influenza, as well as the presence of erythema migrans. The second stage of early disseminated illness is generally distinguished by the presence of neurological problems and musculoskeletal abnormalities. Cardiac anomalies are typically observed during this period. The late stage of infection (stage 3) often manifests from months to years following the first erythema migrans and is distinguished by the presence of monoarthritis or oligoarthritis, primarily affecting the larger joints, alongside neurological symptoms.

Lyme disease has been seen to impact all layers of the heart in a pathological manner (14). The presence of vasculitis affecting intramyocardial vessels may also be seen. The occurrence of valvular dysfunction as a result of Lyme carditis is infrequent, as indicated by a study with a sample size of 15. Lyme carditis is characterized by the presence of myocardial involvement. Diffuse ST-T wave alterations are indicative of cardiac involvement. In the majority of instances, myocardial dysfunction tends to be of a mild kind and has a limited duration (16, 17). The observed elevation in QTcd in patients with Lyme disease in our study can be interpreted as indicative of cardiac involvement.

The occurrence of myocardial involvement resulting in echocardiographic left ventricular dysfunction or clinical congestive heart failure is estimated to be between 10 to 15% in individuals (8). The left ventricular ejection fraction (LVEF) of the patients included in our study had comparable values in both groups. This finding implies that myocardial involvement is less commonly detected in individuals with Lyme disease, especially in cases when the atrioventricular (AV) node is impacted.

There have been reports indicating that early use of antibiotics for Lyme disease can effectively avoid the occurrence of subsequent problems. Nevertheless, the efficacy of antibiotic therapy in

expediting the resolution of cardiac symptoms associated with Lyme disease lacks clinical substantiation (1). The observed rise in Pd and QTcd within our study indicates that cardiac involvement extends beyond the AV node, encompassing both atrial and ventricular regions. Hence, it would be advantageous to devise independent prospective research to assess the impact of antibiotic therapy on electrocardiogram (ECG) outcomes.

QTcd is recognized as a marker of regional heterogeneity in cardiac repolarization. Furthermore, an elevated QTcd is regarded as a non-invasive indicator that signifies the potential for ventricular arrhythmia (18). Hence, it is our contention that heightened QTcd in individuals diagnosed with Lyme disease warrants more vigilance in monitoring.

The Pd waveform is a straightforward electrocardiogram (ECG) observation that is employed to evaluate the durations of intra- and inter-atrial conduction, as well as the transmission of irregular sinus impulses in atria that are prone to atrial fibrillation (19, 20). There is evidence suggesting that extended Pd durations can be linked to the presence of stable angina pectoris (21) and acute coronary syndrome (22). Additionally, such durations have been found in individuals who have undergone coronary artery bypass surgery (23). Hence, exercising caution about atrial arrhythmia in individuals with Lyme disease might prove to be beneficial.

CONCLUSION

In summary, based on the findings of our investigation, it can be inferred that Lyme disease has the potential to induce high-grade AV blocks through its impact on the AV node. Furthermore, it appears to have detrimental effects on several phases of the conduction system in both the atria and ventricles.

Study Limitations

The most important limitation of our study is undoubtedly the small number of Lyme positive patients. However, the fact that cardiac involvement is not very common in Lyme disease seems to be the most important reason for this. Nevertheless, the number of cases related to Lyme endocarditis seems to be acceptable when compared with the studies in the literature. In addition, the fact that it was a retrospective and single-centre study can be said as an additional study limitation.

Ethics Committee Approval: Our study is a retrospective study and institutional permission was obtained to access the retrospective data of the patients after the permission of the clinical research ethics committee (03.02.2023-KAEK-3/36) was obtained. The principles of patient privacy and confidentiality were observed, and data were collected in accordance with the Declaration of Helsinki.

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Evaluation of Seasonal Hazelnut Workers' Emergency Department Applications in Ordu Province: A Retrospective Study

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Abstract

Objective: In Turkey, agricultural worker migration occurs in order to maintain different regulations and management in different seasons. Seasonal agricultural workers (SAWs) may also cause problems such as not knowing the conditions of the region they go to, experiencing health problems due to seasonal conditions, and increased workload in local institutions brought about by population growth due to humidity. This study aimed to evaluate the emergency service applications of seasonal hazelnut workers during the hazelnut harvesting season and to find solutions to possible health problems.

Method: It was a single-center, retrospective study and the applications of seasonal hazelnut workers who applied to the local tertiary emergency department between 01 August 2022 and 30 September 2022 were evaluated. The socio-demographic characteristics of non-pregnant patients aged 18 and over, their reasons for admission to the emergency department, and the treatments they received were recorded.

Results: 400 patients with no missing data were included in the study. 60.2% of the patients included in the study were female and 19% were SAWs who were not registered in the population of Ordu province. It was determined that the most common causes of SAWs in emergency department admissions were allergic reactions with at 37.3% and trauma with at 26%.

Conclusion: It is observed that SAWs increase the rates of emergency service admissions during the hazelnut harvesting season. We think that in this period, the employment of healthcare personnel should be increased, SAWs should be trained in terms of diseases that may occur due to environmental factors and working conditions, and the necessary health plans should be determined in advance.

Key Words: Agricultural worker, Emergency service, Hazelnut, Seasonal

Ordu İlindeki Mevsimlik Fındık İşçilerinin Acil Servis Başvurularının Değerlendirilmesi: Retrospektif bir Çalışma

Özet

Amaç: Tükiye'de farklı bölgelerde ve farklı mevsimlerde tarımsal faaliyetlerin sürdürülmesi için tarımsal işçi göçü meydana gelmektedir. Mevsimlik tarım işçilerin (MTİ) gittikleri bölgenin şartlarını bilmemeleri, mevsim şartlarına bağlı sağlık problemlerinin yaşanması ve göç nedeniyle nüfus artışının getirmiş olduğu yerel kurumlardaki iş yoğunluğunda artma gibi sorunları da beraberinde getirebilmektedir. Bu çalışma, mevsimlik fındık işçilerinin fındık hasat dönemindeki acil servis başvurularını değerlendirmeyi ve olası sağlık problemlerine çözüm üretmeyi amaçlamıştır.

Yöntem: Tek merkezli, retrospektif bir çalışma olup yerel üçüncü basamak acil servise 01 Ağustos 2022 ile 30 Eylül 2022 tarihleri arasında başvuran mevsimsel fındık işçilerinin başvuruları değerlendirilmiştir. 18 yaş ve üzeri gebe olmayan hastaların acil servis başvurusundaki sosyo-demografik özelikleri, başvuru nedenleri ve almış oldukları tedaviler kaydedilmiştir.

Bulgular: Verilerinde eksiklik olmayan 400 hasta çalışmaya dahil edildi. Çalışmaya dahil edilen hastaların %60.2'sinin cinsiyeti kadın ve %19'u Ordu ili nüfusuna kayıtlı olmayan MTİ'lerini oluşturmaktadır. MTİ'lerinin acil servis başvurularındaki en sık neden % 37.3 ile alerjik reaksiyonlar ve %26 ile travma olduğu tespit edildi.

Sonuç: MTİ'lerinin fındık hasat döneminde acil servis başvuru oranlarını arttırdığı görülmektedir. Bu dönemde sağlık personel istihdamının arttırılması ve MTİ'lerinin çevresel faktörler ve çalışma koşulları nedeniyle oluşabilecek hastalıklar açısından eğitilmesi ve gerekli sağlık planlamaların önceden belirlenmesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: Acil servis, Fındık, Mevsimsel, Tarım işçisi

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INTRODUCTION

Individuals who migrate from their provinces to work during planting and harvesting seasons in regions with intensive agricultural activities and return to their original provinces at the end of the season, are defined as seasonal agricultural workers (SAWs). In Türkiye, a significant portion of the employment in agriculture is constituted by SAWs, aimed at sustaining agricultural activities. The need for seasonal workers labor arises due to the necessity of completing the harvest in a short period, the majority of the rural population doing engaging in the same agricultural production, and the decline in rural population due to urban migration (2). Although the number of SAWs working informally in Türkiye is around 300,000 according to the Ministry of Labor and Social Security, it is estimated that the number of individuals affected by seasonal agricultural labor encompasses at least one million people (3).

In Türkiye's hazelnut agriculture, an important sector, as of 2018, 74% of hazelnut planting areas are located in the Eastern Black Sea Region, with 31% in Ordu, 16% in Giresun, 15% in Samsun, 9% in Trabzon, and 9% in Düzce provinces (4). The hazelnut harvest occurs during a short period covering August and September. Due to the inability to shift extensively to mechanized agriculture and the local labor force being insufficient, a large number of SAWs migrate to the region during this period. According to data obtained from local institutional records by the Development Workshop Cooperative for the International Labour Organization (ILO) Office in October 2019, approximately 40-50 thousand seasonal migrant agricultural workers migrate to Ordu, Sakarya, and Düzce provinces to participate in the hazelnut harvest (5).

Various studies have established that seasonal agricultural workers (SAWs) and their families face numerous barriers in to accessing healthcare services. These challenges include transportation difficulties, inadequate sick leave, fear of wage loss or job termination, language barriers with healthcare providers, lack of social security, organizational deficiencies, and limited operational hours of hospital services. SAWs and their families experience health problems similar

to the general population, but they also face unique challenges due to hazardous working conditions, poverty, low living standards, high fertility rates, informality, geographic isolation, nomadic lifestyle, and language and cultural barriers (6,7). These issues lead SAWs and their families to delay seeking health services, particularly those that are monitoring-based and/or require long-term treatment, due to concerns over the inability to continue work and loss of daily wages, until they return to their permanent residences (1,8). Consequently, SAWs and their families often prefer emergency services over other healthcare facilities, believing these will entail less waiting time (9).

In this study, we aim to analyze the emergency department applications of SAWs during the hazelnut harvesting season.

METHODS

Study Design and Population

This is a single-center, retrospective study conducted at the emergency department of a tertiary state hospital between August 1, 2022, and September 30, 2022, following approval from the Ordu University ethics committee. The study included all non-pregnant patients over the age of 18 and the trauma patients under 18 years of age who presented to the Emergency Department during the 2022 hazelnut harvest season.

Data Collection

Hospital records of patients presenting to the Ordu University Emergency Department between August 1, 2022, and September 30, 2022, were retrospectively reviewed. The data collection form recorded patients' age, gender, chronic diseases (Diabetes Mellitus, Hypertension, Coronary Artery Disease, Asthma/COPD, Neurological Disease, Cardiac Disease, Other), and sociodemographic information (residence), presenting complaints, diagnoses, treatments received (including hospital admissions), total daily emergency department visits, total visits by seasonal agricultural workers (SAWs), and the ratio of SAW visits to total emergency department visits.

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for the Social Sciences Statistics for Windows, Version 23.0 (IBM, Armonk, NY, USA). Demographic characteristics of the cases were presented as mean±standard deviation and n (%). Chronic disease data of the cases were also presented in n (%). Additionally, graphical representations were used to show the age distribution and presenting complaints of hazelnut workers.

RESULTS

Between 01 August and 30 September 2022, 22.200 patients who presented to the Emergency Department of Ordu University Training and Research Hospital Ministry of Health, Republic of Türkiye were retrospectively evaluated, and

the study was completed with 400 patients. During the hazelnut harvest period from August 1 to August 31, 2022, there were 11.850 patient admissions, while from September 1 to September 30, 2022, post-harvest, there were 10.350 admissions. Similarly, the total number of patients visiting the emergency department in October was 10.800.

It was found that 60.2% of the patients included in the study were female. 81% were registered residents of Ordu province. Patients' sociodemographic data are shown in Table 1, and age distribution is illustrated in Figure 1. The analysis of the reasons for SAWs' emergency department visits revealed that allergic reactions (37.3%) and trauma (26%) were the top two reasons (Figure 2). When reviewing the medical history of SAWs visiting the emergency department, a majority (57.5%) had a history of chronic illness. Looking at specific chronic conditions, 13.5% had Asthma/COPD, 11.8% had hypertension (HT), and 8% had diabetes mellitus (DM) (Table 2). It was determined that 85.5% of the patients were discharged after outpatient treatment, while 12.7% were admitted for observation and treatment in the emergency department.

Table 1. Analysis of Socio-Demographic Data of Hazelnut Workers Admitted to the Emergency Department

Socio-Demographic Variables		**n**	**%**
Age (Mean ± Std.)	43.9±0.8		
Gender	Male	159	39.8
	Female	241	60.2
Residence	Ordu and Ordu Population Registered	324	81
	Out of the Ordu	76	19
Application Complaint	Infective diseases	47	11.7
	Tick/insect contact	20	5.0
	Trauma	104	26.0
	Allergic reaction	149	37.3
	Other (Headeche, stomache,fewer, et else)	80	20.0
Treatment	Outpatient Treatment/Discharge	342	85.5
	Treatment Follow-up in the ED	51	12.7
	Inpatient Treatment in Hospital	7	1.8
Hospitalization	Yes	7	1,8
	No	393	98.2
Chronic Disease	Present	230	57.5
	Absent	170	42.5

Std: Standard deviation, ED: Emergency Department

Table 2. Chronic Disease Data of Hazelnut Workers Admitted to the Emergency Department

	n	%
HT	47	11.8
DM	32	8
Asthma/COPD	54	13.5
Neurological Disorder	12	3
Cardiac Disorder	14	3.5
Other	56	14

HT: Hypertension, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease

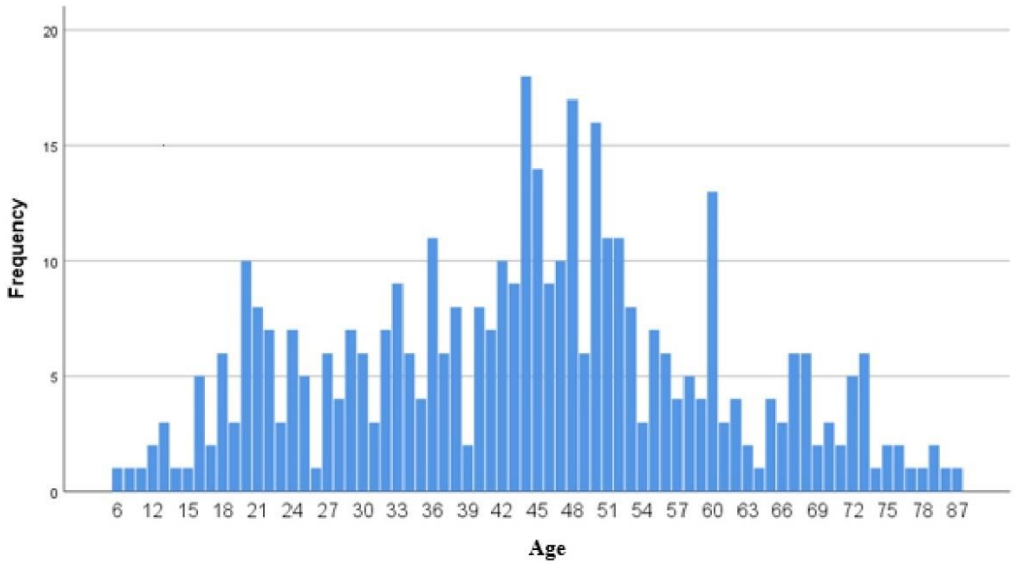

Figure 1. Distribution of hazelnut workers admitted to the emergency department according to age

