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Case Report	1000	200	15	No tables	10 or total of 20 images
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Case Reports

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Exposures Moved from Work to Home as a Public Health Hazard

Bir Halk Sağlığı Tehlikesi Olarak İşten Eve Taşınan Maruziyetler

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ABSTRACT

There are numerous occupational pollutants originating from a wide variety of industrial areas and working environments. These pollutants can be brought inadvertently from workplace to home in various ways and may negatively affect the health of household. In the literature, this situation was known as para-occupational exposures in the past but today it is referred as take-home exposures. In this review article; transport pathway, the diversity of take-home exposures, the population at risk and occupational security deficits were examined and precautions in reducing the take-home exposures were discussed. At the same time, take-home exposures were considered as an important public health problem and the contribution of social inequalities to the extent of the problem was also evaluated. It is aimed to help researchers to have a comprehensive view of take-home exposures and to support preventive efforts.

Keywords: Take-home, occupational pollutants, exposure, contamination, prevention

ÖZ

Çok çeşitli endüstriyel alanlardan ve çalışma ortamlarından kaynaklanan sayısız mesleki kirletici vardır. Bu kirleticiler çalışanlar tarafından değişik yollarla, farkında olmadan, işten eve taşınabilir ve aile bireylerinin sağlığını olumsuz etkileyebilir. Bu durum literatürde geçmişte iş ile ilgili (para-occupational) maruziyetler, günümüzde ise eve taşınan maruziyetler olarak adlandırılmaktadır. Bu derleme makalesinde eve götürülen mesleki kirleticilerin taşınma yolları ve çeşitliliği, risk altında olan nüfus ve mesleki güvenlik açıkları incelenmiş, eve götürülen maruziyetleri önleme yolları tartışılmıştır. Aynı zamanda eve taşınan maruziyetler önemli bir halk sağlığı sorunu olarak ele alınmış, toplumsal eşitsizliklerin sorunun boyutuna katkısı da değerlendirilmiştir. Araştırmacıların eve taşınan işyeri maruziyetleri hakkında kapsamlı bir görüşe sahip olmalarına ve önleme çabalarına yardımcı olmak hedeflenmiştir.

Anahtar Kelimeler: Eve taşınma, mesleki kirletici, maruziyet, kontaminasyon, korunma

Introduction

An emerging hazard in a workplace becomes environmental when it affects employees, when it crosses the boundaries of the workplace and affects those in the wider community. Employees can carry hazardous materials from work to home without realizing it through their clothing, skin, hair, work tools and vehicles. In this case, employees can become "tools" by which occupational hazards are brought into the home environment (1). As a result, various adverse health effects attributed to occupational pollutants may develop in household members by their exposure to hazardous substances (2,3). The importance of these exposures carried to the home has actually been known for a long time, as they are also called "work-related (para-occupational) exposures" (4). For example; Oliver (5) reported in 1914 that the spouses of paint workers who wash their work clothes had lead poisoning. The conceptualization of take-home exposures has emerged over time with the reporting of specific cases such as childhood lead poisoning by the Centers for Disease Control and Prevention.

Evidence from scientific literature shows that a wide variety of occupational chemicals such as pesticides, asbestos, lead, beryllium, halogenated aromatic hydrocarbons can be transported from the workplace to the home environment. Apart from chemical factors, occupational exposures such as various psychosocial stressors and work traumas can also disrupt family and society relations by affecting the behavior of employees (1). However, these behavioral changes were not widely accepted as take-home exposures. At the same time, various allergens (such as cereal dust, animal proteins), radiation and infectious

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agents (such as coxiella, methicillin-resistant *Staphylococcus aureus* (MRSA), scabies) are also take-home exposures that negatively affect family health.

Population at Risk and Structural Sensitivities

The population at risk for the take-home exposures is the household members affected by the employee carrying the pollutants from work to home (Table 1). This also includes homes that function as workplaces (such as farms). Factors such as age, health status, behavior, and education may contribute to varying sensitivity to adverse health effects that occur among the household members (6). Young children with small bodily structures who are in a period of rapid development can be more affected by occupational pollutants carried home by their parents. In addition, their risk of exposure is higher, usually because they spend more time on the ground, they have more hand-to-mouth activities, and their gastrointestinal absorption of pollutants is more than adults (7,8). The susceptibility of the elderly to toxic substances may change, or significant body loads of toxic substances may have accumulated in the elderly before the contaminants carried to the home (9). Women may be particularly at risk because of their tendency to do more housework, including laundry and cleaning. For example; wives of workers exposed to beryllium were exposed to beryllium at home as a result of shaking their husbands' clothes contaminated with gray-black beryllium soot before washing (10). This behavior suggests that both workers and their spouses are unaware of the risk of beryllium contamination taken home.

Transport of Occupational Pollutants

Low occupational hygiene awareness of employees and their family members and the lack of personal protective equipment use of employees play an important role in the transportation of occupational pollutants. However, the risk may persist when employees are aware of workplace hygiene but do not know their right to access protective measures, and feel that their demands for safer conditions or better training will not be met (11).

Jones and Burstyn (1) mentioned external contamination as one of the steps in which occupational pollutants are brought home by developing a conceptual model (Figure 1). Employees can carry occupational contaminants on their skin, clothes (especially shoes), vehicles, work tools and other objects. Many studies have shown that pollutants are released directly into the home environment in these ways. Pollutants from the workplace can be in chemical, physical or biological form and affect workers and their families through dermal, inhalation or oral exposure. A comprehensive mathematical explanation of the distribution and accumulation of external contamination at home was provided by Zirschky (12).

Table 1. Structural vulnerabilities of the population at risk and other influential social-ecological elements

Household members	Age
	Gender
	Health condition
	Behavior
	Education
	Occupation
	Geographical features of the living area
	Industrial features of the living area
	Legal regulations/legislations

After the external contamination of the employee, exposure of household members at home can be direct or indirect. Direct exposure includes direct contact between contaminated objects and household members. For example; by hugging their child, an employee can transfer occupational contaminants to the child's body or clothing. In indirect exposure, contamination is mediated by the home environment (such as carpets), and situations such as washing contaminated and uncontaminated clothes together can lead to cross contamination between clothes (13).

1. Employee's Skin

The skin of the workers is thought to play an important role in the transmission of occupational pollutants. Many studies report contamination in workers' hands, forearms, forehead, and feet (14). Skin contamination often occurs among those who do not adhere to hygiene practices such as hand washing and showering before leaving their workplace or who do not shower immediately upon arrival. For example, in facilities with appropriate infrastructure, workers washing their hands and showering at the end of the shift led to low skin lead levels at the end of the shift (15). Pollutants carried on the skin of the workers can be transferred to the vehicles (10) and the home floor (16).

2. Contaminated Hair

Although there is little evidence to support the hypothesis that occupational pollutants are carried home by hair, measurements of potentially transported allergens in workers' homes in this way have

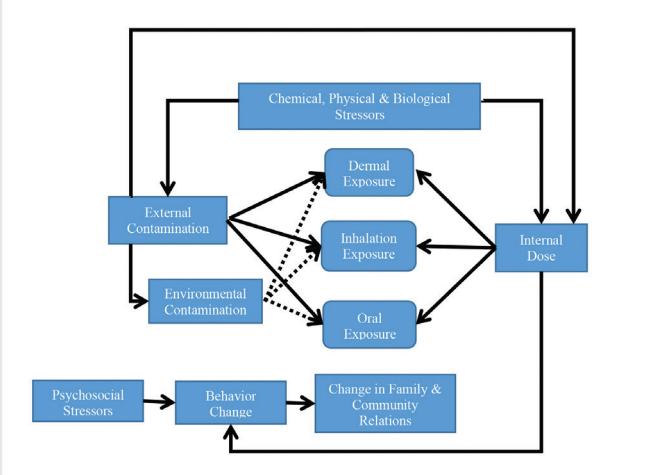

Figure 1. Chemical, physical, biological and psychosocial workplace exposures are carried home by employees through 3 ways (external contamination, internal dose and behavioral change in the worker). Workplace exposures can affect workers and their families through dermal, inhalation, and oral exposure. Dashed arrows represent the impact of environmental pollution on household members from employee's workplace exposure

[Adapted from ':Rachael M. Jones & Igor Burstyn (2018) A conceptual model for take-home workplace exposures, Journal of Occupational and Environmental Hygiene, 15:1, D8-D11']

been reported (17,18). The study by Krop et al. (17) shows that hair can be a source of animal allergen transport to an environment that does not contain allergens.

3. Contaminated Clothing and Shoes

Studies in the literature have shown evidence based on indirect and direct measurements that pollutants can be transported home through contaminated clothing and shoes. Significant levels of pollution have been found in locker rooms where clothes contaminated with occupational pollutants are changed. Based on these findings, contaminated clothing was thought to be a potential source of contamination in workers' homes. Another evidence showing that clothing is a potential source of contamination is the detection of high pollutant levels in children whose parents wear contaminated clothing at home (19). In their study, Lu et al. (20) reported that the rate of pesticides taken home by means of boots was high in the swab samples taken from parents' work boots.

4. Items Moved Home from Work

Employees can take work tools and equipment with them, carry them in their vehicles, or take them from work to home for their own use (6). For example; it is possible for agricultural workers to get pesticides from the workplace to use in their homes.

5. Contaminated Vehicles

Tools can mediate the home transport of occupational pollutants, both as a "reservoir" and as a "vector". They also serve as a microenvironment where pollutants can contaminate all family members (2). A significant relationship has been found between home and vehicle concentrations of occupational pollutants and urine metabolite levels in workers and their children (21).

6. Workplace Visit of Family Members

Workplace visits by family members may also result in occupational contaminants being moved home, although this is different from exposures carried home by parents. For example; immunoglobulin E antibodies specific to laboratory animal allergens were detected in children who developed a cough and rhinitis clinic after they visited the workplace of their parents working in an animal laboratory (22).

7. Professional Preferences and Hobbies

It is an issue that should be taken into account that the parenting profession is also maintained by children. Children exposed to pollutants through the parent's occupation may increase their risk of sensitization if they continue the same profession in their adulthood. Another factor to consider is the exposures associated with hobbies. It is useful and necessary to detail the anamnesis to include these areas as well as the occupation questions.

Main Take-home Exposures and Health Effects

Current information on take-home exposures and health effects is not sufficient. It is almost impossible to predict which occupational exposure factors may pose a threat to employees and their families in the future. In evidence from scientific literature; lead, beryllium, pesticides, and asbestos are prominent examples of take-home exposures. Workplace pollutants can be in chemical, physical or biological form and can contaminate workers and their families through dermal, inhalation, or oral exposure.

Hazardous pollutants can enter the employee's body in various ways and affect household members in various ways through contact (respiratory secretions, blood, urine, etc.) or the body fluids they are fed (such as breast milk). This situation has been called the internal dose of the pollutant (1). For example; workers who have occupational exposure to products containing polybrominated diphenyl ether (PBDE) used as flame retardants have higher serum PBDE levels than the general population (23). PBDE's breast milk levels are proportional to serum levels, and breastfed babies of workers may be exposed to PBDE in this way (24). In addition; occupational exposures of female workers may result in intrauterine exposure of a developing fetus through the placenta. It can cause genotoxicity and decreased fertility by affecting the germ cells of male and female workers.

1. Chronic Beryllium Disease (Berylliosis)

In the literature, there are case series and cohort studies reported in the families of the employees regarding this potentially fatal granulomatous lung disease (25,26). It is found in the families of employees who are exposed to beryllium in the workplaces involved in the production of fluorescent lights, beryllium and gyroscopes, and in the nuclear and aviation industries.

2. Asbestos and Its Effects

In studies evaluating the health effects of asbestos on families of asbestos workers, diseases such as asbestosis, mesothelioma, pleural plaques and cancer have been reported. Twenty percent of mesothelioma cases were attributed to take-home exposures (27), and it was reported that a large number of asbestos fibers were found in the lungs of family members of exposed workers (28). An increased risk of mesothelioma was found in a large cohort study conducted among the spouses of asbestos workers in Italy, but no relation with lung cancer was found (29).

3. Lead and Its Effects

It is evidence-based information that lead poisoning causes a variety of problems in children, ranging from behavioral disorders to brain damage. High blood lead levels may adversely affect the reproductive system in women and men, and cause irreversible neurological damage in pregnant women by affecting the fetus (30). In a meta-analysis study conducted in the United States of America (USA), it has been suggested that the risk of detecting high blood lead levels is higher in the children of workers exposed to lead (31). According to this meta-analysis, it is predicted that 723,500 employees in the USA work in industries that have the potential to take lead home, and two-thirds of them have a significant risk of taking home. In the study conducted by Whelan et al. (8), it was found that children of construction workers who were exposed to lead were six times more likely to have high blood lead levels compared to the children of those who were not exposed, and also their homes had higher lead dust levels.

4. Pesticide and Its Effects

Home transport of pesticides (main organophosphates) by agricultural workers has been well documented in the literature since the mid-1990s. The agricultural jobs of the parents were found to be significantly associated with taking home pesticides (32). Studies have consistently found high levels of organophosphate (33) in the homes of agricultural workers and high levels of metabolites (20) in the urine of their children. In the studies conducted, high organophosphate levels (33) and high metabolite levels in the urine of their children (20) were found in the homes of agricultural workers. Agricultural based take-home pesticide exposure is a major health problem among children in rural communities.

5. Arsenic and Its Effects

Agricultural use of pesticides and herbicides containing arsenic can pollute the home environment. Klemmer et al. (34) concluded that arsenic could be carried home through work clothes. In a study, extremely high levels of arsenic dust were found in the homes of families working in the wood processing field in Hawaii (4). It has also been emphasized that arsenic coming from the workplace may cause cancer development in children. Four cases of hepatic angiosarcoma, a rare tumor in children, have been reported in the literature. One of the cases was associated with arsenic exposure moved home from work (35).

6. Mercury and Its Effects

Toxic mercury exposure is a health problem that is becoming common worldwide. Recent studies show that mercury exposure may be mediated by the occupational and home environment with an increasing ratio, as well as from the general environment. Children are particularly vulnerable to mercury poisoning, as it can lead to pulmonary and nephrotic damage as well as a developing central nervous system disorder. In a study, children of employees who work in a facility producing mercury thermometers were found to have higher urine mercury levels in the study group compared to the control group. At the same time, higher levels of mercury in air were measured in the homes of workers who work in facilities producing thermometers (36). This study showed that toxic mercury can be carried home through shoes or clothing.

7. Polycyclic Compounds and Their Effects

One of the leading reports of a disease in family members attributed to workplace pollutants was published in 1943. This disease was associated with Halowax, a mixture of pentachloronaphthalene, hexachloronaphthalene and chlorinated biphenyl, used for insulation of electrical cables. Acneiform lesions (chloracne) called "Halowax Acne" developed in 52 isolation workers exposed to Halowax. Workers' spouses also had similar acneiform lesions, most likely due to contact exposure with contaminated workwear (37). Similar clinical pictures occurring in workers and their families at similar production sites where polycyclic compounds are used have been reported in the literature.

8. Synthetic Estrogens

There are few studies in the literature on exposure to synthetic estrogens that are brought home as occupational pollutants. Gynecomastia has been reported in the sons of several employees of a chemical plant producing synthetic animal estrogen called zeranol in the Indianapolis city of the USA. In the later examination, zeranol was found in the work clothes of the workers (38).

9. Radioactive Contamination

Radioactive agents as occupational pollutants transported to the home have been less studied and there is insufficient data in the relevant literature. In a study, samples taken from the hair of employees working in the nuclear energy, pharmaceutical and biotechnology industries using C14 radionuclide, were evaluated in terms of contamination with the help of accelerator mass spectrometry. C14 contamination was detected in the analyzes, but it could not be clearly distinguished whether there was an occupational contamination (39). Another case example was reported as an industrial accident due to careless handling of a source of Cs-137, a radionuclide, by the worker. Contamination was found in the urine sample of the spouse of the employee who was exposed to radionuclide body load of the employee (40).

10. Infectious Agents

Hospital and laboratory workers and agricultural workers can transmit infectious pollutants such as scabies, *Coxiella Burnetti* (Q fever agent) and MRSA to household members through their skin and clothing. Workers can mediate the home transport of these pollutants, both as a "reservoir" and as a "vector". In studies conducted, MRSA contamination was found in samples taken from the homes and in the family members of healthcare workers who are MRSA carriers (41). In another study, it was determined that the spouse of a goat farm worker who was diagnosed with Q fever was also diagnosed with the same disease months later, and it was thought that the contamination occurred as a result of washing the contaminated work clothes (42).

11. Nanomaterials

If at least one dimension of the material is between 1 and 100 nm, that material is called a nanomaterial. All over the world, interest in this sector is increasing day by day. Nanomaterials are widely used in many sectors due to their superior properties, so the number of employees exposed to these materials is also increasing. The precautions to be taken during the use, transportation and most importantly the production of these materials (43), which are newly emerging with a wide variety of harmful effects on human health and which are also proven to have asbestos-like properties, are of great importance. Nanoparticles can be dispersed in the working environment by means of air, water and clothing. Therefore, it has become necessary to clean workwear in a specialized facility in order not to transport nanoparticles (especially carbon nanotubes) and limit the risk of contamination of workers' homes (44). Despite the existence of various studies and studies in the literature, the effect of nanotoxicity on human health is not yet fully understood (45). Studies to investigate the health effects of nanomaterials, which have the potential to be moved home as an occupational pollutant, on employees and their families should be developed and continued.

Take-home Exposures as a Public Health Problem

Occupational exposures-related diseases are increasingly recognized as an important public health problem and awareness of the issue is

increasing. The proven existence of take-home exposures has required some countries to make regulations in their labor legislation. In the USA, the "Law for the Protection of Working Families" was passed in 1992. This law necessitates to investigate the risks arising from dangerous substances that are moved to the house and affect household members. The National Institute for Occupational Safety and Health (NIOSH) mentioned about the exposure associated with the contamination of employees' homes with hazardous chemicals transported from the workplace in 1995 and its adverse health effects (3). Effective measures against occupational pollutants carried home by NIOSH are described. But today, as in diagnosis of many occupational diseases; diagnosis of take-home exposure by occupational pollutants that affect family members is also missed.

This problem continues to grow in sectors where prevention is insufficient and in countries where legal regulations are not implemented adequately. In addition, workers with take-home exposure contamination often work in hazardous, temporary or seasonal jobs (8). In most cases, families of immigrant labor work in sectors such as agriculture and construction in high-income countries are mostly affected (46). Syrian refugees working in Turkey have also been found to work in dangerous and temporary locations where there is a risk of moving occupational pollutants home (47). Given this, it can be said that the most affected groups are less likely to benefit from existing standards in occupational health policies and practices. Low socioeconomic status can lead to limited access to health care for workers and their families exposed to toxic workplace pollutants, and when this is combined with poor health care and unhealthy diet, it increases the risk of adverse health effects (6). The exposure is greater in sectors that consist of large numbers of small businesses, such as the service, construction and agriculture sectors, or that carry out high-risk tasks by outsourcing. At the same time, low political power of employee organizations may cause managers to feel little pressure to change policies to improve job security and may play a role in the continuation of the problem.

Prevention and Protection of Take-home Exposures

It is emphasized that a three-layer approach that includes prevention efforts at the workplace, at home and at the community level together is required to prevent exposures taken to the home in a comprehensive way (48). It also requires well-functioning control strategies and workplace hygiene standards that can be supported through public policies (32,49). It is aimed to identify and reduce workplace pollutants that may be responsible for primary protection, which is the most effective and proactive approach. However, these efforts need to be complemented by secondary and tertiary protection measures. Current legal regulations may enable the accumulation of chronic exposure pests and home transport even in full compliance with primary protection measures. Therefore, secondary and tertiary protection measures are also required. At the same time, the presence of occupational pollutants that are not yet known and may pose a threat in the future supports this requirement.

Primary protection includes reducing the use of the most problematic chemicals, better safety protocols and training, mandatory regulatory adaptations, and participation of worker organizations in safety control strategies. It is aimed to determine the effects of occupational pollutants identified in secondary protection at an early stage. Secondary protection includes biological monitoring of home chemicals in children, workplace and home controls including education, and assessing the health of employees, families and communities. Educational intervention programs involving employers, employees, children, teachers, parents, physicians and other health professionals should be developed for prevention. For example; hygienists can visit the workplaces and take the necessary measurements to show whether existing decontamination procedures are effective in preventing contaminants from being carried home. In addition, clinicians should be aware of occupational contaminants transported to the home, and the medical history should include questions about the profession of the parents or spouse (2). It is aimed to alleviate the related health problems in tertiary prevention. Tertiary protection includes community-based programs, improved access to health care for all family members and government programs.

The main recommendations for preventing and controlling workplace pollutants from being taken home can be listed as following: (i) reducing exposure in the workplace by observing safety practices, (ii) regular wet cleaning of floors and work surfaces, avoiding dry dusting and brushing, (iii) using appropriate and effective washing methods to ensure decontamination from the skin, (iv) to take a shower before leaving the workplace, (v) to take a shower immediately upon arrival if it cannot be done at the workplace, (vi) to change work clothes and work shoes before going home, (vii) leaving the contaminated clothing and shoes at workplace to be properly cleaned by the employer (viiii) disposal of the disposable coveralls and shoe covers properly, (ix) keeping street clothes or shoes in separate areas in the workplace to prevent contamination, (x) washing the contaminated clothing separately from family laundry if it is necessary to wash at home, (xi) prohibition of bringing contaminated work items home (xii) separation of work areas from living areas (for those who work in their homes), (xiii) separation of work vehicles from personal vehicles, (xiv) regular cleaning of vehicles used for work, (xv) preventing family members from visiting workplaces and informing family members about this (xvi) proper storage and disposal of hazardous materials for those who work in their homes.

Conclusion

There are numerous occupational contaminants originating from a wide variety of industrial areas and working environments. These pollutants can be carried from work to home by employees without realizing it through their clothing, skin, hair, work tools and vehicles. Apart from chemical, biological, radioactive occupational pollutants, various psychosocial stressors should also be considered as an exposure factor that can affect the behavior of employees and disrupt family and social relations, and this should be taken into account when applying appropriate intervention methods. As a result of all these, other than occupational diseases or injuries that may occur in the employee, various adverse health effects attributed to occupational pollutants may also develop in employee's family members. In addition to individual sensitivities that can change within the family, it has been observed that socio-cultural and socioeconomic differences in the society can also change the exposure rates of employees and their

families from occupational pollutants. For these reasons, take-home exposures are a major problem not only for occupational health but also for public health. In this review article, transportation ways and variety of pollutants taken home, population at risk and occupational vulnerabilities are examined, and measures to prevent take-home exposures are discussed. It was aimed to help researchers to have a comprehensive view of take-home exposures.

The proven existence of take-home exposures and their adverse health effects made it mandatory to make regulations in the labor legislation. Prevention of exposures in the workplace by considering safety practices is the most important step in the primary prevention strategy. However, in the literature, it has been found that current information about exposures taken to home and their adverse health effects is not sufficient, and more studies are required to be conducted. It is clear that it is almost impossible to predict which occupational exposure factor may pose a future threat to employees and their families. For this reason, it should be taken into consideration that besides primary prevention, which is the most effective and proactive approach, secondary and tertiary prevention may have defining features for new diseases in addition to their complementary features. In fact, a well-functioning control strategies and ensuring compliance with the determined workplace hygiene standards supported by healthy public policies after awareness of take-home exposures can be very effective in preventing this important public health problem.

The first of the action principles proposed in the first part of the "Closing the gap in a generation, 2008" report by the World Health Organization Commission on Social Determinants of Health is "Improve the daily living conditions in environments where people are born, grow up, live, work and age". Exposures carried from work to home should be addressed within the integrity and interaction of the work environment, sheltering-housing conditions and settlement, and not only in physical terms, but also in social and sociocultural scope.

Ethics

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - İ.B., B.P.; Design - İ.B., B.P.; Literature Search - İ.B., B.P.; Writing - İ.B., B.P.

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Local and Regional Flap Approaches for the Repair of Postsurgical Tissue Defects in the Head and Neck Region

Baş ve Boyunda Cerrahi Sonrası Oluşan Defektlerin Onarımında Lokal ve Rejyonel Fleplerin Kullanımı

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ABSTRACT

Introduction: In this retrospective study, the indications and success, complication and mortality rates of local and regional flaps used in head and neck reconstruction were investigated.

Methods: Patients operated for head and neck reconstruction between the years 2014 and 2019 were included in this retrospective study.

Results: A total of 41 patients were included in the study. The mean patient age was 60.3±20.6 (range: 8-89). In 39.0% (n=16) of patients, the pectoralis major muscle flap was used for reconstruction. In 17.1% (n=7) of patients, the local advancement flap was used. In all, 29% (n=12) of patients had squamous cell carcinoma, 19.5% (n=8) had basal cell carcinoma, and 14.6% (n=6) of patients had tracheoesophageal fistula. The overall complication rate was 29.2%. The mortality rate was 2.4% (n=1).

Conclusion: In this retrospective study, it was objectively demonstrated that local regional pedicle flaps can be used safely in the repair of head and neck defects with correct patient analysis, wound site and defect evaluation, and flap planning.

Keywords: Head and neck reconstruction, local flaps, regional flaps

ÖZ

Amaç: Bu retrospektif çalışmada baş ve boyun cerrahisinde kullanılan lokal ve rejyonel fleplerin endikasyonları, başarı komplikasyon ve mortalite oranları incelendi.

Yöntemler: Çalışma retrospektif olarak planlandı. Bu çalışmaya baş ve boyun rekonstrüksiyonu amacıyla 2014 ve 2019 yılları arasında kliniğimizde lokal ve rejyonel opere edilen hastalar dahil edildi.

Bulgular: Kırk-bir hasta çalışmaya dahil edildi. Ortalama hasta yaşı 60,3±20,6 (aralık: 8-89) idi. Hastaların %39'unda (n=16) pektoral majör kas flebi, %17'sinde (n=12) lokal ilerletme flebi kullanıldı. Etiyoloji hastaların %29'unda (n=12) sküamöz hücreli karsinom, %19,5'inde (n=8) bazal hücreli karsinom ve %14,6'sında (n=6) trakeaözofageal fistül idi. Genel komplikasyon oranı %29,2 olarak hesaplandı. Mortalite oranı %2,4 (n=1) idi.

Sonuç: Bu retrospektif çalışmada lokal rejyonel pediküllü fleplerin doğru hasta, yara ve defekt analizi ve uygun planlama ile baş ve boyun defektlerinde güvenli bir şekilde ve yüksek başarı oranı ile kullanılabileceği objektif verilere dayanarak gösterilmektedir.

Anahtar Kelimeler: Baş ve boyun rekonstrüksiyonu, lokal flepler, rejyonel flepler

Introduction

Head and neck reconstruction is an important issue due to the special structure of the face and scalp. In particular, the facial region contains important and specific functional anatomical structures, especially the nose, ear, eye, and mouth. Reconstructive needs arise after various operative procedures, especially tumor surgery or events that cause soft tissue and skeletal damage, such as trauma. Reconstructing the most functional and stable structure possible should be the main goal of reconstructive surgery in cases that disrupt the normal anatomy of the orbital cavity, oral cavity, nasal pyramid, and ear. Tissue repair is performed according to the plastic surgery reconstruction pyramid that progresses from simple to more complex. According to this pyramidal approach, soft tissue repair is preferably performed with primary suturing, partial or full thickness skin graft, local flap, regional flap, and free flap options. Sometimes, these options are applied in combination to the patient's defect (1-4).

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If possible, the damaged skeletal support tissue is repaired by rigid fixation of the broken fragments in a straight line with plate screws. If primary skeletal repair is not possible, the defect is repaired using a free bone graft, vascularized autogenous bone grafts, or allograft materials. The primary consideration is the patient's point of view. Accordingly, the correct approach is the simplest one for the patient. A free flap should not be considered if repair with other options is possible, and we should not use this trump card in the future, considering the need for further surgery. In most patients, a free flap is not required unless there is a strain on the surgical indication, and existing defects can be repaired with other options at a much lower risk of donor-site morbidity (5-7).

In this study, our aim was to evaluate the indications and success, complication, and mortality rates of local and regional flaps used in head and neck reconstruction.

Methods

The study was designed as a retrospective study. Patients operated on for head and neck reconstruction with regional and local flaps between the years 2014 and 2019 were included in the study. Ethics approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2474, date: 10.07.2020). Informed consent was obtained from all the patients. Patients who had primary and secondary graft repairs and microsurgical reconstructions were not included. The complication and mortality rates, pathological features, and success rates were investigated (Figure 1-4).

Local regional flaps were planned for chronic wound healing problems such as fistulas and repair of soft tissue defects after primary surgical interventions such as tumor excision, vascular malformation surgery, and cochlear implant placement. Scalp flaps with an axillary pattern (based on the occipital and posterior auricular vessels) were used, and skin grafts were applied to the flap donor areas in large scalp defects and defects after tumor surgery. Pectoralis muscle flaps with an axial circulation pattern were used for extensive tissue defects and chronic draining wounds after tracheoesophageal fistula or tumor excision and neck dissection surgery. Pectoral flap donor areas were mostly closed primarily. In late and simultaneous repairs of patients with cochlear implants exposing scalp defects with discharge and defects in the facial region after tumoral surgery, random transformation and rotation flaps were used, and donor areas were closed primarily.

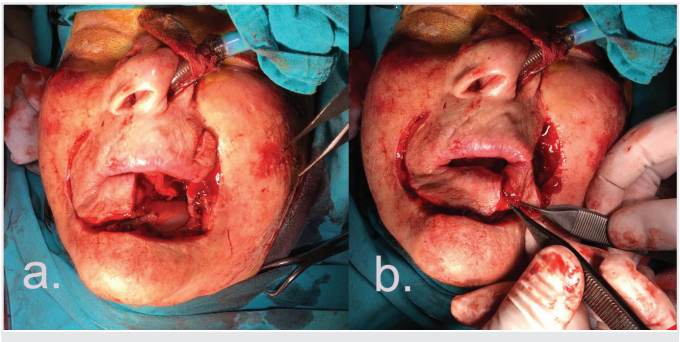

Figure 1. Peroperative photographs of a 68-year-old patient with a lower lip defect following squamous carcinoma excision (a) and reconstruction using Karapandzic and Estlander flaps (b)

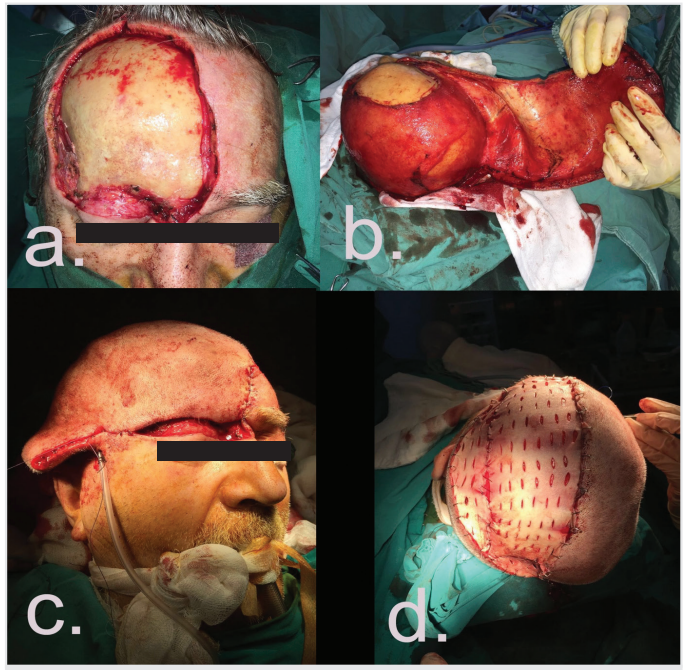

Figure 2. A 60-year-old patient with frontotemporal defect reconstruction using a scalp flap following microcystic adenoid carcinoma excision. Preoperative view of the defect. (a) Flap elevation (b) and insertion of the flap into the defect (c). Split thickness skin grafting was used to cover the donor area defect (d)

Figure 3. An 82-year-old patient with an infraorbital defect following dermal sarcoma excision (a) was repaired using a Mustarde cheek advancement flap (b). Photographs of the patients 1 week (c) and 1 month (d) following surgery

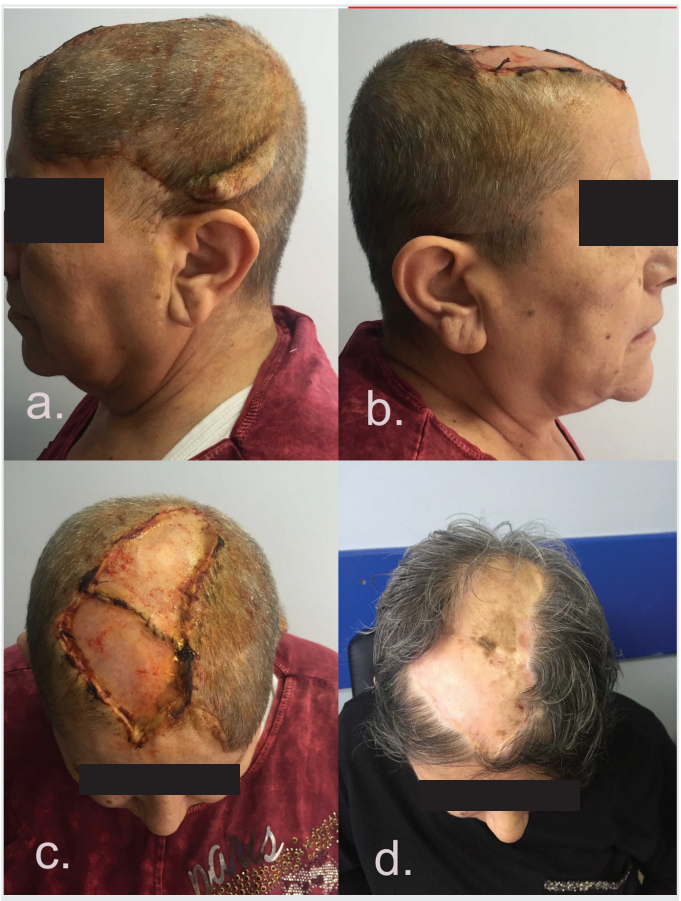

Figure 4. A 55-year-old patient with scalp flap reconstruction (a) following a skin defect due to wound infection and cerebrospinal fluid leak following vascular malformation surgery. The flap was based on superficial temporal and occipital vessels. The donor was repaired with a split thickness skin graft (b-d)

Statistical Analysis

Descriptive analysis was performed using GraphPad Prism 7.0 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results

A total of 41 patients were included in the study. The mean patient age was 60.3±20.6 (range: 8-89), 33 of the patients were male, and 8 of the patients were female. The mean follow-up time was 3.1±1.2 years (Table 1). In 39.0% (n=16) of patients, the pectoralis major muscle flap was used for reconstruction. In 17.1% (n=7) of patients, a local advancement flap was used (Table 2). In all, 29% (n=12) of patients had squamous cell carcinoma, 19.5% (n=8) had basal cell carcinoma, and 14.6% (n=6) had tracheoesophageal fistula (Table 3). The overall complication rate was 29.2%. In all, 3, 4, and 5 patients encountered hematoma, infection, and wound dehiscence in the postoperative period, respectively. Four revision surgeries were performed. The mortality rate was 2.4% (n=1). One patient died in the early postoperative period due to massive bleeding in the neck area (Table 4). Most infections resolved with local and systemic antibiotherapy. Suture line detachments and superficial

Table 1. Patient demographics (n=41)

	Mean (standard deviation)	Range
Mean age (years)	60.3±20.6	3-89
Mean follow-up time (years)	3.1±1.2	1-6

Table 2. List of reconstructive methods (n=41)

	Number	Percentage
Pectoralis major flap	16	39.0%
Local advancement flap	7	17.1%
Frontal flap	4	9.8%
Nasolabial flap	2	4.9%
Limberg flap	2	4.9%
Karapandzic flap	2	4.9%
Fasciocutanous scalp flap	2	4.9%
Transposition flap	2	4.9%
Mustarde flap	1	2.4%
Estlander flap	1	2.4%
Rotation flap	1	2.4%
Deltopectoral flap	1	2.4%

Table 3. Pathological features of the patients

	Number	Percentage
Squamous cell carcinoma		
*Nasal squamous cell carcinoma	3	7.3%
*Lip squamous cell carcinoma	5	12.2%
*Ear squamous cell carcinoma	1	2.4%
*Intraoral squamous cell carcinoma	1	2.4%
*Neck squamous cell carcinoma	1	2.4%
*Cheek squamous cell carcinoma	1	2.4%
Basal cell carcinoma		
*Nasal basal cell carcinoma	4	9.8%
*Upper lip basal cell carcinoma	2	4.9%
*Ear basal cell carcinoma	2	4.9%
Tracheoesophageal fistula	6	14.6%
Cochlear implant exposition	4	9.8%
Larynx ca	3	7.3%
Pharyngocutaneous fistula	2	4.9%
Facial malignant melanoma	1	2.4%
Intraoral retromolar epidermoid tumor	1	2.4%
Microcystic adnexial carcinoma	1	2.4%
Pleomorphic dermal sarcoma of right maxilla	1	2.4%
Neck metastasis of lingual squamous cell carcinoma	1	2.4%
Recurrent frontal mass	1	2.4%

Table 4. Complication and mortality rates following surgery

	Number	Percentage
Hematoma	3	7.3%
Infection	4	9.7%
Wound dehiscence	5	12.1%
Revision surgeries	4	9.7%
Overall complication rate	12	29.2%
Mortality rate	1	2.4%

wound healing problems were treated with appropriate dressings. No significant flap contraction was observed in the late period.

Discussion

In our study, the majority of patients were operated on with a pectoralis major flap. The complication rates were low, and the success rate was high. The pectoralis flap can be used in head defects up to the superior border of the temporalis muscle. Fasciocutanous scalp flaps can be used in scalp areas where the pectoralis flap is out of reach. The utilization of these two flaps alone can eliminate the need for microsurgical reconstruction in the majority of patients that require head and neck reconstruction. The only major group of patients that required microsurgical reconstruction in the head and neck region were those with major bone defects such as tumors of the mandible. In our series, there was only one mortality. This mortality was not directly related to the flap surgery but rather due to postoperative abundant bleeding in the cervical lymph node dissection area.

Both random and axial pattern loco regional flaps were included the study. Local flaps with random and axial circulation patterns are the commonly preferred flap options in the reconstruction of the head and neck region and can be applied easily in direct proportion to the surgical experience when planned correctly. Random pattern local flaps are fed randomly from the subcutaneous vascular network and do not have a distinct feeder vessel, depending on the circulation pattern. Axial pattern flaps, on the other hand, are flaps with a distinct dominant nourishment vessel and are lifted over their pedicle. They can be planned much longer and narrower than random flaps and can even be designed as an island flap only on the vascular pedicle. Thus, it is an advantage to have a much wider range of motion axis. We also designate local flaps with names such as transposition flap, rotation flap, bilobed flap, or advancement flap, according to the surgical design of the flap (8-11).

