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Amaç ve Kapsam

Journal of Academic Research in Medicine-JAREM, yayın dili Türkçe-İngilizce olan, açık erişimli, bağımsız ve önyargısız çift-kör hakemlik prosedürlerine bağlı olarak yayın yapan uluslararası bir dergidir. Dergide deneysel ve klinik tıp alanlarında yapılan araştırmalar, güncel konularla ilgili derlemeler, editöre mektuplar ve tıp eğitimiyle ilgili yazılar yayınlanır. Dergi, Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanmaktadır. Derginin finansmanı Sağlık Bilimleri Üniversitesi Gaziosmanpaşa Eğitim ve Araştırma Hastanesi tarafından sağlanmaktadır.

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The aim of JAREM is to publish research on recent topics at an international level. Moreover, reviews, editor's note and images are also published in the journal. The target audience of readers and authors is composed of educators, academics, researchers, specialists and general practitioners, and all publication process and procedures comply with the standards of ICMJE, WAME and COPE. JAREM is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, Index Copernicus, Gale, CINAHL, J Gate, Türk Medline and CAB International (CABI).

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JOURNAL OF ACADEMIC RESEARCH IN MEDICINE

Yazarlara Bilgi

Journal of Academic Research in Medicine-JAREM, çift-kör hakemli, açık erişimli bir dergi olarak, tıp alanında yapılan deneysel, temel, özgün klinik çalışmaları; mezuniyet sonrası eğitim, tıp tarihi, yayın ve araştırma etiğiyle ilgili yazıları yayınlar. Editörlerin yazı seçiminde temel unsur olarak dikkate alacağı hakemler, yurt içi ve yurtdılında konusunda uzman olan dış bağımsız kişilerden seçilir. Dergi, Nisan, Ağustos ve Aralık aylarında olmak üzere yılda 3 sayı yayınlanmaktadır.

Deneysel, klinik ve ilaç araştırmaları için ilgili uluslararası anlaşmalara uygun etik komisyon raporu gerekmektedir. (Helsinki Declaration of 1975, revised 2008-http://www.wma.net/en/30publications/10policies/b3/index.html, "Guide for the care and use of laboratory animals - www.nap.edu/catalog/5140.html)

Tüm yazarlar bilimsel katkı ve oranlarını ve ilgili sorumluluklarını; ayrıca çıkar çatışması olmadığını bildiren toplu imzaları ile yayına katılmalıdırlar. Araştırmalara kısmi de olsa yapılan nakdi ya da ayni yardımların hangi kurum, kuruluş, ilaç-gereç firmalarınca yapıldığı dip not olarak bildirilmelidir. (ICMJE Potansiyel Çıkar Çatışmaları Bildirim Formu)

Makalelerin formatı ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2018 - http://www.icmje.org/icmje-recommendations.pdf) kurallarına göre düzenlenmelidir.

Orijinal Araştırmalar ve Derlemeler'in sunumu çalışma bildirimi kılavuzlarına göre düzenlenmelidir: randomize çalışmalar için CONSORT, gözlemsel çalışmalar için STROBE, tanısal değerli çalışmalar için STARD, sistematik derleme ve meta-analizler için PRISMA, hayvan deneyli çalışmalar için ARRIVE, randomize olmayan davranış ve halk sağlığına müdahale çalışmaları için TREND.

Orijinal Araştırma için genel etik kurallar çerçevesinde yayının yapıldığı kurumun yetkililerinin hazırladığı etik kurul onayı ya da eşdeğeri bir kabul yazısının sunulması şarttır. Yazılardaki düşünce ve öneriler tümüyle yazarların sorumluluğunda olup, Editör ve yardımcıların kanaatlerini yansıtmaz.

Dergide basılması amacıyla gönderilen yazılar başka yerde yayınlanmamış olmalıdır. Daha önce bilimsel toplantılarda sunulan 200 kelimeyi geçmeyen özet yayınları, durumu açıklanmak koşulu ile kabul edilebilir.

İşlemleri yürütülüp karar aşamasına yaklaşmış olan yazıların, makul bir neden olmadan geri çekilme talebi "ret" kapsamına girmektedir. Yayına kabul edilen yazılar için birinci yazar, Türkçe ve İngilizce açısından olduğu gibi, metinde temel değişiklik yapmamak kaydı ile düzeltmelerin Editörlerce yapılmasını kabul etmiş sayılır.

Yazıların dergide yayınlanmak üzere kabul edilmesi için; atıf alabilme olasılığı, orijinal ve bilimsel akademik üst düzeyde olması ön koşuldur.

Genel Kurallar

Yazılar sadece derginin çevrimiçi makale kabul sistemi www.jarem.org üzerinden gönderilebilir. Yayına kabul edilmeyen yazılar, sanatsal resimler dışında geriye gönderilmez. Tüm yazılar, Editör başta olmak üzere, Editör danışmanı ve yardımcıları, istatistik danışmanları ve en az iki hakem tarafından incelenir. Yazı konusunun en önde gelen otörü olan, fakat çalışmanın dışında olup yazarlarla ve kurumları ile ilişkisi-bilgisi olmayan üç kişinin ilk yazar tarafından hakem olarak önerilmesi dergi için çok önemlidir.

Editör, hakemlere yazıyı göndermeden önce aşağıda bildirilen biçimsel kurallara uygunluğunu araştırır. Düzeltmeler orijinal metinde değil, düzeltilmesi istenen bölümlerle kısıtlı olmalıdır. Yazılar gönderilmeden önce yazım ve çizim hatalarından tam olarak arındırılmalıdır.

Yazım Kurallarına uygun hazırlanmayan makaleler değerlendirmeye alınmayacaktır.

Araştırma Yazıları

1. Özgün Araştırmalar: Yazının tamamı 5000 kelimeyi geçmemeli ve yalnızca içeriği anlamak için gerekli olan sayı ve içerikte tablo ve grafik desteği olmalıdır. Kaynakların 50'den az olması inandırıcılık için genelde yeterlidir. Özgün Araştırma yazılarının yazar sayısı 5 ile sınırlandırılmıştır. İstisnai durumlarda bu sayı artırılabilir ancak sorumlu yazar tarafından gerekçesi dergiye gönderilmelidir.

1.1 Kapak sayfası: Birinci sayfadır ve ayrı MS Word dosyası olarak düzenlenir. Yazarların tam ve açık isimleri, son aldıkları akademik unvanlar ile 50 karakteri geçmeyecek şekilde yazının başlığı yazılır. Yazarların ilgili oldukları kurum, bölüm ve şehir sıra ile bildirilmelidir. Birden fazla yerde yapılan çalışmalar sembollerle açıklanır. Bu sayfanın altına yazışmaya yetkili ve düzeltmeleri yapacak yazarın açık adı, posta ve e-posta adresi, telefon ve faks numaraları yazılır. Ayrıca çalışma bilimsel toplantıda önceden bildirilen koşullarda tebliğ edildi ya da özeti yayınlandı ise açıklaması yapılır.

1.2 Orijinal araştırma makalesi için bölümlü özet: Özetler 250 kelimeyi aşmayacak şekilde çalışmanın amacını, tipini, çalışmadaki ana bulguları ve kısaca çalışmanın sonucunu içermelidir.

Özetler; Amaç, Yöntemler, Bulgular, Sonuç şeklinde alt başlıklarla düzenlenmelidir.

NLM MESH terimleri ile uyumlu en az 3, en fazla 6 tane anahtar kelime bölümlü özetin altında verilmelidir (http://www.nlm.nih.gov./mesh/MBrowser.html).

1.3 Metin: Makale Başlığı, Giriş, Yöntemler (alt başlıklı), Bulgular, Tartışma, Çalışma kısıtlamaları ile Sonuçlar ve Kaynaklar kısımlarını içermelidir. Metnin özellikle yöntemler, bulgular ve tartışma kısmının alt başlıklara bölünmesi yararlı olabilir. Metin toplam 5000 kelimeyi geçmemeli ve Times New Roman yazım sitili ile 12 puntoda yazılmalıdır. En son bölüme teşekkür yazılacak ise, ciddi bilimsel katkı dışında araştırmanın yürütülmesine önemli katkıda bulunanlarla, yazının son şeklinin verilmesine yardım edenler yazılır. Bu bilginin e-posta ile gönderilmesi gerekir veya ayrı MS Word dosyasında "Teşekkür Notu" olarak sisteme yüklenir.

1.4 İstatistiksel Analiz: Tıbbi dergilerdeki istatistik verilerini bildirme kurallarına göre yapılmalıdır (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). İstatistiksel analiz için kullanılan yazılım tanımlanmalıdır. Sürekli değişkenlerin karşılaştırılmasında parametrik testler kullanıldığı zaman verilerin ortalama±standart sapma olarak bildirilmesi gerekir. Parametrik olmayan testler için de Medyan (Minimum-Maksimum) veya Medyan (25'inci ve 75'inci persantiller) değerleri olarak bildirilmesi gerekir. İleri ve karmaşık istatistiksel analizlerde, göreceli risk (RR, relative risk), olasılık (OR, odds ratio) ve tehlike (HR, hazard ratio) oranları güven aralıkları (confidence intervals) ve p değerleri ile desteklenmelidir.

1.5 Kaynaklar: Metin içinde geçiş sırasına göre numaralandırılır ve ayrı sayfada yazılır. Kişisel bilgi, yayınlanmamış veriler, "baskıda gibi" ulaşılamayan kaynaklar burada değil, metin içinde parantez ile sunulur. İki yıldan eski özetler kaynakçaya alınmaz; alınanlar parantezde (abstr.) şeklinde verilir. Kaynakların gerçekliğinden yazarlar sorumludur. Atıf yapılırken en son ve en güncel yayınlar tercih edilmelidir. Yazarlar 10 yıldan eski yayınlara atıf yapmamaya özen göstermelidir. Dergimizde eski kaynakların kullanımı %15 ile sınırlı tutulmaktadır.

Dergiler

Dergi isimlerinin kısaltmaları Index Medicus/Medline/PubMed listesine göre yapılır (dergilerin kısaltmaları için NLM tarafından her yıl yayınlanan MEDLINE dergilerin listesine http://www.nlm.nih.gov/tsd/serials/lji.html adresinden ulaşılabilir). Altı ve daha yazarlı makalelerde tüm isimler yazılır. Yedi ve fazla yazarlı olanlarda ilk altı isim yazılır ve "et al." ilave edilir. Yazar isimlerinden sonra, o yazının tam başlığı, yıl, cilt ve sahifeler sıralanır.

Örnek: Müller C, Büttner HJ, Petersen J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000; 101: 590-3.

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Yazarlara Bilgi

Kitaplar

Kitap içinde bölüm: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St Louis: Mosby; 1974. p.273-85.

Tek yazarlı kitap: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Yazar olarak Editör (ler): Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Toplantıda sunulan makale: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P. 1561-5.

Bilimsel veya teknik rapor: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Tez: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Elektronik formatta makale

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

1.6 Şekiller, Tablolar ve Resimler: Şekil ve resimler, hasta, doktor ve kurum isimleri gözükmeyecek şekilde hazırlanmalıdır. Metinden ayrı olarak, metin içinde geçiş sırasına göre numaralandırılarak verilir. Başlık ve altyazılar ayrı bir sayfada sunulur. Grafiklerde yeteri kalınlıkta çizgi kullanılır. Böylece gerekli küçültmelerde kayıplar en aza iner. Genişlikler en fazla 9 ya da 18 cm. olmalıdır. Çizimlerin profesyonellerce yapılması faydalı olacaktır. Gri renkler kullanılmamalıdır. Kullanılan kısaltmalar alt kısımda alfabetik sıra ile mutlaka açıklanmalıdır. Tablo ve Şekil başlıklarında ve tablonun yazı içinde anılmasında Roma rakamları kullanılmamalıdır. Metin, Tablo ve Şekillerde kullanılan ondalık sayılar Türkçe metinlerde virgül İngilizce metinlerde ise nokta ile ayrılmalıdır. Özellikle tablolar metni açıklayıcı ve kolay anlaşılır hale getirmek amacı ile hazırlanmalı ve metnin tekrarı olmamalıdır.

Video Görüntüler

Özgün Görüntüler'de yer alan resimlere ek olarak video/hareketli görüntüler ve ekstra imaj/statik görüntüler aşağıdaki teknik özelliklerde gönderildiği takdirde web sayfamızda yayınlanacaktır.

1. İmaj/statik görüntü formatında sunumlar: JPG, GIF, TIFF, BMP

2. Video/hareketli görüntü formatında sunumlar: MPEG, VMF.

3. Dosya boyutu maksimum 2 MB olmalıdır.

4. Resimlerde ve özellikle video görüntülerinde doktor, kurum, şehir ve hasta tanımlamaları tümü ile silinerek gönderilmelidir.

Makalenizde yer alan tablolar, şekiller ve resimler için orijinal oldukları ayrıca bildirilmelidir. Orijinali dışında ve başka kaynaktan alındıklarında mutlaka alınan kaynağa atıfta bulunmalı ve alınan kaynağın "hardcopy" veya elektronik formatta versiyonları Telif Hakkı sahibinden (yayınevi, dergi veya yazar) alınan izinler ile birlikte Baş Editör ofisine sunulmalıdır. Kaynaklar, şekiller ve tablolar ile ilgili kurallar tüm makale türleri için geçerlidir.

Özel Bölümler

2. Davetli Derlemeler: Editör ofisinin kararıyla davetli yazarlar tarafından hazırlanabilir. Bir bilgi ya da konunun klinikte kullanılması için son vardığı düzeyi anlatan, tartışan, değerlendiren ve ileride yapılacak çalışmalara yön belirleyen düzeyde olmalıdır. Yazarının konusunda otör olması ve atıfta bulunulmuş yazılarının olması gerekir.

Bölümsüz özet: Araştırma makalelerindeki kelime sayıları burada da geçerlidir, sadece bölümlü olmayacaktır. NLM MESH terimleri (http://www.nlm.nih.gov./mesh/MBrowser.html adresinde bulunabilir) ile uyumlu en az 3, en fazla 6 tane anahtar kelime bölümlü özetin altında verilmelidir. Kelime sayısı 5000, kaynak sayısı 50 ile sınırlıdır.

3. Editöryel Yorum: Dergide çıkan bir araştırmanın o konunun otörü veya iyi değerlendirme yapan hakem tarafından kısaca değerlendirilmesi amacı güder. Sonunda; klinik anlam ve kısa özet bulunur.

4. Bilimsel Mektup: Yeni bilimsel buluş ve verileri duyurmayı amaçlayan, klinik açıdan önemli ancak ön bildiri niteliğinde olan yazılar bilimsel mektup olarak yayına kabul edilir. Bilimsel mektuplar içerik olarak alt başlıksız olup toplam 900 kelimeyi aşmamalıdırlar. Kaynak sayısı 10, tablo ve resim sayısı ise 2 ile sınırlı olmalıdır.

4. Editöre Mektuplar: Derginin temel yayın amaçlarından birini oluşturmaktadır. Yayınlanan bir yazının önemini, gözden kaçan bir yapısını ya da noksanını tartışır. Yazarlar, yayınlanan makaleler hakkında yorum içeren mektuplar dışında da okurlarımızın ilgi alanlarına giren konular veya özellikle eğitici vakalar hakkında da Editöre Mektup formatında yorumlarını sunabilirler. Kaynak sayısı 5, metin ise 500 kelimeyi geçmemelidir, alt başlıkları bulunmaz.

6. Eğitim: Son yıllarda araştırma sonuçları ile kesinleşen, akademik düzeydeki eğitimde yerini alan ve klinik uygulamada yer bulan bilgiler ayrıntıları ile sunulur.

Bölümsüz özet: Araştırma makalelerindeki kelime sayıları burada da geçerlidir, sadece bölümlü olmayacaktır. NLM MESH terimleri (http://www.nlm.nih.gov./mesh/MBrowser.html adresinde bulunabilir) ile uyumlu en az 3, en fazla 6 tane anahtar kelime bölümlü özetin altında verilmelidir. Kelime sayısı 5000, kaynak sayısı 50 ile sınırlıdır.

7. Özgün Görüntü: Klinik bilime dayalı önemli bulguları yansıtan, hastalıkların temel mekanizmalarına ışık tutan, anormallikleri vurgulayan veya yeni tedavi yöntemlerini aydınlatan çarpıcı ve nadir görüntüler yayına kabul edilir. Video görüntüsü olanların basılma şansı yüksektir. Başlığı ile beraber tanımlayıcı metin ve resim alt yazıları (kaynaksız) toplam 250 kelimeyi geçmemelidir.

8. Tarihten Notlar: Türkiye için özellikle tıp tarihindeki önemli olayları açıklayan, hastalıkların tanı ve tedavisinin tarihi ile ilgili yeni bilgileri ortaya çıkaran makalelerdir. Yeni tarihsel bulgular konu ile ilgili uygun araştırma çalışmalarının sonucu olmalıdır. Tarihten notların içeriği altbaşlıksız olmalıdır ve metin 900 kelime kaynak sayısı ise 10 ile sınırlıdır.

9. Yayın Etiği: Derginin bu bölümünde yayın etiği ile ilgili aktüel bilgi ve yorumlara yer veren makaleler ve etik ihlali vakaları yayınlanır. Metin 900 kelime, kaynak sayısı ise 10 ile sınırlıdır.

JAREM

JOURNAL OF ACADEMIC RESEARCH IN MEDICINE

Instructions to Authors

Journal of Academic Research in Medicine (JAREM), as an open access journal with double-blind reviewing process, publishes experimental, basic and original researches conducted in the field of medical sciences; post-graduate training reports, and articles on history of medicine, and publication and research ethics. Reviewers whom opinions are of priority in the decision of approval are selected by the editors among independent local and international individuals that have specialized on their respective fields. The journal is published three times per year; in April, August and December.

An approval of research protocols by an ethical committee in accordance with international agreements (Helsinki Declaration of 1975, revised 2008-http://www.wma.net/en/30publications/10policies/b3/index.html, "Guide for the care and use of laboratory animals - www.nap.edu/catalog/5140.html) is required for experimental, clinical and drug studies.

All submissions must be accompanied by a signed statement of scientific contributions and responsibilities of all authors and a statement declaring the absence of conflict of interests. Any institution, organization, pharmaceutical or medical company providing any financial or material support, in whole or in part, must be disclosed in a footnote (ICMJE Disclosure Form for Potential Conflict of Interest(s)).

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The presentation of Original Researches and Reviews must be designed in accordance with trial reporting guidelines: randomized study-CONSORT, observational study-STROBE, study on diagnostic accuracy-STARD, systematic reviews and meta-analysis PRISMA, animal experimental studies-ARRIVE, nonrandomized behavioural and public health intervention studies-TREND.

An approval of ethic committee or an equivalent acceptance letter prepared by the officials of the institution in accordance with general ethics is mandatory for Original Research. The concept and suggestions presented in the manuscript are the sole responsibility of the authors and do not reflect the opinions of Editor and his/her associates.

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Articles not conforming to the instructions will not be taken into consideration.

Research Articles

1. Original Research: Full text of the paper should not exceed 5000 words and should include tables and graphs in sufficient number and content to allow understanding. Number of references being less than 50 is sufficient for plausibility. Number of authors should be limited to 5 with original articles. When there are more than 5 authors the editorial board should be informed about the justification of this situation by the corresponding author.

1.1 Title page: It is the first page of the manuscript and prepared separately as MS Word document. It must include full names of the authors; highest academic degrees and the title of the article not exceeding 50 characters. Affiliations of the authors, departments and city names must be stated in order. Studies conducted in more than one centre must be marked with symbols. Full name, postal and e-mail addresses, phone and fax numbers of the author responsible for correspondence and corrections must be stated at the bottom of this page. It must be also explained if the study was previously presented in a scientific congress in accordance with aforementioned terms or if the abstract was published.

1.2 Structured abstract for original research article: The abstracts should contain the objective of the study, its type, the results, in sum, conclusion of the study without exceeding 250 word limit.

Abstracts must be structured as to include subheadings of Objective, Methods, Results and Conclusion.

At least 3, at most 6 keywords compatible with NLM MESH terms should be included following abstract (http://www.nlm.nih.gov./mesh/MBrowser.html).

1.3 Text: The text must include; Title, Introduction, Methods (with subheadings), Results, Discussion, Limitations of the study, Conclusion, and References. It may be useful to divide methods, results and discussion sections into subheadings. The text must not exceed 5000 words and should be written in Times New Roman, 12 point font. If acknowledgements will be included at the end of the manuscript, those contributed to the conduction of the study or assisted in finalizing the document are mentioned apart from those having substantial scientific contribution. This information must be sent by e-mail or uploaded to the system in a separate MS Word document with the name of "Acknowledgements".

1.4 Statistical Analysis: Analysis must be performed in accordance with statistical data reporting rules in medical journals (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Software used in statistical analysis must be stated. If parametric tests are used for the comparison of continuous variables, data must be presented as mean±standard deviation. For non-parametric tests, Median (Minimum-Maximum) or Median (25th and 75th percentile) values must be indicated. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supplemented with confidence intervals (CI) and p values.

1.5 References: References should be numbered consecutively in the order cited in the text and are typed in a separate page. Inaccessible references such as personal information, unpublished data, "in press" are not typed in the references section but cited in parenthesis within the text. Abstracts published two years ago are not included in references; if included, they must be written as (abstr.) in parenthesis. Authors are responsible for the accuracy of the references. While citing publications, preference should be given to the latest, most up-to-date publications. Authors should avoid using references that are older than ten years. The limit for the old reference usage is 15% in the journal.

Journals

Journal names must be abbreviated according to the list of Index Medicus/Medline/PubMed (the list of MEDLINE journals and their abbreviations published annually by NLM can be accessed at http://www.nlm.nih.gov/tsd/serials/lji.html). All author names are listed for articles having less than 6 authors. If the article contains 7 or more authors, names of the first 6 authors are written and followed by "et al.". Names of the authors are followed by the title of the manuscript, year, volume and page numbers.

Example: Müller C, Büttner HJ, Petersen J, Roskomun H. A randomized comparison of clopidogrel and aspirin versus ticlopidine and aspirin after the placement of coronary-artery stents. Circulation 2000; 101: 590-3.

JAREM
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Instructions to Authors

Books

Section in a book: Sherry S. Detection of thrombi. In: Strauss HE, Pitt B, James AE, editors. Cardiovascular Medicine. 2nd ed. St Louis: Mosby; 1974. p.273-85.

Book with single author: Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

Editor(s) as author: Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York: Churchill Livingstone; 1996.

Article presented at a meeting: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. P. 1561-5.

Scientific or technical report: Smith P. Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX) Dept. of Health and Human Services (US). Office of Evaluation and Inspections: 1994 Oct. Report No: HHSIGOE 169200860.

Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (dissertation). St. Louis (MO): Washington Univ. 1995.

Manuscript in electronic format

Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

1.6 Figures, Tables and Pictures: Figures and images must be prepared as not to include names of the patient, doctor and the institution. They must be provided separately from the document and numbered according to their sequence within the text. Legends and footnotes are typed in a separate page. The drawings in the graphs must be in sufficient thickness. Therefore, loss of detail will be minimal while zooming out. The width should be maximum 9 or 18 cm. It may be useful if the drawings are made by professionals. Grey colour should not be used. Abbreviations must be defined below in alphabetical order. Roman numbers should not be used in Tables and Figure Captions and in the citation of the tables within the text. Decimal numbers in the text, Tables and Figures must be given with a point. The tables should be prepared to make the text more explanatory and understandable and should not repeat the text.

Video Images

In addition to images in the Original Images; video images/motion pictures, extra images/static images will be published at our website if they comply with the following technical requirements.

1. Presentations in image/static image format: JPG, GIF, TIFF, BMP
2. Video images/motion pictures: MPEG, VMF.
3. File size must be maximum 2 MB.
4. Names of doctor, institution, city, and patient and descriptions in the images and particularly in video images must be deleted before sending.

Originality of the tables, figures and images in your manuscript must be stated. If a material is used from another source, either the original source or a source citing the original one, the source must be cited; hardcopy or electronic versions must be obtained from Copyright owner (publication house, journal or author) and presented to the Editor in Chief with the permissions. Terms relevant to the references, figures and tables are applicable to all types of articles

Specific Sections

2. Invited Review Articles: Can be prepared by the invited authors upon decision of the Editorial Office. An information or a subject must explain, discuss, and evaluate the latest level that has been reached and must be at a particular degree directing the future studies in order to be used in clinic. The author must have a high reputation in his/her field and must have published manuscripts that have been cited.

Unstructured abstract: Word counts determined for research articles are also applicable herein but they will be unstructured. At least 3, at most 6 keywords compatible with NLM MESH terms (available at http://www.nlm.nih.gov./mesh/MBrowser.html) should be included following abstract. They are limited to 5000 words and 50 references.

3. Editorial Note: The purpose of editorial note is to make brief evaluation of the published research by reputable authors on that particular field or by reputable reviewers. Clinical significance and short summary is included at the end of the text.

4. Scientific Letter: Manuscripts that aim to announce scientific discoveries and data or preliminary reports that are of clinical significance are accepted for publication as scientific letter. Scientific letters do not contain subheadings and should not exceed 900 words. Number of references should be limited to 10 and the number of tables and figures should be limited to 2.

5. Letters to the Editor: Are one of the major aims of publication of the journal. The significance of a published manuscript or overlooked or missed aspects are discussed. Apart from letters commenting on the published manuscripts, authors can present their comments on subjects attracting the readers' interest or on educational cases in the form of Letters to the Editor. Number of references should not exceed 5 and the text should be limited to 500 words; the text does not contain subheadings.

6. Education: Scientific knowledge that has been proved with the results latest research, that set out in academic training, and that taken a place in clinical practice is presented in details.

Unstructured abstract: Word counts determined for research articles are also applicable for this section; but this will be unstructured. At least 3, at most 6 keywords compatible with NLM MESH terms (available at http://www.nlm.nih.gov./mesh/MBrowser.html) should be included following abstract. The text should be limited to 5000 words and number of references is limited to 50.

7. Original Images: Striking and rare images reflecting important findings in clinical sciences, shedding light on basic mechanisms of the diseases, emphasizing the abnormalities or revealing new treatment methods are accepted for publication. Those containing video images have higher chance of publication. Figure caption, legends, and footnotes (without reference) should not exceed 250 words.

8. Historical Notes: Historical notes are the articles that enlighten important events in the history of medicine and elucidate new information on the historical progress of the diagnosis and treatment of diseases. New historical discoveries must be the results of appropriate researches conducted on the subject. The content of historical notes should not contain subheadings and be limited to 900 words and 10 references.

9. Publication Ethics: Articles providing contemporary information and comments on publication ethics and cases of violation of ethics are published in this section of the journal. The text is limited to 900 words and the number of references is limited to 10.

JOURNAL OF ACADEMIC RESEARCH IN MEDICINE

İçindekiler / Contents

Özgün Araştırmalar / Original Investigations

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İçindekiler / Contents

Olgu Sunumları / Case Reports

İndeks / Index

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J Acad Res Med 2021;11(3):234-40

Türkiye'de Eğitim Kurumlarında Görevli Akademik Anesteziyoloji ve Reanimasyon Uzmanlarının Bilimsel Üretimlerinin H-indeks ve Bibliyometrik Parametreler ile Analizi

H-index and Bibliometric Analysis of Scientific Production Parameters of the Assistant Academic Anesthesiology and Reanimation Specialist in Educational Institutions in Turkey

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ÖZ

Amaç: Bibliyometrik çalışmalar, yayın sayıları, atıf sayıları ve h-indeksi gibi parametrelerinin değerlendirildiği ve bilim alanındaki üretim hakkında bilgi sahibi olunmasını sağlayan çalışmalardır. Çalışmamızda ülkemizde eğitim kurumlarında görev yapan anesteziyoloji ve reanimasyon uzmanlarının, Scopus veri tabanı kullanılarak belirlenen yayın, atıf sayıları, h-indeksleri ile cinsiyet, çalıştıkları kurum ve unvanın bunlara etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: TARD Eğitim Kurumları Rehberi ve kurumların web siteleri aracılığı ile belirlenen ülkemizde eğitim kurumlarında çalışan anesteziyoloji ve reanimasyon uzmanlarının yayın sayıları, alıntı sayıları ve h-indeksleri, Scopus veri tabanı kullanılarak belirlendi.

Bulgular: Çalışmamıza ülkemizde eğitim kurumlarında anesteziyoloji ve reanimasyon alanında çalışan toplam 1.512 akademisyen dahil edidi. Anesteziyoloji ve reanimasyon alanındaki akademisyenlerin Scopus veri tabanındaki yayın sayısı ortalaması 20,27±23,90, atıf sayısı ortalaması 148,32±270,41 ve h-indeks ortalaması 4,57±4,36 olarak belirlendi. Profesörlerin yayın sayıları, atıf sayıları ve h-indeks ortalamaları, doçent, doktor öğretim üyesi, öğretim üyesi uzman ve uzmanlardan anlamlı olarak yüksek bulundu. Erkek anesteziyoloji ve reanimasyon uzmanlarının yayın sayıları, atıf sayıları ve h-indeks ortalamaları, kadın anesteziyoloji ve reanimasyon uzmanlarından anlamlı olarak yüksek bulundu.

Sonuç: Çalışmamız ülkemizde eğitim kurumlarında çalışan anesteziyoloji ve reanimasyon uzmanlarının bilimsel üretimlerini gösteren önemli bibliyografik parametrelerin ve h-indekslerinin değerlendirildiği ilk çalışmadır. H-indeksi akademik gücü ortaya koymada etkili bir parametredir ve çalışmamızda cinsiyet, çalışılan kurum ve unvanın bibliyografik parametreler üzerine etkili olduğu belirlenmiştir.

Anahtar kelimeler: H-indeks, cinsiyet, unvan, anesteziyoloji ve reanimasyon, akademik

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ABSTRACT

Objective: Thanks to bibliomethric analysis; it is possible to learn more about productivity in science by evaluating parametres such as number of studies, citations and h-index. Purpose of our study is to evaluate the factors that affect the h-index of academician anesthesiologists. In our study, it was aimed to evaluate the effects of anesthesiology and reanimation specialists working in educational institutions in our country, the number of publications, citations, h-indexes, gender, institution and title determined using the Scopus database.

Methods: Academicians were chosen by TARD Education Institues and websites of different institues. Those academicians' number of articles, citations and h-index were determined by using Scopus.

Results: A total of 1,512 academicians working in the field of anaesthesiology and reanimation in educational institutions in our country were included in our study. The number of publications in the Scopus database of anaesthesiology and reanimation academicians was 20.27±23.90, the average number of citations was 148.32±270.41 and the mean h-index was 4.57±4.36. The number of publications, citation numbers and h-indexes of the professors were found to be higher than those of associate professors, doctor lecturers, faculty members, experts and experts. The number of publications, number of citations and h-indexes of male anesthesiology and reanimation specialists were found to be higher than their female colleagues.

