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New targets for Turkish childhood national immunization schedule

Türkiye'de çocukluk çağı ulusal aşı takviminde yeni hedefler

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Abstract

Aim: The National Immunization Schedule (NIS) of Childhood has high coverage, but the administration of non-NIS vaccines (rotavirus, human papilloma virus, meningococcal, influenza, adult type pertussis vaccines [Tdap]) is not widespread in Turkey, despite recommendations by immunization experts. This report intended to explore the administration rates of these vaccines and their reasons in this province.

Methods: This questionnaire based cross-sectional study was conducted in a small city in middle northern Turkey. The target population was the family physicians of this city. The participants filled a survey containing questions about their sociodemographic and professional features and attitudes about non-NIS vaccines via email or telephone interviews.

Results: Seventy-eight (72%) of 108 physicians were enrolled in the study. The most and least recommended vaccines in daily practice and for addition to NIS were rotavirus and Tdap vaccines, respectively. The main reason of not administrating non-NIS vaccines was lack of knowledge and experience.

Conclusion: Vaccination is the safest and cheapest way of protecting from infectious diseases. Family physicians are the leaders of these procedures in the field. Education should be provided to help them reach current knowledge regarding immunizations. Community pediatricians can provide expert consultation. These vaccines should be covered by social security.

Keywords: Immunization, Family physician, Attitude

Öz

Amaç: Türkiye'de Çocukluk Çağı Ulusal Bağışıklama Programının kapsayıcılığı yüksektir; bu programda yer almayan rotavirüs, human papilloma virüs, meningokok, influenza ve erişkin tip boğmaca aşılarının uygulaması bağışıklama ile ilgili uzmanlar tarafından önerilmesine rağmen yaygın değildir. Bu çalışmada bu aşıların uygulanma oranının ve nedenlerinin belirlenmesi hedeflendi.

Yöntemler: Ankete dayalı kesitsel bir çalışma olarak planlanan bu çalışma Orta Kuzey Anadolu'da küçük bir il merkezinde aile hekimleri ile yürütüldü. Katılımcılar tarafından elektronik posta veya telefon görüşmeleri ile sosyodemografik ve mesleki özelliklerini, Çocukluk Çağı Ulusal Aşı Programı dışındaki aşılar konusunda tutumlarının sorulduğu anket formları dolduruldu.

Bulgular: Çalışmaya 108 aile hekiminin 78'i (%72) katıldı. Rotavirus aşısı hem günlük çalışma hayatında, hem de Ulusal Aşı Takvimi'ne dahil edilme önerisi konusunda en yaygın aşı idi. Tdab her iki durumda da en az önerilen aşı idi. Takvimde olmayan aşıların uygulanmaması konusunda en sık neden olarak hekimlerin konuyla ilgili bilgi ve deneyimlerinin yetersiz olması saptandı.

Sonuç: Aşılar enfeksiyon hastalıklarından korunmanın en güvenilir ve ucuz yoludur, bu hizmetlerin sahada yürütülmesini sağlayan kaptanlar aile hekimleridir. Onların bağışıklama ile ilgili güncel bilgi ve gelişmelere ulaşmasını sağlamak için eğitim programları düzenlenmelidir. Çocuk sağlığı izlemelerinde Sosyal Pediatri hekimleri bağışıklama konusunda danışmanlık verebilir. Ek olarak, bu aşılar sosyal güvenlik sisteminin geri ödeme kapsamına alınmalıdır.

Anahtar kelimeler: Bağışıklama, Aile hekimi, Tutum

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Etik Kurul Onayı: Amasya Üniversitesi, Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu (karar no: 15386878-044; toplantı tarihi: 5 Aralık 2019) çalışmayı onayladı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Introduction

The morbidity and mortality of infectious diseases can be reduced with high immunity rates. Vaccines provide simple, reliable, cheap, and effective ways for improvement of public health, and they are the most available means of protection from infectious diseases [1]. In Turkey, the National Immunization Schedule (NIS) is implemented meticulously under the control of Health Ministry of Turkish Republic (HMTR). The NIS includes vaccines against thirteen diseases [2]. All vaccines are supplied and administered freely at primary health care centers by family physicians. Although rotavirus (RVV), human papilloma virus (HPVV), adult type pertussis (Tdap), influenza and conjugated meningococcal vaccines are licensed and available for procurement, they are not included in NIS and defined as "non-NIS vaccines." Their administration is voluntary, and costs are covered by families themselves. The application depends on the recommendation of physicians or the requisition of the families. Although these immunizations are strongly advocated, lack of knowledge about the diseases or immunization facilities, safety concerns, personal beliefs, other priorities, and financial problems are the impediments of non-NIS vaccines [3]. The rate of recommendation and application of non-NIS vaccines are lower than expected, even in developed countries and Turkey [4,5].

Rotavirus infection is a common agent of pediatric acute gastroenteritis, with a prevalence of 22.5% in Turkey [6]. The prevalence is similar in developed and undeveloped countries, which reveals that improved sanitary conditions are insufficient in preventing the infection. It is more frequent in children under five years of age and causes electrolyte imbalance with dehydration [7]. More than 2.7 million episodes of diarrhea, 400,000 outpatient office visits, and 55,000–70,000 hospitalizations per year are attributed to rotavirus in the United States (US) [8]. Vaccination is cost-effective and reduces the disease burden [9,10]. Advisory Committee on Immunization Practices (ACIP) recommends the vaccine to all infants unless contraindicated [7].

Meningococcal disease is an acute, potentially severe, and mortal illness caused by *Neisseria meningitidis.* It is one of the leading causes of bacterial meningitis and sepsis with high morbidity and mortality. Immunodeficiencies related with complement pathway or asplenia are risk factors for invasive meningococcal disease (IMD) [7]. It was the most common agent of bacterial meningitis in Turkey with the serogroups of W-135 (38.1%), B (26.1%), A (8.4%), Y (0.9%) and non-groupable strains (26.4%) [11]. In addition, nasal carriage, which is the most important notion in the epidemiology of IMD rate, is also remarkable, and the serogroup distribution is similar to disease-causing agents [12]. Meningococcal seroepidemiology of Turkey is different from other countries as serogroups W and B are the predominant strains of IMD during childhood. Serogroup C has not been reported for years. The adolescent peak is not observed, and the infection is more common under five years of age [11,12]. Two types of vaccines containing serogroups MenACWY and serogroup MenB are recommended for Turkey. MenACWY is administered to candidate pilgrims before Hajj as one of the travel vaccines, which is one of the finest ways to prevent nasal carriage [12].

HPV infections are usually asymptomatic, but clinical manifestations include anogenital warts, recurrent respiratory papillomatosis, cervical intraepithelial neoplasia, genital and oropharyngeal cancers [7]. As it is one of the most common agents of sexually transmitted disease (STD), it is recommended before the onset of sexual activity. That is why adolescent coverage of the immunization is particularly important [7]. The prevalence of HPV and annual cervical cancer in women is 4.2-25% and 1.43/100000, respectively [13]. HPV is known as one of the preventable reasons of cancer.

Pertussis is one of the frequent reasons of lower respiratory tract infections in infants (LRTI). It causes severe respiratory distress with paroxysms of rapid coughs in infants and prolonged coughing attacks in adolescents. Neither having the infection nor vaccination provides lifelong immunity, but the severity of symptoms decreases with increasing age. People with mild symptoms may transmit the infection to susceptible individuals, such as unimmunized or incompletely vaccinated infants. Acellular pertussis vaccine cannot be administered before six weeks of age and at least three doses are necessary for protection [7]. Tdap is usually recommended to adolescents, pregnant women and adults who are in contact with infants to form a "cocoon" around them. The last dose of tetanus vaccination (Td) during pregnancy or adolescent dose of Td can be administered as Tdap [14,15].

Seasonal influenza is a preventable, highly contagious infection and it can result in fatal complications in risky populations. It is a public health problem because the infection increases heath care costs while causing loss of labor and school time [16]. The infection can be complicated with LRTI in infants or children with chronic illnesses such as asthma, congenital heart diseases, immune deficiency, diabetes, etc. Influenza vaccination is recommended to all children aged between 6-59 months and every individual with a chronic health problem [7]. It should be considered as one of the components of cocooning strategy with Tdap [7,17]. Protection from these high-burden infections via non-NIS vaccines is possible because vaccines are available and strongly recommended. However, in Turkey, their coverage and recommendation are low. Primary healthcare workers are the main leaders of immunization services in the field and their attitude about the new applications in public health is important. The aim of this study is to determine the recommendation rate of non-NIS vaccines and the attitude of family physicians about these administrations in our province.

Materials and methods

This study was designed as a cross-sectional study based on a survey. It was conducted with the family physicians working at the primary health care centers of Amasya, a small city in middle northern Turkey, between December 15, 2019 and May 15, 2020. The data source of the study was a non-standardized questionnaire prepared by the researcher by summarizing the literature, comprising six sections with 35 questions (Appendix 1). The questions were about sociodemographic and professional features of the attendees, their knowledge and attitude about RVV, HPVV, Tdap,

influenza and meningococcal vaccines, experience about the related diseases and their personal intentions about the inclusion of each vaccine to NIS. Complicated diseases were defined as "cases requiring treatment by hospitalization due to clinical condition or laboratory abnormalities such as electrolyte imbalance." The researcher reached each physician by phone and asked whether they wanted to take part in the study. The questionnaires were filled via email or on-call interviews with the physicians who accepted to enroll. Informed consent was obtained before answering the questions.

Ethics

This study was approved by the Ethics Committee of Non-Invasive Clinical Research of the Amasya University with a decision number: 15386878-044 in December.

Statistical analysis

The analyses were performed with a statistical package program (SPSS v15.0 [SPSS Inc., Chicago, IL, USA]). Descriptive statistics were presented as frequency, percentages, arithmetical mean (standard deviation) (arithmetical mean [SD]), and median (minimum, maximum). Nominal variables were compared with Pearson's chi-square, Yate's corrected chi-square, and Fisher's exact test as appropriate. The distribution patterns of the variables were investigated by visual/analytical methods (Kolmogorov-Smirnov test/histograms). A p-value of less than 0.05 was considered statistically significant. The answers such as "I do not know" or "I do not have an idea" were accepted as not answered.

Results

In Amasya, the total number of family physicians is 108, and all were asked to enroll in the study. The researcher could not communicate with two physicians, ten physicians could not participate because of health problems and eighteen physicians were unwilling. Seventy-eight of 108 family physicians enrolled in the study, the participation rate was 72%. None of the physicians who filled the questionnaires was excluded from the study. The median age of the participants was 44 years (min-max: 27-65 years) and the median of active professional time was 20 years (min-max: 3-37 years). Fifty-three (67.9%) of the participants were males and 52.6% (n=41) were working in urban areas.

Seventeen (21.8%) participants declared that their knowledge about non-NIS vaccines was sufficient and 18 (23.1%) had received courses on the subject. RVV was the most prescribed vaccine (n=35; 45.5%) and the main source of recommendation was family will. Tdap was the least prescribed vaccine due to lack of knowledge and experience (n=43; 55.9%).

All participants (n=78) completed the RVV part of the survey. The estimated average rate of complicated acute gastroenteritis was 20%, half of which was attributed to RV infection. The average number of prescriptions per year was 4, and 38 (48.7%) of the participants had not prescribed RVV in the previous year. The most frequent reason of not prescribing RVV was lack of knowledge and experience about the vaccine (n=18; 38.3%). Fifty-two (66.7%) of the participants declared that they recommended the vaccine to their own siblings and relatives, 43 (55.1%) believed that RVV should be included in NIS.

The participation rate in questions about meningococcal vaccines was 100% (n=78). Twenty-three (29.5%) participants observed meningococcal disease during their education or professional time. Sixty-three (80.8%) participants had not prescribed meningococcal vaccines in the previous year. The main reason of not prescribing was lack of knowledge and experience about the vaccine (n=41; 52.5%). Fifty-five (70.5%) participants declared that they recommended the vaccine to their own siblings and 59% (n=46) thought that meningococcal vaccines should be included in NIS.

Seventy of the seventy-eight physicians answered the question about HPV infections. Thirty-two (41%) had HPV infected patients and 19 (24.4%) had patients with HPV-related malignancies. All participants answered the questions about the vaccine. The maximum number of vaccine prescriptions per year was five, and 66 (84.6%) participants had not prescribed the vaccine in the previous year. The main reason of not prescribing was lack of knowledge and experience about the vaccine (n=43; 55.1%). Forty-nine (62.8%) participants declared that they recommended the vaccine to their own siblings and relatives. Forty-one (52.6%) thought that HPV should be included in NIS.

All participants answered the Tdap section of the questionnaire. The estimated average acute LRTI and hospitalization rates were 10% and 5%, respectively. None of the participants had prescribed Tdap in the previous year due to lack of knowledge and experience about the vaccine (n=43; 55.1%). Thirty-two (41%) participants declared that they recommended the vaccine to their own siblings and relatives and 32 (41%) considered that Tdap vaccine should be included in NIS. The target population was declared as pregnant women by 6.4% (n=5), adolescents by 3.8% (n=3), and both by 31.1% (n=24).

The participation rate to the influenza section was 100%. The estimated average acute upper respiratory tract infection (URTI) and hospitalization rates were 26.5% and 10%, respectively. The average number of prescriptions per year was five and 24 (30.7%) participants had prescribed the influenza vaccine in the previous year. However, 48 (61.5%) physicians did not prescribe the vaccine, and 32% (n=25) of the non-prescribers declared that they thought pediatricians should recommend the vaccine. Forty-five (57.7%) participants declared that they recommended the vaccine to their own siblings and relatives and 25 (32.1%) believed that influenza vaccines should be included in NIS.

The gender, working place, age, and duration in the profession had no significant effect on recommending non-NIS vaccines and their addition to NIS (Table 1 and Table 2). At the end of the questionnaire, the participants were asked which vaccine they would recommend for addition to NIS if they were a member of the advisory committee of immunization of HMTR. RVV was the most popular answer to this question (n=20; 25.6%) and the reason was that the infection is common and complicated both for children and their parents.

Table 1: The sociodemographic, professional features of the family physicians and their recommendation rate of non-NIS vaccines to patients

	Rotavirus Vaccine Recommend/ Do not recommend		HPV Vaccine Recommend/ Do not recommend		Meningococcus vaccine Recommend/ Do not recommend		Influenza vaccine Recommend/ Do not recommend		Tdap vaccine Recommend/ Do not recommend	
Gender	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	19 (35.8%)/ 34 (64.2%)	12 (48%)/ 13 (52%)	4 (7.5%)/ 49 (92.5%)	5 (20%)/ 20 (80%)	8 (15.1%)/ 45 (84.9%)	6 (24%)/ 19 (76%)	16 (30.2%)/ 37 (69.8%)	8 (32%)/ 17 (68%)	0	0
P-value	0.43		0.22		0.52		0.87			
Working place	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural
	19 (46.3%)/ 22 (53.7%)	12 (32.4%)/ 25 (67.6%)	5 (12.2%)/ 36 (87.8%)	4 (10.8%)/ 33 (89.2%	9 (22%)/ 32 (78%)	5 (13.5%)/ 32 (86.5%)	15 (36.6%)/ 26 (63.4%)	9 (24.3%)/ 28 (75.7%)	0	0
P-value	0.31		0.85		0.50		0.35			
Age	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old
	16 (39%)/ 25 (61%)	15 (40.5%)/ 22 (59.5%)	3 (7.3%)/ 38 (92.7%)	6(16.2%)/ 31 (83.8%)	5 (12.2%)/ 36 (87.8%)	9 (24.3%)/ 28 (75.7%)	12 (29.3%)/ 29 (70.7%)	12 (32%)/ 25 (67.6%)	0	0
P-value	0.90		0.22		0.27		0.76			
Professional time	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years
	17 (35.4%)/ 31 (64.6%)	14 (46.7)/ 16 (53.3%)	4 (8.3%)/ 44 (91.7%)	5 (16.7%)/ 25 (83.3%)	7 (14.6%)/ 41 (85.4%)	7 (17.9%)/ 23 (76.7%)	14 (29.2%)/ 34 (70.8%)	10 (33.3%)/ 20 (66.7%)	0	0
P-value	0.45		0.45		0.50		0.90			

Table 2: The sociodemographic, professional features of the family physicians and their attitude about addition of non-NIS vaccines to NIS

	Rotavirus Vaccine to NIS Yes/No		HPV Vaccine to NIS Yes/No		Meningococcus vaccine to NIS Yes/No		Influenza vaccine to NIS Yes/No		Tdap to vaccine NIS Yes/No	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
	26 (49.1%) 12 (22.6%)	17 (68%)/ 4 (16%)	25 (47.2%)/ 14 (26.4%)	16 (64%)/ 5 (20%)	29 (54.7%)/ 7 (13.2%)	17 (68%)/ 3 (12%)	13 (24.5%)/ 22 (41.5)	11 (44%)/ 7 (28%)	21 (39.6%)/ 20 (37.7%)	11 (44%)/ 9 (36%)
P-value	0.28		0.37		0.31		0.13		0.53	
Working place	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural
	21 (51.2%)/ 8 (19.5%)	22 (59.5%)/ 8 (21.6%)	17 (41.5%)/ 12 (29.3%)	24 (64.9%)/ 7 (18.9%)	23 (56.1%)/ 5 (12.2%)	23 (62.2%)/ 5 (13.5%)	12 (29.3%)/ 12 (29.3%)	12 (32.4%)/ 17 (45.9%)	16 (39%)/ 15 (36.6%)	16 (43.2%)/ 14 (37.8%)
P-value	0.35		0.20		0.63		0.26		0.81	
Age	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old	≤40 years old	>40 years old
	26 (63.4%)/ 9 (22%)	17 (45.9%)/ 7 (18.9%)	27 (65.9%)/ 8 (19.5%)	14 (37.8%)/ 11 (29.7)	29 (70.7%)/ 5 (12.2%)	17 (45.9%)/ 5 (13.5%)	12 (29.3%)/ 19 (46.3%)	12 (32.4%)/ 10 (27%)	17 (41.5%)/ 16 (39%)	15 (40.5%)/% 13 (35.1%)
P-value	0.11		0.08		0.09		0.20		0.73	
Professional time	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years	≤20 years	>20 years
	28 (58.3%)/ 12(25%)	15 (50%)/ 4 (13.3)	30 (62.5%)/ 10 (20.8%)	11 (36.7%)/ 9 (30.0%)	32 (66.7%)/ 6 (12.5%)	14 (46.7%)/ 4 (13.3%)	14 (29.2%)/ 20 (41.7%)	10 (33.3%)/ 9 (30%)	20 (41.7%)/ 18 (37.5%)	12 (40%)/ 11 (36.7%)
P-value	0.10		0.15		0.26		0.40		0.46	

Discussion

The coverage of non-NIS immunizations is low in the world and in our city. Although most of the participants recommended these vaccines to their relatives and approved their inclusion in NIS, the recommendation rate was exceptionally low. This study established that most of the family physicians in our province lacked knowledge about non-NIS vaccinations. The financial burden and need of expert consultation were the other reported significant problems in this study. Rotavirus was the most recommended vaccine, like the other studies conducted in Turkey [5]. RV causes a highly contagious infection, and the dissemination chain cannot be broken easily because the virus is resistant to sanitary precautions. Therefore, vaccination is the most effective way of protection. However, concerns about the safety, cost, efficiency, and efficacy of the vaccine reduce recommendation and administration rates. Many healthcare workers think that acute gastroenteritis can cause serious problems unless well treated, but vaccination is not considered a priority [18]. The vaccines are safe and efficient in reducing the severity of the symptoms and the cost-effectiveness of the vaccine was established by several studies [7,9]. However, the rates of recommendation and administration were much lower than desired in this study.

Meningococcal vaccines were the second highest recommended and offered vaccine for NIS in this study group. While most physicians had no clinical experience, the high morbidity and mortality rates intimidate the physicians. In Turkey, nasal carriage is high and Hajj season is important. The vaccine is recommended in immune deficiency, but passive smoking, crowded family life, and upper respiratory tract infections can facilitate the infection, which make it a significant public health problem [7]. In another study, the physicians stated that the reason of hesitation was that the serotypes of the agent in Turkey were not fully compatible with the vaccine content. Children must be vaccinated with both Men ACWY and Men B for protection. Two different vaccines for one disease increase the cost and injections [5]. However, insufficient knowledge and expert consultation requirement were the most common reasons of not recommending this vaccine in this study group.

HPV vaccine was not recommended frequently, but the physicians declared that it should be added to NIS because the infection rate is high, and the potential of malign transformation cannot be neglected. The most common reason for not offering was lack of knowledge and experience about the vaccine. In the literature, the barriers against HPV vaccination are cost of the vaccine, concerns about adverse effects and parental concerns of the vaccine rendering sexual activity easier and influencing it to happen at an earlier age. In developing countries, adolescent marriages must be considered as early sexual activity [7]. The rate of recommendation was 45.6% in Turkey, and the reasons for not recommending were the cost and not considering HPV a priority [5]. In Japan, the coverage of HPV vaccine (HPVV) was around 70.6% when it was first introduced to NIS but dropped to 0.6% because of adverse events following immunization [19]. In

another study from Japan, the recommendation rate of HPVV was 21%, although 53% of participants declared the necessity of immunization [20]. The effectiveness of the vaccine is high, so opportunities to prevent cancer should be seized [7]. Women's and children's health are the indispensable parts of public health.

Tdap is a new vaccine in the Turkish market. In many studies, it is the least recommended vaccine because the knowledge and experience about it is limited [5,21]. Although Tdap is recommended as the last dose of Td in childhood-adolescent and pregnancy immunization schedules in developed countries [22], pertussis was not considered a primary healthcare problem [5]. As mentioned before, it is a part of cocooning strategy for the sake of infants who are at risk of severe, complicated LRTI [17].

Seasonal influenza vaccination is recommended to every individual who is at risk of complicated infection, including chronically ill people, pregnant women, children under five years of age, people who have to work in crowded places and may have role in the transmission of the infection in the society such as health care workers, nursery staff, etc. [7]. The coverage of influenza vaccination is lower than expected in adolescents as it is available as "voluntary vaccine" in Japan and supplied by the families with charge [20]. Adolescent vaccination is a part of cocooning strategy of infants for influenza and pertussis unless there is a risk factor for the receiver [7]. In the USA, it is recommended to all children [22]. In Turkey, influenza is under the cover of social security insurance in chronically ill people and the recommendation of the vaccine is usually limited with this population [21]. It is recommended to healthcare workers, too; the acceptance rate was under 50% even in the pandemic season due to disbelief in the necessity of vaccination, concerns about adverse effects, inability to get vaccinated, debates about the vaccine [23]. In this study, family physicians declared that they needed expert consultation for influenza immunization.

In the literature, there are some studies revealing that gender, working place or age and active professional time significantly affect the recommendation of some vaccines. For example, HPVV and Tdap were recommended by female physicians more frequently than male physicians. HPPV is one of the main reasons of gynecologic cancers and Td is in the routine schedule of pregnancy immunizations, which may have increased the awareness of female physicians on the subject. In addition, younger physicians who are new in their professions tend to recommend new vaccines which may be related with possessing current information about immunization [5,24]. However, in this study, none of these variables had statistically significant effects on recommending non-NIS vaccines.

The attitude of physicians about recommending the non-NIS vaccines to their relatives establish their opinion about the vaccine and their attitude about the addition of vaccines to NIS [25]. In this study, approximately 60% of the physicians recommended RVV, HPVV, meningococcus and influenza vaccines to their relatives and their attitudes about addition of these vaccines to NIS were similar. However, Tdap was the least recommended vaccine to their relatives and NIS, which may be related with lack of knowledge and experience about Tdap since it is relatively new for Turkey.

Limitations

This study established the attitude of family physicians, the leaders of immunizations services in the field, about non-NIS vaccines. However, the study setting was a small city and participation was limited. The data were obtained by a non-standardized survey based on personal declaration during that limited time. The limited number of participants and the survey, although it was prepared after reviewing the literature, were the sources of bias in this study. Also, pediatricians were not included. These limitations make it difficult to generalize the results. New multi-center studies with broad participation and standardized investigation tools should be planned.

Conclusion

Family physicians should be educated, and immunizations should be administered under the coverage of social security insurance to increase the recommendation of non-NIS vaccines. Current affairs should be shared at the formal websites of the HMTR and stakeholders. Community Pediatrics should be approved as a subspecialty of Pediatrics in Turkey and immunization consultation should be managed with family physicians at the primary health care centers during pediatric control visits. The patients should not visit hospitals, which carry disease burdens, for these procedures. In addition, families should be aware of the immunization opportunities of their children to benefit from these services. Family physicians have important roles in detecting the priorities of public health and their attitude about new vaccines is important. The authorities believe that adding a new vaccine to NIS is a right and chance for every child to become a healthy individual, and it is everyone's duty to build up herd immunity.

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The utility of mean platelet volume as a predictor of postoperative atrial fibrillation following coronary artery bypass grafting

Koroner arter baypas greftleme sonrası postoperatif atriyal fibrilasyonun bir prediktörü olarak ortalama trombosit hacminin kullanımı

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Abstract

Aim: Atrial fibrillation is the most common arrhythmia following coronary artery bypass grafting (CABG). The predictors of postoperative atrial fibrillation (POAF) following CABG are controversial. The aim of this study was to evaluate the predictivity of mean platelet volume (MPV) in the development of atrial fibrillation following CABG and other risk factors affecting POAF.

Methods: A total of 227 patients who underwent on-pump CABG in the cardiovascular surgery department of our hospital between May 2016 and January 2019 were included in this retrospective cohort study. Patients were divided into two groups as those who underwent POAF and those who did not (non-POAF group). Patients' demographic data such as age, gender, height, weight and BMI, biochemical parameters, comorbidities, smoking status, ejection fraction, the number of bypassed vessels, the use of intra-aortic balloon pump and inotropic agents, total drainage, neurological and other complications, operation time, duration of admission in intensive care unit and in the ward, and mortality status were recorded and comparatively analyzed.

Results: No statistically significant differences were found between the groups in terms of gender, body mass index, the incidences of diabetes mellitus, hypertension, chronic obstructive pulmonary disease, pulmonary arterial hypertension, renal failure, smoking status, the number of bypassed vessels, the use of intra-aortic balloon pump, inotropic agents, and biochemical parameters (P<0.05 for all) except red cell distribution width (RDW), urea and mean platelet volume (MPV). MPV, RDW and urea values were significantly higher in the POAF group (P=0.004, P=0.018 and P=0.006, respectively). Multivariate regression analysis revealed that age, MPV and the amount of total drainage were independent risk factors for developing POAF (OR=1.080, OR=1.371, OR=1.001; P=0.001, P<0.001, P=0.024, respectively).

Conclusion: MPV can be used as a predictor for the development of POAF following on-pump CABG. MPV is a quite simple parameter, which can be readily obtained in routine complete blood count. However, our results should be supported by further prospective, multicenter and large-scale studies.

Keywords: Postoperative atrial fibrillation, Mean platelet volume, Coronary artery bypass grafting, Biochemical parameters

Öz

Amaç: Atriyal fibrilasyon koroner arter baypas greftleme (KABG) sonrası en sık görülen aritmidir. CABG'yi takiben postoperatif atriyal fibrilasyonun (POAF) belirleyicileri tartışmalıdır. Bu çalışmanın amacı, CABG'yi takiben POAF gelişimi ve POAF'ı etkileyen diğer risk faktörleri için ortalama trombosit hacminin (MPV) kullanımını değerlendirmektir.

Yöntemler: Bu retrospektif kohort çalışmamıza Mayıs 2016-Ocak 2019 tarihleri arasında hastanemizin kardiyovasküler kliniğinde pompalı CABG uygulanan toplam 227 hasta dahil edildi. Hastalar, POAF ve POAF olmayan gruplar olarak iki gruba ayrıldı. Hastaların yaş, cinsiyet, boy, kilo ve BMI gibi demografik verileri, biyokimyasal parametreler, komorbiditeler, sigara içme durumu, ejeksiyon fraksiyonu, baypas edilen damar sayısı, aort içi balon pompası (IABP) ve inotropik ajanlar, toplam drenaj, nörolojik ve diğer komplikasyonlar, operasyon süresi, yoğun bakım ünitesinde ve koğuşta yatış süresi ve mortalite durumu kaydedildi ve karşılaştırmalı olarak analiz edildi.

Bulgular: Gruplar arasında cinsiyet, vücut kitle indeksi, diabetes mellitus insidansı, hipertansiyon, kronik obstrüktif akciğer hastalığı, pulmoner arteriyel hipertansiyon, böbrek yetmezliği, sigara içme durumu, baypas edilen damar sayısı, IABP, inotropik ajanlar ve biyokimyasal parametreler (kırmızı hücre dağılım genişliği (RDW), üre ve MPV hariç anlamlı bir fark bulunmadı. MPV, RDW ve üre değerleri POAF grubunda POAF olmayanlara göre istatistiksel olarak anlamlı derecede yüksekti (sırasıyla P=0,004, P=0,018 ve P=0,006). Çok değişkenli regresyon analizinde, yaş ve toplam drenaj miktarı POAF gelişiminin bağımsız risk faktörleri olarak bulundu (sırasıyla OR=1,080, OR=1,371, OR=1,001; P=0,001, P<0,001, P=0,024).

Sonuç: MPV, pompalı CABG'yi takiben POAF gelişimi için bir belirteç olarak kullanılabilir. MPV, rutin tam kan sayımında kolayca elde edilebilen oldukça basit bir parametredir. Ancak, sonuçlarımız prospektif, çok merkezli ve büyük ölçekli çalışmalarla desteklenmelidir.

Anahtar kelimeler: Postoperatif atriyal fibrilasyon, Ortalama trombosit hacmi, Koroner arter baypas greftleme, Biyokimyasal parametreler

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Introduction

Postoperative atrial fibrillation (POAF) is the most common arrhythmia following coronary artery bypass grafting (CABG). The incidence of POAF has been reported between 10% and 40% after CABG operation [1,2]. Although it is usually self-limiting, POAF is an important predictor of morbidity and mortality and increased healthcare costs. POAF is accompanied by cerebrovascular accidents, increased cardiac insufficiency and decreased left ventricular hemodynamic performance [3,4]. The risk of POAF following cardiac surgery is also influenced by several pre-existing cardiac and pulmonary disorders in addition to epidemiological and intraoperative factors. There are studies in the literature investigating the reasons underlying POAF [5]. The most commonly reported risk factor for POAF is age [6]. The other reported risk factors include male gender, low ejection fraction, chronic obstructive pulmonary disease, chronic renal dysfunction and preoperative withdrawal of beta-blockers [7,8]. However, there is no an exact consensus on the risk factors affecting the development of POAF.

Platelets are associated with thrombosis and inflammation, both of which play crucial roles in the pathogenesis of AF [9]. Large platelets increase thrombotic potency. The mean platelet volume (MPV), which corresponds to the average platelet size in the blood, is a readily measurable marker for reflecting platelet activation. MPV increases with the production of platelets. An elevated MPV level shows a higher tendency of coagulation in the blood, which increases the risk of thrombosis, stroke and cardiovascular disease [10]. MPV is a focus of interest as an independent cardiovascular risk factor. Recently, the mean platelet volume, a parameter that is routinely detected in complete blood count and is usually not paid attention to by clinicians, has been examined as a new expression of markers in several diseases including atherosclerosis, cerebral infarction and active inflammatory disorders [11,12]. Easy availability of MPV measurement without any additional cost encourages its wider use in clinical practice. MPV values have been found higher in persons with increased cardiovascular risk [13]. However, the number of studies investigating the relationship between MPV and the development of postoperative AF is limited [2,14]. Therefore, the objective of this study was to retrospectively evaluate the practicability of MPV level for the development of POAF following CABG and the other risk factors affecting POAF.

Materials and methods

Patient population & study design

A total of 227 patients who underwent coronary artery bypass grafting operation in the cardiovascular clinic of our hospital between May 2016 and January 2019 were included in this study. Preoperative standard 12-lead electrocardiography was routinely obtained in all patients and those with sinus rhythms were enrolled in the study. Patients were divided into two groups as those who developed postoperative AF and those who did not (POAF group and non-POAF group). Patients' demographic data such as age and gender, height, weight and BMI values, biochemical parameters, comorbidities, smoking status, ejection fraction, the number of bypassed vessels, the usage of an intra-aortic balloon pump (IABP), administrated inotropic agents, total drainage, neurological and other complications, operation time, and duration of admission in intensive care unit (ICU) and in the ward, and mortality status were recorded and retrospectively analyzed. Patients with significant valvular heart disease, pulmonary or neurological disease, acute coronary syndrome, congestive heart failure, atrial flutter, peripheral vascular disease, those with infections, malignancy, overt hypothyroidism or hyperthyroidism, chronic renal or hepatic disease and overt/active hematological disorders, and patients taking anti-arrhythmic drugs previously and those with current use of oral contraceptives were excluded from the study.

Evaluations

Standard on-pump CABG operation requiring cardiopulmonary bypass was performed in all included patients by the same surgeon. Following anesthesia induction, the patient was given supine position. The operations were performed through median sternotomy, with aortic cannulation at mild hypothermia using a single right atrial cannula, membrane oxygenator, a single cross clamp, and a roller pump with initially antegrade and then retrograde blood cardioplegia via the coronary sinus.

The patients were continuously monitored with a five-lead telemetry during admission in the ICU. Following discharge from the ICU, the patients were followed-up with 12-lead electrocardiography (ECG) every day. New-onset POAF was defined as AF occurring during hospitalization following CABG as specified by the Society of Thoracic Surgeons. Accordingly, atrial fibrillation (AF) lasting at least 10 minutes on the telemetry and requiring medical treatment following surgery in a patient without preoperative AF was defined as POAF.

Complete blood count was performed in patients undergoing CABG by obtaining blood samples following a 12-hour fasting period. Pre- and postoperative hemoglobin (Hb), hematocrit (Hct), white blood cell (WBC), red cell distribution width (RDW), MPV, neutrophil (Neut), platelet count (PLT), C-reactive protein (CRP), urea, creatinine, aspartate transaminase (AST), alanine transaminase (ALT) and troponin levels were measured. In addition, systolic and diastolic blood pressure were measured preoperatively and at the 1^{st}, 2^{nd}, 4^{th}, 8^{th}, 16^{th} and 24^{th} postoperative hours. The parameters obtained were compared between the patients with and without POAF. MPV values were measured from blood samples collected in 2 mL tubes containing tripotassium ethylenediaminetetraacetic acid using an automatic blood counter (Beckman Coulter LH 750, Fullerton, CA, USA).

Ethical statement

The study protocol was approved by the ethics committee of Pamukkale University Medical Faculty. All patients were informed about the study objectives in detail and gave verbal and written consent. The study was conducted in accordance with the principles of Declaration of Helsinki.

Statistical analysis

Data obtained in the study were statistically analyzed with SPSS 20.0 for Windows (SPSS, IBM Inc., Chicago, IL, USA) package software. Normality of the data was analyzed with the Kolmogorov-Smirnov test. The continuous variables were expressed as mean (SD), and the categorical variables, as

frequency and percentage. Since the data were normally distributed, continuous variables were compared between the two groups with Mann-Whitney U test. Categorical variables were compared with the Chi-square or Fisher Exact tests. The data were subjected to univariate regression analysis in order to determine the risk factors affecting POAF. The significant data in the univariate analysis were then subjected to multivariate analysis in order to detect the independent risk factors for POAF development. *P*-value <0.05 was considered statistically significant.

Results

Among 227 patents included in the study, 23.3% (n=53) were females and 76.7% (n=174) were males. Forty-four (19.4%) patients developed AF following CABG. No statistically significant difference was observed between the patients with and without POAF in terms of gender (*P*=0.928). The mean age in POAF and non-POAF patients, and overall were 69.89 (7.44) years, 62.79 (10.21) years and 64.17 (10.12) years, respectively. The mean age of the POAF group was statistically significantly higher compared to the non-POAF group (*P*<0.001). The mean body mass index (BMI) was 27.95 (4.45) kg/m^2 in POAF patients, and 28.49 (5.25) kg/m^2 in patients without POAF. No statistically significant difference was found between the POAF and non-POAF patients in terms of BMI (*P*=0.768). Comorbidities and smoking statuses of the patients are presented in Table 1.

There were no statistically significant differences between the patients with and without POAF in terms of diabetes mellitus, hypertension, COPD, pulmonary arterial hypertension (PAH), and renal failure incidences or smoking status (for all *P*>0.05).

The mean left atrial diameters of those in the POAF and non-POAF groups were similar, with 4.21±1.05 cm and 4.02±0.74 cm, respectively (*P*=0.442). One vessel was bypassed in 2 (4.5%) patients, 2 vessels in 7 (15.9%) patients, 3 vessels in 15 (34.1%) patients, 4 vessels in 12 (27.3%) patients, 5 vessels in 5 (11.4%) patients, 6 vessels in 2 (4.5%) patients and 7 vessels in 1 (2.3%) patient in the POAF group, and in the non-POAF group, 1 vessel was bypassed in 10 (5.5%) patients, 2 vessels in 19 (10.4%) patients, 3 vessels in 58 (31.7%) patients, 4 vessels in 58 (31.7%) patients, 5 vessels in 28 (15.3%) patients, and 6 vessels in 10 (5.5%) patients. No statistically significant was observed between the patients with and without POAF in terms of the number of vessels bypassed (*P*=0.436). Intra-aortic balloon pump (IABP) was used in 7 (15.9%) patients with POAF and 7 (39%) patients without POAF. The rate of patients with IABP was statistically significantly higher in the POAF group (*P*=0.008). Inotropic agents were used in 15 (34.9%) and 41 (22.9%) patients with and without POAF, respectively. There was no statistically significant difference between the two groups in terms of the use of inotropic agents (*P*>0.05). The mean ejection fraction (EF) was 49.27 (8.52) in patients with POAF, and 51.7 (9.38) in those without. EF value was significantly lower in POAF group (*P*=0.042). The total amount of drainage was 75.49 (648.4) mL and 585.4 (402.06) mL in POAF and non-POAF groups, respectively, which was significantly higher in patients with POAF (*P*=0.011). Biochemical outcomes of the patients are presented in Table 2.

Table 1: Clinical characteristics and comorbidities of patients with and without POAF

		AF		Non-AF		*P*-value
		n	%	n	%	
Gender	Female	11	25.0	42	23.0	0.928
	Male	33	75.0	141	77.0	
DM	Yes	19	45.2	70	40.0	0.656
	No	23	54.8	105	60.0	
HT	Yes	24	57.1	88	50.3	0.531
	No	18	42.9	87	49.7	
COPD	Yes	0	0.0	12	6.6	0.13
	No	44	100.0	169	93.4	
PAH	Yes	7	15.9	17	9.3	0.313
	No	37	84.1	166	90.7	
RF	Yes	2	4.5	15	8.2	0.537
	No	42	95.5	168	91.8	
Smoking	Yes	18	43.9	85	48.3	0.739
	No	23	56.1	91	51.7	

DM: diabetes mellitus; HT: hypertension, COPD: chronic obstructive pulmonary disease, PAH: pulmonary arterial hypertension, RF: renal failure

Table 2: Biochemical parameters of patients with and without POAF

	AF		Non-AF		*P*-value
	Mean	SD	Mean	SD	
Hb	13.11	1.54	13.36	1.96	0.411
Hct	40.23	4.86	40.63	5.72	0.715
WBC	8.68	2.68	8.32	2.61	0.284
RDW	16.52	1.25	16.32	2.65	0.018
MPV	9.82	2.92	8.37	1.52	0.004
NEUT	6.3	2.86	6.22	3.05	0.501
PLT	235.16	63.85	228.6	65.88	0.349
CRP	18.57	33.11	15.06	25.52	0.731
Urea	46.05	14.32	42.34	22.87	0.006
Creatinine	1	0.25	1	0.6	0.101
AST	28.7	26.94	42.77	54.97	0.159
ALT	22.02	24.44	25.41	20.87	0.096

Hb: hemoglobin, Hct: hematocrit, WBC: white blood cells, RDW: red cell distribution width, MPV: mean platelet volume, NEUT: neutrophils, PLT: platelets, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Hemoglobin, hematocrit, WBC, neutrophil and platelet count, CRP, creatinine, AST, and ALT values were similar between the two groups (*P*>0.05 for all). However, the mean MPV value was significantly higher in the POAF group (*P*=0.004), along with RDW (*P*=0.018) and urea (*P*=0.006) values.

