



THE TURKISH JOURNAL OF GASTROENTEROLOGY

OFFICIAL JOURNAL OF THE TURKISH SOCIETY OF GASTROENTEROLOGY

Moving Beyond Animal Models

Top and left images: © Institute for Viro Sciences



5

September 2015
Vol. 26 Issue 5





THE TURKISH JOURNAL OF GASTROENTEROLOGY

EDITORS

Editor in Chief

Hakan Şentürk

Associate Editors

Mehmet Arhan
Ömer Başar
Metin Başaranoğlu
Billur Canbakan
Emel Canbay
Şahin Çoban
Ahmet Danalıoğlu
Tarkan Karakan
Seyfettin Köklü

International Associate Editors

Erman Aytaç, USA
Lakshmi Bala, India
Saurabh Chawla, USA
Andrea Furka, Hungary
Ahmet Gürakar, USA
Chen Huang, China
Sachin B Ingle, India
Saud Ishaq, UK
Maria Kapritsou, Greece
Sergey Konstantinov, The Netherlands
Zhanju Liu, China
Stephen Malnick, Israil
Hiroyuki Matsubayashi, Japan
Vincenzo E. Morabito, Italy
Dongren Ren, China
Kireev Roman, Spain
Cosimo Sperti, Italy
Veysel Tahan, USA
Giovanni Li Volti, Italy

Past Editor in Chief

Cihan Yurdaydın

EDITORIAL BOARD

Ulus Salih Akarca	Abdülkadir Dökmeci	Aydın Şeref Köksal
Erdem Akbal	Fuat Ekiz	Necati Örmeci
Meral Akdoğan	Levent Erdem	Ersan Özarslan
Hakan Akın	Selim Gürel	Erkan Parlak
Hikmet Akkız	Saadettin Hülagu	Tuğrul Pürnak
Akif Altunbaş	Ramazan İdilman	Murat Tuncer
Yusuf Bayraktar	Abdurrahman Kadayıfçı	İlker Turan
Fatih Beşışık	Çetin Karaca	Ahmet Uygun
Yavuz Beyazıt	Zeki Karasu	Yücel Üstündağ
Mehmet Cindoruk	Sabahattin Kaymakoğlu	Cihan Yurdaydın
İbrahim Doğan	Erdem Koçak	Osman Yüksel
Enver Dolar		

INTERNATIONAL ADVISORY BOARD

Sami Akbulut, Turkey	Cleber Rosito Pinto Krueel, Brasil
Naim Alkhouri, USA	Anne Marie Lennon, USA
Magdy Hamed Abdel-Fattah Attwa, Egypt	Hao Liu, China
Onur Başer, USA	Edouard Louis, Belgium
Ali Canbay, Germany	Kaushal Kishor Prasad, India
Mehmet Çelikkbilek, Turkey	Vittal Sree Rama Rao, UK
Guruvayoorappan Chandrasekaran, India	Fuat H. Saner, Germany
Feng Yih Chai, Malaysia	Erwin Santo, Israel
Yunfeng Cui, China	Olfat G. Shaker, Egypt
Marc Giovannini, France	Vishal Sharma, India
Chuanyong Guo, China	Vikesh Singh, USA
Gianluca Ianiri, Italy	Ebubekir Şenates, Turkey
Muhammad Idrees, Pakistan	Hala Ahmed Sherif Talkhan, Egypt
Enver İlhan, Turkey	Timuçin Taner, USA
Kalpesh Jani, India	Benjamin Tharian, USA
Ali Kabir, Iran	Zhen Yang, China
Mouen Kashab, USA	Eugenia Yiannakopoulou, Greece
Panagiota Kitsanta, Greece	Yuwei Zhang, USA



Publisher
İbrahim KARA
Publication Director
Ali ŞAHİN
Deputy Publication Director
Gökhan ÇİMEN
Publication Coordinators
Esra GÖRGÜLÜ
Ebru MUTLU