Conclusion: Our study is the first study in which the number of publications, number of citations and h-indexes, which are important bibliographic parameters showing the scientific production of all anesthesiology and reanimation specialists working in educational institutions in our country, were evaluated. The h-index is an effective parameter in revealing academic strength, and in our study, it was determined that gender, institution and title were effective on bibliographic parameters.

Keywords: H-index, gender, title, anesthesiology and reanimation, academic

GİRİŞ

Bibliyometrik çalışmalar, akademik üretkenliğin nicel yöntemlerle değerlendirildiği, bilimsel yayınların ve bilim üretenlerin etkinlikleri konusunda bilgi sahibi olunmasını sağlayan çalışmalardır (1-3). İlk bibliyometrik çalışma 1987 yılında Garfield tarafından "The Journal of the American Medical Association (JAMA)" da "JAMA'da Yayınlanan En Çok Atıf Alan 100 Makale" başlığı ile yayınlanmıştır. O zamandan beri farklı akademik alanlarda pek çok bibliyometrik çalışma yapılmıştır ve bibliyometrik parametreler akademik üretkenliğin değerlendirmesinin önemli bir parçası haline gelmiştir (4,5). Birçok parametre yazarları ve dergileri değerlendirmek için kullanılmaktadır. Bunlar arasında, yayın sayısı, atıf sayısı, Hirsch-indeksi (h-indeksi), m-bölüm, hc-indeksi, e-indeks, g-indeksi, i-10 [in] indeksi, derginin etki faktörü, Eigenfactor, makale etki skoru, SCImago dergi sıralaması, yayın başına kaynağa göre normalleştirilmiş etki gibi ölçümler ve indeksler sayılabilir (1-3).

H-indeksi, akademik üretkenliği değerlendirmenin önemli bir ölçüsü olarak yaygın şekilde kabul edilmiştir (6). Bilim insanlarının hem üretkenliğini hem de alıntı etkisini ölçen bir metriktir (7). Basitçe bilim insanının makalelerinden aldığı atıflara, en çok alıntı yapılan makalelerine ve yayın sayısına dayanmaktadır (8). İndeks ayrıca akademik dergilerin, bölümlerin, üniversiteler veya ülkeler gibi bir grup bilim insanının üretkenliğini ve etkisini ölçmek için de uygulanabilir (9).

Scopus veri tabanı, 2004 yılında Elsevier tarafından başlatılan, en büyük çevrimiçi bibliyometrik veri tabanıdır. PubMed'de yer almayan sosyal ve fiziksel bilimlerden makaleler de dahil olmak üzere, 1966'dan itibaren tüm ana disiplinlerden yayınlanan dergi makalelerini içerir (10). Scopus veri tabanının önemli bir avantajı, makaleleri bağlılık ve ortak yazarlar temelinde yazara göre gruplandıran, yazarın çalışma yerini de içeren, bireysel yazar kimliğidir. Benzer adlara sahip yazarlar, listelerinin doğruluğunu korumak için hataları veya eksiklikleri bildirebilirler ve bu özellikler ile ayırt edilebilirler (11). Bunun aksine, PubMed, Google Scholar ve Web of Science, yazarları gruplandırmak için belirli metin dizelerini arar, böylece benzer adlara sahip yazarlar ayrılmamış olur. Bunun yanında Google Scholar bir abonelik ve kayıt sistemi de içermektedir ve bu nedenle kayıt ya da abone olmayan akademisyen Google Scholar taramasında görülememektedir (12).

Tıbbın pek çok alanında h-indeksi ile ilişkili çalışmalar yapılmıştır (13-15). Farklı ülkelerde yapılan geçmiş çalışmalarda cinsiyetin ve akademik unvanın h-indeks ve bibliyometrik parametreler üzerine etkili olduğu, akademi içerisinde cinsiyet eşitsizliğinin bulunduğu vurgulanmıştır (13-15). Yaptığımız literatür analizinde farklı ülkelerde akademisyen olarak çalışan anesteziyoloji uzmanlarının h-indekslerinin Scopus veri tabanında araştıran ve bibliyometrik verileri kullanan çalışmalar olmasına rağmen, ülkemizde Scopus veri tabanının kullanıldığı böyle bir çalışma bulunmamaktadır.

Çalışmamızda amacımız ülkemizde akademik kadrolarda görev alan tüm anesteziyoloji ve reanimasyon uzmanlarının, Scopus veri tabanında belirlenen yayın sayısı, atıf sayısı ve h-indeksi analizini yapmak ve cinsiyet, çalışılan kurum ile unvanın bibliyometrik parametreler üzerine etkisini değerlendirmektir.

YÖNTEMLER

Dokuz Eylül Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan onay alındıktan sonra (karar no: 2020/16-05, tarih: 13.07.2020), TARD Eğitim Kurumları Rehberi ve T.C. Sağlık Bakanlığı'nın, devlet ve özel üniversitelerin, eğitim ve araştırma hastanelerinin anonim kullanıma açık olan kurumsal web sitelerinde bir eğitim kurumunda halen çalışmakta olan anesteziyoloji ve reanimasyon uzmanlarının listesi 15.07.2020 tarihine kadar olacak şekilde taranarak; ülkemizde üniversiteler ve eğitim araştırma hastaneleri bünyesinde görev yapmakta olan anesteziyoloji ve reanimasyon uzmanlarının listesi oluşturuldu. Veri analizine dahil edilen anesteziyoloji ve reanimasyon uzmanlarının tarama tarihindeki profesör, doçent, yardımcı doçent, doktor öğretim

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üyesi, öğretim üyesi uzman ya da uzman doktor olarak akademik unvanları, cinsiyetleri, anabilim dalı başkanı olup olmadıkları kayıt edildi. Eksik cinsiyet verileri Google, LinkedIn aracılığıyla belirlendi. Akademik kadroları tam olarak belirlenemeyen öğretim üyeleri ve emekli öğretim üyeleri çalışmadan çıkarıldı. Scopus veri tabanından her öğretim üyesinin yayın sayıları, h-indeksi, alıntı sayıları bibliyometrik veri olarak kayıt edildi.

İstatistiksel Analiz

İstatistiksel analiz için SPSS 24.0 istatistik paket programı kullanıldı. Sıklık belirten veriler sayı ve yüzde, sürekli değişkenler ortalama ± standart sapma, ortanca (minimum-maksimum) olarak gösterildi. Sıklık belirten verilerin analizinde ki-kare testi kullanıldı. Devamlı değerler alan verilerin analizinde öncelikle verilerin normal dağılım gösterip göstermediğinin belirlenmesi amacıyla Kolmogorov-Smirnov testi kullanıldı. Test sonucunda verilerin normal dağılım göstermedikleri belirlendi. Verilerde ikiden fazla grup olması durumunda Kruskal-Wallis testi, iki grup olması durumunda Mann-Whitney U testi ile analiz uygulandı. P değerinin 0,05'ten küçük olması anlamlı farklılık olarak kabul edildi.

BULGULAR

Analize dahil edilen 1.512 anesteziyoloji ve reanimasyon uzmanının Scopus veri tabanındaki yayın sayısı ortalaması 20,27±23,90, ortanca değeri 12 (0-233), atıf sayısı ortalaması 148,32±270,41, ortanca değeri 44 (0-2.906) ve h-indeks ortalaması 4,57±4,36, ortanca değeri 3 (0-25) olarak belirlendi.

Çalışmamıza dahil edilen anesteziyoloji ve reanimasyon uzmanlarının 306'sı (%20,2) profesör, 218'i (%14,4) doçent, 157'si (%10,4) doktor öğretim üyesi, 22'si (%4,8) öğretim üyesi uzman doktor, 759'u (%50,2) uzman olarak görev yapmaktaydı.

Çalışmaya dahil edilme kriterlerini karşılayan, eğitim kurumlarında çalışan, anesteziyoloji ve reanimasyon uzmanlarının 872'sinin (%57,7) kadın, 640'ının (%42,3) erkek olduğu belirlendi. Kadın akademisyenlerden, 159'u (%18,2) profesör, 117'si (%13,4) doçent, 67'si (%7,7) yardımcı doçent, 46'sı (%5,3) öğretim üyesi uzman, 483'ü (%55,4) uzman unvanlarına sahipti. Erkek akademisyenlerden, 147'si (%23) profesör, 101'i (%15,8) doçent, 90'ı (%14,1) yardımcı doçent, 26'sı (%4,1) öğretim üyesi uzman, 276'sı (%43,1) uzman unvanlarına sahipti. Profesör, doçent, öğretim üyesi uzman ve uzman sayılarında kadın akademisyen sayıları, erkek akademisyenlerden yüksek olarak bulundu (p<0,001, ki-kare testi) (Tablo 1). Kadın akademisyenlerin 54'ünün (%6,2), erkek akademisyenlerden 57'sinin (%8,9) anabilim dalı başkanı olduğu belirlendi (p=0,046, ki-kare testi).

Profesörlerin yayın sayıları, atıf sayıları ve h-indeks ortalamaları, doçent (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi), doktor öğretim üyesi (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi), öğretim üyesi uzman doktor (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) ve uzmanlardan (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) anlamlı olarak yüksek bulundu (Tablo 2).

Doçentlerin yayın sayıları, atıf sayıları ve h-indeks ortalamaları profesörlerden anlamlı olarak düşük (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi), doktor öğretim üyeleri (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi), öğretim üyesi uzman doktor (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) ve uzmanlardan (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) anlamlı olarak yüksek bulundu (Tablo 2).

Doktor öğretim üyelerinin, yayın sayıları, atıf sayıları ve h-indeks ortalamaları profesörlerden (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) ve doçentlerden (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) anlamlı olarak düşük, öğretim üyesi uzman doktor (sırasıyla p=0,001, p=0,045, p=0,005, Mann-Whitney U testi) ve uzmanlardan (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi) anlamlı olarak yüksek bulundu (Tablo 2).

Öğretim üyesi uzman doktorların, yayın sayıları, atıf sayıları ve h-indeks ortalamaları profesörlerden (sırasıyla p<0,001, p<0,001, p<0,001, Mann-Whitney U testi), doçentlerden (sırasıyla p<0,001, p<0,001, p<0,001 Mann-Whitney U testi) ve doktor öğretim üyelerinden anlamlı olarak düşük (sırasıyla p=0,001, p=0,045, p=0,005, Mann-Whitney U testi), uzmanlardan (sırasıyla p=0,004, p=0,035, p=0,010, Mann-Whitney U testi) anlamlı olarak yüksek bulundu (Tablo 2).

Kadın anesteziyoloji ve reanimasyon uzmanlarının Scopus veri tabanındaki yayın sayısı ortalaması 17,74±22,72 ortanca 9 (0-233), atıf sayısı ortalaması 120,43±222,65 ortanca 34 (0-2.296) ve h-indeks ortalaması 4,03±3,99 ortanca 3 (0-25) olarak belirlendi. Erkek anesteziyoloji ve reanimasyon uzmanlarının Scopus veri tabanındaki yayın sayısı ortalaması 23,51±24,98 ortanca 18 (0-153), atıf sayısı ortalaması 183,19±322,81 ortanca 73,5 (0-2.906) ve h-indeks ortalaması 5,27±4,71 ortanca 4 (0-24) olarak

Tablo 1. Cinsiyete göre, akademik unvan dağılımı

	Kadın	Erkek	Toplam
Profesör	159 (%18,2)	147 (%23,0)	306 (%20,2)
Doçent	117 (%13,4)	101 (%15,8)	218 (%14,4)
Doktor öğretim üyesi	67 (%7,7)	90 (%14,1)	157 (%10,4)
Öğretim üyesi uzman	46 (%5,3)	26 (%4,1)	72 (%4,8)
Uzman	483 (%55,4)	276 (%43,1)	759 (%50,2)
Toplam	872 (%100)	640 (%100)	1512 (%100)

ki-kare testi, p<0,001

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Tablo 2. Anesteziyoloji ve reanimasyon alanında akademik unvan ve cinsiyete göre Scopus veri tabanından belirlenen yayın sayıları, atıf sayıları ve h-indeks ortalamaları (ortalama ± standart sapma) ortanca (minimum-maksimum) değerleri

	Kadın			Erkek			Toplam		
	Yayın sayısı	Atıf sayısı	H-indeksi	Yayın sayısı	Atıf sayısı	H-indeksi	Yayın sayısı	Atıf sayısı	H-indeksi
Profesör doktor	41,60±31,89* 36,5 (1-233)	330,55±342,72* 256 (1-2.296)	8,64±4,65* 8 (1-25)	48,15±28,40 40 (12-153)	448,80±471,43 293.5 (57-2.906)	10,39±4,63 9 (3-24)	44,76±30,38[†‡€£] 38,5 (1-233)	387,88±413,75[†‡€£] 273 (1-2.906)	9,48±4,71[†‡€£] 9 (1-25)
Doçent doktor	23,31±13,56** 22 (1-65)	117,21±104,90** 92 (0-518)	5,00±2,49** 5 (0-11)	28,72±17,03 25 (1-114)	162,01±144,16 135,5 (1-905)	6,02±2,63 6 (1-14)	25,76±15,43[¥αβ] 24 (1-114)	137,41±125,82[¥αβ] 111 (0-905)	5,46±2,60[¥αβ] 5 (0-14)
Doktor öğretim üyesi	12,13±10,58 8 (1-57)	35,67±41,39 19,5 (0-195)	2,58±1,64 2 (0-8)	14,54±12,02 11 (1-51)	52,11±75,80 28 (0-418)	3,24±2,26 3 (0-10)	13,52±11,46[ΦΨ] 9 (1-57)	45,15±63,87[ΦΨ] 24 (0-418)	2,96±2,04[ΦΨ] 3 (0-10)
Öğretim üyesi uzman doktor	7,34±7,08 4.5 (0-27)	22,18±35,06 13 (1-187)	1,90±1,07 2 (1-4)	9,68±8,98 6 (2-29)	39,36±51,26 20 (0-203)	2,26±1,52 2 (0-6)	8,21±7,84[θ] 5 (0-29)	28,58±42,17[θ] 15 (0-203)	2,04±1,26[θ] 2 (0-6)
Uzman doktor	5,49±6,26 3 (0-37)	25,52±63,34 8 (0-710)	1,65±1,54 1 (0-11)	6,12±7,72 3 (0-55)	28,44±64,49 6 (0-423)	1,81±1,97 1 (0-12)	5,72±6,84 3 (0-55)	26,62±63,71 7 (0-710)	1,71±1,71 1 (0-12)
Toplam	17,74±22,72 9 (0-233)	120,43±222,65 34 (0-2.296)	4,03±3,99 3 (0-25)	23,51±24,98 18 (0-153)	183,19±322,81 73.5 (0-2.906)	5,27±4,71 4 (0-24)	20,27±23,90 12 (0-233)	148,32±273,41 44 (0-2.906)	4,57±4,36 3 (0-25)

*p<0,05 profesör unvanına sahip kadın akademisyenler ile erkek akademisyenler arasında, Mann-Whitney U testi, **p<0,05 doçent unvanına sahip kadın akademisyenler ile erkek akademisyenler arasında, Mann-Whitney U testi, †p<0,05 profesörler ile doçentler arasında, Mann-Whitney U testi, ‡p<0,05 profesörler ile doktor öğretim üyeleri arasında, Mann-Whitney U testi, €p<0,05 profesörler ile öğretim üyesi uzman doktorlar arasında, Mann-Whitney U testi, £p<0,05 profesörler ile uzman doktorlar arasında, Mann-Whitney U testi, ¥p<0,05 doçentler ile doktor öğretim üyeleri arasında, Mann-Whitney U testi, αp<0,05 doçentler ile öğretim üyesi uzman doktorlar arasında, Mann-Whitney U testi, βp<0,05 doçentler ile uzman doktorlar arasında, Mann-Whitney U testi, Φp<0,05 doktor öğretim üyeleri ile öğretim üyesi uzman doktorlar arasında, Mann-Whitney U testi, Ψp<0,05 doktor öğretim üyeleri ile uzman doktorlar arasında, Mann-Whitney U testi, θp<0,05 öğretim üyesi uzman doktorlar arasında, Mann-Whitney U testi

belirlendi. Erkek anesteziyoloji ve reanimasyon uzmanlarının yayın sayıları, atıf sayıları ve h-indeks ortalamaları, kadın anesteziyoloji ve reanimasyon uzmanlarının anlamlı olarak yüksek bulundu (sırasıyla p<0,001, p<0,001, p<0,001 Mann-Whitney U testi) (Tablo 2).

Profesör unvanına sahip erkek anesteziyoloji ve reanimasyon uzmanlarının Scopus veri tabanındaki yayın sayısı ortalamaları (p=0,020, Mann-Whitney U testi), atıf sayısı ortalamaları (p=0,005, Mann-Whitney U testi) ve h-indeks ortalamaları (p=0,002, Mann-Whitney U testi) profesör unvanına sahip kadın anesteziyoloji ve reanimasyon uzmanlarından anlamlı olarak yüksek bulundu (Tablo 2).

Doçent unvanına sahip erkek anesteziyoloji ve reanimasyon uzmanlarının Scopus veri tabanındaki yayın sayısı ortalamaları (p=0,030, Mann-Whitney U testi), atıf sayısı ortalamaları (p=0,008, Mann-Whitney U testi) ve h-indeks ortalamaları (p=0,010, Mann-Whitney U testi) doçent unvanına sahip kadın anesteziyoloji ve reanimasyon uzmanlarından anlamlı olarak yüksek bulundu (Tablo 2).

Doktor öğretim üyesi, öğretim üyesi uzman ve uzman unvanına sahip kadın ve erkek anesteziyoloji ve reanimasyon uzmanlarının Scopus veri tabanındaki yayın sayısı, atıf sayısı ve h-indeks ortalamaları arasında anlamlı farklılık yoktu (p>0,05, Mann-Whitney U testi) (Tablo 2).

Çalışmaya dahil edilen akademik anesteziyoloji ve reanimasyon uzmanlarının çalışma yerleri olan üniversiteler ve eğitim araştırma hastanelerinde çalışma durumlarına göre yayın sayısı, atıf sayısı ve h-indeksleri incelendiğinde, üniversite hastanelerinde çalışan toplam 802 (%54,4) akademisyenin yayın sayısı ortalaması 27,06±26,45, ortanca 22 (0-233), atıf sayısı ortalaması 199,27±319,87, ortanca 97 (0-2906), h-indeks ortalaması 5,91±4,66, ortanca 5 (0-25); eğitim araştırma hastanelerinde çalışan toplam 690 (%45,6) akademisyenin yayın sayısı ortalaması 10,11±14,41, ortanca 4 (0-94), atıf sayısı ortalaması 58,81±117,70, ortanca 13 (0-877), h-indeks ortalaması 2,51±2,79, ortanca 1 (0-18) olarak belirlendi. Çalışmamızda eğitim araştırma hastanesinde çalışan akademisyenlerin yayın sayısı, atıf sayısı ve h-indeks ortalamaları üniversitelerde çalışan akademisyenlerden anlamlı olarak düşük bulunmuştur (sırasıyla p<0,001, p<0,001, p<0,001 Mann-Whitney U testi).

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TARTIŞMA

Ülkemizde akademik kurumlarda görev yapan anesteziyoloji ve reanimasyon uzmanlarının bibliyografik verileri ve buna etki eden faktörlerin analizini yapmayı amaçladığımız bu çalışmamızda; ülkemizde akademik kurumlarda görev yapan 1.512 anesteziyoloji ve reanimasyon uzmanı bulunduğunu, profesör, doçent, öğretim üyesi uzman ve uzman sayılarında kadın akademisyen sayılarının, erkek akademisyenlerden yüksek olduğu ve anesteziyoloji ve reanimasyon uzmanlarının cinsiyetlerine göre akademik unvanlarının dağılımı açısından anlamlı farklılık bulunduğu, erkek anabilim dalı başkanı sayısının kadın anabilim dalı başkanı sayısından anlamlı olarak yüksek olduğu, erkek anesteziyoloji ve reanimasyon uzmanlarının yayın sayıları, atıf sayıları ve h-indeks ortalamalarının, kadın anesteziyoloji ve reanimasyon uzmanlarından anlamlı olarak yüksek olduğu, cinsiyet farkının ve akademik unvanın bibliyografik parametreler üzerine etkili olduğu belirlenmiştir.

Tıbbın birçok alanında, mutlak değeri uzmanlık alanına göre değişmekle beraber, akademik unvanın ilerlemesi ile h-indeksinde de bir artış görülmektedir (14). Pagel ve Hudetz (15), ABD'de 24 akademik anesteziyoloji departmanında öğretim üyelerinin bibliyografik verilerini inceledikleri çalışmalarında, h-indeksi, yayın sayısı, toplam atıflardaki artışların akademik unvanın yükselmesi ile korelasyon gösterdiğini bulmuşlardır. Moppett ve Hardman (16) İngiltere'de anesteziyoloji alanında 23 akademik departmanda görev yapan 104 akademisyenin toplam yayın sayısı, toplam atıf sayısı, h-indeks ile g-indeks değerini incelemişler ve profesör olmayanlarla profesörleri karşılaştırdıklarında tüm bibliyografik parametrelerin profesörlerde anlamlı olarak yüksek olduğunu belirlemişlerdir. ABD'de görevli akademik kardiyotorasik anesteziyologların bibliyografik verilerini inceleyen Pagel ve Hudetz (17), akademik unvanın yükselmesinin h-indeks, toplam yayın ve toplam atıf sayılarını artırdığını belirlemiştir. Toronto Üniversitesi'nde görevli 268 akademik anesteziyoloğun değerlendirildiği diğer bir çalışmada, akademik unvanın yükselmesi ile h-indeksin yükseldiği vurgulanmıştır (18). Spearman ve ark. (19) akademisyen beyin cerrahları arasında yaptıkları çalışmalarında akademik unvanın yükselmesi ile h-indeks artışını anlamlı bulmuşlardır. Kuzey Amerika'da pediatrik beyin cerrahlarında yapılan başka bir çalışmada akademik unvan yükselmesiyle h-indeks artışının anlamlı olduğu bulunmuştur (20). Çalışmamızda da akademik unvan yükseldikçe, anlamlı bir şekilde yayın sayısı, atıf sayısı ve h-indeksinin arttığı tespit edilmiştir.

Türkiye Kamu Hastaneleri Kurumu tarafından 2014 yılında yayınlanan 'İnsan Gücü Raporu'na göre Türkiye Kamu Hastaneleri Kurumu'nda çalışan 13.759 (%41,84) kadın, 19.129 (%58,16) erkek uzman hekim olmak üzere, toplam 32.888 uzman hekim bulunmaktadır (21). Aynı raporda cinsiyete göre en çok kadın uzman hekimin görev yaptığı on branş verilmiştir. Anesteziyoloji ve reanimasyon dalında 1.562 (%61,54) kadın, 976 (%38,46) erkek olmak üzere toplam 2.538 uzman hekim bulunmaktadır. Çalışmamızda ülkemizde akademik çalışma ortamları olan üniversiteler ve Sağlık Bakanlığı eğitim ve araştırma hastaneleri incelediğinde, anesteziyoloji ve reanimasyon alanında profesör, doçent, öğretim üyesi uzman ve uzmanlar arasında kadın akademisyen sayıları, erkek akademisyenlerden anlamlı olarak yüksek bulundu. Bu veri Türkiye Kamu Hastaneleri Kurumu tarafından 2014 yılında yayınlanan 'İnsan Gücü Raporu' ile uyumlu olarak değerlendirildi.

Çalışmamızda kadın anesteziyoloji ve reanimasyon uzmanlarının yayın sayısı, h-indeks ve atıf sayısı ortalamalarının erkek anesteziyoloji ve reanimasyon uzmanlarından anlamlı olarak düşük olduğu belirlenmiştir. Pagel ve Hudetz (15) de ABD'de 24 akademik anesteziyoloji departmanında görev yapan erkek akademisyenlerin h-indeksi, yayın sayısı ve toplam atıf ortalamalarının kadın akademisyenlerden anlamlı olarak yüksek olduğunu bulmuşlardır. Kanada'da yapılan bir çalışmada erkek anesteziyologların, kadın anesteziyologlar ile karşılaştırıldığında, h-indeks, yayın sayısı ve atıf sayılarının daha yüksek olduğu belirlenmiştir (22). Pagel ve Hudetz (23), 397 akademik anesteziyoloğun bibliyografik verilerini inceledikleri çalışmalarında kadın anestezistlerin h-indekslerinin erkek anestezistlerden daha düşük olduğunu belirlemiştir. Myers ve ark. (24), kadın cerrahların erkeklerden daha düşük h-indekslerine sahip olduklarını belirlemişlerdir. Hill ve ark. (25), jinekolojik onkologların h-indekslerinin, erkek cinsiyet ile ve akademik unvan yükseldikçe arttığını bulmuşlardır. Kuzey Amerika'da pediatrik beyin cerrahlarında yapılan bir çalışmada da erkek cinsiyetle h-indeks artışının anlamlı olduğu bulunmuştur (20).

Çeşitli çalışmalardan elde edilen sonuçlara göre, kadınlar akademik kademelerde daha yavaş ilerlemektedir ve daha düşük yayın oranlarına sahiplerdir (25,26). Yapılan çalışmalarda kadınların liderlik pozisyonlarında olma oranlarının daha düşük ve akademik tıptan ayrılma olasılıklarının daha yüksek olduğu vurgulanmaktadır (26). Kadın akademisyenlerin geri çekilmelerine katkıda bulunan faktörler olarak, mentor eksikliği, elverişsiz çalışma kültürü, araştırma önündeki engeller, kadınların toplumsal rolleri gösterilmektedir (25,26). Tıpta cinsiyet eşitsizliğinin günümüzde devam etmesinin nedenleri çok yönlüdür. Bireysel olarak kadın akademisyenler, aile ve kültürel beklentiler ile akademik rolleri arasında kalmaktadır. Kurumsal alanda ise cinsiyet ayrımcılığının nedenlerini en iyi o kurumun iklimi ile açıklamak mümkündür. Kadın akademisyenler için kurum iklimleri "soğuk" olarak tanımlanmaktadır (27). Kurumların içinde bulundukları toplumların kültürel kodlarının uzantısı olduğu düşünülecek olursa, yerleşik toplumsal uygulamaları değiştirmek ve liderlik rollerinin kadınlar için de uygun olduğuna dair örgütsel iklim oluşturmak sorunun çözümüne yardım edebilir. Kurumlar, cinsiyet eşitsizliğini gidermek için çalışmalıdır (27-29).

Çalışmamızda akademisyenlerin çalışma yerlerine göre yayın sayıların atıf sayıları ve h-indeksleri incelendiğinde, üniversitelerde çalışan akademisyenlerin, eğitim araştırma hastanelerinde çalışan akademisyenlere kıyasla yayın ve atıf sayıları ile h-indeks değerlerinin anlamlı olarak daha yüksek olduğu belirlenmiştir. Ülkemizde eğitim araştırma hastanelerinin hizmet yükünün daha fazla olmasının, üniversitelerin ise daha multidisipliner yapılara sahip olması ve araştırmaya yönelme oranlarının daha yüksek olmasının bu sonuca neden olduğunu düşünmekteyiz. Ülkemizde

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çalışmamızın yapılması sonrasında olan düzenlemeler ile eğitim araştırma hastanelerinin bir kısmının sağlık bilimleri üniversitesi çatısı altında toplanmasının, ileride bu konuda yapılacak çalışmaların değerlendirilmesini zorlaştıracağını düşünmekteyiz. Yaptığımız literatür analizinde ülkemizde ve dünya literatüründe bu yönde bir bilimsel veriye rastlanmamıştır. Gelecekte farklı dallarda yapılacak çalışmalarda bu konunun araştırılması gerektiğini düşünmekteyiz.

Çalışmanın Kısıtlılıkları

Çalışmamızın bazı kısıtlılıkları da mevcuttur. Çalışmamızda veri elde etmek amacıyla kullanılan web sitelerindeki listelerde bilgi yanlışlıkları bulunabilir. Ayrıca kadın akademisyenler evlendikten sonra soyadlarında değişiklik yapmış olabilirler. Bu nedenle soy isim değişikliğinden önce ve sonra yapılan yayınların, h-indeksinin veya akademik parametrelerin sayısını ilişkilendirmek ve değiştirmek için kurumların web sitelerinden kontrol edildi.

SONUÇ

Çalışmamız Türkiye'de akademik kadrolarda bulunan anesteziyoloji ve reanimasyon uzmanlarının sayılarının, cinsiyet dağılımlarının, akademik unvan dağılımlarının, idari görev dağılımlarının, Scopus veri tabanında bulunan yayın sayısı, atıf sayısı ve h-indekslerinin değerlendirildiği ilk çalışmadır. Çalışmamızda, ülkemizde 1.512 anesteziyoloji ve reanimasyon uzmanı bulunduğu, profesör, doçent, öğretim üyesi uzman ve uzmanlarda kadın akademisyen sayılarının, erkek akademisyen sayısından yüksek olduğu; yayın sayısı, atıf sayısı ve h-indeks değerinin, anesteziyoloji ve reanimasyon uzmanlarının akademik unvanları, çalıştıkları kurum ve cinsiyetleri ile istatistiksel olarak anlamlı ilişkisi olduğu belirlenmiştir.

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The PR Interval Predicted Major Adverse Cardiovascular Events in Patients with Acute Coronary Syndrome Who Underwent Percutaneous Coronary Intervention: 3 Years Follow-up Results

Primer Perkütan Koroner Girişim Uygulanan Akut Koroner Sendrom Hastalarında PR Mesafesi Majör İstenmeyen Olayları Öngörmüştür: 3 Yıllık Takip Sonuçları

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ABSTRACT

Objective: It is crucial to identify the high-risk group in acute coronary syndrome (ACS) patients who underwent percutaneous coronary intervention (PCI). To date, various stratification tools have been developed to predict adverse events. However, the PR interval is a readily available parameter in routine clinical practice. This study aimed to investigate the role of the PR interval in predicting major adverse cardiovascular events (MACE) in patients with ACS who were performed PCI.

Methods: Patients diagnosed with ACS and who underwent PCI between January 2015 and July 2018 were included in the study. Patients were followed up for an average of 3.2 years. Electrocardiogram was obtained from all patients on admission to the hospital. The PR interval was measured by the semi-automatic application tool. The primary outcome was all-cause mortality, new-onset decompensated heart failure, cerebrovascular event, and recurrent revascularization.

