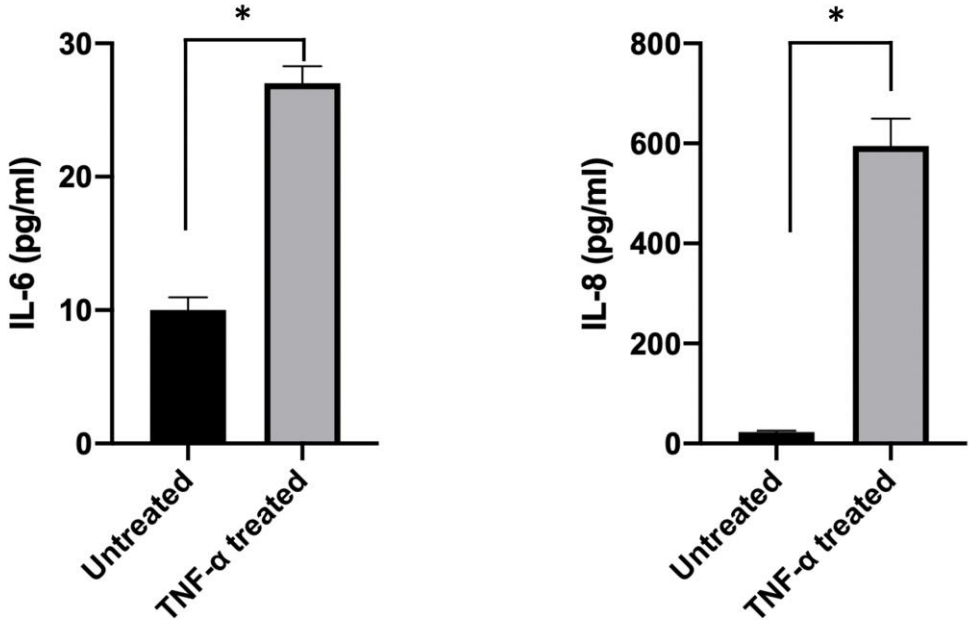
April 2020, Vol 7, No 4

MSD

Medical Science & Discovery



International Journal of Medical Science and Discovery
Open Access Scientific Journal
www.medscidiscovery.com,
Lycia Press London UK ISSN: 2148-6832

Medical Science and Discovery (**http://www.medscidiscovery.com**) is an international open access, peer-reviewed scientific research journal that provides rapid publication of articles in all disciplines of human health, clinical and basic medical science such as Biophysics, Biochemistry, Histology, Physiology, Genetics, Pathology, Toxicology, Anatomical Sciences, Pharmacology, Embryology, Internal and Surgical Medicine.

The policy of top priority of MSD is to put forward and highlight medical innovations and inspiring patents.

MSD offers an exceptionally fast publication schedule including prompt peer-review by the experts in the field and immediate publication upon acceptance. The editorial board aims at reviewing the submitted articles as fast as possible and promptly including them in the forthcoming issues.

This journal is published under ethical publishing policy of international scientific Bioethics and publication rules.

MSD supports the Open Access Initiative. Abstracts and full texts (HTML and PDF format) of all articles published by MSD are freely accessible to everyone immediately upon publication.

Indexed Databases: Chemical Abstracts (CAS), Index Copernicus, Open Air, ULRICHS Database, ProQuest, Advanced Science Index, Turkish Citation Index, Research Bible, Scholar Google, NLM Catalog

Medical Science and Discovery is an international open access, peer-reviewed scientific research journal.

ISSN: 2148-6832 (Print) E-ISSN: 2148-6832 (Online)

Category: Multi Disciplinary Health Science Journal

Abbreviated key title: Med. Sci. Discov.

Frequency: Monthly

Review System: Double Blind Peer Review

Circulation: Globally, Online, Printed

Article Processing Charge (APC): Free

Licensing: CC-BY-NC 4.0 International License Environmental

Editor-in-Chief: Assoc. Prof. Dr. Dr. Ahmad Rajabzadeh, Anatomical Department of lorestan, University of Medical Sciences, Tabriz, Iran

Established: 30.04.2014

Web address: www.medscidiscovery.com

E-mail : editor [at] medscidiscovery.com

Phone : +44 020 3289 9294

Design and preparation of PDFs, Language editing, Web site design, Graphical design Services of international Journal of Medical Science and Discovery has been contracted with Lycia Press LONDON, UK (as Publisher), by the MSD Board of Directors

Publisher: Lycia Press Inc.

Address: 3rd Floor 86 - 90 Paul Street, EC2A 4NE, London, UK

Web address: www.lycians.com

Phone : +44 020 3289 9294

E-mail : office [at] lycians.com

E-mail : info [at] lycians.com

Instruction for Authors

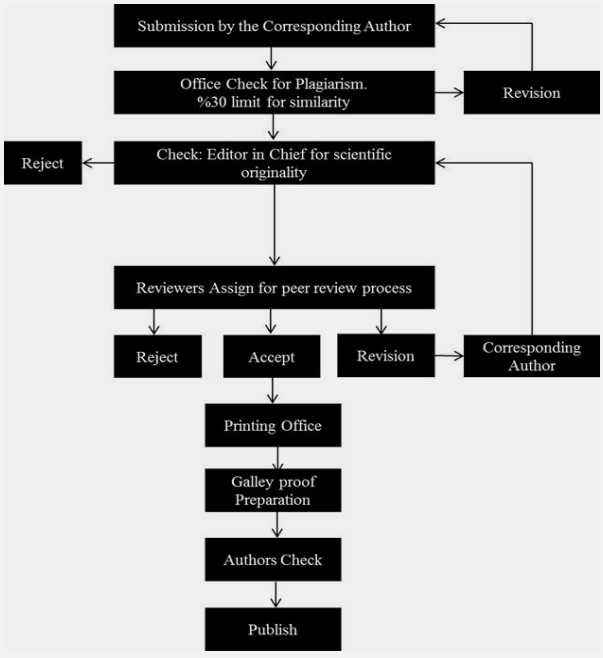
- **Important**
- MSD journal team, is committed to deterring plagiarism, including self-plagiarism. Your manuscripts will be screened for similarity detection with iThenticate, Similarity rate is expected under the %30 except for material and method section.
- For research studies using human or animal subjects, the trial's design, conduct and reporting of results must conform to Good Clinical Practice guidelines (such as the Good Clinical Practice in Food and Drug Administration (FDA)-Regulated Clinical Trials (USA) or the Medical Research Council Guidelines for Good Clinical Practice in Clinical Trials (UK)) and/or to the World Medical Association (WMA) Declaration of Helsinki
- Dear Authors, please upload just these three files to the manuscript submission system for article submissions.
- **1- Title Page Sample**
- **2- Manuscript Sample**
- **3- Copyright Transfer and Author Consent Form**
- Please select Keywords from the MESH source
- (https://www.nlm.nih.gov/mesh/MBrowser.html)
- Manuscripts should be prepared in accordance with the "Uniform Requirements for Manuscripts Submission to Biomedical Journals" proclaimed by the International Committee of Medical Journal Editors (www.icmje.org).
- MSD uses vancouver reference style, please prepare articles due to Vancouver reference style rules.
- Manuscript Preperation Rules
- 1.Cover letter
- a- A statement that the manuscript has been read and approved by all the authors.
- b- That the requirements for authorship have been met for all the authors, based on the criteria stated by ICMJE.
- c- Approval of all the authors regarding the order in which their names have appeared.
- d- That each author confirms the manuscript represents honest work.
- e- The name, address, and telephone number of the corresponding author who is responsible for communicating with other authors about revisions and final approval.
- f- The letter should give any additional information that may be helpful to the editor, such as the type or format of the article. If the manuscript has been submitted previously to another journal or in another language, it is helpful to include the previous editor's and reviewers' comments with the submitted manuscript, along with the authors' responses to those comments. Submitting previous evaluatory review of another journal accelerates the review process.
- g- For accepted manuscripts, the authors are requested to fill and sign the journal's cover letter to express their consent for its publication.
- h- To reproduce published material, to use illustrations or tables or report information about identifiable people, the author should submit a copy of the permission with the manuscript to the journal.
- 2.Top Ethic Committee Approval
- Inclusion of the approval letter from the relevant Ethics Committee or Institution's Review Board regarding the research protocol and the rights of the subjects (if applicable to the study)
- 3.Top Consent Form
- Attach a copy of the consent form to the letter, if applicable. Consent forms would be evaluated by the Ethics Committee and then signed by the participant.
- 4.Top RCT or NCT Registration
- Emailing the letter denoting registration of RCTs or NCTs in domestic or international databases (The trial's registration number needs to be mentioned, too).
- 5. Manuscripts submitted in English, must be type written, double-spaced, on good quality A4 paper, or paper of similar format. Authors are requested to reserve margins of at least 2.5cm all around the paper. Original drawings of photos, tables and figures should be furnished together with the manuscripts.
- 6. Manuscripts should be kept to a minimum length and should be subdivided into labeled sections (Title page, Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, Conclusion, Acknowledgement, and References).
- 7. A title page is to be provided and should include the title of the article, authors' names with full first name (with degrees), authors' affiliation, suggested running title and corresponding author. The affiliation should comprise the department, institution (usually university or company), city and state (or nation). The suggested running title should be less than 50 characters (including spaces) and should comprise the article title or an abbreviated version thereof. For office purposes, the title page should include the name and complete mailing address, telephone and fax number, and email of the one author designated to review proofs.
- 8. An abstract no longer than 250 words for reviews and research articles is to be provided as the second page. Abstract should be structured as objective(s) (including purpose setting), materials and methods, results, and conclusion..

Instruction for Authors

- 9. A list of 3-8 keywords, chosen from the Medical Subject Headings(MeSH) listhttp://www.nlm.nih.gov/mesh/MBrowser.html, is to be provided directly below the abstract. Keywords should express the precise content of the manuscript, as they are used for indexing purposes. Provide abbreviations and nomenclature list in an alphabetical order and non-standard abbreviations contained in the manuscript (excluding references) with definitions after the keywords. Use abbreviations sparingly and only when necessary to save space, and to avoid repeating long chemical names or therapeutic regimes. In a figure or table, define the abbreviations used in a footnote.
- 10. Tables in limited numbers should be self- explanatory, clearly arranged, and supplemental to the text. The captions should be placed above.
- 11. Figures should be utilized only if they augment understandability of the text. The captions should be placed below. Drawings and graphs should be professionally prepared in deep black and submitted as glossy, black and white clean Photostats. Professionally designed computer generated graphs with a minimum of 300 DPI laser printer output is preferable. Color photographs are welcomed.
- 12. The same data should not be presented in tables, figures and text, simultaneously.
- 13. MSD uses Vancouver referencing Style. References in limited numbers and up-to-dated must be numbered consecutively in order of citation in the text (number in parentheses). Periodical titles should be abbreviated according to the PubMed Journals Database (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=journals). Print surnames and initials of all authors when there are six or less. In the case of seven or more authors, the names of the first six authors followed by et al. should be listed.
- Please check all references with EndNote referencing System. Please check out and Download Vancouver Endnote Style.
- **Type of Articles**
- Type of articles are based on PubMed definitions. For more info please refer to: http://dtd.nlm.nih.gov/publishing/tag-library/3.0/n-w2d0.html
- **Editorial :**
- Editorial is Opinion piece, policy statement, or general commentary, typically written by staff of the publication (The similar value "article-commentary" is reserved for a commentary on a specific article or articles, which is written by an author with a contrasting position, not an editor or other publication staff.)
- **Letters to the Editor about a recent journal article :**
- Letters referring to a recent article in this journal must be received within three months of its publication. For example, a letter referring to an article published in the January issue must be submitted online no later than March 31st. Letters submitted after the allowed time will not be considered.
- The text, not including references, must not exceed 700 words. A maximum of three authors and 10 references are allowed. Neither tables nor figures are allowed.
- Letters to the Editor NOT referring to a recent journal article :
- Original research that is of interest but does not fulfill all the requirements needed for publication as a full-length manuscript can be submitted as a letter to the editor. The letter must have a title and a maximum of three authors.
- The text, not including references, tables, figures or legends must not exceed 700 words. No more than 10 references and either one table or one figure are allowed.
- Word Count Limit: Letters should contain 500 - 700 words, maximum number of references is 10, maximum Number of illustrations/Tables is 1.
- **Original Article:**
- The content of the paper must justify its length. For reports of original investigative work, traditional division into sections is required: Title, Keywords, Addresses and which author address for correspondence, Structured abstract, Background, Objectives, Materials/Patients and Methods, Results, Discussion, References and Acknowledgements, Legends for display items (Figures and Tables).
- Original Research articles should contain 2500 - 3500 words, maximum number of references is 35, maximum Number of illustrations/Tables is 5.
- **Review Article :**
- Review Articles should contain 3500 - 4000 words, maximum number of references is 50, maximum number of illustrations/Tables is 5. In a review article both abstract and text of the manuscript, include following items:
- 1) Context: Include 1 or 2 sentences describing the clinical question or issue and its importance in clinical practice or public heath.
- 2) Evidence Acquisition: Describe the data sources used, including the search strategies, years searched, and other sources of material, such as subsequent reference searches of retrieved articles. Explain the methods used for quality assessment and the inclusion of identified articles.
- 3) Results: Address the major findings of the review of the clinical issue or topic in an evidence-based, objective, and balanced fashion, emphasizing the highest-quality evidence available.
- 4) Conclusions: Clearly state the conclusions to answer the questions posed if applicable, basing the conclusions on available evidence, and emphasize how clinicians should apply current knowledge.

Instruction for Authors

- **Case Report**
- A case report is a case study, case report, or other description of a case that should contain 1500 - 2000 words with a structured abstract of 200 words maximum. Case reports should comprise sections of Introduction, Case Presentation, and Conclusions in Abstract and Introduction, Case Presentation, and Discussion in full text with not more than 2 tables or figures and up to 20 references.
- **Brief Report**
- Brief Reports should contain 1000 - 2000 words with a structured abstract of 200 words maximum. Short reports should comprise sections of Background, Objectives, Materials & Methods, Results and Discussion with not more than 2 tables or figures and up to 20 references.
- **Short Communication**
- Short Communication, follow the instructions for original articles, except that the total word number of the main text (excluding references, tables and figure legends) is limited to 2000 with no more than 2 figures and/or tables and no more than 15 references. An abstract, not exceeding 150 words, should be presented at the beginning of the article.
- **News**
- News should contain 1000 - 2000 words with a structured abstract of 200 words maximum. News should comprise sections of Background, Objectives, Materials & Methods, Results and Discussion with not more than 2 tables or figures and up to 20 references.
- **Publication Policies**
- Manuscripts, or the essence of their content, must be previously unpublished and should not be under simultaneous consideration by another Journal. The authors should also declare if any similar work has been submitted to or published by another Journal. By virtue of the submitted manuscript, the corresponding author acknowledges that all the co-authors have seen and approved the final version of the manuscript. The corresponding author should provide all co-authors with information regarding the manuscript, and obtain their approval before submitting any revisions. Manuscripts are only accepted for publication on the understanding that the authors will permit editorial amendments, though proofs will always be submitted to the corresponding author before being sent finally to press. Prior to the initial submission of a new manuscript, please carefully consider that all authors' names are included as no change to authors' details will be permitted after the acceptance. The decision to accept a contribution rests with the Editorial Board of the MSD.
- Manuscripts will be considered for publication in the form of original articles, Case report, short communications, Letter to editor and review articles. The work should be original or a thorough by an authoritative person in a pertinent field.
- **Peer review process**
- All submissions will be reviewed anonymously by at least two independent referees. All manuscripts will be acknowledged upon presenting to the Journal office, provided that all stated requirements are met. Authors are encouraged to suggest names of three expert reviewers, but selection remains a prerogative of the Editor. The whole review process depends on receiving referees comments and revising the manuscripts based on these comments to the author. On receipt of the revised article from the author, and after final approving by referees, the letter of acceptance is issued to the author. Authors have the right to communicate to the editor if they do not wish their manuscript to be reviewed by a particular reviewer because of potential conflicts of interest. No article is rejected unless negative comments are received from at least two reviewers. **MSD employs double blind reviewing process, where both the referee and author remain anonymous throughout the process**.



