ISSN 2149-5807 • EISSN 2149-6048

Indexed in Web of Science

EPAT 1999 Emergency Physicians Association of Turkey

EAJEM

Eurasian Journal of Emergency Medicine

Citation abbreviation: Eurasian J Emerg Med

AVES

Volume: 16 • Issue: 1 • March 2017

www.eajem.com

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Acil Tıp Uzmanları Derneği adına sahibi ve Sorumlu Yazı İşleri Müdürü / Owner and Responsible Manager on behalf of the Emergency Medicine Physicians Association of Turkey: Başar Cander • Yayın türü / Publication Type: Yerel süreli / Local periodical • Basım yeri / Printed at: Matsis Matbaa Hizmetleri San. ve Tic. Ltd. Şti., 2. Tevfikbey Mahallesi Dr. Ali Demir Cad. No:51 34290 Sefaköy, İstanbul, Turkey (+90 212 624 21 11) • Basım tarihi / Printing Date: Mart 2017 / March 2017 • Acil Tıp Uzmanları Derneği tarafından yayınlanmaktadır / Published by Emergency Medicine Physicians Association of Turkey, Yukarı Ayrancı Güleryüz Sok. No: 26/19 06550 Çankaya, Ankara, Türkiye (+90 312 426 12 14)

AVES

Publisher
İbrahim KARA

Publication Director
Ali ŞAHİN

Deputy Publication Director
Gökhan ÇİMEN

Publication Coordinators
Betül ÇİMEN
Zeynep YAKIŞIRER
Gizem KAYAN
Melike Buse ŞENAY
Özlem ÇAKMAK

Project Coordinator
Hakan ERTEN

Project Assistants
Aylin ATALAY
Şükriye YILMAZ

Graphics Department
Ünal ÖZER
Neslihan YAMAN
Deniz DURAN

Contact:
Address: Büyükdere Cad. 105/9
34394 Mecidiyeköy, Şişli, İstanbul, Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Osama Kentab
Paediatrics and Emergency Medicine, King Saud Bin Abdulaziz University, Saudi Arabia

Rasha Buhumaid
Emergency Department and Assistant Program Director, Sheikh Khalifa Medical City, Abu Dhabi, UAE

S. Saravana Kumar
Department of Emergency Medicine, Mehta Hospital, Chennai, India

S.V Mahadevan
Department of Emergency Medicine, Stanford University Faculty of Medicine, Stanford, USA

Saleh Saif Fares
Department of Emergency Medicine, Deputy Head of Zayed Military Hospital's, Abu Dhabi, UAE

Salim Satar
Clinic of Emergency Medicine, Adana Numune Training and Research Hospital, Adana, Turkey

Samad Shams Vahdati
Department of Emergency Medicine and Critical Care, Amrita Institute of Medical Sciences, Kochi, India

Şahin Aslan
Department of Emergency Medicine, Atatürk University School of Medicine, Erzurum, Turkey

Yunsur Çevik
Department of Emergency Medicine, Keçiören Training and Research Hospital, Ankara, Turkey

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Aims and Scope

Eurasian Journal of Emergency Medicine (Eurasian J Emerg Med) is the open access, scientific publication organ of the Emergency Medicine Physicians' Association of Turkey that is published in accordance with independent, unbiased, double blind peer review principles. The journal is published 4 times in a year in March, June, September and December.

The journal aims to publish scientifically high quality articles which can contribute to the literature and written in the emergency medicine field and other related fields. Review articles, case reports, editorial comments, letters to the editor, scientific letters, education articles, original images and articles on history and publication ethics which can contribute to readers and medical education are also published.

The journal's target audience includes Emergency Medicine experts, School members who conduct scientific studies and work in the Emergency Medicine field, researchers, experts, assistants, practicing physicians and other health sector professionals.

Editorial and publication processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE). The journal is in conformity with Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Eurasian Journal of Emergency Medicine is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EMCare, DOAJ, EBSCO, CINAHL, GALE and ProQuest.

Processing and publication are free of charge with Eurasian Journal of Emergency Medicine. No fees are requested from the authors at any point throughout the evaluation and publication process. All manuscripts must be submitted via the online submission system which is available through the journal's web page at www.eajem.com. Journal's guidelines, technical information and the required forms are available on the journal's web page.

All expenses of the journal are covered by the Emergency Medicine Physicians' Association of Turkey. Pharmaceutical advertisements may be published in the printed copies of the journal. Potential advertisers should get in contact with the Editorial Office. Advertisement images are only published upon Editor in Chief's approval.

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Eurasian Journal of Emergency Medicine, the editors, the editorial board and/or the publisher, AVES; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials.

All published content is available online free of charge at www.eajem.com.

Eurasian Journal of Emergency Medicine is distributed internationally and free of charge to its target audience. Archive of the journal is available online at www.eajem.com, free of charge.

The journal is printed on an acid-free paper.

OPEN ACCESS

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Instructions to Authors

Eurasian Journal of Emergency Medicine (Eurasian J Emerg Med), as a double-blind peer reviewed journal published by the Emergency Medicine Physicians' Association of Turkey, publishes original articles on clinical, experimental and basic sciences in the Emergency Medicine field, review articles covering basic and up-to-date subjects, case reports, short editorial manuscripts and manuscripts covering medicine history and publication and research ethics.

Editorial and publication processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE). The journal is in conformity with Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

Originality, high scientific quality and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not be previously presented or published in an electronic or a printed medium. Editorial Board should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. Submission of previous reviewer reports will expedite the evaluation process. Manuscripts that have been presented in a meeting should be submitted with detailed information on the organization including the name, date and location of the organization.

Manuscripts submitted to Eurasian Journal of Emergency Medicine will go through a double blind peer review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in the field in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or the editorial board members of the journal. The Editor in Chief is the final authority in the decision making process of all submissions.

An approval of research protocols by Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", amended in October 2013, www.wma.net) is required for experimental, clinical and drug studies and some case reports. If required, ethics committee reports or an equivalent official document may be requested from the authors. For manuscripts concerning experimental research on humans, a statement should be included that shows informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee and the ethics committee approval number should also be stated in the materials and methods section of the manuscript. It is the authors' responsibility to carefully protect the patients' anonymity. For photographs that may reveal the identity of the patients, releases signed by the patient or their legal representative should be enclosed.

All submissions are screened by a similarity detection software (iThenticate by CrossCheck).

In the event of an alleged or suspected research misconduct, including plagiarism, citation manipulation, and data falsification/fabrication, among others, the Editorial Board will follow and act in accordance with COPE guidelines.

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

2. Drafting the work or revising it critically for important intellectual content; AND

3. Final approval of the version to be published; AND

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their coauthors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Eurasian Journal of Emergency Medicine requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.eajem.com) during the initial submission process in order to act appropriately to authorship rights and prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship", the submission will be rejected without further review. As part of submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Eurasian Journal of Emergency Medicine requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest.

Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board and to disclose potential conflicts of interest ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of potential conflicts of interest of editors, authors and reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

Editorial Board of the journal handles appeal and complaint cases within the scope of COPE guidelines. Authors should get in direct contact with the editorial office regarding their appeals and complaints. When needed, an ombudsperson can be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision making process of appeals and complaints.

When submitting a manuscript to the Eurasian Journal of Emergency Medicine, authors accept to assign the copyright of their manuscript to Emergency Medicine Physicians' Association of Turkey. If rejected for publication, the copyright of the manuscript will be assigned back to the authors. Eurasian Journal of Emergency Medicine requires each submission to be accompanied by a Copyright Transfer Form (available for download at www.eajem.com). When using previously published content, including figures, tables, or any other material in both print and electronic formats, authors must obtain permission from the copyright holder.

Statements or opinions expressed in the manuscripts published in Eurasian Journal of Emergency Medicine reflect the views of the author(s) and not the opinions of the editors, the editorial board or the publisher; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

Manuscript Preparation

The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2015 -

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

http://www.icmje. org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.eajem.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript is prepared and submitted in accordance with the journal's guidelines. Submissions that don't conform the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the;

- Copyright Transfer Form,

- Author Contributions Form,

- and ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.eajem.com

Title page: A separate title page should be submitted with all submissions and this page should include;

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

- Name(s), affiliations and major degree(s) of the author(s)

- Grant information and detailed information on the other sources of support,

- The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author,

- Acknowledgement of the individuals who contributed to the preparation of the manuscript but do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for letters to the editor. The abstract of Original Articles should be structured with subheadings (Aim, Materials and Methods, Results and Conclusion).

Keywords: Each submission must be accompanied by a minimum of three and a maximum of six keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations.

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Materials and Methods (with subheadings), Results, Discussion, Study Limitations, Conclusion subheadings. Please check Table 1 for limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with the international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and statistical software that was used during the process must certainly be specified. Data must be expressed as mean±standard deviation when parametric tests are used to compare continuous variables. Data must be expressed as median (minimum-maximum) and percentiles (25th and 75th percentiles) when non-parametric tests are used. In advanced and complicated statistical analyses, relative risk (RR), odds ratio (OR) and hazard ratio (HR) must be supported by confidence intervals (CI) and p values.

Editorial Comments: Editorial comments aim at providing brief critical commentary by the reviewers having expertise or with high reputation on the topic of the research article published in the journal. Authors are selected and invited by the journal. Abstract, Keywords, Tables, Figures, Images and other media are not included.

Review Articles: Reviews which are prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into high volume of publication and higher citation potential are taken under review. The authors may be invited by the journal. Reviews should be describing, discussing and evaluating the current level of knowledge or topic used in the clinical practice and should guide future studies. Please check Table 1 for limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in the diagnosis and treatment, those offering new therapies or revealing knowledge not included in the books, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, Conclusion subheadings. Please check Table 1 for limitations for Case Reports.

Letters to the Editor: This type of manuscripts can discuss important parts, overlooked aspects or lacking parts of a previously published article. Articles on the subjects within the scope of the journal that might attract the readers' attention, particularly educative cases can also be submitted in the form of "Letter to the Editor". Readers can also present their comments on the published manuscripts in the form of "Letter to the Editor". Abstract, Keywords, Tables, Figures, Images and other media are not included. The text should be unstructured. The manuscript that is being commented on must be properly cited within the manuscript.

Scientific letter: Manuscripts with prior notification characteristics, announcing new, clinically important scientific developments or information are accepted as Scientific Letters. Scientific Letters should not include sub-headings and should not exceed 900 words. Number of references should be limited to 10 and number of tables and figures should be limited to 2.

Clinical Imaging / Visual Diagnosis: Images must be typical for diagnosis, and should facilitate rapid diagnosis for emergency medicine and / or should be educational. Except for the header and references, it must consist of maximum 400 words. A maximum of three authors name, six images and five refecences should be included.

History: This type of manuscript explains events related to emergency and general medicine and presents information on the history of diagnosis and treatment of diseases. Historical findings should be a result of relevant research studies. Manuscript should not include sub-headings, should not exceed 900 words and total number of references should be limited to 10.

Publication ethics: This type of manuscript includes current information on research and publication ethics and presents cases of ethics infringement. Main text should not exceed 900 words and total number or references should be limited to 10.

Tables

Tables should be included in the main document, presented after the reference list and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide an easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

Table 1. Limitations for each manuscript type.

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000 (Structured)	200	50	6	7 or total of 15 images
Review Article	5000	200	50	6	10 or total of 20 images
Case Report	1500	200	10	No tables	10 or total of 20 images
Letter to the Editor	500	N/A	5	No tables	No media
Scientific letter	900	N/A	10	No tables	2 or total of 4 images
Clinical Imaging/ Visual Diagnosis	400	N/A	5	No tables	3 or total of 6 images
History	900	N/A	10	No tables	3 or total of 6 images
Publication ethics	900	N/A	10	No tables	No media

Figures and Figure Legends
Figures, graphics and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300DPI. To prevent delays in the evaluation process all submitted figures should be clear in resolution and large in size (minimum dimensions 100x100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and the main text. The abbreviation should be provided in parenthesis following the definition.

When a drug, product, hardware, or software mentioned within the main text product information, including the name of the product, producer of the product, city of the company and the country of the company should be provided in parenthesis in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables and figures should be referred to within the main text and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks and shortcomings of original articles should be mentioned in the "Discussion" section before the conclusion paragraph.

References
While citing publications, preference should be given to the latest, most up to date publications. If an ahead of print publication is being cited the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ Medline/PubMed (for journal abbreviations consult the List of Journals indexed for MEDLINE, published annually by NLM). When there are 6 or fewer authors, all authors should be listed. If there are 7 or more authors the first 6 authors should be listed followed by "et al". In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples:

Journal article: Lewin MR, Stein J, Wang R, Lee MM, Kernberg M, Boukhman M, et al. Humming is as effective as Valsalva's maneuver and Trendelenburg's position for ultrasonographic visualization of the jugular venous system and common femoral veins. Ann Emerg Med 2007; 50: 73-7.

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

Books 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.

Conference Proceedings: 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.

Manuscripts accepted for publication, not published yet: Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med In press 1997.

Epub ahead of print Articles: Sarıtaş A, Güneş H, Kandiş H, Çıkman M, Çandar M, Korkut S, et al. A Retrospective Analysis of Patients Admitted to our Clinic with Aortic Dissection. Eurasian J Emerg Med 2011 Dec 10. doi: 10.5152/jaem.2011.035. [Epub ahead of print]

Manuscripts published in electronic format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIEID/cid.htm.

REVISIONS
When submitting a revised version of a paper, the author must submit a detailed "Response to reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30 day period is over.

PROOFS AND DOI NUMBER
Manuscripts accepted for publication are provided with a DOI number immediately after acceptance. Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed it is published online on the journal's webpage as an ahead of print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

PERMISSIONS AND REPRINTS
Permission requests for reproduction of published content and reprint orders should be directed to the Editorial Office.

Please get in direct contact with the Editorial Office if you have any questions or comments regarding the journal.

EAJEM
Eurasian Journal of Emergency Medicine
Citation abbreviation: Eurasian J Emerg Med

CONTENTS

EURASIAN JOURNAL OF EMERGENCY MEDICINE

The Public Health Role of Medical Toxicology

Medical Toxicology is a core component of public health, environmental and occupational health and medicine. The pharmacologic and toxicologic education in medical school and residency has advanced throughout the world in the last 40 years. When I first began my training in emergency medicine in the 1970s, there were few early textbooks of emergency medicine and none in medical toxicology. As I began my career, I saw daily overdoses of heroin, caustics, lead, salicylates, hydrocarbons, barbiturates and ethanol. Yet there were no resources or mentors in the field. Poison Control Centers had begun in Europe and the United States but few physicians or pharmacists played critical roles, and case databases, evidence based information and research were nearly nonexistent.

Today many medical schools have transformed pharmacologic education to incorporate medical toxicology, most often taught by emergency physicians who are also subspecialized in medical toxicology. Today many residencies such as Pediatrics and Internal Medicine incorporate education in medical toxicology, whereas almost all residencies in emergency medicine have extensive training in medical toxicology.

We have created a specialty focusing on poisoning and overdose, homicide and suicide and occupational and environmental exposure. Medical toxicology ranges from the care of the neonate suffering abstinence from opioids, the infant unintentionally exposed to a household toxin, an adolescent experimenting with drugs such as amphetamines or cannabinoids, a worker suffering an occupational exposure, a medical error in hospital or a geriatric patient with an adverse drug event. All of these possibilities became the work of the specialist in medical toxicology. Two year Fellowships in medical toxicology have been developed in our department and many others since the early 1980s. These fellowship trained individuals are currently working at the Centers for Disease Control and Prevention (CDC), the Agency for Toxic Substance and Disease Registry (ATSDR), the National Institute of Health (NIH) and the National Institute of Drug Abuse (NIDA). They work in every Poison Control Center in America, almost all academic departments of emergency medicine have medical toxicologists and these individuals work side by side with specialized clinical pharmacists.

These leaders have transformed national standards of care, defined essential antidotes, worked on enhancing awareness, creating laboratories and regulatory services. The goals for all of us in emergency medicine are to create an educational and research environment that will improve development of knowledge and the transmission of evidence to the caregiver who will assure that each patient receives comprehensive integrated care. Each emergency physician, medical toxicologist and poison center is a critical part of the public health system. Each poisoning is an unnecessary event that must be addressed as a failure in the public health system that we endeavor to prevent from reoccurring (1). Our intellectual rigor, clinical excellence and academic commitment in medical toxicology will assist governmental decision making, improve pharmacologic practice and improve the health of our nations (469 of 507).

Lewis R. Goldfrank, MD
Herbert W. Adams Professor of Emergency Medicine
New York University School of Medicine
Ronald O. Perelman Department of Emergency Medicine
Bellevue Hospital Center
Medical Director, New York City Poison Center

References

1. Forging a Poison Prevention and Control System, Committee on Poison Prevention and Control, Board on Health Promotion and Disease Prevention. Institute of Medicine of the National Academies. The National Academies Press, 2004, Washington, D.C. www.nap.edu.

DOI: 10.5152/eajem.2017.00001

Prognostic Value of Red Cell Distribution Width in Critically Ill Patients and Comparison with Intensive Care Unit Scoring Systems

Emin Fatih Vişneci[1], Başar Cander[2], Mehmet Gül[2], Zerrin Defne Dündar[2], Ali Dur[2], Abdullah Sadık Girişgin[2]

[1]Clinic of Emergency Medicine, Konya Training and Resarch Hospital, Konya, Turkey
[2]Department of Emergency Medicine, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey

Abstract

Aim: This study aimed to investigate the prognostic value of lactate and red cell distribution width (RDW) parameters of patients admitted to emergency service and critical care unit (CCU).

Materials and Methods: A total of 147 patients hospitalized in the CCU of Necmettin Erbakan University, Meram Faculty of Medicine, Department of Emergency Medicine, were included in the study. Vital signs, laboratory results, lactate, and RDW values of the patients were recorded. Acute Physiology and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were calculated. Duration of hospitalization and intensive care unit stay and mortalities were recorded. Chi-square, Fisher's exact chi-square, and Student t tests were used for statistical analyzes, and Mann-Whitney U test was used for comparing nonparametric data that were not compatible with a normal distribution. $P<0.05$ were accepted as statistically significant. Spearman correlation analysis was used to assess whether a linear correlation existed between the parameters.

Results: A statistically significant correlation was found between the duration of stay in the CCU for <7 days and total duration of hospitalization ($p<0.001$). Also, statistically significant correlations were observed between mortalities of 28 days and 3 months, APACHE II and SOFA scores, and mean lactate (for 24 h and during hospitalization) and RDW values ($p<0.001$, $p<0.001$, $p<0.001$, and $p<0.05$, respectively). Moreover, correlations were noted between APACHE II scores, lactate value during the first admission, and SOFA scores ($p<0.001$). Correlations were also observed between 48-h SOFA scores and RDW and lactate values ($p<0.001$).

Conclusion: SOFA and APACHE II are the scoring systems used in practice. Efficiencies for mortality assessment of critical patients were confirmed. This study showed that lactate and RDW values, which were compatible with the scoring systems, could be used for assessing prognosis. Wider and more comprehensive studies that can assess scoring systems and lactate and RDW values together for prognostic identification are required to validate the findings.

Keywords: Acute physiology and chronic health evaluation II score, critical patient, intensive care, lactate, red cell distribution width, sequential organ failure assessment score

Introduction

Emergency services and emergency critical care units (CCUs) are the most frequently visited departments for the diagnosis and follow-up of critically ill patients (1). CCUs are the optional units among emergency services in Turkey where intensive care patients are followed up. The CCU of Necmettin Erbakan University, Meram School of Medicine, Department of Emergency Medicine, is also a tertiary intensive care unit (ICU). Longer durations for the diagnosis and transfer of critical patients to the other clinics increase the importance of emergency CCUs. Remarkable knowledge of critical patient follow-ups and close follow-up of prognostic signs are necessary. Blood lactate level is one of the most frequently used parameters (2). Tissue hypoxia during shock and the condition after shock resuscitation are the indicators of prognosis for critical cases in terms of identification of severity and mortality risk of diseases and must be considered a useful indicator for conditions such as etiologic diagnosis (3, 4). Red cell distribution width (RDW) is one such indicator. RDW is an index for the variability of erythrocyte volumes and can be used for detecting the anisositosis grade. The RDW value is known to increase in many types of anemia,

This study was presented at the 1st International Critical Care and Emergency Medicine Congress, 06-08 November 2013, İstanbul, Turkey.

Correspondence to: Emin Fatih Vişneci e-mail: drfatihvisneci@hotmail.com

Received: 03.01.2017 • **Accepted:** 06.02.2017

DOI: 10.5152/eajem.2017.43531

hemoglobinopathies, and conditions such as blood transfusion. Recent studies have shown that RDW increases in cardiopulmonary diseases, such as coronary artery disease, heart failure, and pulmonary hypertension, and is strongly correlated with the prognosis (5, 6).

Acute Physiology and Chronic Health Evaluation II (APACHE II) and sequential organ failure assessment (SOFA) are highly efficient scoring systems for assessing disease severity and mortality of patients in ICUs.

The aim of this study was to detect the prognostic value of RDW and lactate for the patients admitted to emergency services and those in CCUs and to compare them with regard to scoring systems.

Materials and Methods

This was a prospective and observational study conducted in the CCU of Necmettin Erbakan University, Meram School of Medicine, Department of Emergency Medicine. Ethical approval was obtained. Male and female patients aged >18 years who provided informed consent and filled the study form completely were included in the study. Exclusion criteria were as follows: patients who received erythrocyte suspension during their stay in the CCU and in the last 2 weeks, cases with known hematologic malignancy, patients diagnosed with myelodysplastic syndrome, pregnant patients, and patients with malignancies and bone marrow invasion. A total of 647 patients were hospitalized in the CCU during the study period, and 164 of these, whose examinations were completed and who met the inclusion criteria, were included in the study. Three patients were excluded on their or relatives' request; eight patients due to their transfer to another center and six patients based on their blood transfusion needs were excluded from the study. Thus, 147 patients were included in the study. Demographic data, vital signs, and laboratory examinations of the patients were recorded starting from their stay in the CCU. The mean lactate values at the first admission, during the first 24 h, at 48 h, and during the CCU stay were recorded. In addition, the mean RDW value at the first admission, at 48 h, and during the follow-up in the CCU was recorded. Moreover, APACHE II and SOFA scores at first admission and 48 h were calculated. Total hospitalization durations were identified for the patients who stayed in the CCU for <7 days and >7 days. Mortalities at 28 days and 3 months were recorded.

Statistical analysis

The data were statistically assessed using Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA). The chi-square test and when necessary Fisher's exact chi-square test were used for categorical data. The Student *t* test was used for parametric data, and the Mann-Whitney U test was used for comparing non-parametric data that were not compatible with a normal distribution. $p<0.05$ was accepted as statistically significant. The Spearman correlation analysis was used to assess whether a linear correlation existed between some parameters and if the correlation coefficient (*r*) was 0.00-0.25 accepted as extremely weak, 0.26-0.49 accepted as weak, 0.50-0.69 accepted as moderate, 0.70-0.89 accepted as high, and 0.90-1.00 accepted as extremely high.

Results

The mortality and discharge rates of 147 patients included in the study according to their gender are shown in Table 1; 78 patients (53.1%) were males and 69 (46.9%) were females. The mean±stard deviation age was 67±15 years; 59 patients (40.1%) died in the hospital, and 88 (59.9%) were discharged.

Table 1. In-hospital mortality and discharge rates according to patient gender

	Death, n (%)	Discharge, n (%)	Total, n (%)
Male	34 (57.6)	44 (50)	78 (53.1)
Female	25 (42.4)	44 (50)	69 (46.9)
Total	59 (100)	88 (100)	147 (100)

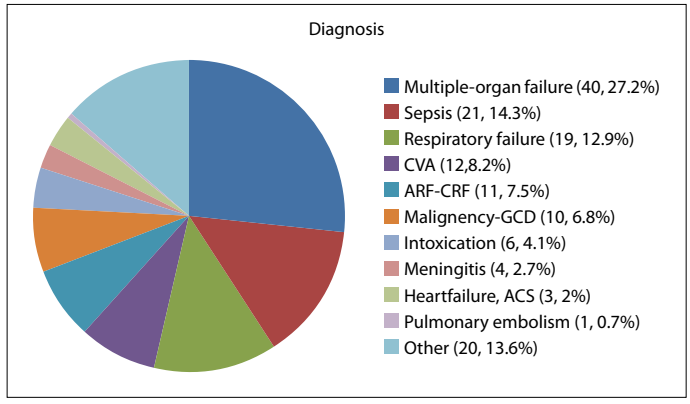


Figure 1. Distribution of patients according to diagnosis
CVA: cerebro vascular accident; ARF: acute renal failure; CRF: chronic renal failure; GCD: general condition disorder

The distribution of the patients according to their diagnoses is shown in Figure 1. The most frequent diagnoses were sepsis and multiple organ failure.

The mean APACHE II score at the first hospitalization in the CCU was 16±6.5. The SOFA score at first hospitalization and at 48 h was 5.6±2.8 and 5.9±2.9, respectively. The mean RDW value at the first hospitalization, at 48 h, and during their stay in the CCU was 13.8±2.5, 13.8±2.6, and 13.8±2.5, respectively. The mean lactate value at first admission in the CCU, at 24 h, mean value at 24 and 48 h was 2.6±2.5, 1.9±1.6, 2.2±1.7, and 1.7±1.3, respectively. The mean lactate value for the period of stay in the CCU was 1.9±1.

The mean duration of the stay in the CCU was 10.9±11.8 days (the shortest was 1 d and the longest was 88 d). The mean duration of total hospital stay was 14±13 days (the shortest was 2 d and the longest was 88 d).

Patients who were followed up in the CCU for <7 days and >7 days were compared with the those who survived and those who died in 28 days and 3 months in terms of lactate and RDW values and APACHE II and SOFA scores. Age, gender, and APACHE II and SOFA scores at first admission and at 48 h, mean RDW values at first admission and at 24 h, mean value at 24 and 48 h, and mean lactate value during the whole hospital stay were compared between the groups. Also, the total duration of stay and the duration of stay in the CCU were compared between groups. Patients diagnosed with respiratory failure were excluded while assessing RDW.

The comparison of statistics of the patients followed up in the CCU for <7 days and >7 days is shown in Table 2. The total duration of stay of the patients followed up in the CCU for <7 days was 7.5±6.2 days. The total duration of stay of the patients followed up in the CCU for ≥7 days was 20.1±14.4 days ($p<0.001$).

The comparison of statistics for the patients who survived and those who died in 28 days is shown in Table 3. A statistically signif-

Table 2. Comparison of age, gender, APACHE II score, SOFA score, duration of stay, mean lactate, and RDW values of the patients for the duration of stay in the CCU shorter than 7 days and longer than 7 days

Duration of stay	<7 Days		≥7 Days		P
Age, year (mean±SD)	67±15		67.6±16		0.834
	n	%	n	%	
Gender					
Male	35	50.7	43	55.1	0.593
Female	34	49.3	35	44.9	
APACHE II	15±6.3		17±6.9		0.080
SOFA at first admission	5.3±2.7		5.8±2.9		0.301
SOFA at 48 h	5.5±3.3		6.2±2.7		0.144
RDW at first admission	13.8±2.4		13.9±2.6		0.724
RDW at 48 h	13.9±2.7		13.9±2.6		0.989
Mean RDW (during stay)	13.7±2.5		14±2.6		0.381
Lactate at first admission	2.2±1.4		2.9±3.1		0.749
Lactate at 24 h	2.2±2		1.7±1		0.418
Mean lactate value during 24 h	2.3±1.8		2.2±1.7		0.561
Lactate at 48 h	1.8±1.6		1.7±1		0.256
Mean lactate (during stay)	1.9±1.3		1.8±0.9		0.796
Duration of stay in the CCU	3.8±1.4		17.2±13.5		0.000
Total duration of stay	7.5±6.2		20.1±14.4		0.000

APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; RDW: red cell distribution width; CCU: critical care unit

Table 3. Comparison of age, gender, APACHE II score, SOFA score, duration of stay, mean lactate, and RDW values in terms of 28-day mortality

Clinical result	Dead		Alive		p
Age, year (mean±SD)	70±13.2		65.8±16.6		0.114
	n	%	n	%	
Gender					
Male	31	59.6	47	49.5	0.239
Female	21	40.4	48	50.5	
APACHE II	18.6±6.7		14.7±6.2		0.001
SOFA at first admission	6.8±3		4.9±2.5		0.000
SOFA at 48 h	7.2±3.3		4.9±2.3		0.000
RDW at first admission	14.±2.6		13.6±2.4		0.013
RDW at 48 h	14.5±2.9		13.4±2.2		0.029
Mean RDW (during stay)	14.5±2.6		13.4±2.3		0.021
Lactate at first admission	3.2±3		2.2±2		0.032
Lactate at 24 h	2.7±2.1		1.4±0.7		0.000
Mean lactate value during 24 h	3±2.2		1.7±1		0.000
Lactate at 48 h	2.1±1.7		1.5±0.9		0.001
Mean lactate (during stay)	2.4±1.4		1.6±0.7		0.000
Duration of stay in the CCU	9.2±6.2		11.9±14		0.704
Total duration of stay	10.2±6.6		16.4±15		0.045

APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; RDW: red cell distribution width; CCU: critical care unit

icant difference was observed between the patients who survived and died in 28 days in terms of APACHE II score (p=0.001). A statistically significant difference was found between the SOFA scores at the first admission and at 48 h (p<0.001). Moreover, a statistically significant difference in the lactate level at the first admission was observed (p=0.032). A statistically significant difference was noted between lactate values at 24 h, mean value at 24 h, and mean value during the hospital stay (p<0.001). Also, a statistically significant difference was observed in lactate values at 48 h (p=0.001). Moreover, a statistically significant difference was found in the RDW values at first admission and at 48 h and the mean RDW value (p=0.013, p=0.029, and p=0.021, respectively).