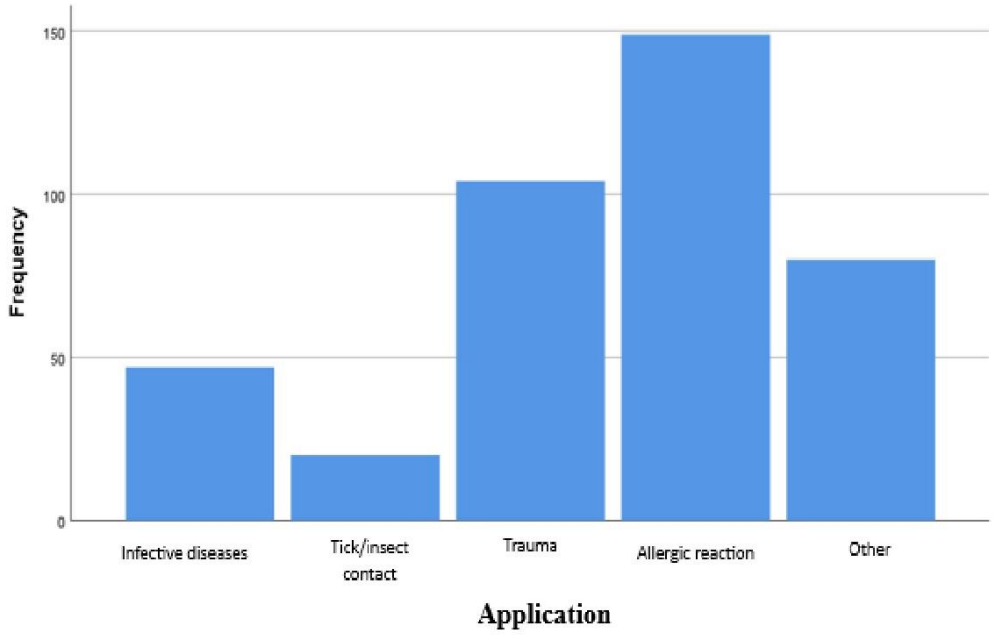

Figure 2. Distribution of hazelnut workers admitted to the emergency room according to complaints

DISCUSSION

With the migration of SAWs, there is an increase in the population, consequently leading to a rise in emergency department visits. During the hazelnut harvest period in Ordu, from August 1, 2023, to August 31, 2023, there were 11.850 patient admissions, and it was observed that the number of emergency department visits in August, the hazelnut harvest season, was higher compared to other months. Hazelnut farm workers are exposed to various allergens due to their working conditions. Agricultural chemicals, machinery oils, and biological agents like insect and animal bites are among the most common allergens they encounter (10,11). A study by Uzunoglu E. et al. showed that Paederus dermatitis is common among hazelnut workers, especially during the harvest season (12). Additionally, the sudden onset of allergic reactions often leads to swift healthcare facility visits. Therefore, we believe that allergic reactions were the most common reason for emergency department visits among hazelnut workers in our study. Due to the geographical structure of the Black Sea region, the geography of hazelnut cultivation consists of mountainous and rocky slopes (13). This increases the risk of trauma to people in these areas. Trauma patients typically present to the emergency department in the acute phase. In our study, trauma was the second most common reason for visits, which we believe is due to the geography of the region.

When examining the medical history of the patients included in the study, although Asthma/COPD and Hypertension (HT) were the most common, visits to the emergency department for respiratory and hypertensive emergencies were less frequent. This is thought to be due to the lack of sick leave for workers, financial concerns, fear of job loss, and lack of health insurance. In contrast, conditions like allergic reactions and trauma occur suddenly and necessitate immediate access to healthcare facilities. SAWs reside in designated camp areas in the regions they visit. Although these areas are equipped with sanitation and toilet facilities, the infrastructure may sometimes be inadequate. During events like floods and heavy rains, these areas may face outbreaks of infectious diseases like gastroenteritis. Additionally, the low socio-cultural level and poor self-care of SAWs also contribute to the prevalence of infectious diseases. Therefore, we believe that 11.7% of the emergency department visits by SAWs were due to infectious diseases.

SAWs face numerous challenges, including the fear of job loss, which leads them to focus solely on work during working hours and postpone other needs, including health. Additionally, transportation difficulties and low socio-cultural levels are other barriers to accessing primary health care services. Consequently, SAWs often bypass the tiered health system and directly visit emergency departments. This increases the

workload of emergency departments during harvest seasons. In our study, we found that 85.5% of the SAWs who visited the hospital received outpatient treatment and were discharged. We believe this percentage includes patients who did not seek primary healthcare services. We learned that 81% of the SAWs were registered residents of Ordu province. Accordingly, we found that the most majority of SAWs are actually from Ordu but reside outside of Ordu. This suggests that the majority of SAWs are actually people from Ordu living in other provinces who return to Ordu during the harvest season. This seasonal migration contributes to the increase in emergency department visits during these periods.

When we examined the age distribution graph of SAWs visiting the emergency department, we found that the majority of visits were made by individuals aged between 40-60 years. As mentioned in Bayram H.'s studyAccording to Erik Erikson, psychosocial development continues throughout life, and the age range of 30-60 years is characterized by productivity versus stagnation, with individuals being productive during this stage (14). We believe that the majority of SAWs are in their productive years, hence the high number of emergency department visits in this age group.

CONCLUSION

In conclusion, although it covers a small part of the year, factors such as increased migration to the region during the hazelnut harvest period, low socioeconomic status of SAWs and their families, adverse environmental factors, and difficult working conditions increase the number of emergency room admissions and thus the workload of emergency services. This periodic intensity in emergency services brings with it the need for personnel and equipment. We also see that this burden increases significantly when we consider the geographical conditions and endemic diseases that SAWs and their families are not used to. To manage this effectively and ensure uninterrupted health services, accurate personnel, and resource planning are essential. Additionally, planning for potential illnesses during these periods is also crucial.

Ethics Committee Approval: Approval was obtained from Ordu University clinical research ethics committee (14.04.2023, No:2023/102).

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A Developed Graphical User Interface-Based on Different Generative Pre-trained Transformers Models

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Abstract

Objective: The article investigates the integration of advanced Generative Pretrained Transformers (GPT) models into a user-friendly Graphical User Interface (GUI). The primary objective of this work is to simplify access to complex Natural Language Processing (NLP) tasks for a diverse range of users, including those with limited technical background.

Method: The development process of the GUI was comprehensive and systematic: Needs Assessment: This stage involved understanding the requirements and expectations of potential users to ensure the GUI effectively addresses their needs. Preliminary Design and Development: The initial designs were created and developed into a functional GUI, emphasizing the integration of features supporting various NLP tasks like text summarization, translation, and question-answering. Iterative Refinement: Continuous improvements were made based on user feedback, focusing on enhancing user experience, ease of navigation, and customization capabilities.

Results: The developed GUI successfully integrated GPT models, including GPT-4 Turbo and GPT-3.5, resulting in an intuitive and adaptable interface. It demonstrated efficiency in performing various NLP tasks, thereby making these advanced language processing tools accessible to a broader audience. The GUI's design, emphasizing user-friendliness and adaptability, was particularly noted for its ability to cater to both technical and non-technical users.

Conclusion: In conclusion, the article illustrates the significant impact of combining advanced GPT models with a Graphical User Interface to democratize the use of NLP tools. This integration not only makes complex language processing more accessible but also marks a pivotal step in the inclusive application of AI technology across various domains. The successful implementation of the GUI highlights the potential of AI in enhancing user interaction and broadening the scope of technology usage in everyday tasks.

Key words: Graphical User Interface (GUI), Generative Pretrained Transformers (GPT) models, Natural Language Processing (NLP), User-Friendly, Accessibility

Farklı Üretken, Önceden Eğitimli Dönüştürücüler Modellerine Dayalı Geliştirilmiş Grafik Kullanıcı Arayüzü

Özet

Amaç: Makale, gelişmiş Üretken Önceden Eğitimli Dönüştürücüler (GPT) modellerinin kullanıcı dostu Grafik Kullanıcı Arayüzü'ne (GUI) entegrasyonunu araştırmaktadır. Bu çalışmanın temel amacı, sınırlı teknik altyapıya sahip kullanıcılar da dahil olmak üzere çeşitli kullanıcıların karmaşık Doğal Dil İşleme (NLP) görevlerine erişimini kolaylaştırmaktır.

Yöntem: GUI'nin geliştirme süreci kapsamlı ve sistematikti: Gereksinim Değerlendirmesi: Bu aşama, potansiyel kullanıcıların gereksinimlerini ve beklentilerini anlamayı içeriyordu ve GUI'nin bu gereksinimleri etkili bir şekilde ele almasını sağlamak için yapıldı. Ön Tasarım ve Geliştirme: İlk tasarımlar, metin özetleme, çeviri ve soru cevaplama gibi çeşitli NLP görevlerini destekleyen özelliklerin entegrasyonunu vurgulayan işlevsel bir GUI olarak oluşturuldu ve geliştirildi. Yinelemeli İyileştirme: Kullanıcının geri bildirimlerine dayalı olarak kullanıcı deneyiminin, gezinme kolaylığının ve özelleştirme yeteneklerinin geliştirilmesine odaklanan sürekli iyileştirmeler yapıldı

Bulgular: Geliştirilen GUI, GPT-4 Turbo ve GPT-3.5 gibi GPT modellerine başarılı bir şekilde entegre edildi ve sezgisel ve uyarlanabilir bir arayüz ortaya çıkarıldı. Farklı NLP görevlerini etkili bir şekilde gerçekleştirme yeteneği göstererek, bu gelişmiş dil işleme araçlarını daha geniş bir kitleye erişilebilir hale getirdi. Kullanıcı dostu ve uyarlanabilirliği vurgulayan GUI tasarımı, teknik ve teknik olmayan kullanıcılara hitap etme yeteneği özellikle dikkat çekti.

Sonuç: Sonuç olarak, makale, gelişmiş GPT modellerini Grafik Kullanıcı Arayüzü ile birleştirmenin NLP araçlarının kullanımını demokratikleştirmedeki önemli etkisini göstermektedir. Bu entegrasyon, karmaşık dil işleme araçlarını sadece daha erişilebilir hale getirmekle kalmaz, aynı zamanda çeşitli alanlarda yapay zeka (AI) teknolojisinin kapsayıcı uygulamasında da bir dönüm noktası işaret eder. GUI'nin başarılı bir şekilde uygulanması, AI'nin kullanıcı etkileşimini geliştirme potansiyelini ve günlük görevlerde teknoloji kullanımının kapsamını genişletme potansiyelini vurgular.

Anahtar kelimeler: Grafik Kullanıcı Arayüzü (GUI), Üretken Önceden Eğitimli Dönüştürücüler (GPT) modelleri, Doğal Dil İşleme (NLP), Kullanıcı Dostu, Erişilebilirlik

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INTRODUCTION

Language serves as the fundamental basis for human communication and influences our interactions with the external environment. The advent of natural language processing (NLP) has revolutionized our interaction with machines. NLP has transformed communication by enabling humans to interact with technology in a more authentic and intuitive way. The rapid increase in the amount of written information available online has driven the progress of NLP. The field of NLP has undergone substantial advancements, progressing from rudimentary rule-based systems to intricate deep learning-based models (1). Due to the intricate nature of human language, natural language interpretation and generation have historically posed significant challenges in the field of NLP, despite notable progress. Nevertheless, recent breakthroughs have paved the way for innovative strategies to address these issues. The development of the Generative Pre-Trained Transformer (GPT) is a significant achievement in the field of NLP. (2).

GPT rose to prominence with the debut of ChatGPT by OpenAI, a research firm focused on creating AI technology (3). GPT is a deep learning model that has been pre-trained on huge corpora of text data and may be fine-tuned for tasks such as language synthesis, sentiment analysis, language modeling, machine translation, and text categorization. GPT's transformer architecture is a huge step forward over earlier techniques to NLP, such as RNN and CNN. It employs a self-attention method to enable the model to consider the context of the full phrase while creating the next word, enhancing the model's capacity to understand and produce language. The decoder is in charge of producing the output text depending on the input representation (4).

GPT is capable of a wide range of NLP tasks. Natural language understanding (NLU) is one of its primary features; it can evaluate and grasp the meaning of text, including detecting entities and relationships in phrases. It's also skilled at natural language generation (NLG), which means it can generate text output such as creative material or detailed and insightful answers to inquiries. GPT may also be used as a code generator, writing

computer code in languages such as Python or JavaScript.

GPT may also be used to answer questions, which means it can offer factual summaries or build tales depending on the supplied text. Furthermore, GPT may summarize material, such as delivering a concise review of a news story or research paper, and it can be used for translation, allowing text to be translated from one language to another. Overall, GPT's capacity to handle a wide range of NLP tasks with high accuracy and precision makes it a useful tool for industries such as finance, healthcare, marketing, and others. As NLP technology advances, we may expect GPT and other language models to become progressively more complex and powerful, allowing us to connect with machines more naturally and efficiently.

GPTs have revolutionized NLP, enabling rapid advancements in various industries. Despite its widespread adoption, there is a lack of comprehensive understanding of GPT's architecture and capabilities. This gap not only hampers optimization but also limits the technology's full potential. Therefore, a detailed study is essential to explore its architecture, supporting technologies, potential applications, current challenges, and future prospects. This unexplored territory and the need for a nuanced understanding served as the driving forces behind our research endeavor.

This article presents the design and implementation of a graphical user interface (GUI) that leverages the capabilities of GPT models for various natural language processing tasks.

METHODS

Objective and Scope

The primary aim of this research is to develop a user-friendly Graphical User Interface (GUI) that integrates GPT for executing a range of NLP tasks. The scope includes text summarization, translation, and question-answering functionalities.

Research Design and Methodology

Needs Assessment: Conducting surveys and interviews to identify user requirements and the NLP tasks that the GUI should support.

Preliminary Design: Sketching initial wireframes and integrating a base GPT model.

Development: Actual coding, leveraging Python rest api endpoints and Angular WEB UI for user interaction.

Evaluation: Performance metrics and user feedback are collected to assess the GUI's efficiency and usability.

Iteration: Refinements are performed based on the evaluation results.

Technical Stack

Programming Language: Python 3.x

Python Libraries: OpenAI, Flask, Flask - Cors

GUI Framework: Angular 16.2, PrimeNg 16.3, PrimeFlex 3.3.1

Deployment: Docker

Version Control: Git

Hardware Specifications

Processor: Virtual 2 Core CPU

RAM: 4GB RAM

Storage: 20GB SSD

Operating System: Debian 12.1.0

System Architecture

The system is modular, consisting of:

User Interface Layer: The User Interface (UI) Layer of our system is meticulously crafted using the Angular Framework. Angular stands out as a premier TypeScript-based open-source web application framework, spearheaded by the esteemed Angular Team at Google, with active contributions from a vibrant community of individuals and corporations alike. Renowned for its versatility and robustness, Angular offers a sophisticated platform that empowers developers in the creation of dynamic and responsive client-side web applications.

In summary, the User Interface Layer of our system, developed using the Angular Framework, embodies the epitome of modern web development practices. With its powerful features, comprehensive toolset, and thriving community, Angular empowers developers to build sophisticated, scalable, and visually stunning web applications that delight users and drive business success.

Business Logic Layer: At the heart of our system lies the Business Logic Layer, a pivotal component that orchestrates the functionality and intelligence of our application. This layer seamlessly integrates cutting-edge GPT (Generative Pre-trained Transformer) models, serving as the backbone for handling a myriad of tasks ranging from natural language processing to text generation and beyond.