Results: The mean age of total 177 ACS patients was 58.7±10.3 years and 150 (84.7%) of them were male. MACE developed in 38 patients (21.4%) who were older (p<0.001) with a male preponderance (p=0.032). The PR interval was shorter in the MACE (+) group than the MACE (-) group (154.2±21.2 vs 164.1±18.1 ms, p=0.004). Backward multivariable Cox regression analysis revealed that male gender [hazard ratio (HR)=3.667, 95% confidence interval (CI): 1.501-8.961, p=0.004], PR interval [HR=0.981, 95% CI:0.961-0.996, p=0.019], and left ventricular ejection fraction [HR=0.906, 95% CI:0.873-0.941, p<0.001] were independent predictors of MACE during long-term follow-up.

Conclusion: The PR interval and male gender were independent predictors of long-term MACE in patients with ACS without atrioventricular conduction defect.

Keywords: Acute coronary syndrome, electrocardiography, PR interval, percutaneous coronary intervention, sympathetic activity, major adverse cardiovascular event

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ÖZ

Amaç: Akut koroner sendrom (AKS) hastalarında yüksek riskli grupları belirlemek önemlidir. Şimdiye kadar çeşitli sınıflandırma araçları geliştirilmiştir. PR intervali rutin günlük pratikte kolay elde edilebilir bir parametredir. Bu çalışmada perkütanöz koroner girişim (PCI) yapılmış AKS hastalarında PR mesafesinin uzun dönem majör istenmeyen advers olayları (MACE) öngörmedeki etkisini araştırmayı amaçladık.

Yöntemler: Ocak 2017 ile Temmuz 2017 tarihleri arasında PCI uygulanan toplamda 177 AKS hastası çalışmaya dahil edildi. Ortalama 3,2 yıl boyunca hastalar takip edildi. Elektrokardiyografi verileri tüm hastalardan başvuru anında elde edildi ve yarı otomatik uygulama aracılığıyla PR aralıkları ölçüldü. Primer sonlanım noktası tüm sebeplere bağlı ölüm, yeni başlayan dekompanse kalp yetmezliği, serebrovasküler olay ve tekrarlayan revaskülarizasyon olarak belirlendi.

Bulgular: Çalışmaya dahil edilen toplam 177 hastanın yaş ortalaması 58,7±10,3 yıl ve 150 (%84,7) kişi erkekti. Hastaların 38 tanesinde (%21,4) MACE gelişti ve bu grupta erkek cinsiyeti hakimiyeti olmakla beraber (p=0,032) daha yaşlı olduğu görüldü (p<0,001). PR intervali MACE (+) grubunda MACE (-) grubuna göre daha kısaydı (154,2±21,2 vs 164,1±18,1, p=0,004). Cox regresyon analizinde erkek cinsiyet [risk oranı (RO)=3,667, %95 güven aralığı (GA): 1,501-8,961, p=0,004], PR mesafesi [RO=0,981, 95% GA:0,961-0,996, p=0,019] ve sol ventrikül ejeksiyon fraksiyonu [RO=0,906, %95 GA: 0,873-0,941, p<0,001] bağımsız MACE öngördürücüsüydü.

Sonuç: Atriyoventriküler ileti kusuru olmayan AKS hastalarında PR mesafesi ve erkek cinsiyet uzun dönem istenmeyen olayların bağımsız öngördürücüsüdür.

Anahtar kelimeler: Akut koroner sendrom, elektrokardiyografi, PR mesafesi, perkütan koroner girişim, sempatik aktivite, majör istenmeyen advers olay

INTRODUCTION

The prognosis of patients with the acute coronary syndrome (ACS) improved considerably with recent developments in medical and interventional treatment options. However, ACS is still one of the leading causes of morbidity and mortality worldwide (1). Thus, determining the high-risk patient population is essential to prevent future adverse events and regulate the aggressivity of treatment modalities (2).

The surface electrocardiogram (ECG) is an easily obtainable, cost-effective, and routinely used diagnostic tool that has a vital role in diagnosing and treating patients with ACS (3). The significant prognostic roles of depolarization and repolarization parameters such as QRS duration, QT interval, T-wave peak to T-wave end interval (TPE) interval were shown in previous studies. In addition, conduction disorders including right bundle branch block, left bundle branch block, atrioventricular (AV) block, and fascicular blocks were also demonstrated to be predictors of adverse events in patients with ACS (4-6). Moreover, elevated heart rate was an independent predictor of long-term major adverse cardiovascular events (MACE) in patients with ACS. This result was linked to increased sympathetic activity (7,8).

The PR interval is the duration of the electrical stimulus that has arisen from the sinus node (SN) and travels to the ventricle. The impulse conduction is slowed by the AV node because of the electrophysiological properties of AV nodal tissue (9). Therefore, increased sympathetic and/or decreased parasympathetic stimulation causes shortening of the PR interval by providing more frequent stimulation from the SN and reducing the delay in the AV node (10). Hence, we aimed to investigate the predictive role of PR interval on MACE development in patients with ACS without AV conduction defect.

METHODS

Study Population

This is a prospective and observational cohort study. A total of 177 consecutive patients with a diagnosis of ACS between January and July 2017 were enrolled. Patients were diagnosed with ACS in accordance with the currently recommended ESC/AHA guidelines (11,12). The study was carried out following the principles stated in the Declaration of Helsinki. The Local Ethics Committee approved the study protocol (decision no: E-64247179-799, date: 26.05.2021).

The same cardiologist at admission recorded sociodemographic data and medical history. The systolic and diastolic pressure, previous history of coronary artery disease (CAD), arterial hypertension (AH), diabetes mellitus (DM), hyperlipidemia, smoking status, and family history of premature CAD were evaluated. The patient's use of antihypertensive drugs or systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg in two or more measurements were defined as AH. The presence of DM was diagnosed according to at least one of the following criteria: i) history of DM and taking any anti-diabetic medication; ii) randomly measured blood glucose value of 200 mg/dL or higher; iii) HbA1c values are 6.5 percent or higher. Regular smokers in the last six months were considered as a smoker. The following formula calculated body mass index (BMI): BMI = weight (kg)/height (meters)^2. All data were stored in the database of our institution.

12-Lead Standard Electrocardiogram Records

Standard 12-lead ECG (Schiller, Cardiovit AT-10 plus) (filter 150 Hz, 25 mm/s, 10 mm/mV) was recorded by experienced nurses at admission in all patients. ECG images were magnified eight times using a semi-automatic application tool. Standard intervals (HR, PR, QRS, and QT intervals) and amplitudes (R, S, and T waves and J and ST segments) on the ECG were analyzed by the experienced cardiologist. In addition, measurements of the PR interval were carried in lead II. The PR interval was assessed as the milliseconds from the initial-up point of the P wave to the initial-up point of the R wave or the initial-down point of the q wave. The onset of the P wave was determined as the deviation point up or down from the isoelectric line. The R wave was determined as the first upward deviation point from the isoelectric line, whereas the q wave was

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the first downward deviation point. The PR interval was calculated as the average duration of 3 consecutive beats.

Exclusion Criteria

End-stage liver or kidney disease (7 patients), collagen tissue disease (2 patients), malignancy (3 patients), acute or chronic infectious disease (10 patients), moderate to severe valvular heart disease (7 patients), congenital heart disease (1 patient), and pulmonary embolism (2 patients) were excluded from the study. In addition, patients with atrial fibrillation (AF) (11 patients), AV blocks (10 patients), and percutaneous coronary intervention (PCI)-related complications were not included in the study. Patients taking medications such as beta-blockers and calcium channel blockers before PCI, which may alter the PR interval (10 patients) were also excluded.

In accordance with the principle of the clinical trials, patients who did not sign the informed consent form, refused PCI, and patients whose information could not be accessed (25 patients) from the hospital's medical system records, national death database system, or telephone numbers were excluded from the study.

Coronary Angiography and Percutaneous Coronary Intervention

Coronary angiography was performed urgently by the trans-femoral Judkins technique preferably. However, the trans-radial Judkins technique was used in case of difficulties in accessing the ascendant aortic artery. The left anterior descending and circumflex coronary arteries were viewed from the right and left cranial and caudal angles. The right coronary artery was visualized from at least two different angles. Patients were given the loading dose of acetylsalicylic acid and clopidogrel or ticagrelor according to the preference of the invasive cardiologist who performed the procedure. At the beginning of the procedure, 5,000 or 10,000 IU intra-venous heparin was administered according to the patients' weight. After the invasive procedure, all patients were taken to the coronary critical care unit and followed until stabilization was achieved.

Echocardiography

Detailed two-dimensional echocardiography was performed in all patients before discharge. Echocardiography was conducted in the left lateral decubitus position with Philips Epiq 7 systems (Philips Medical Systems, Andover, MA) using a 2.5-3.5 Mhz transducer. Left ventricular ejection fraction (LVEF) was measured using the modified Simpson's method. Conventional Doppler echocardiography and tissue Doppler imaging data were also obtained from all patients. The physicians who performed echocardiography were blinded to the other clinical conditions of the patients.

Clinical and Laboratory Data Assessment

At admission, routine biochemistry, hemogram, creatinine kinase-MB fraction (CK-MB), troponin-I, glucose, and C-reactive protein (CRP) were measured. Glucose, creatinine, and lipid parameters were measured with standard methods. Peak CK-MB and peak troponin levels were measured at admission and 4-hour apart. Peak values were included in the analysis. Since laboratory measurements of 50 ng/mL and above are stated as >50 ng/mL in our institution, if the peak value exceeds 50 ng/mL, troponin was included as "50" in the statistical analysis.

Clinical Follow-up and The Primary Outcome

The patients were followed up for an average of 3.2 years. The composite primary endpoint of the study was all-cause mortality, new-onset decompensated heart failure (HF), cerebrovascular event, and recurrent revascularization. Mortality data were obtained by the query of the hospital and national databases or with direct phone calls to relatives of relevant patients. Most of the patients were examined at 1st, 3rd, 6th, 12th, 24th months, and clinical and laboratory findings were regularly recorded to the hospital database system. For patients who were not admitted to the hospital for regular control, relevant medical histories were obtained through the medical system records of the hospital. Typical HF symptoms, including shortness of breath, swelling of ankles, palpitation, weakness, jugular venous fullness, pulmonary congestion, and peripheral edema, were assessed at the examinations. Patients with the symptoms mentioned above and physical examination findings and those with LVEF under 40% were accepted as decompensated heart failure (CHF).

Statistical Analysis

SPSS software package (Version 23.0, SPSS, Inc., Chicago, IL) was used to analyze the data. The normal distribution of the data was assessed by the visual (histograms, probability plots) and analytical methods such as Kolmogorov-Smirnov (if the number of related parameters is more than 50) and Shapiro-Wilk's test (if the number of related parameters is less than 50). Levene's test was used to check the homogeneity of variances. The mean ± standard deviation was used to represent the continuous variables, median. The interquartile range was used for non-normally distributed continuous variables, and the percentages were used to present the categorical variables. The chi-square or Fisher's Exact test was used for comparing the categorical groups. The two-tailed Student t-test was used for normally distributed parameters, while the Mann-Whitney U test was performed for the non-normally distributed continuous variables. The effects of the various variables on MACE were determined by univariate regression analysis. In univariate analyses, the variables with unadjusted $p<0.05$ and considered to be related to MACE were identified as confounding factors and included in the multivariable Cox regression analyses to determine the independent predictors of MACE. A p-value (2-tailed) of less than 0.05 was considered to have statistical significance. Kaplan-Meier curve was drawn to show the PR interval in predicting MACE.

RESULTS

A total of 177 patients were included in this study. The mean age was 58.7±10.3 years and 150 patients (84.7%) were male. The

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patients were divided into two groups according to the presence of MACE which occurred in 38 patients (21.4%). Of those, 7 (18%) died, 19 (50%) had decompensated HF, 6 (8%) had cerebrovascular event, and 9 (23%) had recurrent revascularization. MACE (+) group was older (63.9±11.5 vs 57.28±9.6, p<0.001) and more likely to be male (73.7% vs 12.2%, p=0.032). While LVEF (48.7±10.8 vs 56.2±6.5, p<0.001) and eGFR (81 vs 89.5 mL/min/1.73 m^2, p=0.020) were lower, peak troponin (28.5±22.5 vs 19.2±20.4 ng/mL, p=0.015) and CRP (1.1 vs 0.6 mg/dL, p=0.005) were higher in MACE (+) group. Type of ACS (p=0.245) and other demographic features were similar between groups (Table 1).

The PR interval was shorter (154.2±21.2 vs 164.1±18.1 ms, p=0.004), whereas HR was higher in MACE (+) group. However, HR did not reach statistical significance (76.9±15.8 vs 72.1±14.1 bpm, p=0.068). Other electrocardiographic findings did not differ between MACE groups (Table 2). In addition, patients were divided into two groups as longer (above mean 164) and shorter (below mean 164) PR intervals. Demographic characteristics of patients were similar between PR interval groups. However, overall MACE, mortality, and repeated revascularization rates were higher in the shorter PR interval group (Table 3).

The parameters that found significant in univariate analysis were included in backward multivariable Cox regression analysis which revealed that age [HR=3.667, 95% confidence interval (CI): 1.501-8.961, p=0.004], PR interval [HR=0.981, 95% CI:0.961-0.996, p=0.019], and LVEF [HR=0.906, 95% CI:0.873-0.941, p<0.001] were independent predictors of MACE (Table 4). Kaplan-Meier curves demonstrated that longer PR interval (<164 ms) increased the risk of MACE during 3.2 years of follow-up (Figure 1).

DISCUSSION

In the present study, we demonstrated that the admission PR interval, without AV conduction defect, was an independent predictor of long-term MACE in patients with ACS. Thus, to the best of our knowledge, this study is the first in the literature to evaluate the relationship between the PR interval and MACE in patients with ACS.

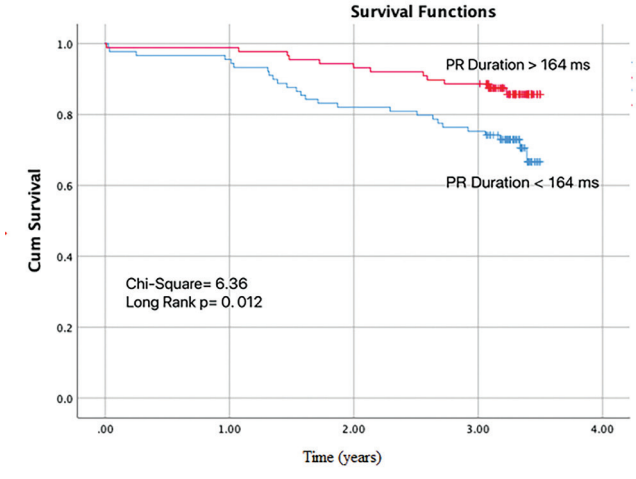

Figure 1. Kaplan-Meier curves demonstrated that PR interval of over 164 ms increased the risk of MACE during 3.2 years of follow-up

MACE: major adverse cardiovascular events

Autonomic nervous system (ANS) activation has an important role in the hemostatic control and the progression of cardiovascular diseases (13). Sympathetic nervous system (SNS) activation increases the HR and left ventricular contraction and accelerates the intracardiac electrophysiological propagation velocity (14). Analysis of adrenergic neural functions can predict adverse events that may develop subsequently. Sinus node activity was increased in the early stage of ACS, and sympathetic activation was associated with adverse outcomes (15). Graham et al. (16) showed that LVEF was lower in the late-stage in patients whose sympathetic activity was higher in patients with acute myocardial infarction (AMI). Xiong et al. (17) demonstrated in their experimental studies that adverse remodeling and LV systolic dysfunction after AMI were of a lesser extent in patients who underwent sympathetic neural ablation. In Takatsubo cardiomyopathy, hyperactivation of the adrenergic activity was blamed for the aneurysm in the apical segment of the left ventricle (18). In addition, increased sympathetic activity and/or decreased vagal activity were shown to induce malignant arrhythmias in various populations. Furthermore, stimulation of arrhythmias by increased sympathetic activity becomes more apparent at higher HR. Especially, acute ischemic episodes of myocardium trigger malignant arrhythmia at higher HR furtherly (19). The mortality rate was shown to reduce considerably employing shifting the autonomic balance in favor of vagal tonus with medical or interventional treatment modalities. Thus, activating parasympathetic activity with beta-blockers and reducing sympathetic tonus with angiotensin-converting enzyme inhibitors are the main focuses of improving survival (20).

ANS activity is evaluated by indirect methods in daily practice frequently. Functional tests such as observing the responses of the organs to certain stimuli and invasive structural tests, such as skin biopsy, microneurography SNS activity, and sural nerve biopsy, are currently practiced methods (21). On the other hand, the variability of HR and arterial blood pressure analyses are cost-effective methods and are frequently used to test the adrenergic activity in routine practice (22,23). The HR reflects the balance between sympathetic and parasympathetic activities. Elevated HR was shown to be the risk factor for CAD, sudden cardiac death, and stroke developments. Moreover, it was demonstrated to predict all-cause mortality in the general population (8,22). Although HR indicates sympathetic activity, it was affected by various conditions such as age, gender, BMI, smoking, physiological and oxidative stress, metabolic factors, and inflammation. Therefore, easily obtainable, cost-effective, and solid indices reflecting the sympathetic activity would contribute to interpreting the adrenergic functions better than HR. Typically, PR interval shortens with increased HR. Besides, the amount of decrease in PR interval with exercise was shown to be beyond the increase in HR (23,24). Therefore, we may speculate that the PR interval has more predictive value than HR reflecting the autonomic balance.

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Table 1. Comparison of the characteristic features of patients with and without MACE

Variables	MACE (-) (n=139)	MACE (+) (n=38)	All patients (n=177)	p
Demographic characteristics				
Gender (male) n (%)	122 (87.8)	28 (73.7)	150 (84.7)	0.032
Hypertension n (%)	62 (44.6)	18 (47.4)	80 (45.2)	0.762
Smoking n (%)	17 (12.2)	7 (20)	24 (13.2)	0.323
Hyperlipidemia n (%)	47 (33.8)	10 (26.3)	57 (32.2)	0.381
Diabetes mellitus n (%)	51 (36.7)	14 (36.8)	65 (36.7)	0.986
Previous CAD n (%)	12 (13.5)	6 (20)	119 (67.2)	0.389
Age (year)	57.28±9.6	63.9±11.5	58.7±10.3	<0.001
Body mass index (kg/m^2)	29.3±4.6	30.7±6.2	29.6±5	0.159
Admission SBP (mmHg)	126.8±19.3	132±21.4	127.9±19.8	0.155
Admission DBP (mmHg)	76.7±11.6	79.9±16.8	77.4±12.9	0.175
LVEF (%)	56.2±6.5	48.7±10.8	54.2±8.5	<0.001
Mortality n (%)	0 (0)	7 (18)	7 (39)	<0.001
Decompensated HF n (%)	0 (0)	19 (50)	19 (11)	<0.001
Repeated revascularization n (%)	0 (0)	9 (23)	9 (1)	<0.001
Cerebrovascular event n (%)	0 (0)	6 (8)	6 (0.5)	<0.001
Type of AMI				
USAP/NSTEMI n (%)	98 (70)	23 (60)	121 (69)	0.245
STEMI n (%)	41 (29)	15 (39)	56 (31)	
IRA				
LAD n (%)	35 (41)	17 (48)	52 (43)	0.425
RCA n (%)	31 (36)	11 (31)	42 (34)	
CX n (%)	20 (23)	7 (20)	27 (22)	
Stent type n (%)				
BMS stent type n (%)	11 (14)	4 (11)	15 (12)	0.203
DES stent type n (%)	70 (78)	25 (71)	95 (76)	
BMS+DES stent type n (%)	8 (9)	6 (17)	14 (11)	
Final TIMI flow n (%)				
0-1 n (%)	2 (2)	3 (10)	5 (4)	0.113
2 n (%)	6 (6)	1 (3)	7 (5)	
3 n (%)	95 (92)	26 (86)	121 (90)	
Admission laboratory				
Serum creatinine (mg/dL)	0.92±0.19	0.95±0.21	0.93±0.19	0.495
eGFR (mL/min/1.73m^2)*	89.5 (75.7-98.2)	81 (71.5-92)	84.1±17	0.020
Peak troponin (ng/mL)	19.2±20.4	28.5±22.5	21.2±21.1	0.015
Glucose (mg/dL)	133.3±53.1	142.3±59.5	135±54.5	0.371
HgbA1c	5.9 (5.7-6.7)	6 (5.7-7.3)	5.9 (5.7-6.7)	0.877
CRP (mg/dL)*	0.63 (0.32-1.14)	1.1 (0.61-2.63)	1.08±1.8	0.003
Hemoglobin (g/dL)	14.5±1.7	14.3±1.8	14.4±1.7	0.748
WBC 10^3/µL	10.4±3.5	9.9±2.4	10.3±3.3	0.486
Medication at discharge				
Aspirin n (%)	116 (100)	31 (96.9)	147 (99.3)	0.998
Clopidogrel n (%)	59 (50.9)	18 (56.3)	77 (50)	0.598
Prasugrel n (%)	12 (10.3)	2 (6.3)	14 (9.5)	0.483
Ticagrelor n (%)	41 (35.3)	10 (31.3)	51 (28.8)	0.666
ACEI n (%)	72 (62.1)	14 (43.8)	86 (58.1)	0.063
ARB n (%)	22 (19)	11 (34.4)	33 (18.6)	0.064
Beta-blocker n (%)	87 (75)	25 (78.1)	112 (75.7)	0.715
OAD/insulin n (%)	51 (36.7)	14 (36.8)	31 (20.9)	0.986

Continuous variables are given as mean ± standard deviation. *Median, interquartile range [range, (25%-75%)]. MACE: major adverse cardiovascular events, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, HF: heart failure, AMI: acute myocardial infarction, USAP: unstable angina pectoris, NSTEMI: non-ST-segment elevated myocardial infarction, IRA: infarct-related artery, LAD: left anterior descending, RCA: right coronary artery, CX: circumflex, TIMI: thrombolysis in myocardial infarction, CRP: C-reactive-protein, WBC: white blood cell, OAD: oral antidiabetic drug

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Table 2. Electrocardiographic findings of patients

Variables	MACE (-)	MACE (+)	All patients	p
Heart rate (beat/min)	72.1±14.1	76.9±15.8	73±14.6	0.068
P wave duration (ms)	110±15.6	104.9±19.3	108.9±16.4	0.094
P wave peak time (ms)	55.5±13.3	52.8±13.9	54.9±13.4	0.285
P wave dispersion (ms)	22.6±15.3	22.5±16.7	22.6±15.9	0.950
PR interval (ms)	164.1±18.1	154.2±21.2	162±19.1	0.004
P wave amplitude (mm)	0.88±0.27	0.80±0.28	0.8±0.2	0.134
P wave terminal force (ms)	64.4±29.9	57.9±34.6	63±31	0.294
QRS duration (ms)	89.7±14.1	91.1±14.7	90±14.2	0.615
AIAB n (%)	11 (7.9)	2 (5.3)	13 (7.3)	0.579
PAİAB n (%)	42 (30.2)	8 (21.2)	50 (28.2)	0.266
QT dispersion n (%)	54 (45.4)	10 (32.2)	64 (36.1)	0.188
QTc interval (ms)	427.2±34.8	432.2±30	428.2±33.8	0.143
QT interval (ms)	395.3±37.2	387±42.2	393.5±38.3	0.457
QT dispersion (ms)	39.6±22.9	33.03±21.9	38.3±22.8	0.147
TPE (ms)	81.9±16.8	82.9±14.9	81.8±16.5	0.758
TPE/QT rate	0.21±0.04	0.21±0.03	0.2±0.03	0.980
QT/QTc rate	0.92±0.09	0.89±0.09	0.92±0.09	0.076
TPE/QTc rate	0.2±0.035	0.2±0.034	0.2±0.034	0.990

Min: minute, TPE: T-wave end interval

Hence, even though HR was higher in the MACE (+) group, it did not reach significance predicting MACE in this study.

The SN, AV node, and ventricular myocardium are under the grip of the autonomic nervous innervation. However, sympathetic and parasympathetic nerve distribution and tissue sensitivity to ANS differ in each part of the heart. Thus, the autonomic stimulus is distinct in the SN, AV node, and myocardium. The AV node has parasympathetic innervation dominantly and, by this way, regulates the HR by reducing stimuli arising from the SN (14,24). Thus, autonomic nerve distribution and AV conduction properties may be altered, followed by AMI due to loss of neural innervation, secondary to the ischemia. Chen et al. (25) reported that autonomic neural denervation and subsequent sympathetic heterogeneous hyperinnervation triggered the malignant arrhythmias and sudden cardiac death in the post-MI phase. That being the case, it can be asserted that autonomic nerve distribution and activity could be better interpreted by examining the PR interval in those with a steady AV conduction system (26).

PR interval is defined as AV block if it is over 200 ms. In a recent study, patients were grouped according to the presence of the first-degree AV block. It was revealed that those with the AV block were more likely to have AF, HF, CAD, and mortality (27). In addition, in some previous trials, both PR interval prolongation and shortening are associated with adverse events in patients with CAD. However, the Atherosclerosis Risk in Communities study showed that while PR interval prolongation was not related to the development of AF, PR interval shortening could predict the occurrence of the AF (28). Moreover, several studies demonstrated that PR shortening had more predictive usefulness than PR prolongation on the development of AF. Conversely, the PR interval prolongation reflects a more fibrotic and/or inflammatory environment in the AV conduction pathway.

On the other hand, the PR interval shortening was an indicator of increased sympathetic burden or parasympathetic withdrawal on the heart (29). In the current study, patients with AV conduction abnormalities were excluded. Hence, it was aimed to evaluate the pure effect of the sympathetic and parasympathetic effect on MACE by measuring the PR interval. Furthermore, given the value of PR interval is crucial in ANS activity estimation, this cost-effective parameter may be added to other prognostic clinical factors to prognosticate future adverse events in MACE prediction better in all CAD patient groups. Various electrophysiological abnormalities were reported to be foreshadowing of the adverse cardiovascular events in patients with ACS. Therefore, ordinary parameters hidden in apparently normal ECG could be studied to predict MACE without expecting pathological effects of MI on ECG (30).

In addition, p wave duration indicates atrial depolarization time and is the first component of the PR interval. The effect of P wave prolongation on MACE was reported in previous studies (31). Although the p wave duration was higher in the MACE (+) group, our study did not reach statistical significance. The PR interval shortening predicted MACE despite the prolonged p wave duration. Thus, it can be emphasized that the PR interval has a substantial value in predicting MACE in patients with ACS. This is a single-center study with a limited number of patients. Therefore, a more extended follow-up period is required better to interpret the role of PR interval on MACE.

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Table 3. Comparison of the characteristic features of patients according to the PR interval

Variables	Short PR interval (n=85)	Long PR interval (n=92)	p
Demographic characteristics			
Gender (male) n (%)	70 (82.4)	80 (87)	0.260
Hypertension n (%)	38 (9.4)	16 (17.4)	0.862
Smoking n (%)	8 (12.2)	7 (20)	0.121
Hyperlipidemia n (%)	23 (27.1)	34 (37)	0.159
Diabetes mellitus n (%)	36 (42.4)	29 (31.5)	0.135
Previous CAD n (%)	9 (15.8)	9 (14.5)	0.846
Age (year)	59.1±10.8	58.3±9.9	0.594
Body mass index (kg/m^2)	29.5±5.2	29.8±4.8	0.697
Admission SBP (mmHg)	127.2±19.6	128.6±20	0.636
Admission DBP (mmHg)	76±13.8	78±11.9	0.160
LVEF (%)	53.4±8.8	55.1±8.1	0.275
MACE n (%)	26 (30.6)	12 (13)	0.006
Mortality n (%)	7 (8.2)	0 (0)	0.005
Decompensated HF n (%)	11 (12.9)	8 (8.7)	0.362
Repeated revascularization n (%)	8 (9.4)	1 (1.1)	0.012
Cerebrovascular event n (%)	4 (4.7)	2 (2.2)	0.352
Type of AMI			
USAP/NSTEMI n (%)	58 (68.2)	63 (68.5)	0.972
STEMI n (%)	27 (31.8)	29 (31.5)	
Final TIMI flow n (%)			
0-1 n (%)	4 (6.5)	1 (1.4)	0.310
2 n (%)	3 (4.8)	4 (5.6)	
3 n (%)	55 (88.7)	66 (93)	
Creatinine (mg/dL)	0.91±0.21	0.94±0.17	0.383
eGFR (mL/min/1.73 m^2)*	84.1 (73-86.5)	81 (71.5-92)	0.020
Peak troponin (ng/mL)	25.6±20.9	17.1±20.7	0.009
Glucose (mg/dL)	133.3±53.1	142.3±59.5	0.371
HgbA1c	6.1±(5.6-8.1)	5.8 (5.7-6.2)	0.122
CRP (mg/dL)*	0.711 (0.38-1.44)	0.713 (0.41-1.37)	0.504
Hemoglobin (g/dL)	14.3±1.9	14.5±1.5	0.488
WBC 10^3/µL	10.7±2.9	10.5±3.8	0.264

Continuous variables are given as mean ± standard deviation. *Median, interquartile range [range, (25%-75%)]. MACE: major adverse cardiovascular events, CAD: coronary artery disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, LVEF: left ventricular ejection fraction, HF: heart failure, AMI: acute myocardial infarction, USAP: unstable angina pectoris, NSTEMI: non-ST-segment elevated myocardial infarction,
TIMI: thrombolysis in myocardial infarction, CRP: C-reactive-protein, WBC: white blood cell

Table 4. Multivariable Cox regression analysis of parameters that predicting MACE

	Univariate			Multivariable		
Variables	**OR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	1.052	1.021-1.084	0.001	-	-	-
Gender (male)	0.451	0.219-0.928	0.031	3.667	1.501-8.961	0.004
PR interval (ms)	0.978	0.963-0.993	0.005	0.981	0.961-0.996	0.019
LVEF (%)	0.920	0.889-0.952	<0.001	0.906	0.873-0.941	<0.001
CRP (mg/dL)	1.503	1.141-1.980	0.004	-	-	-
eGFR (mL/min/1.73 m^2)	0.239	0.058-0.993	0.049	-	-	-

OR: odds ratio, CI: confidence interval, MACE: major adverse cardiovascular events, LVEF: left ventricular ejection fraction, CRP: C-reactive-protein, HR: hazard ratio

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CONCLUSION

The PR interval at admission, probably indicating sympathetic dominancy, was an independent predictor of MACE during three years of follow-up in patients with ACS who were performed PCI. Thus, the PR interval may also be used as a non-invasive test to evaluate autonomic function in various patient groups.

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Retrospective Analysis of the Perinatal Outcomes in Preeclampsia and Eclampsia in a Tertiary Care Center

Tersiyer Bir Merkezdeki Preeklampsi ve Eklampsi Olgularının Perinatal Sonuçlarının Retrospektif İncelenmesi

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ABSTRACT

Objective: Preeclampsia is a multisystemic disease of unknown etiology that increases maternal and fetal mortality and morbidity. Early diagnosis and appropriate management of the disease are essential to prevent adverse outcomes. This study aims to report the pregnancy and perinatal outcomes of preeclampsia and eclampsia cases.