Betül ÇİMEN
Nihan GÜLTAN
İrem Naz GÜVEL
Dilşad GÜNEY
Finance Coordinator
Veysel KARA
Project Coordinators
Hakan ERTEN
Zeynep YAKIŞIRER

Graphics Department
Ünal ÖZER
Neslihan YAMAN
Kübra ÇOLAK
Contact
Address: Büyükdere Cad. No: 105/9
34394 Mecidiyeköy, Şişli, İstanbul-Turkey
Phone: +90 212 217 17 00
Fax: +90 212 217 22 92
E-mail: info@avesyayincilik.com



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Aims and Scope

The Turkish Journal of Gastroenterology is the double-blind peer-reviewed, open access, international publication organ of the Turkish Gastroenterology Society. The journal is a bimonthly publication, published on January, March, May, July, September, November and its publication language is English.

The Turkish Journal of Gastroenterology aims to publish manuscripts at the highest clinical and scientific level on original issues of gastroenterology and hepatology at the international level. The journal publishes original papers, review articles, case reports and letters to the editor on clinical gastroenterology and hepatology.

Editorial and publication processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE).

The Turkish Journal of Gastroenterology is indexed in Science Citation Index Expanded and PubMed/MEDLINE.

The Turkish Journal of Gastroenterology financial expenses of the journal are covered by the Turkish Gastroenterology Society.

Permissions and Reprints

Permissions for reproduction of materials published and reprints in the Turkish Journal of Gastroenterology should be requested from the editorial office at tgd@tgd.org.tr.

Advertising

For requests concerning advertising, please contact the Publisher.

Publisher: AVES - İbrahim Kara

Address: Büyükdere Cad. 105/9 34394 Mecidiyeköy, Şişli, İstanbul, Turkey

Phone: +90 212 217 17 00

Fax: +90 212 217 22 92

Web page: www.avesyayincilik.com

E-mail: info@avesyayincilik.com

Instructions for authors

Instructions for authors are published in the journal pages and could be accessed at the web site of the journal www.turkjgastroenterol.org.

Material Disclaimer

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

The journal is printed on an acid-free paper.



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Instructions to Authors

The Turkish Journal of Gastroenterology is the double-blind peer-reviewed, international open-access publication organ of the Turkish Gastroenterology Society. The Turkish Journal of Gastroenterology publishes original papers, review articles, case reports and letters to the editor on clinical gastroenterology and hepatology. The journal is a monthly periodical and its publication language is English.

The Turkish Journal of Gastroenterology discourages the submission of more than one article dealing with related aspects of the same study. Review articles on selected clinical and basic topics of interest will be solicited by the editors. In exceptional cases, non-invited reviews may be considered for publication.

Editorial and publication processes of the journal are shaped in accordance with the guidelines of the international organizations such as the International Council of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME), the Council of Science Editors (CSE), the Committee on Publication Ethics (COPE), the European Association of Science Editors (EASE)

The Turkish Journal of Gastroenterology will only evaluate manuscripts submitted via the journal's self-explanatory online manuscript submission and evaluation system, manuscripts submitted via any other medium will not be evaluated.

Manuscripts are published on the understanding that they are original contributions and do not contain data that have been published elsewhere or are under consideration by another journal. Meeting abstracts are not considered as duplicate publications but should be disclosed in the cover letter accompanying the manuscript.

Authors must obtain written permission from the copyright owner to reproduce previously published figures, tables, or any other material in both print and electronic formats. The original source should be cited within the references and below the reprinted material.

The Turkish Journal of Gastroenterology requires each submission to be accompanied by a Copyright Transfer Form, an Author Contributions Form and an ICMJE Form for Disclosure of Potential Conflicts of Interest.

Statements or opinions expressed in the manuscripts published in The Turkish Journal of Gastroenterology reflect the views of the author(s) and not the opinions of the editors, the editorial board or the publisher; the editors, the editorial board and the publisher disclaim any responsibility or liability for such materials.