Central to the functionality of the Business Logic Layer is its adept handling of various GPT tasks, leveraging the power and versatility of state-of-the-art machine learning models. Whether it's generating coherent text, summarizing documents, or engaging in conversation, the GPT models encapsulated within this layer exhibit a remarkable ability to comprehend and generate human-like responses.

To facilitate seamless interaction with the user interface, the Business Logic Layer exposes its functionality through REST API endpoints. These endpoints serve as the conduit through which data and requests are exchanged between the user interface and the underlying logic of the system. By adhering to RESTful principles, our API endpoints ensure a standardized and intuitive interface for communication, fostering interoperability and ease of integration with external systems.

Underpinning the Business Logic Layer is a robust implementation of the business service layer, meticulously developed using Python and the Flask library. Python, renowned for its simplicity, readability, and versatility, serves as

the foundation for our business logic, enabling rapid development and iteration. Flask, a lightweight and extensible web framework for Python, further augments our business service layer by providing essential features for routing requests, handling HTTP methods, and managing application state.

Through the harmonious interplay of GPT models, RESTful APIs, Python, and Flask, the Business Logic Layer empowers our system with unparalleled intelligence and functionality. Whether it's automating tedious tasks, providing insightful recommendations, or engaging users in meaningful dialogue, this layer serves as the linchpin for delivering a transformative user experience. With its sophisticated capabilities and robust architecture, the Business Logic Layer lays the groundwork for a truly innovative and impactful application.

UI – Service Interaction:

A REST API, sometimes referred to as a RESTful API, is an application programming interface (API) or web API that adheres to the principles and limitations of the REST architectural style. It enables communication and interaction with RESTful web services. REST, an acronym for representational state transfer, was devised by computer scientist Roy Fielding (5).

An Application Programming Interface (API) constitutes a comprehensive set of guidelines and structures for the development and integration of application software. It functions akin to a contractual agreement between a provider of information and a user, delineating the specific data required by the user (termed as the 'call') and the corresponding output necessitated by the provider (referred to as the 'response') (6).

In this work, business logic layer provides set of API interfaces that receives calls from user interface layer, processes it, and transforms to OpenAI API model (7). Service layer has business logic to transform user inputs to Open-AI model also provides additional inputs for better NLP results (8). Figure 1 depicts workflow processes for the design of the proposed system.

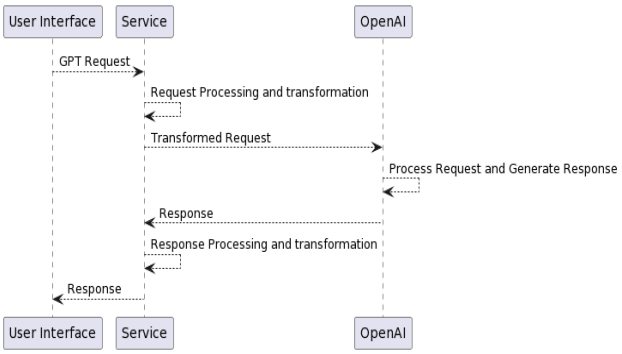

Figure 1. Workflow processes for the design of the proposed system

User Experience Design

Embedded within the core tenets of Human-Centered Design, this particular design ethos places paramount importance on the principles of simplicity and accessibility, meticulously crafted to prioritize the seamless integration of user needs and desires. With a steadfast commitment to enhancing user comfort and ease, the design intricately weaves together intuitive interactions and ergonomic features, forging a symbiotic relationship between user and interface.

At the heart of this design philosophy lies a continuous feedback loop, meticulously curated through a dual-channel approach comprising electronic mail and graphical user interfaces. This comprehensive feedback mechanism serves as the lifeblood of the design process, providing invaluable insights into user experiences and preferences. By leveraging these insights, the design team is empowered to iterate and refine the design iteratively, ensuring its ongoing alignment with evolving user expectations.

Moreover, this iterative refinement process serves as a testament to the design's adaptability and versatility, allowing it to seamlessly cater to the diverse needs of its user base. Each refinement is meticulously crafted to enhance the overall user experience, fostering a sense of inclusivity and accessibility across all touchpoints of interaction.

Furthermore, this commitment to continuous improvement extends beyond mere functionality, delving into the realm of emotional resonance and user delight. Through thoughtful iteration and refinement, the design transcends its utilitarian purpose, forging meaningful connections with users and fostering a sense of loyalty and trust.

In essence, this design philosophy encapsulates the essence of Human-Centered Design, where simplicity, accessibility, and user-centricity converge to create transformative experiences. By embracing a culture of continuous feedback and iterative refinement, this design ethos stands as a beacon of innovation and empathy, enriching the lives of users in profound and meaningful ways.

RESULTS

Figure 2 illustrates the proposed interface's settings and configuration in detail. It showcases the layout and organization of various control elements, demonstrating how users can interact with and adjust the interface. This visualization highlights the user-friendly design, emphasizing ease of navigation and customization options available within the interface. It provides a clear representation of how the interface can be tailored to meet specific user needs, displaying both the default settings and the range of adjustments possible for personalization and efficiency. The figure serves as a comprehensive guide for understanding the interface's functionality and adaptability.

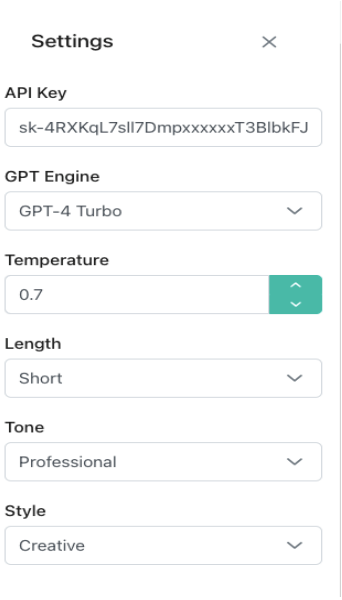

Figure 2. Settings and Configuration of the proposed interface

An API key, also known as an Application Programming Interface key, is a distinct identification utilized for the purpose of authenticating a user, developer, or calling application to an API. API keys are utilized to monitor and regulate the usage of the API, primarily to safeguard against any malicious or abusive activities. The API key serves as both a confidential authentication token and a distinctive identification.

Here API key is provided by OPENAI platform subscription.

GPT Engine: OpenAI provides set of GPT engines, each solves different use cases. The GPT models were sourced from Open-AI. GPT models listed are below in Table 1 [16]:

Table 1. GPT models and algorithms that can be used in the developed software

Models	Description
GPT-4 and GPT-4 Turbo	A set of models that improve on GPT-3.5 and can understand as well as generate natural language or code
GPT-3.5	A set of models that improve on GPT-3 and can understand as well as generate natural language or code
GPT base	A set of models without instruction following that can understand as well as generate natural language or code
DALL·E	A model that can generate and edit images given a natural language prompt
TTS	A set of models that can convert text into natural sounding spoken audio
Whisper	A model that can convert audio into text
Embeddings	A set of models that can convert text into a numerical form
Moderation	A fine-tuned model that can detect whether text may be sensitive or unsafe
GPT-3-Legacy	A set of models that can understand and generate natural language

In this work we have adopted "GPT-4 Turbo, GPT-4 with vision, GPT-4, GPT4-32K and GPT-3-Turbo" models.

Temperature: This parameter is used to control randomness of the output. What sampling temperature to use, between 0 and 2. Higher values like 0.8 will make the output more random, while lower values like 0.2 will make it more focused and deterministic.

Length: This parameter controls length of output. Options are:

- Long
- Medium
- Short

Tone: Defines tone of the output. Options are:

- Professional
- Causal
- Enthusiastic
- Informational
- Funny

Style: Defines style of the output. Options are:

- Creative
- Balanced
- Sensitive

GPT Prompt screen is given in Figure 3.

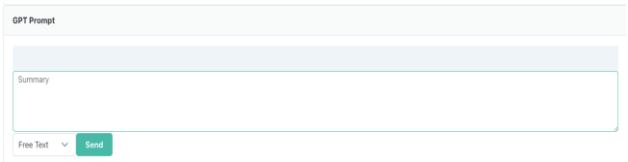

Figure 3. GPT Prompt screen

GPT Prompt screen provides user – GPT interaction. Context provides additional information related with problem.

The Transformer architecture uses contextual embeddings to represent words, meaning that the same word can have different embeddings based on its surrounding words. This allows GPT models to capture nuanced meanings and relationships between words, thereby making better predictions.

In first example, we have not provided any information about the input:

The screen showing that no information is provided regarding the login is given in Figure 4.

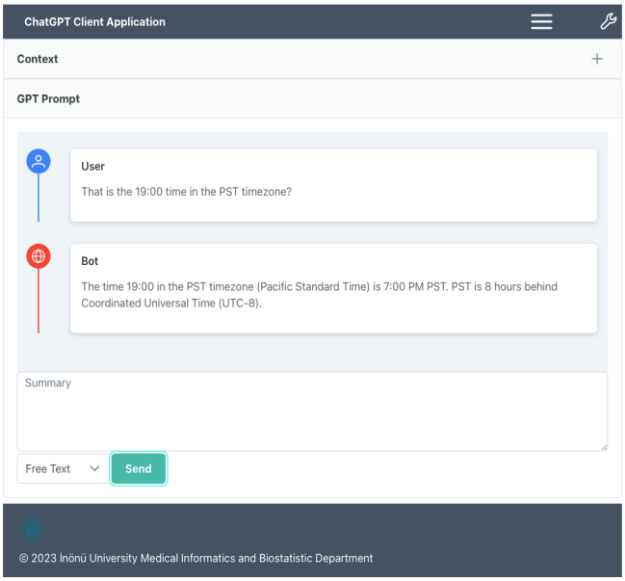

Figure 4. The screen showing that no information is provided about the login

In the second example we have provided context about the input: The screen showing that the context for the entry is provided is shown in Figure 5.

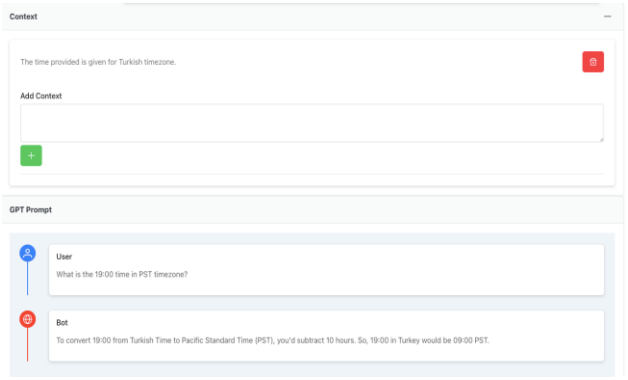

Figure 5. Screen showing that context is provided for the input

Context provides better interpretation and more accurate results for the input.

Free Text Input:

The free text entry screen is shown in Figure 6 below.

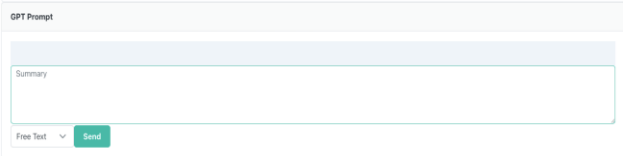

Figure 6. Free text input screen

Free text input provides chat-GPT interaction with user. System sends settings parameters and context to server to support different use cases and optimize responses. User's input text screen is shown in Figure 7 below.

Input:

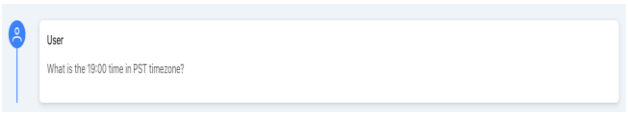

Figure 7. User's input text

Output - 1:

Model: GPT-4 Turbo

Temperature: 0,7

Length: Long

Tone: Funny

Style: Creative

A screenshot of an example of a long response from the system to the user is given in Figure 8 below.

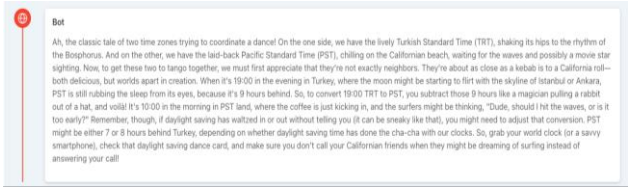

Figure 8. Example of long response from the system to the user

Output - 2:

Model: GPT-4 Turbo

Temperature: 0,7

Length: Medium

Tone: Informational

Style: Balanced

A screenshot of the shorter response sample given by the system to the user is given in Figure 9.

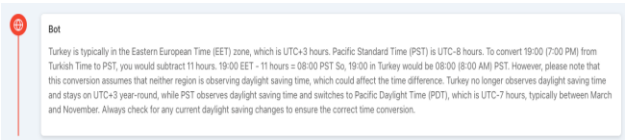

Figure 9. Example of a shorter response given by the system to the user

Text Translate:

Predefined context by software provides information about the input and the transformation to be performed. The results with same transformation will be applied all inputs provided. The image of the screen where the user enters text for text translation is given in Figure 10. The text entered by the user is translated and given as output.

Input:

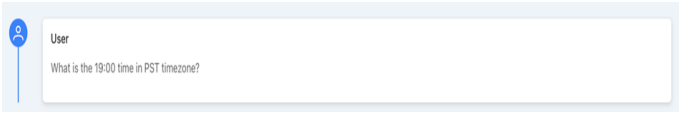

Figure 10. User's input text

File Translate

File translate provides file upload utility to profile external file content as input. Predefined context by software provides information about the input and the transformation to be performed. The transformation is applied to file content provided and result can be viewed with transformed input. The file upload screen for file translation is shown in Figure 11. The file that needs to be translated is selected and uploaded to the system, and the file translation output is obtained from the system.

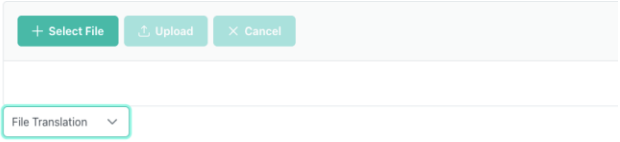

Figure 11. File upload screen for file translate

Cardiovascular Surgery File Translate:

This tool provides pre-defined context and back-end service reads uploaded data, transforms it and uses Open-AI API endpoints with context

and content to perform NLP operations. An example of the text that the user wants translated about cardiovascular disease is given in Figure 12.

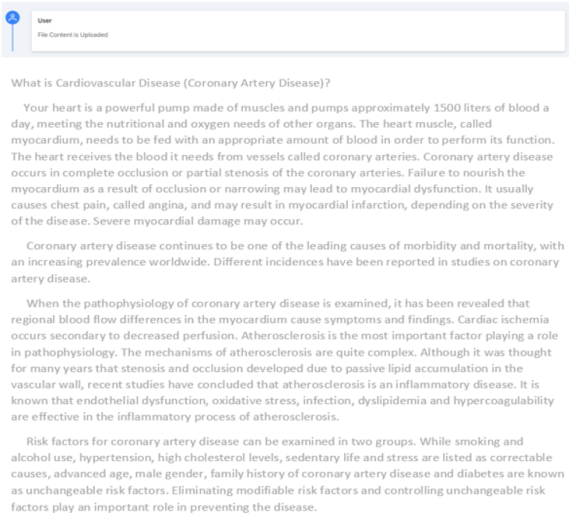

Figure 12. Example of user-uploaded text about cardiovascular disease

Cardiovascular Surgery Paraphrase:

Cardiovascular Surgery Paraphrase provides paraphrasing utility to paraphrase inputs in Cardiovascular Surgery domain. Pre-defined context has been provided by system to control NLP engine. An example of the output where the system comments on the entry after the user enters information about Cardiovascular surgery is shown in Figure 13.