Methods: A total of 510 patients diagnosed with preeclampsia or eclampsia were followed up in our hospital between 2015 and 2020, and they were evaluated retrospectively. Demographic characteristics, laboratory values, maternal, and fetal results of these patients were used for the comparative analysis.

Results: The mean age of the patients, gestational weeks at birth, platelet counts, and birth weight of the newborn were 28 years, 37 weeks, 194,000 cells/mm^3, and 2960 g, respectively. Among the newborns, 34.4% required intensive care. Of the pregnant patients, 48.7% delivered vaginally, while 51.3% delivered by cesarean section. Placental abruption was observed in 2.9%, eclampsia in 2%, and HELLP syndrome was noted in 1% patients.

Conclusion: Preeclampsia is one of the hypertensive diseases of pregnancy that can negatively affect the life of the mother and the baby. Therefore, high-risk pregnant women should be examined in the early weeks of pregnancy. The necessity of referral to tertiary centers is vital for optimal management.

Keywords: Pregnancy, preeclampsia, eclampsia, perinatal outcomes

ÖZ

Amaç: Preeklampsi etiyolojisi bilinmeyen maternal ve fetal mortalite ve morbiditeyi artıran multisistemik bir hastalıktır. Hastalığın erken tanısı uygun yönetimi kötü sonuçları önlemekte önemlidir. Bu çalışmanın amacı preeeklampsi ve eklampsi olgularının gebelik ve perinatal sonuçlarını aktarmaktır.

Yöntemler: 2015-2020 yılları arasında hastanemizde takip edilen preeklampsi ya da eklampsi tanısı alan toplam 510 hasta retrospektif olarak değerlendirildi. Bu hastaların demografik özellikleri, biyokimyasal değerleri, maternal ve fetal sonuçları karşılaştırıldı.

Bulgular: Çalışmada yer alan hastaların ortalama yaşları 28; ortalama doğumda gebelik haftaları 37; ortalama doğum ağırlıkları 2960 gr; ortalama trombosit sayıları 194,000 hücre/mm^3 idi. Olguların %34,4'ü yenidoğan yoğun bakım ünitesine ihtiyaç duymuştu. Olguların %48,7'si vajinal doğum yaparken, %51,3'ü sezeryan ile doğurmuştu. %2,9'unda plasenta dekolmanı ve %2'sinde eklampsi ve %1'inde de HELLP sendromu gelişmiştir.

Sonuç: Preeklampsi anne bebek hayatını olumsuz etkileyebilecek gebeliğin hipertansif hastalıklarındandır. Bu nedenle yüksek riskli gebeler gebeliğin erken haftalarında tespit edilmelidir. Gereğinde tersiyer merkeze sevk optimal yönetim için önemlidir.

Anahtar kelimeler: Gebelik, preeklampsi, eklampsi, perinatal sonuçlar

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Introduction

Preeclampsia is a pregnancy-specific disease characterized by high blood pressure and proteinuria. It increases morbidity and mortality, and its etiology is still unknown. The incidence in nulliparous pregnant women varies from 2% to 7% (1). Hypertensive disorders in pregnancy are responsible for 14% of maternal mortality globally (2). Severe preeclampsia is seen more frequently in patients with risk factors such as preeclampsia history, first pregnancy, multiple pregnancies, presence of chronic hypertension and diabetes mellitus, and history of thrombophilia (1,3). Blood pressure measurement during pregnancy, especially during the second trimester, is important for preeclampsia diagnosis. In preeclampsia, visual and prodromal symptoms such as headache and epigastric pain may accompany hypertension. Preeclampsia findings can also be seen in cases where systemic findings (liver dysfunction, renal failure, cerebral and visual symptoms, pulmonary edema, hemolysis, and the presence of thrombocytopenia) coexist with hypertension (4). Eclamptic crisis or hemolysis, elevated liver enzymes, and decreased platelet count (HELLP syndrome) may develop as a complication of preeclampsia. In preeclampsia, regular controls, early diagnosis and blood pressure regulation, eclampsia prophylaxis, referral to a tertiary center, and timely decisions on the mode of delivery can reduce fetomaternal mortality and morbidity (5).

This study aimed to evaluate the changes in biochemical parameters and report prenatal and maternal outcomes among patients diagnosed with preeclampsia or eclampsia and delivered in our clinic, as well as to share our experiences in a tertiary care center.

METHODS

İstanbul University of Health Sciences Ümraniye Training and Research Hospital Clinical Research Ethics Committee of approved the study (decision no: 386, date: 03.12.2020). The medical records of 510 patients diagnosed with preeclampsia and delivered in the Ümraniye Training and Research Hospital between 2015 and 2020 were retrospectively analyzed. Information was obtained from the computerized files of the patients. Patient consent was not obtained because the study was conducted retrospectively. Patients who were followed up in our clinic and whose files could not be accessed, cases whose births occurred elsewhere or whose babies were transferred to another center, and multiple pregnancies were excluded from the study.

The diagnostic evaluation of these patients was made according to the American College of Obstetricians and Gynecologist preeclampsia diagnostic criteria as follows: systolic pressure ≥140 mmHg and diastolic pressure ≥90 mmHg measured at least four hours apart in pregnant women over 20 weeks of gestation, a protein amount of 300 mg in 24-hour urine or a urine protein/creatinine ratio of 0.3, or if these measurements cannot be performed, +1 protein in dipstick urine (1).

Proteinuria in 24-hour urine and dipstick urine values were not considered since the diagnosis was made using the protein/creatinine ratio in spot urine in our clinic.

The gestational age of the cases was calculated according to the last menstrual period (LMP). In cases of unknown LMP, early fetal biometric measurements were taken into account. Fetal mortality was defined as fetuses older than 22 weeks of gestation without a heartbeat. Babies born before 37 weeks of gestation were considered premature.

Statistical Analysis

Mean, standard deviation, median, range, frequency, and ratio were used for descriptive statistics. Data were entered into Microsoft Excel and were analyzed with the Statistical Package of the Social Sciences Inc., Chicago, IL, USA version 27.0.

RESULTS

The mean ages of the enrolled patients, gestational age at delivery, systolic blood pressure and diastolic blood pressures at diagnosis, spot urine protein/creatinine ratio, platelet count, serum glutamic oxaloacetic transaminase, and serum glutamic pyruvic transaminase values were 28 years (14-48 years), 37 weeks (22-42 weeks), 130 mmHg (100-220 mmHg), 80 mmHg (54-140 mmHg), 0.6 (0.3-26.5), 194.000/mm^3 (16.000-391.000/mm^3), 12 IU/L (6-530 IU/L) and 23 IU/L (8-431 IU / L), respectively. Essential demographic data, blood pressure measurements, and laboratory parameters of patients are shown in Table 1.

The mean infant birth weight was 2690 g (340-5165 g), and 48.7% (n=248) and 51.3% (n=261) of the patients delivered vaginally and by cesarean section, respectively. Eclampsia was observed in 2% (n=10) of the patients, HELLP syndrome in 1% (n=5), placental

Table 1. Demographic data, blood pressure measurements, and laboratory parameters

	min-max			Median
Age	14.0	-	48.0	28.0
Gravida	1.00	-	17.00	2.00
Parity	0.00	-	6.00	1.00
Week of gestation at diagnosis	22.5	-	42.0	37.4
SBP (mmHg)	100.0	-	220.0	130.0
DBP (mmHg)	54.0	-	140.0	80.0
Spot urine protein/creatinine ratio	0.3	-	26.5	0.6
Creatinine (mg/dL)	0.4	-	5.2	0.6
Hemoglobin (g/dL)	8.4	-	17.7	11.7
Platelet (cell/m^3)	16.0	-	391.0	194.0
SGOT (IU/L)	6.0	-	530.0	12.0
SGPT (IU/L)	8.0	-	431.0	23.0
LDH (IU/L)	129.0	-	2148.0	331.0

SBP: systolic blood pressure, DBP: diastolic blood pressure, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvic transaminase, LDH: lactate dehydrogenase, Min: minimum, Max: maximum

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abruption in 2.9% (n=15), and intrauterine death in 1.8% (n=9). Neonatal intensive care unit (NICU) admissions were required in 34.4% (n=175) of cases, mainly due to prematurity (14.9%, n=76), hyperbilirubinemia (11.2%, n=57), respiratory distress syndrome, sepsis, transient tachypnea of the newborn, pneumonia, hypoglycemia, and others. Labor characteristics, fetomaternal outcomes, and NICU admission indications are presented in Table 2. The risk factors for preeclampsia are shown in Table 3.

DISCUSSION

Preeclampsia, which occurs in the second half of pregnancy, is a serious health problem in developing countries because it is associated with high maternal and fetal morbidity and mortality rates (6,7). In the management of preeclamptic cases, early detection, controlling blood pressure, loading $MgSO_4$, and rapid delivery in severe cases are very important. In our clinic, we follow the ISHPP guidelines for diagnosing and managing hypertensive

Table 2. Labor characteristics, fetomaternal outcomes, and NICU admission indications

		min-max			Median	n	%
Newborn's birth weight (g)		340.0	-	5165.0	2960.0		
APGAR 1		0.0	-	7.0	7.0		
APGAR 5		0.0	-	8.0	8.0		
Type of delivery	Vaginal Delivery					248	48.7%
	Cesarean					261	51.3%
Eclampsia	(+)					10	2.0%
HELLP syndrome	(+)					5	1.0%
Abruptio	(+)					15	2.9%
Intrauterin death	(+)					9	1.8%
NICU admission	(+)					175	34.4%
NICU Admission Indications							
Prematurity						76	14.9%
Hyperbilirubinemia						57	11.2%
RDS						16	3.1%
Sepsis						15	2.9%
TTN						43	8.4%
Pneumonia						12	2.4%
Hypoglycemia						2	0.4%
Other						49	9.6%

NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, TTN: transient tachypnea of the newborn, Min: minimum, Max: maximum

Table 3. Risk factors for preeclampsia

	Adjusted OR	95% CI
Age >40 years BMI >25 (kg/m^2)	1.54 2.8	1.1-2.3 1.8-4.7
Nulliparity	1.72	1.26-2.45
Smoking	1.20	0.7-2.20
Chronic hypertension	2.80	1.8-4.20
Assisted reproductive techniques	1.56	1.1-2.20
Prior preeclampsia	3.5	2.2-5.7

BMI: body mass index, OR: odds ratio, CI: confidence interval

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patients (8). Preeclampsia can occur alone or concurrently with other underlying risk factors and superimposed on chronic hypertension (9). The previously reported risk factors of preeclampsia, including maternal age, nulliparity, chronic hypertension, diabetes, multiple gestations, ethnicity, use of assisted reproductive techniques, prior preeclampsia history, and obesity, were confirmed as the independent predictors of preeclampsia. Although advanced maternal age is one of the risk factors of preeclampsia, it can also be observed in adolescent pregnancies (10). In this study, the mean age of the enrolled women was 28 years (range: 14-48 years). A study by Dağdeviren et al. (11) reported the mean age of 35 years in their population. They had never observed preeclampsia in patients younger than 17 years of age. Our rates of adolescent pregnancy were higher; thus, our mean age was younger.

Many complications such as maternal HELLP syndrome, abruption, disseminated intravascular coagulation, renal failure, cerebral hemorrhage, pulmonary edema, fetal intrauterine growth retardation, and intrauterine death may be observed (9,12,13). Eclampsia developed in 2% of our patient group, HELLP syndrome in 1%, and placental abruption in 2.9%. The patients who developed eclampsia (n=10) continued to receive $MgS0_4$ for 48 hours in the postpartum period. No eclamptic seizures were observed in the postpartum period. In 2020, Lai et al. (5) reported similar adverse maternal outcome rates. The definitive treatment of preeclampsia is terminating the pregnancy through delivery (2,14). When adverse events develop, the type of birth becomes, and their timing is crucial. Preeclampsia alone is not an indication for cesarean section. Overall, 48.7% of the patients in our study had a vaginal delivery, and 51.3% delivered through cesarean section. Başol et al. (15) and Dağdeviren et al. (11) also reported similar birth rates. However, the cesarean rates in our region and approach to the delivery methods affected these rates. Three out of the five patients who developed HELLP syndrome were followed up in the intensive care unit, while the other two were followed up with close monitoring. These patients were treated using $MgSO_4$, corticosteroids, antihypertensives, blood products, and supportive treatments.

In a study by Susilo et al. (16) determined that preeclampsia is an independent risk factor for a low 1st minute Apgar score. Asseffa and Demissie (17) reported a NICU admission rate of 11.1% among newborns of preeclamptic/eclamptic mothers, and Adu-Bonsaffoh et al. (18) reported a high rate of NICU admission in preeclampsia compared with other hypertensives disorders in pregnancy. Our NICU admission rate was 34%. Preterm delivery is one of the most critical complications of hypertensive disorders in pregnancy, and preterm babies are more likely to be admitted to the NICU than term infants (12). In our study, the most common reason for hospitalization in the NICU was prematurity (n=76, 14.9%). Our stillbirth rate was 1.8%, while those reported in the literature varied between 0.26% and 6%. In the review by Nicolaides, stillbirth rate was decreased to 0.26% with aspirin use (19). Low molecular weight heparin, folic acid, enoxaparin, PETN, yoga, and vitamin D alone or combined with calcium can be used to prevent preeclampsia and reduce fetomaternal complications (20).

Study Limitations

The limitations of our study include its retrospective nature, the fact that we present only descriptive data that we did not distinguish between primary and recurrent cesarean rates, and the lack of distinction between early and late-onset as well as mild and severe disease.

CONCLUSION

Hypertensive disorders in pregnancy are a significant health problem associated with preventable adverse maternal and fetal outcomes. Therefore, high-risk populations should be screened early and referred to a tertiary center when necessary. In addition, adverse perinatal outcomes could be decreased in experienced and well-equipped clinics. Finally, we require an international program to increase society's awareness toward the adverse perinatal outcomes of hypertensive disorders in pregnancy.

Ethics Committee Approval: İstanbul University of Health Sciences Ümraniye Training and Research Hospital Clinical Research Ethics Committee of approved the study (decision no: 386, date: 03.12.2020).

Informed Consent: Patient consent was not obtained because the study was conducted retrospectively.

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Evaluating Factors Associated with Radiation-induced Erectile Dysfunction After Stereotactic Radiotherapy

Stereotaktik Radyoterapi Sonrası Radyasyona Bağlı Erektil Disfonksiyon ile İlişkili Faktörlerin Değerlendirilmesi

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ABSTRACT

Objective: Erectile dysfunction (ED) is a common side effect of prostate cancer radiotherapy (RT). Stereotactic body RT (SBRT) is a highly conformal RT technique that utilizes ultra-hypofractionated RT with 4-5 fractions, but the effect of SBRT on sexual function remains uncertain. This study aimed to analyze the possible relationship between SBRT and ED in patients with clinically localized prostate cancer.

Methods: Between January 2013 and December 2019, the factors affecting ED were analyzed in 55 patients with preserved potency following SBRT +/− hormone therapy for low- to intermediate-risk prostate cancer. While planning RT, the penile bulb was delineated as an organ at risk (OAR) in the computed tomography scan. A total dose of 35-36.25 Gy was administered in five fractions of 7-7.25 Gy through alternating-day SBRT treatment with CyberKnife. Erectile function was assessed using the International Index of Erectile Function (IIEF-5) scale at baseline and 3 months, 1 year, and 2 years after SBRT. Groups were formed with respect to post-treatment potency, as measured by IIEF-5.

Results: The median patient age was 68.5 years, and the median follow-up duration was 58 months. After SBRT, 56.4% of the patients had preserved potency. Age and inclusion of the proximal seminal vesicles in the planning target volume (PTV) were significantly different between the potency groups in the univariate analysis (p=0.028 and p=0.036). In the multivariable analysis, the PTV and inclusion of the proximal third of the seminal vesicles in the PTV were significant in the development of ED (p=0.038 and p=0.020).

Conclusion: Although modern RT techniques are used in prostate cancer treatment, erectile function may be affected. Considering the complex mechanisms of ED, it would be erroneous to explain the decline in potency based only on dosimetric factors related to OAR doses.

Keywords: Erectile dysfunction, prostate cancer, radiotherapy, stereotactic body radiotherapy

ÖZ

Amaç: Erektil disfonksiyon (ED), prostat kanseri radyoterapisinin sıklıkla gözlenen bir yan etkisidir. Stereotaktik vücut radyoterapi (SBRT), ultrahipofraksiyone (UH)-RT 4-5 fraksiyonda uygulanan RT tekniğidir. SBRT'nin cinsel işlev üzerindeki etkisi halen tartışmalıdır. Bu çalışmanın amacı, klinik olarak lokalize prostat kanseri olan hastalarda SBRT ve ED arasındaki olası ilişkiyi analiz etmektir.

Yöntemler: Ocak 2013 ile Aralık 2019 arasında, düşük-orta riskli prostat kanseri tanısı nedeniyle SBRT +/- hormonoterapi tedavisi uygulanan ve tedavi öncesinde ED olmayan 55 hastada ED'yi etkileyen faktörler analiz edildi. RT planlanırken penil bulb (PB) riskli organ (OAR) olarak tanımlanmıştır. Hastalara fraksiyon başına 7-7.25 Gy, toplam doz 35-36.25 Gy/ 5 fraksiyon olacak şekilde Cyberknife ile gün aşırı SBRT uygulandı. Hastaların erektil fonksiyon durumu tedaviye başlamadan önce ve 3. ayda, 1. yılda ve 2. yılda IIEF-5 skorları kullanılarak değerlendirildi. Hastalar tedavi sonrası potens durumuna göre gruplandırıldı.

Bulgular: Ortanca hasta yaşı 68,5 yıl ve ortanca takip süresi 58 aydı. SBRT'den sonra hastaların %56,4'ünde erektil fonksiyon korunmuştur. Planlanan hedef hacime (PTV) proksimal seminal veziküllerin dahil edilmesi ve hasta yaşı tek değişkenli analizde potens olan ve olmayan gruplar arasında anlamlı olarak farklı bulundu (p=0,028 ve p=0,036). Çok değişkenli analizde, PTV'nin büyük olması ve PTV'ye seminal veziküllerin proksimal üçte birinin dahil edilmesi ED gelişimi açısından istatistiksel olarak anlamlı bulundu (p=0,038 ve p=0,020).

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ÖZ

Sonuç: Prostat kanser tedavisinde her ne kadar modern radyoterapi teknikleri kullanılsa da erektil fonksiyon etkilenebilmektedir. ED'nin karmaşık mekanizması göz önüne alındığında, potensteki düşüşü sadece risk altındaki organların aldığı dozlara bağlamak doğru olmaz.

Anahtar kelimeler: Erektil disfonksiyon, prostat kanseri, radyoterapi, stereotaktik beden radyoterapisi

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer among men worldwide (1). For clinically localized PCa, treatment options include active surveillance, radical surgery, external beam radiotherapy (EBRT), and brachytherapy with or without androgen-deprivation therapy (ADT) (2). SBRT is a form of high-precision conformal EBRT that allows for ultra-hypofractionation (UF) - RT of treatment over 1-5 fractions, and it has comparable efficacy and acceptable toxicities to conventionally fractionated EBRT (3). Based on the low alpha/beta ratio (1.5-3 Gy) in slowly growing PCa, UF-RT may be radiobiologically favorable in PCa treatment (4). Different image-guided RT techniques, such as the CyberKnife robotic radiosurgery system (Accuray, Sunnyvale, CA, USA), can be applied in UF-RT to deliver high-dose radiation with large fraction sizes to the target volumes without increasing the dose to adjacent healthy tissues (5). Prospective nonrandomized trials have reported benefits in terms of biochemical disease-free survival with this method that also resulted in similar levels of gastrointestinal and genitourinary toxicities when compared with UF-RT (6,7). Moreover, a large 5-year randomized trial reported that UF-RT was noninferior to conformal RT in terms of biochemical failure-free survival, overall quality of life, sexual functions, and late toxicity (8).

Nonetheless, erectile dysfunction (ED) is one of the most concerning toxicities following RT. In a meta-analysis, the incidence rates of radiation-induced ED following treatments such as brachytherapy alone, brachytherapy plus EBRT, and EBRT alone were 24%, 40%, and 45%, respectively. Comparatively, in surgical treatments, such as nerve-sparing radical prostatectomy, non-nerve-sparing radical prostatectomy, and cryosurgery, ED is observed in 66%, 75%, and 87% of the patients, respectively (9).

In a recently published meta-analysis, the 5-year prevalence of ED was approximately 50% after RT, but likelihood was dependent on patient age, baseline functions, and comorbidities (10). Furthermore, several studies have reported that ED risk increases with the administration of radiation to the erectile apparatus, particularly the penile bulb (PB) (11,12). However, a review found that no available evidence suggests that avoidance of critical erectile structures during RT was effective in the prevention of these effects (13).

Although veno-occlusive dysfunction of erectile tissues and hemodynamic alterations following RT have been documented, radiation-induced ED is related with more complex mechanisms and remains poorly understood (14). Radiation-induced ED is supposed to be associated with endothelial cell damage on erectile tissues and damage to the arterial supply of the corpora cavernosa regardless of age and comorbidities, in addition to combinations of neurological, vascular, and endocrine disorders (15). However, many studies have shown that decreasing PB dose alone does not directly reduce the incidence of ED, and studies have also suggested performing treatment planning with respect to organs at risk (OARs), such as the neurovascular bundle, internal pudendal artery, and prostatic plexus located posterior of the prostate (16,17).

In recent studies, the optimal RT modality for localized PCa treatment remains under investigation; however, modern RT techniques may reduce the incidence of ED by decreasing the RT volume received by critical structures, such as the PB or vasculature, which are normally exposed to high-dose RT (16,18). Thus, this study aimed to evaluate the factors affecting the incidence of ED in patients with PCa who received SBRT.

METHODS

Patient Selection

In this retrospective analysis, we evaluated 68 patients with histopathologically proven low- or intermediate-risk PCa according to the National Comprehensive Cancer Center (NCCN) guidelines (19), who received SBRT using the CyberKnife at our clinic, from January 2013 to December 2019. Eligible patients were selected according to the following criteria: cT1c-T2c N0 disease, Gleason scores of 6-7, and prostate-specific antigen (PSA) levels of <20 ng/mL. By contrast, those with previous pelvic RT, those who had undergone prostate surgery, and those with high-risk diseases were excluded.

The validated Turkish version of the 5-item International Index Erectile Function (IIEF-5) scoring system was administered before treatment in all 68 patients. Thirteen patients with severe and moderate ED (IIEF-5 ≤11) before RT were excluded from the study, while 55 patients with preserved potency were included to investigate ED following SBRT.

Patients were asked about comorbid diseases such as diabetes mellitus, hypercholesterolemia, or atherosclerosis, which are considered risk factors for ED. Smoking and alcohol consumption were also investigated. Patients receiving ADT were included in the study.

The study protocol was approved by the Ethics Committee of the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 369, date: 22.09.2020).

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Scoring of Erectile Function and Follow-ups

The IIEF-5 questionnaire was administered before RT (baseline) and on the 3rd, 12th, and 24th months after treatment. The IIEF-5 questionnaire is a diagnostic tool for ED, consisting of five items that are based on the ability to obtain erectile function and intercourse satisfaction. A total IIEF-5 score of 5-25 points can be obtained, and ED is divided into five categories: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and none (22-25) (20). After SBRT, 55 patients were subdivided into two groups according to sexual potency. One group consisted of patients with IIEF-5 > 11 (potent group), while the other consisted of those with IIEF-5 ≤ 11 (impotent group).

PSA and total testosterone levels were measured at baseline, at 1 month after treatment, and during follow-up visits every 3 months for the first 2 years and every 6 months thereafter.

Treatment Planning and Delivery

In patients with organ-confined PCa, 4-5 gold fiducial markers were placed transperineally into the prostate through transrectal ultrasonography. RT was delivered with a CyberKnife radiosurgical device with a 6-megavolt linear accelerator mounted on a robotic arm for real-time tracking. Treatment planning scanning was performed 1 week after fiducial markers were implanted to account for the risk of migration.

All patients underwent simulation with computed tomography (CT) with a comfortably full bladder and empty rectum in the supine position. An appropriate fixation device with knee and foot support was used. Planning CT scans were obtained at 1 mm thickness and were fused with magnetic resonance images. CT and magnetic resonance imaging (MRI) datasets were sent for contouring on the CyberKnife planning system. The target definition was based on CT in conjunction with MRI support for a more precise delineation of the anatomical configuration of the prostate, rectum, bladder, and PB. The Evolution of Radiation Therapy Oncology Group protocols were followed while contouring the OAR, such as the bladder, rectum, bowel, PB, and femoral heads (21). The PB was contoured according to the approach previously described by Wallner et al. (22) and evaluated with dose-volume histogram (DVH) analysis during treatment planning by the same radiation oncologists. Other erectile structures, such as the neurovascular bundle, corpora cavernosa, or internal pudendal arteries, were not specifically contoured.

The clinical target volume (CTV) for patients with low-risk ED included only the prostate, whereas the CTV for those with intermediate-risk ED included the prostate and the proximal third of the seminal vesicles. The PTV was defined as the CTV with an additional margin of 5 mm in all directions, except for the posterior direction, which was limited to 3 mm to reduce the risk of rectal toxicity. A total dose of 35-36.25 Gy was prescribed to 95% of the PTV and was administered in five fractions of 7-7.25 Gy through alternating-day treatment. After contouring, DVH was generated from the CyberKnife plan. The goal of the DVH analysis for the PB was to ensure that the volume receiving 30 Gy dosage was limited to <3 cc. The PTV coverage was assessed using the following parameters: PTV95% (PTV receiving 35-36.25 Gy) and the maximum and mean dose delivered to the PTV. V30 (volume of the PB receiving 30 Gy) and D2%, D25%, D50%, D75%, and D90% (mean dose to 90% of the PB) with the maximum and median doses of each DVH was calculated to obtain the delivered dose to the PB (Table 1).

ADT

The intermediate-risk group received luteinizing hormone-releasing hormone agonist as an ADT for 6 months so that the

Table 1. Patient characteristics

Characteristics		**n=55**
Age, mean ± SD (range)		68.56±7.26 (49-85)
Smoking		31 (56.4)
Comorbid disease, n=38 (69.1%)	HT	22 (40%)
	CAD	15 (27.3%)
	DM	5 (9.1%)
	COPD	5 (9.1%)
	Second primary cancer	4 (7.3%)
T score	T2a	35 (63.6%)
	T2b	14 (25.5%)
	T2c	6 (10.9%)
Gleason score	6 (3+3)	41 (74.5%)
	7 (3+4)	10 (18.2%)
	7 (4+3)	4 (7.3%)
D'amico classification	Low risk	25 (45.5%)
	Intermediate risk	30 (54.5%)
Total RT dose	3500	27 (49.1%)
	3625	28 (50.9%)
Initial PSA value	≤10	37 (67.3%)
	>10	18 (32.7%)
Prostate volume, mean ± SD		55.61±31.20
PSA value, mean ± SD		8.73±4.33
Testosterone value, mean ± SD		3,74±1.63
ADT usage		26 (47.3%)
Dosimetric parameters		**Median, (range)**
PB volume, cc		2.24 (0.49-22.58)
V30, cc		0 (0-2.08)
D%25, Gy		11.78 (2.43-37.33)
D%50, Gy		9.16 (2.11-34.48)
D%75, Gy		6.56 (1.75-30.31)
D%90, Gy		4.47 (160-26.73)
D%2, Gy		21.99 (2.80-40.21)
PBmean, Gy		10.11 (2.20-33.51)
PBmax, Gy		23.69 (2.91-40.91)

SD: standard deviation, HT: hypothyroidism, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, PB: penile bulb, PSA: prostate-specific antigen, RT: radiotherapy

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treatment was employed 3 months before RT as an neoadjuvant treatment and concurrent ADT in 3 months according to the NCCN recommendation (19). The low-risk group did not receive ADT.

Statistical Analysis

Categorical variables were presented as number (percentage). Continuous variables were presented with mean ± standard deviation or median (range) according to the normality of the distribution, which was checked using histograms and analytic methods (Shapiro-Wilk test). The change in IIEF-5 scores over time was analyzed with the Friedman test, and the Wilcoxon test was performed to test the significance of pairwise differences using the Bonferroni correction to adjust for multiple comparisons. Chi-square tests were used to compare the distributions of categorical characteristics between the potent and impotent groups after SBRT. The independent samples t-test was used to compare the differences in continuous variables between these two groups. Factors affecting ED were investigated with logistic regression analysis with impotency after SBRT (IIEF-5 score ≤11) as the dependent variable. Any variables demonstrating a p-value of <0.20 in the univariate analysis of the two groups were entered into the multivariable model. Hosmer-Lemeshow goodness-of-fit statistics was used to assess model fit. An overall p-value of <0.05 was considered to show significance. All statistical analyses were performed using the IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

In total, 68 patients with low- and intermediate-risk PCa treated with SBRT using the CyberKnife were included in the study. We examined the factors affecting ED in 55 (80%) patients who were sexually potent at presentation. The median follow-up was 58 (range, 24-78) months. The mean age was 68.6 years. Among these patients, 25 (45.5%) were classified in the low-risk group and 30 (54.5%) in the intermediate-risk group according to the NCCN guideline. ADT was applied in 47.3% of the patients because six patients in the intermediate-risk group refused ADT or the treatment was deemed to be contraindicated because of comorbidities. The characteristics of the patients are summarized in Table 1.

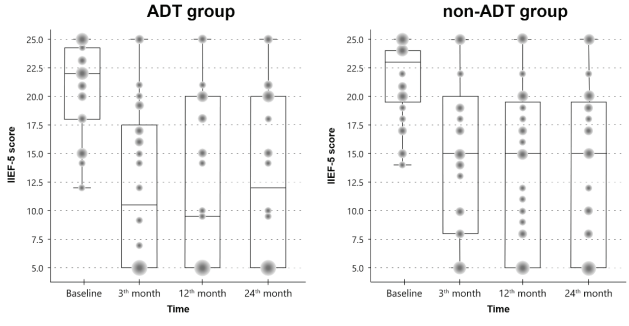

Figure 1. Box plots of the distribution and comparison of IIEF-5 scores with respect to hormone therapy

ADT: androgen-deprivation therapy IIEF-5: 5-item International Index Erectile Function

According to the IIEF-5 scores, 56.4% of the patients remained potent after SBRT. Sexual potency declined steadily throughout the first year of follow-up and plateaued at 12 months. None of the patients reported using sexual aids during the follow-up period.