The comparison of the statistics for the patients who survived and those who died in 3 months is shown in Table 4. No statistically significant difference was found between the patients who survived and those who died in 3 months in terms of age, gender, and total duration of the stay. The APACHE II score at first admission and the SOFA score at 48 h were higher in the patients who died than in those who survived (p<0.001). Lactate values at first admission and at 24 h, mean value at 24 h, and mean value during the hospital stay was different in the patients who died compared to those who survived (p=0.012, p=0.002, and p<0.001, respectively). RDW values at first admission, at 48 h, and during the stay in the CCU were higher in the patients who died than in those who survived (p=0.016, p=0.015, and p=0.024, respectively).

The duration of stay in the CCU was higher in the patients who died than in those who survived. A statistically significant increase in mortality was detected with the increase in the duration of stay in the CCU (p=0.042).

Finally, it was assessed whether a correlation existed in terms of age, gender, APACHE II scores, SOFA scores (at first admission and at 48 h), RDW values (at first admission and at 48 h and mean value during the hospital stay), lactate values (at first admission and at 24 h, mean value at 24 h and 48 h, and mean value during the hospital stay), duration of stay in the CCU, and total hospitalization duration. A correlation was found between the SOFA score at first admission and RDW value at

Table 4. Comparison of age, gender, APACHE II score, SOFA score, duration of stay, mean lactate, and meand RDW values of the patients that died and survived in 3 months

Clinical result	Dead		Alive		p
Age, year (mean±SD)	68.4±14.8		66.7±16.2		0.509
	n	%	n	%	
Gender					
Male	34	57.6	44	50	0.364
Female	25	42.4	44	50	
APACHE II	18.5±6.8		14.5±6		0.000
SOFA at first admission	6.7±2.9		4.8±2.5		0.000
SOFA at 48 h	7.5±3		4.8±2.4		0.000
RDW at first admission	14.4±2.6		13.2±2		0.016
RDW at 48 h	14.4±2.8		13.3±2.2		0.015
Mean RDW (during stay)	14.4±2.6		13.4±2.3		0.024
Lactate at first admission	3.1±2.9		2.2±2.1		0.012
Lactate at 24 h	2.4±1.9		1.5±0.9		0.002
Mean lactate value during 24 h	2.8±2.1		1.7±1		0.000
Lactate at 48.hour	2±1.6		1.5±0.9		0.011
Mean lactate (during stay)	2.3±1.3		1.6±0.7		0.000
Duration of stay in the CCU	13.4±15		9.2±8.8		0.042
Total duration of stay	14.9±15.4		13.7±11		0.865

APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; RDW: red cell distribution width; CCU: critical care unit

first admission, mean RDW value during the hospital stay, and lactate value at first admission (p=0.025, p=0.043, and p=0.011, respectively). A correlation was observed between the SOFA score at 48 h and RDW value at 48 h and mean RDW value during the hospital stay (p=0.04 and p<0.001, respectively). Also, a correlation was observed between the lactate value at 48 h and RDW value at 48 h and mean RDW value during the hospital stay (p=0.003 and p=0.005, respectively). Moreover, a correlation was noted between the APACHE II score and SOFA score at first admission (r=0.682) and the SOFA score at 48 h (r=631; p<0.001 and p<0.001, respectively) (Figure 2).

Discussion

Critical patients are those with unstable life functions, who are receiving supportive treatment, with poor general conditions, and generally treated in ICUs (7).

The lifespan has been prolonged due to the improvement in life conditions and higher access rates of patients to health services with development in medical sciences.

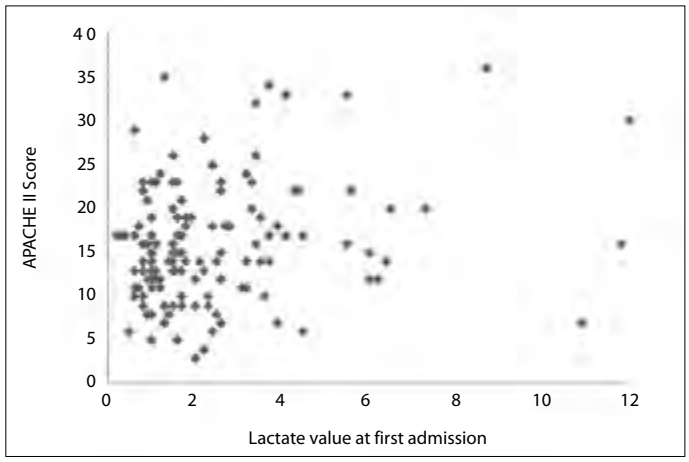
The available literature shows that 46% of the patients hospitalized in the ICUs are older patients (8). This has led to a significant increase in mortality rates of the older patients hospitalized in the ICUs (9-11). Most of the patients in the present study were older patients. However, a 7-day stay in the CCU, 28-day and 3-month mortality, and age were not found to be significantly correlated. This might be due to the differences between diagnoses of age groups, scores, and the lack of classification according to the age groups. It is necessary to assess the influence of age on mortality rates of different patient groups in terms of diagnosis, gender, APACHE II and SOFA scores, and Glasgow Coma Score.

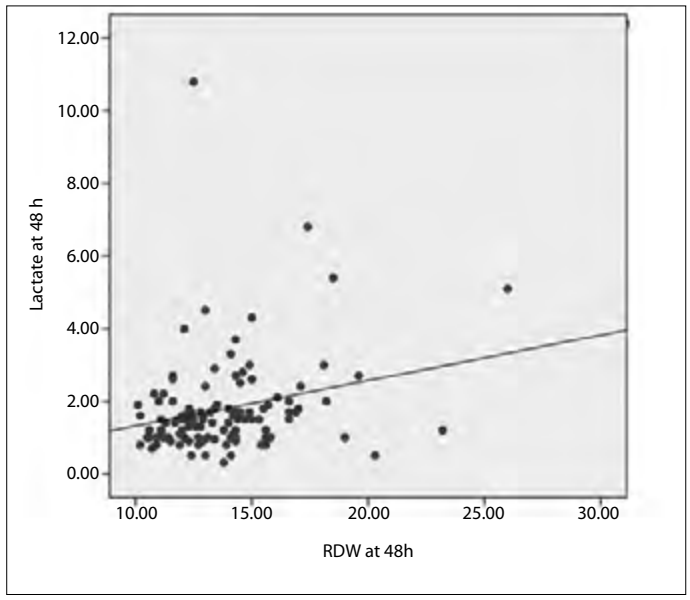
Mahmood et al. (12) explored the relation between age and clinical course and found no significant difference between female and male patients who were aged 50 years and older, but the mortality at the age of 50 years was lower in female patients than in male patients. Jacobson et al. (13) conducted a prospective observational cohort with the patients internalized in the ICU for a 3-year period; with sepsis in the first 24 h, no correlation was found between mortality, hospitalization duration, and gender. The present study found no statistically significant difference between the genders in terms of the 28-day and 3-month mortalities (p>0.05).

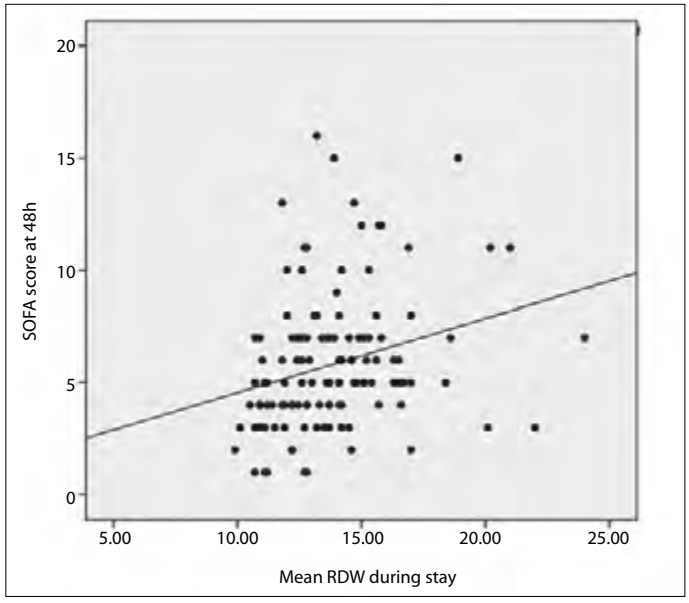
Another study by Wang et al. (14) performed in collaboration with medical and surgical ICUs in Canada assessed 1960 patients, and the most frequent reason for hospitalization was found to be multiple trauma and septic shock, followed by respiratory problems (14). Two and three patients had sepsis and respiratory problems, respectively, in the present study, whereas one patient had multiple organ failure due to several reasons. This might be because the current CCU was a general ICU.

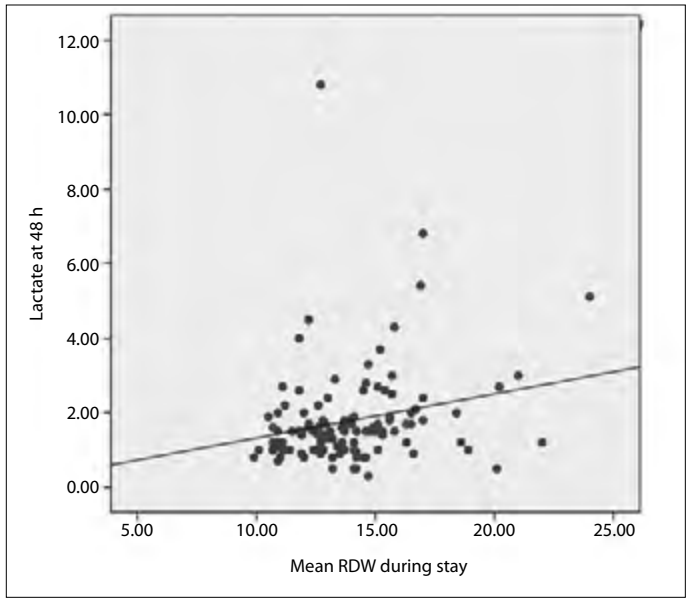
Clinical findings in the ICU and laboratory results are used to estimate the prognosis and death risk of the patients in the ICUs. Lactate is one of the most frequent and easily assessed parameters used in shock and other critical diseases (15). Higher lactate values must be considered as a useful indicator in identifying the severity of diseases and mortality rates (16-19). On the contrary, some studies showed the first lactate values as a weak indicator of mortality (20). The present study found a statistically significant difference between lactate values at first admission and at 24 h, mean values at 24 h, 48 h, and during the stay, and 28-day and 3-month mortalities. However, a higher *P* value was reported for the lactate values at the first admission. Lactate values other than the value at the first admission were more significant.

However, the number of studies on RDW values used in daily practice but not receiving sufficient attention has increased recently. RDW was found to be related to mortality and hospitalization duration. Therefore, RDW is a parameter to be focused on. Physiologic mechanisms (oxidative stress, inflammation, and weak pulmonary function) with higher RDW rates and higher death rates in terms of cardiovascular mortality have been demonstrated but are not completely known (21, 22). Wang et al. (14) found a correlation between higher RDW rates and the APACHE II score. They also found the RDW value to correlate with mortality and duration of stay. Hunziker et al. (23) showed the prognostic value of RDW for ICU mortality, in-hospital mortality, and Simplified Acute Physiology Score (SAPS). The present study found a correlation between RDW value and 28-day and 3-month mortality. Moreover, a correlation was observed between RDW values, SOFA scores at the first admission and at 48 h, and lactate values at 48 h.









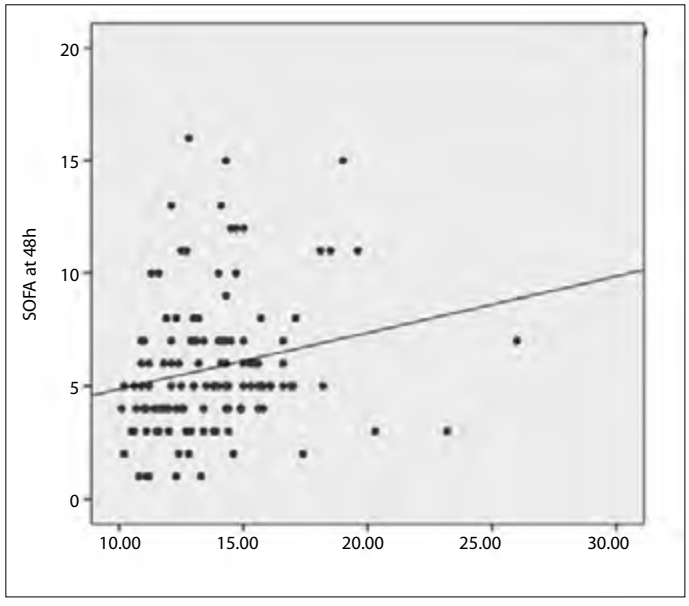


Figure 2. a-e. (a) Correlation between the lactate value at first admission and APACHE II score, (b) Correlation between the mean RDW value during stay and SOFA score at 48 h, (c) Correlation between the RDW value and SOFA score at 48 h, (d) Correlation between the RDW value and lactate value at 48 h, (e) Correlation between the mean RDW value during stay and lactate value at 48 h

APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; RDW: red cell distribution width

The present study found a correlation between one of the most commonly used parameters APACHE II and SOFA scores with 28-day and 3-month mortalities. Hantke et al. (24) assessed SOFA and APACHE II scores in 874 surgical intensive care patients and found the values below the line identified for mortality (0.73 for APACHE II and 0.71 for SOFA). Timsit et al. (25) calculated SOFA scores for each day in a 1-week period for 1685 intensive care patients. For the first week in the ICU, the SOFA score was used to estimate mortality, and was suggested for use to estimate contributions of background diseases to death risk. The estimation of mortality for the patients in the CCU by using APACHE II and SOFA scores in the present study was compatible with the literature. APACHE II and SOFA scores were found to correlate with mortality. Higher statistically significant APACHE II and SOFA scores were observed in the patients who died while assessing the 28-day and 3-month mortalities.

Conclusion

Therefore, APACHE II and SOFA scores continue to be an important guide for estimating mortality. Lactate and RDW values, which are compatible with scoring systems, are considered prognostic indicators. Also, more comprehensive studies will help in assessing the parameters that can be used for the prognosis of critical patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University School of Medicine (18.01.2013, Decision No: 2013-332).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Bektemur G, Osmanbeyoglu N, Cander B. Emergency Department Care Survey. Eurasian J Emerg Med 2015; 14: 1-33. [CrossRef]
2. García Sanz C, Rupérez Lucas M, López-Herce Cid J, Vigil Escribano D, Garrido Cantarero G. Prognostic value of the pediatric index of mortality (PIM) score and lactate values in critically-ill children. An Esp Pediatr 2002; 57: 394-400. [CrossRef]
3. Gotay-Cruz F, Avilés-Rivera DH, Fernández-Sein A. Lactic acid levels as prognostic measure in acutely ill patients. P R Health Sci J 1991; 10: 9-13.
4. Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, et al. Serial lactate for prediction of outcome after cardiac arrest. Medicine (Baltimore) 2004; 83: 274-9. [CrossRef]
5. Karnad A, Poskitt TR. The automated complete blood cell count. Use of the red blood cell volume distribution width and mean platelet volume in evaluating anemia and thrombocytopenia. Arch Intern Med 1985; 145: 1270-2. [CrossRef]
6. Hampole CV, Mehrotra AK, Thenappan T, Gomberg-Maitland M, Shah SJ. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. Am J Cardiol 2009; 104: 868-72. [CrossRef]
7. Cander B, Dundar ZD, Gul M, Girisgin S. Prognostic value of serum zinc levels in critically ill patients. J Crit Care 2011; 26: 42-6. [CrossRef]
8. Aulbert E, Steffens O. Serum ferritin-a tumor marker in malignant lymphomas. Onkologie 1990; 13: 102-8.
9. Trivedi TH, Shejale SB, Yeolekar ME. Nosocomial pneumonia in medical intensive care unit. J Assoc Physicians India 2000; 48: 1070-3.
10. Scott BH, Seifert FC, Grimson R, Glass PS. Octogenarians undergoing coronery artery bypass graft surgery: resource utilization, postoperative mortality and morbidity. J Cardiothorac Vasc Anesth 2005; 19: 583-8. [CrossRef]
11. Seferian EG, Afessa B. Adult intensive care unit use at the end of life: a population-based study. Mayo Clin Proc 2006; 81: 896-901. [CrossRef]
12. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Crit Care 2012; 16: R92. [CrossRef]
13. Jacobson S, Liedgren E, Johansson G, Ferm M, Winsö O. Sequential Organ Failure Assessment (SOFA) scores differ between genders in a sepsis cohort: Cause or effect? Ups J Med Sci 2012; 117: 415-25. [CrossRef]
14. Wang F, Pan W, Pan S, Ge J, Wang S, Chen M. Red cell distribution width as a novel predictor of mortality in ICU patients. Ann Med 2011; 43: 40-6. [CrossRef]
15. Deshpande SA, Platt MP. Association between blood lactate and acid-base status and mortality in ventilated babies. Arch Dis Child Feta Neonatal Ed 1997; 76: F15-20.
16. Cheung PY, Robertson CM, Finer NN. Plasma lactate as a predictor of early childhood neurodevelopmental outcome of neonates with severe hypoxemia requiring extracorporeal membrane oxygenation. Arch Dis Child 1996; 74: F47-50. [CrossRef]
17. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, et al. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med 2001; 27: 74-83. [CrossRef]
18. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med 2004; 32: 1637-42. [CrossRef]
19. Schulman AM, Claridge JA, Carr G, Diesen DL, Young JS. Predictors of patients who will develop prolonged occult hypoperfusion following blunt trauma. J Trauma 2004; 57: 795-800. [CrossRef]
20. Hatherill M, Sajjanhar T, Tibby SM, Champion MP, Anderson D, Marsh MJ, et al. Serum lactate as a predictor of mortality after paediatric cardiac surgery. Arch Dis Child 1997; 77: 235-8. [CrossRef]
21. Horne BD, May HT, Muhlestein JB, Ronnow BS, Lappé DL, Renlund DG, et al. Exceptional mortality prediction by risk scores from common laboratory tests. Am J Med 2009; 122: 550-8. [CrossRef]
22. Garcez, ME, Peres, W, Salvador, M. Oxidative stress and hematologic and biochemical parameters in individuals with Down syndrome. Mayo Clin Proc 2005; 80: 1607-11. [CrossRef]
23. Hunziker1 S, Celi1 LA, Lee J, Howell MD. Red cell distribution width improve Critical Care 2012;16:R89 20.
24. Hantke M, Holzer K, Thöne S, Schmandra T, Hanisch E. The SOFA score in evaluating septic illnesses. Correlations with the MOD and APACHE II score. Chirurg 2000; 71: 1270-6. [CrossRef]
25. Timsit JF, Fosse JP, Troché G, De Lassence A, Alberti C, Garrouste-Orgeas M, et al. Calibration and discrimination by daily Logistic Organ Dysfunction scoring comparatively with daily Sequential Organ Failure Assessment scoring for predicting hospital mortality in critically ill patients. Crit Care Med 2002; 30: 2003-13. [CrossRef]

Comparison of Eosinophil Values with Other Biomarkers in Predicting Perforation of Acute Appendicitis

Serhat Akay[1], Huriye Akay[1], Enver Vardar[2], Zehra Erkul[2]
[1]Clinic of Emergency Medicine, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey
[2]Clinic of Pathology, İzmir Bozyaka Training and Research Hospital, İzmir, Turkey

Abstract

Aim: Perforation is the most common complication of acute appendicitis (AA) and is also a significant cause of infertility among women. One significant challenge for accurate and timely diagnosis of AA before perforation occurs is the limited availability of sensitive and specific blood biomarkers. Although previous studies have proposed hyperbilirubinemia as a biomarker for predicting impending perforation, additional biomarkers with improved specificity and sensitivity are greatly needed. Recently, eosinopenia and altered neutrophil/leukocyte ratio have been proposed as candidate biomarkers for monitoring several emergency situations, such as sepsis. In this study, we aimed to determine whether several peripheral blood parameters, including bilirubin level, total numbers of eosinophils, platelets, and neutrophils, neutrophil/leukocyte ratio, and mean platelet volume, are predictive for impending perforation in patients with AA.

Materials and Methods: All cases with histopathologically confirmed AA who were admitted to our hospital between January 1, 2012 and December 31, 2013 were included in this retrospective study. The bilirubin levels, total numbers of eosinophils, platelets, and neutrophils, neutrophil/leukocyte ratios, and mean platelet volume levels were compared for non-perforated and perforated AA patients. To compare the groups, the post hoc Mann-Whitney-U test was used to analyze non-parametric continuous variables; also, the receiver operating characteristics (ROC) test was used for accuracy.

Results: Among the 590 patients who received a pathological diagnosis of AA, 10.8% progressed to perforation of the appendix. Significant differences in total leukocyte, neutrophil, and eosinophil counts, neutrophil/leukocyte ratios, and bilirubin levels were found between the non-perforated and perforated AA cohorts. The areas under the curve (AUCs) for each parameter were 0.64, 0.63, 0.66, 0.62, and 0.60, respectively. Neutrophil/leukocyte ratios ≥72.2% had the highest sensitivity (84.4%) and eosinophil counts of ≤20/mcl had the highest specificity (76.8%) in predicting perforation.

Conclusion: While eosinopenia alone does not appear to be a marker for perforation, eosinopenia accompanied by higher neutrophil and leukocyte counts, a higher neutrophil/leukocyte ratio, and a higher bilirubin level can be used as a biomarker panel for predicting perforation in cases of AA.

Keywords: Appendicitis, perforation, eosinopenia

Introduction

Acute appendicitis (AA) is a common cause of abdominal pain for patients presenting to emergency departments (EDs); it is the most common cause of acute abdomen-related operations (1). While the gold standard for the diagnosis of AA is physical examination and laboratory results (mainly leukocytosis), one major concern is that the symptoms and signs of AA frequently overlap those of several other acute abdominal emergencies. A delay in diagnosis and surgical intervention inevitably results in perforation, which is a leading cause of morbidity and mortality of AA. Furthermore, complications arising from AA, especially perforation, can result in dysfunction of the fallopian tubes; this usually leads to infertility (2). However, perforation in AA patients is usually diagnosed either intra-operatively by observation or post-operatively by histopathological examination. Thus, timely and accurate diagnosis of perforation is critical, as these complications can be prevented by surgical intervention and successful removal of the appendix.

Many studies have examined biomarkers as diagnostic tools for the diagnosis of appendicitis; however, the number of studies investigating candidate biomarkers for prediction of perforation is limited. Akyildiz et al. (3), in their study comparing perforated and non-perforated appendicitis patients failed to demonstrate differences in leucocyte counts. Studies suggested hyperbilirubinemia as a marker for

Correspondence to: Serhat Akay e-mail: howls_castle@mynet.com
Received: 04.12.2016 • **Accepted:** 23.01.2017

DOI: 10.5152/eajem.2017.99609

perforation (4-7). Sand et al. (4) showed that *Escherichia coli* endotoxin, upon entering the blood stream following perforation, can cause a reduction in bile flow *in vivo*, resulting in hepatocyte dysfunction and increased serum bilirubin levels.

Among other potential markers, Chaudhary et al. (7) have shown that increased leucocyte and neutrophil counts with neutrophil/leucocyte ratio are a poor predictor for perforation, while Abidi et al. (8) suggest that eosinopenia, a recently proposed marker for differential diagnosis of sepsis from systemic inflammatory response in ICU patients, may also be used to predict appendicitis-related perforation. In the study of Becchi et al. (9), furthermore, a change in mean platelet volume (MPV), an indicator of disruption of platelet production in bone marrow, has been shown to be a predictor of death in sepsis patients. In Narci et al. (10) and Tanrikulu et al. (11) studies, MPV has also been shown to decrease in AA cases compared to non-AA patients with acute abdominal symptoms; however, its utility in differentiating perforated AA from non-perforated AA has not yet been determined.

In this study, we aimed to determine whether peripheral blood levels of several biomarkers that were independently evaluated for AA diagnosis, including bilirubin level, total numbers of eosinophils, platelets, and neutrophils, neutrophil/leukocyte ratio, and MVP, can predict impending perforation among AA patients.

Materials and Methods

Patients admitted to a tertiary training hospital ED between January 1, 2012 and December 31, 2013 with operative and histopathological diagnoses of AA were included in this retrospective study. Approval was obtained from the Institutional Ethics Board prior to the start of the study. Laboratory values, pathology reports, operative diagnoses, and clinical data were obtained from patient files and the hospital electronic patient record system. The clinical diagnosis was established preoperatively by means of clinical examination of the attending general surgeon, laboratory results, and radiologic imaging by either ultrasound, performed by the attending radiologist, or intravenous contrast-enhanced computed tomography of the abdomen, interpreted by the attending radiologist.

All excised appendices were sent for pathological examination, and the definitive diagnosis was confirmed by histopathologic examination by the attending pathologist. Perforation was diagnosed either by disruption of the appendix wall intra-operatively in the presence or absence of abscesses or by observation of disruption of the appendix wall during histopathological examination. The exclusion criteria included patients younger than 14 years of age, patients with incomplete charts, patients transferred from another hospital with a diagnosis of AP, patients transferred to another hospital due to unavailable beds, and patients who left the ED or general surgery department on their own. Furthermore, patients with known liver and biliary diseases were excluded due to increased bilirubin levels in this patient group. In addition, patients receiving corticosteroid-containing therapies were excluded because corticosteroids may elevate leucocyte count. Finally, patients with allergic conditions were excluded because such patients may have higher eosinophil counts. Since this was a retrospective study, no informed consents were obtained.

Complete blood counts and full biochemistry panels for each patient were obtained during the initial physical examination by emergency physicians in the ED. The leucocyte and platelet counts, neutrophil and eosinophil differential counts, and MPV were measured using an automated hematology analyzer (BC 5800, Mindray, Shenzhen, China). The upper and lower limits of the reference intervals for leucocyte and platelet counts, neutrophil and eosinophil differential counts, neutrophil/leucocyte ratio, and MPV were 4 to $10x10^3$/mcl, 156 to $373x10^3$/mcl, 2.1 to $6.3x10^3$/mcl, 0 to 500/mcl, 41% to 73%, and 6.9 to 10.8 fl, respectively. Total bilirubin level was measured using a chemistry immune analyzer (AU 680, Olympus, Tokyo, Japan). The upper and lower limits of the reference interval for bilirubin were 0 to 1.2 mg/dL.

Statistical analysis was performed using Statistical Package for Social Sciences 21.0 for Windows (IBM Corp.; Armonk, NY, USA). The normality of distribution was assessed with Levene's test and the Kolmogorov-Smirnov test. To compare groups, the Mann-Whitney U test was used for analysis of non-parametric continuous variables. Continuous variables are presented as the mean and standard deviation, and the receiver operating characteristics (ROC) test was used to determine the accuracy of leucocyte, neutrophil, eosinophil, and platelet counts, neutrophil percentage, and MVP for predicting perforation of appendicitis. To find the optimal cutoff point, we used Youden's index to calculate sensitivity and specificity as well as positive and negative likelihood ratios and predictive values (12). ROC graphs were prepared using Medcalc 16.8 for Windows (Medcalc, Ostend, Belgium). For all statistical tests performed, $p<0.05$ was considered to be statistically significant.

Results

During the two-year period for which our study retrospectively analyzed data, 658 patients were admitted with an initial diagnosis of AA; of these, 590 patients who were conclusively diagnosed with AA based on histopathological findings were included in our study. 423 (71.7%) of patients were male, with an average age of 31.6±13.7 years. 64 (10.8%) patients had perforated appendicitis and 7 (1.2%) patients had wall disruption on histopathologic examination, meanwhile 42 (7.1%) received operative diagnoses and 15 (2.5%) received pathologic and operative diagnoses. When the ages and hospitalization times of patients with non-perforated AA were compared with those of patients with perforated AA, perforated AA patients were significantly older and had significantly longer hospital stays (30.5±12.6 vs 40.8±18.6 years, 2.7±1.4 vs 6.1±4.8 days, both $p<0.001$).

In this study, 142 (24.1%) patients had normal leucocyte counts, 118 (20.2%) had normal neutrophil counts, and 538 (91.2%) had normal total bilirubin counts. When we compared laboratory values between non-perforated and perforated AA patients, the differences in leucocyte, neutrophil, and eosinophil counts, neutrophil/leucocyte ratios, and total bilirubin levels were found to be significant between the two groups; however, the differences in platelet counts and MVP values were not found to be statistically significant when the two diagnosis groups were compared (Table 1).

The ROC analyzes for the leucocyte, neutrophil, and eosinophil counts, total bilirubin, and neutrophil/leucocyte ratio revealed that none of these five values had high accuracy for the diagnosis of perforation in AA, as assessed by the areas under the curve (AUCs) (Table 2). The ROC curves of all five variables show similar accuracies for predicting perforation (Figure 1).

Finally, because all AA patients included in this study underwent operations and the histopathological examination was performed

within our institute, we evaluated the sensitivity and specificity, determined by Youden's index, of perforated appendicitis patients; we found that neutrophil/leucocyte ratios ≥72.2% had the highest sensitivity (84.4%), whereas eosinophil counts ≤20/mcl had the highest specificity (76.8%) in predicting perforation among AA patients (Table 3).

Discussion

The findings of our retrospective study suggest that eosinopenia accompanied with increased leucocyte and neutrophil counts, increased neutrophil/leucocyte ratio, and high total bilirubin level can be used as a predictor for perforation in patients with AA. The independent use of these biomarkers for predicting perforation is not supported statistically; the AUCs of the ROC curves for these values are between 0.6 and 0.7, indicating low accuracy.