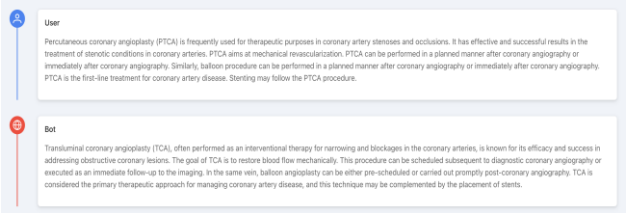

Figure 13. Example of output after the user enters information about Cardiovascular surgery and the system provides a comment on the entry.

DISCUSSION

This work has significant implications for the broader adoption of NLP technologies, particularly for users without a technical background. It opens up new avenues for research and development in the field of user-friendly interfaces for complex machine-learning modelsGPT is an AI language model created by OpenAI, Inc. GPT, an abbreviation for Generative Pre-trained Transformer, is an artificial intelligence system that use a Transformer architecture to generate original material by using a pre-existing dataset during its training phase. GPT was especially designed for NLP tasks that encompass two fundamental elements: (1) comprehending and discerning the semantic meaning of a phrase (natural language comprehension), and (2) producing new phrases based on the inputs (natural language generation). Classical NLP models are rule-based and offer restricted responses by adhering to a predetermined set of encoded rules. As a result, they lack adaptability and struggle to accommodate the dynamic and diverse characteristics of language (9).

The origins of NLP models may be traced back to 1949, with the introduction of Weaver's memorandum which laid the foundation for the notion of machine translation (MT). In the early stages of NLP, the primary focus of algorithms was on machine translation (MT), however there were other models developed with more

extensive capabilities (10). Before 1990, systems were predominantly rule-based and heavily influenced by language ideas. The early 1990s witnessed a significant breakthrough with the implementation of statistical models, which was subsequently accompanied by a transformative move towards machine learning. The rise of deep learning in the early 2000s established the foundation for present-day NLP models. The presentation of the pioneer neural language model by Bengio et al. in 2003 was a significant early advancement (11). This model was a feed-forward neural network with a single hidden layer, and it is thought to be the first model that employed the word embedding technique. The 2010s witnessed a significant advancement in technology due to the rapid growth in computer processing capabilities and the collection of extensive datasets. This advancement resulted in the successful implementation of recurrent neural networks (RNN) and long short-term memory (LSTM) models. These sophisticated network architectures offer significant benefits in forecasting or classifying sequential data. Consequently, two innovations have laid the groundwork for GPT. Initially, novel algorithms were proposed, including sequence-to-sequence learning (2014) (12), attention (2015), and self-attention (2017) (13), which significantly enhanced the effectiveness of generative natural language processing (NLP) models (referred to as "G" in GPT). The second significant development was the introduction of innovative 'word embedding' methods. These methods include representing words as numerical data that captures their importance, frequency of use, and user-defined meanings. This allows words with comparable meanings to have similar numerical values. Word2Vec12 pioneered these techniques in 2013 (14). These methodologies proved to be more effective than previous methods and enabled training on far larger data sets. The concept of large pre-trained language models was introduced in 2016 (15). (The letter "P" in GPT) The Transformer, which is the primary architect of GPT, was launched in 2017, alongside significant technological and conceptual advancements in NLP (16). This innovative architecture facilitated the collection and processing of the semantic significance of words within sentences by NLP models. The first Transformer design has both an encoder and a decoder. The encoder takes inputs for processing and transforms them into a sequence of uninterrupted representations using six identical layers. Afterwards, the decoder sends these representations through six further layers that are comparable in order to produce outputs. Both the encoder and decoder layers comprise a sublayer known as 'multi-head self-attention' and another sublayer known as a 'feed-forward' network, which is fully coupled. Furthermore, within each decoder layer, there exists a sublayer known as 'masked self-attention' that exclusively utilizes

preceding words within a phrase to forecast words at a certain place (auto-regression). The GPT model undergoes a biphasic training phase (17). The initial phase entails the unsupervised training of the model using an extensive collection of unannotated textual input. The model's 'pre-training' involves autonomously acquiring knowledge of linguistic patterns and representations. With a substantial rise in size, GPT showcased its capacity to efficiently acquire new skills with minimal task-specific input, a phenomenon referred to as 'few-shot' learning. As the dimensions of GPT expanded, it exhibited the capacity to proficiently acquire knowledge in new tasks with less task-specific data, a phenomenon referred to as 'few-shot' learning (18).

This article shows how we can implement different use cases with customized inputs for chat-GPT NLP models. In the realm of artificial intelligence, the introduction of OpenAI's API endpoints for ChatGPT represents a significant advancement in democratizing access to sophisticated language models. By providing well-documented and accessible API endpoints, OpenAI has expanded the utility of ChatGPT beyond the confines of research laboratories and specialized applications to a broader audience, including developers, entrepreneurs, and educators. This shift facilitates a more extensive and diverse application of the technology, enabling the incorporation of advanced natural language processing capabilities into a variety of software applications and services. The API's accessibility encourages innovation and experimentation across various fields, fostering a collaborative environment where developers can tailor ChatGPT's capabilities to meet specific needs. This expansion is crucial in bridging the gap between cutting-edge AI research and practical, real-world applications, thereby accelerating the adoption and integration of AI into everyday technology solutions (19).

In academic discourse on artificial intelligence, the optimization of output in GPT for chat completions through context and parameters emerges as a pivotal subject. The efficacy of these language models, hinges significantly on their capacity to interpret and respond to user input within a given context. By meticulously setting parameters – including tone, style, and content specificity – users can significantly refine the model's responses to align more closely with the intended application. This adaptability is crucial in diverse fields ranging from education, where the model can be tuned to provide age-appropriate responses, to customer service, where it can be calibrated for empathetic and solution-oriented interactions. Furthermore, the incorporation of relevant context into prompts enables the model to generate responses that are not only syntactically and semantically accurate but also contextually appropriate, enhancing the overall user experience. These customizable

features underscore the importance of fine-tuning AI models to specific use cases, thereby maximizing their potential and utility in real-world applications (19, 20).

The integration of OpenAI's API endpoints into various applications exemplifies a paradigm shift in the utilization of natural language processing (NLP) techniques, transcending traditional boundaries. By offering a streamlined and accessible gateway to advanced NLP capabilities, these endpoints enable a wide range of applications to harness the power of sophisticated language models like ChatGPT. This integration facilitates diverse functionalities, from semantic analysis and sentiment detection in social media platforms to automated customer support and personalized content creation in digital marketing. Moreover, the adaptability of the API allows for the tailoring of NLP features to specific industry needs, be it in legal text analysis, healthcare communication, or educational content generation. This democratization of NLP technology not only fosters innovation across sectors but also accelerates the development of more intuitive and human-centric AI interfaces. As a result, the OpenAI API endpoints serve as a catalyst, transforming the theoretical potential of NLP into practical, impactful solutions across an array of industries (21).

In conclusion, the article illustrates the significant impact of combining advanced GPT models with a Graphical User Interface to democratize the use of NLP tools. This integration not only makes complex language processing more accessible but also marks a pivotal step in the inclusive application of AI technology across various domains. The successful implementation of the GUI highlights the potential of AI in enhancing user interaction and broadening the scope of technology usage in everyday tasks.

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ARAŞTIMA MAKALES/ RESEARCH ARTICLE

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Evaluation of Single/Multiple Joint Effects of Lipid Profiles on Hypertension, Diabetes Mellitus and Obesity Accompanying Coronary Artery Disease

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Abstract

Objective: Although cardiovascular diseases are among the most prominent causes of mortality/morbidity in the world, they are even more important together with comorbidities. This study aims to reveal the single/multiple effects of total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), and triglyceride (TG) on hypertension (HT), type 2 diabetes mellitus (T2DM) and obesity accompanying coronary artery disease (CAD).

Method: The data were retrospectively achieved from the records of CAD patients undergoing coronary bypass surgery at the Department of Cardiovascular Surgery, Medical Center, University. The medical knowledge discovery process (MKDP) was applied to the data concerning HT, DM, obesity, TC, HDL-C, LDL-C, and TG variables. Different methods were used to determine the optimal cut-off points of lipid profiles. Logistic regression analysis (LRA) was examined the single/multiple effects of lipid profiles on HT, T2DM, and obesity.

Results: TC, LDL-C, TG, and HDL-C lipid profiles categorized according to the cut-off points determined in the current study were analyzed with LRA models. LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) in HT and TC (>190 mg/dL)*TG (>197) mg/dL)*HDL-C (>36.3 mg/dL) in T2DM interaction terms had a moderate effect size. LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) interaction terms in T2DM and TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TK (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) interaction terms in obesity were reported as having a high effect size.

Conclusion: In conclusion, it is recommended to use the approach that analyzes the cut-off points proposed in this study for lipid profiles in predicting HT, T2DM, and obesity.

Keywords: Coronary artery disease, Risk factors, Lipids, Knowledge discovery.

Lipid Profilinin Hipertansiyon, Diabetes Mellitus ve Obezite ile Birlikte Gelen Koroner Arter Hastalığı Üzerindeki Tekli/Çoklu Etkilerinin Değerlendirilmesi

Özet

Amaç: Kardiyovasküler hastalıklar dünya genelindeki önde gelen ölüm/morbidite nedenleri arasında olmasına rağmen, eşlik eden hastalıklarla birlikte daha da önemlidirler. Bu çalışma, total kolesterol (TK), yüksek dansiteli lipoprotein-kolesterol (HDL-C), düşük dansiteli lipoprotein-kolesterol (LDL-C) ve trigliserit (TG)'nin hipertansiyon (HT), tip 2 diabetes mellitus (T2DM) ve obezite üzerindeki tekli/çoklu etkilerini ortaya çıkarmayı amaçlamaktadır.

Yöntem: Üniversitesi Tıp Merkezi … Kardiyovasküler Cerrahi Bölümü'nde koroner bypass cerrahisi geçiren koroner arter hastalarının kayıtlarından retrospektif olarak elde edilmiştir. Hipertansiyon, DM, obezite, TK, HDL-C, LDL-C ve TG değişkenlerine ilişkin veriler için tıbbi bilgi keşfi süreci (TBKS) uygulanmıştır. Lipid profillerinin optimal kesme noktalarını belirlemek için farklı yöntemler kullanılmıştır. Tekli/çoklu etkilerini belirlemek için lojistik regresyon analizi (LRA) lipid profilleri incelenmiştir.

Bulgular: Bu çalışmada belirlenen kesme noktalarına göre kategorize edilen TK, LDL-C, TG ve HDL-C lipid profilleri LRA modelleri ile analiz edilmiştir. HT'de LDL-C (>117 mg/dL)*TK (>191 mg/dL)*HDL-C (>37.2 mg/dL) ve T2DM'de TK (>190 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) etkileşim terimleri orta etki büyüklüğüne sahipti. T2DM'de LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) etkileşim terimleri ve obezitede TK (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TK (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) ve LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) etkileşim terimleri yüksek etki büyüklüğü olarak rapor edilmiştir.

Sonuç: Sonuç olarak, HT, T2DM ve obeziteyi öngörmede lipid profilleri için bu çalışmada önerilen kesme noktalarını analiz eden bir yaklaşımın kullanılması önerilir.

Anahtar kelimeler: Koroner arter hastalığı, Risk faktörleri, Lipitler, Bilgi keşfi

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INTRODUCTION

Cardiovascular diseases, including coronary artery disease (CAD), have increasing importance in terms of being one of the most prominent causes of mortality and morbidity worldwide. In addition, hypertension (HT), type 2 diabetes mellitus (T2DM), obesity, hyperlipidemia, cancer, etc., diseases accompanying CAD can further increase mortality and morbidity. Thence, it is predicted that there will be more than 22 million deaths due to cardiovascular diseases worldwide in 2030 (1). According to the 12-year follow-up data of the heart disease and Risk Factors in Turkish Adults (TEKHARF) study, which has been conducted since 1990 under the leadership of the Turkish Society of Cardiology, it is estimated that there are approximately 2 million coronary heart patients in Turkey and almost 160 thousand people died from coronary heart disease. Approximately 260 thousand coronary events occur throughout the country, and when 85,000 of them are immediately fatal, 175 thousand patients with non-fatal coronary events remain candidates for treatment. Of the 2 million coronary patients, approximately 75-80 thousand additionally die. Thus, the total number of coronary heart patients increases by 90-100 thousand per year. The TEKHARF study found the annual mortality of coronary heart disease in our adults to be 5.2 per thousand in men and 3.2 per thousand in women. Nevertheless, the cause of one out of every eight deaths could not be determined. Among those with known causes, deaths from coronary heart disease were the highest at 42.5%, followed by cancer at a rate of 24% and cerebrovascular event-related deaths at a rate of 12% (2, 3).

When these essential data of TEKHARF (3) and other related studies (4-6) conducted in Turkey are evaluated, it is inferred that preventive medicine practices that can be carried out for the prevention of cardiovascular diseases such as CAD are of great importance to reduce the risk of mortality and morbidity. Lipid profiles are a test that can be used to screen those at risk of developing CAD. Thanks to evaluating these test results, medical information can be obtained to prevent possible risky situations such as heart attack, stroke, etc., in individuals. Lipid profile tests, mainly including total cholesterol (TC) test,

high-density lipoprotein-cholesterol (HDL-C) assay, low-density lipoprotein cholesterol-cholesterol (LDL-C) assay, and triglyceride (TG), are performed for lipids (7). LDL-C plays an important role in developing CAD (8, 9). However, the content of LDL-C particles may show individual variations, and CAD may develop in individuals with normal LDL levels (10). T2DM is a heterogeneous disease and can lead to acute, micro/macro-vascular chronic complications (CAD, stroke, peripheral vascular diseases, etc.). Therefore, it has been reported that the risk of developing CAD in this disease increases 2-4 times (11, 12). T2DM is also defined by several lipid and lipoprotein abnormalities. These abnormalities increased TG level, decreased HDL-C level, increased trim dense LDL-C level, etc., situations (13).

The clinical information, relationships, patterns, and predictive models developed from the existing medical data in the database with data mining/machine learning methods can significantly contribute to clinicians' medical decision-making processes. The medical knowledge discovery process (MKDP) has been used frequently in recent years, especially in medicine and health sciences, because it can extract meaningful and vital information from massive databases and records. MKDP is a process that includes data selection from databases, data pre-processing, transformation, performing data mining methods, and evaluation/interpretation of obtained patterns/relationships (14, 15). MKDP can help physicians make medical decisions by revealing clinically meaningful information from very high-dimensional medical data. Clinical decision support systems are knowledge-based software that support physicians in making the most appropriate medical decisions for patients (16).

The current study aims to reveal the single/multiple effects of TC, HDL-C, LDL-C, and TG on CAD risk factors of HT, T2DM, and obesity, develop an open-source web-based decision support software, and determine the most appropriate cut-off points of the lipid profiles examined.