The final responsibility in regard to the published content rests with the authors.

Each individual listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. <http://www.icmje.org>). Individuals who contributed to the preparation of the manuscript but do not fulfil the authorship criteria should be acknowledged in an acknowledg-

ments section, which should be included in the title page of the manuscript. If the editorial board suspects a case of "gift authorship", the submission will be rejected without further review.

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

A submitted manuscript will not be evaluated for publication until a conflict of interest disclosure is submitted. The disclosure should also be included in the main document before the reference list and in the cover letter. The following information must be provided:

- The author acting as the submission's guarantor and the corresponding author must be identified in the letter to the editor.
- Any financial or editorial assistance received to support the research and/or article should be cleared.
- Identification of any relationships that provided financial or editorial support for the study which may in potential cause competing interests for the submission.

The authors should state in the Materials and Methods section of the main text that experiments have been performed in compliance with the ethical principles of the assigned institutional board or national committee. Application or approval number/year for the study should also be indicated.

It is the author's responsibility to carefully protect the patients' anonymity and to verify that any experimental investigation with human subjects reported in the submission was performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institution(s) with which all the authors are affiliated with. For photographs that may reveal the identity of the patients, signed releases of the patient or of his/her legal representative should be enclosed.

When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration (JAMA 2000;284:3043-3049).

As part of submission of the manuscript, the correspondent author should send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Originality, high scientific quality and citation potential are the most important criteria for a manuscript to be accepted for publication.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript is prepared and submitted in accordance with



THE TURKISH JOURNAL OF GASTROENTEROLOGY

the journal's guidelines. Submissions that don't conform the journal's guidelines will be returned to the submitting author with technical correction requests. Manuscripts that conform the journal's guidelines will be reviewed by at least 3 external peer reviewers during the evaluation process. The Editor in Chief is the final authority in the decision making process.

Authors of a paper accepted for publication in the Turkish Journal of Gastroenterology should be in consent of that editors could make corrections without changing the basic meaning of the text of the manuscript.

All submissions are screened by a similarity detection software. In case there is more than 20% similarity with existing studies, the paper is automatically rejected.

MANUSCRIPT PREPARATION

Manuscripts should be prepared in accordance with the ICMJE - Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (updated in December 2014 - available at www.icmje.org).

Original Investigations and Reviews should be presented according to the guidelines: randomized study - CONSORT, observational study - STROBE, study on diagnostic accuracy - STARD, systematic reviews and meta-analysis PRISMA, nonrandomized behavioural and public health intervention studies - TREND.

Cover letter

A letter of submission must be included in all manuscripts, including revised manuscripts.

This letter may be used to emphasize the importance of the study or new significant points included to the revised manuscript. This letter can be typed or added to the relevant section of the online submission using copy/paste method. In the cover letter of each submission, the authors should briefly state the existing knowledge relevant to the study and the contributions their study make to the existing knowledge.

Title page

A separate title page should be submitted with all submissions and should include the title of the manuscript, name(s), affiliations and major degree(s) of the author(s) and source(s) of the work or study, a short title (running head) of no more than 50 characters. The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be listed on the title page. Grant information and other sources of support should also be included on the Title page. Individuals who contributed to the preparation of the manuscript but do not fulfil the authorship criteria should be acknowledged in the title page.

Main Document

Abstract

All manuscripts should be accompanied an abstract. A structured abstract is required with original articles and it should include the following subheadings: Background/Aims, Materials and Methods,

Results and Conclusion. A structured abstract is not required with review articles and case reports. The abstract should be limited to 250 words for original articles and review articles and 150 words for case reports.

Keywords

Each submission should be accompanied by 3 to 5 key words which should be picked from the Medical Subject Headings (MeSH) list (www.nlm.nih.gov/mesh/MBrowser.html).

