ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2016 June 28; 8(18): 749-784

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

Editorial Board

2014-2017

The *World Journal of Hepatology* Editorial Board consists of 474 members, representing a team of worldwide experts in hepatology. They are from 52 countries, including Algeria (1), Argentina (6), Armenia (1), Australia (2), Austria (4), Bangladesh (2), Belgium (3), Botswana (2), Brazil (13), Bulgaria (2), Canada (3), Chile (1), China (97), Czech Repoublic (1), Denmark (2), Egypt (12), France (6), Germany (20), Greece (11), Hungary (5), India (15), Indonesia (3), Iran (4), Israel (1), Italy (54), Japan (35), Jordan (1), Malaysia (2), Mexico (3), Moldova (1), Netherlands (3), Nigeria (1), Pakistan (1), Philippines (2), Poland (1), Portugal (2), Qatar (1), Romania (6), Russia (2), Saudi Arabia (4), Singapore (1), South Korea (12), Spain (20), Sri Lanka (1), Sudan (1), Sweden (1), Switzerland (1), Thailand (4), Turkey (21), Ukraine (3), United Kingdom (18), and United States (55).

Chile

Luis A Videla, *Santiago*

China

Guang-Wen Cao, *Shanghai*
En-Qiang Chen, *Chengdu*
Gong-Ying Chen, *Hangzhou*
Jin-lian Chen, *Shanghai*
Jun Chen, *Changsha*
Alfred Cheng, *Hong Kong*
Chun-Ping Cui, *Beijing*
Shuang-Suo Dang, *Xi'an*
Ming-Xing Ding, *Jinhua*
Zhi-Jun Duang, *Dalian*
He-Bin Fan, *Wuhan*
Xiao-Ming Fan, *Shanghai*
James Yan Yue Fung, *Hong Kong*
Yi Gao, *Guangzhou*
Zuo-Jiong Gong, *Wuhan*
Zhi-Yong Guo, *Guangzhou*
Shao-Liang Han, *Wenzhou*
Tao Han, *Tianjin*
Jin-Yang He, *Guangzhou*
Ming-Liang He, *Hong Kong*
Can-Hua Huang, *Chengdu*
Bo Jin, *Beijing*
Shan Jin, *Hohhot*
Hui-Qing Jiang, *Shijiazhuang*
Wan-Yee Joseph Lau, *Hong Kong*
Guo-Lin Li, *Changsha*
Jin-Jun Li, *Shanghai*
Qiang Li, *Jinan*
Sheng Li, *Jinan*
Zong-Fang Li, *Xi'an*
Xu Li, *Guangzhou*
Xue-Song Liang, *Shanghai*
En-Qi Liu, *Xi'an*
Pei Liu, *Shenyang*
Zhong-Hui Liu, *Changchun*
Guang-Hua Luo, *Changzhou*
Yi Lv, *Xi'an*
Guang-Dong Pan, *Liuzhou*
Wen-Sheng Pan, *Hangzhou*
Jian-Min Qin, *Shanghai*
Wai-Kay Seto, *Hong Kong*
Hong Shen, *Changsha*
Xiao Su, *Shanghai*
Li-Ping Sun, *Beijing*
Wei-Hao Sun, *Nanjing*
Xue-Ying Sun, *Harbin*
Hua Tang, *Tianjin*
Ling Tian, *Shanghai*
Eric Tse, *Hong Kong*
Guo-Ying Wang, *Changzhou*
Yue Wang, *Beijing*
Shu-Qiang Wang, *Chengdu*
Mary MY Waye, *Hong Kong*
Hong-Shan Wei, *Beijing*
Danny Ka-Ho Wong, *Hong Kong*
Grace Lai-Hung Wong, *Hong Kong*
Bang-Fu Wu, *Dongguan*
Xiong-Zhi Wu, *Tianjin*
Chun-Fang Xu, *Suzhou*
Rui-An Xu, *Quanzhou*
Rui-Yun Xu, *Guangzhou*
Wei-Li Xu, *Shijiazhuang*
Shi-Ying Xuan, *Qingdao*
Ming-Xian Yan, *Jinan*
Lv-Nan Yan, *Chengdu*
Jin Yang, *Hangzhou*
Ji-Hong Yao, *Dalian*
Winnie Yeo, *Hong Kong*
Zheng Zeng, *Beijing*
Qi Zhang, *Hangzhou*
Shi-Jun Zhang, *Guangzhou*
Xiao-Lan Zhang, *Shijiazhuang*
Xiao-Yong Zhang, *Guangzhou*
Yong Zhang, *Xi'an*
Hong-Chuan Zhao, *Hefei*
Ming-Hua Zheng, *Wenzhou*
Yu-Bao Zheng, *Guangzhou*
Ren-Qian Zhong, *Shanghai*
Fan Zhu, *Wuhan*
Xiao Zhu, *Dongguan*

Czech Repoublic

Kamil Vyslouzil, *Olomouc*

Denmark

Henning Gronbaek, *Aarhus*
Christian Mortensen, *Hvidovre*

Egypt

Ihab T Abdel-Raheem, *Damanhour*
NGB G Bader EL Din, *Cairo*
Hatem Elalfy, *Mansoura*
Mahmoud M El-Bendary, *Mansoura*
Mona El SH El-Raziky, *Cairo*
Mohammad El-Sayed, *Cairo*
Yasser M Fouad, *Minia*
Mohamed AA Metwally, *Benha*
Hany Shehab, *Cairo*
Mostafa M Sira, *Shebin El-koom*
Ashraf Taye, *Minia*
MA Ali Wahab, *Mansoura*

France

Laurent Alric, *Toulouse*
Sophie Conchon, *Nantes*
Daniel J Felmlee, *Strasbourg*
Herve Lerat, *Creteil*
Dominique Salmon, *Paris*
Jean-Pierre Vartanian, *Paris*

Germany

Laura E Buitrago-Molina, *Hannover*
Enrico N De Toni, *Munich*
Oliver Ebert, *Muenchen*
Rolf Gebhardt, *Leipzig*
Janine V Hartl, *Regensburg*
Sebastian Hinz, *Kiel*
Benjamin Juntermanns, *Essen*
Roland Kaufmann, *Jena*
Viola Knop, *Frankfurt*
Veronika Lukacs-Kornek, *Homburg*
Benjamin Maasoumy, *Hannover*
Jochen Mattner, *Erlangen*
Nadja M Meindl-Beinker, *Mannheim*
Ulf P Neumann, *Aachen*
Margarete Odenthal, *Cologne*
Yoshiaki Sunami, *Munich*
Christoph Roderburg, *Aachen*
Frank Tacke, *Aachen*
Yuchen Xia, *Munich*

Greece

Alex P Betrosian, *Athens*
George N Dalekos, *Larissa*
Ioanna K Delladetsima, *Athens*
Nikolaos K Gatselis, *Larissa*
Stavros Gourgiotis, *Athens*
Christos G Savopoulos, *Thessaloniki*
Tania Siahanidou, *Athens*
Emmanouil Sinakos, *Thessaloniki*
Nikolaos G Symeonidi, *Thessaloniki*
Konstantinos C Thomopoulos, *Larissa*
Konstantinos Tziomalos, *Thessaloniki*

Hungary

Gabor Banhegyi, *Budapest*
Peter L Lakatos, *Budapest*
Maria Papp, *Debrecen*
Ferenc Sipos, *Budapest*
Zsolt J Tulassay, *Budapest*

India

Deepak N Amarapurkar, *Mumbai*
Girish M Bhopale, *Pune*
Sibnarayan Datta, *Tezpur*
Nutan D Desai, *Mumbai*
Sorabh Kapoor, *Mumbai*
Jaswinder S Maras, *New Delhi*
Nabeen C Nayak, *New Delhi*
C Ganesh Pai, *Manipal*
Amit Pal, *Chandigarh*
K Rajeshwari, *New Delhi*
Anup Ramachandran, *Vellore*
D Nageshwar Reddy, *Hyderabad*
Shivaram P Singh, *Cuttack*
Ajith TA, *Thrissur*
Balasubramaniyan Vairappan, *Pondicherry*

Indonesia

Pratika Yuhyi Hernanda, *Surabaya*
Cosmas RA Lesmana, *Jakarta*
Neneng Ratnasari, *Yogyakarta*

Iran

Seyed M Jazayeri, *Tehran*
Sedigheh Kafi-Abad, *Tehran*
Iradj Maleki, *Sari*
Fakhraddin Naghibalhossaini, *Shiraz*

Israel

Stephen DH Malnick, *Rehovot*

Italy

Francesco Angelico, *Rome*
Alfonso W Avolio, *Rome*
Francesco Bellanti, *Foggia*
Marcello Bianchini, *Modena*
Guglielmo Borgia, *Naples*
Mauro Borzio, *Milano*
Enrico Brunetti, *Pavia*
Valeria Cento, *Roma*
Beatrice Conti, *Rome*
Francesco D'Amico, *Padova*
Samuele De Minicis, *Fermo*
Fabrizio De Ponti, *Bologna*
Giovan Giuseppe Di Costanzo, *Napoli*
Luca Fabris, *Padova*
Giovanna Ferraioli, *Pavia*
Matteo Garcovich, *Rome*
Edoardo G Giannini, *Genova*
Rossano Girometti, *Udine*
Alessandro Granito, *Bologna*
Alberto Grassi, *Rimini*
Alessandro Grasso, *Savona*
Francesca Guerrieri, *Rome*
Quirino Lai, *Aquila*
Andrea Lisotti, *Bologna*
Marcello F Maida, *Palermo*
Lucia Malaguarnera, *Catania*
Andrea Mancuso, *Palermo*
Luca Maroni, *Ancona*
Francesco Marotta, *Milano*
Pierluigi Marzuillo, *Naples*
Sara Montagnese, *Padova*
Giuseppe Nigri, *Rome*
Claudia Piccoli, *Foggia*
Camillo Porta, *Pavia*
Chiara Raggi, *Rozzano (MI)*
Maria Rendina, *Bari*
Maria Ripoli, *San Giovanni Rotondo*
Kryssia I Rodriguez-Castro, *Padua*
Raffaella Romeo, *Milan*
Amedeo Sciarra, *Milano*
Antonio Solinas, *Sassari*
Aurelio Sonzogni, *Bergamo*
Giovanni Squadrito, *Messina*
Salvatore Sutti, *Novara*
Valentina Svicher, *Rome*
Luca Toti, *Rome*
Elvira Verduci, *Milan*
Umberto Vespasiani-Gentilucci, *Rome*
Maria A Zocco, *Rome*

