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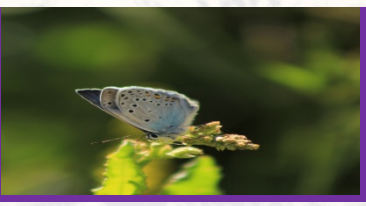

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Letter to the Editor

Optimizing Clinical Decisions in Fournier's Gangrene Using Prognostic Scoring Models

Fournier Gangreninde Prognostik Puanlama Modellerini Kullanarak Klinik Kararların Optimize Edilmesi

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Dear Editor.

I read with great interest the article prepared by Türk and Aslan named "The Effect of Albumin Level and Neutrophil Lymphocyte Ratio on Mortality and Recovery in Fournier's Gangrene" published in the second issue of the fourth volume of your journal (1). I would like to thank the authors and the editorial group for their diagnostic value study evaluating the ability of albumin and neutrophil lymphocyte ratio to predict mortality in Fornier's gangrene (FG). I would like to expand on the two scoring systems mentioned by the authors in the discussion to contribute to the readers.

FG is a rapidly progressing, life-threatening necrotizing infection that affects the perineum, genitalia, and surrounding tissues. Prompt assessment and management are crucial, as delays in treatment can lead to high mortality rates (2,3). The prognostic role of inflammatory markers has been studied in Fournier's gangrene. Lymphocyte-monocyte ratio (LMR) and red cell distribution width (RDW) have been identified as valuable markers in systemic inflammation (4). Elevated LMR and RDW levels are associated with poor prognosis and increased mortality in conditions such as coronary artery disease and critical illness (5).

Based on the inflammatory process of Fournier's gangrene, prognostic scores have been developed utilizing inflammatory markers. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score was developed to differentiate necrotizing infections from other soft tissue infections using initial laboratory parameters. This score is based on C-reactive protein (CRP), white blood cell count, hemoglobin, sodium, creatinine, and glucose levels, with specific points assigned to each parameter. In Fournier's gangrene, the LRINEC score serves as both a diagnostic and prognostic tool. Higher LRINEC scores typically reflect the severity of the disease, the level of systemic inflammation, and the risk of sepsis. Elevated parameters such as CRP and leukocytosis are particularly associated with severe infections and poor outcomes. The score aids in the early diagnosis of Fournier's gangrene and guides patient management. However, the reliability of the LRINEC score in Fournier's gangrene remains debated. Some studies suggest its predictive value for necrotizing infections in this specific patient population is limited. Interpreting the score may be challenging in immunocompromised patients or those with chronic inflammatory conditions (6).

Recently, Yönder et al. developed a novel score based on inflammation and nutrition. Yönder et al. developed the Fournier's Gangrene Mortality Index (FGMI) to predict mortality in Fournier's gangrene patients. This retrospective study included 169 patients treated in Şanlıurfa, Turkey, between 2014 and 2024. FGMI parameters included age, creatinine, albumin, lymphocyte percentage, and neutrophil-to-lymphocyte ratio, with scores ≥5 indicating high mortality risk. Mortality occurred in 11.8% of patients, with significant differences observed in neutrophil and lymphocyte-related markers between survivors and non-survivors. FGMI demonstrated a strong predictive ability for mortality, with an AUC of 0.88, 90% sensitivity, and 70% specificity. In contrast, the LRINEC score lacked effectiveness in mortality prediction. The mentioned study highlights FGMI's utility in early mortality risk assessment (7).

Scoring systems like the FG Severity Index (FGSI) and the Uludağ FG Severity Index (UFGSI) have been developed to aid clinicians in evaluating disease severity, estimating prognosis, and guiding treatment decisions. These tools assess a variety of physiological and biochemical parameters to predict mortality risk, helping physicians to identify patients who may require closer monitoring or more aggressive interventions. Over time, these scoring models have been refined to improve predictive accuracy and support clinical decision-making in managing this challenging condition.

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FGSI is a scoring system used to determine prognosis and predict the risk of mortality in patients with FG. This index helps to evaluate the degree of spread of the disease and the general health status of the patient. FGSI was created by Laor et al. from New York in 1995. They designed that based on Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The data of solely 30 patients with FG treated in 15-year period was evaluated retrospectively. On their data set 13 patients died and 17 patients were survived. An FGSI score above 9 is often associated with a higher risk of mortality, according to data they reported that with a FGSI value of 9 as a threshold, there was a 75% probability of death for scores greater than 9, while a score of 9 or less was associated with a 78% probability of survival. The FGSI is created by measuring the following physiological parameters, with each parameter being given a score between 0 and 4: Body temperature (°C), Heart rate (pulse/minute), Respiratory rate (respiratory rate/minute), Serum sodium level (mmol/L), Serum potassium level (mmol/L), Serum creatinine level (mg/100 ml), Hematocrit (%), White blood cell count (x 103). Each parameter is given a score based on the degree of deviation from normal values (0 is normal, 4 is abnormally high or low). Once the scores are added, the higher the total score, the higher the severity of the disease and the higher the risk of mortality (8). The FGSI helps physicians determine whether they should monitor patients with FG disease more closely and consider aggressive treatment options.

Fifteen years after the work of Laor et al., Yılmazlar et al. from Bursa, developed an updated scoring system named UFGSI, in 2010. The UFGSI is a modified scoring system developed to assess the severity and predict the prognosis of Fournier's gangrene, a rapidly progressing and potentially fatal necrotizing infection of the perineum and genital area. This index builds on previous scoring models, such as the FGSI, by including additional parameters and adjustments to improve predictive accuracy. Yılmazlar et al. recorded their data prospectively for ten years. The dataset in Yılmazlar et al.'s study included 80 patients, comprising 63 survivors and 17 non-survivors. They reported that with a UFGSI threshold value of 9, there was a 94% probability of mortality for patients scoring above 9, while a score of 9 or less was associated with an 81% probability of survival. A secondary analysis was conducted to compare the predictive efficacy of the UFGSI and FGSI scoring systems. Comparison of the area under the curve (AUC) values for mortality prediction demonstrated a statistically significant superiority of the UFGSI (0.947 vs. 0.843). The UFGSI typically evaluates a range of physiological and biochemical parameters, including: Vital signs (e.g., temperature, heart rate, respiratory rate), Blood test values (e.g., hematocrit, white blood cell count, serum sodium, potassium, and creatinine levels), Extent of infection and degree of tissue involvement. Each parameter is scored based on deviations from the normal range, with higher scores indicating more severe physiological derangements. The total score helps clinicians estimate the patient's risk of mortality; a higher score correlates with a higher likelihood of a poor outcome (9). The UFGSI has been particularly valuable for guiding treatment decisions, risk stratification, and resource allocation, as well as aiding in patient counseling and setting expectations for recovery.

In conclusion, scoring systems like the FGSI and UFGSI play a critical role in managing Fournier's gangrene, a severe and rapidly progressing infection. By evaluating key physiological and biochemical parameters, these indices provide a structured approach to assess disease severity and mortality risk. The UFGSI, which builds on the original FGSI with additional parameters, has demonstrated greater predictive accuracy, aiding clinicians in making informed decisions regarding treatment and resource allocation. Higher scores on these indices correlate with increased mortality, underscoring the need for prompt and aggressive management in high-risk patients. Overall, these tools enhance patient outcomes through targeted, risk-adjusted care strategies.

Kind regards

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Case Report

A distal coronary artery perforation caused by guidewire

Klavuz tel kaynakli bir distal koroner arter rupturu

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Abstract

This case report presents a distal coronary artery rupture caused by a guidewire. Although it is generally considered as a benign complication with good prognosis, and less invasive treatment strategies are recommended, the patient required both had to had percutaneous and surgical treatment.

Keywords: coronary angiography, embolization, percutaneous coronary intervention

ÖZ

Bu vaka sunumunda klavuz tele bağlı bir distal koroner arter rüptürü sunulmaktadır. Klavuz tele bağlı koroner rüptürü genelde iyi prognozlu kabul edilse ve tedavi yöntemleri daha çok konservatif olsa da bu vakamızda perkütan ve cerrahi tedavi bir arada gerekmiştir

Anahtar Kelimeler: koroner anjiyografi, embolizasyon, perkütan koroner girişim

Highlights

- Although coronary artery perforations induced by guidewires have been generally considered benign, their treatment can be challenging
- Recommended treatment strategies include reversing anticoagulation with protamine and prolonged balloon inflations
- Various materials including thrombin, collagen, polyvinyl-alcohol, Gelfoam, subcutaneous fat or a part of a balloon can be used for vessel occlusion

Introduction

Coronary artery perforations induced by guidewires have been generally considered benign compared to perforation caused by balloon inflation, stent placement, or the use of debulking devices (1). However, this case report presents a coronary artery distal perforation that required both surgical and percutaneous treatments.

Case Report

A 49-year-old male patient no prior history of coronary artery disease was admitted to the hospital with diagnosis of non-ST elevation myocardial infarction. His psychical examination, transthoracic echocardiography (TTE), ECG, and blood tests were normal except for high troponin level. Coronary angiography revealed totally occluded circumflex artery (CFX) while the other coronary arteries were normal **(Figure 1)**.

The patient received ticagrelor 180 mg in addition to aspirin which was given in the emergency room. And the lesion in CFX was successfully treated with a drug-eluting stent **(Figure 2)**. However, control injections revealed a distal leakage in CFX **(Figure 2)**. Repeated prolonged balloon inflation within the stent was performed, and subsequent contrast injection showed no active leakage. The patient was asymptomatic, and TTE after the procedure showed minimal pericardial effusion. A few hours later, the patient developed mild hypotension (93/60 mmhg) and orthopnea. Repeated TTE showed increased pericardial effusion of less than 2 cm primarily around apex.

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Clinical signs of tamponade were absent; therefore, percutaneous pericardiocentesis was not performed. However, angiography was performed to rule out any active leakage and it revealed the recurrence of distal coronary leakage. The patient has suffered intermittent complete AV block. The temporary pacemaker was implanted, and a 2.0 x 4 cm Prestige coil was used to occlude distal CFX. Control injections confirmed total occlusion of CFX and no leakage **(Figure 3)**. Despite the lack of active coronary leakage and significant pericardial effusion, the patient continued to have mild hypotension and orthopnea. TTE performed the next day revealed a highly echogenic image of the hematoma around the right ventricular free wall, close to apex. Surgical removal of the hematoma resolved the patient's hypotension and orthopnea. The patient was advised to continue aspirin and atorvastatin for life and was discharged in good condition after seven days of hospitalization.

Figure 1. Right anterior oblique caudal view showing total occlusion of the circumflex artery (arrowhead)

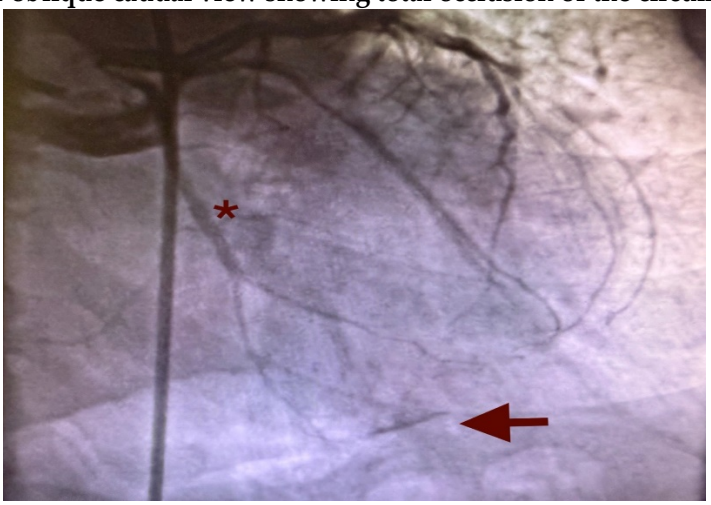

Figure 2. Right anterior oblique caudal view showing distal leakage from the circumflex artery (arrowhead) and stent implanted on mid segment of the circumflex artery (*)

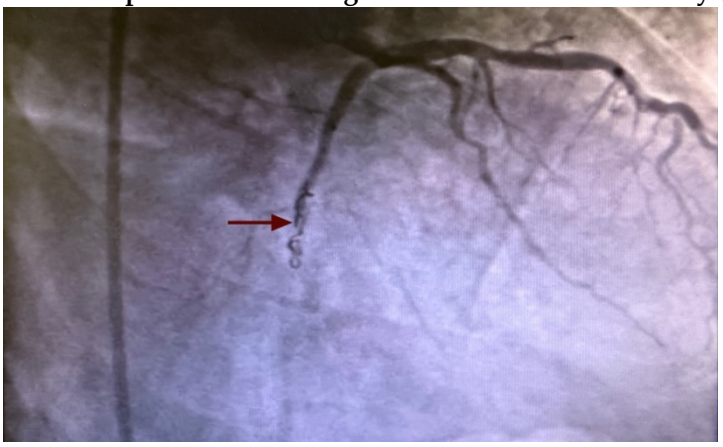

Figure 3. Right anterior oblique caudal view showing occlusion of the circumflex artery with coil (arrowhead)

Discussion

Coronary artery perforation is rare (0.2%-0.6%) but a serious complication of percutaneous coronary intervention (2). Although the guidewire perforations (GWP) are often considered benign, their treatment can be challenging, especially if they are unexpected or poorly managed.

The modified Ellis classification is commonly used to stratify coronary perforations: Type I: extraluminal crater without linear contrast extravasation, suggesting dissection; Type II: myocardial or pericardial blushing; Type III: frank contrast extravasation into the pericardium; and Type IV: perforation with contrast extravasation into the left ventricle, coronary sinus or other vascular areas (3).

Prolonged procedures, stiff or hydrophilic guidewires, and the use of glycoprotein IIb/IIIa platelet inhibitors are common causes of GWP (4). Initially the leakage is often asymptomatic and not associated with significant pericardial effusion on TTE. However, subacute pericardial tamponade may develop (4). In this case, a stiff guidewire was used to cross the total occlusion. TTE after the initial procedure showed no pericardial fluid but significant pericardial effusion noted repeat TTE after few hours.