The mean operational time was 241.43 (43.42) minutes in the patients with POAF and 246.5 (42.56) minutes in patients without, which were similar (*P*=0.409). There were no statistically significant differences between the groups in terms of cross clamp duration, and the durations of admission to the ICU and wards (*P*=0.345 and *P*=0.633, respectively) The most common postoperative complications were low cardiac output syndrome, myocardial infarction, pneumonia, mediastinitis, wound site infections and bleeding. No statistically significant differences were found between the two groups in terms of postoperative complications (*P*=0.624 for all). Two (4.5%) and 3 (1.6%) patients died in the POAF and non-POAF groups, respectively (*P*=0.249).

Age, IABP, EF, RDW, MPV, urea and total drainage variables, all of which were significant in the univariate regression analysis, were included in the multivariate regression analysis. MPV, age and total drainage were the independent risk factors associated with POAF (OR=1.080, OR=1.371, OR=1.001; *P*=0.001, *P*<0.001, *P*=0.024, respectively) (Table 3).

Table 3: Independent risk factors associated with POAF

	OR	95% CI		*P*-value
		Lower	Upper	
Age	1.080	1.031	1.131	0.001
MPV	1.371	1.151	1.634	<0.001
Total drainage	1.001	1.000	1.003	0.024

OR: Odds ratio

Discussion

In this retrospective cohort study, we investigated whether there was a correlation between the mean platelet volume (MPV) and the development of postoperative atrial fibrillation. Our results indicate that MPV was significantly higher in the patients who developed POAF compared to those who did not.

AF is one of the most common complications following CABG. There are numerous studies in the literature reporting risk factors such as age, ejection fraction (EF) and left atrial diameter for the development of POAF [2]. In our study, while the mean left atrial diameter was similar between the groups, the mean age was significantly higher, and EF was significantly lower in patients who developed POAF. In the multivariate analysis we performed to determine the independent risk factors associated with POAF, age was statistically significant. In the present study, the mean age of the patients was 64.17 years. Similarly, in a study by Abeer et al. [15] examining the effect of MPV on acute ischemic stroke, the mean age of the patients was 62.64 years.

The number of studies investigating the relationship between biomedical parameters and the development of POAF are limited [3,14,16]. After understanding the predictive and prognostic value of MPV for many medical conditions, the number of studies on this issue has increased [14-21]. The predictive effect of MPV was examined in many diseases, including cardiovascular disorders. However, there is no consensus in the literature about the correlation between MPV and cardiovascular diseases. For example, some studies found an association between a high MPV level and the risk of stroke [22-24], while others could not [15]. MPV levels were high in patients with arrhythmogenic right ventricular cardiomyopathy or dysplasia (ARVC/D) [17]. In another study by Degerli et al. [18], MPV was a reliable indicator of acute mesenteric ischemia. In a study conducted by Chung et al. [24], MPV was higher in patients with congestive heart failure compared to the control group. Gawlita et al. [20] reported high MPV levels in persons with coronary artery disease. On the other hand, it was reported that MPV levels may be associated with postoperative adverse events [25]. In a study by Icli et al. [26], MPV was significantly higher in patients with mitral valve prolapsus.

MPV is considered to reflect the reactivity or activation of platelets as a simple marker [27,28]. Platelet size has been shown as predictive and prognostic biomarkers of cardiovascular events [29,30]. Larger platelets are metabolically more reactive than smaller ones. Reactive platelets contain a greater amount of prothrombotic materials and are associated with a greater aggregability in response to adenosine diphosphate (ADP), increased thromboxane A2 and B2 and glycoprotein IIb-IIa receptor expression and decreased in-vitro aggregation with prostacyclin [31].

MPV was investigated by many studies as a cardiovascular risk factor. However, the number of studies investigating the association between MPV and atrial fibrillation are limited [2,32]. The results of this study indicate that MPV was statistically significantly higher in the group with postoperative AF compared to the group without. In addition, multivariate analyses revealed that MPV was an independent risk factor for developing POAF. In this regard, our study is one of the limited studies on this issue in the literature.

Limitations

The main limitation of our study was its single-centered, retrospective design. The number of our patients was higher compared to similar studies. The number of parameters studied among the patients with and without postoperative atrial fibrillation constitutes the strong aspect of this study.

Conclusion

The results of our study indicate that MPV can be used as a predictor for the development of POAF after on-pump CABG. MPV is a quite simple parameter, which can be readily obtained in routine complete blood count. We think that this parameter can be a reliable marker of atrial fibrillation, which is one of the common arrhythmias encountered following coronary artery bypass grafting. However, our results should be supported by prospective and multicenter studies.

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Efficacy and toxicity of everolimus plus exemestane in third and later lines treatment of hormone receptor-positive, HER2-negative metastatic breast cancer

Hormon reseptör pozitif HER2-negatif metastatik meme kanseri tedavisinde üçüncü ve sonraki basamaklarda everolimus/eksemestan tedavisinin etkinliği ve toksisitesi

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Abstract

Aim: In daily practice, everolimus plus exemestane therapy has begun to be used in the later-lines as it has been demonstrated that treatments such as cyclin-dependent kinase (CDK) 4/6 inhibitors and fulvestrant, alone or in combination, are more effective in hormone receptor (HR)-positive metastatic breast cancer (MBC). The aim of this study is to evaluate the efficacy and toxicity of everolimus plus exemestane in the third line and later-lines on HR-positive Human Epidermal Growth Factor Receptor 2 (HER2)-negative MBC treatment with real-life data.

Methods: Patients who received everolimus plus exemestane with the diagnosis of HR-positive and HER2-negative MBC between November 2013 and March 2020 were included in this retrospective cohort study. Clinicopathological characteristics of patients and treatment related toxicities were evaluated retrospectively.

Results: The median age of the 33 patients included in the study was 59 (30-77) years. Twenty-three (69.7%) of the patients had visceral metastasis, while 10 (30.3%) had only bone metastasis. Everolimus plus exemestane was used in the third line in 22 (66.6%) patients and later-lines in 11 (33.3%) patients. The median follow-up time was 15.5 months (0.3-35.5). Median progression-free survival (PFS) and overall survival (OS) were 7.0 (5.1-9.0, 95% CI) months and 21.3 (13.4-29.2, 95% CI) months, respectively. Median PFS of patients with only bone metastasis and visceral metastasis were similar (7.2 vs 6.4 months, P=0.96).

Conclusion: Everolimus plus exemestane is an effective and tolerable treatment choice in the later-lines in the treatment of HR-positive HER2-negative MBC.

Keywords: Everolimus, Exemestane, Breast cancer

Öz

Amaç: Siklin bağımlı kinaz 4-6 inhibitörü ve fulvestrant gibi tedavilerin tek başına ya da kombinasyon halinde kullanılmasının hormone reseptör (HR)-pozitif metastatik meme kanseri (MMK) tedavisinde daha etkin olduğunun gösterilmesiyle günlük pratikte everolimus/eksemestan tedavisi daha ileriki basamaklarda kullanılmaya başlamıştır. Bu çalışmanın amacı HR-pozitif HER2-negatif MMK tedavisinde üçüncü ve sonraki basamaklarda everolimus/eksemestan kombinasyon tedavisinin etkinliğini ve toksisitelerini gerçek yaşam verileri ile değerlendirmektir.

Yöntemler: Bu çalışma retrospektif kohort çalışmasıdır. Kasım 2013 - Mart 2020 tarihleri arasında merkezimizde HR-pozitif HER2-negatif MMK tanısıyla everolimus/eksemestan kombinasyon tedavisi alanlar çalışmaya dahil edilmiştir. Hastaların klinikopatolojik özellikleri ve tedavi ilişkili toksisiteler retrospektif olarak incelenmiştir.

Bulgular: Çalışmaya dahil edilen 33 hastanın ortanca yaşı 59'du (30-77). Hastaların 23'ünün (%69,7) visseral metastazı varken 10 (%30,3) hastanın yalnızca kemik metastazı vardı. Everolimus/eksemestan tedavisi 22 (%66,6) hastaya üçüncü basamakta, 11 (%33,3) hastaya ise sonraki basamaklarda verilmişti. Ortanca takip süresi 15,5 (0,3-35,5) aydı. Ortanca progresyonsuz sağkalım (PS) 7,0 (5,1-9,0, 95% CI) ay; ortanca genel sağkalım ise 21,3 (13,4-29,2, 95% CI) aydı. Yalnızca kemik metastazı olan hastalarla visseral metastazı olan hastalar arasında ortanca PS açısından fark yoktu (7,2–6,4 ay; P=0,96).

Sonuç: Everolimus/eksemestan kombinasyonu HR-pozitif HER2-negatif MMK tedavisinde ileriki basamaklarda da etkin ve tolere edilebilir bir tedavi seçeneğidir.

Anahtar kelimeler: Everolimus, Eksemestan, Meme kanseri

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Introduction

Breast cancer is the most common type of cancer in women and ranks second after lung cancer in cancer-related deaths [1]. It is not a single type of disease and is divided into three subgroups with different pathological and clinical features: 'Hormone Receptor (HR)-Positive', 'Human Epidermal Growth Factor Receptor 2 (HER2)-Positive' and 'Triple-Negative' [2-12]. In the last four decades, there have been significant advances in the treatment of 'HR-positive metastatic breast cancer (MBC)' through the process that started with tamoxifen in 1977 [13,14]. Apart from endocrine therapy (ET), significant improvements in survival have been achieved through targeted therapies such as 'phosphoinositide 3-kinase', 'mammalian target of rapamycin (mTOR)' or 'cyclin-dependent kinase (CDK) 4/6' inhibitors [15-21].

The first phase-3 study on efficacy of mTOR inhibitors in the treatment of MBC was conducted in 2012 [17]. In patients with HR-positive and HER2-negative MBC, administration of everolimus in addition to exemestane has been shown to provide an advantage in progression-free survival (PFS). In a later phase-2 study comparing everolimus plus exemestane with capecitabine or exemestane, median PFS were similar between the arms of exemestane plus everolimus and capecitabine [20]. In both prospective studies, everolimus with exemestane was administered as second line treatment. In later retrospective reports, most patients were using everolimus plus exemestane as second line treatment [22,23]. In daily practice, everolimus plus exemestane therapy has begun to be used in the later lines as it has been demonstrated that treatments such as CDK 4/6 inhibitors and fulvestrant, alone or in combination, are more effective in HR positive MBC [24,25].

Our aim in this study is to evaluate the efficacy and toxicity of everolimus plus exemestane in the third and later lines in HR-positive HER2-negative MBC treatment with real-life data.

Materials and methods

This single-center retrospective cohort study was conducted on patients who received everolimus plus exemestane with the diagnosis of HR-positive and HER2-negative MBC between November 2013 and March 2020.

Male patients and those under 18 years of age were excluded from the study.

Demographic features, pathological features (estrogen receptor (ER) expression, Ki67 proliferation index), breast cancer diagnosis date, metastasis date, metastasis regions, everolimus plus exemestane treatment start and end dates, and treatment-related toxicities were evaluated retrospectively via the electronic registration system and manually through the patient files. Side effects were graded by Common Terminology Criteria for Adverse Events version (CTCAE) V.4.03.

Statistical analysis

The analyses were carried out through SPSS software. The time from the onset of everolimus plus exemestane to progression was defined as PFS and time to death was defined as overall survival (OS). Kaplan-Meier curve was used for survival analysis. Log-rank analysis was used for median PFS comparison in subgroups. Values of P <0.05 were considered significant.

Results

The median age of 33 women included in the study was 59 (30-77) years. Characteristics of the patients are presented in table 1. ER status of 26 patients (78.7%) was >80%, and Ki-67 status of 20 patients (60.6%) was >30%.

Table 1: Patient characteristics

	n=33	%
Age		
Median (range) – years	59 (30-77)	
ECOG performance status score		
0 or 1	29	87.9
2	4	12.1
Estrogen receptor expression		
≥ 80%	26	78.7
< 80%	7	21.2
Ki-67 Proliferation index		
≤ 30%	21	63.6
> 30%	12	36.3
Metastatic site		
Bone	29	87.9
Lymph node (non-regional)	21	63.6
Lung	19	57.6
Liver	8	24.2
Brain	3	9.1
Everolimus plus exemestane sequence		
Third line	22	66.6
Fourth line	9	27.2
Fifth line and later	2	6.0

While 23 (69.7%) of the patients had visceral metastasis, 10 (30.3%) had only bone metastasis. Everolimus plus exemestane was used in 22 (66.6%) patients in the third line and 11 (33.3%) patients in later lines. Stable disease (SD) was achieved in 21 (63.6%) patients, while partial response (PR) was achieved in 2 (6.1%) patients.

During the median follow-up period of 15.5 months (0.3-35.5), the disease progressed in 30 (90.9%) patients and 19 (57.6%) patients died. Median PFS was 7.0 (5.1-9.0, 95% CI, figure 1) months, and median OS was 21.3 (13.4-29.2, 95% CI, figure 2) months. There was no significant difference in median PFS between patients with only bone metastasis and those with visceral metastasis (7.2 vs 6.4 months; P=0.96; figure 3).

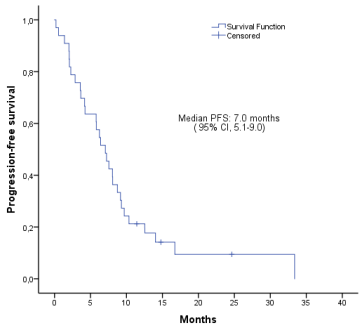

Figure 1: Kaplan–Meier estimates of progression-free survival

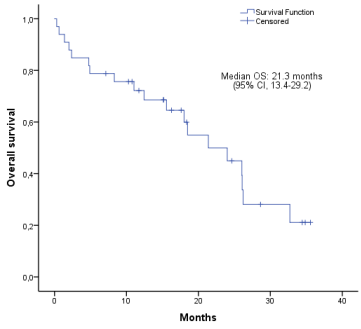

Figure 2: Kaplan–Meier estimates of overall survival

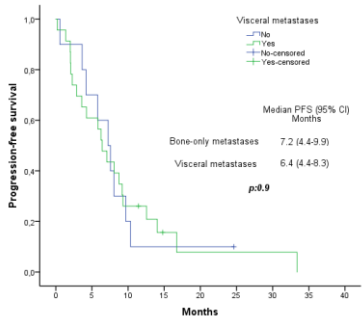

Figure 3: Median PFS on visceral vs bone-only metastases

One (3%) patient died due to acute coronary syndrome and 1 (3%) patient died due to acute renal failure. Eleven (33.3%) patients could not continue with the treatment due to toxicity. Eight (24.2%) patients had dose delay and 7 (21.2%) patients had dose reduction. The most common side effects were stomatitis (n=14, 42.4%) and fatigue (n=13, 39.3%). Treatment-related side effects are shown in table 2.

Table 2: Everolimus related toxicity (n=33)

	Grade 1-2	Grade 3	Grade 4
Stomatitis	12 (36.3%)	2 (6.0%)	0
Fatigue	11 (33.3%)	2 (6.0%)	-
Pneumonitis	5 (15.1%)	0	0
Diarrhea	5 (15.1%)	1 (3.0%)	0
AST/ALT increased	5 (15.1%)	0	0
Anemia	5 (15.2%)	1 (3.0%)	0
Hyperglycemia	4 (12.1%)	1 (3.0%)	0
	n (%)		
Treatment delay	8 (24.2%)		
Dose reduction	7 (21.2%)		
Discontinuation due to toxicity	11 (33.3%)		
Death	2 (6.0%)		

Discussion

To the best of our knowledge, this study is one of the limited number of studies demonstrating the efficacy of everolimus in HR-positive HER2-negative MBC treatment after at least one line of chemotherapy and hormonotherapy in the third and later lines. The median PFS obtained in our study showed that everolimus plus exemestane may be an effective treatment choice in the later lines.

The first study to investigate the effect of mTOR inhibitors in the treatment of HR-positive HER2-negative MBC is BOLERO-2 [17]. This phase-3 study published in 2012 included postmenopausal patients who were refractory to nonsteroidal aromatase inhibitor treatment. Compared to exemestane plus placebo, longer PFS was obtained with everolimus plus exemestane (6.9 vs 2.8 months).

In the phase-2 BOLERO-4 study published in 2018, the efficacy of everolimus combined with letrozole in first line and exemestane in the second line was investigated in HR-positive and HER2-negative MBC patients. Median PFS achieved with everolimus plus letrozole was 22.0 months in the first line and median PFS with everolimus plus exemestane was 3.7 months in the second line [19].

In another phase-2 study, BOLERO-6, published in the same year, the same patient group was randomized into three groups [20]. Median PFS for everolimus, everolimus plus exemestane and capecitabine was 6.8, 8.4 and 9.6 months, respectively. According to the results, everolimus plus exemestane and capecitabine were better than everolimus alone.

In the large retrospective series on 264 HR+ HER2- MBC patients published from Italy, PFS was 11.6, 9.7 and 7.5 months with everolimus plus exemestane in the first, second and third lines, respectively [22]. The median PFS value obtained in our study is similar to the results in BOLERO-2, BOLERO-6 and the study published from Italy. However, our median PFS was better than the 3.7-month PFS in the BOLERO-4 study [17,19,20,22], the difference between which was thought to stem from study design: In BOLERO-4, some patients who received everolimus with exemestane in the second line had received everolimus and letrozole in the first line.

When the tumor response achieved with everolimus plus exemestane was analyzed in the original study, 12% PR and 73% SD were reported compared to central assessment [17]. In our study, the proportion of patients with both PR and SD was slightly lower. The reason for this difference might be the fact that our patients received the treatment in further lines as compared to BOLERO-2.

In the final analysis of BOLERO-2, OS was reported as 31.0 months, while it was reported as 33.0 months in the wide retrospective series [22,27]. In our study, the median OS was 21.3 months. The median PFS we achieved was akin to the pivotal study and retrospective series, while the median OS was shorter. OS difference is thought to be caused by the treatments given after progression.

In visceral metastatic disease, the effectiveness of everolimus with exemestane treatment has been a matter of curiosity. In final analysis of BOLERO-2, it was reported that everolimus plus exemestane treatment was more effective than placebo in the presence of visceral metastasis [17]. In our study 69.7% of the patients had visceral metastasis, and there was no difference in median PFS between visceral metastatic patients and those with only bone metastasis.

The phase 3B BALLET study published in 2017 is one of the most comprehensive studies on the safety of everolimus plus exemestane [28]. In this study, which was conducted on 429 patients, 1% of patients had treatment-related death, 15% could not continue treatment due to side effects and 56% had dose reduction due to side effects. In BOLERO-2, these rates were slightly higher: 1.4% death, 26% could not continue treatment due to side effects, 66% dose reduction or interruption of treatment [17]. In our study we experienced 6% death, 33% of our patients could not continue treatment due to side effects, and 21% of the patients needed dose reduction. Compared to these two comprehensive studies, the rate of patients who could not continue treatment was higher in our real-life experience. Dose reduction in fewer patients was thought to cause more cases to discontinue the treatment.

One of the most common side effects of everolimus plus exemestane is stomatitis, which occurs in approximately 60% of patients [17,28]. In our study, this side effect was observed in 40% of our patients. In our center, the recommendation of prophylactic oral care to each patient at least one week before starting treatment and close follow-up during the treatment has lowered the rate of this side effect. In daily practice, fatigue, pneumonitis, and diarrhea, which are the most common side effects that cause treatment discontinuation, were experienced in our patient group at a rate similar to the previous studies [17,22,28].

Limitations

The limitations of our study were retrospective design and small number of patients. In retrospective studies, the unrecorded side effects are a handicap. However, our study is one of the few studies with real-life data evaluating the efficacy and safety of everolimus plus exemestane in the third and later lines in the treatment of HR-positive HER2 negative MBC.

Conclusion

In conclusion, everolimus plus exemestane is an effective and tolerable treatment choice in the later-lines in the treatment of HR-positive HER2-negative MBC. Novel studies are needed to evaluate the effectiveness of everolimus plus exemestane in patients who progressed with CDK 4-6 inhibitors and fulvestrant.

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Effects of heparin and prednisolone on postoperative intra-abdominal adhesions in Wistar rats

Wistar cinsi ratlarda heparin ve prednizolonun postoperatif intra-abdominal adezyonlara etkisi

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Abstract

Aim: Postoperative intra-abdominal adhesions are one of the complications surgeons want to avoid. It was aimed to compare the effects of physiological saline, heparin, Ringer's lactate, and prednisolone, which have been commonly used for surgical adhesions, with repeated lavage on postoperative adhesions.

Methods: Upon the approval of the Ethics Committee of Fırat University, Faculty of Medicine, 35 Wistar Albino (female) rats were randomized into 5 groups (Heparin BID, Heparin QD, Prednisolone QD, Prednisolone BID, and Control) of 7 rats, and adhesion was created with peritoneal injury model in all rats. The differences in the adhesions created between groups were compared using the macroscopic adhesion scoring system of Linsky.

Results: No significant differences were found between physiological saline-heparin and Ringer's lactate-prednisolone groups in terms of adhesion scores (P=0.06). There was a difference in adhesion severity on the left only in the groups receiving heparin QD and prednisolone QD (P=0.04).

Conclusion: We demonstrated that none of the agents (Physiological saline, Heparin, Ringer's lactate, and prednisolone) we used in our study model reduced adhesions. It is thought that no difference was detected because of the adhesion model we established. Advanced technology-based studies are still needed to prevent postoperative intra-abdominal adhesions that are globally observed to reduce a huge economic burden and decrease mortality and morbidity.

Keywords: Animal models, Heparin, Postoperative intra-abdominal adhesions

Öz

Amaç: Cerrahi sonrası postoperatif batın içi yapışıklıklar halen cerrahların karşılaşmak istemediği bir sorun olarak karşımıza çıkmaya devam etmektedir. Serum fizyolojik, Heparin, Ringer laktat ve prednizolonun mükerrer lavaj ile postoperatif adezyonlar üzerine etkisini karşılaştırmaktır.

Yöntemler: Fırat Üniversitesi Tıp Fakültesi Etik Kurulu'nun onayı alındıktan sonra 7'şerli 5 grup (Heparin günde 2 defa, Heparin günde 1 defa, Prednizolon günde 1 defa, Prednizolon günde 2 defa ve Kontrol) halinde toplam 35 adet Wistar Albino tipi (dişi) rat kullanılmış, tüm ratlarda peritoneal hasar paterni ile adezyon oluşturulmuştur. Her grupta oluşan adezyonlar Linsky'nin kullandığı adezyonları skorlayan, makroskopik adezyon skorlama yöntemiyle gruplar arası farklılıklar kıyaslanmıştır.

Bulgular: Serum fizyolojik-heparin ve Ringer laktat-prednizolon gruplarının karşılaştırılmasında adezyon skoru açısından istatistiksel fark bulunmamıştır (P=0,06). Sadece Heparin günde bir defa ve prednizolon günde bir defa alan gruplarda solda adezyon şiddeti bakımından istatistiksel farklılık bulunmuştur (P=0,04).

Sonuç: Çalışma modelimize göre kullandığımız Serum fizyolojik, Heparin, Ringer laktat ve prednizolonun adezyonları azaltmadığını kanıtladık. Fark olmamasının nedeninin, oluşturduğumuz adezyon modelinden kaynaklandığı düşünülebilir. Tüm dünyada mortalite ve morbiditeyi arttıran postoperatif batın içi adezyonlarını önlemede ileri teknolojik tabanlı çalışmalara ihtiyaç duyulmaktadır.

Anahtar kelimeler: Hayvan modeli, Heparin, Postoperatif intra-abdominal adezyon

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Introduction

Postoperative peritoneal adhesions remain one of the most important causes of mortality and morbidity, resulting in many complications, such as chronic pelvic pain, infertility, and ileus [1]. Despite many novel approaches and surgical developments, there is still no effective method to prevent intra-abdominal adhesions after surgery [2]. In the literature, the intra-abdominal adhesions account for the most crucial factor in the development of postoperative ileus as well as the most frequent reason for referral to the hospital after gynecological or ovarian surgery [3-5].

It is accepted by many clinicians that unexplained female infertility and chronic pelvic pain in women are secondary to intra-abdominal adhesions [6]. One of the most common issues that surgeons still struggle globally is the serious complications that may occur after intra-abdominal adhesions [7]. For this reason, varied materials that might prevent adhesions have been used in many experimental studies. In the literature, many organic and synthetic components have been used to prevent adhesion formation, and numerous studies using the latest technologies are still ongoing. The objective of this study is to investigate the effect of repeated peritoneal lavage on adhesions using the combinations of heparin and physiological saline and prednisolone and Ringer's lactate after abdominal pelvic surgery.

Materials and methods

This study was performed at the Laboratory of Fırat University Experimental Research Center (FÜTDAM) and the Medical Genetics Laboratory of Fırat University. Ethics committee approval of our study was obtained in 2012 with the decision number 76 from Fırat University Experimental Research Center. Thirty-five 12- to 14-week old Wistar Albino adult female rats with regular cycles weighing between 190-220 grams were used in our study. To maintain their regular biological rhythms, they were kept in cages with 5 rats per each at an ambient temperature between 21-23 °C for 12 hours (08.00-22.00) under artificial light and 12 hours in the dark. Animals were fed using standard pellet and city water [8]. Oral feeding was discontinued 18 hours before the experiment, allowing the animals only to drink water. They were anesthetized with chloral hydrate at a dose of 400 mg/kg intraperitoneally. The abdomen was cleaned with a 10% povidone-iodine solution before the surgery. Thirty-five rats were randomly and prospectively divided into 5 groups of 7 rats and placed in the supine position on the operation table. Their abdomens were opened with a midline incision.

The groups established as per the study design and their characteristics are listed below:

Control group (n=7): Laparotomy was performed, all were peritoneally injured, then closed.

Heparin QD group (n=7): In this group, laparotomy was performed to create peritoneal injury, a drain was placed, and abdomens were closed. Peritoneal lavage with 5 ml physiological saline containing 250 IU heparin/ml was performed once a day for 3 days through the drain.

Heparin BID group (n=7): In this group, laparotomy was performed to create peritoneal injury, a drain was placed, and abdomens were closed. Peritoneal lavage with 5 ml physiological saline containing 250 IU heparin/ml was performed twice a day for 3 days through the drain.

Prednisolone QD group: (n=7) In this group, laparotomy was performed to create peritoneal injury, a drain was placed, and abdomens were closed. Peritoneal lavage with 5 ml mixture of 1 vial prednisolone and 1 L Ringer's lactate was performed once a day for 3 days through the drain.

Prednisolone BID group: (n=7) In this group, laparotomy was performed to create peritoneal injury, a drain was placed, and abdomens were closed. Peritoneal lavage with 5 ml mixture of 1 vial prednisolone and 1 L Ringer's lactate was performed twice a day for 3 days through the drain.

The procedure including laparotomy

The animals were anesthetized with chloral hydrate at a dose of 400 mg/kg administered intraperitoneally. The abdomen was cleaned with a 10% povidone-iodine solution before sterile surgical intervention. Thirty-five rats were randomly and prospectively divided into 5 groups of 7 rats. The rats were placed on the operation table in supine position and laparotomy was performed through a 3 cm-long midline incision. A 2x2cm section of the parietal peritoneum was removed from the right side and it was sutured with 3/0 silk. A 2 cm midline parallel straight incision was made on the left side, which was sutured with 3/0 silk. Drains were placed, and the layers of the abdomen and the skin were sutured with 3/0 silk. Rats, which were monitored for blood pressure, heart rate, and fever, were kept in cages of 5 rats per each until the end of the experiment. Regular peritoneal lavage was performed through the drain using 5 ml physiological saline containing Heparin 250IU/ml once a day in the Heparin QD group and 5 ml twice a day in the Heparin BID group for 3 days. Regular peritoneal lavage was performed using a 5 ml mixture of 1 vial prednisolone and 1 L Ringer's lactate once a day in the Prednisolone QD group, and twice a day in the Prednisolone BID group. After 14 days, a relaparotomy was performed to evaluate the adhesions. Powder-free gloves and surgical instruments were used during the operation. The 2x2 cm flap was removed from the right side. Then, repeated peritoneal lavage was performed for 3 days through this drain (Figures 1-6). After surgery, the animals were placed in their cages in separate groups and followed up for 14 days under standard feeding and living conditions.

After 14 days, the animals were anesthetized with chloral hydrate at a dose of 400 mg/kg administered intraperitoneally, and their abdomens were reopened with a midline incision. All adhesions in the abdomen were examined and recorded (Figure 7). The adhesions were scored macroscopically, as shown in Tables 1 and 2, using the scoring system of intra-abdominal adhesions [9].

Statistical analysis

The difference between groups were analyzed with Kruskal Wallis, Mann-Whitney U, and post-hoc Tuckey tests using the SPSS version 15.0 program. Statistical significance was set at $P<0.05$.

Figure 1: Midline incision

Figure 2: Creation of peritoneal injury

Figure 3: Removal of a 2x2 cm flap from the peritoneum

Figure 4: Suturing the removed flap with 3/0 silk

Figure 5: 2 cm straight incision on the left side and suturing with silk 3/0

Figure 6: Placement of drain and closing abdomen.

Figure 7: Midline incision and evaluation of adhesions

Table 1: Macroscopic evaluation of adhesion sizes (Linsky et al. [9])

Score	Adhesion size
0	No adhesion
1	25% of the traumatized area
2	25-50% of the traumatized area
3	50-100% of the traumatized area

Table 2: Macroscopic evaluation of adhesion severity (Linsky et al. [9])

Score	Adhesion severity
0	No resistance to separation
0.5	Some resistance
1	Sharp dissection needed

Results

The mean values of adhesion sizes and severities in the groups that received heparin or prednisolone once and twice daily, along with the control group is presented in Table 3. The comparison of four groups showed a difference in the severity of adhesions on the left side (P=0.328). The sizes of adhesions were similar between the right and left sides and the severity was comparable on the right side among groups (P=0.06, Kruskal Wallis Test). In post-hoc analysis, the severity of left side adhesions was different among the groups in which heparin and prednisolone were used once daily (P=0.08). The comparison of the remaining groups among themselves showed similar results (P=0.06, post-hoc Tukey test).

Table 3: Comparative results of the groups

	Control group	Heparin QD	Heparin BID	Prednisolone QD	Prednisolone BID	*P*-value
Adhesion size, right	2.4	1.6	1.1	2.3	1.4	0.06
Adhesion size, left	2.9	2.7	2.4	2	2.6	0.3
Adhesion severity, right	0.9	0.7	0.4	0.7	0.4	0.08
Adhesion severity left	0.9	1	0.9	0.6*	0.8	0.04

* Groups receiving heparin once daily and Prednisolone once daily were different in terms of adhesion severity on the left.

Discussion

The reason for performing peritoneal lavage repeatedly for 3 days through the drain placed in the abdominal cavity and comparing the fluid barriers was that we thought it could be more effective. Various models, such as the injured uterus horn model, peritoneal injury model, ileal transection model, colonic anastomosis model, bacterial peritonitis model, and clamping model were previously established to create peritoneal adhesions. The peritoneal injury model of our study was chosen as it was close to the surgical procedures performed in clinical practice [9].

The postoperative intra-abdominal adhesions remain to be an issue in general surgery and gynecology since they lead to an elevated level of morbidity and mortality [10]. In the literature, postoperative peritoneal adhesions are among the most common causes of ileus. Today, studies using advanced nanotechnology products and different agents to prevent intra-abdominal adhesions are ongoing at a fast pace and a further step is taken each day to obtain a curative solution [11]. To prevent intra-abdominal adhesions and keep them at the minimum level, many approaches, such as usage of anti-inflammatory agents, antibiotics, fibrinolytic agents, chemical and physical barriers, have been tried [12].

In our study, we compared physiological saline, heparin, Ringer's lactate, and prednisolone, all which have been used against peritoneal adhesions. These agents were chosen because they were safe, simple, cheap, easily accessible, and they each have a different mode of action [13]. We comparatively analyzed the effectiveness of the anticoagulant effects of heparin, reduction of local inflammatory response with prednisolone, removal of fibrin buildup with physiological saline, and its use with fluid barriers and repeated lavage.

In our study, there was no difference in terms of adhesion scores between physiological saline-heparin and Ringer's lactate-prednisolone groups according to the results of Mann-Whitney U test. There was a difference in adhesion severity on the left only in the groups receiving heparin and prednisolone once a day. It is thought that no difference was detected because of the adhesion model we established. There was no difference between these groups in terms of adhesion intensity and size. In conclusion, we found that none of the agents we used in our study model reduced adhesions.

Some basic surgical principles have been widely accepted clinically in the prevention of postoperative intra-abdominal adhesions. These can be listed as gentle handling of the tissues, continuous irrigation, using biologically compliant suture materials, avoiding unnecessary peritoneal dissection, and leaving the peritoneum open [14-16].

However, the fact that the solution to this problem with known pathophysiology remains unknown causes all surgeons to encounter more difficult cases each passing day.

Intra-abdominal adhesions resulting from previous operations are an important problem as they cause reoperations, increase morbidity, mortality, and healthcare expenses. Investigations are ongoing to solve this problem, but despite many positive results, there is no consensus on an absolute method. There are promising studies on biodegradable hyaluronic acid derivatives in the literature [17].

In the current literature, methods such as blockage of immunological factors and mode of actions (tumor necrotizing factor), administration of high dose botulinum toxin, pure olive oil, and platelet-rich plasma have been proven successful in preventing postoperative adhesions by promising studies [18-21].

Limitations

The biggest factor limiting our study is the low sample size and the small number of agents we used.

Conclusion

Since the number of subjects in our study is insufficient, larger, well-planned studies on the effects of different dosages of agents we used for the prevention of adhesions are needed. We believe that further, technology-based research may shed light on this issue.

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The effect of fullerenol C60 on skeletal muscle after lower limb ischemia reperfusion injury in streptozotocin-induced diabetic rats

Streptozotosin ile diyabet oluşturulan ratlarda alt ekstremite iskemi reperfüzyonuna karşı fullerenol C60'ın etkileri

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Abstract

Aim: Fullerenol, a water-soluble C60-fullerene, has been demonstrated to scavenge free radicals in vitro and in vivo. The aim of the study was to investigate the effects of fullerenol C60 on lower skeletal muscles in a rat model of ischemia/reperfusion (I/R).

Methods: After approval of the ethics committee, 30 Wistar Albino rat were divided into 5 groups with six animals per each as follows: Control (C), diabetes (D), diabetes+fullerenol C60 (DF), diabetes+I/R (group DIR) and diabetes I/R+fullerenol C60 (DIR-F) groups. Streptozotocin was administered to the rats to induce diabetes at a dose of 55 mg/kg. Four weeks after the onset of diabetes, rats were subjected to 2 hours of ischemia and 2 hours of reperfusion. At the end of the reperfusion period, skeletal muscle samples were taken from the lower extremity in all groups for histopathological and immunohistopathological examinations.

Results: Myositis and endothelial caspase 3 enzyme activities were high in all groups, particularly DIR. Compared to C, DF and DIR-F groups, inflammation and myositis were significantly higher in the DIR group (P=0.001, P=0.006, P=0.001, respectively, and P=0.001, P=0.022, P=0.001, respectively). Vascular dilatation and congestion were significantly more prominent in all groups compared to the control group (P=0.001 for all).

Conclusion: Our results confirm that fullerenol C60 has protective effects against skeletal muscle damage resulting from I/R in diabetic rats. Future studies conducted to evaluate these effects may help illuminate the action mechanism of fullerenol C60 and pathophysiology underlying the tissue damage related to I/R injury.

Keywords: Ischemia reperfusion, Fullerenol C60, Caspase 3, Rat

Öz

Amaç: Suda çözünür bir fulleren olan Fullerenol C60'ın, serbest radikalleri in vitro ve in vivo temizleyebildiği gösterilmiştir. Çalışmanın amacı, fullerenol C60'ın iskemi reperfüzyon (I/R) sıçan modelinde alt iskelet kasları üzerindeki etkilerini araştırmaktı.

Yöntemler: Etik kurul onayı alındıktan sonra 30 Wistar Albino sıçan; 5 gruba ayrıldı (n: 6); Kontrol (C), diyabet (grup D), diyabet + fullerenol C60 grubu (DF), diyabet + I/R (grup DIR) ve diyabet I/R + fullerenol C60 (DIR-F). Diyabet için sıçanlara 55 mg / kg streptozotosin uygulandı. Diyabet oluşumundan dört hafta sonra sıçanlara 2 saatlik iskemi ve 2 saatlik reperfüzyon uygulandı. Reperfüzyon döneminin sonunda histopatolojik ve immünohistopatolojik incelemeler için tüm gruplardan alt ekstremite iskelet kası örnekleri alındı.

Bulgular: Miyozit ve endotelyal kaspaz 3 enzim aktiviteleri, özellikle DIR ve C, D, DF ve DIR-F grubunda yüksektir. Enflamasyon DIR grubunda C, DF ve DIR-F grubuna göre anlamlı olarak yüksektir (sırasıyla P<0,001, P=0,006, P<0,001). Myosit hasarı da DIR grubunda kontrol, C, DF ve DIR-F grubuna göre anlamlı derecede yüksektir (sırasıyla P<0,001, P=0,022, P<0,001). Vasküler dilatasyon ve konjesyon D, DF, DIR ve DIR-F grubunda kontrol grubuna göre anlamlı olarak yüksektir (P<0,001, tümü).

Sonuç: Sonuçlarımız, fullerenol C60'ın diyabetik sıçanlarda I/R'den kaynaklanan iskelet kası hasarına karşı koruyucu etkileri olduğunu doğrulamaktadır. Fullerenol C60'ın I/R hasarı üzerindeki etkilerini değerlendirmek için yapılacak gelecekteki çalışmalar, fullerenol C60'ın olası koruyucu etkilerini ve I/R hasarına bağlı doku hasarının altında yatan mekanizmaları anlamaya yardımcı olabilir.

Anahtar kelimeler: İskemi reperfüzyon, Fullerenol C60, Kaspaz 3, Sıçan

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Introduction

Ischemia/reperfusion (I/R) results in serious injuries in tissues and organs. I/R is a complex and biphasic process, which causes cell damage and occurs due to numerous factors [1,2]. Ischemia initiates organ damage and the process of death by reducing the formation of energy required to achieve ionic gradient and hemostasis. Reperfusion causes both local and systemic inflammatory response, which may result in widespread microvascular dysfunction [3]. Infra-renal abdominal aorta clamping results in ischemia of distal body parts. Unclamping after a clamping period causes reperfusion injury of local and distant organs/tissues [4,5].

Some nanoparticles can be used for the treatment of injury due to ischemia [6]. Fullerene, with the chemical formulation of C60, is an allotrope of carbon as a nanoparticle and can react with oxygen free radicals [7-9]. Fullerenol (C60(OH)18-22) is one of the water-soluble derivates of C60 fullerenes which is demonstrated to reduce the severity of oxidative damage during an ischemia period by abolishing reactive oxygen species (ROS). C60 fullerenes function as free radical scavengers [7]. Fullerenol is shown to prevent the catabolic activity of vertebral bone marrow stromal cells by reducing ROS, matrix metalloproteinases (MMPs), and tumor necrosis factor-α (TNF-α) and increasing the activation of antioxidant enzymes [10]. Inflammatory cytokines and apoptotic signals are also reduced by fullerenol [11,12]. Fullerenol C60 has no acute toxicity towards cells/tissues [13-16]. C60 fullerenes can easily accumulate inside the cells/organelles as powerful antioxidants.