Japan

Yasuhiro Asahina, *Tokyo*
Nabil AS Eid, *Takatsuki*
Kenichi Ikejima, *Tokyo*
Shoji Ikuo, *Kobe*
Yoshihiro Ikura, *Takatsuki*
Shinichi Ikuta, *Nishinomiya*
Kazuaki Inoue, *Yokohama*
Toshiya Kamiyama, *Sapporo*
Takanobu Kato, *Tokyo*
Saiho Ko, *Nara*
Haruki Komatsu, *Sakura*
Masanori Matsuda, *Chuo-city*
Yasunobu Matsuda, *Niigata*
Yoshifumi Nakayama, *Kitakyushu*
Taichiro Nishikawa, *Kyoto*
Satoshi Oeda, *Saga*
Kenji Okumura, *Urayasu*
Michitaka Ozaki, *Sapporo*
Takahiro Sato, *Sapporo*
Junichi Shindoh, *Tokyo*
Ryo Sudo, *Yokohama*
Atsushi Suetsugu, *Gifu*
Haruhiko Sugimura, *Hamamatsu*
Reiji Sugita, *Sendai*
Koichi Takaguchi, *Takamatsu*
Shinji Takai, *Takatsuki*
Akinobu Takaki, *Okayama*
Yasuhito Tanaka, *Nagoya*
Takuji Tanaka, *Gifu City*
Atsunori Tsuchiya, *Niigata*
Koichi Watashi, *Tokyo*
Hiroshi Yagi, *Tokyo*
Taro Yamashita, *Kanazawa*
Shuhei Yoshida, *Chiba*
Hitoshi Yoshiji, *Kashihara*

Jordan

Kamal E Bani-Hani, *Zarqa*

Malaysia

Peng Soon Koh, *Kuala Lumpur*
Yeong Yeh Lee, *Kota Bahru*

Mexico

Francisco J Bosques-Padilla, *Monterrey*
María de F Higuera-de la Tijera, *Mexico City*
José A Morales-Gonzalez, *México City*

Moldova

Angela Peltec, *Chishinev*

Netherlands

Wybrich R Cnossen, *Nijmegen*
Frank G Schaap, *Maastricht*
Fareeba Sheedfar, *Groningen*

Nigeria

CA Asabamaka Onyekwere, *Lagos*

Pakistan

Bikha Ram Devrajani, *Jamshoro*

Philippines

Janus P Ong, *Pasig*
JD Decena Sollano, *Manila*

Poland

Jacek Zielinski, *Gdansk*

Portugal

Rui T Marinho, *Lisboa*
Joao B Soares, *Braga*

Qatar

Reem Al Olaby, *Doha*

Romania

Bogdan Dorobantu, *Bucharest*
Liana Gheorghe, *Bucharest*
George S Gherlan, *Bucharest*
Romeo G Mihaila, *Sibiu*
Bogdan Procopet, *Cluj-Napoca*
Streba T Streba, *Craiova*

Russia

Anisa Gumerova, *Kazan*
Pavel G Tarazov, *St.Petersburg*

Saudi Arabia

Abdulrahman A Aljumah, *Riyadh*
Ihab MH Mahmoud, *Riyadh*
Ibrahim Masoodi, *Riyadh*
Mhoammad K Parvez, *Riyadh*

Singapore

Ser Yee Lee, *Singapore*

South Korea

Young-Hwa Chung, *Seoul*
Jeong Heo, *Busan*
Dae-Won Jun, *Seoul*
Bum-Joon Kim, *Seoul*
Do Young Kim, *Seoul*
Ji Won Kim, *Seoul*
Moon Young Kim, *Wonu*
Mi-Kyung Lee, *Suncheon*
Kwan-Kyu Park, *Daegu*
Young Nyun Park, *Seoul*
Jae-Hong Ryoo, *Seoul*
Jong Won Yun, *Kyungsan*

Spain

Ivan G Marina, *Madrid*

Juan G Acevedo, *Barcelona*
Javier Ampuero, *Sevilla*
Jaime Arias, *Madrid*
Andres Cardenas, *Barcelona*
Agustin Castiella, *Mendaro*
Israel Fernandez-Pineda, *Sevilla*
Rocio Gallego-Duran, *Sevilla*
Rita Garcia-Martinez, *Barcelona*
José M González-Navajas, *Alicante*
Juan C Laguna, *Barcelona*
Elba Llop, *Madrid*
Laura Ochoa-Callejero, *La Rioja*
Albert Pares, *Barcelona*
Sonia Ramos, *Madrid*
Francisco Rodriguez-Frias, *Córdoba*
Manuel L Rodriguez-Peralvarez, *Córdoba*
Marta R Romero, *Salamanca*
Carlos J Romero, *Madrid*
Maria Trapero-Marugan, *Madrid*

Sri Lanka

Niranga M Devanarayana, *Ragama*

Sudan

Hatim MY Mudawi, *Khartoum*

Sweden

Evangelos Kalaitzakis, *Lund*

Switzerland

Christoph A Maurer, *Liestal*

Thailand

Taned Chitapanarux, *Chiang mai*
Temduang Limpaiboon, *Khon Kaen*
Sith Phongkitkarun, *Bangkok*
Yong Poovorawan, *Bangkok*

Turkey

Osman Abbasoglu, *Ankara*
Mesut Akarsu, *Izmir*
Umit Akyuz, *Istanbul*
Hakan Alagozlu, *Sivas*
Yasemin H Balaban, *Istanbul*
Bulent Baran, *Van*
Mehmet Celikbilek, *Yozgat*
Levent Doganay, *Istanbul*
Fatih Eren, *Istanbul*
Abdurrahman Kadayifci, *Gaziantep*
Ahmet Karaman, *Kayseri*
Muhsin Kaya, *Diyarbakir*
Ozgur Kemik, *Van*
Serdar Moralioglu, *Uskudar*
A Melih Ozel, *Gebze - Kocaeli*
Seren Ozenirler, *Ankara*
Ali Sazci, *Kocaeli*
Goktug Sirin, *Kocaeli*
Mustafa Sunbul, *Samsun*
Nazan Tuna, *Sakarya*
Ozlem Yonem, *Sivas*

Ukraine

Rostyslav V Bubnov, *Kyiv*
Nazarii K Kobyliak, *Kyiv*
Igor N Skrypnyk, *Poltava*

United Kingdom

Safa Al-Shamma, *Bournemouth*
Jayantha Arnold, *Southall*
Marco Carbone, *Cambridge*
Rajeev Desai, *Birmingham*
Ashwin Dhanda, *Bristol*
Matthew Hoare, *Cambridge*
Stefan G Hubscher, *Birmingham*
Nikolaos Karidis, *London*
Lemonica J Koumbi, *London*
Patricia Lalor, *Birmingham*
Ji-Liang Li, *Oxford*
Evaggelia Liaskou, *Birmingham*
Rodrigo Liberal, *London*
Wei-Yu Lu, *Edinburgh*
Richie G Madden, *Truro*
Christian P Selinger, *Leeds*
Esther Una Cidon, *Bournemouth*
Feng Wu, *Oxford*

United States

Naim Alkhouri, *Cleveland*
Robert A Anders, *Baltimore*
Mohammed Sawkat Anwer, *North Grafton*
Kalyan Ram Bhamidimarri, *Miami*
Brian B Borg, *Jackson*
Ronald W Busuttil, *Los Angeles*
Andres F Carrion, *Miami*
Saurabh Chatterjee, *Columbia*
Disaya Chavalitdhamrong, *Gainesville*
Mark J Czaja, *Bronx*
Jonathan M Fenkel, *Philadelphia*
Catherine Frenette, *La Jolla*
Lorenzo Gallon, *Chicago*
Kalpana Ghoshal, *Columbus*
Hie-Won L Hann, *Philadelphia*
Shuang-Teng He, *Kansas City*
Wendong Huang, *Duarte*
Rachel Hudacko, *Suffern*
Lu-Yu Hwang, *Houston*
Ijaz S Jamall, *Sacramento*
Neil L Julie, *Bethesda*
Hetal Karsan, *Atlanta*
Ahmed O Kaseb, *Houston*
Zeid Kayali, *Pasadena*
Timothy R Koch, *Washington*
Gursimran S Kochhar, *Cleveland*
Steven J Kovacs, *East Hanover*
Mary C Kuhns, *Abbott Park*
Jiang Liu, *Silver Spring*
Li Ma, *Stanford*
Francisco Igor Macedo, *Southfield*
Sandeep Mukherjee, *Omaha*
Natalia A Osna, *Omaha*
Jen-Jung Pan, *Houston*
Christine Pocha, *Minneapolis*
Yury Popov, *Boston*
Davide Povero, *La Jolla*
Phillip Ruiz, *Miami*
Takao Sakai, *Cleveland*
Nicola Santoro, *New Haven*
Eva Schmelzer, *Pittsburgh*
Zhongjie Shi, *Philadelphia*
Nathan J Shores, *New Orleans*
Siddharth Singh, *Rochester*
Shailendra Singh, *Pittsburgh*
Veysel Tahan, *Iowa City*
Mehlika Toy, *Boston*
Hani M Wadei, *Jacksonville*
Gulam Waris, *North Chicago*
Ruliang Xu, *New York*
Jun Xu, *Los Angeles*
Matthew M Yeh, *Seattle*
Xuchen Zhang, *West Haven*
Lixin Zhu, *Buffalo*
Sasa Zivkovic, *Pittsburgh*