Transposition flaps can be safely planned with the long side a maximum of three times the length of the short side. Rotation flaps are planned as semicircles adjacent to the defect and are slid over a pivot point. Unlike rotational flaps, advancement flaps are designed adjacent to the defect and are directly advanced to the defect, creating no rotational axis movement. Single and multiple z-plasty, rhomboid flaps, v-y flaps, and w-plasty flaps are other local flap designs that can be considered. Random flaps are local flaps that require good surgical planning; otherwise, their vascular safety may not be very high. We often preferred them to cover small defects in the head and neck area. The random flap donor area is mostly closed primarily, and a second local flap or skin graft is rarely used. Care should be taken to ensure that the adaptation of the flap to the defect area is tension-free. Otherwise, detachments due to marginal necrosis and delays in healing are observed in the suture lines. If the flap is planned with too high length to width ratio, partial or full thickness necrosis is inevitable in its distal area (12-18).

We performed soft tissue repairs by using flaps with a local random circulation pattern and a regional axial pattern in the patients included in our current study. All of these patients with chronic wounds and tissue defects had pioneering surgeries for various reasons. Postoperative recovery problems and soft tissue deficiencies were repaired with local and regional flaps as a result of surgical planning. Axial patterned local and regional flaps are much safer than those fed randomly. Due to their vascular safety, they can be planned much larger and adapted to more distant regional defect areas. According to the course of the dominant nourishing pedicle within the tissues, axial flaps can be elevated as skin flaps, fasciocutaneous flaps, muscle flaps, muscle skin flaps, and muscle skin and bone flaps. It is important to decide the flap to be used according to the size and depth of the defect area, the vascular quality of the wound bed, the presence of infection, and the required tissue deficiency.

Conclusion

The use of local and regional tissues in reconstruction shortens the duration of the surgical procedure, as there is no need for a second surgical team and work area and the need for position adjustment for the patient during the operation is minimal. In addition, since neighboring tissues are used, similar tissue properties are transferred, and better tissue adaptation is achieved. Axial pattern flaps such as the scalp flap and pectoral flap are preferable in more problematic and large defects.

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Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Ethics Committee (approval number: 2474, date: 10.07.2020).

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - D.A., G.T.; Concept - D.A., G.T.; Design - D.A., G.T.; Data Collection or Processing - D.A., G.T.; Analysis or Interpretation - D.A.; Literature Search D.A.; Writing - D.A.

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Is Sarcopenia Related to Mortality in Patients with Chronic Obstructive Pulmonary Disease in the Intensive Care Unit?

Yoğun Bakım Ünitesinde Tedavi Edilen Kronik Obstrüktif Akciğer Hastalarında Sarkopeni Mortalite ile İlişkili midir?

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ABSTRACT

Introduction: On admission to the intensive care unit (ICU), functional and general health stata are important baseline characteristics of critically ill patients with chronic obstructive pulmonary disease (COPD). The measurement of total psoas muscle area (PMA) is under investigation to determine physical frailty and sarcopenia, especially encountered in the elderly, to predict adverse outcomes and mortality in patients requiring in-hospital and ICU management. We aimed to assess the clinical value of total PMA for the prediction of mortality in COPD patients requiring ICU management of acute exacerbations.

Methods: The clinical data of 62 patients whose abdominal computed tomography (CT) scans were available in the hospital Picture Archiving Communication System were collected. The mean duration of stay in the ICU was 7.7±8.8 and 9.4±12.3 days in survivors and non-survivors. The main causes of mortality in non-survivors were respiratory failure and cardiac arrest. For measurements from CT scans, images of the caudal end of the third lumbar vertebra were used. Right and left PMAs were measured to obtain the total PMA and density.

Results: Of 62 patients, 20 (32.2%) were non-survivors (male: 13, female: 7), and 42 were survivors (male: 32, female: 10). There was no significant difference between non-survivors and survivors regarding total PMA and density values ($p>0.05$). In non-survivors and survivors, females had lower total PMA ($p<0.05$). There was no significant association between clinical and PMA data ($p>0.05$).

ÖZ

Amaç: Yoğun bakım ünitesine (YBÜ) kabul aşamasında, ileri derecede kronik obstrüktif akciğer hastalığı (KOAH) olan hastaların fonksiyonel ve genel sağlık durumları önem arz eder. Toplam psoas kas alanının (PKA) ölçümü, hastane ve YBÜ tedavisi gerektiren, özellikle yaşlı hastalarda, olumsuz sonuçları ve mortaliteyi tahmin etmek için, fiziksel kırılganlık ve sarkopeninin araştırılmasında kullanılan bir yöntemdir. Bu çalışmada, KOAH akut alevlenme nedeniyle YBÜ tedavisi gereken hastalarda, mortalitenin tahmini için total PKA'nın klinik değerini araştırmayı amaçladık.

Yöntemler: Bu kesitsel çalışmaya akut KOAH atağı ile YBÜ'de tedavi edilen hastalar alındı. Abdominal bilgisayarlı tomografisi (BT) olan 62 hastanın verileri toplandı. Yoğun bakımda kalış süresi yaşayan hastalar ve ölenlerde ortalama 7,7±8,8 ve 9,4±12,3 gün idi. Mortalite gelişen hastlarda en sık sebepler solunum yetmezliği ve kardiyak arrestti. BT ölçümlerinde 3. lumbal vertebranın kadual ucunun görüntüsü kullanıldı. Total PKA'nın hesaplanması için, sağ ve sol PKA dansite değerleri ile birlikte ölçüldü.

Bulgular: Çalışmaya dahil edilen 62 hastanın 20'si ölmüşken (erkek: 13, kadın: 7), 42'si sağ kalmıştır (erkek: 32, kadın: 10). Ölenler ile yaşayanlar arasında total PKA ve dansite değerleri açısından anlamlı bir fark bulunmadı ($p>0,05$). Kadın hastaların total PKA değeri ölenlerde yaşayanlara göre anlamlı derecede düşük bulunmuştur ($p<0,05$). Hastaların klinik verileri ile PKA değeri arasında anlamlı bir ilişki bulunmadı ($p>0,05$).

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ABSTRACT

Conclusion: The total PMA lacks sufficient power to predict mortality in patients managed with acute exacerbations of COPD in intensive care settings. There is a need for further studies with different sets of findings to assess the contribution of physical frailty and sarcopenia to adverse outcomes in the ICU management of COPD patients.

Keywords: Chronic obstructive pulmonary disease, COPD, frailty, sarcopenia, psoas muscle area, computed tomography

ÖZ

Sonuç: Total PKA, KOAH alevlenme ile YBÜ'de tedavi edilen hastalarda mortaliteyi tahmin etmede yeterli değildir. YBÜ'de yatırılarak tedavi edilen KOAH hastalarında karşılaşılan olumsuz sonuçlara, fiziksel kırılganlık ve sarkopeninin katkısını değerlendirmek için, farklı bulgu grupları ile daha ileri araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı, KOAH, kırılganlık, sarkopeni, psoas kas alanı, bilgisayarlı tomografi

Introduction

Chronic obstructive pulmonary disease (COPD) is a growing healthcare concern that is gaining worldwide importance because of its relatively high prevalence and remarkable morbidity and mortality with the contribution of aging in the population (1,2). COPD can be accompanied by variable comorbidities. COPD exacerbations are associated with a considerable decline of lung function and can significantly worsen survival outcomes, especially in patients who require mechanical ventilation (3). Moreover, the presence of COPD contributes as a prominent risk factor, increasing mortality and morbidity in critically ill patients hospitalized for management of other systemic disorders (4).

During management of in-hospital patients with several systemic disorders, including acute exacerbations of COPD, some of the challenges are related to physical frailty. The presence and severity of frailty can increase the duration and usage of diagnostic and therapeutic procedures during management of main and comorbid disorders; in addition, frailty may impair the overall outcome of patients managed in the intensive care unit (ICU) (2,5).

The all-cause mortality rate in the ICU is higher than in other hospital services. Advanced age, gender, primary disease and its severity, comorbid disorders, and biomarkers such as C-reactive protein, albumin, and ferritin are among the factors considered to increase the risk of fatality (6). Unfortunately, these conditions and biomarkers lack sufficient power to be used directly for the prediction of mortality during management of COPD patients in the ICU. Within this perspective, nowadays, there are also several tools to assess frailty, mainly in the elderly population, to understand patients' basic health conditions; however, their use is not tested adequately in in-hospital patients with various clinical conditions, including the presence of comorbid disorders during intensive care requirements.

With the aging population, the contribution of frailty and pre-frailty as a comorbidity increases considerably in COPD patients (2). Frailty is accepted as a potent predictor of adverse outcomes in various clinical settings (7). Sarcopenia, defined as low muscle mass, is the preferred approach to frailty assessment (8). Sarcopenia is measured commonly by the skeletal muscle mass index (9), and the psoas muscle is the most used muscle for measuring the skeletal muscle mass. Patients managed in the ICU may need to undergo a computed tomography (CT) scan of their body among the diagnostic procedures, and these CT scans may be beneficial for evaluating sarcopenia with total psoas muscle area (PMA). Sarcopenia has the potential to be used as a predictor of the clinical and surgical course and patient morbidity (10,11). Moreover, Yokoyama et al. (12) reported that sarcopenia is a poor prognostic parameter during the management of patients with disordered peripheral arteries.

However, there is not sufficient data to determine the impact of sarcopenia on morbidity and mortality of COPD patients in the ICU. The overall objective of the present trial was to evaluate the association between in-hospital mortality and sarcopenia measured by CT scan with PMA in COPD patients requiring management in the ICU. We hypothesized that sarcopenia is an independent predictor of mortality in COPD patients in the ICU.

Methods

This cross-sectional study included COPD patients managed with acute exacerbations in the ICU of our tertiary care center between May 2012 and May 2017. This study approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Human Research Ethics Committee (approval number:1593, date: 21.12.2018). After informed consent was obtained from the patients or their relatives, selected clinical variables at admission and during follow-up were recorded from the patients' electronic hospital records. COPD patients managed with acute exacerbations in the ICU were accepted as eligible for the study. Patients who had any comorbidities that could influence their outcomes were excluded from the study. Sixty-two COPD patients who had abdominal CT scans for any reason during their hospital stays were included in the study for further evaluation. The diagnosis of COPD was made according to radiographic findings, physical examination, and management plans, including prescriptions that were recorded in the hospital information system of our institution. Medical therapy given to these patients included systemic steroids, inhaled steroids, inhaled anticholinergics, and β2 agonists.

Measurement of PMA

With the available CT scan images, we determined the quantity of skeletal muscle. CT images obtained from 128-slice spiral CT with a 2 mm section thickness (Philips, Holland). For the measurements to obtain information about the skeletal muscle cross-sectional area (cm^2), images of the caudal end of the third lumbar vertebra were used. With these images, right and left PMAs were measured to obtain the total PMA. A radiologist performed these measurements while blinded to the severity and clinical outcomes in the study population. Intraobserver

agreement was found to be adequate with a calculated Kappa value of 0.83. A CT image of the measurement is presented in Figure 1.

Psoas muscle radiation attenuation was also calculated, and mean Hounsfield unit values as density were taken for statistics.

In the study population, selected clinical data were recorded including age, sex, smoking status, length of stay in the ICU, some laboratory measurements, and in-hospital mortality status. The relationship of these clinical parameters with the PMA values was assessed with correlation analyses.

Statistical Analysis

Statistical analyses were performed with SPSS statistical software (IBM SPSS, Version 22.0, IBM Corporation, Armonk, NY, USA). Normality tests for continuous variables were conducted with the Shapiro-Wilk test. Numeric parameters were given as means with standard deviation and analyzed with t- or Mann-Whitney U tests when they were parametric or non-parametric, respectively. Categorical data were presented as numbers with percentages and, where appropriate, they were analyzed with a chi-square test. The relationships between continuous variables were examined with the Spearman's test. A p-value of less than 0.05 was set as the threshold for statistical significance.

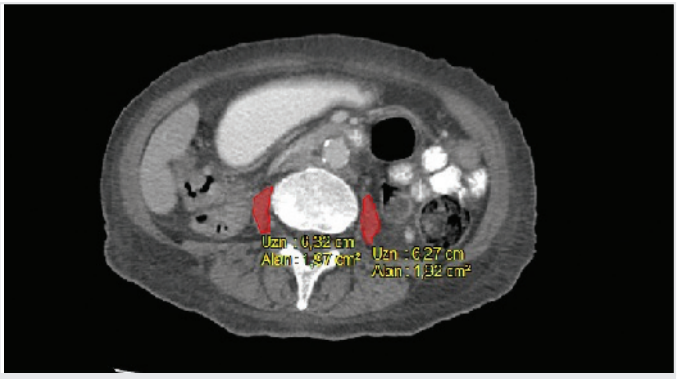

Figure 1. CT image of the measurement of bilateral psoas muscle area
CT: Computed tomography

Results

One hundred six COPD patients were followed in the ICU during the study period. Forty-four of these patients had lung cancer, so they were excluded from the study. Previous CT scans of 62 patients were found by a search in the hospital PACS system and included in the study. The mean duration of stay in the ICU was 7.7±8.8 and 9.4±12.3 days in survivors and non-survivors, respectively. Causes of mortality in non-survivor were mainly respiratory failure and cardiac arrest.

The demographic and some laboratory data of all patients (survivors and non-survivors) are presented in Table 1, and right, left, and total PMA and density values are presented in Table 2. Twenty (32.2%) of 62 patients died during ICU stay. The mean age of the study group was 59.2±15.2 years; 17 of them (27.4%) were female. Although PaO_2 values were higher, and $PaCO_2$ values were lower in survivors, this difference did not reach statistically significance, nor did other parameters (p>0.05). The mean right, left, and total PMA of 62 patients were 6.5±2.7 mm^2, 6.3±2.6 mm^2, and 12.8±5.3 mm^2, respectively. Considering the non-survivors and survivors, the PMA values were found to be comparable (p>0.05) (Table 2).

Table 1. Selected demographic and laboratory data of survivors and non-survivors

	Survivors (n=42)	Non-survivors (n=20)	p
Age (y)	60.3±14.5	56.9±16.6	>0.05
Sex (F/M)	10/32	7/13	>0.05
Albumin (g/dL)	2.9±0.6	2.8±0.8	>0.05
Total protein (g/dL)	6.0±0.7	6.0±0.9	>0.05
CRP (mg/L)	101.0±103.7	141.0±115.6	>0.05
WBC ($x10^3/mm^3$)	13.0±5.0	13.6±14.4	>0.05
Hematocrit (%)	34.3±7.0	34.6±6.8	>0.05
Platelet ($x10^3/\mu L$)	259.4±125.8	208.0±111.1	>0.05
PaO^2 (mmHg)	88.5±62.1	77.3±44.2	>0.05
$PaCO^2$ (mmHg)	49.5±17.7	59.4±25.7	>0.05

Data are presented as means with standard deviation.
F: Female, M: male, CRP: C-reaktif protein, WBC: white blood cell

Table 2. Total PMA and density values of survivors and non-survivors

	Survivors (n=42)	Non-survivors (n=20)	p
Right psoas area (mm^2)	6.4±2.4	6.8±3.3	>0.05
Left psoas area (mm^2)	6.2±2.6	6.4±2.8	>0.05
Total psoas area (mm^2)	12.6±5.0	13.15±6.0	>0.05
Density (HU)	51.5±23.1	46.7±20.1	>0.05

Data are presented as means with standard deviation.
PMA: Psoas muscle area, HU: Hounsfield unit

When we categorized the participants according to gender (Table 3), males in both survivors and non-survivors had higher total PMA values than their female counterparts ($p<0.05$). However, the density values did not differ between survivor and non-survivor males and females ($p>0.05$). There was no significant correlation between participants' demographic, laboratory, and psoas data ($p>0.05$).

Discussion

In the present study, data analyses did not support the value of total PMA and density measured with an approved method using CT images to predict in-hospital mortality in COPD patients admitted to the ICU. Although male patients had higher PMA and density than female patients, overall, the results indicated no significant difference between the 32.25% of patients who did not survive and the 67.75% of patients who survived. We could not determine any correlation among the demographic, laboratory, and PMA data. Another finding of this study was that these patients were somewhat younger than other patients admitted to the ICU. In general, elderly persons need in-hospital management because of acute exacerbations of their chronic disorders that affect several organ systems. It has been reported that 46% of patients admitted to the ICU are seniors (13). In our study, the mean age of patients hospitalized in the ICU was 59.2±15.2 years. In a study by Unal et al. (14), the mean age of patients in the ICU was 73.9 years, and 77.5% of them were in the geriatric age range (>65 years).

Some studies have examined the value of total PMA in the assessment of sarcopenia status to predict outcomes in patients with different disorders. The findings have been contradictory as discussed below. Some authors concluded that total PMA can have prognostic value in patients who undergo emergency surgery, cancer resection, or liver transplantation (15-17). In a study by Waduud et al. (18), total PMA was assessed in patients who had elective abdominal aortic aneurysm repair. Their study did not support the value of total PMA for the prediction of mortality at 30 days, 1 year, or 4 years, and for the requirement of ICU admission, prolonged hospital stay, or readmission within 30 days. On the other hand, Thurston et al. (19) and Newton et al. (20) both reported a longer duration of hospital stay in sarcopenic patients who underwent endovascular aneurysm repair. Contrary to those findings, Kays et al. (21) reported that the presence of sarcopenia was not a determining factor for the development of early or late complications. In accordance with the results of the current study, Heard et al. (22) found that sarcopenia did not influence the decision about the management strategies required after postintervention discharge. Boutin et al. (23) assessed the paravertebral muscle area at the level of T12 and the psoas muscle at the level of L4 in a group of elderly patients requiring hip fracture management. Although they found no meaningful association of decreased cross-sectional area of the psoas muscle with mortality, they noted that patients with decreased PMA also had a lower survival rate. Couch et al. (24) concluded that there was no relationship between the lower mass of psoas area and prognosis after analysis of clinical data in 225 elderly trauma patients. Their findings supported that lean psoas area cannot be used as a predictor for the mortality or complications of trauma. Patients who underwent surgery of major internal organs (25-27) showed an association between PMA and all-cause mortality: low PMA was related to increased mortality rates. Overall, to draw conclusions by comparison of findings from similar studies poses a challenge because of inconsistency among definitions related to the measurement criteria for evaluation of sarcopenia. Garg et al. (28) suggested that no meaningful association existed between PMA and mortality one year later after their management. In contrast, Saji et al. (29) demonstrated an association of PMA with mortality 6 months after their management. Patients with lower levels of PMA had higher mortality rates (30,31).

In this study, measurement of total PMA was preferred as a tool for the measurement of total abdominal muscle area, because after a short training period, the observer was able to determine the suitable area for psoas muscle measurements after performing a short scan. The measurement of total PMA was reported to be a reproducible tool in previous studies, because no intraobserver and interobserver differences considered meaningful was observed. The method is feasible using most standard PACS viewers, so there is no need for any additional resources, and is representative of likely clinical application. However, the Hounsfield-based method of image analysis has a potential benefit, because it is demonstrated that sarcopenic myosteatosis can be associated with increased mortality, suggesting that measuring the PMA may not be enough to accurately assess the actual muscle bulk (21). Therefore, we also calculated the density of the muscle for determining sarcopenia in our cohort.

The patient's gender may be a prominent contributor to the development and course of sarcopenia to predict their mortality. In a study by van Mourik et al. (32), although the PMA of females was found to be correlated with all-cause and cardiac mortality within 2 years, the PMA of males did not present a relationship with mortality. Higher baseline values of PMA were obtained with males than with females, which might serve as a larger reserve before having the negative outcome of a low PMA. Mamane et al. (33) investigated males and females separately

Table 3. Total PMA and density values according to the gender of participants in both survivor and non-survivors

	Non-survivor		
	Male (n=13)	**Female (n=7)**	**p**
PMA (mm^2)	15.1±5.9	9.5±4.7	0.045
Density (HU)	58.7±23.2	38.1±17.2	0.055
	Survivor		
	Male (n=32)	**Female (n=10)**	**p**
PMA (mm^2)	14.3±4.3	7.3±2.7	0.001
Density (HU)	46.4±18.8	46.4±18.8	0.897

PMA: Psoas muscle area, HU: Hounsfield unit

in participants who underwent transcatheter aortic valve implantation. They found higher one-year mortality in males. We also demonstrated higher values of total PMA in males, but sex-based differences were not predictive of mortality. Considering the results of the above studies, there are important differences among the characteristics of those cohorts in terms of their main and comorbid disorders. Our COPD patients were typically older and current or previous smokers with a high rate of cardiovascular and pulmonary comorbid disorders. Therefore, it is important to appreciate that it may be challenging and inadequate to capture the complex nature of the interplay between frailty and the comorbid states of subjects with a single tool such as the assessment of total PMA.

Study Limitation

This study has several limitations, including its retrospective observational nature and the single-center collection of COPD patients, which did not consider the severity of COPD and may therefore not be representative of all cohorts of COPD patients with different severity requiring ICU management. The patients included in this study were somewhat younger than those in most COPD populations. Therefore, the conclusions cannot be extrapolated to the comprehensive and long-term prognostic value of PMA as a screening tool, thereby necessitating a more prolonged follow-up period to determine time-dependent changes in the PMA and to establish its prognostic value in the future.

Conclusion

There is a need to assess physical frailty and sarcopenia in the management of acute exacerbations of COPD requiring ICU services. Overall, according to the results of the current study, the total PMA alone is not a successful tool for the prediction of in-hospital mortality in the acute exacerbations of COPD managed in the ICU. Considering the wide range of variability in its values from patient to patient, the total PMA may be a good alternative to determine the degree and change of sarcopenia during follow-up of COPD patients to improve the success of their management plan, especially in patients over than 65 years of age.

Ethics

Ethics Committee Approval: This is study approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Human Research Ethics Committee (approval number:1593, date: 21.12.2018).

Informed Consent: Informed consent was obtained from the patients. patients.

Peer-review: Externally peer-reviewed.

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Intestinal Atresia: Twenty Years of Experience at a Reference Hospital

İntestinal Atrezi: Referans Bir Hastanenin Yirmi Yıllık Deneyimi

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ABSTRACT

Introduction: The aim of this study was to reveal the factors that affect the clinical outcomes of patients undergoing surgery in our university hospital for intestinal atresia (IA) and to share our experience.

Methods: We analyzed data from 74 newborns with IA who underwent surgical treatment between January 1997 and December 2016.

Results: The study population consisted of 40 female and 34 male newborns with a mean age at diagnosis of 6.4±8.3 days. The mean birth weight was 2.3±0.6 kg, the mean gestational age was 35.6±2.8 weeks, the mean maternal age was 28.9±6.1 years, and the mean hospitalization time was 24.5±25.3 days. Duodenal atresia was the most common diagnosis (n=31, 42%) and colonic atresia the least common (n=2, 3%). The longest and shortest mean hospital stays occurred in patients with jejunal (32.8±41.6 days) and those with colonic (8±0 days) atresia, respectively. Although the survival rates were low in newborns with either intestinal or duodenal atresia (80% or 81%, respectively), all patients with pyloric or colonic atresia survived. Of the patients who died, 82% (9/11) had additional congenital abnormalities (X^2=8.461, p=0.004), which included major cardiac defects (n=3), Down syndrome (n=2), biliary atresia (n=1), esophageal atresia + tracheoesophageal fistula + anal atresia + tracheal atresia (n=1), esophageal atresia + tracheoesophageal fistula (n=1), and microcephaly (n=1). The mean hospital stay of patients with or without additional abnormalities was 26.4±21.4 or 23.04±28.04 days, respectively (p=0.207).

Conclusion: Among newborns with IA, duodenal atresia was the most common diagnosis and colonic atresia the least common. Additional congenital abnormalities negatively affect the hospital stay and mortality rate of newborns with IA.

Keywords: Intestinal atresia, surgical treatment, hospital stay, mortality, newborn

ÖZ

Amaç: Bu çalışmada, bir üniversite hastanesinde intestinal atrezi (İA) endikasyonu ile ameliyat edilen hastaların klinik sonuçlarına etkili olan faktörleri ortaya koymak ve deneyimlerimizi paylaşmak amaçlanmıştır.

Yöntemler: Ocak 1997-Aralık 2016 tarihleri arasında cerrahi tedavi uygulanan 74 İA'lı yenidoğan olgu çalışmaya alındı.

Bulgular: Çalışma popülasyonu, tanı anındaki ortalama yaşı 6,4±8,3 gün olan 40 kız ve 34 erkek yenidoğandan oluşuyordu. Ortalama doğum ağırlığı 2,3±0,6 kg, gebelik yaşı 35,6±2,8 hafta, anne yaşı 28,9±6,1 yıl ve hastanede kalış süresi 24,5±25,3 gündü. En fazla duodenal atrezi (n=31, %42), en az ise kolon atrezisi (n=2, %3) görüldü. En uzun ve en kısa ortalama hastanede kalış süreleri sırasıyla jejunal atrezili (32,8±41,6 gün) ve kolonik atrezili (8±0 gün) olgularda saptandı. Sağkalım oranları multipl İA'da ve duodenal atrezide düşük (sırasıyla; %80 ve %81) olmasına karşın pilorik atrezili ve kolonik atrezili tüm olgular hayatta kaldı. Ölen hastaların %82'sinde (9/11) ek konjenital anomaliler vardı (X^2=8,461, p=0,004). Bunlar majör kardiyak defektler (n=3); Down sendromu (n=2), biliyer atrezi (n=1) ve özofagus atrezisi + trakeoözofageal fistül + anal atrezi + trakeal atrezi (n=1), özofagus atrezisi + trakeoözofageal fistül (n=1) ve mikrosefali (n=1). Ek anomalisi olan ve olmayan hastaların ortalama hastanede kalış süresi sırasıyla 26,4±21,4 gün ve 23,04±28,04 gündü (p=0,207).

Sonuç: İA'lar arasında en sık duodenal atrezi, en az ise kolonik atrezi görüldü. Ek konjenital anomaliler İA'lı yenidoğanlarda hastanede kalış süresini ve mortalite oranını olumsuz etkilemektedir.

Anahtar Kelimeler: İntestinal atrezi, cerrahi tedavi, hastanede kalış süresi, mortalite, yenidoğan

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Introduction

Intestinal atresia (IA) is one of the most common causes of intestinal obstruction in newborns. The IA incidence is 2.5-3 per 10,000 live births (1,2). IA can be classified as follows. Type 1 cases have a transluminal septum accompanied by a proximal dilated bowel in continuity with a collapsed distal bowel (the bowel is usually of normal length). Type 2 refers to cases in which two blind-ending atretic ends are separated by a fibrous cord along the edge of an intact mesentery. Type 3A cases exhibit type 2 findings plus an additional mesenteric defect and a shortened bowel length, while type 3B cases have proximal jejunal atresia, often with malrotation, absence of most of the mesentery, and varying lengths of the ileum surviving after perfusion from the retrograde flow of a single supply artery. Type 4 refers to cases with multiple IAs of types 1, 2, and 3 in sequence (sausage appearance). However, in our study, we did not consider types 3A, B as separate entities; rather, we classified them together as type 3 IA (3). We used the expression "multiple IAs" for cases with more than one type of IA in different regions of the intestinal system.

Approximately 60 years ago, the mortality rate observed in newborns with IA was 30-50%, whereas the current survival rates are 90% or higher (4-6). Advancements in newborn care, total parenteral nutrition (TPN), maternal polyhydramnios/antenatal diagnoses, neonatal anesthesia, and surgical techniques have resulted in higher survival rates among affected patients (2). However, some studies have reported survival rates of 41.7-71.5% (7-9). Despite all efforts, newborns with IA still die due to additional congenital abnormalities, and those who survive may experience prolonged hospitalization due to the need for TPN and the presence of interfering infections.

The aims of this study were to determine the clinical and demographic characteristics of patients undergoing IA surgical treatment in a tertiary pediatric surgery and neonatal intensive care unit and to identify the factors affecting clinical outcome, as well as to share our experience.

Methods

The Fırat University Faculty of Medicine Ethics Committee approved the protocol before study initiation (approval number: 11, date: 16.11.2017). The study included pediatric patients undergoing surgical treatment for IA in the Pediatric Surgery and Newborn Intensive Care Unit of Fırat University Faculty of Medicine between January 1997 and December 2016. We excluded the data from patients with esophageal atresia (EA) only or with isolated anal atresia. We extracted the data from patient files retrospectively. We recorded data such as gestational age, sex, birth weight, age at diagnosis, 5-minute Apgar score, maternal age, prenatal diagnosis, symptoms and findings, direct abdominal radiographic findings, IA site, presence of multiple IAs, concomitant intestinal/systemic abnormalities, major cardiac defects, surgical technique, duration of hospital stay, short-term complications, clinical outcomes, and causes of mortality and morbidity. We compared the patient data according to the site of IA.

Statistical Analysis

For all statistical analyses, we used SPSS 21 for Windows (IBM SPSS Statistics, Armonk, NY, USA). Numerical variables are expressed as means ± standard deviation and categorical variables as percentages (%). We applied the Kruskal-Wallis test to compare variables with a non-normal distribution among more than two groups. We used the chi-square or Fisher's exact test to compare categorical variables. We evaluated binary categorical variables using the binomial test. We applied binary logistic regression to compare patients with and those without mortality. A p-value <0.05 was indicative of statistical significance.

Results

We evaluated 74 patients undergoing surgical treatment for IA. The newborn male to female ratio was 1.2. The mean age at diagnosis was 6.4±8.3 days (range: 1-45 days), the mean birth weight was 2.3±0.6 kg, the mean gestational age was 35.6±2.79 weeks, the mean maternal age was 28.9±6.1 years, the mean hospital stay was 24.5±25.3 days, and the mean 5-minute Apgar score was 7.6±1.7. The IA site was classified as duodenal (n=31, 41.8%), jejunal (n=17, 22.9%), ileal (n=15, 20.2%), multiple (n=5, 6.7%), pyloric (n=4, 5.4%), or colonic (n=2, 2.7%). Table 1 presents the patient characteristics according to the site of the atresia. The most common site was the duodenum. The 5-minute Apgar scores, gestational ages, birth weights, hospital stay durations, and rates of maternal polyhydramnios, multiple IAs or additional intestinal/systemic abnormalities, prematurity, sepsis, and mortality did not differ according to IA site ($p>0.05$). The complication rate was significantly higher in patients with multiple IAs than in those with IA at other sites ($p=0.05$).

Clinically, non-bilious vomiting was the most frequent complaint in patients with pyloric or duodenal atresia, whereas bilious vomiting/nasogastric drainage was the most frequent complaint in all other patients. The most common physical examination finding was abdominal distension. Radiographic findings of the patients revealed massive gastric distension in all patients with pyloric atresia (n=22, 71%) and double-bubble signs (n=8, 26%) and free intraperitoneal air (n=1, 3.2%) in patients with duodenal atresia. Air-fluid levels (n=15, 88%), free intraperitoneal air (n=1, 6%), and ground glass appearance/calcifications (n=1, 6%) were observed in patients with jejunal atresia. Of the 15 patients with ileal atresia, 11 (73%) had air-fluid levels, and 3 (20%) had intraperitoneal free air. The patient with ascending colonic atresia had intraperitoneal free air due to perforation. In addition, the patient with rectal atresia appeared to have a pouch colon. Four of the five (80%) patients with multiple IAs had air-fluid levels, and the remaining one (20%) had a massive gastric appearance.

The incidence of additional abnormalities was 68% in patients with duodenal atresia, 41% in patients with jejunal atresia, 24% in patients with ileal atresia, 80% in patients with multiple IAs, and 100% in patients with colonic atresia. Table 2 lists the additional abnormalities detected in the patients.

Mortality was observed in 4 of 33 (12%) patients undergoing surgery within the first 2 days after birth and in 7 of 41 (17%) patients undergoing surgery after more than 2 days; however, the difference was not statistically significant ($p=0.55$). The complication and mortality rates in patients with type 4 IA (40% and 20%, respectively) were higher than

those in patients with other types of IA. The survival rate of patients with pyloric atresia (n=4) who underwent pyloroplasty and web excision was 100%. The 31 patients with duodenal atresia underwent Kimura's diamond-shaped duodeno-duodenostomy (n=24), duodenotomy + duodenal web excision (n=6), or Kimura's diamond-shaped duodeno-duodenostomy + gastrostomy (n=1). The survival rate of the patients with duodenal atresia was 81%. The 17 patients with jejunal atresia underwent resection anastomosis (n=14), jejunostomy (n=2), or resection anastomosis + gastroschisis repair with a prosthetic patch (n=1). The survival rate of the patients with jejunal atresia was 88%. The 15 patients with ileal atresia underwent resection anastomosis (n=11), ileostomy (n=3), or resection anastomosis with gastrostomy (n=1). The survival rate of the patients with ileal atresia was 87%. The two patients with colonic atresia underwent either resection anastomosis (n=1) or resection anastomosis + colon pull-through (n=1); both patients survived. The patients with multiple IAs (n=5) underwent resection anastomosis (n=4) or resection anastomosis + ileostomy (n=1). Their survival rate was 80%. Table 3 lists the surgical interventions performed on patients with IA, and Table 4 presents the postoperative complications and related treatments.

Table 1. Disease characteristics according to the site of the atresia

Variable	Pyloric atresia (n=4)	Duodenal atresia (n=31)	Jejunal atresia (n=17)	Ileal atresia (n=15)	Colonic atresia (n=2)	Multiple atresias (n=5)	p
Male/female	3/1	13/18	11/6	11/4	1/1	1/4	0.222
Gestational age (weeks)	36.5±3	35.3±2.7	35.8±2.6	36.3±2.8	28.1±1.1	35.7±1.2	0.86
Birth weight (kg)	2.23±0.7	2.2±0.6	2.4±0.6	2.6±0.6	2.0±0.3	2.3±03	0.05
Maternal polyhydramnios (n, %)	2 (50%)	7 (23%)	8 (47%)	4 (27%)	1 (50%)	4 (80%)	0.259
Apgar score at 5 minutes	8.5±1	7.4±1.9	8.1±1.5	7.4±1.6	6±0	7±1.2	0.203
Congenital abnormalities (n, %)	2 (50%)	20 (65%)	4 (24%)	7 (47%)	0 (0%)	4 (80%)	0.078
Additional intestinal abnormalities (n, %)	0 (0%)	14 (45%)	9 (53%)	7 (47%)	1 (50%)	3 (60%)	0.441
Prematurity (n, %)	1 (%25)	15 (48%)	6 (35%)	4 (27%)	1 (50%)	2 (40%)	0.05
Sepsis (n, %)	0 (0%)	10 (32%)	4 (24%)	9 (60%)	0 (0%)	3 (60%)	0.125
Duration of hospital stay (days)	17.2±7.9	20.9±17.6	32.8±41.6	21.2±13.2	8±0	39.2±50	0.259
Complications (n, %)	0 (0%)	6 (19%)	4 (24%)	1 (7%)	0 (0%)	2 (40%)	0.005*
Mortality (n, %)	0 (0%)	6 (19%)	2 (12%)	2 (13%)	0 (0%)	1 (20%)	0.431

*The complication rate was statistically higher in the patients with multiple intestinal atresias

Table 2. Additional abnormalities detected in patients

Type of atresia (n, %)	Duodenal atresia (n=31)	Jejunal atresia (n=17)	Ileal atresia (n=15)	Colonic atresia (n=2)	Multiple intestinal atresias (n=5)
Down syndrome	10 (32.2%)	1 (5.8%)	2 (13.3%)	-	1 (20%)
Cardiac defect	4 (12.9%)	2 (11.7%)	4 (26.6%)	-	2 (40%)
Esophageal atresia	4 (12.9%)	-	1 (6.6%)	-	-
Anal atresia	4 (12.9%)	-	-	-	-
Tracheal atresia	1 (3.2%)	-	-	-	-
Biliary atresia	1 (3.2%)	-	-	-	-
Gastroschisis	1 (3.2%)	1 (5.8%)	-	-	1 (20%)
Choledochal cyst	1 (3.2%)	-	-	-	-
Posterior urethral valve	-	-	1 (6.6%)	-	-
Cleft palate	-	-	1 (6.6%)	-	-
Intestinal perforation	1 (3.2%)*	2 (11.7%)**	3 (20%)	1 (50%)	-
Cystic fibrosis	1 (3.2%)	-	-	-	-
Choanal atresia	-	1 (5.8%)	1 (6.6%)	-	-
Hypothyroidism	1 (3.2%)	-	-	-	-
Microcephaly	1 (3.2%)	-	-	-	-
Pouch colon	-	-	-	1 (50%)	-
Annular pancreas	7 (22.5%)	-	-	-	-
Penoscrotal hypospadias	1 (3.2%)	-	-	-	-

*Gastric perforation, **intrauterine occult jejunal perforation and necrotizing enterocolitis related to gastrointestinal perforation

Table 3. Surgical procedures performed in patients with intestinal atresia

Site of atresia	Number of patients	Primary operation
Pyloric atresia	4	Pyloroplasty
Duodenal atresia	31	Duodeno-duodenostomy (n=24), duodenal web excision (n=6), duodeno-duodenostomy + gastrostomy (n=1)
Jejunal atresia	17	Resection anastomosis (n=14), resection anastomosis + silo formation (n=1), jejunostomy (n=2)
Ileal atresia	15	Resection anastomosis (n=11), resection anastomosis + gastrostomy (n=1), ileostomy (n=3)
Colonic atresia	2	Resection anastomosis (n=1), resection anastomosis + pull through (n=1)
Multiple intestinal atresias	5	Resection anastomosis (n=4), resection anastomosis + ileostomy (n=1)

Table 4. Postoperative complications and relevant treatment options

Complications	Number of cases	Treatment
Wound infection	1	Conservative therapy
Anastomosis stenosis	2	Resection anastomosis
Ileus	2	Adhesiolysis
Pneumothorax	1	Tube thoracostomy
Gastric perforation	1	Gastrostomy
Short bowel syndrome	2	Total parenteral nutrition

The mean hospital stay duration was 17.2±7.9 days (range: 9-25 days) in patients with pyloric atresia, 20.9±17 days (range: 2-75 days) in patients with duodenal atresia, 32.8±41.6 days (range: 7-180 days) in patients with jejunal atresia, 21.2±13.2 days (range: 8-50 days) in patients with ileal atresia, 8±0 days in patients with colonic atresia, and 39.2±50 days (range: 16-90 days) in patients with multiple IA. The longest hospital stay was observed in patients with jejunal atresia. Of the 11 patients who died, 9 (82%) had additional congenital abnormalities (X^2=8.461, p=0.004), which comprised major cardiac defects (n=3), Down syndrome (n=2), congenital biliary atresia (n=1), EA + tracheoesophageal fistula (TEF) + anal atresia + tracheal atresia (n=1), EA + TEF (n=1), and microcephaly (n=1). We found no independent effect of congenital abnormalities on patient mortality in our logistic regression analysis (R^2=0.866, B=5.634, SE=4.161, Wald=1.833, df=1, p=0.176, Exp B (95% confidence interval, 279.722 0.80 to 974627.134). The 5-minute Apgar score was ≤5 in 5 (46%) patients. The age at diagnosis was older than 2 days in 7 (63.6%) patients, and the birth weight was <2 kg in 5 (45.5%) patients. The mean hospital stay of patients with and those without additional abnormalities were 26.4±21.4 and 23.04±28.04 days, respectively (p=0.207).

Discussion

Duodenal atresia is more common in males than females. However, our series included 13 males and 18 females. Prenatal ultrasonography (US) can detect duodenal atresia better than jejunal, ileal, or colonic atresia. Basu and Burge (10) were able to diagnose 31% of small IA cases by antenatal US. In our series, maternal polyhydramnios was detected in 7 of 31 patients with duodenal atresia (23%) via prenatal US. Approximately 50% of the patients with duodenal atresia showed a double-bubble sign via direct abdominal radiography (11). The sign was present in 22 patients (71%) in our series, of whom 26% had massive gastric appearance, and 3% had free intraperitoneal air.