The aim of the study was to investigate the potential protective effects of fullerenol C60 on I/R injury in skeletal muscles in a rat model.

Materials and methods

Animals and experimental protocol

This study was conducted upon the consent of Experimental Animals Ethics Committee of Gazi University. All the procedures were performed according to accepted standards of Guide for the Care and Use of Laboratory Animals.

30 Wistar Albino rats (200- 250 g) were used. The rats were kept at 20-21ºC in cycles of 12 hours of daylight and 12 hours of darkness and had free access to food until two hours before the anesthetic procedure. The animals were randomly separated into five groups, each containing six rats. Control group (C), Diabetes group (D), Diabetes+ Fullerenol C60 (DF), Diabetes+ischemia-reperfusion (DIR), Diabetes+ischemia-reperfusion+ fullerenol C60 (DIR-F).

Diabetes was induced by a single intraperitoneal injection of streptozotocin (Sigma Chemical, St. Louis, MO, USA) at a dose of 55 mg/kg. Seventy-two hours after the injection, the blood glucose levels were measured. Rats were classified as diabetic if their fasting blood glucose (FBG) levels exceeded 250 mg/dl, and only animals with FBGs of >250 mg/dl were included in the diabetic groups (D, DF, DIR, DIR-F). The rats were kept alive for four weeks after streptozotocin injection to allow the development of chronic diabetes before they were exposed to I/R.

Control group (Group C): Only midline laparotomy was performed without any additional surgical intervention. After 4 hours of follow-up, they were sacrificed, and skeletal muscle tissue specimens were collected for histopathological and immunohistopathological investigation.

Diabetes group (Group D): Only midline laparotomy was performed without any additional surgical intervention. After 4 hours of follow-up, they were sacrificed, and skeletal muscle tissue specimens were collected for histopathological and immunohistopathological investigation.

Diabetes-Fullerenol C60 group (Group DF): Midline laparotomy was performed without any additional surgical intervention**.** Fullerenol C60 100 $\mu g.kg^{-1}$ was administered intraperitoneally: After 4 hours of follow-up, all rats received ketamine at a dose of 100 mg/kg intraperitoneally and were sacrificed. Skeletal muscle tissue specimens were collected for histopathological and immunohistopathological investigation.

Diabetes-Ischemia-reperfusion group (Group DIR): Midline laparotomy was performed similarly. Infrarenal aorta was left clamped for 2 hours. After removing the clamp, reperfusion was established for another 2 hours. At the end of 4 hours, rats were sacrificed, and skeletal muscle tissue specimens were collected for histopathological and immunohistopathological investigation.

Diabetes-Ischemia-reperfusion group with fullerenol C60 (Group DIRF): After following the same steps in I/R group, fullerenol C60 was administered (100 $\mu g.kg^{-1}$) intraperitoneally 30 minutes before the ischemia period. At the end of 4 hours, rats were sacrificed, and skeletal muscle tissue specimens were collected for histopathological and immunohistopathological investigation.

Histopathological and immunohistopathological evaluation. Tissues were fixed in 10% formaldehyde for 12 hours at room temperature. Sections (3-4 μm thick) were cut from the fixed tissue samples, embedded in paraffin blocks and mounted on poly-L-lysine-coated slides (Sigma-Aldrich; Merck KGaA, Darmstadt, Germany), all of which were left overnight at 45˚C. The sections were held for 20 minutes at 75˚C, followed by tap fixation and paraffin extraction. Deparaffinization was performed with a Leica Bond-Max automatic immunohistochemical/*in situ* hybridization stainer (Leica Microsystems GmbH, Wetzlar, Germany). Citrate buffer was applied for antigen retrieval for 30 minutes at 75˚C and washed with bond wash solution (Leica Microsystems GmbH). Sections were blocked with 0.3% hydrogen peroxide for 5 minutes at room temperature, then incubated with primary antibodies against caspase-3 (1:400; p11, C-6; cat. no. sc-271759; Santa Cruz Biotechnology, Inc., Dallas, TX, USA) and caspase-8 (1:200; D-8; cat. no. sc-5263; Santa Cruz Biotechnology, Inc.) for 15 minutes. The secondary antibodies (Leica Biosystems Newcastle Ltd., Newcastle Upon Tyne, UK) were incubated with cells for 8 minutes. The Bond™ Polymer Refine Detection system (cat. no. DS9800; Leica Biosystems Newcastle Ltd.) was added as a horseradish peroxidase polymer (a secondary antibody substitute) for 8 minutes. DAB (Leica Microsystems GmbH) was applied to the cells for 6 minutes and the marking became visible. Hematoxylin counterstaining was also performed

at 6 minutes. All steps following blocking of sections with hydrogen peroxide occurred at room temperature.

The stained samples were covered with balsam following washing in water and alcohol and cleared in xylene. The cytoplasmic caspase-3 staining was evaluated in myocyte and endothelia using a light microscope (Nikon Eclipse E600; Nikon Corporation, Tokyo, Japan) at a magnification of x400.

For hematoxylin and eosin staining, slides were kept in an oven at 72˚C for 20 minutes, deparaffinized in xylene solution and washed with alcohol three times. Sections were then incubated in hematoxylin for 4 minutes at room temperature, washed and exposed to acid-alcohol and ammonia solutions for a few seconds, then incubated in eosin for 6 minutes at room temperature, and immersed in a descending alcohol series and xylene. Stained slides were covered with slip and evaluated with a light microscope at a magnification of x400.

Statistical analysis

SPSS (IBM Corp., Armonk, NY, USA; version 20.0) was used for all statistical analysis. Descriptive statistics are presented as mean, standard deviation (SD) values. Group averages were compared with one-way ANOVA. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The myocyte caspase 3 activity in the skeletal muscle tissue was significantly higher in the DIR group as compared to C, D, DF, and DIR-F groups (p=0.001 for all). There was a statistically significant difference between the groups in terms of endothelial caspase 3 enzyme activity in skeletal muscle tissue ($P=0.001$). Endothelial caspase 3 in DIR group was significantly higher than that in C, D, DF, and DIR-F groups ($P=0.001$ for all). Additionally, that of the D group was significantly higher than that of the DIR-F group ($P=0.005$) (Table 1, Figure 1-5).

Inflammation in skeletal muscle tissue in the DIR group was significantly higher than that in C, DF, and DIR-F groups (P=0.001, P=0.006, P=0.001, respectively). In addition, inflammation in D group was significantly higher than that of C, DF and DIR-F groups ($P=0.001$, $P=0.006$, $P=0.001$, respectively) (Table 2, Figures 6–10).

The groups were compared in terms of skeletal myocyte damage ($P=0.001$), which was significantly higher in the D, DF, DIR, and DIR-F groups than that in the C group ($P=0.001$ for all). It was also significantly higher in DIR group compared to C, DF, and DIR-F groups ($P=0.001$, $P=0.022$, $P=0.001$, respectively) (Table 2, Figures 6–10).

Vascular dilatation and congestion were higher in D, DF, DIR, and DIR-F groups compared to the control group ($P=0.001$ for all) (Table 2, Figures 6–10)).

Table 1: Muscle tissue caspase 3 values [Mean (SD)]

	Group C (n=6)	Group D (n=6)	Group DF (n=6)	Group DIR (n=6)	Group DIR-F (n=6)	*P*-value **
Myocyte	0.00 (0.00)*	0.00 (0.00)*	0.00 (0.00)*	2.00 (0.26)	0.00 (0.00)*	0.001
Endothelial	1.17 (0.17)*	2.00 (0.00)*	1.67 (0.33)*	3.33 (0.21)	0.83 (0.17)*,&	0.001

*P***: Significance level with One Way ANOVA test $P<0.05$, *$P<0.05$: Compared with group DIR, &$P<0.05$: Compared with group D, Note: zero value indicates no damage

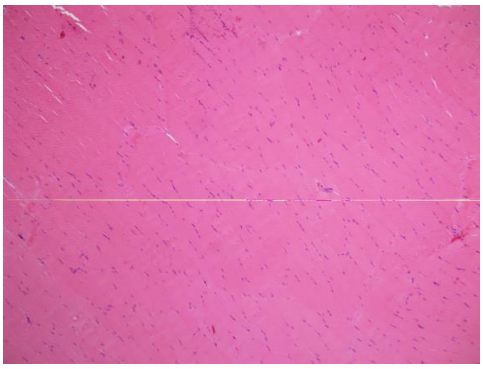

Figure 1: No inflammation, fibrosis or vascular dilation were observed in the muscle tissue taken from the control group (H/E x 100)

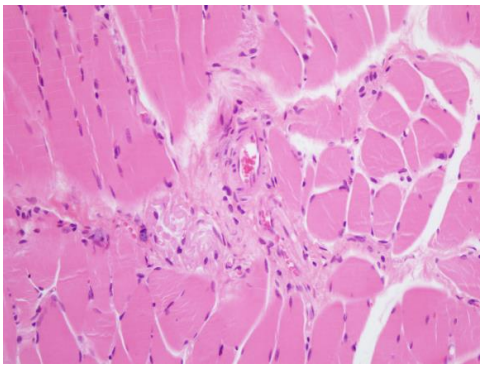

Figure 2: In the muscle sample from the diabetic group, there was minimal inflammation, vascular dilation, congestion between muscle fibers, and damage to myocytes (H/E x 400)

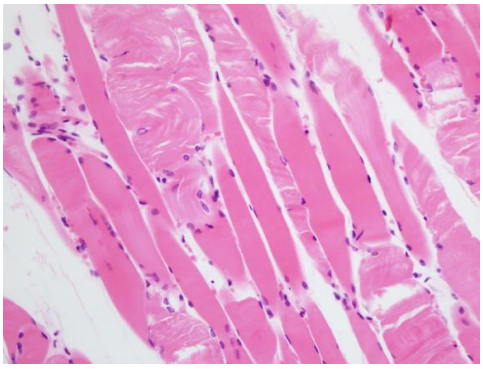

Figure 3: In the muscle sample from the diabetic-ischemia group, there was considerable damage, inflammation, vascular dilation, and congestion in myocytes (H/E x 400)

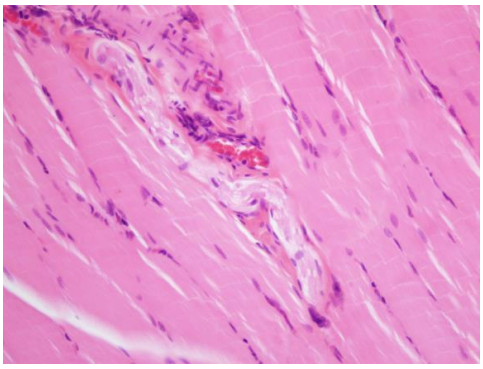

Figure 4: In the muscle sample from the diabetic-fullerenol group, damage, vascular dilation, and congestion were observed in myocytes (H/E x 400)

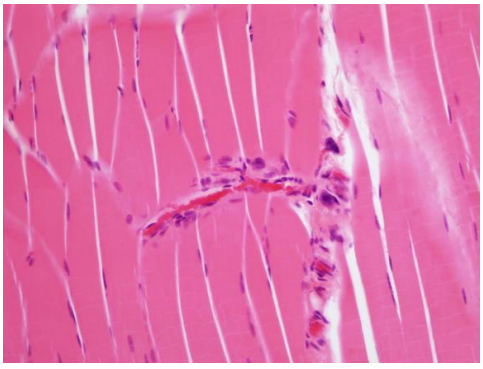

Figure 5: In Diabetic-ischemia-fullerenol group, various myocytes were damaged, vascular dilation, and congestion were observed (H/E x 400)

Table 2: Histopathological examination of muscle tissue [Mean (SD)]

	Group C (n=6)	Group D (n=6)	Group DF (n=6)	Group DIR (n=6)	Group DIR-F (n=6)	*P*-value **
Inflammation	0.00 (0.00)*,&	1.00 (0.00)	0.33 (0.21)*,&	1.00 (0.00)	0.17 (0.17)*,&	0.001
Fibrosis	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-
Vascular dilation	0.00 (0.00)	1.00 (0.00)+	1.00 (0.00)+	1.00 (0.00)+	1.00 (0.00)+	0.001
Congestion	0.33 (0.21)	1.00 (0.00)+	1.00 (0.00)+	1.00 (0.00)+	1.00 (0.00)+	0.001
Steatosis	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-
Myocyte injury	0.00 (0.00)	1.50 (0.22)+,*	1.33 (0.21)+,*	2.67 (0.21)+	1.67 (0.17)+	0.001

*P***: Significance level with One Way ANOVA test $P<0.05$, *$P<0.05$: Compared with group DIR, +$P<0.05$: Compared with group C, Note: zero value indicates no damage

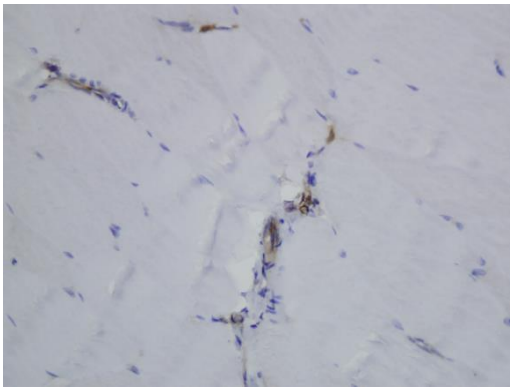

Figure 6: In Caspas-3 immunohistochemical study on muscle tissue in the control group, mild-moderate staining was detected only in endothelial cells(x400)

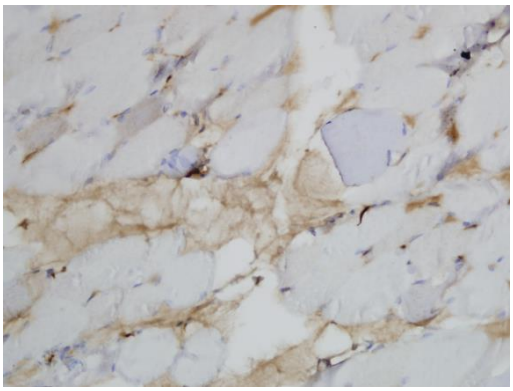

Figure 7: According to Caspase-3 immunohistochemical study of the muscle sample in the diabetic group, there was moderately positive staining in damaged myocytes and endothelial cells (x400)

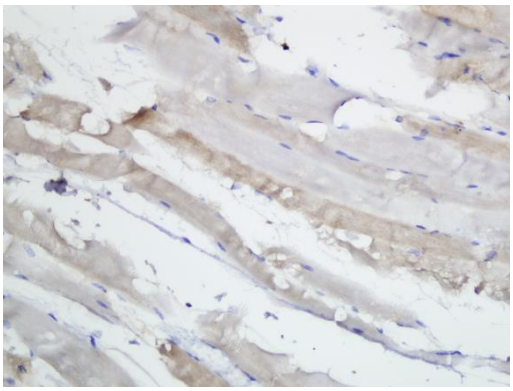

Figure 8: In Caspase-3 immunohistochemical study of the muscle sample in the diabetic-ischemia group, moderate positive staining was observed in the damaged myocytes (x400)

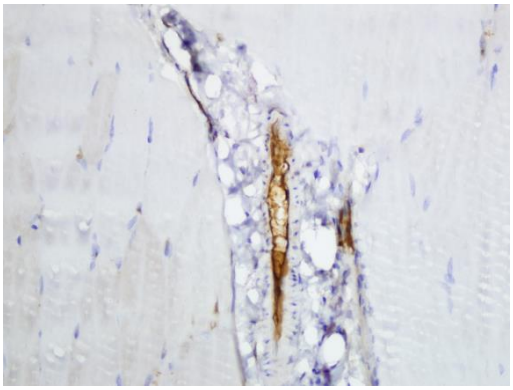

Figure 9: In the muscle sample from the diabetic-fullerenol group, only positive staining detected in the endothelial cells, but no staining in myocytes (x400)

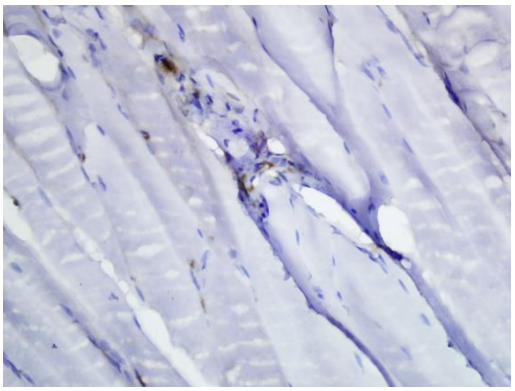

Figure 10: In the muscle sample from diabetic- ischemia-fullerenol group, only positive staining was detected in endothelial cells, but no staining in myocytes (x400)

Discussion

Reperfusion injury is still being studied today [17]. Ischemia reperfusion injury is especially important for not only adjacent organs but distant organs as well, such as the lungs, kidney, and heart [2,18,19]. After ischemia, reperfusion increases the rate of injury caused by the ischemic period and aggravates the damage [2,18]. Reperfusion generates ROS. Then, ROS causes lipid peroxidation in cell membranes [20]. Various I/R injury models have been used [21-24] and many studies have been conducted about I/R [25-27]. It is known microcirculation may be affected by diabetes, along with I/R, which is the reason we used STZ-induced diabetic rats to determine the effects of fullerenol.

Reperfusion injury has some features such as vasoconstriction, thrombosis, edema, leukocyte infiltration, and increased free radicals [28]. Various methods have been described to evaluate muscle injury due to I/R such as mitochondrial enzyme activity, the permeability of vessels, lactate dehydrogenase levels, neutrophil infiltration [28-30]. Histologic examination may also be used in the evaluation of I/R injury [31]. A histologic examination can show myocyte injury directly, including the integrity of the cell membrane, gaps within the cell, and staining intensity [30,32]. In previous studies, morphological changes due to I/R was shown [33-35]. In this study, we used histopathological examination to show I/R injury and the effect of fullerenol on I/R injury of skeletal muscle.

Previous studies found that fullerene derivatives are potent antioxidants [36,37] and have tissue-protective effects against oxidative damage [38,39]. In addition, it is known that C60 can react with up to 34 methyl radicals and release nitric oxide (NO). Therefore, we used fullerene derivates in our study. A previous study demonstrated that fullerenol attenuated ischemia-induced lung injury [36]. Foroshani et al. [40] stated that fullerenol decreased ischemia-induced brain edema. Zavodovsky et al. [41] conducted a study about the influence of C 60 fullerene on I/R injury in the skeletal muscle and found that fullerene reduced ischemic muscle trauma. Erer et al. [42] used iloprost to find that lung injury induced by skeletal muscle I/R was alleviated. Another study showed that fullerene derivates decreased neurological dysfunction and brain edema and had protective effects against ischemia-induced damage [43]. Our findings also revealed that fullerenol C60 has protective effects against lower skeletal muscle damage due to ischemia-reperfusion injury.

Limitations

We have some limitations to our study. First, we investigated the effect of fullerenol C60 on I/R injury in skeletal muscle by using immunohistological examination only. We did not use any grading and scoring methods to show skeletal muscle injury. In addition, we did not examine any biochemical parameters and ROS levels.

Conclusion

We showed that fullerenol C60 has protective effects against skeletal muscle damage after I/R in diabetic rats. We believe that researching nanoparticles, the most important raw material of the future, particularly fullerenol C60, can help understand the possible protective effects and mechanisms underlying I/R damage.

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Examination of the relationship between health literacy, concern and anxiety in adults with diabetes mellitus or hypertension and comparison with individuals without chronic disease

Diyabetes mellitus veya hipertansiyonu olan yetişkin bireylerde sağlık okuryazarlığı, endişe ve anksiyete arasındaki ilişkinin incelenmesi ve kronik hastalığı olmayan bireylerle karşılaştırılması

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Abstract

Aim: The low level of health literacy in our country can cause worry and anxiety. The effect of this situation in individuals with chronic diseases was compared with healthy individuals. In our study, the level of health literacy (HL) of individuals with a chronic disease (Diabetes Mellitus (DM) or Hypertension (HT)) who applied to the Family Medicine outpatient clinic was determined. The effect of HL on anxiety levels in individuals with and without chronic diseases was investigated.

Methods: This cross-sectional study included those with chronic diseases (DM or HT) and healthy individuals. The data were obtained with Adult Health Literacy Scale (AHLS), Anxiety, Anxiety Scale (WAS) and descriptive questionnaire. SPSS 22 statistics program was used for statistical analysis. Descriptive statistics, chi-square analysis, ANOVA and Pearson correlation analysis were used in statistical evaluation.

Results: The mean scores of Adult Health Literacy Scale (AHLS) were 6.21 for individuals with HT, 6.58 for individuals with DM and 14.92 for healthy subjects. The mean scores of Worry and Anxiety Scale (WAS) were 46.42 in individuals with HT, 44.54 in individuals with DM and 34.19 in healthy individuals. The scores of scales were significantly different among individuals with and without chronic diseases (DM or HT) ($P<0.01$). A significant negative correlation was found between the scores of WAS and AHLS among individuals with DM and HT ($P<0.01$, $P<0.01$, r=-0.35, r=-0.45, respectively).

Conclusion: This study showed that individuals with DM and HT had lower health literacy levels and higher worry and anxiety scores than healthy individuals. It was found that low health literacy level was associated with chronic diseases and inversely related to worry and anxiety.

Keywords: Health literacy, Chronic diseases, Worry and anxiety

Öz

Amaç: Ülkemizde sağlık okuryazarlık düzeyinin düşük olması, endişe ve anksiyeteye neden olabilmektedir. Bu durumun kronik hastalıklara sahip bireylerdeki etkisi sağlıklı bireyler ile karşılaştırıldı. Çalışmamızda Aile Hekimliği polikliniğine başvuran, kronik hastalığa sahip (Diyabetes Mellitus (DM) veya Hipertansiyon (HT)) bireyler ile sağlıklı bireylerin sağlık okuryazarlığı (SOY) düzeyi belirlendi. SOY düzeyinin bireylerdeki endişe ve anksiyete üzerindeki etkisi araştırıldı.

Yöntemler: Bu çalışmaya kronik hastalıklara sahip (DM veya HT) ve sağlıklı bireyler dahil edildi. Veriler Yetişkin Sağlık Okuryazarlık Ölçeği (YSOÖ), Endişe ve Anksiyete Ölçeği (EAÖ) ve tanımlayıcı anket ile elde edilmiştir. Araştırma kesitsel tiptedir. Verilerin değerlendirilmesinde SPSS 22 istatistik programı kullanılmıştır. İstatistiki değerlendirmede tanımlayıcı istatistikler, ki kare analizi, ANOVA ve Pearson korelasyon analizi kullanılmıştır.

Bulgular: Araştırmada YSOÖ puan ortalamaları; HT' u olan bireylerde 6,21, DM' u olan bireylerde 6,58, sağlıklı bireylerde 14,92'dir. EAÖ puan ortalamaları; HT' u olan bireylerde 46,42, DM' u olan bireylerde 44,54, sağlıklı bireylerde 34,19' dur. Sağlıklı bireyler, kronik hastalığı olan bireylerle (DM veya HT) kıyaslandığında her iki ölçekte de anlamlı farklılık içermektedir ($P<0,01$). DM ve HT' u olan bireylerin EAÖ puanı ile YSOÖ puanı arasında anlamlı negatif korelasyon bulundu (sırasıyla $P<0,01$, $P<0,01$, r= -0,35, r=-0,45).

Sonuç: Bu çalışma DM ve HT' u olan bireylerin sağlıklı bireylere kıyasla SOY düzeylerinin düşük, endişe ve anksiyete puanının yüksek olduğunu göstermiştir. Düşük SOY düzeyinin kronik hastalıklara eşlik etmesinin yanı sıra endişe ve anksiyete ile de ters ilişkili olduğu bulunmuştur.

Anahtar kelimeler: Sağlık okuryazarlığı, Kronik hastalıklar, Endişe ve anksiyete

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Introduction

Health literacy (HL) is defined as the ability of an individual to comprehend and evaluate the medical information given and develop appropriate behavior. It is classified in three groups. Functional HL refers to an individual's ability to apply basic literacy knowledge to health related materials, communicative HL refers to developing social and cognitive functions, directing them in an environment, and being able to apply them to daily life, while critical HL refers to an individual's ability to make the right decision by analyzing the information with a critical approach on health-related issues, and to ensure his/her individual and social development [1,2]. It was found that HL level was poor in all developed, developing, and underdeveloped countries. It has been reported that poor HL causes difficulty in maintaining glycemic control in diabetic individuals and regulating blood pressure in hypertensive individuals, leading to a higher risk of complications, and resulting in increased levels of anxiety [3-5].

This study was conducted to examine HL levels in individuals with DM or HT, investigate their relationship with anxiety, and compare them with individuals without chronic disease.

Materials and methods

This cross-sectional, descriptive, and analytical study was conducted on 300 individuals who applied to the family medicine department's outpatient clinic in a university hospital. Among all, 100 had DM, 100 had HT and 100 were healthy.

Only otherwise-healthy individuals over the age of 18 years who had a chronic disease (DM or HT) and could communicate were included in the study. Individuals with more than one chronic disease, unable to communicate and those aged under 18 years were not included.

The data of the research were collected using the Adult Health Literacy Scale (AHLS), Anxiety Scale (AS) and a questionnaire form consisting of 12 questions prepared by the researchers by scanning the literature. The questionnaire included questions about socio-demographic data of the individuals (age, gender, marital status, socioeconomic level, educational status, occupation), the presence of chronic diseases, presence of DM or HT, duration of the disease, status of regular checks, regular drug use, and reasons for discontinuation of medications.

AHLS is a scale of 23 questions, consisting of 22 questions related to health information and drug use, and one question to locate and name the organs. Among them, 13 are yes / no questions, 4 are filling the gap, 4 are multiple choice and 2 are matching questions. Possible scores vary between 0-23. HL increases with the score obtained. It has been demonstrated that AHLS is a valid and reliable scale in evaluating health literacy and can be used safely in adult individuals [6].

AS is a Likert-type scale with nine (0-8) points. Score range is between 0 and 80. The scale provides the opportunity to distinguish between those who do and do not comply with the diagnostic criteria of anxiety disorders. It clearly measures anxiety-related helplessness. It has been demonstrated as a valid-reliable scale in measuring anxiety [7].

Prior to the study, approval and necessary permissions were obtained from Yuzuncu Yıl University Ethics Committee (Record Number: 141, Date: 20.06.2018), and data were collected between August 2018 and December 2018.

Statistical analysis

The data obtained from the research were assessed with the SPSS 22 statistical program. Descriptive statistical analysis, chi-square analysis, ANOVA and Pearson correlation analysis were used to evaluate the data. $P<0.05$ was considered statistically significant.

Results

Evaluation of educational status revealed that 67 DM patients (67%) and 68 HT patients (68%) were illiterate or primary school graduates, along with four (4%) healthy individuals. While 87 (87%) DM patients and 84 (84%) HT patients were unemployed, 89 (89%) healthy individuals were pursuing a career. The mean ages of individuals with HT, DM and healthy participants were 61.63 (10.05) years (min 33, max 87 years), 56.74 (8.77) years (min 26, max 80 years), 29.34 (7.51) years.

Forty-one (41%) DM patients and 36 (36%) HT patients had regular check-ups (at least every six months). Forty-one (41%) DM patients and 37 (37%) HT patients did not use their medication regularly. When the reasons for discontinuation of medication were examined, the most common answer was 'I forget' (n=21 (51.2%) and n=18 (50.0%) for DM and HT patients, respectively). The least frequent responses were 'I do not trust my doctor' and 'I do not benefit from treatment' (n=1 (2.4%) for DM and n=2 (5.6%) for HT) among both patient groups. The questionnaire results of the individuals included in the study are shown in Table 1.

Table 1: Questionnaire responses of individuals included in the study (n=300)

		Group			
		DM n (%)	HT n (%)	Healthy n (%)	*P*-value*
Age(mean)		56.74	61.63	29.34	<0.01
Gender	Woman	63(63)	53(53)	55	0.31
	Man	37(37)	47(47)	45	
Marital status	Married	91(91)	82(82)	46	<0.01
	Single	9(9)	18(18)	54	
Education	Illiterate	47(47)	39(39)	0	
	Primary education	20(20)	29(29)	4	<0.01
	Secondary education	19(19)	15(15)	3	
	High School	13(13)	15(15)	11	
	University	1(1)	2(2)	82	
Occupation	Unemployed	87(87)	84(84)	11	
	Public Officer	3(3)	10(10)	26	<0.01
	Worker	10(10)	2(2)	4	
	Health professional	0(0)	0(0)	20	
	Other	0(0)	4(4)	39	
For how many years?	0-1 year	8(8)	7(7)	-	
	>1 year - 5 years	27(27)	26(26)	-	0.56
	>5 years - 10 years	36(36)	29(29)	-	
	More than 10 years	29(29)	38(38)	-	
Regular checks	every 3 months	23(23)	9(9)	-	
	every 6 months	18(18)	27(27)	-	0.23
	when the prescription expires	56(56)	57(57)	-	
	I don't go	3(3)	7(7)	-	
Regular use of medication	I use regularly	59(59)	63(63)	-	0.13
	I sometimes skip	39(39)	30(30)	-	
	I often skip	2(2)	7(7)	-	

* ANOVA, DM: Diabetes mellitus, HT: Hypertension

Among all participants, the mean AHLS scores were significantly higher in men, singles, those with a high education level (high school and university graduates), professionals and individuals without chronic disease ($P<0.05$ for all).

Among patients with a chronic disease (DM and HT), the mean AHLS scores were significantly low in those who have

had the disease for more than 10 years, who do not have regular check-ups (at least every six months) and who do not use medication regularly (P<0.05 for all).

The mean AHLS scores of healthy individuals included in the study was the highest, while that of HT patients was the lowest, with a significant difference between them (P<0.01). The mean AHLS scores of DM and HT patients included in the study were similar (P= 0.32) (Table 2).

Among all participants, the mean AS scores were significantly high in women, those with low socioeconomic statuses, low education levels (primary school and illiterate), nonprofessionals and individuals with a chronic disease (DM or HT) (P<0.05 for all).

Among patients with a chronic disease (DM and HT), the mean AS scores were high in those who have had the disease for more than 10 years, and who do not have regular check-ups (at least every six months) (P<0.05 for all).

The mean AS score of HT patients included in the study was the highest, while that of healthy individuals was the lowest. There was a significant difference between healthy individuals and those with DM or HT (P<0.01). There were no significant differences between the mean AS scores of DM and HT patients included in the study (P=0.36) (Table 3).

Bilateral correlation analysis between the mean AS and AHLS scores of individuals with DM and HT revealed a significant negative correlation, and a non-significant negative correlation was found among healthy individuals (Table 4).

Bilateral correlation analysis was performed for mean AS and AHLS scores of all individuals included in the study to find that mean AHLS scores decreased as AS scores increased and vice versa. A significant negative intergroup correlation was found between the groups (P<0.01, r=-0.43).

Table 2: Comparison of mean AHLS scores in individuals with DM, HT and healthy individuals included in the study (n=300)

	n	Mean Grade	Std. Deviation	Min.	Max.	*P*-value*
HT	100	6.21	4.01	0	20	
DM	100	6.58	4.09	0	16	<0.01
Healthy	100	14.92	2.91	7	20	
Total	300	9.24	5.47	0	20	

*ANOVA, DM: Diabetes mellitus, HT: Hypertension, AHLS: Adult health literacy scale

Table 3: Comparison of mean AS scores in individuals with DM, HT and healthy individuals included in the study (n=300)

	n	Mean Grade	Std. Deviation	Min.	Max.	*P*-value*
HT	100	46.42	13.93	4	70	
DM	100	44.54	13.92	14	74	<0.01
Healthy	100	34.19	18.30	0	77	
Total	300	41.72	16.74	0	77	

* ANOVA, DM: Diabetes mellitus, HT: Hypertension, AS: Anxiety scale

Table 4: Correlation analysis of mean AS scores and mean AHLS scores in individuals with DM, HT and healthy individuals included in the study (n=300)

	r*	*P*-value*
DM	-0.35	<0.01
HT	-0.45	<0.01
Healthy individuals	-0.02	0.78

* Pearson correlation analysis, DM: Diabetes mellitus, HT: Hypertension

Discussion

HL is an important public health problem affecting the entire society, especially individuals with chronic diseases (such as DM and HT). Studies conducted reveal that HL levels are not at a sufficient level neither in our country nor in the world, and the HL levels of individuals with chronic diseases are even below the national average [8,9].

In studies conducted in the USA and Europe, the level of HL in individuals with a chronic disease was highly insufficient (64% and 26%, respectively), and in the studies conducted in our country, the level of HL of individuals with a chronic disease was low (64.6%) [10-12]. In our study, similar to the literature, individuals with a chronic disease had low AHLS scores.

In the studies carried out abroad and our country, the level of HL was higher among men, those with high education levels (high school, university, post-graduate) and those with a profession [13-15]. In harmony with the literature, in our study, the AHLS scores of men, individuals with high educational status and those with a profession were significantly higher. Moreover, in our study, single individuals had higher HL levels compared to married people (P<0.01).

In our study, when individuals with chronic diseases were evaluated among themselves, similar to the literature, the HL levels of those with a disease duration of more than 10 years, those who did not have regular checkups (at least every 6 months) and those who did not use their medication regularly were low (P<0.05 for all) [15,16].

Studies conducted in Konya, Istanbul and Izmir have shown that anxiety is high among individuals with chronic diseases and significantly different from that among healthy individuals [17-19]. In our study, individuals with a chronic disease (DM and HT) had also higher AS scores and showed a significant difference compared to healthy individuals.

We found that those with low HL levels were accompanied by prominent levels of anxiety, and there was a significant negative correlation between these two parameters. Assessment of the three groups (DM, HT, healthy individuals) of our study separately revealed that anxiety decreased as the HL level of individuals with DM and HT increased, and vice versa. In healthy individuals, there was no inverse relationship between these two parameters. In the literature review, there was no study on the correlation between AS and AHLS. Our research may be the first in this regard.

Limitations

The lower mean age of healthy individuals compared to the other groups is among the limitations of our study. It can be said that the number of samples could not be kept larger by adhering to a single outpatient clinic, and chronic diseases other than DM and HT were not included. However, we believe this study is important because it is the first study to compare healthy individuals with those with a chronic disease.

Conclusion

This study revealed that individuals with a chronic disease have low HL levels compared to healthy individuals, however, they are accompanied by anxiety, which decreases with increasing HL level. It may be recommended to increase community-based projects, provide training, and prepare awareness-raising presentations to increase HL levels of all members of the society, especially individuals with chronic diseases. In addition, it will be beneficial to distribute HL booklets including simple illustrations to outpatient clinics in hospitals, which are especially visited by chronic patients. Increasing public spots consisting of short, clear, and simple information will help easily reach every segment of the public, under the leadership of our Ministry of Health. Creating scales suitable for the cultural structure of our country for the exact

determination of HL is of significance. Even if there has been an increase in our country in recent years, it is necessary to conduct current studies on HL, since sufficient levels have not been reached yet.

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Evaluation of Notch1 gene expression in prostate carcinoma

Prostat karsinomunda Notch1 gen ekspresyonunun değerlendirilmesi

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Abstract

Aim: Prostate cancer is one of the most common cancers in the world and its incidence is rapidly increasing. Currently, several new treatment strategies that target specific signaling pathways as well as immunotherapy are being explored for prostate cancer. In the current study, we aimed to investigate the frequency and clinicopathologic features associated with Notch1 gene expression using immunohistochemistry and real-time-polymerase chain reaction in patients with prostate cancer.

Methods: This research was planned as a cohort study. Tissue samples of 60 patients with prostate cancer and 20 patients with benign prostatic hyperplasia were selected from the archives. Twenty patients with benign prostatic hyperplasia were used as the control group. The relative expression levels of Notch1 gene were determined by real-time-polymerase chain reaction while Notch1 protein expression was analyzed using immunohistochemistry.

Results: We found Notch1 gene expression at a significant level in 17 (28.3%) of 60 patients with prostate carcinoma. We found a significant correlation between high Gleason scores (P=0.007), high ISUP (International Society of Urologic Pathologists) grade group scores (P=0.008) and high prostate-specific antigen levels (P=0.018) for Notch1 gene expression.

Conclusions: We conclude that Notch1 is important in prostate carcinogenesis. Therefore, determining Notch1 will be an essential step in targeted therapies in patients with prostate carcinoma.

Keywords: RT-PCR, Immunohistochemistry, Notch1, Prostate cancer, ISUP, PSA

Öz

Amaç: Prostat kanseri dünyada en yaygın görülen kanserlerden biridir ve sıklığı giderek artmaktadır. Şu anda, prostat karsinomu için etkin bir tedavi yöntemi olmamakla birlikte immünoterapiyi ve spesifik sinyal yolaklarını hedefleyen yeni tedavi stratejileri araştırılmaktadır. Biz bu çalışmada prostat kanseri hastalarında immünohistokimya ve Real-Time polimeraz zincir reaksiyonu ile Notch1 gen ekspresyonunu ve klinikopatolojik özellikler ile ilişkisini araştırmayı amaçladık.

Yöntemler: Bu araştırma bir kohort çalışma olarak planlandı. Hastane arşivimizden 60 tane prostat kanseri ve 20 tane benign prostat hiperplazisi olan hastaların parafin blokları seçildi. Benign prostat hiperplazisi olan 20 hasta kontrol grubu olarak kullanıldı. Notchl gen ekspresyonu seviyeleri immünohistokimya ve Real-Time polimeraz zincir reaksiyonu kullanılarak analiz edildi.

Bulgular: Çalışmamızda 60 prostat karsinomu tanılı hastamızın 17'sinde (%28,3) Notch1 gen ekspresyonunu anlamlı düzeyde yüksek bulduk. Ayrıca yüksek Gleason skoru (P=0,07), yüksek ISUP skoru (P=0,008) ve yüksek prostat spesifik antijen düzeyi (P=0,018) ile Notch1 ekspresyonu arasında anlamlı bir korelasyon bulduk.

Sonuçlar: Prostat karsinogenezinde Notch1'in önemli olduğu sonucuna vardık. Bu nedenle, Notch1 prostat karsinomlu hastalarda hedefe yönelik tedavilerde önemli bir adım olacaktır.

Anahtar kelimeler: RT-PCR, İmmünohistokimya, Notch1, Prostat kanseri, ISUP, PSA

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Introduction

Prostate carcinoma (PCa) is the most commonly diagnosed malignancy in men and its incidence is rapidly increasing. Many factors are associated with pathophysiology and progression of PCa [1]. Hormonal imbalances, genetic factors, and many factors such as carcinogens in the diet and infectious agents are all sources that have been determined to contribute to prostate carcinogenesis [1-4]. The prostatic epithelium is composed of two types of cells: Luminal epithelial cells and basal epithelial cells [4]. Primary prostate tumors are almost always characterized by a luminal phenotype suggesting a luminal origin, but recently it has been indicated that both types of these epithelial cells are possible cells of origin for prostate carcinogenesis.