World Journal of Hepatology

Contents

Three issues per month Volume 8 Number 18 June 28, 2016

MINIREVIEWS

749 Quality of life after liver transplantation: State of the art

Onghena L, Develtere W, Poppe C, Geerts A, Troisi R, Vanlander A, Berrevoet F, Rogiers X, Van Vlierberghe H, Verhelst X

ORIGINAL ARTICLE

Retrospective Study

757 Clinical characteristics and progression of liver abscess caused by toxocara

Ha KH, Song JE, Kim BS, Lee CH

EVIDENCE-BASED MEDICINE

762 Treating chronic hepatitis B virus: Chinese physicians' awareness of the 2010 guidelines

Wei L, Jia JD, Weng XH, Dou XG, Jiang JJ, Tang H, Ning Q, Dai QQ, Li RQ, Liu J

META-ANALYSIS

770 Transarterial radioembolization *vs* chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis

Facciorusso A, Serviddio G, Muscatiello N

CASE REPORT

779 Atypical presentation of a hepatic artery pseudoaneurysm: A case report and review of the literature

Luckhurst CM, Perez C, Collinsworth AL, Trevino JG

Contents

World Journal of Hepatology
Volume 8 Number 18 June 28, 2016

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Reem Al Olaby, BSc, MSc, PhD, Pharmacist, Research Associate, Research Fellow, Department of Biotechnology, The American University in Cairo, Doha 22188, Qatar

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ ABSTRACTING

World Journal of Hepatology is now indexed in PubMed, PubMed Central, and Scopus.

FLYLEAF

I-IV Editorial Board

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

Xiu-Xia Song, Vice Director
World Journal of Hepatology
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-59080039
Fax: +86-10-85381893
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
June 28, 2016

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/g_info_20160116143427.htm

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i18.749

World J Hepatol 2016 June 28; 8(18): 749-756
ISSN 1948-5182 (online)

MINIREVIEWS

Quality of life after liver transplantation: State of the art

Louis Onghena, Wouter Develtere, Carine Poppe, Anja Geerts, Roberto Troisi, Aude Vanlander, Frederik Berrevoet, Xavier Rogiers, Hans Van Vlierberghe, Xavier Verhelst

Louis Onghena, Wouter Develtere, Anja Geerts, Hans Van Vlierberghe, Xavier Verhelst, Department of Hepatology and Gastroenterology, Ghent University Hospital, 9000 Ghent, East Flanders, Belgium

Carine Poppe, Roberto Troisi, Aude Vanlander, Frederik Berrevoet, Xavier Rogiers, Department of General and Hepato-biliary Surgery, Liver Transplantation Service, Ghent University Hospital and Medical School, 9000 Ghent, East Flanders, Belgium

Author contributions: Onghena L, Develtere W, Poppe C, Geerts A, Troisi R, Vanlander A, Berrevoet F, Rogiers X, Van Vlierberghe H and Verhelst X collected and analyzed the data and wrote the paper with equal contribution.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other co-authors contributed their efforts in this manuscript.

Manuscript source: Invited manuscript

Correspondence to: Xavier Verhelst, MD, Department of Hepatology and Gastroenterology, Ghent University Hospital, De Pintelaan 185 - 1K12IE, 9000 Gent, East Flanders, Belgium. xavier.verhelst@uzgent.be
Telephone: +32-9-3322371
Fax: +32-9-3324984

Received: February 22, 2016
Peer-review started: February 25, 2016
First decision: April 15, 2016
Revised: May 4, 2016
Accepted: June 1, 2016
Article in press: June 3, 2016
Published online: June 28, 2016

Abstract

Quality of life (QoL) after deceased donor liver transplantation is increasingly recognized as a major outcome parameter. We reviewed recent publications in this rapidly evolving field in order to summarize recent achievements in the field and to define opportunities and perspectives for research and improvement of patient care. QoL does improve after liver transplantation according to a typical pattern. During the first year, there is a significant improvement in QoL. After one year, the improvement does stabilise and tends to decline slightly. In addition to the physical condition, different psychological parameters (such as depression, anxiety, sexual function) and socio-demographic elements (professional state, sex, marital state) seem to impact QoL. Opportunities for further research are the use of dedicated questionnaires and identification of influencing factors for QoL.

Key words: Epidemiologic factors; Liver transplantation; Demographic factors; Quality of life; Mental health; Sociological factors

Core tip: Quality of life (QoL) after deceased donor liver transplantation (LT) is increasingly recognized as a major outcome parameter. This review summarizes a broad spectrum of factors that influence QoL in LT and elucidates the evolution in time of physical and mental QoL after LT. Furthermore attention is given to areas for further investigation and the use of self-report QoL questionnaires in LT. This way, we want to offer a recent and complete overview in this rapidly evolving field.

Onghena L, Develtere W, Poppe C, Geerts A, Troisi R, Vanlander A, Berrevoet F, Rogiers X, Van Vlierberghe H, Verhelst X. Quality of life after liver transplantation: State of the art. *World J Hepatol* 2016; 8(18): 749-756 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i18/749.htm DOI: http://dx.doi.org/10.4254/

wjh.v8.i18.749

INTRODUCTION

In 1967, Thomas Starzl performed the first successful liver transplantation. Over the past few decades liver transplantation (LT) has become a widely accepted treatment for end-stage liver disease, acute liver failure and selected cases of hepatocellular carcinoma with excellent long-term results[1,2]. The first years after the introduction of liver transplantation were characterized by a marked increase of survival rates, due to better pre- and post-operative care, refinement of explanting techniques and organ preservation, better surgical techniques, the development of potent immunosuppressive drugs and improved patient selection. Therefore, mortality and morbidity have decreased[3,4]. Today liver transplantation has a three-month survival rate of about 91.2%, a five-year survival of about 73.3% and a ten-year survival of about 60%[3,5-7].

Survival is the main outcome parameter after liver transplantation and a conditio sine qua non. However, once survival is granted, the real outcome parameter to address the success of liver transplantation on the long term is quality of life (QoL). QoL can be defined as "an overall sense of well-being, including aspects of happiness and satisfaction with life as a whole, which is measurable through mental well being, physical functioning and overall health status"[8]. The World Health Organization defines health as a "state of complete physical, mental and social well-being and not merely the absence of disease and infirmity". A shift of the focus from life expectancy to QoL can be observed in an increasing number of medical fields and is also taking place in organ transplantation research[9]. The goal of liver transplantation is to achieve a health status that is at least as good as it was before liver transplantation.

Since 2010 many authors have addressed the issue of QoL after LT. Our goal was to collect and compare these new insights and controversies in this research area.

METHODOLOGY

We searched for articles in major databases (PubMed, Google Scholar and Science Direct) from 2009 to 2015. English, French and Dutch manuscripts were eligible.

Search terms "Quality of life" and "Liver transplantation" were used as MeSH terms or searched in the title of the article. Exclusion criteria were paediatric LT, living donor liver transplantation (LDLT) and articles published before 2009. Paediatric patients were excluded due to different interpretation of QoL, reliance on parents and difficult data collection. LDLT patients were excluded due to a different psychosocial process pretransplantation. Only articles between 2009 and 2015 were eligible for inclusion.

STUDY RESULTS

Description of selected manuscripts

Thirty-one publications met our criteria for the PubMed search, including 24 original articles and 7 reviews (Figure 1 and Table 1). The last search was performed September 1st, 2015.

Components of QoL

Overall QoL: In general, health related QoL (HRQoL) improves and remains stable throughout the years after transplantation, but does not reach the level of the general population. This can be explained by the presence of comorbidities, the severity of the disease and the transplant procedure[3,8,10-14].

HRQoL tends to increase rapidly during the first two years, and remains stable afterwards once almost normal values have been reached[8,15]. Some authors report a more fluctuating evolution with a rapid increase of QoL during the first six months, followed by a stabilization during the remainder of the first year and a rebound effect during the second year due to adaption to certain psychosocial conditions. Patients are confronted with their new health status and can experience problems with re-enrolment in society and more particular difficulties in their professional life. The rebound effect is due to the fact that patients slowly retrieve peer acceptance and can participate in professional and social activities. After two years, in these patients, an improvement can be found until the fifth year after LT[10].

Overall, many studies have proven significant improvements in general and mental health, vitality, social and physical functioning[1,16].

Physical QoL: Overall, physical health starts improving after the first month after transplantation. This effect lasts the first six months, up to 2 years after transplantation[17]. Fluctuations are not uncommon due to the rebound effect[10,13,16]. A lower physical activity can be seen 10 to 30 years post-transplantation in comparison to the general population. This can be explained by the effect of ageing[11,14]. Due to the rapid evolution in the field of LT, older studies do not reflect the common medical practice and should be read with caution.

In summary, an improvement is seen in physical functioning after LT after the first year, if major medical complications are absent, *e.g.*, cytomegalovirus reactivation, rejection and revision[1,18-22].