We compared the eosinophil counts between the perforated versus non-perforated AA patient groups and found that perforated AA patients have significantly lower eosinophil counts compared to non-perforated patients. In their study, Bass et al. (13), eosinophils accounted for 1% to 3% of leucocytes, and the inflammatory cascade initiated eosinophilic response via adrenal corticosteroids and epinephrine. Same study investigating the utility of eosinophil count in diagnosing sepsis suggested that as the inflammation cascade builds up, chemotactic substances released from inflammatory cells during the inflammatory response lead to the sequestration of circulating eosinophils at the site of inflammation, thus decreasing the number of circulating eosinophils. During the course of AA, when perforation occurs, the infected tissue at the site of appendicitis spills into the peritoneal cavity, resulting in either a localized abscess or diffuse peritonitis; this site may become a focus for sequestration of circulating eosinophils, resulting in a decrease in eosinophil count. The optimal cutoff point for eosinopenia determined by Youden's index in this study is ≤20/mcl; while eosinopenia showed the lowest sensitivity among the five biomarkers included in our study, it showed the highest specificity (53.1% and 76.8%, respectively).

Although other biomarkers were statistically different between perforated and non-perforated cases, we failed to find statistical differences between platelet counts and MPV. In the study of Sevinc et al. (14), authors evaluated the aforementioned markers and found that although differences in both markers exist for perforated and non-perforated AA, only MPV is different between AA and non-AA patients. However, the low AUC values of these

Table 1. Comparison of laboratory values between perforated and non-perforated appendicitis

Laboratory marker	Non-perforated appendicitis	Perforated appendicitis	p
Leucocyte count	13.1±4.3x10^3	15.4±4.5x10^3	<0.001
Neutrophil count	10.1±4.3x10^3	12.2±4.1x10^3	0.010
Neutrophil/leucocyte count	75.0±116%	79.1±8.8%	0.010
Eosinophil count	124.0±133.7	78.1±117.8	<0.001
Platelet count	249.2±60.3x10^3	256.3±75.4x10^3	0.859
Mean platelet volume	9.2±1.3	9.2±1.4	0.565
Total bilirubin	0.7±0.5	0.8±0.5	0.003

Table 2. Areas under the curve (AUCs) of laboratory values for leucocyte, neutrophil, and eosinophil counts, total bilirubin, and neutrophil/leucocyte ratio

Laboratory marker	AUC (95% CI)
Leucocyte count	0.64±0.03 (0.57-0.70)
Neutrophil count	0.63±0.03 (0.57-0.7)
Neutrophil/Leucocyte	0.60±0.03 (0.53-0.67)
Eosinophil count	0.66±0.04 (0.58-0.74)
Total Bilirubin count	0.62±0.03 (0.55-0.69)

AUC: area under curve; CI: confidence interval

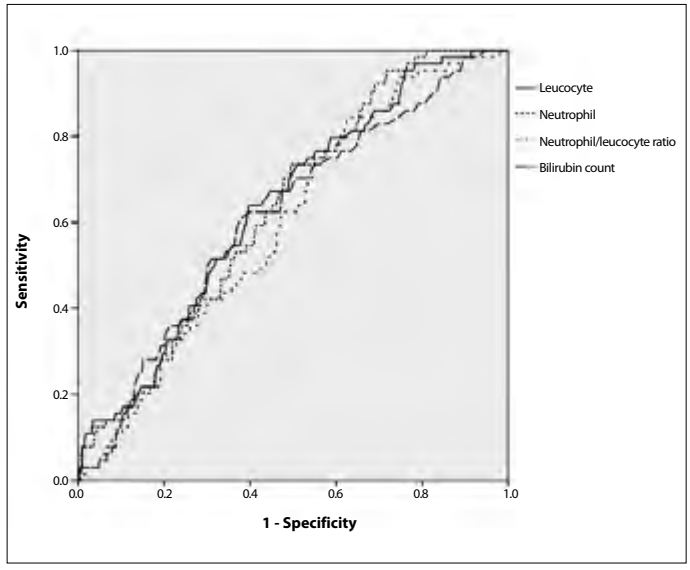


Figure 1. ROC curves of leucocyte, neutrophil, and bilirubin counts, eosinophil count, and neutrophil/leucocyte ratio

Table 3. Sensitivity and specificity for leucocyte, neutrophil, and eosinophil counts, total bilirubin, and neutrophil/leucocyte count

Laboratory marker	Laboratory value	Sensitivity	Specificity	+LR	-LR	+PV	-PV
Leucocyte count	13.900	64.1% (51.1-75.7%)	60.3% (55.9-64.5 %)	1.61	0.60	16.4	93.2
Neutrophil count	9.950	73.4% (60.9-83.7%)	50.6% (46.2-54.9%)	1.49	0.53	15.3	94
Neutrophil/leucocyte count	72.2 %	84.4% (73.1-92.2%)	37.6 (33.5- 41.9%)	1.35	0.42	14.1	95.2
Eosinophil count	20	53.1% (40.2-65.7%)	76.8 (73.0- 80.3%)	2.29	0.61	21.8	93.1
Total bilirubin	0.62	60.9% (47.9-72.9%)	62.0% (57.7- 66.1%)	1.60	0.63	16.3	92.9

+LR: positive likelihood ratio; -LR: negative likelihood ratio; +PV: positive predictive value; -LR: negative predictive value

biomarkers, between 0.5 and 0.6, limit their use. In Temple et al. (15) and Sahm et al. (16) studies, the perforation rates were similar to our study.

Several modalities are available for the diagnosis of AA in ED, including biochemistry panels, urinalysis, and radiologic imaging. While computerized tomography (CT) is highly accurate in detecting appendicitis, the presence of five key signs of perforation (abscess, phlegmon, extraluminal air, appendicolith, and focal defects in the appendiceal wall) can vary between patients. In the study of Horrow et al. (17), in several patients, some or all of these signs may be absent, thus decreasing the sensitivity and the specificity of CT. The lack of access to CT in certain settings, concerns regarding radiation, and potentially inadequate interpretation of CT are among the limitations of CT for the diagnosis of perforation. We strongly believe that eosinopenia along with increased leucocyte and neutrophil counts, increased total bilirubin level, and increased neutrophil/leucocyte ratio can predict perforation as a biomarker panel, especially in settings where CT use is limited or unavailable.

Study limitations

The limitations of this study are shared by other retrospective studies; specifically, we failed to define possible confounding variables and sources of bias. First, our hospital lacks an obstetrics and gynecology department, and most female patients with right lower quadrant pain are transferred to the nearest hospital for gynecological evaluation; this may have resulted in an unequal number of male patients with AA as a selection bias. In addition, the exclusion of patients who were managed non-operatively and the exclusion of patients who were transferred to other hospitals before the completion of treatment should be considered as additional selection biases. Furthermore, all patients with right lower quadrant pain with suspected AA who underwent operations and patients with pathologically proven appendicitis were included; thus, patients with negative laparotomy results were excluded from our study. The retrospective nature of the study limits the definition of confounding variables. We believe a prospective study will overcome these limitations.

Conclusion

We would like to note that while AA patients with eosinopenia prior to operation are more likely to suffer perforation, eosinopenia is not an absolute marker for perforation. Our results support that perforation remains an operative or histopathological diagnosis. Patients with decreased eosinophil counts prior to surgery accompanied by increases in leucocyte and neutrophil counts, with high total bilirubin level and high neutrophil/leucocyte ratio, have an increased risk of perforation. Therefore, meticulous efforts should be made to select the surgical procedure and post-operative clinical course for these patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Izmir Bozyaka Training and Research Hospital (13.01.2015, Decision No: 001).

Informed Consent: Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Yeniocak S, Turkmen S, Uzun O, Karaca Y, Tatlı O, Turedi S, et al. Analysis of patients presenting to emergency department with acute pain. Eurasian J Emerg Med 2012; 11: 212-5. [CrossRef]
2. Mueller BA, Daling JR, Moore DE, Weiss NS, Spadoni LR, Stadel BV, et al. Appendectomy and the risk of tubal infertility. N Engl J Med 1986; 315: 1506-8. [CrossRef]
3. Akyildiz H, Akcan A, Sozuer EM, Kucuk C, Korkut C, Ekici F. Acute appendicitis-perforated appendicitis: Are they differently clinical antities? Eurasian J Emerg Med 2008; 7: 13-5.
4. Sand M, Bechara FG, Holland-Letz T, Sand D, Mehnert G, Mann B. Diagnostic value of hyperbilirubinemia as a predictive factor for appendiciel perforation in acute appendicitis. Am J Surg 2009; 198: 193-8. [CrossRef]
5. Beltrán MA, Almonacid J, Vicencio A, Gutiérrez J, Cruces KS, Cumsille MA. Predictive value of white blood cell count and C-reactive protein in children with appendicitis. J Pediatr Surg 2007; 42: 1208-14. [CrossRef]
6. Khan S. Elevated serum bilirubin in acute appendicitis: a new diagnostic tool. Kathmandu Univ Med J 2008; 6: 161-5.
7. Chaudhary P, Kumar A, Saxena N, Biswal UC. Hyperbilirubinemia as a predictor of gangrenous/perforated appendicitis: a prospective study. Ann Gastroenterol 2013; 26: 325-31.
8. Abidi K, Khoudri I, Belayachi J, Madani N, Zekraoui A, Zeggwagh AA, et al. Eosinopenia is a reliable marker of sepsis on admission to medical intensive care units. Crit Care 2008; 12: R59. [CrossRef]
9. Becchi C, Al Malyan M, Fabbri LP, Marsili M, Boddi V, Boncinelli S. Mean platelet volume trend in sepsis: is it a useful parameter? Minerva Anestesiol 2006; 72: 749-56.
10. Narci H, Turk E, Karagulle E, Togan T, Karabulut K. The role of mean platelet volume in the diagnosis of acute appendicitis: a retrospective case-controlled study. Iran Red Crescent Med J 2013; 15: e11934. [CrossRef]
11. Tanrikulu CS, Tanrikulu Y, Sabuncuoglu MZ, Karamercan MA, Akkapulu N, Coskun F. Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. Iran Red Crescent Med J 2014; 16: e10211. [CrossRef]
12. Perkins NJ, Schisterman EF. The Inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. Am J Epidemiol 2006; 163: 670-5. [CrossRef]
13. Bass DA, Gonwa TA, Szejda P, Cousart MS, DeChatelet LR, McCall CE. Eosinopenia of acute infection: production of eosinopenia by chemotactic factors of acute inflammation. J Clin Invest 1980; 65: 1265-71. [CrossRef]
14. Sevinç MM, Kınacı E, Çakar E, Bayrak S, Özakay A, Aren A, et al. Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: an analysis of 3392 cases. Ulus Travma Acil Cerrahi Derg 2016; 22: 155-62.
15. Temple CL, Huchcroft SA, Temple WJ. The natural history of appendicitis in adults. A prospective study. Ann Surg 1995; 221: 278-81. [CrossRef]
16. Sahm M, Pross M, Lippert H. Acute appendicitis - changes in epidemiology, diagnosis and therapy. Zentralbl Chir 2011; 136: 18-24. [CrossRef]
17. Horrow MM, White DS, Horrow JC. Differentiation of perforated from nonperforated appendicitis at CT. Radiology 2003; 227: 46-51. [CrossRef]

Diagnostic and Prognostic Significance of Neutrophil Gelatinase-Associated Lipocalin and Pentraxin-3 in Acute Coronary Syndrome

Muhammet Raşit Özer[1], Mehmet Ergin[1], İbrahim Kılınç[2], Zerrin Defne Dündar[1], Nejla Özer[2], Mehmet Akif Önal[1], Abdullah Sadık Girişgin[1], Sedat Koçak[1], Mehmet Gül[1], Başar Cander[1]

[1]Department of Emergency Medicine, Necmettin Erbakan University School of Medicine, Konya, Turkey
[2]Department of Biochemistry, Necmettin Erbakan University School of Medicine, Konya, Turkey

Abstract

Aim: The aim was to evaluate the levels of serum pentraxin-3 (PTX-3) and neutrophil gelatinase-associated lipocalin (NGAL) and the efficiency of making a diagnosis and to estimate the prognosis in patients with chest pain.

Materials and Methods: The study was conducted in the Necmettin Erbakan University Meram Medicine School Emergency Department. Patients who had chest pain and met the inclusion criteria were accepted. They were divided into the following groups: acute coronary syndrome (ACS), a diagnosis other than ACS (non-ACS), and control. The patients in theACS and non-ACS groups were divided into five sub-group -groups: ST Elevated Myocardial Infarction (STEMI) Non- ST Elevated Myocardial Infarction (NSTEMI), Unstable Angina Pectoris (USAP), stable angina, and pulmonary embolus. For all patients, serum PTX-3, serum NGAL, troponin I, and creatine kinase-MB fraction (CK-MB) levels were measured.

Results: There were 199 patients in the ACS and non-ACS groups and 30 patientsin the control group. There was no significant difference among the study groups in terms of age and PTX-3 and NGAL levels. When comparing survival and non-survival in terms of in-hospital death, CK-MB and troponin I levels were significantly higher in the ACS and non-ACS groups than in the control groups, whereas there was no significant difference in terms of PTX-3 and NGAL levels.

Conclusion: The results of our study demonstrated that PTX-3 and NGAL are not effective biomarkers in the differential diagnosis and the determination of in-hospital mortality in ACS. However, the limitations of the study should be considered. The results confirmed that CK-MB and Troponin I can be safely used in the differential diagnosis and the prediction of mortality.

Keywords: Acute coronary syndrome, biomarker, neutrophil gelatinase-associated lipocalin, pentraxin-3

Introduction

Chest pain is one of the main reasons for admission to emergency departments (EDs). Among patients with such admissions, 30% to 50% have acute coronary syndrome (ACS). Coronary artery disease (CAD) is the most common cardiovascular diseases and is related to high mortality rates (1, 2).

Chest pain-related admissions to EDs are important ongoing problem for physicians. Despite the clinical experience of physicians and presence of electrocardiogram (ECG) and biochemical parameters, 2%-5% of patients with ACS remain undiagnosed (3). Cardiac troponin is a highly sensitive and specific biomarker that demonstrates myocardial damage. However, it is not specific as high levels of it can also be detected in many clinical conditions (renal failure, gastrointestinal bleeding, respiratory disease, subarachnoid hemorrhage and ischemic stroke) other than ACS (4-8). In spite of this, cardiac troponins have recently been accepted as the gold standard biomarker in ischemic myocardial damage (9).

Pentraxin-3 (PTX-3) and neutrophil gelatinase-associated lipocalin (NGAL) are believed to be involved in the pathophysiology of ACS (10). It has been reported that PTX-3 is secreted from cardiomyocytes in cardiac ischemia and that it is anindicator of myocyte injury. PTX-3 has also been reported to appear with acute myocardial infarction (AMI), which reaches its peak level at the seventh hour, regresses within several days, and finally returns to its normal plasma level (11). NGAL has been shown to be primarily produced in neutrophils and

This study was presented at the 11th National Emergency Medicine Congress and 2nd Intercontinental Emergency Medicine Congress, 16-19 April, Antalya, Turkey.

Correspondence to: Muhammet Raşit Özer e-mail: drrasitozer@gmail.com

Received: 13.01.2017 • **Accepted:** 06.02.2017

DOI: 10.5152/eajem.2017.28290

subsequently in cardiomyocytes, and its levels are elevated in pathological conditions such as atherosclerosis (12-16).

The aim of this study was to investigate whether the new-generation biomarkers NGAL and PTX-3 have a diagnostic value superior to the routinely used biomarkers CK-MB and troponin I in patients suspected of having ACS and to determine the relationship of these biomarkers with hospital mortality rates.

Materials and Methods

The Ethics Committee of Necmettin Erbakan University Meram Medicine School approved this controlled prospective clinical study on January 3, 2014 (number, 2014-570). This study included 229 patients who met with the inclusion criteria, who had presented to the Necmettin Erbakan University Meram Medicine School Emergency Department (ED) with chest pain and equivalent complaints, and who were followed up with a pre-diagnosis of ACS in the ED.

Study groups

Group 1 included patients with ACS (including MI with ST segment elevation (STEMI), MI with non-STEMI (NSTEMI), and unstable angina pectoris (USAP)]; Group 2 included patients with a diagnosis other than ACS (non-ACS) (including pulmonary embolism and stable angina), and Group 3 was the control group, which included patients with a diagnosis other than ACS or non-ACS. The patients were consecutively enrolled. Cardiac biomarkers were evaluated between survival and non-survival groups.

Study protocol

Patients who had presented to the ED with chest pain and who had agreed to participate were physically examined by an emergency physician (EP) and underwent electrocardiography; then, they were taken to the chest pain unit (CPU) for follow-up. The investigators analyzed the patients who were taken to the CPU for compatibility with the inclusion criteria, informed the proper patients, and obtained their consents (Table 1). The demographic characteristics, contact information, and laboratory and radiological examinations requested by the EP were recorded. NGAL and PTX-3 levels of the patients were also determined. The patients were followed up, and their in-hospital clinical courses were recorded.

Table 1. Inclusion and exclusion criteria of patients in the study

A. Inclusion criteria
1. Patients who were ≥18 years of age
2. Patients who agreed to join the study
3. Admission to the ED with chest pain or equivalent complaints
B. Exclusion criteria
1. Female patients who were pregnant or breast feeding
2. Patients who were <18 years age
3. Patients who refused to join the study
4. Patients with a history of chronic renal failure
5. Patients who had a history of active or previous cancer
ED: emergency department

Biochemical evaluation

Having performed tests for the differential diagnosis of chest pain, the sera and plasma of the venous blood drawn at admission from the included patients were used as samples. Blood samples were centrifuged at 4000 g for 5 min. The blood samples to be analyzed for N-GAL and PTX-3 level were transferred into plastic and sealed Eppendorf tubes and storedat -80°C until biochemical analysis. On the day of analysis, they were obtained from the Eppendorf tubes and incubated at room temperature and analyzed. NGAL (Lot no: 5031059529) (Boster®, USA) and PTX-3 (Lot no: 5111059529) (Boster®, USA) levels were determined by ELISA using ELISA kits. An ELISA washer and a semi-automatic ELISA reader were used. CK-MB and troponinI levels were analyzed using a Beckman Coulter DXI 800 instrument by the chemiluminescence method.

Statistical analysis

The data obtained were analyzed using Statistical Package For Social Sciences version 16.0 (SPSS Inc.; Chicago, Illinois, ABD). Descriptive data are expressed as mean±standard deviation and percentage. Normally distributed data (parametric or non-parametric) were analyzed using the Kolmogorov-Smirnov Test. Non-normally distributed variables were expressed as median±the interval between quarters (25%-75%). The Mann-Whitney U and Kruskal-Wallis tests were used for the comparison of non-parametric variables. The chi-square test was used to determine the significance of the differences among the patient and control groups with regard to the demographic characteristics and comorbid situations. The Pearson test was used for correlation analysis. A p value of <0.05 was accepted as statistically significant.

Results

A total of 229 patients were included (Table 2). Their mean age was 60.48±14.84 years. A statistically significant difference was observed among the groups with regard to the mean age (p=0.001). The mean age in patients in Group 2 was lower than those patients in the other groups. Totally, 69% (n=158)of the patients were males and 31% (n=71) were females. No difference was observed amongthe groups with regard to gender distribution (p=0.353). The number of patients with an additional disease in Group 1 was significantly higher than that in the other groups (p=0.001). The number of patients with an atherosclerotic cardiac disease was significantly higher in Group 1 than in the other groups (p=0.013). No difference was observed among the groups with regard to the history of diabetes mellitus, hypertension, hyperlipidemia, and smoking (p=0.174, p=0.063, p=0.075, and p=0.431, respectively) (Table 2).

The patient group that was classified according to the diagnosis included 28% (n=55) NSTEMI, 28% (n=55) STEMI, 24% (n=48) stable angina, 16% (n=32) USAP, and 4% (n=9) pulmonary embolism. Sixteen (7%) patients included in the study died during the course of hospitalization, which was statistically significantly different among the study groups (p=0.024). The mortality rate in Group 1 was 10.6%, and no mortality was observed in Group 3 (Table 2).

A significant difference was observed among the groups with regard to NGAL, CK-MB, and troponin I levels (p<0.001, p<0.001, and p<0.001, respectively). However, no difference was observed among the groups with regard to PTX-3 levels (p=0.978) (Figure 1).

Paired comparisons were made among the groups. NGAL levels were determined to be significantly higher in Group 3 than in groups

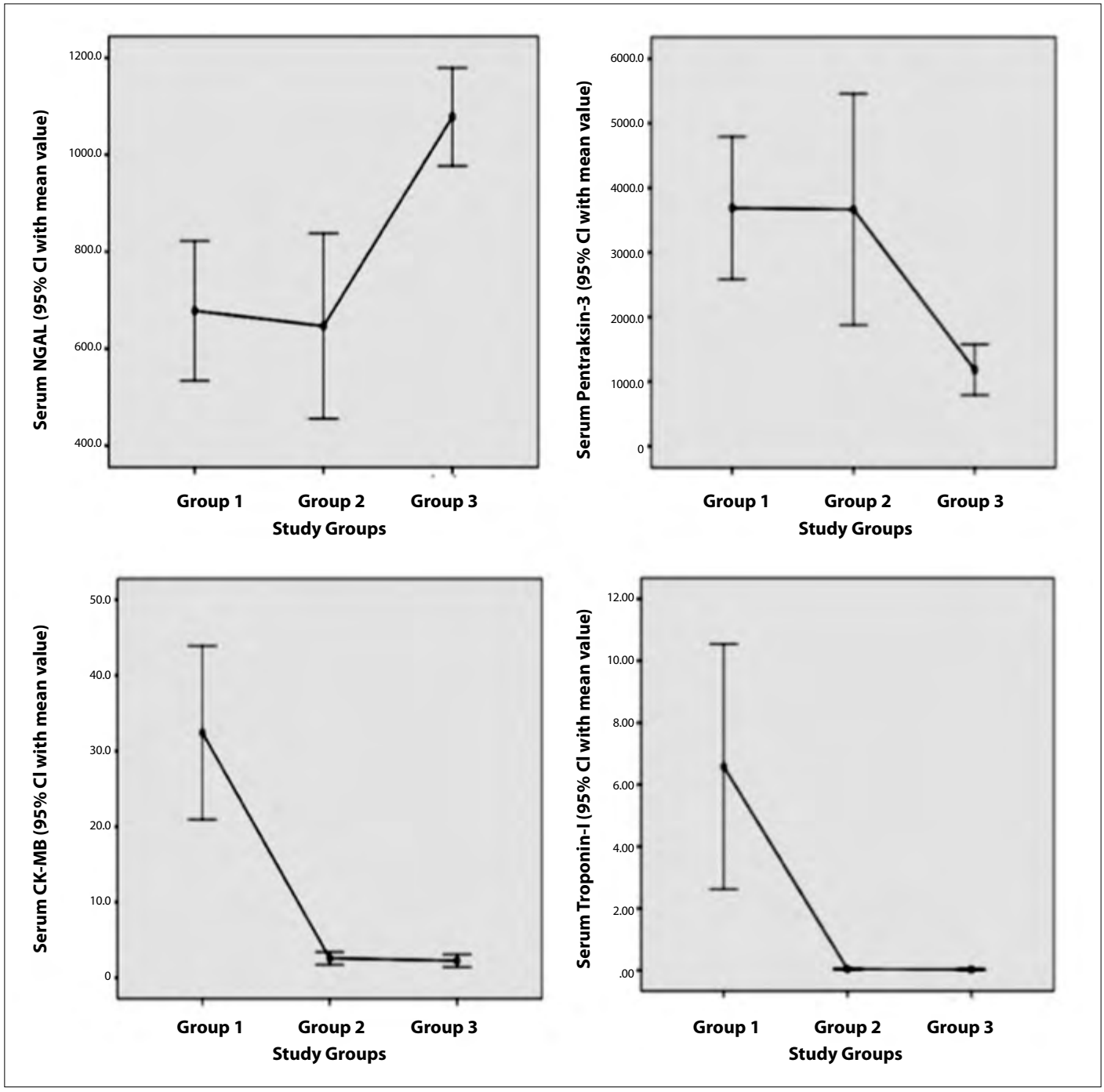


Figure 1. Comparison of the values of groups NGAL, pentraxin-3, CK-MB and troponin I

1 and 2 (p<0.001 and p=0.003, respectively). No difference was observed between groups 1 and 2 with regard to NGAL level (p=0.270). CK-MB levels were significantly higher in Group 1 than group 2 and 3 (p<0.001). No difference was observed between groups 2 and 3 with regard to CK-MB levels (p=0.810). Troponin I levels were significantly higher in Group 1 than in groups 2 and 3 (p<0.001 and p<0.001, respectively). No difference was observed between groups 2 and 3 with regard to Troponin I levels (p=0.675) (Table 2).

The study groups were classified as "survival" and "non-survival" groups according to in-hospital mortality (Table 3). The mean age of the patients in the non-survival group was significantly higher (p<0.001). No difference was observed between the groups with regard to gender or comorbidity (p=0.560 and p=0.540, respectively). No difference was observed between the groups with regard to NGAL and PTX-3 levels, whereas a significant difference was determined for CK-MB and troponin I levels, which were higher in the non-survival group (p=0.547 and p=0.973 vs. p=0.001 and p<0.001, respectively) (Table 3).

When the cardiac biomarkers were evaluated with regard to correlation, a significant correlation was observed only between CK-MB and troponin I (r=0.723, p<0.001). No correlation was determined between the other biomarkers (NGAL and PTX-3).

Table 2. Distribution of gender, age, comorbidities results among the study groups

Groups Parameters	All Groups (n=229)	Group 1 (n=142)	Group 2 (n=57)	Group 3 (n=30)	p
Age (Mean value±standart deviation)	60.48±14.84	63.11±13.67	53.82±15.78	60.67±14.82	0.001
Gender[α]					
Male	158 (69)	102 (71.8)	35 (61.4)	21 (70)	0.353
Female	71 (31)	40 (28.2)	22 (38.6)	9 (30)	
Comorbidity[α]					
Yes	156 (68.1)	109 (76.8)	33 (57.9)	14 (46.7)	0.001
No	73 (31.9)	33 (23.2)	24 (42.1)	16 (52.3)	
ASCD[α]					
Yes	101 (44.1)	70 (49.3)	25 (43.9)	6 (20)	0.013
No	128 (55.9)	72 (50.7)	32 (56.1)	24 (80)	
DM α					
Yes	37 (16.2)	28 (19.7)	6 (10.5)	3 (10)	0.174
No	192 (83.8)	114 (80.3)	51 (89.5)	27 (90)	
Hypertension[α]					
Yes	97 (42.4)	68 (47.9%)	21 (36.8%)	8 (26.7%)	0.063
No	132 (57.6)	74 (52.1%)	36 (63.2%)	22 (73.3%)	
Hyperlipidemia[α]					
Yes	27 (11.8)	22 (15.5)	4 (7)	1 (3.3)	0.075
No	202 (88.2)	120 (84.5)	53 (93)	29 (96.7)	
Cigarette smoking[α]					
Yes	69 (30.1)	45 (31.7)	18 (31.6)	6 (20)	0.431
No	160 (69.9)	97 (68.3)	39 (68.4)	24 (80)	
In-hospital mortality[α]					
Survival	213 (93)	127 (89.4)	56 (98.2)	30 (100)	0.024
Non-survival	16 (7)	15 (10.6)	1 (1.8)	0 (0)	
Biomarkers[β]					
NGAL	223 (33.5-4974.4)	171.55 (33.5-4974.4)	211.1 (39.6-3012.8)	1099.64 (513.7-1568.6)	<0.001
PTX-3	707.75 (13.7-21.000)	709.51 (13.7- 21.000)	705.98 (18.9-21.000)	916.46 (308-4789.3)	0.978
CK-MB	2.6 (0.2-299)	4.2 (0.6-299)	1.8 (0.2-20.5)	1.6 (0.8-13.1)	<0.001
Tn-I	0.03 (0.01-198)	0.14 (0.01-198)	0.01 (0.01-0.51)	0.01 (0.01-0.4)	<0.001

ASCD: atherosclerotic cardiac disease; CK-MB: creatine kinase-MB fraction; DM: diabetes mellitus; NGAL: neutrophil gelatinase associated lipocalin; PTX-3: pentraxin3; Tn-I: troponinI
[α]Described by number (n) and percentage (%)
[β]Described by median value (minimum-maximum values)

The ROC curve of NGAL revealed an area under the curve (AUC) value of 0.729 (p<0.001) (Figure 2). The sensitivity, specificity, and accuracy of NGAL were 62%, 35%, and 54%, respectively, when the optimal threshold value was accepted as 502.1 ng/mL.

Discussion

Despite advances in the diagnosis and treatment of ACS, the mortality, hospitalization, and recurrent infarction rates among patients with ACS remain high (2). Many biomarkers are being used and tested to perform risk analysis for diagnosing ACS that would result in early treatment. Cardiac troponins have high sensitivity and specificity in the diagnosis of myocardial injury. It should not be forgotten that cardiac troponins are currently used as the gold standard. However, an elevation in their levels may be observed in many situations other than cardiac events (17). In light of this information, new biomarkers are required.