Main Text

Original Articles: Acceptance of original papers will be based upon the originality and importance of the investigation. Turkish Journal of Gastroenterology encourages submission of widely readable clinical studies. The journal does not consider animal experiments for evaluation and only prospective or retrospective clinical studies are evaluated as original papers.

Original Articles should be structured with Introduction, Materials and Methods, Results and Discussion subheadings. The number of references cited should not exceed 35 and the main text should be limited to 4000 words. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour.

Introduction: Provide background information that will orient the general reader.

Materials/Patients and Methods: Materials/Patients and Methods: Provide a level of detail such that another investigator could repeat the work for methods that are used without significant modification. Citation of the original work will suffice. For reports of research using human subjects, state that informed consent was obtained from each patient and that institutional ethic committee approval was obtained.

State if informed consent was obtained from each patient and that ethic committee approval was obtained.

Results: Use tables and figures for better understanding. Please refer to the instructions before uploading images to the website.

Discussion: Discuss your results by citations; avoid discussion of other related works. Do not engage in a literature review.

Case Reports: Turkish Journal of Gastroenterology encourages submission of original and interesting case series. Single case reports are not considered for evaluation and publication; however, submission of single case reports in the letter to the editor format is possible and encouraged.

The main text of Case Reports should be limited with 1200 words and should be structured with the following subheadings; Introduction, Case Presentation and Discussion. The maximum number of references cited in a case report should be 10. A case report can be signed by maximum 5 authors unless the report entails a rare disease or condition with a cohort or multi-center.



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Review Articles: Mainly, invited reviews on specific topics are published. In exceptional cases, non-invited reviews may be considered for publication. Individuals interested in writing a review article must correspond with the Editorial Office regarding the topic before submitting the entire manuscript. The subheadings of the review articles should be planned by the authors. However, each review article should include a "Conclusion" section. The main text of review articles should be limited with 5000 words. The number of references cited should not exceed 50.

Editorials: Invited brief editorial comments on selected articles are published in The Turkish Journal of Gastroenterology. Editorials should not be longer than 1000 words excluding references.

Letter to the editor: Letters to the editor, containing case reports or brief reports of studies should not be longer than 400 words excluding references. Letters should include no more than 5 references.

Invited Letters to the Editor: Letters related to articles published in recent issues of the Turkish Journal of Gastroenterology or to topics of gastroenterology are welcomed and will be considered for publication. A publication fee will not be requested for the letters in this category.

- Letters to the editors should be sent within 6 months of publication of the commented article. Should not be longer than 400 words excluding references. Commented article should be cited as a reference. Letters should include no more than 5 references.
- Letters to the editor, containing case reports or brief reports of studies should not be longer than 400 words excluding references. Letters should include no more than 5 references.

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

Statistical analysis should be performed in accordance with guidelines on reporting statistics in medical journals (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. *Br Med J* 1983; 7; 1489-93.). Information on the statistical analysis process of the study should be provided within the main text.

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

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

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

References

References should be numbered consecutively in the order they are referred to within the main text and all references listed in the reference list should be referred to within the main text in parenthesis. Style and punctuation of each reference in the reference list should be in accordance with the examples listed below;

Standard journal article: Journal titles should be abbreviated in accordance with journal abbreviations used in Index Medicus (for journal abbreviations consult List of Journals indexed for MEDLINE published annually by NLM at <http://www.nlm.nih.gov/tsd/serials/lji.html>). When there are six or fewer authors, all authors should be listed. If there are seven or more authors, first 3 should be listed, followed by "et al.". A list of authors should be followed by the full title of the article, journal title, year, volume and page numbers.

Example: Mittal RK, Holloway RH, Penagini R, et al. Transient lower esophageal sphincter relaxation. *Gastroenterology* 1995; 109: 601-10.

Books:

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

Personal author(s): Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Marcel Dekker; 1993.