The Notch was first discovered in 1917 by Thomas Hunt Morgan [6]. Later, Kidd et al. discovered that the loss of Notch expression not only affected the neurodevelopmental phenotype of this Drosophila strain, but also the morphology of the eye, wing, and hair [7]. In later studies, it was found that the disorder of Notch expression is associated with some diseases, for example, T-cell acute lymphoblastic leukemia (T-ALL) patients, CADASIL syndrome (cerebral autosomal- dominant arteriopathy with subcortical infarcts and leukoencephalopathy) and Alagille syndrome [8-10]. The Notch signaling pathway plays a significant role both in embryonic development and the determination of cell fate in organ homeostasis [11]. The main function of the Notch pathway is the regulation of bi-directional cell fate decisions. Furthermore, it has been shown that Notch activation in cancer cells causes abnormal cell proliferation. Mammals have four Notch receptors, Notch1, Notch2, Notch3 and Notch4. There are also five Notch ligands including Jagged1, Jagged2, Delta 1, Delta 3 and Delta 4. In addition, the ligands for the Notch receptor are divided into two groups: Delta-like ligands (DLL1, DLL3, and DLL4) and Serrate-like ligands (JAG1 and JAG2). The Notch gene encodes a 300 kD single-pass transmembrane receptor. The Notch receptor consists of two parts, one intracellular and one extracellular. The large extracellular region contains 36 consecutive EGF (Epidermal Growth Factor) -like repeats and 3 cysteine-rich LIN 12 repeats. EGF repeats allow the Notch receptor to interact with ligands. The intracellular part of the Notch receptor is also called Notch Intracellular Domain (NICD) [12-14].

Many cancer pathways have been investigated to date [15,16]. Recently, studies have been examining the Notch pathway in terms of prostate carcinogenesis, with no full elucidation [17]. Therefore, in this study, we aimed to investigate the frequency and clinicopathologic features associated with Notch1 gene expression using immunohistochemistry and real-time-polymerase chain reaction in patients with prostate cancer.

Materials and methods

Tissue samples

Tissue samples from prostate carcinoma patients who underwent surgery between 2010 and 2017 were selected from the archives of Department of Pathology. The study was performed in accordance with the principles of Declaration of Helsinki and approved by the Ethics Committee of Akdeniz University (Date:30.11.2016, number:625). This study was supported by Akdeniz University Research Fund Accounting (BAP Project no: TTU-2017-2289). All our patients were sampled with suspicion of prostate carcinoma. The blocks with sufficient tumor tissue for the study were selected in historical order since 2017. Hematoxylin-Eosin stained preparations obtained from formalin-fixed, paraffin-embedded blocks were removed from the archive and re-examined. Sixty of our patients had prostate carcinoma; 33 samples were obtained with tru-cut biopsy, 16 with radical prostatectomy and 11 with prostate TUR. Twenty patients with benign prostatic hyperplasia were used as the control group. Notch1 gene expression was examined both immunohistochemically and by RT-PCR in 60 patients with prostate cancer and 20 with benign prostatic hyperplasia. The optimal blocks for immunohistochemistry and real-time-polymerase chain reaction (RT-PCR) were selected. The anamnesis, stage, diagnosis history, PSA values and treatment follow-up times for the cases were obtained from our hospital's automation system, patient follow-up files, and from the patients themselves or their relatives via telephone.

Immunohistochemistry

In retrospectively selected cases, sections with a thickness of 5 μm were obtained from the appropriate paraffin blocks. Immunohistochemistry was performed using Cell Signaling Technology rabbit monoclonal Notch1(D1E11) XP® antibody (Cell Signaling Technology, Danvers, MA, USA) at 1:50 dilution for two hours. The staining procedure was performed on the DAKO Omnis autostainer (Agilent, Santa Clara, CA 95051, USA). Sections were examined using light microscopy (Zeiss, Oberkochen, Germany). Negative controls were performed by replacing the primary antibody with the nonimmune IgG in the same dilutions as the specific antibodies. Positive staining for Notch1 was observed in the cytoplasm and nucleus.

RNA Extraction and RT-PCR (Reverse Transcription Polymerase Chain Reaction)

Total RNA was extracted from FFPE tissue using Purelink FFPE RNA Isolation Kit (Cat No: K156002; Invitrogen) according to the manufacturer's instructions. The amount of total RNA in each sample is measured using NanoDrop (Maestrogen, Taiwan). All samples are diluted to a concentration of 25 ng/μl. The reverse transcription reaction was performed using High Capacity cDNA Reverse Transcription Kit (Appliedbiosystems by Thermo Fisher Scientific). Complementary DNA was prepared from 25 ng of isolated total RNA, with 10xRT Random Primers, according to the manufacturer' s instructions. The program was as follows: 10 minutes at 25 ºC, 2 hours at 37 ºC, 5 minutes at 85 ºC and at 4 ºC thereafter on a polymerase chain reaction thermocycler (Applied Biosystems). The resulting cDNA was diluted to 1/5.

qPCR

The relative expression levels of Notch1 gene were determined by qPCR with TaqMan® Gene Expression Master Mix in Applied Biosystems 7900HT Real-Time PCR System and normalized to 18S. Primers and FAM-MGB hydrolysis probes were TaqMan® Gene expression assays on demand for Notch11 Hs01062014_m1 and 18S (Hs99999901_s1) (Applied biosystems by Thermo Fisher Scientific). All samples were

performed in duplicates. The PCR amplification program was as follows: 20 seconds at 95 ºC, 40 cycles of 1 second at 95 ºC and 20 seconds at 60 ºC. In addition, as the non-template control, ddH2O was analyzed for every plate. To assure that the amplification efficiencies for each real-time-PCR run and each gene were similar, the slope was adjusted for each sample. The data obtained from the qPCR was analyzed by the ΔΔCt-method.

Statistical analysis

Data were evaluated with the SSPS 22® program. Descriptive statistics were presented as mean (standard deviation) and median (minimum-maximum) for normally and non-normally distributed values, respectively. Nominal variables were shown as number (n) and percentage (%). As there were two groups, the significance of the difference between the groups was evaluated with the Student's t-test or the Mann Whitney U-test. Categorical variables were evaluated with the Pearson Chi-square test. A value of $P<0.05$ was considered statistically significant.

Results

Eighty cases, diagnosed at the Akdeniz University Medical Faculty Pathology Department between 2010 and 2017, were selected for this study. Of the patients with prostate adenocarcinoma, 20, 10, 14, 8 and 8 patients had Gleason scores of 6, 7, 8, 9 and 10, respectively. In the 80 cases we evaluated, the youngest and oldest patients were 46 and 81 years old, with a mean age of 65 years.

PSA values ranged between a minimum of 0.16 ng/ml and a maximum of 260 ng / ml. The Gleason score in our prostate adenocarcinoma cases ranged from a minimum of 6, to a maximum of 10. ISUP grade group were scored in 21 patients as ISUP-1, in eight patients as ISUP-2, in one patient as ISUP-3, in 14 patients as ISUP-4 and in 16 patients as ISUP-5. Notch1 gene expression was detected in 17 out of 60 patients by RT-PCR (Table 1). Thirty-three specimens were obtained with tru-cut biopsy, 16 with radical prostatectomy and 11 with prostate TUR material.

In immunohistochemical examination, cytoplasmic and nuclear staining in malignant gland epithelium was considered positive. In 17 of our 60 prostate carcinoma patients, a positive reaction was observed in the malignant gland epithelium. In our control group with benign prostatic hyperplasia, focal staining with Notch-1 was observed in the basal cells and smooth muscles in the stroma. In our control group, no staining was observed in the prostate gland epithelium. Immunohistochemically, going by the RT-PCR results, preexisting cytoplasmic and nuclear immunoreaction was observed in 17 of 60 patients (Figure 1, 2). A significant relationship was found between Notch1 gene expression, increase in Gleason scores ($P=0.007$), and ISUP grade groups (Figure 3).

The Notch1 gene expression of our patients with prostate adenocarcinoma were compared with those with benign prostatic hyperplasia, as evaluated with RT-PCR. Out of 60 patients with prostate adenocarcinoma, 17 had significantly higher levels of Notch1 gene expression than patients with benign prostatic hyperplasia.

In addition, in our study, 10 out of 17 patients with Notch1 gene expression were metastatic, and nine metastatic distant organs were detected. We could not perform a statistical evaluation because our data on metastasis were incomplete. We found that Notch1 gene expression was significantly associated with Gleason score, ISUP grade group increase and PSA elevation (Table 2).

Table 1: Notch-1 gene expression of 60 patients with prostatic adenocarcinoma compared to patients with benign prostatic hyperplasia (Bold texts: Notch-1 positive patients)

Patient number	Notch1 CT	18SrRNA CT	ΔCT	ΔΔCT (8.595)	Fold difference (2^-ΔΔCT)
1	31.98	21.64	10.34	1.745	0.298
2	27.64	15.43	12.21	3.615	0.082
3	**33.95**	**26.14**	**7.81**	**-0.785**	**1.72**
4	**36.146**	**29.16**	**6.99**	**-1.605**	**3.042**
5	29.22	14.78	14.44	5.845	0.017
6	**34.37**	**27.69**	**6.68**	**-1.915**	**3.771**
7	**34.85**	**27.88**	**6.97**	**-1.625**	**3.08**
8	**30.93**	**25.50**	**5.43**	**-3.165**	**8.96**
9	**33.89**	**26.42**	**7.47**	**-1.125**	**2.181**
10	35.11	24.58	10.53	1.935	0.262
11	29.44	16.01	13.43	4.835	0.035
12	35.69	26.76	8.93	0.335	0.79
13	33.97	21.83	12.14	3.545	0.09
14	29.98	16.18	13.8	5.205	0.027
15	**33.214**	**25.079**	**8.135**	**-0.46**	**1.376**
16	31.89	18.37	13.52	4.925	0.033
17	31.86	18.04	13.82	5.255	0.026
18	30.197	17.895	12.30	3.705	0.0389
19	34.38	25.15	9.23	0.635	0.64
20	**36.45**	**27.96**	**8.49**	**-0.105**	**1.08**
21	33.81	23.85	9.96	1.365	0.388
22	**29.89**	**22.14**	**7.75**	**-0.845**	**1.80**
23	**34.18**	**28.63**	**5.55**	**-3.045**	**8.25**
24	30.73	17.14	13.59	4.995	0.031
25	**34.11**	**26.13**	**7.98**	**-0.615**	**1.53**
26	**35.241**	**27.249**	**7.99**	**-0.605**	**1.52**
27	29.531	17.173	12.36	3.765	0.074
28	30.285	16.336	13.95	5.355	0.024
29	28.76	16.75	12.01	3.415	0.09
30	30.999	17.42	13.58	4.985	0.0316
31	29.536	16.135	13.40	4.805	0.058
32	34.501	24.496	10	1.405	0.378
33	31.473	17.895	13.58	4.985	0.032
34	29.86	15.97	13.89	5.295	0.03
35	31.861	20.559	11.30	2.705	0.153
36	31.793	18.893	12.9	4.305	0.051
37	30.1	17.87	12.23	3.635	0.081
38	33.63	23.63	10	1.405	0.38
39	34.43	24.38	10.05	1.455	0.36
40	**33.918**	**25.714**	**8.20**	**-0.395**	**1.315**
41	33.626	22.241	11.39	2.795	0.144
42	**35.059**	**27.177**	**7.88**	**-0.715**	**1.64**
43	31.431	19.075	12.36	3.765	0.074
44	**35.19**	**27.78**	**7.41**	**-1.185**	**2.27**
45	34.39	24.88	9.51	0.915	0.53
46	28.99	15.56	13.43	4.835	0.04
47	30.93	17.03	13.09	4.495	0.044
48	33.84	22.63	11.21	2.615	0.163
49	**35.61**	**27.62**	**7.99**	**-0.605**	**1.52**
50	31.08	15.99	15.09	6.495	0.011
51	30.0	18.29	11.71	3.115	0.12
52	29.099	19.392	9.71	1.115	0.461
53	30.338	15.53	14.81	6.215	0.013
54	30.508	17.225	13.28	4.685	0.0389
55	29.98	16.98	13	4.405	0.047
56	30.167	18.165	12	3.405	0.094
57	33.51	23.50	10.01	1.415	0.38
58	29.392	15.245	14.15	5.555	0.0213
59	29.60	18.76	10.84	2.245	0.22
60	**29.299**	**21.406**	**7.89**	**-0.705**	**1.63**

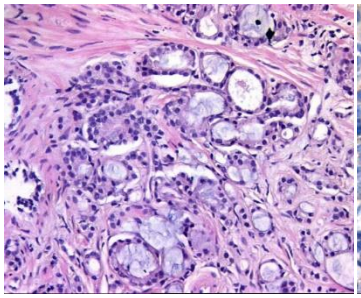

Figure 1: Prostate adenocarcinoma (H&E 20X)

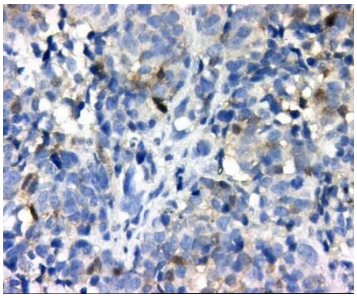

Figure 2: Prostate adenocarcinoma positive with Notch1 (40X)

Table 2: Mean age, PSA, ISUP and Gleason scores of scores in Notch-1 positive and negative patients

	Notch-1 positive (n=17)		Notch-1 negative (n=43)		*P*-value
	mean	SD	mean	SD	
Age	67	9	65	8	0.407
ISUP Grade Group	3.82	1.47	2.58	1.67	0.008
Gleason Score	8.35	1.41	7,23	1,32	0.007
Serum PSA Level	184.51	432.84	24.67	45.10	0.018

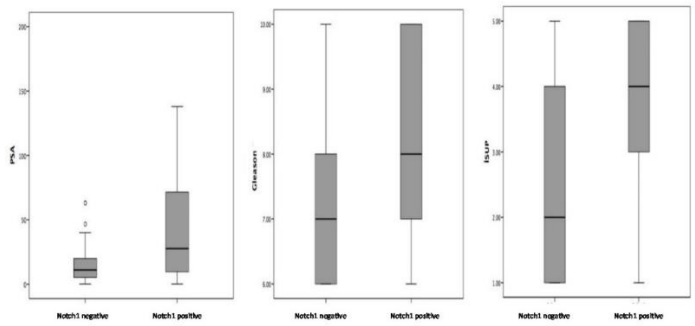

Figure 3: A significant relationship was found between Notch1 gene expression and Gleason score increase, ISUP score increase, and PSA elevation

Discussion

The aim of this study was to investigate the frequency and clinicopathologic features associated with Notch1 gene expression. We demonstrated that high Gleason scores, high ISUP grade group scores and high PSA levels significantly correlated with Notch1 gene expression.

It is well known that Notch signaling regulates normal and cancer development in many tissues including the prostate. The expression of Notch pathway elements clearly shows the regulation of Notch signaling pathway in prostate cancer in cases of established cancer cell lines, transgenic mouse models, and clinical tumor specimens.

The role of Notch ligands and Notch receptors in prostate tumorigenesis is not well defined. In a study in 2006, Notch1 mRNA expression has been reported to be significantly down-regulated in prostate cancers, thus suggesting a potential tumor suppressor role for Notch1 in prostate cancer [18]. This study also examined the expression of the remaining members of the Notch receptor family in prostate cancer but found no significant differences in mRNA levels for Notch-2-3-4 between benign and malignant prostate specimens [18]. Conversely, a study in 2007 revealed that Notch1 protein was overexpressed in malignant prostates compared to benign controls [19]. This suggests a potential carcinogenic role of Notch1 in prostate tumorigenesis. Notch1 protein expression, rather than Notch1 mRNA expression, is a more reliable indicator of Notch1 functionality. Researchers in a study showed that the Notch signal is associated with prostate development and cancer cell growth, and they correlated high grade localized PCa with the gene expression of the Notch signal. Because of the role of basal epithelial cells in the development of prostate carcinoma, they have suggested that PCa and basal epithelial cell relationship should be investigated and discussed [20]. A review of Notch pathway and prostate tissue revealed that Notch pathway was involved in prostate differentiation in benign prostate tissue and associated with lethal potential in prostate cancers [21]. The expression of Immunohistochemical Notch-1 in normal prostate tissue, prostatic intraepithelial neoplasia and PCa was investigated. As a result of this study, stronger staining was observed in prostatic intraepithelial neoplasia than prostatic adenocarcinomas [22].

Prostate cancer most frequently metastasizes to bone, brain, and lymph nodes. Therefore, the relationship between the metastasis of prostate cancers and Notch pathway was investigated [22-29]. As a result of these studies, metastatic prostate cancer was shown to have increased expression levels of the Notch1 receptor ligand, when compared to benign prostate tissue and localized prostate cancer [22-28].

Surgical treatment and chemotherapy are used in the treatment of prostate cancers. Although chemotherapy agents used in prostate carcinomas have exceptionally good response at first, it is known that a rapid resistance to chemotherapeutic agents develops soon. Therefore, resistance mechanisms against chemotherapeutic agents have been investigated. Since the notch pathway is known to play a role in prostate carcinomas, its effect on chemotherapy resistance has been researched. It is concluded that the notch pathway is effective in the progression, metastasis, and chemotherapy resistance of prostate cancer [24,28].

To fully understand the role of Notch1 in prostate carcinogenesis, it may be necessary to assess the possibility that primary tumor growth and metastasis progression may be affected differently by Notch signaling. There is also a need for further study, more mouse models, and cell lines in this regard. If the role of Notch1 in prostate tumorigenesis is better understood, therapeutic strategies for Notch1 can be developed. Therefore, this is an important and urgent need, given the proposed use of anti-Notch compounds for the treatment of cancer, including prostate cancer.

Limitations

Our study had some limitations. Due to our financial limitation, we were able to study a small number of patients and evaluate Notch1 only.

Conclusions

The current study showed that a high Gleason score, high ISUP scores, and high PSA levels and Notch1 gene expression are significantly correlated. Due to the small number of studies related to this topic and the inadequate data obtained, it is important to conduct further studies with wider series to determine the prognosis of PCa patients and manage their treatment.

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Association between coronary artery disease severity and videocapillaroscopic findings of nail fold capillary circulation

Koroner arter hastalığının şiddeti ile tırnak yatağı kapiller dolaşımının videokapilleroskopik bulguları arasındaki ilişki

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Abstract

Aim: Endothelial dysfunction plays a significant role in the etiology of coronary artery disease (CAD), which develops due to atherosclerosis, and is a major cause of morbidity and mortality. Nail fold videocapillaroscopy (NVC) assessment is a surrogate marker of endothelial dysfunction. To the best of our knowledge, the relationship between the microcirculation features on NVC and the severity of coronary atherosclerosis has not previously been investigated. In this study, we aimed to investigate the relationship between severity of coronary atherosclerosis (shown by SYNTAX and Gensini scores) and NVC findings which is an indirect indicator of systemic endothelial damage.

Methods: The study was designed as a retrospective cohort. One-hundred consecutive patients who underwent coronary angiography (CAG) and had at least one lesion in the epicardial coronary arteries, narrowing the lumen by more than 50%, were included. Coronary angiographic images of the patients were evaluated by two experienced interventional cardiologists and SYNTAX and Gensini scores were calculated. Patients were divided into three groups according to the SYNTAX scores (SYNTAX score ≤22, between 23-32, and ≥33) and two groups according to Gensini scores (Gensini score ≥30 and <30). The NVC examinations were performed by a rheumatologist who was experienced in this field, and the reduction in capillary density, presence of dilated capillaries, giant capillary, microhemorrhage, branching, disorganization, tortuosity, avascular area, extravasation, and neoangiogenesis were investigated.

Results: Dilated capillary vessels were more common in diabetic patients (85%) than in non-diabetics (66.7%) (P=0.041). Besides, there was no significant difference in NVC parameters between patients with and without diabetes mellitus (P>0.05 for all), with and without hypertension (P>0.05 for all). There was no significant difference between the SYNTAX groups in terms of NVC findings (P>0.05 for all). The NVC findings were similar between Gensini groups (P>0.05 for all).

Conclusion: The severity of atherosclerosis surrogated by SYNTAX and Gensini scores was not related to the NVC findings. Therefore, NVC is inappropriate for determining the severity of CAD.

Keywords: Coronary artery disease, Nail fold videocapillaroscopy, SYNTAX, Gensini Score

Öz

Amaç: Ateroskleroza bağlı olarak gelişen ve önemli morbidite ve mortalite nedeni olan koroner arter hastalığının (KAH) etiyolojisinde endotel disfonksiyonu önemli rol oynar. Tırnak dibinin videokapilleroskopik (NVC) değerlendirilmesi endotel disfonksiyonun dolaylı bir göstergesidir. NVC ile değerlendirilen mikrosirkulasyona ait verilerle endotel disfonksiyonunun önemli rol oynadığı koroner arterlerdeki aterosklerozun yaygınlığı arasında bir ilişki olup olmadığı daha önce araştırılmamış bir konudur. Biz bu çalışmada sistemik endotel hasarının dolaylı bir göstergesi olan NVC ile tırnak yatağının kapiller dolaşımını değerlendirererek koroner arter hastalığının yaygınlığı gösteren SYNTAX ve Gensini skorları ile muhtemel ilişkiyi araştırmayı amaçladık.

Yöntemler: Bu çalışma retrospektif Kohort çalışması olarak tasarlanmıştır. Koroner anjiyografi (KAG) yapılan ve epikardiyal koroner arterlerde lümeni %50'den fazla daraltan lezyon tespit edilmiş olan ardışık 100 hasta çalışmaya alınmıştır. Çalışmaya katılan hastaların KAG görüntüleri deneyimli iki invaziv kardiyoloji uzmanı tarafından değerlendirilerek SYNTAX ve Gensini skorları hesaplanmıştır. Hastalar SYNTAX skoruna göre ≤22, 23-32 arası ve ≥33 olmak üzere 3 gruba ve Gensini skoruna göre Gensini skoru ≥30 ve <30 olan hastalar olmak üzere 2 gruba ayrılmıştır. Çalışmaya katılan hastaların NVC incelemeleri bu konuda deneyimli olan bir romatoloji uzmanı tarafından yapılmıştır ve dev kapiller arter varlığı, mikrohemoraji, dallanma, disorganizasyon, tortiyozite, avasküler alan, extravazasyon, neogenezis, kapiller dansitede azalma ve dilate kapiller damar varlığı araştırılmıştır.

Bulgular: Diyabetes mellitusu olan hastalarda (%85) dilate kapiller diyabetes mellitusu olmayan hastalardan (%66,7) daha yaygındı (P=0,041). Diyabetes mellitusu olan/olmayan (hepsi için P>0,05), hipertansiyonu olan/olmayan hastalar arasında NVC parametreleri bakımından anlamlı bir fark saptanmadı (hepsi için P>0,05). SYNTAX skoruna göre gruplar arasında NVC parametreleri bakımından anlamlı bir fark saptanmadı (hepsi için P>0,05). Gensini skoruna göre gruplar arasında benzer NVC bulguları saptandı (hepsi için P>0,05).

Sonuç: Koroner arter hastalığının yaygınlığını belirlemede kullanılan SYNTAX ve Gensini skorları ile NVC parametreleri arasında ilişki yoktur. Bu yüzden NVC parametrelerinin koroner arter hastalığının şiddetini belirlemede kullanılması uygun değildir.

Anahtar kelimeler: Koroner arter hastalığı, Tırnak yatağı videokapilleroskopi, SYNTAX, Gensini skoru

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Introduction

Coronary artery disease (CAD) is one of the most common causes of morbidity and mortality in Turkey as well as in the world, and the most prominent etiological factor is atherosclerosis in 85% of patients. Atherosclerosis is a progressive process that is based on endothelial dysfunction and progresses to plaque rupture and thrombosis, causing narrowing and occlusion of the vessel lumen. The endothelial layer covers the inner surface of all vascular structures and has vital functions in the maintenance of blood circulation in the organism. In the capillaries which perfuse the tissues, vessel walls consist of the endothelium, a single-layered cellular arrangement. Endothelial dysfunction plays a significant role in the development of atherosclerosis, which is considered as a systemic disease. Many parameters that indirectly indicate endothelial dysfunction have been studied previously in patients with CAD. Reduction in flow-mediated dilatation (FMD), which reflects endothelial function, has been shown with the presence and severity of CAD previously [1-3]. Gümüşel et al. [4] have shown a strong negative correlation between the Gensini score and FMD in CAD patients. It has been reported that FMD and coronary calcification score, which reflects endothelial dysfunction noninvasively, may provide complementary information in predicting the prevalence and severity of CAD graded by Gensini and SYNTAX scores [5].

Nail fold videocapillaroscopy (NVC) is a noninvasive method used as a complementary test to confirm the diagnosis and to monitor the efficiency of treatment in rheumatic diseases such as systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) by examining the capillary structures in the nail fold [6-13]. The videocapillaroscopic analysis is now included in the ACR / EULAR classification criteria for systemic sclerosis [14]. Reduction of peripheral tissue perfusion is usually associated with microvascular injury in SSc, which can be demonstrated by different methods [15]. In SSc, the association of NVC findings with disease activity, pulmonary HT, efficacy of medical treatment, and involvement of internal organs has been shown previously [7,16-18].

To the best of our knowledge, the relationship between microcirculation on NVC and the severity of coronary atherosclerosis has not previously been investigated. In this study, we aimed to investigate the relation of the severity of coronary atherosclerosis, shown by SYNTAX and Gensini scores, with NVC findings as an indirect indicator of systemic endothelial damage.

Materials and methods

Two experienced interventional cardiologists evaluated coronary angiography images of the patients and calculated the SYNTAX and Gensini scores.

Gensini score

Gensini score indicating the severity and extension of coronary atherosclerosis in CAD patients was calculated as previously described in the literature [19]. This method scores and classifies the severity and extent of the stenosis in epicardial coronary arteries due to atherosclerosis. According to Gensini scoring system, 1-25% stenosis scores 1 point, 26-50% stenosis scores 2 points, 51-75% stenosis, 4 points, 76-90% stenosis, 8 points, 91-99% stenosis,16 points, and total occlusion, 32 points. In addition, each lesion in the epicardial coronary arterial system is multiplied by a factor representing the importance of its localization. The patient's score is multiplied by 5 if the lesion is in the left main coronary artery (LMCA), multiplied by 2.5 in the proximal left anterior (LAD) or in the left circumflex (LCx) artery lesions, multiplied by 1.5 in the middle segment of the LAD and LCx lesions, multiplied by 1 in the distal segment of LAD and LCx, or in the first diagonal and optuse marginalis (OM) branch, or in the right coronary artery lesions, or in the posterior descending artery (PDA) lesions, and multiplied by 0.5 in the second diagonal or OM branch lesions. The total Gensini score is calculated by summation of the scores from all coronary lesions.

SYNTAX score

The SYNTAX score has been developed as a combination of several predetermined angiographic classifications aimed at grading coronary atherosclerotic lesions based on the number, functional impact, localization, and complexity of the lesions [20]. This scoring system is intended to assist in risk classification of patients with severe coronary lumen stenosis who require revascularization and the selection of patients for appropriate revascularization technique [20-22]. It was used in the SYNTAX study for the first time. In this study, the rates of long-term cardiovascular events differed between treatment strategies (coronary artery bypass grafting (CABG) vs percutaneous coronary intervention (PCI)) and among the groups categorized into tertiles according to the SYNTAX score as well. According to the results of the first published SYNTAX trial, the event rates were similar in patients with low (0-22) and moderate (23-32) SYNTAX score tertiles for CABG and PCI, but the rate of long-term adverse cardiovascular event was significantly higher in the PCI group compared to the CABG group in patients with a high SYNTAX score (≥33 indicating most complex disease) [23].

NVC findings

NVC examination of the patients was performed by a rheumatologist who was experienced in capillaroscopy in Rheumatology Clinic by Video Cap 3.0 device. Reduction in capillary density, dilated capillaries, giant capillary structures, microhemorrhage, branching, disorganization, tortuosity, avascular area, extravasation, and neoangiogenesis were investigated [24,25].

Study population

As a result of the sample size analysis based on other research findings in the literature, the minimum number of participants in each group was determined as 17 with a 95% confidence level and 80% power.

The study included 100 consecutive patients who underwent coronary angiography (CAG) and who had ≥50% stenosis in epicardial coronary arteries. Patients were divided into groups according to heart failure (EF ≥50% and EF <50%), presence of HT and DM, SYNTAX score (<23, 23-32, ≥33) and Gensini score (<30 and ≥30) and compared in terms of NVC parameters.

Patients with chronic diseases such as systemic sclerosis, chronic renal failure, chronic liver disease,

decompensated congestive heart failure, any malignancy, dilated cardiomyopathy, congenital heart disease, and pregnant women were excluded from the study.

Statistical analysis

Numerical variables were presented as mean, standard deviation and minimum-maximum values. Categorical variables were given as numbers and percentages. Pearson's chi-square test was used to compare the categorical variables between the study groups. Statistical analyses were performed with Jamovi (Version 0.9.5.12) computer software. $P<0.05$ was considered statistically significant.

Results

The study included 100 patients, 31 females 69 males. The age of patients ranged from 38 to 89 years with a mean age of 62 (11) years. Forty patients had diabetes mellitus (DM), 52 had hypertension (HT).

The highest and lowest SYNTAX scores were 53 and 2, respectively. The mean SYNTAX score of the patients was 18.6 (12.6). According to the SYNTAX scores, 68 had a score of 22 or less, 20 had a SYNTAX score of 23-32, and 12 had a SYNTAX score of 33 or higher.

The highest and lowest Gensini scores were 242 and 4, respectively, with a mean Gensini score of 63.0(49.2). When the patients were divided into 'mild-moderate CAD' and 'severe CAD' groups according to the Gensini score, 27 patients had a Gensini score of <30 and 73 had a Gensini score of ≥30.

In the NVC evaluation of the patients, 16 had reduced capillary density, 74 had dilated capillary structures, 2 had giant capillaries, 4 had microhemorrhage, 36 had branching, 7 had disorganization, 73 had tortuosity, and 15 had an avascular area, one had extravasation, and one had neoangiogenesis.

There was no significant difference between the diabetic and non-diabetic patients in terms of NVC parameters except for the rate of dilated capillary structures, which was higher in diabetic patients than in non-diabetic patients (85% vs. 67%, $P=0.041$). NVC parameters of hypertensive and non-hypertensive patients (Table 1), low, intermediate, and high SYNTAX scores and groups with Gensini scores<30 and ≥30 were comparable among themselves ($P>0.05$ for all) (Table 2, 3).

Table 1: Comparison of CAD patients with and without diabetes mellitus and hypertension in terms of NVC findings

	Non-diabetic (n=60)	Diabetic (n=40)	*P*-value	Hypertensive (n=52)	Normotensive (n=48)	*P*-value
Giant capillaries, n (%)	2 (3.3)	0 (0)	0.52	2 (3.8)	0 (0)	0.50
Microhemorrhage, n (%)	2 (3.3)	2 (5)	0.99	2 (3.8)	2 (4.2)	0.99
Branching, n (%)	21 (35)	15 (37.5)	0.80	17 (32.7)	19 (39.6)	0.47
Disorganization, n (%)	6 (10)	1 (2.5)	0.24	5 (9.6)	2 (4.2)	0.44
Tortuosity, n (%)	42 (70)	31 (77.5)	0.41	38 (73.1)	35 (72.9)	0.99
Avascular area, n (%)	9 (15)	6 (15)	0.99	7 (13.5)	8 (16.7)	0.65
Extravasation, n (%)	1 (1.7)	0 (0)	0.99	1 (1.9)	0 (0)	0.99
Neoangiogenesis, n (%),	1 (1.7)	0 (0)	0.99	1 (1.9)	0 (0)	0.99
Reduced capillary density, n (%)	8 (13.3)	8 (20)	0.37	9 (17.3)	7 (14.6)	0.71
Dilated capillaries, n (%)	40 (66.7)	34 (85)	0.041	40 (76.9)	34 (70.8)	0.49

* The number and percentage of patients with relevant findings are presented.

Table 2: Comparison of NVC findings between the Syntax groups

	<23 (n=68)	23-32 (n=20)	≥33 (n=12)	*P*-value
Giant capillaries, n (%)	2 (2.9)	0 (0)	0 (0)	0.99
Microhemorrhage, n (%)	2 (2.9)	2 (10)	0 (0)	0.25
Branching, n (%)	25 (36.8)	7 (35)	4 (33.3)	0.97
Disorganization, n (%)	4 (5.9)	1 (5)	2 (16.7)	0.39
Tortuosity, n (%)	49 (72.1)	16 (80)	8 (66.7)	0.68
Avascular area, n (%)	11 (16.2)	2 (10)	2 (16.7)	0.83
Extravasation, n (%)	0 (0)	1 (5)	0 (0)	0.33
Neoangiogenesis, n (%),	1 (1.5)	0 (0)	0 (0)	0.99
Reduced capillary density, n (%)	11 (16.2)	2 (10)	3 (25)	0.53
Dilated capillaries, n (%)	49 (72.1)	15 (75)	10 (83.3)	0.71

* The number and percentage of patients with relevant findings are presented.

Table 3: Comparison of NVC findings between the Gensini groups

	Gensini ≥30 (n=73)	Gensini <30 (n=27)	*P*-value
Giant capillaries, n (%)	1 (1.4)	1 (3.7)	0.47
Microhemorrhage, n (%)	3 (4.1)	1 (3.7)	0.99
Branching, n (%)	26 (35.6)	10 (37)	0.99
Disorganization, n (%)	4 (5.5)	3 (11.1)	0.38
Tortuosity, n (%)	55 (75.3)	18 (66.7)	0.39
Avascular area, n (%)	12 (16.4)	3 (11.1)	0.75
Extravasation, n (%)	1 (1.4)	0 (0)	0.99
Neoangiogenesis, n (%),	0 (0)	1 (3.7)	0.27
Reduced capillary density, n (%)	13 (17.8)	3 (11.1)	0.55
Dilated capillaries, n (%)	51 (69.9)	23 (85.2)	0.12

* The number and percentage of patients with relevant findings are presented.

Discussion

To the best of our knowledge, this is the first study to investigate the association between atherosclerosis severity and NVC findings in CAD patients. According to our results, dilated capillary structures were more frequent in diabetic patients than non-diabetic patients. Other NVC findings were similar between the diabetic and non-diabetic patients. The NVC findings between hypertensive and normotensive patients, patients with low-to-intermediate and high SYNTAX scores, and patients with Gensini scores of <30 and ≥30 were also comparable.

Endothelial dysfunction is an early and reversible stage in the development of cardiovascular diseases. It can be used to predict future CAD development before occurrence of atherosclerotic changes in the arterial wall [26]. Carotid intima-media thickness (CIMT) and FMD are noninvasive techniques to evaluate endothelial dysfunction [2,26]. There are studies showing that increased CIMT and decreased FMD are associated with CAD as well as studies showing that increased CIMT is associated with CAD severity [27-30].

Diabetes mellitus is a common disease with frequent complications leading to high mortality and morbidity rates worldwide. Endothelial dysfunction and angiopathy play a key role in the early stage of diabetes complications. Alterations in permeability and capillary flow affect the macrovascular and microvascular structures due to the changes in red blood cell velocity and basement membrane thickness. In patients with diabetes mellitus, increase in tortuosity and angiogenesis have been reported in NVC examination. Microcirculation angiopathy has been reported in 17% of diabetic patients and these patients deserve more attention regarding diabetic vascular complications [31]. In our study, dilated capillary vessels were found more frequently in the NVC examination of diabetic CAD patients while there was no significant difference in capillary density, the presence of giant capillaries, microhemorrhage, branching, disorganization, tortuosity, avascular area, extravasation, and neoangiogenesis compared to non-diabetic CAD patients. We believe that this was due to the presence of endothelial dysfunction underlying CAD because all patients who participated in the study had CAD.

Increased peripheral vascular resistance is associated with essential hypertension. The characteristics of microcirculation contribute to hypertension by determining peripheral vascular resistance. Nail fold videocapillaroscopic examination of hypertensive patients showed a reduction in capillary density and in velocity of red blood cells. Reduction of red blood cells velocity was associated with microcirculation impairment and end-organ damage in hypertensive patients [32]. In our study, reduction in capillary density, the presence of dilated capillaries, giant capillary, microhemorrhage, branching, disorganization, tortuosity, avascular area, extravasation, and neoangiogenesis were similar between hypertensive and normotensive patients. We believe that this was due to the small number of patients enrolled in the study.

Cardiac Syndrome X (CSX) is a clinical status characterized by typical angina pectoris and ST depression on exercise ECG test without any obstructive (≥50%) stenosis in epicardial coronary arteries on CAG. Increase in vasoconstriction sensitivity and/or impairment in relaxation in arterioles and pre-arterioles are believed to play role in the etiopathogenesis of CSX [33]. Reduction in capillary density has been reported in the NVC findings of CSX patients [34].

Coronary slow flow is defined as a delay in filling the vessel lumen by opaque material despite any stenosis in the epicardial coronary arteries on CAG [35]. The pathophysiology of coronary slow flow is implicated in small vessel disease, endothelial dysfunction, atherosclerosis, inflammation, an imbalance in vasoactive substances, and anatomical abnormalities. Nail fold videocapillaroscopic examination of patients with coronary slow flow revealed that tortuosity, microhemorrhage, and capillary dilatation were 5.7 times higher than those with normal coronary blood flow [13].

In our study, the SYNTAX and Gensini scores were calculated on CAG images to determine the severity of atherosclerosis in CAD patients with ≥50% stenosis in epicardial coronary arteries. There was no significant relation between NVC findings and SYNTAX or Gensini scores of CAD patients. Consequently, there was no significant relationship between NVC findings and the severity of atherosclerosis in CAD patients.

Limitations

The main limitation of our study was the absence of a control group with normal coronary arteries as demonstrated with CAG. The lack of a significant difference in the NVC findings between the study groups might be since there was already an underlying endothelial dysfunction, for all patients already had CAD. In addition, the number of sample size might not be high enough to reveal such a difference.

Conclusions

According to our results, there was significant relationship between diabetes mellitus, hypertension, and NVC findings in patients with CAD. Besides, we did not find any relationship between the NVC findings and SYNTAX and Gensini scores, which are used to determine the severity of atherosclerosis in CAD.

To clarify this issue, it may be more appropriate to conduct long-term intermittent NVC examinations of people with normal coronary arteries and compare NVC findings when coronary artery disease is detected, or to study where some patients have normal coronary artery disease and some patients with coronary artery disease.

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The effect of tack number and balloon trocar use on acute post-operative pain scores of patients who underwent TEP repair of inguinal hernia

TEP inguinal herni onarımı yapılan hastalarda tack sayısının akut post-operatif ağrı skoruna etkisi

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Abstract

Aim: As the novel technology on surgical procedures evolve, the management and amelioration strategies for postoperative pain gains importance for surgeons to improve patients' life quality and postoperative outcomes. In this study, we aimed to compare the number of tacks placed during surgery and the use of intra-operative balloon trocars during TEP repair of inguinal hernias with respect to post-operative early pain scores.

Methods: A total of 83 patients were included in this prospective cohort study, 59 being in the 0-1 tack group and 24 in the 2 tacks group. Balloon trocar was used in 32 patients. All patients underwent laparoscopic TEP inguinal hernia repair. Groups were compared with respect to pain scores on 3rd, 12th and 24th postoperative hours.

Results: Pain score was better in no balloon trocar+2 tacks group when compared to balloon trocar+2 tacks and no balloon trocar+0-1 tack group at the 24th postoperative hour (P=0.02 and P=0.007, respectively), and in the balloon trocar+0-1 tack group than that of the no balloon trocar+0-1 tack group (P=0.004). There was no statistically significant difference between these four groups in terms of pain score on the 3rd and 12th hours of surgery (P=0.46 and P=0.24, respectively). Patients in the 0-1 tack group reported less pain on the 24th postoperative hour (3.1 (6.3) vs 14.1 (21.8); P=0.32).

Conclusion: Using less number of tacks and avoiding using balloon trocar result in lower pain scores following laparoscopic TEP repair of inguinal hernias.

Keywords: Tack number; Mesh fixation, Inguinal hernia, Laparoscopy, Post-operative pain

Öz

Amaç: Cerrahi prosedürler yeni teknoloji kullanılarak geliştikçe, postoperatif dönemde hastaların yaşam kalitesinin ve ameliyat sonrası dönemin iyileştirilmesi açısından bu dönemde ağrı yönetimi ve ağrıyı azaltma stratejileri cerrahlar için önem kazanmaktadır. Bu nedenle, çalışmamızda, tack sayısı ve intraoperatif balon trokar kullanımının TEP inguinal herni operasyonu sonrası erken dönem ağrı skorlarına etkisinin retrospektif olarak karşılaştırılması amaçlanmıştır.