One of the important risk factors for ACS is age. The mean ages of patients were 62.6±13, 62.1±12, and 62.83±12.9 years in the studies by Leurent et al. (19), Ariza-Sole et al. (18), and Salama

Table 3. Comparison of serum biomarkers between survival and non-survival groups according to the in-hospital mortality

Groups Parameters	Survival group (n=213)	Non-survival group (n=16)	p
Age (Mean value± standard elevation)	59.25±14.40	76.81±10.48	<0.001
Gender[α]			
Male	148 (69.5)	10 (62.5)	0.560
Female	65 (30.5)	6 (37.5)	
Comorbidity[α]			
Yes	144 (67.6)	12 (75)	0.540
No	69 (32.4)	4 (25)	
Biomarkers[β]			
NGAL	226.3 (33.5-4974.4)	221.3 (51.6-2317.5)	0.547
PTX-3	714.79 (13.7-21000)	616.2 (113.5-21000)	0.973
CK-MB	2.5 (0.2-299)	24.55 (1.9-238.6)	0.001
Tn-I	0.02 (0.01-198)	4.44 (0.01-100)	<0.001

CK-MB: creatine kinase-MB fraction; NGAL: neutrophil gelatinase-associated lipocalin; PTX-3: pentraxin3; Tn-I: troponin I
[α]Described by number (n) and percentage (%)
[β]Described by median value (minimum–maximum values)

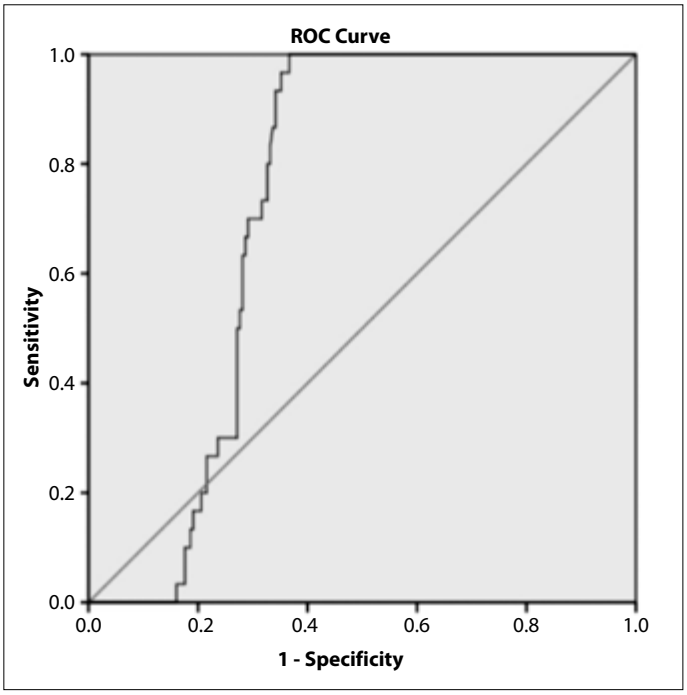


Figure 2. The ROC Curve of NGAL

et al. (20), respectively. In our study, the mean age of the patients was 63.11±13.67 years, which was similar to those reported in the literature.

Various rates of STEMI, NSTEMI, and USAP have been reported in case series published in the literature. In a study including patients presenting to the emergency unit with a complaint of chest pain, 41% of patients had NSTEMI and STEMI, 27% had USAP, and 32% had non-cardiac chest pain; in another study, one-third of the patients with ACS had STEMI and the remaining had NSTEMI and USAP (21, 22). In other studies, various rates have been reported for patients with ACS, such as 54%-61% in NSTEMI and 33%-45.6% in STEMI (20, 23, 24). In our study, 39% of the patients with ACS had NSTEMI, 39% had STEMI, and 22% had USAP.

Hasdai et al. (25) reported the coronary cardiac disease-related mortality rate to be 20% in the 35-55-year age group. In another study, the in-hospital mortality rate among patients with ACS was 4% (26). In another study investigating mortality rates in ACS, the in-hospital mortality rate was 20% for those having STEMI and 10% for those having NSTEMI (27). In our study, the in-hospital mortality rates were 7.2% and 6.3% for patients having STEMI and NSTEMI, respectively.

PTX-3 is an acute-phase reactant that has recently been discovered. Atherosclerosis is known to develop as a reason for an inflammatory process. It was determined that endothelial cells and macrophages are involved in the basic formation of atherosclerosis and that PTX-3 is secreted from atherosclerotic lesions (28). In the study by Matsui et al. (29), elevated serum PTX-3 levels were related to USAP, STEMI, NSTEMI, cardiac failure, and negative cardiovascular events. Ustundag et al. (30) determined the sensitivity and specificity of PTX-3 levels analyzed within the first 6 h to be 98.5% and 92.3%, respectively, in patients with ACS. Buyukkaya et al. (31) investigated PTX-3 levels in patients with cardiac syndrome X and determined a significantly higher PTX-3 level in the study group than in the control group. In many studies conducted on patients with vascular diseases, mortality was seen to have correlated to elevated PTX-3 levels (32, 33). In the study by Latini et al. (32), elevated PTX-3 levels have been suggested to be related to 3-month mortality in patients with MI. However, in our study, serum PTX-3 levels observed in the groups were investigated with regard to the diagnosis and in-hospital mortality, and no significant difference was observed.

Risk factors and correlations for leukocyte activation in atherosclerosis have also been reported in a study, a correlation has been demonstrated between symptomatic cardiovascular diseases and elevated NGAL levels; on the contrary, plasma NGAL levels and non-symptomatic cardiovascular diseases have been demonstrated to be not correlated (34). In another study, the group of patients with CAD confirmed via angiography was compared to the groups of patients with normal coronary arteries, and serum NGAL levels were found to be significantly elevated in the presence of CAD (35). In a similar study, 47 patients with NSTEMI confirmed via angiography were compared to 45 control patients with stable angina (having undergone coronary angiography and determined to have normal coronary arteries), and NGAL levels were positively correlated to lesion complexity and the diffusiveness of CAD in patients with NSTEMI. It was concluded that serum NGAL levels on admission are related to the increased atherosclerotic load in patients with Non-ST elevated Acute Coronary Syndrome(NSTE-ACS)(36).

In the study by Choi et al. (37), serum NGAL levels were determined to be significantly higher in patients with CAD than in the healthy population. Similarly in another study, serum NGAL levels showed an increasing tendency in CAD and AMI, although this was not significant. In the study by Arslan et al. (38) that compared patients with stable CAD and AMI, significantly higher plasma NGAL

levels were detected in the AMI group; however, no difference was found between STEMI and NSTEMI. It was concluded that NGAL NGAL levels are more successful indicator in detecting MI than other inflammatory markers. In our study, NGAL levels were significantly lower in the ACS and non-ACS patient groups (Group 1 and 2) than in the control group, and no difference was detected between the ACS and non-ACS groups.

According to the risk classification of the American College of Cardiology/American Heart Association, a cardiac troponin I level between 0.1 and 1.5 ng/mL indicates a moderate risk, and a level over 1.5 ng/mL indicates a high risk in patients with NSTEMI (39). In another study, troponin levels were observed to increase within 2-3 h after admission to the ED in 80% of patients with MI, and the levels of CK-MB and other cardiac biomarkers were found to start increasing within 6-9 h (40). Similarly, in our study, CK-MB and troponin I had an elevated course in the patient group (group 1 patients), which was statistically significant.

Study limitations

Our study was a single-center prospective study. The control group included patients who had presented to our emergency unit with complaints other than chest pain and whose diagnosis did not comprise chest pain in the differential diagnosis. The amount of time between the onset of chest pain and the time of blood sampling could not be determined. The number of patients was also limited.

Conclusion

In conclusion, the data obtained in our study indicate that NGAL and PTX-3 are not effective biomarkers in the differential diagnosis of chest pain or the prediction of mortality in ACS. This conclusion should be evaluated considering the limitations of our study. The outcomes obtained in this study confirm the use of CK-MB and troponin I, which are used in daily practice, as reliable biomarkers in the differential diagnosis and in the prediction of mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Necmettin Erbakan University Meram School of Medicine (03.01.2014, Decision No: 2014-570).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: This study was supported by Necmettin Erbakan University Scientific Research Project (BAP) (project no: 14158005).

References

1. Solinas L, Raucci R, Terrazzino S, Moscariello F, Pertoldi F, Vajto S, et al. Prevalence, clinical characteristics, resource utilization and outcome of patients with acute chest pain in the emergency department. A multicenter, prospective, observational study in north-eastern Italy. Ital Heart J 2003; 4: 318-24.
2. Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, et al. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007; 28: 1598-660. [CrossRef]
3. Pope JH, Aufderheide TP, Ruthazer R, Woolard RH, Feldman JA, Beshansky JR, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000; 342: 1163-70. [CrossRef]
4. Khan NA, Hemmelgarn BR, Tonelli M, Thompson CR, Levin A. Prognostic value of troponin T and I among asymptomatic patients with end stage renal disease: a meta-analysis. Circulation 2005; 112: 3088-96. [CrossRef]
5. Vasile VC, Babuin L, Rio Perez JA, Alegria JR, Song LM, Chai HS, et al. Long term prognostic significance of elevated cardiac troponin levels in critically ill patients with acute gastrointestinal bleeding. Crit Care Med 2009; 37: 140-7. [CrossRef]
6. Vasile VC, Chai HS, Khambatta S, Afessa B, Jaffe AS. Significance of elevated cardiac troponin T levels in critically ill patients with acute respiratory disease. Am J Med 2010; 123: 1049-58. [CrossRef]
7. Batal O, Jentzer J, Balaney B, Kolia N, Hickey G, Dardari Z, et al. The prognostic significance of troponin I elevation in acute ischemic stroke. J Crit Care 2016; 31: 41-7. [CrossRef]
8. Zhang L, Wang Z, Qi S. Cardiac troponin elevation and outcome after subarachnoid hemorrhage: a systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2015; 24: 2375-84. [CrossRef]
9. Freitas C, Larrivée B, Eichmann A. Netrins and UNC5 receptors in angiogenesis. Angiogenesis 2008; 11: 23-9. [CrossRef]
10. Walz A, Baggiolini M. Generation of the neutrophil-activating peptide NAP-2 from platelet basic protein or connective tissue-activating peptide III through monocyte proteases. J Exp Med 1990; 171: 449 54. [CrossRef]
11. Peri G, Introna M, Corradi D, Iacuitti G, Signorini S, Avanzini F, et al. PTX3, a prototypic long pentraxin, is an early indicator of acute myocardial infarction in humans. Circulation 2000; 102: 636-41. [CrossRef]
12. Eagan TM, Damås JK, Ueland T, Voll-Aanerud M, Mollnes TE, Hardie JA, et al. Neutrophil gelatinase-associated lipocalin: a biomarker in COPD. Chest 2010; 138: 888-95. [CrossRef]
13. Nielsen BS, Borregaard N, Bundgaard JR, Timshel S, Sehested M, Kjeldsen L. Induction of NGAL synthesis in epithelial cells of human colorectal neoplasia and inflammatory bowel diseases. Gut 1996; 38: 414-20. [CrossRef]
14. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, et al. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. Nature 2004; 432: 917-21. [CrossRef]
15. Xu S, Venge P. Lipocalins as biochemical markers of disease. Biochim Biophys Acta 2000; 1482: 298-307. [CrossRef]
16. Bolignano D, Coppolino G, Lacquaniti A, Buemi M. From kidney to cardiovascular diseases: NGAL as a biomarker beyond the confines of nephrology. Eur J Clin Invest 2010; 40: 273-6. [CrossRef]
17. Hamm C, Heeschen C, Falk E, Fox KAA. Acute coronary syndromes: pathophysiology, diagnosis and risk stratification. In: Camm AJ, Luescher TF, Serruys PW, ed. The ESC Textbook of Cardiovascular Medicine. Oxford: UK, Blackwell Publishing; 2006. p333-66.
18. Ariza-Solé A, Formiga F, Lorente V, Sánchez-Salado JC, Sánchez-Elvira G, Roura G, et al. Efficacy of bleeding risk scores in elderly patients with acute coronary syndromes. Rev Esp Cardiol (Engl Ed). 2014; 67: 463-70. [CrossRef]
19. Leurent G, Garlantézec R, Auffret V, Hacot JP, Coudert I, Filippi E, et al. Gender differences in presentation, management and in hospital out come in patients with ST-segment elevation myocardial infarction: Data from 5000 patients included in the ORBI prospective French regional registry. Arch Cardiovasc Dis 2014; 107: 291-8. [CrossRef]
20. Salama M, Çakmak H A, Coşansu K, İkitimur B, Karadağ B, Enar RAkut koroner sendromlarda standart risk skorlamalarıyla birlikte geliştiki NT-proBNP düzeyinin 6 aylık mortalite ve morbiditeye etkileri. Turk Kardiyol Dern Ars 2010; Suppl 2: 136.

21. Gay PC, Nishimura RA, Roth CS, Evans WE, Zinsmeister AR, Kottke BA. Lipoprotein analysis in the evaluation of chest pain in the emergency department. Mayo Clin Proc 1991; 66: 885-91. [CrossRef]
22. Bugiardini R. Risk stratification in acute coronary syndrome: focus on unstable angina non-ST segment elevation myocardial infarction. Heart 2004; 90: 729-31. [CrossRef]
23. El-Menyar A, Zubaid M, Shehab A, Bulbanat B, Albustani N, Alenezi F, et al. Prevalence and impact of cardiovascular risk factors among patients presenting with acute coronary syndrome in the Middle East. Clin Cardiol 2011; 34: 51-8. [CrossRef]
24. Stähli BE, Yonekawa K, Altwegg LA, Wyss C, Hof D, Fischbacher P, et al. Clinical criteria replenish high-sensitive troponin and inflammatory markers in the stratification of patients with suspected acute coronary syndrome. PLos One 2014; 3: 9: e98626.
25. Hasdai D, Topol EJ, Kilaru R, Battler A, Harrington RA, Vahanian A, et al. Frequency, patient characteristics, and outcomes of mild-to-moderate heart failure complicating ST-segment elevation acute myocardial infarction: lessons from 4 international fibrinolytic therapy trials. Am Heart J 2003; 145: 73-9. [CrossRef]
26. Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, Goodman SG, et al. Does simplicity compromise accuracy in acs risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. PLoS One 2009; 4: e7947. [CrossRef]
27. Wiviott SD, Morrow DA, Giugliano RP, Frederick CH, McCabe CP, Cannon EM, et al. Performance of the thrombolysis in myocardial infarction risk index for early acute coronary syndrome in the National Registry of Myocardial Infarction: a simple risk index predicts mortality in both ST and non-ST elevation myocardial infarction. J Am Coll Cardiol 2003; 41: 365-6. [CrossRef]
28. Lusis AJ. Atherosclerosis. Nature 2000; 407: 233-41. [CrossRef]
29. Matsui S, Ishii J, Kitagawa F, Kuno A, Hattori K, Ishikawa M, et al. Pentraxin 3 in unstable angina and non-ST-segment elevation myocardial infarction. Atherosclerosis 2010; 210: 220-5. [CrossRef]
30. Ustundag M, Orak M, Güloğlu C, Sayhan M B, Alyan O, Kale E. Comparative diagnostic accuracy of serum levels of neutrophil activating peptide-2 and pentraxin-3 versus troponin-I in acute coronary syndrome. Anadolu Kardiyol Derg 2011; 11: 588-94. [CrossRef]
31. Büyükkaya E, Karakaş MF, Kurt M, Motor S, Akçay AB, Büyükkaya S, et al. The serum pentraxin-3 is elevated in patients with cardiac syndrome X. Turk Kardiyol Dern Ars 2013; 41: 290-5. [CrossRef]
32. Latini R, Maggioni AP, Peri G, Gonzini L, Lucci D, Mocarelli P, et al. Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. Circulation 2004: 110: 2349-54. [CrossRef]
33. Suzuki S, Takeishi Y, Niizeki T, Koyama Y, Kitahara T, Sasaki T, et al. Pentraxin 3, a new marker for vascular inflammation, predicts adverse clinical outcomes in patients with heart failure. Am Heart J 2008; 155: 75-81. [CrossRef]
34. Elneihoum AM, Falke P, Hedblad B, Lindgärde F, Ohlsson K. Leukocyte activation in atherosclerosis: correlation with risk factors. Atherosclerosis 1997; 131: 79-84. [CrossRef]
35. Zografos T, Haliassos A, Korovesis S, Giazitzoglou E, Voridis E, Katritsis D. Association of neutrophil gelatinase-associated lipocalin with the severity of coronary artery disease. Am J Cardiol 2009; 104: 917-20. [CrossRef]
36. Soylu K, Aksan G, Nar G, Özdemir M, Gülel O, İnci S, et al. Serum neutrophil gelatinase-associated lipocalin levels are correlated with the complexity and severity of atherosclerosis in acute coronary syndrome. Anatol J Cardiol 2015; 15: 450-5. [CrossRef]
37. Choi KM, Lee JS, Kim EJ, Baik SH, Seo HS, Choi DS, et al. Implication of lipocalin-2 and visfatin levels in patients with coronary heart disease. Eur J Endocrinol 2008; 158: 203-7. [CrossRef]
38. Sahinarslan A, Kocaman SA, Bas D, Akyel A, Ercin U, Zengin O, et al. Plasma neutrophil gelatinase-associated lipocalin levels in acute myocardial infarction and stable coronary artery disease. Coron Artery Dis 2011; 22: 333-8. [CrossRef]
39. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, et al. ACC/AHA 2002 guideline update for the management of patients withunstable angina and non-ST segment elevation myocardial infarction-summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002; 40: 1366-74. [CrossRef]
40. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 2012; 33: 2551-67. [CrossRef]

EURASIAN JOURNAL OF EMERGENCY MEDICINE

Demographic Features of Patients with Extremity and Spine Fractures in Emergency Departments

Kenan Koca, Ömer Erşen, Serkan Akpancar, Faruk Akyıldız, Levent Gürer
Clinic of Orthopedic Surgery, Gülhane Training and Research Hospital, Ankara, Turkey

Abstract

Aim: Fractures are a major source of disability in all age groups; however, little is known about their epidemiology despite being quite a few studies on this subject. The aim of this study was to identify the frequency, gender, and seasonal distributions of fractures in an emergency department.

Materials and Methods: Patients who had been admitted to an emergency department because of extremity and spine problems were included in this study. Physical examinations, radiographs, ultrasonography, computed tomography, and magnetic resonance images were recorded. All demographic data such as age and gender, and other data, including season and history, were collected retrospectively. Diagnoses and treatment types (conservative or surgery) were evaluated.

Results: Between January 2012 and January 2014, 190.986 patients (95.619 males and 95.367 females) with various complaints were admitted to an emergency ward. After assessment of 32.300 patients who had pain in an extremity or the spine, 4.036 of them were diagnosed with fractures, with a total of 4.301 fractures being diagnosed. The average age of the patients who presented symptoms in an extremity or the spine was 36.2 years, and the gender ratio (men/women) was 60:40. The most common fractures were at the radius (15.6%), and the least common fractures were at the sesamoid bones (0.04%).

Conclusion: This study showed that 17% of the patients admitted to the emergency ward had extremity or spinal complaints and 2.2% of the patients had fractures. These epidemiological data may be relevant for physicians working in emergency departments when evaluating trauma patients.

Keywords: Demographics, fractures, emergency department

Introduction

Fractures are a major source of disability in all age groups; however, little is known about their epidemiology despite being quite a few studies on this subject. The knowledge of fracture incidence is important for the planning of treatment, to define training priorities, and to gain an understanding of orthopedic and trauma surgery. This study was conducted at a major trauma center that provides health services to patients of all age groups and is responsible for the inpatient and outpatient care of their injuries.

Epidemiology brings together all the knowledge of common diseases that occur in different groups. Epidemiological information is used to plan and evaluate strategies to prevent diseases and guide the management of patients (1, 2). Epidemiological knowledge of fractures is critical for determining the necessary measures to prevent the most common fractures, which is required to develop effective treatment strategies and training programs.

In emergency departments, there is little knowledge about the frequency and types of fractures in the patient population, and the factors that affect their distribution in Turkey. This study will provide a comprehensive perspective for emergency physicians to develop strategies for the most prevalent fractures in specific age groups, to prevent systemic complications due to major fractures and to guide the management of patients.

The purpose of this report to is summarize the available evidence on gender, age, and seasonal distribution of fractures to make recommendations for future needs and research opportunities.

Materials and Methods

This was a retrospective, single-center study conducted in an emergency department during the period from 1st January, 2012 to 1st January, 2014. The study was conducted in Keçiören, a district of Ankara in Turkey. The climate of this area varies through the year. The

This study was presented at the 50th Congress of the European Society for Surgical Research, 10-13 June 2015, Liverpool, United Kingdom.

Correspondence to: Serkan Akpancar e-mail: drserkanakpancar@gmail.com

Received: 09.11.2016 • **Accepted:** 13.01.2017

DOI: 10.5152/eajem.2017.57966

Table 1. Frequency, gender ratio, treatment options and mean patient age for each type of fracture

FRACTURE	n	%	Surgery (%)	Men: Women	Surgical/ conservative	Most frequent season	Mean age
Radius	686	15.9	3.8	56:44	24:76	SUMMER	31
Finger Phalanges	490	11.4	2.6	71:29	23:77	SUMMER	26.5
Femur	480	11.2	10.8	51:49	97:3	WINTER	64.8
Tibia	364	8.4	6.9	67:33	81:19	WINTER	35.9
Fibula	362	8.4	4.4	54:46	52:48	WINTER	40
Metacarpal	351	8.2	2.1	74:26	24:76	SUMMER	27.1
Humerus	298	6.9	5.3	55:45	76:24	WINTER	40.9
Toe Phalanges	271	6.3	1.1	54:46	18:82	SUMMER	32.8
Metatarsal	240	5.6	1.2	54:46	22:78	SUMMER	32.1
Ulna	211	4.9	2.6	64:36	53:47	SUMMER	25.2
Clavicle	117	2.7	0.7	62:38	26:74	SUMMER	19.3
Tarsal Bones	79	1.8	1.2	61:39	67:33	SUMMER	33
Carpal Bones	75	1.7	1.2	73:27	70:30	WINTER	31
Pelvis	63	1.5	1.2	77:23	86:14	SPRING	45.6
Lumbar Spine	59	1.4	0.8	71:29	58:42	AUTUMN	50.5
Coccyx	48	1.1	0.4	29:71	36:64	WINTER	37
Thoracic Spine	47	1.1	0.8	53:47	74:26	AUTUMN	42.7
Patella	32	0.7	0.5	69:41	69:31	SPRING	39.6
Scapula	16	0.4	0.1	69:31	38:62	WINTER	42.3
Cervical Spine	10	0.2	0.2	30:70	80:20	WINTER	56.3
Sesamoid	2	0.04	0	50:50	0:100	WINTER	23
TOTAL	4301	100	100	60:40	47:53	SUMMER	36.2

Table 2. Frequencies of carpal, phalangeal, toe and tarsal bones

Fracture	The most common (%)	The second most common (%)	The third most common (%)	The rarest (%)
Carpal Bones	Scaphoid (89)	Trapezium (4)	Triquetrium (3)	Pisiform (0)
Tarsal Bones	Calcaneus (55)	Talus (20)	Navicular (15)	Cuboid (1)
Metacarpals	5. (59)	4. (18)	1. (10)	2. (4)
Metatarsals	5. (63)	4. (12)	3. (9)	1. (8)
Finger Phalanges	5. (33)	4. (24)	1. (17)	2. (10)
Toe Phalanges	1. (35)	5. (31)	4. (16)	3. (5)

Table 3. Distribution of the fractures according to the anatomical region

Fracture	The most common side (%)	The second most common side (%)	The third most common side (%)	The rarest (%)
Radius	Distal (80)	Proximal (10)	Diaphysis (9)	Diaphysis (9)
Femur	Proximal (70)	Diaphysis (18)	Distal (12)	Distal (12)
Humerus	Proximal (45)	Distal (37)	Diaphysis (18)	Diaphysis (18)
Pelvis	Ramus Pubis (38)	Acetabulum (23)	Sacrum (21)	Iliac crest (18)

average temperature is 23°C in summer and -2°C in winter (3). The number of patients that received treatment in the hospital during 2014 was 872.025. Patients were first evaluated by emergency doctors, and then, those with suspected fractures were evaluated by orthopedic and traumatology consultants. The suspected extremities were initially examined by physical examination, and then, two plain X-ray radiographs were taken. The patients who were suspected of having a fracture (not detected) were evaluated by computed tomography and subjected to radiological expert opinion. All patients who had been diagnosed with a fracture were included in the study. The distribution of fractures according to age group, gender, frequency, applied treatment, and seasons is presented in Table 1-3 and Figure 1, 2.

All data was transferred to Microsoft Excel and analyzed using the Statistical Package of Social Sciences version 15 (SPSS Inc., Chicago, IL, USA) software package. A descriptive analysis was primarily applied. Clinical data were presented as numbers, percentages, and means. The distributions of data were subject to certain year intervals.

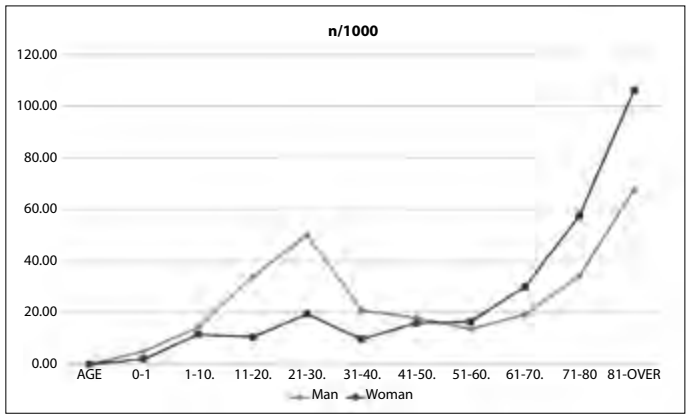


Figure 1. Age and gender distribution of fractures

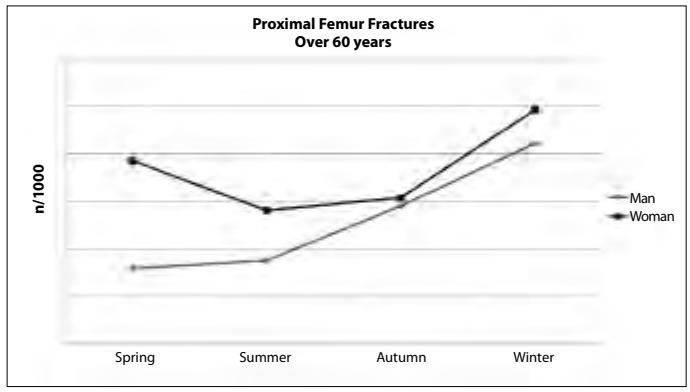


Figure 2. Age and seasonal distribution of proximal femur fractures over 60 years of age

Results

Between 2012 and 2013, 190.986 patients (95.619 males and 95.367 females) with various complaints were admitted to the emergency department. After assessment of 32.300 patients who complained of pain in the extremities or the spine, 4.036 of them were diagnosed with fractures, with a total of 4.301 fractures being diagnosed. The incidence of fractures on the total population was 4.6/1.000/year. The mean age of the patients was 36.2 years, with a gender ratio of 60:40 (male:female). The age and gender distribution of fractures according to each age decade is shown in Figure 1. A slightly undulating frequency in women is observed up to 60 years, with a rapid increase thereafter. In men, the pattern is different; there is an increased incidence in young men who are in their 30s that gradually falls until about 60 years of age. It then rises again, although the peak for older males is lower than for older females. The highest incidence of fracture in women is between 21 and 30 years and after 80 years of age. It is similar to men as there are two similar peaks between 21 and 30 years and after 80 years of age. Table 1 presents data on frequency and gender ratio, treatment options of all fractures observed in the emergency department. The most prevalent fractures were the radius fractures (15.6%) and the least common were the sesamoid bone fractures (0.04%). All sacrum fractures and most of the femur, pelvis, tibia, and cervical spine fractures were treated surgically. All sesamoid fractures and most of the metatarsal, finger phalanx, radius, and clavicle fractures were treated conservatively. The mean patient age for the metacarpal, finger phalanx, ulna, and clavicle fractures was less than 30 years and these could be considered as juvenile fractures. Most of the fractures occurred in men, mainly resulting from high-impact traumas, such as exercise, work casualties, car crash, and squeezing injuries. The mean patient age for the femur, humerus, cervical spine, and pelvis fractures was over 40 years and could be considered as old-age fractures. From the sixth decade onwards, most of the fractures occurred in women and were due to low-impact trauma that resulted in major fractures, usually caused by falling from a standing height. Fractures were most frequent during the summer and least likely to occur in the autumn. Weight-bearing fractures as well as human fractures of large bones, such as the femur, tibia, and fibula, occurred mostly during the winter, while fractures of small bones occurred mostly during the summer. Table 2 shows the frequency of carpal, phalangeal, and tarsal bone fractures. Amongst the carpal bones, the scaphoid was the most commonly broken bone, and the pisiform, the least. Amongst the tarsal bones, the calcaneus was the most commonly broken bone, and the cuboid, the least. The fifth metatarsal, metacarpal, and finger phalanges were the most commonly broken bones, along with the first of the toe phalanges. Table 3 portrays the distribution of the fractures according to the anatomical region. The distal end of the radius, proximal end of the femur, proximal end of the humerus, and the pubic ramus of the pelvis were the most fractured sites. Figure 2 shows the age and seasonal distribution of the proximal femur fractures for patients over 60. In women above 60, fractures of the proximal femur occurred more than in men during all seasons. In the spring, fracture rates in women were 2.43 times higher than those in men, whereas, in autumn, the rates in women were similar to those in men.

Discussion

Gender, age, and seasonal distributions of fractures, the frequency of each type of fractures and the factors that affect the distribution of the fractures were investigated in this study.

In this study, the average age (40.7 years) of the patients with fractures is quite different from the average age (49.1 years) reported in other epidemiological studies (4, 5). This is related to the socioeconomic structure and the different young/elderly ratio in different countries. In this survey, the lower average age (36.2 years) was partially due to a younger population in Turkey. Agreement with the literature in terms of 60% of the patients being male was observed (6). Upon analyzing the overall age and gender frequency curves for females (40% of the cases), a slight undulating frequency was noted until menopause with a rapid apparent increase thereafter, and the percentage of fractures in this age group was higher than in men. This is similar to the type of distributions observed in the literature for women, i.e., unimodal, with a peak appearing around menopause, and increasing over the last decades of life (7). In men, the distribution is represented by a bimodal curve, which is again in agreement with the literature (8). The highest incidence of fractures took place in women in the age range of 21-30 years, especially in active individuals, due to high-impact trauma related to sports activities, crushing, and squeezing injuries, and in the over 80 years group because of inactivity, such as patients with low-impact trauma due to osteoporosis (9). Also, there was an increased incidence in patients of around 60 years old.

According to Johansen et al. (9) fractures of the metacarpals, metatarsals, and finger phalanges are not associated with age. However, fractures of the hip, spine, humerus, and pelvis are more common in the elderly, especially in females. These results agree with the work presented here, with the femur, humerus, spine, and pelvis fractures all occurring in patients over 40 years old. These were fractures associat-

ed with age, more common in the elderly, and were acquired through low-impact trauma. The metacarpal, finger phalanx, ulna, and clavicle fractures mostly occurred in patients younger than 30 years, and were considered as juvenile fractures. Most of the fractures occurred in men primarily from daily activities, workplace injuries, sports, car crash, and squeezing injuries. From the sixth decade onwards, most of the fractures occurred in women and were because of low-impact trauma due to osteoporosis that resulted in major fractures.