Due to the high incidence of renal and cardiac abnormalities that accompany duodenal atresia, such cases should undergo echocardiography and abdominal US (2). Congenital abnormalities are present in more than 50% of patients with IA. In a series evaluated by Escobar et al. (12) that included 169 patients with duodenal atresia, the rate of Down syndrome was 27%, that of maternal polyhydramnios was 33-50%, and that of premature birth was 45%. Congenital abnormalities were detected in 46% of the patients and included congenital cardiac diseases (n=46), EA (n=14), anal atresia (n=6), anal atresia + EA (n=3), renal anomalies (n=8), biliary atresia (n=2), pyloric stenosis (n=1), and Hirschprung's disease (n=1). The incidence of additional abnormalities in the patients with duodenal atresia was 68% in our series, and these abnormalities included primarily Down syndrome (32.2%), major cardiac defects (12.9%), microcephaly (3.2%), type 2 choledochal cyst (3.2%), biliary atresia (3.2%), gastroschisis (3.2%), cystic fibrosis (3.2%), penoscrotal hypospadias (3.2%), anal atresia (9.6%), EA + TEF (6.4%), EA + TEF + anal atresia (3.2%), and EA + TEF + tracheal atresia (3.2%). The most common surgical procedure used to treat duodenal atresia is Kimura's diamond-shaped duodeno-duodenostomy. Concomitant duodenectomy with web excision is a less frequent surgical technique used for cases of type 1 duodenal atresia due to the risk of damage to the ampulla vateri (2). Likewise, Kimura's diamond-shaped duodeno-duodenostomy was performed in 24 patients in our series, duodenotomy + duodenal web excision in 6 patients, and Kimura's diamond-shaped duodeno-duodenostomy + gastrostomy in 1 patient. The mortality rate after duodenal obstruction have been reported at 9% by Rattan et al. (13), at 5.9% by Chen et al. (14), and at 58% by Zamir and Akhtar (15). In our series, the mortality rate was 19%. Sepsis is the most important risk factor for duodenal atresia, with a mortality rate of 50%. Congenital cardiac disease, prematurity, low birth weight, and Down syndrome are other risk factors (13). Sepsis (32%), Down syndrome (32.2%), prematurity (48%), birth weight <2 kg (48%), and major cardiac defects (12.9%) were the most important underlying risk factors for mortality in our patients with duodenal atresia.

The incidence of jejunoileal atresia is approximately 1 in every 5000 live births, and this rate is similar between males and females. Approximately one-third of patients are born prematurely (16,17). In our study, 11 males and 6 females had jejunal atresia, and 11 males and 4 females had ileal atresia. A premature birth history was observed in 35% and 27% of the patients with jejunal and ileal atresia, respectively.

Advancements in newborn care, surgical techniques, TPN, antenatal diagnosis, and neonatal anesthesia have increased the survival rate

of patients with IA from 80% in the 1990s (16) to over 90% in the 21st century (18,19). The survival rates in our study (100% in patients with pyloric atresia, 81% in those with duodenal atresia, 88% in those with jejunal atresia, 87% in those with ileal atresia, 100% in those with colonic atresia, and 80% in those with multiple IAs) were similar to those observed in the literature. The overall mortality rate was 14.9% in our study.

The surgical technique to be performed depends on the gastrointestinal system abnormalities and on the length of the intestine left behind, rather than the type of atresia itself. Whenever possible, wide resection of the proximal intestine and primary anastomosis are recommended with resection of the atretic segment (19). The expanded segment of the intestine of 3-25 cm was excised and anastomosed in our patients. The use of stomas is not recommended because it increases the risks of mortality and morbidity. The practice of stomas reduced from 20% to as low as 10% from the 1970s to 1990s (6). In our series, a stoma was opened in only 7 patients with intestinal perforation (4.5%).

Colonic atresia occurs in 1 in every 40,000 live births and constitutes approximately 1.8-15% of all IAs (20). In our study, colonic atresia was observed in 3 patients (4.1%): isolated colonic atresia in 2 and multiple IAs in 1. In the literature, 47% of colonic atresia cases are accompanied by congenital abnormalities (21). In our series, we did not encounter additional congenital abnormalities in any of the patients with colonic atresia. The mortality rate of colonic atresia is reported to be 25.7% (21). However, none of the patients in our series died.

The mean hospital stay is reported to be 19 days in patients with duodenal atresia, 25 days in patients with jejunal/ileal atresia, and 12 days in patients with colonic atresia in the study by Piper et al. (22). In our study, the mean hospital stay was 21 days in patients with duodenal atresia, 33 days in those with jejunal atresia, 21 days in those with ileal atresia, 8 days in those with colonic atresia, and 39 days in those with multiple IAs.

Early diagnosis and treatment are thought to reduce the mortality of patients with IA (23,24). In our series, 4 of 33 (12%) patients undergoing surgery within the first 2 days died, whereas 7 of 41 (17%) undergoing surgery after 2 days died; however, the difference was not significant. In patients with IA, the abdominal re-operation rates vary between 14% and 25% for postoperative complications (22,25). In our series, the rate of abdominal reoperation was 4% for postoperative complications.

Conclusion

The mean hospital stay in our study was similar to those reported in the literature. Although the mortality rates of patients with multiple and duodenal atresias were consistent with those in the literature, we encountered no deaths in patients with pylorus or colonic atresia. Concomitant severe congenital abnormalities in these patients adversely affect the hospital stay and mortality rate.

Ethics

Ethics Committee Approval: The Fırat University Faculty of Medicine Ethics Committee approved the protocol before study initiation (approval number: 11, date: 16.11.2017).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.S., T.T., Ü.B., A.K.; Concept - M.S., T.T., Ü.B.; Design - M.S., T.T., M.A.; Data Collection or Processing - T.T., Ü.B., İ.A.; Analysis or Interpretation - Ü.B., M.A., İ.A., A.K.; Literature Search – M.S., M.A., İ.A., A.K.; Writing - M.S., T.T., M.A., A.K.

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Oxford Unicondylar Knee Arthroplasty Hybrid and Cementless Fixation: Is There Any Difference in Short-term Follow-up?

Oxford Unikondiler Diz Artroplastinde Hibrid ve Çimentosuz Fiksasyon: Kısa Süreli Takipte Fark Var mı?

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ABSTRACT

Introduction: Despite a faster recovery, low complication rate, and good functional results, it has been reported that unicondylar knee arthroplasty (UKA) may have high revision rates. Aseptic loosening and pain are the most common causes of UKA revision. The use of cementless and hybrid UKA has been presented as a solution to improve the fixation of prosthetic components. The main purpose of this study was to compare the early clinical outcomes and quality of fixation of cementless and hybrid UKA radiologically.

Methods: A retrospective study was established with patients who received 37 cementless and 41 hybrid UKA in a minimum 2-year follow-up period. The patients' clinical outcomes were evaluated using the Oxford knee score, EuroQol-5 dimensions, EuroQol-visual analog scale, knee injury and osteoarthritis outcome score, and knee range of motion. The fixation of UKA components was evaluated with the varus-valgus angle of the tibial-femoral component, and the incidence of the radiolucent (RL) line at both the tibial and femoral component-bone interface on the radiograph.

Results: There was no significant difference in any clinical outcome measurement ($p>0.05$). There was no significant difference between the varus-valgus and flexion-extension angles of the femoral and tibial components in both groups ($p>0.05$). There were significantly more tibial RL in the hybrid group than in the cementless group ($p=0.025$). There was no significant difference in the incidence of RL at the femoral component-bone interface ($p=0.691$).

Conclusion: The cementless group showed significantly less tibial RL than the hybrid group in UKA. Although there were no clinically significant differences between cementless and hybrid UKAs, cementless UKA may be preferred to prevent possible prosthesis loosening.

Keywords: UKA, unicondylar, unicompartmental, cementless, hybrid

ÖZ

Amaç: Her ne kadar daha hızlı iyileşme, düşük komplikasyon oranı ve iyi fonksiyonel sonuçlar olsa da unikondiler diz artroplastisinin (UDA) yüksek revizyon oranlarına sahip olabileceği bildirilmiştir. UDA revizyonunun en yaygın nedenleri aseptik gevşeme ve ağrıdır. Çimentosuz ve hibrit UKA kullanımı, protez bileşenlerinin fiksasyonunu iyileştirmek için bir çözüm olarak sunulmuştur. Bu çalışmanın temel amacı, çimentosuz ve hibrid UDA'nın erken klinik sonuçlarını ve radyolojik olarak fiksasyon kalitesini karşılaştırmaktır.

Yöntemler: En az 2 yıllık izlem süresi içinde 37 çimentosuz ve 41 hibrid UDA uygulanan hastalarda retrospektif bir çalışma tasarlandı. Hastaların klinik sonuçları Oxford diz skoru, EuroQol-5 ölçeği, EuroQol-görsel analog skalası, diz yaralanması ve osteoartrit sonuç skoru ve diz eklem hareket açıklığı ile değerlendirildi. Komponentlerin fiksasyonu ise tibial-femoral komponentin varus-valgus açısı ve radyografide tibial ve femoral komponent-kemik arayüzünde radyolusent (RL) çizgi insidansı ile değerlendirildi.

Bulgular: Hiçbir klinik sonuç ölçütünde anlamlı bir fark yoktu ($p>0,05$). Her iki grupta femoral ve tibial komponentlerin varus-valgus ve fleksiyon-ekstansiyon açıları arasında anlamlı fark yoktu ($p>0,05$). Hibrid grupta çimentosuz gruba göre tibial RL anlamlı olarak daha fazlaydı ($p=0,025$). Femoral komponent-kemik arayüzeyinde RL insidansında anlamlı bir fark yoktu ($p=0,691$).

Sonuç: UDA uygulanan çimentosuz grup hibrid gruba göre anlamlı derecede daha az tibial RL gösterdi. Çimentosuz ve hibrid UDA'lar arasında klinik olarak anlamlı bir fark olmamakla birlikte, olası protez gevşemesini önlemek için çimentosuz UDA tercih edilebilir.

Anahtar Kelimeler: UDA, unikondiler, unikompartmantal, çimentosuz, hibrid

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Introduction

Cemented fixation is the gold standard in total knee arthroplasty (TKA), and successful long-term results have been reported in clinical trials (1,2). However, the lack of remodeling capacity of bone cement has raised questions regarding the long-term results of cemented TKA, especially in young and active patients due to the effect of third-body wear (3). Aseptic loosening is most commonly observed in tibial components in TKA, whether cemented or not (4,5). Since the idea of hybrid components emerged in the late 1980s (6), hybrid TKA has become a preferred method in some centers, and comparable success rates have been reported (7,8).

Whether cemented or not in unicondylar knee arthroplasty (UKA), the general view is that the tibial component is at greater risk of aseptic loosening. In addition, if there is pain in the first year postoperatively due to increased stress in the proximal tibia and subchondral bone marrow edema, it can be easily misdiagnosed as aseptic loosening (9,10).

It is generally accepted that uncemented UKA provides biological adherence to bone through bony ingrowth, with the associated theoretical advantages of eliminating cement complications and shortening operation and tourniquet time (11,12). In spite of these advantages of a cementless prosthesis, there is no clear consensus in the literature on the fixation method of the tibial component. Although there are comparative publications in the literature about cemented and cementless UKA, there are no comparative publications on cementless and hybrid (a combination of an uncemented femoral component and a cemented tibial component) UKA. The aim of this study was to compare the early clinical and radiological results of cementless and hybrid UKA.

Methods

After approval was obtained from University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Local Ethics Board (approval number: 56/07, date: 12.11.2018), this retrospective cohort study was initiated. A retrospective review was performed of 78 consecutive patients with a medial knee arthrosis treated with UKA between January 2014 and December 2018. Radiological data were collected from the picture archiving and communication system.

The clinical and radiological results were compared for patients treated with an Oxford hybrid UKA and uncemented UKA, by a single surgeon (H.A.) with a follow-up of at least 2 years between 2014 and 2017. The demographic properties of the patients are given in Table 1.

The indication for cement usage was given according to the bone hardness test in patients undergoing surgery with the indication of UKA (13). In this test, if the bone surface collapsed (thumb penetrates the bone tissue) when pressure was applied to the trabecular bone surface with the thumb after the tibia was cut, it was deemed unsuitable for the uncemented tibial component, and the cemented one was applied.

The patients' clinical results were evaluated using the Oxford knee score, EuroQol-5 dimensions (EQ-5D-3L), EQ-visual analog scale, and the knee injury and osteoarthritis outcome scores (pain, symptom, daily life, sports, and quality of life). Joint range of motion was measured at the final visits. Radiological examination was performed by two independent orthopedic surgeons. Measurements were performed on the patients' anteroposterior and lateral knee radiographs. The varus-valgus and flexion-extension angles of the tibial and femoral components were measured to determine component alignment on

Table 1. Patients' demographic characteristics and clinical results

	Cementless (n=46)	Hybrid (n=34)	p-value (MWU)
Age	57.4 (47-74)	59.2 (47-72)	0.277 *
Gender (F/M)	28/9	37/4	0.156 ∫
Side (R/L)	22/16	23/24	0.157 ∫
Height (m)	1.62 (1.52-1.7)	1.63 (1.53-1.86)	0.489 *
Weight (kg)	80.6 (55-112)	81.1 (64-108)	0.854 *
BMI (kg/m^2)	29.9 (23.3-34.5)	30.3 (23.1-40.6)	0.719 *
Follow-up (months)	34.1 (25-38)	35.9 (28-65)	0.890 *
Oxford Knee score	41.1 (12-48)	40.6 (20-48)	0.236
EQ-5D-3L	0.80 (0.59-1)	0.79 (0.49-1)	0.625
EQ-VAS	82.8 (55-100)	82.9 (60-100)	0.869
KOOS - pain	81.3 (1.67-100)	83.7 (33.3-100)	0.289
KOOS - symptom	85.3 (42.8-100)	84.5 (42.8-100)	0.512
KOOS - daily life	84.3 (14.7-100)	86.1 (30.8-100)	0.785
KOOS - sports	67.0 (20-100)	68.7 (25.0-100)	0.922
KOOS - quality of life	82.0 (25-100)	79.4 (25-100)	0.245
ROM			
Flexion	112.7° (95°-120°)	111.4° (80°-120°)	0.411
Extension	0.5 (0-0)	0.3 (0-10)	0.793

Reference values are given in parentheses.

BMI: Body max index, F: female, M: male, R: right, L: left, *: t-test, ∫: chi square, KOOS: knee injury and osteoarthritis outcome score, EQ-5D-3L: EuroQol-5 dimensions, EQ-VAS: EuroQol-visual analog scale, MWU: Mann-Whitney U test

radiological evaluation (Figure 1, 2). The incidence of radiological lines at the tibial component-bone and femoral component-bone interfaces was also evaluated.

The bone contact points of the tibial component were divided into six regions according to the technique described by Pandit et al. (14) Zone 1: from the medial tibial plateau to the medial keel, Zone 2: from the medial plateau to the lateral keel, Zone 3: the medial vertical surface of the keel, Zone 4: the lower part of the keel, Zone 5: the lateral vertical surface of the keel, and Zone 6: the lateral to the keel of the medial plateau (Figure 3). Additionally, the bone contact points of the femoral component were measured by a similar technique (Figure 4).

During the follow-up period, insert dislocation occurred in two patients in both groups. All four patients underwent replacement with a 1 mm-thick insert.

Statistical Analysis

The statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, Illinois). Odds ratios and means were compared between groups, with 95% confidence intervals. Results were considered statistically significant at $p<0.05$. A comparison of proportions method was used to calculate the sample size.

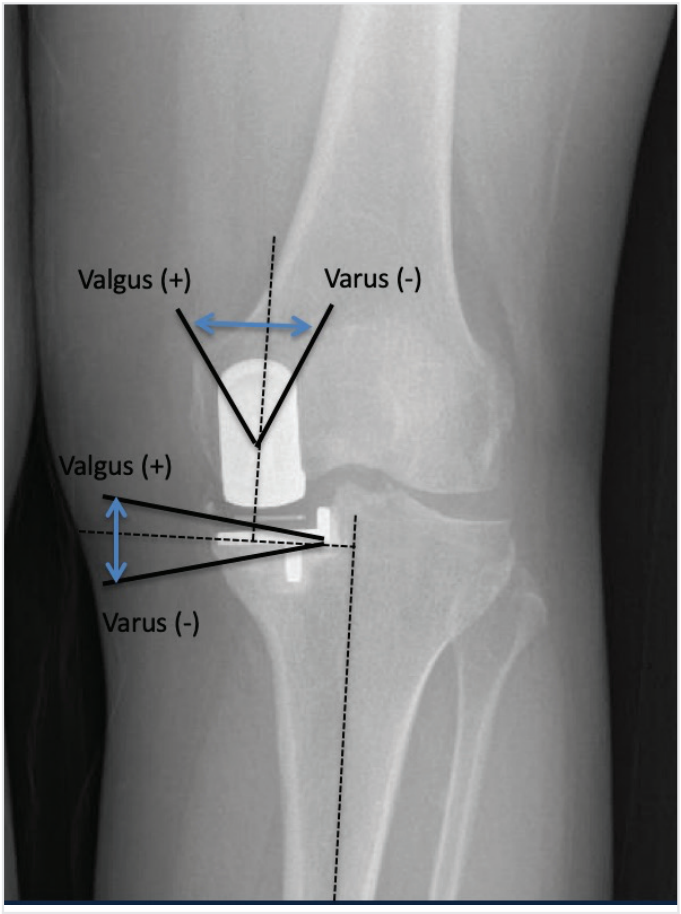

Figure 1. Six zones of RL below the tibial component of the Oxford UKA on anteroposterior radiograph

RL: Radiolucent line, UKA: unicondylar knee arthroplasty

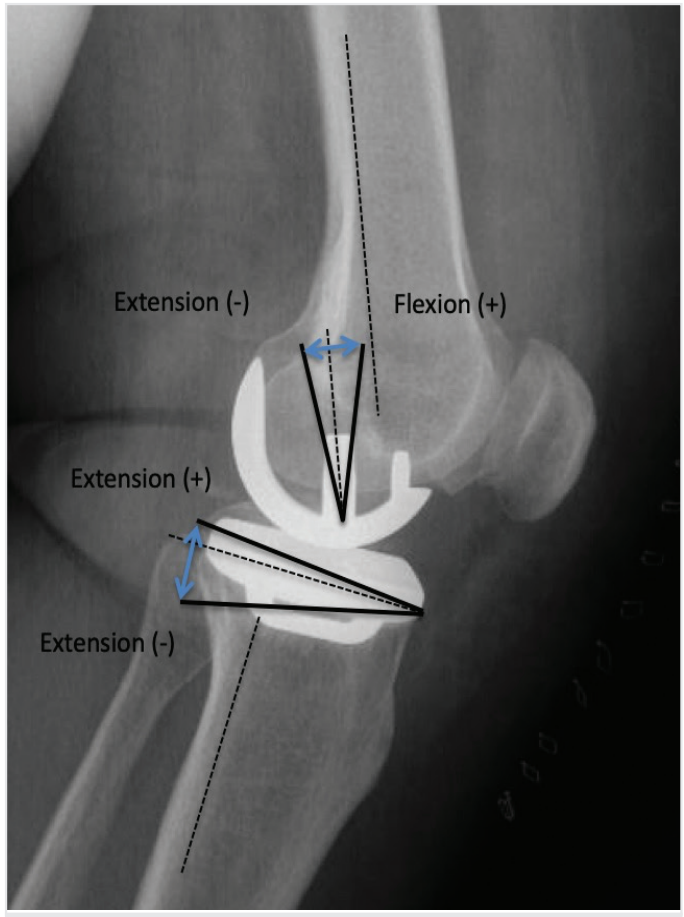

Figure 2. Six zones of RL above the femoral component of the Oxford UKA on lateral radiograph

RL: Radiolucent line, UKA: unicondylar knee arthroplasty

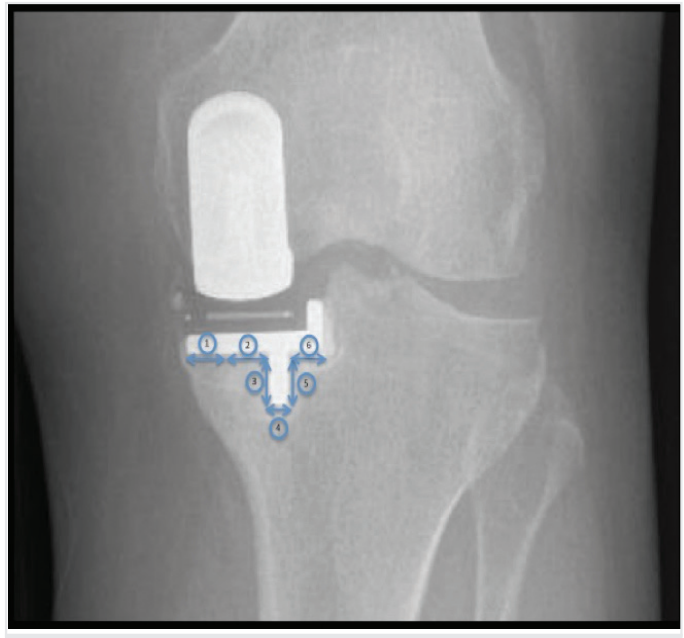

Figure 3. Varus-valgus angles of femoral and tibial components

Results

The clinical results of both the cementless and hybrid groups are given in Table 1. Although there was a proportional difference in clinical results in both groups, there was no statistically significant difference between the two groups.

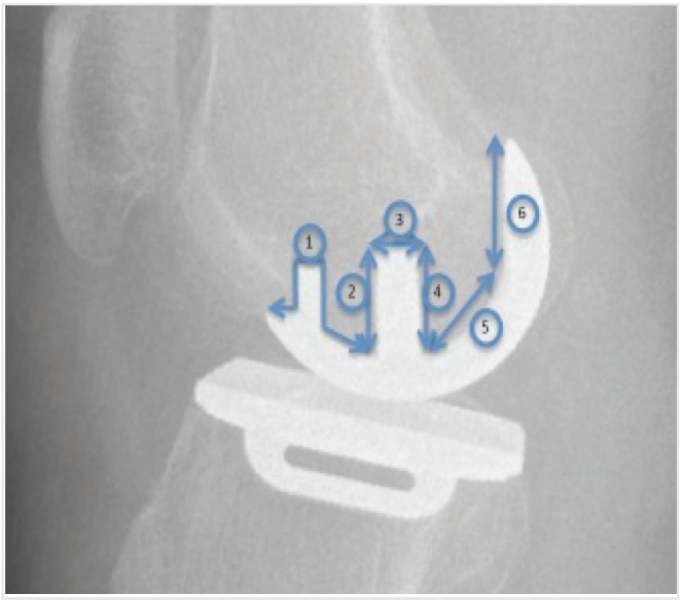

Figure 4. Flexion-extension angles of femoral and tibial components

When the femoral components were evaluated in terms of alignment, in the cementless group, the mean varus-valgus angle was 5.6±2.1 (-6.3-11.0), and the mean flexion-extension angle was 9.4±3.3 (6.5-13.3); in the hybrid group, the mean varus-valgus angle was 7.1±3.3 (-8.4-13.2), and the mean flexion-extension angle was 6.8±4.4 (-5.6-12.2). When the tibial components were evaluated in terms of alignment, the mean varus-valgus angle in the cementless group was -0.5±2.3 (-1.4-4.9), and the mean flexion-extension angle was 4.5±2.7 (-2.6-6.8), and in the hybrid group, the mean varus-valgus angle was -1.1±3.4 (-2.1-5.5), and the mean flexion-extension angle was 4.8±2.5 (0.1-9.3). There was no statistically significant difference between the varus-valgus and flexion-extension angles of the femoral and tibial components in both groups ($p>0.05$).

The radiolucent (RL) areas in each zone, the total number of RL areas, and the numbers of complete and partial RL areas in the patients were compared between the groups (Table 2). When the incidence of RL lines was evaluated in both groups, no complete RL line was observed in any prosthesis. When evaluations were performed of the tibial components alone, a partial RL area was detected in 7 (15.2%) of the cementless group and 12 (35.2%) of the hybrid group. The incidence of the RL line at the tibial component interface was higher in the hybrid group than in the cementless group, but the difference was not statistically significant ($p=0.069$). When partial RL involvement was evaluated according to the region, a total of 13 regions in the cementless group and a total of 32 regions in the hybrid group were detected. This difference was

Table 2. The incidence of radiolucent line

Tibial Component			
	Cementless (n=46)	**Hybrid (n=34)**	**p-value ∫**
Complete RL	0 (0%)	0 (0%)	1.00
Partial RL area (−)	39 (84.8%)	26 (64.8%)	0.069
Partial RL area (+)	7 (15.2%)	12 (35.2%)	
Area 1	1 (2.6%)	9 (19.1%)	0.781
Area 2	4 (10.5%)	5 (10.6%)	1.00
Area 3	3 (7.9%)	2 (4.3%)	0.652
Area 4	2 (5.3%)	4 (8.5%)	0.687
Area 5	3 (7.9%)	7 (14.9%)	0.501
Area 6	0 (0%)	2 (4.3%)	0.500
Total Areas	13	32	0.025
Femoral component			
Total surface RL	0 (0%)	0 (0%)	1.00
Partial RL area (−)	45 (97.4%)	32 (95.7%)	1.00
Partial RL area (+)	1 (2.6%)	2 (4.3%)	
Area 1	0 (0%)	0 (0%)	1.00
Area 2	0 (0%)	0 (0%)	1.00
Area 3	0 (0%)	0 (0%)	1.00
Area 4	0 (0%)	1 (2.1%)	1.00
Area 5	1 (0%)	0 (0%)	0.447
Area 6	0 (0%)	1 (2.1%)	1.00
Total areas	1	2	0.691

RL: Radiolucent line; ∫: chi-square

statistically significant (p=0.025). When all the tibial components were considered in the cementless group, the highest rates of partial RL region involvement were determined in Zone 3 and Zone 5, respectively. The total of all partial RL regions was 13. In the hybrid group, the highest rates of partial RL region involvement in the tibial components were seen in zones 1, 5, and 2, respectively.

When the femoral components were evaluated among themselves, a partial RL area was detected in one patient of the cementless group and in two patients of the hybrid group. There was no statistically significant difference in the incidence of the partial RL line at the femoral component interface (p=0.691).

Discussion

There is no comparative study in the literature regarding hybrid vs all uncemented or all cementless UKA. Therefore, the results of this study could only be compared with the results of hybrid vs cementless fixation in TKA.

Cement application is the most widely used fixation method in TKA compared with the cementless and hybrid options. However, there is confusion as to which is the optimum fixation method. In view of the potential late loosening and third-body wear effects of cement, cementless implants have been developed as an alternative method that allows biological fixation and has potential advantages such as the preservation of bone stock for revisions (3,15,16) However, some studies have reported that cementless fixation leads to instability and loosening, especially in the tibial component (17,18). To avoid these problems in the cementless tibial component, the idea of hybrid application was proposed and successful medium- and long-term results of hybrid TKA have been reported (19-22). Behery et al. (23) found that 76 cases of aseptic loosening comprised 10% with cementless prostheses and 0% cemented. Early weight-bearing and obesity were reported to cause loosening. Another interesting point of that study was that all the loosened tibial components were seen in patients with a cruciate retaining prosthesis. The authors attributed this to the different femoral rollback kinematics in the two design types, with a different pattern of tibial weight-bearing, which could be implicated in micromotion and failure of osseointegration. In the present study, aseptic loosening was not observed in both cementless and hybrid UKA groups. The probable reason for the lack of aseptic loosening in both groups may be the inadequate follow-up period. However, the higher number of tibial RL lines seen in the hybrid group may be a predictor of future aseptic loosening.

In UKA, the fixation evolution of the components undergoes a process similar to that of TKA. Cementless fixation of tibial and femoral components has been accepted as a widely used method in recent years, whereas cemented prosthesis had previously been the generally accepted method (24). As in TKA, the femoral component in UKA is at a lower risk of loosening than the tibial component. However, there are different views on cementless application of the tibial component in patients with high-level activity expectations, obese patients, and patients with osteoporosis. The design group has argued that the use of cementless application in osteoporotic patients is not a contraindication and does not include any indications different from those for cemented versions (25). In a study of 12 cadaveric knees, Jaeger et al. (26) emphasized that bone quality is important in implant choice, and if bone quality is poor, it will lead to subsidence of the implant. Similarly, in the present study, there was no significant difference between the two groups which had patients with similar demographical properties in terms of RL lines seen in the femoral components.

Stempin et al. (13) stated that they made the decision to use cement intraoperatively by observing the quality of bone visually and by applying the bone hardness test. Accordingly, after the tibial cut is made, pressure is applied to the bone surface with the thumb (index finger in small knees), and a slight deflection is observed on the bone surface. If the resected surface collapses, the stiffness of the bone is considered to be insufficient to provide primary stability of the implant and a cemented component is used (13). In contrast, Campi et al. (11) reported that the problem of bone quality will not affect the results. They stated that as the forces primarily transmitted are compressive, the implant works well with cementless fixation, and neither bone density nor patient age affects the success or failure of a cementless fixation (27). The decision to apply the tibial component with or without cement was also made in this present study according to the bone hardness test.

In the literature, no significant difference has been reported between the functional outcomes of cemented and cementless UKA (28).

Likewise, in the present study, there was no significant difference between cementless and hybrid UKA with respect to functional outcomes.

In the current series, as there was no fracture due to press-fit implantation, the risk reduction can be explained by strict adherence to the technique described by Campi et al. (11), including adequate clearing of peg and keel slots, avoidance of damage to the posterior cortical bone, and delicate impaction using a small hammer to avoid causing a fracture.

Another reason for the success of the current series may be that all operations were performed by a single surgeon and the team is experienced in UKA. The learning curve for UKA is considered to be long, so experience provides minimization of surgical errors. Therefore, the postoperative results can be evaluated without the bias of technical errors.

Study Limitation

There are a few limitations associated with this study, primarily its retrospective nature and the limited sample size. For arthroplasty cases, a 2-year follow-up period may not be sufficient. The osteolysis and UKA loosening in this early period may be due to undetected infection, inappropriate surgical technique, and/or the choice of fixation (cemented or cementless). The results of this study describe a single surgeon's experience and, therefore, may not be generalizable.

The most important feature of this study is that it is the first study in the literature to compare the clinical and radiological results of cementless and hybrid UKA.

Conclusion

The most important finding of the study was that cementless tibial components showed significantly less RL than components of the hybrid group. Cementless and hybrid UKA have been used as a popular method in recent years and are preferred by many surgeons, and now it may be possible to predict what problems might be encountered, especially in obese and osteoporotic patients in long-term follow-up.

Ethics

Ethics Committee Approval: This study approval was obtained from University of Health Sciences Turkey, Dışkapı Yıldırım Beyazıt Training and Research Hospital Local Ethics Board (approval number: 56/07, date: 12.11.2018).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.A., M.A.; Concept - H.A., H.A.A., M.A., K.B., H.B.Ç.; Design - H.A., H.A.A., M.A., K.B., H.B.Ç.; Data Collection or Processing - H.A., H.A.A., M.A., K.B., H.B.Ç.; Analysis or Interpretation - H.A., H.A.A., M.A., K.B., H.B.Ç.; Literature Search - H.A., H.A.A., M.A., K.B., H.B.Ç.; Writing - H.A., H.A.A., M.A., K.B., H.B.Ç.

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Predictors of Clinically Significant Prostate Cancer: A Comparative Study of PSA, PSA Density, and MRI Parameters

Klinik Anlamlı Prostat Kanseri Belirteçleri: PSA, PSA Dansitesi ve MRG Bulgularının Karşılaştırılması

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ABSTRACT

Introduction: The purpose of this study was to compare prostate-specific antigen (PSA), PSA density (PSAd), the prostate imaging-reporting and data system (PI-RADS) score, and lesion dimension (four parameters) in clinically significant prostate cancer (PCa) detection.

Methods: This study included 154 patients who underwent multi-parametric prostate magnetic resonance imaging (mpMRI) and 12 quadrant systematic prostate biopsy between 01/2018 and 03/2019. Two radiologists used the PI-RADS version 2.1 to describe the MRI findings by consensus. A Gleason score ≥3+4 was assessed as clinically significant PCa. Areas under the curve (AUC) were calculated using receiver operating characteristics. Youden's index was used to determine ideal cutoffs. DeLong's test was used to evaluate statistically significant differences between the four parameters.

Results: The median age was 66 (±6.9) in this cohort. The median PSA level was 7.8 ng/dL (±18.4, 1.6-109.3), the median PSAd was 0.146 ng/mL/cm^3, and the median lesion dimension was 12 mm. In MRI, the number of cases with the PI-RADS scores from 1 to 5 were 34, 6, 11, 38, and 65, respectively. In terms of pathology, there was no tumor in 44 patients' samples, while insignificant cancer and clinically significant PCa were seen in 33 and 77, respectively. The AUC values of PSA, PSAd, PI-RADS score, and lesion dimension were 0.684, 0.731, 0.856, and 0.858, respectively. The optimal cutoffs were ≥10 ng/mL for PSA, ≥0.22 ng/mL/cm^3 for PSAd, ≥4 for the PI-RADS score and ≥10 mm for lesion dimension. DeLong's tests showed that the PI-RADS score and lesion dimension were significantly superior to PSA and PSAd. There was no significant difference between the PI-RADS score and lesion dimension.

ÖZ

Amaç: Klinik anlamlı prostat kanseri (KAK) tespitinde, prostat-spesifik antijen (PSA), PSA yoğunluğu (PSAd), prostat görüntüleme-raporlandırma ve bilgi sistemi (PI-RADS) skoru ve lezyon boyutu içeren dört parametrenin karşılaştırılması amaçlanmıştır.

Yöntemler: Bu çalışma, 01/2018 ile 03/2019 arasında, multi-parametrik prostat manyetik rezonans görüntüleme (mpMRG) ve 12 kadran sistematik prostat biyopsisi yapılan 154 olguyu kapsamaktadır. MRG bulguları 2 radyolog tarafından konsensüs ile PI-RADS versiyon 2.1 kullanılarak değerlendirildi. Gleason ≥3+4 tümörler KAK olarak tariflendi. Eğrinin altında kalan alan (EAA) alıcı çalışma karakteristik eğrisi (ROC) kullanılarak hesaplandı. Uygun sınır değeri tespit için Youden'in indeksi kullanıldı. Dört parametre arasındaki anlamlı farklılık DeLong testi yardımıyla değerlendirildi.

Bulgular: Kohortda ortanca yaş 66 (±6,9) idi. Ortanca PSA 7,8 ng/dL, PSAd 0,146 ng/mL/cm^3 ve lezyon boyutu 12 mm idi. MRG'de PI-RADS skor 1'den 5'e olgu sayısı sırasıyla 34, 6, 11, 38 ve 65'ti. Patolojide, 44 olguda tümör görülmezken, 33 klinik sessiz kanser, 77 KAK saptandı. PSA, PSAd, PI-RADS skoru ve lezyon boyutu için EAA'lar sırasıyla; 0,684, 0,731, 0,856 ve 0,858 idi. En uygun sınır değerler PSA için ≥10 ng/mL, PSAd için ≥0,22 ng/mL/cm^3, PI-RADS skoru için ≥ skor 4 ve lezyon boyutu için ≥10 mm idi. DeLong testinde PI-RADS skoru ve lezyon boyutu, PSA ve PSAd'den daha üstün bulundu. PI-RADS skoru ile lezyon boyutu arasında anlamlı fark yoktu.

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ABSTRACT

Conclusion: The PI-RADS score and lesion dimension had higher accuracy than PSA and PSAd in clinically significant PCa detection. Lesions ≥10 mm were associated with the risk of clinically significant PCa, and this should be considered in reporting.

Keywords: Multiparametric prostate MRI, PI-RADS category, prostate-specific antigen, prostate biopsy, prostate cancer

ÖZ

Sonuç: KAK tanısında, PI-RADS skoru ve lezyon boyutu PSA ve PSAd'den daha yüksek doğruluğa sahiptir. 10 mm'den büyük lezyonlar KAK için potansiyel riskli olup raporlamada bu dikkate alınmalıdır.

Anahtar Kelimeler: Multi-parametrik prostat MRG, PI-RADS kategori, prostat-spesifik antijen, prostat biyopsisi, prostat kanseri

Introduction

Prostate cancer (PCa) is the second most common cancer in men (1). Digital rectal examination (DRE), prostate-specific antigen (PSA), and transrectal ultrasound-guided biopsy are utilized in screening. Randomized controlled studies have shown that PSA screening decreases disease-specific mortality (2). The serum PSA level may increase in both benign and malignant conditions; therefore, it is often used in combination with other screening methods. However, when these screening methods are used alone or together, they have low specificity in Pca diagnosis. Redundant diagnosis of clinically insignificant cancer is another problem with these methods (3).

Publication of the prostate imaging-reporting and data system (PI-RADS) guidelines has changed the clinical picture. Multi-parametric prostate magnetic resonance imaging (mpMRI) prevented unnecessary biopsies and introduced targeted biopsy, which reduced the diagnosis of indolent cancer and made a beneficial contribution to clinically significant PCa detection (4,5). Although PI-RADS is not directly recommended for management, biopsy should be considered for score 4 or 5 lesions (6).

PSA density (PSAd) is considered superior to serum PSA alone in the diagnosis of PCa (7). In recent studies, the combination of PSAd and mpMRI facilitated detection of clinically significant PCa, and PSAd may help to predict negative biopsy results (7,8). On the other hand, undifferentiated tumours producing less PSA or large prostate volume decreased the capability of PSAd to detect cancer (7,9).

Clinically significant PCa is defined as volume ≥0.5 cc and/or Gleason score ≥3+4 and/or extraprostatic extension (6). An increased tumor volume is associated with aggressive biological behaviour, the risk of extraprostatic extension, PSA recurrence, and metastasis (10,11). Image-guided focal therapy or active surveillance options could be offered more safely with the accurate measurement of preoperative tumor dimensions (12).

This study aimed to compare PSA, PSAd, PI-RADS score, and tumor dimensions in clinically significant PCa detection.

Methods

Study Population

This retrospective study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 18.06.2020/729). Written informed consent was obtained from all participants. One-hundred and fifty-four patients who underwent mpMRI and 12 quadrant systematic biopsies between January 2018 and December 2019 were included. All patients had a clinical suspicion of PCa with either elevated PSA or abnormal DRE. The patients included in this study with PI-RADS score 1 were sampled due to having elevated PSA or abnormal DRE. Cognitive-fusion biopsy was added to systematic biopsy in those who had a transitional zone (TZ) lesion (n=19) on the mpMRI. The patients treated before mpMRI were excluded.