Although GWPs may initially appear benign on angiography, they frequently evolve into Ellis class III perforations, which are associated with poor prognosis (2). Recommended treatment strategies include reversing anticoagulation with protamine and prolonged balloon inflations (2,3), which have been reported to be successful in >50% of patients (3,5). If leakage persists, distal vessel occlusion is advised (4). Various materials including thrombin, collagen, polyvinyl-alcohol, Gelfoam, subcutaneous fat or a part of a balloon can be used for vessel occlusion (4,6).

In this case, repeated prolonged balloon inflations initially appeared to resolve the leakage. However, distal leakage recurred after a few hours later necessitating coil implantation, which successfully occluded the CFX and distal perforation. Despite this, surgical removal of the pericardial hematoma was required to fully resolve patients' symptoms.

Conclusion

This case highlights the importance of carefully reviewing angiography images in all patients. In the presence of any distal rupture initial echocardiography might appear be normal; therefore, TTE should be performed a few hours later even initial TTE is normal. Persistent distal ruptures despite ballon inflations should be treated aggressively. Additionally, pericardial hematoma should be suspected in patients with pericardial effusion who are experiencing hypotension.

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Ethical Approval: *Informed consent for case report was obtained from the patient.*

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Original Article

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Evaluation of the Effect of Ramadan Fasting on Parotid and Submandibular Gland Elasticity with Shear Wave Elastography

Ramazan Orucunun Parotis ve Submandibular Bez Üzerindeki Etkisinin Shear Wave Elastografi ile Değerlendirilmesi

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Abstract

Background: The changes in eating-drinking and sleeping habits during Ramadan cause also changes in daily routines. It was aimed to evaluate the effect of Ramadan fast on parotid and submandibular gland elasticity with shear wave elastography.

Materials and Methods: The anthropometric measurements of the volunteers such as age, gender, height, and weight, and the elastography values of the bilateral parotid and submandibular glands measured on the day before and on the last day of Ramadan were obtained. Five 2D-SWE (Two-dimensional shear wave elastography) measurements were taken at the same depth. The average of these was calculated. In this way, the accuracy of the numerical data obtained was increased. The mean value of five 2D-SWE measurements was used for the statistical analysis. This procedure was repeated for both parotid and submandibular glands. Data obtained in the study were analyzed statistically. A value of $p < 0.05$ was accepted as statistically significant.

Results: There was a statistically significant difference between the mean BMI values measured on the day before Ramadan and the last day of Ramadan fasting ($p<0.001$). No significant difference of elastography values was found between the bilateral parotid and submandibular glands on the day before Ramadan and on the last day of Ramadan.

Conclusions: The intermittent fasting during Ramadan had no effect on the elasticity of the salivary glands, as determined by our studied.

Keywords: Intermittent fasting, Elastography, Parotid gland, Submandibular gland

ÖZ

Amaç: Ramazan ayında yeme-içme ve uyku alışkanlıklarında meydana gelen değişiklikler, günlük rutinlerde de değişikliklere neden olmaktadır. Bu çalışmada, Ramazan orucunun parotis ve submandibular bez elastikiyeti üzerine etkisinin shear wave elastografi ile değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Gönüllülerin yaş, cinsiyet, boy ve kilo gibi antropometrik ölçümleri ile bilateral parotis ve submandibular bezlerin Ramazan'dan bir gün önce ve Ramazan'ın son günü ölçülen elastografi değerleri elde edilmiştir. Aynı derinlikte beş adet 2D-SWE (Two-dimensional shear wave elastography) ölçümü alındı. Bunların ortalaması hesaplandı. Bu şekilde elde edilen sayısal verilerin doğruluğu artırıldı. İstatistiksel analiz için beş 2D-SWE ölçümünün ortalama değeri kullanılmıştır. Bu prosedür hem parotis hem de submandibular bezler için tekrarlandı. Çalışmada elde edilen veriler istatistiksel olarak analiz edilmiştir. $P <0.05$ değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Ramazan'dan önceki gün ve Ramazan orucunun son gününde ölçülen ortalama vücut kitle indeksi (VKİ) değerleri arasında istatistiksel olarak anlamlı bir fark vardı ($p<0.001$). Bilateral parotis ve submandibular bezlerin Ramazan'dan önceki gün ve Ramazan'ın son günündeki elastografi değerleri arasında anlamlı bir fark bulunmamıştır.

Sonuç: Ramazan ayında aralıklı olarak tutulan orucun, çalışmamızda belirlendiği üzere tükürük bezlerinin esnekliği üzerinde herhangi bir etkisi olmamıştır.

Anahtar kelimeler: Aralıklı açlık, Elastografi, Parotis bezi, Submandibular bez

Highlights

- The effect of Ramadan fasting on the elasticity of the parotid and submandibular glands using shear wave elastography.
- What are the effects of dehydration, which occurs intermittently during Ramadan, on the elasticity of the parotid and submandibular glands?
- Elastography is a US-based imaging technique used to evaluate the stiffness of tissues

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Introduction

Fasting in Ramadan is one of the five pillars of Islam. Ramadan is the 9th month of the lunar calendar and moves forward about 11 days each year. Muslims abstain from eating any food, drinking any liquids, from dawn to sunset and fasten. Smoking, parenteral feeding and sexual intercourse are also prohibited during this period. The duration of fasting changes between 9 and 21 hours depending on the geographical situation. Ramadan lasts 29 or 30 days. The changes in eating-drinking and sleeping habits during Ramadan cause also changes in daily routines (1). Several studies have been conducted to demonstrate the effects of fasting on human physiology and the potential impact on the existing diseases (2-4). It has been reported that dehydration occurring during Ramadan fasting can increase the risk of developing acute sialadenitis (5). In another study, it was found that salivary levels of sIgA were elevated during the fasting period, while statherin levels were higher after fasting. These biomarkers are essential for oral health, as they help defend against microbial invasions and regulate the balance of calcium and phosphate ions in saliva (6).

The parotid glands are the largest salivary glands and contribute about 25% of the total saliva production. They secrete a serous fluid rich in electrolytes and enzymes. The submandibular glands, which produce approximately 70% of daily saliva, secrete a mixture of electrolytes, enzymes, and mucins. The sublingual glands, producing a mucus-rich fluid containing antigens and antibodies, drain either directly into the oral cavity or into the submandibular duct (7). Ultrasonography (US) is a non-invasive, inexpensive, repeatable, and portable imaging method (8). It is commonly used in the examination of the parotid and submandibular glands. Elastography is a US-based imaging technique used to evaluate the stiffness of tissues (9). It is a promising tool regarding the diagnosis of several benign and malignant disorders, particularly fibrosis. There are two types of US elastography: Strain Elastography (SE) and Shear Wave Elastography (SWE). In SE, external pressure with the help of a US probe is implemented to create mechanical stimulation. In SWE, mechanical stimulation is created with shear waves produced by the imaging device. In both methods, the elasticity properties of the tissues are evaluated according to the response to the implemented mechanic stimulation (10). The tissue elasticity is measured in kilopascal units or with shear wave velocity (SWV). The real-time quantitative measurement of the tissue elasticity, repeatability, and non-dependence to an operator (as no pressure is implemented), are the advantages of SWE (11).

In this study, it was aimed to investigate with SWE the effects of hunger and thirst, which occur in intermittent durations through Ramadan, on the elasticity of the parotid and submandibular glands.

Material and Methods

Study design

This study approval was obtained from the Harran University Faculty of Medicine, Ethics Committee (number: HRÜ/19.03.43. date: 11.03.2019). Informed consent was obtained from all patients. Healthy male volunteers, who were fastening in Ramadan (between May and June 2019) and working in our institute, were included in our study. Females were not included, because they could not fasten during the menstruation period. This single-center, prospective study had two phases. The first phase was defined as the day before the first day of Ramadan and the second phase was defined as the last day of Ramadan fasting. On the day before the first day of Ramadan and the last day of the Ramadan fasting, the body mass indexes, and the elastography values of the parotid and submandibular glands were measured. In both phases, the measurements were carried out at 12:00 am in order to get the measurement values at the near 8th hour of fasting. Body mass index (BMI) was calculated by dividing the weight (in kilograms) by the height (in square meters) (kg/m^2).

Ultrasound and 2D-SWE

The examinations were performed by using the Siemens ACUSON S2000 US system (Siemens Medical System Solution, CA, USA) with a 9L4 probe. First, the gray-scale US examination of both parotid and submandibular glands was performed, while the volunteers were in the supine position **(Figure 1)**. After the gray-scale ultrasonography showed normal and healthy glands, the US probe was placed on the right parotid gland at the transverse plane following sufficient gel application. In this study, 2D-SWE (Two-dimensional shear wave elastography), the most novel elastography method using acoustic radiation force, was used. Elastography images were obtained by gently placing the US probe in the parotid and submandibular gland. Any pressure was avoided. Patients were instructed not to move to avoid artifacts. Values obtained from moving images were not considered in the analyses. SWE values were measured at the longest longitudinal measurements. A square

region of interest (ROI) was used as the plane. The ROI was placed at a depth of 0.5 cm. Quantitative elasticity values were measured in meters per second (m/s). Tissue elasticity was determined in a color range between dark blue (lowest stiffness) and red (highest stiffness) (**Figure 2 and 3).** Five 2D-SWE measurements were taken at the same depth. The average of these was calculated. In this way, the accuracy of the numerical data obtained was increased. The mean value of five 2D-SWE measurements was used for the statistical analysis. This procedure was repeated for both parotid and submandibular glands.

Statistical analyses

Statistical analyses were performed using the SPSS 24.0 version (SPSS Inc, Chicago, IL) package program. Descriptive statistics were summarized as a number, percentage, mean and standard deviation. The suitability of the variables to the normal distribution was investigated using visual (histogram and probability charts) and analytical methods (Shapiro-Wilk test). When the repeat measurement of the groups was compared, the data with normal distribution (differences between them) were analyzed by paired sample t test. The relationship between normally distributed data was evaluated by Pearson correlation analysis and correlation coefficient (r) was specified. Statistical significance level was accepted as $p < 0.05$ in all statistical analyses.

Results

Twenty-six cases, who were included in the study, were males. The mean age of the subjects was 33.69±8.12 years (min-max: 23-50 years). The mean BMI on the day before the first day of Ramadan was 26.88±3.35 (min- max: 19.23-36.14), while the same value on the last day of the Ramadan fasting was 26.15±3.25 (min-max: 18- 92-35.43). There was a statistically significant difference between the mean BMI values measured on the day before the first day of Ramadan and the last day of Ramadan fasting (Table 1; $p<0.001$). There was no statistically significant difference between the mean SWE values of both parotid glands on the day before the first day of Ramadan and the last day of Ramadan fasting were for the right side (p=0.234) and left side (p=0.261) **(Table 1)**. There was also no statistically significant difference between the mean SWE values of both submandibular glands on the day before the first day of Ramadan and on the last day of Ramadan fasting were for the right side (p=0.108) and left side (p=0.868) **(Table 1)**.

The Pearson's correlation analysis did not reveal any significant relationship between the age of the subjects and the SWE values of the right parotid (r=0.049, p=0.813), left parotid (r=0.012, p=0.953), right submandibular (r=0.133, p=0.516), and left submandibular (r=0.003, p=0.987) glands measured on the day before the first day of Ramadan. The Pearson's correlation analysis did also not show any significant relationship between the BMI values measured on the day before the first day of Ramadan and the SWE values of the right parotid (r=267, p=0.187), left parotid (r=-0.358, p=0.073), right submandibular (r=0.266, p=0.189), and left submandibular (r=0.008, p=0.967) glands.

Table 1. Comparison of body mass index and shear wave elastography values measured one day before and on the last day of Ramadan fast

Variables	One day before ramadan fast Mean ± SD	Last day of ramadan fast Mean ± SD	p^*
BMI (kg/m^2)	26.88±3.35	26.15±3.25	**<0.001**
Left parotid (kPa)	2.75±0.26	2.7±0.3	0.261
Right parotid (kPa)	2.94±0.36	2.88±0.36	0.234
Left submandibular (kPa)	2.72±0.31	2.75±0.36	0.868
Right submandibular (kPa)	2.82±0.32	2.73±0.28	0.108

Abbreviations: *: Paired sample t test; **BMI:** Body mass index; **SWE**: shear wave elastography; **SD**:Standard deviation

Figure 1. Healthy right parotid gland gray scale examination of a 27-year-old male patient

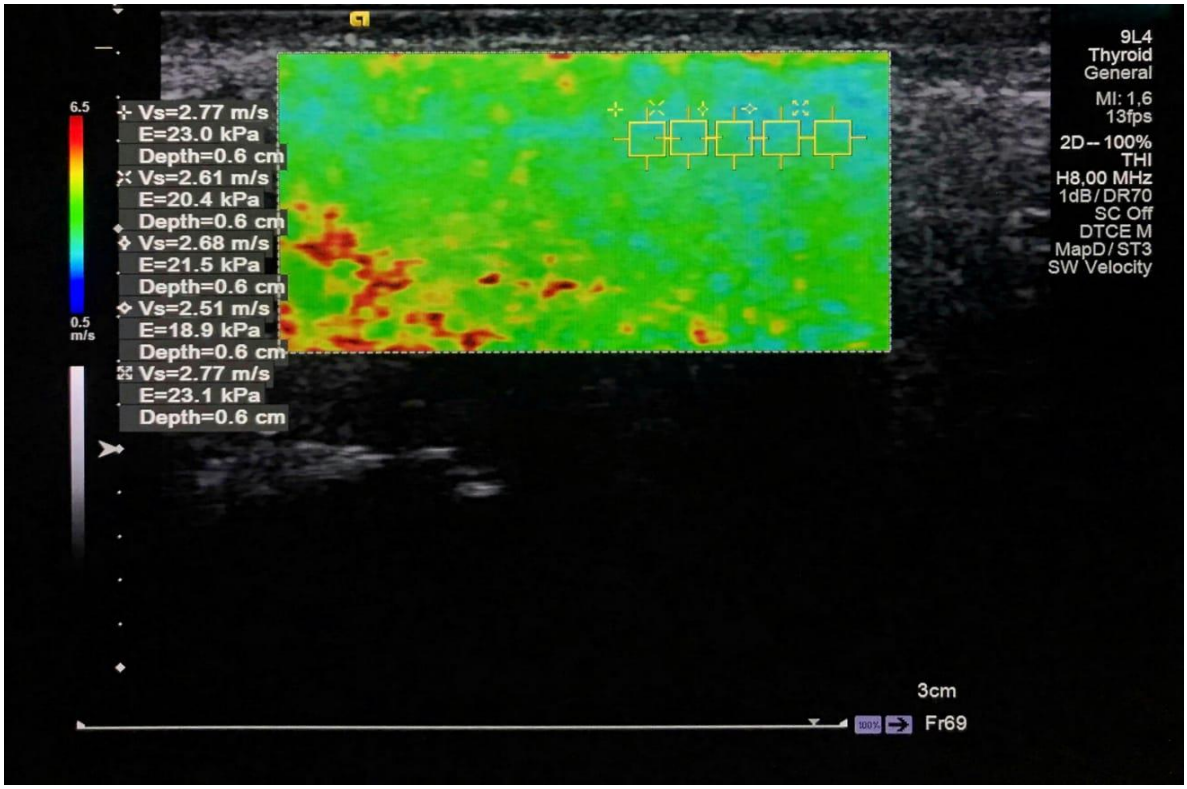

Figure 2. Elasticity values from the right parotid gland in elastography images obtained the day before Ramadan.