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

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

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

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

Article in electronic format: Morse SS. Factors in the emergence of infectious diseases. *Emerg Infect Dis* (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): [24 screens]. Available from: <http://www.cdc.gov/ncidod/EID/cid.htm>.



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Tables

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

Figures and Figure Legends

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

Figure legends should be listed at the end of the main document.

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 Turkish Journal of Gastroenterology 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. The publisher will request the corresponding author to list their correction requests if there are any and approve the publication of the manuscript.

PUBLICATION FEE

A non-refundable charge of 299 USD (795 TL or 265 Euro) for each accepted manuscript must be paid by the author(s) to the Turkish Society of Gastroenterology (Türk Gastroenteroloji Derneği) (Bank account: Türkiye Halk Bankası, Emek Branch Office). The journal will supply all publication expenses including copy-editing service and statistician's endorsement through these funds.

Account numbers:

Turkish Lira (TL):

IBAN CODE: TR88 0001 2009 4010 0016 0000 63

EURO (€):

IBAN CODE: TR60 0001 2009 4010 0058 000112

SWIFT CODE: TRHBTR2A

US Dollars (\$)

IBAN CODE: TR87 0001 2009 4010 0058 000111

SWIFT CODE: TRHBTR2A

In case of acceptance of a manuscript that contains colour illustrations, an additional fee of 50TL (25USD, 12€) is requested to be paid to the same bank account.

PERMISSIONS AND REPRINTS

Permissions for reproduction of materials published and reprints in the Turkish Journal of Gastroenterology should be requested from the editorial office at tgd@tgd.org.tr.

INSTRUCTIONS FOR AUTHORS

Instructions for authors are published in the journal pages and could be accessed at the web site of the journal www.turkjgastroenterol.org.

The journal is printed on an acid-free paper.



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Original Articles

- **363 Epiglottic cyst as an etiological factor of globus sensation**
Bahtiyar Polat, Serdar Karahatay, Mustafa Gerek
- **367 Effect of *H. pylori* infection on gastrin, ghrelin, motilin, and gastroesophageal reflux**
Makbule Eren, Ömer Çolak, Serap Işıksoy, Aslı Yavuz
- **373 Mismatch repair gene expression in gastroesophageal cancers**
Amelia Dracea, Cristina Angelescu, Mihaela Danculescu, Marius Ciurea, Mihai Ioana, Florin Burada
- **378 Lack of association of two common polymorphisms rs2910164 and rs11614913 with susceptibility to gastric cancer: A meta-analysis**
Liwei Zhang, Jiayan Gao, Dan Zhou, Feng Bao
- **386 Prognostic markers for metastatic colon cancer patients undergoing multiple metastasectomies**
Bala Başak Öven Ustaalioğlu, Metin Tilki, Zeynep Gamze Kılıçoğlu, Ahmet Bilici, Ali Sürmelioglu, Recep Ustaalioğlu, Burçak Erkol
- **392 Possible relationship between the resistin gene C-420G polymorphism and colorectal cancer in a Turkish population**
Yiğit Düzköylü, Soykan Arıkan, Saime Turan, İlhan Yaylım, Mehmet Baki Doğan, Serkan Sarı, Feyzullah Ersöz, Ümit Zeybek, Özlem Timırcı Kahraman, Burcu Çelikel, Simge Erdem
- **397 Clinical and genetic analysis of pediatric patients with Wilson disease**
Özlenen Şimşek Papur, Sezin Aşık Akman, Orhan Terzioğlu
- **404 Increased plasma CgA levels associated with nonalcoholic fatty liver disease**
Peng-Bo Wu, Yin-Zhi Deng, Yong-Xiang Shu, Shi-Yun Tan, Ming Li, Guo Fang
- **408 The development of a clinical score for the prediction of nonalcoholic steatohepatitis in patients with nonalcoholic fatty liver disease using routine parameters**
Li Chunming, Sheng Jianhui, Zhang Hongguang, Qiu Chunwu, Huang Xiaoyun, Yang Lijun, Yu Xuejun
- **417 Sedation for gastrointestinal endoscopy with the application of target-controlled infusion**
Yi-Ting Chang, Tzung-Chieh Tsai, Huan Hsu, Yung-Ming Chen, Kuang-Piao Chi, Shih-Yen Peng
- **423 The incidence and risk factors of portal vein system thrombosis after splenectomy and pericardial devascularization**
Shengli Wu, Zheng Wu, Xiaogang Zhang, Ruitao Wang, Jigang Bai
- **429 Gallstones in liver transplant recipients: A single-center study in China**
Rui Shi, Zhong-Yang Shen, Da-Hong Teng, Wei-Ping Zheng, Zhi-Jun Zhu, Yong-Lin Deng, Cheng Pan, Zhongping Tian, Hong Zheng