MR Acquisition Protocol

All MR scans were acquired on a 1.5T scanner (Aera, Siemens Healthineers, Erlangen, Germany). The protocol included the following sequences: turbo spin-echo T2-weighted imaging (T2WI) with axial, sagittal, and coronal orientations (Axial T2WI parameters were as follows: repetition time, 5660 ms; echo time, 99 ms; field of view, 200×180 mm; acquisition matrix, 320×288; slice thickness, 3 mm with no gap; number of excitations, 6), a diffusion-weighted imaging with an axial orientation (repetition time, 4000 ms; echo time, 76 ms; b-values, 0, 200, 600, and 1400 sec/mm^2; field of view, 200×180 mm; acquisition matrix, 100×90; slice thickness, 3 mm with no gap) with apparent diffusion coefficient mapping, and dynamic contrast-enhanced sequences with an axial orientation (repetition time, 2.48 ms; echo time, 1.52 ms; the field of view, 260×215 mm; acquisition matrix, 160×108; slice thickness 3 mm with a 0.3 mm gap; temporal resolution, 7 sec).

Image Analysis

Scoring was performed using the PI-RADSv2.1 (13). Standardized PI-RADSv2.1 is on a five-point scale, which describes clinically significant PCa as follows: 1, extremely unlikely; 2, unlikely; 3, equivocal; 4, likely; or 5, extremely likely. Two radiologists with 5 and 3 years of experience in prostate MRI, blinded to clinical and pathological data assigned the score individually to assess inter-reader agreement. After 1 month, PI-RADSv2.1 scoring was repeated with consensus, and the consensus score was used in statistical analysis.

Prostate volume was calculated on axial and sagittal T2WI using an ellipsoid formula (maximum anterior-posterior × transverse × longitudinal diameter ×0.52) (6). PSAd was obtained using PSA/volume.

Maximum single-axis size was considered a lesion dimension using the sequence in which the lesion was seen best, was mostly axial T2WI since it had highest spatial resolution. When multiple lesions were present, the PI-RADS score and dimension of index lesion were used in the statistical analysis.

Histopathologic and Clinical Evaluation

The pathological evaluation was based on the pathology reports. Tumors were graded by the genitourinary pathologists as proposed by the International Society of Urological Pathology (ISUP) in 2014. Accordingly, Gleason 3+3 tumors were categorized as ISUP 1, Gleason 3+4 tumors as ISUP 2, Gleason 4+3 tumors as ISUP 3, Gleason 4+4 tumors as ISUP 4, and Gleason ≥4+5 tumors as ISUP 5. Gleason ≥3+4 tumors were considered clinically significant PCa as defined in the PI-RADSv2 (6).

Fourty-nine of 154 were underwent radical prostatectomy (RP) after 12 quadrant biopsy. If there was any discrepancy between systematic biopsy and RP, ISUP results of RP were considered in statistical analysis. To match the lesions on the mpMRIs with histopathology, we first localized the index lesion on the mpMRI to the corresponding PI-RADS sector map and then recorded the biopsy/prostatectomy results for the relevant regions.

Statistical Analysis

The Kappa statistic was used to determine inter-reader agreement. Accordingly, it was classified as follows: 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and 0.81-0.99, almost perfect.

The PI-RADSv2.1 score and ISUP grade correlation were analysed using the Spearman's rank correlation. Pearson correlation analysis was used to determine the relationship between PSA, PSAd, dimension, and ISUP grade.

PSA, PSAd, the PI-RADS score, and lesion dimension were compared using receiver operating characteristic (ROC) curves in clinically significant PCa detection. Youden's index was used to determine ideal cutoff values and sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were computed. The area under the curve (AUC) was calculated for each ROC curve. DeLong's test was used to evaluate statistically significant differences between them.

All analyses were conducted using SPSS version 20 (IBM®, Armonk, NY, USA) and Medcalc® 19.12.0 (MedCalc Software bvba, Ostend, Belgium). Results were considered statistically significant at $p<0.05$.

Results

The median age of 154 cases was 66 (standard deviation ±6.9, range: 46-81). The median PSA level was 7.8 ng/dL (±18.4, 1.6-109.3), median PSAd 0.146 ng/mL/cm^3 (±0.402, 0.036-3.090), and median lesion dimension 12 mm (±16, 0-118) (Table 1).

There were no lesions in 34 patients. Fourteen patients had multifocal lesions. The total number of lesions was 138. Nineteen lesions (13.8%) were localized in TZ.

There were no tumors in 44 patients. The cognitive fusion biopsy results in 19 lesions were as follows: no tumor 2; ISUP 1 tumor 6; ISUP 2 tumor 7; ISUP 3 tumor 1; and ISUP 4 tumor 3. The numbers of cases with ISUP scores 1 to 5 were 33, 36, 24, 11, and 6, respectively (Table 2). There were 77 patients who had clinically significant PCa. The number of cases with the PI-RADS scores from 1 to 5 were 34, 6, 11, 38, and 65, respectively. There was no clinically significant PCa in patients assigned a PI-RADS score of 1. The ISUP ≥2 cancer detection rate was 18% in patients with a PI-RADS score of 2. The clinically significant PCa detection rate was 34% in patients with a PI-RADS score of 3, 80% in those with a score of 4, and 82% in those with a score of 5. As the PI-RADS score increased, the ISUP grade increased significantly (Figure 1) ($p<0.001$).

Inter-reader agreement was moderate (Kappa: 0.536). There was a strong correlation between PSA, PSAd, tumor dimension, and ISUP

Table 1. Summary of patient and lesion characteristics

Parameters	Number	Median	Standard deviation	Minimum	Maximum
Age	154	66	6.9	46	81
PSA (ng/mL)	154	7.8	18.4	1.6	109.3
PSAd (ng/mL/cm^3)	154	0.146	0.402	0.036	3.090
Dimesion (mm)	154	12	16	0	118
Lesion detected	138	-	-	-	-
Peripheral zone	119 (86.2%)	-	-	-	-
Tranzitional zone	19 (13.8%)	-	-	-	-

PSA: Prostate-specific antigen, PSAd: prostate-specific antigen density

Table 2. Values of the PI-RADSv2.1 score and ISUP grade

PI-RADSv2 score	No tumor	ISUP 1	ISUP 2	ISUP 3	ISUP 4	ISUP 5	Total
1	29	5	0	0	0	0	34
2	5	0	1	0	0	0	6
3	1	6	3	1	0	0	11
4	7	13	13	3	2	0	38
5	2	9	19	20	9	6	65
Total	44	33	36	24	11	6	154

PI-RADSv2.1: prostate imaging-reporting and data system version 2.1, ISUP: International Society of Urological Pathology

(p<0.001 for all). Pearson correlation coefficients were 0.373, 0.432, 0.629, respectively.

The AUC values of PSA, PSAd, the PI-RADS score, and lesion dimension were 0.684, 0.731, 0.856, and 0.858, respectively (Figure 2). The cut-offs calculated using Youden's index were ≥10 ng/mL for PSA, ≥0.22 ng/mL/cm^3 for PSAd, PI-RADS score ≥4, and ≥10 mm for lesion dimension in clinically significant PCa detection. For those cutoffs, sensitivity, specificity, PPV, and NPV were 53.2%, 79.2%, 71.9%, and 62.9% for PSA; 58.4%, 87%, 81.8%, and 67.7% for PSAd; 93.5%, 59.7%, 69.9%, and 90.2% for the PI-RADS score; and 88.3%, 66.2%, 72.3%, and 85% for lesion dimension, respectively (Table 3).

DeLong's tests showed that PSA and PSAd had similar accuracy in clinically significant PCa detection (p=0.162). The PI-RADS score was significantly superior to PSA and PSAd (p<0.001 and p=0.004, respectively). The accuracy of lesion dimension was also higher than those of PSA and PSAd (p<0.001 and p=0.002, respectively). There was no significant difference between the PI-RADS score and lesion dimension (p=0.915) (Figure 3, 4).

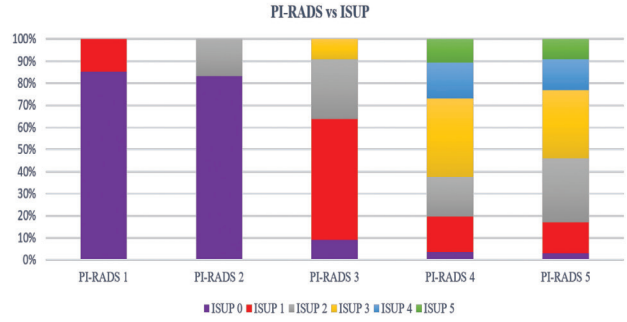

Figure 1. Percentages of ISUP grades in different PI-RADSv2.1 scores

ISUP: International Society of Urological Pathology, PI-RADSv2.1: prostate imaging-reporting and data system version 2.1

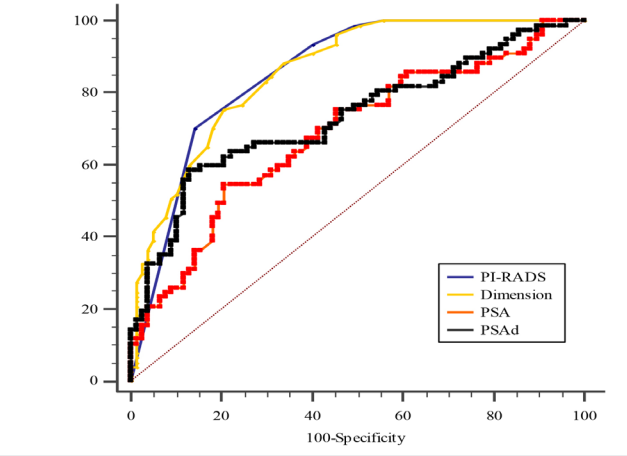

Figure 2. ROC curves of PSA, PSAd, the PI-RADSv2.1 score, and lesion dimension in clinically significant prostate cancer detection

ROC: PSA: prostate-specific antigen, PSAd: prostate-specific antigen density, PI-RADSv2.1: prostate imaging-reporting and data system version 2.1

Discussion

PSA is the first-line screening test in the diagnosis of PCa. However, mpMRI is the rising star of the new era in this field with a high sensitivity. In this study, the PI-RADS score and lesion dimension performed better in clinically significant PCa detection compared with PSA and PSAd. The

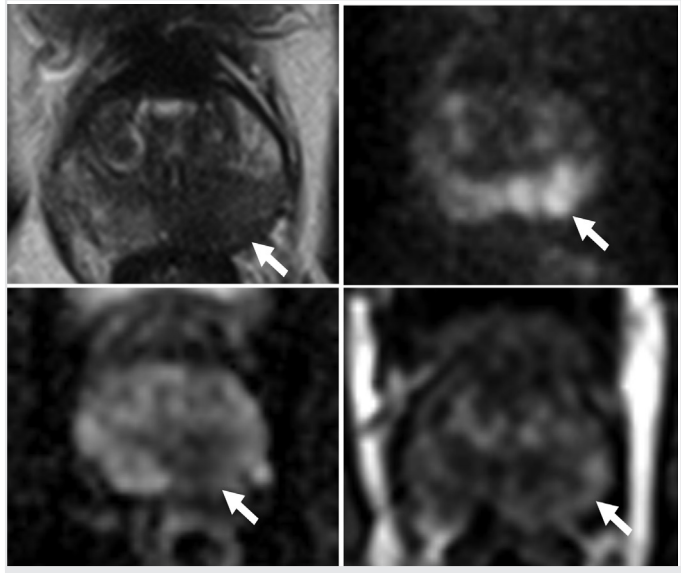

Figure 3. A 77-year-old patient with a PSA of 30 ng/mL, PSAd of 0.882 ng/mL/cm^3, and a 20 mm lesion localized in left mid peripheral zone (arrows). The lesion was slightly heterogeneous and moderately hypointense on T2WI (a), markedly hyperintense on a high b-value image (b), hypointense on an ADC map (c), and focally enhanced on DCE (d). Reader 1, reader 2, and consensus PI-RADSv2.1 scores were 5 for all. RP specimen revealed an ISUP-2 tumor with 23% involvement of the whole mount

PSA: Prostate-specific antigen, PSAd: prostate-specific antigen density, T2WI: T2-weighted imaging, ADC: apparent diffusion coefficient, DCE: dynamic contrast-enhanced, PI-RADSv2.1: prostate imaging-reporting and data system version 2.1, RP: radical prostatectomy, ISUP: International Society of Urological Pathology

Table 3. Diagnostic performance of PSA, PSAd, the PI-RADSv2.1 score, and lesion dimension in clinically significant prostate cancer detection

Parameters	Cutoff (≥)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
PSA	10 ng/mL	53.2	79.2	71.9	62.9
PSAd	0.22 ng/mL/cm^3	58.4	87	81.8	67.7
PI-RADS	Score 4	93.5	59.7	69.9	90.2
Dimension	10 mm	88.3	66.2	72.3	85

PSA: Prostate-specific antigen, PSAd: prostate-specific antigen density, PI-RADSv2.1: prostate imaging-reporting and data system version 2.1, PPV: positive predictive value, NPV: negative predictive value

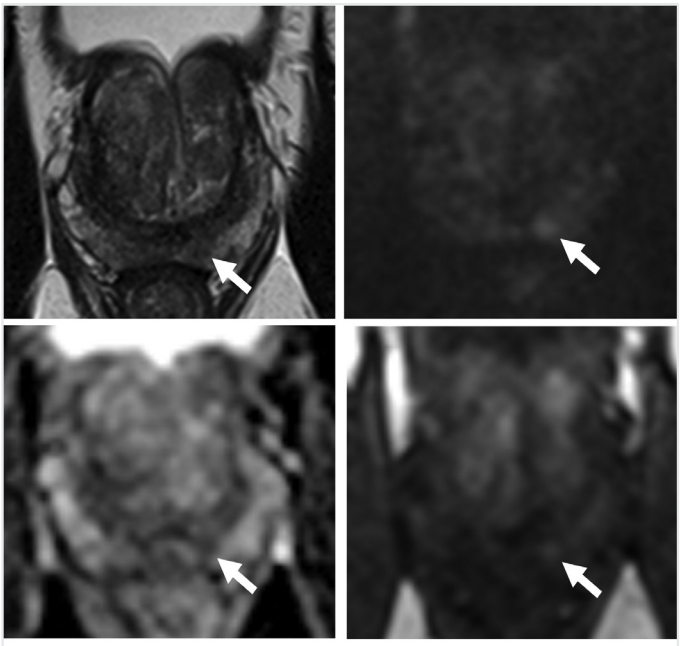

Figure 4. A 74-year-old patient with a PSA of 9.8 ng/mL, PSAd of 0.153 ng/mL/cm^3, and mpMRIs from a to d; T2WI, DWI, ADC, and DCE, respectively. An 9 mm lesion localized on the left mid-base peripheral zone (arrows). Reader 1, reader 2, and consensus PI-RADSv2.1 scores were 2, 3, and 3, respectively. TRUS systematic biopsy revealed an ISUP 1 tumor with 5% involvement in the relevant core

PSA: Prostate-specific antigen, PSAd: prostate-specific antigen density, mpMRI: multi-parametric prostate magnetic resonance imaging, T2WI: T2-weighted imaging, DWI: diffusion-weighted imaging, ADC: apparent diffusion coefficient, DCE: dynamic contrast-enhanced, PI-RADSv2.1: prostate imaging-reporting and data system version 2.1, RP: radical prostatectomy, ISUP: International Society of Urological Pathology

optimal cut-off values were ≥10 ng/mL, ≥0.22 ng/mL/cm^3, ≥4, and ≥10 mm for PSA, PSAd, the PI-RADS score, and lesion dimension, respectively.

Biopsy was traditionally recommended when PSA was ≥4 ng/dL (14,15). D'Amico et al. (16) classified low-risk patients as those with a Gleason score <7, T1c-T2a, and PSA ≤10 ng/mL; PSA >10 ng/mL increased the risk, regardless of Gleason score and T-staging (16). Catalona et al. (14) found sensitivity, specificity, PPV, and NPV of 27.7%, 93.1%, 54.1%, and 84.1%, respectively, with a cut-off of greater than 10 ng/mL for all ages. Therefore, better markers are required since PSA has low sensitivity and/or specificity in clinically significant PCa detection.

PSAd is one of the reliable parameter in the prediction of clinically significant PCa (7,8). Kundu et al. (17) showed that the clinically significant PCa detection rate was 10% in PSAd less than 0.1, whereas it was 45% in those PSAd greater than 0.19 ng/mL/cm^3 and pointed out that higher PSAd was correlated with a worsening pathological outcome. Corcoran et al. (9) have reported that PSAd was the strongest predictor compared with PSA, clinical stage, number of positive cores, and tumor volume in upgrading from a Gleason score of 3+3 to >3+3 and from 3+4 to >3+4 but not in upgrading from Gleason 7 to >7. It was emphasized that higher grade tumors produced less PSA, and PSAd lost its predictive ability with increasing grade (9). On the other hand, Cuocolo et al. (18) reported that the combination of PSAd and biparametric MRI did not significantly improve the diagnostic performance of mpMRI alone. Aminsharifi et al. (15) reported that clinically significant PCa was less common in gray zone patients with a PSA between 4 and 10 ng/mL when PSAd was <0.08 ng/mL/cm^3. In the risk classification of the National Compherensive Cancer Network, PSAd <0.15 ng/mL/cm^3 was defined as very low risk (19). Despite, the threshold was determined as <0.2 ng/mL/cm^3 in the PRIAS active surveillence protocol (20). In the present study, the optimal cut-off value was calculated as ≥0.22 ng/mL/cm^3 in clinically significant PCa detection with a sensitivity of 58.4%, specificity of 87%, PPV of 81.8%, and NPV of 67.7%. It seemed to be inconvenient to use as a marker alone in detection of clinically significant PCa in consequence of having lower performance than the PI-RADS score and tumor dimension. However, it may be used in addition to the PI-RADS score since PSAd had high specificity.

The PI-RADS score is a significant predictor in clinically significant PCa detection (21,22). It is quite successful to exclude to clinically significant PCa with high NPV. Also, it shows anterior tumours that can be overlooked by systematic biopsy (21,22). A PI-RADS score ≥4 was reported to be associated with clinically significant PCa (22,23). Nevertheless, Greer et al. (24) stated that there was no difference between scores of 3 and 4, and score ≥3 lesions needed to be biopsied. PI-RADS score ≥3 lesions were indicated for biopsy and, in the current randomized controlled trials, cited as PROMIS and PRECISION (25,26). This revealed that there has been no clear consensus in the literature about the threshold PI-RADS score yet. In our study, the optimal cut-off value was PI-RADS score ≥4 in clinically significant PCa detection with a sensitivity of 93.5%, a specificity of 59.7%, PPV of 69.9%, and NPV of 90.2%.

Clinically significant PCa was defined as a volume ≥0.5 cc and/or Gleason score ≥3+4 and/or extraprostatic extension in the PI-RADS guideline (6). Maximum tumor diameter was a significant and independent predictor of biochemical recurrence (10). Nelson et al. (11) reported that tumor volume was strongly correlated with pathological stage, extraprostatic extension, and biochemical recurrence in RP specimens. Tumor volume was revealed as a potential predictor of prognosis (11). Vargas et al. (27) showed that lesions ≥1 cm^3 were detectable independently of Gleason score. The PI-RADS primarily recommended single diameter measurement, whereas volume assessment was an alternative option (6). Single diameter measurement was more reproducible than volume according to the PRECISE panel (28). In this study, the maximum single axis was measured. There was a strong correlation between lesion dimension and ISUP grade ($p<0.001$). The optimal cut-off value was ≥10 mm in clinically significant PCa detection, with a sensitivity of 88.3%, specificity of 66.2%, PPV of 72.3%, and NPV of 85%. Lesion dimension had the highest AUC in clinically significant PCa detection and performed better than PSA and PSAd. These results showed that lesion dimension had a diagnostic value at least as high as the PI-RADS score.

The only size criterion was 15 mm, which raised the score from 4 to 5 in the PI-RADSv2.1 guideline (13). Rosenkrantz et al. (29) argued that a threshold of 15 mm was empirically used in PI-RADSv1 and was required of supporting data. They proposed 10 mm as a new threshold for a score of 5 since 56.4%-61.9% of the lesions measured between 10 and 14 mm were clinically significant PCa (29). An et al. (30) found this threshold to be 16 mm for the TZ lesions and 14 mm for the peripheral zone lesions and pointed out that the current 15 mm criterion was reasonable.

However, this study included only patients with PI-RADS score 4 and 5 lesions (30). The threshold for clinically significant PCa definition is 0.5 cc, corresponding to 1 cm in a single measurement. In our study, the optimal cut-off was 10 mm, independent of the PI-RADS score. Lesions ≥10 mm had a potential risk for clinically significant PCa, and this could be considered in reporting.

Study Limitation

The present study has some limitations. First, this was a retrospective study in which selection bias may exist. Second, 12 quadrant systematic biopsy was the reference test. That may have decreased the correlation of mpMRI with pathology and underestimated mpMRI performance. mpMRI is a candidate diagnostic tool for the screening test. If the study only included RPs, it would only include high-risk patients; however, this would not be compatible with the intended use. It may be claimed that it reflected daily practice better. Third, the consensus PI-RADSv2.1 score was considered as a definite score, but both readers may have made mistakes which limited the generalizability of the results. There was no actual solution to this limitation since interreader agrement was moderate and the major problematic issue of the PI-RADS guidelines. Fourth, this was a single-center study with a relatively small population. These data require support by large and prospective cohorts with multiple readers.

Conclusion

The PI-RADS score and lesion dimension performed better in clinically significant PCa detection compared to PSA and PSAd. The optimal cut-off values were ≥4 in the PI-RADS score and ≥10 mm in dimension. Lesions ≥10 mm were associated with the risk of clinically significant PCa and should be considered in reporting.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Non-Interventional Clinical Research Ethics Committee of İzmir Katip Çelebi University (approval number: 18.06.2020/729).

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

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.C., Y.A., C.G.; Concept - M.C., Y.A., İ.Ö., C.G., M.E.U.; Design - M.C., E.M.H.D., Y.A., İ.Ö., C.G., M.E.U.; Data Collection or Processing - M.C., E.M.H.D.; Analysis or Interpretation - M.C., E.M.H.D., C.G., M.E.U.; Literature Search - M.C.; Writing - M.C., E.M.H.D., M.E.U.

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A Novel Marker Affecting Survival in Acute Non-variceal Upper Gastrointestinal Bleeding: Cardiac Troponin I

Akut Varis Dışı Üst Gastrointestinal Kanamada Sağkalımı Etkileyen Yeni Bir Belirteç: Kardiyak Troponin I

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ABSTRACT

Introduction: Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is an important public health problem with high rates of morbidity and mortality. ANVUGIB results in hypovolemia, hypotension, and shock, increasing cardiac oxygen use and may cause elevated serum levels of cardiac troponin (cTn). In this study, we aimed to evaluate whether elevated cTnI has clinical significance in patients with ANVUGIB.

Methods: A total of 62 patients diagnosed with ANVUGIB whose serum cTnI levels were studied at the time of admission and follow-up in our clinic from January 2015 to January 2016 were included in the study. Patients with acute cardiac diseases that may cause elevated cTn were excluded from the study.

Results: Forty-three of the patients were male (69.4%), and the mean age of all patients was 71.52±13.30 years. The mean cTnI level was 0.042±0.097 in all patients, with cTnI levels higher than the reference value in nine (14.5%) patients. In logistic regression analysis, the factors found to contribute to cTnI were tachycardia, chronic kidney disease, and coronary artery disease. In receiver operating characteristic analysis, cut-off values of 0.025 and 6.5 were found for cTnI and the Rockall score, respectively. In addition, cTnI and the Rockall score were shown to affect survival [log-rank (Mantel-Cox) test: p=0.011; log-rank (Mantel-Cox) test: p=0.014; respectively].

Conclusion: We believe that serum cTnI levels studied during the first admission will be found useful as a biomarker in addition to the other existing risk determination systems, in order to identify patients at risk, even if findings of acute coronary syndrome are not observed in patients presenting with ANVUGIB.

Keywords: cTnI, upper gastrointestinal bleeding, rockall score

ÖZ

Amaç: Akut varis dışı üst gastrointestinal sistem kanaması (AVDÜGSK) yüksek mortalite ve morbiditeye sahip önemli bir sağlık sorunudur. AVDÜGSK'leri hipovolemi, hipotansiyon ve şok tablosu oluşturarak kardiyak oksijen kullanımını artırır ve serum kardiyak troponin (kTn) düzeyinin yükselmesine neden olabilir. Biz bu çalışmada AVDÜGSK'si olan hastalarda kTnI yüksekliğinin klinik bir öneme sahip olup olmadığını değerlendirmeyi planladık.

Yöntemler: Kliniğimize Ocak 2015-Ocak 2016 tarihleri arasında başvuran, AVDÜGSK tanısı konan, başvuru anında serum kTnI bakılmış olan 62 hasta çalışmaya dahil edildi. kTn yüksekliğine sebep olabilecek akut kardiyak hadisesi olan tüm hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya alınan hastaların 43'ü erkek (%69,4) olup tüm hastaların ortalama yaşı 71,52±13,30 (25-92) idi. Tüm hastaların ortalama kTnI düzeyi 0,042±0,097 olup 9 (%14,5) hastanın kTnI düzeyi referans aralığının üzerinde idi. Yapılan lojistik regresyon analizinde kTnI düzeyi yüksekliğine katkı yapan faktörler taşikardi, kronik böbrek yetmezliği ve koroner arter hastalığı idi. Yapılan alıcı işletim karakteristiği analizinde kTnI ve rockall skoru için eşik değeri sırasıyla; 0,025 ve 6,5 olarak saptandı ve kTnI ile rockall skorunun yükseliğinin sağkalım üzerinde etkili olduğu gösterildi [sırasıyla; log-rank (Mantel-Cox) testi: p=0,011, log-rank (Mantel-Cox) testi: p=0,014].

Sonuç: AVDÜGSK ile başvuran hastalarda akut koroner sendrom bulguları olmasa bile ilk başvuruda serum kTnI düzeyinin bakılmasının riskli hastaların belirlenmesi açısından mevcut diğer risk belirleme yöntem ve skorlama sistemleriyle birlikte, bir biyobelirteç olarak kullanım alanı bulabileceği kanaatindeyiz.

Anahtar Kelimeler: kTnI, üst gastrointestinal sistem kanaması, Rockall skoru

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Introduction

Acute non-variceal upper gastrointestinal bleeding (ANVUGIB) is an important health problem with high rates of morbidity and mortality (1). Mortality from ANVUGIB reaches up to 40%, especially in patients who develop hemodynamic instability. Therefore, by detecting and treating the locale and cause of bleeding in the early period, hemodynamic stabilization is ensured and has vital importance (2).

Cardiac troponin I (cTnI) is an invaluable cardiac marker with high sensitivity and specificity in the diagnosis of myocardial necrosis and the classification of cardiac risk (3). cTnI plays an important role together with cTnC and cTnT in the regulation of cardiac muscle contraction. cTnI is not found in skeletal muscle and has high sensitivity, even under conditions causing severe muscle damage, such as severe muscle trauma, surgery, muscle diseases, and comprehensive exercise (4). Although elevation of cTn is a marker of myocardial necrosis, its level may also be increased in diseases that cause no myocardial damage, such as sepsis, pulmonary embolism, heart failure, and renal failure (5). Elevated cTnI has an important role in the diagnosis, treatment, and follow-up of acute coronary syndrome when evaluated together with the presence of risk factors and the clinical picture. There are studies reporting that serum cTnI levels elevated due to noncardiac causes may be associated with a poor prognosis in these diseases (6-8).

ANVUGIB may lead to hypovolemia, hypotension, and septic shock picture, increase cardiac oxygen use, and cause elevation of serum cTn levels (9). Among the other diseases causing an increase in serum cTn levels through a similar mechanism are sepsis, septic shock, systemic inflammatory response syndrome, and emergency noncardiac critical conditions (6,10,11). There are studies in the literature evaluating the association of ANVUGIB and myocardial infarction (12). Considering that cTnI may also be elevated in various noncardiac diseases, in the present study, we aimed to investigate serum cTnI levels in patients with ANVUGIB in whom acute myocardial pathologies were ruled out and whether elevated cTn1 has clinical significance.

Methods

A total of 62 patients who presented to our university gastroenterology and emergency department between January 2015 and January 2016, were diagnosed with ANVUGIB, whose serum cTnI were examined at the time of admission, and in whom the concomitant presence of acute coronary syndrome was ruled out with necessary investigations were included in this study. The study was approved by Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee (approval number: 2017/811, date: 24.02.2017). All participants provided written consent for participation in the study. Patients with stable coronary artery disease (CAD), hypertension controlled with drugs, or chronic kidney disease (CKD) in addition to ANVUGIB were included in the study; patients with acute myocardial infarction, arrhythmias, heart failure, aortic dissection, valvular heart disease, cardiac contusion or hypertensive crisis, those with pulmonary embolism or severe pulmonary diseases, patients with myocarditis or pericarditis, those with acute cerebrovascular events determined, patients with infiltrative diseases such as hemochromatosis or amyloidosis, those with rhabdomyolysis due to any cause, patients with sepsis or septic shock, those with a severe burn above 30%, cancer patients, those with cardiac arrest, and patients who underwent resuscitation and electrical cardioversion were excluded from the study.

Admission data on the patients included in the study were obtained by retrospective screening of the medical records that were prospectively recorded in the database and automation-recording program of our hospital. The records were examined, and patients' admission data including demographic features (age, gender etc), hemodynamic findings (blood pressure, pulse), administered drugs (antithrombotic, anticoagulant, and nonsteroidal anti-inflammatory drugs), laboratory data [serum cTnI, hemoglobin (Hb), leukocyte count, creatinine, urea, other laboratory investigations], and comorbidities (CKD, CAD etc) were recorded. The types and numbers of blood products transfused were determined for patients who received blood product transfusion during hospitalization in intensive care units (ICU) or wards.

The patients were divided into two groups according to cTnI values. Accordingly, patients with a serum cTnI value within the normal range (cTnI: 0.00-0.06 mg/L) were classified as group A, and those with a serum cTnI value, which was so high as to require clinical follow-up (cTnI ≥0.06 mg/L) as group B. Patients with an admission systolic blood pressure <90 mmHg were considered as hypotensive, and those with a peripheral pulse rate >90 as tachycardic. The Glasgow-Blatchford score (13) and the Rockall score (14), determined by evaluating endoscopy reports, were calculated for each patient. The lesions detected on endoscopy were grouped according to the Forrest classification (15). The 30-day mortality rate was calculated. We allocated the surviving patients to group 1 and the patients who died to group 2.

Statistical Analysis

Statistical analysis was performed using the "IBM SPSS Statistics for Windows, Version 19.0" (Armonk, NY, IBM Corp.) software package. Continuous variables were expressed as mean ± standard deviation, and categorical data as frequency and percentage (n, %). The normality of continuous variables was tested with the Kolmogorov-Smirnov method. In the comparison of two groups, an Independent-Samples t-test was used for normally distributed variables and a Mann-Whitney U test for non-normally distributed variables. In order to determine the linear correlation between variables, Pearson's correlation test was used for the parametric variables and Spearman's correlation test for non-parametric variables. A logistic regression model was used to investigate whether various variables are independent risk factors for elevation of cTnI. In the multivariate analysis, independent effects of the possible risk factors in the prediction of survival were examined with the backward elimination method using Cox-regression analysis. In order to analyze survival, the cutoff value for cTnI was determined using receiver operating characteristic (ROC) curves. The effect of cTnI levels on survival was analyzed with a log-rank (Mantel-Cox) test. Survival rates were calculated with the Kaplan-Meier method. Differences were considered statistically significant at $p<0.05$.

Results

A total of 62 patients who presented due to ANVUGIB between January 2015 and January 2016 were included in the study. Of all patients, 43 (69.4%) were male, and their mean age was 71.52±13.30 years.

All patients underwent endoscopy within the first 12 hours after presentation. When endoscopy results were evaluated, bleeding was found to originate from a duodenal ulcer in 27 (43.5%), gastric ulcer in 19 (30.6%), Mallory-Weiss lesions in 6 (9.7%), and non-variceal various esophageal lesions in 10 (16.2%) patients. When endoscopic findings of the patients with bleeding due to duodenal ulcer were examined, Forrest 1b ulcer was found in 1 (3.7%) patient, Forrest 2a in 7 (25.9%) patients, Forrest 2b in 1 (3.7%) patient, Forrest 2c in 10 (37%) patients, and Forrest 3 ulcer in 8 (29.6%) patients. When endoscopic findings of the patients with bleeding due to gastric ulcer were examined, Forrest 1b ulcer was found in two (10.5%) patients, Forrest 2a in five (26.3%) patients, Forrest 2b in one (5.3%) patient, Forrest 2c in three (15.8%) patients and Forrest 3 in eight (42.1%) patients.

Of all patients, 13 (21%) were using anti-thrombotics, 12 (19.4%) anti-coagulants, 4 (6.5%) both antithrombotic and anticoagulant drugs, 4 (6.5%) nonsteroidal anti-inflammatory drugs, 2 (3.2%) both non-steroidal anti-inflammatory and anti-thrombotic drugs, and one (1.6%) anti-coagulant, anti-thrombotic, and non-steroidal anti-inflammatory, while 26 (41.9%) were not using any anti-coagulant, anti-thrombotic, or non-steroidal anti-inflammatory drug.

Serum cTnI levels were above the reference range in 9 (14.5%) of the 62 patients, and the mean serum cTnI level was 0.042±0.097 mg/L in all patients. There were 53 patients in group A (85.5%) and 9 patients in group B (14.5%). The mean serum cTnI level was found to be 0.017±0.015 mg/L in group A and 0.19±0.20 mg/L in group B, and the difference between the two groups was statistically significant (p<0.001). The mean age was found to be 70.15±13.70 years in group A and 79.60±6.0 years in group B, and the difference was statistically significant (p=0.04). The mean Hb level was found to be 8.6±2.7 g/dL in group A and 7.3±2.9 g/dL in group B, and the difference was not statistically significant (p=0.072). Demographic and laboratory data on the patients in groups A and B are given in Table 1.

When the patients in group A and group B were compared in terms of the need for blood transfusion, a mean of 4.74±4.6 units of erythrocyte suspension was transfused in the patients in group A during hospitalization, while this amount was 7.44±7.7 units in the patients in group B. The difference between the groups was not statistically significant (p=0.350). The mean serum creatinine levels were 1.12±0.55 mg/dL and 1.69±0.68 mg/dL in the patients in group A and group B, respectively, and the difference between the two groups was statistically significant (p=0.012).

The mean duration of hospitalization was 8.60±5.30 days in all patients. The mean durations of hospitalization found were 8.50±5.20 days and 9.33±6.40 days in group A and group B, respectively. There was no significant difference between the groups in terms of the duration of hospitalization (p=0.666). The mean length of stay in the ICU was 4.56±4.80 days. The mean length of stay was found to be 4.40±4.85 days in group A and 5.55±4.66 days in group B. There was no statistically significant difference between the groups in terms of the length of stay in the ICU (p=0.393).

When the patients' hemodynamic values at the time of admission were evaluated, tachycardia was found in 24 (45.3%) patients and hypotension in 16 (30.0%) of the patients in group A. In group B, seven (77.8%) patients had tachycardia, and four (44.4%) patients had hypotension at the time of first admission. Hb examined during the first admission was <7 g/dL in 17 of 53 patients (32.1%) in group A, and 5 (55.6%) patients in group B. When patients were examined in terms of comorbidities; a history of CKD was found in 5 (9.4%), CAD in 23 (43.4%), and diabetes mellitus (DM) in 15 (28.3) patients in group A, while a history of CKD was found in 3 (33.3%), CAD in 8 (88.8%) and DM in 1 (11.1%) patient in group B.

In the logistic regression analysis performed with several factors such as gender and the presence of tachycardia or hypotension at the time of admission, an initially measured Hb <7 g/dL, and the presence of CKD, DM, and stable CAD; tachycardia found during the first admission; and presence of a history of accompanying CKD or CAD were determined as the independent risk factors in terms of elevated serum cTnI levels. Estimated relative risks [odds ratio (OR)] calculated for the presence of tachycardia, CKD, and stable CAD during the first admission were found

Table 1. Clinical, demographical and laboratory data of the groups

	Group A cTnI <0.06 mg/L (n=53) (85.5%)	Group B cTnI ≥0.06 mg/L (n=9) (14.5%)	All patients (n=62)	p
Age	70.15±13.7 (25-92)	79.6±6.0 (73-87)	71.5±13.3	0.040
Male (%)	39 (73.6)	4 (44.4)	43 (69.4)	0.106
Hb (gr/dL)	8.6±2.7 (3.7-15.5)	7.3±2.9 (5.1-14.7)	8.36±2.7 (3.7-15.5)	0.072
WBC ($\times 10^3$)	13.6±9.6 (2.3-67.3)	11.9±3.7 (4.6-16.0)	13.3±8.9 (2.3-67.3)	0.96
Creatinine (mg/dL)	1.12±0.55 (0.53-2.99)	1.69±0.68 (0.88-2.5)	1.2±0.6 (0.53-2.99)	0.012
BUN	104.5±51.7 (28.6-236)	149±84 (41.9-281)	110.9±58.8 (28.6-281)	0.134
Mean number of ES transfusions	4.74±4.6	7.44±7.7	5.13±5.2	0.350
Length of stay in ICU (days)	4.40±4.85 (0-26)	5.56±4.66 (1-15)	4.56±4.80 (0-26)	0.393
Hospitalization (days)	8.50±5.20 (3-30)	9.33±6.40 (2-21)	8.60±5.60 (2-30)	0.666
Glasgow-Blatchford score	12.34±3.1 (5-18)	15.55±2.96 (10-18)	12.80±3.21 (5-19)	0.03
Rockall score	5.47±1.56 (2-9)	7.44±1.50 (5-9)	5.76±1.69 (2-9)	0.03

Hb: Hemoglobin, WBC: white blood cell, BUN: blood urea nitrogen, ES: erythrocyte suspension ICU: intensive care unit, cTnI: cardiac troponin I

as 11.2 [95% confidence interval (CI): 1.3-96.9], 11.5 (95% CI: 1.1-120.47), and 20.4 (95% CI: 1.75-238.6), respectively. The results of the logistic regression model examining the factors that contributed to elevation of cTnI are given in Table 2.

When the patients' 30-day mortality rates were evaluated, seven (11.3%) patients died during daily follow-up due to various causes related to bleeding, whereas five (9.4%) patients in group 1 died within 30 days from bleeding-related causes, this rate was 22.2% (two patients) in group 2. There was no statistically significant difference between the groups in terms of 30-day mortality rates (p=0.262). Patients included in the study were divided into two groups according to mortality data. Patients who survived at the end of 30 days were assigned to group 1, and those who died within 30 days due to bleeding-related causes as group 2. Demographic and laboratory data of group 1 and group 2 are given in Table 3.

The mean serum cTnI level was found as 0.038±0.095 mg/L in group 1 and 0.077±0.11 in group 2. The difference between the two groups was not statistically significant (p=0.067). When the groups were compared in terms of the length of stay in the ICU; the mean length of stay in the ICU was found to be 4.36±4.95 days in group 1 and 6.14±3.34 days in group 2. The mean length of stay in the ICU was longer in the patients in group 2, although the difference was not statistically significant (p=0.058). However, the statistical analysis revealed that the patients in group 2 required more blood transfusions during their hospitalization. A mean of 4.51±4.5 units erythrocyte suspension was transfused in group 1, while this amount was 10.0±7.7 units in group 2, and the difference was statistically significant (p=0.012).

The mean Rockall and Glasgow scores found were 5.76±1.69 and 12.80±3.21 in all patients, respectively. In Pearson correlation analysis, it was found that the Rockall and Glasgow scores were correlated with serum cTnI levels, length of stay in the ICU, and the total number of erythrocyte suspensions given to patients during their hospitalization. Correlation analyses are summarized in Table 4.