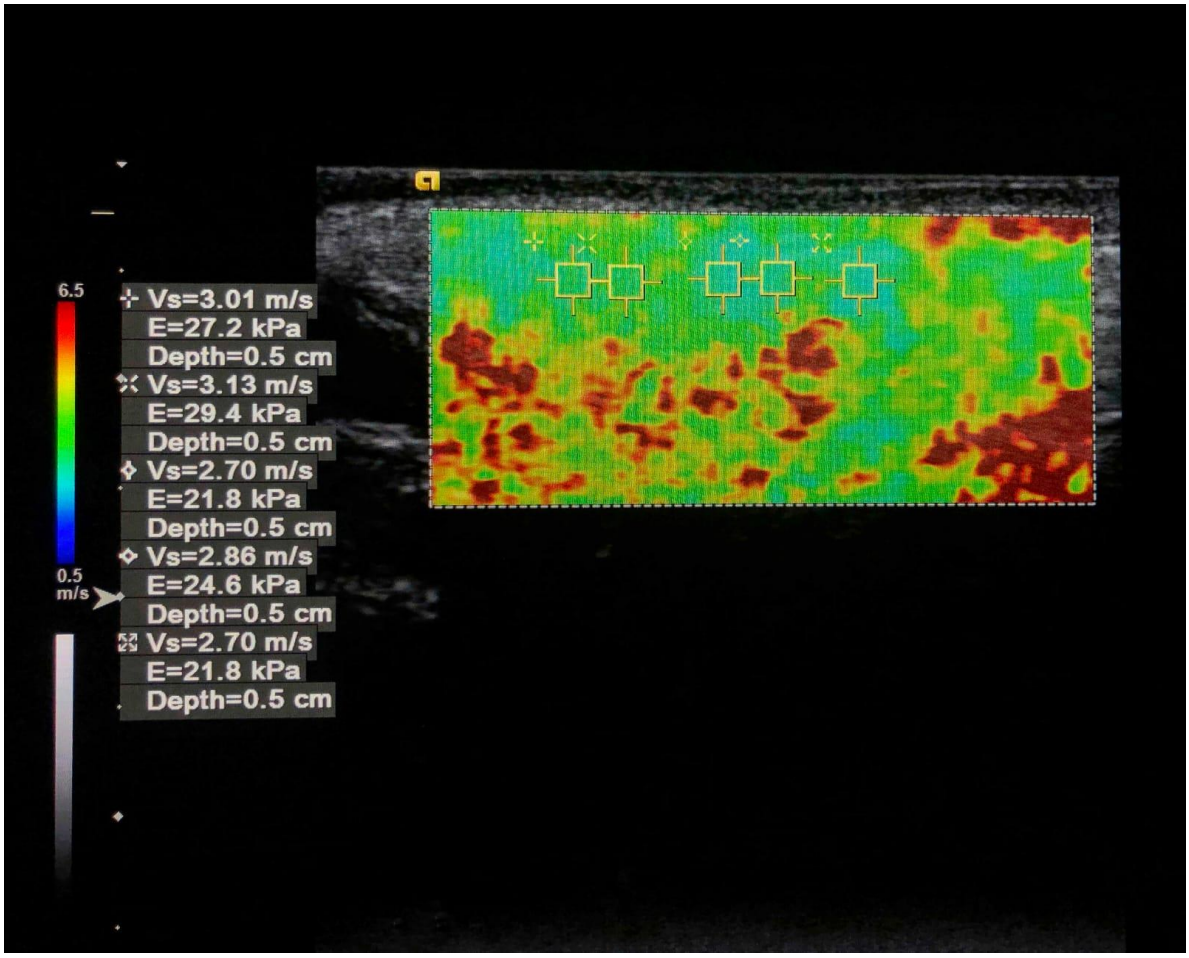

Figure 3. Elasticity values from the right parotid gland in elastography images on the last day of Ramadan

Discussion

During Ramadan fasting, Muslims are prohibited to eat and drink from dawn to sunset, and they are allowed to eat and drink from sunset to dawn. Therefore, fasting Muslims experience intermittent hunger and thirst throughout Ramadan. In this study, we investigated the cumulative effect of Ramadan fasting on the elasticity of both parotid and submandibular glands.

Like in previous studies, we determined a decrease in BMI values of the participating volunteers at the end of Ramadan (12, 13). This decrease in the BMI values might be a result of the reduced calorie intake. The previous studies had been focused rather on the changes in the biochemical and immunological components in the salivary secretion, which might emerge as a result of fasting, instead of the effects on the structural characteristics. Develioğlu et al. (13) investigated the effects of Ramadan fasting on the concentrations of serum IgG, IgM, and salivary IgA and they found that IgG values declined but remained within the normal limits and the serum IgM levels were not affected. They also determined that there was a statistically significant decrease in the levels of salivary IgA. Sariri et al. (14) conducted a study to investigate the possible changes in the salivary glucose levels during Ramadan fasting and detected a drop in the mean salivary glucose concentration during Ramadan fasting compared to the concentrations before Ramadan. Khaleghifar et al. (15) investigated the effects of Ramadan fasting on the biochemical analysis of the salivary fluid and measured the uric acid concentration, alkaline phosphatase (ALP) and aspartate aminotransferase (AST) activity before, during, and after fasting. They reported a significant decline in the salivary uric acid and AST concentrations and a significant elevation in the ALP activity. In a study on the effect of Ramadan fasting on sleep patterns conducted by Bahaham et al., it was found that melatonin levels obtained from saliva samples declined significantly below basal levels, despite the fact that the circadian pattern was retained during Ramadan (16). Another study by Joachim et al. demonstrated that sialadenitis developed more than twice as frequently in patients who fasted during Ramadan than in non-fasting months. According to the researchers, this situation occurred as a result of dehydration (17).

US elastography is increasingly being utilized to diagnose both benign and malignant diseases of the salivary

glands. Elastography studies reveal promising outcomes, particularly in diseases that involve inflammatory alterations and fibrosis in the major salivary glands, such as primary Sjögren's syndrome (pSS) (18-20). In a study on pSS, sicca syndrome, and a healthy control group, Dejaco et al. found that patients with pSS had higher elastography scores (21). Wierzbicka et al. observed that parotid gland stiffness increased in all patient groups compared to the control group in patients with pSS, sialolitis, Stensen's duct stenosis, and chronic inflammation (22). Similarly, in another study utilizing the acoustic radiation force imaging method, Turnaoglu et al. reported that mean SWV values in pSS patients were higher than in the control group (23). In a study performed by Arslan et al., higher SWE and elastic modulus values were obtained in patients with pSS compared to the control group (24).

Our aim in this study was to investigate the physiological changes that intermittent hunger and thirst may cause in salivary secretion during the month of Ramadan and the reflections of its possible effects on the elasticity of the tissue on the major salivary glands. To the best of our knowledge, this is the first study demonstrating the effects of Ramadan fasting on the elasticity of the salivary glands. Ratchatasettakul et al. (25) conducted a study to investigate the effects of food intake on liver stiffness and measured the hepatic elasticity in the 15th, 30th, 45th, 60th, and 120th minutes after overnight fasting. The measurements were repeated after the overnight fasting every 30 minutes until they returned to the basal level. The liver elasticity returned to baseline by 150 minutes. Mederacke et al. (26) performed a similar study to show the effects of food intake on liver stiffness in patients with chronic or resolved hepatitis C virus infection. Researchers found that liver stiffness significantly increased immediately after food intake for up to 60 min and normalizing after 180 min. In our current study, no similar changes were detected in the salivary glands.

As the measurements were performed on the day before the first day of Ramadan and after 8-hour fasting on the last day of Ramadan in our study, we believe that the elasticity of the parotid and submandibular glands was probably returned to baseline values. According to the results of this study, intermittent hunger, and thirst like in Ramadan fasting did not have any effect on the elasticity of the parotid and submandibular glands.

Study limitations

One of the limitations of our study is that comparing the control group not only at the beginning and end of the Ramadan month, but also during other periods, could have added further value to our paper. The second limitation is the small number of voluntary participants. The third limitation is that, since the study sample consisted solely of healthy young men, the results cannot be generalized to other age groups.

Conclusion

The intermittent fasting during Ramadan had no effect on the elasticity of the salivary glands, as determined by our studied. Further multicenter clinical studies with larger sample sizes are needed to demonstrate to confirm these findings.

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Ethical Approval: *This Study approval was obtained from the Harran University Faculty of Medicine, Ethics Committee (number:* HRÜ/19.03.43. *date: 11.03.2019). Informed consent was obtained from all patients.*

Author Contributions: *Concept: F.D, O.D. Literature Review: F.D, O.D. Design: F.D, O.D. Data acquisition: F.D, O.D. Analysis and interpretation: F.D, O.D. Writing manuscript: F.D, O.D. Critical revision of manuscript: F.D, O.D.*

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Emergency Visits in Cancer Patients: Predictors of Hospitalization and Palliative Care Needs

Kanser Hastalarında Acil Servis Başvuruları: Yatışı Öngören Faktörler ve Palyatif Bakım İhtiyaçları

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Abstract

Background: Cancer patients frequently visit emergency departments due to acute complications related to their disease or treatment. Identifying visit patterns and predictors of adverse outcomes can guide targeted interventions to improve care and reduce emergency reliance.

Materials and Methods: This retrospective cohort study analyzed visit patterns, common complaints, and predictors of hospitalization and mortality among cancer patients at a tertiary hospital. We reviewed 753 patients with active cancer who visited emergency department. Data on demographics, clinical presentation, admissions, and mortality were analyzed. Regression analysis was performed to determine the predictors of hospitalization and mortality. Mortality rates were assessed based on visit frequency.

Results: Among 753 patients with 1609 visits, gastrointestinal (36.5%) and respiratory (20.7%) cancers were the most common. Abdominal pain (18.15%) and nausea/vomiting (18.09%) were leading complaints. Hospitalization occurred in 34.6% of visits. Significant predictors included anorexia-cachexia (OR=3.84, 95% CI: 2.18–6.77, p<.001), altered mental status (OR=3.14, 95% CI: 1.81–5.44, p<.001), shortness of breath (OR=2.15, 95% CI: 1.52–3.03, p<.001), fever (OR=1.86, 95% CI: 1.40–2.48, p<.001), and abdominal pain (OR=1.61, 95% CI: 1.22–2.12, p<.001). The two-year mortality rate was 20.19%, highest in gastric (32.65%), pancreatic (25.0%), and lung cancers (24.8%). Patients with ≥5 visits had a 25% mortality rate.

Conclusions: Cancer patients frequently visit emergency services and anorexia-cachexia, altered mental status, shortness of breath, fever and abdominal pain increase the hospitalization risks. Recurrent visits (≥5) have higher mortality, highlighting the need for better palliative care integration and strategies to reduce emergency dependence for this vulnerable population.

Keywords: Cancer, Emergency Department, Mortality, Palliative Care

ÖZ

Amaç: Kanser hastaları, hastalıkları veya tedavileriyle ilişkili akut komplikasyonlar nedeniyle sıklıkla acil servislere başvurmaktadır. Başvuru paternlerinin ve olumsuz sonuçları öngören faktörlerin belirlenmesi, bakım kalitesini iyileştirmek ve acil başvurularını azaltmak için hedefe yönelik palyatif çözümlere rehberlik edebilir.

Gereç ve Yöntem: Bu retrospektif kohort çalışması, üçüncü basamak bir hastanede Acil service başvuran aktif kanserli 753 hastayı kapsamaktadır. Demografik veriler, klinik başvurular, yatış oranları ve mortalite verileri incelenmiştir. Hastaneye yatış ve mortalite ilişkili semptomları belirlemek için regresyon analizi yapılmış ve başvuru sıklığına göre mortalite oranları ayrıca değerlendirilmiştir.