Mental QoL: The World Health Organisation defines mental health as "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community"[23]. This vague definition complicates the assessment of mental health QoL after liver and impedes the comparison of different studies. Some authors assessed the mental QoL by measuring anxiety

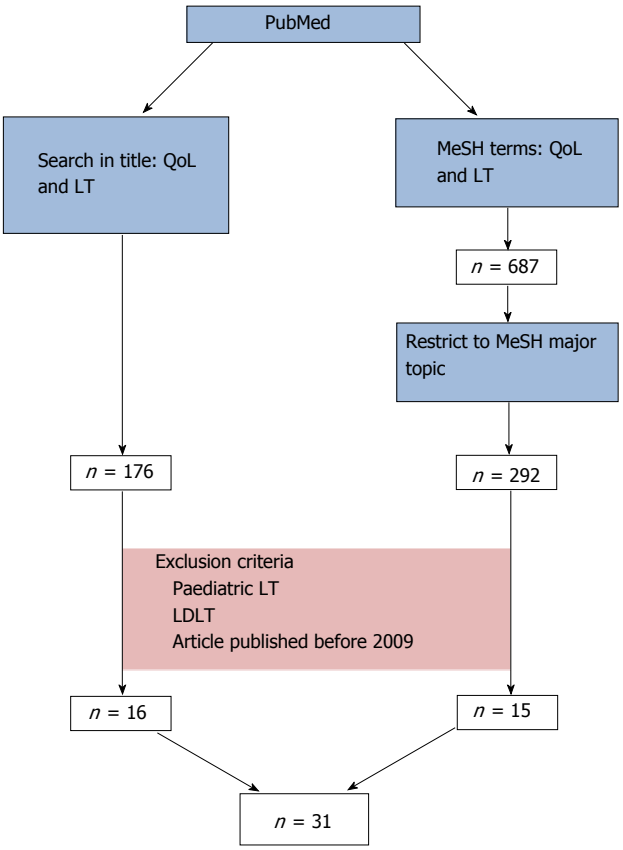

Figure 1 Summary of the search method. LT: Liver transplantation; LDLT: Living donor liver transplantation; QoL: Quality of life.

and depression, because of the high correlation with these mental diseases. Burra and Germani[14] showed in their systematic review an increase of depression and anxiety scores during the first year, followed by a decrease afterwards. However, another study reported a significant improvement of depression and anxiety rates especially during the first year after LT in the absence of complications such as biliary events, endocrine disorders, physical and psychiatric problems[11,15]. The relief of the stressful time-lapse awaiting transplantation combined with a better physical health status could be a logical explanation. Furthermore, differences might be related to the presence of underlying psychiatric morbidities. Affective illness, maladjustment and severe anxiety have been diagnosed in 19%-54% of patients during psychiatric evaluation. Obsessive-compulsive, somatization, anxiety and depression symptoms were frequently found. The transplantation and stay at intensive care unit have been considered as traumatic stressors that diminish QoL and can cause overall mental distress. These patients are prone to some psychiatric disorders (*e.g.*, anxiety and affective disorders, post-traumatic stress disorder) and a low QoL after LT[21,24-31].

The short form-36 questionnaire (SF-36) is extensively used to assess the health-related QoL, which is a reliable and standardized tool comparing as well the mental [the mental component summary score (MCS)] as the physical [physical component summary score (PCS)] aspects of QoL. During the first month after liver transplantation, studies show a rapid improvement of the MCS; the improvement of the PCS is slower though more durable and remains at higher levels six to twelve months after transplantation[13,15]. Side effects of immunosuppressive drugs and unmet expectations after liver transplantation can also hamper the improvement of MCS[17].

In summary an improvement is seen in the mental health status within the first months after transplantation and can be influenced by complications such as rejection, infections and biliary events. These are interesting targets for improvement[13-15,27].

Factors influencing QoL after transplantation

Aetiology of liver disease: The original liver disease leading might influence QoL afterwards. Patients transplanted for non-cholestatic liver diseases report a significantly lower QoL after LT in comparison to those with a cholestatic liver disease[12]. Patients with viral hepatitis tend to suffer more from anxiety after LT than patients with alcoholic liver disease[13]. However, others challenge these data[10,14,21]. The influence of aetiology on QoL needs further investigation, since it influences all aspects of QoL[2,14].

Socio-demographic factors: The influence of gender on QoL remains a matter of debate, and data are conflicting[8,11,18].

Relational status however, does impact QoL. Married patients have a better QoL after liver transplantation than single or non-married patients[8,19,28]. This might be explained by a better social support.

Employment after LT is a crucial factor influencing QoL. Unfortunately, only 25% will return to work after two years. Restarting an active professional life after LT generates an income, but also restores the functional role of the patient in society. In employed patients, physical functioning is also improved and this results in an overall better QoL[10,12-14,21].

Early retirement, which is often observed in these patients, negatively impacts QoL. Patients with former alcoholic liver disease have a lower chance to return to work after transplantation, compared to other aetiologies, which can be related to the psychosocial burden present before liver transplantation. This can be explained by the psychosocial burden attached to addiction.

Professional activity before transplantation has a major impact on the general outcome after LT, which improves the activation grade after LT. As one might expect, the type of activities will determine the possibility to return to work, favouring higher educated patients compared to lower educated patients involved in physically demanding manual labour[1,3,13].

Patients regaining professional activities after only one year had a better QoL on the long term with less emotional problems[1,3,8,10,28]. A possible bias could be that only patients in good general condition will resume

Table 1 Summary of used articles

Ref.	Title	Study design	Population (*n*)	Instruments used to assess QoL	Main conclusions
Masala *et al*[1]	Quality of life and physical activity in liver transplantation patients: Results of a case-control study in Italy	Case-control	45 transplant patients 108 controls	SF-36 IPAQ	Transplant recipients are more subject to psychological/emotional distress and low physical function than the general population
Lankarani *et al*[2]	Outcomes of liver transplantation for patients with acute liver failure	Retrospective cross-sectional study	12 ALF patients 20 cirrhotic patients	N/A	Liver transplantation is safe, effective and should be considered in patients diagnosed with ALF
Drent *et al*[3]	Symptom experience, nonadherence and quality of life in adult liver transplant recipients	Review	N/A	N/A	Health-related quality of life is satisfactory, but below the level of the general population
O'Mahony *et al*[4]	The future of liver transplantation	Review	N/A	N/A	Improvements in surgical techniques, postoperative care, and donor and recipient selection have all contributed to the increased success of OLT and to higher survival rates in patients with advanced liver disease
Saidi[5]	Current status of liver transplantation	Review	N/A	N/A	New problems that include severe organ shortage, recurrence of primary disease, opportunistic infections, and development of de novo malignancies are the major problems affecting further implementation of LT
Butt *et al*[8]	Quality of life, risk assessment, and safety research in liver transplantation: New frontiers in health services and outcomes research	Review	N/A	N/A	Recipient quality of life is an area that has grown in importance in the published literature, but several important questions remain unanswered in these areas that merit programmatic, interdisciplinary research
Jay *et al*[9]	A review of quality of life instruments used in liver transplantation	Review	N/A	N/A	There are no available instruments that allow for the precise and reliable assessment of the full QoL impact of liver transplantation
Wang *et al*[10]	Health-related quality of life after liver transplantation: The experience from a single Chinese center	Case-control	60 post-LT, 55 benign end-stage liver disease, 50 controls	SF-36	LT patients generally have a good HRQoL although some respects of their HRQoL remains to be improved. Lower family income and poor education are important factors relating to the poor HRQoL of LT patients
Chen *et al*[11]	Health-related quality of life of 256 recipients after liver transplantation	RCT	256	SF-36, BAI, SDS	Age > 45 yr at time of transplant, DDLT, full-time working, no complications, anxiety and depression were possible factors influencing postoperative HRQoL in liver recipients
Braun *et al*[12]	Quality of life after liver transplantation	Case-control	123 recipients, 40 patients on the waiting list and a cohort of healthy controls	EORTC QLQ C30 and a liver transplant specific module	Retransplantation was accompanied by a significant loss of QoL. Cyclosporine-treated recipients displayed a better QoL compared with those treated with tacrolimus. The influence of medical parameters, such of co-morbidity or immunosuppression, needs to be further established with reference to QoL
Cannesson *et al*[13]	Vie quotidienne, grossesse, qualité de vie après transplantation hépatique	Review	N/A	N/A	The global perception of quality of life increases after liver transplantation, but remains lower than in healthy subjects
Burra *et al*[14]	Vie quotidienne, grossesse, qualité de vie après transplantation hépatique	Review	N/A	N/A	Liver transplantation is associated with an improvement in overall QoL. However, this improvement is lower than expected. QoL improves significantly early after liver trans-plantation, but it seems to decrease after the first year after transplantation
Zaydfudim *et al*[15]	Reduction in corticosteroids is associated with better health-related quality of life after liver transplantation	Retrospective analysis of prospective, longitudinal data	186	SF-36, BAI, and Center for Epidemiologic Studies Depression Scale	High-dose steroid use for post-transplant immunosuppression in liver transplant recipients is associated with reduced physical and mental HRQoL and increased symptoms of anxiety
Sirivatanauksorn *et al*[16]	Quality of life among liver transplantation patients	Case-control	57 pre-LT 95 post-LT	SF-36, CLDQ	OLT improved HRQoL of end-stage liver patients and their spouses or caregivers