In the ROC analysis, the optimal cut off values for serum cTnI concentrations and Rockall scores were found to be 0.025 mg/L and 6.5, respectively. In the comparison of survival curves plotted according to the conditions of serum cTnI concentrations and Rockall scores being under or above the cut off values; there was a statistically significant difference in terms of survival for both serum cTnI concentrations (Mantel-Cox test: chi-square 6.426, p=0.011) and Rockall scores (Mantel-Cox test: chi-square 6.055, p=0.014). Kaplan-Meier curves are seen in Figure 1, 2. According to Cox-regression analysis, the presence of CKD

Table 2. Factors contributing to elevated cTnI in the logistic regression analysis

	Group A cTnI <0.06 mg/L (n=53) (85.5%)	Group B cTnI >0.06 mg/L (n=9) (14.5%)	All patients (n=62)	OR (95% CI)
Male (n, %)	39 (73.6)	4 (44.4)	43 (69.4)	NS
Tachycardia (%)	24 (45.3)	7 (77.8)	31 (50)	11.2 (1.3-96.9)
Hypotension (%)	16 (30)	4 (44.4)	20 (32.3)	NS
Hb <7 g/dL (%)	17 (32.1)	5 (55.6)	22 (35.5)	NS
Cardiac disease presence (%)	23 (43.4)	8 (88.1)	31 (50)	20.4 (1.75-238.6)
Chronic kidney disease (%)	5 (9.4)	3 (33.3)	8 (12.9)	11.5 (1.1-120.47)
Diabetes mellitus presence (%)	15 (28.3)	1 (11.1)	16 (25.8)	NS

cTnI: Cardiac troponin I, OR: odds ratio, CI: confidence interval, Hb: hemoglobin, NS: not significant

Table 3. Clinical, demographic, and laboratory data of the groups

	Group1 survived patients (n=55) (88.7%)	Group 2 died patients (n=7) (11.3%)	All patients (n=62)	p
Age	71.51±13.6 (25-92)	71.6±11.1 (58-88)	71.5±13.3 (25-92)	0.828
Male (%)	40 (72.7)	3 (42.9)	43 (69.4)	0.106
Hb (gr/dL)	8.5±2.8 (3.7-15.5)	6.9±1.9 (4.0-10.1)	8.4±2.7 (3.7-15.5)	0.133
WBC ($\times 10^3$)	13.6±9.6 (2.3-67.3)	11.9±3.7 (4.6-16.0)	13.3±8.9 (2.3-67.3)	0.151
Creatinine (mg/dL)	1.22±0.62 (0.53-2.99)	1.15±0.5 (0.54-1.93)	1.2±0.6 (0.53-2.99)	0.879
BUN	113.2±61.3 (28.6-281)	93.4±30 (41.9-137.6)	110.9±58.8 (28.6-281)	0.616
cTnI	0.038±0.095 (0.0-0.68)	0.077±0.11 (0.0-0.32)	0.042±0.097 (0.0-0.68)	0.067
Rockall Score	5.51±1.57 (2-9)	7.71±1.58 (6-9)	5.76±1.69 (2-9)	0.003
Glasgow Blatchfort score	12.50±3.15 (5-18)	15.14±2.97 (10-19)	12.80±3.21 (5-19)	0.045
Mean number of ES transfusions	4.51±4.5 (0-21)	10.0±7.7 (0-25)	5.1±5.2 (0-25)	0.012
Length of stay in ICU (days)	4.36±4.95 (0-26)	6.14±3.34 (0-11)	4.56±4.80 (0-26)	0.058

Hb: Hemoglobin, WBC: WBC: white blood cell, BUN: blood urea nitrogen, ICU: intensive care unit, cTnI: cardiac troponin I, ES: erythrocyte suspension

Table 4. Correlation of cTnI with other factors

	Rockall score		Glasgow-Blatchford score		Number of ES transfusions		Length of stay in ICU (days)	
	p	P	p	P	p	P	p	P
cTnI	0.001	0.396	0.007	0.337	0.217	0.089	0.007	0.340
Rockall score	-	1	0.001	0.400	0.002	0.381	0.006	0.347
Glasgow-Blacthford score	0.001	0.400	-	1	<0.001	0.520	0.003	0.368
Number of ES transfusions	0.002	0.002	<0.001	0.520	-	1	<0.001	0.709

P: Pearson correlation coefficient, cTnI: cardiac troponin I, ES: erythrocyte suspension, ICU: intensive care unit

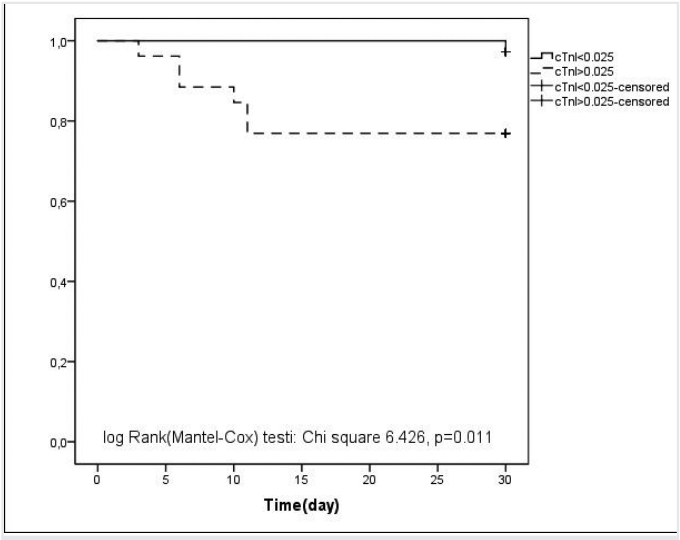

Figure 1. Correlation of cTnI levels with mortality
cTnI: Cardiac troponin I

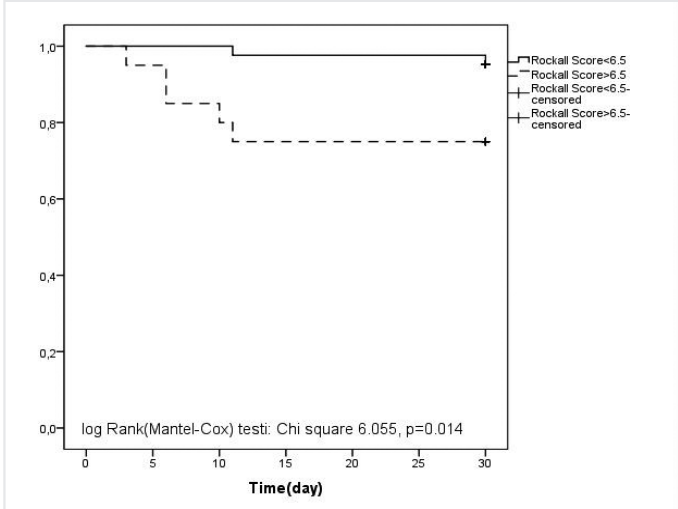

Figure 2. Correlation of Rockall score with mortality

as a comorbidity was found to be an independent risk factor associated with mortality in patients presenting with ANVUGIB (OR: 11.47, 95% CI: 1.35-97.63). On the other hand, the number of erythrocyte suspensions given to the patients during hospitalization, presence of hypotension or tachycardia at the first admission, gender, length of stay in the ICU, and presence of comorbidity (DM and CAD) alone were not mortality-related independent risk factors.

Discussion

Risk stratification, determination of low- and high-risk patients in an early period, and planning appropriate follow-up and treatment are crucial in patients with ANVUGIB (16,17). At present, there is no ideal model used in the prediction of mortality in ANVUGIB. The Rockall score is one of the most commonly used scoring systems for this purpose. Although the effectivity of the Rockall score in the prediction of mortality and re-bleeding has been confirmed by many studies, its use is limited, especially in patients with unstable hemodynamics. Non-endoscopic factors such as age, shock, and comorbidity are involved in the calculation of the Rockall score, although the presence and characteristics of the lesion causing bleeding are important, and thus the calculation and use of the Rockall score is limited, especially in patients with unstable hemodynamics (14,18-20). There are similar problems in the other various risk scoring systems, and there is still a need for an optimal marker to predict mortality and morbidity in ANVUGIB.

In the present study, serum cTnI levels were above the reference value that requires clinical follow-up (>0.06 mg/L) in 14.5% of all patients. All of these patients were investigated for the presence of acute coronary syndrome, which was then ruled out by clinical findings, electrocardiography, echocardiography, and clinical follow-up. In logistic regression analysis, CKD, CAD, and tachycardia were found as the independent risk factors affecting elevation of serum cTnI levels. In fact, there are various studies in the literature reporting elevated serum cTnI levels due to various reasons other than acute coronary syndrome. In a study by Alcalai et al. (7), serum cTnI levels were measured in all patients who presented to the hospital for various reasons within a 10-month period, and 53% of 635 patients with high serum level of cTnI were diagnosed with acute coronary syndrome, while elevated serum cTnI levels did not result from thrombotic causes in 41% of patients. In the same study, no explanation was for elevated serum cTnI levels in 6% of the patients. According to that study, an important proportion of patients with elevated serum cTnI levels had no CAD. In the same study, patients with elevated serum cTnI levels that did not result from thrombotic causes were examined, and non-ischemic cardiac events such as myocarditis and arrhythmia were found in 11%, sepsis in 8%, pulmonary diseases in 7%, cerebrovascular events in 5%, surgical conditions (trauma, intensive gastrointestinal bleeding, intestinal obstruction etc) in 5%, and renal failure in 2% of the patients, while 2% of the patients underwent cardiopulmonary resuscitation. Elevated serum cTnI levels are not easy

to interpret in patients with CKD (21). Elevated serum cTnI levels in these patients may be related to subclinical myocardial damage, chronic inflammatory responses, and chronic volume load due to CKD. Many studies have shown that an elevated cTnI level was more significant and specific when patients with CKD were excluded. Data obtained from a smaller group of patients with renal failure showed that serum cTnI levels were associated with several complications, including increased rates of mortality (21,22). Serum cTnI levels have also been reported to increase in patients with hypotension and sepsis (10,23). It has been shown in coronary angiography or autopsy examinations that a large proportion of patients with sepsis and elevated serum cTnI levels had no CAD (10,24). Although definitive cause of elevated cTnI levels in sepsis is not clear, several factors, such as cytotoxic endotoxins, inflammatory mediators, septic microemboli, vasoactive drugs used in the treatment, and accompanying hypotension, are thought to be responsible for this elevation (25,26). Studies have shown that elevated serum cTnI levels were associated with the severity of sepsis, multiple organ failure, and mortality, and that increased cTnI levels were especially observed in streptococcic sepsis and gram-negative sepsis (27).

Today, serum cTnI levels are recognized as one of the independent predictors of risk in acute coronary syndrome (3). In addition, there are studies reporting that elevated serum cTnI levels occurring for various reasons other than acute coronary syndrome have short- and long-term prognostic value in various diseases (10,21,24). Perioperative cTnI levels have been shown to be significant in the determination of cardiac risk after open cardiac surgery (28). In studies including asymptomatic dialysis patients with CKD and excluding patients with angina pectoris and acute coronary syndrome, cTnI levels were found to be high; the same studies also showed that in addition to cardiac death, noncardiac death was also increased in patients with high serum cTnI levels (29). It has been shown that serum cTnI levels were increased, in the acute exacerbation period in patients with chronic obstructive pulmonary disease (COPD), length of stay in ICU and the need for ventilation were increased in patients with high serum cTnI levels, and it has been proposed that cTnI levels can be used in determination of high-risk groups in terms of acute exacerbation attacks in COPD patients, but an association between serum cTnI levels and mortality could not be demonstrated (30). On the other hand, there are studies reporting that an elevated serum cTnI level was correlated with short- and long-term mortality and morbidity in patients who had an ischemic stroke (31,32). An elevated serum cTnI level has been shown to be an independent predictor of mortality in patients hospitalized in the ICU due to pneumonia who had no acute coronary syndrome (33).

Based on the results of this study, we believe that elevated serum cTn1 levels in patients with ANVUGIB without acute coronary syndrome might result from relative cardiac ischemia caused by bleeding and volume loss, tachycardia, and hemodynamic instability. In fact, one of the noteworthy points of the study was that patients with elevated serum cTn1 levels were more hemodynamically unstable. It was found that Hb values at admission were lower, hypotension and tachycardia during the first admission were more common, length of stay in the ICU was longer, the need for transfusion was more common, and the 30-day mortality rate was higher in patients with elevated serum cTn1 levels. However, although the numerical difference was significant for most of these parameters, the difference was not statistically significant due to the small number of patients. Therefore, we plan to confirm these results with a prospective study to be conducted with a sufficient number of cases.

Another remarkable point of this study was that even a serum cTnI level above the cut-off point that was determined as much lower than the level requiring clinical follow-up (0.025 mg/L) affected mortality. Given that there is still no optimal method to determine risk in the management of patients with ANVUGIB, the serum cTnI level could be used as a non-invasive and inexpensive biomarker for risk stratification in patients with ANVUGIB.

Study Limitation

The most important limitation of this study was its retrospective design and relatively small number of patients. Due to the small number of patients, despite significant numerical differences between the groups in terms of various parameters, these differences did not reach statistical significance.

Conclusion

Serum cTnI levels may be elevated in patients with ANVUGIB, even in the absence of acute coronary syndrome, and high serum cTnI levels are associated with mortality in these patients. Therefore, we believe that investigation of serum cTnI levels during initial admission of patients presenting with ANVUGIB, even if they have no acute coronary syndrome, will be found useful among the other risk stratification methods and scoring systems in terms of the determination of high-risk patients.

Ethics

Ethics Committee Approval: The study was approved by Necmettin Erbakan University, Meram Faculty of Medicine Ethics Committee (approval number: 2017/811, date: 24.02.2017).

Informed Consent: All participants provided written consent for participation in the study.

Peer-review: Externally peer-reviewed.

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Investigation of the Effects of Splenectomy on Bone Healing (Experimental Study)

Splenektominin Kemik İyileşmesine Etkilerinin Araştırılması (Deneysel Çalışma)

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ABSTRACT

Introduction: This study is an experimental setup to examine the effects of splenectomy, applied to multi-trauma patients who are commonly seen in emergency traumatology practices and on fracture healing processes with respect to histopathological, biomechanical, and radiological aspects.

Methods: Further, 32 male Sprague Dawley rats (10 months old; average weight 394.5±28.3 g) are included in the study. In a dark environment, rats are fed at 22 °C for 12 hours with standard rodent food ad libitum. They are divided into two groups: splenectomy (total splenectomy and long bone fracture healing) and control (only long bone fracture healing n=16). Four months after surgery, rats are killed, and callus tissues in fractured femurs were examined histopathologically, radiologically, and biomechanically.

Results: In the radiological analysis of the femur materials in relation to the case and control groups, there was no substantial difference in the Goldberg classification score (p>0.05). Similarly, no substantial difference was observed (p>0.05) in histopathological examinations and biomechanical analysis conducted in femur samples.

Conclusion: When all of the results obtained in our study are evaluated together, it was concluded in the rats to which splenectomy is applied that this did not affect fracture healing histopathologically, biomechanically, and radiologically, despite the modification of immune modulators.

Keywords: Bone healing, splenectomy, immune

ÖZ

Amaç: Bu çalışma acil travmatoloji pratiğinde sıkça görülen bir durum olan multi travma hastalarında yapılan splenektominin kırık iyileşme sürecine olan etkilerini histopatolojik, biyomekanik ve radyolojik açıdan incelemek için oluşturulmuş bir deneysel düzenektir.

Yöntemler: Çalışmaya 32 erkek Sprague Dawley rat alındı (10 aylık; ortalama ağırlık, 394,5±28,3 g). Sıçanlar, karanlık bir ortamda 12 saat boyunca 22 °C'de standart kemirgen gıda ad libitumu ile beslendi. Splenektomi (toplam splenektomi ve uzun kemik kırık iyileşmesi) ve kontrol grubu (sadece uzun kemik kırık iyileşmesi n=16) olmak üzere iki gruba ayrıldı. Ameliyattan dört hafta sonra, sıçanlar sakrifiye edildi ve kırılan femurlarındaki kallus dokuları histopatolojik, radyolojik ve biyomekanik olarak incelendi.

Bulgular: Olgu ve kontrol grubunda gönderilen femur materyallerinin radyolojik incelemesinde yapılan Goldberg sınıflama skorlamasında anlamlı (p>0,05) farklılık göstermemiştir. Yine gönderilen femur numunelerinde yapılan histopatolojik incelemeler ve biyomekaniksel analizlerde de anlamlı (p>0,05) farklılık gösterilememiştir.

Sonuç: Çalışmamızdan elde edilen tüm sonuçlar birlikte değerlendirildiğinde splenektomi yapılan sıçanlarda immün modülatörler üzerinde oluşturduğu modifikasyon değişikliğine rağmen kırık iyileşmesini histopatolojik, biyomekanik ve radyolojik olarak etkilemediği sonucuna varılmıştır.

Anahtar Kelimeler: Kemik iyileşmesi, splenektomi, bağışıklık

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Introduction

In orthopedics and traumatology clinics, fracture healing is of great significance. Before discussing the factors influencing fracture healing, it would be beneficial to mention the fracture healing process. Fracture healing consists mainly of three stages: inflammation stage, repairing stage, and reshaping stage. Furthermore, major factors affecting this process are smoking cigarettes, soft tissue damage, infection, insufficient fracture stabilization, poor nutrition, age, and use of pharmacological agents (1-3). Fracture healing has two types: the first is primary fracture healing which occurs in the form of unification in fractures, and the second is secondary fracture healing which defines the unification of the fracture that is not determined.

There is an interaction at the cellular level between the immune system and the musculoskeletal system (4). Wound healing is positively affected by a decrease in CD8 cytotoxic T-lymphocyte count. Again, studies have shown that there is an increase in bone formation when there are no B lymphocytes following trauma (5).

The spleen is a core immune system organ where old and damaged erythrocytes and other circulating blood components and microorganisms are cleaned. Additionally, it is the second largest lymphoid organ due to its dense macrophage and dendritic cell content, including half of the body's lymphocytes. Since the spleen is the central organ of cellular and humoral immunity, immune function is its most important function (6). Lymphocytes are effector cells of the adaptive immune system, and their contribution to regenerative processes has been demonstrated (7). Some research has also shown a relationship between spleen function and bone metabolism at the cellular level. Despite this circumstance, the effect of the spleen on bone metabolism and remodeling has not yet been fully explained (8). However, bone resorption and formation are modulated by the interaction between T and B lymphocytes, dendritic cells, and cytokines on the immune system (9,10).

The interaction between the immune system and bone metabolism has been discussed in numerous studies; however, to our knowledge, no study has considered the effects of the spleen and immune system on muscle and tendon metabolism. We also know that spleen-induced cytokines and cells play a significant role in tendon healing. Therefore, we assume that the spleen and immune system components may affect bone healing. Investigating this possibility, we designed a study model that examines the histopathological, radiological, and biomechanical mechanism of bone healing in patients with large bone fractures simultaneously in splenectomized rats. Our hypothesis before the study was to obtain better histopathological, immunohistochemical, and biomechanical results for the healing of femoral fractures in animals where splenectomy was performed. We figured this was because the rate of pro-inflammatory/anti-inflammatory cytokines in rats with splenectomy shifted in favor of anti-inflammatory cytokines and decreased inflammatory cells from the spleen.

Methods

According to the surgical procedures to be examined, 36 rats were randomly selected and divided into two groups of equal numbers. During the analysis, the rats were given unlimited tap water (ad libitum) and standard rodent feed. The animals were monitored at 22 degrees Celsius (°C) in order to stay 12 hours in the light and 12 hours in the dark. Each group was operated by the same surgeon on the same day. Before surgery, a single dose of gentamicin 8 mg/kg was administered subcutaneously from the nape of the skin under the literature. The animals, with the requisite follow-up and preparations, were taken to the operating room. Moreover, the anesthetic drug dose was calculated by weighing each rat on an electronic scale. As an anesthetic, isoflurane was started at a 4% induction dose and continued at 2% for maintenance. The right knee areas of the rats were shaved and then stained with povidone-iodine (Batticon®, ADEKA, Turkey). Anteromedially, the skin was passed through a 2 cm longitudinal incision. The joint capsule was opened from the medial patella. Patella was laterally overturned and knee flexed. The femur canal would be exposed, and the femur canal has been prepared using 1 mm Kirschner wire (TST, Istanbul) and electric drill (note: supplied by us) among the femur condoms. Then, the 0.8 mm Kirschner wire (TST, İstanbul) was placed in the prepared channel where the wire was compressed, pulled back 3-4 mm, and cut from the femoral condyle level. Furthermore, the residual wire in the channel was pushed back into the channel so that it did not come out of the condyle, the patella was reduced by extending the knee, the capsule was sutured with 3/0 vicryl (Atramat®, Mexico) and skin with 2/0 silk (Sterisilk®, Turkey), and the wound is closed. Then, a 0.5 cm longitudinal incision was made at the midshaft level from the lateral of the thigh and was osteotomized from the femoral mid-soft (middle body) by applying even pressure through the costa scissors. In addition, the incision was closed following the skin and subcutaneous anatomy (Figure 1). Subsequently, a 3 cm midline incision was made in the abdomen, and the spleen was inspected and separated from its ligaments and removed from the abdomen. The veins in the spleen hilus and punch are dissected and ligated and cut, and the spleen is taken out of the abdomen. Following the clinical examination, the fracture was radiologically examined with a direct radiography on the surgery table with a portable X-ray device (Figure 2). All rats were sacrificed under general anesthesia by cervical dislocation in the 4th week after all of these procedures. Further, 8 out of 16 rats in each group are sent for biomechanical examination after their bilateral femurs were removed, while the remaining 8 rats are sent for pathology after operated sides were amputated. All 16 rats in each group were X-rayed (Figure 2); this procedure was applied to all groups. All the radiographs obtained were scored by two separate orthopedists,

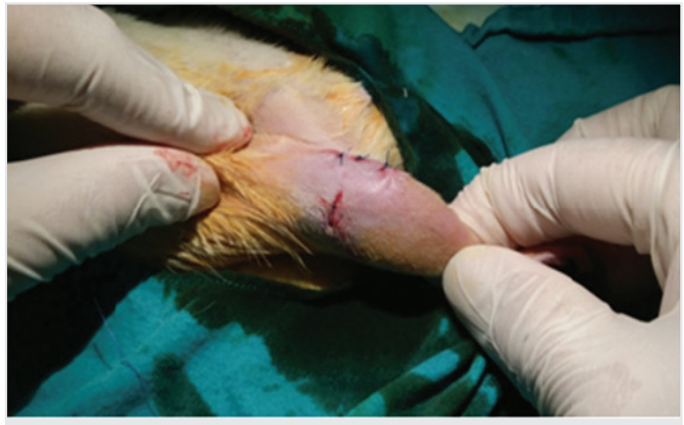

Figure 1. Creation of a femur fracture with a mini open incision

independent of the experiment according to the Goldberg classification. Materials sent to pathology were made according to the histological healing scale published by Huo et al. (10) with respect to histological classification of healing (Figure 3). On the other hand, the materials sent to the biomechanics laboratory were also sent to Yıldız Technical University Faculty of Mechanical Engineering and Biomechanical Engineering with a wet sponge, frozen at -20 °C and analyzed in terms of biomechanics. Then, the radiological and histological findings of the control and drug groups were evaluated using the Kruskal-Wallis test. As a result, the difference between the splenectomy group and the group that was not applied splenectomy was compared in terms of fracture healing. The study was approved by the Animal Experiments Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital, Turkey (approval number: HADYEK/2014-26, date: 23.07.2014).

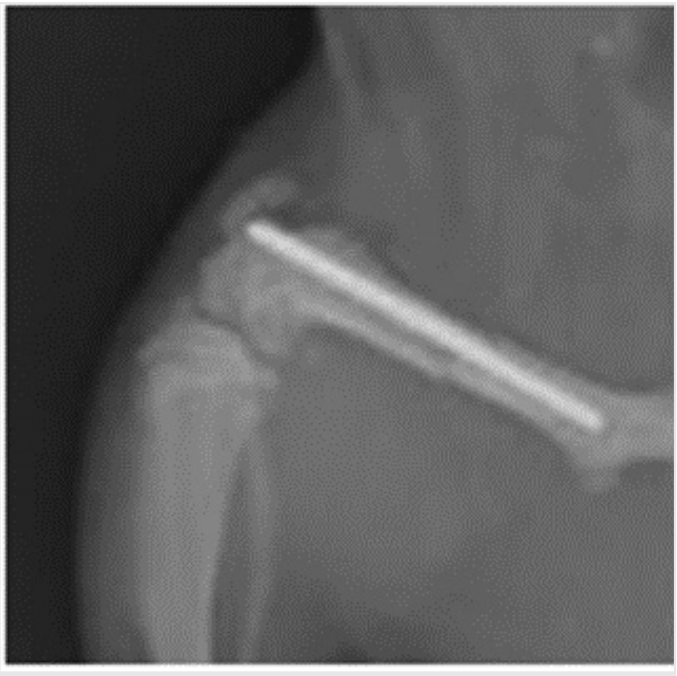

Figure 2. Early postoperative X-ray

Statistical Analysis

The SPSS 22.0 software was used in the analysis. Average, standard deviation, and median lowest and highest values were used in the descriptive statistics for all data collected. The distribution of variables is measured by the Kolmogorov-Smirnov test. In the analysis of quantitative data, the Mann-Whitney U test and Independent Samples t-test were used. The Paired Samples t-test was used for the study of repeated measurements. Moreover, the Kappa fit test was used for fit analysis.

Results

In the case and control group, the Goldberg classification score did not vary significantly (p>0.05). Also, the histopathological score did not differ significantly in the case and control groups (p>0.05) (Table 1).

The Goldberg classification assessment of the first and second orthopedists was substantially in conformity (p=0.000/Kappa=0.619) (Table 2).

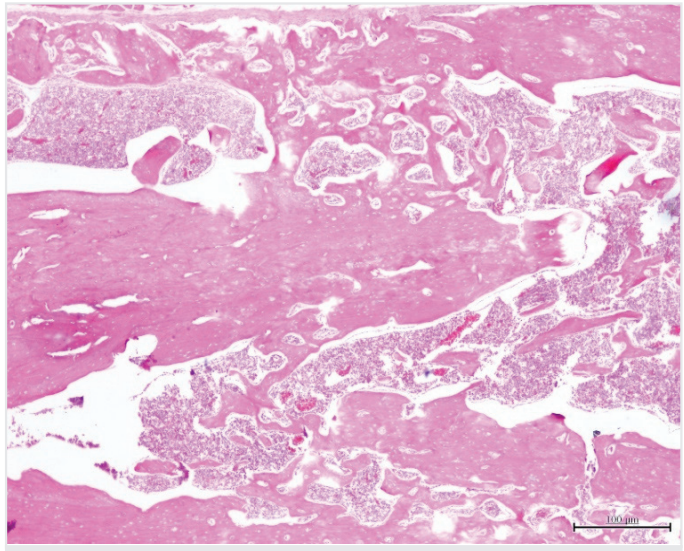

Figure 3. Mature bone (hematoxylin-eosin staining x40 magnification)

Table 1. Analysis of radiological and histopathological results

	Control group		Case group		p
	Mean ± SD	Med (min-max)	Mean ± SD	Med (min-max)	
Goldberg classification	2.8±0.4	3.0 2.0-3.0	2.6±0.6	2.9 1.0-3.0	0.361
Histopathologic score	6.9±0.9	6.5 5.5-8.0	6.9±1.2	7.0 5.0-8.3	0.957

Independent sample t-test, Mann-Whitney U test, SD: standard deviation, min: minimum, max: maximum

Table 2. Compatibility analysis table among orthopedists

		Orthopedic surgeon 2 Goldberg scores				% Conformity	Kappa	p
		1	2	2.5	3			
Orthopedic surgeon 1 Goldberg scores	1	1	0	0	0	93%	0.619	0.000
	2	0	6	0	2			
	2.5	0	1	0	2			
	3	0	0	1	19			

Kappa conformity test

In the case and control groups, the robust biomechanical measurements did not differ significantly (p>0.05). In addition, in the case and control groups, the broken side biomechanical measurements did not vary significantly (p>0.05). However, in the control group, the biomechanical measurement of the broken side was significantly lower (p=0.001) from the strong side. Also, in the case group, the broken side biomechanical measurement was significantly lower (p=0.001) from the strong side (Table 3).

Discussion

In this experimental study, we examined and compared the effect of splenectomy on the healing of femoral fractures in rats that were treated with splenectomy and in rats not treated with splenectomy. Despite having positive and negative effects in the literature, we could not show any effect differently. In other words, the healing process in rats with and without splenectomy was biomechanically, radiologically, and histopathologically indifferent. In this regard, there are studies with different study designs in the literature, and we compared some of them with the results of our study. Zhang et al. (11) showed that the anti-inflammatory effect of splenectomy reduces the amount of cerebral infarction. However, the anti-inflammatory mechanism of action that emerged after splenectomy could not be explained in the same study. These researchers showed that the number of CD4+ and CD3+ T lymphocytes decreased after splenectomy (11). However, in a 2011 study by Milićević et al. (12), it was shown that the number of B lymphocytes increased 3 months after splenectomy, but there was no change in the number of T lymphocytes, natural killer cells, macrophages, neutrophils, and monocytes. Also, in their studies, Arakawa et al. (13) demonstrated the anti-inflammatory effect of splenectomy on the portal system.

In a recent study, immune function changes after splenectomy had an effect on fracture healing. For this reason, it was said that the spleen should be preserved in order to heal the fracture (14). In the same study, low levels of IL-1β and TNF-α, which are pro-inflammatory cytokines, were detected. Furthermore, they also showed that splenectomy negatively reduced RANKL expression and affected collagen synthesis and fibroblast differentiation and that these changes cause a delay in bone healing. However, according to our study, their weak points were that they did not biomechanically investigate bone healing. In their study in the splenectomized rats, Sun et al. (15) and Toben et al. (16) showed that splenectomy increased bone formation.

Sun et al. (15) reported that T lymphocytes had a negative effect on bone healing and had negative effects at the early stage of fracture healing. This process was clarified by increased interaction between T lymphocytes and RANK-RANKL and increased osteoclastogenesis. They also emphasized that the reduction of pro-inflammatory cytokines released from activated T lymphocytes, monocytes, and macrophages is effective in these processes. In parallel with this study, lower levels of IL-1 TN, TNF-α, and IFN-γ were observed, as well as higher levels of IL-10 and IL-4.

Nakamichi et al. (17) showed that TNF-α levels decreased after splenectomy and that this resulted in a decrease in the number of osteoclasts and that, as a consequence of all these inflammatory changes, splenectomy had a positive impact on bone healing. Lehmann et al. (18) showed in their study that the decrease in TNF-α signal reduced fracture healing and that the positive or negative effect of TNF-α was dose-dependent. Toben et al. (16) emphasized that IFN-γ levels were low in lymphatic rats and reduced macrophage activation and tissue destruction (16). Another study found that IL-10 levels increased in immune system deficiency, inhibiting the secretion of pro-inflammatory cytokines, which had a positive effect on bone healing (19). IL-2 is considered to be an important T-cell growth factor (20). One study found that rats with immune deficiencies (excluding IL-2 deficiency) increased bone healing. In the same study, the level of IL-2 in the splenectomy group was found to be high as other other anti-inflammatory cytokines (21). In a recent study, immune function changes after splenectomy affect fracture healing. For this reason, it was said that the spleen should be preserved in order to heal the fracture.

Conclusion

Although there is no consensus in all the studies being conducted, the works that are realized have deficient aspects. The most important indicator of the healing process in orthopedic practice is how much the bone can be restored in terms of biomechanics. Other healing markers are changes in microlevel, and the most noticeable parameter of the clinical outcome is the resistance level of the callus. In our study, biomechanical, histopathological, and radiological effects of splenectomy on fracture healing were not shown. However, the shortcomings of our study are that the level of immunofluorescence and inflammatory mediators cannot be measured and that the amount of callus is not quantitatively measured by micro-CT. Therefore, we recommend that the extended study plans be made by completing the limitations of our study.

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Table 3. Biomechanical values of the groups' solid and broken sides (Newton)

		Control group			Case group			p
		Mean ± SD		Med (min-max)	Mean ± SD		Med (min-max)	
Biomechanics	Solid side	178.2±23.2	177	151-220	199.8±33.5	202	154-244	0.186
	Broken side	92.9±24.4	99	56-125	84.3±21.6	79	56-123	0.499
Difference p		0.001			0.000			

Independent sample t-test, Paired sample t-test, SD: standard deviation, min: minimum, max: maximum

Ethics

Ethics Committee Approval: The study was approved by the Animal Experiments Ethics Committee of University of Health Sciences Turkey İstanbul Bağcılar Training and Research Hospital, Turkey (approval number: HADYEK/2014-26, date: 23.07.2014).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.Z.G., S.Y., E.A., Ş.Ö., M.A.G.; Concept - M.Z.G., S.Y., E.A., Ş.Ö., M.A.G.; Design - M.Z.G., S.Y., E.A., Ş.Ö., M.A.G.; Data Collection or Processing - M.Z.G., S.Y., A.A., M.A.G., Z.B.; Analysis or Interpretation - M.Z.G., A.A., Z.B.; Literature Search - M.Z.G., Z.B.; Writing - M.Z.G., Z.B.

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Common Findings in Endoscopic Gastric Biopsies in Southeastern Anatolia: Effects of Eating Habits and *Helicobacter Pylori* Infection

Güneydoğu Anadolu'da Mide Endoskopik Biyopsilerinde Sık Rastlanan Bulgular: Beslenme Alışkanlıklarının ve *Helicobacter Pylori* Enfeksiyonunun Etkisi

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ABSTRACT

Introduction: Roasted and spicy food (mainly hot pepper) consumption is very common in Southeastern Anatolia. Smoked and spicy diets and *Helicobacter pylori (H. pylori)* infection are known risk factors for gastric cancer. The aim of this study was to investigate the effects of eating habits on the gastric mucosa, to investigate the rate of *H. pylori* positivity, and to examine the association of these factors with histopathological features in this region.

Methods: Histopathological findings in endoscopic biopsies of 943 consecutive patients were retrospectively evaluated.

Results: More than half of the patients were female (54%; n=505), and the median age was 47±17.27 (range: 18-96). The most common non-gastritis histopathologic diagnosis was gastric carcinoma (2.5%; n=24), followed by polypoid lesions (1.6%; n=16). The vast majority of patients (92%) had chronic gastritis, and neutrophilic activity was present in 61% (n=537). The frequencies of atrophy, intestinal metaplasia, and regenerative mucosal changes were significantly correlated with the severity of neutrophilic activity ($p<0.05$). Patients with atrophy and intestinal metaplasia were significantly older than those without atrophy and intestinal metaplasia ($p<0.001$; mean age: 47 and 46 vs 56 and 55, respectively). More than 50% were infected with *H. pylori* (57%; n=542), and *H. pylori* positivity was associated with the presence of chronic and chronic active gastritis, as well as lymphoid hyperplasia ($p<0.001$). In contrast, erosion, atrophy, and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis ($p<0.05$).

Conclusion: *H. pylori* infection and spicy food consumption are key risk factors for gastritis in Southeastern Anatolia. Prospective epidemiological studies are needed to better demonstrate the causal interaction between dietary factors and gastritis.

Keywords: Eating habits, endoscopic biopsy, gastritis, *Helicobacter pylori*, histopathology

ÖZ

Amaç: Közlenmiş ve baharatlı yemekler Güneydoğu Anadolu Bölgesi'nde sık tüketilmektedir. Tütsülenmiş ve baharatlı besinler ile *Helicobacter pylori (H. pylori)* enfeksiyonunun mide kanseri için risk faktörü olduğu bilinmektedir. Bu çalışmanın amacı; Güneydoğu Anadolu'da beslenme alışkanlıklarının mide mukozasına etkisini, *H. pylori* pozitifliğini araştırmak ve bu faktörlerin histopatolojik özelliklerle ilişkisini değerlendirmektir.

Yöntemler: Ardışık 943 hastada mide endoskopik biyopsilerindeki histopatolojik özellikler retrospektif olarak değerlendirildi.

Bulgular: Olguların çoğu kadındı (%54; n=505) ve ortanca yaş: 47±17,27'ydi (yaş aralığı: 18-96). Gastrit dışı en sık tanı gastrik karsinom (%2,5; n=24) ve gastrik polipti (%1,6; n=16). Olguların büyük kısmında (%92) kronik gastrit ve bunların %61'inde (n=537) nötrofilik aktivite mevcuttu. Atrofi, intestinal metaplazi ve rejeneratif mukozal değişiklikler nötrofilik aktivitenin derecesi ile anlamlı düzeyde ilişkiliydi ($p<0,05$). Atrofi ve intestinal metaplazisi olan olgular, olmayanlara göre, anlamlı düzeyde daha yaşlıydı ($p<0,001$; ortalama yaş sırasıyla; 47 ve 46'ya karşı ve 56 ve 55). Olguların %57'si (n=542) *H. pylori* pozitifti ve *H. pylori* varlığı kronik ve kronik aktif gastrit ve lenfoid hiperplazi varlığı ile anlamlı düzeyde ilişkiliydi ($p<0,001$). Öte yandan; erozyon, atrofi ve nöroendokrin hücre hiperplazisi *H. pylori* gastriti olan bireylerde daha az orandaydı ($p<0,05$).

Sonuç: *H. pylori* enfeksiyonu ve baharatlı (acı) yiyeceklerin sürekli tüketilmesi Güneydoğu Anadolu'da yaşayan bireylerde gastrit oluşumu için anahtar faktörlerdir. Beslenme alışkanlıkları ile gastrit arasındaki nedensellik ilişkisinin tam olarak gösterilebilmesi için prospektif epidemiyolojik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Beslenme alışkanlığı, endoskopik biyopsi, gastrit, *Helicobacter pylori*, histopatoloji

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Introduction

In Southeastern Turkey, people often consume roasted and spicy food such as roasted hot peppers and red meat directly exposed to heat and flames. While polycyclic hydrocarbons in overcooked meat is considered carcinogenic, there is no consensus on the possible carcinogenic and anticarcinogenic effects of capsaicin, the active ingredient in hot peppers (1-4). Smoked, spicy, and salty diets are widely known to be risk factors for gastric cancer. It has even been suggested that eating habits may affect the course of *Helicobacter pylori (H. pylori)* infection, which is another important risk factor for gastric cancer; however, this association remains to be fully elucidated (5).

The aim of this study was to investigate the effects of eating habits on the gastric mucosa, display the histopathologic features, determine the *H. pylori* positivity rate, and investigate the association between these parameters in a population in southeastern Turkey.

Methods

The study protocol was approved by the Adıyaman University Faculty of Medicine Institutional Ethics Committee (approval no: 2017/9-8, date: 19.12.2017). Informed consent was not sought due to the retrospective nature of the study. The endoscopic biopsies of 943 consecutive patients (adults) who were diagnosed in our center between January 01, 2015 and December 31, 2016 were reviewed for the presence/absence of the following findings: acute and/or chronic inflammation, atrophy, metaplasia, erosion, ulceration, dysplasia, regenerative changes, neuroendocrine cell hyperplasia, *H. pylori*, lymphoid hyperplasia (LH), and malignancy. LH was defined as reactive lymphoid follicles forming germinal centers in the lamina propria. Gastritis, atrophy, metaplasia, and *H. pylori* density were scored using the Sydney system (6,7). For better demonstration of intestinal metaplasia and *H. pylori* infection, periodic acid Schiff-Alcian blue (Dako, California, USA) and Warthin Starry (Dako, California, USA) stained slides were reviewed. Clinical data were obtained from patient files.