Bulgular: Bulgular: Toplam 753 hastanın 1609 başvurusu incelenmiştir. En sık görülen kanser türleri gastrointestinal (%36,5) ve solunum sistemi kanserleri (%20,7) olup, en yaygın semptomlar karın ağrısı (%18,15) ve bulantı/kusma (%18,09) olarak belirlenmiştir. Başvuruların %34,6'sı yatış ile sonuçlanmış olup Anoreksi-kaşeksi (OR=3.84, 95% CI: 2.18–6.77, p<.001), bilinç değişikliği (OR=3.14, 95% CI: 1.81–5.44, p<.001), nefes darlığı (OR=2.15, 95% CI: 1.52–3.03, p<.001), ateş (OR=1.86, 95% CI: 1.40–2.48, p<.001) ve karın ağrısı (OR=1.61, 95% CI: 1.22–2.12, p<.001) yatış için anlamlı prodüktörlerdir. İki yıllık mortalite oranı %20,19 olup, en yüksek oran gastrik (%32,65), pankreatik (%25,0) ve akciğer (%24,8) kanserlerinde saptanmıştır. Beşten fazla başvurusu olan hastaların mortalitesi %25 saptanmıştır.

Sonuç: Sonuç: Kanser hastaları sıkça acil servise başvurmakta olup, anoreksi-kaşeksi, bilinç değişikliği, nefes darlığı, ateş ve karın ağrısı hastaneye yatış riskini artırmaktadır. Beş ve üzeri tekrar eden acil servis başvuruları, daha yüksek mortalite oranları ile ilişkilidir. Bu durum, palyatif bakımın iyileştirilmesi ve bu hassas popülasyonda acil servise bağımlılığı azaltmaya yönelik stratejilerin acilen gerekliliğini vurgulamaktadır

Anahtar kelimeler: Kanser, Acil Servis, Mortalite, Palyatif Bakım

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Highlights

- *High Emergency Department Utilization by Cancer Patients:* 30% of cancer patients visit the ED during treatment, with frequent visits linked to disease progression.
- *Key Predictors of Hospitalization Identified:* Symptoms such as anorexia-cachexia, altered mental status, shortness of breath, fever, and abdominal pain significantly increase hospitalization risk.
- *Frequent ED Visits Linked to Mortality:* Patients with five or more ED visits face a 25% two-year mortality rate, underscoring the need for early interventions.

Introduction

Up to 30% of cancer patients may visit the Emergency Department (ED) at least once during their treatment course (1–3). Cancer incidence and cancer caused by mortality are rising due to prolonged life expectancy and enhanced diagnostic capabilities. For many patients the ED is the point of attention for the assessment and treatment of acute problems related to cancer or its therapies (1–3).

However, ED's have some limitations in providing comprehensive oncology care which leads to increased length of stay, poor symptom control and avoidable admissions.

The most frequent complaints observed in the ED among patients with cancer are nausea and vomiting, abdominal pain, dyspnea, and fatigue (4–6). These symptoms require a lot of diagnostic testing, and the patients may require intervention on an urgent basis. The frequency of ED visits has been associated with disease progression as well as worse outcomes including higher mortality rates (7,8).

Research evidence has pointed out that the implementation of palliative care and the establishment of coordinated outpatient oncology services can decrease the frequency of visits to the ED and produce better patient-oriented results (9–12). Nevertheless, many healthcare organizations do not have the necessary structure to provide palliative specific care.

Our study aimed to fill the gap in current research regarding ED utilization by specific cancer subtypes by describing patterns of ED utilization, identify common presenting symptoms, and determine predictors of hospitalization and mortality among patients with active cancer. These insights may guide strategies to optimize oncology care, enhance symptom management, and reduce the burden on emergency services and improve outcomes of this vulnerable population.

Material and Methods

Study Design and Setting: This study was designed as a single-center, retrospective cohort study and was conducted at a tertiary care university hospital ED. Used records from January 2016 to January 2018. The hospital had a comprehensive cancer center and is one of the largest cancer hospitals that receive about 34,000 ED visits on an annual basis. In this study, STROBE guidelines for observational research were followed.

Participants: Inclusion criteria were adults (≥18 years) with active cancer (receiving chemotherapy, palliative intent, or documented recurrence), who visited the ED with cancer-related problems. Exclusion criteria included patients in remission or those presenting to the hospital due to trauma or any other visits that were not related to cancer. We excluded patients with incomplete records, which included missing demographic or outcome data. Patients were identified using ICD-10 code (C34 for lung cancer, C50 for breast cancer, C18 for colon cancer etc.) documented in the hospital's electronic health system.

Data Collection: Two experienced ED nurses, who are familiar with the process of abstraction of data, re-viewed the records. The data collected included the patients' demographic data, cancer diagnosis, symptoms presented at the ED, diagnostic investigations, and management in the ED, hospital admission and mortality. Mortality was established through the patients' charts and phone contact made six months after the end of the study. The data includes 1609 ED visits made by 753 patients.

Variables: We collected the following variables: patient characteristics (such as age, gender, cancer type, symptoms at presentation), diagnostic investigations (laboratory tests and imaging), treatments (fluids, analgesics, and transfusions), hospital admission and mortality. The symptoms were classified according to the organ system affected while the diagnostic investigations included the standard laboratory and imaging procedures.

Ethics: This Study approval was obtained from the Koc University Hospital Faculty of Medicine, Non-Interventional Clinical Research Ethics Committee (Approval No. 2021.176. IRB1.060 date: 24.03.2021). As this was a retrospective study, patient data were reviewed in compliance with institutional regulations and national

data protection laws. Only data from patients who had provided informed consent for the use of their information and communication permissions during hospital admission were included. We ensured the patient's confidentiality and followed the principles of the Declaration of Helsinki.

Statistical analyses

We used descriptive statistics to summarize demographic and clinical characteristics. Continuous variables were tested for normality using the Shapiro-Wilk test and presented as mean ± SD for normally distributed data or median with interquartile range (IQR) for non-normally distributed data. Variance homogeneity was assessed using Levene's test. Categorical variables expressed as frequencies and percentages. To identify predictors of hospitalization, we performed logistic regression analysis. Variables with a p-value <0.10 in the statistical analysis were included in a multivariate logistic regression model to control potential confounders. Results of the regression analysis are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Given the binary nature of the dependent variable (hospitalization: yes/no), binary logistic regression was applied. We considered p<0.05 significant. Analyses were conducted using SPSS version 20.0 (IBM Corp., Armonk, NY).

Results:

Patient Characteristics: A total of 753 patients made 1,609 ED visits. The mean age was 62 ± 14 years (range: 19–94), and the gender distribution was balanced (49.3% male, 50.7% female). Gastrointestinal cancers were most common (36.5%), followed by respiratory (20.7%), hematopoietic/lymphatic (12.4%), genitourinary (11.0%), and gynecologic (5.0%) malignancies. Lung, colon, and pancreatic cancers were frequent diagnoses (Table 1).

Number of Hospitalizations and Discharges by Cancer Type: Of the 1,609 ED visits, lung cancer alone was seen to be the most common (19.9%), and 31.2% of these visits ended up being hospitalized. Colon cancer (30.1%) and pancreatic (38.9%) cancer also had high rates of hospitalization, respectively. Although colon cancer accounted for only 10.9% of visits while pancreatic cancer was 10.1%. However, gastric cancer had almost half (48.5%) of the visits resulting in hospitalization. On the other hand, all the testis cancer patients were discharged without being admitted.

Thus, 65.4% of patients (n= 1,052) were discharged and 34.6% of patients (n=557) were hospitalized **(Table 1)**.

Presenting Symptoms: The most frequent symptom was abdominal pain (18.2%), followed by nausea/vomiting (18.1%), fever (15.9%), malaise/fatigue (15.7%), and shortness of breath (9.8%). Other less common symptoms were diarrhea, cough, altered mental status, anorexia-cachexia and chest pain **(Table 2)**. The analysis of ED revisit rates based on presenting symptoms highlights specific predictors of repeated visits. Patients presenting with abdominal distention and dizziness demonstrated the highest revisit rates (1.91 each), followed by abdominal pain (1.9), nausea and vomiting (1.9) and fever (1.9).

Predictors of Hospitalization: Of the 1609 visits 34.6% (n= 557) resulted in hospitalization. Anorexia-cachexia, altered mental status, shortness of breath, fever and abdominal pain symptoms were found to be significantly higher in hospitalized patients (p<0.001, for all). Anorexia-cachexia (OR=3.84, 95% CI: 2.18–6.77, p: < 0.001), altered mental status (OR=3.14, 95% CI: 1.81–5.44, p: <0.001), shortness of breath (OR=2.15, 95% CI: 1.52–3.03, p: < 0.001), fever (OR=1.86, 95% CI: 1.40–2.48, p: < 0.001) and abdominal pain (OR=1.61, 95% CI: 1.22–2.12, p: < 0.001) were identified as significant predictors by the multivariate logistic regression analysis respectively **(Table 3)** .

Admission Trends: The attendance at ED was seen to have spikes at certain times of the day between 10:00 to 18:00 and between 20:00 to 23:00. Patients waited for an average of 136 ± 67.8 minutes. Of these, 40.4% visited the ED more than once and 11.3% visited the ED five or more times **(Figure 1).**

Mortality: We calculate the two-year mortality as 20.19%. The highest mortality was observed in gastric cancers (n=16, 32.65%), the next being pancreatic cancers (n=16, 25.0%) and lung cancers (n=36, 24.8%) the other cancers mortality rate was (n=84, 18%). Of the patients who visited the ED more than five times, mortality was 25% while 2% of the patients who visited once **(Figure 2)**.

Diagnostic and Treatment Patterns: Common investigations included complete blood counts (83.4%), biochemistry tests (81.9%), and coagulation profiles (21.9%). Imaging studies, such as X-rays (27.5%) USG's (%24.7) and Computed Tomography (15.4%), were frequently performed. Interventions included fluid therapy (36.4%) and analgesics (25.9%); blood transfusions were rare (1.9%).

Table 1: Cancer Types, Gender, and Age Distribution of Patients

Cancer Types	Patients* (n, %)	Male* (n, %)	Female* (n, %)	Age (Mean ±SD)	Discharge** (n, %)	Hospitalization** (n, %)	Total Visits** (n, %)
Lung Cancers[1]	145 (19.3)	79 (54.5)	66 (45.5)	64 ± 6	220 (20.9)	100 (18.0)	320 19.9)
Colon Cancers[2]	75 (10.0)	39 (52.0)	36 (48.0)	63 ± 6	123 (11.7)	53 (9.5)	176(10.9)
Pancreas Cancers[2]	64 (8.5)	33 (51.6)	31 (48.4)	62 ± 6	99 (9.4)	63 (11.3)	162 10.1)
Lymphoma[3]	56 (7.4)	29 (51.8)	27 (48.2)	61 ± 6	82 (7.8)	35 (6.3)	117 (7.3)
Gastric Cancers[2]	49 (6.5)	24 (49.0)	25 (51.0)	65 ± 6	51 (4.8)	48 (8.6)	99 (6.2)
Breast Cancers	48 (6.4)	0 (0.0)	48 (100.0)	55 ± 5	61 (5.8)	21 (3.8)	82 (5.1)
Rectum Cancers[2]	41 (5.4)	20 (48.8)	21 (51.2)	58 ± 5	61 (5.8)	25 (4.5)	86 (5.3)
Prostate Cancers[5]	33 (4.4)	33(100.0)	0 (0.0)	72 ± 7	44 (4.2)	22 (3.9)	66 (4.1)
Brain Cancers	23 (3.1)	11 (47.8)	12 (52.2)	62 ± 6	42 (4.0)	21 (3.8)	63 (3.9)
Bladder Cancers[5]	27 (3.6)	15 (55.6)	12 (44.4)	64 ± 6	23 (2.2)	31 (5.6)	54 (3.4)
Liver Cancers[2]	26 (3.5)	14 (53.8)	12 (46.2)	63 ± 6	33 (3.1)	13 (2.3)	46 (2.9)
Leukemia[3]	23 (3.1)	13 (56.5)	10 (43.5)	60 ± 6	22 (2.1)	14 (2.5)	36 (2.2)
Connective Tissue Cancers	22 (2.9)	12 (54.5)	10 (45.5)	59 ± 5	24 (2.3)	18 (3.2)	42 (2.6)
Ovarian Cancers[4]	18 (2.4)	0 (0.0)	18 (100.0)	58 ± 5	30 (2.9)	16 (2.9)	46 (2.9)
Kidney Cancers[5]	14 (1.9)	9 (64.3)	5 (35.7)	65 ± 6	19 (1.8)	15 (2.7)	34 (2.1)
Thyroid Cancers	14 (1.9)	2 (14.3)	12 (85.7)	56 ± 5	22 (2.1)	2 (0.4)	24 (1.5)
Multiple Myeloma[3]	14 (1.9)	9 (64.3)	5 (35.7)	62 ± 6	12 (1.1)	10 (1.8)	22 (1.4)
Cervix Uteri Cancers[4]	12 (1.6)	0 (0.0)	12 (100.0)	55 ± 5	16 (1.5)	7 (1.3)	23 (1.4)
Throat Cancers[1]	10 (1.3)	6 (60.0)	4 (40.0)	63 ± 6	10 (1.0)	6 (1.1)	16 (1.0)
Testis Cancer[5]	9 (1.2)	9 (100.0)	0 (0.0)	28 ± 2	16 (1.5)	0 (0.0)	16 (1.0)
Esophagus Cancers[2]	8 (1.1)	4 (50.0)	4(50.0)	62 ± 6	10 (1.0)	12 (2.2)	22 (1.4)
Endometrial Cancers[4]	8 (1.1)	0(0.0)	8 (100.0)	59 ± 5	11 (1.0)	4 (0.7)	15 (0.9)
Gall Bladder Cancers[2]	6 (0.8)	4 (66.7)	2 (33.3)	61 ± 6	12 (1.1)	6 (1.1)	18 (1.1)
Biliary Tract Cancers[2]	6 (0.8)	4 (66.7)	2 (33.3)	61 ± 6	8 (0.8)	12 (2.2)	20 (1.2)
Adrenal Cancers	1 (0.1)	1 (100.0)	0 (0.0)	57 ± 0	1 (0.1)	2 (0.4)	3 (0.2)
Larynx Cancers[1]	1 (0.1)	1 (100.0)	0 (0.0)	58 ± 0	0 (0.0)	1 (0.2)	1 (0.1)
Total	753(100.0)	371(49.3)	382 (50.7)	62 ± 14	1052 (100.0)	557 (100.0)	1609(100)