Case Report

- **435 Squamous cell carcinoma of the cecum developing in a patient with long-standing ulcerative colitis and a coexistent carcinoid tumor in the appendix: A case report**
Saqib Ahmad, Nicholas Watson, Kiran Shamim, Achyuth Menon, Khorrum Abdullah



THE TURKISH JOURNAL OF GASTROENTEROLOGY

Letters to the Editor

- **438 Prevalence of Barrett's esophagus in Lebanon**
Sebahat Başıyigit, Ferdane Pirinçci Sapmaz, Ayşe Kefeli
- **439 How to evaluate gastroesophageal sphincter incompetence**
Onur Keskin, Çağlar Keskin
- **440 Eosinophilic colitis presenting with lower gastrointestinal bleeding: An uncommon entity with a rare presentation**
Ayşe Kefeli, Abdullah Özgür Yeniova, Sebahat Başıyigit, Nedim Güneş
- **442 Important factors determining prognosis based on SUVmax in PET imaging**
Ertan Şahin, Abdullah Barış Akcan
- **443 Chronic recurrent emesis in a geriatric patient with jejunal cavernous hemangioma misdiagnosed as diabetic gastroparesis**
Li-Yan Liu, Xun Sun, Yan Zhu, Xiang-Wei Meng, Quan Wang, Yuan-Jie Sun
- **446 ERRATUM**



THE TURKISH JOURNAL OF GASTROENTEROLOGY

From the Editor

MOVING BEYOND ANIMAL MODELS

Since I became the Editor in Chief of the Turkish Journal of Gastroenterology 18 months ago, this publication has only accepted manuscripts reporting research that did not directly involve the use of animals. This policy is still in effect, and will continue to be because it embodies the high scientific and ethical standards that researchers expect from our journal.

There is a growing concern about the lack of applicability of animal research to humans. The U.S. Food and Drug Administration, for example, reports a 92% failure rate of clinical trials following preclinical success in animal studies (1), and this number was reported to be as high as 95% more recently (2).

Animal models may not be the right way to go

Many reasons for this overwhelming failure have been discussed, including reporting and publication bias, poor study design, inadequate sample size and inappropriate statistical analysis, and low reproducibility in animal studies, leading researchers to conclude that “it is nearly impossible to rely on most animal data to predict whether or not an intervention will have a favorable clinical benefit-risk ratio in human subjects.” (3). These concerns should be taken seriously, and measures should be implemented accordingly, including journal editors avoiding publishing this misleading work.

Aside from the limitations of preclinical study design and reporting, however, there is a bigger and deeper problem that does not have any easy solution, and that is the influence of intrinsic species differences. Several systemic reviews have pointed out that animals are poor models for human pathophysiology. For example, “Animal models of stroke mimic at best less than 25% of all strokes”, and all of the 100 experimental neuroprotective drugs failed in clinical trials despite promising results in animal models (4). Furthermore, it has been more than 10 years since the recommendations of Stroke Therapy Academic Industry Roundtable criteria, yet even with the best studies that adhere to the criteria “the ultimate proof that plain standardization of procedures in fact increases the rate of successful translation from bench to bedside in stroke research is still missing.” (4). Genetic differences have contributed to the failure of acute inflammation (such as sepsis, trauma and burns) research using mice (5). It has been shown that “Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts” (5). There have been nearly 150 clinical trials testing inflammatory drugs in critically ill patients, and all of them