METHODS

Research sample and characteristics

The present research protocol was approved by the İnönü University Clinical Research Ethics Committee (Research protocol no: 2016/159). The material of this retrospective case-control study consisted of medical records taken from the database of approximately 2400 coronary artery patients who underwent coronary bypass surgery between January 1, 2002, and September 1, 2018, in Inönü University Faculty of Medicine, Turgut Ozal Medical Center, Department of Cardiovascular Surgery. Individuals who had more than 50% stenosis angiographically in at least one of the major epicardial arteries and underwent coronary bypass surgery were included in the study. However, individuals with

less than 50% stenosis in at least one of the epicardial arteries or less than 40% stenosis in the left main coronary artery were excluded from the study. Data collected on coronary artery patients in this study were collected as follows.

- Gender (male/female),
- Age (years),
- HT (diastolic blood pressure > 90 mmHg and/or systolic blood pressure > 140 mmHg),
- T2DM,
- Obesity (body mass index (BMI)>30),
- TC (mg/dL),
- HDL-C (mg/dL),
- LDL-C (mg/dL),
- TG (mg/dL).

The current research was evaluated in accordance with the STROBE guideline (17).

Surgical Technique

All surgical operations were performed under cardiopulmonary bypass (CPB) with the aid of a membrane oxygenator (Dideco D 708 Simplex, 41037 Mirandola-Italy), a roller pump (Cobe Cardiovascular INC, Arvada CO 80004-3599 USA) and a non-pulsatile flow. Antegrade and retrograde blood cardioplegia were used for myocardial protection (Medtronic CardioTermTM CT 400 BR CA 92807 USA). All patients were systemically cooled to 28-32 ˚C. Distal anastomoses were performed using 7.0 prolene sutures under a cross-clamp in all surgical operations. Proximal anastomoses were applied to the proximal aorta using 6.0 or 7.0 prolene sutures. After completing the proximal anastomoses, retrograde warm blood cardioplegia was given. In cases with left ventricular aneurysm and left ventricular thrombus, aneurysm repair, thrombectomy, and proximal anastomoses under cross-clamp were performed before distal anastomoses. Cardiopulmonary bypass was performed with moderate hypothermia (28-30°C) and high perfusion pressure (60-70 mmHg). Surgical strategies were exiting cardiopulmonary bypass at low body temperature (35 °C), striving to shorten the times of cross-clamping and CPB, and avoiding hypotension in the intraoperative and early postoperative periods. In the intraoperative evaluation, great attention was paid to the cannulation area in cases with plaques in the ascending aorta. No narcotic analgesics or deep sedative drugs were administered to the operated patients after they were admitted to the intensive care unit. All patients were extubated as early as possible. After the drainage tubes were removed from the patients, antiaggregant treatment was applied with acetylsalicylic acid at a dose of 300 mg/day. The patients were contacted to come in for the normal outpatient controls on the 10th postoperative day, in the second and sixth months, and then once a year (18).

Biochemical Analysis

The lipid profiles discussed in this study are studied with the Abbott brand Architect C16000

model device (in the same device) in the central laboratory of Inonu University Turgut Ozal Medical Center. Comprehensive information on the determination of relevant lipid profiles is presented below.

TC determination: TC determination is studied by the enzymatic method (cholesterol esterase and cholesterol oxidase) (Ref no: 7D62-21). The system can measure up to 705 mg/dL directly, and for higher results, the sample can be diluted 1:4 initially with automatic or manual dilution, and the result can be obtained automatically by multiplying its concentration with the appropriate dilution factor. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external quality control (Biorad EQAS External Quality Assurance Service) is performed once a month. Interassay values were 2.5% for control 1 and 2.7% for control 2. Intraassay values are 2.1% CV for control 1 and 2.3% for control 2.

TG determination: TG determination is made by the enzymatic method (lipase, glycerol kinase, and glycerol phosphate oxidase) (Ref no: 7D74-21). The system can measure up to 1420 mg/dL directly, and for higher values, the sample can be diluted 1:4 initially with automatic or manual dilution, and the result can be obtained automatically by multiplying its concentration with the appropriate dilution factor. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external control quality control (Biorad EQAS External Quality Assurance Service) is performed once a month. Interassay values are 2.9% CV for control 1 and 3.1% CV for control 2. Intraassay values are 2.2% CV for control 1 and 2.5% CV for control 2 (19).

HDL-C determination: This procedure is performed by the colorimetric endpoint reaction technique (Ref no: 02R06-31, 02R06-21). The method is linear up to 200 mg/dL. Calibration is repeated at least every 20 days as needed, internal quality control is evaluated every day (two controls), and external control is performed once a month. Interassay values were 3.8% CV for control 1 and 4.1% for control 2. Intraassay values are 2.3% CV for control 1 and 2.2% CV for control 2.

Determination and calculation of LDL-C: The colorimetric method is carried out (Ref no: 02R05-31, 02R05-21). The method is linear up to 600 mg/dL. The calibration process is repeated at least every 20 days, and internal quality control is performed every day. The normal value is <100 mg/dL. Interassay values are 4.3% CV for control 1 and 4.5% for control 2. Intraassay values are 2.4% CV for control 1 and 2.8% CV for control 2. Friedewald's formula (20) calculates LDL-C according to the following equation when TG<400 mg/dL (21).

LDL-C= TC – (HDL-C + TG/5)

Sample Size

In patients with CAD, a priori power analysis revealed a minimum of 515 in each group (1030 individuals in total) considering the estimated difference in HT rate between the two groups of 0.10, type I error (α) of 0.05, Type II error (β) of 0.10 (power=0.90), and the assumed effect size of 0.20 (22). In this research study, to increase the validity and reliability of the research findings, all data on 2831 CAD patients were obtained from the records of the cardiovascular surgery department.

Medical Knowledge Discovery Process (MKDP)

In this research, MKDP, which is explained in Figure 1, 2 and the details given below, was applied for the selection, pre-processing, transformation, data mining, and evaluation of the data.

I. Data selection: Absence or presence of CAD risk factors of HT, T2DM, and obesity were dependent/output/outcome variables (binary categorical features), and TC, HDL-C, LDL-C, and TG lipid profiles were explanatory/independent/input variables.

II. Data pre-processing: The missing data were completed with the help of the assignment approach based on the Random Forest method. Extreme/outlier observations were detected with the local outlier factor (LOF). LOF values were calculated according to the k=5 neighborhood value, and the extreme value threshold was determined as 2.5.

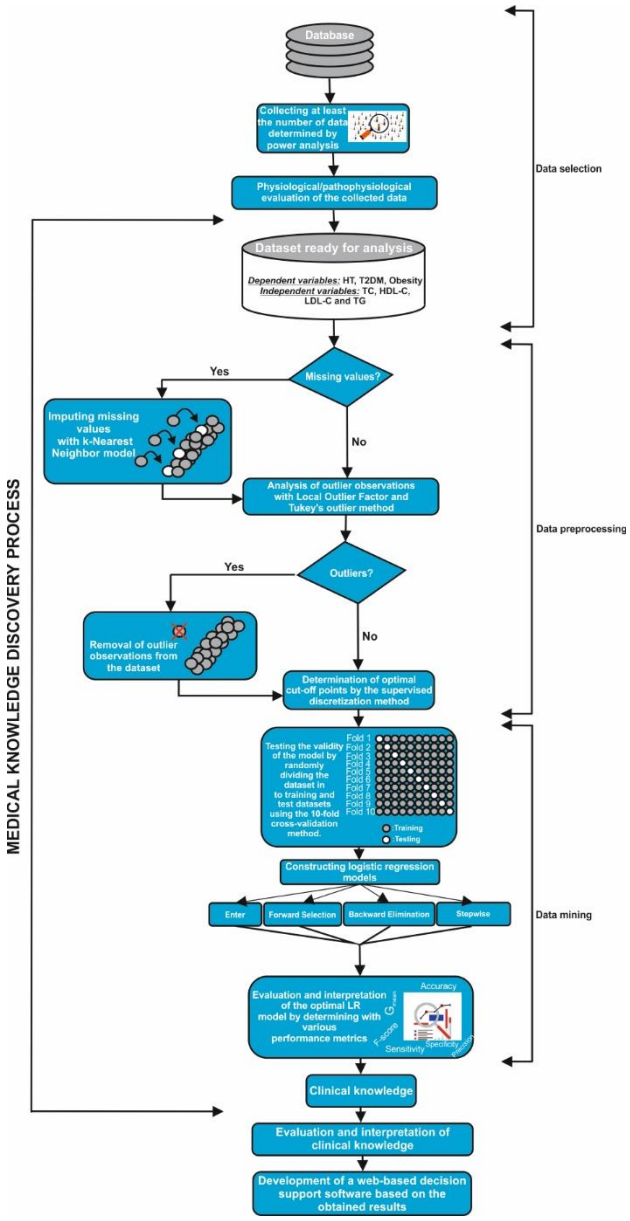

Figure 1. Graphical abstract

III. Data transformation: No transformation techniques were applied to quantitative data.

IV. Data mining: In the modeling stage, multiple logistic regression (LR) analysis (LRA) was used for the relationships between the absence or presence of CAD risk factors of HT, DM, and obesity (dependent/output/outcome variable) and

lipid profiles of TC, HDL-C, LDL-C and TG (explanatory/independent/input variables. The most appropriate (optimal) LR model was selected by applying the Akaike Information Criterion (AIC) based stepwise feature selection. The 10-fold cross-validation method was used to examine the accuracy of the models. LRA models were obtained by stepwise feature selection techniques. AIC statistics were used in selecting the variables that could be included in the models. In this stage, single and multiple joint effects of TC, HDL-C, LDL-C, and TG lipid profiles on HT, DM, and obesity were investigated for risk assessment.

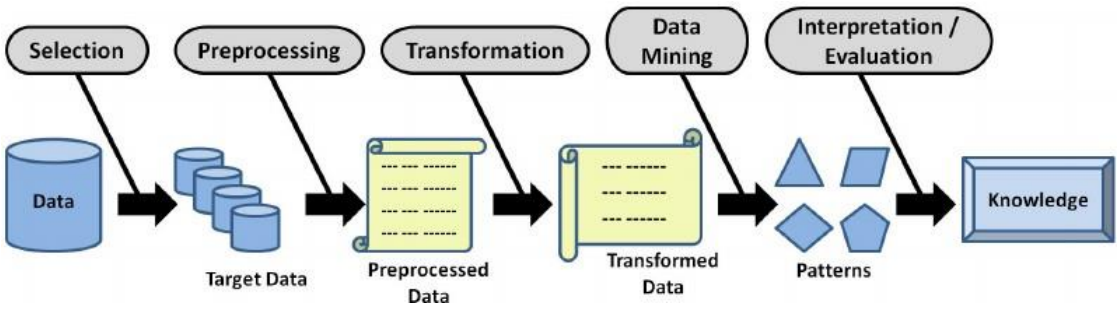

Figure 2. Detailed stages for the MKDP approach

The goodness of the fit of the established LR models was examined by the Hosmer-Lemeshow test and the Akaike Information Criterion (AIC). In addition, McFadden, Nagelkerke, and Cox-Snell summary statistics were given for the LR models. Interpretations for OR with 95% confidence intervals, the measure of effect size (ES) in this study, were made according to the relevant reference study (23).

V. Interpretation and evaluation: In the performance evaluation of the models estimated in this study, accuracy, sensitivity, specificity, positive/negative predictive values, F-score and Gmean were calculated. The 95% confidence intervals of the relevant performance criteria were performed using the 1000 repetitive bootstrap technique, one of the non-parametric methods.

Biostatistical Data Analysis

Quantitative data are summed up as mean and standard deviation or median and interquartile range, and numbers and percentages summarize qualitative data. In data analysis, controls and necessary actions were taken to prevent missing and erroneous data and excessive variability problems. Normality assessment of the variables was performed by the Kolmogorov-Smirnov test. Since the normality assumptions were not met, the differences between the classes of qualitative variables in terms of lipid profiles were examined

with the help of the Mann-Whitney U test. The effect size (ES) for the Mann-Whitney U test is the square of epsilon (ε2) was interpreted as low for values of 0.01 to <0.08, moderate for values of 0.08 to <0.26, and high for values ≥ 0.26 (24). Correlations between quantitative variables were calculated using the Spearman rho technique as the data did not show normal distribution. The effect size for correlations was evaluated as low for 0.10 - <0.30, moderate for 0.30 - <0.50, and high for ≥ 0.50 (25). All p<0.05 values were considered statistically significant. The optimal cut-off points of the lipid profiles examined according to the risk factors for CAD, HT, T2DM, and obesity were determined with the help of an approach based on the logistic regression model with the supervised/supervised discretization method. In all analyses and models, R software and IBM SPSS Statistics Premium version 26.0 for Windows package program were used where appropriate.

Risk Calculation Tool

A web-based open-source "Risk Calculation Tool" was developed using the significant coefficients from the multiple LR analysis for the relevant tasks. Shiny (26), a package available in R, was utilized throughout the development of the tool. In addition, the following packages – shinyWidgets (27), shinyLP (28), shinythemes (29), and shinydashboard (30)- were employed to design the graphical user interface. The proposed web-based software is freely available at the internet address: http://161.9.167.247/RiskCalcTools/. Figure 3 provides a perspective on the relevant portions of the tool and descriptions.

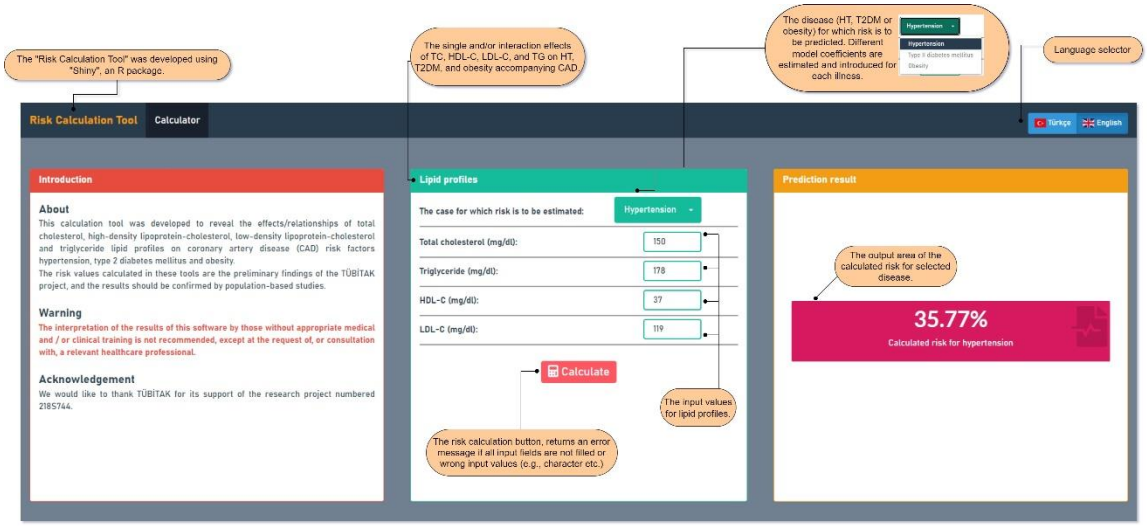

Figure 3. A perspective on the relevant portions of the tool and descriptions

RESULTS

The study consisted of 2828 people, 2137 men (75.6%) and 691 women (24.4%). The mean age

of the individuals is 60.84±9.71 years, the mean age of men is 60.12±9.77 years, and the mean age of women is 63.07±9.15 years.