Abbreviations:*Percentages are based on patients (n = 753),** Percentages are based on emergency department visits (n = 1609),[1]Respiratory system cancers (Lung, Throat, Larynx): 20.7%,[2]Gastrointestinal cancers (colon, pancreas, gastric, rectum, liver, gall bladder, and biliary tract cancers): 36.5%,[3]Hematopoietic and Lymphatic System (Lymphoma, Leukemia, Multiple Myeloma): 12.4%,[4]Gynecologic cancers (Ovarian, Cervix uteri, Endometrial cancer): 5.04%,[5]Genitourinary Cancers (Prostate Cancers, Bladder Cancers, Kidney Cancers, Testis Cancer): 11.02%

Table 2: Most Frequent Symptoms Reported According to Admissions

Symptoms	n, (%)*	Symptoms	n, (%)*
Abdominal Pain	292 (18.15)	Thrombophlebitis	26(1.62)
Nausea or vomiting	291 (18.09)	Urine Retention	22(1.37)
Fever	255 (15.85)	Hypertension	18(1.12)
Malaise and fatigue	252 (15.66)	Hematuria	15(0.93)
Shortness of breath	158 (9.82)	Hemoptysis	12(0.75)
Diarrhea	83(5.16)	Hyperglycemia	9(0.56)
Cough	65(4.04)	Hypotension	8(0.50)
Altered Mental Status	63(3.92)	Drug overdose	5(0.31)

Anorexia and Cachexia	61(3.79)	**Anxiety**	2(0.12)
Chest Pain	61(3.79)	**Fall**	38(2.36)
Ascites	60(3.73)	**Palpitation**	35(2.18)
Constipation	45 (2.80)	**Syncope**	26(1.62)
Loss of Appetite	42(2.61)	**Dizziness**	41(2.55)
Gastrointestinal hemorrhage	33(2.05)	**Headache**	40(2.49)

Abbreviations: **Percentages are based on emergency department visits (n = 1609).*

Table 3: Predictors of Hospitalization

Symptoms	OR (95% CI)	p
Anorexia-Cachexia	3.84 (2.18–6.77)	<0 .001
Altered Mental Status	3.14 (1.81–5.44)	<0 .001
Shortness of Breath	2.15 (1.52–3.03)	<0 .001
Fever	1.86 (1.40–2.48)	< 0.001
Abdominal Pain	1.61 (1.22–2.12)	<0 .001
Nausea/Vomiting	1.25 (0.95–1.65)	0.095
Diarrhea	1.10 (0.88–1.37)	0.216
Dizziness	0.95 (0.72–1.26)	0.356
Cough	0.85 (0.66–1.09)	0.452
Chest Pain	0.82 (0.64–1.06)	0.483
Weakness	0.78 (0.60–1.01)	0.510
Back Pain	0.75 (0.58–0.97)	0.618
Palpitations	0.70 (0.54–0.91)	0.658
Hemoptysis	0.68 (0.52–0.89)	0.702

Abbreviations: *OR: Odds Ratio CI: Confidence Interval*

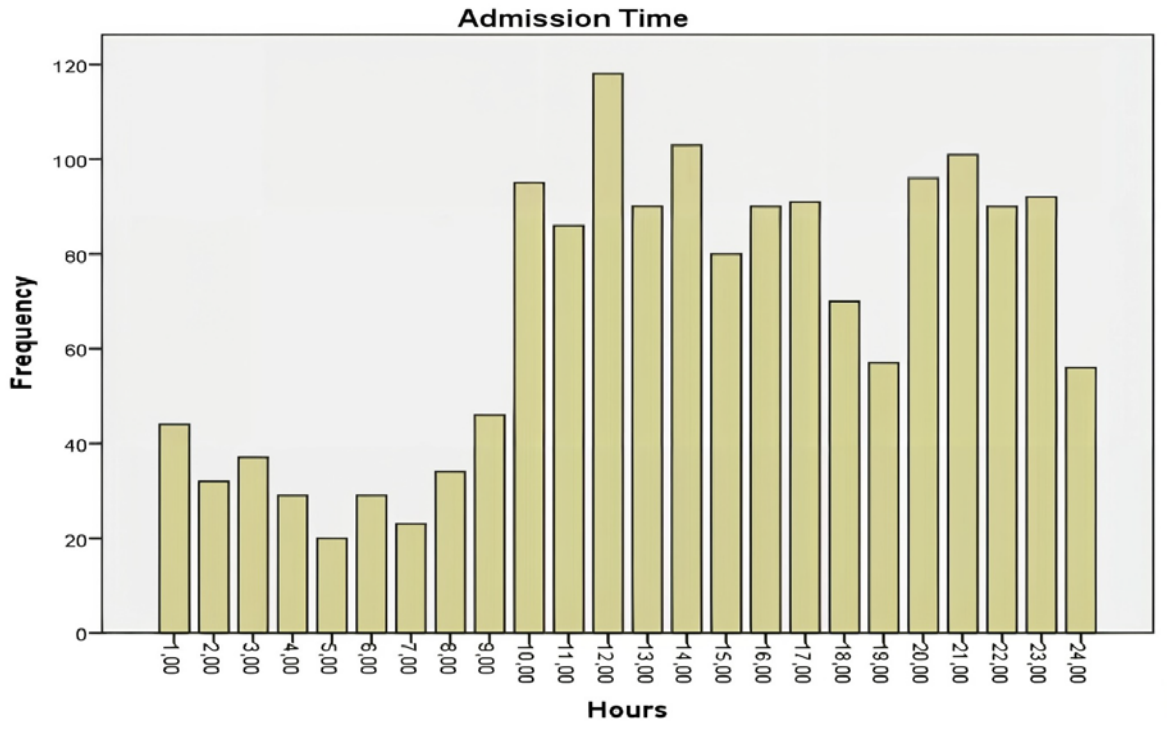

Figure 1. Admission Trends

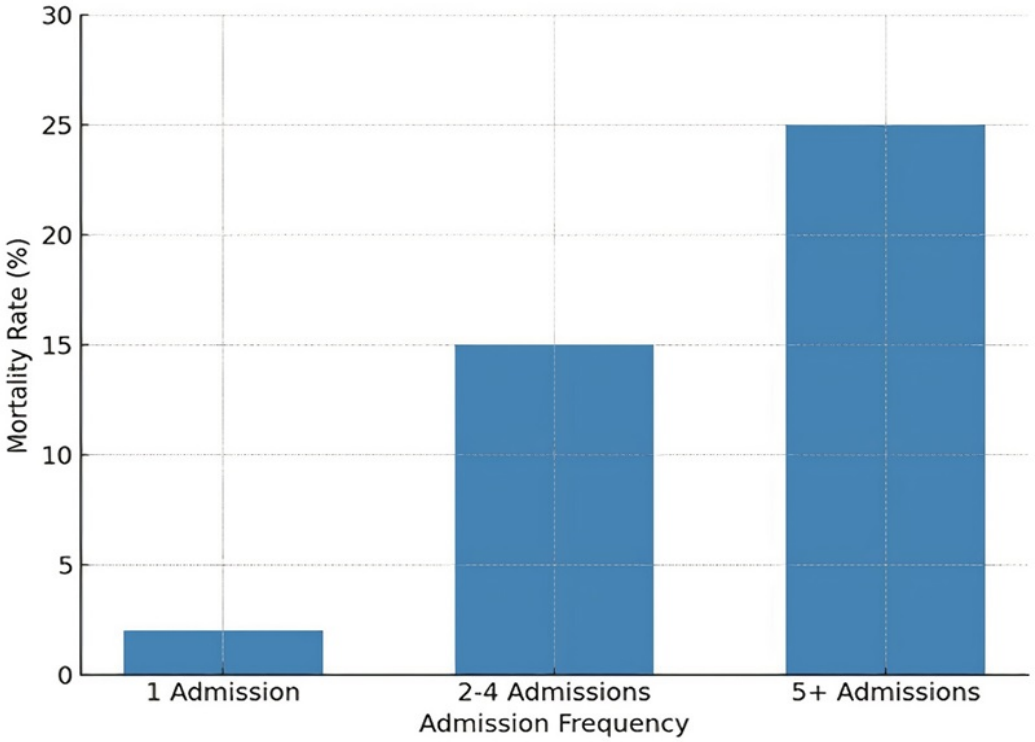

Figure 2. Mortality rate by Admission counts

Discussion

Our study also supports the fact that cancer patients constitute a heavy burden on the EDs due to high revisit rates, frequent admissions and high mortality. These patterns indicate late-stage disease, complex symptoms and poor coordination of care in the outpatient setting. Specifically, some of the high-risk presentations, for instance anorexia-cachexia or altered mental status were found to predict both hospitalization and mortality.

Even more, the frequent ED utilization (at least 5 visits) was associated with significantly higher mortality, which supports the importance of early inpatient admission and multimodal palliative care. Our results concur with the existing literature that frequent ED visits near the end of life indicate suboptimal community support (2,3,7,13). Thus, well-directed, proactive interventions targeting patients with gastric, lung or pancreatic cancer are necessary to prevent acute events, decrease the load on the ED, and enhance the outcomes of the patients.

Emergency Department Utilization: The findings from our study demonstrate that a large proportion of patients with cancer visit the ED highlight with existing literature that has established enhanced acute care utilization due to severe symptoms, treatment related toxicity and disease progression (4–6,14).The graph of visits and the peaks seen during late morning and early evening hours are in conformity with the findings of Barbera et al. which highlights the fact that both patient and institutional factors are key in determining the ED utilization patterns (3). Our findings also support the need to vary the attendance of the staff and resources to meet the challenges of increased patient throughput.

Symptom Profiles and Predictors of Hospitalization: As in prior research, the symptoms reported included nausea, abdominal pain, and fatigue as the common symptoms observed among the patients (8,15). Thus, symptoms such as anorexia-cachexia and altered mental status were identified as the major factors that are associated with increased risk of hospitalization, which in turn leads to early mortality, as in the literature reported before (12,16). In our research, we identified the factors that include shortness of breath and fever as the predictors of the outcome may be indicative of other conditions such as infections, respiratory complications or worsening of the disease (17). If these symptom clusters are recognized at an early stage, then this may allow for appropriate management and possibly minimize the need for admission. Elevated revisit rates for symptoms such as abdominal distention, dizziness,

abdominal pain, nausea, vomiting, and fever underscore the necessity for targeted interventions during initial emergency department evaluations. These symptoms may indicate complex underlying conditions that, if not thoroughly addressed, could lead to repeat visits. Future research should focus on identifying the etiologies and developing effective management strategies for these high-risk presentations.

Cancer-Specific Trends: Of the cancer types considered, lung, pancreatic and colon cancers were the most frequent and accounted for the highest rates of ED visit and hospitalization. These results are consistent with prior research, which has connected lung cancer to late-stage disease, severe symptoms and frequent acute on chronic admissions (3,4). Pancreatic cancers which also characterized by severe pain and gastrointestinal distress at late stages of the disease leading to high admission rates (6). On the other hand, cancers which are generally less aggressive and therefore may not cause much distress such as testicular and thyroid cancers, were rarely hospitalized (8). Thus, such differences are an emphasis on the need for cancer care pathways and the triage that can identify those at high risk of clinical worsening.

Mortality and Frequent Admissions: The observed two-year mortality rate was 20.2% as well as its correlation with the frequent ED visits are consistent with previous research that has demonstrated that frequent presentations are a marker of worsening disease, inadequate community support or unmet palliative requirements (13,18,19). Thus, the results of the study revealed that patients who visited the ED at least five times had a high mortality rate, which emphasizes the importance of intensive and comprehensive management at the onset of the disease. With the integration of palliative care into oncology which has been seen to lower the rates of ED visit and enhance the quality of life through home based and outpatient palliative care programs, it could reduce the acute presentations (8,12,20,21).

Diagnostic and Treatment Patterns: Our findings on diagnostic and treatment practices are in conformity with the usual practice in the ED when dealing with a patient with cancer and acute problems. The use of laboratory investigations and imaging in the assessment of the patient's clinical state is therefore quite frequent as seen in literature too (22,23). The use of fluids and analgesics is understandable given that this is a very symptomatic population. Transfusion rates were lower than reported in literature before. This may be due to varying local practice, patient characteristics, or disease severity or pathways that restrict giving transfusions in ED (6). Further research may be done to examine the effects of using standardized plans for management of cancer patients in the emergency department with an aim of enhancing diagnostic value and symptom control.

Implications for Practice: Based on these findings, health systems should emphasize the early incorporation of palliative care and supportive care services as an integral part of the oncology care to minimize the dependence on the ED, enhance symptom control could improve the outcome as reported in existing literature (20,24). Especially, it is crucial to identify effective intervention for such high-risk patients as gastric cancer, lung cancer, pancreatic cancer, and symptoms such anorexia-cachexia, altered mental status, shortness of breath, fever and abdominal pain to avoid hospitalization and death. Furthermore, those patients who are likely to present at the ED frequently are at high risk of mortality and this emphasizes the need for early admission and prompt instituting of palliative measures for this vulnerable population.

Study limitations

Limitations and Future Directions: The use of a single center and retrospective cohort design may pose some limitations to the external validity of the study. Further investigation should be carried out into larger cohorts and in more than one center to validate our findings and assess the effects of interventions meant to decrease the dependence on the ED. Research on the possible palliative care delivery modals, specialized triage tools and telemedicine-based follow-up may help in identifying the best ways to manage such high-risk patients.