Fractures were most frequent during summer and least frequent during autumn. However, weight-bearing fractures and human fractures of long bones, such as the femur, tibia, and fibula, were most prevalent during the winter, whereas fractures of small bones occurred mostly in the summer. The climatic conditions of the area where the study was conducted are ideal for presenting a seasonal distribution of fractures, as there are four distinct seasons. All the sacrum (100%) fractures, and most of the femur (97%), pelvis (86%), tibia (81%), and cervical spine (80%) fractures were treated surgically. All the sesamoid and most of the metatarsal, finger phalanx, radius, and clavicle fractures were treated conservatively.

Studies suggest that osteoporotic fractures are increasing and mainly occur in women. Up to 10 different fracture types are considered to be potentially osteoporotic (10). Proximal femur fractures are one of the representative fractures that can indicate osteoporosis. Fractures occurring in patients over 60 account for the majority of hospitalization and mortality events (11). In this study, 70% of the femur fractures occurred on the proximal end, and the majority of these fractures were observed in patients over 60, probably as a result of osteoporosis (12). It is known that the mortality rate is increased in patients who have already suffered a hip fracture within the first year following the fracture event (13, 14). This is because of comorbidities, advanced age, and actual fracture stress impact on overall health due to fracture. The distribution of proximal femur fractures according to seasons is shown in Figure 2. Fractures occurred more in women than in men in all seasons. In spring, the rate of fractures for women was 2.43 times higher than that for men; however, the rate decreased in summer. The rates leveled off in autumn, followed by an increase in winter again. This demonstrates that immobilization and sun deprivation lead to osteoporotic fractures much more frequently in women than in men.

Study limitations

The limitations of this study were retrospective nature and there are many shortcomings in this study of orthopedic epidemiology in Turkey. In an attempt to correctly define the epidemiology of fractures in the local population, a study should be conducted with individuals visiting only one orthopedic trauma unit.

Conclusion

By analyzing the data related to 4.301 fractures in 4.036 patients admitted to the emergency services of the Gülhane Military Medical Academy, the frequency of fractures according to age group, gender, and season were determined. The knowledge of fracture incidence is important for the planning of treatment, to establish priorities in training, and to gain an understanding of orthopedic traumatology.

In Turkey, osteoporotic fractures are increasing in patients over the age of 50, especially in women. Immobilization and sun deprivation in winter and spring result in osteoporotic fractures in women. This clearly has significant implications for the detection, prevention, and treatment of osteoporosis and the prevention and treatment of osteoporotic fractures. Efforts are potentially geared towards educating the population and, consequently, reducing osteoporosis rates.

Further epidemiological studies are needed for treatment initiatives. In an attempt to correctly define the epidemiology of fractures in the local population, all individuals participating in a study should visit only one orthopedic trauma unit in Turkey.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors would like to thank Harun Yasin Tüzün, Hasan Turgut, Nuray Can, Murat Durusu and İbrahim Arziman for their valuable contributions.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Aschengrau A, Seage G. Essentials of Epidemiology in Public Health. Jones & Bartlett Learning; 2008.
2. Pearce N. Traditional epidemiology, modern epidemiology, and public health. Am J Public Health 1996; 86: 678-83. [CrossRef]
3. Sensoy S, Demircan M, Ulupınar Y, Balta İ. Climate of Turkey. 2007. Devlet Meteoroloji İşleri Genel Müdürlüğü, 13 Feb. 2009 Available at: http://www.dmi.gov.tr/index.aspx.
4. Braga Junior MB, Das Chagas Neto FA, Porto MA, Barroso TA, Lima ACM, Silva SM, et al. Epidemiologic profile and satisfaction level of patients presenting musculoskeletal trauma assisted in a public emergency hospital in Brazil. Acta Ortop Bras 2005; 13: 137-40.
5. Court-Brown CM, Caesar B. Epidemiology of adult fractures: a review. Injury 2006; 37: 691–7. [CrossRef]
6. de Albuquerque AL, de Sousa Filho PG, Braga Junior MB, Cavalcante Neto Jde S, de Medeiros BB, Lopes MB. Epidemiology of fractures in patients from small towns in Ceará treated by the SUS. Acta Ortop Bras 2012; 20: 66-9.
7. Sobania LC, Tatesuji BS, Pacheco CES. Acidentes de tráfego, um problema de saúde pública: análise de 160 pacientes acidentados e internados em hospitais de pronto socorro. Rev Bras Ortop 1989; 24: 13–22.
8. Court-Brown CM, Caesar BC. The epidemiology of fractures. In: Bucholz RW, Heckman JD, Court-Brown CM, eds. Rockwood & Green's Fractures in Adults. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.p.96-113.
9. Johansen A, Evans RJ, Stone MD, Richmond PW, Lo SV, Woodhouse KW. Fracture incidence in England and Wales: a study based on the population of Cardiff. Injury 1997; 28: 655-60. [CrossRef]
10. Mandıracıoğlu A. Demographic characteristics of the elderly population in Turkey and the world. Ege J Med 2010; 4: 39-45.
11. Abrahamsen B, Van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. Osteoporos Int 2009; 20: 1633-50. [CrossRef]
12. Silveira VA, Medeiros MM, Coelho-Filho JM, Mota RS, Noleto JC, Costa FS, et al. Hip fracture incidence in an urban area in Northeast Brazil. Cad Saude Publica 2005; 21: 907-12. [CrossRef]
13. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B, Oglesby AK. The components of excess mortality after hip fracture. Bone 2003; 32: 468-73. [CrossRef]
14. Kanis JA, Odén A, McCloskey EV, Johansson H, Wahl DA, Cooper C. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int 2012; 23: 2239-56. [CrossRef]

EURASIAN JOURNAL OF EMERGENCY MEDICINE

Usage of Pediatric Emergency Department for Non-Urgent Complaints

Raziye Dut
Clinic of Pediatrics, Health Sciences University, Süleymaniye Gynecologic-Obstetrics and Children Ilness, Training and Research Hospital, Istanbul, Turkey

Abstract

Aim: The number of visits to pediatric emergency departments is increasing. To determine the epidemiological profile of patients that are being examined by a pediatrician at emergency departments (EDs) is essential for planning medical care.

Materials and Methods: 12.535 pediatric patients that had visited a pediatric emergency department (PED) due to a non-urgent complaint were enrolled. Demographic features such as gender and age; the nature of the presenting complaint; timing of the visit, i.e., frequency of the visits according to seasons, days of the week, times of the day; and other factors including admission rates, length of stay, and rates of treatment upon observation were reviewed.

Results: Of the 12.535 patients included in the study, 5645 (45.0%) were girls, 6890 (54.9%) were boys, and the mean age was 4.9 years old. Most patients were 1-4y (33.8%) and patients older than 15y (3.2%) were the smallest group. The results revealed that the most common complaints were fever (38.5%), coughing (20.7%) and vomiting (11.1%). The inpatient admission rate was 0.69% and the rate of patients being treated upon observation was 5.9%. The most common visiting times were 18:00-23:59 (42.9%). Furthermore, 65% of visits took place during workdays and 35.0% during weekends. Most visits took place on Monday (15.5%). The length of stay was different amongst the different age groups (p=0.009).

Conclusion: Pediatric patients typically are admitted to EDs for common pediatric complaints rather than uncommon complaints or accidents. The result of the present study may be useful in the management planning of pediatric emergency departments.

Keywords: Emergency department, complaints, pediatrician

Introduction

Emergency department (ED) usage has been increasing in Turkey and in the world. Of all children in the U.S., 20% will visit an ED at least once each year (1, 2). Patients ≤18 years old account for about 25% of the total number of ED visits (3). ED usage due to non-urgent conditions is very high (4).

The percentage of non-urgent visits to pediatric EDs (PEDs) has been identified to be 15% to 60%, and from 11% to 83% in general EDs. Non-urgent ED visits are defined as visits for conditions in which a delay of several hours would not increase the likelihood of an adverse outcome, and these visits can involve admission to hospital, diagnoses, vital sign assessment, complaint, timing of visit, arrival to ED, and procedures and/or tests being ordered. These type of visits are characterized by the patient's ability to wait for evaluation or care (5). Billings et al. (6) examined data on adult emergency visits, excluding visits due to injury, mental health complaints, and alcohol or substance abuse, and found that 4 to 5 visits were due to non-urgent conditions that could have otherwise been managed in a primary care setting or through preventive measures (6).

The usage of PEDs for non-urgent complaints has saturated the capacity of PEDs and is leading to excessive healthcare spending, as well as unnecessary testing and treatments, preventing the efficient and effective usage and quality of PEDs. Visiting PEDs for non-urgent concerns may unnecessarily crowd the department, leading to longer waiting times, adverse events due to delays in care and increased costs. Many of the PED visits could have been managed in a primary care setting, and this has been shown to improve health outcomes. Parents take their children to PEDs for non-urgent care because of the advantages of PED care (7).

In a study, Lowe and Abbuhl argue that social, economic, and practical factors contribute to such visits, and that the societal context of the

This study was presented at the 52nd Congress of Turkish Pediatric Association ,15-19 May 2016, Antalya, Turkey.

Correspondence to: Raziye Dut e-mail: raziyedut@gmail.com

Received: 05.11.2016 • **Accepted:** 15.01.2017

DOI: 10.5152/eajem.2017.63935

visits must be assessed to determine if these visits are appropriate (8, 9). Sempere-Selva et al. (10) concluded that patients preferred to use PED services because of their greater convenience and accessibility. Several studies have examined PED usage with the aim of developing interventions to increase the efficiency of EDs and decrease costs (11).

Descriptive research has identified the demographic characteristics of those using PEDs for non-urgent care, as it is vital to prevent unnecessary crowding of PEDs and improve medical care.

In the present study, visits to PEDs due to non-urgent complaints were investigated in the Acıbadem Maslak Hospital, a private hospital of Istanbul, Turkey. This study was conducted to understand the causes leading to crowding in PEDs and to highlight this issue for future research, thus helping to achieve a cost-effective usage of PEDs.

Materials and Methods

Non-urgent visits to PEDs (<16 yr old) were analyzed. This is a single-center, retrospective study on PED usage, which included 12.535 patients who visited a PED and were examined by a pediatrician. We particularly looked at non-urgent patients who were examined by a pediatrician to show the epidemiological characteristics of processing medical care. Informed consent is not necessary due to the retrospective nature of this study.

Data regarding patients' demographic features, complaints upon presentation, timing of the visits (season, day of the week, time of the day), inpatient admission rates, length of stay (LOS), and treatment upon observation were extracted.

We classified patients according to age, as follows: <1y, 1-4y, 5-9y, 10-14y and >15y. We analyzed the characteristics of non-urgent visits to PEDs: 1) age and sex of the patient; 2) timing of the visits (season, day of the week, time of the day, i.e., 00:00-05:59, 06:00-11:59, 12:00-17:59, 18:00-23:59); 3) waiting times at the emergency department, i.e., time elapsed between admission and departure(discharge) ; 4) rates of treatment upon observation, admission, discharge.

We determined the number of admissions for each age group and month, and results were compared. Although the complaints could be considered as non-urgent, admission can be necessary. We also obtained data regarding non-urgent, non-vital, possible treatments at home of the emergency departments. Trauma, injury, car crash, status epilepticus, convulsion with or without fever, respiratory arrest, drug abuse, intoxication, other vital urgent conditions, and chronic and recurrent conditions were excluded.

Ethics Committee Approval was taken from Ethical Committee of Acıbadem University for this study.

Statistical analysis

The Number Cruncher Statistical System (NCSS) 2007 statistical software program (Utah, USA) was used. Descriptive statistical analysis, single direction analysis, the Tukey multiple comparative test, chi-square test, and Fisher reality test were employed. A p value <0.05 was considered statistically significant. Data excluded from the analysis are indicated in the text and tables.

Table 1. Age groups and their presenting complaints

	<1 y		1-4 y		5-9 y		10-14 y		>15 y		
	N	%	N	%	N	%	N	%	N	%	p
Fever	554	37.4	2712	43.6	1589	37.4	471	29.4	115	28.4	<0.001
Cough	264	17.8	1142	23.7	888	20.9	252	15.7	59	14.5	<0.001
Vomiting	120	8.1	506	10.5	527	12.4	215	13.4	34	8.4	<0.001
Nausea	9	0.6	46	0.9	117	2.7	92	5.7	44	10.8	<0.001
Abdominal Pain	10	0.6	109	2.2	335	7.9	166	10.3	34	8.4	<0.001
Rash	109	7.3	215	4.4	176	4.1	58	3.6	11	2.7	<0.001
Ear Pain	13	0.8	287	5.9	379	8.9	78	4.8	17	4.2	<0.001
Headache	2	0.1	9	0.1	66	1.5	59	3.6	19	4.6	<0.001
Diarrhea	58	3.9	213	4.4	162	3.8	83	5.1	22	5.4	0.116
Stomatitis	9	0.6	29	0.6	6	0.1	3	0.1	0	0.0	0.001
Foot-Leg Pain	0	0.0	15	0.3	13	0.3	3	0.1	0	0.0	0.177
Throat Pain	16	1.0	157	3.2	342	8.0	183	11.4	67	16.5	<0.001
Rhinorrhea	69	4.6	240	4.9	138	3.2	46	2.8	22	5.4	<0.001
Stuffiness	32	2.1	52	1.0	26	0.6	12	0.7	4	0.9	<0.001
Fatigue	21	1.4	42	0.8	56	1.3	31	1.9	21	5.1	<0.001
Urine pain	3	0.2	39	0.8	16	0.3	3	0.1	0	0.0	0.001
Hyperemic Eye	16	1.0	28	0.5	20	0.4	6	0.3	0	0.0	0.025
Constipation	23	1.5	41	0.8	9	0.2	2	0.1	0	0.0	0.001
Restlessness	166	11.2	59	1.2	5	0.1	1	0.0	0	0.0	0.001

Table 2. Number of visits for every season, days of the week and hours of the day; observation unit care and admission for every age group

		<1 y		1-4 y		5-9 y		10-14y		>15y		
		N	%	N	%	N	%	N	%	N	%	p
Sex	Girl	672	45.4	2157	44.8	1899	44.8	711	44.4	206	50.8	0.197
	Boy	808	54.5	2656	55.1	2339	55.1	888	55.5	199	49.1	
Season	Winter	99	6.6	379	7.8	429	10.1	170	10.6	31	7.6	<0.001
	Spring	95	6.4	371	7.7	390	9.2	153	9.5	43	10.6	
	Summer	407	27.5	1190	24.7	758	17.8	311	19.4	66	16.3	
	Autumn	879	59.3	2873	59.6	2661	62.7	965	60.3	265	65.4	
Visiting Day	Monday	243	16.4	717	14.9	652	15.3	262	16.3	70	17.2	0.002
	Tuesday	175	11.8	606	12.5	519	12.2	194	12.1	73	18.0	
	Wednesday	190	12.8	605	12.5	474	11.1	222	13.8	51	12.5	
	Thursday	170	11.4	574	11.9	537	12.6	198	12.3	60	14.8	
	Friday	203	13.7	613	12.7	504	11.8	187	11.6	49	12.1	
	Saturday	226	15.2	725	15.0	678	16.0	242	15.1	46	11.3	
	Sunday	273	18.4	973	20.2	874	20.6	294	18.3	56	13.8	
Total Day	Workday	981	66.2	3115	64.7	2686	63.3	1063	66.4	303	74.8	<0.001
	Weekend	499	33.7	1698	35.2	1552	36.6	536	33.5	102	25.1	
Visiting Hours	00:00-05:59	205	13.9	561	11.7	375	8.9	120	7.5	33	8.2	<0.001
	06:00-11:59	223	15.1	913	19.1	804	19.1	317	20.0	78	19.5	
	12:00-17:59	343	23.3	1239	25.9	1251	29.7	490	30.9	105	26.2	
	18:00-23:59	698	47.5	2066	43.2	1780	42.2	658	41.5	184	46.0	
Observation Unit care		90	6.0	280	5.8	251	5.9	95	5.9	25	6.1	0.976
Admission		24	1.6	31	0.6	26	0.6	4	0.2	1	0.2	<0.001

Results

Demographic data

We studied 12.535 patients, of which 5645 (45.0%) were girls and 6890 (54.9%) were boys, with a median age of 4.9 years old. Of the patients, 1480 (11.8%) were <1y, 4813 (38.4%) were 1-4y, 4238 (33.8%) were 5-9y, 1599 (12.8%) were 10–14y, and 405 (3.2%) were >15y. No difference was found between girls and boys in terms of age distribution (p=0.197).

Presenting complaints

The most common complaints upon presentation at the PED were fever (38.5%), cough (20.7%), and vomiting (11.1%). Coughing was more common in boys (p=0.001). Vomiting, ear pain, and throat pain was more common in girls (p=0.018), (p=0.023), (p=0.006), respectively.

Complaints upon presentation according to age are shown in Table 1. Fever was more common among 1-4y than in the other age groups (p=0.0001). Coughing was less frequent in those <1y and >15y compared to the other age groups (p=0.0001). In the >15y group, nausea was more common than in the other age groups (p=0.0001). In the <1y and 1-4y groups, abdominal pain was less common compared to the other age groups (p=0.0001). When compared to the other age groups, in the 10-14y and >15y groups, the incidence of rash was lower (p=0.0001), but headache was more common (p=0.0001). In the <1y group the incidence of ear pain was lower than in the other age groups (p=0.0001). Incidence of diarrhea was not different amongst the age groups (p=0.116). Stomatitis was not found in the >15y group, (p=0.0001). Throat pain was less common for the <1y and 1-4y groups compared to the other age groups (p=0.0001). Rhinorrea was less frequent in the 5-9y and 10-14y groups compared to the other age groups (p=0.0001). Stuffiness was more common in the <1y and 1-4y groups than in the other age groups (p=0.0001). Fatigue was more common in the >15y than in other age groups (p=0.0001). Complaints of painful urination, constipation, and restlessness were less common in the >15y group than in the other age groups (p=0.0001). Incidence of dyspnea was not different amongst the <1y, 1-4y, 5-9y, 10-14y, and >15y groups (p=0.153). Restlessness was more common in the <1y group (p=0.0001).

Length of stay (LOS)

In the studied PED visits, there was no difference in the LOS between girls and boys (p=0.246). However, LOS was different between the age groups (p=0.009). The length of stay for the <1y was longer than for the 1-4y (p=0.0001) and the 5-9y (p=0.01), but there was no difference between the other age groups (p>0.05) and there was no difference between seasons (p=0.0001); however, in winter, LOS was longer than in spring (p=0.002) or autumn (p=0.0001).

Table 3. Visiting hours and presenting complaints

Visiting Hours/Presenting Complaints	00:00-05:59		06:00-11:59		12:00-17:59		18:00-23:59		p
Fever	512	39.57%	891	38.16%	1275	37.19%	2.118	39.32%	0.192
Cough	193	14.91%	559	23.94%	826	24.10%	1.003	18.62%	<0.001
Vomiting	234	18.08%	284	12.16%	336	9.80%	539	10.01%	<0.001
Nausea	26	2.01%	73	3.13%	83	2.42%	122	2.27%	0.097
Abdominal Pain	79	6.11%	127	5.44%	164	4.78%	278	5.16%	0.304
Rash	34	2.63%	97	4.15%	151	4.40%	282	5.24%	<0.001
Ear Pain	119	9.20%	132	5.65%	172	5.02%	349	6.48%	<0.001
Headache	11	0.85%	26	1.11%	42	1.23%	75	1.39%	0.401
Diarrhea	55	4.25%	130	5.57%	133	3.88%	216	4.01%	0.008
Stomatitis	3	0.23%	6	0.26%	18	0.53%	20	0.37%	0.305
Foot-Leg Pain	8	0.62%	2	0.09%	8	0.23%	13	0.24%	0.022
Throat Pain	24	1.85%	144	6.17%	262	7.64%	325	6.03%	<0.001
Rhinorrhea	23	1.78%	100	4.28%	170	4.96%	221	4.10%	<0.001
Stuffiness	10	0.77%	27	1.16%	37	1.08%	49	0.91%	0.590
Fatique	9	0.70%	24	1.03%	48	1.40%	87	1.62%	0.031
Urine Pain	3	0.23%	7	0.30%	17	0.50%	34	0.63%	0.127
Hyperemic Eye	1	0.08%	14	0.60%	25	0.73%	29	0.54%	0.061
Constipation	8	0.62%	8	0.34%	16	0.47%	43	0.80%	0.068
Restlessness	66	5.10%	16	0.69%	34	0.99%	112	2.08%	<0.001

Season/day/admission/observation

Of the 12.535 patients, 86 (0.69%) were admitted and 741 (5.9%) were treated upon observation.

No differences were found between girls and boys as regards presentation to the PED with respect to season (p=0.266), day of the week (p=0.850), workday and weekend (p=0.929), time of the day (p=0.504), admission rates (p=0.553), and rates of treatment upon observation (p=0.226).

Presentation rates according to season, day of the week, time of the day, rates of treatment upon observation, and admission rates are shown in Table 2.

The number of visits to the PED in summer was higher for the <1y and 1-4y groups compared to the other age groups (p=0.0001). There were less visits to the PED on weekends for the >15y group compared to the other age groups (p=0.0001).

There was no difference in the rates of treatment upon observation amongst the age groups (p=0.976). Admission rates for the <1y were higher compared to the other age groups (p=0.0001).

Treatment rates upon observation were lower in spring than in the other seasons (p=0.0001). There were no admissions in spring (p=0.001). For the <1y group, the number of visits in summer and autumn was higher than in the other seasons (p=0.0001). There were less visits during winter workdays (p=0.0001). There were less visits during the 12:00-17:59 time slot in summer than in other seasons (p=0.0001). Fever was the most common complaint in autumn compared to the other seasons (p=0.0001).

Visiting times

For any given day of the week, the most common , visits took place during the 18:00–23:59 time slot (42.9%), followed by 12:00-17:59 (27.3%), 06:00-11:59 (18.6%), and 00:00-05:59 (10.3%).

are shown in Table 3. Restless, vomiting and ear pain were more common at 00:00–05:59 compared to other times of the day (p=0.0001), (p=0.0001), (p=0.0001), respectively. Coughing and throat pain were less common complaints during the 00:00–05:59 time slot compared to other times of the day (p=0.0001), (p=0.0001), respectively.

For the <1y and 1-4y groups, there were more visits during the 00:00–05:59 times, compared to the other age groups (p=0.0001).

Discussion

Pediatric emergency departments are commonly used by pediatric patients due to non-urgent reasons, which could have been managed by their primary care provider. Often, pediatric patients visit PEDs during days and hours in which the primary care pediatric centers are closed, particularly on the weekends and in the evenings (12).

The Healthcare Cost and Utilization Project (Agency for Healthcare Research and Quality) categorizes the top 10 reasons for PED visits as the same top 10 reasons for visits to primary care centers. This suggests that these conditions could be appropriately cared for in a primary care setting (13). A publication on PEDs shows that one third of pediatric patients visit PEDs for observation and treatment of common illnesses (14).

In that study, of all children visiting PEDs, 54.9% were boys and the most common age group was 1-4y. For children under one year old, immunization scale is very hard and routine control at primary care is more common. But after one year, immunization scale is not that hard and routine controls are becoming not frequently. These findings agree well with the literature. In the literature, the age group that visited PEDs the most was the 1-4y group (42.3%); of those children, 59.1% were boys (15). Many authors found age as a predictor for inappropriate ED visits (7, 16-19). Detailed clinical, familial and social data are needed to determine the true reasons for frequent visits to PEDs in this age group. The neonatal period (<28 days old) is a vulnerable period of pediatric health where emergencies can certainly occur. For newborns, hospital care after birth and early primary care may have a significant impact on healthcare service usage. We investigated this group into <1y, did not assess them seperately.

It is known that 10-19y period is considered as adolescent period. In Turkey, children ≤16y are examined at pediatric clinics and PEDs. Pediatric physicians should understand their psychosocial requirements, and discuss HEADSS (Home, Education/Employment, Activity, Drugs, Sexuality, Suicide) assessment topics. Adolescents do not bring up complaints easily, so trust is more important for them. They contact their primary care provider more than PEDs, and in practice on how to specifically provide for the unique needs of this age population (20, 21). Adolescents who visit PEDs due to non-urgent complaints are a vulnerable group and are more likely to report urgent concerns such as drug use/abuse, suicide, unintentional injuries, or crashes (22). In that study, non-urgent complaints were found. Fatique and headache were more common in the adolescent group.

The rate of admission was 0.69%, and the rate of treatment upon observation was 5.9%. These results show that patients who visit PEDs are usually discharged. The lower admission rate and higher rate of treatment upon observation suggests that PEDs have a higher workload for hospitals. One of the most important functions of an emergency department is to assess patient status so as to categorize the patient as inpatient or outpatient. With rapid, appropriate assessment of patient status, the incidence of emergency department overcrowding can also be reduced, thereby reducing treatment delay and mortality (23-25).

Observation unit care for pediatric short-course treatments (typically <24 hours) and frequent reassessments are very important, as using inpatient beds for short-stay patients may delay the admission for children requiring a longer inpatient stay. Another advantage of the observation unit is the lower cost of care (26, 27).

Overall, workday visits were the most common (65.0%), followed by weekend visits (35.0%). The number of visits to PEDs was higher on Mondays (15.5%) than on the other workdays. Regarding visits to PEDs on weekends, the number of visits on Sunday (19.7%) was higher than on Saturday (%). Overall, visits to PEDs on Sunday ED were the most common. In the literature, visits to PEDs on Sunday are reported to be 23.7%, which is similar to the result for this study (15).

Complaints differed according to season and the number of visits during different seasons differed according to age group. In winter, the LOS in PEDs was longer than in spring and autumn, but did not differ from summer. Overall, the number of non-urgent visits is high during autumn. This needs to be investigated to understand the nature of the diagnoses according to the seasons and the national data on viral or allergic diseases.

We found that complaints were different depending on the time of the PED visit. Visits to PEDs most commonly occurred during 18:00-23:59 (42.9%). Visits during 00:00-05:59 were more frequent for the <1y and 1-4y groups. This probably reflects higher anxiety and need for reassurance in parents.

A 2006 study from the State Children's Health Insurance Program of New York City suggested that during daytime hours, only 20% of parents brought their children to PEDs because of the perceived need of hospitalization, i.e., care that could not be provided in a primary care setting (28). Generally, a pediatrician or a general practitioner in a primary care center is available during office hours, from 8 A.M to 6 P.M during workdays and from 9 A.M to 2 P.M on Saturdays. Many parents who seek outpatient treatment care during the evening hours prefer to take their children to a pediatrician in a primary care center, but visit a PED because of the lack of primary care access during those hours. The idea that extended office hours in primary care settings can reduce ED usage has recently been raised in studies with adult patients (29). This idea may be applicable for pediatric patients so as to receive a higher quality of care. Thus, after-hour pediatric services could reduce PED usage. The effect of extended hours in pediatric primary care clinics on PED usage (with respect to season, timing of after-hour visits, age of patients, presenting complaint, parent perceptions, and preferences for emergency care) should be evaluated.

Parents often overestimate the severity of their child's condition as urgent; parents need to be educated by physicians, as most of the pediatric conditions can be prevented. When illnesses arise, only a few are genuinely urgent conditions; thus, illnesses may be acute but usually do not require an extensive all-inclusive treatment at a PED.

Furthermore, this study would be a reference for upcoming research aimed at studying why parents visit PEDs so frequently, and highlights the importance of reducing PED usage due to non-urgent complaints.

Study limitations

This study has certain limitations. It included only one private hospital in Istanbul, such that the results cannot be readily generalized. Thus, there may be variation in the reasons for non-urgent pediatric care in other PEDs and other regions of the country. It will be important to examine the trends of other public hospitals in future studies.