Statistical Analysis

Statistical analysis was performed using the software SPSS Statistics, Version 24.0 (Armonk, NY: IBM Corp). Non-parametric tests (χ^2 to compare frequencies; Kruskal-Wallis test to compare independent variables between two groups) and descriptive analyses were used. Results were considered significant at $p<0.05$.

Results

More than half of the patients were female (54%; n=505), and the median age was 47±17.27 (range: 18-96). The most common clinical diagnosis (75%; n=706) was gastritis, and the gastric antrum (83%; n=783) was the most common biopsy location (Table 1).

The vast majority of patients (92%) had chronic gastritis, and neutrophilic activity was present in 61% (n=537) (Figure 1A, B). The severity of chronic inflammation decreased significantly with age, and gastric ulcer was more common in older patients ($p<0.001$). The frequencies of atrophy, intestinal metaplasia, and regenerative mucosal changes were significantly correlated with the severity of neutrophilic activity, and foveolar hyperplasia was also more common in patients with

Table 1. Clinical characteristics of the study group

Median age	47±17.27 (range: 18-96)
Gender	
Female	54% (n=505)
Male	46% (n=438)
Clinical (endoscopic) diagnosis	
Gastritis	75% (n=706)
Ulcer	3.5% (n=33)
Erosion	5% (n=49)
Suspicion of malignancy and/or dysplasia	7% (n=68)
Atrophy	1% (n=9)
Intestinal metaplasia	1% (n=9)
Polyp/polypoid lesion	2.8% (n=26)
Biopsy location*	
Antrum	83% (n=783)
Corpus	12% (n=116)
Fundus	1.2% (n=11)
Cardia	0.7% (n=7)
Pylorus	0.7% (n=7)
Other/unknown	3% (n=26)

*Some patients had multiple biopsies from different locations

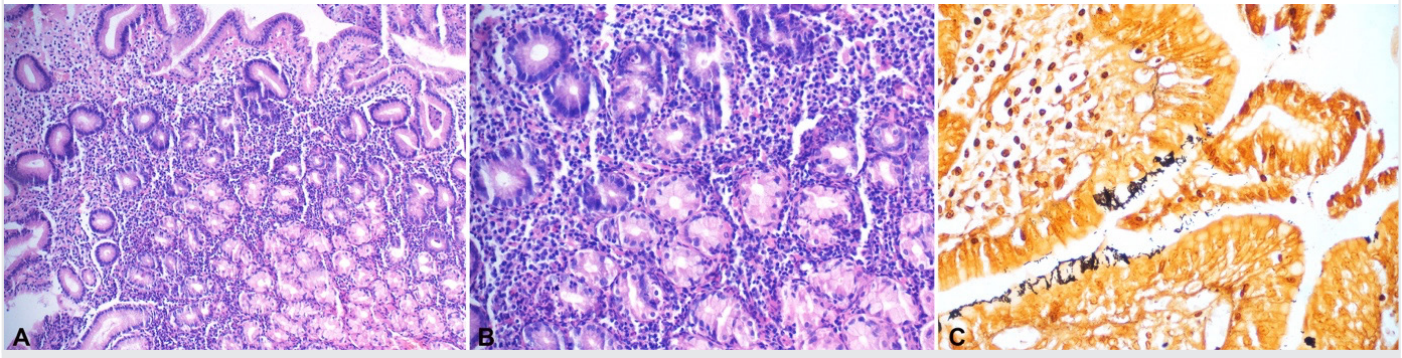

Figure 1. Chronic gastritis was the most common finding, with neutrophilic activity present in more than half of the patients. A-B) Mixed inflammatory cells within the lamina propria, also infiltrating occasional glands. Hematoxylin-eosin, original magnification x100 and x200. C) *Helicobacter pylori* infection was observed in a large proportion of the study group. Whartin-Starry, x400

severe chronic active gastritis (p<0.05). Atrophy was also significantly associated with intestinal metaplasia and neuroendocrine cell hyperplasia (p<0.001). Approximately 6% (n=55) had atrophic gastritis with intestinal metaplasia, and 4% (n=38) had atrophic gastritis without intestinal metaplasia. Patients with atrophy and intestinal metaplasia were significantly older than those without atrophy and intestinal metaplasia (p<0.001; mean age: 47 and 46 vs 56 and 55, respectively). More than half of the patients were infected with *H. pylori* (57%; n=542) (Figure 1C), and *H. pylori* positivity was associated with the presence of chronic gastritis, chronic active gastritis, LH, and regenerative mucosal changes (p<0.001). The density of *H. pylori* and lymphoid aggregates decreased significantly with age (p<0.001). The severity of chronic gastritis and chronic active gastritis were also significantly correlated with *H. pylori* density (p<0.001). In contrast, erosion, atrophy, and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis (p<0.05). Sixty-eight patients (7%) with *H. pylori* infection showed intestinal metaplasia without mucosal atrophy. Only 45 (8%) of *H. pylori*-positive patients had atrophic gastritis.

The most common non-gastritis histopathologic diagnosis was gastric carcinoma (2.5%; n=24), followed by polypoid lesions (1.6%; n=16) (Table 2). Patients with malignant tumors, dysplasia, and polypoid lesions were significantly older than those with gastritis and/or erosion/ulceration (median: 71.5±15.5 vs 47±17; p<0.001), but there was no significant association between gender and lesion type, although polypoid lesions tended to be more common among women (Table 3).

Discussion

In this study, we observed that the majority of patients (92%) had chronic gastric inflammation, and more than half (57%) had chronic active gastritis. The relatively high proportion (57%) of patients with *H. pylori* infection within the study group and the significant association of *H. pylori* positivity with the presence of both chronic and chronic active inflammation suggest that *H. pylori* infection is a major cause of gastritis. On the other hand, the *H. pylori* positivity rate was strikingly lower than previously reported in southeastern Anatolia (57% vs 89%) (8), despite the fact that our study group consisted of symptomatic patients. Moreover, of the 360 *H. pylori*-negative patients, 334 had chronic and 138 had chronic active gastritis, indicating that gastritis is common in the region regardless of *H. pylori* status. Recently, in a study of patients with chronic gastritis, barbecue and spicy foods were associated with dyspeptic symptoms (9). While *H. pylori* acts both as a cause and an exacerbating factor for gastritis, the regional habit of consuming mainly roasted hot peppers and spicy food is probably another major source of gastric mucosal irritation and inflammation. However, data on the effect of capsaicin (i.e., the active ingredient of pepper) on the gastric mucosa is controversial. It was reported to induce acute erosive gastritis in 1970s (10), but recent studies have shown that capsaicin inhibits gastric acid output by vagal inhibition (11), inhibits in vitro proliferation of *H. pylori*, and decreases gastric neutrophilic infiltration (12) in animal studies. Mózsik et al. (13) have demonstrated that the effects of capsaicin on the gastric mucosa is dose- and time-dependent: while a small dose of capsaicin inhibits gastric acid secretion, a high dose causes hyperacidity and associated mucosal damage. It has been suggested that capsaicin-sensitive afferent nerves are involved in the course of gastritis, regardless of *H. pylori* infection (14) and that these nerves may exhibit both pro- and anti-inflammatory effects (15). The dose-dependent nature of the relationship explains the conflicting results reported in the literature. We also found a significant association between erosive gastritis and *H. pylori* negativity, which may be attributable to the hyperacidity-inducing effects of high-dose capsaicin, in this case, consuming large amounts of

Table 2. Histopathologic characteristics

Frequency of inflammatory lesions	
Chronic gastritis	92% (n=875)
Mild	24% (n=229)
Moderate	38% (n=361)
Severe	30% (n=285)
Chronic active gastritis	57% (n=537)
Mild	22% (n=205)
Moderate	23% (n=220)
Severe	12% (n=112)
Gastric ulcer	2% (n=19)
Erosion	1% (n=10)
Frequency of *Helicobacter pylori* infection 57% (n=542)	
Frequency of inflammation associated mucosal changes	
Regenerative/reactive changes	27% (n=254)
Foveolar hyperplasia	8% (n=77)
Atrophy	10% (n=93)
Intestinal metaplasia	19% (n=176)
Neuroendocrine cell hyperplasia	4.5% (n=42)
Frequency of dysplastic/neoplastic lesions 3.1% (n=30)	
Low-grade dysplasia	0.2% (n=2)
High-grade dysplasia	0.4% (n=4)
Adenocarcinoma	1.6% (n=15)
Diffuse type (signet ring cell) carcinoma	0.6% (n=6)
Neuroendocrine carcinoma	0.1% (n=1)
Mucinous carcinoma	0.1% (n=1)
Melanoma	0.1% (n=1)
Frequency of polypoid lesions 1.6% (n=16)	
Hyperplastic polyp/polypoid foveolar hyperplasia	1.2% (n=11)
Fundic gland polyp	0.4% (n=4)
Adenomatous polyp	0.1% (n=1)

Table 3. Association of histopathologic diagnosis with age and gender

	Gastritis/erosion/ulceration	Reflux gastropathy	Polyps	Dysplasia	Malignant	Normal	p
Gender (female/male ratio)	1.16	1 female	2.75	0.5	0.5	1.18	0.146
Mean/median age ± SD	48/46±17	n=1; age: 49	66/65±14	66/67±12	68/72±16	52/51±12	<0.001

SD: Standard deviation

spicy food. However, given that this is a cross-sectional, retrospective study, it is not possible to determine a precise causal relationship between diet and chronic gastritis. A prospective study design may be helpful in this regard. Of note, a similar dose-dependent effect of capsaicin has also been documented for gastric cancer formation (4).

The significant association between the severity of neutrophilic activity and reactive changes such as regenerative mucosal changes and foveolar hyperplasia is not surprising. It is somewhat unexpected that atrophy and neuroendocrine cell hyperplasia were less common in patients with *H. pylori* gastritis, considering that long-term and/or persistent *H. pylori* infection is known to cause atrophic gastritis. This finding indicates that the predominant mechanisms for atrophic gastritis in the study group are autoimmune pathway and environmental factors, including a high-fat diet (16) and high salt intake (17), although the evaluation of multifocal atrophic gastritis was limited due to the small number of patients with concurrent antrum and corpus biopsies. Patients with atrophy and intestinal metaplasia were significantly older, consistent with previous studies reporting that atrophic gastritis is more common in older age groups (17,18), which most likely results from decreasing repair capacity with aging (19). The decreasing tissue repair capacity with aging may also be responsible for the increased frequency of occurrence of gastric ulcer in older patients. A decrease in gastric mucosal surface hydrophobicity with age has also been suggested to contribute to gastric ulcer formation in older individuals (20).

The association between age and inflammatory activity was another noteworthy finding. The severity of chronic inflammation, density of *H. pylori* positivity, and associated lymphoid aggregates decreased significantly with age. Other than the possibility of earlier *H. pylori* eradication, this may be a result of a reduction in T-cell response with aging (21) and the accompanying decrease in B-cell stimulation within the mucosa-associated lymphoid tissue. Therefore, it would be reasonable to claim that while the chronic inflammatory response decreases with age, acute responses such as ulceration become predominant in older individuals due to impaired mucosal defense mechanisms.

Gastric cancer is the fifth most common type of cancer in Turkey (22). The frequency of gastric malignancy in our study group was 2.5%. The tumor type was adenocarcinoma in most of them, and the tumor was located in the antrum in 54%. Curiously, one patient was diagnosed with melanoma but unfortunately was lost to follow-up, and the distinction between primary and metastatic melanoma could not be made. Although rare, primary melanoma occurs in the stomach (23,24); however, detailed clinical and radiological examinations should be performed to rule out a primary tumor elsewhere in the body. We observed that patients with malignant tumors, dysplasia, and polypoid lesions were significantly older than those with inflammation. This may be attributed to longer exposure to carcinogens and the accumulation of mutations. Considering the two risk factors for gastric cancer, the high incidence of *H. pylori* infection and frequent intake of spicy foods, closer monitoring may be beneficial to detect gastric cancer cases at early stages in this region. It should also be noted here that preinvasive neoplastic and dysplastic lesions may also occur, especially due to *H. pylori* gastritis. While the frequency of dysplasia was <1% in our series, the frequency of high-grade dysplasia (0.4%) was slightly higher than the annual incidence of high-grade dysplasia (0.18%) recently reported from a different geographic region of Turkey (25), suggesting that tight monitoring may be an efficient method of following up with individuals in higher-risk regions.

Conclusion

H. pylori infection and frequent spicy food intake seem to be the key factors in the development of gastritis among inhabitants of Southeastern Anatolia. However, prospective epidemiological studies are needed to better demonstrate the causal effect of dietary factors in the pathogenesis of gastritis in patients with dyspeptic symptoms in this region.

Ethics

Ethics Committee Approval: The study protocol was approved by the Adıyaman University Faculty of Medicine Institutional Ethics Committee (approval no: 2017/9-8, date: 19.12.2017).

Informed Consent: Informed consent was not sought due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Z.B.; Concept - B.P., B.A.T., S.İ., Z.B.; Design - B.P., B.A.T.; Data Collection or Processing - B.P., B.A.T., S.İ., Z.B.; Analysis or Interpretation - B.P.; Literature Search - B.P.; Writing - B.P., B.A.T., S.İ., Z.B.

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Prediction of Prognostic Factors in the Survival of Non-small-cell Lung Cancer Patients with Multiple Brain Metastases

Çoklu Beyin Metastazlı Küçük Hücreli Dışı Akciğer Kanserli Hastaların Sağkalımında Prognostik Faktörlerin Öngörülmesi

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ABSTRACT

Introduction: We aimed to investigate the factors affecting survival in non-small-cell lung cancer (NSCLC) patients with multiple brain metastases.

Methods: One hundred thirty patients who were diagnosed with NSCLC at the time of presentation or during disease follow-up were evaluated at University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Radiation Oncology between 2012 and 2017.

Results: In univariate analysis, significant effects of age >60 (p=0.006), stage 4 at the time of diagnosis (p<0.001), Karnofsky Performance score (KPS) <70 (p<0.001), extracranial metastasis presentation (p=0.014), uncontrolled primary tumor (p=0.002), headache (p=0.037), and recursive partitioning analysis (RPA) Class III (p<0.001) were observed in predicting early mortality. In multivariate Cox regression analysis, stage 3 at the time of diagnosis [hazard ratio (HR): 0.419, 95% confidence interval (CI): 0.217-0.809, p=0.010], KPS ≥70 (HR: 14.515, 95% CI: 5.470-38.519, p<0.001), and RPA Class I-II (HR: 0.192, 95% CI: 0.102-0.362, p<0.001) had a positive effect on overall survival.

Conclusion: Predicting prognostic factors when making whole- brain radiotherapy decisions in NSCLC patients with multiple brain metastases will help in treating such patients appropriately. In multiple brain metastases with NSCLC patients, stage 3 at the time of diagnosis, KPS ≥70, and RPA Class I-II have a positive effect on overall survival.

Keywords: Non-small-cell lung cancer, multiple brain metastases, survival

ÖZ

Amaç: Çoklu beyin metastazı olan küçük hücreli dışı akciğer kanseri hastalarında sağkalımı etkileyen faktörleri araştırmayı amaçladık.

Yöntemler: 2012-2017 yılları arasında Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi, Radyasyon Onkoloji Kliniği'nde, ilk başvuru anında veya hastalığın takibi sırasında beyin metastazı gelişen küçük hücreli dışı akciğer kanseri tanılı 130 hasta değerlendirildi.

Bulgular: Tek değişkenli analizde, yaş >60 (p=0,006), tanı anında evre 4 hastalık (p<0,001), Karnofsky Performans skoru (KPS) <70 (p<0,001), ekstrakraniyal metastaz varlığı (p=0,014), primerin kontrol altında olmaması (p=0,002), baş ağrısı (p=0,037) ve RPA sınıfı III (p<0,001) erken mortaliteyi tahmin etmede istatistiksel anlamlı olarak gözlendi. Çok değişkenli Cox regresyon analizinde, ilk başvuru anında evre 3 hastalık (HR: 0,419, 95% CI: 0,217-0,809, p=0,010), 70≥ KPS [hazard ratio (HR): 14,515, 95% CI: 5,470-38,519, p<0,001] ve RPA Sınıf I-II'nin (HR: 0,192, 95% CI: 0,102-0,362, p<0,001) genel sağkalım üzerinde olumlu etkisi vardı.

Sonuç: Çoklu beyin metastazı olan küçük hücreli dışı akciğer kanseri hastalarında tüm beyin radyoterapisi kararı verirken prognostik faktörlerin öngörülmesi hastaların uygun şekilde tedavi edilmesine yardımcı olacaktır. İlk başvuru anında evre 3 hastalık, KPS ≥70 ve RPA sınıf I-II çoklu beyin metastazı olan küçük hücreli dışı akciğer kanseri hastalarında genel sağkalımı olumlu yönde etkiler.

Anahtar Kelimeler: Küçük hücreli dışı akciğer kanseri, çoklu beyin metastazı, sağkalım

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Introduction

The most commonly known cancers that metastasize to the brain are lung cancer, breast cancer, and melanoma. Lung cancer is the main cause of cancer mortality and a type of malignancy in which brain metastases are often observed (1). For patients with solid tumors, brain metastasis shortens life expectancy. It is related to a lower quality of life and survival (2). Approximately 10% of patients with non-small-cell lung cancer (NSCLC) will have brain metastasis detected during diagnosis, and 30%-50% will develop brain metastasis (3,4). Early diagnosis is attained with a suitable frequency of neurological imaging during magnetic resonance imaging (MRI) screening and treatment follow-up.

The approach to the treatment of brain metastases may be whole-brain radiotherapy (WBRT), surgery, or stereotactic radiosurgery (SRS) (5). The goal of WBRT is to eliminate unrecognized micrometastases on imaging, increase intracranial control, and reducing the risk of mortality due to neurological causes. Survival in patients with symptomatic brain metastases is lower than in asymptomatic patients, independent of the treatment administered (6,7). The most commonly used method to predict the prognosis of a patient with brain metastasis is recursive partitioning analysis (RPA), which includes information on age, extracranial metastasis status, whether the primary tumor is under control, and the Karnofsky Performance score (KPS) (8).

In this study, we aimed to investigate the factors affecting survival in NSCLC patients with multiple brain metastases.

Methods

This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 1858, date: 14.06.2019). Due to the retrospective analyzes of data from medical records, informed consent was waived. One hundred thirty patients who were diagnosed with NSCLC during follow-up were assessed at the Radiation Oncology Clinic between 2012 and 2017. OS was determined by calculating the interval between the diagnosis of brain metastasis and the time of final control or death.

The criteria for exclusion from the study were the following: 1) patients with leptomeningeal metastasis, 2) pre-WBRT SRS (the use of high-dose radiotherapy in a single fraction in the treatment of intracranial lesion application), 3) small-cell lung cancer histology, and 4) single brain metastases.

WBRT was performed using opposing lateral fields; a gantry tilt of 3°-5° was used to avoid divergence into the eyes, and multi-leaf collimation blocks were used to ensure proper coverage of the cribriform plate, temporal lobe, and brainstem while shielding the eyes, nasal cavity, and oral cavity. The inferior border was generally set at C1-2. WBRT was administered using a schedule of 20 Gy in 5 fractions of 4 Gy/fx or 30 Gy in 10 fractions of 3 Gy/fx, for 5 days a week. WBRT (20 Gy-30 Gy) applied to all patients with three-dimensional conformal radiotherapy or intensity-modulated radiotherapy using 6 MV (megavolts) of photon energy.

When WBRT was complete, we reassessed the patients in the first month and every three months thereafter with contrast MRI. Additionally, local recurrence and distant metastasis follow-up examinations were performed every three months. The intracranial answer was assessed with 1.1 new response evaluation criteria in solid tumors (9).

Statistical Analysis

The characteristics of the patients in the two groups were compared using the chi-square test for categorical variables and the Mann-Whitney U test for non-categorical variables. Potential prognostic factors were evaluated using the Kaplan-Meier method (log-rank test) for univariate analysis of the OS and also using a multivariate survival analysis of the Cox regression model. The results were reported as risk ratios hazard ratio (HR) and the corresponding 95% confidence interval (CI). Results were considered statistically significant at $p<0.05$. Statistical analyzes were conducted with SPSS (version 22.0; IBM Corp., Armonk, NY, USA).

Results

The median age of the patients was 60 (range: 25-82) years. Fifteen patients were female, and 115 patients were male. Seventy (54%) of the patients had adenocarcinoma histology. The most common reference complaint was a headache in 48 (37%) patients. The most common location of metastases was bilateral hemispheres in 74 (57%) patients.

In univariate Kaplan-Meier survival analysis, of age >60 ($p=0.006$), stage 4 at the time of diagnosis ($p<0.001$), KPS <70 ($p<0.001$), extracranial metastasis presentation ($p=0.014$), uncontrolled primary tumor ($p=0.002$), headache ($p=0.037$), and RPA Class III ($p<0.001$) were observed to predict early mortality (Table 1).

In multivariate Cox regression analysis, stage 3 at the time of diagnosis (HR: 0.419; 95% CI: 0.217-0.809; $p=0.010$), KPS ≥70 (HR: 14.515; 95% CI: 5.470-38.519; $p<0.001$), and RPA Class I-II (HR: 0.192; 95% CI: 0.102-0.362; $p<0.001$) had a positive effect on overall survival (OS) (Table 2).

The median follow-up duration was three months (range: 1-56 months, 95% CI: 2.239-3.761). The 1-year OS in RPA Class I was 66%, in RPA Class II, 12%, and in RPA Class III, none. The median OS was 12, 6, and 2 months for patients with RPA Class I, RPA Class II, and RPA Class III, respectively ($p<0.001$) (Figure 1).

One-year OS was 58% in patients with KPS ≥70. In multivariate analysis, KPS ≥70 had a positive effect on OS (Figure 2).

The 1-year OS of patients with stage III at the time of diagnosis was 55%. Moreover, stage 3 at the time of diagnosis had a positive effect on OS (Figure 3).

Discussion

The brain is the most common area where hematogenous metastasis occurs in patients with lung cancer. While the mean survival of patients with brain metastasis is frequently less than 6 months, it is well recognized that in some subgroups, the mean survival is longer (10).

Table 1. Clinical characteristics and results of the univariate analysis (Kaplan-Meier, log-rank test) of OS of patients with multiple brain metastases

	Number of patients (%)	Median OS (months)	95% CI	p
Age				
≤60	68 (52)	4	2.099-5.901	**0.006**
>60	62 (48)	3	2.252-3.748	
Gender				
Female	15 (12)	4	2.832-5.168	0.998
Male	115 (88)	3	2.167-3.833	
Histology				
Adeno	70 (54)	3	2.463-3.537	0.196
Others	60 (46)	4	2.130-5.870	
Stage (at the time of diagnosis)				
III	27 (21)	12	10.192-13.808	**<0.001**
IV	103 (79)	3	2.555-3.445	
Extracranial metastases				
Absent	68 (52)	5	3.308-6.692	**0.014**
Present	62 (48)	3	2.478-3.522	
KPS				
≥70	39 (30)	12	11.083-12.917	**<0.001**
<70	91 (70)	2	1.543-2.457	
Primary under control				
Yes	53 (38)	4	1.656-6.344	**0.002**
No	77 (62)	3	2.356-3.644	
Headache				
Yes	48 (37)	4	1.574-6.426	**0.037**
No	82 (63)	3	2.124-3.876	
Epilepsy				
Yes	15 (12)	3	1.909-4.091	0.103
No	115 (88)	4	3.169-4.831	
Dizziness				
Yes	25 (19)	5	2.062-7.938	0.116
No	105 (81)	3	2.455-3.545	
Loss of balance				
Yes	11 (9)	2	1.191-2.809	0.062
No	119 (91)	4	3.193-4.807	
Hemiparesis				
Yes	34 (26)	3	1.147-4.853	0.087
No	96 (74)	3	2.172-3.828	
Vision loss				
Yes	2 (2)	1	-	0.348
No	128 (98)	3	2.245-3.755	
Localization of metastasis				
Bilateral	74 (57)	3	2.401-3.599	0.082
Temporal	18 (14)	6	0.879-11.121	
Frontal	15 (11)	4	2.106-5.894	
Cerebellum	12 (9)	1	-	
Parietal	6 (5)	3	0.000-6.601	
Occipital	5 (4)	5	0.706-9.294	
RPA				
Class I	27 (21)	12	11.098-12.902	**<0.001**
Class II	31 (24)	6	4.923-7.077	
Class III	72 (55)	3	2.239-3.761	

OS: Overall survival, CI: confidence interval

Several studies have shown that patients under 60 years of age are at an increased risk of brain metastasis (11,12). An analysis of 482 patients with stage 3b-4 NSCLC found that, statistically, the risk of brain metastasis was significantly higher in patients less than 60 years of age and in patients with adenocarcinoma (13). In another study with 157 patients, age was identified as a prognostic factor (14). Age was determined to be significant in univariate analysis; however, it was not a prognostic factor in the present study.

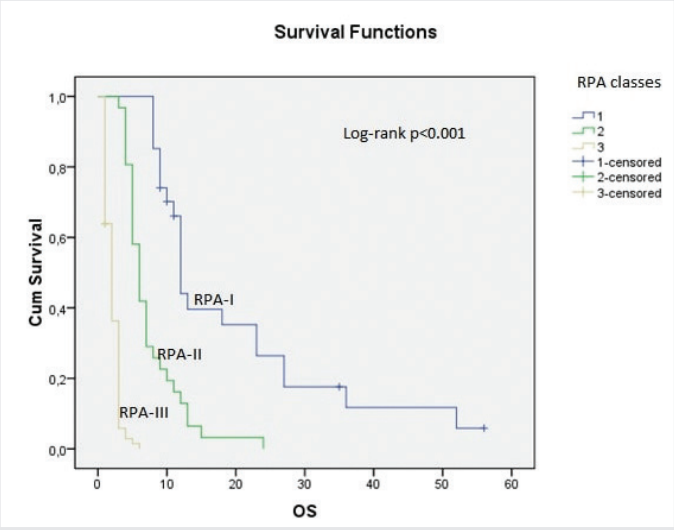

Figure 1. RPA classes
RPA: Recursive partitioning analysis, OS: overall survival

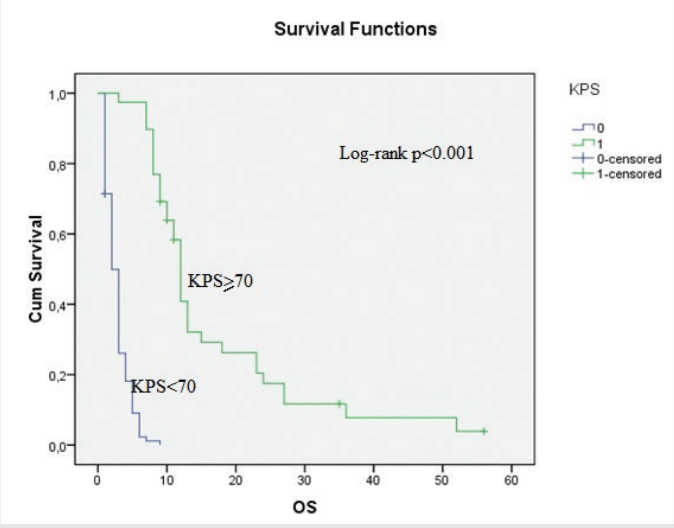

Figure 2. KPS
KPS: Karnofsky Performance score, OS: overall survival

The prognostic function of gender in brain metastases is unclear. Some studies have demonstrated that, particularly in advanced-stage NSCLC patients, the influence of gender on brain metastases is constrained (15,16). A meta-analysis of risk factors for brain metastases showed that gender could not be used as a marker (17). Nevertheless, some studies show that in early-stage NSCLC patients, the female gender may have predictive value for the incidence of brain metastases (18,19). Gender could have predictive value in early-stage NSCLC but is not appropriate for advanced-stage NSCLC. It has been shown in our study that gender is not a prognostic factor.

We know that lung adenocarcinoma often leads to hematogenous metastasis, whereas epidermoid cell carcinoma often causes lymphatic metastasis (20). The predisposition of NSCLC to brain metastasis is greater in patient subgroups with adenocarcinoma (54.8%) and undifferentiated carcinoma (31.7%) than in those with squamous cell carcinoma (21). Again, other studies have also shown that patients with adenocarcinoma and large-cell carcinoma histology have a higher risk of developing brain metastasis compared with squamous cell carcinoma histology (22,23).

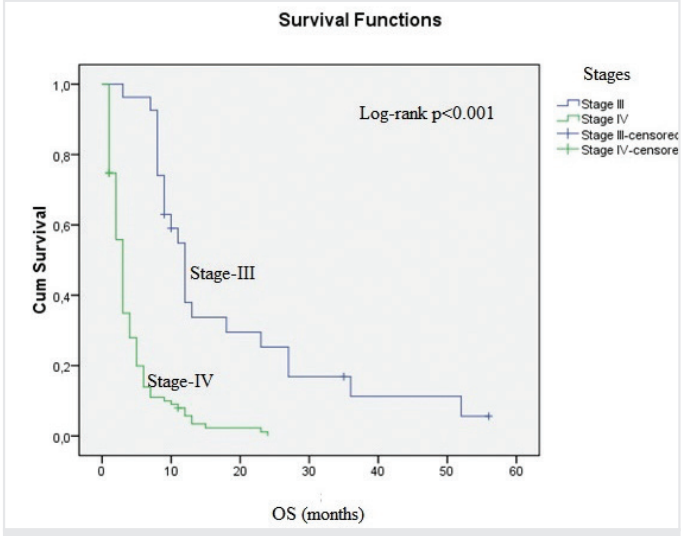

Figure 3. Stages
OS: Overall survival

Table 2. Results of the multivariate Cox regression analysis of OS of patients with multiple brain metastasis

	HR	95 % CI	p
Age <60 vs ≥60	1.031	0.692-1.536	0.880
Stages 3 vs 4 at the time of diagnosis	0.419	0.217-0.809	**0.010**
Extracranial metastases absent vs present	0.759	0.521-1.105	0.150
KPS ≥70 vs <70	14.515	5.470–38.519	**<0.001**
Primary under controlled vs uncontrolled	0.875	0.583-1.312	0.518
Headache present vs absent	1.157	0.771-1.734	0.481
RPA Class I-II vs III	0.192	0.102-0.362	**<0.001**

OS: Overall survival, HR: hazard ratio, CI: confidence interval

In the present study, the majority of patients were diagnosed with adenocarcinoma (54%). We found no statistically significant differences between the histological subtypes. In our retrospective study, ALK, EGFR, and KRAS mutations were not tested in most patients (only ~5% were evaluated). The reason for that at the time of presentation, 79% of patients were in the metastatic stage and lived a short time.

In two studies, one with patients who developed brain metastasis after surgically resected NSCLC (24) and another with patients who received chemotherapy after cranial radiotherapy (25), the presence of extracranial metastasis was found to be a negative prognostic factor. Another showed extracranial metastasis to be significant in univariate analysis but not significant in multivariate analysis (26). In our study, we found it to be significant in univariate analysis.

In a study which evaluated 1,218 patients, they found that brain metastasis developed as the first site of relapse in patients with NSCLC who underwent curative surgery and had high pT and pN stages (27). In another study that evaluated 105 patients, it was shown that as NSCLC progresses, the time until brain metastasis decreases. Delayed growth of brain metastases was associated with a better prognosis but not increased survival (28). The tumor stage at the time of diagnosis was found to be an important factor in OS.

RPA provides a standard for the clinical comparison of brain metastasis patients, and the safety of this standard has been demonstrated by some clinical studies (29,30). Furthermore, in a different study, adenocarcinoma histology and RPA Class I and II (KPS ≥70) were related to better OS (31). In our study, RPA Class I-II and KPS ≥70 were also related to better OS.

Study Limitation

The limitations of this study were that it was performed in a single center, and the majority of patients were not assessed for chemotherapy because chemotherapy could not be administered; therefore, few patients underwent targeted therapy.

Conclusion

Radiotherapy is one of the basic treatments for brain metastasis. The survival of patients with multiple brain metastases is affected by numerous factors. In our study, stage 3 at the time of diagnosis, KPS ≥70, and RPA Class I-II were determined as prognostic factors affecting OS. Predicting prognostic factors when making WBRT decisions in NSCLC patients with multiple brain metastases will help in treating such patients appropriately.

Ethics

Ethics Committee Approval: This study was approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (approval number: 1858, date: 14.06.2019).

Informed Consent: Due to the retrospective analyzes of data from medical records, informed consent was waived.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - B.İ.; Concept - Ö.M.; Design - B.İ., A.H.Y.; Data Collection or Processing - Ö.M., B.İ.; Analysis or Interpretation - Ö.M., A.H.Y.; Literature Search - A.H.Y.; Writing - Ö.M.

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

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Insulinoma: Spectrum of Clinicopathological Features in a Tertiary Center

İnsülinoma: Üçüncül Bir Merkezdeki Klinikopatolojik Özelliklerin Spektrumu

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ABSTRACT

Introduction: Insulinoma is the most common functional neuroendocrine tumor of the pancreas. There are different methods for the preoperative localization of insulinoma, such as Computed Tomography (CT) scan, Magnetic Resonance Imaging and Endoscopic Ultra Sonography (EUS). In this study, we report on the clinicopathological features of insulinoma in 43 patients.

Methods: The hospital records of 43 patients with suspicion of insulinoma based on biochemical diagnostic criteria, referred to İmam Khomeini Complex Hospital, Tehran, Iran between 2006 and 2016, were reviewed retrospectively.

Results: Of the 43 studied patients, 28 were female. The mean age of the patients was 45.4±13.3 years. The most frequent clinical presentation of insulinoma was neurogenic and neuroglycopenic symptoms (81.4%). Mean glucose, insulin, and C-peptide in patients with hypoglycemic crisis were 39.13±13.15 mg/dL, 32.15±32.53 µUI/mL, and 4.77±2.88 ng/mL, respectively. Mean tumor size was 2.13±1.22 cm. The most common site of insulinoma was the tail of the pancreas. Surgery was the treatment of choice and performed in 31 patients. Of 21 tumors studied microscopically, 7 were invasive.

Conclusion: In non-diabetic patients with manifestations of hypoglycemia, a diagnosis of insulinoma should be considered. During the past decade, the diagnostic delay for insulinoma has been reduced in our country by improving imaging technologies. EUS and CT scan are the best modalities for localization and size measurement of insulinoma. Tumor size has decreased compared with previous decades, probably due to a reduced delay in diagnosis.

Keywords: Insulinoma, hypoglycemia, neoplasm, pancreas

ÖZ

Amaç: İnsülinoma pankreasın en sık görülen fonksiyonel nöroendokrin tümörüdür. Bilgisayarlı Tomografi (BT) tarama, Manyetik Rezonans Görüntüleme ve Endoskopik Ultrasonografi (EUS) gibi insülinomaların preoperatif lokalizasyonu için farklı yöntemler vardır. Bu çalışmada 43 hastada insülinomun klinikopatolojik özellikleri sunulmaktadır.

Yöntemler: 2006-2016 yılları arasında Tahran, İran'da İmam Humeyni Kompleks Hastanesi'ne atıfta bulunulan biyokimyasal tanı kriterlerine göre insülinoma şüphesi olan 43 hastanın retrospektif olarak hastane kayıtları incelendi.

Bulgular: Çalışılan 43 hastanın 28'i kadındı. Hastaların ortalama yaşı 45,4±13,3 idi. İnsülinomun en klinik görünümü nörojenik ve nöroglikopenik semptomlardı (%81,4). Hipoglisemik kriz hastalarında ortalama glikoz, insülin ve C-peptit sırasıyla; 39,13±13,15 mg/dL, 32,15±32,53 µUI/mL ve 4,77±2,88 ng/mL idi. Ortalama tümör boyutu 2,13±1,22 cm idi. En yaygın insülinoma bölgesi pankreas kuyruğuydu. Cerrahi tedavi tercih edildi ve 31 hastaya uygulandı. Mikroskobik incelemeli 21 tümörden 7'si invazivdi.

Sonuç: Hipoglisemi belirtileri olan diyabetik olmayan hastalarda insülinoma tanısı düşünülmelidir. Son on yılda, görüntüleme teknolojilerini geliştirerek ülkemizde insülinomun tanısal gecikmesi azalmıştır. EUS ve BT taraması insülinoma lokalizasyonu ve boyut ölçümü için en iyi yöntemlerdir. Muhtemelen tanıdaki gecikmenin azalması nedeniyle tümör boyutu önceki on yıllara göre azalmıştır.

Anahtar Kelimeler: İnsülinoma, hipoglisemi, neoplazm, pankreas

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Introduction

Pancreatic cancers may arise from exocrine or neuroendocrine cells of the pancreas. Most pancreatic cancers are exocrine cancers, and neuroendocrine tumors are rare pancreatic masses that originate from the islets of Langerhans (1). Neuroendocrine neoplasms are the second most common pancreatic tumors and account for 1%-2% of all pancreatic neoplasms (2). In the recent decade, the incidence of pancreatic neuroendocrine neoplasms (pNEN) has increased significantly and reached 1/100,000 population per year (3,4). This increased rate may be due to the improved diagnostic imaging techniques as well as increased knowledge and awareness of physicians about these neoplasms (5). The age range of most patients with pNEN is from 30 to 60 years, and there is no gender difference (3,4).

pNENs are divided into two groups: functional and non-functional. As non-functional tumors have no symptoms, they are usually diagnosed at a more advanced stage of disease than functional tumors such as insulinoma.

Insulinoma is a functional pNEN and the most common type (6). Insulinoma is the main cause of hypoglycemia due to endogenous hyperinsulinemia. Insulinomas are benign in 90% of cases (7).

Insulinoma is a rare tumor with an incidence rate of 0.15%-0.4% (8). It represent 1%-2% of all pancreatic neoplasms (9) and is the cause of 70%-75% of hyperinsulinemia cases (8). However, the prevalence rate is unknown, as the incidence rate in autopsy reports is higher (0.8%-10%) (10,11).

The diagnostic hallmark of insulinoma is Whipple's triad, which includes the simultaneous presence of three symptoms of hypoglycemia, compatible adrenergic (neurogenic) and/or neuroglycopenic signs, and symptom relief upon administration of glucose (8).

Insulinoma in most cases is sporadic; however, in 4%-10% of cases, it may be associated with multiple endocrine neoplasia type-1 (MEN1) syndrome, which tends more to be malignant (12).

The main goal of this study was to present clinicopathological characteristics of insulinoma in a series of 43 patients.

Methods

In a retrospective study, the hospital records of all patients with insulinoma tumors, referred to İmam Khomeini Hospital (a tertiary center), Tehran, Iran from 2006 to 2016, were reviewed.

In this study, all patients with clinical manifestations of hypoglycemia and positive biochemical tests results including low blood sugar and high insulin and C-peptide levels, as well as those with hypoglycemic symptoms such as palpitation, tremor, sweating, and a histological report of insulinoma, even without any information about laboratory results (including low blood sugar and high insulin and C-peptide levels), were included in the study.