Telles-Correia *et al*[17]	When does quality of life improve after liver transplantation? A longitudinal prospective study	Cohort study	60	SF-36	Our findings suggested that quality of life improved early after liver transplantation (1 mo). Between the first and the sixth months, there only was a significant improvement in the physical quality of life
Bownik *et al*[18]	When does quality of life improve after liver transplantation? A longitudinal prospective study	Review	N/A	N/A	Greater attention must be paid to patients' postoperative expectations and the effects of social influences (such as gender, education level, and socioeconomic and ethnic background)
Duffy *et al*[19]	When does quality of life improve after liver transplantation? A longitudinal prospective study	Prospective, cross-sectional study	168	SF-36, liver disease quality of life	More than 50% of LT recipients survive 20 yr, achieve important socioeconomic milestones, and report quality of life superior to patients with liver disease or other chronic conditions
Narumi *et al*[20]	Importance of awareness of perioperative social and physical situations of living donors for liver transplantation	Case-control study	31	SF-36, Hamilton's depression and anxiety scores	We must pay attention to depression and anxiety among living donors
Thiel *et al*[21]	Contributors to individual quality of life after liver transplantation	Cross-sectional study	71	SF-36, SEIQoL-DW	The five most nominated areas related to QoL are not related to health. By focusing on health, the importance of health-related factors is overrated, and the impact of non-medical effects is under- represented
Volk *et al*[22]	Organ quality and quality of life after liver transplantation	Retrospective cross-sectional study	171	SF-36	No association between organ quality and QOL after liver transplantation is found
Baranyi *et al*[24]	Overall mental distress and health-related quality of life after solid-organ transplantation: Results from a retrospective follow-up study	Retrospective follow-up	123	TERS, SCL-90-R SF-36	Transplantation recipients may face major transplantation- and treatment-related overall mental distress and impairments to their HRQoL. Further, overall mental distress is a high-risk factor in intensifying impairments to patients' overall quality of life
Jurado *et al*[25]	Coping strategies and quality of life among liver transplantation candidates	Observational	93	SF-36, MCMQ	Cirrhosis etiology is not a determinant factor of quality of life, whereas the acceptance-resignation coping strategy might lead to lower self-perception of quality of life
Lobo *et al*[26]	Care complexity, mood, and quality of life in liver pre-transplant patients	Cross-sectional	60	SF-36, HADS, INTERMED, EuroQol	High frequency of complexity in liver transplant candidates in European hospitals, but wide between-center differences suggest that local studies in specific hospitals and/or countries may be necessary to document care needs
Martín-Rodríguez *et al*[27]	Affective status in liver transplant recipients as a function of self-perception of general health	Cross-sectional	168	SF-36, HADS	Transplant recipients with worse self-perception of general health presented the same anxiety-depressive levels as patients with severe liver disease in the pretransplantation phase
Santos *et al*[28]	Affective status in liver transplant recipients as a function of self-perception of general health	Observational, descriptive and transversal	73	SF-36, BDI, structured interviews	Psychological aspects related to transplants require psychological intervention because they can affect the recuperation process, the quality of life, and the adherence to treatment for potential transplant patients
Stilley *et al*[29]	Pathways of psychosocial factors, stress, and health outcomes after liver transplantation	Longitudinal	130	N/A	A number of strong bidirectional relationships exist between coping style, self-regulatory ability, hostility, the caregiver relationship and family environment, personal and transplant-related stress over the second half of the first post-transplant year, and health (especially mental) outcomes at 12 mo post-transplant
Telles-Correia *et al*[30]	Predictors of mental health and quality of life after liver transplantation	Cross-sectional	60	SF-36	Quality of life improved early after liver transplantation (1 mo). Between the first and the sixth months, there only was a significant improvement in the physical quality of life
Telles-Correia *et al*[31]	Mental health and quality of life in alcoholic liver disease patients after liver transplantation: A prospective controlled study	Cross-sectional	45	SF-36, HADS, brief coping inventory	There is a favorable adjustment of alcoholic liver disease patients after transplantation as shown in coping mechanisms evolution, which might explain the improved mental health and quality of life dimensions

Poppe *et al*[32]	Improving quality of life in patients with chronic kidney disease: Influence of acceptance and personality	Cross-sectional	99	SF-36, ICQ, NEO-FFI	Acceptance is an important positive variable in accounting for health-related quality of life
Åberg *et al*[33]	Cost of a quality-adjusted life year in liver transplantation: The influence of the indication and the model for end-stage liver disease score	Cross-sectional	333	15D	The cost/QALY ratio for LT appears favorable, but it is dependent on the assessed time period and the severity of the liver disease
Fernández-Jiménez *et al*[34]	Comparison of quality of life between two clinical conditions with immunosuppressive therapy: Liver transplantation and multiple sclerosis	Cross-sectional	62	SF-36	Transplant recipients belong to a population that still requires special health care. Bio-psychosocial functioning is not fully restored

IPAQ: International Physical Activity Questionnaire; ALF: Acute liver failure; LT: Liver transplantation; QoL: Quality of life; HRQoL: Health related QoL; CLDQ: Chronic liver disease questionnaire; SF-36: Short form-36; OLT: Orthotopic liver transplantation; DDLT: Deceased donor liver transplantation; BAI: Beck anxiety inventory; SDS: Sheehan disability scale; EORTC QLQ: European Organization for Research and Treatment of Cancer, quality of life questionnaire; RCT: Randomized controlled trial; SEIQoL-DW: The schedule for the evaluation of individual quality of life - direct weighting; MCMQ: Medical coping modes questionnaire; SCL-90-R: Symptom checklist-90-revised; TERS: Transplant evaluation rating scale; HADS: Hospital anxiety and depression scale; BDI: Beck depression inventory; QALY: Quality-adjusted life year; ICQ: Illness cognition questionnaire; NEO-FFI: Neuroticism-extraversion-openness five-factor inventory; N/A: Not available.

work. Unemployment leads to a circulus vitiosus: Unemployed patients are less active, therefore less motivated which leads to reduced physical functioning and to lower employment. Professional reactivation should be stimulated after liver transplantation and is an interesting target for improvement of QoL.

Depression and anxiety: Patients with anxiety disorders or depression before LT report a lower QoL. Generally, it is assumed that mental disorders such as anxiety disorders and depression are mostly correlated with the severity of the disease pre-transplant and the occurrence of complications. However, some studies show that the acceptance of the disease is more predictive for a good or bad QoL than the severity of the disease[13,32].

Importantly, high levels of depression may double the chances of mortality. More than half of the recipients experience at least one episode of anxiety disorder or depression within the first two years after transplantation. This negatively impacts MCS[8,11].

Sexual function: An aspect of QoL that often remains taboo, is sexual function after LT. We found some conflicting results. As expected, sexual dysfunction seems to be related to old age, a positive post-transplant status and the presence of depression[14]. In a study of Cannesson *et al*[13], 70% of the liver transplant recipients declare to have a satisfactory sexual life after LT, even though a decrease is seen in libido, sexual potency and starting of new sexual relationships, caused by bodily changes and immunosuppressive side effects. This high percentage may be caused by a reserve of patients to communicate openly about this topic. Sexual function after liver transplantation is a research area with unmet needs.

Immunosuppressive therapy: Intensified immunosuppressive therapy during the first six months after transplantation can cause uncomfortable side effects[5]. These side effects are common and remain a challenge on the long term[3]. Transplant recipients take a variation of immunomodulating drugs, such as mTOR and calcineurin inhibitors. Their side effects include diabetes mellitus, renal failure, hypertension, tremor, obesity and hypercholesterolemia[4,11,15]. Furthermore, corticosteroids, often used in the first 3 mo can cause insomnia, mood swings and anxiety[15]. Especially high doses of corticosteroids are associated with physical and mental health, however this correlation is not seen with low-dose corticosteroids. Corticosteroid restricting strategies can reduce long-term complications and support QoL[4,15]. Noteworthy, some observations report better QoL in patients using cyclosporines than patients using tacrolimus[8]. However, rejection and re-transplantation affect QoL, and should be avoided by proper immunosuppressive therapy[8,12,13]. We can conclude that the maximal reduction of side effects has a beneficial effect on QoL[12,33,34].

Waiting list: Waiting for a liver transplantation can be long and stressful. The QoL of patients on the waiting list is significantly lower than the QoL of the general

population. Length of time spent on the waiting list has a negative impact on QoL. Thirty-eight percent of these patients are fearful (for rejection, death, recurrence of illness), 53% struggle with keeping up with their work-related functions and 23% experience social isolation. Anxiety and negative mood are known to get worse with increasing waiting time[13]. Nevertheless, some authors do not describe an increase in psychosocial stress[28]. More than half of the patients on the waiting list express a need for psychological counselling, which decreases during the waiting time[27].

Areas of controversy

Areas for further investigation: Although QoL has been extensively studied, we identified several areas of ambiguity. Identifying influencing factors of QoL is crucial to increase QoL after liver transplantation and needs further research[3,12]. In this line some interesting areas of research are: The influence of the underlying condition on QoL, gender, length of stay, immunosuppressive regimens, the influence of the recurrence of the initial liver disease, sexual function and professional reactivation. The development of more liver transplant specific outcome measures could be helpful[13,14].

Self-report QoL questionnaires: For the assessment of QoL more than 50 different instruments are used, measurement is not standardized and generic health assessment questionnaires are very commonly used. The largest part of these instruments has not been designed to evaluate the health status of liver transplant patients. Consequently it is difficult to interpret the results of these questionnaires in a meaningful way[9,14]. The SF-36 is the most commonly used generic questionnaire. It offers broad-spectrum questions applicable to a variety of patient groups and enables comparison between different populations[1,9]. These questionnaires can be distributed before and after LT.

Alternative questionnaires are the Transplant Effects Questionnaire, the Positive Effects of Transplant Scale, the schedule for the evaluation of individual expects of QoL - direct weighting (SEIQoL-DW)... The SEIQoL-DW allows patients to name areas important for him/herself and weigh each area to the relative importance and fulfilment level. On the downside, it is a qualitative interview-based assessment with his inherent disadvantages[21]. This complicates its use in clinical studies and does not enable repeated questioning of the same patient. Other questionnaires are the International Physical Activity Questionnaire and the Chronic Liver Disease Questionnaire. Only 16% of the reported authors used disease-specific instruments[1,9,16].