Conclusion

The present study described the demographic features, complaints, and seasonal and time patterns of visits to PEDs for pediatric examination due to non-urgent complaints. The results revealed that typically, pediatric patients visit PEDs due to common pediatric complaints rather than uncommon complaints or accidents. This leads to an increased number of visits, which in turn leads to longer waiting times, causing patient dissatisfaction. Overcrowding also cause many patients to leave the PED without having been examined by a physician. So, a combination of high patient volumes and limited emergency care capabilities represent a serious problem. Monitoring of frequent visits to PEDs may have the potential to be useful as a quantitative marker for patient health and/or quality of health care delivery. Most PED visits could have been managed by the primary care provider (PCP). Access to primary care/preventative care and

providing parental education about how to address childhood illnesses have all been associated with a decreased number of visits to PEDs due to non-urgent complaints. The future investigations to exclude why parents come children to PED with non-urgent conditions would be planned. Also, parents should be trained about urgent and non-urgent conditions to reduce PED overcrowding and improve cost efficiency.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Acıbadem University (Decision No: 2014-571).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Acknowledgements: The author would like to thank all of the nurses and health care workers of Acıbadem Maslak Hospital, Emergency Department.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Alpern ER, Clark AE, Alessandrini EA, Gorelick MH, Kittick M, Stanley RM, et al. Recurrent and high-frequency use of the emergency department by pediatric patients. Acad Emerg Med 2014; 21: 365-73. [CrossRef]
2. Alpern ER, Stanley RM, Gorelick MH, Donaldson A, Knight S, Teach SJ, et al. Epidemiology of a pediatric emergency medicine research network: the PECARN Core Data Project. Pediatr Emerg Care 2006; 22: 689-99. [CrossRef]
3. Mistry RD, Cho CS, Bilker WB, Brousseau DC, Alessandrini EA. Categorizing urgency of infant emergency department visits: agreement between criteria. Acad Emerg Med 2006; 13: 1304-11. [CrossRef]
4. Vedovetto A, Soriani N, Merlo E, Gregori D. The burden of inappropriate emergency department pediatric visits: why Italy needs an urgent reform. Health Serv Res 2014; 49: 1290-305. [CrossRef]
5. Uscher-Pines L, Pines J, Kellermann A, Gillen E, Mehrotra A. Emergency department visits for nonurgent conditions: systematic literature review. Am J Manag Care 2013; 19: 47-59.
6. Billings J, Parikh N, Mijanovich T. Emergency department use in New York City: a survey of Bronx patients. Issue Brief (Commonw Fund) 2000; (435): 1-5.
7. Berry A, Brousseau D, Brotanek JM, Tomany-Korman S, Flores G. Why do parents bring children to the emergency department for nonurgent conditions? A qualitative study. Ambul Pediatr 2008; 8: 360-7. [CrossRef]
8. Chin NP, Goepp JG, Malia T, Harris L, Poordabbagh A. Nonurgent use of a pediatric emergency department: a preliminary qualitative study. Pediatr Emerg Care 2006; 22: 22-7. [CrossRef]
9. Lowe RA, Abbuhl SB. Appropriate standards for "appropriateness" research. Ann Emerg Med 2001; 37: 629-32. [CrossRef]
10. Sempere-Selva T, Peiró S, Sendra-Pina P, Martínez-Espín C, López-Aguilera I. Inappropriate use of an accident and emergency department: magnitude, associated factors, and reasons--an approach with explicit criteria. Ann Emerg Med 2001; 37: 568-79. [CrossRef]
11. Mistry RD, Hoffmann RG, Yauck JS, Brousseau DC. Association between parental and childhood emergency department utilization. Pediatrics 2005; 115: e147-51. [CrossRef]
12. Hummel K, Mohler MJ, Clemens CJ, Duncan B. Why parents use the emergency department during evening hours for nonemergent pediatric care. Clin Pediatr (Phila) 2014; 53: 1055-61. [CrossRef]
13. Merrill CT, Owens PL, Stocks C. Pediatric emergency department visits in community hospitals from selected states, 2005: Statistical brief #52. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD) 2006.
14. Scribano PV, Wiley JF 2nd, Platt K. Use of an observation unit by a pediatric emergency department for common pediatric illnesses. Pediatr Emerg Care 2001; 17: 321-3. [CrossRef]
15. Kwak YH, Kim DK, Jang HY. Utilization of emergency department by children in Korea. J Korean Med Sci 2012; 27: 1222-8. [CrossRef]
16. Carret ML, Fassa AG, Kawachi I. Demand for emergency health service: factors associated with inappropriate use. BMC Health Serv Res 2007; 7: 131. [CrossRef]
17. Ben-Isaac E, Schrager SM, Keefer M, Chen AY. National profile of nonemergent pediatric emergency department visits. Pediatrics 2010; 125: 454-9. [CrossRef]
18. Davis JW, Fujimoto RY, Chan H, Juarez DT. Identifying characteristics of patients with low urgency emergency department visits in a managed care setting. Manag Care 2010; 19: 38-44.
19. Brousseau DC, Nimmer MR, Yunk NL, Nattinger AB, Greer A. Nonurgent emergency-department care: analysis of parent and primary physician perspectives. Pediatrics 2011; 127: e375-81. [CrossRef]
20. Hicks CF, Ward MJ, Platt SL. Adolescents' and young adults' perspectives on their emergency care. Pediatr Emerg Care 2014; 30: 529-33. [CrossRef]
21. Pitts SR, Niska RW, Xu J, Burt CW. National hospital ambulatory medical care survey: 2006 emergency department summary. Natl Health Stat Report 2008; 7: 1-38.
22. Wilson KM, Klein JD. Adolescents who use the emergency department as their usual source of care. Arch Pediatr Adolesc Med 2000; 154: 361-5. [CrossRef]
23. Weiss SJ, Ernst AA, Sills MR, Quinn BJ, Johnson A, Nick TG. Development of a novel measure of overcrowding in a pediatric emergency department. Pediatr Emerg Care 2007; 23: 641-5. [CrossRef]
24. Chamberlain JM, Patel KM, Pollack MM. Association of emergency department care factors with admission and discharge decisions for pediatric patients. J Pediatr 2006; 149: 644-9. [CrossRef]
25. Chaiyakulsil C, Pandee U. Validation of pediatric early warning score in pediatric emergency department. Pediatr Int 2015; 57: 694-8. [CrossRef]
26. Conners GP, Melzer SM, Committee on Hospital Care, Committee on Pediatric Emergency Medicine, Betts JM, Chitkara MB, et al. Pediatric observation units. Pediatrics 2012; 130: 172-9. [CrossRef]
27. Cator AD, Weber JS, Lozon MM, Macy ML. Effect of using pediatric emergency department virtual observation on inpatient admissions and lengths of stay. Acad Pediatr 2014; 14: 510-6. [CrossRef]
28. Stockwell MS, Findley SE, Irigoyen M, Martinez RA, Sonnett M. Change in parental reasons for use of an urban pediatric emergency department in the past decade. Pediatr Emerg Care 2010; 26: 181-5. [CrossRef]
29. Göransson KE, De Waern M, Lindmarker P. Patients' pathway to emergency care: is the emergency department their first choice of care? Eur J Emerg Med 2013; 20: 45-50. [CrossRef]

EURASIAN JOURNAL OF EMERGENCY MEDICINE

Efficacy of Use of Red Cell Distribution Width as a Diagnostic Marker in Acute Appendicitis

Birsen Ertekin[1], Hasan Kara[2], Esma Erdemir[1], Emine Doğan[3], Tarık Acar[1], Lütfi Saltuk Demir[4]

[1]Clinic of Emergency Medicine, Beyhekim State Hospital, Konya, Turkey
[2]Department of Emergency Medicine, Selçuk University School of Medicine, Konya, Turkey
[3]Department of Emergency Medicine, Başkent University School of Medicine, Konya, Turkey
[4]Department of Public Health, Necmettin Erbakan University Meram School of Medicine, Konya, Turkey

Abstract

Aim: We aimed to investigate the increase in values of red cell distribution width (RDW) and also the dependence of RDW on leukocyte count (WBC) and C-reactive protein (CRP) values in acute appendicitis (AA).

Materials and Methods: This study includes data collected from 407 patients who were admitted between January 2012 and July 2014 to the emergency service and underwent an operation owing to a diagnosis of AA confirmed by a pathology report. These patients were divided into two groups, namely, non-complicated and complicated appendicitis, according to the results of the operation. The control group consisted of 100 adult patients with similar complaints not having acute abdominal conditions. The age, gender, and WBC, RDW, and CRP levels of the patients on admission were recorded retrospectively.

Results: A total of 350 (86%) of the patient group were diagnosed with non-complicated appendicitis, 34 (8.4%) with plastron appendicitis, and 23 (5.6%) with perforated appendicitis. No significant difference was observed with respect to WBC, RDW, and CRP levels between the AA groups ($p>0.05$). The WBC, RDW, and CRP values were found to be significantly different in the AA groups from the control group ($p<0.05$). The sensitivity and specificity of the WBC, RDW, and CRP values in the AA group were 70% and 60%, 41% and 30%, and 51% and 40%, respectively. No dependence of RDW values on WBC or CRP levels was found.

Conclusion: RDW values were found to be significantly higher in the AA group than in the control group. The low sensitivity and specificity values of the RDW test reduce the possibility that it might become a hematologic marker to be used in the definitive diagnosis of AA.

Keywords: Red cell distribution width, acute appendicitis, diagnosis, marker

Introduction

Red cell distribution width (RDW) is a quantitative measurement of difference in the size of circulating erythrocytes, which has a high value if greater heterogeneity in cell dimensions is present (i.e., anisocytosis). RDW is a parameter that is easy and cheap to measure and is routinely checked as part of the full blood count. Normal RDW values range between 11.5% and 14.5% (1). Increased RDW values might be observed in many situations such as a higher production of inactive erythrocytes (hemolysis, which causes the release of premature erythrocytes into the circulation, after blood transfusions, or in cases of deficiencies in iron, vitamin B12, and folic acid). In recent studies, RDW was claimed to be useful for the detection of a risk of mortality in patients that have cardiovascular disease, acute dyspnea, acute pancreatitis, community-acquired pneumonia, and sepsis (2-5). Acute appendicitis (AA) is the most common cause of acute abdominal pain that requires an emergency surgical operation in adults (6). Individuals have a 7% risk of AA over the course of a lifetime (7). In addition, most patients have characteristic symptoms and findings on physical examination. However**,** the definitive diagnosis of cases that require emergency operations is not always easy. The important requirement in the case of AA is to perform an emergency operation on an immediate diagnosis. The rate of correct diagnosis of AA is 76%-92% owing to developments and improvements in medicine (8). Rates of perforation and negative appendectomy have not decreased, even though the mortality rate has decreased with recent

Correspondence to: Birsen Ertekin e-mail: biceacil@hotmail.com

Received: 01.10.2016 • **Accepted:** 17.01.2017

DOI: 10.5152/eajem.2017.75047

improvements in diagnostic techniques (9). Thus, a diagnosis should be rapidly established using the easiest methods. Otherwise, the development of mortal complications is inevitable in cases where a diagnosis is delayed. A blood test that supports the findings of clinical and physical examinations and imaging of the patient is required for a diagnosis of AA. Currently, there is no marker for the definitive diagnosis of AA prior to performing AA surgery. The need for interventions such as radiological imaging methods and inflammatory tests, as well as invasive procedures such as laparoscopy, has increased owing to the high rates of negative appendectomy and perforation (10). The detection of inflammatory parameters (leukocyte count [WBC], C-reactive protein [CRP] values, etc.) and serial follow-ups are also significant in terms of the diagnosis of AA (11). The aim of our study is to investigate the increase in RDW values, in addition to the dependence of RDW on WBC and CRP values, in AA.

Materials and Methods

In this study, patients diagnosed with AA at Konya Beyhekim Public Hospital emergency service between January 2012 and July 2014 who underwent surgery for AA were investigated following the approval of the Selçuk University School of Medicine ethical committee (number of issue: 2013-336). The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the institutional review committee on human research. Because the study was a retrospective study, informed consent couldn't be obtained from each patient. Female and male patients older than 18 years who were admitted to the emergency service with a complaint of abdominal pain and/or nausea and vomiting and whose symptoms were compatible with a diagnosis of AA according to their history, findings on physical examination, and laboratory results on admission were examined by abdominal ultrasonography (US) and/or abdominal computed tomography (CT) by radiologists. Patients who were treated medically without surgery were excluded from the study. In total, 407 patients whose diagnoses were confirmed as AA via a pathology report were included in the study. Those diagnosed with AA were divided into two subgroups-non-complicated and complicated (plastron or perforated) appendicitis-according to the results of the operation. The control group consisted of 100 adult patients with similar complaints but with the exclusion of acute abdominal conditions. These patients had diseases such as gastroenteritis, urinary tract infections, renal colic, and non-specific abdominal pain. The age, gender, and WBC, RDW, and CRP levels of the patients on admission were recorded retrospectively.

Biochemical analysis

White blood cell and RDW values were determined from blood samples collected from the patients upon admission (Sysmex XT 2000i). CRP levels were measured using a nephelometric technique (Siemens BN II).

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences 18.0 program (SPSS Inc.; Chicago, USA) Groups were compared using the t-test for continuous variables. The Pearson correlation test was used for the detection of correlation of RDW with other variables. The results were expressed as the mean±standard deviation. The cut-off values of parameters were identified using the analysis of receiver operating characteristic (ROC) curves for the differentiation of groups. Values of sensitivity and specificity were calculated using different cut-off values. A value of $p \leq 0.05$ was accepted as being statistically significant.

Table 1. Comparison of WBC, CRP, and RDW levels of subjects with complicated and non-complicated acute appendicitis*

	Non-complicated group (n=350)	Complicated group (n=57)	p
WBC (K/µL)	11.8±4.5	12.5±4.3	0.99
RDW (%)	13.6±2.1	13.6±2.1	0.94
CRP (mg/L)	27.8±55.8	20.1±45.7	0.11

WBC: white blood cell; RDW: red blood cell distribution width; CRP: C-reactive protein
*Data reported as mean±SD.

Table 2. Comparison of demographic features and WBC, CRP, and RDW levels of subjects in the acute appendicitis and control groups*

	Acute appendicitis group (n=407)	Control group (n=100)	p
Age	31.9±12.7	38.7±11.6	0.001
Male/female	260/147	47/53	0.002
WBC (K/µL)	11.9±4.5	9.1±4.6	0.001
RDW (%)	13.6±2.1	13±1.4	0.012
CRP (mg/L)	26.7±54.5	6.9±9.8	0.026

WBC: white blood cell; RDW: red blood cell distribution width; CRP: C-reactive protein
*Data reported as number or mean±SD.

Results

In total, 407 patients with a definitive diagnosis of AA and 100 patients in the control group were investigated. A total of 350 (86%) of the patient group were diagnosed with non-complicated appendicitis, 34 (8.4%) were diagnosed with plastron appendicitis, and 23 (5.6%) were diagnosed as having perforated (complicated) appendicitis. No significant difference was observed with respect to the WBC, RDW, and CRP levels between the complicated and non-complicated AA subgroups ($p>0.05$) (Table 1). Of the AA group, 260 (63.9%) were male and 147 (36.1%) were female, whereas 47 (47%) of the control group were male and 53 (53%) were female. The mean age of the AA group was 31.9±12.7 years, whereas this was 38.7±11.6 years in the control group. A significant difference was observed between the AA and control groups with respect to age and gender ($p<0.05$). The mean WBC values were 11.9±4.5 in the AA group and 9.1±4.6 in the control group. RDW values were found to be significantly different between the AA group and the control group ($p<0.05$) (Table 2). The area under the curve (AUC) was calculated from the ROC curves for the WBC, RDW, and CRP values of the patient groups. The AUC was found to be 0.710 ($p=0.001$) for WBC, 0.385 ($p=0.001$) for RDW, and 0.432 ($p=0.034$) for CRP. Sensitivity was 70% and specificity was 60% according to the ROC curve for WBC, whereas the optimum cut-off was 8.99. Sensitivity was 41% and specificity was 30% according to the ROC curve for RDW, whereas the optimum cut-off was 13.1. Sen-

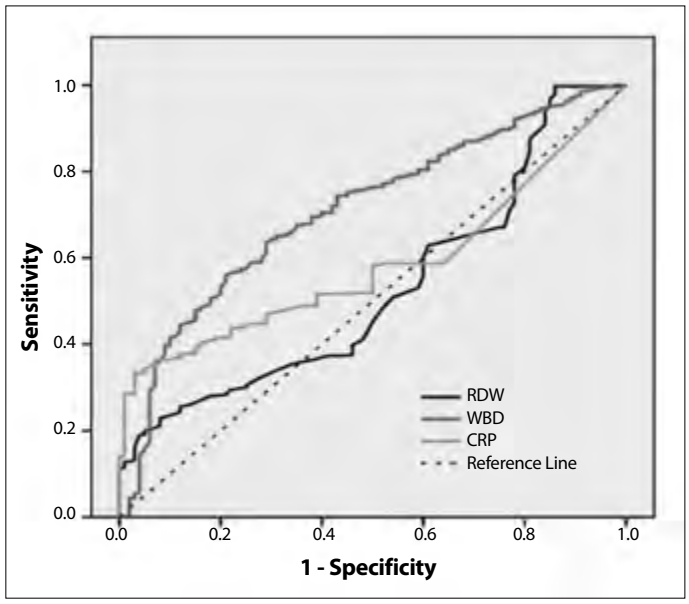


Figure 1. Receiver operating characteristic (ROC) Curves for red blood cell distribution width (RDW), white blood cell (WBC), and C-reactive protein (CRP) in plasma in the diagnosis of acute appendicitis (AA)

sitivity was 51% and specificity was 40% according to the ROC curve for CRP, whereas the optimum cut-off was 3.3 (Figure 1). A significant correlation was found between WBC and CRP (p=0.000) (correlation coefficient=0.221), whereas there was no correlation between RDW and WBC or CRP.

Discussion

This study investigated the relationship between RDW and the severity of disease in AA patients. Significant differences were observed when the median RDW values were compared between the groups. We think that RDW on admission might be useful for prediction of the severity of disease. RDW can be measured by a low-cost laboratory test that is quickly and easily performed using automatic cell counters. RDW, which is a marker that indicates variations in the size of red blood cells (RBCs) in circulation, is usually restricted to the diagnosis of anemia (12). Increases in RDW levels are related to increases in inflammatory markers such as CRP, erythrocyte sedimentation rate, and interleukins (13). We investigated the correlation between RDW, WBC, and CRP, which are inflammatory markers in patients diagnosed with AA. Increased RDW values are related to various medical disturbances and nutritional deficiencies, and are a predictor of early mortality (14). We predicted that RDW might have exceptional value clinically as an independent predictor of the diagnosis of AA, because it is measured by a test commonly performed by clinicians. Recently, inflammation has been stated to be a possible independent predictor of the diagnosis of AA, and RDW might be correlated to inflammatory parameters (15).

Acute appendicitis is the most common cause of acute abdominal surgery, and morbidity and mortality in AA significantly decrease in the event of early diagnosis (6). Mortality has decreased by 85% and operation rates have decreased by 63% with developments in the diagnosis and treatment of AA, whereas discharge rates of patients with abdominal pain have increased by 88% (16). Difficulties in the diagnosis of AA continue despite improvements in diagnostic methods, and rates of negative appendectomy and perforation are still high (17). Bachmann et al. (18) stated that because the tests used for the diagnosis of AA cannot be used in actual practice, their use can only be suggested. Many parameters (CRP, WBC, neutrophil/lymphocyte ratio, interleukins 4, 5, 6, 10, and 12, tumor necrosis factor-alpha, endoxin erythrocyte sedimentation rate, procalcitonin, fibrinogen, etc.) have been investigated for the diagnosis of AA in the literature. WBC is used for the diagnosis of AA. Demircan et al. (19) claimed that clinical findings, WBC, other inflammatory markers, abdominal US, and CT should be used as supportive tests for diagnosis. Yang et al. (20) reported that increases in WBC were proportional to the extent of histological inflammation and that CRP values were higher in patients with perforation. Sensitivity was 85% and specificity was 31.9% for WBC in the same study. WBC levels were also significantly higher in the AA group than in the control group in our study. However, no significant difference was observed with respect to WBC, CRP, and RDW levels between the non-complicated and complicated AA subgroups. Sensitivity was found to be 70% and specificity was found to be 60% for WBC.

In all cases of acute inflammation, CRP is a sensitive acute-phase protein of which the level increases according to the duration and severity of inflammation (21). Hallan and Asberg (22) stated that WBC, CRP, and neutrophil levels increase the accuracy of the diagnosis of AA. They also reported a sensitivity of 40%-99% and a specificity of 27%-90%. Asfar et al. (21) claimed that normal CRP levels most probably indicated a non-inflamed normal appendix. They concluded that CRP is more sensitive than WBC and neutrophil count and significantly increases the sensitivity and specificity if used simultaneously. CRP levels were significantly higher in the AA group than in the control group in our study. Sensitivity was 51% and specificity was 40% for CRP.

In numerous recent studies, RDW was found to have extraordinary prognostic value for the prediction of mortality in many clinical conditions (23-25). In addition, RDW is thought to be a marker for many pathological conditions (rheumatoid arthritis, inflammatory bowel disease, colon cancer, celiac disease, etc.) (26-29). Chronic inflammation, aging, malnutrition, and anemia are thought to be underlying factors, but the pathophysiological basis of this relationship is uncertain (30). Similarly, in another study 28-day mortality in patients with sepsis and septic shock has been demonstrated to be related to RDW. (31). This situation supports the relationship between inflammation and RDW. Because AA is an inflammatory process, our study supports the use of RDW as a marker like other inflammatory markers such as CRP and WBC (20-21). Inflammation might be helpful for explaining the relationship between RDW and mortality. It allows the release of abundant new reticulocytes with symptoms of sepsis, and this situation is related to increases in RDW. In addition, high levels of oxidative stress cause increases in RDW by shortening the lifespan of RBCs and promoting the release of abundant immature RBCs into the circulation. In addition, inflammation contributes to morphological changes in RBCs by altering membrane glycoproteins and ion channels in RBCs (32). Şenol et al. (5) emphasized that a high RDW value on admission is an independent marker of mortality in patients with acute pancreatitis and might be used as a prognostic marker. Narci et al. (33) stated that RDW levels in an AA group were low when compared with a control group, and they therefore cannot be used as a suitable marker. They detected a sensitivity of 47% and a specificity of 67% when the optimum cut-off value was 15.6% according to ROC analysis. Similarly, Tanrıkulu et al. (34) stated that there was no significant relationship between RDW and AA in their study. However, in our

study RDW values were found to be higher in the AA group than in the control group and therefore RDW is a marker of inflammation and might have predictive value. The sensitivity of RDW was calculated to be 41% and the specificity was calculated to be 30% when the optimum cut-off value was 13.1. As we mention in the Limitations section of our study, the level of RDW may vary with the duration and severity of inflammation. In addition, initial RDW values may be influenced by hospital admission or discharge by the physician. The low sensitivity and specificity of RDW in our study may be caused by this factor. Because the time between the onset of symptoms in our patients, admission to the emergency service, and the onset of treatment is not known, because our study is retrospective, this may have affected sensitivity and specificity (35). There are studies in the literature that show a strong correlation between RDW and inflammatory markers such as CRP and sedimentation rate (15). In our study, no significant correlation was found between RDW, CRP, and WBC.

Study limitations

The most important limitation of this study is that the sample size (patient number) was statistically low. Secondly, because acute changes in RDW might be affected by blood loss or hemolysis, a single measurement of RDW is not sufficient. We could not evaluate changes in RDW levels and did not take variations with time into consideration. Thirdly, samples for RDW measurements were collected in a single center. RDW values in samples collected from different populations for a comparison of clinical outcomes might exhibit differences. Finally, levels of iron, vitamin B12, and folic acid were not measured because the study was retrospective.

Conclusion

It is thought that a rapid, easy, low-cost blood test that supports clinical experience and imaging techniques, gives information about tissue damage in the appendix, and can be performed at the patient's bedside would be optimal. The employment of a specific marker that can lead to early detection even in small centers will enable a safe method of diagnosis in emergency situations, giving a choice of treatment for patients at risk.

Red cell distribution width levels were found to be significantly higher in patients diagnosed with AA in comparison to the control group. The commonly used, low-cost RDW test may be an important hematological parameter for the diagnosis of AA. Its low levels of sensitivity and specificity decrease the possibility of the use of RDW as a marker for the definitive diagnosis of AA. Therefore, further studies are required to investigate the correlation between AA and hematological markers, and, by studying the pathophysiology, to confirm whether or not the correlation is accurate.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Selçuk University School of Medicine (Decision No: 2013-336).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer-review: Externally peer-reviewed.

Acknowledgements: The authors would like to thank Specialist Dr. Feridun Koyuncu and İbrahim Kayıtmazbatır for their contributions.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Sadaka F, O'Brien J, Prakash S. Red cell distribution width and outcome in patients with septic shock. J Intensive Care Med 2013; 28: 307-13. [CrossRef]
2. Patel KV, Semba RD, Ferrucci L, Newman AB, Fried LP, Wallace RB, et al. Red cell distribution width and mortality in older adults: a meta-analysis. J Gerontol A Biol Sci Med Sci 2010; 65: 258-65. [CrossRef]
3. Ku NS, Kim HW, Oh HJ, Kim YC, Kim MH, Song JE, et al. Red blood cell distribution width is an independent predictor of mortality in patients with gram-negative bacteremia. Shock 2012; 38: 123-7. [CrossRef]
4. Hunziker S, Celi LA, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. Crit Care 2012; 16: R89. [CrossRef]
5. Şenol K, Sağlam B, Kocaay F, Tez M. Red cell distribution width as a predictor of mortality in acute pancreatitis. Am J Emerg Med 2013; 31: 687-9. [CrossRef]
6. Mentes O, Eryilmaz M, Harlak A, Yaman H, Yigit T, Ongoru O, et al. The importance of urine 5-hydroxyindoleacetic acid levels in the early diagnosis of acute appendicitis. Am J Emerg Med 2009; 27: 409-12. [CrossRef]
7. Ma KW, Chia NH, Yeung HW, Cheung MT. If not appendicitis, then what else can it be? A retrospective review of 1492 appendectomies. Hong Kong Med J 2010; 16: 12-7.
8. Andersson RE, Hugander A, Ravn H, Offenbartl K, Ghazi SH, Nyström PO, et al. Repeated clinical and laboratory examinations in patients with an equıvocal of diagnosis appendicitis. World J Surg 2000; 24: 479-85. [CrossRef]
9. Blomqvist PG, Andersson RE, Granath F, Lambe MP, Ekbom AR. Mortality after appendectomy in Sweden, 1987-1996. Ann Surg 2001; 233: 455-60. [CrossRef]
10. Mengucuk M, Ayten R, Bulbuller N, Godekmerdan A, Basbuğ M, Mungan İ. Role of C-reactive protein, procalsitonin and neopterin in the diagnosis of acute appendicitis. Firat Med J 2010; 15: 40-3.
11. Paajanen H, Mansikka A, Laato M, Ristamäki R, Pulkki K, Kostiainen S. Novel serum inflammatory markers in acute appendicitis. Scand J Clin Lab Invest 2002; 62: 579-84. [CrossRef]
12. Tonelli M, Sacks F, Arnold M, Moye L, Davis B, Pfeffer M. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. Circulation 2008; 117: 163-8. [CrossRef]
13. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. Arch Intern Med 2009; 169: 588-94. [CrossRef]
14. Kho AN, Hui S, Kesterson JG, McDonald CJ. Which observations from the complete blood cell count predict mortality for hospitalized patients? J Hosp Med 2007; 2: 5-12. [CrossRef]
15. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009; 133: 628-32.
16. Pledger G, Stringer MD. Childhood deaths from acute appendicitis in England and Wales 1963-97; Observational population based study. BMJ 2001; 323: 430-1. [CrossRef]
17. Burd RS, Whalen TV. Evaluation of the child with suspected appendicitis. Pediatr Ann 2001; 30: 720-5. [CrossRef]
18. Bachmann LM, Bischof DB, Bischofberger SA, Bonani MG, Osann FM, Steurer J. Systematic quantitative overviews of the literature to determine the value of diagnostic tests for predicting acute appendicitis: study protocol. BMC Surg 2002; 2: 2. [CrossRef]

19. Demircan A, Aygencel G, Karamercan M, Ergin M, Yılmaz TU, Karamercan A. Ultrasonographic findings and evaluation of white blood cell counts in patients undergoing laparotomy with the diagnosis of acute appendicitis. Ulus Travma Acil Cerrahi Derg 2010; 16: 248-52.
20. Yang HR, Wang YC, Chung PK, Chen WK, Jeng LB, Chen RJ. Laboratory tests in patients with acute appendicitis. ANZ J Surg 2006; 76: 71-4. [CrossRef]
21. Asfar S, Safar H, Khoursheed M, Dashti H, al-Bader A. Would measurement of C-reactive protein reduce the rate of negative exploration for acute appendicitis? J R Coll Surg Edinb 2000; 45: 21-4.
22. Hallan S, Asberg A. The accuracy of C-reactive protein in diagnosing acute appendicitis-a meta-analysis. Scand J Clin Lab Invest 1997; 57: 373-80. [CrossRef]
23. Makhoul BF, Khourieh A, Kaplan M, Bahouth F, Aronson D, Azzam ZS. Relation between changes in red cell distribution width and clinical outcomes in acute decompensated heart failure. Int J Cardiol 2013; 167: 1412-6. [CrossRef]
24. Hong N, Oh J, Kang SM, Kim SY, Won H, Youn JC, et al. Red blood cell distribution width predicts early mortality in patients with acute dyspnea. Clin Chim Acta 2012; 413: 992-7. [CrossRef]
25. Braun E, Domany E, Kenig Y, Mazor Y, Makhoul BF, Azzam ZS. Elevated red cell distribution width predicts poor outcome in young patients with community acquired pneumonia. Crit Care 2011; 15: R194. [CrossRef]
26. Tecer D, Sezgin M, Kanık A, İncel NA, Çimen ÖB, Biçer A, Şahin G. Can mean platelet volume and red blood cell distribution width show disease activity in rheumatoid arthritis? Biomark Med 2016; 10: 967-74. [CrossRef]
27. Akkermans MD, Vreugdenhil M, Hendriks DM, van den Berg A, Schweizer JJ, van Goudoever JB, et al. Iron deficiency in inflammatory bowel disease: the use of zincprotoporphyrin and red blood cell distribution width. J Pediatr Gastroenterol Nutr 2016. [CrossRef]
28. Ay S, Eryilmaz MA, Aksoy N, Okus A, Unlu Y, Sevinc B. Is early detection of colon cancer possible with red blood cell distribution width? Asian Pac J Cancer Prev 2015; 16: 753-6. [CrossRef]
29. Harmanci O, Kav T, Sivri B. Red cell distribution width can predict intestinal atrophy in selected patients with celiac disease. J Clin Lab Anal 2012; 26: 497-502. [CrossRef]
30. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. Arch Intern Med 2009; 169: 515-23. [CrossRef]
31. Jo YH, Kim K, Lee JH, Kang C, Kim T, Park HM, Kang KW, Kim J, Rhee JE. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. Am J Emerg Med 2013; 31: 545-8. [CrossRef]
32. Song CS, Park DI, Yoon MY, Seok HS, Park JH, Kim HJ, et al. Association between red cell distribution width and disease activity in patients with inflammatory bowel disease. Dig Dis Sci 2012; 57: 1033-8. [CrossRef]
33. Narci H, Turk E, Karagulle E, Togan T, Karabulut K. The role of red cell distribution width in the diagnosis of acute appendicitis: a retrospective case-controlled study. World J Emerg Surg 2013; 8: 46. [CrossRef]
34. Tanrikulu CS, Tanrikulu Y, Sabuncuoglu MZ, Karamercan MA, Akkapulu N, Coskun F. Mean platelet volume and red cell distribution width as a diagnostic marker in acute appendicitis. Iran Red Crescent Med J 2014; 16: e10211. [CrossRef]
35. Lee SM, Lee JH, Kim K, Jo YH, Lee J, Kim J, et al. The clinical significance of changes in red blood cell distribution width in patients with community-acquired pneumonia. Clin Exp Emerg Med 2016; 3: 139-47. [CrossRef]

Acute Flank Pain: Multi-detector Computed Tomographic Evaluation in the Emergency Room

Yeliz Aktürk, Serra Özbal Güneş, Baki Hekimoğlu
Clinic of Radiology, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ankara, Turkey

Abstract

Acute nontraumatic pathological conditions of the kidneys include frequent hematuria, renal colic, and acute renal failure. Infections and renal vascular problems are frequently encountered in an emergency department. In this pictorial review, we aim to discuss patterns of acute renal pathologies and explain hints for differential diagnosis with computed tomographic findings.