Instruction for Authors

- **Ethical Rules and Rights**
- **Conflicts of interest**
- Conflicts of interest arise when authors, reviewers, or editors have interests that are not fully apparent and that may influence their judgments on what is published. They have been described as those which, when revealed later, would make a reasonable reader feel misled or deceived. (The Committee on Publication Ethics (COPE) states in its Guidelines on Good Publication Practice 2003).
- Authors should disclose, at the time of submission, information on financial conflicts of interest or other interests that may influence the manuscript. Authors should declare sources of funding for the work undertaken.
- **Authors Responsibilities**
- 1. Authors must certify that their manuscript is their original work.
- 2. Authors must certify that the manuscript has not previously been published elsewhere, or even submitted and been in reviewed in another journal.
- 3. Authors must participate in the peer review process and follow the comments.
- 4. Authors are obliged to provide retractions or corrections of mistakes.
- 5. All Authors mentioned in the paper must have significantly contributed to the research. Level of their contribution also must be defined in the Authors Contributions section of the article.
- 6. Authors must state that all data in the paper are real and authentic.
- 7. Authors must notify the Editors of any conflicts of interest.
- 8. Authors must identify all sources used in the creation of their manuscript.
- 9. Authors must report any errors they discover in their published paper to the Editors.
- 10. Authors must not use irrelevant sources that may help other researches/journals.
- 11. Authors cannot withdraw their articles within the review process or after submission, or they must pay the penalty defined by the publisher.
- **Editorial Responsibilities**
- 1. Editors (Associate Editors or Editor in Chief) have complete responsibility and authority to reject/accept an article.
- 2. Editors are responsible for the contents and overall quality of the publication.
- 3. Editors should always consider the needs of the authors and the readers when attempting to improve the publication.
- 4. Editors should guarantee the quality of the papers and the integrity of the academic record.
- 5. Editors should publish errata pages or make corrections when needed.
- 6. Editors should have a clear picture of a researchs funding sources.
- 7. Editors should base their decisions solely one the papers importance, originality, clarity and relevance to publications scope.
- 8. Editors should not reverse their decisions nor overturn the ones of previous editors without serious reason.
- 9. Editors should preserve the anonymity of reviewers (in half blind peer review journals).
- 10. Editors should ensure that all research material they publish conforms to international accepted ethical guidelines.
- 11. Editors should only accept a paper when reasonably certain.
- 12. Editors should act if they suspect misconduct, whether a paper is published or unpublished, and make all reasonable attempts to persist in obtaining a resolution to the problem.
- 13. Editors should not reject papers based on suspicions; they should have proof of misconduct.
- 14. Editors should not allow any conflicts of interest between staff, authors, reviewers and board members.
- 15. Editors must not change their decision after submitting a decision (especially after reject or accept) unless they have a serious reason.
- **The Journal's Policy on Plagiarism**
- Any practice of plagiarism will not be tolerated by the journal regarding submitted manuscripts. Non-identifiable quoted segments of articles or close paraphrases from other author/s or even submitting the author's previously published work are known as the act of plagiarism by this journal unless proper use of quotations or paraphrasing with decent citation or referencing are in place. Heavy use of one or a couple of articles is discouraged, even if paraphrased fully. Advertent practice of plagiarism will abort reviewing process or later submission to this journal. All submitted articles will evaluate by iThenticate software belonged to cross check for stop any plagiarism and improve publication quality.

Instruction for Authors

- **The Journal's Policy on Plagiarism**
- Any practice of plagiarism will not be tolerated by the journal regarding submitted manuscripts. Non-identifiable quoted segments of articles or close paraphrases from other author/s or even submitting the author's previously published work are known as the act of plagiarism by this journal unless proper use of quotations or paraphrasing with decent citation or referencing are in place. Heavy use of one or a couple of articles is discouraged, even if paraphrased fully. Advertent practice of plagiarism will abort reviewing process or later submission to this journal. All submitted articles will evaluate by iThenticate software belonged to cross check for stop any plagiarism and improve publication quality.
- **Statement of Human and Animal Rights**
- All submitted articles involving human experiments should be performed only in accordance with the ethical standards provided by the responsible committee of the institution and in accordance with the Declaration of Helsinki (as revised in Edinburgh 2000), available at http://www.wma.net/en/30publications/ 10policies/b3/index.html. Papers describing animal experiments can be accepted for publication only if the experiment conforms the National Institute of Health Guide (National Institute of Health Publications No. 80-23, Revised 1978) for the care and use of Laboratory Animals for experimental procedure. Authors must provide a full description of their anesthetics and surgical procedures. All manuscripts reporting the results of experimental investigations involving human subjects should include a statement confirming the informed consent was obtained from each subject or subject's guardian.
- Humans: When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). If doubt exists whether the research was conducted in accordance with the Helsinki Declaration, the authors must explain the rationale for their approach and demonstrate that the institutional review body explicitly approved the doubtful aspects of the study.
- Animals: When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.
- All animal or human subjects should be used after approval of the experimental protocol by a local ethics committee.
- **Acknowledgements**
- Contributors: In acknowledgement section, name people for their contributions or their permission to reproduce their published material, to use their illustrations or provide information about them- try to fully name people who have helped from the conception of the idea to adoption of the hypothesis, to finalization of the study, etc., earnestly. Statement of financial support: Aside from the title page, state any financial or other relationships that might lead to a conflict of interest.
- **Copyright**
- After acceptance and publication; Medical Science and discovery allows to the author's to hold the copyright without any restriction. Please complete copyright form and send via email to editor. Download MSD Copyright Transfer and Author Consent Form
- **Creative Commons License**
- This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.(CC BY NC).
- **Copyright 2019:** The Author(s); This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. All Rights reserved by international journal of Medical Science and Discovery.
- **Disposal of material**
- Once published, all draft copies of the manuscript, correspondence and artwork will be held at least for 6 months before disposal. Authors and Readers may find original PDF file of article on backup servers such as LOCKSS (https://www.lockss.org/)
- **Digital Object Identifier DOI**
- Once a manuscript is accepted for publication it will be provided with a registered DOI number following the acceptance decision. Manuscripts accepted for publication by the MSD will be published as ahead of print articles prior to the printing date of their scheduled issue. Corresponding author will be provided with a PDF Proof by the publisher once the production process of an accepted manuscript is over.

Instruction for Authors

- **Article Processing Charge** is Fee
- MSD Article Submission Fee: Free
- MSD Fast Evaluation Process Fee: Free
- MSD Article Evaluation Fee: Free

- Please write your text in good English (American or British usage is accepted, but not a mixture of these). In case of insufficient writing on grammar and language, the authors may be directed to editing service of the journals publisher to eliminate possible grammatical or spelling errors (Lycia Press). Lycia Press proofreading service Fee for MSD is 40GBP /1000 words . for PDF design; service Fee for MSD is 40GBP /1000 words

- **MSD revenue sources and Sponsorships**
- All costs arising from the publications are covered by the Sponsor Companies. Sponsorship request evaluates by the MSD Journal Management Board, Lycia Press and the sponsor company logos will be included on the back page of printed magazine and in the sponsor section of journal website

- **References**
- Committee on Publication Ethics (COPE). (2011, March 7). Code of Conduct and Best-Practice Guidelines for Journal Editors. Retrieved from http://publicationethics.org/files/Code_of_conduct_for_journal_editors_Mar11.pdf
- World Association of Medical Editors (WAME). Principles of Transparency and Best Practice in Scholarly Publishing. http://www.wame.org/about/principles-of-transparency-and-best-practice

Medical Science and Discovery, April 2020, Vol.7, No.4

Contents

Research Article

http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):450-4

Research Article Doi: 10.36472/msd.v7i4.366

The evaluations of ESWL, RIRS and m-PCNL treatments in kidney stones smaller than two centimeters

Hüseyin Saygın[1]*, Gökhan Gökce[1], Esat Korgalı[1]

Abstract

Objective: The aim of the current study was to compare the outcome of minimal invasive treatment (RIRS, m-PCNL) with the ESWL, Micro-Percutaneous Nephrolithotomy (m-PCNL), and Retrograde intrarenal surgery (RIRS) in patients with renal calculi less than two centimeters in size.

Methods: Preoperative renal ureter-bladder (KUB) film and computed tomography (CT) used to imaging stone size and localization in all patients. Ninety consecutive patients were randomized equally to three groups. We evaluated age, gender, stone size, length of hospitalization, stone-free rates, X-ray duration that patients were exposed during the processes, general anesthesia time, Visual Analogue Scale values, Modified Clavien Complication Scale scores after RIRS, mPCNL, and ESWL on renal stones smaller than 2 cm.

Results: At the end of the first month, stone-free rate for the lower calyx stones was 33.3% (3 patients out of 10) in ESWL, 83.3% (10 patients out of 12) in RIRS, and 90.9% (10 patients out of 11) in m-PCNL. ESWL's success in the lower-calyx stones was found to be low. Our rates for the stones in renal pelvis, middle, and upper calyx were % 85.7 (18 patients out of 21) in ESWL, % 94.4 (17 patients out of 18) in RIRS and % 94.7 (18 patients out of 19) in m-PCNL. No difference was observed in the duration of hospitalization among patients who underwent RIRS and m-PCNL. The VAS scores in ESWL group were higher than other groups. There were no significant differences for fluoroscopy time between the groups. Decrease in hemoglobin values before and after the procedure were found to be significant in m-PCNL group ($p<0.05$).

Conclusions: We compared three minimal invasive treatments for less than 2 cm renal stones; m-PCNL and RIRS methods were found to be more effective than ESWL, especially aspects of the stone free rates.

Keywords: ESWL, RIRS, m-PCNL

Introduction

In European Association of Urology (EAU) guidelines; first choice of treatment for kidney stones smaller than two centimeters (cm) reported as Extracorporeal shock wave lithotripsy (ESWL) or other endourologic approaches. If there is no suitability for ESWL for 10-20mm, lower calyx stones endourologic initiatives are recommended as the first choice (1). If the standard of care for renal calculi is larger than 2 cm in size, it is called as percutaneous nephrolithotomy (1). However, nowadays, there is no consensus on the best treatment modality for renal calculi less than 2 cm in size. There are many treatment options including ESWL, standard /mini / micro PCNL, and RIRS (1). The success of ESWL, which is a minimally invasive method, is relatively low due to the rate of stone clearance in lower calyceal stones and the need for repetition in hard stones (2). The disadvantage of RIRS treatment is ureteral injury, necessity of anesthesia, and high instrument cost (3-4). Modified PCNL technique m-PCNL is a minimally invasive method for the treatment of renal stones smaller than 2 cm (3). The target of minimal invasive procedures of stone treatments is to decrease the complication rates, the length of hospitalization, morbidity, and mortality with high the success rates (5-6).

Based on our literature research, there is no any study which comparing the clinical outcome of RIRS, m-PCNL, and ESWL for renal calculi less than 2 cm in size. Especially, in lower pole stone clearance rates are lower than stones in other location with ESWL and there is no study comparing these treatment modalities for lower calix stones. The aim of the current study was to compare the outcome of minimal invasive treatment with the ESWL, m-PCNL, and RIRS in patients with renal calculi less than 2 cm in size. The hypothesis is that the stone clearance rates with the microperc and RIRS will be higher than the ESWL.

Received 12-03-2019 **Accepted** 09-04-2020 **Available Online** 17-04-2020 **Published** 30-04-2020
1 Cumhuriyet University, Faculty of Medicine, Department of Urology, Sivas, Turkey
*** Corresponding Author:** Hüseyin Saygın **E-mail:** dr.saygin@hotmail.com

http://dx.doi.org/10.36472/msd.v7i4.366

Materials and Methods

This study was prospectively designed in adult patients with renal stones smaller than 2 cm in a tertiary center. The local ethics committee approved this study and written consent was obtained from all the participants. Ninety consecutive patients with renal stones smaller than 2 cm were randomized into m-PCNL, RIRS, and ESWL groups.

Preoperative renal ureter-bladder (KUB) film and computed tomography (CT) used to imaging stone size and localization in all patients. Adult patients with single stone smaller than 2 cm in kidney were included in the study. Patients with multiple kidney stones, coagulopathy, patients with active urinary tract infection and non-adult patients were excluded from the study.

Shock Wave Lithotripsy

The therapy was usually started at a lower power of 12 kV and then increased gradually to 20 kV. A maximum of 2000 shocks were delivered for each session (ELMED multimed classic Ankara, Turkey). One week after the ESWL session, patients were evaluated with renal-ureter-bladder (KUB) film for residual stone fragmentation. Repeated ESWL sessions were performed if inadequate fragmentation of the stone encountered, a maximum of 3 sessions.

Micro-PCNL

After general anesthesia, 6-F ureter catheter was inserted into the renal pelvis in the lithotomy position under cystoscopy. After moving to the prone position, contrast material was administered through the ureteral catheter to define the calyceal anatomy. After selection of a suitable calyx, with visualization of fluoroscopy 4.85 all-seeing needle (PolyDiagnost, Pfaffenhofen, Germany), it was advanced to the desired calyx. The clearness of the vision and wash out of stone fragments were obtained by the irrigation pump system that was controlled with a foot pedal. The stones were fragmented using (5-10 Hz, 0.5-1.2 joule) holmium:YAG laser (StoneLight Laser , AMS, Minnesota, USA) fiber under direct visualization. A 6-F ureteric catheter was removed approximately about 1 day postoperatively.

Retrograde Intrarenal Surgery

All procedures were performed with 7.5 F FLEX-XC flexible ureteroscopes (Karl Storz, Tuttlingen, Germany) and a 272-mm laser fiber was used for laser lithotripsy. The use of the ureteral access sheath was determined by the surgeons preference. At the end of the operation, a 4.8F JJ stent was routinely inserted.

Treatment success rate was defined as completely stone free rate (SFR) or presence of clinically insignificant residual fragment (<3 mm) on x-ray KUB and USG after 1 month of last procedure in both groups. Complications were classified according to the modified Clavien Clasification System. Mean procedure time, mean fluoroscopy time, hospitalization time, pain score on day 1 using visual analog scale, and complications using modified Clavien Clasification Scale were collected in the study groups.

Statistical analysis

Datas were presented as the mean ± SD and percentage. Datas were processed using SPSS-14 for Windows (SPSS Inc., Chicago, IL, USA). Statistical analysis was performed with chi-square, t, and ANOVA tests. After ANOVA, Tukey test was used as a post hoc test if a significance found. A p value of less than 0.05 was considered as significant.

Results

The selected demographics and stone characteristics of the ESWL, RIRS, and m-PCNL groups were found similar ($p>0.05$) (Table 1). The Table 2 presents operative and postoperative data of the study groups. There was no significant difference with regard to the operation times between the RIRS and the m-PCNL groups (42.3 ± 0.4 vs. 48 ± 18.6 min; $p>0.05$). Although the operating time of ESWL group was significantly longer compared to other study groups (66.0 27.7 min vs. 42.3 ± 0.4 vs. 48 ± 18.6 min, respectively; $P= 0.001$); however, the ESWL patients did not receive general anesthesia as related to the nature of procedure.

Considering 3 groups by detected on X-ray KUB 1 months after surgery, nine patients in the ESWL group, three patients in RIRS group, and two patients in m-PCNL group were detected with residual fragment. The stone clearance rates at 1 month follow-up were 70 %, 90%, and 93,3% for the ESWL, RIRS and m-PCNL groups in the order of writing. The lower pole stone clearance rates were lower than other groups for the ESWL group (Table 3). The stone clearance rates of RIRS and m-PCNL techniques were found similar ($p>0.05$).

In the m-PCNL group, one patient with solitary kidney who underwent nephrectomy for stony atrophic kidney, on the first postoperative day, urinary system ultrasonography was performed because of pain and decreased urine output. Pelvicaliectasis was detected and a jj stent was placed on the first postoperative day. In addition, one patient in the m-PCNL group underwent (CT) due to postoperative decrease in hemoglobin and 18x10x9 cm hematoma was detected in the retroperitoneum.

In the RIRS and m-PCNL groups, hemoglobin decrease was significantly higher. When we consider the RIRS and m-PCNL groups, the decrease in hemoglobin was significantly lower in the RIRS group (Table 4). No statistically significant difference was found between the groups in terms of stone size and fluoroscopic time.