In this study, the lipid profiles examined for coronary artery patients were classified according to the optimal cut-off points determined by the supervised discretization method. Optimal cut-off points determined in this study for HT accompanying CAD were given below:

• > 191 mg/dL for TC,

• > 117 mg/dL for LDL-C,

• > 181 mg/dL for TG,

• > 37.2 mg/dL for HDL-C.

In relation to T2DM accompanying CAD, the following optimal cut-off values were identified:

• > 190 mg/dL for TC,

• > 115 mg/dL for LDL-C,

• > 197 mg/dL for TG,

• > 36.3 mg/dL for HDL-C.

Similarly, the optimal threshold points below were calculated for obesity concomitant with CAD:

• > 192 mg/dL for TC,

• > 117 mg/dL for LDL-C,

• > 193 mg/dL for TG,

• > 36.8 mg/dL for HDL-C.

Statistics from multiple LRA models regarding the possible effects of clinically categorized lipid profiles on HT, T2DM, and obesity are summarized in Table 1. According to the modeling results, the goodness of fit criteria of the models established to evaluate the multiple effects of categorized lipid profiles on HT, T2DM, and obesity were statistically significant (Hosmer & Lemeshow test; $p>0.05$).

Considering the values given in Table 1, in the model for the HT response variable, TC (>191 mg/dL)*HDL-C (>37.2 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) and LDL-C (>117 mg/dL)*TC (≥191 mg/dL)*HDL-C (>37.2 mg/dL) interactions were statistically significant ($p<0.05$). Other coefficients in the model were insignificant ($p>0.05$). LDL-C (>115 mg/dL), TG (>197 mg/dL), HDL-C (>36.3 mg/dL), and TC (>190 mg/dL)*LDL-C (the terms >115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) were statistically significant ($p<0.05$).

In the model equation estimated for obesity, TG (>193 mg/dL), LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (> 36.8 mg/dL), TG (>193 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and LDL-C (>117 mg/dL)*TG (> 193

mg/dL)*HDL-C (>36.8 mg/dL) terms were found to be significant ($p<0.05$).

While the ES levels of the OR were "Low" for TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) and LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) interactions for the HT dependent variable, the ES values were "Moderate" for LDL-C (>117 mg/dL)*TC (≥191 mg/dL)*HDL-C (>37.2 mg/dL).

In the equation established for the T2DM output variable, the ES levels for OR were also obtained as "Low". For LDL-C (>115 mg/dL), TG (>197 mg/dL), HDL-C (>36.3 mg/dL), TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL).

In the multiple LR equation estimated for obesity, ES was calculated at "High" levels for TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TC (>192 mg/dL)*TG (>193 mg/dL)* HDL-C (>36.8 mg/dL), and was determined to be "Moderate" for TG (> 197 mg/dL). in the same way, the ES level was found to be "Low" for LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL), TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) and TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)). The coefficients of determination for each model for all dependent variables were calculated as small degrees

Table 1. Statistics from multiple LRA models on the effects of lipid profiles classified by optimal cut-off points from this study on HT, T2DM, and obesity

HT	TC (>191 mg/dL)*TG (?181 mg/dL)*HDL-C (>37.2 mg/dL)	-0.5708	0.3528	2.6175	1	0.1057	0.5651	0.28-1.1195	Low	NPV	0.644 (0.626-0.661)
	LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL)	0.8329	0.3628	5.2714	1	**0.0217**	2.3001	1.1382-4.7314	Moderate	F-score	-
										G_{Mean}	-
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	0.018	8	1	3685.2				2.38E-03	4.26E-03		3.10E-03
	Statistics on coefficients									***Performance metrics***	***Values (95% CI)***
	Variables	**ß**	**SE**	**Wald**	**DF**	***p***	**OR**	**95% CI**	**ES**		
	Constant	-1.0596	0.0814	169.5454	1	**<0.0001**	0.3466	-	-	Accuracy	0.742 (0.727-0.76)
	LDL-C (>115 mg/dL)	-0.3816	0.1886	4.0912	1	**0.0431**	0.6828	0.4661-0.9782	Low	Specificity	0.005 (0-0.01)
	TG (>197 mg/dL)	0.4023	0.1131	12.6596	1	**0.0004**	1.4953	1.1971-1.8652	Low	Specificity	0.998 (0.996-1)
	HDL-C (>36.3 mg/dL)	-0.2147	0.1027	4.3726	1	**0.0365**	0.8068	0.6594-0.9862	Low	PPV	0.500 (0.091-0.875)
	TC (>190 mg/dL)*LDL-C (>115 mg/dL)	0.3102	0.1963	2.499	1	0.1139	1.3638	0.9369-2.0257	Low	NPV	0.743 (0.727-0.759)
	TC (>190 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)	0.5735	0.308	3.4681	1	0.0626	1.7745	0.9627-3.235	Moderate	F-score	0.011 (0.001-0.019)
T2DM	**LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)**	1.2535	0.7427	2.8487	1	0.0914	3.5027	0.7783-15.7846	High	G_{Mean}	0.052 (0.014-0.105)
	TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL)	-1.7372	0.813	4.566	1	**0.0326**	0.176	0.0344-0.8999	Low		
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	2.32	8	0.969385	3199.7				1.37E-02	2.28E-02		1.55E-02
	Statistics on coefficients									***Performance metrics***	***Values (95% CI)***
	Variables	**ß**	**SE**	**Wald**	**DF**	***p***	**OR**	**95% CI**	**ES**		
	Constant	-1.6778	0.0899	348.677	1	**<0.0001**	0.1868	-	-	Accuracy	0.817 (0.803-0.832)
	TG (>193 mg/dL)	0.6017	0.1611	13.9484	1	**0.0002**	1.8251	1.3268-2.4967	Moderate	Specificity	0.000 (0.000-0.001)
	HDL-C (>36.8 mg/dL)	0.2587	0.1479	3.0601	1	0.0802	1.2953	0.967-1.7277	Low		
	TC (>192 mg/dL)*HDL-C (>36.8 mg/dL)	-1.1199	0.6105	3.365	1	0.0666	0.3263	0.0776-0.9277	Low	Specificity	1.000 (0.999-1.000)
	LDL-C (>117 mg/dL)*TG (>193 mg/dL)	-0.4205	0.2123	3.9228	1	**0.0476**	0.6567	0.4309-0.992	Low		
	LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)	-0.7531	0.3709	4.1236	1	**0.0423**	0.4709	0.2132-0.9278	Low	PPV	-
	TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	-0.9927	0.4111	5.8293	1	**0.0158**	0.3706	0.157-0.7987	Low		
Obesity	**TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL)**	1.7271	0.7169	5.8036	1	**0.016**	5.6245	1.5627-27.8208	High	NPV	0.817 (0.802-0.830)
	TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	1.6448	0.7747	4.5074	1	**0.0337**	5.18	1.2501-27.9009	High	F-score	-
	LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL)	2.7606	0.8729	10.0023	1	**0.0016**	15.8094	2.7805-89.6744	High	G_{Mean}	-
	Model significance and goodness of fit statistics										
	Hosmer & Lemeshow test			**AIC**				**Pseudo R^2 values**			
	$?^2$	**DF**	***p***					**McFadden**	**Nagelkerke**		**Cox-Snell**
	3.45E-13	8	1	2684.2				1.15E-02	1.77E-02		1.09E-02

SE: Standard error, DF: Degrees of freedom, OR: Odds ratio, CI: Confidence interval, ES: Effect Size; HT: Hypertension, T2DM: Type 2 diabetes mellitus, TC: total cholesterol; HDL-C: high-density lipoprotein-cholesterol; LDL-C: low-density lipoprotein-cholesterol; TG: Triglyceride; AIC: Akaike Information Criterion; PPV: Positive predictive value; NPV: Negative predictive value

DISCUSSION

Atherosclerotic cardiovascular diseases are a substantial cause of death in developed and

developing countries. Dyslipidemia is one of the most important preventable risk factors that increase the risk of atherosclerotic cardiovascular diseases. Dyslipidemia is the main factor in the pathogenesis of atherosclerosis. According to clinical studies, approximately 80% of the adult population in Turkey is exposed to dyslipidemia. Thanks to early diagnosis and timely measures, cardiovascular disease risk can be reduced. Since blood lipids can be measured easily, quickly, inexpensively, and reliably, screening for dyslipidemia can accurately calculate the future risk of atherosclerotic cardiovascular disease. Although the incidence of diseases such as obesity, T2DM, and HT is increasing worldwide, it also leads to a gradual increase in the incidence of dyslipidemia. Dyslipidemia is not only a lifestyle disorder; but also has a genetic background such as familial hypercholesterolemia, which is an autosomal dominant single-gene disease. Familial cases of hypercholesterolemia develop with increased high cholesterol levels and progression of early atherosclerotic cardiovascular diseases, regardless of lifestyle. In a part of familial dyslipidemia, LDL-C and TG elevation are present together, while in some others, only TG is present (31, 32). In light of these data, the possible single/multiple effects of TC, LDL-C, TG, and HDL-C lipid profiles on obesity, T2DM, HT, etc., illnesses can be evaluated in planning, rearranging, and improving preventive/curative health services.

Many studies have shown that disorders in the lipid profile are risk factors in atherosclerotic diseases. In large-scale screening studies, the critical cut-off value(s) was/were determined as an atherosclerotic risk factor for lipid levels (33). The risk of atherosclerotic disease increases when the single and multiple analyses of the values that make up the lipid profile are above the critical value. However, changes in lipid profile and single/multiple relationships between them may show differences, especially in those with different diseases such as DM, obesity, and HT, which are other risk factors of atherosclerosis. Establishing these differences is very important in determining the type, duration, and dose of dyslipidemia treatment, especially in individuals with atherosclerotic risk factors who have not had the disease and in patients who have the disease and whose treatment is ongoing. In patients with atherosclerosis risk factors, instead of evaluating the lipid profiles individually, single/multiple examinations of the accompanying risk factors and the values that make up the lipid profile are of great importance both in the prevention of atherosclerosis and in demonstrating the success of the treatment of patients with atherosclerotic cardiovascular disease. Also, determining these lipid profile values, and their interrelationships will help determine the targeted lipid profile level(s) in

those with additional risk factors such as DM, HT, and obesity and determine the single/multiple dose and duration of the medical treatment to be given to these patients.

The prevalence of obesity and T2DM continues to increase worldwide, particularly in low-income and developing countries, with the increasing adoption of lifestyles associated with low energy expenditure and high-calorie intake. Although easily diagnosed, T2DM and HT are complex and heterogeneous phenotypes associated with an increased risk of life-threatening cardiovascular disease. Their common presence in the same individual can be attributed to the pathophysiology of obesity and insulin resistance. HT and T2DM are common comorbidities, and the most important cause of morbidity and mortality in diabetes is cardiovascular disease exacerbated by HT. In this regard, T2DM and HT are intimately connected due to similar risk factors such as endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity. There is also significant overlap in the cardiovascular complications of T2DM, HT, and obesity, mainly associated with micro/macro-vascular disease(s) (34). TG and LDL-C levels at the start of the Helsinki Heart Study trial group (n = 4,081) were examined concerning the occurrence of cardiac endpoints in the 5-year randomized coronary primary prevention study among dyslipidemic middle-aged men. The related study concluded that serum TG concentration had predictive significance in measuring coronary heart disease risk and predicting the effect of gemfibrozil therapy, particularly when combined with HDL-C and LDL-C (35).

Lipid profiles are a common test that can be used to screen those at risk of developing CAD. Thanks to the evaluation of these test results, information can be obtained to prevent possible risky situations such as heart attack, stroke, and stroke in individuals. Lipid profile tests are mainly; total TC is performed for lipids such as HDL-C, LDL-C, and TG (7). Single and multiple joint effects of lipid profiles on HT, T2DM, and obesity are discussed in the current study. Based on the related analyses for obesity, the most significant interaction was LDL-C (>117 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) term (OR=15.8094; 95% CI: 2.7805-89.6744), followed by TC (>192 mg/dL)*LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL) interaction (OR=5.6245; 95% CI: 1.5627-27.8208), TC (>192 mg/dL)*TG (>193 mg/dL)*HDL-C (>36.8 mg/dL) (OR=5.18; 95% CI: 1.2501-27.9009) and TG (>193 mg/dL) (OR=1.8251; 95% CI: 1.3268-2.4967), respectively. The reported factors had high and moderate ES for the estimated model concerning obesity, and the other three interactions (i.e., LDL-C (>117 mg/dL)*TG (>193 mg/dL), LDL-C (>117 mg/dL)*HDL-C (>36.8 mg/dL) and TG

(>193 mg/dL)*HDL-C (>36.8 mg/dL)) were also significant and had low ES levels. In relation to T2DM, the estimated model suggested the most significant factors/interaction of TG (>197 mg/dL) (OR=1.4953; 95% CI: 1.1971-1.8652), LDL-C (>115 mg/dL) (OR=0.6828; 95% CI: 0.4661-0.9782) and TC (>190 mg/dL)*LDL-C (>115 mg/dL)*TG (>197 mg/dL)*HDL-C (>36.3 mg/dL) (OR=0.176; 95% CI: 0.0344-0.8999), respectively. As for HT, LDL-C (>117 mg/dL)*TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) interaction was the most prominent factor having moderate ES level (OR=2.3001; 95% CI: 1.1382-4.7314), pursued by TC (>191 mg/dL)*HDL-C (>37.2 mg/dL) (OR=1.6465; 95% CI: 1.0254-2.6907; ES: Low) and LDL-C (>117 mg/dL)*HDL-C (>37.2 mg/dL) (OR=0.5507; 95% CI: 0.3407-0.8688; ES: Low), consecutively. In this research, single and joint effects of the lipid profiles on T2DM, HT, and obesity are relied on the estimated optimal cut-off points based on supervised learning. As far as known, the current clinical research puts forth the preliminary results of single and joint effects of the categorized lipid profiles on T2DM, HT, and obesity accompanying CAD for the first time, and proposes a "Risk Calculation Tool" available for free with a web-based approach using Shiny in R programming language.

The present paper has a few limitations. Initially, though the sample size was calculated based on the priori power analysis, multicenter studies, which are the update of this research and include more patients, may provide more clinically reliable results. Secondly, even though internal validation was completed on the proposed tool's accessible data in this research, external validation should be undertaken on separate and larger patient groups in the later stages of this study.

In conclusion, it is recommended to use the approach that analyzes the cut-off points proposed in this study for lipid profiles in predicting HT, T2DM, and obesity clinically accompanying CAD. However, there is a need for a comprehensive evaluation of the results by applying the proposed model to independent datasets. The developed web-based decision support tool can be accessed as open access at http://161.9.167.247/RiskCalcTools/

Ethics Committee Approval: The present research protocol was approved by the Malatya Clinical Research Ethics Committee (Research protocol no: 2016/159).

Peer-review: Externally peer-reviewed

Author Contributions: Concept: CC, AKA, NE, ST, BA, Design: CC, AKA, NE, ST, BA, İS, CÇ, HP, Literature search: CC, AKA, NE, ST, BA, İS, CÇ, HP, Data Collection and Processing: CC, AKA, CÇ, HP, Analysis or Interpretation: CC, AKA, NE, ST, BA, İS, CÇ, HP, Writing: CC, AKA, NE, ST, BA, İS, CÇ, HP,

Conflict of Interest: The authors declared no conflict of interest.