The patients were followed for a minimum of 24 months after SBRT, and the IIEF-5 scores decreased after RT in all patients (p<0.001). When patients with and without ADT were analyzed separately, the IIEF-5 scores were significantly lower than values before RT and at the 3rd and 12th months in both groups (p<0.001 and p<0.001), regardless of ADT (Figure 1) (Table 2). No difference was found in IIEF-5 scores among the measurements at the 3rd, 12th, and 24th months after treatment.

Significantly larger PTV was observed in the impotent group. The proportion of the patients in whom the seminal vesicle was added to the target volume was higher in the impotent group. No significant differences were observed between the potent and impotent groups with respect to smoking, alcohol consumption, comorbidities (hypertension, diabetes mellitus, coronary artery disease, and chronic obstructive pulmonary disease), T-stage, administration of hormone therapy, and RT dose. No correlation was found between the ED and prostate volume, PB dose (mean or maximum dose), and dose distribution in the PB (Table 3).

In the univariate analysis, age and the inclusion of the proximal seminal vesicles in the PTV significantly associated with ED following SBRT (p=0.028, p=0.036). Smoking, ADT usage, comorbid diseases, RT dose, and PB doses were not significant. The multivariable analysis showed that the PTV and inclusion of the proximal seminal vesicles in the PTV were significantly associated with ED likelihood (p=0.038, p=0.020) (Table 4).

DISCUSSION

In this study, we evaluated 55 patients with PCa who, before SBRT, had no worse than moderate ED. These patients had undergone RT with or without ADT and attended follow-up for at least 1 year after RT. The use of ADT and the PB dose were not associated with ED, but logistic regression showed that the higher PTV and the inclusion of the proximal third of the seminal vesicle into the CTV were associated with ED.

Randomized trials comparing patients receiving UF-RT with those receiving conventional fractionation showed similar biochemical control rates and toxicity (gastrointestinal and genitourinary), while enabling the delivery of highly conformal RT (8,23). A study recommends a total dose of 35-36.25 Gy (BED = 70 Gy vs. 74 Gy, assuming alpha/beta of 3) given in five fractions (7-7.25 Gy), while utilizing image-guided RT techniques in SBRT (24). Besides gastrointestinal and genitourinary toxicity, ED is a known prevalent side effect of PCa treatment; however, research is limited with respect to data concerning sexual outcomes following SBRT (25).

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Table 2. Distribution and comparison of IIEF-5 scores in the overall group and with respect to hormone therapy

	IIEF-5 questionnaire	Median (range)	p value (Friedman test)	p value (Wilcoxon test)
Total (n=55)	Baseline	22 (12-25)	<0.001	<0.001[a]
	3rd month	14 (5-25)		<0.001[b]
	12th month	12 (5-25)		0.359[c]
	24th month	14 (5-25)		0.500[d]
with ADT (n=26)	Baseline	22 (12-25)	<0.001	<0.001[a]
	3rd month	10.5 (5-25)		<0.001[b]
	12th month	9.5 (5-25)		0.607[c]
	24th month	12 (5-25)		0.180[d]
non-ADT (n=29)	Baseline	23 (14-25)	<0.001	<0.001[a]
	3rd month	15 (5-25)		<0.001[b]
	12th month	15 (5-25)		0.138[c]
	24th month	15 (5-25)		0.593[d]

a: Baseline vs. 3rd month, b: Baseline vs. 12th month, c: 3rd month vs. 12th month d: 12th month vs. 24th month, ADT: androgen-deprivation therapy, IIEF-5: 5-item International Index Erectile Function

Studies that evaluated the relationships between ED and EBRT have shown decreased potency in patients with PCa (26,27). In the majority of the studies investigating radiation-induced ED, the PB/crura is considered an anatomic surrogate in which the application of high-dose RT can lead to ED (28,29), but a recent study found no relationship between ED and RT (30). However, previous studies have recommended limiting the mean dose to 95% of the PBV <50 Gy with conventionally fractionated EBRT (31,32). In the very recent CHHIP trial, the relationship between ED and dose to the PB indicated that the PB dose was predictive of ED development after RT - with a threshold mean dose of approximately 20 Gy (33). Recommended PB dose constraints for hypofractionated schedules have not been determined yet (34), and the standard fractionations stated in the Quantitative Analyses of Normal Tissue Effects in the Clinic review need to be validated using data from patients treated with different regimens (13). In the present study, only the PTV was related with ED incidence, regardless of the PB dose. Although the target volume and PTV margin reduction were enabled by SBRT and provided the capability to ensure that the PB volume of receiving 30 Gy did not exceed 3 cc, ED was detected in nearly half of the patients. This could be explained by the effects of dose variations delivered to the structures for erectile function; therefore, the effects of RT on ED appear to be associated with other factors in addition to previously shown relationships with the PB dose.

In contrast to gastrointestinal and genitourinary side effects, it is difficult to explain radiation-induced ED only with dosimetric factors linked to OAR doses after SBRT (35). Pretreatment baseline factors should be considered associated with ED. Attributing ED to only RT is difficult because erectile function is closely related with age and other comorbidities, such as cardiovascular disease, hypertension, diabetes, and behavioral risk factors (i.e., obesity, smoking, sedentary lifestyle, and alcohol consumption) (36). Some authors have also suggested that ED can be explained by the effects of post-RT ED (37). In a recent epidemiologic study, older patients were found to have experienced a decline in erectile functions similar to patients without PCa, while ED was observed in up to 44% of men aged 60-69 years (38). Consistent with epidemiological data, ED is expectedly seen in approximately half of the patients in this age group, regardless of RT; therefore, treatments should be tailored according to age groups and the current status of the patients (39). In the present study, age (>70 years) was observed as a significant variable associated with ED in the univariate analysis. Comorbidities and lifestyle habits were not identified as prognostic factors for ED following SBRT. Similarly, Dess et al. (37) found that other comorbidities were not significant factors for ED, except for older age.

ED was a common side effect in 60% of the patients at 2 years post-RT follow-up, and the largest decline in erectile function occurs within the first year after radiation-based treatments and increases with time, predominantly during the first 1-3 years (40,41). In recently published trials, decreased potency was observed in nearly 50% of the patients following SBRT, with the greatest decline seen during the first year after RT (37,42). This result is similar to our findings that 46.3% of our patients showed a decline in sexual potency following SBRT in the 3rd and 12th months. The follow-up period was not enough to analyze the factors associated with late sexual side effects and/or to assess the whole group in terms of changes or stabilization of erectile functions; therefore, these may be short-term ED outcomes in patients with PCa treated with SBRT. Despite these results, none of the patients used sexual aids before or after RT, and the most reliable explanations were the high cost of these treatments and no coverage by social health insurance.

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Table 3. Comparison of potent and impotent patients

	Potent (IIEF-5 > 11) n=31	Impotent (IIEF-5 ≤ 11) n=24	p-value
Age (>70 years)	9 (29%)	12 (50%)	0,112
Adding SV	14 (45.2%)	17 (70.8%)	0.057
ADT usage	14 (45.2%)	12 (50%)	0.721
Smoking	19 (61.3%)	12 (50%)	0.402
RT dose (3625 cGy)	17 (54.8%)	11 (45.8%)	0.437
Comorbid disease	20 (64.5%)	18 (75%)	0.404
HT	11 (35.5%)	11 (45.8%)	0.437
CAD	6 (19.4%)	9 (37.5%)	0.134
DM	3 (9.7%)	2 (8.3%)	0.863
COPD	3 (9.7%)	2 (8.3%)	0.863
Second primary cancer	3 (9.7%)	1 (4.2%)	0.435
	Mean ± SD	**Mean ± SD**	
PSA value	8.12±4.06	9.51±4.64	0.244
Testosterone	3.79±1.87	3.68±1.29	0.798
Prostate volume	63.11±31.21	65.05±42.53	0.714
PTV, cc	84.76±38.99	110.10±59.68	0.023*
PB volume, cc	3.08±3.78	2.31±1.19	0.298
PBmean, Gy	13,68±9.35	11,69±8.79	0.812
PBmax, Gy	23.65±12.80	20.76±11.57	0.675
D%2, Gy	22.23±12.80	18.98±11.85	0.624
D%25, Gy	17.05±11.34	14.26±10.84	0.651
D%50, Gy	13.03±9.66	11.20±9.17	0.835
D%75, Gy	10.04±8.36	8.82±7.40	0.598
D%90, Gy	8.51±7.38	7.37±6.17	0.302
V30, cc	0.29±0.56	0.19±0.46	0.406

*Significant result, ADT: androgen-deprivation therapy, IIEF-5: 5-item International Index Erectile Function, PSA: prostate-specific antigen, PB: penile bulb, SD: standard deviation, HT: hypothyroidism, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease

Patients who received ADT were not considered ideal in investigating the effect of RT on sexual outcomes, so they were excluded from most of the previous studies. In some studies, no significant difference was found in the erectile function results with the inclusion of the ADT group and no differences were found in the frequency or recovery of sexual potency in the RT alone or RT + ADT groups (43,44). Similarly, ADT had no significant effects on ED in the present study.

This study has several limitations. First, this was a retrospective study from a single center and included a limited number of patients. Therefore, patient characteristics and interpretations may be biased. Second, despite the promising results, data regarding long-term potency preservation after SBRT are lacking. Third, the method of ED measurement by using the IIEF-5 scoring system limited the findings because it is a patient-reported instrument, and this feature may affect the quantification of sexual function. Finally, other erectile structures, such as the neurovascular bundle, corpora cavernosa, or internal pudendal arteries, were not contoured specifically, and only the PB dose was evaluated as a critical component that could contribute to ED.

CONCLUSION

Although SBRT allows for delivery of highly conformal EBRT, related with risk reduction by avoidance of erectile tissues such as the PB, the risk for radiation-induced ED is similar to other radiation therapy techniques. It appears that explaining the decline in potency based only on dosimetric factors associated with SBRT may be erroneous. Therefore, sexual function is a multifactorial process and should be considered when evaluating ED. Radiation-induced ED will require more studies with high-quality data and sufficient follow-up.

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Table 4. Factors predicting erectile dysfunction

p-value		Univariate analysis			Multivariable analysis		
		Odds ratio	95% CI	p value	Odds ratio	95% CI	
Age (>70 years)	-	0.028*	3500	1.144-10.706	0.155	2.531	0.703-9.112
Inclusion of the seminal vesicle in PTV	-	0.036*	3.363	1.083-10.441	0.020*	4.806	1.275-18.121
ADT usage	-	0.522	1.417	0.488-4.115	-	-	-
Smoking	-	0.256	0.534	0.181-1.574	-	-	-
PSA value	-	0.319	1.066	0.940-1.209	-	-	-
Testosterone value	-	0.908	0.979	0.681-1.407	-	-	-
RT dose	-	ref			-	-	-
-	-	0.351	0.601	0.206-1.752	-	-	-
Comorbid disease	-	0.670	1.286	0.404-4.089	-	-	-
HT	-	0.581	1.357	0.459-4.012	-	-	-
CAD	-	0.189	2.250	0.670-7.555	0.115	2.995	0.764-11.734
DM	-	0.798	0.783	0.120-5.096	-	-	-
COPD	-	0.798	0.783	0.120-5.096	-	-	-
Second primary cancer	-	0.409	0.375	0.037-3.850	-	-	-
Prostate volume, cc	-	0.884	1.001	0.986-1.016	-	-	-
PTV, cc	-	0.072	1.011	0.999-1.023	0.038*	1.015	1.001-1.028
PB volume, cc	-	0.419	0.880	0.646-1.199	-	-	-
PBmean, Gy	-	0.623	0.861	0.475-1.562	-	-	-
PBmax, Gy	-	0.522	0.866	0.558-1.344	-	-	-
D2, Gy	-	0.469	0.851	0.551-1.316	-	-	-
D25, Gy	-	0.518	0.852	0.523-1.386	-	-	-
D50, Gy	-	0.695	0.892	0.503-1.582	-	-	-
D75, Gy	-	0.834	0.930	0.471-1.835	-	-	-
D90, Gy	-	0.806	0.906	0.412-1.991	-	-	-
V30, cc	-	0.503	0.963	0.863-1.075	-	-	-

*Significant result, ADT: androgen-deprivation therapy, PSA: prostate-specific antigen, PB: penile bulb, SD: standard deviation, RT: radiotherapy, PTV: planning target volume, CI: confidence interval, HT: hypothyroidism, CAD: coronary artery disease, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital (decision no: 369, date: 22.09.2020).

Informed Consent: Retrospective study.

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The Clinico-radiologic Evaluation and Risk Factor of Ventilator-associated Pneumonia in a Pediatric Care Unit of a Tertiary Center

Üçüncü Basamak Bir Merkezin Pediatrik Yoğun Bakım Ünitesinde Ventilatörle İlişkili Pnömoninin Risk Faktörleri ve Klinik-radyolojik Değerlendirmesi

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ABSTRACT

Objective: Ventilator-associated pneumonia (VAP) is the second most common form of hospital-acquired infection. Prediction of possible etiologic agents and initiation of appropriate and narrow-spectrum antibiotherapy is crucial to reduce morbidity and mortality. Clinical and radiologic variable analyses may help clinicians to foresee the usual cause of VAP.

Methods: This was a retrospective observational study evaluating the clinico-radiologic characteristics of VAP in a pediatric intensive care unit (PICU) of a tertiary referral university hospital between January 2011 and December 2016.

Results: A total of 1,323 patients in the PICU were followed during the study period, wherein 78 with a median age of 10 months (1-188) were detected to have VAP. Patients were divided into two groups according to the etiologic agents as gram-positive (n=16, 20.5%) and gram-negative VAP (n=62, 79.5%). Radiologic findings included peribronchial thickening (n=32, 41.0%), diffuse interlobular septal thickening (n=38, 48.7%), patchy infiltrate (n=54, 69.2%), consolidation (n=54, 69.2%), and pleural effusion (n=21, 26.9%). The presence of consolidation and pleural effusion were significantly more common among the patients with gram-positive VAP (p-values are 0.004 and 0.02).

Conclusion: Clinical and radiologic evaluation of patients may be a clue for the estimation of the microbiology of VAP, which is highly recommended before the initiation of empirical antibiotherapy.

Keywords: Ventilator-associated pneumonia, pediatric intensive care, clinico-radiologic evaluation

ÖZ

Amaç: Ventilatör ilişkili pnömoni (VİP), hastane kaynaklı enfeksiyonun ikinci en yaygın şeklidir. Olası etiyolojik ajanın öngörülmesi ve uygun, dar spektrumlu antibiyotik tedavisinin başlatılması, morbidite ve mortaliteyi azaltmak için çok önemlidir. Klinik ve radyolojik değişkenlerin analizi, klinisyenlerin VİP'nin olağan şüphesini önceden görmelerine yardımcı olabilir.

Yöntemler: Bu çalışma, Ocak 2011 ile Aralık 2016 arasında üçüncü basamak bir üniversite hastanesinin pediatrik yoğun bakım ünitesinde VİP'nin kliniko-radyolojik özelliklerini değerlendiren retrospektif bir gözlemsel çalışmaydı.

Bulgular: Çalışma süresi boyunca çocuk yoğun bakım ünitesinde 1.323 hastayı takip ettik. Ortanca yaşı 10 ay olan (1-188) 78 hastada VİP tespit edildi. Hastalar etiyolojik etkenlere göre Gram-pozitif (n=16, %20,5) ve Gram-negatif ilişkili VİP (n=62, 79,5). Radyolojik bulgular arasında peribronşiyal kalınlaşma (n=32, %41,0) olmak üzere iki gruba ayrıldı. Diffüz interlobüler septal kalınlaşma (n=38, %48,7), yamalı infiltrat (n=54, %69,2), konsolidasyon (n=54, %69,2) ve plevral efüzyon (n=21, %26,9). Konsolidasyon varlığı ve plevral efüzyon, Gram-pozitif ventilatör ilişkili pnömonisi olan hastalarda anlamlı olarak daha yaygındı (p değerleri; 0,004 ve 0,02).

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ÖZ

Sonuç: Hastaların klinik, risk faktörleri ve laboratuvar parametreleriyle birlikte radyolojik olarak değerlendirilmesi VİP'nin olası etkeninin öngörülmesinde fayda sağlayarak, uygun etkene yönelik antibiyoterapinin kısa sürede başlanmasına olanak tanıyabilir.

Anahtar kelimeler: Ventilatör ilişkili pnömoni, pediatrik bakım, kliniko-radyolojik değerlendirme

INTRODUCTION

Ventilator-associated pneumonia (VAP), which is defined as pneumonia occurring >48-72 h of mechanical ventilation (MV) is an important cause of nosocomial mortality (1) and is most common in adults and the second most common form of hospital-acquired infection (HAI) in the bloodstream of pediatric patients (2). The average risk of VAP is reported between 3% and 19% in children, with a cumulative incidence of 1.1-27.1 per 1,000 ventilator days (2-4). Together with VAP attributable mortality, which is nearly 13%, several reports also highlight the VAP-related undesirable outcomes, such as prolonged MV duration and length of hospital stay (LOS), economic burden, and tremendous healthcare work use (5-7).

Another unwanted consequence of increased VAP incidence is the emergence of resistant nosocomial pathogens. These patients require longer durations and several courses of antibiotherapy, thus pre-designed rational policies should be conducted in the facilities. Recent guidelines are recommended to utilize empiric antibiotherapy options of narrow-spectrum and shorter duration therapies to minimize the patient's exposure to unnecessary medicine and decrease antibiotic resistance rates (1). Dual gram-negative and empiric methicillin-resistant *Staphylococcus aureus* (MRSA) antibiotic regimens are suggested to be limited and selection should be patient-tailored. Therefore, possible etiologic agent prediction and appropriate initiation of narrow-spectrum antibiotherapy are crucial to reduce morbidity, mortality, and many other VAP-related complications. Clinical and radiologic variable analyses may help clinicians to foresee the usual causes of VAP. As far as we know; a very limited number of studies were reported that particularly investigated the relationship between radiologic characteristics and microbiology of VAP. Children's data are even rarer.

Proceeding from this point of view, the clinico-radiologic characteristics of pediatric patients who were diagnosed with VAP in a referral university hospital were evaluated.

METHODS

Study Design and Hospital Setting

This was a retrospective observational study evaluating the clinico-radiologic characteristics of VAP in a pediatric intensive care unit (PICU) of a tertiary referral university hospital between January 2011 and December 2016. Our PICU is a 6-bed unit, accepting complicated pediatric patients aged 1 month to 18 years old. It has 2, each with 3 patient beds, without an isolation room. The patient-to-nurse ratio is 2:1.

Medical records of patients were retrospectively evaluated using standardized surveys. Information regarding, age, gender, underlying disease, LOS before PICU admission, previous antibiotic use, duration and nature of MV (intubation/tracheostomy), antibacterial therapy regimen and duration, and clinical outcomes were recorded.

Laboratory and Microbiologic Evaluation

Laboratory evaluation included the results of complete blood count, C-reactive protein, and procalcitonin analyses that were ordered throughout the therapy. Microbiological culture reports of tracheal aspirate material (from the endotracheal tube and the tracheostomy cannula) of patients, together with antimicrobial susceptibility results, were recorded.

The tracheal aspirate specimen was initially investigated with gram stain; cultured in 5% sheep blood agar (Becton Dickinson, Germany) and chocolate agar (Oxoid, England) which was incubated in 5% CO_2 atmosphere; and cultured on Mac Conkey agar (Oxoid, England) and incubated in the normal atmosphere for 24-48 h. For anaerobic conditions, the GasPak system (Becton Dickinson, USA) was used. Isolated pathogens were identified with conventional methods (gram stain, catalase, oxidase, DNase, carbohydrate fermentation, urease effect, use of citrate, lysine decarboxylase, Voges Proskauer, motility and indole test, etc.).

Antimicrobial susceptibility was performed, according to the Clinical Laboratory Standards Institute (CLSI) recommendations, in Mueller Hinton agar (Oxoid, England) by the Kirby Bauer disc diffusion method. Minimal inhibitory concentration analysis was performed using E-test (bioMeriéux, France) and results were evaluated according to the CLSI criteria (8).

Definition of Terms

Since January 2010, infection control nurses assigned from the Hospital Infection Control Committee have performed active monthly surveillance of HAIs in PICU, with pediatric infectious disease specialists. VAP diagnosis was performed according to the Center for Disease Control and Prevention definition criteria (9). According to this, at least one of the following should be present: a new or progressive infiltrate; consolidation, cavitation, or pleural effusion evident on chest radiography, with at least one episode of fever (>38 °C) attributable to no other recognized cause; leukopenia [<4,000 white blood cells (WBC)/mm^3] or leukocytosis (≥12,000 WBC/mm^3); and at least two signs of new-onset purulent sputum (a change in sputum characteristics, an increased amount of respiratory secretion or in suctioning requirements, new-onset or worsening cough, dyspnea or tachypnea, rales or

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bronchial breath sounds, or a worsening gas exchange profile (i.e., O_2 desaturation; PaO_2/FiO_2 level ≤240), an increased oxygen requirement, or an increased ventilation need) (10).

VAP incidence was calculated as follows: (number of cases with VAP/total number of patients who received MV x100) = VAP rate per 100 patients.

The terms of the radiologic classification used the glossary of the Fleischner Society for thoracic imaging (11). Peribronchial thickening was defined as thin circular increased density, which was peribronchially observed. Interlobular septal thickening was accepted as affecting one of the components of the septa that might be responsible for the thickening and so render septa visible (Figure 1). Infiltrate was accepted as patchy opacification with undefined borders on chest X-ray and widespread ground glass appearance on computed tomography (CT) (Figure 2). Homogeneous dense lobar-segmental opacification with the air bronchogram and loss of silhouette sign on chest X-ray and lobar/segmental increased density on CT was defined as consolidation (Figure 3). Pleural effusion was defined as blunting of the costophrenic or cardiophrenic angle or a meniscus laterally seen and gently sloping medially (Figure 4).

Clinico-radiological characteristics between the gram-positive and gram-negative-related VAP were compared in the end.

Radiologic Evaluation

Radiologic modalities (chest X-ray and/or computerized thorax tomography), which were performed on the day of VAP diagnosis were evaluated by a pediatric radiologist from the hospital computer system. Findings were classified into 5 groups as a peribronchial thickening, interlobular septal thickening, patchy infiltrate (separate patchy opacification with uncertain borders), lobar/segmental consolidation, and pleural effusion.

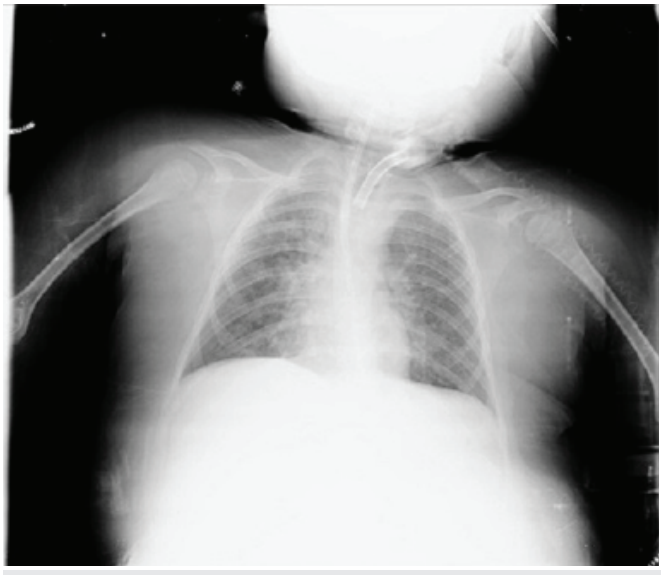

Figure 1. X-ray reveals "diffuse interlobular septal thickening" in both lungs

Statistical Analysis

Statistical analysis of data was performed using the statistical package for social science for Windows version 21.0 (SPSS 21.0, SPSS Inc. USA). Normality was assessed using the Shapiro-Wilk tests and histogram graphics. Data are presented as median,

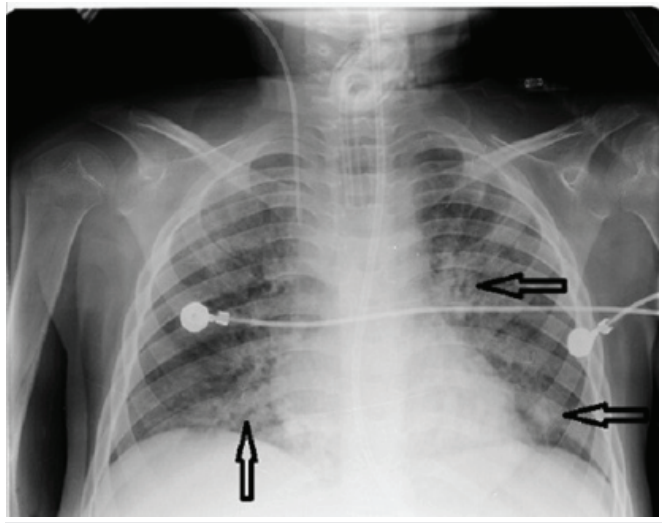

Figure 2. The X-ray revealed the scattered and patchy opacifications with uncertain borders that do not erase the contour of the heart or diaphragm representing an "infiltrate"

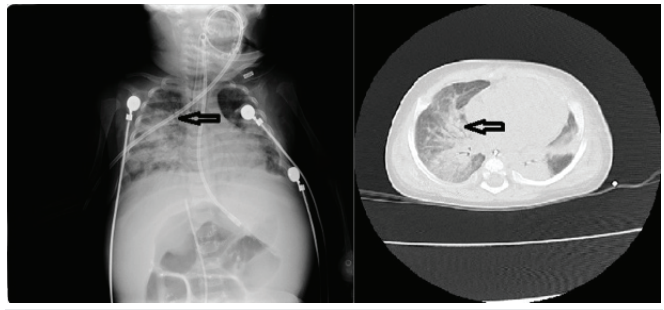

Figure 3. Lobar/segmental consolidations are detected on X-ray (right) and CT (left) of the lungs. Air-bronchograms are seen (arrows)

CT: Computed tomography

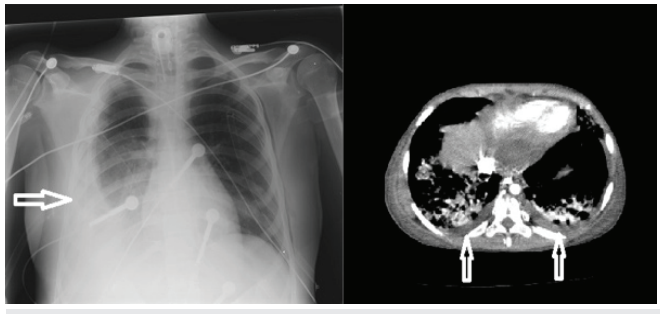

Figure 4. The pleural fluid is demonstrated on X-ray (right) and CT (left) (arrows)

CT: Computed tomography

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minimum, maximum, frequency, and percentage. Categorical variables between the groups were compared with the Pearson χ^2 test or the Fisher exact test when the expected cell size was <5. The Mann-Whitney U test was used for continuous variables, which are not normally distributed. All p-values are based on 2-tailed statistical analyses and a p-value of <0.05 was considered statistically significant. The significant predictors of gram-positive and gram-negative-related VAP with p≤0.05 in univariate analysis were fitted to perform a logistic regression analysis model to identify independent risk factors.

Ethical Committee and Informed Consent

This study was performed with the permission of the İstanbul University İstanbul Faculty of Medicine Clinical Research Ethical Committee (decision no: 772, date: 29.05.2018). This was a retrospective case-control study, thus informed consent was not obtained.

RESULTS

During the study period, a total of 1,323 patients attended to PICU, wherein 78 patients with the median age of 10 months (1-188) were detected to have VAP. Twenty-six patients (33.3%) were female. VAP incidence was 10.3/1,000 ventilator days. Patient characteristics were presented in Table 1.

Table 1. Characteristics of patients

Age [months, median (range)]	**10 (1-188)**
Gender, female, n (%)	26 (33.3)
PRISM score on PICU admission	9 (2-18)
Gram-positive organisms, n (%)	
MRCNS	9 (11.5)
MRSA	4 (5.1)
Streptococcus pneumonia	2 (2.6)
Corynebacterium spp	1 (1.3)
Gram-negative organisms, n (%)	
Pseudomonas aeruginosa	22 (28.2)
Acinetobacter baumannii	22 (28.2)
Kleibsiella pneumonia	6 (7.7)
Escherichia coli	1 (1.3)
Serratia marcescens	2 (2.6)
Stenotrophomonas maltophilia	9 (11.5)
LOS before PICU admission, d, mean ± SD	24 (10-128)
Length of PICU stay before the diagnosis of VAP, d, median (range)	28 (4-188)
Length of MV before the diagnosis of VAP, d, median (range)	14 (2-184)
Clinical outcome	
PICU mortality, n (%)	10 (12.8)
VAP cured	55 (70.6)
Tracheostomies	13 (16.6)

SD: standard deviation, PICU: pediatric intensive care unit, VAP: ventilator-associated pneumonia, MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase-negative *staphylococcus*

The patients were divided into two groups according to etiologic agents as Gram-positive (n=16, 20.5%) and Gram-negative-related VAP (n=62, 79.5%). The most common Gram-positive microorganism was methicillin-resistant coagulase-negative staphylococcus, whereas *Pseudomonas aeruginosa* and *Acinetobacter baumannii* were the most common Gram-negative bacteria (n=22, 28.2%). The etiologic distribution of VAP was shown in Table 1.

The most common cause of PICU admission was respiratory-related conditions (n=36, 46.2%), followed by neurologic conditions (n=21, 26.9%), post-operative follow-up (n=11, 14.1%), cardiovascular disorders (n=9, 11.5%), and decompensation of underlying metabolic disease (n=1, 1.3%). When admission diagnostic category was compared between Gram-positive and gram-negative-related VAP, no significant difference was achieved (Table 2).

Underlying chronic illnesses were noted in 59 (75.6%) patients, of which, the most common was chronic neurologic disorder (n=23, 29.5%). Gram-positive-related VAP was significantly more common among patients with chronic cardiovascular disorders (p=0.049). Possible risk factors for the development of VAP were compared between etiologic agents in Table 2. The history of surgery and thorax drainage were significantly more common in the Gram-positive-related VAP group (p-values are 0.038 and 0.026, respectively); whereas the incidence of rectal carbapenem-resistant *Klebsiella pneumonia* (CRKP) colonization was significantly higher in patients with gram-negative-related VAP (p=0.014). Empirical glycopeptide and carbapenem use were significantly higher in patients with gram-negative-related VAP (p-values are <0.001 and 0.001, respectively)

The mean LOS before PICU admission was 24 (10-128) days and the mean length of PICU stay before the diagnosis of VAP was 28 (4-188) days. The length of MV before the diagnosis of VAP was significantly longer among the patients with Gram-negative-related VAP [17 (4-184) days] compared with that of the Gram-positive ones [9 (2-33) days] (p=0.024). No significant difference was achieved in terms of laboratory variables between the two groups (p>0.05) (Table 2).