Yöntemler: Bu prospektif kohort çalışmasına toplam 83 hasta dahil edildi; 59'u 0-1 tack kullanılan grupta ve 24'ü 2 tack kullanılan grupta idi. 32 hastada balon trokar kullanıldı. Tüm hastalara laparoskopik TEP inguinal herni onarımı yapıldı. Gruplar ameliyat sonrası 3., 12. ve 24. saatlerde ağrı skorlarına göre karşılaştırıldı.

Bulgular: Ameliyattan sonraki 24. saatte balon trokar kullanılmayan ve 2 tack kullanılan grupta balon trokar + 2 tack ve balon trokar + 0-1 tack grubuna göre ağrı skoru daha iyi idi (Sırasıyla P=0,02 ve P=0,007). Ağrı skoru balon trokar + 0-1 tack grubunda, balon trokar kullanılmayan ve 0-1 tack kullanılan gruba kıyasla daha iyiydi (P=0,004). Ameliyatın 3. ve 12. saatlerinde ağrı skoru açısından bu dört grup arasında istatistiksel olarak anlamlı bir fark saptanmadı (Sırasıyla P=0,46 ve P=0.24). 0-1 tack grubundaki hastalar postoperatif 24. saatte daha az ağrı hissettiklerini bildirdi (3,1 (6,3)'e karşı 14,1(21,8); P=0,32).

Sonuç: İnguinal hernilerin laparoskopik TEP onarımını takiben daha az sayıda tack kullanımı ve balon trokar kullanımının sınırlanması, daha iyi postoperatif ağrı skoru ile ilişkilidir.

Anahtar kelimeler: Tack sayısı, Mesh fiksasyonu, İnguinal herni, Laparoskopi, Postoperatif ağrı

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Introduction

Inguinal hernia repair is one of the most frequent surgical operations worldwide. Following the first report of laparoscopic hernia repair in 1993, and introduction of mesh placement, post-operative complication and recurrence rates decreased dramatically [1,2]. Similar to physicians in other disciplines of medicine, surgeons are continuously seeking novel methodologies to reduce post-operative pain and increase the life quality of patients who underwent surgical procedures.

Endoscopic totally extraperitoneal (TEP) repair is one of the minimally-invasive (laparoscopic) methods for inguinal hernia repair and despite its negative sides such as longer learning period and difficulties in performing, TEP is highly preferred by surgeons since it offers lower rate of complications including acute postoperative pain, chronic postoperative inguinal pain, recurrence, and its requirement of less number of closing material [3,4]. In the laparoscopic inguinal hernia repair (LIHR) using TEP approach, a prosthetic mesh is placed to cover all current and future possible hernia sites in order to fix the herniated bowel and prevent recurrence through an extraperitoneal incision [5,6].

Sometimes mesh material requires fixing with different techniques, such as tack, stapler, fibrin glue, or suture. The correct replacement and fixation of mesh to the fasciomuscular layer of the abdominal wall is crucial to reinforce the posterior wall and prevent future recurrences [2].

Although tack closure is shown to be associated with less post-operative pain, nerve injury and hematoma and also is time-saving, the effects of tacks on the bowel are reportedly etiological factors in the development of an intestinal fistula following LIHR [7-9].

Even though laparoscopy is associated with less incidence and ratio of postoperative pain, patients who underwent inguinal hernia repair still report post-operative pain and often require analgesia medication including even opioids. The number of tacks and the replacement sites of tacks on the mesh have significant impact on prevention of post-operative acute pain [10]. And inadequate control of the acute pain following the surgery has been shown to be associated with postoperative chronic pain [11].

In the present study, we analyzed and compared the clinical outcomes of laparoscopic TEP using different number of tacks for mesh fixation and accessing the peritoneal cavity with or without use of balloon trocar. We investigated whether the use of a smaller number of tacks may be beneficial in reducing acute postoperative pain in patients underwent TEP repair for the treatment of inguinal hernia.

Materials and methods

Patients and surgical procedure

This is a prospective cohort study on patients who underwent laparoscopic repair of inguinal herniation. It was approved by the Ethical committee of Istanbul Education and Research Hospital (Date: 12/06/2020. Approval Number: 2447). Our laparoscopic inclusion criteria consisted of patients aged 18 years or more, those with unilateral hernia (direct or indirect), ASA score of I, II or III, and patients with hernias between 2-5 cm in size. Those with hernias less than 2 cm and greater than 5 cm, ASA score IV, bilateral and/or recurrent hernia were excluded. Patients with significant comorbidity and not those suitable for pneumoperitoneum were also excluded. Informed consent was obtained from all patients prior to surgery. All cases were elective, and none were transferred emergently.

The hernias were classified according the criteria defined by Schumpelick-Arit. All laparoscopic repairs were performed by following the same surgical protocol by two specialist surgeons highly experienced in laparoscopic inguinal hernia repair. All patients were given prophylaxis against infectious conditions and antithrombotic agents were used when necessary.

A standardized TEP approach under general anesthesia was performed using three different ports, one inserted just below the umbilicus through a 1 cm incision, one placed above the pubic symphysis, and one placed between the other two ports. Hasson trocar was fixed by present sutures on both sides of the trocar wings to prevent air discharge through the port incision. If the operating surgeon preferred using the balloon trocar, it was introduced to provide a passageway through the peritoneum into the abdomen after insufflation with 30 cc air.

Following the definition of anatomical structures in the inguinal region, the hernia defect was closed with a polypropylene or polyvinylidene fluoride mesh of appropriate size. The mesh was then secured with 0-1 5 mm titanium tacks, one being on the pubic tubercle, and then on the anterior superior iliac spine if second tacks were needed. Decision for replacement of a second tack was made by the operating surgeon depending on the characteristics of the hernia. Whenever possible, our decision was to use the least number of tacks for mesh fixation. Following mesh fixation, the trocars were removed, and the fascial scars were closed.

While we evaluated our LIHR patients retrospectively, we created four different groups:

Balloon trocar + 0-1 tack; Balloon trocar + 2 tacks; No balloon trocar + 0-1 tack, and No balloon trocar + 2 tacks. The purpose of this subgrouping was to define whether the tacks used for mesh fixation results in a tissue injury led to an increased pain score during the postoperative period. Since the number of the patients with 0 tacks were low for creation of an individual subgroup, we defined a single group for the patients with 0-1 tacks.

Pain score

Postoperative pain scores were evaluated on the 3rd, 12th, and 24th postoperative hours using a personal pain scoring method. Patients were given a grading scale where a score of 0 points meant no pain and 100 points meant intense and the worst pain experienced so far by the patient. The questionnaire was applied by the same supervising nurse of the general surgery ward. The education levels of all patients were similar between the groups, and all were literate. The baseline educational level of all subjects were high school, corresponding to at least 12-years of schooling in the country's educational system.

They were allowed to resume normal diet and mobilized as soon as possible.

A self-controlled analgesia device and oral paracetamol or a non-steroidal anti-inflammatory drug were provided for the patients to use when needed.

Statistical analysis

The demographic data of the patients were given as number and percentages, and numerical variables were presented as mean (SD). Normality of the data distribution was tested using Kolmogorov-Smirnov test. Statistical analysis was performed using Analysis of Variance (ANOVA) test between the study groups. The lowest *P*-values were reported in the tables. Comparison of two data were performed using a Chi-square test for percentages. A *P*-value of <0.05 was considered statistically significant. All statistical analysis was carried out using the GraphPad Prism 8.0 statistical package. The comparisons of the significant results in the Kruskal Wallis test were re-evaluated with post-hoc correction. Sample sizes for each group were calculated using the equations determined by MacCallum et al [12]. A power analysis determined the minimum sample size. Briefly the formula as follows was used for sample size calculation: Effect size f=0.40; α err prob=0.05; Power (1-β err prob)=0.80; number of groups=4 ; Output: Total sample size=76.

Results

Patient and operation characteristics and are summarized in Table 1. Eighty-three patients were enrolled in the study, including 71 males (85.5%) and 12 females (14.5%). The mean age was 44.7 (15.4) years. The mean BMI was 26.5 (2.85) kg/m^2. The mean hernia size was 2.08 (0.53) cm in diameter. The hernia was localized on the right side in 51 (61.6%) patients and left side in 32 (38.4%). The most common hernia type was Mc II (Combined hernia with hernia orifice 3 cm) in 39 patients followed by L II (Lateral (indirect) hernia with hernia orifice 3 cm) in 15. The mean operation time was 71(26) minutes (24-200; median: 50).

Polypropylene was the most commonly used mesh [66 (79.5%) patients] whereas polyvinylidene was used in 17 (20.5%) patients. Intraoperative balloon trocar was not used in 51 (61.5%) of the patients. The number of tacks used was 0-1 in 59 (71.0%) patients and 2 in 24 (29.0%) patients (Table 2). A tack number of more than 2 was not administered to any of the patients.

When patients were divided into subgroups and compared in terms of intraoperative balloon trocar use and number of tacks, pain score was better in no balloon trocar+2 tacks group when compared to balloon trocar+2 tacks and no balloon trocar+0-1 tack group at the 24th hour following the surgery (*P*=0.02 and *P*=0.007, respectively), and in balloon trocar+0-1 tack group than that of the no balloon trocar+0-1 tack group (*P*=0.004). The mean pain scores on the 3rd, 12th and 24th post-operative hours were depicted in Table 2. There was no statistically significant difference between these four groups in terms of pain score at the 3rd and 12th hours of surgery (*P*=0.46 and *P*=0.24, respectively).

While we evaluated tack number alone, patients in the 0-1 tack group reported less total mean pain at the 24th postoperative hour (3.1(6.3) vs. 14.1(21.8); *P*=0.32) (Table 3).

The patients with polyvinylidene mesh fixation reported significantly higher pain compared to the patients with polypropylene mesh at the 24th postoperative hour (42.9(32.5) vs. 6.1(10.1); *P*<0.001). The ratio of self-administered pain medication use was shown in Table 3. There was no statistically significant difference between the ratios of pain medication use among the tack number specified groups on the 3rd, 12th, and 24th hours postoperatively (*P*=0.60, *P*=0.39 and *P*=0.67, respectively).

The median post-operative hospital stay was 2 days (1-5). There were no reports of any post-operative early complications in patients.

Table 1: Demographics of the patients and intraoperative specifications

Parameters	n=83
Male/Female	71/12
Age (years)	44.7(15.4)
BMI	26.50(2.85)
Location of the hernia	
Left	32 (38.3%)
Right	51 (61.7%)
Hernia size (cm)	2.08(0.53)
Duration of operation (minutes)	71.0(26.0)
Type of hernia (According to Aachen classification)	
L I (Lateral (indirect) hernia with hernia orifice <1.5 cm)	9 (10.9%)
L II (Lateral (indirect) hernia with hernia orifice 3 cm)	15 (17.8%)
M II (Medial (direct) hernia with hernia orifice 3 cm)	5 (5.5%)
M III (Medial (direct) hernia with hernia orifice >3 cm)	7 (8.2%)
Mc I (Combined hernia with hernia orifice <1.5 cm)	2 (2.7%)
Mc II (Combined hernia with hernia orifice 3 cm)	39 (46.6%)
Mc IIII (Combined hernia with hernia orifice >3 cm)	6 (8.2%)
Number of tacks used for mesh fixation	1.16±0.5
Type of mesh used	
Polypropylene	66 (79.5%)
Polyvinylidene	17 (20.5%)
Intraoperative balloon trocar use	
Yes	32 (38.5%)
No	51 (61.5%)

Table 2: Pain scores of the patients sub-grouped according to intra-operative tack number and balloon trocar use

Intraoperative variables	Pain score			Age	M/F	BMI
	3rd hour	12th hour	24th hour			
Balloon trocar + 0-1 tack (n=18)	20(20.8)	11(9.9)	7(12.2)	41.7(11.2)	5.8	25.4(2.56)
Balloon trocar + 2 tacks (n=14)	30(17.3)	10(10.0)	10(10.0)	43.4(11.7)	4.2	27.2(3.02)
No balloon trocar + 0-1 tack (n=41)	26(12.8)	16.2(11.4)	15.8(6.0)	47.6(8.9)	4.8	24.8(3.16)
No balloon trocar + 2 tacks (n=10)	17(11.6)	11(7.3)	1(3.1)	42.2(14.1)	5.4	26.7(1.86)
P-value	0.46	0.24	0.004	0.89	0.32	0.67

Table 3: Pain scores of the patients sub-grouped according to intra-operative tack number, type of mesh used, and self-administration of postoperative analgesia

	Pain score		
Number of tacks used for mesh fixation	3rd hour	12th hour	24th hour
0-1 tack (n=59)	25.1 (17.3)	13.4 (10.9)	3.1 (6.3)
2 tacks (n=24)	27.7 (12.3)	10.8 (7.6)	14.1 (21.8)
P-value	0.38	0.44	<0.05
Type of mesh used			
Polypropylene (n=66)	23.3 (13.3)	12.7 (9.9)	6.1 (10.1)
Polyvinylidene (n=17)	40 (43.5)	13.4 (15.2)	42.9 (32.5)
P-value	0.08	0.90	<0.001
Number of patients used postoperative pain medication			
0-1 tack (n=59)	12 (20.3%)	14 (23.7%)	4 (6.7%)
2 tacks (n=24)	8 (33.3%)	10 (41.6%)	2 (8.3%)
P-value	0.60	0.39	0.67

Discussion

Despite its long duration of learning and cost, laparoscopic repair of inguinal hernias is preferred for its favorable effects on quality of life, short duration for return to daily activities and work, and less pain among other positive sides such as lower rate of complications and recurrence as well as better cosmetic results [10,13].

The use of mesh in LIHR is related with a low rate of complications and recurrence, along with better effects on resuming normal daily activities [14]. Fixation of the mesh in appropriate measures might be the most crucial step of LIHR, since rolling of the mesh, inflammatory reaction and fibrous tissue production around the mesh were shown to be related with chronic post-operative pain and recurrence [6]. Different mesh fixation techniques have various advantages or disadvantages when compared with each other. Cost, intra-operative

complication and recurrence rates, post-operative pain, and operative time are among the indicators on the decision-making process by the surgeon when choosing one over another [2].

Post-operative acute pain within 48 hours after the surgery is still an issue to be solved by different intra- and post-operative approaches to mitigate the general well-being of the patients [15]. Different intra-operative interventions were recruited to reduce suture-site pain including injection of local anesthetic agents to the suture region [16]. Post-operative acute pain is a restricting factor for the patients for return to daily activities, and pain medications including morphine equivalents are prescribed for the patients.

The use of a balloon trocar to approach the hernia region might be related with intra-operative bleeding, and post-operative pain on the trocar site and peritoneum. In a large group of hernia patients, Belyansky et al. [10] showed increased ratio of post-operative pain after LIHR in patients with more than >10 tacks and when adjustments were made for tack number, they could not find a relationship between the operation type (modified Lichtenstein, TAPP or TEP) and pain score. It has been shown that various techniques used for LIHR and mesh fixation are related with different recurrence rates. Thus, since TEP repair and tack fixation were shown to be related with less recurrence rate, we use the combination of these two when available and appropriate for the patient. Furthermore, combination of these has also been shown to be related with less post-operative acute pain [17,18].

Our study aimed to evaluate the pain scores of patients who underwent TEP repair of inguinal hernias in terms of number of tacks used for mesh fixation and introduction of a balloon trocar to go forward through the peritoneal cavity.

In our study, patients reported significantly better pain scores in no balloon trocar+2 tacks group when compared to balloon trocar+2 tacks and no balloon trocar+0-1 tack group on the next day of the operation. Although we expected to find that use of more number of tacks and balloon trocar have an exacerbating effect on post-operative pain score, we could not find this correlation in all comparisons. In the patients without balloon trocar introduction, the reason for a more comfortable post-operative process with less pain might be resulting from the better placement of the mesh with two tacks, hence providing a better intra-abdominal fixation and relief.

Additionally, despite the exclusion of patients who chose to receive self-controlled pain medication with opioids, other medications such as Paracetamol and NSAIDs might be reducing the pain and complicating the evaluation process between these groups. However, the ratios of self-administered pain medication on the pain score evaluation visits was similar between the study groups.

Furthermore, pain score was worse in balloon trocar+0-1 tack group than that of the no balloon trocar+0-1 tack group, showing that balloon trocar use might be a cause of acute post-operative pain after LIHR. While we evaluated tack number alone and excluding balloon trocar use as a variable, patients in the 0-1 tack group reported significantly less pain at the 24th postoperative hour. Although the pain score on the 3rd, 12th and 24th post-operative hours were worse for the balloon trocar+2 tacks group, this finding did not reach significance for all inter-group comparisons.

Among our patients, some patients did not require mesh fixation, thus no tack was used for these group of patients since non-fixation of mesh was shown to be adopted routinely and safely in LIHR by different studies worldwide [19].

Despite providing valuable data to evaluate TEP repair patients with different intra-operative approaches, our study has some limitations. Personal specifications such as gender, age, educational and social status, economic wealth are among the most common indicators of pain perception by an individual [20]. However, these factors except age were not been recorded and evaluated in the context of our study. Replacing 0-1 or 2 tacks did not have a significant influence on operating time, so we did not use operation time between the groups as a variable. Patients' duration until return to daily activities, comfort, and life quality a few months after the operation and presence of any chronic post-operative pain also have not been recorded. Most post-operative complications are preventable depending on the operating surgeon's anatomy knowledge and laparoscopic experience. The operations presented here were performed by two different surgeons with similar experience, using the same procedure for LIHR. Although inter-individual variations might apply to our study too, both surgeons were raised from the same teaching clinic and share similar experience and operation number performed.

Limitations

Our study has several limitations to declare. First, the number of the individuals in comparison groups are not equal. Furthermore, we did not subgroup the patients depending on the type of hernia, thus, a more severe form of hernia and complicated repair process might be a cause of the increased pain score irrespective of the balloon trocar or the number of the tacks used. Further studies with homogenous patient groups are required for better understanding of the effect of these variables on postoperative pain scores in inguinal hernia patients,

Conclusion

While surgeons worldwide are seeking novel methodologies and techniques in hernia surgery to keep complications at minimum, LIHR using TEP procedure is a convenient procedure in terms of pain control together with small number of tack use for mesh fixation. Introduction of balloon trocar also provides disadvantages due to tissue injury during the creation of a passage to the hernia site. Our suggestion is the use of possible lowest number of tacks for mesh fixation and limited use of balloon trocar for the laparoscopic TEP repair of inguinal hernias.

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The evaluation of calcium as a prognostic factor in non-traumatic cardiopulmonary arrests

Travmatik olmayan kardiyopulmoner arrestlerde kalsiyumun prognostik bir faktör olarak değerlendirilmesi

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Abstract

Aim: Cardiopulmonary arrests (CPA) should be rapidly responded to in emergency departments (ED). Arrests associated with coronary cardiac diseases are held responsible for about 90% of sudden mortality over the age of 18 years. In our study, the effect of calcium on prognosis was investigated in patients who were admitted to our emergency department with non-traumatic CPA and underwent cardiopulmonary resuscitation (CPR).

Methods: The data of 132 non-traumatic CPA patients who were admitted to the emergency room between 1 January 2017 and 31 December 2019 were examined from the hospital registry for this cohort study. The demographic features (age, gender, mortality, and the presence of diseases in their medical history) were noted. Blood was collected from patients at the time of admission to the ED. Adjusted serum Ca^{+2}, potassium (K^{+}) and sodium (Na^{+}) electrolyte levels were evaluated among patients who were either admitted to the intensive care unit or died.

Results: Fifty-eight (43.93%) patients died in the emergency department, and 74 (56.07%) were admitted to intensive care units. There were no comorbid diseases in 50.76%. Coronary artery disease, respiratory diseases and others were found in 23.46%, 6.06% and 19.7% of the patients, respectively. In the patient group declared "exitus" in the intensive care unit after CPR, serum adjusted calcium levels were significantly higher compared to the surviving patient group (P=0.041)

Conclusion: It was noted that adjusted Ca^{+2} concentration can be a beneficial parameter in determining the prognosis in non-traumatic arrest cases.

Keywords: Adjusted calcium level, Cardiopulmonary resuscitation, Prognosis

Öz

Amaç: Kardiyopulmoner arrestler (KPA), acil servislerin en hızlı müdahale edilmesi gereken durumlardan birini oluşturmaktadır. Koroner kalp hastalıklarına bağlı arrestler, 18 yaş üstü ani ölümlerin yaklaşık %90'nından sorumlu tutulmaktadır. Çalışmamızda acil servisimize nontravmatik KPA olarak getirilen ve kardiyopulmoner resüsitasyon (KPR) yapılan hastalar üzerinde, kalsiyumun prognoza olan etkisi araştırdık.

Yöntemler: 1 Ocak 2017-31 Aralık 2019 yılları arasında acil servise başvuran 138 travmatik olmayan KPA hastasının verileri hastanenin otomasyon sisteminden kohort çalışması olarak incelendi. Olguların demografik özellikleri (yaş, cinsiyet, mortalite ve tıbbi geçmişlerinde hastalık varlığı) incelendi. Acil servise başvuru anında serum kalsiyum (Ca^{+2}), potasyum (K) ve sodyum (Na) düzeyleri ölçüldü. Daha sonra, exitus olan grup ile yoğun bakım ünitesine yatırılan hasta grupları arasında düzeltilmiş serum Ca^{+2} elektrolit düzeyleri değerlendirildi.

Bulgular: Bu hastaların 58'i (%43,93) acil serviste exitus kabul edildi ve 74'ü (%56,07) yoğun bakım ünitelerine yatırıldı. Hastaların %50,76'sında komorbid hastalıklar bulunmadı. Koroner arter hastalığı %23,46, solunum sistemi hastalığı %6,06, diğer hastalıklar %19,7 olarak bulundu. KPR sonrası yoğun bakım ünitesinde exitus olarak bildirilen hasta grubunda serum düzeltilmiş Ca^{+2} düzeyleri sağ kalan hasta grubuna göre istatistiksel olarak anlamlı derecede yüksek bulundu (P=0,041).

Sonuç: Düzeltilmiş Ca^{+2} konsantrasyonunun, travmatik olmayan arrest vakalarda prognozun belirlenmesinde faydalı bir parametre olabileceği düşünüldü.

Anahtar kelimeler: Düzeltilmiş kalsiyum seviyesi, Kardiopulmoner resusistasyon, Prognoz

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Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Kafkas University Medical School (date: 9/25/2019, issue: 80576354-050-99/203). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Introduction

Cardiopulmonary arrest (CPA) is a consequence of various conditions, such as ceased respiration and circulation, and is characterized by inability to get a pulse and sudden loss of consciousness [1]. Cardiopulmonary resuscitation (CPR) is defined as the revival effort to correct respiratory and circulatory functions [2]. The most common reason for cardiac arrest in adult patients is ischemic cardiovascular diseases [3]. Throughout the duration of the arrest, vital organs cannot function without external support. Unless rapidly intervened, the patient will be in somatic death within 8 minutes [4]. Studies have reported that the ischemia-reperfusion injury damages the organs in patients who underwent resuscitation after CPA [5,6].

It is known that serum Ca^{+2} level is related to the prognosis of many diseases. The Ca^{+2} ion plays a significant role in stimulating and contracting the heart muscle [7]. We therefore think that serum Ca^{+2} level can be associated with the prognosis of cardiac arrests.

In this study, we aimed to determine whether serum adjusted Ca^{+2} levels are indicative for prognosis in successful resuscitation in patients who were brought to the emergency department with CPA.

Materials and methods

One hundred and thirty-two cases over the age of 18 years brought to our hospital's ED with non-traumatic CPA between 2017-2019 were examined in this retrospective cohort study. Data were obtained from the hospital registry. The demographic features (age, gender, mortality status and the presence of comorbid diseases in medical history) of the cases were evaluated. With the routine biochemistry analyzer (Cobas c501, Roche, Germany) total Ca^{+2} levels were measured upon arrival at the ED. The adjusted Ca^{+2} levels were calculated using the relevant formula in the literature, and the results were presented as the adjusted Ca^{+2} levels [8]. Patients whose hospital records could not be accessed, whose blood could not be examined during CPR, those with liver cirrhosis, malnutrition, hypo-hyperparathyroidism, patients with impaired serum electrolyte metabolism or patients who underwent a parathyroid operation, patients with malignancy, metabolic diseases, missing information in the patient files and cases of arrest under the age of 18 years were excluded. We examined our non-traumatic CPA cases in two groups, those who survived (surviving group) or died (exitus group) after CPR.

Statistical analysis

SPSS Windows 20 statistics program was used in all data analysis. The results were given as mean standard deviation (SD). Student's t test and Chi-square tests were applied to compare the variables between two groups. In all the tests, $P<0.05$ was considered significant.

Results

Between the study dates, 207 traumatic and non-traumatic CPA patients were admitted to ED. A total of 138 non-traumatic CPA patients were included in this study. However, six patients were excluded from the study because their laboratory data were insufficient. Flow diagram with exclusion criteria is summarized in Figure 1. When the demographic data of the 132 cases in the study was examined, it was found that 58 (43.93%) patients were terminated as exitus, and 74 (56.07%) were admitted to intensive care units.

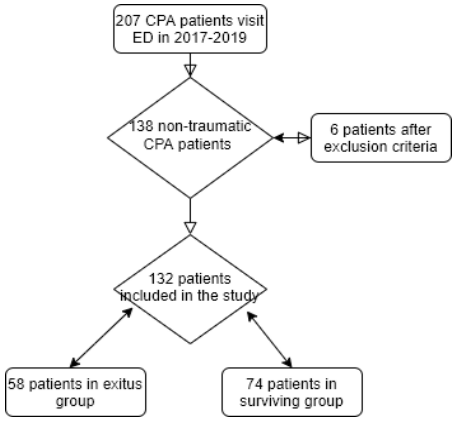

Figure 1: Flow diagram of the study ED: Emergency department, CPA: Cardiopulmonary arrest)

The mean age of all patients was 68.50 (13.45) years. The mean ages of the surviving and exitus groups were 68.86 (13.59) and 68.17 (13.33) years, respectively, which were similar (P=0.617) (Table 1). Among all, 56.06% (n=74) were male and 43.93% (n=58) were female. No statistically significant difference was found between the two groups in terms of the effect of gender on survival (P=0.214). No comorbid diseases were found in 50.76% of patients, whereas coronary artery disease was found in 23.48%, respiratory system diseases were found in 6.06%, and other diseases (diabetes mellitus, stroke, neurological diseases etc.) were present in 19.7%. No differences were found between exitus group and surviving group with respect to comorbid disease (P=0.552).

No statistically significant differences were found between the exitus and surviving groups in terms of average serum K (4.9 (0.17) mmol/L and 4.73 (0.12) mmol/L, respectively) and Na (139.9 (5.6) mmol/L and 138.49 (4.2) mmol/L, respectively) levels (P=0.398, P=0.118, respectively). Adjusted serum Ca^{+2} levels were higher in the exitus group than the surviving group (11.87 (1.4) mg/dL vs 9.77 (1.3) mg/dL) (P=0.041) (Table 2).

Table 1: Age comparison between the exitus and surviving groups

	Group	Mean	SD	*P*-value
Age	Surviving	68.86	13.59	0.617
	Exitus	68.17	13.33	

SD: Standard deviation

Table 2: Serum potassium, sodium, and calcium levels of the surviving and exitus groups

Serum levels	Surviving group (n=74)		Exitus group (n=58)		*P*-value
	Mean	SD	Mean	SD	
Potassium (K) mmol/L	4.73	0.12	4.9	0.17	0.398
Sodium (Na) mmol/L	138.49	4.2	139.9	5.6	0.118
Calcium (Ca) mg/dL	9.7	1.3	11.87	1.4	0.041

SD: Standard deviation

Discussion

CPAs, known as the sudden cease of respiratory and cardiac functions, have a prominent place in hospital morbidity and mortality [9]. The most common (60%) reason for sudden deaths in adults is arrests related to coronary cardiac diseases. On the other hand, the most commonly observed mortal arrhythmia in this patient group is ventricular fibrillation. Approximately 15-20% of mortalities consist of sudden cardiac deaths [10].

When the demographic data about cardiac arrest cases in the literature is examined, it has been noted that it is more

commonly found in males rather than females in terms of the distribution of the disease [11,12]. In our study, the number of male patients were insignificantly higher than that of females. The ages of the youngest and oldest of the patients included in the study were 24 and 95 years, respectively, with a mean overall age of 69.37 (13.64) years. In the study conducted by Geçmen et al. [13], the average age of cardiac arrest cases in the hospital was found as 61.7 (14.6) years.

In Özen's dissertation study [14] on the relationship between the ventricle movement examined via ultrasonography in patients who underwent CPR and prognosis, the mean age of CPA cases was 65.18 ± 16.3 years. The mean age of non-traumatic cardiac arrest cases admitted to our hospital was in consistency with the literature. The province our hospital is in and the surrounding provinces it serves have low populations, and thus the number of cases in our study was lower compared to international studies. Another reason is that the study we conducted is a 2-year retrospective study while other international studies are long-term cohort studies. The number of patients in our study was consistent the number of patients in national studies [12].

Cardiopulmonary arrests are examined in two groups according to their causes, as those related or unrelated to trauma. The patient group of this study consists of non-traumatic CPA cases. When previous studies are examined, the success rate for CPR in non-trauma cardiac arrests is reported as 14-17% [15]. In our study, the success rate was 56% after CPR in 132 patients were admitted to our ED with non-traumatic CPA. The reason for the high successful resuscitation rate can be explained with low population, a short transportation time of emergency ambulances due to transportation issues, the prompt initiation of medical first aid, and the sufficient number of medical staff serving in the ED.

It has been stated that various biochemical markers can be used as an early determiner of prognosis after cardiac arrest [12,16]. However, no studies showing the relationship between non-traumatic cardiopulmonary arrests admitted to the emergency room and adjusted Ca^{+2} levels to determine their prognosis are found. Thus, this study is the first to present the role of Ca^{+2} in determining prognosis in CPA patients. Although it is known that calcium has a critical role in bone mineralization, cardiac conductivity and contractility, vascular smooth muscular tonus regulation, coagulation and decreasing nervous conduction, the relationship between calcium and the heart muscle contraction is yet to be clarified [17]. In every heart cycle, with the stimulation of the heart muscle, extracellular Ca^{+2} ions start entering the cell [18]. In situations such as coronary failure and ischemia, Ca^{+2} release from sarcoplasmic reticulum, from where Ca^{+2} is released the most, is disrupted. After ischemia, the ion concentration in the cell starts changing; Ca^{+2}, K^{+} and Na^{+} increase. As the ischemia continues, the oxygen level in the tissue decreases and the oxidative mechanisms start malfunctioning. As the $Na^{+}K^{+}$ATPase pump malfunctions the Na^{+} ions moving into the cell increase, which causes the cell to swell, leading to necrosis [19]. In cardiac arrests, the cardiac ischemia is relevant. Therefore, as the arrest duration increases, the Ca^{+2} entrance from the SR to the cytoplasm increases. $Na^{+}K^{+}$ATPase pump loses its function and induces necrosis. In the study conducted by Ovbiagele et al. [20], it was noted that in ischemic stroke cases, serum Ca^{+2} levels measured early (the first 4,5 hours) were higher compared to later (72-96 hours) measurements of serum Ca^{+2} levels. However, it was found that this had no prognostic importance [20]. In our study, it has been revealed that there was a significant difference in the adjusted serum Ca^{+2} levels between the surviving group and the exitus group after CPR. Serum Ca^{+2} levels have been higher in patients accepted as exitus. We think the reason that the results of the study conducted by Ovbiagele et al. [20] is statistically different from our study results is the adjusted Ca^{+2} levels have not been examined.

Measuring the adjusted Ca^{+2} levels is important when CPR is being performed in ED. Thus, requesting serum albumin levels should not be ignored. For example, in traumatic situations such as burns and injuries with loss of blood, albumin concentration decreases. Moreover, it can also be affected by non-traumatic situations such as malnutrition, cirrhosis, hyperparathyroidism, hypoparathyroidism, malignancies, drug use and metabolic diseases.

Limitations

The limitations of our study included the more prominent elderly population of our province and collection of data from a single hospital.

Conclusion

It is known that electrolyte changes affect necrosis and tissue ischemia. Calcium levels increase in the serum depending on necrosis after ischemia. We compared some serum electrolyte differences between survivors after CPA and those who died. Only serum Ca^{+2} level was found to be significantly higher in exitus cases. In addition, we think that adjusted serum Ca^{+2} levels can be used as a successful resuscitation indicator in CPA cases. In this regard, we believe that further multicenter studies with larger sample sizes are needed.

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Use of platelet large cell ratio as a new biomarker in the diagnosis of acute appendicitis

Akut apandisit tanısında yeni bir biyobelirteç olarak trombosit büyük hücre oranının kullanımı

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Abstract

Aim: Acute appendicitis (AA) is one of the common causes of acute abdomen. Despite classical signs and symptoms, it may not always be easily and quickly diagnosed. Although many laboratory and imaging methods and risk scoring systems are available, studies are currently underway to find new biomarkers. In this study, we aimed to investigate whether Platelet-Large Cell Ratio (P-LCR), one of the platelet parameters, can be used as a new biomarker.

Methods: This retrospective cross-sectional study was performed by scanning the hospital records of AA patients, as determined with histopathological examination, who were diagnosed between 01 January-November 2019.The patients were divided into three as normal appendectomy (Group 1), non-complicated appendicitis (Group 2) and complicated appendicitis (Group 3) groups, which were compared in terms of P-LCR and other platelet parameters.

Results: A total of 425 patients were included in the study. The number of female patients in Groups 1, 2 and 3 were 12 (36.4%), 42 (45.7%), and 121 (40.3%), respectively. The mean age of the patients was 27.2 (16.1) years. Among all, complicated and uncomplicated appendectomy groups had significantly higher WBC and lower PDW and P-LCR values compared to the normal appendectomy group (P=0.007, P=0.027 and P=0.036, respectively). The cut-off values of WBC and P-LCR were 11.47 (71.9% sensitivity, 51.5% specificity) and 19.85 (75.8% sensitivity, 32.4% specificity), respectively. The WBC and P-LCR values had strong distinguishing features compared to other parameters (AUC=0.630, P=0.013 and AUC=0.604, P=0.047, respectively).

Conclusion: This is the first study investigating the P-LCR value in the diagnosis of AA. We found that WBC, PDW and P-LCR values, which are whole blood count parameters, can be used in the diagnosis of AA.

Keywords: Acute appendicitis, Platelet large cell ratio, Platelet count, Mean platelet volume, Platelet distribution volume

Öz

Amaç: Akut apandisit, akut karnın yaygın nedenlerinden biridir. Klasik belirti ve semptomlara rağmen, her zaman kolay ve hızlı bir şekilde teşhis edilemeyebilir. Birçok laboratuvar ve görüntüleme yöntemi ve risk skorlama sistemi mevcut olmasına rağmen, yeni biyobelirteçleri bulmak için çalışmalar devam etmektedir. Bu çalışmada trombosit parametrelerinden biri olan Trombosit-Büyük Hücre Oranının (P-LCR) yeni bir biyobelirteç olarak kullanılıp kullanılamayacağını araştırmayı amaçladık.

Yöntem: Çalışma, retrospektif tanımlayıcı bir çalışma olarak planlanarak, 01 Ocak 2019 ve Kasım 2019 tarihleri arasında gerçekleştirildi. Akut apandisit tanılı hastaların kayıtları tarandı. Hastalar histopatolojik sonuçlarına göre normal apendektomili, non-komplike apandisitli ve komplike apandisitli olmak üzere üç gruba ayrıldı. Gruplar P-LCR ve diğer trombosit parametreleri açısından karşılaştırıldı.

Bulgular: Toplam 425 hasta çalışmaya dâhil edildi. Gruplardaki kadın hasta sayıları sırasıyla 12 (%36,4), 42 (%45,7) ve 121 (%40,3) idi. Hastaların yaş ortalaması 27,2 (16,1) idi. Komplike ve komplike olmayan apendektomi grupları, normal apendektomi grubu ile karşılaştırıldığında, anlamlı derecede yüksek WBC düzeyleri ve düşük PDW ve P-LCR değerleri saptandı (P=0,007; P=0,027 ve P=0,036). WBC sayısı eğri altındaki alan (AUC) 0,63 idi ve diğer parametrelere göre güçlü ayırt edici özelliğe sahip idi (P=0,013). WBC'nin cut-off değeri 11,47 alındığında sensitivitesi %71,9, spesifisitesi %51,5 bulundu. P-LCR'nin cut-off değeri 19,85 alındığında ise sensitivitesi %67,6, spesifisitesi %32,4 idi (AUC=0,396; P=0,047).

Sonuç: P-LCR'nin akut apandisit tanısında kullanılabilirliği ile ilgili yapılan bu ilk çalışmada, tam kan sayımı parametreleri olan WBC, PDW ve P-LCR değerlerinin akut apandisit tanısında kullanılabileceği bulunmuştur.

Anahtar kelimeler: Akut apandisit, Trombosit büyük hücre oranı, Trombosit sayısı, Ortalama trombosit hacmi, Trombosit dağılım hacmi

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Introduction

Acute appendicitis (AA) is one of the most common causes of acute abdominal surgery in all age groups [1,2]. The probability of having AA in any period of life is 7-8% [3]. It is more common in developed countries and males [4,5]. The diagnosis of AA in patients admitted to the emergency department is usually based on the patient's history, physical examination, laboratory parameters, and radiological tests. Several risk scoring systems have also been developed to avoid missing the diagnosis [6-8]. Despite this, some patients are still misdiagnosed, who may later present with perforated appendicitis. In such cases, the risk of mortality increases, and the healing process is prolonged. However, patients who were operated for suspected appendicitis had normal appendectomy pathology postoperatively.

Complete blood count (CBC) is one of the most frequently requested tests by the emergency department physicians. It is also routinely requested by surgeons preoperatively to evaluate inflammatory pathologies [9]. Although elevated white blood cells (WBC) and neutrophil count, which are among the CBC parameters, are early indicators of AA, their sensitivity and specificity may vary according to the duration of symptoms and population [10,11]. These laboratory tests cannot definitively diagnose or exclude AA but may support its diagnosis [11]. Various biomarkers and blood parameters have been studied for the diagnosis of AA. Leukocyte count and C-reactive protein (CRP) levels are widely used in emergency departments [10,12-14]. Recently, platelet count (PC) and morphological tests have also been frequently investigated for the diagnosis of AA [1,2]. It was emphasized that these tests may have a prominent place in various gastrointestinal diseases and surgical outcomes [15].

The appendix is a structure with intense lymphatic activity. Excessive lymphatic activity in inflammation of the appendix may have the potential to affect platelet parameters. Early diagnosis of AA is sometimes impossible despite classical symptoms and clinical findings. Recent studies suggest that platelet parameters play a significant role in inflammation and may be inflammatory biomarkers [16,17]. There has been no previous research on platelet-large cell ratio (P-LCR) levels in acute appendicitis.

We assessed platelet-large cell ratio (P-LCR) levels in acute appendicitis, as well as the relationship between AA and PC, mean platelet volume (MPV), platelet distribution volume (PDW), plateletcrit (PCT) and WBC levels.

Materials and methods

Study design and population

This study was conducted on patients admitted to the emergency department of a third-level university hospital. It was a single-center retrospective analysis of patients diagnosed with AA between January 01, and November 2019. Approval was obtained from Ataturk University Medical Faculty Ethics Committee with the date and number of 07.11.2019/07-51. Information about patients diagnosed with AA and the procedures performed were obtained from the hospital registry.