The mean Visual Analogue Scala (VAS) was significantly higher in the ESWL group than the other groups. No statistically significant difference was found between the groups in the Modified Clavien Classification Scale. However, grade 2 complications in 7 patients in the RIRS group and grade 3B complications in the m-PCNL group of 2 patients were observed. In the m-PNL group one patient, who had solitary kidney, required JJ stent on the following day after surgery due to anuria. In the RIRS group, antipyretic and antibiotic drugs were used due to high fever after the operation.

http://dx.doi.org/10.36472/msd.v7i4.366

Table 1. Demographic data and stone size (Mean ± SD).

	ESWL (n=30)	RIRS (n=30)	m-PCNL (n=30)	Significance
Age, y	42.2 ± 14,3	44.3 ± 11,8	36.1 ± 14.9	P=0.06
Gender				
Male	22 (73%)	19 (63%)	16 (53%)	
Female	8 (27%)	11 (37%)	14 (47%)	P=0.275
Stone size, cm	1.0 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	P= 0.058

Table 2. Comparison of operative and postoperative data.

	ESWL	RIRS	m-PCNL	Significance
Operating time, min	66.0 ± 27.7[a]	48.0 ± 18.6	42.3 ± 10.4	P= 0.001
Fluoroscopy time, sec	61.7 ± 24.9	50.3 ± 32.3	55.4 ± 30.4	P= 0.118
Visual analogue score (VAS)	5.0 ± 1.2[b]	3.2 ± 0.6	3.2 ± 0.8	P= 0.001
Hospital stay, day	-	1.1 ± 0.4	1.6 ± 0.9	P=0.107

Visual analogue score (VAS): Post op 1 day, scale 1–10. [a,b]P<0.05, SWL vs. RIRS and m PNL. *p<0.05

Table 3. Stone clearance rates

	Patients	Lower pole stone patients, n (%)	Complete stone clearance, n (%)	Lower pole stone clearance, n (%)	Significance
ESWL	30	9 (%30)	21(%70)	3(%33.3)	p=0.004*
RIRS	30	12(%40)	27(%90)	10(%83.3)	p=0.320
m-PCNL	30	11(%36.6)	28(%93.3)	10(%90.9)	p=0.685

*p<0.05

Table 4 Preoperative and postoperative hemoglobin value

	Preoperative hemoglobin (g/dl)	Postoperative hemoglobin (g/dl)	Significance
ESWL	14.7 ± 1.5	14.4 ± 1.4	t= 2.52 P= 0.07
RIRS	14.7 ± 1.9	13.9 ± 1.8	t= 5.78 * P= 0.001 *
m-PCNL	14.4 ± 1.7	13.3 ± 1.9	t= 6.90 P= 0.001 *

Discussion

Minimal invasive endourologic procedures are recommended for lower calyx stones (10-20 mm) as the first choice in the presence of unsuitable conditions for ESWL or failure (1). RIRS provides a significantly higher stone-free rate and lower retreatment rate compared with ESWL (7). m-PCNL has been shown to have a good stone clearance rate and similar complication rates when compared with RIRS (8). In this study, we confirmed that RIRS, m-PCNL, and ESWL are safe and effective methods for the treatment of renal stones smaller than 2 cm. The stone clearance rates of RIRS and m-PCNL techniques were found similar. The lower pole stone clearance rates were lower than other groups for the ESWL group. We excluded patients with high body mass index and patients with recurrent renal stone disease history from the study.

ESWL is an outpatient treatment without hospitalization and can be applied without general anesthesia to patients with high tolerance. It does not require hospitalization and patients can turn back to their daily activities after couple of hours from the process. In this study, ESWL was performed to 30 patients (22 male, 8 female) who had kidney stones smaller than 2 cm in our clinic (9 patients with lower pole calculi, 21 patients with middle, upper pole or renal pelvis calculi). Yoon et al. found stone free rates as %74.7 for 79 patients with lower calyx stones in 142 renal stone patients who underwent ESWL (9). Compared with this study, although we found similar results with Yoon et al. for middle and upper calyx stones, the stone-free rates for lower calyx stones were lower in our study. Singh et al. compared ESWL and RIRS in 35 patients with the average stone size of 16.4 ± 2.3 mm in ESWL group and 15.0 ± 3.6 mm in RIRS group, they found stone-free rate as 48.6 % and the first day VAS score as 2.40 ± 0.64 in ESWL group. Also their stone-free rate was %82.8 and the first day VAS score was 4.3 ± 0.4 and the operation time was 78.7 ± 20.0 minutes in RIRS group (10). In our study, the average stone

http://dx.doi.org/10.36472/msd.v7i4.366

size in the ESWL group was 1.0 ± 0.3 mm. We found 70% of stone-free rate in ESWL group. However, stone-free rate in our ESWL and RIRS groups were higher. VAS scores of our ESWL group (5.00 ± 1.23) at the first day of procedure were higher. In another study; ESWL, RIRS, and m-PCNL in 251 patients with the average stone size of 14,9 ± 2.9 mm in ESWL group and 15.6 ± 3.4 mm in RIRS group, they found stone-free rate as 65 % in ESWL group. Also their stone-free rate was %87 and the operation time was 43.1±17 minutes in RIRS group (11). These results are similar with our studies.

In this study, RIRS was performed to 30 patients (19 male, 11 female) who had kidney stones smaller than 2 cm in our clinic. (12 patients with lower pole calculi, 18 patients with middle, upper pole or renal pelvis calculi). Stephan Kruck et al. compared ESWL and RIRS in 202 patients, stone-free rate was 58.4 % in ESWL group. Also their stone-free rate was %77.88 and the hospitalization time was 2.3 ± 2.6 days in RIRS group. (12). Stone-free rates in our ESWL and RIRS groups were higher than this study, and the hospitalization time (1.1 ± 0.4 day) of our RIRS group was lower than this study. The study of Sabnis et al. was comparing RIRS and m-PCNL in 70 patients with the average stone size of 1.04 ± 0.25 mm in RIRS group and 1.1 ± 0.2 mm in m-PCNL group, they found stone-free rate as 94.3% and the first day VAS score as 1.6 ± 0.8 and hospitalization time 49 ± 18 hours in RIRS group. Also their stone-free rate was 97.1% and the first day VAS score was 1.9 ± 1.2 and the operation time was 51.6 ± 18.5 minutes and hospitalization time 57 ± 22 hours in m-PCNL group. (13) In our study, the average stone size in the RIRS group was 1.2 ± 0.3 mm. We found stone-free rate as 90% in RIRS group. VAS scores of our RIRS group (3.2 ± 0.6) and m-PCNL (3.2 ± 0.8) procedure were higher than this study.

In our study, m-PCNL was performed to 30 patients (16 male, 14 female) who had kidney stones smaller than 2 cm in our clinic. (11 patients with lower pole calculi, 19 patients with middle, upper pole or renal pelvis calculi). In Kiraç et al. study; RIRS and m-PCNL in 73 patients, they found stone-free rate as 88.8 % and hospitalization time was 24.5 ± 4.6 hours and operating time was 66.4 ± 15.8 minutes and fluoroscopy time was 72.5 ± 23.7 seconds in RIRS group (14). Also their stone-free rate was 89.1% and hospitalization time was 42.6 ± 13.6 hours and operating time was 53.0 ± 14.5 minutes and fluoroscopy time was 130.5 ± 49.5 in seconds in m-PCNL group. In our study, operative time and fluoroscopy time was lower than this study. Hatipoğlu et al. found stone free rates as 82.1% for 62 patients with lower calyx stones in 140 renal stone patients who undergone m-PCNL (15). In this study, they reported that average stone size of 15.1 ± 5.1 mm, operation time 55.8 ± 30.8 minutes, fluoroscopy time 107.4 ± 79.1 seconds and hospitalization time 1.8 ± 0.6 day. In our study, stone-free rate was higher and operation and fluoroscopy times were lower than this study.

Conclusions

ESWL, RIRS, and m-PCNL are minimal invasive treatments for renal stones smaller than 2 cm. For these stone sizes, ESWL technique is usually more preferred. But in this study, we compared patients with renal stones less than 2cm; m-PCNL and RIRS methods were found to be more effective than ESWL. However studies with larger number of patients are needed to confirm our results.

Acknowledgments: None

Author Contributions: HS, GG, EK: Design of project, Patient examination, Data analyzes and statistics **HS:** Revisions

Conflict of Interest: The authors declare that they have no conflict of interest

References

1. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU guidelines on interventional treatment for urolithiasis. European urology. 2016; 69: 475-482.

2. Srisubat A, Potisat S, Lojanapiwat B, Setthawong V, Laopaiboon M. Extracorporeal shock wave lithotripsy (ESWL) versus percutaneous nephrolithotomy (PCNL) or retrograde intrarenal surgery (RIRS) for kidney stones. Cochrane database of systematic reviews. 2014 ;11.

3. Knoll T, Jessen J. P, Honeck P, Wendt-Nordahl G. Flexible ureterorenoscopy versus miniaturized PNL for solitary renal calculi of 10–30 mm size. World journal of urology. 2011; 29: 755-759.

4. Traxer O, Thomas A. Prospective evaluation and classification of ureteral wall injuries resulting from insertion of a ureteral access sheath during retrograde intrarenal surgery. The Journal of urology. 2013; 189: 580-584.

5. Jackman S. V, Docimo S. G, Cadeddu J. A, Bishoff J. T, Kavoussi L. R, Jarrett T. W. The "mini-perc" technique: a less invasive alternative to percutaneous nephrolithotomy. World journal of urology. 1998; 16: 371-374.

6. Monga M, Oglovie S. Minipercutaneous nephrolithotomy. Journal of endourology. 2000; 14: 419-421.

7. El-Nahas A. R, Ibrahim H. M, Youssef R. F, Sheir K. Z. Flexible ureterorenoscopy versus extracorporeal shock wave lithotripsy for treatment of lower pole stones of 10–20 mm. BJU international. 2012; 110: 898-902.

8. Sabnis R. B, Jagtap J, Mishra S, Desai M. Treating renal calculi 1–2 cm in diameter with minipercutaneous or retrograde intrarenal surgery: a prospective comparative study. BJU international. 2012; 110: E346-E349.

9. Yoon C. Y, Kim D. S, Lee J. G. Stone free rate of SWL in renal calyceal stone according to its location. Korean Journal of Urology. 1999; 40: 138-142.

10. Singh B. P, Prakash J, Sankhwar S. N, Dhakad U, Sankhwar P. L, Goel A, Kumar M. Retrograde intrarenal surgery vs extracorporeal shock wave lithotripsy for intermediate size inferior pole calculi: a prospective assessment of objective and subjective outcomes. Urology. 2014; 83: 1016-1022.

11. Resorlu B, Unsal A, Ziypak T, Diri A, Atis G, Guven S, Oztuna D. Comparison of retrograde intrarenal surgery, shockwave lithotripsy, and percutaneous nephrolithotomy for treatment of medium-sized radiolucent renal stones. World journal of urology. 2013; 31: 1581-1586.

12. Kruck S, Anastasiadis A. G, Herrmann T. R, Walcher U, Abdelhafez M. F, Nicklas A. P, Nagele U. Minimally invasive percutaneous nephrolithotomy: an alternative to retrograde intrarenal surgery and shockwave lithotripsy. World journal of urology. 2013; 31: 1555-1561.

13. Sabnis R. B, Ganesamoni R, Doshi A, Ganpule A. P, Jagtap J, Desai M. R. Micropercutaneous nephrolithotomy (microperc) vs retrograde intrarenal surgery for the management of small renal calculi: a randomized controlled trial. BJU international. 2013; 112: 355-361.

14. Kirac M, Bozkurt Ö. F, Tunc L, Guneri C, Unsal A, Biri H. Comparison of retrograde intrarenal surgery and mini-percutaneous nephrolithotomy in management of lower-pole renal stones with a diameter of smaller than 15 mm. Urolithiasis. 2013; 41: 241-246.

15. Hatipoglu N. K, Tepeler A, Buldu I, Atis G, Bodakci M. N, Sancaktutar A. A, Gurbuz C. Initial experience of micro-percutaneous nephrolithotomy in the treatment of renal calculi in 140 renal units. Urolithiasis. 2014; 42: 159-164.

http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):455-8

Research Article Doi: 10.36472/msd.v7i4.369

Comparisons of neutrophil, monocyte, eosinophil, basophil and lymphocyte ratios among the fibromyalgia syndrome and healthy individuals

Nihal Tezel[1]*, Selcan Gültuna[2]

Abstract

Objective: To evaluate the basophil lymphocyte ratio (BLR) and eosinophil lymphocyte ratio (ELR) values in the fibromyalgia syndrome (FMS) that previously reported being used as an indicator of inflammation in autoimmune rheumatic diseases and smokers.

Material and Methods: We retrospectively analyzed 4500 fibromyalgia (FM) patients who were registered in the network system with the M79-ICD code and 2000 healthy controls. A total of 216 FM patients and 194 healthy controls were included in the study.

Results: The blood BLR levels were significantly higher in FM patients than in healthy controls. ($p< 0,02$). The two groups did not show significant differences in terms of the other parameters ($p> 0.05$).

Conclusion: In the present study, neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), platelet lymphocyte ratio (PLR), ELR, platelet distribution width (PDW) are independent markers for early diagnosis and for the inflammatory predictive process. BLO levels were low revealed. To use these rates as disease markers should be supported by large-scale studies.

Keywords: Neutrophil-lymphocyte ratio; monocyte-lymphocyte ratio; eosinophil-lymphocyte ratio; basophil-lymphocyte ratio; fibromyalgia syndrome; inflammatory marker.

Introduction

Fibromyalgia syndrome (FMS) is a common chronic pain syndrome with female predominance characterized by diffuse stiffness, pain, tenderness, and somatic symptoms (like sleep problems, headache, fatigue) (1). The incidence of FMS in the general population is 2-4% (2). Although the etiology and pathogenesis of FMS have remained unknown until now, genetic and epigenetic causes have been suggested in which the FMS etiopathogenesis pain regulation system is impaired (3). In FMS, which cannot be diagnosed by any laboratory or imaging, the diagnosis can be made with clinical and examination findings. In FMS, where somatic symptoms are intensely observed, it is important to exclude other diseases in which these symptoms can be common. Therefore, laboratory support is very important in the diagnosis. According to previous findings, an increase of Pro-inflammatory cytokines like IL 8, IL 6 has been detected in fibromyalgia (FM) patients (4). However, these biomarkers cannot be used in clinical practice. In recent years, neutrophil- neutrophil-lymphocyte (NLR) and Platelet Distribution Width (PDW) have been identified as two important systemic inflammation markers.

And, many studies have reported that NLR and PDW were associated with inflammatory activity and prognosis in FMS (5). However, there are studies indicating otherwise (6).

The aim of the study is to evaluate the BLR and ELR values in FMS that previously reported to be used as an indicator of inflammation in autoimmune rheumatic diseases and smokers (7,8).

Received 01-04-2019 **Accepted** 19-04-2020 **Available Online** 20-04-2020 **Published** 30-04-2020
1 Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Physical Medicine and Rehabilitation, Ankara, TR
2 Ministry of Health Ankara Diskapi Yildirim Beyazit Training and Research Hospital, Immunology and Allergy, Ankara, TR
*** Corresponding Author:** Nihal Tezel **E-mail:** nihaltezel@gmail.com

Material and Methods

Patients diagnosed with fibromyalgia (FM) who applied to the physical therapy and rehabilitation outpatient clinic between January 2018 and November 2018 were scanned. Patients with disease that may affect the blood count (diabetes, B12, vitamin D, ferritin deficiency, hypothyroidism, hypercholesterolemia, high acute phase reactants or have comorbidities) both patient and control groups were excluded from the study.

We retrospectively analyzed 4500 FM patients who were registered in the network system with the M79-ICD code and 2000 healthy controls. 4284 FM patients and the 1806 healthy controls excluded from the study due to comorbidities and the reasons that can be affected the blood values. A total of 216 FM patients and 194 healthy controls were included in the study. All participants' age, gender, lökosit, neutrophil, lymphocyte, eosinophil, basophil, monocyte and platelet counts; PDW; and MPV data were recorded. The study protocol was approved by the local Ethics Committee. (approve date:04.02.2019, approve number:59/06) The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The statistical analysis was performed using the SPSS for Windows 11.5 package program (SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk's test) to determine whether or not normally distributed.