Conclusion

Our study demonstrates that frequent admissions to the ED by patients with cancer are often associated with late-stage disease, high symptom burden or inadequate community management. The results reveal that high-risk presentations which include anorexia-cachexia, altered mental status, shortness of breath, fever and abdominal pain or frequent ED admissions are associated with high hospitalization. Patients with ≥5 ED visits had a 25% mortality rate. Establishing effective follow-up and treatment protocols for cancer patients presenting to the emergency department may be effective in reducing emergency department visits and hospitalizations for these patients.

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Original Article

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In Vitro Investigation of the Effect of Mouthwashes on Fertility Tests

Ağız Çalkalama Solüsyonlarının Doğurganlık Testleri Üzerindeki Etkisinin İn Vitro Değerlendirilmesi

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Abstract

Background: Mouthwashes are not devoid of side effects like other drugs and may affect the clinical outcomes of the patients. The aim of this study is to experimentally investigate the interference effect of mouthwashes containing different chemical components on fertility tests.

Materials and Methods: A (BisBiguanide), CH (QuaternaryAmmonium), L (EssentialOils), CO (QuaternaryAmmonium), and M (StannousFloride) were added (20 µL) to the N Protein Control SL/Low (180 µL) control solution. Samples were studied in immunoassay autoanalyzer. The same process was done by adding distilled water (20 µL) to the control solution.

Results: The bias formula was used to calculate how much the obtained results deviated from the target value. No test showed negative interference exceeding 10% in any mouthwash. The TESTO test had positive interference at a rate of 36.85% in CH. Interference was observed in the DHEAS test at a rate of 23.73% in A and 18.97% in CO. This was followed by Estradiol with 14.92%, Beta HCG with 12.82% in A and DHEAS with 11.45% in M.

Conclusions: This study has shown that the interaction potential of commercial kits with mouthwash solution contents may cause erroneous measurements in terms of hormone test results. Chlorhexidine should be prescribed with careful questioning. Essential oils seem to be safer than other mouthwashes in terms of interference.

Keywords: mouthwashes, interference, bias, fertility tests, immunoassay autoanalyzer, deviations

ÖZ

Amaç: Ağız gargaraları diğer ilaçlar gibi yan etkilerden yoksun değildir ve hastaların klinik sonuçlarını etkileyebilir. Bu çalışmanın amacı farklı kimyasal bileşenler içeren ağız gargaralarının doğurganlık testleri üzerindeki interferans etkisini deneysel olarak araştırmaktır.

Gereç ve Yöntem: A (BisBiguanide), CH (QuaternaryAmmonium), L (EssentialOils), CO (QuaternaryAmmonium), and M (StannousFloride) N Protein Control SL/Low (180 µL) kontrol solüsyonuna eklendi (20 µL). Örnekler immunoassay otoanalizöründe incelendi. Aynı işlem kontrol solüsyonuna distile su (20 µL) eklenerek yapıldı.

Bulgular: Elde edilen sonuçların hedef değerden ne kadar saptığını hesaplamak için bias formülü kullanıldı. Hiçbir test herhangi bir ağız gargarasında %10'u aşan negatif interferans göstermedi. TESTO testi CH'de %36,85 oranında pozitif interferansa sahipti. DHEAS testinde A'da %23,73 ve CO'da %18,97 oranında interferans gözlendi. Bunu A'da %14,92 ile Estradiol, %12,82 ile Beta HCG ve M'de %11,45 ile DHEAS izledi.

Sonuç: Bu çalışma, ticari kitlerin gargara solüsyonu içerikleriyle etkileşim potansiyelinin hormon test sonuçlarında hatalı ölçümlere neden olabileceğini göstermiştir. Klorheksidin dikkatli sorgulama ile reçete edilmelidir. Esansiyel yağlar, interferans açısından diğer gargaralardan daha güvenli görünmektedir.

Anahtar kelimeler: gargaralar, interferans, bias, doğurganlık testleri, immunoassay otoanalizörü, sapmalar.

Highlights

- The interference effect of mouthwashes should not be ignored in the evaluation of test results.
- The test that shows the most bias from the target value is DHEAS, and the mouthwash that causes the most bias is Bis Biguanide Antiseptic.
- Essential oil components seem to be safer than other mouthwashes in terms of interference.

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Introduction

Mouthwash are medicated liquid held in the mouth by the movements of the perioral muscles to eliminate oral pathogens (1). In the 1960s, Harald Loe showed that the chlorhexidine (CHX) compound could prevent the formation of dental plaque (2). Today, it is well documented that CHX is not devoid of side effects like other drugs such as increased staining of teeth and taste disturbance in long-term use (3). Recently, many herbal-containing mouthwashes on the market have been subjected to extensive research for their potential to prevent oral diseases. These mouthwashes have been claimed to be effective in reducing and preventing the formation of bacterial dental plaque, tooth decay and bad breath (1,4). The use of natural antimicrobials can contribute to controlling the erratic growth of the oral microbiota and overcoming the problems caused by strains resistant to conventional antimicrobial agents (5,6). The current situation supports the use of CHX, which still complies with the standards and can be labeled as the 'gold standard' (7).

Drug-drug interactions are very common during dental treatments. Drug interaction is defined as the change of the effect of one drug by another drug and may affect the clinical outcomes of the patients (8). This interaction is a situation that clinicians can predict and be aware of, and there are many studies on this subject (9). Also, low-level exposure to CHX may cause cross-resistances to antibiotics. Moreover, some mechanisms that allow CHX resistance in bacterial organisms include mutations in efflux pumps and cell membrane structure. It has been shown to have adverse effects on human tissues as well as multidrug resistance (6,7). Another condition that may indirectly affect the clinics of patients is 'interference'. Drug interference may develop due to metabolites or additives of a drug (10).

There is not enough data on how much mouthwashes and mouth rinse solutions prescribed during or after dental treatments interfere with laboratory parameters with diagnostic and prognostic importance and whether they affect the test results and cause false results. Interference is defined as "the effect of a substance in the sample that alters the true value of the result, usually expressed as concentration or activity for the analyte" (11) and there is no guidance on which drug affects which test. This lack of knowledge may even lead to incorrect test measurements and related malpractice in the therapeutic use of mouthwashes. Demonstrating and publishing possible errors before they occur will guide clinicians.

Most of the hormones evaluated in fertility tests are determined using immunoanalytical methods (12). Interference in analyzing using the immunoassay method is a serious problem that many clinicians are not aware of or even unknown (13). Since the kits in which the immunoassay method is used contain complex biological reagents (especially immunoglobulins), they are sensitive to different types of interference with other complex molecules during measurement. Immunoglobulins can also cause false positives or false negatives in test results by competing with enzyme-labeled immunoglobulins in the reagents of the immunoassay method or by forming an immunocomplex (14,15). Interference can thus obscure accurate test results, leading to unnecessary clinical investigations and inappropriate therapy for the patient. The focus of this study is to experimentally investigate the interference effect of mouthwashes containing different chemical components on fertility tests.

Material and Methods

Study design

"N Protein Control SL/Low (Siemens, Marburg, Germany, lot: 084654)" control solution was used in the study. The solutions obtained by adding BisBiguanide (A), QuaternaryAmmonium (CH and CO), EssentialOils (L), and StannousFloride (M) (20 µL) containing mouthwashes to 180 µL control solution were mixed with vortex for 5 seconds before the study. Obtained samples were studied in e601 (Roche, Germany) fully automatic immunoassay autoanalyzer. To determine the target value, the same process was done by adding distilled water (20 µL) to the control solution, and all measurements were repeated 3 times, and the average values were taken into account. The bias formula was used to calculate how much the obtained results deviated from the target value (16). Since this study was an experimental study that did not use any blood or tissue samples, it does not require ethics committee approval.

Statistical analyses

Statistical analysis was calculated with Microsoft Office Excel Program. In the Bias (%) formula used when calculating the deviation rates from the target value, C1 refers to the measurement result made from the distilled water mixture, and C2 refers to the measurement result prepared with the antibody. Bias (%) = ((C2-C1)/C1)x100. Negative deviation indicates false negative, positive deviation indicates false positive. The size of the percent

value indicates the amount of deviation and thus the severity of the interference.

Results

Mouthwashes are evaluated as different groups such as their mechanism of action, ingredients, chemical structures and usage area. The content, category, active ingredient and letter code given to the mouthwash are shown in **Table 1.** The deviations of five different mouthwashes from the target value were calculated. As a result, interference rates below 10% were considered normal **(Table 2), (Figure 1)**.

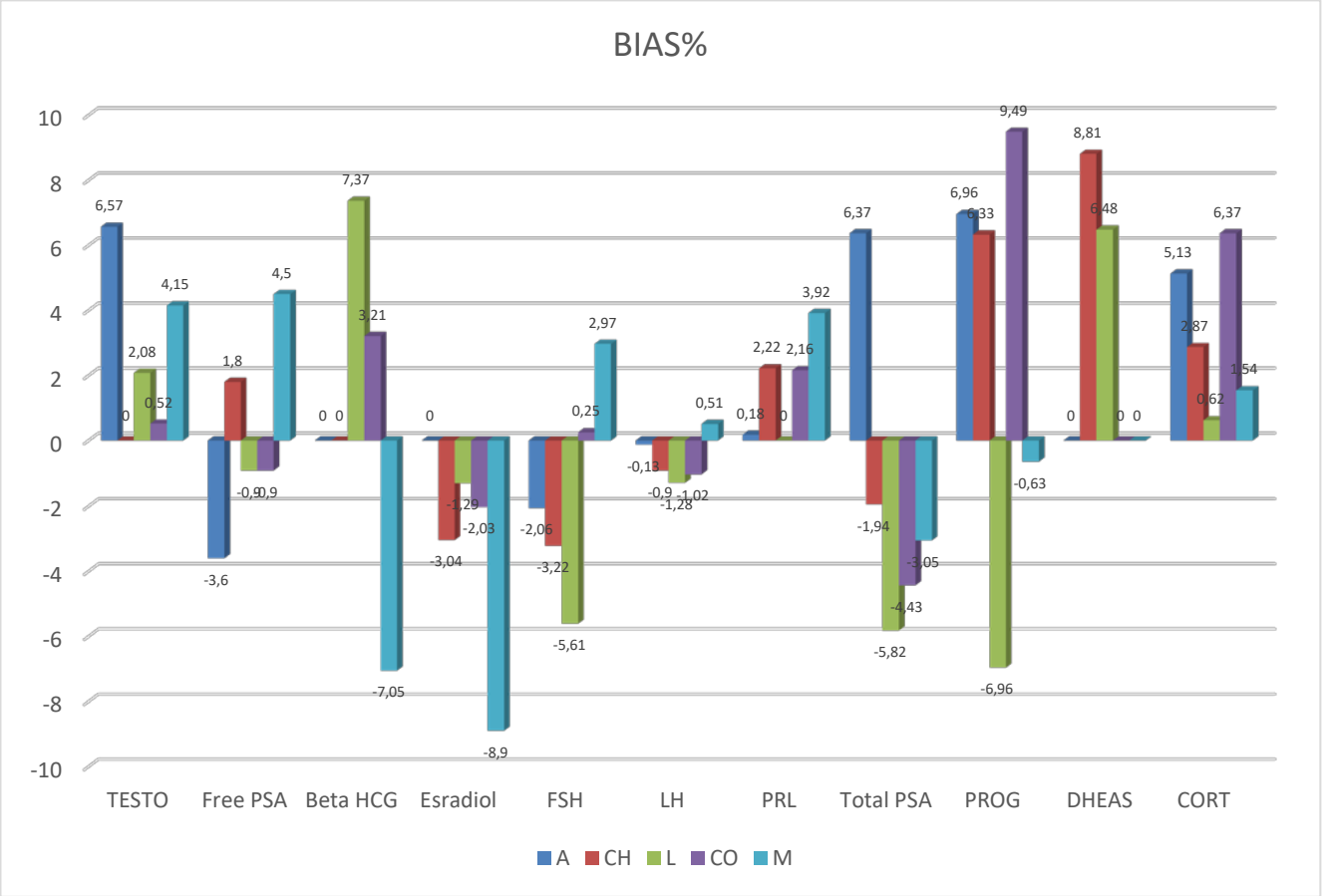

Figure 1. Percentage deviations from target value (%BIAS)

Tests with negative interference

Free prostate specific antigen (Free PSA) and follicle stimulating hormone (FSH) in An exposure; Estradiol, FSH, luteinizing hormone (LH), Total PSA in CH exposure; Free PSA, Estradiol, FSH, LH, Total PSA, Progesterone (PROG) in L exposure; Free PSA, Estradiol, LH, Total PSA in CO exposure; Beta human chorionic gonadotropin (Beta HCG), Estradiol, Total PSA, PROG showed negative interference in M exposure.

Among all tests, the most negative interference occurred in the Estradiol test with -8.90% in M exposure. This was followed by Beta-HCG with -7.05% in M exposure. No test showed negative interference exceeding 10% in any mouthwash.

Tests with positive interference

The Testosterone (TESTO) test had the highest bias (36.85%) with positive interference in CH exposure. The deviation of the Dehydroepiandrosterone sulfate (DHEAS) test, which showed positive interference was 23.73% in an exposure and 18.97% in CO exposure. This was followed by Estradiol with 14.92% and Beta HCG with 12.82% in an exposure. And DHEAS with 11.45% in M exposure.