Three groups were formed based on the histopathological findings of the patients operated for AA. The groups were categorized by histopathological reports as those with normal appendices (normal appendectomy group), positive appendicitis findings (non-complicated appendicitis group), and complicated cases with abscesses, perforation, gangrene, phlegmon, and plastron (complicated appendicitis group).

Patients with hematologic disease, chronic infectious disease or inflammatory disease, heart failure, liver disease, cancer, vascular disease, medications that could affect platelet counts and indices, and data deficiency were excluded from the study. P-LCR, PC, PDW, MPV, PCT, and WBC values were compared between the appendicitis vs. non-appendicitis and complicated vs. non-complicated groups.

Laboratory examination

Blood samples were collected into ethylene diamine tetraacetate (EDTA) sample tubes for CBC in our hospital, which was performed using a Sysmex XN-1000 hematology analyzer. The reference ranges of the parameters used for the study are as follows: Red blood cells (RBC = 4.7-6.1X10^6 /μL), MPV (5.91–11.32 fl), PCT (0.17-0.39%), PDW (12.2-15.9%), WBC (3.9-10.8X103 /μL), hemoglobin (HBG: 14.4-18.3 g/dL), PC (145–344 × 103 /μL) and P-LCR (17.5-42.5%).

Statistical analysis

SPSS 25 Statistics version (IBM Corporation, New York, NY, USA) software package was used for statistical analysis. Data were presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of continuous variables was analyzed by Shapiro Wilk test. To calculate the difference between the groups, ANOVA and Kruskal Wallis tests were used for normally and non-normally distributed data, respectively. Tukey test was used as a post hoc test between the groups. The receiver operating characteristic (ROC) curve analysis was performed to identify the role of CBC parameters in AA diagnosis between the groups. The comparison between the categorical variables was made using the Chi-square test and Fisher's Exact test. The statistical significance level was $P<0.05$.

Results

A total of 469 patients' electronic files were accessed from the hospital automation system. Forty-four patients were excluded after the implementation of the exclusion criteria, which left 425 patients to be included in the study. The inclusion and exclusion status of the participants were briefly given in the Figure 1. The histopathological reports of 76.6% (n=300) of the patients was compatible with uncomplicated appendicitis, since they did not have abscess, perforation, gangrene, phlegmon, and plastron in histopathological examination.

There were 250 males (58.8%). The mean age of the patients was 27.2 (16.1) years. Complicated and uncomplicated appendectomy groups had significantly higher WBC levels and lower PDW and P-LCR values compared to the normal appendectomy group (P=0.007, P=0.027 and P=0.036, respectively). Other demographic characteristics and laboratory findings of the patients are presented in Table 1.

According to ROC analysis shown in Table 2, PDW, WBC and P-LCR values were statistically significant in the

differential diagnosis of acute appendicitis, but only WBC number (AUC=0.63) had a strong distinguishing feature (P=0.013). The cut off value of WBC was 11.47 with a sensitivity and specificity of 71.9% and 51.5%, respectively (AUC=0.630, P=0.013).

The cut-off value of P-LCR was 19.85, with a sensitivity and specificity of 75.8% and 32.4%, respectively (AUC=0.604, P=0.047), which were enough for discrimination between the groups (Table 2, Figure 2).

All other parameters had an AUC of less than 0.60 and were insufficient for differential diagnosis. In the diagnosis of acute appendicitis, the cut off value of PDW was 10.05, with a sensitivity and specificity of 63.3% and 30.3%, respectively (AUC=0.397, P=0.049).

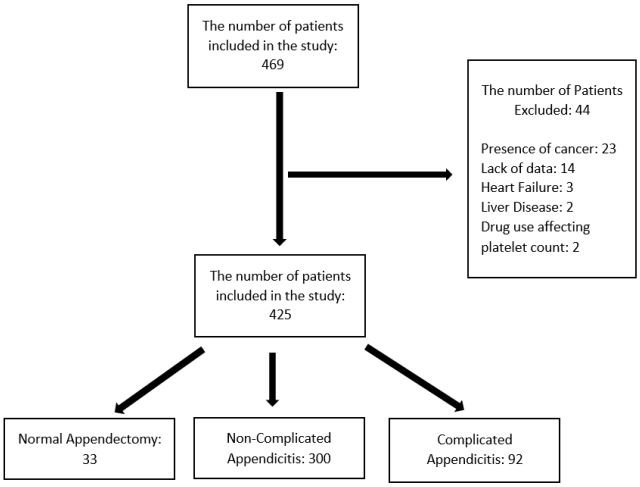

Figure 1: Flow chart of study

Table 1: Comparison of demographic and laboratory values in normal appendectomy, complicated appendicitis and non-complicated appendicitis groups

Characteristic	Normal appendectomy (n=33)	Complicated appendicitis (n=92)	Non-complicated appendicitis (n=300)	*P*-value
Age, years	28.6 (20.6) (3-81)	26.9 (17.7) (3-88)	27.2 (15.1) (3-82)	0.042[a]
Gender Female n (%)	12 (36.4%)	42 (45.7%)	121 (40.3%)	0.560[b]
RBC(10^6/µL)	4.8 (0.7) (3.1-5.6)	4.9 (0.6) (2.8-6.1)	4.9 (0.6) (3.2-6.3)	0.683[b]
MPV (7,4-10,4 fL)	10.6 (1.2) (8.5-14)	9.8 (0.8) (8.5-12)	9.9 (0.9) (8.2-13.7)	0.052[c]
PCT (%)	0.3 (0.1) (0.1-0.9)	0.3 (0.1) (0.1-0.5)	0.3 (0.1) (0.1-0.6)	0.555[c]
PDW (%)	11.9 (3) (8.3-24.1)	10.8 (1.4) (8.4-15.2)[d]	11 (2.1) (7.9-23.2)[d]	0.027[b]
WBC (10^3/µL)	11.9 (3.6) (5.7-19.8)	14.8 (4.7) (3.4-27.2)[d]	13.8 (4.9) (3.4-39.5)[d]	0.007[c]
HGB (g/dL)	13.7 (2) (8.6-17.2)	13.8 (1.9) (8.9-17.4)	14 (2.2) (8.6-38.1)	0.884[c]
PC (10^3/µL)	287.5 (148.4) (130-917)	272.3 (81.8) (110-569)	267.9 (79.4) (60-608)	0.736[c]
P-LCR (%)	27 (9.2) (13.9-53)	23.2 (5.9) (12.3-38.7)[d]	23.8 (7.5) (10.7-53.6)[d]	0.036[b]

[a] Pearson Chi-Square Test, [b] One Way ANOVA Test, [c] Kruskal Wallis Test, [d] Complicated and uncomplicated appendectomy were significant compared to normal appendectomy (P<0.05)

Table 2: Receiver operating characteristic curve for the predictors of cases with positive appendectomy

Parameter	Cut off	AUC	*P*-value	Sensitivity (%)	Specificity (%)	95% CI
RBC(10^6/µL)	>4.75	0.504	0.946	63.8	39.4	0.394-0.613
MPV (fL)	>9.45	0.399	0.053	64.3	24.2	0.297-0.501
PCT (%)	>0.235	0.466	0.513	63	33.3	0.355-0.576
PDW (%)	>10.05	0.397	0.049	63.3	30.3	0.289-0.505
WBC (10^3/µL)	>11.47	0.630	0.013	71.9	51.5	0.538-0.723
HGB (g/dL)	>13.25	0.521	0.686	65.8	36.4	0.412-0.631
PC (10^3/µL)	>231.5	0.498	0.972	65.1	39.4	0.386-0.610
P-LCR (%)	>19.85	0.604	0.047	75.8	32.4	0.291-0.501

CI: confidence interval, AUC: area under curve

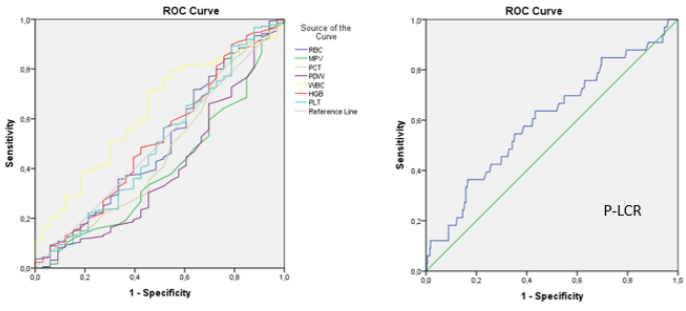

Figure 2: ROC curve of parameters for the diagnosis of acute appendicitis

Discussion

With this study, P-LCR test results are assessed in the diagnosis of AA for the first time in the literature. Although P-LCR was statistically significant in its diagnosis, ROC analysis revealed that AUC was low, and it was negatively correlated with AA. Also, the increase in the number of WBC was important in the diagnosis of AA, while the increase in other CBC parameters was not.

Despite developing laboratory and radiological imaging methods, the differential diagnosis of acute appendicitis can still lead to complications due to delayed or incorrect diagnosis in some atypical cases [9]. Imaging methods may not be available in various health centers. More easily accessible and inexpensive methods are being tried out to reduce these complications. Since AA is an inflammatory process, CBC parameters are one of the most commonly used methods in studies predicting AA.

There are many studies on CBC parameters in the diagnosis of AA, the results of which differ. Some parameters deemed useful in diagnosis by numerous studies have been contrarily reported in others [2,9,11,14,15,18]. In these studies, it was emphasized that WBC was useful and available in predicting the diagnosis of AA. A consensus is yet to be reached on the other CBC parameters. In our study, WBC was significant in the prediction of AA, with a sufficient AUC value in ROC analysis and a positive correlation with AA.

Recently, platelet and indices of these parameters have been investigated frequently. Platelets have been found to play significant roles in inflammation. The activity and function of platelets have been associated with their size. Larger platelets are thought to be younger and more reactive [1,2,9,19]. Our study contradicts these studies in terms of PC, and the statistical significance of PC in the diagnosis of AA could not be determined.

Among platelet indices, PDW and MPV are markers which indicate platelet activation. Several studies in the literature have also given conflicting results with many diseases. Some have emphasized that they can be used in the diagnosis while others reported conflicting results. Boshnak et al. [9] emphasized that high WBC and PDW values can be used as diagnostic tests for diagnosis of acute appendicitis, and MPV cannot. Biomarkers such as WBC and CRP have been considered useful in predicting AA, but some studies have reported that these do not safely exclude AA [1]. Yigit et al. [1] determined that MPV and PDW values could not be used as biomarkers in the diagnosis of AA. Gunes et al. [20] emphasized that high WBC and PCT levels support AA diagnosis, while other parameters, MPV and PDW, do not. Sepas et al. [2] reported that MPV and PDW values may be significantly associated with AA and used as new biomarkers in its diagnosis. As a result of this study, we foresee that WBC can be conveniently used for the diagnosis of AA and other CBC parameters cannot.

P-LCR represents the percentage of circulating platelets greater than 12 fL and is more reactive than other platelet parameters [21]. In the literature, P-LCR has not been reported for use in the diagnosis of acute appendicitis, rather, its elevation is investigated in atherosclerotic vascular diseases and its relationship with coronary vessel diseases is assessed. While some argued that P-LCR may be related to coronary vascular

diseases, further studies stated otherwise [21-23]. Cerit et al. [22] compared coronary ischemia with platelet parameters and found that P-LCR value was significantly higher in coronary artery patients than in the control group. In their study on coronary artery diseases, De Luca et al. [23] emphasized that P-LCR levels could not be used in coronary diseases. Our study is the first in the literature investigating whether P-LCR level can be used to predict AA diagnosis.

Limitations

The retrospective and single-center design of the study were its main limitations. Due to its retrospective nature, we could not question whether patients used drugs affecting platelet parameters. Only drugs used from hospital data could be accessed. Our other limitation was hematological malignancies, which were undiagnosed and more common in the elderly population. Only appendiceal malignancies were excluded. Further prospective and multi-center studies are needed.

Conclusion

In our study, hemogram parameters were investigated in patients with normal appendices, non-complicated appendicitis, and complicated appendicitis with histopathological identification of acute appendicitis. From these parameters, it was determined that WBC, PDW and PLCR can be used in the differential diagnosis of acute appendicitis.

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Investigation of the relationship of corneal densitometry, corneal volume and central corneal thickness with age in healthy individuals

Sağlıklı bireylerde korneal dansitometrinin, kornea hacminin ve santral korneal kalınlığın yaş ile ilişkisinin değerlendirilmesi

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Abstract

Aim: Many changes occur in the body with aging, from which the eye is also affected. In this study, we aimed to investigate the relationship of corneal densitometry (CD), corneal volume (CV), and central corneal thickness (CCT) with age in healthy individuals.

Methods: This prospective cross-sectional study included 89 healthy individuals aged between 18-79 years. CD, CV, CCT measurements were performed with Pentacam HR (Oculus, Wetzlar, Germany) with a Scheimpflug camera. CD measurements were performed manually in the central 6 mm optical zone, 90-270 degrees plane. The data obtained were analyzed with SPSS 21 program.

Results: CD correlated positively, and CV correlated negatively with age (P=0.01, r=0.25 and P=0.04, r=-0.213, respectively). There was no significant correlation between age and CCT (P=0.42, r=-0.08).

Conclusion: Age is a crucial factor affecting overall health. It positively correlated with CD and negatively correlated with CV in healthy individuals. According to these results, these parameters responsible for vision health may be affected by age.

Keywords: Age, Cornea densitometry, Central corneal thickness, Cornea volume, Pentacam

Öz

Amaç: Yaş ile beraber vücutta farklı mekanizmalara bağlı birçok değişiklik meydana gelmektedir. Buna bağlı olarak bu değişimlerden göz de etkilenmektedir. Bu sebeple, çalışmamızda sağlıklı bireylerde kornea dansitometrisinin (KD), kornea hacminin (KH) ve santral korneal kalınlığın (SKK) yaş ile olan ilişkisini araştırmayı amaçladık.

Yöntemler: Bu prospektif, kesitsel çalışmaya yaşları 18-79 yaş arasında değişen 89 sağlıklı birey dahil edildi. Bireyler yaşlarına göre 18-40 ve 41-79 yaş olmak üzere iki gruba ayrıldı. KD, KH, SKK ölçümleri Scheimpflug kameraya sahip Pentacam HR (Oculus, Wetzlar, Almanya) ile yapıldı. KD ölçümü, santral 6 mm'lik optik zonda, 90-270 derece düzleminde, manuel olarak ölçüldü. Elde edilen veriler Spss 21. programı ile analiz edildi.

Bulgular: KD'nin yaş ile pozitif yönde, KH'nin yaş ile negatif yönde korelasyon gösterdiği bulundu (sırasıyla P=0,018 r=0,25 ve P=0,04 r=-0,213). SKK ile yaş arasında anlamlı bir korelasyon bulunamadı.

Sonuç: Yaş, vücut sağlığını etkileyen önemli bir faktördür. Sağlıklı bireylerde yaşın KD ile pozitif yönde, KH ile negatif yönde korelasyon gösterdiği bulunmuştur. Bu sonuçlara göre görme sağlığından sorumlu bu parametreler yaştan etkileniyor olabilir.

Anahtar kelimeler: Yaş, Kornea dansitometrisi, Santral korneal kalınlık, Kornea hacmi, Pentacam

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Introduction

The cornea is the transparent anterior structure of the eye with refractive features. Microscopically, it consists of six layers: front to back the epithelium, bowman, stroma, dua layer, descement, and endothelium. It provides 70% of the refractive power of the eye with approximately 43 dioptric refractive power. Especially the regular structure of collagen in the stroma layer is responsible for the transparency of the cornea. In cases such as previous corneal surgery, trauma, and keratitis, the transparency of the cornea may be impaired. This results in a decrease in the degree of vision and quality in patients [1].

Corneal densitometry (CD) is a noninvasive and quantitative measurement that provides information about the transparency of the cornea. It is used to evaluate the response to treatment and follow-up in corneal diseases. There are several studies about the use of CD in keratoconus, bacterial keratitis, photorefractive keratectomy, cross-linking, and Lasik surgery [2-6]. CD, measured with Pentacam HR with a Scheimpflug camera, is affected by keratoconus and various systemic diseases [7,8].

As is known, central corneal thickness (CCT) is important in intraocular pressure measurements. On the other hand, corneal volume (CV) is a parameter that is parallel to CCT and affected by various diseases. Also, CV has been shown to decrease with age [9].

In the literature, several studies are investigating CD, CV, and CCT. All these three parameters are related to vision health together. Our study is the first in our country that examines the relationship of all these three parameters with age. In our study, we aimed to investigate whether CD, CCT, and CV are related with age in normal healthy people.

Materials and methods

Eighty-nine eyes of 89 participants, aged between 18 and 79 years, who were admitted to Pamukkale University Training and Research Hospital Cornea Clinic from June 2019 to September 2019 were included in this prospective, cross-sectional study. Patients with trauma, previous ocular surgery, glaucoma, uveitis, collagen tissue disease, autoimmune disease history, more than + 3 hypermetropia, and -3 myopia were excluded from the study. A total of 110 participants were evaluated in the cornea clinic, 21 of which were excluded from the study due to several reasons (not meeting inclusion criteria, corneal problems, scars, opacity, keratoconus, low test quality). The flow diagram is shown in Figure 1.

The participants were divided into two groups as those aged between 18-40 and 41-79 years. The rationale of dividing participants with this age cut off was based on physiological differences between two age groups. After the visual acuity, biomicroscopic examinations, and fundus examinations of the participants, measurements were made with Pentacam HR, Scheimpflug camera (Oculus, Wetzlar, Germany). CD was measured manually in the central 6 mm optical zone, 90-270-degree plane (Figure 2). The two groups were compared in terms of CD, CV and CCT values. The relationship between CD, CV, and CCT with age and gender were investigated. Our study was carried out following the Helsinki Declaration principles with the approval of the Pamukkale University Ethics Committee (date: 5/21/2019, number: 10). Detailed informed consent was obtained from the participants of the study.

Statistical analysis

The data were evaluated with SPSS 21 package program. Student's t-test was used to compare patients over and under 40 years of age. Correlation between CD, CCT, and CV with age was measured by the Pearson correlation test. *P*-values below 0.05 were considered significant.

Results

The mean age of the patients was 41.17 (15.78) years. Thirty-nine (43.8%) were male and 50 (56.2%) were female. The mean ages of males and females were 38.82 (17.40) and 43.02 (14.31), respectively, which were similar (P=0.07). There was no difference between genders in terms of CD, CV, and CCT values (P=0.54, P=0.37, P=0.65, respectively) (Table 2). The mean CD value of individuals between the ages of 18-40 and 41-79 years were 12.00 (0.97) and 12.37 (1.23), respectively. There were no significant differences between these two groups in terms of CD, CV, and CCT values (P=0.39 P=0.63 P=0.39, respectively) (Table 3). A significant positive correlation was observed between CD and age (P=0.01, r=0.25). The mean CCT and CV values of participants were 543.67 (31.92), and 59.68 (3.85), respectively. While CCT was not correlated with age (P=0.425, r= -0.086), CV was (P=0.04, r=-0.213).

Table 1: CD, CV, CCT measurements according to gender

	Male	Female	*P*-value
CD	12.28 (1.39)	12.13 (0.87)	0.54
CV	59.89 (4.00)	59.52 (3.77)	0.37
CCT	547.12 (32.78)	540.98 (31.30)	0.65

CD: Cornea densitometry, CV: Cornea volume, CCT: Central corneal thickness

Table 2: CD, CV, and CCT measurements according to age groups

	Group 1 (18-40 age)	Group 2 (41-79 age)	*P*-value
CD	12.0 (0.97)	12.19 (0.97)	0.39
CV	59.86 (4.02)	60.27 (3.65)	0.63
CCT	539.97 (26.44)	554.28 (33.48)	0.39

CD: Cornea densitometry, CV: Cornea volume, CCT: Central corneal thickness

Discussion

Transparency of the cornea in the central 6 mm area is important for visual clarity. In our study, a significant positive correlation was observed between the central 6 mm CD and age, which was consistent with the literature [10-13]. Contrary to these studies, there are numerous studies indicating that the CD is not affected by age in the central 6 mm area [14]. In another study, CD was found to positively correlate with age, and negatively correlate with corneal endothelial cell density [15]. It is known that corneal endothelial cells decrease with age. In fact, it has been shown that there is a 0.6% loss of cells every year [16]. Corneal endothelium plays a significant role in corneal transparency [17], which may be one of the reasons for CD increase with age.

In our study, there was no significant difference between patients aged below and above 40 years of age. Alzahrani et al. [18] classified 97 patients between the ages of 10 and 69 years at 10-year intervals, and found the CD values of participants in the 10-19 and 40-49 age groups higher, and attributed this to hormonal changes in the body in these age groups. We divided the participants into two groups since the age of 40 is a sensitive period for hormonal changes in the body but

observed that this does not affect CD. Similarly, we observed that the two groups did not differ in terms of CV and CCT. Studies with more participants are needed to thoroughly investigate this situation.

In our study, no differences were observed between male and female genders in terms of CD, CV, and CCT. In a recent study, total CD was significantly higher in women than in men. It is emphasized by the authors that this result has no specific reason and can be neglected in clinical practice [19]. In another study, it was emphasized that gender does not affect CD [13]. Although studies are stating that CCT differs with gender, there are studies that state otherwise [20,21].

In some studies, CCT has been shown to decrease with increasing age [20,21], while in others, it was unrelated [19]. In a study conducted in our country, it was stated that CCT increased in older age groups [22]. In our study, no significant relationship was found between CCT and age. In addition, numerous studies reported that CV decreases with increasing age (9). In our study, it was found that CV correlates with age negatively.

It is known that corneal endothelial cells decrease with aging. It is thought that CD has changed due to this decrease. It has been shown in previous studies that CV also varies with age and is associated with CCT [9]. It would not be wrong to say that all three parameters are somehow related to each other in the light of previous studies. Therefore, investigating the effect of aging on these parameters can shed light on changes in visual quality with age.

Limitations

Our study has several limitations. We think that our study may be affected by the factors that depend on the participants since it is a study involving a limited number of patients at a certain time. It is also possible that racial characteristics will affect these parameters. On the other hand, corneal endothelial functions were not measured in this study. Also, CD measurements were made only from the central 6 mm area. Therefore, there is a need for studies in which more corneal parameters are included and the peripheral parts of the cornea are also measured.

Conclusion

CD, CV, CCT are parameters which are responsible for the quality of vision. In our study, it was found that CD correlated positively with age, and CV correlated negatively. Age seems to affect the corneal parameters which are responsible for visual clarity.

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Evaluation of scoliosis in patients with lumbosacral transitional vertebra

Lumbosakral tranzisyonel vertebralı hastalarda skolyozun değerlendirilmesi

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Abstract

Aim: Lumbosacral transitional vertebra and scoliosis both have the potential to alter spinal balance, along with psoas muscles, which are important in the maintenance of spinal alignment. In this study we aimed to evaluate the relationship between lumbosacral transitional vertebrae and their potential influence on lumbar alignment.

Methods: In this cross-sectional study, lumbar Magnetic Resonance Imaging (MRI) studies that are referred to our Radiology Department between January 2017 and July 2017 were evaluated. 125 patients with lumbosacral transitional vertebra and 125 patients without any history of previous spinal surgery, trauma, inflammatory or infectious diseases were included. Type of transitional vertebra (unilateral/bilateral), presence of scoliosis and psoas muscle diameter-area measurements were evaluated.

Results: Among the transitional vertebra group, 75 patients had unilateral and 50 had bilateral sacralization. Among sacralization patients, 52.8% also had scoliosis. The presence of scoliosis was significantly lower in patients with bilateral sacralization compared to those with unilateral sacralization (P=0.001). The psoas muscle cross-sectional area and diameters were also further evaluated for the presence of asymmetry in the scoliosis group. Measurements were made twice by one radiologist and the mean value was used for statistical analysis. Results showed that area and transverse diameter asymmetries were statistically significant in patients with scoliosis (P=0.001 and P=0.003, respectively).

Conclusions: Lumbosacral transitional vertebra deteriorates spinal alignments and particularly when unilateral, may cause scoliosis and psoas muscle asymmetry. The pathophysiology of psoas muscle asymmetry, however, is controversial and should be further evaluated.

Keywords: Lumbosacral transitional vertebra, Magnetic resonance imaging, Scoliosis, Psoas muscles

Öz

Amaç: Lumbosakral tranzisyonel vertebra ve skolyozun her ikisinin de spinal dengeyi değiştirebilecek potansiyel etkileri bulunmaktadır. Psoas kasları ise spinal dengenin sağlanmasında önemli göreve sahiptir. Bu çalışmada lumbosakral tranzisyonel vertebra ile spinal dizilim arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Bu kesitsel çalışmada hastanemizin Radyoloji Bölümü'nde Ocak 2017-Temmuz 2017 tarihleri arasında çekilen Lomber Manyetik Rezonans Görüntüleme tetkikleri retrospektif olarak değerlendirildi. Tranzisyonel vertebralı 125 hasta ile spinal cerrahi, travma, inflamatuar ya da enfeksiyöz bir hastalık öyküsü bulunmayan 125 hasta control grubu olarak çalışmaya dahil edildi. Tranzisyonel vertebranın yönü (unilateral, bilateral), skolyoz varlığı ve psoas kası çap ile alanları değerlendirildi.

Bulgular: Tranzisyonel vertebralı hastaların 75'i unilateral 50'si ise bilateral sakralizasyona sahipti. Sakralizasyonu olan hastaların %52,8'inde aynı zamanda skolyoz mevcuttu. Bilateral sakralizasyonu olan hastalarda unilateral sakralizasyonu olan hastalara kıyasla skolyoz anlamlı derecede daha az saptandı (P=0,001). Skolyoz grubunda psoas kası asimetri durumunu saptamak için psoas kas çapları ve kesitsel alanları değerlendirildi. Ölçümler aynı radyolog tarafından iki kere yapılarak ortalama değer istatistiksel değerlendirmede kullanıldı. Skolyozlu hastalarda psoas kaslarının alanlarında ve transvers çaplarında anlamlı oranda asimetri olduğu görüldü (sırasıyla P=0,001 ve P=0,003).

Sonuç: Lumbosakral tranzisyonel vertebra spinal dizilimi bozmakta ve özellikler tek taraflı olduğunda skolyoza ve psoas kası asimetrisine neden olmaktadır. Psoas kası asimetrisinin altındaki patofizyoloji kesin olmayıp ileri çalışmalarla desteklenmelidir.

Anahtar kelimeler: Lumbosakral tranzisyonel vertebra, Manyetik rezonans görüntüleme, Skolyoz, Psoas kası

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Introduction

According to Becker et al. [1], lumbar pain is recognized as a common cause of hospital visits and is mostly not related to any one single mechanism. Notably, Lumbosacral Transitional Vertebrae (LSTV) are anomalies that involve the sacralization of the lower lumbar vertebrae and lumbarization of the upper sacral vertebrae, with a reported frequency of 4-21% in the population [2,3]. Castellvi et al. [4] defined four LSTV types, varying from dysplastic transverse process to complete fusion with sacral ala, both of which can be seen unilaterally or bilaterally. As reported by Almeida et al. [5] and Paajanen et al. [6], Bartolotti Syndrome was established as the cause of lumbar pain in 1917, and its relationship with back pain and disc degeneration in adjacent segments was studied by various researchers.

Scoliosis is a spinal deformity which may be related to congenital abnormalities or various neuromuscular diseases. It may also develop secondarily to degenerative changes [7]. Additionally, in degenerative scoliosis, asymmetry in facet joint orientation and degeneration as well as an asymmetric compression fracture are thought to be the cause of the scoliosis [8]. The lumbar muscles are structures that support the stability of the spine along with discs and facet joints [9]. Muscle strength is directly proportional to the cross-sectional area of the muscle and the fibers contained in the muscle, and in many studies, muscle planimetry was used to assess muscle strength [2].

The present study aimed to determine the relationship between LSTV and scoliosis and evaluate psoas muscle asymmetry at the scoliosis level.

Materials and methods

Population

In this cross-sectional study, Lumbar MRI examinations performed in our institution for lower back pain between January and July 2017 were reviewed. Approval of Gelisim University Ethics Committee (14.02.2019, 2019-3-6) was obtained. Patients with a history of surgery, trauma, and malignancy, and patients who underwent an MRI examination due to inflammatory or infectious diseases of the spinal cord and vertebrae were excluded in order to minimize the potential additional causes that may disturb spinal alignment. Patients who had LSTV with lumbarization of the first sacral vertebra were not included in our study. The study included two groups: A population of 125 patients with an LSTV anomaly with unilateral or bilateral sacralization of the last lumbar vertebra, and a control group of 125 whose MRI examinations reported "lumbar MRI examination within normal limits". Both groups had an equal gender distribution of (52.8% female, 47.2% male). The age of participants in the LSTV with sacralization group ranged from 15 to 78 years, with a mean of 44.62 (14.84) years. The age of the control group ranged from 13 to 70 years, with a mean value of 39.09 (11.85) years.

Image analysis

All lumbar MRI images were performed according to the standard lumbar MRI protocol (Axial T2-weighted fast spin echo; TR: 3800, TE: 100, Sagittal T2-weighted fast spin echo; TR: 2500, TE: 100, Sagittal T1-weighted spin echo TR:500, TE:10) with a 1.5 T Philips Achieva MRI device (Philips Healthcare, Best, The Netherlands). The images were evaluated at the workstation (INFINITT PACS, Infinitt Healthcare, South Korea) by a radiologist with >5 years of experience in spinal imaging. LSTV anatomy and type were determined based on full spine coronal plane localizer images and verified with the roentgenogram of the patients as well as with axial MR images by the presence of articulation, pseudo-articulation, or fusion of the fifth lumbar vertebra with sacrum (sacralization) (Figure 1). Coronal localizer images were evaluated for the presence of scoliosis and lumbar vertebral roentgenograms of patients were further checked for their Cobb angle measurement (Figure 2). Following the measurement, we determined the curvature type. Right-sided curvature of the scoliosis is called dextroscoliosis and its left-sided counterpart is levoscoliosis. Axial T2A MRI sections were used for psoas muscle area and diameter measurements.

Figure 1: Bilateral sacralization and pseudoarticulation of L5 vertebra with sacrum is seen on axial T2-weighted MR image.

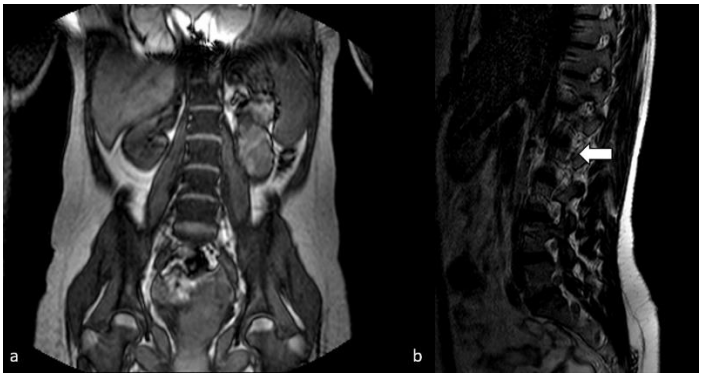

Figure 2: Coronal lumbar survey image (a) showing the scoliosis and T2-weighted sagittal image (b) of the same patient. Not all the vertebrae are on the same line because of scoliosis, also showing the suspected apex of the curvature (arrow).

Measurements were made on the Infinitt PACS system at the level of cross-sections between the lower limit of the L4 vertebrae and the upper limit of the L5 vertebra. Area measurements were calculated in mm² by drawing the psoas muscle limits manually using polygonal ROI. Anteroposterior (AP) diameter measurement was made such that it would pass through the midpoint of the sagittal plane of the psoas muscle, and the transverse diameter measurement was made such that it would pass through the middle section of the psoas muscle in the coronal plane (Figure 3). Measurements were made by the same radiologist twice, and the mean value of two measurements was used in statistical data.

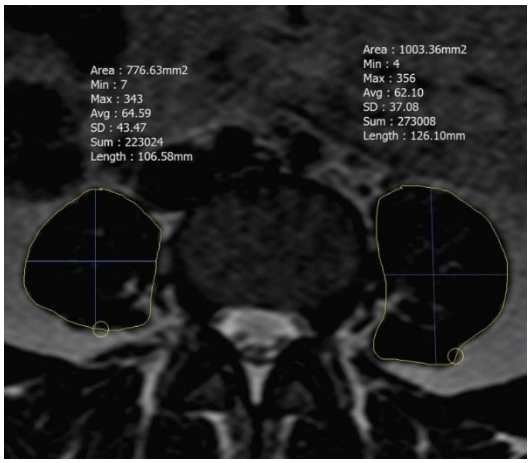

Figure 3: Axial T2-weighted image, psoas muscle area measurements are done with polygonal ROI (yellow) and diameter measurements (anterior-posterior and transverse) are seen (blue).

Statistical analysis

Statistical analysis of the data was made by using SPSS (Statistical Package for the Social Sciences) version 15.0. Data of the continuous variables were indicated as the mean (standard deviation), median and interval, and categorical variables frequency and percentage. The Pearson correlation test was used for correlations, Fisher's exact test and Chi-Square test for the categorical variables in the analyses in which the intergroup comparisons were made, and Student's t-test and Mann Whitney U test for the continuous variables. The results were evaluated with a 95% confidence interval, and the significance level was accepted as $P<0.05$.

Results

In patients with sacralization, unilateral sacralization was detected in 75 (right: 32, left: 43) and bilateral sacralization in 50. Simultaneous scoliosis was detected in 52.8% (n=66) of patients with sacralization. The mean (SD) Cobb angle was 14.3 (1.1)° in scoliosis patients. The apex of scoliosis was mostly at the L3 level (31.2%), followed by L2 (6.4%), L1 and L4 (4.8%), T12 (3.2%) and T11 (2.4%) respectively. Among scoliosis patients, 40 patients had levoscoliosis and 26 had dextroscoliosis.

When the relationship between unilateral or bilateral sacralization and the presence and direction of scoliosis were evaluated, the presence of scoliosis was significantly lower in the patient group with bilateral sacralization than in the unilateral sacralization group ($P<0.001$) (Table 1).

In the group of patients with unilateral sacralization, the frequency of dextroscoliosis was significantly higher in patients with right-sided sacralization ($P=0.003$) (Table 2). In patients with left-sided sacralization, the percentage of dextroscoliosis and levoscoliosis were the same ($P=0.06$) (Table 3).

The difference in the right-left psoas area and psoas transverse diameter were significantly greater in the scoliosis group when compared to the group without scoliosis ($P=0.001$ and $P=0.003$, respectively). The difference in right-left psoas AP diameter was higher but not statistically significant ($P=0.179$) (Table 4).

The right-left psoas area, psoas AP diameter, and psoas transverse diameter differences were significantly higher in the concave side of the curvature in the scoliosis group when compared with the control group ($P=0.001$) (Table 5).

Table 1: The presence of scoliosis regarding unilateral sacralization and bilateral sacralization

	Unilateral sacralization		Bilateral sacralization		*P*-value
	n	%	n	%	
Scoliosis					
(-)	24	32.0	35	70.0	0.001
(+)	51	68.0	15	30.0	

Table 2: Scoliosis status only by the presence of right sacralization

	Right Sacralization (+)		*P*-value
	n	%	
Dextroscoliosis			
(-)	15	46.9	0.003
(+)	17	53.1	
Levoscoliosis			
(-)	24	75.0	0.497
(+)	8	25.0	

Table 3: Scoliosis status only by the presence of left sacralization

	Left Sacralization (+)		*P*-value
	n	%	
Right scoliosis			
(-)	30	69.8	0.759
(+)	13	30.2	
Left scoliosis			
(-)	30	69.8	0.060
(+)	13	30.2	

Table 4: Comparison of the presence of scoliosis and psoas measurements in patients with sacralization

Right-left difference	Scoliosis (+) Patient Group			Scoliosis (-) Patient Group			*P*-value
	Mean	SD	Median	Mean	SD	Median	
Psoas area	1.1894	1.0826	0.950	0.7017	0.7406	0.400	0.001
Psoas AP diameter	0.3939	0.3167	0.350	0.2983	0.2169	0.200	0.179
Psoas TRV diameter	0.4258	0.3045	0.300	0.2729	0.2219	0.200	0.003

SD: Standard deviation, AP: Anteroposterior, TRV: Transverse

Table 5. Comparison of the differences between right and left psoas areas and diameters of scoliosis patients and control group

Right-left difference	Scoliosis (+) Patient Group			Control Group			*P*-value
	Mean	SD	Median	Mean	SD	Median	
Psoas area	1.1894	1.0826	0.950	0.4720	0.3505	0.400	0.001
Psoas AP diameter	0.3939	0.3167	0.350	0.1864	0.1973	0.200	0.001
Psoas TRV diameter	0.4258	0.3045	0.300	0.1928	0.1587	0.100	0.001

SD: Standard deviation, AP: Anteroposterior, TRV: Transverse

Right-left psoas AP diameter and psoas TRV diameters were statistically significantly higher in patients without scoliosis than the control group ($P<0.001$ and $P=0.016$, respectively). The mean difference of the right-left psoas area was higher, yet not statistically significant ($P=0.203$) (Table 6).

The right-left psoas muscle area and diameter differences of the patient group with scoliosis, the patient group without scoliosis, and the control group are shown in Figure 4.

Table 6: Comparison of right-left psoas area and diameters of patients without scoliosis and control group

Right-left difference	Scoliosis (-) Patient Group			Control Group			*P*-value
	Mean	SD	Median	Mean	SD	Median	
Psoas area	0.7017	0.7406	0.400	0.4720	0.3505	0.400	0.203
Psoas AP diameter	0.2983	0.2169	0.200	0.1864	0.1973	0.200	<0.001
Psoas TRV diameter	0.2729	0.2219	0.200	0.1928	0.1587	0.100	0.016

SD: Standard deviation, AP: Anteroposterior, TRV: Transverse

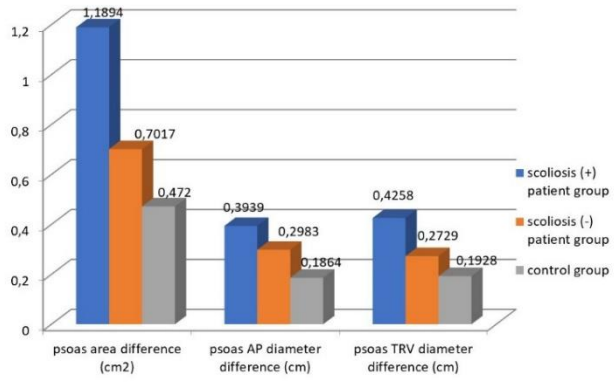

Figure 4: Right-left psoas muscle area and diameter differences of the patient group with scoliosis, a patient group without scoliosis, and the control group (cm: centimeter, AP: Anteroposterior, TRV: Transverse)

Discussion

Intervertebral discs, alignment of vertebrae, facet joints, and paraspinal muscle groups play an essential role in the stability of the spine. For efficient and normal functioning facet joints, disc and alignment are significant. Based on this, we created the following hypothesis: In the presence of pseudo-articulation or fusion formation of sacrum with the transverse process of L5 vertebrae (L5 sacralization), the regular anatomy of the lumbosacral junction would deteriorate so that the mechanical balance in this area would also be disrupted. This, in turn, would result in scoliosis – especially in patients with unilateral LSTV. According to Nardo, et al. [10] and deBruin, et al. [11], the relationship between LSTV and both the lumbar pain and degenerative changes in adjacent segments were depicted. However, their relationship with scoliosis is not clear. Technically, the results of our study confirmed our hypothesis, and scoliosis was lower in patients with bilateral sacralization than in the unilateral group. In patients with unilateral sacralization, the scoliosis curvature opening was seen towards the side of the sacralization. While this relationship was statistically significant on the right side, and there was a similar but insignificant relationship on the left side. Scoliosis curvature concavity towards the sacralization side cannot be explained by the spasm that occurred in the psoas muscle on the side where the mechanic is deteriorated, because in this case, the top of the scoliosis curve would be on the side where the sacralization was, and the concavity would face the opposite side [12]. The lack of statistical significance may be related to the fact that the number of patients with left-sided scoliosis was less than the right-sided group.