Normally distributed continuous variables were expressed as mean±standard deviation (s.d) while the continuous variables that do not have normal distribution were expressed as median (minimum-maximum). Also, categorical variables were summarized as counts (percentages). Comparisons of normally distributed continuous variables between groups were tested using the Student's test. For non-normally continuous variables, differences between groups were tested using the Mann-Whiney U test. ROC curve analysis was used to test the hallmark of BLO in predicting FM. A two-sided p-value of less than 0.05 was considered as statistically significant.

Results

Age and gender data for 174 FM patients and 194 healthy controls were shown in Table 1. A total of 196 FM patients (176 women, 20 men) and 194 healthy control (174 women, 20 men) included in the study. The mean age for the patients and control groups were 44,43±8,69 and 42,53±9,60 years respectively. There were no statistically significant age and gender differences between the groups.

Laboratory data has been shown in Table 2. The blood BLR levels were significantly higher in FM patients than in healthy controls. (p< 0,02)

The two groups did not show significant differences in terms of the other parameters (p> 0.05).

ROC analysis The area under the curve (AUC) was 0.42.

Table 1 Demographics of the patients (SD: Standard Deviation)

	Group 1 (n=216)	Group 2 (n=194)
Male (%)	20 (9,3)	20 (10,3)
Female (%)	196 (90,7)	174 (89,7)
Age, Mean±SD	44,43±8,69	42,53±9,60

Table 2 Comparison of NLR, PLR, ELR, BLR, MLO, MPV, RDW between fibromyalgia patients and healthy controls

	Group 1 (n=216)	Group 2 (n=194)	p*
NLR, median min-max	1,84 (0,54-7,00)	1,80(0,29-11,33)	0,262
PLR, median min-max	119,41(41,67-823,33)	119,87 (54,55-783,33)	0,702
ELR, median min-max	0,58 (0-0,67)	0,06 (0-0,36)	0,084
BLR, median min-max	0 (0-1,11)	0 (0-1,4)	**0,002***
MLO, median min-max	0,21 (0,06-6,33)	0,21 (0,03-1,33)	0,678
MPV, mean±SD	8,75±1,32	8,94±1,39	0,370
RDW, mean ±SD	13,76±1,31	13,67±1,22	0,434
WBC, mean ±SD	7,41±1,73	7,25±1,50	0,489
NEU, mean ±SD	4,38±1,422	4,18±1,22	0,264
MONO, mean ±SD	0,51±0,18	0,49±0,14	0,337
LYM, mean ±SD	2,30±0,59	2,29±0,61	0,607
EOS, mean ±SD	0,16±0,13	0,17±0,10	0,113
BASO, mean ±SD	0,04±0,15	0,05±0,15	0,463
PLT, mean ±SD	269,65±58,34	272,30±58,93	0,596
PDW, mean ±SD	16,37±1,32	16,16±1,22	0,176

NLR: neutrophil lymphocyte ratio; PLR: platelet lymphocyte ratio; ELR: eosinophil lymphocyte ratio; BLR:basophil lymphocyte ratio; MLO:monocyte lymphocyte ratio; MPV:mean platelet volume; RDW: Red Blood cell distribution width; WBC: white Blood cell; NEU: neutrophil; MONO:monocyte; LYM: lymphocyte; EOS: eosinophil; BASO: basophil; PLT: platelet; PDW: platelet distribution width; min-max:minimum-maximum; SD: Standard deviation.

Discussion

FMS is a multifactorial disease with unknown etiology. In early diagnosis and treatment, typically there are no laboratory abnormalities specifically associated with FMS. In FM patients, NLR, PLR rates, MPV and RDW Blood distribution parameters have been previously evaluated in various studies, and different results have been revealed (5). To our knowledge, this is the first study to evaluate NLR, MLR, ELR, and BLR levels in FMS. In the present study, we did not find any difference in NLR, PLR, ELR ratios and MPV and RDW values between FM patients and healthy controls. In FM patients, BLR was lower than the control group.

Zhang et al (7) found that NLR, MLR levels were significantly higher in the inflammatory rheumatic disease and were closely related to AFR. Similarly, Uslu et al (9) found the relationship between NLR and PLR levels and DAS-28 scores. And they indicated that these ratios can be used as inflammatory markers in rheumatoid arthritis.

Aktürk et al. (5) found NLR levels high in FM patients but did not find a correlation with AFR. The NLR has been reported as a prognostic marker to determine the systemic inflammatory response.

Similar to our study, Karataş et al. (6) did not found any difference between healthy controls and FM patients in NLR, MLR, and PLR levels. They suggested that FMS is not an inflammatory disease.

Taşoğlu et al. (10) evaluated the correlation between severe knee osteoarthritis with NLR and reported that patients with severe knee osteoarthritis had higher BLR and NLR values compared to those with mild knee osteoarthritis. However, in this study, there was a significant difference in ages between the groups. Fest et al. (11) found the distribution of the NLR and PLR was different between age categories. Also in osteoarthritis (OA), the inflammatory reaction can trigger the OA changes (12). These differences can be explained by age or inflammation in severe osteoarthritis.

Ilgun et al. did not find an association between FM NLR and found a correlation between tender scores with PLR scores (13). In this study, the diagnosis of FM was made according to the 1990 ACR criteria. However, clinical experience and epidemiological data show that FMS patients frequently report other symptoms such as sleep disturbances, fatigue, irritable bowel syndrome, and others.

Taş et al. (14) investigated the NLR and PLR in rest leg syndrome, one of the central sensitization syndromes such as FMS. They found no difference similar to our study.

Qin et al (15) investigated NLR and PLR in patients with SLE patients. The rates were significantly higher in the patient group and correlated with C-Reactive protein and nephritis.

Monocyte-lymphocyte ratio (MLR), were not evaluated in FMS before. It has been related to diabetic retinopathy and the predictive value of the prognosis of some tumors (16,17). In the present study, we did not find any MLO differences between groups.

Eosinophil and basophil in normal blood tend to be low as has been known, increases in these two types of leukocytes are used to reflect allergic diseases and parasitic infections. In our study, we found that BLR levels were decreased. Like the present study, a clinical study also found a decrease in basophil ratio in SLE patients. In this study, although BLR levels were found to be low in SLE patients, they did not find any correlation with inflammatory and immune markers. Indeed, they indicate that basophil cells are effective in SLE pathogenesis, there is no such literature on FM (7).

Hematologic parameters such as neutrophil, lymphocyte, and platelet counts can easily be affected by various conditions such as ethnicity, age, sex, eating habits, and environmental factors (18). One of the reasons for differences in results between similar studies can be explained by this.

The role of systemic inflammation in the pathogenesis of FMS has not been clear. We can see significant differences in blood distribution parameters are mostly detected in inflammatory processes. The meaning of inflammatory mechanisms and blood distribution parameters in FMS should be supported by much larger studies.

The strengths of our study are that the number of patients screened was high, blood counts ratios used as an inflammatory marker in some diseases which have not been previously evaluated in FMS were investigated, and we have determined methodological exclusion criteria well.

Limitation of the study as the network database is examined. The patients cannot be evaluated in terms of disease severity or quality of life.

Conclusion

Discovering new biomarkers of inflammation becomes important in order to help diagnostic accuracy and provide prognostic information about fibromyalgia. Our study demonstrated that BLR levels are markedly decreased in FMS. The literature has comprehensive results about the fibromyalgia and NLR, MLR, PLR, ELR, PDW relations.

In the present study, NLR, MLR, PLR, ELR, PDW are independent markers for early diagnosis and for the inflammatory predictive process. BLO levels were low revealed. It is our opinion that to use these rates as disease markers must be supported by large-scale studies.

Acknowledgments: None

Author Contributions: NT, SG: Design of research, data collection, **SG;** Statistical analysis**, NT:** Writing of manuscript and revisions**.**

Conflict of Interest: The authors declare that they have no conflict of interest

References

1. Lichtenstein A, Tiosano S, Amital H. The complexities of fibromyalgia and its comorbidities . Curr Opin Rheumatol. 2017, 30:94-100.

2. Clauw DJ, D'Arcy Y, Gebke K, Semel D, Pauer L, Jones KD. Normalizing fibromyalgia as a chronic illness. Postgrad Med 2018; 130: 9-18.

3. Cabo-Meseguer A, Cerdá-Olmedo G, Trillo-Mata JL. Fibromyalgia: Prevalence, epidemiologic profiles and economic costs. Med Clin 2017;149:441–8.

4. Rodriguez-Pinto I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett. 2014;161(2):200–203.

5. Aktürk S, Büyükavcı R. Evaluation of BLRod neutrophil-lymphocyte ratio and platelet distribution width as inflammatory markers in patients with fibromyalgia. Clin Rheumatol. 2017;36(8):1885-1889.

6. Karataş G, Gündüz R. The Significance of inflammation markers in complete blood count in patients with fibromyalgia. Med Sci Discov. 2020 ;7(1):364-7.

7. Zhang Y, Yin Y, Kuai S, Shan Z, Pei H, Wang J. Combination of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio as diagnostic biomarker for rheumatoid arthritis. Int J Clin Exp Med. 2016; 9: 22076- 22081.

8. Çekici Y, Yılmaz M, Seçen O. New inflammatory indicators: association of high eosinophil to-lymphocyte ratio and low lymphocyte-to-monocyte ratio with smoking. Journal of International Medical Research.2019;(47)9:4292–4303.

9. Uslu AU, Kucuk A, Sahin A, Ugan Y, Yılmaz R, Güngör T et al. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheum Dis 2015; 18(7): 731– 735.

10. Tasoglu O, Boluk H, Onat SS, Tasoglu I, Ozgirgin N. Is blood neutrophil-lymphocyte ratio an independent predictor of knee osteoarthritis severity?Clin Rheumatol 2016;35 (6):1579-1583.

11. Fest J, Ruiter R, Ikram MA, Voortman T, Van Eijck CHJ, Stricker BH. Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study.Sci Rep 2018; 8:10566.

12. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. J Pain Res. 2018;11:2189–96.

13. İlgün E, Akyürek Ö, Kalkan AO, Demir F, Demirayak M, Bilgi M. Neutrophil/Lymphocyte Ratio and Platelet/Lymphocyte Ratio in Fibromyalgia. Eur J Gen Med. 2016;13(2):100-4.

14. Tak AZA, Şengül Y. Evaluation of Inflammation with Neutrophil-to-lymphocyte Ratio and Platelet-to-lymphocyte Ratio in Restless Legs Syndrome. Turk J Neurol. 2018; 24(3): 259-263.

15. Qin B, Ma N, Tang Q, Wei T, Yang M, Fu H, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. Mod Rheumatol.2016; 26(3), 372–6 .

16. Feng F, Tian Y, Liu S, Zheng G, Liu Z, Xu G, et al. Combination of PLR, MLR, MWR, and tumor size could significantly increase the prognostic value for gastrointestinal stromal tumors. Medicine 2016;95:3248.

17. Li J, Jiang R, Liu WS, Liu Q, Xu M, Feng QS, et al. A large cohort study reveals the association of elevated peripheral BLRod lymphocyte-to-monocyte ratio with favorable prognosis in nasopharyngeal carcinoma. PLoS ONE 2013;8:83069.

18. El-Hazmi MA, Warsy AS. Normal reference values for hematological parameters, red cell indices, HB A2 and HB F from early childhood through adolescence in Saudis. Ann Saudi Med 2001;21:165-169.

http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):459-65

Research Article Doi: 10.36472/msd.v7i4.370

Inflammatory markers and clinical factors which affecting the survival in metastatic renal cell carcinoma

Mahmut Büyükşimşek[1]*, Ali Oğul[1]

Abstract

Objective: According to metastatic renal cell carcinoma treatment protocol, after the use of tyrosine kinase inhibitors (TKI) has been achieved significant improvements for the treatment of metastatic renal cell carcinoma (mRCC). In this study, we aimed to investigate the effect of neutrophil-to-lymphocyte ratio (NLR) and prognostic nutritional index (PNI) on survival in patients with mRCC treated with sunitinib or pazopanib.

Material and Methods: Medical data for 38 patients with mRCC were reviewed retrospectively. NLR and PNI values were dichotomized based on receiver operating characteristic (ROC) curve analysis (cut-off values: 3 and 46, respectively). Univariate and multivariate analyses were performed to identify prognostic factors for progression free survival (PFS) and overall survival (OS) using a Cox proportional hazards model.

Results: Median PFS and OS were 12 and 27 months, respectively. Median PFS was 10 months in patients with NLR ⩾ 3 while 14 months in patients with NLR <3 (p: 0.008). Median OS was 18 months in patients with NLR ⩾3 while 31 months in patients with NLR <3 (p: 0.003). In patients with PNI ⩾ 46, PFS was 21 months and OS was 47 months whereas in patients with PNI < 46, PFS was 8 months and OS was 13 months (p values were <0.001, <0.001 respectively). In multivariate analysis, PNI was the independent risk factor for both PFS and OS, while NLR was the independent risk factor for OS only.

Conclusion: In patients with mRCC that using sunitinib or pazopanib, NLR and PNI values can be used as easily accessible prognostic markers.

Keywords: Renal cell carcinoma, Tyrosine kinase inhibitors, Neutrophil-to-lymphocyte ratio, Prognostic nutritional index.

Introduction

Renal cell carcinoma (RCC) is an aggressive malignancy with a 40% recurrence risk after nephrectomy for localized tumor, with a 5-year survival rate below 20% in advanced stage. Today, despite the increase in early detection of small renal masses, up to 20% of the patients with RCC apply to health centers in the metastatic phase (1). In clinical studies with tyrosine kinase inhibitors (TKI) such as sunitinib, pazopanib, sorafenib; prolonged progression-free survival (PFS) and overall survival (OS) have been obtained in patients with metastatic renal cell carcinoma (mRCC). New prognostic and predictive markers are needed for these agents that cause significant changes in mRCC management (2).The relationship between cancer development and inflammation has increased interest in the prognostic significance of inflammatory markers (3). The neutrophil-to-lymphocyte ratio (NLR), an index formed by dividing absolute neutrophil count into absolute lymphocyte count, is an inflammatory marker that has attracted researchers' attention due to its potential prognostic effect and has been identified as an independent prognostic factor in many types of cancer (4,5). Although a relationship between increased NLR and poor prognosis was demonstrated in patients with RCC (6); data on its role in patients with mRCC treated with sunitinib or pazopanib are insufficient. The Prognostic Nutritional Index (PNI), which is calculated using serum albumin concentration and total lymphocyte count in peripheral blood, was first used to obtain an idea about the immune nutritional status and surgical risk in patients undergoing gastrointestinal surgery (7). However, it was found that preop nutritional and immunological status was not only associated with postoperative complications but also associated with prognosis in malignancy patients, and currently PNI is used prognostically in various types of cancer (8-10). However, the prognostic role of PNI in mRCC patients using tyrosine kinase inhibitors has not been fully established. In this study, we aimed to evaluate the effects of NLR and PNI and also clinicopathological factors on progression-free

Received 10-04-2019 **Accepted** 19-04-2020 **Available Online** 21-04-2020 **Published** 30-04-2020
1 University of Health Sciences, Adana Health Practice and Research Center, Dept of Medical Oncology, Adana, TR
*** Corresponding Author:** Mahmut Büyükşimşek **E-mail:** mahmutbuyuksimsek@gmail.com

http://dx.doi.org/10.36472/msd.v7i4.370

survival (PFS) and overall survival (OS) in mRCC patients treated with sunitinib or pazopanib.

Materials and Methods

Study Design and Population

We evaluated data of 64 patients with mRCC treated in the medical oncology department between January 2014 and December 2018. The data were obtained retrospectively from medical records, laboratory results and patient files. This study included patients who were treated with tyrosine kinase inhibitors (TKI) such as sunitinib or pazopanib for mRCC, Eastern Cooperative Oncology Group (ECOG) performance score ⩽2, over 18 years of age and with clear cell subtype.