Table 1. Product code, category and ingredients

Product Code (antiseptic, antiplaque mouthwashes)	Product Category	Content (active ingredients)	Content (Inactive Ingredients)
A	Bis Biguanide Antiseptics	0.15% Benzydamine Hydrochloride, 0.12% Chlorhexidine Gluconate	Mint Flavor, Sorbitol (E420), Patent Blue V, Glycerol, Polysorbate 20, Tartrazine (E102), Ethanol, Water
CH	Quaternary Ammonium Compounds	0.075% Cetylpyridinium Chloride	Aqua, Glycerin, Propylene Glycol, Sorbitol, Tetrapotassium Pyrophosphate, Polysorbate 20, Tetrasodium Pyrophosphate, Zinc Citrate, PVM/MA Copolymer, Aroma, Benzyl Alcohol, SodiumFluoride, Sodium Saccharin, Bambusa Vulgaris Shoot Extract, 15510, Charcoal Powder, CI 15510, CI 17200, CI 19140, CI 42051.
CO	Quaternary Ammonium Compounds	0.075% Cetylpyridinium Chloride	Aqua, Glycerin, Propylene Glycol, Sorbitol, Poloxamer 407, Aroma, Cetylpyridinium Chloride, Potassium Sorbate, Sodium Fluoride, Menthol, Sodium Saccharin, Cl 42051.
L	Phenol And Essential Oils	Essential Oils (Thymol, Eucalyptol, Menthol, Methyl Salicylate)	Zinc Chloride, Fluoride, Mint Flavor
M	Short-Acting Agents Containing Stannous Floride	Olaflur (Aminfluoride) and Stannous Floride, Fluoride Content 250 ppm	Aqua, Xylitol, Polyvinylpyrrolidone (PVP), Polyethylene Glycol (PEG-4) Hydrogenated Castor Oil, Olaflur, Aroma, Stannous Fluoride, Sodium Saccharin, CI 42051.

Tablo 2. Percentage of deviations from target value (BIAS) for tests with 180 µL of control solution added to 20 µL of mouthwash.

	Dis.Wat	A		CH		L		CO		M		
Test	**R**	**R**	**B%**	**R**	**B%**	**R**	**B%**	**R**	**B%**	**R**	**B%**	**Unit**
TESTO	0.58	0.62	6.57	0.79	36.85*	0.59	2.08	0.58	0.52	0.60	4.15	ng/mL
Free PSA	0.11	0.11	-3.60	0.11	1.80	0.11	-0.90	0.11	-0.90	0.12	4.50	ng/mL
Beta HCG	0.62	0.70	12.82*	0.70	12.50*	0.67	7.37	0.64	3.21	0.58	-7.05	mIU/mL
Esradiol	64.46	74.08	14.92*	62.50	-3.04	63.63	-1.29	63.15	-2.03	58.72	-8.90	pg/mL
FSH	12.13	11.88	-2.06	11.74	-3.22	11.45	-5.61	12.16	0.25	12.49	2.97	mIU/mL
LH	7.81	7.80	-0.13	7.74	-0.90	7.71	-1.28	7.73	-1.02	7.85	0.51	mIU/mL
PRL	17.11	17.14	0.18	17.49	2.22	17.11	0	17.48	2.16	17.78	3.92	ng/mL
Total PSA	0.36	0.38	6.37	0.35	-1.94	0.34	-5.82	0.35	-4.43	0.35	-3.05	ng/mL
PROG	1.58	1.69	6.96	1.68	6.33	1.47	-6.96	1.73	9.49	1.57	-0.63	ng/mL
DHEAS	94.48	116.90	23.73*	102.80	8.81	100.60	6.48	112.40	18.97*	105.30	11.45*	ug/dL
CORT	9.74	10.24	5.13	10.02	2.87	9.80	0.62	10.36	6.37	9.89	1.54	ug/dL

Abbreviations: Dis.Wat: Distilled Water, A: BisBiguanide Ch and CO: QuaternaryAmmonium, L:EssentialOils, M:StannousFloride, R:Result, B: Bias, TESTO: Testosterone, PSA: Prostate specific antigen, HCG: Human chorionic gonadotropin, E2: Estradiol, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, PRL: Prolactin, PROG: Progesterone, DHEAS: Dehydroepiandrosterone sulfate, CORT: Cortisol, PRG: Progesterone, *Values deviating from the target value by more than 10%.

Discussion

This in-vitro study examining the interference effect of mouthwashes is the first pilot study. CHX. which is one of the bisbiguanides with wide pharmacological effects. breaks down the cell membrane of many microorganisms. stops their growth depending on its concentration and provides inhibition of proteolytic enzymes (17). In addition. due to its cationic structure. it can adhere to mucous membranes and tooth surface. and exhibits long-term release (18). In our study. the tests that had more than 10% positive interference in an exposure. containing 0.12% CHX as the active ingredient. were DHEAS (23.73%). Esradiol (14.92%) and Beta HCG (12.82%). respectively. DHEAS also showed highly positive interference in CO and M exposure (18.97% and 11.45%. respectively). It showed highly positive interference in three of the five mouthwashes and deviated the most from other fertility tests.

Moreover. A is the only mouthwash with positive interference of estradiol (14.92%). which has shown negative interference not exceeding 10% with other tested mouthwashes. Estradiol is the most potent estrogen. the level of which increases in hormone-producing tumors and ovarian cysts (12). Significant changes in test values. negative or positive. may lead to misdiagnosis and treatment. So, individuals should be questioned whether they use any mouthwash before being tested.

DHEAS with the most positive interference in exposure (23.73%) is the most abundant circulating steroid hormone in humans. Normal values in humans vary widely with age. gender and ethnicity and are affected by daily changes in corticosteroid production. alcohol intake. smoking. body mass index. medications. and thyroid function. While individual variables make interpretation of test results difficult (19); this study showed the DHEAS was least interfered with L exposure (6.48%).

EssentialOil is a combination product of essential oils such as thymol and eucalyptol. which acts non-specifically against bacteria and is widely used as a disinfectant and antiseptic. but can cause burning sensation and staining of oral tissue (20). It aimed to overcome the problems caused by strains resistant to traditional antimicrobials (21.22). In alternative medicine. most of the plants consist of flavonoids that have an antibacterial effect on bacterial cells by disrupting the cytoplasmic membrane and inhibiting enzymatic activity (22). In addition. it reduces bacterial load by decreasing plaque mass and prevents plaque maturation. thereby reducing pathogenicity (23). Mouthwashes, in which essential oils are active antiseptic substances, contain alcohol (e.g. ethanol) at rates exceeding 25% to dissolve the active ingredients. but the mouthwashes we chose in this study are alcohol-free. None of the hormone tests in our study showed positive or negative interference exceeding 10% in L exposure. According to this result. alcohol-free essential oils may be a safe mouthwash considering the interference of fertility tests. Clinical studies can be conducted to test the accuracy of the study design in real situations.

Information on circulating concentrations of more than a hundred steroid compounds can lead to problems in interpretation with current technology (12) TESTO (36.85%) and Beta HCG (12.50%) showed the highest positive interference in mouthwash exposure containing Charcoal. Testosterone is the main androgen that influences the development of primary and secondary sexual characteristics and forms the basis of spermatogenesis together with FSH activity in men (24). Determination of testosterone level is indicated in the differential diagnosis of testicular and ovarian endocrine function. Testosterone is a useful marker for diagnosis and monitoring of tumor-associated androgen production and androgenation disorders (25). Mouthwash containing charcoal is a quaternary ammonium compound whose active ingredient is 0.075% Cetylpyridinium Chloride. Like bisbiguanides. quaternary ammonium compounds have a positive charge and interact with the bacterial cell membrane and impair its permeability. They adhere to the mucosal surfaces, but this adhesion is weaker than bisbiguanides (17.26.27). It has been shown that mouthwashes containing cetylpyridinium chloride at 0.07% concentrations inhibit periodontopathogens (28). and in another study, they are effective in antibacterial. antiplaque and antigingivitis (29). Cetylpyridinium chloride has a history of safe and effective use in oral care (30.31). In addition to its limited side effects such as gingival irritation and mild tooth staining (32. 33). it is also known to be safe for use during pregnancy (34). However. because clinical and laboratory evidence to support the therapeutic efficacy and safety of the use of charcoal-based mouthwashes is insufficient. dentists should advise their patients to be cautious when using these non-prescription mouthwashes (35). The fact that a high testo-positive interference value of 36% was observed only in mouthwash containing charcoal in our study confirms the lack of clinical information regarding the mechanism of action of such mouthwashes. The different bias percentages of different mouthwashes may be due to the interaction of the chemicals in their content. Studies can be conducted on the effects of the active ingredients of bis biguanide. quarterner ammonium and essential oils. Considering the possibility that drug-test interactions may lead to clinical inconsistencies in test results and affect the risk of morbidity and mortality. commercial companies may need to update their measurement methods (36).

In addition. CO which is a mouthwash containing a quaternary ammonium compound. showed a high positive interference value (18.97%) on DHEAS. This was followed by DHEAS with 11.45% in exposure to M. whose active ingredient is fluoride components. Beta HCG. which showed positive interference in other mouthwashes. showed negative interference (-7.05%) only with M. Beta hCG can be used to detect pregnancy as early as 10 days following pregnancy and may cause false negative biases in the individual using a short-acting fluoride-containing mouthwash such as M. Or vice versa. it can cause false positive deviations with a bias of 7.37% in an individual using L. Stannous fluoride (SnF2). which is the active ingredient in M. is a broad-spectrum antimicrobial agent with effects on dental plaque and gingivitis (37) and is still considered superior to other fluoride compounds. SnF2 reduces the prevalence of bacteria in the biofilm composition when SnF2 toothpaste is combined with an essential oil-containing mouthwash (38). In this study. PSA. FSH. LH. PRL. PROG and CORT tests showed positive and negative interferences not exceeding 10%. The test that shows the most bias from the target value is DHEAS. and the mouthwash that causes the most bias is CHX. Chlorhexidine. the only agent that can be prescribed in our country. should be prescribed with careful questioning (39).

Study limitations

The study is experimental and needs to be supported by in vivo studies to increase its applicability in the clinical setting. Its limitation is that it was studied with control solutions similar to human blood. The density of the human blood matrix and the thermodynamic interactions it will show may reveal different bias values during interference. Further studies are needed using biological fluids such as human serum or plasma that better reflect mouthwashes clinically. Another limitation of the study is the lack of sufficient data on the relationship between the use of mouthwashes and the rate of passage from the mucosa (oral or gastrointestinal) to the systemic circulation.

Conclusion

Mouthwashes with essential oil components seem to be safer than other mouthwashes in terms of interference. This study has shown that the interaction potential of commercial kits with mouthwash solution contents may cause erroneous measurements in terms of hormone test results. Questioning the use of mouthwash in patients with suspicious hormone results may be a method to reach the correct result.

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Diagnostic Value of HMGB1 Protein Levels in Colorectal and Gastric Cancer

Kolorektal ve Gastrik Kanserde HMGB1 Protein Düzeylerinin Tanısal Değeri

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Abstract

Background: High Mobility Group Box-1 (HMGB1), a nuclear protein, regulates the transcription of multiple genes. The study aimed to ascertain the diagnostic utility of HMGB1 protein levels in colorectal and gastric cancers.

Materials and Methods: This was a cross-sectional study. The patients were categorized into groups based on their histopathological diagnoses. Preoperative and pre-chemotherapy blood samples were collected from the patients. The analysis procedures were replicated twice for each sample utilizing the sandwich enzyme immunoassay technique.

Results: The study included 20 controls and 70 patients in total. Of the 70 patients, 24 had a gastric cancer diagnosis, and 46 had a colorectal cancer diagnosis. The patient group did not differ in any of the following categories from the control group: gender, age, body mass index (BMI), alcohol consumption, or smoking. ($p > 0.005$) Pathologic diagnoses did not differ between adenocarcinoma and signet ring cells in gender, BMI, HMGB1 serum levels, smoking, or alcohol consumption ($p>0.005$). The High Mobility Group Box-1 variable was not statistically significant between colorectal and gastric cancer groups in adenocarcinoma patients, who were excluded from the pathology results of 7 signet ring cell carcinoma patients ($p=0.885$).

Conclusions: In conclusion, HMGB-1 protein levels were not different in patients with colorectal and gastric carcinoma compared to those in healthy subjects. HMGB-1 level measurement may not make a diagnostic difference in the presence of colorectal carcinoma and gastric carcinoma.

Keywords: High Mobility Group Box-1, colorectal cancer, gastric cancer, signet ring cell carcinoma

ÖZ

Amaç: Nükleer bir protein olan Yüksek Mobilite Grup Kutusu-1 (HMGB1), birden fazla genin transkripsiyonunu düzenler. Çalışmanın amacı, kolorektal ve gastrik kanserlerde HMGB1 protein düzeylerinin tanısal faydasını belirlemektir.

Gereç ve Yöntem: Bu kesitsel çalışmada hastalar histopatolojik tanılarına göre gruplara ayrıldı. Hastalardan ameliyat öncesi ve kemoterapi öncesi kan örnekleri toplandı. Analiz prosedürleri her örnek için sandviç enzim immünoassay tekniği kullanılarak iki kez tekrarlandı.

Bulgular: Çalışmaya toplam 20 kontrol ve 70 hasta dahil edildi. 70 hastanın 24'ünde mide kanseri tanısı, 46'sında ise kolorektal kanser tanısı vardı. Hasta grubu, cinsiyet, yaş, vücut kitle indeksi (VKİ), alkol tüketimi ve sigara kullanımı kategorilerinden hiçbirinde kontrol grubundan farklı değildi. ($p > 0,005$) Patolojik tanılar, adenokarsinom ve signet halka hücreleri arasında cinsiyet, VKİ, HMGB-1 serum düzeyleri, sigara kullanımı veya alkol tüketimi açısından farklılık göstermedi ($p>0,005$). HMGB-1 değişkeni, 7 signet halka hücreli karsinom hastasının patoloji sonuçlarından hariç tutulan adenokarsinom hastalarında kolorektal ve gastrik kanser grupları arasında istatistiksel olarak anlamlı değildi ($p=0,885$).