When psoas asymmetry was evaluated in the presence of scoliosis accompanying sacralization, we found that there was significant psoas asymmetry between the right and left side both in patients with scoliosis, compared to the control group, and in the patients with sacralization but without scoliosis. In this asymmetry, we found that the psoas area and diameters were greater on the concave side where the opening of the scoliosis was observed. However, here it is controversial whether scoliosis or psoas asymmetry develops first. According to Panjabi [12], the psoas muscle and paravertebral muscles are clearly the dynamic stabilizers of the vertebrae. Accordingly, Panjabi suggested that the cross-sectional areas of the psoas and multifidus muscles would be more on the convex side in people with scoliosis and further maintained that this was a compensation mechanism to establish the coronal balance.

Similarly, Kim, et al. [13], evaluated the cross-sectional areas of paravertebral and psoas muscles in degenerative scoliosis, finding that the areas on the convex side were more significant at the top level of scoliosis. However, the present study showed that the psoas areas were larger on the concave side, a result which corresponds to the hypothesis that the muscles on the concave side should be shorter and thicker, as the muscles on the convex side – due to the asymmetry in the coronal plane of the vertebra in scoliosis – should be more taut and thin. In this hypothesis, psoas asymmetry is a result rather than a cause. In the present study, psoas asymmetry was statistically significant in sacralization patients with and without scoliosis, suggesting the presence of LSTV – an essential parameter in our study – was effective on the development of scoliosis. The fact that the frequency of scoliosis was higher in patients with unilateral sacralization than in patients with bilateral sacralization also supports this hypothesis. In this context, scoliosis may develop primarily in patients with unilateral sacralization, and psoas asymmetry may then subsequently occur. However, the causal mechanism in the development of scoliosis is unclear.

Dangaria et al. [14] investigated the relationship between disc herniation and psoas muscle area and found a reduction in muscle area on the affected side. Danneels et al. [8], however, revealed that there was no difference in the psoas muscles of people with lumbar pain. In another study, Wan et al. [15] investigated the changes in paraspinal muscles in people with lumbar pain and found a reduction in paraspinal muscle areas due to reflex inhibition on the side with pain. LSTV and scoliosis were evaluated as factors of to affect psoas muscle in our study. No evaluation was made for the presence of pain in patients. Therefore, the relationship between reflex inhibition and pain and atrophy secondary to the process in our study is unknown. However, when it is considered that the pain is on the side of sacralization – the primary pathology – the absence of atrophy on the ipsilateral psoas muscle in our study suggests that this mechanism does not affect the current pathology.

When we evaluated our study results in comparison with other studies in which the psoas muscle on the convex side of scoliosis was expected to have a smaller diameter, in our study, conversely, the psoas muscle dimensions were more prominent. This was the result of a cause-effect relationship rather than a compensation mechanism. In light of these findings it may be that scoliosis develops primarily on the side of sacralization in patients with LSTV and that the muscles consequently become shorter and thicker on the openness-side, and longer and thinner on the other side.

Limitations

Limitations of the present study include the fact that paraspinal muscles which provide spinal stability were not evaluated, and only the psoas muscle was assessed. The control group consisted of patients with lumbar complaints even though they had standard lumbar MRI images. We only included patients with sacralization that was confirmed on axial and survey images and we excluded patients with lumbarization among transitional vertebra patients and that may be a potential source of bias.

Conclusions

This study shows that the mechanical balance which provides spinal stability in LSTV patients is deteriorated, especially in patients with unilateral LSTV, and that this may lead to the development of scoliosis and psoas muscle asymmetry in these patients. Psoas muscle cross-sectional areas tend to be more prominent and thicker on the concave side in patients with sacralization accompanied by scoliosis, and the causative mechanism is unclear. The presence of sacralization and its unilaterality are risk factors in the development of scoliosis and related pathologies. We believe that an awareness of this information would be helpful in planning patient-specific treatment to prevent the development of scoliosis.

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Assessment of preoperative risk scoring systems in geriatric and non-geriatric coronary bypass surgery patients

Koroner bypass cerrahisi uygulanan geriatrik ve geriatrik olmayan hastalarda preoperatif risk puanlama sistemlerinin değerlendirilmesi

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Ethics Committee Approval: Ethical approval of was obtained from Lokman Hekim University, Non-Interventional Clinical Research Ethics Committee (date: 20/05/2020, number: 53875521-050-E.249). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etik onay Lokman Hekim Üniversitesi, Girişimsel Olmayan Klinik Araştırma Etik Kurulu'ndan (tarih: 20/05/2020, sayı: 53875521-050-E.249) alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: The need to predict mortality in patients undergoing cardiac surgery has resulted in the development of numerous preoperative risk scoring systems, which are being successfully implemented in clinical practice. Although the criteria of scoring systems use patient age as a risk factor, their effectiveness should also be evaluated in the subgroups of these systems.

Methods: Our retrospective cohort study includes all patients who underwent isolated CABG surgery at Private Akay Hospital Cardiovascular Surgery Clinic between May 2012 and March 2014. Patients were subdivided into two cohorts as geriatric (≥65 years) and non-geriatric (<65 years) patients. In this study, intraoperative deaths and deaths within 30 days postoperatively were considered as mortality. We retrospectively evaluated demographic data, preoperative risk factors, preoperative treatments, postoperative data, postoperative complications, laboratory findings, and mortality and morbidity outcomes from patient files and the hospital database.

Results: The coherence between observed and EuroSCORE II-predicted mortality, logistic Euro-SCORE-predicted mortality and Parsonnet-predicted mortality were 93%, 94%, and 89%, respectively for patients aged 65 and older, and 78%, 77%, and 71%, respectively for patients aged below 65 years (P=0.01 for all).

Conclusion: In general, we observed that EuroSCORE II, Log EuroSCORE and Log Parsonnet scoring systems are more effective in predicting mortality among elderly coronary bypass surgery patients compared to younger patients.

Keywords: Preoperative risk scoring systems, Geriatric patient, Coronary bypass

Öz

Amaç: Kalp cerrahisi uygulanacak olan hastalarda mortaliteyi öngörmeye duyulan ihtiyacın sonunda birçok preoperatif risk skorlama sistemleri oluşturulmuştur. Günümüzde de bu preoperatif skorlama sistemleri başarıyla kullanılmaktadır. Skorlama sistemleri kriterlerinde hasta yaşını risk faktörü olarak kullansada, bu sistemlerin alt gruplarında da etkinliklerinin değerlendirilmesi gerekmektedir.

Yöntemler: Retrospektif kohort çalışmamızda Özel Akay Hastanesi Kalp ve Damar Cerrahisi Kliniği'nde Mayıs 2012 – Mart 2014 tarihleri arasında ardışık olarak CPB altında izole CABG operasyonu geçiren tüm hastalar çalışmaya dâhil edildi. Hastalar geriatrik (≥65 yaş) ve geriatrik olmayan (<65 yaş) hastalar olmak üzere iki gruba ayrıldı. Çalışmamızda meydana gelen intraoperative ve postoperatif 30 gün içinde olan ölümler mortalite olarak kabul edildi. Retrospektif olarak hastalara ait demografik veriler, preoperatif risk faktörleri, preoperatif tedaviler, postoperatif veriler, postoperatif komplikasyonlar, laboratuar bulguları, gözlenen mortalite ve morbidite kayıtları hasta dosyaları ve hastane veri tabanından elde edilmiştir.

Bulgular: Altmış beş yaş üzerindeki hastalar için Euroscore 2 beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %93 olduğu, 65 yaş altındaki hastalar için Euroscore 2 beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %78 olduğu izlenmiştir (P=0,01). Altmış beş yaş üzerindeki hastalar için Logistic Euroscore (Log Euroscore) beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %94 olduğu, altmış beş yaş altındaki hastalar için Log Euroscore beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %77 olduğu izlenmiştir (P=0,01). Altmış beş yaş üzerindeki hastalar için Logistic Parsonnet (Log Parsonnet) beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %89 olduğu, altmış beş yaş altındaki hastalar için Log Pars beklenen mortalitenin gerçekleşen mortaliteye göre uyum düzeyinin %71 olduğu izlenmiştir (P=0,01).

Sonuç: Genel olarak bakıldığında Euroscore 2, Log Euruscore ve Log Parsonnet skorlarlama sistemlerinin koroner bypass olacak geriatrik hastalar üzerinde mortalitenin belirlenmesinde daha etkin sonuçlar verdiği görülmüştür.

Anahtar kelimeler: Preoperatif risk skorlama sistemleri, Geriatrik hasta, Koroner bypass

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Introduction

The assessment of surgical outcomes and quality has become particularly important in recent years. Various surgical techniques have been compared to reduce postoperative mortality and morbidity, especially in elderly patients [1]. This process was initially introduced for research purposes but has now become a source of data demanded by hospital administrations, families, insurance companies, government agencies, and even legal courts. For this reason, researchers have started developing scoring systems that aim to assess the difficulties of different types of surgeries.

Risk scoring systems allow the physician to preoperatively determine the postoperative mortality risk of the patient, inform the patients and their relatives accurately, determine cost and length of hospital stay, and retrospectively compare patients of different risk groups among themselves [2]. However, creating a perfectly accurate scoring system is problematic since patients have varying characteristics, and hence requires extensive patient data.

Approximately 19 different scoring systems have been developed in multiple countries depending on their own demagogic structures [3]. Logistic EuroSCORE, EuroSCORE II, and logistic Parsonnet scoring systems are the ones most used globally [4-6].

Elderly patients make up a significant portion of all cardiac surgeries. The gradually aging populations increase the prevalence of chronic diseases and acute disorders, and subsequently, the elderly constitute a major group of patients in many departments of hospitals, including cardiac surgery [7]. Cardiac surgery handles a considerable amount of elderly patients.

People over the age of sixty-five are considered the elderly population [8]. Increasing age itself is an important risk factor for surgical patients [9]; however, elderly people have medical conditions that can negatively affect surgical care and outcomes that need to be taken into consideration [10].

In addition, older patients are under the risk of being excluded from standard surgical treatments and clinical trials compared to younger age groups [11,12]. In western countries, the elderly constitute the fastest-growing demographic group, and the number of elderly individuals that require surgical intervention is also expected to increase in the coming years [13]. The average life expectancy has similarly increased in Turkey as well, which translates into an increased proportion of elderly patients that require treatment for cardiovascular diseases [14].

Age is used as a parameter in all three scoring systems. However, it is not known how effective the scoring systems are in the geriatric population.

In this study, we have evaluated the EuroSCORE II, Logistic EuroSCORE, and Logistic Parsonnet scores, all of which are used for preoperative risk scoring in coronary bypass surgery patients aged ≥65 years and <65 years. The main purpose of our evaluation to observe the effectiveness of these currently used preoperative risk scoring systems in geriatric patients.

Materials and methods

This retrospective study was granted ethical approval by Lokman Hekim University, Non-Interventional Clinical Research Ethics Committee (date: 20/05/2020, number: 53875521-050-E.249).

We retrospectively evaluated demographic data, preoperative risk factors, preoperative treatments, postoperative data, postoperative complications, laboratory findings, and mortality and morbidity outcomes from patient files and the hospital database. All patients who underwent isolated coronary artery bypass grafting (CABG) under cardiopulmonary bypass (CPB) between May 2012 and March 2014 in Private Akay Hospital Cardiovascular Surgery Clinic were included in this study. Patients were subdivided into two cohorts as geriatric (≥65 years) and non-geriatric (<65 years) patients. In this study, intraoperative deaths and deaths within 30 days postoperatively were considered as mortality.

Scoring systems (EuroSCORE II, Log EuroSCORE and Log Parsonnet)

The most effective way of stratifying cardiac surgical patients according to operative risk is to use one of several available risk prediction algorithms that incorporate multiple variables to derive a risk score. One of the most widely used algorithms for this purpose in the Europe is the EuroSCORE [5,15]. EuroSCORE was developed to predict in-hospital mortality after cardiac surgery and published in 1999. As a result of progress in preoperative screening, surgical techniques and intensive care, the risk associated with cardiac surgery have gone down. The original EuroSCORE was felt no longer appropriate for risk stratification. The EuroSCORE II was developed based on a more current patient database and appears to reduce the overestimation of the calculated risk. This algorithm incorporates patient age, gender, mobility, severity of angina, urgency and variables reflecting comorbidities. The logistic model is a better risk predictor especially in high-risk patients and may be of interest to institutions engaged in the study and development of risk stratification. Another scoring system is log Parsonnet scoring system which is simple, additive and grades the severity of illness of patients into five groups. We stratified our all patients in this study according to the operative risk by using EuroSCORE II, Log EuroSCORE and Log Parsonnet perioperatively.

CABG surgical technique

All cases were operated under general anesthesia using the standard anesthesia protocol that is used in our clinic. In all patients, the operation was performed with a median sternotomy. In all CABG patients, cardiopulmonary bypass was achieved with an arterial cannula in the aorta and the two-stage venous cannulation of the right atrium. After cardiac arrest was achieved with antegrade and retrograde cold crystalloid cardioplegia and topical hypothermia following cross-clamp, the continuation of the arrest was done with intermittent retrograde cold blood cardioplegia. The operation was completed under moderate hypothermia (28 °C). In all CABG patients, the left internal mammary artery (LIMA) was used to bypass the left anterior descending artery. A saphenous vein graft was used to bypass other coronary arteries. Warm blood cardioplegia was given before unclamping the cross clamp.

Exclusion criteria

The study only includes patients that underwent isolated coronary bypass surgery. Patients that underwent a combination of CABG and other procedures (valve surgery, aneurysm repair, etc.) were excluded from the study. The cases where LIMA was not used were also excluded for sample standardization. Death after postoperative day 30 was not considered as postoperative mortality.

Statistical analysis

In the study, the patients' general and clinical characteristics and scores are presented as means, standard deviations, percentages, and frequencies. The demographic and clinical characteristics of the patients were analyzed according to age groups using the chi-square test. Independent samples t-test was used to determine the association between patients' scores and mortality outcomes. The paired sample t-test was used to determine the association between age groups and clinical scores. ROC (Receiver-Operating Characteristic) analysis was performed and ROC curves were generated to determine the agreement between scoring systems (EuroSCORE II, Log EuroSCORE and Log Parsonnet) predictions and actual mortality. The area under the receiver operating characteristic (AUROC) was calculated for comparison of the areas under ROC curves. Data were analyzed using SPSS for Windows version 19.0 (Statistical Package for the Social Sciences, Chicago, IL, USA) and α=0.05 was determined as the critical decision criterion.

Results

The survival outcomes were not different between the two groups. The mortality rates for patients aged <65 years and ≥65 years were 2.9% and 2.3%, respectively, which were similar (P=0.30).

The male-to-female ratios of the two groups were alike. The prevalence of diabetes mellitus (DM), hypertension (HT), family history (FH), hyperlipidemia (HL), and obesity were not different between the two groups (P=0.20, P=0.05, P=0.12, P=0.91, P=0.51, respectively).

Smoking rates were significantly higher in the group of patients aged <65 years (P=0.03), along with the prevalence of chronic obstructive pulmonary disease (COPD) (P=0.04).

The prevalence of extracardiac arteriopathy was significantly higher in patients aged ≥65 years (P=0.01). The prevalence of neurological dysfunction was similar between patients aged <65 years and ≥65 years (P=0.59), along with that of emergency operations, chronic renal failure (CRF), critical preoperative state, left ventricular (LV) aneurysm, incidence of postoperative intra-aortic balloon pump (IABP) and postoperative inotropic support (P=0.63, P=0.66, P=0.47, P=0.62, P=0.61, and P=0.08, respectively).

The mean age was 70.62 years for patients aged ≥65 years, 50.65 years for patients aged <65 years, and 55.70 years for all patients (Table 1). The results of all three scoring systems were significantly higher in patients aged ≥65 years (P=0.01 for all) (Table 2).

The length of hospital stays, duration of intubation, and length of ICU stays were alike between the two groups (P=0.43, P=0.49, P=0.68, respectively) (Table 3).

Table 1: The examination of the characteristics of the age groups

Group		Age group ≥65 years n	%	Age group <65 years n	%	*P*-value
Survival	Death	12	2.9%	28	2.3%	0.30
	Survived	396	97.1%	1175	97.7%	
Gender	Female	129	31.6%	451	37.5%	0.09
	Male	279	68.4%	752	62.5%	
Diabetes mellitus	Yes	90	22.1%	290	24.1%	0.20
	No	318	77.9%	913	75.9%	
Hypertension	Yes	197	48.3%	513	42.6%	0.05
	No	211	51.7%	690	57.4%	
Family History	Yes	159	39.0%	523	43.5%	0.12
	No	249	61.0%	680	56.5%	
Hyperlipidemia	Yes	205	50.2%	600	49.9%	0.91
	No	203	49.8%	603	50.1%	
Obesity	Yes	74	18.1%	238	19.8%	0.51
	No	334	81.9%	965	80.2%	
Smoking status	Yes	151	37.0%	519	43.1%	0.03
	No	257	63.0%	684	56.9%	
chronic obstructive pulmonary disease	Yes	34	8.3%	59	4.9%	0.04
	No	374	91.7%	1144	95.1%	
Extracardiac arteriopathy	Yes	35	8.6%	46	3.8%	0.01
	No	373	91.4%	1157	96.2%	
Neurological Dysfunction	Yes	9	2.2%	35	2.9%	0.59
	No	399	97.8%	1168	97.1%	
Reoperation	Yes	1	0.2%	9	0.7%	-
	No	407	99.8%	1194	99.3%	
Emergency Operation	Yes	11	2.7%	41	3.4%	0.63
	No	397	97.3%	1162	96.6%	
Chronic renal failure	Yes	11	2.7%	(17).	1.4%	0.66
	No	397	97.3%	1186	98.6%	
Active Endocarditis	Yes	0	0.0%	0	0.0%	-
	No	408	100.0%	1203	100.0%	
Critical Preoperative State	Yes	4	1.0%	20	1.7%	0.47
	No	404	99.0%	1183	98.3%	
Left Ventricle aneurysm	Yes	4	1.0%	17	1.4%	0.62
	No	404	99.0%	1186	98.6%	
Post-MI Ventricular Septal Defect	Yes	0	0.0%	1	0.1%	-
	No	408	100.0%	1202	99.9%	
Aortic Surgery	Yes	0	0.0%	0	0.0%	-
	No	408	100.0%	1203	100.0%	
Preoperative Intra-Aortic Balloon Pump	Yes	2	0.5%	3	0.2%	-
	No	406	99.5%	1200	99.8%	
Postoperative Intra-Aortic Balloon Pump	Yes	15	3.7%	17	1.4%	0.61
	No	393	96.3%	1186	98.6%	
Postop Inotropic Support	Yes	41	10.0%	85	7.1%	0.08
	No	367	90.0%	1118	92.9%	

MI: Myocardial Infarct

Table 2: The examination of scores according to age groups

Measurement	Age group	n	Observed mortality rate	X (SD)	*P*-value
EuroSCORE II	≥65 years	408	2.9%	2.92 (3.01)	0.01
	<65 years	1203	2.3%	1.80 (2.11)	
Log EuroSCORE	≥65 years	408	2.9%	3.05 (3.00)	0.01
	<65 years	1203	2.3%	1.99 (2.15)	
Log Parsonnet	≥65 years	408	2.9%	3.58 (2.93)	0.01
	<65 years	1203	2.3%	2.5 (2.48)	

X: Mean, SD: Standard deviation, Log: Logistic

Table 3: The examination of the length of hospital stay according to age groups

Measurement	Age group	n	X (SD)	*P*-value
Length of Hospital Stay (days)	≥65 years	408	6.13 (1.90)	0.43
	<65 years	1203	6.24 (2.52)	
Duration of Intubation (minutes)	≥65 years	408	15.50 (21.97)	0.49
	<65 years	1203	14.65 (21.45)	
Length of ICU Stay	≥65 years	408	1.78 (2.07)	0.68
	<65 years	1203	1.72 (2.70)	
Age	≥65 years	408	70.62 (4.14)	-
	<65 years	1203	50.65 (7.65)	

EuroSCORE II, log EuroSCORE II and Log Parsonnet scores were significantly higher in patients who died from both groups compared to those who survived (P=0.01 for all) (Table 4). The coherence between observed and EuroSCORE II-predicted mortality for patients aged ≥65 years and <65 years were 93% (89% sensitivity and 75% specificity) and 75% (79% sensitivity, 70% specificity), respectively, which were significantly different (P=0.01). There was a prominent level of agreement between observed and EuroSCORE II-predicted mortality (P=0.01).

The coherence between observed and Log EuroSCORE-predicted mortality for patients aged ≥65 years and <65 years were 94% (90% sensitivity and 74% specificity) and 77% (79% sensitivity, 70% specificity), respectively, which were

significantly different (P=0.01). There was a prominent level of agreement between observed and Log EuroSCORE-predicted mortality (P=0.01).

The coherence between observed and Log Parsonnet-predicted mortality for patients aged ≥65 years and <65 years were 89% (82% sensitivity and 70% specificity) and 71% (71% sensitivity, 64% specificity), respectively, which were significantly different (P=0.01). There was a prominent level of agreement between observed and Log Parsonnet-predicted mortality (P=0.01) (Table 5, Figures 1 and 2).

Table 4: Scores and survival outcomes according to age groups

Age group	Score	Survival	n	X (SD)	*P*-value
≥65 years (n=408)	EuroSCORE II	Death	12	9.25 (3.92)	0.01
		Survived	396	2.72 (2.77)	
	Log EuroSCORE	Death	12	9.54 (3.71)	0.01
		Survived	396	2.85 (2.75)	
	Log Parsonnet	Death	12	8.51 (3.91)	0.01
		Survived	396	3.44 (2.76)	
Under 65 (n=1203)	EuroSCORE II	Death	28	3.88 (3.47)	0.01
		Survived	1175	1.75 (2.05)	
	Log EuroSCORE	Death	28	4.14 (3.64)	0.01
		Survived	1175	1.93 (2.08)	
	Log Parsonnet	Death	28	5.54 (5.22)	0.01
		Survived	1175	2.43 (2.33)	

Table 5: The evaluation of the effectiveness of scores according to age groups

ROC	Age ≥65 years (n=408)			Age <65 (n=1203)		
	EuroSCORE II	Log EuroSCORE	Log Parsonnet	EuroSCORE II	Log EuroSCORE	Log Parsonnet
Sensitivity	89%	90%	82%	79%	79%	71%
Specificity	75%	77%	70%	70%	70%	64%
Diagnostic accuracy	93%	94%	89%	78%	77%	71%
P-value	0.01	0.01	0.01	0.01	0.01	0.01

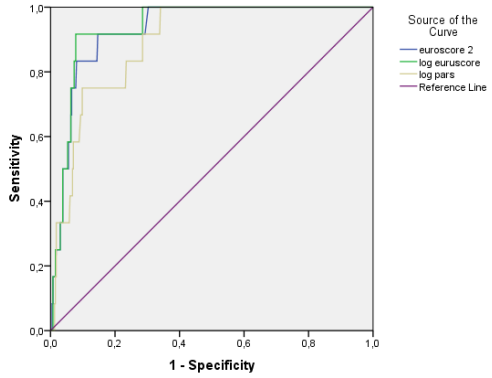

Figure 1: The evaluation of the effectiveness of scores according to age; ROC curve for patients aged ≥65 years

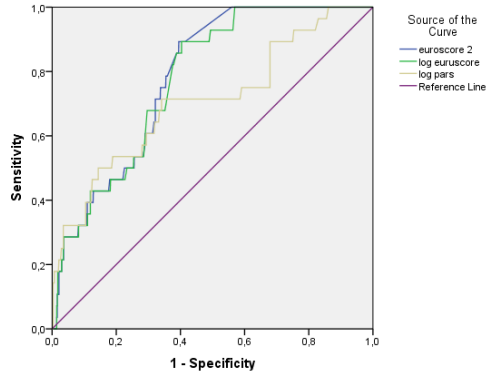

Figure 2: The evaluation of the effectiveness of scores according to age; ROC curve for patients aged <65 years

Discussion

In the last 50 years, the population over the age of sixty-five has tripled as a result of the global improvement in living standards and developments in medicine. This has not only increased the number of geriatric patients that need to be treated in clinics but also deepened the discussion regarding the surgical indications in this weak and vulnerable age group [16]. The increase in the population aged sixty-five and older that resulted from improved living standards and medical developments, which also reflected in the number of cardiac surgery operations required by this age group [2].

The costs and outcomes of open-heart surgery in elderly patients is of interest to researchers due to the higher mortality and complication rates and prolonged length of hospital stay associated with old age [17-20].

However, new medical systems may partially rationalize expensive treatments such as cardiac operations. With recent advances in myocardial protection and intensive care, the risks and costs associated with cardiac operations in elderly people may have reduced compared to the previous years [21].

Therefore, choosing the optimal intervention for each patient will always maintain its importance in terms of patient wellbeing and costs. Hence, predicting mortality outcomes before the intervention is critical for appropriate decision-making. In this regard, our study analyzes the preoperative risk scoring of coronary bypass surgery in the geriatric patient group in detail, and leads the physicians in making the correct surgical decision and, accordingly, helps accurately estimate treatment outcomes and hospital costs.

One study found that changes in organ functions, comorbidities, morbidity, and mortality increased in elderly patients compared to younger patients and that more than 50% of patients over seventy years of age had concomitant diseases, and 30-40% had 2 or more comorbidities [3].

In our study, it can be said that the demographic characteristics of our patients were largely homogeneous for the two groups, excluding extracardiac arteriopathy, COPD, and smoking. Furthermore, considering both the size and homogeneity of the sample, we believe that our results have increased predictive value and can correctly demonstrate the effects of the age parameter since they are minimally affected by differences in comorbidities.

Proper postoperative patient care in elderly patients requires careful preoperative evaluation, preoperative risk assessment, careful comorbidity assessment, optimal surgical technique, and correct surgical decision and anesthesia management [9].

Advances in perioperative treatments in the past decade have led to better outcomes for general cardiac surgery, and it has been suggested that better results can be achieved in select geriatric patients [22]. Accordingly, cardiac surgery in elderly patients can be performed with acceptable mortality rates, provided that the physician properly makes a multi-factor risk assessment and right treatment decisions [13].

The fact that the mortality rates were not significantly different for patients aged ≥65 years and <65 years that underwent coronary bypass surgery in our study indicate that the patients were selected adequately. By allowing us to compare the observed and predicted mortality results in these two sets of patients that underwent the same procedure, our results also become an index of care quality [23].

In our study, the duration of intubation, length of ICU stay, and length of hospital stay was not different for the two

groups. This finding suggests that, contrary to what is expected, old age alone does not result in morbidities such as prolonged intubation, prolonged intensive care stay, and prolonged hospital stay.

Although not evaluating the effectiveness of scoring systems, there are studies in the literature supporting our results which indicate geriatric patients significantly benefit from coronary artery bypass surgery with an increased quality of life and successful long-term outcomes despite higher mortality and morbidity rates compared to young patients [24].

Our results indicate that all three scoring systems more accurately predicted mortality rates in patients aged ≥65 years compared to patients aged <65 years. In addition, the effectiveness evaluations and ROC analysis indicate that all three scoring systems are more reliable in patients aged ≥65 years compared to patients aged <65 years. Therefore, EuroSCORE II, Logistic EuroSCORE, and Logistic Parsonnet scores more effectively predict mortality in coronary bypass surgery patients over the age of sixty-five compared to those under the age of sixty-five. In addition, the effectiveness results of the three scoring systems were not statistically different. Hence, all three scoring systems are equally effective in assessing patients aged ≥65 years.

Another conclusion from our study is that the scoring systems are adequately effective in both age groups. This shows us that these scoring systems maintain their effectiveness.

Limitations

Our retrospective cohort study was a single center study. Multicenter studies are needed for further assesment of the scoring systems (EuroSCORE II, Log EuroSCORE and Log Parsonnet). However, number of patients in the study was valuable factor even if it was a single-center study. The other limitation reducing the number of patients in our study was that the data for patients before 2012 were not included in the study, because scoring systems had not been developed yet.

Conclusion

EuroSCORE II, logistic EuroSCORE, and logistic Parsonnet systems, all of which are preoperative risk scoring systems that are currently used in coronary bypass surgery, give more accurate results in geriatric patients compared to non-geriatric patients. Future studies can help better understand the effects of patient age, gender, and physiological changes caused by chronic diseases on organs and systems and help divide preoperative risk scoring systems into sub-scales to increase practical accuracy.

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Assessment of diagnosis and treatment of geriatric patients in otorhinolaryngology

Otorinolaringolojide geriatrik hastaların tanı ve tedavilerinin değerlendirilmesi

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Ethics Committee Approval: Ethical approval of was obtained from Kutahya University of Health Sciences Institutional Ethics Committee for Non-Invasive Researches (date: 04/06/2020, reference no: 2020/09-07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Otorhinolaryngological problems worsen the social interaction of the elderly and cause addiction and depression in patients. There are a limited number of studies in the literature that examine the otorhinolaryngological disorders of the geriatric population. Through analysis of ENT patients' demographic features, diagnostic distributions, and service processes in ENT inpatient ward, this study aims to obtain data that can guide the efforts in improving future service offered for these patients.

Methods: In this cross-sectional study, the records of patients aged 65 years and over who were consulted from outpatient or emergency clinics and other departments, such as the intensive care unit to the ENT Department of KSBU Evliya Çelebi Training and Research Hospital between 01.01.2017 and 31.12.2019 (including 31.12.2019) were scanned retrospectively. Diagnoses, laboratory, radiological and audio-vestibular evaluations, and treatment processes of the patients included were analyzed.

Results: Among 12509 patients included in the study, 5792 were female (46.3%) and 6717 (53.7%) were male. The most frequent consultation to the ENT outpatient clinic was due to otological complaints with 8594 (68.7%) patients. The main tests used in the evaluation of patients were 5272 audiometric tests, 1585 laboratory tests (hemogram - biochemistry), and 508 computed tomography. The most common diagnoses were hearing loss (24.89%), followed by cerumen impaction (22.07%). Various surgical interventions were performed on 332 (2.65%) patients included in the study. Most common surgical operations were head/neck surgery (134 surgeries), and the most common surgical intervention was tracheotomy (46 patients).

Conclusion: Majority of geriatric patients are outpatients and frequently present with autological complaints. Surgical operation was performed to geriatric patients mostly due to oncological disorders.

Keywords: Geriatrics, Otorhinolaryngology, Epidemiology

Öz

Amaç: Otorinolaringolojik problemler, yaşlıların sosyal etkileşimini daha da kötüleştirmekte, hastalarda bağımlılık ve depresyona neden olabilmektedir. Literatürde geriatrik populasyonun otorinolaringolojik rahatsızlıklarını inceleyen sınırlı sayıda çalışma bulunmaktadır. Bu çalışma ile KBB hastalıkları bölümüne başvuran yaşlı hastaların demografik özelliklerini, tanı dağılımlarını, KBB hastalıkları yataklı servisindeki süreçlerini analiz etmek suretiyle gelecekte kendilerine sunulacak hizmetin kalitesini artırmaya yönelik çabalarda yol gösterici olabilecek veriler elde etmeyi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışmada; 01.01.2017 – 31.12.2019 (31.12.2019 dahil) tarihleri arasında ayaktan polikliniğe başvuran ve acil-tıp kliniği, yoğun bakım gibi farklı branşlardan KSBÜ Evliya Çelebi eğitim ve araştırma hastanesi KBB bölümüne konsülte edilen 65 yaş ve üstü hastaların dosyaları retrospektif olarak tarandı. Çalışmaya dahil edilen hastaların tanıları, laboratuvar, radyolojik ve odyo-vestibüler değerlendirmeleri ve tedavi süreçleri analiz edildi.

Bulgular: Çalışmaya dahil edilen 12509 hastanın 5792'si kadın (%46,3), 6717'si (%53,7) erkekti. KBB polikliniğine en sık başvurunun 8594 (%68.7) hasta ile otolojik şikayetler nedeniyle yapıldığı görüldü. Hastaların değerlendirilmesinde kullanılan başlıca tetkikler 5272 odyometrik test, 1585 laboratuvar testi (hemogram - biyokimya), 508 bilgisayarlı tomografidir. Hastalıklar sıklık sırasına göre incelendiğinde ilk ikisi sırasıyla; işitme kaybı %24,89 ve sıkışmış serümen %22,07'dir. Çalışmaya dahil edilen hastalardan 332'sine (%2,65) muhtelif cerrahi müdahaleler yapılmıştır. En sık cerrahi operasyonların baş/boyun cerrahisi (134 ameliyat), en sık yapılan cerrahi girişimin ise trakeotomi açılması (46 hasta) olduğu tespit edildi.

Sonuç: Geriatrik hastaların çoğunluğunun ayaktan tedavisinin yapıldığı ve sıklıkla otolojik şikayetlerle başvurdukları görülmüştür. Geriatrik hastalara çoğunlukla onkolojik rahatsızlıklar nedeniyle cerrahi operasyon yapılmıştır.

Anahtar kelimeler: Geriatri, Kulak burun boğaz hastalıkları, Epidemiyoloji

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Introduction

The human lifespan has increased thanks to the advancements in health services and easier access. Corresponding with the decrease in fertility rates, the rate of elderly people in the population is increasing day by day [1]. The increased rate of the geriatric population in developing countries is faster than that of all populations' and parallel to this, the ratio of the elderly population to the general population is increasing. The elderly constituted only 2% of the population in the USA a century ago. Today, this rate is over 12% and estimates indicate that 20% of all population will consist of the elderly in 2050 [2]. The average life expectancy is estimated as 78 years in the world [3]. According to the Turkish Statistical Institute data, while 7% (5,083,414) of our country's population consisted of people aged 65 years and over in 2009; this rate increased to 9,01% (7,550,727) by 2019 [2].

Epidemiological studies on the geriatric population will play an influential role in the planning and development of preventive health services. As a result of the increase in chronic diseases and drug consumption with aging, extreme use of health institutions, disabilities, and deaths occur. In numerous studies, the rate of emergency room consultations of geriatric patients was 9-19% [4,5]. Gülalp et al. [6] found this rate to be 22.68%. The factors underlying these variations are country, city, location of the health institution, and the population distribution of that region.

This study aims to analyze the demographic characteristics, diagnosis distributions, and the processes in the ear-nose-throat (ENT) diseases inpatient services (hospitalization, types of surgery, referral, death, etc.) of the elderly patients who apply to the ENT diseases department, and to obtain data that can guide the efforts to improve the quality of future services.

Materials and methods

This study was approved by KUHS Institutional Ethics Committee for Non-Invasive Researches with the date and number of 04/06/2020 and 2020/09-07.

While the United Nations defines old age as 60 years and older, the World Health Organization (WHO) has drawn a chronological border and defined old age as 65 years and older. In this study, files of patients aged 65 years and over who applied to the ENT Diseases Department of Kütahya University of Health Sciences Evliya Çelebi Training and Research Hospital from the outpatient or emergency clinics and consultations from other departments such as the intensive care unit between 01.01.2017 - 31.12.2019 were scanned. After evaluation of demographic information such as age and gender, patients were divided into three groups. The first group consisted of patients aged between 65-74 years (younger elderly), the second group, between 75-84 years (elderly) and the third group, aged 85 years and over (aged elderly). The diagnoses and laboratory, radiological and audiovestibular evaluations of the patients included in the study were analyzed. The reasons for inpatients' hospitalization, and if performed, the types of surgical operations were noted, and the data obtained were compared between the groups.

Statistical analysis

The data obtained from the study were evaluated using open source software 'Jamovi' (version 1.1.9) and $P<0.05$ was considered statistically significant [7]. In the statistical evaluation of the data obtained from the study, categorical data were presented as frequency (n) and percentage (%). Chi-square, Fisher's Exact, and Likelihood Ratio Tests were utilized as cross-table statistics for the statistical evaluation between categorical variables. In the comparison of numerical variables between the two groups, Independent Samples T-test were used.

Results

The total number of patients is 12509, among which 5792 were female (46.3%) and 6717 (53.7%) were male. The mean age of these patients was 72.92 (6.28) years.

The demographic findings of the patients are summarized in Table 1. In 2017, 2018, and 2019, the application rates of young elderly patients were statistically significantly higher than that of the elderly and aged elderly patients ($P=0.003$). No significant difference was observed between the total number of patients admitted, the number of patients admitted by age groups, the mean age, and gender rates between years (Table 1). Only laryngological disorders that are non-gastroesophageal reflux were significantly higher in men (175 patients) compared to women (61 patients) ($P=0.023$) (Table 2).

Otological complaints were the most frequent cause of outpatients consulted to ENT clinic ($P<0.001$). Distribution of patients' complaints by ENT disease sub-branches is summarized in Figure 1. The first five diseases were hearing loss is 24.89%, cerumen impaction 22.07%, tinnitus 7.24%, allergic rhinitis 6.01% and dizziness (vertigo) 5.58%. The distribution of patients according to their diagnosis is summarized in Table 2.

Table 1: Demographic findings

	2017	2018	2019	Total
Number of patients	4142	4140	4227	12509
65-74 years old	2664	2709	2770	8143
75-84 years old	1229	1164	1241	3634
>85 years old	249	267	246	762
Male/Female	2192/1950	2161/1979	2364/1863	6717/5792
Patient mean age	72.76 (6.21)	73.08 (6.36)	73.04 (6.33)	72.92 (6.28)

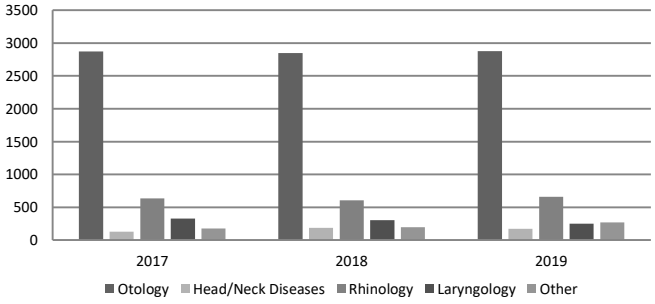

Figure 1: Distribution of consultations to ENT sub-branches by years

Distribution of the main tests used in the evaluation of patients were as follows: 5272 audiometric tests, 1585 laboratory tests (hemogram - biochemistry), 508 computed tomography (CT), 448 ultrasonography (USG), 269 magnetic resonance imaging (MRI), 217 videonistagmography (VNG), 40 auditory brainstem response (BERA) and 20 positron emission tomography - CT (PET-CT) (Table 3).