Demographic data including age and gender, interferon use, risk groups according to Memorial Sloan Kettering Cancer Center (MSKCC) risk criteria, surgical status were recorded from patient files. Complete blood count, serum calcium, albumin, LDH levels of all patients were recorded within a week before the TKI treatment. Patients with chronic diseases such as chronic heart failure, liver cirrhosis, systemic lupus erythematous, myeloproliferative disease and those with secondary malignancy were excluded. 26 patients were excluded from the final analysis for the following reasons: other type of tyrosine kinase inhibitor therapy (n = 9), no survival outcome data (n = 13), concomitant chronic disease or secondary malignancy (n = 4). Ethics committee approval was obtained from the ethics committee of University of Health Sciences-Adana Health Practice and Research Center. All the procedures were performed according to the 1964 Helsinki declaration.

Treatment Regimens

38 patients who used sunitinib (sutent; pfizer) or pazopanib (votrient; novartis) treatment were included in the study. Sunitinib was administered 50 mg once daily on 28 consecutive days of a given 6-week cycle and pazopanib was administered continuously 800 mg once daily. During the treatment of TKI according to the severity, treatment interruption or dose reduction for side effect management was performed according to the standard guidelines. Treatment continued until unacceptable adverse events were observed, disease progression was detected on imaging, or death occurred. Disease progression was assessed using the modified Response Evaluation Criteria in Solid Tumors version 1.1. (11).

Statistical analyses

PFS was considered as the time from the onset of TKI treatment to disease progression in imaging or death from any cause. OS was considered as the time from the first day of treatment to last follow up or death. NLR was calculated dividing the neutrophil counts by lymphocyte counts. PNI was calculated with the formula '(10 × albumin (g/L) + (0.005 × total lymphocyte count)'. The most sensitive and specific cut-off values for NLR and PNI were determined by using receiver operating characteristic (ROC) curve analysis.

The association between survivals and clinical and laboratory variables was evaluated using univariable Cox regression analysis, followed by multivariable analysis using the Cox proportional hazards model. The log rank test was used to determine differences between groups. Kaplan-Meier curves were used to estimate the time to event distribution. All analyses were performed using the SPSS statistical software package (SPSS statistics 21.0) and $p< 0.05$ was considered as statistically significant.

Results

A total of 38 patients, including 10 males and 28 females, were included in the study and the median age was 59 (range 38-76). The ECOG performance score was 0-1 in 25 patients, and 2 in 13 patients. All patients were from the clear cell subtype and the number of patients with Fuhrman grade 1, 2, 3 and 4 were 2, 2, 9, and 25, respectively.

According to the Memorial Sloan Kettering Cancer Center (MSKCC) index, 5 patients were in favorable, 20 patients were intermediate and 13 patients were in poor risk group. 25 patients received sunitinib therapy while 13 patients received pazopanib therapy. In response to the first treatment, 11 (28.9%) patients developed progression, 10 (26.3%) patients had partial response, and 17 patients had stable disease (44.8%). While 11 patients had a single metastatic focus, 27 patients had multiple foci of metastatic lesions. Metastasectomy was performed in 5 patients with a single metastatic focus. Twenty-eight patients underwent radical nephrectomy. The relationship of the clinical and demographic data of the patients with survival is shown in Table 1.

The median follow-up time was 20 months. Median PFS and OS were 12 and 27 months, respectively. ROC analysis was performed to determine cut off values for NLR and PNI and the results were shown in Table 2. Median PFS was 10 months in patients with NLR ⩾3 and 14 months in patients with NLR <3 (p: 0.008). Median OS was 18 months in patients with NLR ⩾3, and 31 months in patients with NLR <3 (p: 0.003). In patients with PNI ⩾46, PFS was 21 months and OS was 47 months; in patients with PNI <46, PFS was 8 months and OS was 13 months (p values <0.001, <0.001, respectively). Independent risk factors for survival were evaluated by Cox regression analysis and for this purpose, the number of metastatic fields, ECOG performance status, MSKCC index, and NLR and PNI values were included in this analysis (Table 3 and 4).

ECOG performance status, number of metastatic fields and MSKCC index were determined as independent risk factors for PFS and OS. Cox regression analysis showed that pretreatment NLR value was not an independent risk factor for PFS [HR: 1.282 (0.808-1.816 95% CI), p: 0.147] but it was an independent risk factor for OS [HR: 1.632 (1.112-2.442 95% CI), p: 0.034]. As important finding of our results, the low PNI was determined as an independent risk factor for shorter PFS and OS [HR: 1.934 (1.244-2.978 %95 CI), p: 0.033; HR: 1.568 (1.030-2.466 %95 CI), p: 0.044, respectively].

Table 1. Clinical and demographic data of patients

	n (%)	PFS Median, months	p value	OS Median, months	p value
Age					
Median(range)	59 (38-76)				
Gender					
Female	14 (36.8)	13	0.95	37	0.75
Male	24 (63.2)	12		22	
ECOG					
0-1	25 (65.8)	34	**<0.001**	50	**<0.001**
≥ 2	13 (34.2)	6		11	
MSKCC index			**<0.001**		**<0.001**
Favorable	5 (13.2)	21		NR	
Intermediate	20 (52.6)	16		29	
Poor	13 (34.2)	4		11	
Nephrectomy			0.34		0.56
Yes	28 (73.7)	15		30	
No	10 (26.3)	9		20	
Number of Metastatic Site			**0.004**		**0.002**
1	11 (28.9)	21		55	
≥ 2	27 (71.1)	7		15	
Use of INF-α			0.5		0.66
Yes	15 (39.5)	10		31	
No	23 (60.5)	14		24	
Sunitinib	25 (65.8)	12	0.9	26	0.95
Pazopanib	13 (34.2)	13		28	
Status					
Alive	11 (28.9)				
Death	27 (71.1)				
Overall	38 (100)	12			27

PFS: Progression-free survival, OS: Overall survival, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center index

Table 2. ROC analysis results for NLR and PNI

	Cut off Value	AUC	95% CI for AUC Lower Bound	Bound Upper	Sensitivity	Specificity	p value
NLR	3	0.724	0.55	0.89	70.4	72.2	0.032
PNI	46	0.779	0.62	0.94	82	77.8	0.008

CI: Confidence interval, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

Table 3. Univariate and Multivariate Analysis of Potential Prognostic Factors for Progression-Free Survival

Parameters	Univariate		Multivariate	
	HR (95% CI)	p value	HR (95% CI)	p value
ECOG performance score	1.626 (1.124-2.348)	<0.001	1.354 (1.046-2.128)	**0.005**
Number of metastatic site (0-1 vs ≥ 2)	1.650 (1.154-2.455)	0.004	1.432 (1.054-2.122)	**0.035**
MSKCC index				
Favorable		Ref		
Intermediate	1.642 (1.104-2.450)	0.001	1.268 (1.116-2.096)	**0.044**
Poor	3.454 (1.760-5.870)	<0.001	2.876 (1.136-3.986)	**0.001**
NLR	1.764 (1.242-2.432)	0.008	1.282 (0.808-1.816)	0.147
PNI	2.450 (2.052-3.985)	<0.001	1.934 (1.244-2.978)	**0.033**

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

Tablo 4. Univariate and Multivariate Analysis of Potential Prognostic Factors for Overall Survival

Parameters	Univariate HR (95% CI)	p value	Multivariate HR (95% CI)	p value
ECOG performance score	2.154 (1.348-3.246)	<0.001	2.114 (1.264-3.175)	**0.006**
Number of metastatic site (0-1 vs ≥ 2)	1.856 (1.124-2.774)	0.002	1.356 (1.084-2.243)	**0.038**
MSKCC index				
Favorable		Ref		
Intermediate	1.784 (1.108-2.789)	0.001	1.456 (1.008-2.564)	**0.013**
Poor	4.876 (1.986-8.142)	<0.001	3.468 (1.126-7.168)	**<0.001**
NLR	1.936 (1.237-2.652)	0.003	1.632 (1.112-2.442)	**0.034**
PNI	2.875 (1.984-3.964)	<0.001	1.568 (1.030-2.466)	**0.044**

HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, MSKCC: Memorial Sloan Kettering Cancer Center, NLR: Neutrophil-to-lymphocyte ratio, PNI: Prognostic nutritional index

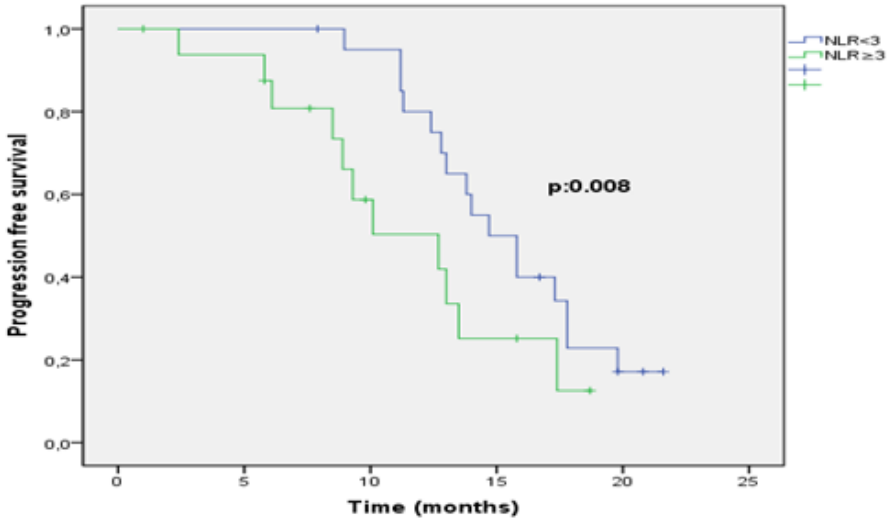


Figure 1a. Progression free survival times according to NLR

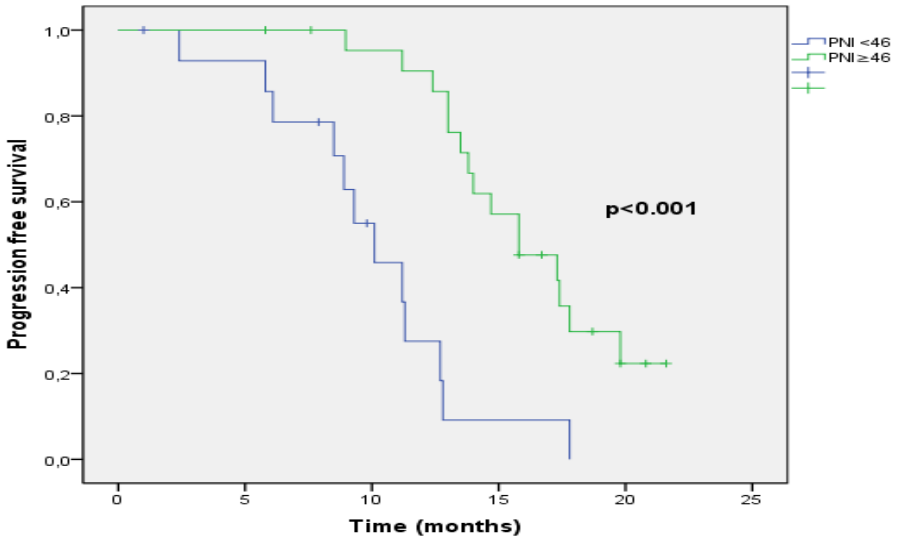


Figure 1b. Progression free survival times according to PNI

http://dx.doi.org/10.36472/msd.v7i4.370

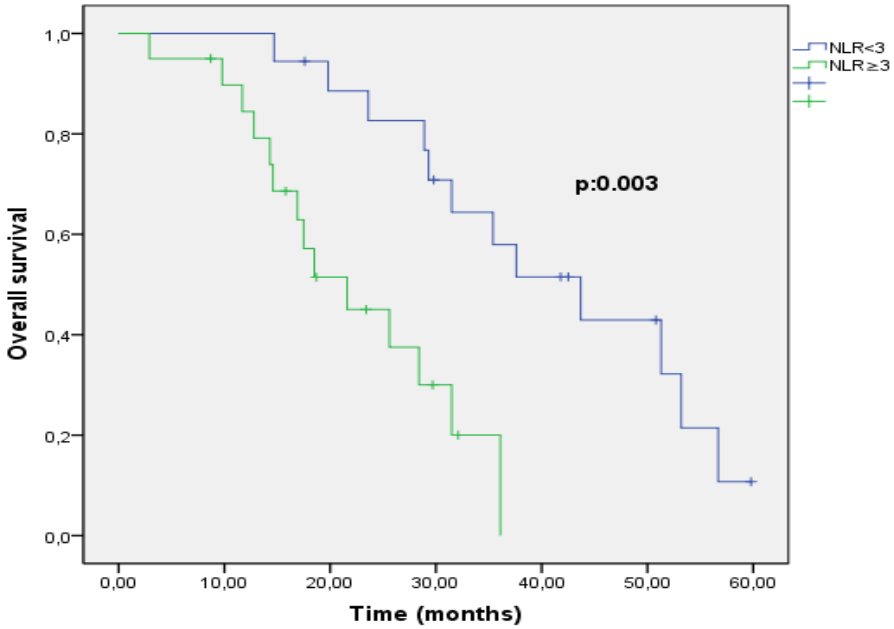


Figure 2a. Overall survival times according to NLR

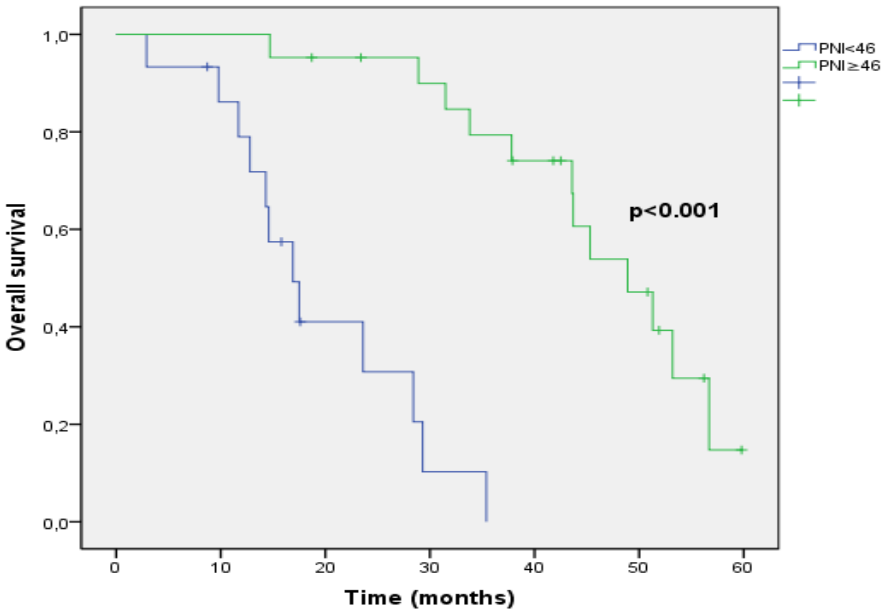


Figure 2a. Overall survival times according to PNI

Discussion

RCC is the most common cancer of the kidney, and about half of the patients with RCC eventually move on to the metastatic stage, where 5-year survival is quite low. In the literature it was showed that significant advances have been achieved in mRCC management by proving the therapeutic effects of TKIs such as sunitinib, pazopanib sorafenib that increase PFS and OS in patients with mRCC (12). However, new prognostic clinical markers are needed for these targeted agents. We evaluated the clinicopathological results of 38 patients with mRCC who used sunitinib or pazopanib as primary care targeted therapy, and found that NLR was an independent prognostic marker for OS and PNI was an independent prognostic marker for PFS and OS in our study. In our study, we analyzed the factors affecting PFS and OS in patients using sunitinib or pazopanib as a first-line tyrosine kinase inhibitor with or without previous history of using INF-α. Similar survivals have been demonstrated in the use of both agents in patients with mRCC, and there has been an overall survival expectancy of 22.9 to 26.4 months (13, 14) and is consistent with our study. The relationship between tumor development and inflammation has been evaluated for many years, and tumor-promoting inflammation is now considered as an important step in the cancer development (15,16). It is also known that tumor progression is not only related to the biological structure of the tumor, but also it is associated

with acute phase proteins such as albumin, C-reactive protein, and serum levels of components that make up the inflammatory response such as lymphocyte, platelet, white blood cells, etc. (17). Similarly, neutrophils are inflammatory markers known to be the main component of the tumor microenvironment, which are produced in response to cytokines with increased release due to aggressive tumor biology and tumor load (18,19). Recently, various combinations of these factors have been investigated quite frequently as inflammatory markers in determining the prognosis of various cancers. High NLR value before treatment has been shown to be an independent risk factor for short survival in many types of cancer such as gastric cancer (20), ovarian cancer (21), pancreatic cancer (22). In a study conducted by Keizman D et al. (23) in patients with mRCC receiving sunitinib, the cut off value 3 for NLR was found to be an independent risk factor for PFS and OS. In our study, in which the same cut off value was taken for NLR, the high NLR value was prognostic for short PFS and OS, but it was only an independent risk factor for OS. NLR was not determined as an independent risk factor for PFS, and this may be related with the limited number of patients included in the study. PNI, calculated by serum albumin level and total lymphocyte count in peripheral blood, gives an idea about the nutritional and immunological status of patients and can be used as a prognostic marker for survival rates (24). Albumin is frequently used as an indicator of nutritional status, and studies have proven that its low concentration is an independent indicator of long-term outcomes in various types of cancer, such as breast (25), colorectal (26), and hepatocellular cancer (27). Lymphocytes are an important component of cell-mediated immunity, which plays an important role in defending against cancer. Low lymphocyte count may be associated with inability to defend against cancer by causing weakness in immunological response (28). In addition, tumor-infiltrating lymphocytes are an important component of the anti-tumor response and more tumor-infiltrating lymphocytes are associated with stronger antitumor response and better survival (29-31). All these findings brought to mind the idea that PNI can be used as a prognostic marker for survival in cancer patients, and this theory has been supported by a growing number of recent studies (32, 33). In our study, PNI level was significantly associated with OS and PFS in univariate and multivariate analyzes, and longer survival was achieved in patients with high PNI level. In the non-inferiority study, it has been proven that pazopanib and sunitinib are equally effective in the treatment of mRCC. Also in this study, MSKCC index and performance status were determined as factors that were affecting the survival (34). When we evaluated patients receiving sunitinib and pazopanib as a single group and made their survival analysis, MSKCC index and ECOG performance status were determined as independent factors affecting survival in accordance with the literature.