Patients with a positive sulfonylurea test, those with positive biochemical test results but different histology (other than insulinoma), and those with a known history of treated insulinoma in previous years that were referred due to liver metastasis, were excluded from the study.

Patients' information, including personal information, clinical symptoms, laboratory tests results, imaging and pathology reports, and treatment modality, was recorded in a questionnaire.

The study protocol was approved by the Ethics Committee at Imam Khomeini Hospital, and the study was conducted according to the Helsinki declaration (approval number: IR.TUMS.IKHC.REC.1396.3105, date: 07.08.2017).

Statistical Analysis

Data were presented as mean and standard deviation for numerical data and number and percentage for categorical data. Independent Samples t-tests and chi-square tests were used to compare numerical data with a normal distribution and categorical data, respectively. For comparison of more than two groups, analysis of variance and the Kruskal-Wallis test were used for data with and without a normal distribution, respectively. Data analysis was performed using SPSS software version 20.00 for Windows, and results were considered significant at $p<0.05$.

Results

Demographics

Finally, 43 patients with insulinoma were included in the study. Of them, 38 were selected on the basis of positive laboratory evidence of insulinoma and 5 on the basis of a pathological report of insulinoma.

The patients' demographic characteristics are presented in Table 1. Of 43 patients, 28 were aged below 50 years and 15 above 50 years.

Clinical Presentation

The number of hypoglycemic crisis was registered in 25 patients. Of them, the number of crises varied from 4 crises in a day and 1 in a month, with a mean of 18 crises in a month. Other information regarding clinical presentation, symptoms, and biochemical parameters is shown in Table 1.

Weight changes were registered in 20 patients. Of them, 2 patients had no change in weight and 18 had variable changes in weight from 10 kg weight loss to 31 kg weight gain (mean of 7 kg weight gain).

There was no significant association between age (below and above 50 years) and changes in weight (7.07±3.00 vs 6.8±14.61, respectively) or between the number of crises in a week (4.90±6.8 vs 3.00±2.09, respectively) and the duration of the 72-hour fasting test (11.58±8.37 vs 12.91±19.29) ($p>0.05$). Also, no significant association was found between age (below and above 50 years) and the mean glucose level during a hypoglycemic crisis (40.25±14.20 vs 37.80±17.46, respectively) ($p>0.05$).

The mean serum insulin level during a hypoglycemic crisis in patients aged less than 50 years was significantly higher than in those aged above 50 years (39.32±37.45 and 17.80±9.69, respectively) ($p<0.05$). However, serum C-peptide levels were not significantly different between the two age groups (5.22±3.37 in patients below 50 years and 3.87±1.19 in those above 50 years old).

There was a significant correlation between the number of crises in week and weight changes ($r=0.62$, $p=0.03$). Also, a significant direct

correlation was found between the number of crises in a week and the time interval between disease onset and referral (r=0.50, p=0.01).

There was no significant correlation between the number of crises in a week and the duration of the fasting test (r=0.44, p=0.23). In addition, no significant correlation was observed between weight changes and the time interval from disease onset to referral (r=0.07, p=0.81). There was a significant correlation between insulin and the C-peptide level at the end of the fasting test (r=0.64, p<0.001).

Tumor Size and Location

Of 43 patients, tumor size was determined in 21 cases based on the pathology report, and the accuracy of size measurement by computed tomography (CT) scan and endoscopic ultrasonography (EUS) was compared with the size reported by pathology as the gold standard. According to this analysis, correlation of the size reported by pathology was more compatible with the CT report than the EUS report in these 21 cases. In other cases without a pathology report, tumor size was considered according to the CT scan report, and in those without a CT scan report, the size reported by EUS was considered as the tumor size. Therefore, 31 of 43 patients had a definite tumor size: in 21 patients according to the pathology report, in 6 based on the CT scan report, and in 4 based on EUS. The mean tumor size available in 21 patients according to the pathology report was 2.13±1.22 cm (0.6-5.5 cm).

The tumor location of was available in 25 patients (based on the pathology report or surgery report): 10 in the head, 4 in the body, and 11 in the tail of the pancreas.

Regarding imaging, in 35 patients, EUS had been performed, and the related findings are shown in Figure 1. In three patients, tumor size had not been reported. The mean tumor size in 24 patients with tumor size reported by EUS was 1.67±0.60 cm (0.6-3.2 cm).

Another imaging study was CT scan, which had been performed for 35 patients. Tumor location by CT scan is depicted in Figure 2. In two cases, tumor size had not been reported. Mean tumor size according to CT scan, available for 17 patients, was 1.7±0.86 cm (0.5-3.9 cm).

Mean tumor size for the head, body, and tail was 2.06±1.12, 1.22±0.69, and 2.13±1.48 cm, respectively, and tail tumors were larger.

By using CT scan and EUS 77.5% (31 cases) of insulinoma tumors were localized. Of 40 patients with available recorded imaging reports, the tumor was not localized in 9 cases (22.5%).

In 25 cases with a pathology report of the tumor location, CT scan imaging had been performed for 22 cases. For localization of the tumor by considering pathological study as the gold standard, the sensitivity of

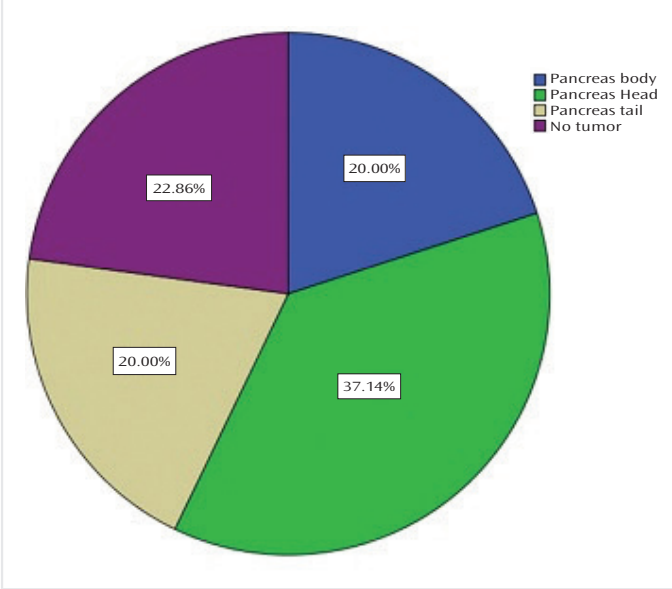

Figure 1. Tumor location by EUS
EUS: Endoscopic ultrasonography

Table 1. Demographic, clinical, and paraclinical characteristics of 43 patients with insulinoma

Variable	n	Value
Age (mean ± SD)	43	45.4±13.3 (21-70) years
Gender, n (%)	43	F 28 (65.11), M 15 (34.89)
Clinical presentation		
Neurogenic symptoms, n (%)	43	4 (9.30)
Neuroglycopenic symptoms, n (%)		4 (9.30)
Both symptoms, n (%)		35 (81.4)
Symptoms in		
Fasting, n (%)	43	38 (88.40)
Postprandial, n (%)		1 (2.30)
Both conditions, n (%)		4 (9.30)
Interval between onset of symptoms and referral, average (ranges)	43	2 years (1 month-10 years)
Glucose level in hypoglycemic crisis, mean ± SD (range)	40	39.3±13.15 mg/dL (10-74 mg/dL)
C-peptide level in hypoglycemic crisis mean ± SD (range)	39	4.77±2.88 ng/mL (1.36-18 ng/mL),
Insulin level in hypoglycemic crisis, mean ± SD (range)	39	32.15±32.53 µUI/mL (5.6-154 µUI/mL)
Duration of fasting test, mean (range)	18	12 (3-30) hours

SD: Standard deviation, F: female, M: male

CT scan was 68.18%, and its positive predictive value (PPV) was 72.22%. According to the tumor location, sensitivity and PPV of CT scan for the head, body, and tail tumor was 55.55% and 100%, 100% and 75%, and 66.66% and 83.33%, respectively.

EUS had been performed for 23 patients. Sensitivity and PPV of EUS for localization of the tumor was 95.65% and 77.27%, respectively. According to the tumor location, the sensitivity and PPV of EUS for pancreas head, body, and tail tumors was 100% and 87.5%, 100% and 75%, and 90.90% and 70%, respectively.

Regarding tumor size measurement by considering histological examination as the gold standard, there was a significant correlation between tumor size reported by EUS and histology as well as between CT scan and histology (r=0.837 and r=0.948 for EUS and CT scan, respectively). Correlation between CT scan and histology was stronger than between EUS and histology and the accuracy of CT scan in the estimation of tumor size was higher than that of EUS.

Among the studied patients, there were two cases of MEN1 syndrome. As the first one was a known case of MEN1 and had died in intensive care unit after surgery, this case was excluded from the study.

There was no significant association between age (below and above 50) and tumor size (1.97±1.14 vs 1.64±1.19, respectively).

No significant association was found between weight change, the mean glucose level during hypoglycemia, duration of the fasting test, and tumor size (less than 2 cm and greater than 2 cm).

Glucose and insulin levels at the end of the fasting test were not different between those with tumors less and greater than 2 cm (32.89±13.98 vs 43.55±16.43 mg/dL for glucose and 26.53±20 vs 46.38±43.91 for insulin level, respectively).

The number of hypoglycemic crises per week in patients with tumor sizes greater than 2 cm was significantly higher than those with tumor sizes less than 2 cm (9.25±11.98 vs 2.95±2.45). Also, the C-peptide level during hypoglycemia was higher in tumors greater than 2 cm than in tumors less than 2 cm (6.36±4.73 vs 4.01±1.41).

There was no significant difference in the interval from the onset of disease to referral between those with a tumor size greater and less than 2 cm.

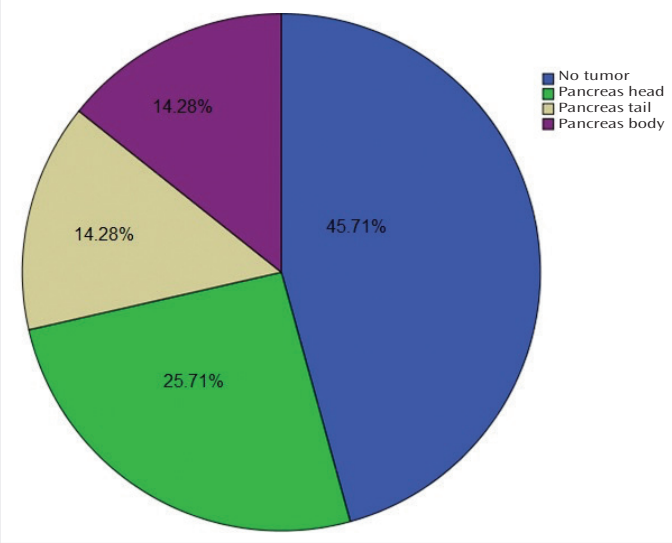

Figure 2. Tumor location by CT scan
CT: Computed tomography

Treatment

Treatment had been recorded in 39 of 43 patients. Of 39 patients with available data, 31 (79.49%) underwent operation and 8 (20.51%) received medical treatment.

Tumor Pathology

Among 43 patients, insulinoma had been reported as a pathological condition in 21cases. Pathological slides were re-studied, and specific staining was performed in available cases. Pathological characteristics are shown in Table 2.

There was a significant difference in mitotic activity between pancreatic head, body, and tail tumors.

Regarding mitotic activity and tumor size in available data in 21 cases, all 11 tumors sized lesser than 2 cm were grade 1 and of 10 tumors sized greater than 2 cm, 6 were grade 1, 3 grade 2, and one was grade 3. There was a significant association between tumor size and mitotic activity (p=0.018).

There was no significant association between mitotic activity and tumor invasion.

Tumor invasion was seen in 33.3% of patients (7 cases). The highest rate of invasion was seen in pancreatic tail insulinomas (50% in comparison to 33% in the body and 22.2% in the head). In microscopic evaluation, malignant insulinoma with invasion to adjacent tissues was identified in 7 of 21 studied cases (33.33%) and among those with malignant

Table 2. Pathological characteristics of studied patients with insulinoma

Variable	n	Value
Microscopic pattern		
Solid, n (%)	19	8 (42.10)
Gyriform, n (%)		7 (36.84)
Other patterns, n (%)		4 (21.05)
Mitotic activity		
Grade 1, n (%)	21	17 (80.95)
Grade 2, n (%)		3 (14.28)
Grade 3, n (%)		1 (4.76)
Amyloid rate		
No	15	10 (66.66)
Low		3 (20.00)
High		2 (13.33)
Cell cytoplasm		
Eosinophilic, n (%)	17	10 (58.82)
Some eosinophilic some clear, n (%)		3 (17.64)
Other types, n (%)		4 (23.52)

insulinoma, liver metastasis, and vascular and lymph node invasion as well as invasion to the splenic artery was observed in one patient. Vascular invasion was detected in three cases, vascular and lymphatic invasion in two cases and invasion to adjacent adipose tissue in one patient.

There was no relationship between tumor invasion and patient age (46±10.08 and 46.57±13.55 years for those with and without invasion, respectively).

The mean tumor size in the invasive group was 2.85±1.70 cm, which was significantly higher than the mean tumor size in the noninvasive group (1.76±0.82 cm).

There was no relationship between tumor location and tumor invasion. Also, the mean age of patients with tail tumors was higher than that of patients with the head and body tumors (44.30±14.69, 44.25±4.27, and 52.54±11.48 years for the head, body, and tail, respectively).

Discussion

This retrospective study reported on the clinicopathological characteristics of insulinoma in 43 patients. Insulinoma is the most common functional pancreatic NEN, as 76% of pancreatic NEN were insulinoma in a study by Cheng et al. (13). Insulinoma may occur in all ages, and there is no age limitation. However, the age of most patients is between 30 and 60 years, and the median age is in the fifth decade of life (5,14). In the current study, patients ranged from 21 to 70 years of age, and most patients were aged below 50 years (28 patients/65.11%) with a mean age of 45.4±13.3 years, which is less than previous studies that reported insulinoma in the fifth decade of life (5,13,14). However, the mean age of patients in the study by Peltola et al. (15) in Finland was 52 years, and in the study of Cheng et al. (13), 46 years, which is higher than in our study, while it was 39 years in the previous study in Iran, which is less than the current study (16). Insulinoma occurs in both genders without gender predominance or a slightly higher rate in the female gender (5,14). In the present study insulinoma was observed in both genders, but more than half of the cases were female (65.11%). However, the proportion of females in our study (65.11%) was less than that in the Finnish study (70%) (15). In contrast to the current study, in a previous study in Iran on 68 insulinoma cases, males slightly outnumbered females (53% vs 47%, respectively) (Table 2) (16).

The mean tumor size in the current study was 2.13±1.22 cm (0.6-5.5 cm), whereas in the previous study in Iran the mean tumor size was 2.9 cm (1-8.5 cm) (Table 2) (16). However, tumor size in some previous studies was lower than in ours (14,17-19).

Clinical Manifestations

Due to high insulin levels, patients with insulinoma experience hypoglycemia symptoms that are categorized as either neuroglycopenic and neurogenic (catecholamine response) (20). These symptoms are improved by glucose administration (Whipple's triad) (8) and aggravated by fasting or exercise.

In the current study, both neurogenic and neuroglycopenic symptoms were seen in most insulinoma patients (81.39%). In the study by Peltola et al. (15) in Finland, prevalence of neuroglycopenic and autonomic symptoms was 96% and 77%, respectively. The rate of neuroglycopenic symptoms in that study (96%) (15) was slightly higher than in ours (90.69%). In the previous study in Iran, neuroglycopenic symptoms were observed in 97% of patients, which is higher than the current study, and adrenergic symptoms were observed in 89.6% of cases (16).

Insulinoma symptoms may occur in the postprandial state, in the fasting state, or even with no relationship to eating (21). In the present study, the majority of patients (88.37%) showed symptoms in the fasting condition, and others showed symptoms in the postprandial or both conditions.

Weight gain in insulinoma occurs due to frequent eating to prevent hypoglycemic symptoms (22). In our study, 65% of patients experienced weight gain.

Diagnosis

The mean diagnosis delay in the present study was 2 years, while it was 13 and 15 months in Peltola et al. (15) and Cheng et al. (13), respectively which is less than in our study (15). However, the mean diagnosis delay in a previous study in our country was 39.9 months, which is higher than the one in the current study (Table 3) (16).

The presence of low plasma glucose associated with high serum insulin and C-peptide levels in a symptomatic patient is the basis for the biochemical diagnosis of insulinoma after exclusion of other causes of hyperinsulinemic hypoglycemia (23).

Table 3. Findings of our study compared to previous studies about insulinoma

Study	Number of patients	Year	Mean age (year)	Sex (M/F), (n)	Mean/median diagnosis delay (month)	Mean tumor size (cm)	MEN1 cases (n)
Current study	43	-	45.4	15/28	24	2.13	1
Peltola et al. (15)	79	2018	52	24/55	13	-	2
Yu et al. (14)	17, 9	2017	47, 51	9/8, 4/5	11, 1	1.5, 2.1	-
Iglesias et al. (19)	29	2015	48.7	6/23	-	1.7	3
Tsang et al. (18)	36	2016	48.2	18/18	-	1.47	3
Cheng et al. (13)	76	2016	46.2	26/50	24	2.2	-
Larijani et al. (16)	68	2005	39	36/32	40	2.9	2
Goh et al. (17)	17	2009	50	7/10	3	1.5	-

M: Male, F: female, MEN: multiple endocrine neoplasia

Imaging

Due to the risk of developing diabetes following major pancreatic resection, pancreas-preserving surgery is the treatment of choice for insulinoma (20). Therefore, preoperative localization of the tumor is required for planning the appropriate surgical approach (24). However, without preoperative tumor localization, 10%-27% of insulinomas remain undetected during surgery (25).

In our study, in 22.5% (nine) of cases, imaging could not localize the tumor while in Finland study the tumor was not identified in nine cases (11%) by imaging. This difference may be due to more imaging methods being used in that study compared with ours (15).

The sensitivity of EUS in tumor localization was 95.65% in our study, while it was 78% in Finland study (15). In that study EUS had the best sensitivity for detecting tumors less than 1 cm (15). Sensitivity of CT scan in tumor localization in Finland study was 51%, and the mean sensitivity of CT scan in previous studies was 43%, while in our study it was 68.18%, which is higher than in previous studies (15,26). In the study by Cheng et al. (13), the sensitivity of EUS and CT scan for the localization of pancreatic NEN was 100% and 91.5%, respectively. In that study, abdominal ultrasonography, CT scan, MRI, and EUS were the most commonly used imaging modalities for preoperative localization of pancreatic NEN (13). Dynamic MRI, CT scan, and EUS are the most useful imaging modalities for the evaluation of insulinoma (27). The sensitivity of EUS is 70%-95%, which in combination with 3-phase CT scan, reaches 100% (27). As conventional sonography, CT scan, and MRI are commonly available modalities, they can be applied as first-line imaging methods for detection and localization of insulinoma (28). The success rate of tumor localization with a combination of intraoperative ultrasound and operative palpation reaches nearly 100% (29,30).

Treatment

In our study, 79.49% of patients underwent surgery, and 20.51% received medical treatment, while in the Finland study 90% of the patients underwent curative surgery and 3% palliative surgery, which resulted in an overall rate of surgery higher than ours (15).

Lack of assessment of treatment outcomes in patients with insulinoma as well as limited access to data due to retrospective nature of the study were the main limitations of the current study that should be considered in future studies. Another limitation is the lack of detailed assessment of symptoms in each category.

Pathology

Most cases of insulinoma are benign, and approximately 10% of cases are malignant (5,26). The diagnostic criteria for insulinoma malignancy include local invasion and lymph node or distant metastasis. Benign insulinomas are usually small and measure approximately 1-2 cm (31). In the present study, 7 cases (33.33%) were identified as malignant insulinoma with invasion to adjacent tissues, while in a previous study in Iran, 5.8% were malignant, which is lower than the percentage in our study (16). The rate of malignancy in our study is close to that of Yu et al. (14) (35%), which is higher than that of Peltola et al. (15) (14%).

In the current study, 80.95% of insulinoma tumors were grade 1. In a study by Tsang et al. (18), 86.1% of tumors belonged to G1, which is higher than in ours while in a study by Yu et al. (14), 44.4% of tumors were G1 which is lower than in ours. Also, according to Yu et al. (14), 44.4% of tumors were G2, while in our study this rate was 14.3%.

According to Tsang et al. (18), 8.3% of insulinomas were a component of MEN1 syndrome, while in our study, only in 2.32% of insulinoma cases was MEN1 syndrome diagnosed. In the previous study in Iran two cases of MEN1 syndrome (2.94%) were identified, which is similar to the current study (Table 3) (16).

Study Limitation

Lack of assessment of treatment outcomes in patients with insulinoma as well as limited access to data due to the retrospective nature of the study were the main limitations of the current study that should be considered in future studies. Another limitation is the lack of assessment of symptoms in detail in each category.

Conclusion

This study presented the picture of insulinoma in the past decade in Iran. According to the results, the diagnostic delay of insulinoma has been reduced in our country during the past decade by improved imaging technologies but needs to be reduced further. For localization of insulinoma tumors, EUS and CT scan are the best modalities, while for size measurement, the accuracy of CT scan is greater than that of EUS. Also, it appears that the malignancy rate has increased in insulinoma tumors, and the tumor size has decreased compared with previous decades, probably due to the reduced diagnostic delay.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee at Imam Khomeini Hospital, and the study was conducted according to the Helsinki declaration (approval number: IR.TUMS.IKHC.REC.1396.3105, date: 07.08.2017).

Informed Consent: Retrospective study.

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Stability of Cardiac Troponin-I in Whole Blood and Plasma in Patients with Acute Myocardial Infarction

Akut Miyokard Enfarktüslü Hastalarda, Tam Kan ve Plazma Kardiyak Troponin-I Stabilitesi

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ABSTRACT

Introduction: In this study, we aimed to investigate the short-term stability and variability of cardiac troponin T (cTnI) in ethylenediamine tetraacetic acid (EDTA) whole blood, heparinized whole blood, and EDTA plasma.

Methods: Thirteen patients with myocardial infarction were included. Venous blood samples (24 mL) from all patients were collected into vacuum tubes with EDTA and heparin (Becton Dickinson-USA), and analyses were performed on four different groups (one group for repeatability and three groups for stability).

Results: There was no statistically significant difference in cTnI concentrations at baseline, 2, 4, 6, 12, 24, and 48 hours between the heparinized whole blood, EDTA whole blood, and EDTA plasma groups (group 2) ($p>0.05$). In the heparinized whole blood and EDTA plasma groups, there was a statistically significant difference between cTnI concentrations at baseline, 2, 4, 6, 12, 24, and 48 hours. In the EDTA whole blood group, there was no statistically significant difference between any time points.

Conclusion: The interclass and intraclass correlation coefficients of the EDTA whole blood group were sufficiently high, which indicates better stability. EDTA whole blood samples are preferable for cTnI measurement because they are stable for 48 hours. EDTA-containing tubes are easy to find in clinical laboratories and do not need to be centrifuged, which saves time and effort.

Keywords: Cardiac troponin-I, acute myocardial infarction, plasma, whole blood

ÖZ

Amaç: Bu çalışmada EDTA tam kan, heparinize tam kan ve EDTA plazmasındaki kısa-süreli kardiyak troponin T (cTnI) stabilitesini ve değişkenliğini araştırmayı amaçladık.

Yöntemler: Miyokard enfarktüsü geçiren 13 hasta dahil edilmiştir. Tüm hastalardan 24 mL venöz kan örnekleri EDTA ve heparinli vakum tüplerine alındı (Becton Dickinson-ABD) ve analizler 4 farklı grupta (tekrarlanabilirlik için 1 grup ve stabilite için 3 grup) gerçekleştirildi.

Bulgular: Heparinize tam kan, EDTA tam kan ve EDTA plazma grupları arasında başlangıç, 2., 4., 6., 12., 24 ve 48. saat cTnI konsantrasyonları arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0,05$). Heparinize tam kan ve EDTA plazma gruplarında, başlangıç, 2., 4., 6., 12, 24, 48 saat cTnI konsantrasyonları arasında istatistiksel anlamlı fark vardı. EDTA tam kan grubunda tüm saatler arasında istatistiksel olarak anlamlı fark yoktu.

Sonuç: EDTA tam kan grubunun sınıflar arası ve sınıflar arası korelasyon katsayıları yeterince yüksekti, bu da daha iyi bir stabilite olduğunu göstermektedir. EDTA tam kan örnekleri cTnI ölçümünde tercih edilebilir, çünkü 48 saat stabildir. EDTA içeren tüplerin klinik laboratuvarlarda bulunması kolaydır ve santrifüjlemeye gerek kalmaz, zamandan ve emekten tasarruf sağlar.

Anahtar Kelimeler: Kardiyak troponin-I, akut miyokard enfarktüs, plazma, tam kan

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Introduction

Cardiac troponin-I (cTnI) is widely used as the gold standard marker of myocardial cell damage. The quantitative measurement of cTnI is very important for the diagnosis and treatment of myocardial infarction (MI). Following myocardial cell damage, cytosolic troponin is released first, and as further damage occurs, troponin present in the sarcomere is released into the circulation. For this reason, troponin is both an early and late marker of acute myocardial infarction (AMI).

The kinetics of cTnI release after damage are as follows: levels of cTnI start increasing 4-9 hours after AMI and peak at 12-24 hours. They can remain elevated for up to 14 days.

A rise in circulating cTn with at least one value above the 99th percentile upper reference limit is indicative of the presence of AMI and is useful within the particular diagnosis of ST segment elevation but especially non-ST-elevation myocardial infarction (1). Measurement of cTn plays a critical role in the rapid assessment of patients admitted to the emergency department with acute coronary syndrome (2). By using troponin-specific antibodies, cTn levels can be determined in the blood. More than one assay is available for cTnI, and each antibody measures different epitopes and fragments (3). Therefore, there is no standardization between assays. Different assays have different cut-off limits. Also, the complex release of cTn (in the form of cTn-T, I, and C complex) may cause different results between measurements, because some of the antibodies used in the measurements are not able to recognize some of the cTn forms in the complex, which cause lack of standardization in cTnI measurement (4,5). cTnI measurements are influenced by multiple factors, including proteolytic degradation, heparin, heterophile antibodies, human-animal antibodies, autoimmune antibodies, rheumatoid factors, cTnI-specific autoantibodies, hemolysis, and fibrin (6). These variations in troponin measurements can cause diagnostic problems, so the stability of troponin is crucial, especially in the area of AMI.

In this study, the aim was to evaluate how the cTnI test results of patients diagnosed with MI were affected when blood samples were collected into tubes containing different anticoagulants and when analyzed under different storage conditions.

Methods

A total of 13 patients 18 years and older and diagnosed with AMI in the emergency room were included in the study prospectively. MI is diagnosed when blood levels of sensitive and specific biomarkers such as cTn or CK-MB are increased in the clinical setting of acute myocardial ischemia. Patients with chronic kidney disease, acute infection, congestive heart failure, or chronic obstructive pulmonary disease at admission were excluded because of the risk of false positivity. This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee (approval number: 2014/09/01, date: 14.07.2014). All participants' rights were protected, and written informed consent was obtained before the procedures, according to the Helsinki Declaration (2013). Venous blood samples (24 mL) were collected from all patients into vacuum tubes with ethylenediamine tetraacetic acid (EDTA) and heparin (two EDTA tubes BD, 10 mL K2 EDTA, Cat. No: 367525 and two heparin tubes BD, 4 mL lithium heparin, Cat. No: 367883).

The first samples that arrived in the laboratory were defined as baseline cTnI value (0 minutes), and troponin-I analyses were completed within 30 minutes after arrival. The whole blood samples collected into tubes with EDTA and heparin were kept at room temperature, and troponin-I analyses were repeated after 2, 4, 6, 12, 24, and 48 hours. Additional EDTA samples were centrifuged immediately, and the first aliquoted plasma samples were analyzed for troponin-I, whereas the other aliquots were frozen and kept at -20 °C. Troponin-I analyses were repeated after 2, 4, 6, 12, 24, and 48 hours from frozen plasma samples.

cTnI was analyzed with the AQT90 analyzer closed-tube system (Radiometer Medical Aps, Denmark) using the time resolve fluorometry method. The minimum sample volume was 2 mL.

Analyses were performed on four different groups (one group for repeatability and three groups for stability). The first group of blood samples (n=10) were analyzed as whole blood with EDTA, and all repeatability studies were completed within 6 hours on the day of collection. All analyses were performed 10 times for each patient.

The second group of whole blood samples with EDTA (n=10) was centrifuged at 1000 g for 5 minutes within 30-60 minutes, and plasma samples were obtained. Baseline levels were recorded, then other plasmas were melted after the appropriate incubation period, and all analyses were completed within 30 minutes.

The third group of blood samples with EDTA (n=7) and the fourth group with heparin (n=10) were analyzed, and after measurement of baseline levels, the next set of samples was analyzed within 30 minutes after the appropriate incubation period.

Statistical Analysis

In this study, statistical analyses were performed with the Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) package program. In the data analysis, descriptive statistical methods (mean, standard deviation) were used, as well as repetitive variance analysis in multiple groups, Newman-Keuls multiple comparison test in subgroup comparisons, and One-Way analysis of variance in between-group comparisons.

Intraclass correlation coefficients (ICCs) were calculated for measurement of reliability. The results were evaluated at a significance level of $p<0.05$.

Results

The cTnI levels of a total of 13 AMI patients were tested on three different samples in two different collection tubes at seven different time points. For the reliability of EDTA whole blood measurement (group 1), the results are listed in Table 1. The ICC was calculated, and the reliability coefficient was found to be 0.997 (0.995-0.999). The variability of the measurements was found to be 1.7%, which indicates high reliability of EDTA whole blood measurements (Table 2).

There was no statistically significant difference between cTnI concentrations at baseline, 2, 4, 6, 12, 24, and 48 hours in the EDTA plasma group (group 2), EDTA whole blood (group 3), and heparinized whole blood (group 4) ($p>0.05$) (Table 3). In the EDTA plasma group (group 2), there was a statistically significant change in the cTnI concentration

between baseline and 2, 4, 6, 12, 24, and 48 hours (p=0.028) (Table 3). In the EDTA whole blood group (group 3), no significant difference was observed between cTnI concentrations at baseline and 2, 4, 6, 12, 24, and 48 hours (p=0.107) (Table 3). In the heparinized whole blood group (group 4), there was a statistically significant difference in cTnI concentrations between baseline and 2, 4, 6, 12, 24, and 48 hours (p=0.002) (Table 3).

In multiple comparison analyses of groups 2 and 4, the baseline values were statistically significantly higher than the 12-, 24-, and 48-hour measurements (p=0.048, p=0.049, p=0.013) (Table 4). The 48-hour values were statistically significantly lower than those at 4, 6, 12, and 24 hours (p=0.018, p=0.011, p=0.049, p=0.027), and no significant difference was observed between the other time points (p>0.05) (Table 4). The 4-hour values were significantly lower than the baseline and 12-hour values (p=0.012, p=0.026). The 24-hour values were significantly lower than the 12-hour values (p=0.017). The other time points did not differ statistically significantly (p>0.05) (Table 4).

Discussion

In our study, no significant intraclass and interclass difference in cTnI values was found in EDTA whole blood. The interclass and ICCs of the EDTA whole blood group were sufficiently higher, which indicates better stability compared with the other two groups.

There was also no statistically significant difference between cTnI levels in whole heparinized blood, EDTA whole blood, and EDTA plasma samples at the same hours, which showed a similar safety profile.

No differences in stability were reported between whole EDTA blood, EDTA plasma, and serum (7) or between heparinized whole blood and plasma (8).

In a study by Chapelle et al. (6), heparinized whole blood and plasma samples were collected from 85 patients with suspected MI, and no statistically significant difference was found between the two sample types, as in our study. There were significant differences between intraclass (baseline, 4-, 6-, 12-, 24-, and 48-hour) measurements of the heparin whole blood group (6). Binding of heparin to cTnI may cause

Table 1. Results of patients in EDTA whole blood (group 1)

Sample ID	Number of repeats	Minimum value	Maximum value	Mean ± SD
1	10	0.84	1.1	0.946±0.075
2	10	1.3	1.5	1.41±0.056
3	10	2.8	3.1	2.97±0.094
4	10	3.7	4.1	3.9±0.019
5	10	1.9	2	1.96±0.032
6	10	1.1	1.3	1.18±0.030
7	10	0.53	0.67	0.579±0.042
8	10	1.4	1.5	1.45±0.052
9	8	2.1	2.3	2.175±0.103
10	8	1.3	1.6	1.4±0.092

SD: Standard deviation, EDTA: Ethylenediaminetetraacetic tetraacetic acid

Table 2. Variability of group 1 (EDTA whole blood)

	Variability %	ICC	95% CI	
			Lower bound	Upper bound
EDTA whole blood	1.7	0.997	0.995	0.999

ICC: Intraclass correlation coefficient, CI: confidence interval, EDTA: Ethylenediaminetetraacetic tetraacetic acid

Table 3. Comparison of groups 2, 3, and 4

	Heparinized whole blood (group 4)	EDTA whole blood (group 3)	EDTA plasma (group 2)	p
Baseline	3.25±2.58	2.06±0.91	2.87±2.13	0.753
2. hours	3.11±2.43	2.03±0.93	2.76±1.99	0.866
4. hours	3.06±2.3	2±0.99	2.67±1.95	0.767
6. hours	3.11±2.46	2.02±0.91	2.79±2.06	0.781
12. hours	3.01±2.34	1.92±0.81	2.8±1.96	0.674
24. hours	3.02±2.48	1.88±0.83	2.66±1.84	0.761
48. hours	2.86±2.27	1.99±0.82	2.73±2.03	0.893
p	0.002	0.107	0.028	

EDTA: Ethylenediaminetetraacetic tetraacetic acid

Table 4. Comparison of groups 2 and 4

Multiple comparison test	Heparinized whole blood (group 4)	EDTA plasma (group 2)
Baseline/2. hours	0.173	0.107
Baseline/4. hours	0.107	0.012
Baseline/6. hours	0.169	0.062
Baseline/12. hours	0.048	0.362
Baseline/24. hours	0.049	0.121
Baseline/48. hours	0.013	0.135
2. hours/4. hours	0.429	0.061
2. hours/6. hours	0.931	0.490
2. hours/12. hours	0.084	0.478
2. hours/24.hours	0.480	0.205
2. hours/48. hours	0.025	0.667
4. hours/6. hours	0.719	0.122
4. hours/12. hours	0.238	0.026
4. hours/24. hours	0.310	0.858
4. hours/48. hours	0.018	0.257
6. hours/12. hours	0.066	0.734
6. hours/24. hours	0.141	0.156
6. hours/48. hours	0.011	0.291
12. hours/24. hours	0.611	0.017
12. hours/48. hours	0.049	0.230
24. hours/48. hours	0.027	0.588

EDTA: Ethylenediaminetetraacetic tetraacetic acid

lower measured values by masking specific epitopes. In addition, therapeutic heparin treatment during the early hours of AMI may also interfere with these samples. These effects may give us an idea to explain the intraclass differences in the heparin whole blood group. Also, in the EDTA plasma group, there was a statistically significant intraclass difference.

EDTA, as an anti-coagulant, may cause discrepancies, especially in assays utilizing antibodies that differentially recognize free and complexed cTnI. EDTA can cause partial unfolding of the calcium-dependent troponin complex and changes the three-dimensional structure of the troponin complex by binding calcium. Partial unfolding of the cTnI-TnC complex in the absence of calcium would thus facilitate blockage of some cTnI epitopes by the interfering factor. In the presence of calcium, the cTnI-TnC complex will stay more tightly together, reducing the interaction of the interfering factor with cTnI (9).

No significant difference was observed in cTnI concentrations in the EDTA whole blood group, between baseline and 2, 4, 6, 12, 24, and 48 hours. When compared with the EDTA whole blood group, the heparin whole blood and EDTA plasma groups did not differ significantly. This was the key part of our study. The interclass and ICCs of the EDTA whole blood group were sufficiently high, which indicate better stability.

There is substantial heterogeneity in cTn assays, and different cut-off values are used from one assay to the other and from one laboratory to another. In addition, there are preanalytical and analytic problems associated with samples for the measurement of cTn (10).

All studies must report the specific metrics utilized for the evaluation of cTn in all biomarker papers, compliant with the Standards for Reporting Diagnostic Accuracy guidelines (11).

Conclusion

EDTA whole blood samples are preferred for cTnI measurement, because they are stable for 48 hours. EDTA-containing tubes are easy to find in clinical laboratories, and there is no need for centrifugation, which saves time and effort.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital Local Ethics Committee (approval number: 2014/09/01, date: 14.07.2014).

Informed Consent: All participants' rights were protected, and written informed consent was obtained before the procedures, according to the Helsinki Declaration (2013).

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Subgroup Analysis in Multiple Myeloma Patients under Sixty Years: A Single-Center Study

Altmış Yaş Altı Multipl Miyelom Hastalarında Subgrup Analizi: Tek Merkez Çalışma

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ABSTRACT

Introduction: Multiple myeloma (MM) constitutes approximately 10% of hematological malignan-cies with abnormal proliferation of plasma cells, which causes an abnormal increase of monoclonal immunoglobulin light chains. We aim to examine our young myeloma cases' data and compare light chain disease with other subtypes, which are known to have a worse prognosis in all age groups.

Methods: Fifty-five MM patients diagnosed and treated between January 2010 and 2020 under 60 years old, were analyzed retrospectively. Their demographic data, laboratory, treatment subtypes, MM subtypes, CRAB findings (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment, and responses to the first-line treatment were analyzed. The patients were divided into two groups, the light chain and other myeloma subgroups, and compared statistically.

Results: Seventeen patients were female (30.9%), and 38 were male (69.1%). The median age was 54 (range: 34-59) years. The median duration of follow-up was 30 (range: 3-108) months. The MM sub-types examined were: immunoglobulin G (IgG)/Kappa 13 (23.6%), kappa light chain 10 (18.2%), lambda light chain 10 (18.2%), IgG/Lambda 9 (16.4%), IgA/Lambda 8 (14.5%), and IgA/Kappa 5 (9.1%). There was no significant difference between the two groups except for albumin and calcium values. In the other myeloma subtype group, albumin and calcium values were significantly lower ($p<0.05$) than the light chain group.

Conclusion: The myeloma distribution under the age of 60 was different from that in the general my-eloma population. The light chain was more at the forefront, which appears to be related to lytic le-sions, kidney failure, and amyloidosis. Moreover, albumin, an independent prognostic indicator for myeloma, decreased in the other myeloma subgroup compared with the light chain subgroup. They are first mentioned in the literature in patients under 60 years old.

Keywords: Multiple myeloma, young patients, light chain, albumin, prognosis

ÖZ

Amaç: Multipl miyelom (MM), hematolojik malignitelerin yaklaşık %10'unu oluşturan; monoklonal immünglobulin artışına eşlik eden serbest hafif zincir salınımına neden olan anormal proliferasyon gösteren, malign plazma hücrelerinin oluşturduğu bir hastalıktır. Çalışmamızda, tanı anında 60 yaş altında olan genç miyelom olgularımızın verilerini, retrospektif olarak ortaya koymayı ve kötü prognoza sahip olduğu bilinen hafif zincir hastalığı ile diğer miyelom alt tiplerini karşılaştırmayı amaçladık.