have failed, prompting researchers to suggest the need of “higher priority for translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases” (5). The influence of genetic differences is not limited to species that are less similar to humans. In fact, even chimpanzees and other primates have critical genetic differences that make translation to humans unreliable (6-8). There have been more than 200 clinical trials for vaccines against human immunodeficiency virus (HIV), but none of them made it through despite preclinical success in chimpanzees and other non-human primates (9). The Institute of Medicine has determined that “most current biomedical use of chimpanzees is unnecessary” (10) and the National Institute of Health (NIH) of the United States has stated that experiments on chimpanzees—who are more genetically similar to humans than any other animals— “rarely accelerated new discoveries or the advancement of human health for infectious diseases.” (11). The list goes on and on.

The problems with the use of animals in biomedical research are widely recognized. Dr. Don Nicholson, former vice president of the pharmaceutical giant Merck, acknowledged that “The limitations of animals as stand-ins for human

The Institute of Medicine has determined that “most current biomedical use of chimpanzees is unnecessary”

patients are a major reason [for failure]. Animal disease doesn't faithfully replicate asthma, for instance. The condition is uniquely human, and animal models can't capture the constriction of airways and all of the other characteristics of the disease.” “We have found great mechanisms that can control asthma in an animal,” he says. “And most of them have failed” in humans (12). Dr. Richard Klausner, former director of the National Cancer Institute, said “The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades—and it simply didn't work in humans.” (13). Dr. Elias Zerhouni, former director of the U.S. NIH has stated: “We have moved away from studying human disease in humans,” he lamented. “We all drank the Kool-Aid on that one, me included.” With the ability to knock in or knock out any gene in a mouse—which “can't sue us,” Zerhouni quipped—researchers have over-relied on animal data. “The problem is that it hasn't worked, and it's time we stopped dancing around the problem...We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans.” The current director of NIH, Dr. Francis Collins, has also agreed that the failure of animal



THE TURKISH JOURNAL OF GASTROENTEROLOGY

models in the area of sepsis, for example, is “a heartbreaking loss of decades of research and billions of dollars” and announced NIH’s commitment to developing novel non-animal methods known as organs on chips [14].

A 2014 BMJ article discussing systematic reviews of the translation of animal research concluded, “if animal researchers continue to fail to conduct rigorous studies and synthesise and report them accurately, if research conducted on animals continues to be unable to reasonably predict what can be expected in humans, the public’s continuing endorsement and funding of preclinical animal research seems misplaced.” [15].

The history of cancer research has been a history of curing cancer in the mouse

I agree. The scientific community has been too content with animal experiments and even applauded serendipitous findings from animal studies, not realizing that the opportunistic approach is dangerous and misleading.

When we recognize that the reliance on inherently flawed animal models of human disease are largely responsible for clinical failure—beyond the limitations of study design and reporting and selective use of species that are genetically further from humans—it does not make sense to continue to promote this practice. Human-relevant approaches should be more aggressively developed and utilized instead. Fortunately, non-animal research methods like established clinical, computational and *in vitro* models abound, [16] and new technologies like guts [17] and other organs-on-chips [18] are constantly being developed and validated. With the implementation of these modern technologies, scientists do not need to rely on experiments that harm animals and that we know will likely never improve human health.

We challenge other scientific journals to do the same!

As a scientific publication, we have a special role in steering the direction of future endeavor. Researchers have warned that “Each time... potential treatments is observed to be effective based upon animal research, it propagates numerous further animal and human studies consuming enormous amounts of time and effort to prove that the observation has little or no relevance to human disease or that it may have been an artifact of the animal model itself.” [19].