Keywords: Renal, tomography, flank pain

Introduction

Various renal pathologies can be detected by computed tomography (CT) in patients referring to the emergency room with acute abdominal pain. Emergency physicians and radiologists often play an important role in the evaluation and management of acute renal diseases.

In the diagnosis of acute renal pathologies, anamnesis, clinical and laboratory findings, and physical examination are of primary importance. Imaging methods are of equal importance as these diagnostic methods. Often, ultrasonography is the first choice for imaging. However, there are clinical limitations with ultrasonography. Some of these limitations are: the need for patient cooperation, the presence of artifacts due to intestinal gases, and some technical disadvantages in diagnosing the vascular pathologies. It is also easier to exclude other non-kidney causes such as acute appendicitis, psoas abscess, diverticulitis, which cause abdominal pain with CT. Although CT involves radiation exposure, contrast agent allergy, and contrast nephropathy risks (in some patients), it is a fast performing modality with a high diagnostic value that should be preferred when ultrasonography is insufficient. It provides more anatomical details than ultrasonography. Renal perfusion defects and parenchymal vascularization problems can also be demonstrated using contrast media.

Early recognition, diagnosis, and management of renal disease have important implications for long-term morbidity and mortality.

Acute pathological conditions of the kidneys may be classified as traumatic and non-traumatic. The non-traumatic admissions to the emergency department are frequent hematuria, renal colic, and acute renal failure. Infections and renal vascular problems are also frequently encountered in the emergency department. In this pictorial review, we aim to discuss patterns of acute non-traumatic renal pathologies and explain hints for differential diagnosis with findings from CT imaging.

Hematuria

Hematuria is commonly seen in a wide spectrum of urinary diseases (1). The causes of gross hematuria are urinary system infections, urolithiasis, and neoplasms of genitourinary system (2).

Hematuria may be evaluated by multi-detector CT (MDCT) of nephrographic, excretory phase, or without contrast. MDCT without contrast helps evaluate nephrolithiasis which is one of the main reasons of hematuria and allows imaging from the kidney to the bladder (3).

A typical CT urography procedure obtains non-contrast images, and nephrographic phase images are obtained 90-100 s after intravenous nonionic contrast injection (100-150 mL of 300 mg I/mL at 2-4 mL/s, 2.5- to 5-mm slice thickness) (4).

Correspondence to: Yeliz Aktürk e-mail: yelizakturk@yahoo.com
Received: 21.06.2016 • **Accepted:** 15.01.2017

DOI: 10.5152/eajem.2017.02986

Renal parenchymal abnormalities, especially masses, are best visualized via nephrographic phase images by which other abdominal organs can also be evaluated. Delayed thin slice images from the kidneys to the bladder reveal contrast distended urinary system and are used to detect uroepithelial diseases (3). Pyelographic phase images are obtained 5-15 min after contrast administration and are used to evaluate uroepithelium. However, economical analyses reveal that MDCT are most cost-effective in patients with persistent hematuria and normal ultrasonographic findings (4).

Renal cell carcinoma and transitional cell carcinoma have typically higher density than urine and their densities are measured to be 5-30 Hounsfield units (HU) in CT without contrast administration. Malignant renal and urothelial tumors show early contrast enhancement and washout (4, 5). Thus, in the nephrographic phase, contrasted urothelial lesions may be detected in urine with low density (Figure 1).

Increase in density up to more than 20 HU after contrast administration is a sign of malignancy (4, 6). Infiltration may cause focal delays in contrast enhancement. Ureteric obstruction maybe best visualized in nephrographic phase and can be easily distinguished from a stone. The other findings of transitional cell carcinoma are thickening of the wall, stenosis, and infiltration of periurethral fat tissue (4).

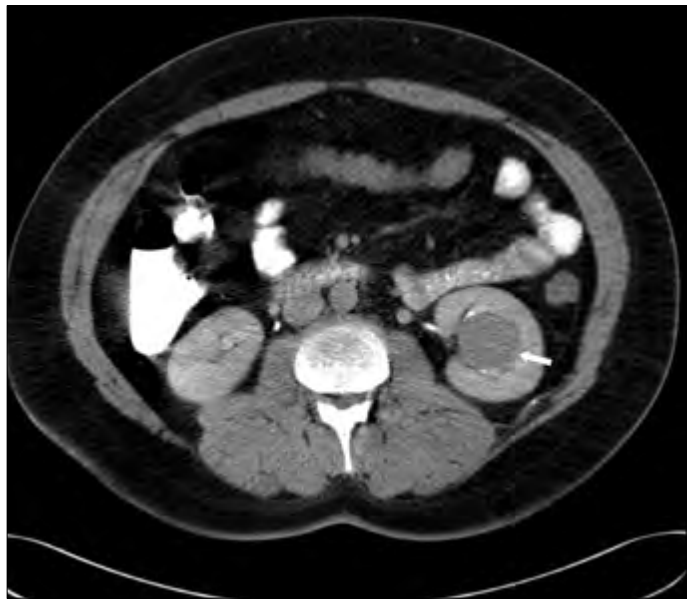


Figure 1. The axial abdominal computed tomography (CT) images of a patient obtained in the nephrogram phase because of hematuria. The lesion was diagnosed as transitional cell carcinoma (white arrow) which fills the left renal sinus and shows contrast enhancement, solid lesion with a density higher than urine

Renal colic and urolithiasis

Acute flank pain and renal colic are commonly encountered in emergency departments. The lifetime incidence of urolithiasis is approximately 12% (7, 8). The patients are generally between 30 and 60 y, and the occurrence is three times more common in men (7). It has been shown in many studies that abdominal CT without contrast administration has a higher specificity and sensitivity for detecting stones in the urinary system compared with other modalities (9).

Multi-detector CT without contrast is a fast and reliable diagnostic method for urinary stones. There is no requirement of intravenous contrast administration and thus allergic--anaphylactic reactions and nephrotoxicity risks do not exist. The analysis maybe performed in a very short time and has a high sensitivity for distinguishing stones and other causes of renal colic (7). However, there is radiation exposure in CT. Thus, nowadays low-dose tomographic studies are gaining importance. Researchers have reported that in patients with acute abdomen who refer to the hospital with urinary colic CT examinations with low-dose radiation (25 mAs) have the same diagnostic sensitivity as the examinations with standard radiation dose (100 mAs) (10). McLaughlin and colleagues stated that the use of iterative reconstruction techniques increases diagnostic ability (11).

However, on some occasions of renal anomaly and variations such as duplication of renal collective system, CT urographic study, which includes excretory phase after intravenous contrast administration, may be useful for diagnosis (Figure 2).

Increase in kidney dimensions may be observed because of swelling and edema in acute obstructions. This has been reported at an incidence of 36%-71% in different studies. Perinephritic edema has been reported in 36%-82% of the patients. Decrease in renal density due to obstruction may be seen in patients with kidney stone (9). Hydronephrosis, hydroureter, and perinephritic fat stranding have a predictivity of 90% for obstruction of the urinary system due to stone disease (4, 12).

Urinary tract infections

Bacterial nephritis has a wide spectrum ranging from acute pyelonephritis (APN) to renal abscess and emphysematous pyelonephritis (EPN) (13). Recent reports imply the importance of early imaging. Shen and Brown stated that early imaging is cost-effective and advocate imaging in people who are going to be hospitalized by APN (14, 15). Yoo et al. (14) reported that there are clinically significant findings in 16% of the patients. MDCT is important for the detection of abscess and APN. It is superior to ultrasound in renal abnormalities such as perinephric stranding, inflammatory masses, delayed or diminished contrast enhancement, kidney enlargement, or gas formation (13).

Contrasted studies are needed to demonstrate the changes in renal parenchymal perfusion and contrast excretion. The most common findings of APN are areas of wedge shape, focal or global diminished attenuation with unclear borders. Linear bands of hyper- or hypoattenuation parallel to the axis of tubules and collecting ducts may be seen.

The other findings are loss in corticomedullary distinction in early arterial phase and delay in cortical nephrogram. Occasionally, focal pyelonephritis areas may mimic renal tumors (14).

Renal abscess is accumulation of purulent material in renal parenchyma and is caused by hematogenous gram-positive bacteria or ascending gram-negative microorganisms (Figure 3). On MDCT, hypodense lesion due to necrosis and hyperdense peripheral border, which holds contrast, may be encountered (16).

Emphysematous pyelonephritis is a rare, necrotizing infection characterized by gas production in the renal parenchyma (17). Most patients are diabetic, and obstructive uropathy is reported as a risk factor in 90% in different series. It is unilateral in 90% of the cases. The most common pathogens are *Escherichia coli*, *Klebsiella pneu-*

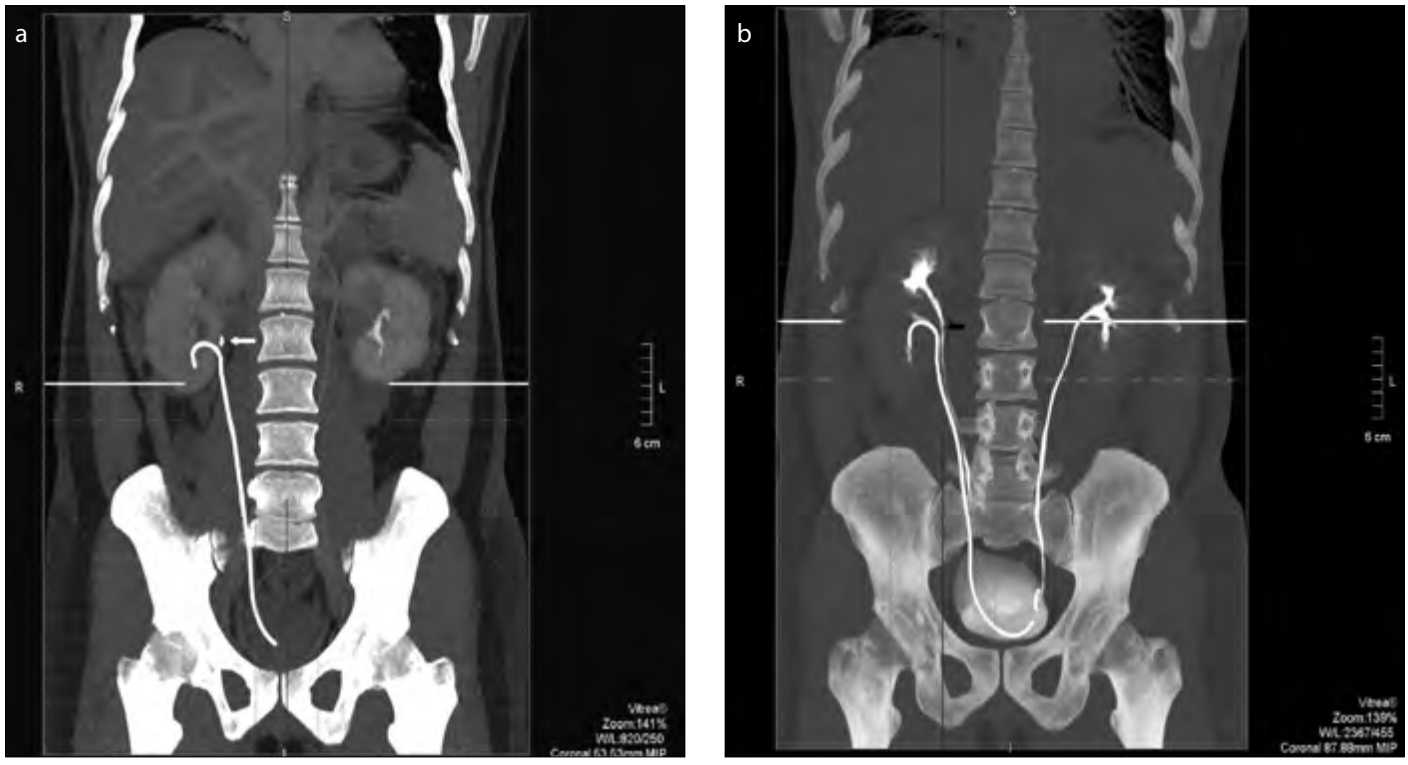


Figure 2. a, b. (a) Ureterolithotomy was performed on a 42-year-old male patient because of a ureter stone seen in his radiogram. The stone could not be found endoscopically in the operation and hence a catheter was placed. Postoperatively, a multi-detector CT (MDCT) in the pyelogram phase was performed. On coronal imaging, urethral duplication, urethral stone in the superior part of the superior ureter (white arrow), and the catheter extending from the collecting structures to the internally located ureter were seen, (b) Coronal image in excretory phase shows dilatation in superior collecting structures and the filling defect in superior ureter (black arrow)

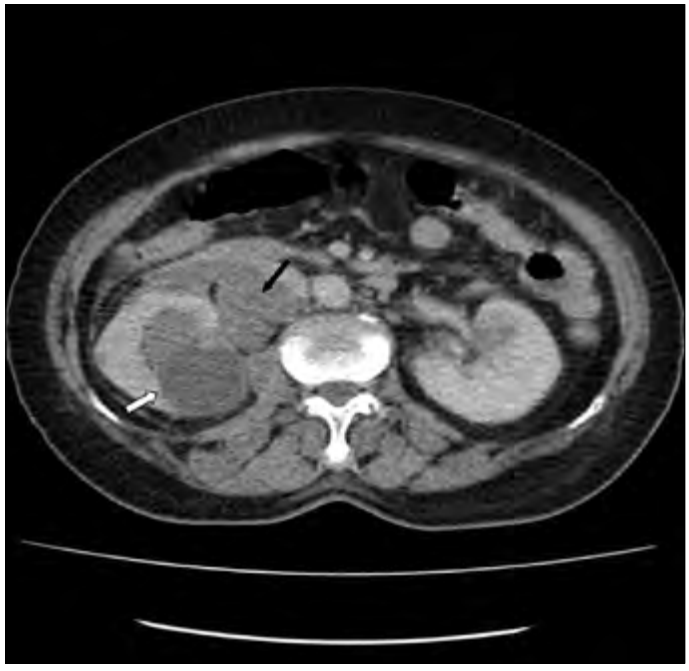


Figure 3. A 53-year-old female patient was admitted to the emergency with fever and flank pain. Axial computed tomography (CT) images in nephrogram phase reveal a lesion in the posterior middle section of the right kidney. Fluid density and minimal peripheral contrast enhancement are consistent with abscess (white arrow). In addition to that, fluid accumulations in the perirenal area (black arrow), perirenal stranding, and thickening of Gerota fascia are visible

moniae, *Proteus mirabilis,* and *Pseudomonas aeruginosa* (18). The prognosis may be mortal if evaluated by X-ray graphy, because the gas in the renal parenchyma may be confused with the intestinal gas (19). CT is useful in detecting the extension of the infection, parenchymal gas formation, and the evaluation of complications (18, 19). There are subtypes of EPN according to the images on the CT. In Type 1, there is parenchymal destruction but no fluid collection or gas extension from medulla to cortex. Subcapsular or perinephral crescentic gas formation may be seen. The nonexistence of fluid collection is the result of a weak immune response. Mortality rate is high (66%). However, in type 2, there exist confined, bubbly, intrarenal gas pattern, renal and perirenal fluid collections, and gas formation in renal pelvis. Mortality rate is nearly 18% (19). Formation of gas may reach perirenal region, renal vein, and inferior vena cava (Figure 4, 5).

Renal vascular pathologies

Arterial dissections are frequent in malignant hypertension, atherosclerosis, trauma, fibromuscular dysplasia, connective tissue diseases such as Marfan syndrome, Ehler-Danlos syndrome (20-22). Cocaine abuse and extracorporeal shock wave lithotripsy cases were also reported (22). The most common localization of primary dissection of perinephric arteries is renal arteries (20). The extension of false lumen may cause a narrowing in the true lumen, and diminished renal blood flow may cause renal infarct. Less than 25% of renal artery dissections occur spontaneously and frequently in men of fourth

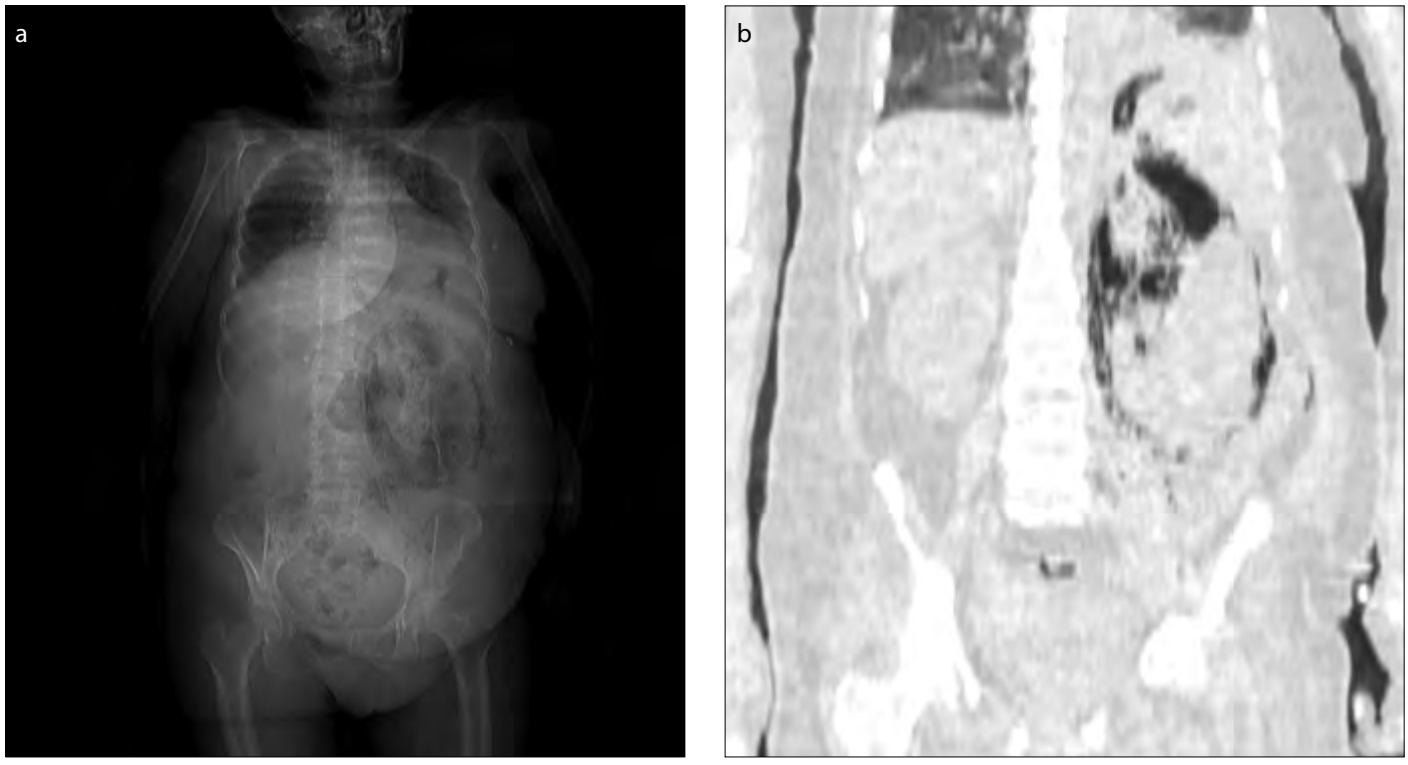


Figure 4. a, b. (a) Abdominal scans of a 56-year-old female patient who was admitted to the emergency department with high fever and flank pain and (b) reconstructed image in coronal lung window. In the upper left quadrant, in the left renal region, there is abundant air which can be differentiated from the intestinal gas

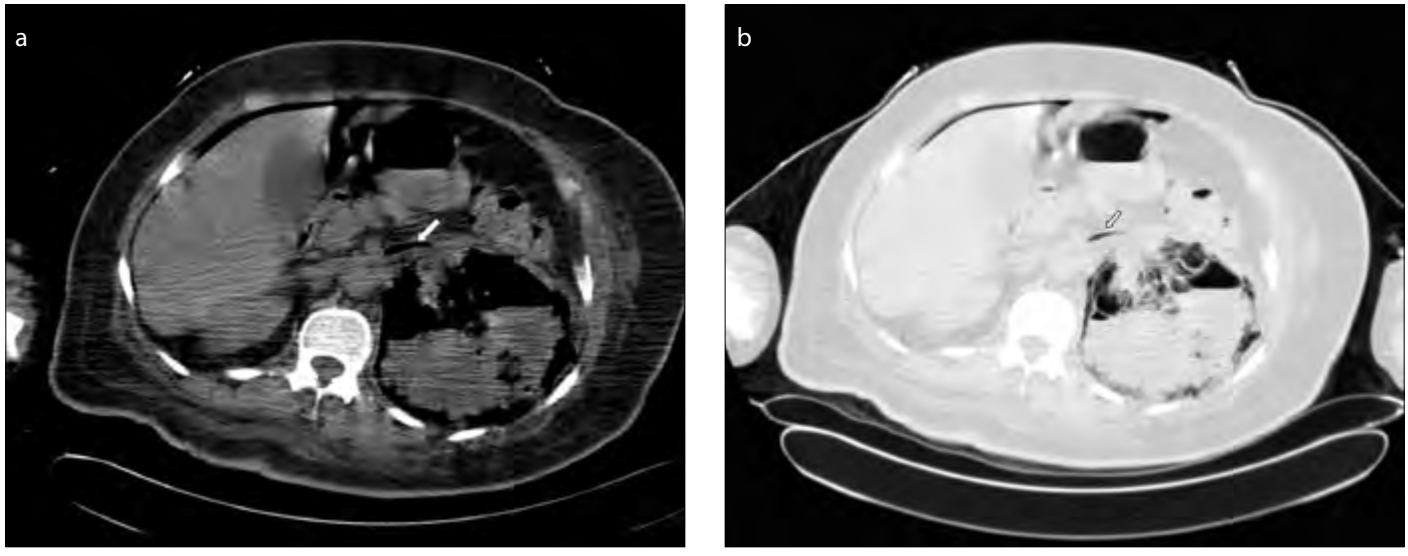


Figure 5. a, b. (a) Axial images after contrast administration: parenchymal and (b) lung window. Left renal dimensions are enlarged. In the renal cortex, renal pelvis, and perirenal region, there is abundant air density and the borders of renal cortex and medulla are lost. Air density extends into the left renal vein (arrow)

and fifth decades with no previous health problems (20, 23). The most common clinical presentation is persistent and severe hypertension with an acute onset. However, severe upper abdominal pain resembling a renal colic may also be seen (24). Because of this, even if there is no history of trauma in a patient with acute flank pain and hypertension, isolated renal artery dissection may also be taken into consideration (20, 25). Angiography with catheter is a gold standard in diagnosis; however, it is possible to evaluate by CT angiography noninvasively (22, 25). In CT renal perfusion defects, areas without contrast enhancement and hypodense image in renal artery may be seen (Figure 6).

Conclusion

Acute renal pathologies are a wide spectrum of diseases which may be life-threatening. Early diagnosis is important in prognosis,

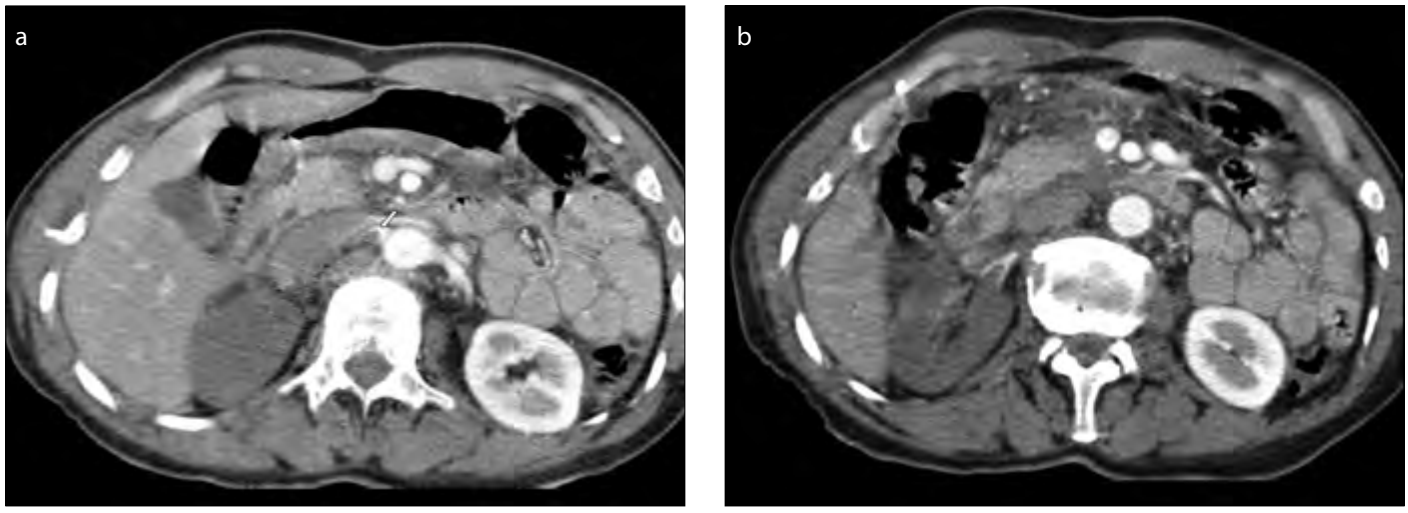


Figure 6. a, b. (a) Axial abdominal computed tomography (CT) of a patient after contrast administration. The patient is 45- years-old and he has right flank pain with hematuria and hypertension with no history of trauma. The sign of a false lumen without contrast filling at the level of the right renal artery orifice (arrow) and delay in the nephrogram phase in the right renal parenchyma, (b) There is no contrast enhancement in the right kidney even if the left kidney is in nephrogram phase

early onset of therapy, and in decreasing complications. MDCT is an important modality in acute renal pain.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Song JH, Beland MD, Mayo-Smith WW. Incidental clinically important extraurinary findings at MDCT urography for hematuria evaluation: Prevalence in 1209 consecutive examinations. AJR AM J Roentgenol 2012; 199: 616-22. [CrossRef]
2. Dames EL, Ng LG, Tay KH. Congenital renal arteriovenous malformation presenting with gross hematuria after a routine jog: a case report. J Med Case Rep 2014; 8: 65-70. [CrossRef]
3. Joffe SA, Servaes S, Okon S, Horowitz M. Multi-detector row CT urography in the evaluation of hematuria. Radiographics 2003; 23: 1441-55. [CrossRef]
4. O'Connor OJ, McLaughlin P, Maher MM. CT Urography. AJR Am J Roentgenol 2010; 195: 201-6. [CrossRef]
5. Lang EK, Macchia RJ, Thomas R, Watson RA, Marberger M, Lechner G, et al. Improved detection of renal pathologic features on multiphasic helical CT compared with IVU in patients presenting with microscopic hematuria. Urology 2003; 61: 528-32. [CrossRef]
6. Silverman SG, Leyendecker JR, Amis ES Jr. What is the current role of CT urography and MR urography in the evaluation of the urinary tract? Radiology 2009; 250: 309-23. [CrossRef]
7. Patatas K, Panditaratne N, Wah TM, Weston MJ, Irving HC. Emergency department imaging protocol for suspected acute renal colic: re-evaluating our service. Br J Radiol 2012; 85: 1118-22. [CrossRef]
8. Kirpalani A, Khalili K, Lee S, Haider MA. Renal colic: comparison of use and outcomes of unenhanced helical CT for emergency investigation in 1998 and 2002. Radiology 2005; 236: 554-8. [CrossRef]
9. Akay H, Akpınar E, Ergun O, Ozmen CA, Haliloğlu M. Unenhanced multidetector CT evaluation of urinary stones and secondary signs in pediatric patients. Diagn Interv Radiol 2006; 12: 147-50.
10. Licheng J, Yidong F, Ping W, Keqiang Y, Xueting W, Yingchen Z, et al. Unenhanced low-dose versus standard-dose CT localization in patients with upper urinary calculi for minimally invasive percutaneous nephrolithotomy (MPCNL). Indian J Med Res 2014; 139: 386-92.
11. McLaughlin PD, Murphy KP, Hayes SA, Carey K, Sammon J, Crush L, et al. Non-contrast CT at comparable dose to an abdominal radiograph in patients with acute renal colic; impact of iterative reconstruction on image quality and diagnostic performance. Insights Imaging 2014; 5: 217-30. [CrossRef]
12. O'Connor OJ, McSweeney SE, Maher MM. Imaging of hematuria. Radiol Clin North Am 2008; 46: 113-32. [CrossRef]
13. Lim SK, Ng FC. Acute pyelonephritis and renal abscesses in adults--correlating clinical parameters with radiological (computer tomography) severity. Ann Acad Med Singapore 2011; 40: 407-13.
14. Yoo JM, Koh JS, Han CH, Lee SL, Ha US, Kang SH, et al. Diagnosing acute pyelonephritis with CT, Tc-DMSA SPECT, and doppler ultrasound: a comparative study. Korean J Urol 2010; 51: 260-5. [CrossRef]
15. Shen Y, Brown MA. Renal imaging in pyelonephritis. Nephrology (Carlton) 2004; 9: 22-5. [CrossRef]
16. Piccoli GB, Consiglio V, Deagostini MC, Sera M, Biolcati M, Ragni F, et al. The clinical and imaging presentation of acute non complicated pyelonephritis: a new profile for an ancient disease. BMC Nephrol 2011; 12: 68. [CrossRef]
17. Arsene C, Saste A, Arul S, Mestrovich J, Kammo R, Elbashir M, et al. A case series of emphysematous pyelonephritis. Case Rep Med 2014; 2014: 587926. [CrossRef]
18. Nasr AA, Kishk AG, Sadek EM, Parayil SM. A case report of emphysematous pyelonephritis as a first presentation of diabetes mellitus. Iran Red Crescent Med J 2013; 15: e10384. [CrossRef]
19. Saxena D, Aggarwal L, Tudu SK, Thomas S. Emphysematous pyelonephritis-a rare surgical emergency presenting to the physician: a case report and literature review. Indian J Surg 2013; 75: 272-4. [CrossRef]
20. Bayram Y, Turgut F, Kırbas I, Kanbay M. Idiopathic spontaneous renal artery dissection: a rare case. Turk Neph Dial Transpl 2010; 19: 206-8. [CrossRef]

21. Alamir A, Middendorf DF, Baker P, Nahman NS Jr, Fontaine AB, Hebert LA. Renal artery dissection causing renal infarction in otherwise healthy men. Am J Kidney Dis 1997; 30: 851-5. [CrossRef]
22. Afshinnia F, Sundaram B, Rao P, Stanley J, Bitzer M. Evaluation of characteristics, associations and clinical course of isolated spontaneous renal artery dissection. Nephrol Dial Transplant 2013; 28: 2089-98. [CrossRef]
23. Lok SY, Chalvardijan A, Common AA. Primary renal artery dissection. Can Assoc Radiol J 1995; 46: 54-6.
24. Kanofsky JA, Lepor H. Spontaneous renal artery dissection. Rev Urol 2007; 9: 156-60.
25. Tandon G, Sukhija R. Isolated spontaneous renal artery dissection: a case report and review. Int J Angiol 2012; 21: 99-102. [CrossRef]

One of the Rare Reasons of Abdominal Pain-Chilaiditi's Syndrome

Eylem Kuday Kaykısız[1], Özgür Özer[2], Zübeyir Dalgıç[1]
[1]Clinic of Emergency Medicine, Bitlis State Hospital, Bitlis, Turkey
[2]Clinic of Radiology, Bitlis State Hospital, Bitlis, Turkey

Abstract

Chilaiditi's sign is the anatomical description of the interposition of the colon between the liver and the diaphragm; when it is accompanied with clinical symptoms, it is known as Chilaiditi's syndrome. Most commonly, it is an asymptomatic radiological finding and is considered a rare entity, and therefore, it is often misdiagnosed in clinical practice; however, it may be accompanied by a series of severe complications. Here we report a patient with Chilaiditi's syndrome, owing to its rarity, and the typical radiological findings of this syndrome. A 22-year-old female was admitted to the hospital, presenting with a 2-day history of nausea and worsening right upper quadrant pain. Vital signs were stable. The physical examination revealed a soft abdomen with mild right upper abdominal tenderness. Laboratory assays showed no abnormalities. A plain abdominal X-ray showed an abnormal gas shadow in the subhepatic space and a segment of gaseous distended colon. A computarized tomography (CT) scan of the abdomen showed a loop of colon interpositioned between the liver and the right hemidiaphragm, mimicking free air. The patient consulted with a general surgery physician, and was admitted to the general surgery service to follow up on treatment and operation, if indicated. The patient was managed conservatively. During the course of her hospital stay, her abdominal pain resolved without surgical intervention. She was then able to tolerate a regular diet, and was discharged after two days of hospital stay. Although Chilaiditi's syndrome is not common, it is important, and can be easily mistaken for pneumoperitoneum. Most of the cases with Chilaiditi's syndrome can be resolved with nasogastric decompression and repeated laxatives. Surgical intervention is reserved for patients with signs of systemic toxicity or peritonitis. Owing to the rarity of this syndrome and its typical radiological findings, we aimed to present this case.