Table 2: The distribution of patients according to their diagnosis

	2017				2018				2019			
	65-74 age	75-84 age	>85 age	Total	65-74 age	75-84 age	>85 age	Total	65-74 age	75-84 age	>85 age	Total
Otology	**1772**	**902**	**196**	**2870**	**1818**	**827**	**203**	**848**	**1883**	**857**	**186**	**2876**
Chronic otitis media	60	12	2	74	62	18		80	64	15	6	85
Middle ear infections (acute otitis media, acute serous otitis media)	59	9	4	72	61	16	2	79	44	15	1	60
Sudden hearing loss	6	2		8	9	1		10	2			2
Dizziness (vertigo)	172	61	3	236	172	39	5	217	194	62	14	270
Facial nerve paralysis	14	3		17	6	1	1	8	11	3		14
Otitis externa	56	27	7	90	171	32	9	212	101	40	5	146
Meniere's disease	6			6	2	1		3	4			4
Hearing loss	587	356	91	1034	574	328	104	978	637	371	93	1101
Cerumen impaction	559	339	80	978	530	301	71	902	532	289	60	881
Tinnitus	222	82	8	312	236	80	6	322	215	52	5	272
Acoustic neuroma					1			1	2			2
Temporomandibular joint syndrome	27	9		36	13	6	2	21	23	6		29
Foreign body in the outer ear canal	4	2	1	7	9	4	3	16	4	4	2	10
Head and Neck Surgery	**83**	**38**	**8**	**129**	**126**	**51**	**10**	**187**	**115**	**52**	**7**	**174**
Benign soft tissue masses	9	12	3	24	27	11	2	40	29	10	2	41
Intraoral malignancies					3			3	1	3		4
Acute tonsilitis	32	10	1	43	44	17	2	63	42	15	2	59
Acute lymphadenitis	13	5	1	19	20	11	3	34	25	10	1	36
Tongue / lip diseases	17	6	2	25	16	8	1	25	8	5		13
Salivary gland diseases	9	5		14	11	3	2	16	7	5		12
lymphoma	2		1	4	5	1		6	3	3	3	9
Laryngology	**189**	**112**	**27**	**328**	**205**	**85**	**13**	**303**	**192**	**54**	**4**	**250**
Acute laryngitis	16	3		19	6	2		8	8	2		10
Foreign body in the larynx	1			1		1		1	1	1		2
Vocal cord paralysis	8	1		9	9	1		10	1	1		2
Laryngeal diseases	24	8		34	34	14	1	49	19	7		26
Laryngeal malignancies	2		1	3	6	3		9	4			4
Dysphagia	3	2	1	6	9	4		13	2	1		3
Voice disorder	10	3		13	2	3		5	7	2		9
Gastroesophageal reflux	125	95	23	243	139	57	12	208	150	40	4	194
Rhinology	**492**	**127**	**18**	**637**	**438**	**150**	**20**	**608**	**444**	**185**	**31**	**660**
Upper respiratory tract infection (acute pharyngitis nasopharyngitis)	107	12	3	122	118	37	7	162	102	47	8	157
Allergic rhinitis	221	57	7	285	163	68	8	239	154	64	10	228
Nasal bone fracture		2	1	3	5		1	6	22	3	3	28
Acute sinusitis	65	25	2	92	54	10	3	67	63	37	3	103
Epistaxis	55	26	4	85	43	26	1	70	43	27	4	74
Nasal polyposis	7			7	9	2		11	8	1	1	10
Nasal septum deviation	10			10	12	4		16	15	1	1	17
Sleep apnea	21	1		22	25	2		27	10			10
Lacrimal canal stenosis					2			2	1			1
Nasopharyngeal / paranasal sinus malignancies					2			2	3			3
Headache	6	4	1	11	5	1		6	23	5	1	29
Other	**118**	**50**	**10**	**178**	**122**	**51**	**21**	**194**	**156**	**93**	**18**	**267**
Total	**2664**	**1229**	**247**	**4142**	**2709**	**1164**	**267**	**4140**	**2740**	**1241**	**243**	**4227**

Table 3: The distribution of the main tests used in the evaluation of patients

	2017				2018				2019			
	65 -74 age	75-84 age	>85 age	Total	65 -74 age	75-84 age	>85 age	Total	65 -74 age	75-84 age	>85 age	Total
Audiological examination	845	487	106	1438	988	508	108	1602	1564	497	171	2232
BERA	10	1		11	1	5	2	8	8	8	5	21
Vestibular tests (Caloric test, VNG, v- HIT)	40	10		50	83	12	1	96	53	13	5	71
Ultrasonographic examination	74	28	3	105	70	30	3	103	159	68	13	240
Computed tomography (brain, neck, temporal, maxillofacial)	109	29	8	146	114	31	5	150	181	55	18	254
Magnetic resonance imaging (brain, neck, nasopharynx, internal acoustic channel)	55	18	3	76	58	28	3	89	69	29	6	104
Pet - CT	1			1	4			4	10	5		15

BERA: Auditory Brainstem Response, VNG: Videonystagmography, v-HIT: Video head impulse test, Pet-CT: Positron emission tomography- computed tomography

Various surgical interventions were performed on 332 (2.65%) of the patients included in the study. The most common surgical operations were head and neck surgery (134 surgeries), and the most common surgical intervention was tracheotomy (46 patients). The distribution of patients according to surgical interventions are summarized in Table 4.

In 2019, 31 patients were admitted to the ENT inpatient clinic for medical treatment. Twelve had attacks of vestibular neuritis, 8 had attacks of epistaxes, 4, malignant external otitis, and 3 patients, Meniere's disease. No patients who underwent medical or surgical admittance were dispatched to external health institutions. There were no death cases in geriatric patients who received treatment in our clinic within 3 years.

Table 4: The distribution of patients according to surgical interventions

	2017				2018				2019				Total
	65-74 age	75-84 age	>85 age	Total	65-74 age	75-84 age	>85 age	Total	65-74 age	75-84 age	>85 age	Total	
Head and neck surgery				**45**				**47**				**42**	134
Benign soft tissue tumor excision	9	6	1	**16**	8	1	1	**10**	7	2		**9**	35
Neck dissection	4	2	2	**8**	6	7	1	**14**	6	4		**10**	32
Tongue / Lip malignant tumor resection	6	1	1	**8**	9	3		**12**	4	2		**6**	26
Excision of malignant skin tumors	2	2		**4**	1			**1**	2	2	3	**7**	12
Salivary gland surgery (Superficial / total Parotidectomy, submandibular gland excision)	5		1	**6**	5	2		**7**	2	1		**3**	16
Thyroidectomy (total / lobectomy)	1			**1**						1		**1**	2
Intraoral malignancies excision	1			**1**	1	2		**3**	4	2		**6**	10
Tonsillectomy	1			**1**									1
Rhinology				**19**				**11**				**14**	44
Endoscopic nasal and nasopharyngeal tumor surgery	1		1	**2**						1	1	**2**	4
External nose surgery	2		1	**3**	1			**1**	2			**2**	6
Closed reduction of nasal fractures		1		**1**		1		**1**	2			**2**	4
Caldwell-Luc surgery	1			**1**									1
Functional endoscopic sinus surgery	5	1		**6**	5		1	**6**	5			**5**	17
Nasopharyngeal Biopsy	1		1	**2**									2
Oro-antral fistulas repairment	1			**1**					1			**1**	2
Septoplasty	2			**2**	3			**3**	2			**2**	7
Uvulopharyngoplasy	1			**1**									1
Otology				**21**				**17**				**25**	63
Auricular excision, scoop surgery							3	**3**	1			**1**	4
Canal Wall Down tympanoplasty	8	1		**9**	9	1		**10**	12	2		**14**	33
Outer ear canal, radical excision of malignant parts			1	**1**									1
Tympanoplasty	5			**5**	2	1		**3**	6	1		**7**	15
Facial nerve decompression	1			**1**									1
Placement of implantable bone hearing aids	1			**1**	1			**1**	2			**2**	4
Ventilation tube application	3	1		**4**					1			**1**	5
Laryngology				**32**				**34**				**25**	91
Direct laryngoscopy / cordectomy / stripping	9	3	1	**13**	2	9	1	**12**	11	2	1	**14**	39
Partial / total Laryngectomy	1			**1**	2			**2**					3
Voice prosthesis application		1		**1**	1			**1**	1			**1**	3
Tracheotomy	8	8	1	**17**	5	7	7	**19**	5	4	1	**10**	46
Total	79	27	11	**117**	61	32	14	**109**	76	24	6	**106**	332

Discussion

Turkish Statistical Institute data shows a change from 7% to 9% in the ratio of the geriatric population to the general population, which corresponds to an increase of approximately two and a half million [2]. With these data, we can estimate that geriatric patients will constitute an important portion of our clinical patients for years to come. Although there is an increase in the geriatric population rate in our country's demographics, there are quite a limited number of studies in the literature, which evaluate how this increase does and will directly affect the field of ENT diseases. The results of this study will provide an idea about the epidemiological features of elderly patients seen in the ENT practice of a tertiary hospital for a period of 3 years.

In many studies examining the geriatric population, there is a gender difference; women have been shown to apply more to hospitals. It was postulated that this is due to women having a higher life expectancy compared to men [8,9]. However, we observed almost no difference between genders; in fact, more men have consulted to the ENT Diseases Department than women.

According to the literature, while the most common head and neck malignancy in the general population is oral cavity and lip cancers, it is laryngeal cancer in our country [10,11]. The male to female ratio is 3:1 in the general population worldwide, this ratio is 4.4:1 in our country [12]. In the context of sub-branches, laryngological disorders that are non-gastroesophageal reflux were statistically significant for men and laryngological surgical interventions other than opening tracheotomy were more common in men than in women. The larynx malignancy male to female ratio is 7.4:1. However, this rate includes our surgical patients only. Patients who prefer radiotherapy/chemotherapy treatment and those who refuse treatment or want to receive treatment in other centers are not included.

Epidemiological studies have found that hearing impairment is the most common ENT morbidity [13]. According to WHO data, hearing loss is observed in 30-35% of people over 60 years of age, and in 40-45% of people over 70 years of age [14]. In this study, the most common reason for outpatient clinic application was otological complaints (68.7%). Creighton et al. [15] reported an increase in otological complaints with age, and a reduction in rhinological, head and neck surgery diseases. Okoye and Onotai [16] reported that the most common ENT applications in geriatric patients were due to otological disorders, followed by rhinology and laryngology. Among otological complaints, hearing loss is the most common. Epidemiological studies conducted in various populations are in support of the findings of this study [13,17]. Hearing loss can seriously affect the life quality of patients, increasing isolation, depression, and even suicidal tendencies [12]. Therefore, immediate treatment/rehabilitation has the utmost importance.

According to Timsit et al. [18], the most frequent geriatric patient complaints after hearing loss are epistaxis and foreign body aspirations. Özler et al. [19] ranked epistaxis, vestibular problems, and pharyngotonsillitis pathologies as the most common complaints, after ear and hearing problems. In our research, hearing impairment, cerumen impaction, tinnitus, seasonal allergic rhinitis, and dizziness were the most common complaints. We also observed that, in parallel to similar studies, ear and hearing complaints were in the foreground. In contrast, epistaxis-related applications were less common. We think this is because patients consult primarily to the emergency room, rather than the ENT clinic. In addition, our clinical experience in the study area is that allergic conditions are more common in the general population than in other regions. This suggests that seasonal allergic rhinitis occurs as the most common disorder among rhinological disorders due to regional differences.

One of the most common otological complaints in the elderly is vertigo. Although in our study, 5.8% of the patients

often complained of vertigo, studies have shown that vertigo cause restrictions in daily activities of 30% of people over the age of 70 [20]. As a result of the decrease in vestibular functions due to aging, a decrease in mobility, imbalance, and frequent falls are seen in the geriatric population, which increases morbidity/mortality.

Epidemiological studies investigating the geriatric population are quite limited in the literature. In these studies, only the diagnosis and surgery of the patients were emphasized, and no study mentioned the tests used to evaluate the patients. In our study, we examined the most frequent audiological tests for evaluating geriatric patients and found that the most common are audiological tests. It is not surprising that audiological tests are the most common, where the most frequent causes for consultation are hearing complaints. The most preferred radiological imaging method in the evaluation of patients was found to be CT.

All organs and systems are affected by the aging process. Loss of function in organs also affects surgical results. Any kind of surgical intervention in geriatric patients with more co-morbid diseases than the young population causes high mortality and morbidity [19]. For this reason, surgeons should plan surgery considering the physiological reserves of patients; otherwise, undesirable conditions such as a decrease in organ functions and organ failure due to surgical stress, unexpected complications, prolonged hospital stay, and adverse effects on morbidity/mortality may be encountered. 189 (56,9%) of 332 patients who underwent a surgical operation in our clinic did so due to suspected malignancy or malignancy. Al-Qurayshi et al. [21] reported that the most common surgical intervention in the geriatric population was due to oncological diseases, similar to our study. In our clinic, surgical intervention was performed most frequently due to diseases related to the head and neck (134 surgeries). The most common surgical operation related to laryngology is tracheotomy (46 patients). Most of the patients treated in intensive care and hospitalized in palliative treatment centers are elderly patients and these patients require tracheotomy because of prolonged intubation [22]. Therefore, it is not surprising that tracheotomy surgery is high in geriatric patients.

The geriatric population is increasing day by day and takes up more space in our daily practice. In their study evaluating 131,700 patients who were consulted to the ENT clinic for the first time in 6 years, Creighton et al. [15] found that otorhinolaryngological complaints of patients belonging to different age groups vary. In this study, the rates of pediatric and geriatric patients were 14.3 and 14.9%, respectively. While the most common reason for consultancy in patients within the pediatric age group is rhinological disorders, in the geriatric age group, it is otological disorders [16]. Although pediatric ENT is a subspecialty in the ENT practice, no geriatric ENT subspecialty exists. To better evaluate diseases related to the geriatric population, we advise special training and seminars to be given in the future and geriatric ENT to be considered as a sub-branch, just as pediatric ENT.

The rate of geriatric population in the general population is increasing day by day both in the world and in our country. This study has shown that ENT consultations are mostly related to otological complaints in outpatients. Health problems of older people cause addiction and depression; otorhinolaryngological problems -especially otological disorders- make the patient's social interaction worse. Therefore, autological treatment and rehabilitation should be given importance. Although it does not seem high in proportion, vertigo in geriatric patients is of special importance. Vertigo can accompany other otological symptoms. It can be due to central and multiple peripherical causes and shows a significant correlation with mortality/morbidity.

Limitations

The most important limitation of our study is that it is based on cross-sectional retrospective file scanning. Unfortunately, this design prevents establishing the relationship between cause and effect. With these results, mortality cannot be predicted for geriatric patients hospitalized for surgical or long-term medical treatment. In addition, this is a single-center study. Therefore, this data may not represent our country. A multi-center study will be useful in obtaining more detailed information.

Conclusion

This study is the biggest series study in the ENT field in Turkey that conducts an epidemiological evaluation of geriatric patients. Epidemiological studies on the geriatric population will guide the planning of healthcare services to be provided to patients and the development of preventive healthcare services.

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Can C-reactive protein to albumin ratio be used as a predictor of amputation development in acute lower extremity ischemia?

C-reaktif protein - albümin oranı akut alt ekstremite iskemisinde amputasyon gelişiminin öngörücüsü olarak kullanılabilir mi?

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Abstract

Aim: Acute lower limb ischemia is a cardiovascular emergency that occurs due to embolic and thrombotic causes. Inflammatory biomarkers obtained from routine blood parameters have been used in the diagnosis and progression of many cardiovascular diseases. In this study, we aimed to reveal the predictive value of C reactive protein to albumin ratio (CAR) in predicting limb loss, which is a significantly morbid result of thromboembolectomy.

Methods: Patients who were admitted to our clinic with acute lower extremity ischemia between March 15, 2015-March 15, 2018 and who underwent thromboembolectomy were included in this retrospective cohort study. The patients in which no extremity amputation was performed after the surgery were included in Group 1 and those in which amputation was performed in the early post-operative period (in-hospital) were included in Group 2. Multivariate logistic regression analysis was utilized to predict parameters supporting amputation in patients with lower extremity thromboembolism.

Results: There were 207 patients in Group 1 and 32 in Group 2. Amputation was performed above the knee in 5 patients (15.6%), below the knee in 23 patients (71.8%) and below the ankle in 4 patients (12.5%) in Group 2. The mean age of patients in Groups 1 and 2 were 58.7 (9.8) years and 68.3 (10.3) years, respectively (P<0.001). In the regression analysis, advanced age (OR: 1.045, CI 95%: 1.004-2.144, P=0.011), CAR (OR: 1.679, CI 95%: 1.224-3.794, P=0.005) and hospital admission time (OR: 1.054, CI 95%: 1.010-1.458, P=0.022) were determined as independent predictors for amputation.

Conclusion: The CAR value obtained from routine blood parameters obtained before the procedure may be a good predictor of amputation risk.

Keywords: Inflammation, Amputation, Embolectomy, Lower extremity

Öz

Amaç: Akut alt ekstremite iskemisi embolik ve trombotik nedenlerden dolayı ortaya çıkan kardiyovasküler acil bir durumdur. Rutin kan parametrelerinden elde edilen inflamatuar biyobelirteçler birçok kardiyovasküler hastalığın tanısında ve progresyonunda kullanılmıştır. Bu çalışmada, tromboembolektominin önemli bir morbid sonucu olan ekstremite kaybının öngörülmesinde C reaktif proteinin albümin oranının (CAR) prediktif değerini ortaya koymayı amaçladık.

Yöntemler: Kliniğimize akut alt ekstremite iskemi durumu olan 15 Mart 2015-15 Mart 2018 tarihleri arasında başvuran ve tromboembolektomi uygulanan hastalar bu retrospektif kohort çalışmasına dahil edildi. Ameliyat sonrası ekstremite amputasyonu yapılmayan hastalar Grup 1, ameliyat sonrası erken dönemde (hasteneiçi) amputasyon yapılan hastalar Grup 2 olarak kaydedildi.

Bulgular: Hastaların 207'si Grup 1'e, 32'si Grup 2'ye dahil edildi. 5 hastada (%15,6) diz üstünde, 23 hastada (%71,8) diz altında ve 4 hastada (%12,5) ayak bileği altında amputasyon yapıldı. Grup 1'deki hastaların ortalama yaşı 58,7 (9,8) iken, Grup 2'deki hastalar 68,3 (10,3) idi (P<0,001). Alt ekstremite tromboembolizmi olan hastalarda amputasyonu destekleyen parametreleri tahmin etmek için çok değişkenli lojistik regresyon analizi kullanıldı. Bu değerlendirmede, ileri yaş (OR: 1,045, CI% 95: 1,004-2,144, P=0,011), CAR (OR: 1,679, CI %95: 1,224-3,794, P=0,005) ve hastaneye başvuru zamanı (OR: 1,054, CI %95: 1,010-1,458, P=0,022) amputasyonu göstermek için bağımsız prediktörler olarak belirlendi.

Sonuç: Sonuç olarak, işlemden önce alınan rutin kan parametrelerinden elde edilen CAR değeri amputasyon riskinin iyi bir prediktörü olabilir.

Anahtar kelimeler: Enflamasyon, Amputasyon, Embolektomi, Alt ekstremite

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Introduction

Acute lower limb ischemia is a cardiovascular emergency that occurs due to embolic and thrombotic causes [1]. Surgery or endovascular intervention should be planned as soon as these patients are diagnosed. Despite advances in endovascular methods, surgical thromboembolectomy remains the gold standard. If not intervened on time as necessary, undesirable results such as limb loss, renal failure and mortality may occur [2]. Loss of extremity is a significant problem because it extends hospital stay, causes loss of workforce and psychosocial problems, thus increases treatment costs.

Inflammatory biomarkers obtained from routine blood parameters have been used in the diagnosis and progression of many cardiovascular diseases [3,4]. One of the most important among these, C reactive protein (CRP), is a nonspecific acute phase reactant synthesized in the liver. Studies have shown that CRP value may be effective in the progression of vascular diseases [5,6]. Albumin is an important compound for humans, and low albumin has poor prognostic importance for cardiovascular diseases [7]. Therefore, the value of CRP to albumin ratio (CAR) is considered an important parameter. Its predictive value has been shown in cardiovascular diseases [8,9].

In this study, we aimed to reveal the predictive value of CAR in predicting limb loss, a significant morbid result of thromboembolectomy.

Materials and methods

Patients who were admitted to our clinic with acute lower extremity ischemia between March 15, 2015 and March 15, 2018 and who underwent thromboembolectomy were included in this retrospective study, which began after approval was granted by Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee (Approval No: 2011-KAEK-25 2019/10-09). The data of the patients were accessed from the hospital registry system and patient files. Demographic data, pre- and perioperative features of the patients were recorded. Patients who previously had peripheral vascular surgery or intervention, patients with malignancy, those with hematological or inflammatory diseases, patients with vasculitis, liver disease, irreversible tissue loss at the time of admission, and those with active infection were excluded. After the implementation of exclusion criteria, 239 consecutive patients were included in the study. Hospital admission time was defined as the time from the occurrence of the first symptoms to admission to the hospital. Amputation decision was taken together with the Department of Orthopedics in patients with standing ischemia, in whom demarcation line occurred following surgical interventions. Patients in which no extremity amputation was performed after the surgery were included in Group 1 and those who underwent amputation in the early post-operative period (in-hospital) were included in Group 2.

Diagnosis of acute lower extremity ischemia and surgical thromboembolectomy technique

Detailed anamnesis was obtained from all patients and physical examinations were performed. Clinical diagnoses were supported by Doppler ultrasonography. Angiography was performed in patients with extensive atherosclerotic disease. All operations were performed urgently under local anesthesia and mild sedation. After the incision was made in the femoral region, superficial femoral, main femoral and deep femoral artery were rotated and suspended by rotating with vascular loops. 100U / kg iv heparin was administered before vascular clamps were placed. Then, embolectomy was performed with a Fogarty (3F-7F) catheter. After sufficient backflow was provided, arteriotomy was repaired. After the operation, patients were followed up in intensive care unit for at least one day and given heparin infusion on the first day after the operation. Later, low molecular weight heparin was introduced. Thromboembolism etiology was investigated peroperatively with echocardiography and abdominal ultrasonography. Discharge medical treatments were arranged according to the etiology of thromboembolism.

Evaluation of blood parameters

Blood samples of all patients were obtained from peripheral veins after hospitalization. Hematological and biochemical evaluations were performed with an automatic analyzer. CAR was calculated as follows:

CAR= (C reactive protein level(g/dL)/Albumin level(mg/dL))

Statistical analysis

Statistical analysis was performed with SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program. Student's t-test was used for numerical values with normal distribution, and Mann-Whitney U test was utilized for numerical data without normal distribution. Numerical values were expressed as mean (standard deviation) or mean and interquartile range. Chi-square test was used to compare categorical variables. $P<0.05$ was considered statistically significant. Multivariate logistic regression analysis was utilized to evaluate significant parameters in the univariate analysis for predicting amputation. Receiver Operating Characteristic (ROC) analysis was performed to evaluate the predictive value of CAR for amputation and the area under the curve (AUC) was calculated.

Results

There were 207 and 32 patients in Groups 1 and 2, respectively. Amputation was performed above the knee in 5 patients (15.6%), below the knee in 23 patients (71.8%) and below the ankle in 4 patients (12.5%) in Group 2. The mean ages of patients in Groups 1 and 2 were 58.7 (9.8) years and 68.3 (10.3) years, respectively. The mean age of Group 2 was statistically significantly higher compared to Group 1 ($P<0.001$). There was no statistically significant difference between the groups in terms of gender, smoking, diabetes mellitus, chronic obstructive pulmonary disease, coronary artery disease, hypertension and hyperlipidemia rates ($P>0.05$ for all). Peripheral arterial disease rates and hospital admission times were significantly higher in Group 2 ($P=0.012$, $P<0.001$, respectively) (Table 1).

Laboratory values of the patients are presented in Table 2. There was no difference between the groups in terms of hematocrit, platelet, white blood cell, neutrophil, lymphocyte, total protein, albumin, urea and creatinine values ($P>0.05$ for all). C-reactive protein (CRP), NLR and CAR values were

significantly higher in Group 2 (P=0.002, P=0.018, P<0.001, respectively).

Multivariate logistic regression analysis was utilized to predict parameters supporting amputation in patients with lower extremity thromboembolism (Table 3). Advanced age (OR: 1.045, CI 95%: 1.004-2.144, P=0.011), CAR (OR: 1.679, CI 95%: 1.224-3.794, P=0.005) and hospital admission time (OR: 1.054, CI 95%: 1.010-1.458, P=0.022) were determined as independent predictors for amputation.

ROC analysis revealed that the cut-off value for CAR was 3.81 (AUC=0.747, 95%CI:0.638-0.857, P<0.001, 76.9% sensitivity, 56.7% specificity) (Figure 1).

Table 1: Demographic properties of the patients

Variables		Group 1 (n=207)	Group 2 (n=32)	*P*-value
Age(years) (mean(sd))		58.7 (9.8)	68.3 (10.3)	<0.001†
Male gender, n(%)		109 (52.6%)	21 (65.6%)	0.182*
Hyperlipidemia, n(%)		63 (30.4%)	11 (34.3%)	*0.654**
Hypertension, n (%)		95 (45.8%)	17 (53.1%)	0.527*
Diabetes mellitus, n (%)		33 (15.9%)	8 (25%)	0.206*
Smoking, n (%)		48 (23.1%)	9 (28.1%)	0.696*
COPD, n(%)		26 (12.5%)	16(18.7%)	0.596*
CAD, n(%)		74 (35.7%)	14 (43.7%)	0.446*
PAD, n(%)		33 (15.9%)	12 (37.5%)	*0.012**
Atrial Fibrillation, n(%)		89 (42.9%)	17 (53.1%)	*0.378**
Hospital admission time, hours		2 (1-12)	4 (1-72)	*<0.001*
Location of occlusion	İliofemoral, n(%)	88 (42.5%)	11 (34.3%)	0.279*
	Femoropopliteal, n(%)	119 (57.4%)	21 (65.6%)	0.218*

†Student's t test, *Chi-square test, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, PAD: Peripheral arterial disease

Table 2: Preoperative laboratory values of the patients

Variables	Group 1 (n=207)	Group 2 (n=32)	*P*-value[m]
White blood Cell (10^3/μL)	9.1 (6.2- 15.9)	9.7 (5.4- 16.2)	0.118
Hematocrit (%)	41.8 (33.4- 53.7)	39.7 (34.3- 54)	0.289
Platelet (10^3/μL)	243.3 (156- 494)	244 (139- 455)	0.412
Neutrophil (10^3/μL)	5.1 (2.2- 11)	5.4 (2.6- 12.3)	0.094
Lymphocyte(10^3/μL)	2.1 (0.8- 4.3)	1.5 (0.7- 3.2)	0.102
Total protein (g/dL)	6.8 (5.5-8.5)	6.4 (5.5-8.2)	0.154
Albumin (g/dL)	3.6 (3.4-5.5)	3.4(3 - 5.4)	0.094
Urea (mg/dL)	18 (12- 46)	16 (18- 42)	0.377
Creatinine (mg/dL)	1.2 (0.7- 2.4)	1.2 (0.8- 2.2)	0.228
C Reactive protein (mg/dL)	8.5 (5.5- 13.6)	13.9(6.8- 21.8)	0.002
NLR	3.7 (2.1-8.8)	4.2 (2.8-9.1)	0.018
CAR	2.47 (1.3-4.6)	4.34 (2.3-6.2)	<0.001

[m] Mann Whitney U test (Data is expressed as median (interquartile range)) CAR: C reactive protein to albumin ratio

Table 3: Multivariate logistic regression analysis to identify factors affecting amputation rate in patients with femoral thromboembolism

Variables	*P* value	Exp(B) Odds Ratio	95% C.I. Lower-Upper
Age	0.011	1.045	1.004-2.144
PAD	0.109	0.789	0.556- 1.194
NLR	0.085	1.078	0.867- 1.496
CAR	0.005	1.679	1.224- 3.794
Hospital admission time	0.022	1.054	1.010-1.458

CAR: C reactive protein to albumin ratio, NLR: Neutrophil to lymphocyte ratio, PAD: Peripheral arterial disease

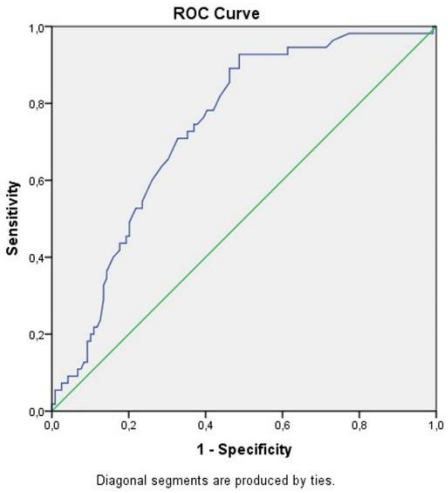

Figure 1: Receiver operation characteristic (ROC) curve and area under the curve (AUC) for C reactive protein to albumin ratio (cut-off=3.81, AUC: 0.747, 95% CI: 0.638- 0.857, P<0.001, 76.9% sensitivity, 56.7% specificity)

Discussion

Acute lower limb thromboembolism is an important clinical condition that requires immediate intervention. Acute arterial occlusion is the most common cause among all acute lower limb ischemia with a rate of about 35%. This clinical situation is due to embolization from an embolic focus or thrombosis due to atherosclerotic plaque rupture [10]. One of the most feared consequences of this disease is limb loss. With this current study, we have revealed that the CAR value obtained from the blood samples taken at the time of admission is an independent predictor in predicting amputation.

The relationship between inflammation and pathogenesis and progression of diseases has been the subject of research in many medical fields. Atherosclerosis, the cause of most cardiovascular diseases, is closely related to chronic inflammation. Endothelial dysfunction occurs with muscle proliferation in the vascular structure and the formation of fibrous plaque structures. These plaque structures contain leukocytes and are activated by interleukin 1 and tumor necrosis factor. These inflammatory pathways play an active role in the development of rupture, especially in plaque structures [11,12].

C reactive protein is an acute phase reactant, a good indicator of systemic inflammatory response. Studies have shown that CRP is effective in the development of atherosclerosis [13]. In addition, it has been demonstrated that high CRP values play an effective role in the deterioration of the stable structure in the atherosclerotic plaque [14,15]. CRP shows these effects by disrupting fibrinolysis, increasing collagen degradation in monocytes and activating the complement system [15]

Albumin has important effects on anti-inflammatory, antioxidant, anticoagulation systems and osmotic pressure in the human body [7]. Decreased serum albumin levels have been shown to increase mortality and morbidity in cardiovascular diseases [16,17]. In a study on patients with acute coronary syndrome, low albumin was found to be associated with extensiveness of coronary artery disease and in-hospital mortality [18]. In addition, low levels of albumin are associated with increased blood viscosity, impaired endothelial functions, increased platelet activation and aggregation [19,20]. All these factors also increase cardiovascular mortality and morbidity.

When all these effects of low albumin and CRP are revealed, CAR emerges as a valuable predictor for cardiovascular system diseases. In the study of Karabag et al. [21] which included 1217 ST-elevation myocardial infarction patients, the predictive value of inflammatory parameters was investigated in predicting the development of no-reflow after percutaneous intervention. The authors found that CAR value was more predictive of no-reflow than NLR, albumin and CRP values. The relationship between the severity of coronary artery disease and CAR in patients with acute coronary syndrome was investigated by Cagdas et al. [22] on 344 consecutive patients, and a significant relationship between CAR values and angiographic severity of coronary artery disease was observed by the authors. In another study, it was found that the CAR value has a poor prognostic value in patients admitted to hospitals with acute medical problems [23]. In our study, we revealed that there is a significant relationship between the development of

amputation, which is a catastrophic result of surgical thromboembolectomy, and CAR.

In the study conducted by Saskın et al. [24], the place of inflammatory parameters was investigated in predicting amputation after thromboembolism operations (Lower and upper extremities). 123 patients were included in the study and preoperative mean platelet volume and CRP values were determined as independent predictors of amputation. In addition, a positive correlation was found between NLR value and amputation risk. Similarly, in our study, although we found a significant correlation between NLR value and amputation, NLR was not an independent predictor in multivariate analysis. Unlike this study, our study included more patients and consisted only of patients with lower extremity thromboembolism.

In our study, we determined that advanced age and the length of time from the first complaint until admission to the hospital were independent predictors for amputation in addition to the CAR value. Prolonged ischemia time increases tissue damage after reperfusion, thereby increasing the risk of amputation. Advanced age is a bad prognostic factor in many cardiovascular diseases. Patients who developed acute lower extremity ischemia were divided into two groups as those under 80 years of age (41 patients) and over (24 patients) by Kubat et al. [25] and compared in terms of results. Although amputation rates were higher in patients over 80 years of age after the surgeries, there was no statistically significant difference. However, the small number of patients may have been effective in this statistical result.

Limitations

The most important limitations of our study are its retrospective and single-center design. In addition, because our study was retrospective, we may have missed possible hereditary hypercoagulation diseases. Our study needs to be supported by multicenter prospective studies.

Conclusion

Acute lower extremity ischemia is an emergency cardiovascular condition that can have mortal and morbid consequences. Surgical thromboembolectomy remains the gold standard treatment method. In these patients, the CAR value obtained from routine blood parameters obtained before the procedure may be a good predictor of the risk of amputation.

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Case report
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Pneumobilia after blunt trauma of abdominal wall caused by car crash with hepatic rupture

Araba kazasının neden olduğu karın duvarı künt travmasında gelişen karaciğer rüptürü sonrası pnömobili

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Abstract

Pneumobilia is the presence of air in the biliary system. It mostly indicates a connection between the biliary system and the gastrointestinal tract, although it can also occur after trauma. The best diagnostic modality of pneumobilia is computed tomography (CT). We herein present a 32-year-old male patient with pneumobilia due to hepatic rupture caused by abdominal trauma after car crash. The instability of the patient and hepatic rupture were the reasons of surgical treatment. The surgeon should know that pneumobilia and portal venous gas are easily confused. While mortality risk of pneumobilia is lower than that of portal venous gas, in such conditions the patient should be operated, because chance of cure is quite high.
Keywords: Pneumobilia, Hepatic rupture, Abdominal trauma, Blunt trauma

Öz

Pnömobili, biliyer sistemde hava varlığıdır. Çoğunlukla biliyer sistem ile gastrointestinal sistem arasındaki bağlantıyı gösterir, ancak travmadan sonra da ortaya çıkabilir. En iyi tanısal radyolojik tetkik, bilgisayarlı tomografidir (BT). Bu yazıda, trafik kazası dolayısıyla gelişen karın travmasının neden olduğu hepatik rüptüre bağlı pnömobili ile prezente olan, 32 yaşında bir erkek hasta sunulmaktadır. Hastanın cerrahi endikasyonları, instabilitesi ve hepatik rüptürdü. Cerrahlar pnömobili ve portal venöz gazın kolayca karıştığını bilmelidirler. Pnömobilinin mortalite riski portal venöz gazınkinden daha düşük olmakla birlikte, bu gibi durumlarda hasta kesinlikle ameliyat edilmelidir, çünkü iyileşme şansı oldukça yüksektir.
Anahtar kelimeler: Pnömobilya, Hepatik rüptür, Karın travması, Künt travma

Introduction

Pneumobilia is presence of gas in the biliary tree. There are several conditions associated with pneumobilia: 1) Dysfunction of the Oddi sphincter (OD), 2) Spontaneous biliary fistula, 3) Surgical biliary-enteric anastomosis [1] and rarely, 4) Abdominal trauma [2]. Pneumobilia caused by blunt trauma is exceedingly rare and does not need any specific treatment. We herein present a case of a 32-year-old male patient with pneumobilia due to liver rupture after abdominal blunt trauma.

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Case presentation

A 32-year-old male was admitted to the emergency department after a car accident. He was driving at 60 kilometers per hour and not wearing a seatbelt. Physical examination showed bruises on the extremities and epigastric area. The abdomen was diffusely tender. Laboratory values were as follows: WBC: 8.84 x 10^3, HGB: 7.8 g/dL, elevated liver function tests (aspartate transaminase 943 iU/L, alanine transaminase 897 IU/L), blood pressure: 90/50 mm Hg, heart rate (HR): 130 beats/min, respiratory rate (RR): 23 breaths/min, and oxygen saturation (SpO_2): 91% while breathing room air. An abdominal X-ray showed fluid in the abdomen.

The initially performed brain computed tomography (CT) did not show any cerebral lesions and the clinical condition was marked by hypotension and confusion. Later an abdominal CT showed Grade 3 liver laceration that involved hepatic rupture (crosses) (Figure 1), hemoperitoneum and pneumobilia (arrows) (Figure 2). An exploratory laparotomy was performed; about 1.5 liters of blood was observed in the right and left quadrants and a rupture was seen between 5^{th} and 6^{th} segments of the liver. All abdominal viscera were otherwise normal. The liver rupture was coagulated, a hemostatic sponge was placed, and the rupture was sutured with 3-0 vicryl. The peritoneal cavity was irrigated with physiologic solution. The layers of the abdomen were closed after achieving hemostasis. Postoperative period was uneventful. Patient's written consent and ethical approval were obtained (Decision No: LMC CS008.

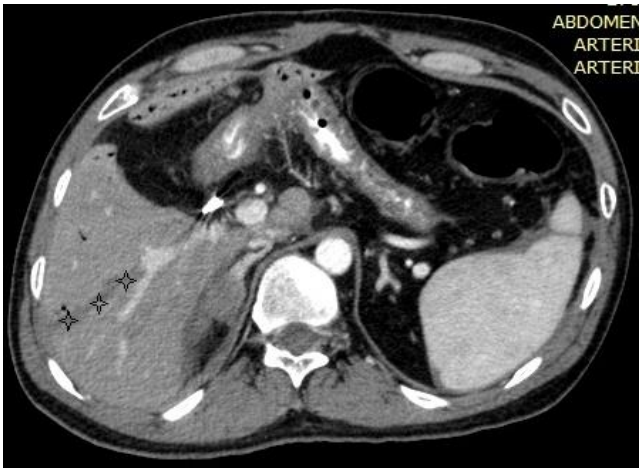

Figure 1: Hepatic rupture (crosses)

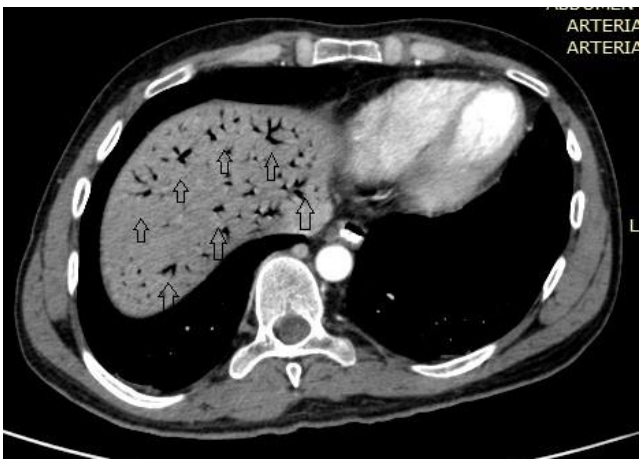

Figure 2: Pneumobilia (arrows)

Discussion

Air present in the intrahepatic biliary tract is called pneumobilia [3]. When there is no surgically formed entero-billiary anastomosis, most pneumobilia cases are related to gallstones. Other causes include emphysematous cholecystitis, pyogenic cholangitis, and abdominal trauma [4]. Pneumobilia is diagnosed with ultrasonography, plain radiography, or CT. In ultrasonographic examination, the liver is observed to have a "stripped appearance." Plain radiography showed sword-shaped lucency in the area where air is present. However, CT is the easiest way of detecting pneumobilia, which readily reveals gas within the liver [5]. It is important to differentiate pneumobilia from portal venous gas. In pneumobilia, air follows the centripetal flow of bile and locates around the hilum. In portal venous gas, air follows the centrifugal flow and can be found near the hilum and towards the periphery [6]. Portal venous gas is associated with a high mortality rate (75-90%) [7].

In our case, in the absence of gallstones, cholecystitis, cholangitis and Oddi sphincter dysfunction lead us to believe that it is due to liver rupture. Pneumobilia and hepatic rupture were diagnosed while a CT was performed to identify the source of fluid in abdomen. According to the World Society of Emergency Surgery (WSES) liver injury scale, all instable patients with Grade IV laceration should be operated immediately [8]. Asymptomatic pneumobilia patients with bilioenteric fistula need surgical treatment while those with pneumobilia caused by blunt trauma does not [9]. In this case the operation was performed because of the instability and the hepatic rupture.

Conclusion

After investigating the literature and many cases of pneumobilia, we found that blunt abdominal trauma was a rare cause of pneumobilia. In comparison to portal venous gas, pneumobilia due to blunt trauma has a lower mortality risk which makes it treatable with surgery.

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