Radiologic findings included peribronchial thickening (n=32, 41.0%), diffuse interlobular septal thickening (n=38, 48.7%), patchy infiltrate (n=54, 69.2%), consolidation (n=54, 69.2%), and pleural effusion (n=21, 26.9%) (Figures 1-4). The presence of consolidation and pleural effusion were significantly more common among the patients with gram-positive-related VAP (p-values are 0.004 and 0.020, respectively).

A logistic regression analysis including the parameters with a p-value of <0.05 found in the univariate analysis was used. Empirical glycopeptide and carbapenem were found to be independent risk factors for the development of Gram-negative-related VAP, whereas the same applied to the presence of consolidation with Gram-positive-related VAP (Table 3).

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Table-2. Comparison of VAP according to etiologic microorganism

	Gram-positive	Gram-negative	p
Age [months, median (range)]	9 (1-190)	27 (2-157)	0.17
Comorbid conditions, n (%)	10 (62.5)	49 (79)	0.17
Chronic cardiovascular disease	5 (31.3)	7 (11.3)	**0.049**
Neurologic disorder	3 (18.8)	20 (32.3)	0.23
Metabolic disease	1 (6.3)	8 (12.9)	0.45
Chronic respiratory disease	-	2 (3.2)	0.63
Chronic kidney disease	-	5 (8.1)	0.30
Malignancy	-	2 (3.2)	0.63
Chronic liver disease	1 (6.3)	5 (8.1)	0.64
Admission diagnostic category, n (%)			
Respiratory	6 (37.5)	30 (48.4)	0.43
Cardiovascular	2 (12.5)	7 (11.3)	0.59
Neurological	5 (31.3)	16 (25.8)	0.66
Post-operative	3 (18.8)	8 (12.9)	0.40
Metabolic disorder	-	1 (1.6)	0.79
Risk factors			
Tracheostomy	3 (18.8)	5 (8.1)	0.20
Percutaneous endoscopic gastrostomy	1 (6.3)	2 (3.2)	0.50
Immunosuppression	2 (12.5)	5 (8.1)	0.44
Surgery	6 (37.5)	9 (14.5)	**0.038**
Renal replacement therapy	-	4 (6.5)	0.39
Central venous catheterization	15 (93.8)	62 (100)	0,2
Thorax drainage tube	3 (18.8)	1 (1.6)	**0.026**
Total parenteral nutrition	16 (100)	60 (96.8)	0.63
Rectal VRE colonization	4 (25.0)	20 (32.3)	0.40
Rectal CRKP colonization	2 (12.5)	28 (45.2)	**0.014**
Empirical antibiotic use before a diagnosis of VAP, n (%)			
Carbapenems	2 (12.5)	45 (72.6)	**<0.001**
Glycopeptides	9 (56.3)	58 (93.5)	**0.001**
Anti-pseudomonal penicillin	10 (62.5)	51 (82.3)	0.08
Aminoglycosides	11 (68.8)	51 (82.3)	0.19
Linezolid	-	6 (9.7)	0.23
LOS before PICU admission, d, mean ± SD	23 (10-94)	26 (12-128)	0.78
Length of PICU stay before the diagnosis of VAP, d, mean ± SD	24 (4-175)	32 (4-188)	0.44
Length of MV before the diagnosis of VAP, d, mean ± SD	9 (2-33)	17 (4-184)	**0.024**
Laboratory parameter, median (range)			
White blood cell count	14,600 (8,300-15,900)	11,340 (4,600-33,000)	0.99
Neutrophil count	10,000 (4,700-12,400)	7,000 (1,800-16,000)	0.61
Lymphocyte	3,800 (2,100-7,100)	2,050 (650-11,300)	0.98
CRP	307 (69-545)	90 (0.1-259)	0.52
PCT	14.1 (4.7-36)	1.2 (0.23-17.5)	0.27
Radiologic findings			
Peribronchial thickening	5 (31.3)	27 (43.5)	0.37
Diffuse interlobular septal thickening	9 (56.3)	29 (46.8)	0.49
Patchy infiltrate	13 (81.3)	41 (66.1)	0.24
Consolidation	14 (87.5)	30 (48.4)	**0.004**
Pleural effusion	8 (50)	13 (21)	**0.020**

*MRSA: methicillin-resistant *Staphylococcus aureus*, MRCNS: methicillin-resistant coagulase-negative *staphylococcus*, MV: mechanical ventilation, PICU: pediatric intensive care unit, S: standard deviation, VAP: ventilator-associated pneumonia, CRP: C-reactive protein, PCT: procalcitonin

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Table 3. Multivariate analysis of the risk factors in predicting the VAP etiology

Variable	p	Adjusted OR	95 CI
Carbapenems	0.010	30.6	2.25-416.7
Glycopeptides	0.031	10.7	1.25-93.1
Consolidation	0.045	3.2	1.05-12.3

CI: confidence interval, OR: odds ratio, VAP: ventilator-associated pneumonia

DISCUSSION

The National Healthcare Safety Network reports a steady decline in the VAP incidence in the United States; however, it is not valid for the low and middle-income countries, which range from 8.87 to 18.7/1,000 ventilator days (12-14). The incident reports from our country vary between different centers and between pediatric and adult ICUs. A multicenter study regarding patients in the adult ICU reports VAP incidence as high as 26.5/1,000 days, whereas the National Surveillance report of 2015 estimated a VAP incidence in PICUs as 4.7 patients per 1,000 ventilator days (15,16). A similar incidence was also reported by Şevketoğlu et al. (17) in their PICU study. Our VAP incidence was 10.3/1,000 ventilator days, which may be related to the complexity of our patients and the longer duration of PICU stay.

Most of the national and international reports highlight the dominance of Gram-negative etiology of VAP. Aerobic Gram-negative bacilli like *E. coli, Klebsiella pneumonia, Enterobacter* spp, *Pseudomonas aeruginosa* and *Acinetobacter* spp, and Gram-positive cocci (*S. aureus*, MRSA, and *Streptococcus* spp) constitute the majority of cases, whereas viruses and fungi are exceptional (18,19). The Extended Prevalence of Infection in Intensive Care study reported that 62% of the cases were related to gram-negative microorganisms (20). In our study cohort, consistent with previous reports, the majority of patients (79.4%) had Gram-negative-associated VAP. Empirical glycopeptide and carbapenem use were found to be independent risk factors for Gram-negative-related VAP. Similarly, rectal CRKP colonization incidence was higher among those patients. This may be related to the decomposition of intestinal microbiota, which is also more common in patients with longer PICU stay.

Recent guidelines recommended the initial antimicrobial therapy, including the coverage for *S. aureus, Pseudomonas aeruginosa,* and other gram-negative bacilli (1). MRSA coverage, in the first place, is not recommended unless there is an increased risk for MRSA, such as patients treated in units where the resistance of *S. aureus* isolates is >10-20% or unknown. The golden standard for diagnosis is bacterial growth; however, it requires a specific time, which is extremely important in the pediatric age group. Hopefully, newer molecular techniques will be developed and would be more widely used shortly (21). For all that, traditional methods, such as portable chest radiographs, may help to predict the etiologic agent in the early phase. Conventional radiology was used for the diagnosis of VAP in children for a long time. However, specific definitions, like consolidation or cavity formation, were used for the definition of VAP, other than estimating the etiologic agent.

Several reports defined the radiologic differences between viral and bacterial agents or characteristic imaging findings for specific pathogens (22-24). Okada et al. (22) reported that ground-glass attenuation and bronchial wall thickening on CT were demonstrative for *Pseudomonas aeruginosa*-related pneumonia. Another study of the same facility found that pleural effusion was significantly more frequent in patients with MRSA pneumonia than those with MSSA pneumonia (24). Our literature research in the English language could not reveal any study evaluating the differences between the Gram-positive and negative etiology of VAP. In our study, the presence of pleural effusion and consolidation were higher among the patients with Gram-positive microorganisms, which can be accepted as an important finding since the interpretations were performed by a pediatric radiologist. There is an instructive report, which is pointing the importance of specialist evaluation since opinions between clinicians and radiologists are contradicting, particularly for the discrimination of atelectasis and consolidation (25). Therefore, we highly recommend to the consulate conventional radiographs with a specialist if possible.

The onset of VAP may also be important for the estimation of the etiologic agent. Some investigators found that MSSA was the major bacterium grown in early VAP cases (the cases occurring within 4 days of MV), whereas MRSA and *Acinetobacter baumannii* were the most common bacteria in late VAP, which others declared no specific correlation (26,27).

Compatible with former studies, the median length of MV in our study cohort was significantly more common among the patients with gram-negative-related VAP. In addition, the history of surgery, thorax drainage tube, and presence of chronic cardiovascular disorders were higher in the gram-positive-related VAP group. Therefore, empirical antibiotherapy with broadened gram-positive coverage, including MRSA, may be recommended in cases with formerly specified risk factors.

Study Limitations

Study limitations include the retrospective design of the study, relatively small number of patients and third-level center, high presence of underlying chronic disease, and long hospital stays in patients, which affect the heterogeneity in the study cohort.

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CONCLUSION

In conclusion, clinical and radiologic evaluation of patients may be a clue for the estimation of the microbiology of VAP, which is highly recommended before the initiation of empirical antibiotherapy.

Ethics Committee Approval: This study was performed with the permission of the İstanbul University İstanbul Faculty of Medicine Clinical Research Ethical Committee (decision no: 772, date: 29.05.2018).

Informed Consent: This was a retrospective case-control study, thus informed consent was not obtained.

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Meme Kanserli Hastalarda Aksiller Evrelemede Preoperatif Ultrasonografi ve Ultrasonografi Eşliğinde İnce İğne Aspirasyon Biyopsisinin Güvenilirliğinin Değerlendirilmesi

Evaluation of the Reliability of Preoperative Ultrasonography and Ultrasonography-guided Fine Needle Aspiration Biopsy in Axillary Staging in Patients With Breast Cancer

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ÖZ

Amaç: Çalışmamızın amacı meme kanseri tanısı ile aksiller ultrasonografi (AUS) ve ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi (US-İİAB) yapılan hastalarda bu yöntemlerin doğruluğunu değerlendirerek klinik olarak aksillanın negatif olduğu hasta grubunda sentinal lenf nodu biyopsisi (SLNB) ve/veya aksiller lenf nodu diseksiyonunun ihmal edilebileceği bir grup olup olmadığını araştırmaktır.

Yöntemler: Çalışmaya Ocak 2013-Nisan 2020 tarihleri arasında meme kanseri tanısı ile AUS ile değerlendirilen ve şüpheli lenf noduna US-İİAB yapılan hastalar dahil edilmiş, tedaviye neoadjuvan kemoterapi (NAK) ile başlanan hastalar çalışmadan dışlanmıştır. AUS ve US-İİAB'nin sensitivite, spesifisite, pozitif prediktif değer (PPD), negatif prediktif değer (NPD) ve doğruluğu hesaplanıp bunu etkileyen faktörler değerlendirilmiştir.

Bulgular: Çalışmaya katılan hastaların yaş ortalaması 51,1±10,76 idi. Ortalama tümör boyutu 18,84±9,87 mm olarak bulundu. AUS ile görüntülemede benign olduğu düşünülen 95 hastanın 14'ünde (%14,74) final patolojik değerlendirmede makrometastaz görülürken, şüpheli veya malign görüntü özelliklerine sahip 20 hastanın 8'inde (%40) final patolojide makrometastaz mevcuttu. US-İİAB ile aksiller metastaz düşünülen hastalar NAK'ye yönlendirilip çalışmadan dışlandıkları için US-İİAB ile değerlendirilip metastaz düşünülmeyen 25 hasta çalışmaya dahil edildi ve başlangıçta İİAB ile metastaz düşünülmeyen bu hastaların 8'inde (%32) final patolojide makrometastaz saptandı. US sensitivite %36,36, spesifisite: %87,10, PPD: %40, NPD: %85,26 ve doğruluk: %77,39 iken, US-İİAB için spesifisite: %100, NPD: %68,00 ve doğruluk: %68 idi. Palpe edilen lenf nodu varlığı yalancı pozitiflik üzerine etkili bir faktör olarak değerlendirildi (p<0,05).

Sonuç: Deneyimli kişilerce uygulanan AUS ve US-İİAB aksiller hastalığı dışlamada değerli bir yöntemdir. Ancak günümüz şartlarında aksillayı değerlendirmek için SLNB yapılması halen standart yöntem olarak kalmaya devam etmektedir.

Anahtar kelimeler: Meme kanseri, aksiller ultrasonografi, ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi

ABSTRACT

Objective: Our study aimed to evaluate the accuracy of axillary ultrasonography (AUS) and ultrasonography-guided fine-needle aspiration biopsy (US-FNAB) methods in patients diagnosed with breast cancer. In addition, to investigate the group that does not need sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection among the clinically negative axilla patients.

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ABSTRACT

Methods: The patients diagnosed with breast cancer and an AUS scan with US-FNAB to the suspected lymph node between January 2013 and April 2020 were included, and the patients whose treatment started with neoadjuvant chemotherapy were excluded. Sensitivity, specificity, positive predictive value (PPD), negative predictive value (NPD), and accuracy of AUS and US-FNAB were calculated, and the factors affecting were evaluated.

Results: The mean age of the patients in the study was 51.1±10.76 years. The mean tumor size was 18.84±9.87 mm. While 14 of 95 patients (14.74%) considered benign with AUS had macrometastases in the final evaluation. In addition, 8 (40%) of 20 patients with suspicious or malignant image features had macrometastases. Twenty-five patients evaluated with US-FNAB but did not detect metastasis were included. However, 8 (32%) of these patients who were not initially considered for metastasis by FNAB had macrometastases in the final pathology. While US sensitivity was 36.36%, specificity: 87.10%, PPD: 40%, NPV: 85.26%, and accuracy: 77.39%, specificity for US-FNAB was 100%, NPV: 68.00%, and accuracy: 68%. The presence of palpable lymph nodes was observed as a factor in false positivity ($p<0.05$).

Conclusion: AUS and US-FNAB applied by experienced staff are valuable methods in excluding axillary disease. However, SLNB remains the standard method to evaluate the axilla nowadays.

Keywords: Breast cancer, axillary ultrasonography, ultrasonography-guided fine-needle aspiration biopsy

GİRİŞ

Meme kanseri dünya genelinde milyonlarca kadını etkiler. Yapılan araştırmalarda 2020 yılında 2,3 milyon yeni meme kanseri olgusu bildirilmiştir (1). Erken evre tümörlerde moleküler subtipe de bağlı olarak tedaviye cerrahi ile başlansa da, lokal ileri evre tümörlerde veya aksiller lenf nodu tutulumu varsa başlangıç tedavisi neoadjuvan kemoterapi (NAK) olmaktadır (2). Tedavi kararını belirlemedeki en etkili faktörler; tümör boyutu, aksiller lenf nodu tutulumu ve moleküler subtiptir. Aksiller lenf nodu tutulumu tedavi seçeneğini etkilemek dışında halen en önemli prognostik faktörlerdendir (3).

Geleneksel yaklaşımda meme kanseri tedavisinde aksiller lenf nodu diseksiyonu (ALND) çok uzun süre kullanılsa da, erken evre ve aksilla klinik negatif meme kanserli hastalarda güncel yaklaşım sentinel lenf nodu biyopsisidir (SLNB) (2,4). ALND ile palpe edilen lenf nodu olan hastaların %70'inde ve palpe edilen lenf nodu olmayan erken evre hastaların %90'ında gereksiz diseksiyon yapıldığı bildirilmiştir (5). Ayrıca aksiller nodal tutulumu değerlendirmek için daha az invaziv bir metot olan SLNB ile nodal tutulum olmadığı anlaşılan hastalarda ALND'nin lenfödem, sinir hasarı ve omuz disfonksiyonu gibi morbiditelerinden kaçınılabilir (6).

Bir yandan görüntüleme tekniklerinin aksiller metastazı saptamada sensitivitesinin yetersiz olduğu düşünülse de diğer yandan son yıllarda yapılan bazı çalışmalarda aksiller ultrasonografi (AUS) negatif iken SLNB'nin gerekliliği değerlendirilmeye başlanmıştır (7). 2017 yılında yayınlanan bir çalışmada erken evre (T_{1-2} N_0) meme kanserli hastalar arasında AUS ile lenf nodu tutulumu düşünülmeyen gruptakiler SLNB ve non-SLNB olarak randomize edilmiş ve ortalama 17 aylık takip ile klinik olarak anlamlı aksiller nüks olmadığı görülmüştür (8). Yine benzer şekilde prospektif olarak dizayn edilen ve halen devam eden SOUND çalışmasında ≤2 cm, aksilla klinik negatif olup meme koruyucu cerrahi planlanan hastalar SLNB ve non-SLNB olarak randomize edilmiş ve bu çalışma ile preoperatif görüntülemenin aksiller nodal yükü belirleyebileceği düşünülmüştür (9).

Yapılan çalışmalarda preoperatif aksiller nodal yükü belirlemede, sensitivite ve spesifite sırası ile AUS için %56,6-92 ve %81-100 arasında ve ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi (US-İİAB) için %39,5-71 ve %95,7-100 arasında bildirilmiştir (10-12).

Ayrıca AUS ve US-İİAB için yalancı negatiflik (YN) oranları da SLNB ile yakın sonuçlar göstermektedir (13).

Bu çalışmaların varlığı gereksiz müdahaleleri önlemek için AUS ve US-İİAB'nin güvenilirliğini tekrar sorgulamamıza neden oldu. Bu amaçla hastanemizde erken meme kanseri tanısı aldıktan sonra AUS ve US-İİAB ile değerlendirilip daha sonra ameliyatta SLNB ve/veya ALND yapılan hastaları karşılaştırarak bu yöntemlerin sensitivite, spesifisite, pozitif prediktif değer (PPD), negatif prediktif değer (NPD) ve doğruluğunu hesaplamayı, aynı zamanda klinik olarak aksillanın negatif olduğu hasta grubunda SLNB'nin ihmal edilebileceği bir grup olup olmadığını araştırmayı amaçladık.

YÖNTEMLER

Hasta Grubu

Retrospektif olarak tasarlanan bu çalışmada, hastanemizin bağlı bulunduğu Gaziosmanpaşa Eğitim ve Araştırma Hastanesi Etik Kurul Komitesi'nden etik kurul onayı alındı (onay numarası: 267 tarih: 05.05.2021). Kimliği gizlenmiş idari verilerin geriye dönük kullanımı nedeniyle hasta bilgilendirilmiş onayına gerek görülmedi. Çalışmaya Ocak 2013-Nisan 2020 tarihleri arasında meme kanseri tanısı aldıktan sonra cerrahi tedavi öncesi AUS ile değerlendirilen ve aksilladaki şüpheli lenf noduna US-İİAB yapılan 115 hasta dahil edildi. Cerrahi tedaviyi kabul etmeyen ve lokal ileri meme kanseri tanısı ile tedaviye NAK ile başlanan hastalar çalışmaya dahil edilmedi.

Hastaların yaş, fizik muayene (uzman meme cerrahları tarafından yapılan değerlendirme), tıbbi hikaye, meme US bulguları, meme ve aksilla biyopsisi ile final patoloji sonuçları tıbbi kayıtlardan retrospektif olarak derlendi.

Çalışma Tasarımı

Hastalar preoperatif US bulguları, US-İİAB bulguları ve final patoloji sonuçları üzerinden değerlendirildi. Aksiller lenf nodlarının hem US, hem de US-İİAB ile metastaz açısından değerlendirilmesi final patoloji ile karşılaştırılarak sensitivite, spesifite, PPD, NPD, YN, yalancı pozitiflik (YP) ve doğruluk ayrı ayrı hesaplandı ve iki yöntem

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bu değerler açısından karşılaştırıldı. US-İİAB ile malign olduğu düşünülen hastalar NAK için yönlendirildiğinden bu grupta sadece sitopatolojik olarak benign tanısı alan hastalar çalışmaya dahil edildi.

Görüntüleme Metotu ve Görüntü Analizi

Ultrason muayeneleri, 5-14 MHz lineer dizilimli prob ile Toshiba Aplio 500 yazılım sürümü 6.0 (Toshiba Corporation, Tokyo, Japonya) olan ultrason cihazı kullanılarak meme görüntülemede 10 yıllık deneyime sahip deneyimli iki radyolog (N.U. ve Y.K.) tarafından yapıldı. Ultrasonografik olarak yapılan değerlendirmede diffüz, ince hipoekoik korteksi (<3 mm) ve santral yağlı hilumu olan hiperekoik lenf nodları benign olarak değerlendirilirken, asimetrik fokal veya diffüz kortikal kalınlığı olan (>3 mm), lobule konturlu, deri altı dokuya göre hipoekoik/anekoik kortekse sahip veya oblitere olan, ayrıca yağlı hilumu distorsiyone olan ve net görülemeyen lenf nodları şüpheli-malign olarak değerlendirildi (14).

Biyopsi Metotu

AUS ile yapılan değerlendirmede metastaz açısında şüpheli veya malign görünümlü lenf nodlarına aynı radyoloji uzmanları (N.U. ve Y.K.) tarafından US-İİAB uygulandı. US eşliğinde İİAB, 21 G'lik şırınga ile korteksin en kalın veya fokal olarak kalınlaşmış kısmından birkaç kez yapıldı. Sitopatolojik sonuçlar metastaz açısından negatif, atipik sitoloji, pozitif ve yetersiz olarak gruplandırıldı. Atipik sitoloji pozitif gruba dahil edilirken yetersiz olarak değerlendirilen örnek istatistiksel değerlendirmede negatif gruba dahil edildi.

Sentinal Lenf Nodu Biyopsisi

Tümörün drene olduğu ilk lenf nodu sentinel nod olarak adlandırıldı. AUS bulgularında metastaz düşünülmeyen hastalara ve US-İİAB sonucu benign-yetersiz olarak değerlendirilen hastalara peroperatif SLNB ile değerlendirme yapılıp aksiller diseksiyon kararı yapılan SLNB sonucuna göre belirlendi. SLNB tekniğinde tüm hastalara mavi boya yöntemi ile (isosülfan blue dye) ile görüntüleme tercih edildi. Yöntemde anestezi indüksiyonu sonrası; 5 cc %1 isosülfan blue subareolar dokuya enjekte edildikten sonra memeye beş dakika masaj yapılıp ardından meme koruyucu cerrahi yapılan hastalarda aksiller insizyonla, mastektomi yapılan hastalarda ise üst flep kesisi ile aksillaya girilip mavi boyalı lenf nodları ve eğer varsa şüpheli olarak palpe edilen lenf nodları çıkartılarak histopatolojik olarak değerlendirildi. Peroperatif yapılan değerlendirmede SLNB sonucunda aksiller metastaz düşünülen hastalara ve isosülfan blue enjeksiyonu sonrası aksillada mavi boyalı lenf nodu bulunamayan hastalara aksiller metastazı atlamamak için ALND yapıldı.

Histopatolojik Değerlendirme

Histopatolojik değerlendirme final patoloji sonucu üzerinden yapıldı. İncelemede tüm sentinal lenf nodları formalinde fikse edilip ikiye bölündü ve parafine gömüldü. 50-150 µm aralıklar ile minimum 6 seviye kesildi. Patolojik değerlendirme hemotoksilen-eosin ve immünohistokimyasal boyama ile yapıldı. Meme rezeksiyon materyallerinin histopatolojik değerlendirilmesi en büyük tümör çapı, histopatolojik tanı, histolojik derece, östrojen, progesteron, Ki-67 ve insan epidermal büyüme faktör reseptörü-2 (HER-2) durumları açısından incelendi. Histolojik derece belirlenmesinde Bloom-Richardson sistemi Nottingham modifikasyonu kullanıldı. Tümör evresi 2017 AJCC Kanser Evreleme Kılavuzu 8. baskısına ve 2019 CAP Kılavuzu'na göre değerlendirildi (15,16).

Aksilla için yapılan değerlendirmede makrometastaz varlığı pozitif kabul edilirken, benign histopatolojik özellikteki lenf nodları, makrometastaz saptanmayan olgular, mikrometastaz ve izole tümör hücresi varlığı negatif olarak değerlendirildi. Ancak negatif kabul edilen olguda mikrometastaz varlığı ayrıca belirtildi. Metastatik lenf nodunun boyutu ve çapı değerlendirmeye dahil edildi.

İstatistiksel Analiz

Sürekli değişkenlerin normallik kontrolü Shapiro-Wilk ile değerlendirilmiştir. US'nin final patoloji sonucuna göre elde edilen doğru pozitif, doğru negatif, yanlış pozitif ve yanlış negatif kararlarına göre yaş ve tümör boyutu için verilerin normalliğine bağlı olarak One-Way ANOVA ve Kruskal-Wallis testleri uygulanmıştır. US-İİAB'nin final patoloji sonucuna göre elde edilen doğru negatif ve yanlış negatif kararlarına göre yaş ve tümör boyutu için verilerin normalliğine bağlı olarak Student's t-test, Mann-Whitney U testi kullanılmıştır. Kategorik değişkenlerin analizinde ise chi-square test (Pearson chi-square) ve Fisher's exact test kullanılmıştır. US ve US-İİAB'nin final patoloji sonucuna göre diagnostik değerlerinin incelenmesinde sensitivite, spesifisite, PPD, NPD ve doğruluk değerleri hesaplanmıştır.

BULGULAR

Çalışma, dahil etme kriterlerine sahip 115 meme kanserli hasta üzerinden yapıldı. Tüm hastalar AUS ile değerlendirilmiş ve 25 hastaya US-İİAB yapılmıştı. Hastaların ortalama yaşı 51,1±10,76 olarak hesaplandı. Ortalama tümör boyutu 18,84±9,87 mm idi. Çalışmaya dahil edilen hastaların 15'inde (%13,04) aksillada palpe edilen lenf nodu vardı. Hastalara ait demografik veriler ve tümör özellikleri Tablo 1 ile gösterildi.

AUS ve US-İİAB ile Değerlendirme Sonuçları

AUS ile yapılan değerlendirmede hastaların 95'inde (%82,60) aksiller lenf nodları benign (negatif) olarak değerlendirilmiş, 20 hastada (%17,40) şüpheli ve malign özellikte lenf nodu görülmüştü. US ile aksiller lenf nodları benign olarak değerlendirilen 95 hastanın 81'inde (%85,26) final patolojide negatif idi [72'sinde (%75,79) benign histopatolojik bulgular, 9 hastada (%9,47) mikrometastaz mevcuttu]. US ile aksiller lenf nodları benign olarak değerlendirilen 95 hastanın 14'ünde (%14,74) ise final değerlendirmede aksiller metastaz saptandı. US ile şüpheli veya malign görüntü özelliklerine sahip 20 hastanın 8'inde (%40) final patolojide makrometastaz varken ve 12'sinde final patoloji negatif idi [2'sinde (%10) mikrometastaz ve 10'unda (%50) benign histopatolojik bulgular]. US ve ek olarak manyetik rezonans görüntüleme ile şüpheli olarak değerlendirilen 25 (21,73%) hastaya US-İİAB ile örnekleme yapılmıştı. US-İİAB ile malign olarak

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değerlendirilen hastalar NAK'ye yönlendirilmiş ve biyopsi yapılıp preoperatif histopatolojik değerlendirme ile benign olduğu düşünülen 25 hastanın final patoloji değerlendirmesi yapıldığında, 8'inde (%32) makrometastaz saptanırken, 17 (%68) hasta final patolojide negatif olarak değerlendirilmişti [14 (%56) hastada benign histopatolojik bulgular ve 3 (%12) hastada mikrometastaz]. US-İİAB sonrası hiçbir hastada komplikasyon görülmemişti. US ve US-İİAB için sensitivite, spesifisite, PPD, NPD ve doğruluk oranları Tablo 2 ile gösterildi.

Tablo 1. Hastalara ait demografik veriler ve tümör özellikleri

Hasta özellikleri	**Ortalama ± SS (min-maks)**
Yaş (yıl)	51,1±10,76 (25-80)
Tümör boyutu (mm)	18,84±9,87 (5-60)
ALN boyutu (mm)	13,17±7,18 (0-34)
Tümöre ait özellikler	**n (%)**
Tümör yerleşimi	
Üst dış kadran	59 (51,3)
Alt dış kadran	16 (13,9)
Üst iç kadran	19 (16,5)
Alt iç kadran	14 (12,2)
Merkezi	0 (0)
Multisentrik	7 (6,1)
Tümör tipi	
İnvazif duktal kanser	79 (68,7)
İnvazif lobuler kanser	12 (10,4)
Diğerleri	24 (20,9)
Moleküler subtip	
Luminal A	55 (47,8)
Luminal B	46 (40)
HER-2 zengin	6 (5,2)
Üçlü negatif	8 (7)
T-evresi	
T_{is}	0 (0)
T_1	68 (59,6)
T_2	43 (37,7)
T_3	3 (2,6)
T_4	0 (0)
Tümör derecesi	
G1	14 (12,6)
G2	74 (66,7)
G3	23 (20,7)
Aksiller US	
Benign	95 (82,6)
Malign	20 (17,4)
US-İİAB	
Malign	25 (21,7)
Final patoloji	
Benign	82 (71,3)
Mikrometastaz	11 (9,6)
Makrometastaz	22 (19,1)

SS: standart sapma US: ultrasonografi, US-İİAB: ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi, HER-2: insan epidermal büyüme faktör reseptör 2, min: minimum, maks: maksimum

Tedavi üzerine etkisi açısından sonuçları değerlendirirsek, US ile metastaz düşünülmeyen hastaların %14,74'ünde metastaz saptanmış, US-İİAB ile benign olarak tanı alan hastaların ise %32'sinde final patoloji malign olarak değerlendirilmişti.

Final patoloji ile US ve final patoloji ile US-İİAB arasında doğruluğu etkileyen faktörlere baktığımızda; palpe edilen lenf nodu varlığında hem gerçek pozitiflik (GP), hem de YP lenf nodu palpe edilmeyen hastalara göre daha yüksek oranda, gerçek negatiflik (GN) ise daha düşük oranda saptanmıştı ($p<0,05$). GP hastalarda tümör boyutları YP ve GN olanlara kıyasla daha yüksek gözlenmişti ($p<0,05$). Tümör boyutu ve aksillada palpe edilen lenf nodu olması YN üzerine etkili faktörlerdi. Bulgular Tablo 3, 4 ile gösterildi.

TARTIŞMA

ALND uygulamalarından sonra 1991 yılında Giuliano ve ark. (17) tarafından SLNB'nin uygulanmaya başlaması büyük bir gelişme olarak yorumlanmıştır ve zamanla SLNB N_0 meme kanserli hastalarda bölgesel lenfatik değerlendirme için standart olmuştur (18).