Keywords: Chilaiditi's syndrome, abdominal pain, colon interposition

Introduction

Chilaiditi's sign is the anatomical description of the interposition of the colon between the liver and the diaphragm. It was first described by Demetrius Chilaiditi in 1910 (1). Chilaiditi's sign has an incidence of 0.025%-0.28% worldwide, with a marked male predominance (male to female, 4:1) (2, 3). Most commonly, it is an asymptomatic radiological finding and is considered as a rare entity, and therefore, it is often misdiagnosed in clinical practice; however, it may be accompanied by a series of severe complications, such as bowel obstruction and perforation (4). The differential diagnosis of Chilaiditi's syndrome includes pneumoperitoneum, pneumobilia, and hepatic-portal venous gas. The therapy for Chilaiditi's syndrome consists of conservative nasogastric decompression and bed rest. Surgical intervention is rarely indicated (4).

Case Presentation

A 22-year-old female was admitted to the Emergency Department of the Bitlis State Hospital in December 2016, presenting with a 2-day history of nausea and worsening epigastric and right upper quadrant pain. The pain was sharp and radiated to the right shoulder. She denied dysphagia, early satiety, fever, chills, night sweats, melena, hematochezia, or any changes in her bowel habits. She did not recall having a similar experience before. The patient had no history of surgery. On original presentation, she was afebrile, with a blood pressure of 126/91 mmHg, pulse of 77 beats/min, respiratory rate of 20 beats/min, and oxygen saturation of 99% on room air. The physical examination revealed a soft abdomen with mild right upper abdominal tenderness; no rebound tenderness or muscle guarding was identified. The cardiovascular and respiratory exams were unremark-

Correspondence to: Eylem Kuday Kaykısız e-mail: eylemkuday@hotmail.com
Received: 13.01.2017 • **Accepted:** 14.01.2017

DOI: 10.5152/eajem.2017.81300

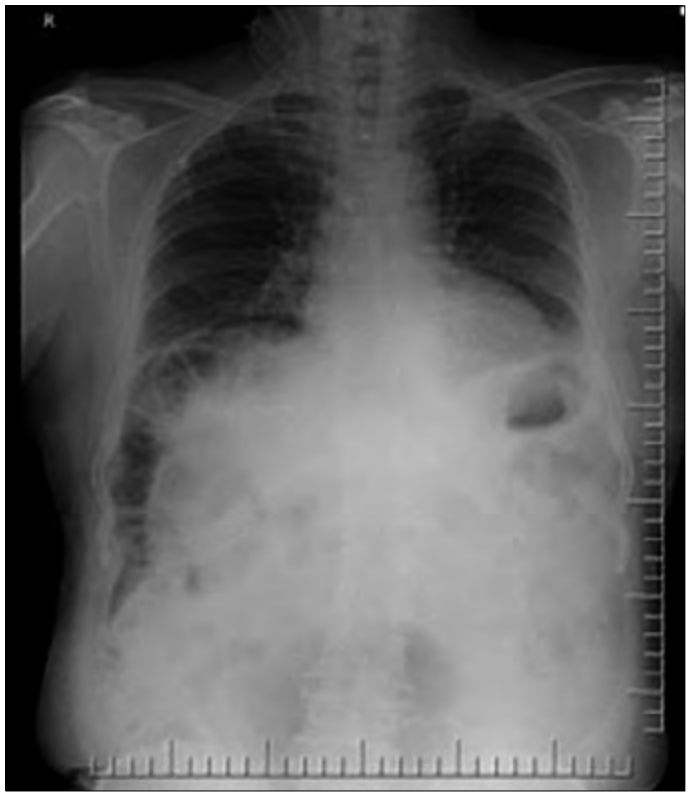


Figure 1. X-ray showed an abnormal gas shadow in the right subhepatic space, and a segment of gaseous distended colon, which was located on the right side of the abdominal cavity; this was interposed between the liver and the right diaphragm

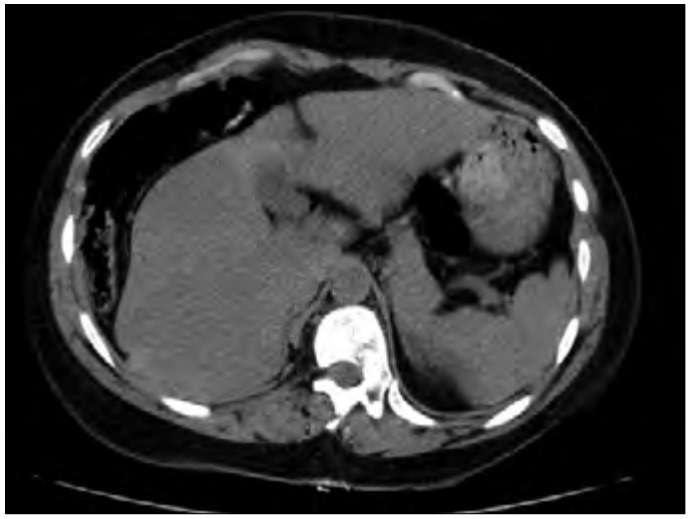


Figure 2. Computarized tomography (CT) scan of the abdomen and pelvis showed a loop of colon interpositioned between the liver and the right hemidiaphragm, mimicking free air

able. Laboratory assays, including hemogram, biochemistry, and full urinalysis showed no abnormalities.

A plain abdominal X-ray showed an abnormal gas shadow in the right subhepatic space, and a segment of gaseous distended colon, which was located on the right side of the abdominal cavity; this was interposed between the liver and the right diaphragm (Figure 1). Further imaging by a Computarized Tomography (CT) scan of the abdomen and pelvis showed a loop of colon interpositioned between the liver and the right hemidiaphragm, mimicking free air (Figure 2). After that, the patient consulted with a general surgery physician, and was admitted to the general surgery service to follow up on treatment and operation, if indicated. The patient was managed conservatively with Intravenous (IV) fluid hydration and pain management. During the course of her hospital stay, her abdominal pain resolved without surgical intervention. She was then able to tolerate a regular diet, and was discharged after two days of hospital stay.

Informed consent was obtained from the patient.

Discussion

Chilaiditi's sign is the anatomical description of the interposition of the colon between the liver and the diaphragm. When it is accompanied with clinical symptoms, such as abdominal pain, nausea, vomiting, and constipation, it is known as Chilaiditi's syndrome (4). Several causes, including absence of suspensory ligaments of the transverse colon, atrophic or small liver, segmental agenesis of the right lobe of the liver, abnormality of the falciform redundant mesocolon, redundant or dilated colon, and volvulus of the colon have been reported to be associated with Chilaiditi's syndrome (5, 6).

Chilaiditi's sign is often an incidental finding and is asymptomatic. Therefore, obtaining the medical history and performing a careful physical examination are important for surgeons. However, old patients or patients with dementia can scarcely state their complaints on their own, and it is also difficult to obtain their medical history or perform a thorough physical examination. In our case, the patient had 2 days of nausea and worsening epigastric and right upper quadrant pain, and was believed to have biliary colic. She was saved from a surgical procedure due to a careful examination.

Radiological studies may be helpful in this situation. Most of the patients with Chilaiditi's sign can be easily diagnosed via chest X-ray. However, the haustral folds of bowel loops may not be seen in a chest X-ray. Sato et al. (7) reported that ultrasound is helpful in diagnosing Chilaiditi's syndrome. Most of the cases that can be diagnosed by X-ray and CT of the abdomen provide more information. However, ultrasound may be helpful in distinguishing between Chilaiditi's syndrome and pneumoperitoneum. In our case, X-ray and ultrasound diagnostic tools were unremarkable, so we performed a CT scan. A CT scan of the abdomen and pelvis, with intravenous contrast, showed a loop of colon interpositioned between the liver and the right hemidiaphragm, mimicking free air.

The management of Chilaiditi's syndrome varies due to its different etiologies, and includes both, operative and nonoperative approaches. Saber and Boros (5) reported that 26% of patients needed operative management, while the majority required nonoperative treatment, including bowel decompression and repeated radiography. If the symptoms were persistent, surgical intervention may be indicated. Bowel decompression may be both, diagnostic and therapeutic (5). In our case, the patient was managed conservatively with IV fluid hydration and pain management.

Conclusion

Although Chilaiditi's syndrome is not common, it is important, and can be easily mistaken for pneumoperitoneum. Most of the patients with Chilaiditi's sign are found incidentally. When it is accom-

panied with clinical symptoms, it is known as Chilaiditi's syndrome. Most of the cases with Chilaiditi's syndrome can be resolved with nasogastric decompression, repeated laxatives, and enemas. Surgical intervention is reserved for patients with signs of systemic toxicity or peritonitis. In our case, the patient was initially believed to have biliary colic pain. However, considering the possibility of Chilaiditi's syndrome protected the patient from an unnecessary procedure, such as operation. Owing to the rarity of this syndrome and the typical radiological findings associated with it, we aimed to present this case.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. D. Chilaiditi, "Zur Frage der Hepatoptose und Ptose im Allgemeinen im Anschlussan Drei Falle von Temporarer, Partieller Lebererlagerung," Fortschr Geb Rontgenstr Nu- klearmed Erganzungsband 1910; 16: 173-208.
2. Alva S, Shetty-Alva N, Longo WE. Image of the month. Chilaiditi sign or syndrome. Arch Surg 2008; 143: 93-4 . [CrossRef]
3. Yin AX, Park GH, Garnett GM, Balfour JF. Chilaiditi syndrome precipitated by colonoscopy: a case report and review of the literature. Hawaii J Med Public Health 2012; 71: 158-62.
4. Orangio GR, Fazio VW, Winkelman E, McGonagle BA. The Chilaiditi Syndrome and associated volvulus of the transverse colon. An indication for surgical therapy. Dis Colon Rectum 1986; 29: 653-6. [CrossRef]
5. Saber AA, Boros MJ. Chilaiditi's syndrome: what should every surgeon know? Am Surg 2005; 71: 261-3.
6. Kurt Y, Demirbas S, Bilgin G, Aydin Y, Akin L, Yildiz M, et al. Colonic volvulus associated with Chilaiditi's syndrome: report of a case. Surg Today 2004; 34: 613-5. [CrossRef]
7. Sato M, Ishida H, Konno K, Hamashima Y, Naganuma H, Komatsuda T, et al. Chilaiditi syndrome: sonographic findings. Abdom Imaging 2000; 25: 397-9. [CrossRef]

EURASIAN JOURNAL OF EMERGENCY MEDICINE

A Misdiagnosed Patient with Recurrent Abdominal Pain: Nutcracker Syndrome

Eylem Kuday Kaykısız[1], Ali Fırat Sarp[2], Ramazan Güven[1]
[1]Clinic of Emergency Medicine, Bitlis State Hospital, Bitlis, Turkey
[2]Clinic of Radiology, Bitlis State Hospital, Bitlis, Turkey

Abstract

Nutcracker phenomenon is characterized by impeded outflow from the left renal vein into the inferior vena cava because of extrinsic left renal vein compression. Because of its rarity and excessive misdiagnosis, we report the case of a 30-year-old female patient who was admitted to the emergency department of our hospital with recurrent left flank and lower abdominal pain andwas diagnosed with nutcracker syndrome. A 30-year-old female patient was admitted tothe emergency department of our hospital with recurrent left flank and lower abdominal pain. Physical examination showed a flaccid abdomen, which was painful onpalpation of the lower portion and left flank, without any signs of peritoneal irritation as well as theabsence of vulvar or lower limb varices. In the work-up, abdominal computed tomography with intravenous contrast was used and revealed compression of the left renal vein between the aorta and superior mesenteric artery. Therefore, the patient was referred to the vascular and endovascular surgery department to evaluate the possibility of a minimally invasive treatment. There is a wide spectrum of clinical presentations of nutcracker syndrome, and the diagnostic criteria are not well defined, frequently resulting in delayed or incorrect diagnosis. From the number of cases reported in the literature, it is obvious that this condition is not very common. Therefore, nutcracker syndrome must kept in mind in patients with recurrent flank and lower abdominal pain duringdifferential diagnosis.

Keywords: Nutcracker syndrome, renal vein entrapment, recurrent abdominal pain

Introduction

Nutcracker phenomenon is characterized by impeded outflow from the left renal vein into the inferior vena cava because of extrinsic left renal vein compression.

Because of its rarity and excessive misdiagnosis, we report the case of a 30-year-old female patient who was admitted to emergency department of our hospital with recurrent left flank and lower abdominal pain anddiagnosed with nutcracker syndrome.

Case Presentation

A 30-year-old female patient was admitted to the emergency department of our hospital with recurrent left flank and lower abdominal pain. Before this, she was admitted to the emergency department of another hospital and urology policlinic but remained misdiagnosed. The patient had no known disease, medications, and history of surgery, except for caesarean section.Her vital signs were stable. Physical examination showed a flaccid abdomen, which was painful onpalpation of the lower portion and left flank, without any signs of peritoneal irritation as well as theabsence of vulvar or lower limb varices. Findings of initial laboratory tests, including hemogram, biochemistry, and complete urinalysis, were unremarkable. Urinary ultrasonography was performed, and emergent sonopathology was not performed. In the work-up, abdominal computedtomography with intravenous contrast was used and revealed compression of the left renal vein between the aorta and superior mesenteric artery (Figure 1). Therefore, the patient was referred to the vascular and endovascular surgery department to evaluate the possibility of a minimally invasive treatment.

Discussion

Nutcracker phenomenon, also known as left renal vein entrapment, is characterized by impeded outflow from the left renal vein into the inferior vena cava because of extrinsic left renal vein compression (1). Although the terms nutcracker syndrome and nutcracker phenomenon are sometimes used interchangeably in the litera-

Correspondence to: Eylem Kuday Kaykısız e-mail: eylemkuday@hotmail.com
Received: 18.01.2017 • **Accepted:** 23.01.2017

DOI: 10.5152/eajem.2017.21920

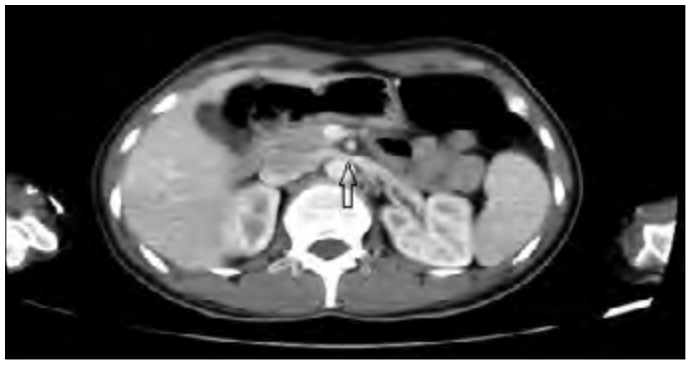


Figure 1. Computed tomography revealed compression of the left renal vein between the aorta and superior mesenteric artery

ture, Shin and Lee (2) have emphasized that the nutcracker anatomy is not always associatedwith clinical symptoms and that some anatomicfindings suggestive of a nutcracker may represent a normalvariant. There is a wide spectrum of clinical presentations and diagnostic criteria are not well defined, frequently resulting in delayed or incorrect diagnosis (3).

Because of uncertainties, some authors have focused on the characteristic anatomic and hemodynamic findings, referring to them asnutcracker phenomenon rather than nutcracker syndrome (4). The earliest pathologic descriptionof this phenomenon was made by Grant in 1937, following which the first clinical report was presented by El-Sadr and Mina (5, 6).

The syndrome is manifested by left flank and abdominal pain, with or without unilateral macroscopic or microscopic hematuria. However, it should be noted that hematuria is not always present (7). In our case, recurrent hematuria was present for 10 years but findings of complete urinalysis wereclear by then.

The other common mode of presentation is a symptom complex called "pelvic congestion syndrome," characterized by symptoms of dysmenorrhea, dyspareunia, postcoital ache, lower abdominal pain, dysuria, and pelvic varices (8). Similarly, compression of the left renal vein can cause left renal-to-gonadal vein reflux, resulting in lower limb varices and varicoceles in males (9). When getting a detailed history, our patientsexperienced symptoms suggestive of pelvic congestion syndrome. Systemic manifestations have also been reported in adolescents, including headache, abdominal pain, fainting, and tachycardia mimicking clinical symptoms of an orthostatic disturbance (10).

In summary, the classical manifestations of nutcracker syndrome include flank and lower abdominal pain, unilateral microscopic or macroscopic hematuria, pelvic congestion syndrome, and rarely, varicose manifestations. Its diagnosis is based on history and physical examination as well as basic laboratorytests to exclude other causes of hematuria. Surveillance is appropriate in cases of mild symptoms and either microscopic or insignificantmacroscopic hematuria with no evidence of significant blood loss. Open surgical interventions, although effective, are associated with higher surgical morbidity. If the long-term outcomes remain as good as the short-term results reported to date, stenting (extravascular/intravascular) may become the treatment of choice.

Conclusion

From the number of cases reported in the literature, it is obvious that this condition is not very common but the prevalence is probably much higher than its diagnosis because the presence of characteristic anatomic changes does not always cause symptoms. Therefore, nutcracker syndrome must kept in mind in patients with recurrent flank and lower abdominal pain duringdifferential diagnosis.

Informed Consent: Verbal informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

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

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Rudloff U, Holmes RJ, Prem JT, Faust GR, Moldwin R, Siegel D. Mesoaortic compression of the left renal vein (nutcracker syndrome): case reports and review of the literature. Ann Vasc Surg 2006; 20: 120-9. [CrossRef]
2. Shin JI, Lee JS. Nutcracker phenomenon or nutcracker syndrome? Nephrol Dial Transplant 2005; 20: 2015. [CrossRef]
3. Kurklinsky AK, Rooke TW. Nutcracker phenomenon and nutcracker syndrome. Mayo Clinic Proc 2010; 85: 552-9. [CrossRef]
4. Takahashi Y, Sano A, Matsuo M. An ultrasonographic classification for diverse clinical symptoms of pediatric nutcracker phenomenon. Clin Nephrol 2005; 64: 47-54. [CrossRef]
5. Grant JCB. Method of Anatomy. Baltimore, MD: Williams & Wilkins; 1937:158.
6. El-Sadr AR, Mina E. Anatomical and surgical aspects in the operative management of varicocele. Urol Cutaneous Rev 1950; 54: 257-62.
7. Takahashi Y, Sano A, Matsuo M. An effective "transluminal balloon angioplasty" therapy for paediatric chronic fatigue syndrome with nutcracker phenomenon. Clin Nephrol 2000; 53: 77-8.
8. d'Archambeau O, Maes M, De Schepper AM. The pelvic congestion syndrome: role of the "nutcracker phenomenon" and results of endovascular treatment. JBR-BTR 2004; 87: 1-8.
9. Little AF, Lavoipierre AM. Unusual clinical manifestations of the nutcracker syndrome. Australas Radiol 2002; 46: 197-200. [CrossRef]
10. Takemura T, Iwasa H, Yamamoto S, Hino S, Fukushima K, Isokawa S, et al. Clinical and radiological features in four adolescents with nutcracker syndrome. Paediatr Nephrol 2000; 14: 1002-5. [CrossRef]

EURASIAN JOURNAL OF EMERGENCY MEDICINE

Pneumocephalus as a Cause of Postoperative Headache

Yasin Yıldız, Mine Kayacı Yıldız, Serkan Emre Eroğlu
Clinic of Emergency Medicine, Ümraniye Training and Research Hospital, İstanbul, Turkey

A 53-year-old woman presented to our emergency department with headache 7 days after an endoscopic endonasal skull base surgery with a transnasal transsphenoidal approach for pituitary adenoma. Clinical examination at the time of admission revealed normal findings; her Glasgow coma scale was 15 and all other vital signs were normal. There was no focal neurological deficit on central nervous system examination. Noncontrast head CT demonstrated bifrontal and convexial (intrahemispheric) intracranial air, also known as pneumocephalus (-1000 Hounsfield units), on the bone window. There was no midline shift (Figure 1-3). She was referred to the neurosurgery clinic and admitted to the clinic for repair surgery. Three days later, she underwent duraplasty and lumbar drainage.

The presence of gas or air within the cranial cavity is called pneumocephalus. It is usually associated with surgical interventions through the skull or traumatic injury. Serious clinically morbidity rarely occurs in case of pneumocephalus (1). Postoperative pneumocephalus in the frontal or intraventricular locations is rarely associated with postoperative cerebrospinal fluid (CSF) leak. However, pneumocephalus in the interhemispheric fissure, convexity, and parasellar/sellar/perimesencephalic areas is usually related to a postoperative CSF leak (2).

In case of tension pneumocephalus, there is a one-way valve mechanism that draws air into the skull. A serious intracranial mass effect can occur (1). It may result in altered mental status, generalized convulsions with/without focal signs, restlessness, or cardiac

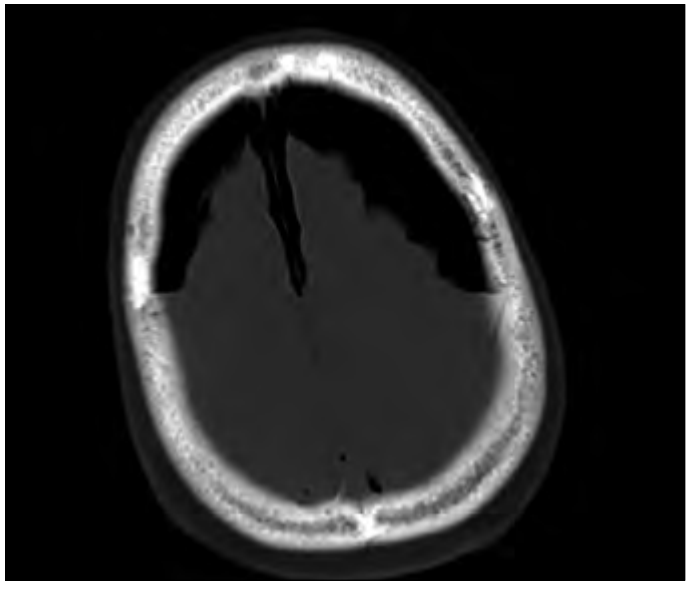


Figure 1. Bifrontal and intrahemispheric pneumocephalus

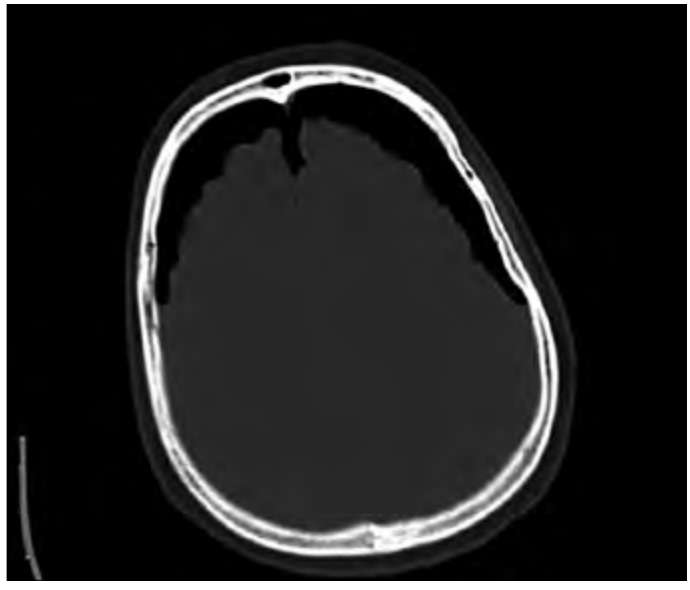


Figure 2. Bifrontal and intrahemispheric pneumocephalus

Correspondence to: Serkan Emre Eroğlu e-mail: drseroglu@gmail.com
Received: 06.01.2017 • **Accepted:** 05.02.2017

DOI: 10.5152/eajem.2017.30502

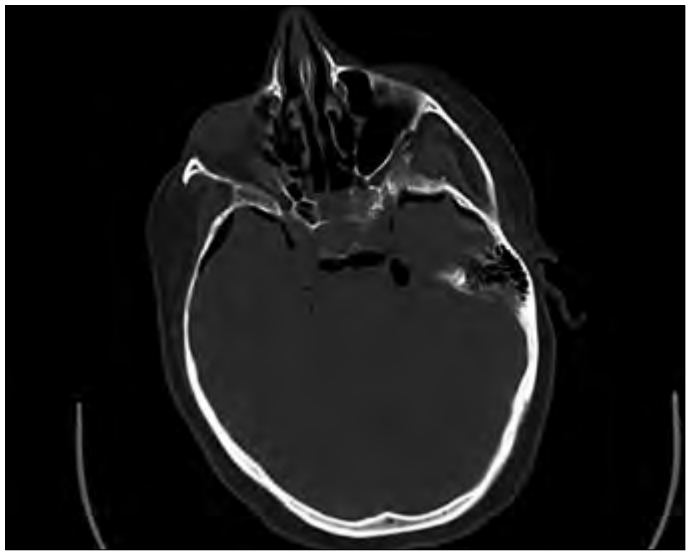


Figure 3. Parasellar pneumocephalus

arrest. Early diagnosis and treatment are important because it is a life-threatening complication (3).

In conclusion, one cause of the occurrence of postoperative headache after neurosurgical procedures can be pneumocephalus. Urgent intervention is necessary to avoid tension pneumocephalus.

References

1. Goodwin CR, Boone CE, Pendleton J, Elder BD, Wei Z, Hsu W, et al. Pneumocephalus leading to the diagnosis of cerebrospinal fluid leak and esophageal perforation after cervical spine surgery. J Clin Neurosci 2016: 26: 141-2. [CrossRef]
2. Banu MA, Szentirmai O, Mascarenhas L, Salek AA, Anand VK, Schwartz TH. Pneumocephalus paterns following endonasal endoscopic skull base surgery as predictors of postoperative CSF leaks. J Neurosurg 2014: 121: 961-75. [CrossRef]
3. Biyani N, Silbiger A, Ben-Ari J, Constantini S. Postoperative brain stem tension pneumocephalus causing transient locked-in syndrome. Pediatr Neurosurg 2007; 43: 414-7. [CrossRef]