The fact that the study was retrospective, single-centered and with a small sample size may have caused bias in the analysis of the results, and this is the major limitation of our study. The other limitation was the inability to form a homogenous group in terms of the use of INF-α and the relationship between dynamic changes of the inflammatory markers and the survival during the treatment

Conclusion

After the use of TKI in the treatment of mRCC, and there has been a need for markers to predict the treatment response. Our study showed that PNI was an independent prognostic marker for PFS and OS and NLR was an independent prognostic marker only for OS in mRCC patients using sunitinib or pazopanib. While the NLR value reflects the only inflammatory state but the PNI value also shows the nutritional state, and the fact that the nutritional state is an important prognostic factor for mRCC may have caused this condition.

Acknowledgments, Funding: None

Conflict of interest and financial disclosure: The authors declare that there is no conflict of interest and financial relationships.

Author's contiributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Mahmut Buyuksimsek and Ali Ogul. The first draft of the manuscript was written by Mahmut Buyuksimsek and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conceptualization: Mahmut Buyuksimsek, Methodology: Ali Ogul; Formal analysis and investigation: Mahmut Buyuksimsek; Writing - original draft preparation: Mahmut Buyuksimsek; Writing - review and editing: Mahmut Buyuksimsek; Supervision: Ali Ogul.

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Kang M, Yu J, Sung HH, Jeon HG, Jeong BC, Park SH, et al. Prognostic impact of the pretreatment aspartate transaminase/alanine transaminase ratio in patients treated with first-line systemic tyrosine kinase inhibitor therapy for metastatic renal cell carcinoma. Int J Urol. 2018 Jun;25(6):596–603.

2. Escudier B, Albiges L, Sonpavde G. Optimal management of metastatic renal cell carcinoma: Current status. Drugs. 2013 Apr;73(5):427–38.

3. Kowalewska M, Nowak R, Chechlinska M. Implications of cancer-associated systemic inflammation for biomarker studies. Biochim Biophys Acta. 2010 Dec;1806(2):163–71.

4. Xin-Ji Z, Yong-Gang L, Xiao-Jun S, Xiao-Wu C, Dong Z, Da-Jian Z. The prognostic role of neutrophils to lymphocytes ratio and platelet count in gastric cancer: A meta-analysis. Int J Surg. 2015 Sep;21:84–91.

5. Peng B, Wang YH, Liu YM, Ma LX. Prognostic significance of the neutrophil to lymphocyte ratio in patients with non-small cell lung cancer: A systemic review and meta-analysis. Int J Clin Exp Med. 2015 Mar;8(3):3098–106.

6. Huang J, Dahl DM, Dong L, Liu Q, Cornejo K, Wang Q, et al. Preoperative Neutrophil-to-Lymphocyte Ratio and Neutrophilia Are Independent Predictors of Recurrence in Patients with Localized Papillary Renal Cell Carcinoma. Biomed Res Int. 2015 Sep;2015.

7. Onodera T, Goseki N, Kosaki G. Prognostic Nutritional Index in gastrointestinal surgery of malnourished cancer patients [in Japanese]. Nihon Geka Gakkai Zasshi 1984 Sep;85:1001-5.

8. Schwegler I, Von Holzen A, Gutzwiller JP, Schlumpf R, Mühlebach S, Stanga Z. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. Br J Surg. 2010 Jan;97(1):92–7.

9. Ray-Coquard I, Cropet C, Van Glabbeke M, Sebban C, Le Cesne A, Judson I, et al. Lymphopenia as a prognostic factor for overall survival in advanced carcinomas, sarcomas, and lymphomas. Cancer Res. 2009 Jul;69(13):5383–91.

10. Lien YC, Hsieh CC, Wu YC, Hsu HS, Hsu WH, Wang LS, et al. Preoperative serum albumin level is a prognostic indicator for adenocarcinoma of the gastric cardia. J Gastrointest Surg. 2004 Dec;8(8):1041–8.

11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228–47.

12. Na N, Yao J, Cheng C, Huang Z, Hong L, Li H, et al. Meta-analysis of the efficacy of the pretreatment neutrophil-tolymphocyte ratio as a predictor of prognosis in renal carcinoma patients receiving tyrosine kinase inhibitors. Oncotarget. 2016 Jul;7(28):44039–46.

13. Motzer RJ, Hutson TE, Tomczak P,Michaelson MD, BukowskiRM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan;356:115-24.

14. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010 Feb 20;28(6):1061-8.

15. Lu H, Ouyang W, Huang C. Inflammation, a key event in cancer development. Mol Cancer Res. 2006 Apr;4(4):221–33.

16. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. Nat Rev Immunol. 2004 Aug;4(8):641–8.

17. Maeda K, Shibutani M, Otani H, Nagahara H, Ikeya T, Iseki Y, et al. Inflammation-based factors and prognosis in patients with colorectal cancer. World J Gastrointest Oncol. 2015 Aug;7(8):111.

18. Crusz SM, Balkwill FR. Inflammation and cancer: Advances and new agents. Nat Rev Clin Oncol. 2015 Oct;12(10):584–96.

19. Mantovani A, Cassatella MA, Costantini C, Jaillon S. Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol. 2011 Jul;11(8):519–31.

20. Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. The baseline ratio of neutrophils to lymphocytes is associated with patient prognosis in advanced gastric cancer. Oncology. 2008 Apr;73(3–4):215–20.

21. Cho H, Hur HW, Kim SW, Kim SH, Kim JH, Kim YT, et al. Pre-treatment neutrophil to lymphocyte ratio is elevated in epithelial ovarian cancer and predicts survival after treatment. Cancer Immunol Immunother. 2009 Jan;58(1):15–23.

22. An X, Ding PR, Li YH, Wang FH, Shi YX, Wang ZQ, et al. Elevated neutrophil to lymphocyte ratio predicts survival in advanced pancreatic cancer. Biomarkers. 2010 Sep;15(6):516–22.

23. Keizman D, Ish-Shalom M, Huang P, Eisenberger MA, Pili R, Hammers H, et al. The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. Eur J Cancer. 2012 Jan;48(2):202–8.

24. Pinato DJ, North B V., Sharma R. A novel, externally validated inflammation-based prognostic algorithm in hepatocellular carcinoma: The prognostic nutritional index (PNI). Br J Cancer. 2012 Apr;106(8):1439–45.

25. Lis CG, Grutsch JF, Vashi PG, Lammersfeld CA. Is serum albumin an independent predictor of survival in patients with breast cancer? J Parenter Enter Nutr. 2003 Jan-Feb;27(1):10–5.

26. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY, et al. Low preoperative serum albumin in colon cancer: A risk factor for poor outcome. Int J Colorectal Dis. 2011 Apr;26(4):473–81.

27. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: A systematic review of the epidemiological literature. Nutr J. 2010 Dec;9(1):1–16.

28. Fogar P, Sperti C, Basso D, Sanzari MC, Greco E, Davoli C, et al. Decreased total lymphocyte counts in pancreatic cancer: An index of adverse outcome. Pancreas. 2006 Jan;32(1):22–8.

29. Ivan JC, Ronald B. Impact of the Tumor Microenvironment on Tumor-Infiltrating Lymphocytes: Focus on Breast Cancer. Breast Cancer (Auckl). 2017 Sep;11:1-12

30. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: Results from the FinHER trial. Ann Oncol. 2014 Aug;25(8):1544–50.

31. Berghoff AS, Ricken G, Wilhelm D, Rajky O, Widhalm G, Dieckmann K, et al. Tumor infiltrating lymphocytes and PD-L1 expression in brain metastases of small cell lung cancer (SCLC). J Neurooncol. 2016 Oct;130(1):19–29.

32. Migita K, Takayama T, Saeki K, Matsumoto S, Wakatsuki K, Enomoto K, et al. The prognostic nutritional index predicts long-term outcomes of gastric cancer patients independent of tumor stage. Ann Surg Oncol. 2013 Aug;20(8):2647–54.

33. Nozoe T, Kohno M, Iguchi T, Mori E, Maeda T, Matsukuma A, et al. The prognostic nutritional index can be a prognostic indicator in colorectal carcinoma. Surg Today. 2012 Jun;42(6):532–5.

34. Motzer RJ, Hutson TE, McCann L,Keith D, Choueiri TK.Overall survival in renal-cell carcinoma with pazopanib versus sunitinib. N Engl J Med. 2014 May;370:1769–70.

http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):466-9

Research Article Doi: 10.36472/msd.v7i4.368

TNF-alpha Induces Pro-Inflammatory Factors in Colorectal Cancer Microenvironment

Ahu Pakdemirli[1]*, Gizem Calibasi Kocal[2]

Abstract

Objective: The tumor microenvironment has a crucial role in organizing cancer malignancy, progression, drug resistance and survival. It consists of cellular and non-cellular components. These non-cellular components such as cytokines, extracellular matrix, growth factors and metabolites are responsible for shifting the action from pro-cancer to anti-cancer effects. Twenty percent of all cancers occur in association with chronic inflammation via cytokines. Even cancers that are not caused by chronic inflammation, present high levels of cytokine expression pattern in their tumor microenvironment. Tumor necrosis factor-alpha (TNF-α) and some interleukins are characterized as pro-tumorigenic cytokines and they were involved in cancer by presenting their ability to activate the oncogenic transcription factors. The aim of this study is to evaluate the remodeling of colorectal cancer tumor microenvironment by TNF-α.

Material and Methods: TNF-α (5ng/ml) was applied to HT-29 colorectal cancer cells, then human soluble factors were determined by using Human Cytokine Group 1, 8 plex Panel (Bio-Rad Laboratories Inc. USA) and Magpix Luminex instrument and xPONENT software (version 4.2, Luminex Corp, Austin, Texas, US). The results were normalized to total protein concentration estimated via Bradford assay.

Results: Current research highlights the effect of TNF-α on the tumor microenvironment. Interleukin-6 and interleukin -8 soluble factors were higher in TNF-α treated colorectal cancer cells when compared with untreated control group.

Conclusion: The results of the study show that TNF-α is responsible for elevating the levels of interleukin-6 and interleukin-8, which are associated with inflammation in the tumor microenvironment.

Key words: Colorectal Cancer, Tumor Microenvironment, Cytokines, TNF-α, Interleukin-6, Interleukin-8

Introduction

Colorectal cancer is the third most common cancer in males, while it is in the second most occurring cancer in females. In 2018, 1.8 million newly diagnosed colorectal cancer patient and approximately 861.000 deaths related to colorectal cancer are recorded by the World Health Organization. (GLOBOCAN, 2018) There are plenty of factors that cause colorectal carcinogenesis. One of these factors is a chronic inflammation that could trigger angiogenesis, evading from apoptosis, gene mutations, cell proliferation, epigenetic changes related to cancer development. Despite thorough proofs signifying a crucial role for inflammation colorectal cancer promotion and progression, still, there is comparably little knowledge on inflammation-associated microenvironmental alteration related to neoplasia/hyperplasia development and its progression through invasive colorectal adenocarcinoma (1).

The tumor microenvironment (TME) has a crucial role in organizing of cancer malignancy, progression, drug resistance and, survival, etc. Tumor genotype and phenotype are related to varying of cellular and non-cellular components in TME. The cellular components in TME are immune cells, adipocytes, cancer-associated fibroblasts, pericytes, etc. The non-cellular secreted elements of heterogeneous TME consist of cytokines, DNA, RNA, growth factors, metabolites, matricellular proteins, etc. These non-cellular substances are regulating numerous ways which providing cancer survival and progression via numerous growth signals, metabolites, energy, drug resistance-related environment, evading immune surveillance. These secreted components which are responsible for shifting the action from pro-cancer to anti-cancer effects are considered as novel targets in drug resistance and cancer therapeutics (2).

Received 25-03-2019 **Accepted** 28-04-2020 **Available Online** 29-04-2020 **Published** 30-04-2020
1 University of Health Sciences, Gulhane School of Medicine, Department of Physiology, Kecioren, Ankara, TR
2 Dokuz Eylul University, Institute of Oncology, Department of Translational Oncology, Inciralti, Izmir, TR
*** Corresponding Author:** Ahu Pakdemirli **E-mail:** ahu@pakdemirli.com

Almost 20% of all cancer appears in association with chronic inflammation and infection. Even if those cancers do not arise as a result of inflammation show a wide range of inflammatory infiltrates with increased cytokine expression levels in TME. (3) Cytokines elevate two-way interaction through paracrine signaling between cancer-associated cells in the environment and tumor cells. (4-6) A specific number of those cytokines with different functions such as interleukins (IL), tumor necrosis factor family, TGF-beta family of proteins and interferon family exist in the TME. Cytokines could take part in effect the tumor formation by acting indirectly by stimulating inflammatory cell type and directly as a growth-promoting factor on tumor cells. (7) Tumor necrosis factor-alpha (TNF-α) is one of those inflammatory mediators that is induced in carcinogenesis, via taking a part of chronic inflammatory diseases. (8) Other pro-inflammatory cytokines with a typical pro-tumorigenic effect are IL-6 and 8. Elevated serum IL-6 and 8 levels were discovered in patients with systemic cancers as compared to patients with benign diseases or healthy controls. (9-10)

In the current study, TNF- α induced pro-inflammatory factors interleukin 6 and 8 have been evaluated as inflammation modulators in the tumor microenvironment.

Material and Methods

Cell Culture

HT-29 cell line (CCL-247, ATCC, Rockville, CT, USA) was grown in McCoy's 5A media supplemented with 10% FBS, 2mM L-Glutamine at 37o C in a humidified incubator of %5 CO2. Cells were exposed to 5ng/ml TNF-α (Sigma, St Louis, Missouri, USA) for 48 hours, then soluble factors were measured.

Analysis of Soluble Factors via Multiplexing Assay

According to Bio-Plex Pro assays instruction manual, Human Cytokine Group 1, 8 plex Panel (Bio-Rad Laboratories Inc. USA) was achieved. At first 50 µl of 1x beads were added to the assay plate then wells were washed 2 times with 100 µl wash buffer (Bio-Rad Laboratories Inc. USA) which was provided with kit. After that 50µl of sample were added to each well.