Given the limitations of animal models, publishing animal studies would mislead the scientific community into futile

research and give the general public false hope. This is unethical. We encourage submissions of studies with human-relevant approaches such as clinical, *in vitro*, *in silico*, and other non-animal methods, and we challenge other scientific journals to do the same. The Turkish Journal of Gastroenterology is a “cruelty-free journal”, to both humans and non-human animals, and we believe that this policy would foster positive changes in the current research system and facilitate much-needed medical progress.

Hakan Şentürk
Editor in Chief

References

1. Food and Drug Administration. Innovation or stagnation: challenge and opportunity on the critical path to new medical products. Washington, DC: Food and Drug Administration. 2004.
2. Hartung T. Food for Thought Look Back in Anger – What Clinical Studies Tell Us About Preclinical Work. ALTEX 2013; 30; 275–91.
3. Ioannidis JPA. Extrapolating from Animals to Humans. Science Translational Medicine 2012; 4: 151ps15.
4. Sutherland BA, Minnerup J, Balami JS, Arba F, Buchan AM, Kleinschnitz C. Neuroprotection for ischaemic stroke: translation from the bench to the bedside. International Journal of Stroke: Official Journal of the International Stroke Society 2012; 7: 407–18.
5. Seok J, Warren HS, Cuenca AG, Mindrino MN, Baker HV, Xu W, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proceedings of the National Academy of Sciences 2013; 110: 3507–12.
6. Bailey J. Lessons from chimpanzee-based research on human disease: the implications of genetic differences. Alternatives to Laboratory Animals: ATLA 2011; 39: 527–40.
7. Boffelli D, Martin DIK. Epigenetic Inheritance: A Contributor to Species Differentiation? DNA and Cell Biology 2012; 31(Suppl 1): S11–S16.
8. Bailey J. Monkey-based research on human disease: the implications of genetic differences. Alternatives to Laboratory Animals: ATLA 2014; 42: 287–317.
9. Esparza J. A brief history of the global effort to develop a preventive HIV vaccine. Vaccine 2013; 31: 3502–18.
10. Altevogt BM, Pankevich DE, Shelton-Davenport MK, Kahn JP. Chimpanzees in biomedical and behavioral research: assessing the necessity. National Academies Press 2011.
11. National Institutes of Health. Council of Councils Working Group on the Use of Chimpanzees in NIH-Supported Research. Retrieved from http://dpcpsi.nih.gov/council/pdf/FNL_Report_WG_Chimpanzees.pdf. 2013.
12. Rockoff JD. Forget Lab Rats: Testing Asthma Drugs on a Microchip. Wall Street Journal. Retrieved from <http://www.wsj.com/articles/SB10001424127887324049504578545154163286708>. 2013.
13. Cimonis M, Getlin J, II THM. Cancer Drugs Face Long Road From Mice to Men. Los Angeles Times. Retrieved from <http://articles.latimes.com/1998/may/06/news/mn-46795>. 1998.
14. Collins DF. Of Mice, Men, and Medicine. Retrieved from <http://directorsblog.nih.gov/2013/02/19/of-mice-men-and-medicine/>. 2013.
15. Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? BMJ 2014; 348: g3387.
16. Knight A. Non-animal methodologies within biomedical research and toxicity testing. ALTEX 2008; 25: 213–31.
17. Kim HJ, Ingber DE. Gut-on-a-Chip microenvironment induces human intestinal cells to undergo villus differentiation. Integrative Biology: Quantitative Biosciences from Nano to Macro 2013; 5: 1130–40.
18. Esch EW, Bahinski A, Huh D. Organs-on-chips at the frontiers of drug discovery. Nature Reviews Drug Discovery 2015; 14: 248–60.
19. Wiebers DO, Adams HP, Whisnant JP. Animal models of stroke: are they relevant to human disease? Stroke; a Journal of Cerebral Circulation 1990; 21: 1–3.