Yapılan çalışmalara baktığımızda aksiller hematom, lenfödem, omuz hareket kısıtlılığı ve parestezi gibi postoperatif yan etkilerin SLNB uygulanan grupta ALND yapılan gruba göre daha az görüldüğü bildirilmiştir (19,20). Yine de SLNB tamamen masum bir yöntem değildir. YN oranı genel olarak %10'un altında olarak bildirilen bu yöntemde hastaya ikinci bir ameliyat gerekliği ortaya çıkmaktadır (21,22). Ayrıca hastaneye yatış gerekmekte ve postoperatif dönemde enfeksiyon, lenfödem, seroma, sinir hasarı ve omuz hareket kısıtlılığı ALND'ye göre daha az da olsa görülebilmektedir (23).

Aksiller diseksiyon sonrası SLNB'nin doğruluğunu değerlendiren bir çalışmada doğruluk %96,9, sensitivite %91,2, spesifisite %100 ve YN %8,8 olarak bulunmuştur (19).

Giderek daha az invaziv metotların uygulanmaya konması, SLNB için de US-İİAB'nin alternatif olarak değerlendirilmesi düşüncesini akla getirir. AUS ve US-İİAB hastaneye yatış gerektirmeyen, ucuz ve morbiditesi düşük yöntemlerdir ancak doğruluğu yüksek oranda işlemi yapan kişinin tecrübesine bağlıdır.

Meme kanserinde AUS ve US-İİAB'nin güvenilirliğini değerlendirmek için güncel literatürü incelediğimizde; Chowdhury ve ark. (13) >50 yaş, primer meme lezyonu <1,5 cm östrojen reseptörü pozitif ve HER-2 reseptörü negatif hastalar üzerinde yaptıkları bir çalışmada AUS'un YN oranını %10,7 olarak bularak bunun SLNB ile benzer olduğunu belirtmişlerdir. Çalışmada AUS'nin aksiller hastalığı dışlamadaki sensitivitesi %89,3 olarak bulunmuştur (13).

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Tablo 2. US ve US-İİAB için sensitivite, spesifisite, PPD, NPD ve doğruluk oranları

İstatistik	US için diagnostik güç	US-İİAB için diagnostik güç
Sensitivite	36.36 (17.20-59.34)	0.00 (0.00-36.94)
Spesifisite	87.10 (78.5-93.15)	100.00 (80.49-100.00)
Pozitif prediktif değer	40.00 (23.69-58.88)	-
Negatif prediktif değer	85.26 (80.69-88.90)	68.00 (68.00-68.00)
Doğruluk	77.39 (68.65-84.67)	68.00 (46.50-85.05)

US: ultrasonografi, US-İİAB: ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi, PPD: pozitif prediktif değer NPD: negatif prediktif değer

Tablo 3. US ile görüntülemede final patolojinin doğruluğunu etkileyen faktörler

	US & final patoloji								Toplam		
	GP		YP		YN		GN				
	n	%	n	%	n	%	n	%	n	%	p1
ER											
Yok	0	0,0	2	13,3	0	0,0	13	86,7	15	13,0	0,253
Var	8	8,0	10	10,0	14	14,0	68	68,0	100	87,0	
PR											
Yok	2	7,7	5	19,2	0	0,0	19	73,1	26	22,6	0,084
Var	6	6,7	7	7,9	14	15,7	62	69,7	89	77,4	
HER-2											
Yok	7	6,7	11	10,6	12	11,5	74	71,2	104	90,4	0,91
Var	1	9,1	1	9,1	2	18,2	7	63,6	11	9,6	
Moleküler subtip											
Luminal A	4	7,3	5	9,1	7	12,7	39	70,9	55	47,8	0,893
Luminal B	4	8,7	5	10,9	7	15,2	30	65,2	46	40,0	
HER-2 zengin	0	0,0	1	16,7	0	0,0	5	83,3	6	5,2	
Üçlü negatif	0	0,0	1	12,5	0	0,0	7	87,5	8	7,0	
PLN											
Yok	1	1,1	5	5,3	14	14,7	75	78,9	95	82,6	**<0,001**
Var	7	35,0	7	35,0	0	0,0	6	30,0	20	17,4	
Tümör derecesi											
Düşük	0	0,0	1	7,1	3	21,4	10	71,4	14	12,6	0,783
Orta	7	9,5	7	9,5	8	10,8	52	70,3	74	66,7	
Yüksek	1	4,3	3	13,0	3	13,0	16	69,6	23	20,7	
Tümör yerleşimi											
Üst dış	4	6,8	7	11,9	8	13,6	40	67,8	59	51,3	0,777
Alt dış	0	0,0	0	0,0	3	18,8	13	81,3	16	13,9	
Üst iç	1	5,3	3	15,8	1	5,3	14	73,7	19	16,5	
Alt iç	2	14,3	1	7,1	2	14,3	9	64,3	14	12,2	
Multisentrik	1	14,3	1	14,3	0	0,0	5	71,4	7	6,1	
	Ortalama ± SS		**Ortalama ± SS**		**Ortalama ± SS**		**Ortalama ± SS**		**Ortalama ± SS**		**p2**
Yaş (yıl)	51,63±8,38		48,67±9,44		50,43±9,73		51,53±11,4		51,1±10,76		0,849
Tümör boyutu (mm)	32,13±10,6		20±17,94		22,36±7,15		18,84±9,87		20,31±11,14		**0,011***

Değerlendirme satır yüzdeleri üzerinden yapıldı. p1: chi-square test, p2: One-Way ANOVA (*Kruskal-Wallis test), US: ultrasonografi, ER: östrojen reseptörü, PR: progesteron reseptörü, HER-2: insan epidermal büyüme faktörü reseptör-2, PLN: palpe edilen lenf nodu, GP: gerçek pozitif, GN: gerçek negatif, YP: yalancı pozitif, YN: yalancı negatif, SS: standart sapma

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Tablo 4. US-İİAB ile değerlendirmede final patolojinin doğruluğunu etkileyen faktörler

	US-İİAB & final patoloji				Total		
	YN		GN				
	n	%	n	%	n	%	p1
ER							
Yok	0	0,0	3	100,0	3	12,0	0,527*
Var	8	36,4	14	63,6	22	88,0	
PR							
Yok	2	25,0	6	75,0	8	32,0	1,00*
Var	6	35,3	11	64,7	17	68,0	
HER-2							
Yok	7	30,4	16	69,6	23	92,0	1,00*
Var	1	50,0	1	50,0	2	8,0	
Moleküler subtip							
Luminal A	4	33,3	8	66,7	12	48,0	0,633
Luminal B	4	40,0	6	60,0	10	40,0	
Her-2 zengin	0	0,0	1	100,0	1	4,0	
Üçlü negatif	0	0,0	2	100,0	2	8,0	
PLN							
Yok	1	14,3	6	85,7	7	28,0	0,362*
Var	7	38,9	11	61,1	18	72,0	
Tümör derecesi							
Düşük	0	0,0	1	100,0	1	4,2	0,563*
Orta	7	38,9	11	61,1	18	75,0	
Yüksek	1	20,0	4	80,0	5	20,8	
Tümör yerleşimi							
Üst dış	4	28,6	10	71,4	14	56,0	0,858
Üst iç	1	25,0	3	75,0	4	16,0	
Alt iç	2	50,0	2	50,0	4	16,0	
Multisentrik	1	33,3	2	66,7	3	12,0	
	Ortalama ± SS		**Ortalama ± SS**		**Ortalama ± SS**		**p²**
Yaş (yıl)	51,63±8,38		50,18±11,25		51,1±10,76		0,75
Tümör boyutu (mm)	32,13±10,6		19,82±14,93		20,31±11,14		**0,002***

Değerlendirme satır yüzdeleri üzerinden yapıldı. p1: chi-square test (*Fisher's exact test), p2: Student's t-test (*Mann-Whitney U test), US-İİAB: ultrasonografi eşliğinde ince iğne aspirasyon biyopsisi, SS: standart sapma, ER: östrojen reseptörü, PR: progesteron reseptörü, HER-2: insan epidermal büyüme faktörü reseptör-2, PLN: palpe edilen lenf nodu, GN: gerçek negatif, YN: yalancı negatif

Ancak bu çalışmanın aksine meme kanseri tanısı ile ameliyat edilen hastalarda AUS ve US-İİAB'nin doğruluğunu değerlendiren bir başka çalışmada US ve US-İİAB için YN %42,4 bulunmuş ve final patolojide aksillada sadece tek lenf nodu metastazı olan hastalarda bu oranın %57,6'ya çıktığı gösterilmiştir. Aynı çalışmanın sonuçlarına göre, östrojen reseptörü pozitif hastalarda YN daha yüksek bulunmuştur (24).

Park ve ark. (10) 382 hastayı değerlendirdikleri çalışmada AUS'nin aksiller metastazı öngörmede sensitivitesi %56,6, spesifitesi %81,0, PPD %60,3, NPD %78,5 ve doğruluğu %72,8 olarak hesaplanmıştır. US-İİAB için ise sensitivite, spesifite, PPD, NPD ve doğruluk oranları sırası ile %39,5, %95,7, %82,3, %75,6 ve %76,7 olarak bulunmuştur. Beklenenin aksine US-İİAB'nin sensitivitesinin düşük olma sebebi, yetersiz sitoloji olarak değerlendirilen grupta final patolojide metastaz saptanması olarak belirtilmiştir. Çalışmada US-İİAB ile metastaz saptanan hastalar değerlendirildiğinde, hastaların %16,2'sinde preoperatif evreleme için gereksiz yapılacak SLNB'den kaçınılabileceği vurgulanmıştır. Çalışmada palpe edilen ve palpe edilmeyen tümörlü hastalar karşılaştırılarak, palpe edilen tümöre sahip hastaların olduğu grupta sensitivite daha yüksek olsa da iki grup arasında istatistiksel olarak sensitivite ve spesifisite için fark olmadığı gösterilmiştir (10).

Baruah ve ark.'nın (25) yaptıkları çalışmada final patolojide aksiller lenf nodunda metastaz saptanan hastaların %28,5'inde ve tüm

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hastaların %7,8'inde US-İİAB ile preoperatif tanı konulduğu ve bu hastalarda SLNB'den kaçınıldığı bildirilmiştir. Çalışmada US-İİAB'nin sensitivite, spesifite, PPD, NPD ve doğruluk oranları sırasıyla %28,5, %100, %100, %78,8 ve %80,5 olarak bulunmuştur (25).

Benzer bir çalışmada Van Rijk ve ark. (26) preoperatif AUS ve şüpheli lenf nodlarına yapılan US-İİAB sonuçlarını değerlendirmişler, AUS ile US-İİAB'nin sensitivitesini %35 ve %62, spesifitesini %82 ve %99 olarak bulmuşlardır. Çalışmanın sonucunda hastaların %8'inde preoperatif SLNB yapılamadan metastazın tanınabileceği ve hastaların NAK'ye yönlendirilebileceğini savunmuşlardır (26). Ancak hastanemizde güncel kılavuzlara uygun olarak bu uygulama tercih edilmemektedir ve SLNB NAK öncesi yapılmayıp US-İİAB sonucuna göre NAK planlanmaktadır (27).

Houssami ve ark. (28) meta analizlerinde US-İİAB'nin aksiller hastalığı öngörmedeki sensitivitesini %79,6, spesifitesini %98,3 ve PPD %97,1 olarak hesaplamışlardır ve US-İİAB'nin aksiller lenf nodunun değerlendirilmesindeki doğruluğunun çok iyi olduğunu belirtmişlerdir.

Singh ve ark.'nın (5) AUS ve US-İİAB'nin doğruluğunu değerlendirmek için yaptıkları prospektif çalışmanın sonuçlarında; AUS ve US-İİAB için sensitivite, spesifite, PPD, NPD ve doğruluk oranlarını sırası ile %61,5-83, %75,6-100, %69,5-100, %68,5-72,6 ve %69-88,1 olarak hesaplanmıştır. Çalışmada hastaların %24'üne US-İİAB ile metastaz kanıtlandıysa SLNB yapılmadan direk ALND yapılabileceğini göstermişlerdir (5).

Gurleyik ve ark.'nın (29) aksillanın klinik olarak negatif olduğu hastaları değerlendirdikleri çalışmada ise, US-İİAB ile aksiller lenf nodu metastazı saptanan hastalara direk ALND uygulanmıştır ve YN US için %23,7 ve US-İİAB için %31,8 olarak bulunmuştur.

Yapılan çoğu çalışma US-İİAB ile lenf nodu metastazı saptanan hastaların ne kadarında preoperatif evreleme için gereksiz SLNB yapıldığı ve bundan ne kadar kaçınılabileceğini değerlendirmeye yöneliktir. Ancak güncel durumda US-İİAB ile aksiller metastaz tanımlanan hastaların büyük bir kısmında tedaviye NAK ile başladığından odaklanmamız gereken US-İİAB ile metastaz saptanmayan hastaların ne kadarında peroperatif aksillaya cerrahi müdahaleden (SLNB/ALND'den) kaçınılabileceği sorusu yani US-İİAB'nin aksiller hastalığı dışlamadaki sensitivitesi olmalıdır.

Bizim araştırmamızda olduğu gibi Fayyaz ve Niazi (30) NAK alan hastaları değerlendirmeye katmadan yaptıkları araştırmada sensitivite, spesifite, PPD, NPD ve doğruluk oranlarını US-İİAB için sırası %77,22, %92,59, %91,04, %80,65 ve %85,0 olarak bulmuşlardır. Bizim çalışmamızda sensitivite, spesifite, PPD, NPD ve doğruluk AUS için sırası ile %36,36, %87,10, %40,00, %85,26 ve %77,39 bulundu. US-İİAB için ise spesifisite %100, NPD ve doğruluk %68,00 olarak hesaplandı. Preoperatif US ile metastaz olmadığı düşünülen hastaların %85,26'sında ve US-İİAB ile metastaz saptanmayan hastaların %68'inde final patoloji ile de metastaz saptanmadı. Ancak US ile metastaz düşünülmeyen hastaların %14,74'ünde ve US-İİAB ile metastaz saptanmayan hastaların %32'sinde final patolojide metastaz olduğu görüldü. Palpe edilen lenf nodu varlığı YP üzerine etkili idi.

Çalışmanın Kısıtlılıkları

Çalışmamızın limitasyonu, tek merkezli olup sınırlı sayıda hasta içermesidir. Ayrıca preoperatif değerlendirmede aksiller metastaz düşünülen hastalarda tedaviye NAK ile başlandığı için değerlendirme daha çok metastaz saptanmamış hastalar üzerinden yürütülmüştür. NAK alan hastalarda tedavi sonrası kemoterapi yanıtına bağlı olarak aksiller lenf nodlarındaki tutulum değişebileceği için değerlendirmeye dahil edilmemiştir. Ayrıca meme ve aksillanın fizik muayene ile değerlendirilmesi subjektif bir yöntemdir.

SONUÇ

Deneyimli kişilerce uygulanan AUS ve US-İİAB aksiller hastalığı dışlamada, meme kanserinin preoperatif değerlendirilmesinde ve tedavi planının yapılmasında değerli bir yöntemdir. Ancak AUS ve US-İİAB'nin negatif olması SLNB'den kaçınmayı sağlayacak doğruluğa ulaşmamıştır. Yine de yakın dönemde özellikle meme koruyucu cerrahi yapılıp radyoterapi planlanacak belli hasta gruplarında AUS ve US-İİAB ile değerlendirme aksillaya cerrahi girişimi ortadan kaldırabilir.

Teşekkür: Sayın Asena Ayça Özdemir'e bu makaleye yaptığı yardım ve katkılardan dolayı teşekkür ederiz.

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Diagnostic and Prognostic Value of M30 and M65 in Laryngeal Squamous Cell Carcinoma

M30 ve M65'in Larenksin Skuamöz Hücreli Kanserlerinde Tanısal ve Prognostik Değeri

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ÖZ

Amaç: Çalışma ameliyat öncesi ve sonrası plazma M30 ve M65 düzeylerinin larenks skuamöz hücreli kanserlerinde (SHK) prognostik değer, klinik evre, histolojik farklılaşma ve lenf nodu metastazı ile ilişkisini araştırmak üzere dizayn edilmiştir.

Yöntemler: Çalışmaya dahil edilen 29 larenks SHK'lı (grup 1) ve 19 sağlıklı bireyden (grup 2) ameliyat öncesi ve ameliyat sonrası birinci ayda alınan venöz kanda M30 ve M65 seviyeleri enzime bağlı immünosorbent deneyi ile belirlendi.

Bulgular: Grup 1 ve grup 2 serum M30 seviyeleri arasındaki fark istatistiksel olarak anlamlı idi (sırası ile medyan değer: 233,94 U/L'ye karşı 95,17 U/L) (p=0,001). M65 değerleri arasında ise anlamlı fark saptanmadı (sırası ile medyan değer: 350,67 U/L ve 309,94 U/L) (p<0.387).

Sonuç: Laringeal karsinomlu hastalarda preoperatif ve postoperatif serum M30 ve M65 düzeylerini değerlendirdiğimiz çalışmada M30 düzeyleri sadece ileri evre tümörlerde değil erken evre tümörlerde de yüksekti. Dolayısıyla M30 seviyesinin takip edilmesi larenks kanserlerinin erken teşhisi için faydalı olabilir.

Anahtar kelimeler: Keratin-18, M30, M65, apoptozis, laringeal skuamöz hücreli karsinom

ABSTRACT

Objective: This study aimed to investigate the preoperative and postoperative plasma M30 and M65 levels in laryngeal squamous cell carcinoma (LSCC) and its relationship with the prognostic value, clinical stage, histological differentiation, and lymph node metastasis.

Methods: This study was prospectively conducted, which included 29 patients with LSCC (group 1) and 19 healthy individuals (group 2). The venous blood was collected from all patients in the preoperative and first postoperative months. Serum M30 and M65 levels were determined by enzyme-linked immunosorbent assay.

Results: A statistically significant difference was found in serum M30 levels between groups 1 and 2. (Median: 233.94 U/L vs. 95.17 U/L) (p=0.001), whereas no significant difference was found in serum M65 values in groups 1 and 2 (median: 350.67 U/L vs. 309.94 U/L) (p<0.387).

Conclusion: The preoperative and postoperative serum M30 and M65 levels in the patients with laryngeal carcinoma were evaluated, which evaluated M30 levels were high not only in advanced-stage tumors but also in early staged tumors. Thus, following the M30 level may be useful for the early diagnosis of laryngeal cancers.

Keywords: Keratin-18, M30, M65, apoptosis, laryngeal squamous cell carcinoma

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INTRODUCTION

Laryngeal squamous cell carcinoma (LSCC) is one of the most common malignancies in males and the second most common malignancy in the head and neck region (1,2). Moreover, 2.4% of all newly diagnosed malignancies are added to the total number annually (1,2). Early-stage laryngeal cancers have a better prognosis than advanced stage cancers (3). Thus, early detection of laryngeal cancer provides more curative treatment functional and preservative surgery. Late presenting malignancies reduce the treatment efficacy and increase the recurrence rate (4). Therefore, new diagnostic markers for early LSSC detection will be useful and helpful in outcome prediction.

M30 and M65 are different circulating fragments of cytokeratin-18 (CK-18), which is an important constituent of the intermediate filament system. They are primary insoluble molecules that play a substantial role in cellular mechanisms (cellular manner, motility, division, and cell-cell contact). CK-18 is a cytoskeletal protein that is primarily found in the epithelial cell lining of the respiratory and gastrointestinal tracts and is usually expressed during malignant transformation (5). Necrosis of malignant and normal epithelial cells releases CK-18 (6,7). Caspase-mediated cleavage of the CK-18 contributes to the degradation of the intracellular cytoskeleton if epithelial cells undergo apoptosis (8).

After plasma concentrations of both full-length CK-18 (M65) and caspase-cleaved CK-18 fragments (M30) that is measured by enzyme-linked immunosorbent assay (ELISA), the studies on specific tumor types, including the lungs, breast, prostate, head and neck, colorectal, and testicular tumors were initiated (6,9-16). This study was designed to show the diagnostic and prognostic value of M30 and M65 in LSCC.

METHODS

Patients

This study was conducted at the Otolaryngology Department of İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine and included 29 patients with primary LSCC, of which diagnosis was confirmed by preoperative histological biopsy, as group 1. Additionally, group 2 (n=19) included participants of similar age, who smoked without any systemic diseases, as the control. Patients with active infection, immunosuppression, and other malignancies were excluded from the study. The study was approved by the İstanbul University-Cerrahpaşa Ethics Committee (approval number: B.30.2.İST.0.30.90.00/19047, date: 16.07.2021). This study was supported by the Scientific Research Projects Coordination Unit of İstanbul University (project number: 25617).

Patients were staged according to the tumor, node, and distant metastasis (TNM) classification of the International Union against cancer (17). Tumor extent, nodal involvement, and distant metastasis of the LSCC were assessed by physical examination, panendoscopy, and imaging studies (positron emission tomography, computed tomography, and magnetic resonance imaging). All patients were surgically treated, either by partial or total laryngectomy with or without neck dissection according to the tumor stage. Postoperative radiotherapy (RT) or chemoradiotherapy (CRT) was planned by postoperative definitive pathologic findings. Informed consent was obtained from all participants.

Samples

Serum samples were obtained after 12-h fasting by centrifugation of clotted specimen within 30 minutes to determine the M30 [caspase-cleaved keratin 18 (ccK18 or M30 neo-epitope)] and M65 [soluble keratin 18 (K18)]. The separated serum samples were stored in several small aliquots at -70 °C until assayed. In group 1, the first blood samples were taken before surgery and the second at the first month after surgery, and before the RT and/or CRT.

Laboratory Methods

ELISA procedure was used to determine the serum M30 and M65 levels (Peviva AB, Bromma, Sweden; Cat No: 10010 and 10020; respectively). The M65 ELISA assay measures total soluble K18 that are released from dead cells (necrotic and apoptotic). Whereas, M30 ELISA assay specifically detects apoptotic death. Combining the two assays may be useful for assessing cell death mode. Our study performed all determinations according to the manufacturer's instructions. The final step of the procedures measured the absorbance in a microplate reader at 450 nm. By plotting a standard curve, the M30 and M65 levels were expressed as U/L from known concentrations versus measured absorbance. The measuring ranges of M30 and M65 kits were 0-1,000 U/L and 0-2,000 U/L, respectively.

Statistical Analysis

The Statistical Package for the Social Sciences Version 21.0 (SPSS Inc., Chicago, IL., USA) was used for statistical analysis. The normal distribution of data was analyzed with the Kolmogorov-Smirnov test, and Levene's tests were used to assess homogeneity. The Wilcoxon signed-rank test and Mann-Whitney U test were used to compare the groups. The statistically significant level was set as a p-value of <0.05.

RESULTS

Group 1 (study group, n=29) included 3 (10.3%) female and 26 male (89.7%) patients, with a mean age of 58.1 (minimum: 34; maximum: 74) years. Group 2 (control group, n=19) included 2 female (10.5%) and 17 (89.5%) healthy males with a mean age of 57 (minimum: 30; maximum: 70) years.

All patients were treated by surgery, and 3 received adjuvant CRT (10%), 10 received adjuvant RT (34%), and 1 received adjuvant CRT. Neck dissection was not performed on 5 patients with early stage glottic carcinoma who were graded as N_0 according to preoperative assessments.

The difference between preoperative serum M30 levels in groups 1 and 2 were statistically significant ($p<0.05$) (Table 1, Figure 1). The difference between preoperative serum M65 levels in groups 1 and 2 were not statistically significant ($p>0.05$) (Table 1). Increased

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postoperative M30 and M65 serum levels were found in group 1; however, the comparison of preoperative and postoperative serum M30 and M65 levels was not statistically significant (p>0.05) (Table 1).

The statistical analysis according to nodal status (N+, N_0) revealed that preoperative and postoperative serum M30 and M65 levels were not statistically significant (p>0.05). The comparison according to the stage (early, advanced) revealed 13 patients with early and 16 patients with advanced laryngeal carcinoma. When the difference between the preoperative and postoperative serum M30 and M65 level in patients with early and advanced stages were not statistically significant (p>0.05). The group analyses according to T-stage (T_{1-2}, T_{3-4}) revealed that the comparison of preoperative and postoperative M30 and M65 levels in patients with T_{1-2} (n=20) and T_{3-4} tumors (n=9) was not a significantly different (p>0.05) (Table 2).

Table 3 represents preoperative M30 and M65 values of N_0, N+, T_{1-2}, T_{3-4}, and advanced and early stages in patients from group 1, and the data was compared with group 2. The preoperative M30 values in N_0, N+, T_{1-2}, T_{3-4}, and early and advanced stages were significantly higher than the control group, whereas the preoperative M65 values did not show any statistically significant difference (p>0.05) (Table 3).

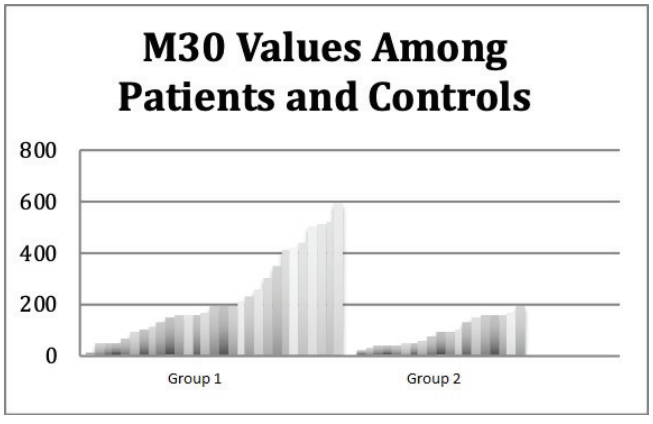

Figure 1. Preoperative serum M30 levels in groups 1 and 2

DISCUSSION

The survival rate of patients with advanced laryngeal cancer is low according to early-stage laryngeal cancer and is estimated to be 73-92% for early-stage (stages 1 and 2) laryngeal cancer, conversely 35% to 64% for late-stage laryngeal cancer (stages 3 and 4) (17,8,10). Late diagnosis is one of the most important reasons. Mortality and morbidity are increasing by invasion and metastatic potential and high recurrence rate in advanced laryngeal carcinoma. Therefore, some diagnostic tests may be useful for its early diagnosis.

CKs have been attested to play a role in the filtration of tumors into the surrounding tissue. The two forms of CK-18 appear to designate the proportion of apoptosis within the total cell death (8,18). M30 and M65 are considerably new markers that designate different circulating forms of the epithelial cells' structural protein, CK-18. M30 levels remark the caspase-cleavage form of CK-18 in the serum, whereas M65 remarks a broad epitope present in full-length protein, as well as in the caspase-cleaved fragment, thereby identifying CK-18 set free by tissue necrosis in addition to apoptosis (6). They are biomarkers for tumor cell death (18). M65 measures both caspase-cleavage (apoptosis) and cellular release of intact CK-18 during necrosis (18). Additionally, M65 was demonstrated to be a marker of tumor growth in control animals (18), which can be detected both in the plasma and serum of patients. Greystoke et al. (19) reported that M30 and M65 assays were reliable in the serum compared in plasma. Serum M30 and M65 were resistant to processing variation, including delays.

Serum M30 and M65 have been studied in a variety of cancers. Ueno et al. (20) found higher M30 levels in patients with breast cancer compared to healthy subjects. However, any relation between M30 levels and prognosis was not found (20). Dive et al. (21) reported that the median M65 levels in patients with metastatic pancreatic cancer were higher than those with locally advanced or resectable pancreatic cancer. However, M65 levels both in healthy control and patients with pancreatic cancer were not compared (21).

Ulukaya et al. (10) evaluated only M30 levels among patients with non-squamous cell lung cancer (NSCLC) or benign lung disease and healthy group and reported that M30 levels were higher in

Table 1. Preoperative (preop) and postoperative (postop) M30 and M65 values of patients and controls

	Preop M30, mean ± SD, (min-max) (median)	Postop M30, mean ± SD, (min-max) (median)	p-value*	Preop M65, mean ± SD (min-max) (median)	Postop M65 mean ± SD (min-max) (median)	p-value*
Group 1 (n=29)	293,93±165.56 (15,957-513,150) (193,160)	255,93±157,72 (58,265-582,480) (193,160)	0.627	350,67±143,24 (126,920-668,330) (332,09)	372,64 ± 224,09 (128,830-993,780) (303,24)	0.754
Group 2 (n=19)	95,17±56,15 (17,038-196,587) (97,380)	95.17±56,15 (17,038-196,587) (97,380)		309,94 ± 93,52 (162,082-580,367) (297,619)	309,94 ± 93,52 (162,082-580,367) (297,619)	-
p-values	0.002**	0.0001**		0.393	0.858	

*Wilcoxon signed-rank test, **Mann-Whitney U test, p<0.05, SD: standard deviation, min-max: minimum-maximum

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patients with NSCLC. Moreover, they found a relation between poorer survival and increasing M30 levels of patients (10). Hou et al. (11) reported that M30, M65, and circulating tumor cells were higher in patients with small-cell lung cancer. Yaman et al. (22) found that both serum M30 and M65 levels were significantly increased in patients with advanced gastric cancer compared to the control group, and patients with metastatic disease had significantly higher M30 levels compared to patients with locally advanced disease. Bilici et al. (23) reported that plasma M65, but not M30 levels, was significantly increased in patients compared

Table 2. Preoperative and postoperative M30 and M65 values and their comparison in patients who are grouped according to TNM classification

Nodal metastasis	n	Preop M30, mean ± SD, (min-max), (median)	Postop M30, mean ± SD, (min-max), (median)	p*	Preop M65, mean ± SD (min-max), (median)	Postop M65, mean ± SD, (min-max), (median)	p*
N_0	15	226,913±149,239 (49,902-513,150) (194,31)	215,286±162,323 (58,265-565,330) (176,31)	0.82	334,189±136,13 (153,070-641,930) (312,99)	321,604±179,719 (128,830-859,870) (291,94)	0.532
N+	14	241,454±186,923 (15,957-442,600) (177,845)	299,47±145,811 (164,020-480,370) (276,71)	0.363	368,318±153,591 (126,920-668,330) (351,15)	427,317±259,137 (340,130-993,780) (350,005)	0.331
p**		0.930	0.116	-	0.662	0.247	-
Stage							
Early	13	247,576±149,797 (49,902-513,150) (215,47)	207,173±164,577 (58,265-565,330) (165,48)	0.463	339,798±138,911 (153,070-641,930) (312,99)	328,396±189,376 (128,830-859,870) (291,94)	0.422
Advanced	16	222,848±181,459 (71,215-442,600) (158,52)	295,539±145,043 (164,020-582,480) (276,71)	0.179	359,495±150,601 (126,920-668,330) (351,15)	408,584±248,946 (193,260-993,780) (350,01)	0.326
p**		0.405	0.065	-	0.759	0.392	-
T-stage							
$T_{1,2}$	20	236,225±155,496 (15,957-513,150) (189,00)	267,361±170,883 (58,265-582,480) (201,01)	0.601	366,429±150,664 (126,920-668,330) (359,84)	415,936±244.181 (128,830-993,780) (344,77)	0.351
$T_{3,4}$	9	228,838±196,16 (52,600-522,587) (193,16)	230,519±129.105 (79,138-388,546) (182,55)	0.767	315,635±126.118 (177,907-472,110) (258,31)	276,421±138,028 (184,788-371,497) (211.46)	0.441
p**	-	0.777	0.604	-	0.370	0.081	-

*Wilcoxon signed-ranks test, **Mann-Whitney U test, TNM: tumor, node, and distant metastasis, SD: standard deviation, (min-max): minimum-maximum

Table 3. Comparison of preoperative M30 and M65 levels in patients and controls according to N status, disease stage, and T-stage

Parameter	Subgroup	Preoperative median	Control median	p
M30 (U/L)	N+	177,845	97,380	0.014*
	N_0	194,31		0.002*
	T_1-T_2	189,00	97,380	0.031*
	T_3-T_4	193,16		0.026*
	Early-stage	215,47	97,380	0.003*
	Advanced-stage	158,52		0.007*
M65 (U/L)	N+	177,845	97,380	0.321
	N0	194,31		0.648
	T_1-T_2	189,00	97,380	0.912
	T_3-T_4	193,16		0.387
	Early-stage	215,47	97,380	0.782
	Advanced-stage	158,52		0.714

*Mann-Whitney U test, $p<0.05$

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to healthy control in advanced gastric cancer. A study performed by De Haas et al. (16) revealed that serum M30 level was an important prognostic factor, such as lactate dehydrogenase, alpha-fetoprotein, and β-human chorionic gonadotropin, in testicular cancer. Additionally, another study that focused on the urogenital system reported that M30 levels were correlated with the grade, stage, and Ki-67 index of endometrial cancer (24).