In conclusion, the best way to measure QoL after LT is the combination of generic questionnaires and disease-specific questionnaires, which offers a broad and thorough assessment of QoL. Jay *et al*[9] proposed the consistent use of validated, treatment-specific QoL instruments. This will result in a more accurate assessment of QoL in LT and lead to an increasing number of studies with comparable endpoints.

DISCUSSION

Quality of life should be a major concern for health workers involved in transplant medicine and should be the final "major outcome" to evaluate the success of liver transplantation on the long term. Fortunately, authors report a significant increase in QoL during the first year after liver transplantation, which remains stable afterwards. In general an improvement is seen both in physical and mental QoL. However, they express distinct dynamics after transplantation with a slower but more durable increase for the physical QoL compared to the mental QoL. An integrated biopsychosocial approach is the preferred model to evaluate QoL after liver transplantation.

QoL in liver transplantation is definitely influenced by numerous factors: Mental health, sociodemographic factors, underlying liver disease, immunosuppressive therapy, time on the waiting list, *etc*.

Our minireview has several limitations. Studies with different endpoints were used, since a lot of studies use different questionnaires to measure QoL. A general image of QoL in LT is given. Consequently not all aspects of QoL are reviewed in detail.

The latter could also be seen as strength of this article since we looked into almost all the aspects of QoL in liver recipients.

We can conclude that in order to further increase the QoL in LT recipients, multidisciplinary interventions of biosocial and psychological treatment are needed. An integrated approach of rehabilitation programs, psychological treatment and thorough repetitive medical follow-up seems to be helpful in these patients with physical and social problems, and stimulates the rehabilitation progress[8,10,28]. Longitudinal monitoring of QoL could increase insight into dynamics of QoL after LT and identify patients at risk for more thorough and individualized follow-up. This is a growing field of research with a lot of unanswered questions and opportunities for improvement strategies.

REFERENCES

1 **Masala D**, Mannocci A, Unim B, Del Cimmuto A, Turchetta F, Gatto G, Santoro R, Ettorre GM, Boccia A, La Torre G. Quality of life and physical activity in liver transplantation patients: results of a case-control study in Italy. *Transplant Proc* 2012; **44**: 1346-1350 [PMID: 22664013 DOI: 10.1016/j.transproceed.2012.01.123]

2 **Lankarani KB**, Eshraghian K, Malek-Hosseini SA, Janghorban P, Geramizadeh B, Eshraghian A. Outcomes of liver transplantation for patients with acute liver failure. *Arch Iran Med* 2013; **16**: 64-67 [PMID: 23360625]

3 **Drent G**, De Geest S, Dobbels F, Kleibeuker JH, Haagsma EB. Symptom experience, nonadherence and quality of life in adult liver transplant recipients. *Neth J Med* 2009; **67**: 161-168 [PMID: 19581664]

4 **O'Mahony CA**, Goss JA. The future of liver transplantation. *Tex Heart Inst J* 2012; **39**: 874-875 [PMID: 23304042]

5 **Saidi RF**. Current status of liver transplantation. *Arch Iran Med* 2012; **15**: 772-776 [PMID: 23199251]

6 **United Network for Organ Sharing**. Richmond, VA (United States of America), 2014. [accessed 2014 Dec]. Available from: URL: http://www.unos.org

7 **European Liver Transplant Registry**. Villejuif (France), 2014. [accessed 2014 Dec]. Available from: URL: http://www.eltr.org/spip.php?article4

8 **Butt Z**, Parikh ND, Skaro AI, Ladner D, Cella D. Quality of life, risk assessment, and safety research in liver transplantation: new frontiers in health services and outcomes research. *Curr Opin Organ Transplant* 2012; **17**: 241-247 [PMID: 22476225 DOI: 10.1097/MOT.0b013e32835365c6]

9 **Jay CL**, Butt Z, Ladner DP, Skaro AI, Abecassis MM. A review of quality of life instruments used in liver transplantation. *J Hepatol* 2009; **51**: 949-959 [PMID: 19775771 DOI: 10.1016/j.jhep.2009.07.010]

10 **Wang GS**, Yang Y, Li H, Jiang N, Fu BS, Jin H, Yang JX, Chen GH. Health-related quality of life after liver transplantation: the experience from a single Chinese center. *Hepatobiliary Pancreat Dis Int* 2012; **11**: 262-266 [PMID: 22672819]

11 **Chen PX**, Yan LN, Wang WT. Health-related quality of life of 256 recipients after liver transplantation. *World J Gastroenterol* 2012; **18**: 5114-5121 [PMID: 23049223 DOI: 10.3748/wjg.v18.i36.5114]

12 **Braun F**, Teren K, Wilms P, Günther R, Allmann J, Broering DC, Küchler T. Quality of life after liver transplantation. *Transplant Proc* 2009; **41**: 2564-2566 [PMID: 19715975 DOI: 10.1016/j.transproceed.2009.06.030]

13 **Cannesson A**, Boleslawski E, Declerck N, Mathurin P, Pruvot FR, Dharancy S. [Daily life, pregnancy, and quality of life after liver transplantation]. *Presse Med* 2009; **38**: 1319-1324 [PMID: 19586750 DOI: 10.1016/j.lpm.2009.06.003]

14 **Burra P**, Germani G. Long-term quality of life for transplant recipients. *Liver Transpl* 2013; **19** Suppl 2: S40-S43 [PMID: 23960031 DOI: 10.1002/lt.23725]

15 **Zaydfudim V**, Feurer ID, Landman MP, Moore DE, Wright JK, Pinson CW. Reduction in corticosteroids is associated with better health-related quality of life after liver transplantation. *J Am Coll Surg* 2012; **214**: 164-173 [PMID: 22137824 DOI: 10.1016/j.jamcollsurg.2011.10.006]

16 **Sirivatanauksorn Y**, Dumronggittigule W, Limsrichamrern S, Iramaneerat C, Kolladarungkri T, Kositamongkol P, Mahawithitwong P, Asavakarn S, Tovikkai C. Quality of life among liver transplantation patients. *Transplant Proc* 2012; **44**: 532-538 [PMID: 22410064 DOI: 10.1016/j.transproceed.2011.12.056]

17 **Telles-Correia D**, Barbosa A, Mega I, Mateus E, Monteiro E. When does quality of life improve after liver transplantation? A longitudinal prospective study. *Transplant Proc* 2009; **41**: 904-905 [PMID: 19376385 DOI: 10.1016/j.transproceed.2009.01.051]

18 **Bownik H**, Saab S. Health-related quality of life after liver transplantation for adult recipients. *Liver Transpl* 2009; **15** Suppl 2: S42-S49 [PMID: 19876941 DOI: 10.1002/lt.21911]

19 **Duffy JP**, Kao K, Ko CY, Farmer DG, McDiarmid SV, Hong JC, Venick RS, Feist S, Goldstein L, Saab S, Hiatt JR, Busuttil RW. Long-term patient outcome and quality of life after liver transplantation: analysis of 20-year survivors. *Ann Surg* 2010; **252**: 652-661 [PMID: 20881772 DOI: 10.1097/SLA.0b013e3181f5f23a]

20 **Narumi S**, Umehara M, Toyoki Y, Ishido K, Kudo D, Kimura N, Kobayashi T, Sugai M, Hakamada K. Importance of awareness of perioperative social and physical situations of living donors for liver transplantation. *Transplant Proc* 2012; **44**: 328-331 [PMID: 22410008 DOI: 10.1016/j.transproceed.2012.01.049]

21 **Thiel C**, Landgrebe K, Knubben E, Nadalin S, Ladurner R, Grasshoff C, Königsrainer A, Schenk M, Thiel K. Contributors to individual quality of life after liver transplantation. *Eur J Clin Invest* 2013; **43**: 11-19 [PMID: 23078202 DOI: 10.1111/eci.12007]

22 **Volk ML**, Hagan M. Organ quality and quality of life after liver transplantation. *Liver Transpl* 2011; **17**: 1443-1447 [PMID: 21898767 DOI: 10.1002/lt.22425]

23 **World Health Organisation**. Copenhagen (Denmark), 2014. [accessed 2014 Dec]. Available from: URL: http://www.who.int/features/qa/62/en/

24 **Baranyi A**, Krauseneck T, Rothenhäusler HB. Overall mental distress and health-related quality of life after solid-organ transplantation: results from a retrospective follow-up study. *Health Qual Life Outcomes* 2013; **11**: 15 [PMID: 23391215 DOI: 10.1186/1477-7525-11-15]

25 **Jurado R**, Morales I, Taboada D, Denia F, Mingote JC, Jiménez MÁ, Palomo T, Rubio G. Coping strategies and quality of life among liver transplantation candidates. *Psicothema* 2011; **23**: 74-79 [PMID: 21266145]

26 **Lobo E**, Stiefel F, Söllner W, Santabarbara J, Lobo A, Huyse F, Marcos G, Michaud L, Hohenberger W, Ludwig G. Care complexity, mood, and quality of life in liver pre-transplant patients. *Clin Transplant* 2013; **27**: 417-425 [PMID: 23488869 DOI: 10.1111/ctr.12104]

27 **Martín-Rodríguez A**, Pérez-San-Gregorio MA, Domínguez-Cabello E, Fernández-Jiménez E, Pérez Bernal J. Affective status in liver transplant recipients as a function of self-perception of general health. *Transplant Proc* 2012; **44**: 2619-2621 [PMID: 23146474 DOI: 10.1016/j.transproceed.2012.09.052]

28 **Santos GG**, Gonçalves LC, Buzzo N, Mendes TA, Dias TP, da Silva RC, da Silva RF, de Felicio HC, Santos Júnior R, Miyazaki MC. Quality of life, depression, and psychosocial characteristics of patients awaiting liver transplants. *Transplant Proc* 2012; **44**: 2413-2415 [PMID: 23026609 DOI: 10.1016/j.transproceed.2012.07.046]