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ODU TIP DERGİSİ/ODU MEDICAL JOURNAL (ODU MED J) **April 2024;11(1):49-54**

OLGU SUNUMU / CASE REPORT **DOI:** 10.56941/odutip.1354398

Disappeared Third Molar Tooth: A Case Report

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Abstract

Many complications can be encountered during diagnosis and treatment in healthcare. These can range from the simple to the serious enough to be life-threatening. Preventing complications before they occur is essential. However, they can occur despite all the precautions taken. When they develop, the process needs to be managed properly.

Foreign body ingestion and aspiration are among the most important complications in dentistry. While complications can be overcome more easily in cases of ingestion, emergency intervention may be required in cases of aspiration. In both cases, medical doctors and dentists must work in coordination and the process must be managed.

In this case report, the diagnosis of a third molar tooth that was ingested during extraction and the subsequent process is shared.

Keywords: Aspiration, Ingestion, Third Molar.

Gözden Kaybolan Üçüncü Molar Diş: Olgu Sunumu

Özet

Sağlıkta tanı ve tedaviler sırasında birçok komplikasyonla karşılaşılabilir. Bunlar basitten, hayatı tehdit edecek kadar önemli düzeyde olanlara kadar değişebilir. Komplikasyonların meydana gelmeden önlenmesi esastır. Ancak alınan bütün önlemlere rağmen meydana gelebilirler. Geliştiklerinde sürecin doğru bir şekilde yönetilmesi gerekmektedir.

Yabancı cisim yutulması ve aspirasyonu, diş hekimliği alanında meydana gelen en önemli komplikasyonlardandır. Yutma olgularında komplikasyon daha kolay atlatılabilirken, aspirasyon olgularında acil müdahale gerekebilmektedir. Her iki durumda da mutlaka tıp hekimleri ile diş hekimleri koordineli çalışmalı ve süreç yönetilmelidir.

Bu olgu sunumunda çekim sırasında yutulan bir üçüncü molar dişin tanısı ve sonrasında gelişen süreç paylaşılmaktadır

Anahtar Kelimeler: Aspirasyon, Yutma, Üçüncü Molar Diş

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INTRODUCTION

Health is an important and indispensable value for human life. Its deficiency is unthinkable. Because health affects whole life. The disorder in the structure and functions of the organism makes

it impossible to continue life in an ideal way. Disorders in health are defined as diseases and they must be diagnosed and treated (1).

A certain amount of knowledge is required for the treatment of diseases. In addition, it is essential that the application be performed with the utmost care and attention to interventional treatments. However, the occurrence of negativities may be inevitable in some cases no matter how meticulously the physician works. These situations are called complications (2).

Physicians encounter complications in many treatments that they apply throughout their professional lives. These can range from simple to dangerous for patients. Prevention of complications is one of the most important duties of the physician. If it develops despite all kinds of precautions, it is also among the duties of the physician to manage and eliminate it and inform the patient and their relatives if necessary (3).

In the field of dentistry, many complications can be encountered during treatments. Foreign body ingestion or aspiration is among the most important of these (4). In case of ingestion, there is not much to be done, it is usually expected to come out from digestive tract. However, its aspiration can cause serious complications (5). Because of this, it is very important that the process is managed correctly and that dentists work in coordination with the medical doctors of the relevant departments.

Tooth extractions are among the important treatments in dentistry in which the mentioned complications are observed. Indications for tooth extraction include caries, pulp necrosis, impacted or semi-impacted teeth, association with pathological lesions, and some systemic problems of the individual. On the other hand, tooth extraction is contraindicated in individuals with severe pericoronitis, whose systemic condition is not suitable for surgery, and whose tooth is adjacent to malignant lesions (6).

In this case report, the aim is to share the detection of an ingested tooth during extraction and the subsequent process.

CASE REPORT

A 21-year-old female patient came to our clinic with swelling on the left side of the lower jaw. In her anamnesis, it was learned that she did not have any systemic disease. She reported swelling and pain in her left lower jaw occasionally and this situation improved after antibiotic treatment. In the clinical examination, it was determined that the distal half of tooth 38 was impacted and swelling and hyperemia developed in the soft tissues around the tooth. Panoramic radiography showed that the development of the tooth continued and there was an S-shaped curvature in the mesial root. It was confirmed that there was no other pathology or dental caries in this region (Figure 1).

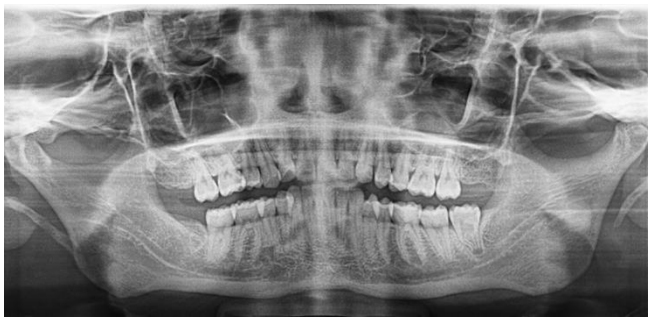

Figure 1. Patient’s panoramic radiography.

Extraction of the tooth for the treatment was recommended to the patient. Detailed information about the procedure was given and all possible risks were explained. After that, the patient's written consent was obtained, and the extraction of the tooth was started. The flap was removed after local anesthesia. The tooth was fully raised with the elevator. It was observed that the patient developed a nausea reflex while holding the tooth with extraction forceps, and then the tooth was not in place.

The inside of the mouth was checked in detail. The surgical area and its neighbors were searched, but no teeth were found. A periapical radiograph revealed that the tooth had come out of the socket totally (Figure 2). The surgical field was sutured. In this whole process, no symptoms were observed in the patient like a cough, shortness of breath, etc. The patient, who was thought to have ingested the tooth, was immediately referred to the emergency department. A detailed consultation about the situation was written and given to the patient. An hour later, the patient came back to the clinic and declared that several radiographies were taken in the emergency department and that the tooth was not in the lungs and stomach. Thereupon, the clinic was searched again, but the tooth was not found.

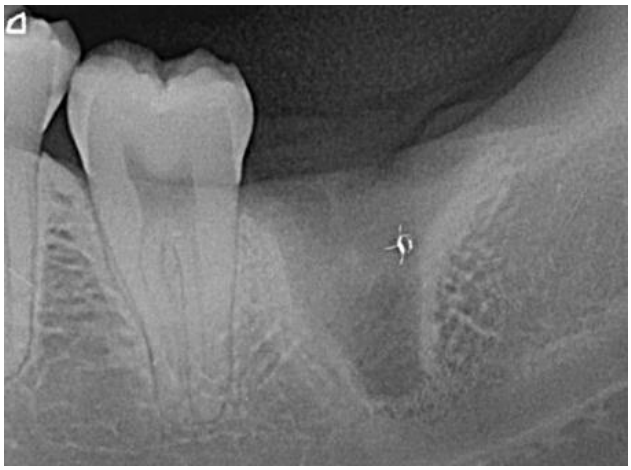

Figure 2. Patient’s periapical radiography after extraction.

Then the radiographies taken in the emergency department were opened and analyzed via the online system with the patient's permission (Figure 3a-3b). A tooth superposed with the L5 vertebra was detected in the direct abdominal radiography (Figure 4). It was told to the patient that she ingested the tooth, and it would come out digestive tract without damaging any part of the digestive system and, stool follow-up would be beneficial just in case. A phone number was given to her to keep in touch with the clinic and report the situation. It was told that she should apply to the emergency department if an unexpected situation develops. The patient who called on the second day after the procedure said that the tooth had come out from the body.

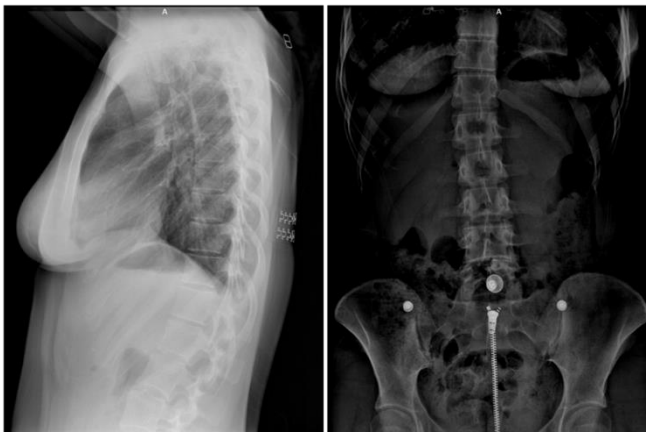

Figure 3a-3b. Patient's lateral lung and direct abdomen radiographies.

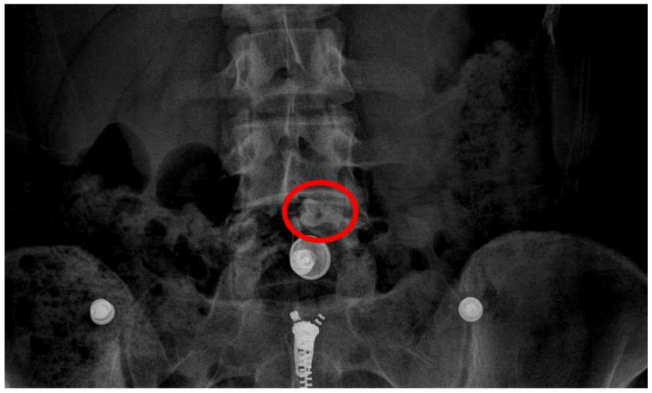

Figure 4. The tooth which seen on patient's direct abdomen radiography.

DISCUSSION

Loss of a material used during dental treatments and an extracted tooth, or a tooth piece may occur. The main thing to avoid such problems is to take all necessary precautions and prevent complications. If encountered, the first thing to do is to check the oral cavity and clinic. If not found, it should be considered to go down the oropharynx. Aspiration or ingestion may have occurred here. Which of these occurred should be determined without delay and a course should be followed accordingly (5,6).

Foreign body aspirations are serious complications. Severe cough, pain, shortness of breath, and complete airway obstruction may be seen after aspiration. Some cases may be asymptomatic and serious lung infection may develop in them. In case of aspiration, the patient should be referred to the emergency service as soon as possible and the necessary intervention should be made by the relevant physician (6).

Ingestion foreign bodies is undesirable. However, it is a complication that can be overcome more easily than aspiration. If the object is not pointed, protruding, toxic, etc., it can be easily removed from the digestive system without the need for any intervention. It can be checked whether the object has come out with stool follow-up or radiographs taken at intervals (3).

The patient should be given the necessary information and told that there is no cause for concern in both cases. Always stay in contact with the patient and the patient should be followed up until the complication disappears and the process should be managed ideally.

Medical doctors may not have detailed information about the anatomy of the mouth, teeth, jaw and surrounding tissues, and the diagnosis and treatment of diseases in this region. The same is true for dentists who constantly work in the head and neck region. Therefore, in some cases, the coordinated work of medical doctors and dentists is important.

Emergency departments are the busiest places where health care is provided. Sudden diseases, accidents, injuries, and life-threatening conditions are diagnosed and treated in these units, which work 24 hours a day. Diagnosis and treatment must be carried out quickly due to its nature. This means intense physical and mental workload. Emergency departments physicians, who must make quick and accurate decisions, may make mistakes when deciding on the right diagnosis and treatment under intense physical and mental workload like any physician. For this reason, every effort should be made to prevent unnecessary referrals and individual applications to emergency departments (7,8).

CONCLUSION

Although Adult Still's Disease should be kept in mind in terms of making a differential diagnosis from other diseases and iniating treatment quickly. In this case, we presented a case of resistant AOSD that was resistant to systemic corticosteroids and complicated by MAS and DAH. The use of tocilizumab after corticosteroids in the treatment of such complicated cases seems promising.

Ethics Committee Approval: The presented study is qualitative, and consent was obtained by giving information about the study by one-to-one interviews with the subjects who agreed to participate. The study was carried out by paying attention to the Declaration of Helsinki.

Author Contributions: Concept: EY, Design: EY, Supervision: EY, Data Collection and/or Processing: EY, Analysis and/or Interpretation: EY, Writing: EY.

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Capecitabine-induced hand foot syndrome: a brief look at possible pathways that may be associated with inflammation

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Abstract

Hand foot syndrome is a toxic reaction related to certain chemotherapy agents. Capecitabine is a prodrug used in the treatment of many cancers, such as gastrointestinal, biliary tract and breast cancers. It is associated with hand and foot syndrome (HFS), which preferentially affects palms and soles. There is still no consensus on effective international standard therapeutic strategies for the treatment and prevention of HFS because the underlying physiological and pharmacological mechanisms leading to the development of HFS have not been adequately explained. HFS is rarely life-threatening, but it may deteriorate the patient's quality of life. Quitting or a reduction in the dose of the causative drug mostly provide the amelioration of the symptoms. The aim of this review is to briefly evaluate the possible inflammatory mechanisms that may be associated with capecitabine- induced HFS.

Keywords: Capecitabine, Hand foot syndrome, Cyclooxygenase 2

Kapesitabine bağlı el ayak sendromu: enflamasyonla ilişkili olabilecek olası yolaklara kısa bir bakış

Özet

El ayak sendromu, belirli bazı kemoterapi ajanlarıyla ilişkili toksik bir reaksiyondur. Kapesitabin, gastrointestinal sistem, safra yolları ve meme kanserleri gibi birçok kanserin tedavisinde kullanılan bir ön ilaçtır. Tercihen avuç içi ve ayak tabanlarını etkileyen el ve ayak sendromu (HFS) ile ilişkilidir. HFS gelişimine yol açan altta yatan fizyolojik ve farmakolojik mekanizmalar yeterince açıklanamadığından, HFS'nin tedavisi ve önlenmesi için etkili uluslararası standart tedavi edici stratejiler üzerinde hala bir görüş birliği yoktur. HFS nadiren yaşamı tehdit eder, ancak hastanın yaşam kalitesini bozabilir. Sebep olan ilacın bırakılması veya dozunun azaltılması çoğunlukla semptomların düzelmesini sağlar. Bu derlemenin amacı, kapesitabin ile indüklenen HFS ile ilişkili olabilecek olası enflamatuvar mekanizmaları kısaca değerlendirmektir.

Anahtar Kelimeler: Kapesitabin, El ayak sendromu, siklooksijenaz-2

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INTRODUCTION

Achievements in cancer therapy and chemotherapeutics provide more treatment options and more exposure to adverse effects associated with them. A large number of mucocutaneous side effects, the exact mechanism of which is still unknown, can be induced by chemotherapeutic agents. 'Palmar plantar erythrodysesthesia (PPE)' is a cutaneous drug reaction. It is mostly developed by chemotherapeutic agents (1). 'Chemotherapy-induced acral erythema' is also termed 'palmar-plantar erythrodysesthesia', 'hand-foot syndrome (HFS)', 'Burgdorf reaction' and 'toxic erythema of palms and soles' (1,2). Hand-foot syndrome was first reported by Zuehlke et al. in 1974 as 'erythematous eruption of the palms and soles' due to mitotane therapy (3).

Most patients present with erythema, swelling, and sensory abnormalities, such as a tingling sensation and dysesthesia in the palms or soles. In severe cases, the affected skin tissue exhibits desquamation or turns into an ulcerated or blistered formation (1,4-12). HFS is rarely life-threatening, but daily activities of the patient, such as walking or holding objects, may be restricted (1,5,10). It has been shown that it can deteriorate the quality of life (5,6,8,13,14).