Then the plate was incubated for an hour in dark at RT with shaking at 300 RPM. After incubation, The plates have been (Bio-Rad Laboratories Inc. USA) washed with wash buffer for three times. Subsequently, 25 µl antibody solution (Bio-Rad Laboratories Inc. USA) was added to each well for incubation for 30 min. After that the plate was washed with wash buffer for three times.

The 50 µl Streptavidin-PE (Bio-Rad Laboratories Inc. USA) was added to each well for incubation for 30 min. Finally, the plate was washed with 120 µl of assay buffer (Bio-Rad Laboratories Inc. USA) which was provided with kit.

The fluorescent signal was measured by a CCD imager and the concentrations of the analyte were determined with both Bio-Plex Manager and MAGPIX®- Luminex xPONENT software (Bio-Rad Laboratories Inc. USA).

Statistical analysis: SPSS V.15.0 (SPSS, Chicago, Illinois, USA) was used for the data analysis. The mean ± the SE (standard error) was used for numerical values found in the figures and text.

A non-parametric Mann Whitney U test was used to determine the statistical significance. All p-values <0.05 were considered statistically significant.

Results

In this study remodeling of colorectal cancer tumor microenvironment after TNF-α induction was evaluated. The graph showed that significantly elevated IL-6 and 8 levels after 48 hours of TNF-α exposure (Figure 1) (p-value <0.05). Data for each group with mean and standard error showed on Table 1.

In TNF-α treated group, IL-6 amount was measured as 27 pg/ml, while untreated group IL-6 amount was 10 pg/ml. Overall IL-6 level was increased 2.7 fold in TNF-α treated group. IL-8 level was elevated more than IL-6. In TNF-α treated group, IL-8 amount was measured as 595 pg/ml, while untreated group was 23 pg/ml. IL-8 level was increased 25.9 fold when compared with untreated control group.

Table 1. Stimulated levels of IL-6 and IL-8 cytokines (pg/ml) after a 48-h exposure with TNF-α.

	Interleukin-6		Interleukin-8	
	Untreated	TNF-α treated	Untreated	TNF-α treated
Mean (pg/ml)	10	27	23	595
Min-Max	8 - 12	24 - 30	18 - 28	493 - 697
SEM	0.9522	1.299	2.380	54.73
P-Value	0.0003		< 0.0001	
Fold change	2.7		25.9	

http://dx.doi.org/10.36472/msd.v7i4.368

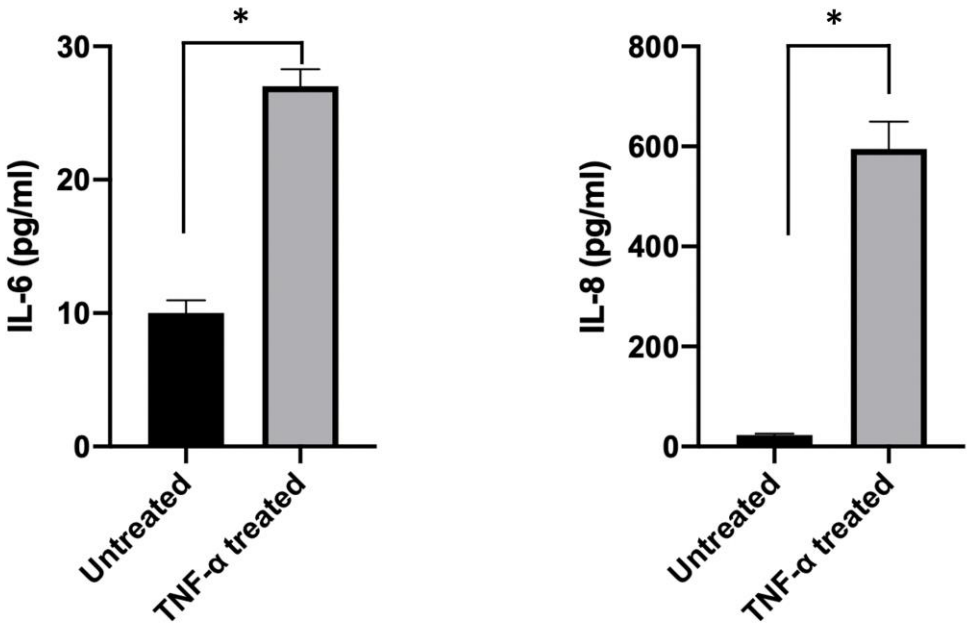


Figure 1. The expression pattern of IL-6 and IL-8 soluble factors in TNF-α treated and control (untreated) group.

Discussion

Inflammation in cancer is guided by chemokines, cytokines and soluble factors. These factors are secreted by tumor cells or tumor microenvironment secretes them by their recruited cells. Cytokines encourage tumor cell growth, differentiation, and survival. Most of the cytokines play roles in metastasis, epithelial-mesenchymal transition, angiogenesis, invasion, proliferation via transforming the intestinal epithelial cells (IECs) and, apoptosis. Cytokines trigger cancer-associated fibroblasts to secrete growth factors that inflect tumor microenvironment (1). Inflammatory (or pro-inflammatory) cytokines are secreted by macrophages, helper T cells and other certain cell types that develop inflammation. Pro-inflammatory interleukins consist of IL-1, IL-2, IL-6, IL-8, and TNFα (11). Fundamental secretion of the pro-inflammatory interleukins leads to an inflammation in the intestine and is thought to increase the risk for colon and rectal cancer development (12). Increased expression of IL-6 is associated with an expanded risk of colorectal adenomas. IL-6 is also a strong stimulator of colon cancer cell growth and proliferation. This growth implicates the expansion of other cancer cell lines and primary tumors.

TNF-α and IL-6 or transcription factors of these cytokines, such as NF-κB and STATs, certainly appear as potential targets for anticancer therapy (13). The tumor-promoting features of TNF-α are presumably linked to its capacity to activate NF-κB and AP-1 signaling pathways that provoke cell proliferation and survival (14). In our study, it was observed that TNFα increases the secretion levels of IL-8 and IL-6 on HT-29 colorectal cancer cell line. Similarly, Edwardson et al. evaluated that an increased amount of cytokines expands the effectiveness of the drug in the cell microenvironment (15).

Conclusion

TNF- α and IL-6 are presumably the best identified pro-tumorigenic cytokines and they were primarily suspected to be involved in cancer development because of their ability to activate the oncogenic transcription factors STAT3 (IL-6), AP-1 (TNF) and NF-κB in epithelial cells.

Even though preclinical data are highly supportive about the effect of drugs that target pro-inflammatory tumor microenvironment on tumor cell growth and survival, clinical trials will need to arrange to approve their impact in patients. Also, these drugs should be determined whether they will be beneficial as single agents or should they be used in combination with standard cytotoxic therapies (13).

Acknowledgments: We sincerely thank to Ezgi DAŞKIN, Tolga SEVER and Aslıhan KARADAG for their support during the entire study process

Conflict of interest and financial disclosure: The authors declare that there is no conflict of interest and financial relationships.

Author's contiributions: HP, GCK: Design of study, Invitro studies, Data analyzes and statistics, Revisions

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Patel H, Nilendu P, Jahagirdar D, Pal JK, et al. Modulating secreted components of tumor microenvironment: A masterstroke in tumor therapeutics. Cancer Biol Ther. 2018;19(1): 3–12.

2. Colotta F, Allavena P, Sica A, Garlanda C, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30:1073-81.

3. Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation. Nature. 2008;454:436–44.

4. Matsumoto S, Hara T, Mitsuyama K, et al. Essential Roles of IL-6 Trans-Signaling in Colonic Epithelial Cells, Induced by the IL-6/soluble-IL-6 Receptor Derived From Lamina Propria Macrophages, on the Development of Colitis-Associated Premalignant Cancer in a Murine Model J Immunol. 2010;184: 1543–51.

5. Ernst M, Najdovska M, Grail D, et al. STAT3 and STAT1 mediate IL-11-dependent and inflammation-associated gastric tumorigenesis in gp130 receptor mutant mice. J Clin Invest. 2008;118: 1727–38.

6. Becker C, Fantini MC, Wirtz S, et al. IL-6 signaling promotes tumor growth in colorectal cancer. Cell Cycle. 2005;4:217–20.

7. Rigby RJ, Simmons JG, Greenhalgh CJ, et al. Suppressor of cytokine signaling 3 (SOCS3) limits damage-induced crypt hyper-proliferation and inflammation associated tumorigenesis in the colon. Oncogene. 2007;26:4833–41.

8. Popa C, Netea MG, Van Riel P. LCM, et al. The Role of TNF-alpha in Chronic Inflammatory Conditions, Intermediary Metabolism, and Cardiovascular Risk. J Lipid Res. 2007;48(4):751–62.

9. Kumari N, Dwarakanath, BS, Das A, Bhat AN. Role of interleukin-6 in Cancer Progression and Therapeutic Resistance. Tumor Biol. 2016;37(9):11553–72.

10. Bărbălan A, Streața I, Ivan ET, et al. Interleukin-8 mRNA Expression in Locally Advanced Colorectal Cancer Patients. Curr Health Sci J. 2017;43(3):209–13.

11. Bondurant KL, Lundgreen A, Herrick JS, et al. Interleukin Genes and Associations with Colon and Rectal Cancer Risk and Overall Survival. Int J Cancer. 2013;132(4):905-15.

12. Janos Terzić 1, Sergei Grivennikov, Eliad Karin, Michael Karin. Inflammation and Colon Cancer. Gastroenterology. 2010;138(6):2101-14.

13. Klampfer L. Cytokines, Inflammation and Colon Cancer. Curr Cancer Drug Targets. 2011;11(4):451-64.

14. Grivennikov SI, Karin M. Inflammatory Cytokines in Cancer: Tumour Necrosis Factor and Interleukin 6 Take the Stage. Ann Rheum Dis. 2011;70(1):104-08.

15. Edwardson DW, arissenti AM, Kovala AT. Chemotherapy and Inflammatory Cytokine Signalling in Cancer Cells and the Tumour Microenvironment. Adv Exp Med Biol. 2019;1152:173-215.

http://www.medscidiscovery.com

OPEN ACCESS JOURNAL ISSN: 2148-6832

MSD Medical Science and Discovery
2020; 7(4):470-4

Research Article Doi: 10.36472/msd.v7i4.372

Bone marrow plasma cell ratio, is it must to evaluate before autologous stem cell transplantation in multiple myeloma?

Semih Başcı[1], Tuğçe Nur Yiğenoğlu[1], Mehmet Bakırtaş[1], Bahar Uncu Ulu[1], Derya Şahin[1], Tahir Darçın[1], Jale Yıldız[1], Dicle İskender[1], Nuran Ahu Baysal[1], Mehmet Sinan Dal[1], Merih Kızıl Çakar[1], Fevzi Altuntaş[1]

Abstract

Objective: Complete remission in multiple myeloma (MM) is a defined as having a <5% bone marrow plasma cell (BMPC) ratio plus negative serum and urine immunofixation tests. However, it is necessary to reassess whether or not the bone marrow plasma cell ratio should be determined before transplantation in secretory multiple myeloma patients. A significant decrease in monoclonal protein levels or having negative serum and urine immunofixation tests after induction therapy might be enough to indicate chemo-sensitivity.

Material and Methods: In this study, the data of 177 multiple myeloma patients that underwent autologous stem cell transplantation (ASCT) in our center were retrospectively evaluated.

Results: We found a statistically significant difference in the post-ASCT response rates between the patients with a pre-ASCT BMPC ratio <5% vs BMPC ratio ⩾5% (p:<0.001*). The 2-year progression-free survival (PFS) of the patients with BMPC ratio <5% and ⩾5% post-ASCT was found 24% and 25% (median PFS 11 months (95% CI; 6,68-15,31) vs 12 months (95% CI; 9,47-14,53)) respectively (p: 0.900). The 2-year overall survival (OS), was 67% and 63% (median OS 35 months (95% CI; 25,59-44,41) vs 40 months (95% CI; 27,52-52,47)) respectively (p: 0.341).

Conclusion: Patients with decreasing monoclonal protein in serological tests, the pre-ASCT BMPC ratio was not found to have an impact on neutrophil and platelet engraftment durations, transplantation related mortality (TRM), PFS and OS. Our study suggests that in MM patients with measurable disease, it is not required to evaluate the BMPC ratio if serologic response exists.

Keywords: multiple myeloma, bone marrow, plasma cell ratio, stem cell transplantation

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy. It is originated from monoclonal malignant plasma cells. The peak incidence of MM is in the seventh decade. Significant improvements in prognosis are observed with the addition of many novel agents to treatment options (1-5). Currently, induction therapy with novel agents followed by high-dose melphalan conditioning and autologous stem cell transplantation (ASCT) are considered to be the standard of care in newly diagnosed eligible MM patients (6,7).

Complete remission (CR) in MM is defined as having a <5% bone marrow plasma cell (BMPC) ratio with negative serum and urine immunofixation (IFE) tests (8). Besides, International Myeloma Working Group (IMWG) recommended a more advanced complete remission category described as having normal serum free light chain (FLC) ratio and absence of clonal cells in bone marrow (9). Yet, a few studies were conducted to clarify the significance of BMPC ratio in CR (10-12).

Applying novel agents provided deeper treatment responses and CR rates increased, and the reevaluation of the prognostic effect of achieving CR pre-ASCT became a requisite condition. Kim et al. showed that pre-ASCT CR is an important prognostic factor for better survival. In their study, they assumed all patients with negative serum and urine IFE tests as CR. Bone marrow evaluation was not necessary for patients to be assumed as a CR (12).

In the era of novel agents, there is a need to reevaluate the definition and also the importance of pre-ASCT CR. Besides, it was believed that residual MM cells persisting in the bone marrow despite myeloablative chemotherapy, play a major role in relapse but studies on different purging technics pre-ASCT could not provide a significant non-relapse survival advantage.

Received 14-04-2019 **Accepted** 28-04-2020 **Available Online** 29-04-2020 **Published** 30-04-2020
1 University of Health Sciences, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, Dept of Hematology and Bone Marrow Transplantation Center Ankara, TR
*** Corresponding Author:** Semih Başcı **E-mail:** dr.semihbasci@gmail.com

http://dx.doi.org/10.36472/msd.v7i4.372

Therefore it is needed to reveal whether it is really necessary to evaluate pre-ASCT BMPC ratio in patients with measurable monoclonal (M) protein levels at diagnosis and now having a serological treatment response after induction chemotherapy (CR or lower).

In this study, the data of MM patients who underwent ASCT were retrospectively analyzed to find out whether or not the evaluation of pre-ASCT BMPC ratio before had an additional prognostic impact in addition to urine and serum IFE.

Material and Methods

The results of 177 MM patients with measurable M protein levels at diagnosis, underwent ASCT at our center between 2009 and 2018 were analyzed retrospectively. The study was approved by the local ethical committee. The patients' characteristics, myeloma related data and pre-ASCT response are given in Table 1.

Table 1: Patients characteristics

Parameters	Patient Population (n=177)
Age (median)	56 (29-81)
Gender	
Female	69
Male	108
ISS	
ISS I	50
ISS II	53
ISS III	45
Not evaluated	29
Durie Salmon	
DS1	6
DS2	14
DS3	152
Not evaluated	5
Pre-transplantation response	
CR	74
VGPR	45
PR	41
Stable	12
Refractory	5
Chemotherapy line(s)	
1 line	47
2 lines	101
3 lines	22
4 lines	2
5 lines	1
Not evaluated	4
Melphalan	
140mg/m^2	21
200mg/m^2	156
Renal Failure (GFR<50 ml/min)	
Present	9
None	168
Radiotherapy	
Applied	29
None	148
CD34$^+$ cells infused	4.62 x10^6 /kg (2-13,4)

All patients underwent peripheric blood stem cell (PBSC) harvesting. Mobilization of 130 patients were with granulocyte-colony stimulant factor (G-CSF, 10µg/kg), 21 patients were with cyclophosphamide (4.000 mg/m2) plus G-CSF and 6 patients were with plerixafor. 20 patients data regarding mobilization was not available or were applied the non-standard mobilization regimens. Patients older than 70 and/or patients with creatinin higher than 2 mg/dL received lower dose of melphalan 140 mg/m2 as the conditioning regimen, and the other patients received standard dose 200 mg/m2. Patients underwent tandem ASCT were not included in the study.