The study that was conducted by Ozturk et al. (13) was the first study on M30 and M65 levels in patients with advanced head and neck squamous cell carcinomas (HNSCC), which found a statistical significance between the M30 levels of the patient and control groups. The average serum M65 levels were higher in patients with HNSCC; however, statistical significance was not found. They also revealed no correlation between age, sex, stage, and localization of the tumor and serum M30 and M65 levels. Our study analyzed the availability of serum M30 and M65 concentrations as a diagnostic test and a prognostic marker in patients with laryngeal carcinoma and found that plasma M30 levels in patients with laryngeal cancer were significantly higher than healthy controls, but not M65. Moreover, the comparison of serum M30 levels in early and late-stage laryngeal carcinoma found no statistically significant difference between M30 levels. Thus, the M30 level may be useful for the early diagnosis of laryngeal cancers.

Patients were analyzed according to the T-stage, which revealed no significant difference in M30 and M65 levels in T_{1-2} and T_{3-4} tumors. This study included patients with early-stage tumors in addition to advanced-stage laryngeal cancers like previous studies. Therefore, increased M30 levels in both patients with advanced and early stages were one of the important study results. Many studies suggest that cervical lymph node metastasis is the most important prognostic factor for laryngeal cancer (25,26). Jose et al. (27) showed that the 5-year survival rate decreased by approximately 50% in patients with cervical lymph node metastasis. In this study, the comparison of preoperative and postoperative M30 and M65 levels in patients with or without cervical lymph node metastasis revealed no significant difference.

Study Limitations

The limitation of this study is the small number of participants.

CONCLUSION

The preoperative and postoperative serum M30 and M65 levels in the patients with laryngeal carcinoma were evaluated. Serum M30 levels in patients with LSCC were higher compared to healthy subjects. Moreover, M30 levels were high, not only in advanced-staged tumors but also in early-stage tumors that were not previously studied. Therefore, M30 could serve as a promising biomarker candidate in LSCC. The levels of M30 and M65 were not significantly different in patients with nodal metastasis or advanced tumor stage, which may indicate that M30 and M65 cannot be used as prognostic markers in laryngeal carcinoma. Future prospective studies are needed to evaluate the prognostic importance of these markers on laryngeal cancer.

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa Ethics Committee (approval number: B.30.2.İST.0.30.90.00/19047, date: 16.07.2021).

Informed Consent: Informed consent was obtained from all participants.

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Safety Evaluation of Early Active and Passive Motion Without Immobilization in Metacarpal Fractures

Metakarp Kırıklarında İmmobilizasyon Olmaksızın Erken Aktif ve Pasif Hareket Güvenli Midir? Sonuçlar Üzerinde Geleneksel Rehabilitasyon Programlarından Daha Etkili Midir?

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ABSTRACT

Objective: Early motion after surgical treatment of metacarpal fractures is important to prevent joint motion limitation. Contrarily, the loss of reduction in the fracture line with an early motion negatively affects the results. This study aimed to evaluate the reliability of early active and passive motion without immobilization after surgical treatment and compare the results with the traditional rehabilitation program.

Methods: This study included 86 patients who were fixed with miniplate screws. Patients were divided into two groups according to the rehabilitation programs. The first group had immobilization with orthosis and traditional rehabilitation program for 4 weeks, whereas the second group had an early active and passive joint range of motion exercises without immobilization. The first group included 37 males and 16 females with a mean age of 34.92±12.97 years who were followed for an average of 43.19±13.03 months. The second group included 23 males and 16 females with a mean age of 31.82±11.92 years who were followed for an average of 39.05±12.74 months.

Results: No significant differences were determined between the groups in terms of age, female-male ratio, time from injury to surgery, follow-up period, fractured extremity, and dominant-non-dominant ratio. Additionally, no significant differences were found between the groups in terms of grip strength and time to return to work at the final follow-up. The total joint range of motion and Quick Disabilities of the Arm, Shoulder, and Hand scores were significantly better in the second than the first group. Union at the fracture line without reduction loss was observed in both groups at the final follow-up.

Conclusion: Fixation with miniplate screws provides stable fixation in extra-articular metacarpal fracture. Early active and passive motion without immobilization does not cause complications at the fracture line with this stable fixation. Contrarily, more successful results were obtained than the traditional rehabilitation program in terms of the range of motion and functional results.

Keywords: Metacarpal fracture, rehabilitation, early active motion, early passive motion

ÖZ

Amaç: Erken hareket metakarp kırıklarının cerrahi tedavisi sonrası eklem hareket kısıtlılığının önlenmesinde önemlidir. Diğer taraftan erken hareketle oluşan kırık hattındaki redüksiyon kaybı sonuçları olumsuz etkiler. Bu çalışma ile cerrahi tedavi sonrası immobilizasyon olmaksızın erken aktif ve pasif hareketin güvenilirliğini değerlendirmeyi ve geleneksel rehabilitasyon programı ile sonuçları karşılaştırmayı amaçladık.

Yöntemler: Mini plak vidaları ile tespit edilen 86 hasta çalışmamıza dahil edildi. Hastalar rehabilitasyon programlarına göre 2 gruba ayrıldı. Birinci gruba 4 hafta boyunca ortez ile immobilizasyon ve geleneksel rehabilitasyon programı uygulandı. İkinci gruba immobilizasyon olmaksızın erken aktif ve pasif eklem hareket açıklık egzersizleri uygulandı. Birinci grupta yaş ortalaması 34,92±12,97 olan 37 erkek ve 16 kadın ortalama 43,19±13,03 ay takip edildi. İkinci grupta yaş ortalaması 31,82±11,92 olan 23 erkek ve 16 kadın ortalama 39,05±12,74 ay takip edildi.

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ÖZ

Bulgular: Gruplar arasında yaş, kadın erkek oranı, yaralanmadan ameliyata kadar geçen süre, takip süresi, kırık ekstremite ve dominant nondominant oranı açısından anlamlı fark yoktu. Kavrama kuvvetleri ve işe dönüş süreleri açısından gruplar arasında anlamlı fark yoktur. Toplam eklem hareket açıklığı ve Kol, Omuz ve Elin Hızlı Engelleri skorları ikinci grupta daha iyi bulundu. Son kontrollerde kırık hattında kaynama vardı ve her iki grupta da redüksiyon kaybı görülmedi.

Sonuç: Ekstraartiküler metakarp kırıklarında mini plak vidalarla uygulanan tespit stabil fiksasyon sağlar. Bu stabil fiksasyon ile immobilizasyon olmaksızın uygulanan erken aktif ve pasif hareket kırık hattında komplikasyonlara neden olmaz. Aksine hareket açıklığı ve fonksiyonel sonuçlar açısından geleneksel rehabilitasyon programlara göre daha başarılı sonuçlar elde edilir.

Anahtar kelimeler: Metakarpal kırık, rehabilitasyon, erken aktif hareket, erken pasif hareket

INTRODUCTION

Hand fractures are the most common fractures in the human skeleton. Metacarpal fractures constitute 30-50% of hand fractures (1), which are more common in young adults (2). Patients are frequently encountered in the rehabilitation clinics with the expectation of early return to work after the fracture (3). Consensus is unavailable on the optimal treatment option for extra-articular metacarpal fractures. However, prolonged immobilization carries a potential risk of joint stiffness in closed reduction casting and pinning (4,5). Fixation with miniplate screws provides a rigid and stable fixation for early motion (4). However, a risk of motion limitation may develop due to friction and adhesions caused by plates and screws (6). Tendon adhesions, joint motion limitation, and strength and functional loss can develop after open surgery. Early postoperative rehabilitation is effective in preventing these complications (7). Early rehabilitation aimed to achieve a more successful result in joint range of motion and functional result, to provide an early return to normal life and work-life, and to prevent tendon adhesions (8). However, the loss of reduction in the fracture line due to early forced action negatively affects the results (9). Therefore, early passive motion is not started in the traditional rehabilitation program, but an only early active movement. The patient also uses a splint or orthosis for immobilization. (10).

We hypothesize that early active and passive motion without immobilization will provide better results in both joint ranges of motion and functional results. This study aimed to compare early active and passive motion without immobilization with traditional rehabilitation in clinical and functional aspects.

METHODS

This study retrospectively evaluated 144 patients who are fixed with 2.0 and 2.4 mm miniplate screws between January 2016 and June 2020 due to extra-articular metacarpal fracture. Patients with first metacarpal fracture and those under 18 years of age as well as 19 patients who did not come for regular control, 11 who could not be regularly rehabilitated, 28 who had an additional fracture in the upper extremity before surgery or during follow-up, open fractures, and tendon, nerve, and vascular repair with fracture were excluded from our study. Final controls of 86 patients were performed.

The study protocol was approved by the University of Health Sciences Turkey Ethics Committee of Gaziosmanpaşa Training and Research Hospital (approval number: 302-2021).

Patients were evaluated under two groups according to the rehabilitation program. The first group had immobilization with the orthosis and traditional rehabilitation program for 4 weeks, whereas the second group had no immobilization and early active and passive joint range of motion was started. The coarse clothing of patients was reduced in both groups, and rehabilitation was started under the guidance of a physiotherapist on postoperative day 3. The incision area was massaged with lotion, three times for 10 min, every day after the stitches were removed. Elevation, cold application, and compression bandages were applied to reduce edema formation. The decongestive exercise was started. The hand was placed higher than the elbow and the elbow higher than the shoulder, and the affected hand was massaged starting from the fingertips to the axilla.

Orthosis was used for the whole day for 4 weeks in the first group. Additionally, the metacarpal bones were immobilized in the intrinsic plus position [wrist in 30 degrees extension, metacarpophalangeal (MCP) joints in 70-degree flexion, and proximal interphalangeal (PIP) joints in full extension]. Immobilization was performed with one finger on the radial and ulnar sides of the fractured finger. Only one adjacent finger was included in the immobilization in the 2nd and 5th metacarpal fractures. Contrarily, immobilization was not applied in the second group. Active joint range of motion was started in the first group under the guidance of a physiotherapist after postoperative day 3. Isometric exercises were started for muscle strengthening in the orthosis. Isometric exercises were started in the second week to strengthen the intrinsic muscles. Paraffin treatment for 20 min before the exercises was started 2 days after the sutures were removed. Active joint range of motion exercises under the guidance of a physiotherapist for 45 min was applied for 5 days in a week in the first 2 weeks and 3 days in a week in weeks 3 and 4. Passive range of motion exercises and gentle ball squeezes and dough exercises were started for muscle strengthening at week 4. Additionally, gentle and resistance abduction exercises were started. Active joint range of motion exercises against resistance was started for muscle strengthening after week 6.

Active, actively assisted, and passive joint range of motion exercises and isometric exercises for muscle strengthening was started under the guidance of a physiotherapist in the second group after the postoperative day 3. Paraffin treatment for 20 min before the exercises was started 2 days after the sutures were removed. Active, active assisted, and passive joint range of motion exercises

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for 45 min was applied for 5 days a week in the first 2 weeks and 3 days a week in weeks 3 and 4. Hand therapeutic dough and grip strengthening exercises for 10 min were started in each session in addition to the range of motion exercises after postoperative week 2. Isometric exercises were also started to strengthen the intrinsic muscles in the second week. The home exercise program was explained to the patients by an experienced physiotherapist on the contralateral intact extremity before hospital discharge. Additionally, informative brochures were given to the patients and were recommended to perform a 30-min home exercise program after 10 min of hot application twice a day.

The total joint range of motion (TJROM) and grip strength were evaluated. TJROM measurements were made by recording the sum of the flexion and extension angles of the MCP, PIP, and distal interphalangeal joints with the aid of a goniometer while the hand was in full flexion and full extension (11). Handgrip strength was measured with a Jamar dynamometer (Asimow Engineering, Los Angeles, USA) in the shoulder with 0° adduction, elbow with 90° flexion, and forearm at neutral rotation. Each measurement was repeated three times and the average was recorded as kg (8). Quick Disabilities of the Arm, Shoulder, and Hand (Q-DASH) scoring was used for satisfaction assessment (3). The time to return to work was evaluated through the Social Security Institution's incapacity report system.

Statistical Analysis

Statistical analyses were performed by Statistical Package for the Social Sciences version 20 computer software. All measured data are descriptively presented. Data were presented as numbers, mean, and standard deviation. The Shapiro-Wilk test was used to determine normal data distribution. Differences in clinical details were assessed using the chi-squared test for categorical variables, such as gender, hand side, hand dominance, and affected finger, and the Student's t-test for continuous variables, such as age, period injury to operation, and return to work period. The relationship between the rehabilitation modalities and TJROM, grip strength, Q-DASH, and return to work period were analyzed using the tests (Samples t, Mann-Whitney U, chi-square, Fisher's Exact). The significance level was considered at p-values of <0.05.

RESULTS

No statistically significant differences were found between the groups in terms of age, gender, time from injury to surgery, fractured extremity side, dominant-nondominant extremity ratio, and mean follow-up time (p>0.05; Table 1).

Handgrip strength was 40.87±6.41 kg in the first group and 39.20±11.52 kg in the second group at the final follow-up, without statistically significant differences between the groups (p=0.4066; Table 2). The mean TJROM score was 229.80±15.99° in the first group and 244.05±12.88° in the second group. The mean Q-DASH score was 3.15±3.53 in the first group and 0.98±1.91 in the second group. The results of TJROM and Q-DASH were statistically significantly better in the second group than in the first group (p<0.05). The mean time to return to work was 32.19±8.94 days in the first group, whereas 29.58±6.63 days in the second group,

Table 1. Demographic values, period from injury to surgery, and mean follow-up period of the patients

	First group	Second group	p-values
Age (years)	34.91±12.97	31.82±11.92	0.2531
Male/female	31/16	23/16	0.6578
Right hand/left hand	30/17	29/10	0.3097
Dominant/non-dominant	32/15	31/8	0.3449
Effected finger			
2nd metacarpal	6	6	
3rd metacarpal	11	6	
4th metacarpal	9	8	0.8271
5th metacarpal	21	19	
Period injury to operation	2.36±1.88	2.75±2.05	0.3653
Mean follow-up period	43.19±13.03	39.05±12.74	0.1416

Table 2. Grip strength, range of motion, functional results, and time taken to return to work at final follow-ups

	First group	Second group	p-values
Grip strength (kg)	40.87±6.41	39.20±11.52	0.4066
Total joint range of motion	229.80±15.99	244.05±12.88	<0.0001
Quick disabilities of the arm, shoulder, and hand	3.15±3.53	0.98±1.91	0.0005
Return to work period	32.19±8.94	29.58±6.63	0.1259

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without statistically significant difference (p=0.1259). Proximal humerus fracture was observed in one patient due to falling in 22 days in the second group. The reoperated patient was excluded from the study. One patient had delayed wound healing in the first group. The dressing was followed up with rehabilitation after the stitches were removed. The wound completely healed without the need for extra intervention within 30 days.

DISCUSSION

The hand is a region where many movements are intertwined in a small area. Minor injuries can result in a major functional loss (12). A wide variety of treatment options are available for metacarpal fractures (13,14). Surgical treatment is preferred in fractures with high rotational displacement and shortness at the fracture line. Surgery is also applied in multipart fractures and displaced fractures, which cannot be closely reduced.

Miniplate screw system has developed a lot with implant technology developments. Starting early motion after fixation with miniplate screws in metacarpal fractures was possible. Gaining an early joint range of motion shortens the patient's return to work days (11,15). Early motion after rigid fixation is ideal in metacarpal fractures; however, it is not without problems (16). Adhesions and plate screw irritations may occur in the extensor tendons after fixation (17). Complication rates after metacarpal fractures are between 32% and 36%. Joint stiffness is the most frequently reported complication with a rate of 76%. TJROM has been reported to be <220° in these patients (18).

The literature demonstrated that early motion can be started after rigid fixation with miniplate screws (4). Immobilization is applied in the first 2 weeks to prevent potential reduction loss in the traditional rehabilitation program (3). Active motion exercises are under the direct control of the patient through osseous structures and musculotendinous structures. Active motion exercises generate tendon gliding, promote strength, endurance, and exchange lymphatic drainage. Passive motion exercises are applied by the physiotherapist to overcome tissue resistance and are not under the control of the patient, which is usually painful and is not applied early in classical rehabilitation to avoid tissue injuries and possible implant failure.

An animal study revealed that early controlled passive movement in unstable extra-articular metacarpal fractures helps to create a more stable biomechanically union without disturbing the callus tissue and reduces dorsal angulation at the fracture line. Additionally, an early controlled passive motion was determined to cause a mechanical stimulus that triggered healing and tissue differentiation at the fracture line (19). A biomechanical study has determined that the use of miniplate screws in metacarpal fractures is sufficiently resistant to controlled passive motion exercise cyclic loads (20).

Implant failure was not observed in patients who underwent traditional rehabilitation and in patients who started active, actively assisted, and passive joint range of motion exercises after the postoperative day 3 in our study. An early passive motion was determined to be started after osteosynthesis with miniplate screws.

Success after hand rehabilitation is associated with pain, strength gain, and total active range of motion, and functional gain. The mean handgrip strength at week 6 was 33.9 (22-51) kg in patients who underwent immobilization for 1 week after surgical treatment (21). The clinical results of the classical rehabilitation program and home exercise program were compared in patients who underwent fixation with plate screws in a study. An average of 35 kg grip strength was reached in both groups at the end of 12 weeks (3). The mean grip strength was 39.20±11.52 kg in patients who were not immobilized but applied early passive and active exercise, whereas 40.87±6.41 kg in patients who underwent conventional rehabilitation in our study. No significant differences were found in the handgrip strength between the two groups. The mean handgrip values of our study, which were higher than the values of both studies, are thought to be associated with a longer follow-up period.

The mean TJROM value was evaluated according to the rehabilitation applied in a study conducted with patients who underwent fixation with miniplate screws, which was 256° in patients who received the home program and 245° in patients who underwent rehabilitation under the guidance of a physiotherapist. Significantly, better results were achieved in patients who underwent rehabilitation under the guidance of a physiotherapist (3). Another study evaluated 54 metacarpal fractures of 42 patients who were immobilized with an orthosis in the intrinsic plus position that allows finger movement and revealed a mean TJROM of 241° at week 6 and 253° at week 12 (5). A study evaluated closed reduction percutaneous pinning in 33 patients who were immobilized for 30.9±5.8 days and revealed a mean TJROM of 249±40° at 2.9±2.4 months. Additionally, open reduction and plate screws fixation was performed in 23 patients who were immobilized for 20±5.6 days and revealed a mean TJROM of 234.3±58.5° at 4.2±5.6 months (4). The mean TJROM was 244.05±12.88° in patients who underwent early passive and active exercise without immobilization in our study. The mean TJROM was 229.80±15.99° in our patients who underwent conventional rehabilitation. TJROM value was significantly better in patients who applied early passive and active exercise without immobilization.

A study clinically evaluated 37 metacarpal fractures fixed with plate screws, wherein the patients underwent a traditional rehabilitation program with immobilization after surgical treatment. The mean Q-DASH score was 3.6 at 32 months (22). In our study, the mean Q-DASH score was 3.15±3.53 in patients who underwent conventional rehabilitation. Similar results were obtained in Q-DASH scores with this study. Better Q-DASH results (0.98±1.91) were obtained in patients who started early active and passive motion without immobilization. Starting early active and passive motion without immobilization was revealed to give better results than traditional rehabilitation in our study.

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Study Limitations

The rehabilitation of patients was started in the same rehabilitation center; however, the rehabilitation of patients after hospital discharge continued under the guidance of different physiotherapists. Different surgeons performed the operations. The metacarpal fracture fixation was performed with miniplate screws; however, the same brand of the implant was not used in all patients. The randomization method was not used in the distribution of patients into groups. Pretreatment values are unknown because prefracture evaluations of patients could not be made. No difference was found between the groups in terms of age, male-female ratio, and dominant extremity involvement, thus no significant difference was found between the groups in terms of pretreatment values.

CONCLUSION

Fixation with miniplate screws provides a stable fixation in extra-articular metacarpal fractures. This stable fixation allows passive, as well as active motion, in the early period without immobilization. Initiation of active and passive motion in the early period without immobilization provides better functional results and joint range of motion. Our study determined that early active and passive motion without immobilization is required to achieve more successful results after fixation of extra-articular metacarpal fractures with miniplate screws.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Gaziosmanpaşa Training and Research Hospital (decision no: 302, date: 23.06.2021).

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Anesthesia and Postoperative Analgesia for a Patient with Mungan Syndrome, Autosomal Recessive Familial Visceral Myopathy: A Case Report

Mungan Sendromlu Bir Hastada Anestezi ve Postoperatif Analjezi, Otozomal Resesif Ailesel Viseral Miyopati: Olgu Sunumu

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ABSTRACT

Mungan syndrome, a type of familial visceral myopathy, is a rare autosomal recessive genetic disorder characterized mainly by pseudo-obstruction caused by visceral myopathy. There are different components of this syndrome, such as Barret's esophagus, megaduodenum and cardiac abnormalities. Anesthetic management and procedures for postoperative analgesia are essential for patients with this syndrome to prevent complications such as ileus caused by pseudo-obstruction. This report presents our experience managing anesthesia during total hip replacement surgery performed on a 39-year-old female patient diagnosed with Mungan syndrome.

Keywords: Anesthesia, Mungan syndrome, myopathy, pseudo-obstruction, Barret's esophagus

ÖZ

Ailesel viseral miyopati türü olan Mungan sendromu, esas olarak viseral miyopatinin neden olduğu psödo-obstrüksiyon ile karakterize, nadir görülen otozomal resesif bir genetik bozukluktur. Bu sendromun Barrett's özofagusu, megaduodenum ve kardiyak anormallikler gibi farklı bileşenleri vardır. Anestezi yönetimi ve postoperatif analjezi sağlamaya yönelik prosedürler, bu sendromlu hastalar için psödo-obstrüksiyonun neden olduğu ileus gibi komplikasyonları önlemek için önemlidir. Olgu sunumuzda, MGS tanısı alan 39 yaşındaki kadın hastaya total kalça protezi ameliyatında anestezi yönetimine ilişkin deneyimimizi sunmaktayız.

Anahtar kelimeler: Anestezi, Mungan sendromu, miyopati, psödo-obstüksiyon, Barret özofagus

INTRODUCTION

Familial visceral myopathies are rare genetic disorders with idiopathic chronic intestinal pseudo-obstruction syndromes (1). In these diseases, pathological findings are general degeneration and fibrotic replacement of the smooth muscles of the gastrointestinal system. In addition, the uterus and the external ophthalmoplegia of the eye may also be affected in some patients. There are many subtypes of this disease in the literature: type 1 is autosomal dominant, type 2 is autosomal recessive with ptosis and external ophthalmoplegia, and type 3 is autosomal recessive with complete gastrointestinal tract dilation (2). Mungan syndrome (MGS), an autosomal recessively inherited disorder, is familial visceral myopathies. The case reports of patients with MGS were first published in 2003 by Mungan et al. (3) Following that, the term MGS was first described in 2007 in the literature. Genetic studies are still in progress, and linkage analysis identifies a syndromic locus on the chromosome 8q23-q24 about this syndrome (4). Its primary manifestation is chronic intestinal pseudo-obstruction caused by visceral myopathy. Gastrointestinal hypomotility, mega duodenum, and Barret's esophagus are other gastrointestinal

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manifestations of MGS. Patients with this syndrome may also have bilateral ptosis on the eyes, renal hypoplasia, vesicoureteral reflux, and cardiac abnormalities such as membranous ventricular septal defect, pulmonary valve regurgitation, tricuspid valve regurgitation, pulmonary valve stenosis, and supravalvular pulmonary stenosis. Management of patients with visceral myopathies is challenging due to the high risks of gastrointestinal and cardiovascular complications. As far as we know, there is no case report regarding anesthetic management of familial visceral myopathies. This report presents a successful case of anesthetic management of a patient who had MGS operated for coxarthrosis by the orthopedic surgery department.

CASE PRESENTATION

A 39-year-old female patient was scheduled for total hip replacement surgery for coxarthrosis. Written informed consent was obtained from the patient. Her medical history revealed glaucoma, transient ischemic attack, and MGS components, including Barrett's esophagus confirmed by endoscopy and vesicourethral reflux. She had many constipation-diarrhea periods and acute gastroenteritis attacks because of the pseudo-obstructive symptoms of the syndrome. Her family history was positive for familial visceral myopathy. One of her brothers died because of ileus caused by MGS, and the other brother died when he was a child for an unknown reason. Her physical examination was normal, and she had no constipation and diarrhea complaints in the preoperative period. An echocardiogram determined degenerative changes on the mitral and aortic valves. Routine non-invasive monitoring was performed, including non-invasive blood pressure, heart rate, pulse oximetry (SpO_2), electrocardiography, and temperature (˚C) monitoring. An epidural catheter was uneventfully placed through the L3-L4 vertebral space for postoperative analgesia. Anesthesia was induced with midazolam (0.05 mg/kg), fentanyl (1 mcg/kg), propofol (2-2.5 mg/kg) and vecuronium (0.1 mg/kg). The trachea was intubated, and anesthesia was maintained with total intravenous anesthesia (TIVA) with propofol (0.1-0.2 mg/kg/min) and remifentanil (0.25-0.5 mcg/kg/min) infusion and oxygen/air for the duration of the procedure. Cefazolin (25 mg/kg), ranitidine (1 mg/kg) and metoclopramide (10 mg) were administered intravenously. The bispectral index and invasive blood pressure were also monitored. The patient had episodes of hypertension whose systolic blood pressure reached 180 mmHg, and we used a bolus of 1 mg/kg followed by an esmolol infusion of 0.15 mg/kg/min. The intraoperative blood loss was 500 mL, and the patient received 50 mL/kg crystalloid solution during surgery. There was no need for blood and blood products. The duration of the operation was three hours. The trachea was extubated, and she was taken to the intensive care unit (ICU) and was discharged one day later. After the test dose (3cc of 2% lidocaine) was administered, 0.125% bupivacaine was administered as an epidural infusion for 48 hours at a rate of 3 cc/h. She had no pseudo-obstructive symptoms after the operation, and her bowel movements were normal. The patient had an uncomplicated surgery and an uneventful hospital stay.

DISCUSSION

Patients with MGS may have different symptoms in a wide range of severity. While some of these patients show no symptoms throughout their lifetime, some of them can be taken to operation for exploratory laparotomy for suspected mechanical obstruction, and some of them even die because of ileus. The physician needs to be careful and consider postoperative gastrointestinal complications such as constipation and ileus (2). Consumption of fewer opioid drugs for postoperative analgesia with multimodal analgesia methods and early mobilization are essential interventions to prevent pseudo-obstructive symptoms. In our case, we offered combined spinal-epidural anesthesia to the patient, but she refused to have surgery under regional anesthesia. She just accepted an epidural catheter for postoperative analgesia., So, we preferred to place the epidural catheter to relieve the patient's postoperative pain, reduce opioid consumption, and early mobilization. Patients with MGS have decreased lower esophageal sphincter tone for visceral myopathy, so some precautions, including pharmacologic agents, should be taken to prevent aspiration prophylaxis (3). Hypertension was probably a coincidental finding for our patient, but it may also be a component of the syndrome in the future. Hypertensive episodes constituted a risky situation in terms of intraoperative bleeding, so we used esmolol, the short-acting beta-blocker infusion, to overcome the intraoperative hypertension problem. The surgery was performed in the lateral decubitus position, and supports were placed on the back for positioning. Considering the possibility of displacement of the epidural catheter due to the supports placed and the risk of increased blockage or spinal injection in the procedure performed under general anesthesia, we did not prefer epidural infusion in our patient for blood pressure and pain management. Effective fluid management is crucial to prevent postoperative cardiac and pulmonary complications as MGS also has cardiac components. We used arterial pulse contour analysis to determine the patient's volume status. To achieve goal-directed fluid therapy, we set our threshold limits of pulse pressure and stroke volume variation as 12%. We preferred to use TIVA in our patient, for the possible relationship between MGS and malignant hyperthermia has not yet been rule out in the literature. She was transferred to the ICU for follow-up in malignant hyperthermia risk and to monitor the return of bowel movements.

MGS is composed of different components, and its primary manifestation is gastrointestinal symptoms related to familial visceral myopathy and pseudo-obstruction. In addition, there are other symptoms such as Barret's esophagus, cardiac abnormalities, and vesicourethral reflux (3). Therefore, in anesthesia and postoperative pain management of patients with MGS, each component of this syndrome must be considered to prevent postoperative complications by utilizing some methods such as multimodal analgesia, early mobilization, and goal-directed fluid therapy. Furthermore, dynamic monitoring methods such as pulse control analysis should be considered to evaluate patients' volume status and avoid adverse consequences of cardiac pathologies.

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