Different classifications for grading the degree of severity of HFS have been developed by; the 'National Cancer Institute (NCI) of the United States of America', the 'World Health Organization', and Blum et al. (1,15,16). The severity of HFS is mostly graded according to the 'National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)' or the 'World Health Organization (WHO) HFS grading scale' (1,7,12,15,17).

Although many conventional or novel agents may cause HFS, the most frequently implicated agents are 'PEGylated liposomal doxorubicin (PLD), capecitabine, 5-fluorouracil (5-FU), cytarabine, docetaxel, and tyrosine kinase inhibitors. Of these, the incidence of HFS is higher with capecitabine (between 50% and 60%) (4,8,10). Chemotherapy-induced erythrodysesthesia is termed as classic hand foot syndrome (HFS). Capecitabine-induced HFS is also involved in this group. However, 'multikinase-associated skin toxicities' are commonly termed as 'hand foot skin reaction (HFSR)' (12). Capecitabine was developed as a prodrug of 5-FU in the class known as fluoropyrimidines, including 5-FU and Tegafur. It is taken orally and is converted in vivo to cytotoxic 5-FU, which has antineoplastic activity in many cancers (1,18). Capecitabine has been used in the treatment of numerous malignancies, such as the gastrointestinal tract, pancreas, biliary tract, breast, liver, head and neck, prostate, and genitourinary tracts, due to its high bioavailability, acceptable tolerability, and targeted intratumoral activation, as indicated in its prescribing information: 'for advanced or metastatic colorectal cancer and for advanced or metastatic breast

cancer as a single agent if an anthracycline- or taxane-containing chemotherapy is not indicated or as a regimen with docetaxel after disease progression on prior anthracycline-containing chemotherapy' (18,19). Hyperbilirubinemia, diarrhea, and HFS are the most commonly seen dose-limiting adverse effects related to capecitabine use (18).

Development and the degree of severity of HFS may be affected by multiple factors, such as the type and dose of the chemotherapeutic agent, gender, and genetic variations involved in drug metabolism, and this makes the determination of the incidence of the reaction challenging (7,9,10,20). However, it has been reported that patients treated with antineoplastic drugs develop HFS in a range of 6% to 64% (1,4,10,21-23). The exact cause of HFS remains unknown. The severity and incidence of HFS are associated with the dose administered (4,24,25). The highest incidence rates of HFS have been reported in patients treated with capecitabine and pegylated liposome-encapsulated doxorubicin treatment (7,10,20,26). HFS was found to be present in 22%–77% of patients taking capecitabine in previous studies (10,11,14). In a study of capecitabine using the Blum et al. classification system, the incidence of HFS was reported to be 68.3% (26). The minimum incidence rate of HFS in the prescribing information of capecitabine is even stated as 54% (19). It is a dermatologic toxic reaction that has a dose-dependent manner and rechallenge of patients with the causative drug mostly generates the reaction (4,5,22,26,27). Loss of fingerprints can be detected and may cause identification problems in certain patients (28). Hyperpigmentation may be seen as a consequence of capecitabine-induced HFS in African American patients (10). Quitting or a reduction in the dose of the causative drug generally improves the recovery of the symptoms (5,6,26,27). It may also cause a notable reduction in the patient's quality of life. It may require drug withdrawal or reduction, which may result in a decrease in the effectiveness of treatment and thus a disruption in the chemotherapy plans (5,14,29,30).

Pathogenesis of Capecitabine –Induced Hand Foot Syndrome

There is still no consensus on effective international standard therapeutic strategies for the treatment and prevention of HFS because the underlying physiological and pharmacological mechanisms leading to the development of HFS have not been adequately explained. The pathogenesis of HFS is thought to be different for each class of drug (4,11,29,31). Beard et al. proposed that it might be the host-versus-altered-host response, an immune-mediated response, in patients administered a continuous infusion of 5-FU (32). It is also emphasized that this mechanism may not be generalizable to drugs other than 5-FU and capecitabine (1,7,32). Another explanation for capecitabine-induced HFS has been impaired renal function, as the elimination of the metabolites is

primarily through the kidneys (8). Another theory suggests that, as a consequence of the elimination of capecitabine by the eccrine system (sweat secretion), and since the hands and feet have an increased number of eccrine glands, the accumulation of capecitabine in this specific area may lead to HFS (5,6,8,31,33,34).

Even though, the toxic metabolite/metabolites of capecitabine induced HFS are not clearly understood, one theory regarding HFS mediated by capecitabine implies that it may be related to the accumulation of capecitabine and its metabolites (5,6,31). Thymidine phosphorylase (TP), capecitabine-activating enzyme, is also angiogenic, and its expression is increased in various tumors. Asgari et al. reported that TP is found in high concentrations in keratinocytes on the palms (5,35). They also concluded in their 1999-dated study that its expression and activity show a correlation to the degree of differentiation of normal keratinocytes (35). Expression of the capecitabine-activating enzyme TP was identified as higher in the palmar skin, and it is suggested that this may be associated with the high concentration of active components level in this area. Accumulation of the capecitabine metabolite because of upgraded levels of thymidine phosphorylase in keratinocytes may lead to an increased probability of developing HFS (5,6,35). Complementary to this hypothesis, another study planned on healthy volunteers reported that intrapatient comparison of the evaluation of the difference between the palm and back areas of the hand exhibited significantly higher reactivity of TP (activating enzyme) and dihydropyrimidine dehydrogenase (DPD) (catabolic enzyme) and the proliferation marker Ki67 in the palm when compared to the back area. This higher expression of TP and DPD in the palm area results in local activation of capecitabine and this may be an explanation for the preferential specificity of HFS for the palms (36). It is suggested that the increased level of TP expression in the palm may result in cytotoxic effects related to the locally elevated production of 5-FU during capecitabine treatment, and the increased proliferation rate detected in the palm contributes to this by making these cells more sensitive to the cytotoxic effects of 5-FU that are produced locally (36). The contribution of a higher proliferation rate also supports the explanation for the localized activation of capecitabine and the preferential concentration of HFS in the palms (36). A previous supportive theory came from another study, and it was shown that patients treated with 5-FU and a DPD inhibitor and with an inherited DPD deficiency exhibited a more diminished frequency of HFS (8,37,38). These aforementioned studies make a contribution to the previous theory regarding the possible mechanism of HFS, which is based on the idea that increased vascularization, temperature, and pressure in the hands and feet may be associated with capecitabine-induced HFS (5,6). It is concluded

that this may be related to the angiogenic effects of TP, whose expression is upgraded in keratinocytes, and that angiogenic effect-mediated vascularization is implicated in playing a role in capecitabine-induced HFS (6,35,36).

A recent study also broadened the point of view on this subject and the theory that capecitabine-induced HFS may be related to the accumulation of capecitabine and its metabolites. This study, with metabolomic analysis of HFS-positive and negative cancer patients taking capecitabine, detected nine novel metabolites of capecitabine. It was shown that newly detected acetylation metabolites of capecitabine, M9/M10, formed primarily by N-acetyltransferase 2 (NAT2) and with a minor contribution by N-acetyltransferase 1 (NAT1), exhibited inhibition over the growth of HaCaT cells in a dose-dependent manner. Hydroxylation, methylation, degradation, and acetylation have been demonstrated as novel metabolic pathways of capecitabine in patients with HFS. It has been suggested that the metabolism of capecitabine may be affected by the polymorphic variants of NAT1 and NAT2 (39).

Evaluation of the histopathology of HFS exhibited epidermal changes, such as 'basal layer vacuolar degeneration, full-thickness necrosis, hyperkeratosis or parakeratosis' (1,10). Inflammatory changes, dilatation of the blood vessels, oedema, and infiltration of white blood cells were detected in the tissues affected by HFS (1,5-8,26). Cianchi et al. have shown that up-regulation of cyclooxygenase 2 (COX-2) gene expression may be associated with tumor angiogenesis in human colorectal cancer. COX-2 and vascular endothelial growth factor (VEGF) were significantly correlated with microvessel density, and it is suggested that VEGF is likely one of the most considerable mediators of the COX-2 angiogenic pathway (40). However, the exact pathogenesis of HFS remains poorly understood; its inflammatory basis has been kept in mind from the very beginning as one of the possible underlying mechanisms of HFS. It has previously been hypothesized that HFS may be a type of inflammation related to the overexpression of COX-2 formed extensively in the palm of hand and plantar of the foot that capecitabine or its metabolites may trigger directly or indirectly (6,31,41-43). In regard to this theory, a retrospective study carried out by Lin et al. has indicated that celecoxib, a specific inhibitor of COX-2, diminished the incidence of HFS in 67 metastatic colorectal cancer patients, using capecitabine (41). A prospective study carried out by Zhang et al. has also indicated that celecoxib could decrease the incidence of HFS associated with capecitabine in patients with metastatic colorectal cancer (43). The prevention of moderate to severe HFS with celecoxib was reported in a 2014-dated meta-analysis by Macedo et al (29). The potential prophylactic efficacy of oral celecoxib use for capecitabine-associated HFS was reported in a meta-analysis by Huang et al.,

highlighting the need for long-term studies of celecoxib use in order to evaluate its adverse effects (44). Another meta-analysis by Pandy et al., using only randomized controlled trials to compare the efficacy of prophylactic agents (urea cream, pyridoxine, and celecoxib) versus no prophylaxis in preventing HFS in cancer patients administered systemic cancer treatment, reported that celecoxib may be more effective for HFS associated with capecitabine (for all grades) (12). It is reported in the literature that further studies are needed in this area to provide reliable and relevant information to guide clinical practice.

The investigation of the efficacy of celecoxib in the treatment of HFS still continues, with new studies evaluating the change in its route of administration. To overcome the systemic adverse effect of celecoxib's reported gastrointestinal and cardiovascular toxicity, seen with its long-term use, a topical application form of celecoxib (a topical hydrogel of celecoxib, 1%) was recently evaluated in a pilot trial as a safe alternative for HFS associated with chemotherapy in cancer patients. Its systemic adverse effects and absorption are limited by topical application. It penetrated the stratum corneum and was distributed in the epidermis and dermis. It is emphasized that most of the drug was retained in the epidermis in this hydrogel application, and it ameliorated the HFS (45). Recently, another supportive study evaluating a different member of the family of non-steroidal anti-inflammatory drugs, diclofenac, has also been published. The effectiveness of topical 1% diclofenac gel in the prevention of capecitabine-induced HFS has been reported (46).

An alternative hypothesis for the mechanism of capecitabine-induced HFS concentrated on an inflammatory response associated with abnormal autoimmune regulation instead of previously thought COX-2-mediated inflammation (47). A clinical study was conducted to evaluate the potential diagnostic and capecitabine-related adverse effects biomarkers on urinary endogenous metabolites. It analyzed the metabolic profiles of 139 colorectal patients, 50 non-neoplastic controls, and also colorectal patients with or without capecitabine- related adverse effects. The authors of the study suggested that erroneous cell proliferation, differentiation, potential metabolic pathways, and an excessive immune response may make patients with cancer more sensitive to capecitabine-related adverse effects (47).

Another study that evaluated the contribution of keratinocytes to capecitabine-induced HFS concluded that mitochondria-associated apoptosis is activated in keratinocytes by capecitabine therapy. It has been shown that dysfunction of mitochondria contributes to apoptosis associated with capecitabine, stimulating the cell deaths of keratinocytes, and may cause a direct and irreversible reduction of the corneuos layer (48). This experimental animal study investigated the relationship between alterant keratinocytes and the

development of capecitabine-induced HFS and concluded that keratin and the corneous layer were decreased in HFS associated with capecitabine. The result of the study further implicated that capecitabine and its metabolites increased the cell death of keratinocytes through the activation of apoptosis signaling pathways. It has been shown that capecitabine actuated mitochondrial-associated apoptosis in keratinocytes. Determination of the up-regulation of apoptosis-related proteins and a decline in mitochondrial membrane potential revealed that mitochondrial apoptosis was notably associated with capecitabine- induced HFS. It was reported in the study that capecitabine-induced HFS has been shaped through mithochondrial dysfunction, activated caspase-dependent apoptosis, induced cell death of keratinocytes, and, as a consequence of these reactions, an irreversible and direct reduction of the corneous layer. Differing from the other previous studies, skelemin or ionic channel have been postulated to be more adequate to describe capecitabine-induced HFS rather than inflammatory and immune pathways (48).

Furthermore, another study combining metabolomics with cell RNA sequencing has recently demonstrated that the inflammation mechanism of capecitabine-associated HFS may be related to abnormal expression of interleukin (IL) 6 or IL8 and not solely to overexpression of COX-2. It is reported that the involvements of the P38MAPK, NF-κB, and JAK-STAT3 signaling pathways, which may be associated with overexpression of IL6 or IL8, were detected as potential pathways taking part in hand foot syndrome associated with capecitabine. The exposure of skin cells to capecitabine and its metabolites exhibited much higher expression levels of IL6 or IL8 than those of COX-2, as well (49). Another study, differing from other previous studies hypothesizing the idea that cell death related to fluoropyrimidine may be associated with apoptosis, has suggested that pyroptosis may be involved in the development of HFS associated with capecitabine. The pyroptosis of keratinocytes induced by 5-DFUR, an active metabolite of capecitabine, may be gasderminE (GSDME) dependent, and this pyroptosis may trigger persistent inflammation. In addition, TP is implicated in the pyroptosis of keratinocytes induced by 5-DFUR in vitro. Tipiracil, a TP inhibitor administered topically, exhibited a reversal effect in HFS associated with capecitabine without impacting the antitumor effect (50).

In addition to these aforesaid theories that may interact with inflammatory pathways, enzymes that are responsible for the metabolism, the transporters involved in the absorption of capecitabine, and pharmacogenomics may (‘thymidine phosphorylase, uridine phosphorylase, dihydropyrimidine dehydrogenase, cytidine deaminase, N-acetyltransferase 1, N-acetyltransferase 2, thymidylate synthase methylenetetrahydrofolate

reductase, ATP binding cassette transporters, solute carrier proteins SLC22, SLC28, SLC29 transporters') take part in capecitabine-induced HFS, and it is not discussed in this review. However, it is suggested that there may be an association between dihydropyrimidine dehydrogenase and thymidylate synthase variants and capecitabine toxicity. Variability seen in the activity of dihydropyrimidine dehydrogenase and thymidylate synthase enzymes related to genetic polymorphisms and capecitabine toxicity may interact (31). Transporters involved in the absorption have been suggested to be related to HFS associated with capecitabine. The adverse effects seen in colorectal cancer patients associated with fluoropyrimidine treatment interactions with the polymorphisms of the ATP-binding cassette subfamily B member 1 (ABCB1) gene and interactions between certain members of SLC transporters ['in particular, human Organic Anion Transporter 2 (h OAT2), human Concentrative Nucleoside Transporter (hCNT1), and human Equilibrative Nucleoside Transporter 1 (h ENT1) of the SLC 22, SLC28, and SLC 29 families, respectively'] and 5-FU have also been reported in the literature (31).

CONCLUSION

Hand-foot syndrome is an expected adverse effect of some chemotherapeutic agents, mostly seen with capecitabine. Quitting or dose reduction may disrupt the treatment of patients. It may be further suggested that non- adherence to the treatment may arise. The exact mechanism is poorly understood. However, the evolving literature with new hypotheses is an area that is improving. It is of crucial requirement to investigate the underlying mechanism of HFS in order to establish a standard treatment consensus. Therefore, further evaluations are essential in the prevention and treatment of HFS for the progress and betterment of patient care.

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