29 **Stilley CS**, Flynn WB, Sereika SM, Stimer ED, DiMartini AF, deVera ME. Pathways of psychosocial factors, stress, and health outcomes after liver transplantation. *Clin Transplant* 2012; **26**: 216-222 [PMID: 21518004 DOI: 10.1111/j.1399-0012.2011.01467.x]

30 **Telles-Correia D**, Barbosa A, Mega I, Monteiro E. Predictors of mental health and quality of life after liver transplantation. *Psychother Psychosom* 2011; **80**: 60-61 [PMID: 21088450 DOI: 10.1159/000317539]

31 **Telles-Correia D**, Barbosa A, Mega I, Monteiro E, Barroso E. Mental health and quality of life in alcoholic liver disease patients after liver transplantation: a prospective controlled study. *Transplant Proc* 2011; **43**: 184-186 [PMID: 21335183 DOI: 10.1016/j.transproceed.2011.01.002]

32 **Poppe C**, Crombez G, Hanoulle I, Vogelaers D, Petrovic M. Improving quality of life in patients with chronic kidney disease: influence of acceptance and personality. *Nephrol Dial Transplant* 2013; **28**: 116-121 [PMID: 22822093 DOI: 10.1093/ndt/gfs151]

33 **Åberg F**, Mäklin S, Räsänen P, Roine RP, Sintonen H, Koivusalo AM, Höckerstedt K, Isoniemi H. Cost of a quality-adjusted life year in liver transplantation: the influence of the indication and the model for end-stage liver disease score. *Liver Transpl* 2011; **17**: 1333-1343 [PMID: 21770017 DOI: 10.1002/lt.22388]

34 **Fernández-Jiménez E**, Pérez-San-Gregorio MA, Martín-Rodríguez A, Domínguez-Cabello E, Navarro-Mascarell G, Bernardos-Rodríguez A. Comparison of quality of life between two clinical conditions with immunosuppressive therapy: liver transplantation and multiple sclerosis. *Transplant Proc* 2012; **44**: 2609-2611 [PMID: 23146471 DOI: 10.1016/j.transproceed.2012.09.051]

P- Reviewer: Feier FH, Gutierrez JA, Mittal PK, Srivastava M
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i18.757

World J Hepatol 2016 June 28; 8(18): 757-761
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Clinical characteristics and progression of liver abscess caused by toxocara

Kyung Ho Ha, Jung Eun Song, Byung Seok Kim, Chang Hyeong Lee

Kyung Ho Ha, Department of Internal Medicine, Daegu Medical Center, Daegu 41845, South Korea

Jung Eun Song, Byung Seok Kim, Chang Hyeong Lee, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Daegu Catholic University, Daegu 42472, South Korea

Author contributions: Ha KH searched literature, drafted the manuscript, incorporated corrections by coauthors into final manuscript and organized details for submission of manuscript; Song JE and Kim BS supervised the manuscript; Lee CH contributed to writing the manuscript, reviews and corrections, final approval and submissions.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Daegu Catholic University.

Informed consent statement: Because of retrospective and anonymous character of this study, the need for informed consent was waived by the institutional review board.

Conflict-of-interest statement: The authors have no conflict of interest related to this publication.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Chang Hyeong Lee, MD, Professor, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Daegu Catholic University, 33, Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, South Korea. chlee1@cu.ac.kr

Telephone: +82-53-6503067
Fax: +82-53-6284050

Received: February 15, 2016
Peer-review started: February 16, 2016
First decision: March 24, 2016
Revised: April 7, 2016
Accepted: June 1, 2016
Article in press: June 3, 2016
Published online: June 28, 2016

Abstract

AIM: To evaluate the clinical characteristics and progression of liver abscess caused by toxocara.

METHODS: We retrospectively reviewed the medical records of patients with serum IgG antibody to *Toxocara canis* and liver abscess diagnosed using abdominal computed tomography between February 2010 and February 2015. Among 84 patients exhibiting serum IgG antibody to *Toxocara canis*, 34 patients were diagnosed with liver asbscess and treated with albendazole. A follow-up period of 1 year was conducted.

RESULTS: Mean patient age was 53 (34-79) years, with 26 (76.5%) patients being male. Twenty-one (61.7%) patients were moderate or heavy drinkers, 23 (67.6%) patients had a history of eating raw meat or liver and 6 (17.6%) patients owned pet dogs or cats. Main patient symptoms consisted of right upper quadrant pain, fever, and fatigue; 18 (52.9%) patients, however, presented with no symptoms. Lung involvement was detected in 444 (11.7%) patients. The eosinophil count increased in 29 (85.3%) patients at initial diagnosis, and decreased in most patients after albendazole treatment. The initial serum IgE level increased in 25 (73.5%) patients, but exhibited various response levels after albendazole treatment. Liver abscess formation improved in all patients.

CONCLUSION: The liver abscess was improved with albendazole treatment.

Key words: Toxocariasis; Liver abscess; Eosinophilia

Core tip: This is a retrospective study to evaluate the clinical characteristics and progression of liver abscess caused by toxocara. Eating uncooked food was a more common route of infection than contact with pet animals. Alcohol consumption, sex (male), and ingestion of raw meat or liver were considered to be significant risk factors for toxocariasis. Patients can present with no specific symptoms, eosinophilia, and/or increased levels of serum IgE. Liver abscess caused by toxocara has characteristic radiologic findings. Even if a few patients experience relapse or migration of abscess posttreatment, a good prognosis exists for the overall clinical course.

Ha KH, Song JE, Kim BS, Lee CH. Clinical characteristics and progression of liver abscess caused by toxocara. *World J Hepatol* 2016; 8(18): 757-761 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i18/757.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i18.757

INTRODUCTION

Toxocariasis is a parasitic infection caused by *Toxocara canis* or *Toxocara cati*. It is known as a main cause of eosinophilia[1]. Clinical manifestations of toxocariasis range from asymptomatic infection to involvement of various organs. Visceral larva migrans (VLM) means toxocara infection associated with various internal organs of the body[2]. Liver abscess represent one type of VLM, which differs from pyogenic liver abscess in displaying specific histologic and radiologic findings[3,4]. Hepatic VLM or liver abscess caused by toxocara can occasionally be detected as an abnormal finding at ultrasonography screening and therefore be misdiagnosed as a malignancy in patients with chronic liver disease or a history of other cancer(s)[5]. A thorough understanding of the clinical characteristics and progression of hepatic VLM or liver abscess caused by toxocara is necessary in order to determine potential factors that may help improve diagnosis, as well as avoid unnecessary testing and improper disease treatment.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients with serum IgG antibody to *Toxocara canis* and liver abscess diagnosed by abdominal computed tomography (CT) at Daegu Catholic University Hospital between February 23, 2010 and February 24, 2015. We investigated patients about a history of moderate or heavy alcohol consumption, raw meat or cow's liver ingestion, and owning pet dogs or cats. We obtained liver transaminase levels, peripheral blood eosinophil counts, serum IgE levels, hepatitis B surface antigen and antibody and anti-hepatitis C virus antibody results. In addition, we obtained any history of underlying disease and other organ(s) involvement. Eosinophilia was defined as an absolute peripheral blood eosinophil count $\geqslant$ 500/μL. Elevated serum levels of IgE were defined as IgE levels $\geqslant$ 100 IU/mL. We treated patients with liver abscess with 400 mg orally twice daily for 5 d. The follow-up protocol consisted of obtaining repeat eosinophil counts and serum IgE levels, as well as performing abdominal CT scans at various intervals for 1 year.

RESULTS

Among a total of 84 patients exhibiting serum IgG antibody to *Toxocara canis*, 34 patients were diagnosed with liver abscess. Mean patient age was 53 years, with serum IgG antibody to *Toxocara canis* being three times more prevalent in men than in women (Table 1). Twenty-three (67.6%) patients had a history of eating raw meat or liver and 6 (17.6%) patients owned pet dogs or cats (Table 1). Four patients had no specific history of eating uncooked food or owning pet animals. Main patient symptoms consisted of right upper quadrant pain, fever, and fatigue. Eighteen (52.9%) patients were asymptomatic (Table 1). Five patients revealed involvement of other organs including the lung, a leg muscle, and the brain in addition to liver involvement (Table 1). One of four patients with lung involvement demonstrated concomitant brain involvement. Aspartate transaminase and alanine transaminase levels were normal in all patients except one who had alcoholic hepatitis. Twenty-nine (85.3%) patients initially presented with eosinophilia. Among these 29 patients, 17 had mild eosinophilia, 7 had moderate eosinophilia, and 5 had severe eosinophilia (Table 1). Twenty-five of 26 patients who had repeat serum IgE levels had initially increased IgE levels (Table 1). The remaining patient demonstrated an upper normal serum IgE level of 99 IU/mL. Liver abscess on dynamic CT included multiple lesions in 19 patients and a single lesion in 15 patients (Table 1). The lesions were seen as ill-defined, low-attenuating, oval nodules. They were faintly seen on arterial and equilibrium phase images and best seen on the portal venous phase. All of these 34 patients were treated with albendazole. After treatment, the eosinophil count was normal in 16 patients, decreased in 8, and remained the same in one (Table 2). The eosinophilic response pattern was divided into two groups: Continuously decreasing (15 patients, 62.5%) and fluctuating (9 patients, 37.5%). We were unable to evaluate the eosinophilic response in 9 patients. Among those patients, 5 had normal eosinophil counts at initial diagnosis and 4 did not participate in the follow-up protocol posttreatment. Fifteen of 24 patients who showed an eosinophilic response did so within 1 mo posttreatment. Six months after treatment, the serum