Sonuç: Sonuç olarak, kolorektal ve gastrik karsinomlu hastalarda HMGB-1 protein düzeyleri sağlıklı bireylere göre farklı bulunmamıştır. HMGB-1 düzeyi ölçümü kolorektal karsinom ve gastrik karsinom varlığında tanısal bir fark yaratmayabilir.

Anahtar kelimeler: Yüksek Mobilite Grubu Kutu-1, kolorektal kanser, mide kanseri, yüzük hücreli karsinom

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Highlights

- High Mobility Group Box-1 (HMGB1), a nuclear protein, regulates the transcription of multiple genes.
- HMGB-1 protein levels were not different in patients with colorectal and gastric carcinoma compared to those in healthy subjects.
- HMGB-1 level measurement may not make a diagnostic difference in the presence of colorectal carcinoma and gastric carcinoma.

Introduction

Colorectal and gastric cancers are gastrointestinal cancers with high mortality rates. Gastric cancer has remained the fifth most common type of cancer worldwide, despite a steady decline over the last 50 years (1). By 2020, more than one million people worldwide had been diagnosed with gastric cancer, accounting for 5.6% of all cancer cases. While gastric cancer was the leading cause of cancer-related deaths until the mid-1990s, it is now the third leading cause of cancer-related deaths (2). Colorectal cancer (CRC) is steadily increasing worldwide. Given demographic projections, the number of CRC cases worldwide is expected to increase by 60% by 2030, reaching more than 2.2 million new cases and approximately 1.1 million deaths annually. Currently, Eastern Europe, Asia and South America are experiencing rapid increases in both CRC incidence and mortality (3). Although effective therapeutic strategies for CRC have been developed over the past decades, five-year overall survival rates remain poor. This is due to the presence of poor prognostic factors such as vascular and neural invasion, low lymphocyte-monocyte ratio (LMR), late diagnosis and tumor stage. According to estimates, approximately 20% of CRC patients have already progressed to metastatic status at the time of diagnosis (4,5). In addition to surgery, chemotherapy and radiotherapy, new methods such as immunotherapy have recently been used in the treatment of these cancers. The poor prognosis despite these treatments has led to the search for new prognostic and predictive markers. Identification of new targets in treatment is also gaining importance. HMGB1, a high-mobility group box-1 protein, is known to be a nuclear protein that resides in the nucleus and controls the transcription of multiple genes (6). This protein is composed of 215 amino acids and contains two DNA-binding domains, Box-A and Box-B, as well as a C-terminal region that is negatively charged. Recent studies have shown that HMGB1 serves not only as a core protein, but also as a separate cytokine that enhances the production of proinflammatory cytokines. HMGB1 is released from necrotic cells through passive leakage, but it is actively released from inflammatory cells and has a strong tendency to bind to certain receptors (7). HMGB1 serves as an external signaling molecule in processes such as inflammation, cell differentiation, cell migration, and tumor metastasis. It has been observed that HMGB1 protein and the receptor for advanced glycation end products (RAGE), which are crucial for the growth of tumor cells, have been identified as a ligand-receptor pair (8). HMGB1 has been associated with several different types of cancer. Specified cancers include melanoma, prostate, pancreatic and breast cancer (9). High expression of HMGB1 in many of these cancers is often associated with invasion and metastasis. This suggests that HMGB1 plays an important role in cell growth, invasion and cancer metastasis (10). This study was conducted to investigate the expression status and predictive value of HMGB1 in primary colorectal and gastric cancer.

Material and Methods

Study Design and Setting: This study was conducted in the context of a cross-sectional study. The study included patients with histopathologically confirmed primary gastric and colorectal cancer, who were diagnosed at SANKO University Medical Oncology Clinics and had not yet received treatment. Additionally, healthy volunteers, who applied to the SANKO University Check-up outpatient clinic and agreed to participate in the study, were also included. Patients, who had prior exposure to chemotherapy or radiotherapy, were below 18 years old, had undergone surgery, had a previous malignancy, declined to participate in the study, were pregnant, had any autoimmune disease, collagen tissue disease, or severe psychological disorder, and had a history of polypharmacy were not included in the study.

The volunteers were excluded if they had undergone chemotherapy or radiotherapy, surgical intervention, had a history of another malignancy, refused to participate in the study, were pregnant, had any autoimmune disease, collagen tissue disease, severe psychological disorder, or a history of polypharmacy.

The study involved a review of the patients' files to gather information such as age, gender, and routine laboratory test results. The patients were categorized into groups based on their histopathological diagnoses. Pre-

treatment blood samples were collected prior to initiating first-line systemic chemotherapy.
Each volunteer in the study provided approximately 4-5 cc of venous blood, which was collected in a biochemistry tube. The blood was then kept at room temperature for 20 minutes before being centrifuged at 4000 rpm for 10 minutes. This process resulted in the separation of the serum portion. The serum that had been separated was allocated into labeled eppendorf tubes and kept in the deep freezer at -80 ºC in the SANKO University laboratory until the day of the study. The control group underwent the same method of study, using identical parameters. The HMGB1 serum levels were quantified using Rel Assay Brand commercial kits in the designated laboratory, following the instructions provided by the manufacturer. The analysis procedures were replicated twice for each sample utilizing the sandwich enzyme immunoassay technique.
The assay's concentration/absorption graphic curves of the test and calculations regarding the results were performed by using 450 nm wavelenght on the program of the Biotek_ELx808 (Winooski, Vermont, USA) device. The test was determined to have a sensitivity of 0.09 ng / mL and detection range of 1-32 ng / mL. Intra-assay and inter-assay variation coefficients were determined as 8.7% and 5.3% respectively

Ethics: This Study approval was obtained from the SANKO University, Clinical Research Ethics Committee (Approval No. 2022/21.01. date: 22.12.2022). Data from patients who gave informed consent for the use of their information and permission for contact were included in the study. We ensured the patient's confidentiality and followed the principles of the Declaration of Helsinki.

Statistical analyses
To analyze the variables, we employed the statistical software SPSS 26.0, developed by IBM Corporation, headquartered in Armonk, New York, United States.The Shapiro-Wilk-Francia test was used to determine whether or not the data followed a normal distribution, and the Levene's test was used to determine whether or not the fluctuations in the data were consistent with one another. A T test with independent samples and Bootstrap results, as well as a Mann-Whitney U test with Monte Carlo results, were utilized in order to compare two independent groups in terms of quantitative variables. The Pearson Chi-Square Fisher test was utilized for the purpose of comparing categorical variables. The Monte Carlo simulation method was utilized in order to test the exactness of the tests. In the tables, quantitative variables were presented in the form of mean (standard deviation) and median (minimum or maximum), whereas categorical variables were presented in the form of n (percent). A level of confidence of 95% was used to conduct the analysis of the variables, and a p-value of less than 0.05 was regarded as statistically significant.

Results:
A total of 70 patients and 20 controls participated in the study. 24 of the 70 patients were diagnosed with gastric carcinoma, and 46 were diagnosed with colorectal carcinoma. When compared to the control group, the patient group did not differ from the control group in terms of gender, age, body mass index (BMI), smoking, or alcohol consumption. ($p > 0.005$) Additionally, there was no difference in the levels of HMGB1 serum found between the control group and the carcinoma patient group ($p > 0.005$). In terms of gender, age, HMGB1 serum levels, smoking, and alcohol consumption, there was no difference between patients with colorectal carcinoma and patients with gastric carcinoma when the patient group was analyzed in detail ($p > 0.005$). Between the two groups, the only thing that was found to be different was the BMI. In the group that had colorectal carcinoma, the body mass index (BMI) was statistically lower ($p = 0.011$). In terms of pathologic diagnoses, there was no difference between the groups of adenocarcinoma and signet ring cells in terms of gender, body mass index (BMI), HMGB1 serum levels, smoking, or alcohol consumption ($p>0.005$). The only individuals who had a younger mean age were those, who had signet ring cell carcinoma (55.9 years compared to 44.9 years $p = 0.001$). A comprehensive presentation of the demographic and clinicopathologic data pertaining to the groups can be found in Table 1. The comparison of the High Mobility Group Box-1 variable between colorectal and gastric cancer groups in the adenocarcinoma patients, who were excluded from the pathology results of 7 patients with signet ring cell carcinoma, did not show any statistical significance ($p=0.885$).

Table 1: Cancer Types, Gender, and Age Distribution of Patients

	Gender		Age, years	BMI, kg/m²	HMGB-1	Smoke		Alcohol	
	Female, (%)	Male, (%)				No, (%)	Yes, (%)	No, (%)	Yes, (%)
Groups									
Control (n=20)	10 (50.0)	10 (50.0)	54.7± 11.8	25.2± (1.8)	22.6 (13.2-74.2)	9 (45.0)	11 (55.0)	12 (60.0)	8 (40.0)
Patient (n=70)	31 (44.3)	39(55.7)	58.4 ± 11.0	25.3 ± (1.4)	18.3 (8.3 -118.4)	25 (35.7)	45 (64.3)	51 (72.9)	19 (27.1)
p	0.800 [c]		0.236 [t]	0.879 [t]	0.139 [u]	0.602 [c]		0.407 [c]	
Type of CA									
Colon (n=46)	18 (39.1)	28(60.9)	61 (38-80)	24.8 (22-27.7)	18.8 (11.1 - 118.4)	14 (30.4)	32 (69.6)	33 (71.7)	13 (28.3)
Gastric (n=24)	13 (54.2)	11(45.8)	59 (27-67)	25.4 (24.1- 29.1)	18.3 (8.3 -117.7)	11 (45.8)	13 (54.2)	18(75.0)	6(25.0)
p	0.312 [c]		0.194 [u]	0.011 [u]	0.600 [u]	0.293 [c]		0.788 [c]	
Pathology result									
Adenocarcinoma (n=63)	27 (42.9)	36(57.1)	59.9± 9.8	25.3± 1.4	18.3 (8.3-118.4)	21 (33.3)	42 (66.7)	46 (73.0)	17 (27.0)
Stone ring cell (n=7)	4 (57.1)	3 (42.9)	44.9 ± 12.2	25.1 ± 0.4	16.5 (13.2-32.7)	4 (57.1)	3 (42.9)	5 (71.4)	2 (28.6)
p	0.692 [f]		0.001 [t]	0.342 [t]	0.419 [u]	0.239 [f]		0.999 [f]	
Total (n=90)	41 (45.6)	49(54.4)	57.5 ± 11.2	25.2± 1.5	19.7 (8.3-118.4)	34 (37.8)	56 (62.2)	63 (70.0)	27 (30.0)

Abbreviations: *[t] Independent Samples T Test (Bootstrap), [u] Mann Whitney U Test (Monte Carlo), [c] Pearson Chi Square Test (Monte Carlo), [f] Fisher Exact Test(Monte Carlo), HMGB-1: (High Mobility Group Box B-1)*

Discussion

HMGB-1 is a protein with intracellular and extracellular functions. It is structurally defined as a nucleoprotein that binds to DNA and plays an important role in the regulation of gene expression. HMGB-1 acts as an active mediator in the processes of inflammation, tissue repair and cell death. When released into the extracellular environment, it can act as a proinflammatory cytokine and trigger various cellular responses (9-10). In CRC related research, increased levels of HMGB-1 have been observed to have significant effects on the course and prognosis of CRC disease. Patients with high HMGB-1 expression have been found to have more advanced TNM stages of disease, shorter overall survival and disease-free survival, and a higher likelihood of disease recurrence and metastasis (11). It has also been observed in studies that increased expression of HMGB-1 may be associated with damage to the intestinal mucosal physical barrier and alteration of the local immune barrier (12). HMGB-1 is thus considered an independent risk factor for death and relapse risk in CRC patients and a potential marker for a better understanding of the diagnosis and prognosis of CRC. However, definitive data are still lacking in the literature (13). Although some studies have shown some associations of HMGB-1 protein with CRC, it has not been reported to be associated with certain clinical features and to have any diagnostic utility. In particular, HMGB-1 was not associated with gender, age, tumor diameter and nerve invasion (14). In our study, there was no difference in protein levels between the patient population and controls. A recent study also revealed that high levels of HMGB1 have been observed in exosomes derived from gastric cancer cells, which may contribute to cancer progression by inducing M2-like macrophage polarization (15). Therefore, the document focuses on data showing a negative association between HMGB1 and gastric cancer. Studies have shown that HMGB-1 protein plays an important role in the growth, invasion and spread of gastric cancer and is also involved in mechanisms that promote cancer cell survival. HMGB1 has been shown to affect the growth and invasion of gastric cancer cells through the NF-kB pathway and also to promote autophagy-mediated survival of gastric cancer cells through RAGE activation. Furthermore, it is suggested that targeting HMGB1 and its related pathways may be a potential strategy for the treatment of gastric cancer (16-17). These data suggest that HMGB-1 protein is an important factor in the pathogenesis of gastric cancer and can be considered as both a prognostic indicator and a potential therapeutic target. However, in our study, no correlation was found between gastric cancer and HMGB-1 levels. When we evaluate these two results together, although a prognostic relationship with HMGB-1 levels has been reported in the literature, according to the results of our study, no relationship was found with the presence of gastric or colorectal carcinoma. The limitations of our study

include the lack of subgroups according to tumor staging, the lack of concomitant gene expression levels while working at the protein level, and the lack of specific protein determinations such as western blot at the tissue level. Even after excluding the signet ring cell carcinoma subgroup, which is a pathologic subtype with a poor prognosis, still no significant difference was observed in HMGB-1 levels. Another limitation of our study is that the sample was small in number, consisting of patients diagnosed at a single center and volunteers. It is important to remember that when the sample is small, it will be difficult to find significant correlations in the data. Repeating the study with a larger sample will contribute to the literature.

Study limitations

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Conclusion

HMGB-1 protein levels were not different in patients with colorectal and gastric carcinoma compared to those in healthy subjects. HMGB-1 level measurement may not make a diagnostic difference in the presence of colorectal carcinoma and gastric carcinoma.

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