Yöntemler: Ocak 2010 ile Ocak 2020 arasında 60 yaşın altında tanı alarak tedavi edilen elli beş MM hastası retrospektif olarak incelendi. Demografik veriler, laboratuvar parametreleri, tedavi alt tipleri, MM alt tipleri, CRAB bulguları (hiperkalsemi, böbrek yetmezliği, anemi ve litik kemik lezyonlarının varlığı), tedavi ve birinci basamak tedaviye yanıtları analiz edildi. Hastalar hafif zincir ve diğer miyelom alt grupları olarak iki gruba ayrıldı ve istatistiksel olarak aynı başlangıç parametreleri açısından karşılaştırıldı.

Bulgular: On yedisi kadın (%30,9) ve 38'i erkek (%69,1) idi. Ortanca yaş 54 bulundu (aralık: 34-59). Medyan takip süresi 30 aydı (aralık: 3-108). MM alt tipleri incelendiğinde; immünoglobulin G (IgG)/Kappa 13 (%23,6), kappa hafif zincir 10 (%18,2), lambda hafif zincir 10 (%18,2), IgG/Lambda 9 (%16,4), IgA/Lambda 8 (%14,5) ve IgA/Kappa 5 (%9,1) idi. Hafif zincir ve diğer miyelom alt grupları istatistiksel olarak karşılaştırıldı. İki grup arasında albümin ve kalsiyum değerleri dışında anlamlı bir farklılık saptanmadı. Diğer miyelom alt tipi grubunda, albümin ve kalsiyum değerleri hafif zincir grubuna göre anlamlı olarak düşüktü ($p<0,05$).

Sonuç: Çalışmamızda 60 yaşın altındaki miyelom dağılımının, genel miyelom popülasyonu ile aynı olmadığı görülmüş olup; litik lezyon, böbrek yetmezliği ve amiloidoz ile daha çok birliktelik gösteren hafif zincir hastalığı daha fazla görülmüştür. Ayrıca miyelom için bağımsız bir prognositik gösterge olarak görülen albümin, diğer miyelom alt grubunda, hafif zincir grubuna göre anlamlı olarak azalmıştı. Bu bulgular 60 yaş altı miyelom olgularında ilk kez ortaya konulmaktadır.

Anahtar Kelimeler: Multipl miyelom, genç hasta, hafif zincir, albümin, prognoz

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Introduction

Multiple myeloma (MM) constitutes approximately 10% of hematological malignancies. It is a disease caused by malignant plasma cells, which is abnormal proliferation, causing free light chain release accompanying the increase in monoclonal immunoglobulin (Ig) (1). It is possible to say that the data obtained from many publications are seen around 7 in 100,000, and the median age is 65 years old (2-4). Clinical manifestations appear as renal failure, anemia, hypercalcemia, and lytic bone lesions. Although positron emission tomography/computed tomography (PET/CT) is often preferred for the detection of lytic bone lesions, magnetic resonance imaging (MRI), CT, and plain radiographs also contribute to the diagnosis.

The most common MM subtypes are those that show the IgG monotype followed by the IgA monotype (5,6). The light chain subtype is seen at a rate of 15% and appears to have a worse prognosis (6). In the light chain subtype, renal failure, bone lesions, and light chain amyloidosis are more common. It is seen at an earlier age and has a worse prognosis than other subtypes (7,8).

Autologous stem cell transplantation, which forms an integral part of the treatment, also provides the basis for approaching patients in terms of age and sheds light on the definition of "young myeloma." Although there is no exact cut-off to guide treatment determination and demonstration, we see 65 years old as a possible cut-off because of transplantation. Today, the approach to young myeloma, which constitutes approximately 37% of all cases, is particularly critical in planning the treatment process, obtaining an optimal response, and preventing treatment-related toxicities (9).

Our study aims to analyze the data of our young myeloma cases retrospectively and compare light chain disease, which is known to have a worse prognosis in all age groups.

Methods

The data of 55 MM patients under 60 years old who were diagnosed and treated between January 2010 and January 2020 in the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology Outpatient our hospital were analyzed retrospectively. Demographic data of patients (age and gender), hemoglobin, albumin, protein, lactate dehydrogenase (LDH), beta-2 microglobulin, creatinine, calcium, treatment subtypes, and the number of cures applied, and MM subtypes. Also, the preferred detection methods of lytic lesions and rates (PET/CT, CT, and MRI), chromosome analysis at diagnosis and myeloma fluorescence in situ hybridization panel results (if available), CRAB findings at the time of diagnosis (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment and responses to the first-line treatment, autologous stem cell transplantation rate, duration of follow-up, and final status were analyzed retrospectively. Patients were divided into two groups, the light chain, and other myeloma subgroups, and statistically compared the same baseline parameters. All light chain patients were checked for the presence of IgD and IgE monoclonality.

The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethic Committee and the Ministry of Health (approval number: 2241, date: 27.04.2020). Informed consent was obtained from our patients to publish the presentation.

Statistical Analysis

Average, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov-Smirnov test. An Independent Samples t-test and the Mann-Whitney U test were used in the analysis of independent quantitative data. In the analysis of independent qualitative data, the chi-square test was used. Fisher's exact test was used when chi-square test conditions were not met. The SPSS 26.0 program was used in the analysis.

Results

Data of a total of 55 patients were examined. Seventeen were female (30.9%), and 38 were male (69.1%). The median age was found to be 54 (range: 34-59) years. The median duration of follow-up was 30 (range: 3-108) months.

When MM subtypes are examined, IgG/Kappa was 13 (23.6%), kappa light chain 10 (18.2%), lambda light chain 10 (18.2%), IgG/Lambda 9 (16.4%), IgA/Lambda 8 (14.5%), and the number of patients diagnosed with IgA/Kappa was 5 (9.1%). The number of patients with lytic lesions detected by any imaging method was 43 (78.2%). All patients had a PET/CT at the time of diagnosis; 38 patients had lytic lesions detected by PET/CT (69.1%) (Table 1).

Fifteen (27.3%) of the patients were at the International Staging System (ISS) stage 1, 39 at stage 2 (70.9%), one at stage 3 (1.8%). There were 16 (29.1%) patients with initial renal failure, 21 (38.2%) with anemia, and five patients (9.1%) with hypercalcemia. In the first-line treatment, vincristine-adriamycin-dexamethasone was preferred for 36 patients (65.5%) and bortezomib-cyclophosphamide-dexamethasone (34.5%) for 19 patients. While there were two patients (3.6%) with complete remission after first-line treatment, 12 patients showed progressive disease (21.8%). A total of 45 patients underwent autologous bone marrow transplantation (81.8%). In the final status assessment, 15 patients dropped out (27.3%) (Table 2).

The patients were divided into two groups as light chain and other myeloma subgroups and compared statistically in terms of baseline parameters. Ages, gender distribution, LDH, beta-2 microglobulin, creatinine, hemoglobin value, lytic lesion rate, ISS and Revised-international Staging System stages, renal failure, anemia, and hypercalcemia rate did not differ significantly in the light chain and the other group. In the other myeloma subtype group, albumin and calcium values were significantly lower ($p<0.05$) than the light chain group (Table 3).

Discussion

It is still not possible to talk about curative treatment for MM. Although recent years began a new era with the advent of new immunomodulators and target cell treatments, it also fell short regarding delivering a precise treatment. The main population affected by the disease is older individuals. In this population, mortality is based on chronic and non-myeloma causes, while myeloma is controlled with long-term treatments. Considering the older age of individuals in this age group and their tendency to have comorbidities, it is difficult to talk about curability (10).

Table 1. Demographic data, laboratory results, myeloma subtypes, presence of lytic lesions

		Min-max	Median	Mean ± SD (n, %)
Age		34.0-59.0	54.0	52.1±6.2
Gender	Female	-	-	17 (30.9%)
	Male	-	-	38 (69.1%)
Albumin (g/L)		2.0-5.7	3.8	3.7±0.8
Lactate dehydrogenase (U/L)		104.0-499.0	194.0	198.7±67.3
Beta-2 microglobulin (mg/L)		1.5-43.3	3.1	5.7±7.0
Creatinine (mg/dl)		0.5-6.2	0.9	1.4±1.1
Hemoglobin (g/L)		5.5-15.1	11.3	11.0±2.3
Calcium (mg/dL)		7.9-16.5	9.4	9.7±1.3
Corrected calcium (mg/dL)		7.9-16.3	9.2	9.5±1.3
Number of cycles in first-line treatment		1.0-6.0	2.0	2.9±1.3
Multiple myeloma subtypes	IgG/Kappa	-	-	13 (40%)
	Kappa	-	-	10 (18.2%)
	Lambda	-	-	10 (18.2%)
	IgG/Lambda	-	-	9 (16.4%)
	IgA/Lambda	-	-	8 (14.5%)
	IgA/Kappa	-	-	5 (9.1%)
Presence of lytic lesions	(-)	-	-	12 (21.8%)
	(+)	-	-	43 (78.2%)
PET/CT	(-)	-	-	17 (30.9%)
	(+)	-	-	38 (69.1%)

SD: Standard deviation, Ig: immunoglobulin, PET: positron emission tomography, CT: computed tomography, Min: minimum, Max: maximum

Table 2. ISS scores, CRAB findings (hypercalcemia, renal failure, anemia, and presence of lytic bone lesions), treatment and responses, last status

		Min-max	Median	Mean ± SD (n, %)
ISS	I	-	-	15 (27.3%)
	II	-	-	39 (70.9%)
	III	-	-	1 (1.8%)
R-ISS	I	-	-	14 (25.5%)
	II	-	-	40 (72.7%)
	III	-	-	1 (1.8%)
Renal failure	(-)	-	-	39 (70.9%)
	(+)	-	-	16 (29.1%)
Anemia	(-)	-	-	34 (61.8%)
	(+)	-	-	21 (38.2%)
Hypercalcemia	(-)	-	-	50 (90.9%)
	(+)	-	-	5 (9.1%)
First-line treatment	VAD	-	-	36 (65.5%)
	VCD	-	-	19 (34.5%)
Response	CR	-	-	2 (3.6%)
	PD	-	-	12 (21.8%)
	PR	-	-	9 (16.8%)
	SD	-	-	25 (45.5%)
	VGPR	-	-	6 (10.9%)
	No information	-	-	1 (1.8%)
Stem cell transplantation	(-)	-	-	10 (18.2%)
	(+)	-	-	45 (81.8%)
Follow-up period (month)		3-108	30	36.3±27.8
Drop-out	(+)	-	-	15 (27.3%)
	(-)	-	-	40 (72.7%)

ISS: The International Staging System, R-ISS: Revised-international Staging System, CR: complete response, PD: progressive disease, PR: partial response, SD: stable disease, VGPR: very good partial response, SD: standard deviation, Min: minimum, max: maximum

When speaking to a younger age group, discussions about treatment procedures for an incurable disease warrants a very different approach. Effective treatment requires getting a response to the disease and maintaining it for a meaningful length of time. The preferred treatment subtypes and toxicities explain the essential points in young age myeloma (11-14).

In our study, as in the general population, MM is a male-dominated disease in the patient group under 60. There may be a significant difference regarding the distribution of myeloma subtypes. While the IgG/Kappa myeloma subtype is followed by IgA/Kappa in the general population, in our study, the subtype of IgG/Kappa myeloma is followed by kappa and lambda light chain myeloma. Considering that renal failure, bone lesions, and AL amyloidosis are seen in the light chain myeloma, it seems quite possible to expect these three parameters to be prominent under 60. However, in our study, no significant difference was observed in the group under 60 years of age regarding renal insufficiency at the time of diagnosis. As mentioned earlier, considering the literature, there was significantly more involvement of light chain

Table 3. Statistical analysis of parameters

		Light chain subgroup		Other subgroup		p	
		Mean ± SD (n, %)	Median	Mean ± SD (n, %)	Median		
Age		53.5±5.5	55.0	51.4±6.5	54.0	0.232	m
Gender	Female	8 (40%)	-	9 (25.7%)	-	0.270	X^2
	Male	12 (60%)	-	26 (74.3%)	-		
Albumin (g/L)		4.0±0.8	4.2	3.5±0.7	3.4	0.019	t
Lactate dehydrogenase (U/L)		200.3±54.5	195.5	197.8±74.3	188.0	0.898	t
Beta-2 microglobulin (mg/L)		4.7±4.2	2.6	6.3±8.2	3.85	0.164	m
Creatinine (mg/dl)		1.6±1.3	1.1	1.2±0.9	0.89	0.426	m
Hemoglobin (g/L)		11.4±2.2	11.6	10.8±2.3	11.1	0.375	t
Calcium (mg/dL)		10.2±2.0	9.9	9.3±0.7	9.2	0.043	m
Corrected calcium (mg/dL)		9.8±1.9	9.3	9.4±0.8	9.2	0.793	m
Number of cycles in first-line treatment		3.0±1.3	3.0	2.8±1.4	2.0	0.530	m
Presence of lytic lesions	(-)	2 (10%)	-	10 (28.6%)	-	0.109	X^2
	(+)	18 (90%)	-	25 (71.4%)	-		
PET/CT	(-)	5 (25%)	-	12 (34.3%)	-	0.473	X^2
	(+)	15 (75%)	-	23 (65.7%)	-		
ISS	I	6 (30%)	-	9 (25.7%)	-	0.977	X^2
	II	14 (70%)	-	25 (71.4%)	-		
	III	0 (0%)	-	1 (2.9%)	-		
R-ISS	I	6 (30%)	-	8 (22.9%)	-	0.792	X^2
	II	14 (70%)	-	26 (74.2%)	-		
	III	0 (0%)	-	1 (2.9%)	-		
Renal failure	(-)	12 (60%)	-	27 (77.1%)	-	0.178	X^2
	(+)	8 (40%)	-	8 (29.9%)	-		
Anemia	(-)	13 (65%)	-	21 (60%)	-	0.714	X^2
	(+)	7 (35%)	-	14 (40%)	-		
Hypercalcemia	(-)	17 (85%)	-	33 (94.3%)	-	0.342	X^2
	(+)	3 (15%)	-	2 (5.7%)	-		
First-line treatment	VAD	9 (45%)	-	27 (77.1%)	-	0.016	X^2
	VCD	11 (55%)	-	8 (22.9%)	-		
Stem cell transplantation	(-)	4 (20%)	-	6 (17.1%)	-	0.899	X^2
	(+)	16 (80%)	-	29 (82.9%)	-		
Follow-up period (month)		41.4±27.9	38.5	33.4±27.6	28.0	0.308	t
Drop-out	(-)	17 (85%)	-	23 (65.6%)	-	0.122	X^2
	(+)	3 (15%)	-	12 (34.4%)	-		

x,t,m: Mann-Whitney U test, X^2: chi-square test, t: Independent Samples t-test, PET: positron emission tomography, CT: computed tomography, SD: standard deviation, ISS: The International Staging System, R-ISS: Revised-international Staging System, VAD: vincristine-adriamycin-dexamethasone, VCD: bortezomib-cyclophosphamide-dexamethasone

patients in lytic lesions. In contrast, no significant difference was found in our study with light chain myeloma.

In our study, the initial calcium and albumin values were significantly lower in the other myeloma subtypes compared with the light chain group. However, there was no significant difference in the corrected calcium levels. Serum albumin level is defined as an independent risk factor in MM. In a 2009 study (15), patients diagnosed with 373 MM and their data were analyzed. While the patient group with serum albumin 3.5 and below were older, they had lower hemoglobin levels and worse performance status than other groups. Also, beta-2 microglobulin, serum M protein, and the bone marrow plasma cell ratio were higher in this group. In our study, the albumin level was significantly lower in the other myeloma subtypes group than the light chain group. Considering that light chain patients have a worse disease course in the general population, it should be emphasized that this finding is new in the patient group under 60 years old.

In the first treatment series, the combination of bortezomib-adriamycin-dexamethasone was frequently preferred in our case series. Until about three years ago, the use of this combination was mandatory in primary care in accordance with the health system legislation in our country. Today, we use combinations of cyclophosphamide or lenalidomide and bortezomib dexamethasone as the first-line therapy. Reports in the literature also focus on combinations of lenalidomide bortezomib and autologous stem cell transplantation (9).

Conclusion

Our study contains important results concerning MM subgroup data and clinical features in the group under 60 years old. The disease subtype distribution under the age of 60 different from the general myeloma population, and the light chain was more at the forefront. Albumin decreased in the other myeloma subgroup compared with the light chain group. This investigation is the first in the literature to study patients under 60 years old, regarding data revealed by albumin, which is seen as an independent prognostic indicator for myeloma. However, the comparison was not possible concerning the group's treatment heterogeneity and the number of patients.

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We respectfully remember all the colleagues we lost in the COVID-19.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethic Committee and the Ministry of Health (approval number: 2241, date: 27.04.2020).

Informed Consent: Informed consent was obtained from our patients to publish the presentation.

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Giant Anterior Staphyloma After Bomb Explosion

Bomba Patlaması Sonrası Gelişen Dev Anterior Stafilom

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ABSTRACT

A 64-year-old male patient was admitted to our clinic complaining of pain in his left eye. Three years ago, the patient was hit in the left eye by a metal object during an in-car bomb explosion. The patient had a giant anterior staphyloma in his left eye that prevented the eyelids from closing. In the shiotz tonometer measurement, the left intraocular pressure was 26 mmHg. In computed tomography, the distance between the staphyloma endpoint and the lens was 7.17 mm. After open glob trauma, patients should be checked at short intervals for regular follow-up for ocular surface infections. The ophthalmologist responsible for the patient should regularly assess the patient's compliance with the drug and the eye's response to the drug. Early surgery should be applied if necessary to prevent staphyloma and similar eye complications.

Keywords: Anterior staphyloma, Somalia, fungal keratitis, trauma, eye

ÖZ

Altmış dört yaşında erkek hasta sol gözünde ağrı şikayeti ile kliniğimize başvurdu. Hastanın 3 yıl önce sol gözüne araç içi bomba patlaması sırasında metal bir cisim çarpmıştı. Hastanın sol gözünde kapakların kapanmasını engelleyen dev anterior stafilom vardı. Shiotz tonometre ölçümünde sol göz içi basıncı 26 mmHg idi. Bilgisayarlı tomografide stafiloma uç noktası ile lens arasındaki mesafe 7,17 mm idi. Açık glob travmasından sonra hastalar, oküler yüzey enfeksiyonları açısından düzenli takip için kısa aralıklarla kontrol edilmelidir. Hastadan sorumlu göz doktoru, hastanın ilaca uyumunu ve gözün ilaca verdiği yanıtı düzenli olarak değerlendirmelidir. Stafilom ve buna benzer göz komplikasyonlarının oluşmasını önlemek için gerekirse erken cerrahiye başvurulmalıdır.

Anahtar Kelimeler: Ön stafilom, Somali, fungal keratit, travma, göz

Introduction

Anterior staphyloma means that in corneal tears, the iris comes forward and covers the defect and then integrates with the corneal scarification. There are 4 types of staphyloma. These are anterior, intercalary, equatorial, and posterior staphylomas. Perforant injuries, peripheral corneal ulcers, absolute glaucomas, sclerites and pathological myopies can cause weakening of the outer sphere of the eye and ultimately staphyloma (1,2).

Anterior staphylomas located in front of the equator are called calare type if they are above the ciliary body; intercalare type if they are between the ciliary body and the limbus (3). It is probably due to a combination of infection and high intraocular pressure (3). Patients' complaint of admission is an opaque, enlarged and protruded eye that usually accompanies vision loss. In differential diagnosis, malignant melanoma, buphthalmus, axial myopia and coloboma should be considered. Penetrating keratoplasty and enucleation have a place in treatment.

Case Report

A 64-year-old male patient was admitted to our clinic complaining of pain in his left eye. His left eye was normal. Written consent was obtained from the patient. A detailed history of the patient found out that he had a history of trauma to the left eye 3 years ago. A metal object ricocheting off a car bomb detonated in Somalia hit his left eye. He later described being admitted to a local clinic in the area where he was found and the metal object was removed from his eye and his eye was covered with tight bandages. Afterwards, he was diagnosed with post-traumatic fungal keratitis at another eye clinic he had been admitted to, but he had not responded to treatment. After a long time, the patient was brought to our clinic by his relatives.

In a detailed eye examination, the best adjusted visual acuity was 10/10 in the right eye and the level of light sensation in the left eye. On a biomicroscopic examination, the right cornea was transparent, the crystallized lens was natural, and the anterior chamber was shaped. The patient had a giant anterior staphyloma in his left eye that prevented

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the eyelids from closing (Figure 1, 2). Crystallized lens and fundus in the same eye could not be evaluated. The intraocular pressure in the right eye was 19 mmHg with the Goldmann aplanation tonometer. In the schiotz tonometer measurement, the left intraocular pressure was 26 mmHg.

The patient had no history of systemic disease. Computed tomography showed no foreign body and the lens was in normal position, the distance between the lesion endpoint and the lens was 7.17 mm (Figure 3).

The patient was diagnosed with total anterior staphyloma, a rare pathology of the anterior segment that occurs as a result of protrused uveal tissue from the damaged area of the cornea or sclera as a result of trauma or corneal ulcer. Sclero-keratoplasty was recommended for treatment. Because the patient did not accept surgery, he was given brimonidine and dorzolamide + timolol eye drop treatment due to the height of intraocular pressure.

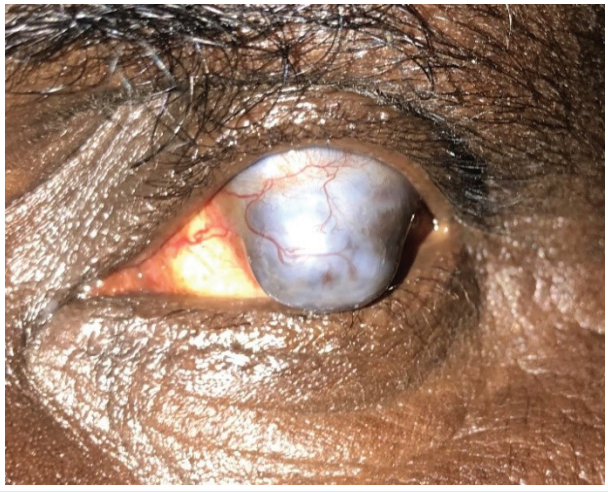

Figure 1. Anterior staphyloma, vascularized, white in color

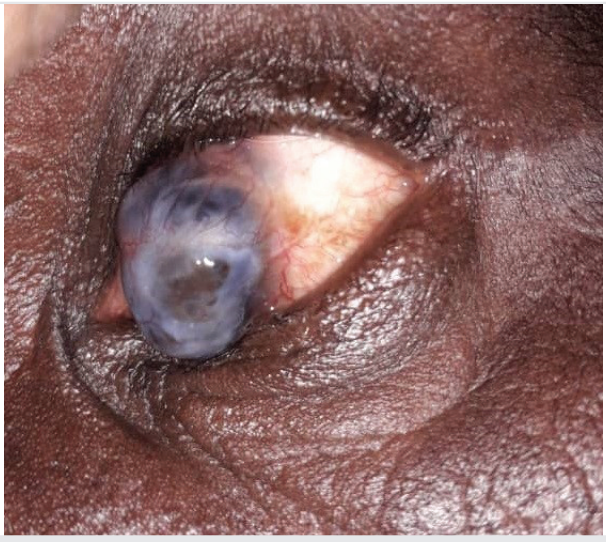

Figure 2. Lateral appearance of anterior staphyloma in vascularized, white color

Discussion

Anterior staphyloma typically occurs in low-income countries due to lack of post-traumatic care followed by infectious keratitis (4). In this patient, a noticeable piece of metal after the bomb explosion punctured the ocular sphere and caused the uveal tissue to protrude from the cornea.

Similar to our case, anterior staphyloma occurs when corneal perforations are not treated or there is no response to treatment initiated due to penetrating injury. When the cornea becomes lasere, the iris clogs the incision site and forms a pseudocornea above the wound. Simultaneous increased intraocular pressure increases the protrusion of the iris (5).

Ocular trauma cannot be avoided, but its consequences can be avoided. From this point of view, first diagnosis and then treatment are very important. Anterior staphyloma treatment is usually based on removing the tissues that make up the staphyloma from the eyeball and restoring the eyeball using the sclero-keratoplasty technique (6). Currently, total anterior staphylomas are quite rare due to the ease of access to treatment.

Neovascular glaucoma, endophthalmia and uveal-choroidal melanoma are important in the differential diagnosis of anterior staphyloma. The fact that our patient complained of pain suggested that there may be a case of anterior staphyloma accompanied by neovascular glaucoma.

Uvea melanoma is the most common primary malignant intraocular neoplasm in adults, and the 10-year mortality after diagnosis and treatment is around 30-50% (7,8). The separation of anterior staphyloma from uveal malignant melanoma is very important both in terms of treatment and follow-up. The absence of pain in staphyloma is a clinically important finding in moving away from the diagnosis of malignant melanoma. But our patient complained of pain in the eye, suggesting the possibility of malignant melanoma. After anti-glaucomatous treatment, which we started due to high intraocular pressure, the eye pain had passed. This case has shown that we should be alert to the possibility of malignant melanoma in cases that look like a anterior staphyloma in appearance, but appear as a painful eye.

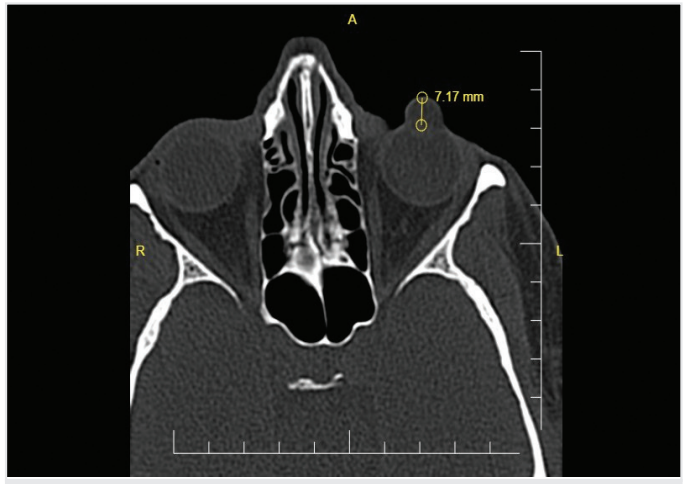

Figure 3. In computed tomography, the distance between the lesion endpoint and the lens is 7.17 mm

Conclusion

After open glob trauma, patients should be checked at short intervals for regular follow-up for ocular surface infections. The patient's ophthalmologist should regularly assess the patient's compliance with the drug and the eye's response to the drug. Early surgery should be sought if necessary to prevent the occurrence of eye complications such as anterior staphyloma. Uveal malignant melanoma should be kept in mind in painful eyes with total anterior staphyloma.

Ethics

Informed Consent: Written consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - İ.A.H., İ.A.K.; Concept - İ.A.K., M.K.; Design - İ.A.K., M.S.K.; Data Collection or Processing - İ.A.H.; Analysis or Interpretation - İ.A.H., İ.A.K., M.S.K., M.K.; Literature Search - İ.A.H.; Writing - İ.A.H., İ.A.K., M.K.

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Simultaneous Cranial Subarachnoid Hemorrhage-Subdural Hematoma and Spinal Subarachnoid Hemorrhage

Eşzamanlı Kraniyal Subaraknoid Kanama-Subdural Hematom ve Spinal Subaraknoid Kanama

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ABSTRACT

Patients with traumatic intracranial subarachnoid hemorrhage (SAH) rarely develop spinal subarachnoid hemorrhage (SSAH) without direct spinal injury. We present the case of a 76-year-old male patient with traumatic intracranial SAH and subdural hematoma, back pain and weakness in the both lower limbs radiating to the legs three days after the trauma. After worsening of pain and numbness, the patient underwent a lumbar magnetic resonance imaging 7 days after the trauma, in which blood was seen in the spinal canal in the lumbosacral region. The bleeding was considered SSAH because of the liquid level. The patient underwent conservative treatment because the patient was found to be at high cardiac risk and the neurological deficit was mild. In patients with traumatic intracranial hemorrhage and delayed pain or neurological deficits, SSAH should be suspected in the first period of trauma.

Keywords: Intracranial bleeding, spinal subarachnoid hemorrhage, back pain, magnetic resonance imaging

ÖZ

Çok nadiren, travmatik intrakraniyal subaraknoid hemorojisi (SAH) olan hastalarda, doğrudan omurga yaralanması olmadan spinal subaraknoid kanama (SSAH) ortaya çıkabilir. Travmatik intrakraniyal SAH ve subdural hematomu olan 76 yaşındaki erkek hastada, yoğun bakım takibi sırasında travmadan üç gün sonra bacaklarına yayılan sırt ağrısı ve bilateral alt ekstremitede güçsüzlük ortaya çıktı. Ağrı ve uyuşmanın kötüleşmesi üzerine, travmadan 7 gün sonra hastaya lomber manyetik rezonans görüntüleme yapıldı. Lumbosakral bölgede intraspinal kanama görüldü. Kanamanın sıvı seviyesi göstermesi sebebiyle SSAH olarak değerlendirildi. Hasta kardiyak açıdan yüksek riskli bulunduğu için ve nörolojik defisiti hafif olduğu için konservatif tedavi uygulandı. Travmatik intrakraniyal kanaması olan ve gecikmiş ağrı veya nörolojik defisitleri olan hastalarda, travmanın ilk döneminde, intraspinal kanamadan şüphelenilmelidir.

Anahtar Kelimeler: İntrakraniyal kanama, spinal subaraknoid kanama, sırt ağrısı, manyetik rezonans görüntüleme

Introduction

Spinal subdural hematoma (SDH) and traumatic spinal subarachnoid hemorrhage (SSAH) are rare, and the exact mechanism for their pathogenesis is not clearly understood (1). Spinal SDH is most common in the thoracic and thoracolumbar regions (1). The causes of spinal SDH-SSAH include hemorrhagic disorders, traumas, the transition of subarachnoid hemorrhage (SAH) to the subdural space, vascular malformation, anticoagulation use, spinal surgery, lumbar puncture, or spinal anesthesia (1,2). In addition, spinal tumors, diabetes, chronic kidney failure, and alcoholism have been reported as causes of spinal SDH (1). Traumatic intracranial bleeding can cause spinal bleeding without direct damage to the spine. Traumatic SSAH or spinal SDH is thought to be caused by the migration of intracranial traumatic SAH or SDH without direct spinal injuries (3).

There are a few reported cases with simultaneous cranial SDH-SAH and SSAH (3). In this article, we present a male patient with post-traumatic cranial SAH-SDH and simultaneous spinal SAH.

Case Report

A 76-year-old man is rushed to the emergency room for a head trauma, with a history of hypertension, diabetes, and coronary artery bypass surgery 20 years ago. The physical and clinical examinations revealed a temperature of 37.5 °C, pulse rate of 110 beats/min, blood pressure of 125/80 mmHg, respiratory rate of 19 breaths/min, and oxygen saturation

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of 96% at room air. On neurological examination, the general condition was medium, he was cooperative and orientated, was dysarthric, had a good comprehension, and a GCS of 15. His pupils were isochoric, and his eyes were free in all directions. He had no facial asymmetry, upper and lower extremity examination was unremarkable, he presented no motor and sensory loss, and the cerebellar tests were unremarkable. He was on aspirin but did not take anticoagulants. A brain computed tomography (CT) was performed to assess the patient's impaired consciousness; SAH was observed in both hemispheric cortical sulci, basal cystern, bilateral silvian and interhemispheric fissures (Figure 1). We found a 12 mm thick SDH in the left temporoparietal region (Figure 2). The patient was hospitalized in neurosurgery intensive care unit. No aneurysm was detected on cranial CT angiography. Three days after the trauma, he developed back pain radiating to his legs and weakness in the bilateral lower extremities. A lumbar magnetic resonance imaging (MRI) was performed on day 7 after the trauma to investigate the increased pain and numbness. On lumbar MRI, the L5-S2 vertebra corpus projections were leveled in the subarachnoid area, with mild hyperintensity on T1AG and mild hypointensity on T2AG, and a 50x10 mm SAH was detected (Figure 3). We proposed a conservative treatment instead of surgery due to his heart disease, signs of infection, and the mild neurological deficit. After one month of follow-up, the patient was discharged with no neurological deficit and a good mobilization and oral intake. We obtained an informed consent from the patient.

Discussion

Spinal SDH-SSAH usually occurs due to trauma, coagulopathy, vascular malformation, spinal puncture, lumbar instrumentation, and other invasive procedures, or may occur spontaneously (4). SSDH may occur in patients with traumatic intracranial SDH (3), and is most common in the thoracic region. It manifests as a sudden back pain radiating to the upper or lower extremities or trunk, and can cause motor dysfunction, sensory deficiency, and autonomic dysreflexes (5). It commonmy occurs in adults over 50 years old (1).

The spinal subdural space is avascular and a hemorrhage is thought to be from the subarachnoid region (1). This is supported by the presence of accompanying SAH in several cases with spinal SDH. When the arachnoid membrane is torn, bleeding from the subarachnoid space extends into the subdural space (5). If there is a rupture in the arachnoid, intracranial SDH leaks from the subarachnoid space to the arachnoid, this facilitates spontaneous resolution and migration of the SDH (3). Also, a raised intracranial pressure due to the intracranial SDH can push the hematoma directly into the skull base or spinal canal through the subdural space (1).

The spinal subdural space is void of large blood vessels or bridging veins that serve as a source for SDH (6). The simultaneous occurrence of cranial SAH and spinal SDH in different regions is extremely rare. The cranial SAH can extend to the spinal SAH and then through the arachnoid membrane to extend to the spinal subdural space. The opposite form, which moves from the spinal to the cranial region, can also be seen (6). In addition, the large amount of SAH extending from the cranium to the spinal area can compress the spinal cord or cause laceration in the arachnoid membrane, causing SSDH (1).

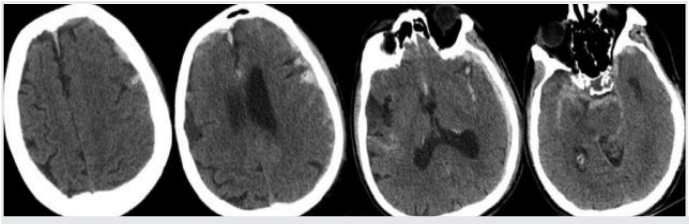

Figure 1. SAH is observed in bilateral hemispheric cortical sulcus, basal cystern, and bilateral silvian fissure and interhemispheric fissure

SAH: Subarachnoid hemorrhage

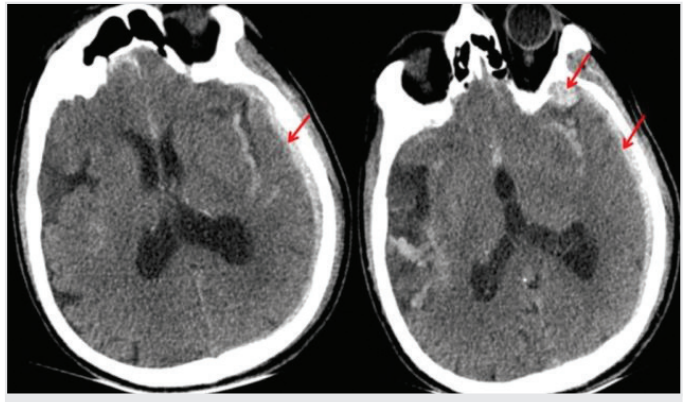

Figure 2. SDH is observed in the left temporoparietal (red arrow)

SDH: Subdural hematoma

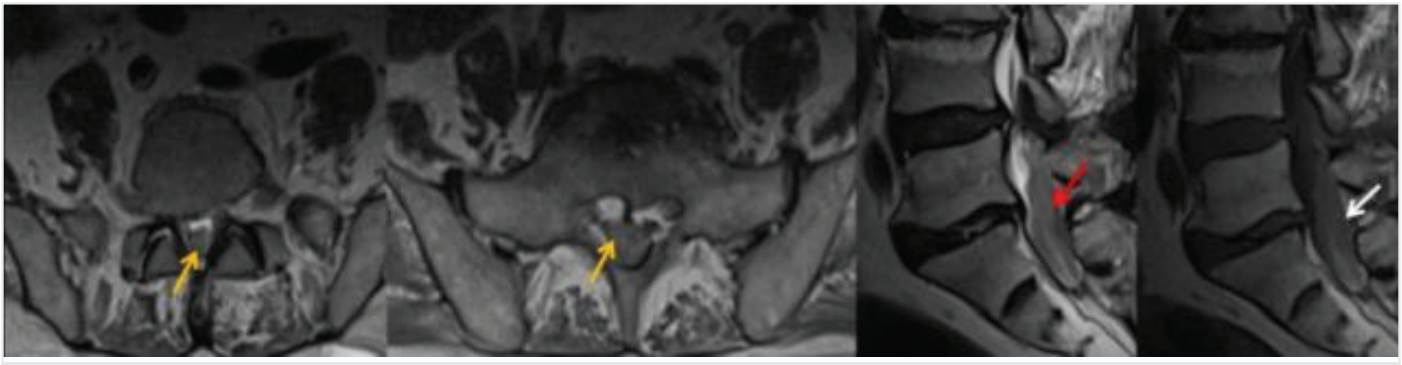

Figure 3. L5-S2 vertebral corpus projections at the level of the subarachnoid, mild hypointensities in T2AG on axial (yellow arrow) and sagittal (red) views, mild hyperintensities on the sagittal T1AG (white arrow), and SAH is observed

SAH: Subarachnoid hemorrhage

The anterior and posterior spinal cisternes are lined to the posterior cranial fossa cystern via the foramen magnum. Therefore, blood can pass from the intracranial subarachnoid to the spinal subarachnoid. This migration occurs most likely with large SAHs or after the patient's early uprising (7). The authors argued that blood in the intracranial subarachnoid space may migrate to the subarachnoid space in the most caudal part of the spinal canal (8). In this article, SSAH was detected in the lumbosacral region on a lumbar MRI done seven days later in the patient with traumatic intracranial SDH and SAH.

SSAH is located intradural extramedullary. It extends across multiple vertebral corpus levels and can also be seen as a focal clot. The hematoma typically shows the liquid-fluid level at the bottom of the dural sac or other dependant parts (thoracic vertebra in the supine position). However, a hematoma is located in the ventral spinal cord/cauda equina (9). SDHs are crescentric in shape, they do not show liquid-liquid leveling, and the dura dark signals separate this collection from the epidural adipose tissue. Spinal SDH and SAH can occur simultaneously (9).

Emergency decompressive surgery is the first treatment option for spinal SDH-SAH in patients with worsening neurological conditions. Conservative treatment is a good option for patients with minimal neurological disorders (3), which has been be proven to have a good clinical outcome (6). Syringomyelia SSAH and arachnoid cysts associated with arachnoiditis are rare complications (10).

Patients with traumatic brain injury may present with delayed spinal bleeding. Patients presenting with traumatic intracranial SAH or SDH with delayed pain or neurological deficits should be evaluated immediately for spinal SAH or SDH in the first period of trauma, even in the absence of symptoms of direct spinal injury or spinal injury.

Ethics

Informed Consent: Written informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - H.K., V.K.; Concept - A.T.; Design - H.K., O.K.; Data Collection or Processing - H.K., V.K., O.K.; Analysis or Interpretation - H.K., V.K.; Literature Search - H.K., A.T.; Writing - H.K., O.K.

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

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