The overall survival (OS) was termed as the period of time to death or latest follow-up for surviving patients. The progression-free survival (PFS) was termed as the period of time to progression or death or latest follow-up for patients in remission. Engraftment was defined, without any support following 3 days for neutrophil to have absolute neutrophil count (ANC) >500/mm3 and for platelet to have >20000/mm3 (13-17).

Bone marrow aspiration and biopsy were performed before PBSC mobilization. Plasma cell counts were evaluated after CD138 immune staining. To verify the plasma cell, lambda and kappa immune staining were performed. Bone marrow aspiration evaluation was carried out with 500 cell counts.

International Staging System (ISS) and Durie-Salmon Stages (DS) were used staging at diagnosis and treatment response was determined according to the criteria of IMWG (18). Serological CR was described as the absence of identifiable M protein in serum and urine protein electrophoresis (PEP) plus negative IFE.

IBM SPSS Statistics (version 21) was used for statistical analysis. Descriptive statistics were applied to present the data. Categorical data was presented as a ratio, and numerical data was presented as median and mean ± standard deviation. The differences between neutrophil and platelet engraftment times between bone BMPC ratio groups (<5% vs ⩾5%) were investigated by the non-parametric Mann Whitney U test. Chi-square and Fisher exact tests were used to determine the difference between post-transplant response and BMPC ratio groups. Kaplan-Meier survival analysis was applied for PFS and OS and log-rank test were used to examine the factors affecting survival. P values of ⩽0.05 were considered statistically significant.

Results

The 108 (61%) of the 177 MM patients included in the study were females, and 69 (39%) were males. The median age was 56 (range 29-81) and the median disease duration before ASCT was 10 months (range 3-67 months). Median post-transplant follow up was 26 months (range 1 -109 months). Durie-Salmon stages I, II, and III at diagnosis constituted 3.4%, 7.9%, and 85.9% of the patients respectively. 2.8% of the patients' stages at the time of diagnosis could not be reached from the records.

http://dx.doi.org/10.36472/msd.v7i4.372

Before PBSC mobilization, we obtained complete response (CR) in 74 (41.8%) patients, very good partial response (VGPR) in 45 (25.4%) patients and partial response (PR) in 41 (23.2%) patients among 177 patients. According to the immunohistochemical examination of bone marrow biopsy performed before PBSC mobilization, we found 128 (72.3%) patients with bone marrow plasma cell (BMPC) ratio <5% and 49 with (27.7%) ⩾ 5%.

All patients with negative serum and urine IFE were found to have a BMPC ratio <5%. We found that patients with VGPR response, BMPC ratio <5% was in 30 (66.7%) patients and BMPC ratio ⩾5% was in 15 (33.3%) patients. We found among the patients with PR response, BMPC ratio <5% was in 18 (43.9%) patients and BMPC ratio ⩾ 5% was in 23 (56.1%) patients.

The neutrophil and platelet engraftment durations of the patients with pre-ASCT BMPC ratio <5% and BMPC ratio ⩾5% was found similar. In both groups, neutrophil engraftment occurred in median of 11 days whereas platelet engraftment occurred in median of 12 days.

While the transplant-related mortality (TRM) rate was 1.1% among the patients with pre-ASCT BMPC ratio <5% TRM rate was found 0.6% in patients with BMPC ratio ⩾ 5%. No statistically significant difference was found between groups regarding TRM rates (p:0.825).

Among the patients with pre-ASCT BMPC ratio <5%, the post-ASCT response rates were 78.9% CR, 10.2% VGPR and 6.3% PR respectively (4.6% of the patients' post-ASCT response rates could not be reached from the records).

Among the patients with pre-ASCT BMPC ratio ⩾5%, the post-ASCT response rates were 49% CR, 8.2% VGPR, 26.5% PR, 6.1% stable disease, and 6.1% progressive disease respectively (4.1% of the patients' post-ASCT response rates could not be reached from the records).

We found a statistically significant relationship between groups regarding the post-ASCT response rates (p: <0.001*).

Among the patients with BMPC ratio <5% and ⩾5%, the 2-year PFS was 24% and 25% (median PFS 11 months (95% CI; 6,68-15,31) versus 12 months (95% CI; 9,47-14,53)) respectively. No statistically significant relationship was found between the BMPC ratio and PFS post-ASCT (p: 0.900, Fig. 1). Among the patients with BMPC ratio <5% and ⩾5%, the 2-year OS was 67% and 63% (median OS 35 months (95% CI; 25,59-44,41) versus 40 months (95% CI; 27,52-52,47)) respectively. No statistically significant relationship was found between the BMPC ratio and OS post-ASCT (p:0.34, Fig.2).

The patients were divided into 5 groups according to their response rates before transplantation and BMPC ratio (CR and <5% BMPC ratio; VGPR and <5% BMPC ratio; VGPR and ⩾5% BMPC ratio; PR and <5% BMPC ratio; PR and ⩾5% BMPC ratio). When these 5 groups were compared with respect to PFS and OS, we did not find a statistically significant difference among the groups (p=0.439 and p=0.823 respectively) (Table 2).

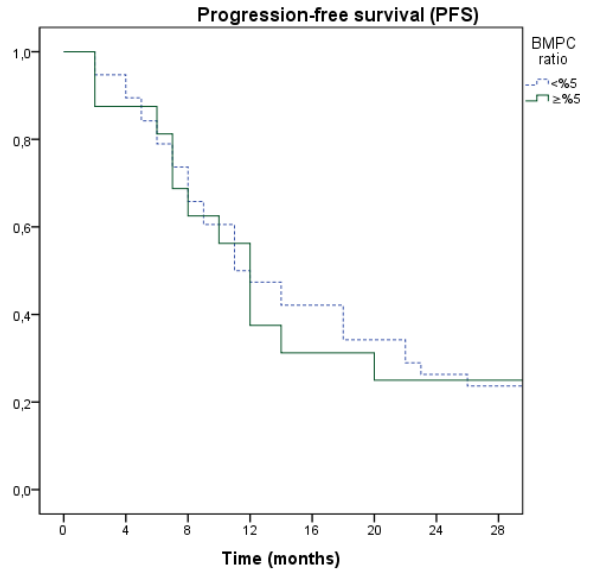


Figure 1: Progression-free survival and Bone Marrow Plasma Cell Ratio

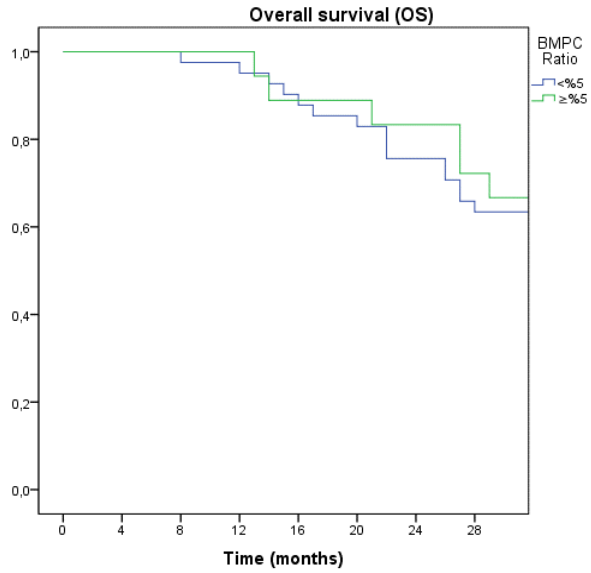


Figure 2: Overall survival and Bone Marrow Plasma Cell Ratio

 http://dx.doi.org/10.36472/msd.v7i4.372

Table 2: The relationship between Pre-transplantation response, Bone Marrow Plasma Cell (BMPC) Ratio and Progression-Free Survival (PFS), Overall Survival (OS)

Pre- transplantation response, Bone marrow plasma cell ratio	n	PFS (months) 95% CI Median(min-max)	OS (months) 95% CI Median(min-max)
CR, BMPC ratio< 5%	74	14 (0,85-27,14)	38 (24,85-51,14)
VGPR, BMPC ratio < 5%	30	11 (6,61-15,38)	33 (15,47-50,53)
VGPR, BMPC ratio ≥ 5%	15	14 (5,41-22,58)	27 (0-79,92)
PR, BMPC ratio < 5%	18	9 (3,86-14,13)	34 (28,15-39,84)
PR, BMPC ratio ≥ 5%	23	8 (2,83-13,16)	40 (26,05-53,94)
P Value		p=0.439	p=0.823

CR: complete remission, VGPR: very good partial remission, PR: partial remission, CI: confidence interval

Discussion

CR is described as having a <5% BMPC ratio in addition to para-protein absence that could be identified with serum and urine IFE negativity lasting for at least 6 weeks (8-12,18-19). However, it is necessary to evaluate whether or not the BMPC ratio should be determined before ASCT in patients MM with measurable disease at diagnosis and have a treatment response after induction therapy. Regression in the initial M protein levels might be enough to indicate chemo-sensitivity in secretory MM patients. Therefore, studies comparing the transplantation outcome of the CR patients and serologically CR with BMPC ratio ⩾5% are required. However, the number of studies conducted on this subject is quite limited. Similarly, studies researching the impacts of BMPC ratios during and after the transplantation in secretory MM patients with serological response are required. In such secretory MM patients, it could be specified whether or not the evaluation of bone marrow plasma ratio is necessarily required along with an absence of M protein in serum and urine IFE or its decrease for the prediction of the ASCT outcome.

In the study conducted by Lee et al. with 106 MM patients, the evaluation of BMPC ratio performed before PBSC mobilization in addition to the serological evaluation with serum and urine IFE on MM patients that underwent ASCT was indicating as a predictor of the disease progression. The prognostic impact of the BMPC ratio has been more evident found out between groups of serological CR and not having a serological CR. Among the patients with not having a serological CR, when the patients with BMPC ratio <5% and ⩾5% were compared, longer PFS and OS were found in patients with BMPC ratio <5% (20). However, in our study, we did not have any patients having a serological CR and BMPC ratio ⩾5% before PBSC mobilization. In the response evaluation conducted before PBSC mobilization, we did not find a statistically significant difference between OS and PFS durations when VGPR and PR response patients were compared after grouped as BMPC ratio <5% and ⩾5%.

These results also suggest that finding a decrease of M protein with serum and urine IFE after an induction treatment of MM patients with measurable disease at diagnosis is sufficient, and the evaluation of the BMPC ratio is not necessarily required.

Because our results indicated that the BMPC ratio evaluation carried out pre-ASCT did not have any impacts on OS and PFS after transplantation. As the BMPC ratio evaluation did not have any impacts on predicting OS and PFS in post-ASCT, its effect on the process of ASCT could not be displayed, either. We did not find any statistically significant difference between the BMPC ratio <5% and ⩾ 5% conducted pre-ASCT with respect to the duration of neutrophil and platelet engraftment and TRM.

Regardless of serological response, the higher CR rate was found in response evaluation after 3 months post-ASCT in patients with pre-ASCT BMPC ratio <5% in comparison to BMPC ratio ⩾5%; however, this did not reflect on PFS and OS.

Conclusion

The number of studies conducted on the impact of the BMPC ratio carried out pre-ASCT on the transplantation outcome is quite limited. In our study, we did not find any impacts of the evaluation of the BMPC ratio before ASCT on the durations of neutrophil and platelet engraftment, TRM rates, and PFS and OS duration in the patients whose M protein were found decreased in the serological test. Limitation of the study was, we did not have any serological CR patients with ⩾5% BMPC ratio, we were unable to evaluate BMPC ratio impacts on serological CR patients. As a conclusion, our study suggests that in MM patients who have measurable disease at diagnosis, it is not required to evaluate the BMPC ratio if serologic response exists.

Author's contributions: Design of the study: **S.B., T.N.Y.**; Literature search: **T.N.Y., M.B.**; Material preparation: **B.U.U. T.D.**; Data collection: **M.B., D.Ş.**; Analysis: **S.B., J.Y.**; Preparation of article and revisions: **S.B., D.İ., N.A.B., T.N.Y.**; Supervision and critical review: **M.K.Ç., M.S.D., F.A.**

Conflict of interest and financial disclosure: The authors declare that there is no conflict of interest and financial relationships.

Ethical issues: Author declare, originality and ethical approval of research. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

References

1. Brenner H, Gondos A, Pulte D. Recent major improvement in long-term survival of younger patients with multiple myeloma. Blood 2008; 111: 2521–2526.

2. Kumar SK, Rajkumar SV, Dispenzieri A et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111: 2516–2520.

3. Kastritis E, Zervas K, Symeonidis A et al. Improved survival of patients with multiple myeloma after the introduction of novel agents and the applicability of the International Staging System (ISS): an analysis of the Greek Myeloma Study Group (GMSG). Leukemia 2009; 23: 1152–1157.

4. Kyle RA, et al. Long-term survival in multiple myeloma. N Engl J Med. 1983; 308(6): 314–316.

5. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.

6. Palumbo A, Cavallo F. Have drug combinations supplanted stem cell transplantation in myeloma? Hematology Am Soc Hematol Educ Program 2012; 2012: 335–341.

7. Harousseau JL. Autologous transplantation for multiple myeloma. Ann Oncol 2008; 19 (Suppl 7): vii128–vii133.

8. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol. 1998; 102(5):1115-1123.

9. Kyle RA and Rajkumar SV, "Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma," Leukemia 2009; vol.23, no.1, pp.3–9.

10. Rajkumar SV, Fonseca R, Dispenzieri A et al., "Effect of complete response on outcome following autologous stem cell transplantation for myeloma," Bone Marrow Transplantation 2000; vol.26, no.9, pp.979–983.

11. Rajkumar SV, Fonseca R, Lacy MQ, et al., "Beta2-microglobulin and bone marrow plasma cell involvement predict complete responders among patients undergoing blood cell transplantation for myeloma," Bone Marrow Transplantation 1999; vol.23, no.12, pp.1261–1266.

12. Kim JS, Kim K, Cheong J-W, Min YH, Suh C, Kim H, et al. Complete Remission Status Before Autologous Stem Cell Transplantation Is an Important Prognostic Factor in Patients with Multiple Myeloma Undergoing Upfront Single Autologous Transplantation. Biol Blood Marrow Transplant [Internet]. 2009; 15(4):463–70.

13. Dreger P, Klöss M, Petersen B et al. Autologous progenitor cell transplantation: prior exposure to stem cell-toxic drugs determines yield and engraftment of peripheral blood progenitor cell but not of bone marrow grafts Blood 1995; 86: 3970-3978

14. Schmitz N, Linch DC, Dreger P et al. Randomized trial of filgrastim-mobilized peripheral blood progenitor cell transplantation versus autologous bone-marrow transplantation in lymphoma patients (erratum: Lancet 1996; 347: 914) Lancet 1996; 347: 353-357

15. Davies SM, Kollman C, Anasetti C et al. Engraftment and survival after unrelated-donor bone marrow transplantation: a report from the national marrow donor program Blood 2000; 96: 4096-4102

16. Bensinger WI, Martin PJ, Storer B et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers New Engl J Med 2001; 344: 175-181

17. Laughlin MJ, Barker J, Bambach B et al. Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors New Engl J Med 2001; 344: 1815-1822

18. Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–1473.

19. Lee S-E, Yahng S-A, Cho B-S, Eom K-S, Kim Y-J, Kim H-J, et al. Lymphocyte subset analysis for the assessment of treatment-related complications after autologous stem cell transplantation in multiple myeloma. Cytotherapy 2012; 14(4):505–512.

20. Lee S-E, Yoon J-H, Shin S-H, Eom K-S, Kim Y-J, Kim H-J, et al. Bone Marrow Plasma Cell Assessment before Peripheral Blood Stem Cell Mobilization in Patients with Multiple Myeloma Undergoing Autologous Stem Cell Transplantation. BioMed Research International 2014; Volume 2014, Article ID 982504, https://doi.org/10.1155/2014/982504

MSD

Medical Science & Discovery

International Journal of
Medical Science and Discovery
Open Access Scientific Journal
ISSN: 2148-6832
Lycia Press LONDON U.K.
www.medscidiscovery.com

lycians

www.lycians.com