Table 1 Baseline characteristics of patients with liver abscess caused by toxocara

Patients, *n*	34
Mean age, yr	53
Male, *n* (%)	26 (76.5)
Underlying disease, *n* (%)	
Hypertension	9 (26.5)
Diabetes	4 (11.8)
Tuberculosis	3 (8.8)
Liver cirrhosis	2 (5.9)
Chronic viral hepatitis	2 (5.9)
Cancer history	2 (5.9)
None	9 (26.5)
Alcohol drinking, *n* (%)	
Heavy drinking	14 (41.2)
Moderate drinking	7 (20.6)
No drinking	9 (26.5)
Unknown	4 (11.8)
Transmission, *n* (%)	
Eating raw meat or liver	23 (67.6)
Keeping pet dogs or cats	6 (17.6)
No specific history	4 (11.8)
Unknown	7 (20.6)
Symptoms, *n* (%)	
Asymptomatic	18 (52.9)
RUQ pain	6 (17.6)
Fever	4 (11.8)
Fatigue	4 (11.8)
Anorexia	2 (5.9)
Cough	2 (5.9)
Weakness of legs	2 (5.9)
Involvement of other organs, *n* (%)	
Lung	4 (11.8)
Muscle of legs	1 (2.9)
CNS	1 (2.9)
Mean AST/ALT, IU/L	31/31
Eosinophilia, *n* (%)	
Normal (< 500/μL)	5 (14.7)
Mild (500-1500/μL)	17 (50.0)
Moderate (1500-5000/μL)	7 (20.6)
Severe (> 5000/μL)	5 (14.7)
Serum IgE, *n* (%)	
Normal (< 100 IU/mL)	1 (2.9)
Mild elevated (100-500 IU/mL)	10 (29.4)
Severe elevated (> 500 IU/mL)	15 (44.1)
Unknown	8 (23.5)
Liver abscess, *n* (%)	
Single	15 (44.1)
Multiple	19 (55.9)

Liver abscess caused by toxocara was related to sex (male), alcohol drinking, eating raw meat or liver. Laboratory characteristics showed normal liver enzymes, peripheral blood eosinophilia, and elevated level of serum IgE. RUQ: Right upper quadrant; CNS: Central nervous system; AST: Alanine aminotransferase; ALT: Aspartate aminotransferase.

IgE level increased in 7 patients, decreased in 8, and remained the same in 3 (Table 2). We were unable to evaluate the serum IgE response in 16 patients. Among these patients, 8 patients did not undergo check serum IgE level tests initially and the other 8 patients did not participate in the follow-up protocol. A follow-up CT was performed for 22 patients. Among these patients, 15 demonstrated disappearance of liver abscess within 3 mo and 21 within 6 mo. Relapse or migration of liver abscess was observed in 3 patients.

Table 2 Therapeutic response after treatment with albendazole *n* (%)

Eosinophilia (*n* = 25)	
Normalized	16 (64)
Decreased	8 (32)
No change	1 (4)
Serum IgE (*n* = 18)	
Increased	7 (38.9)
Decreased	8 (44.4)
No change	3 (16.7)
Liver abscess (*n* = 22)	
Improved	22 (100)
Not improved	0

Most eosinophil counts were normalized or decreased and all of the abscesses were improved on computed tomography after 1 year, but the levels of serum IgE showed variable response after 6 mo.

DISCUSSION

Toxocariasis is a worldwide disease. The overall seroprevalence of toxocariasis has been reported as 13.9% in Unites States[6], 2%-5% and 14%-37% respectively in the urban and rural areas of France[7], 18% in China, 20% in Malaysia, 68% in Indonesia, and 81% in Nepal[8]. In South Korea the seroprevalence has been reported as 5% in Gangwon-do[9], 6% in Seoul, and 11% in Gyeongsangnam-do[10]. The seroprevalence of toxocariasis in patients with eosinophilia has been reported as 64.9%-86.7% in Seoul[8,11], 50.5% in Chungcheongnam-do[12], and 62% in Pohang[13]. These reports confirm that toxocariasis is known to be a main cause of eosinophilia. Toxocara infection is caused by ingestion of embryonated eggs from the soil and pet animals or by ingestion of encapsulated larva while eating uncooked paratenic hosts[14]. In this study, eating uncooked food was a more common route of infection than contact with pet animals (67.6% *vs* 17.6%). Choi *et al*[8] suggested that ingestion of raw cow liver was related to an increased risk of toxocariasis, but not ingestion of raw meat or animal blood and owning dogs. Based on the results of our epidemiologic study, demonstrating that men are three times more susceptible to toxocariasis than women, and revealing that approximately 60% of the patients consumed alcohol, we consider sex (male) and alcohol consumption as risk factors for toxocariasis.

The most commonly utilized serologic test for toxocariasis is the detection of the serum IgG antibody to the toxocara excretory/secretory antigen (TES Ag) with a toxocara ELISA kit (Bordier Affinity Products, Crissier, Switzerland)[15]. Eosinophilia, elevated serum IgE levels or increased eosinophil cationic protein is helpful for the diagnosis of active toxocariasis[16-18]. Although the toxocara ELISA test possesses high sensitivity and specificity[15], the test cannot differentiate present from past infections[16] and may produce cross-reactivity with other parasites such as *Clonorchis sinensis*, *Sparganum*, *Fasciola hepatica*, and *Paragonimus westermani*[2]. Infected larva can penetrate the intestinal wall through vessels and invade various organs such as the liver, lung, muscle,

eye, heart and central nervous system, *etc*[19,20]. We investigated other organ(s) involvement in 84 patients who had the IgG antibody for *Toxocara canis*, and found the organs involved, displayed in order of frequency, were the liver (40.5%), lung (27.4%), eye (8.3%), skin (3.6%), muscle (1.2%), and brain (1.2%). Lung involvement occurred in 11.8% of patients with liver abscess (Table 1). This occurrence, therefore, creates the necessity of assessing the possibility of lung involvement in patients with liver abscess caused by toxocariasis. TES Ag secreted from the epicuticle of the moving larva causes an immune reaction, which produces increased serum IgE and eosinophilia[21]. Liver abscess, histologically described as eosinophilic abscess or granuloma, results from eosinophilic inflammation which develops when larva remain in the liver[22].

Approximately 50% of patients were asymptomatic. A small number of patients had right upper quadrant pain, fever, and fatigue (Table 1). It remains impossible to rule out liver abscess in patients with toxocariasis using only symptom information. In contrast to patients with hepatic visceral larva migrans or liver abscess caused by toxocara, approximately 90% of patients with pyogenic liver abscess have fever and approximately 70% have abdominal pain[23]. The possibility of abscess caused by toxocara must be considered if liver abscess is inadvertently detected upon abdominal ultrasonography during routine medical exams. CT finidngs of liver abscess caused by toxocara usually include lesions that measure approximately 1-1.5 cm in diameter; possess an oval shape, obscure margin, multiplicity, and hypodensity[3]. In contrast to hepatocellular carcinoma, CT finindgs for liver abscess include lesions that are regular, not round, and striking at portal venous phase[24]. We can confirm the CT findings cited in this study; however, one finding that differs from the previous study[24] is that data from this study reveal that a relatively high number of patients with single abscess existed.

Toxocariasis is a self-limiting disease; therefore, patients with mild symptoms do not necessarily require medication[2]. However, if patients have moderate or severe symptoms due to visceral larva migrans, they should be treated with albendazole[24]. Previous literature has recommended treating liver abscess regardless of symptom status because, compared with the control group, the albendazole group demonstrated accelerated liver abscess healing[5]. Twenty-four of 25 patients who presented with eosinophilia and had been treated with albendazole displayed decreased eosinophil counts. Fifteen of these patients (62.5%) had checked their eosinophil count within 1 mo posttreatment. All patients experienced decreased eosinophil counts. Previous literature has reported an eosinophilic response occurred 1 mo posttreatment[16]; therefore, we concluded that the eosinophilic response could be evaluated 1 mo posttreatment. In addition, if the eosinophilic count initially decreases, but continually increases during the posttreatment period, relapse or migration of lesions should be considered. Transient eosinophil count fluctuations, which can occur among eosinophilic response patients as observed in this study, must also be considered. Abdominal CT and repeat eosinophil counts at follow-up can help distinguish relapse or migration from eosinophilic fluctuation. Repeat serum IgE levels at follow-up provides an inadequate evaluation measurement of treatment response because serum IgE responds unpredictably[16]. CT follow-up was performed within 3 mo for 68.2% of patients and liver abscess disappeared in all of them. We therefore concluded that CT scan results could be evaluated 3 mo posttreatment. We encountered relapse or migration of lesions in three patients at 4, 6 and 8 mo posttreatment. Eosinophilia developed in only one of these patients, while the other two experienced continuously decreasing eosinophil levels despite relapse or migration of lesions. Two of these three patients were retreated with albendazole, while the other was only observed. Subsequently, all lesions of all three patients disappeared. If this phenomenon is observed posttreatment, the possibility of reinfection also needs to be considered. No evidence exists confirming that patients who are experiencing relapse or migration of liver abscess, regardless of clinical symptoms or eosinophilia, should be retreated with albendazole. It is reasonable, however, to retreat relapsed or migrated lesions with albendazole because albendazole is inexpensive, easily available over the counter and has no significant side effects. Existence of toxocara-specific IgG antibody can persist for years after the disappearance of liver abscess. One study reported that the mean duration of IgG antibody existence in the body was 2.7 years[25]. IgG antibody detection was conducted at 3, 9, 18, 24 mo and 5 years each in five patients from this study. All patients persistently displayed IgG antibody during the follow-up period, therefore, excluding detection of serum IgG antibody testing from the follow-up protocol[16].

The study has limitations as a retrospective study, so our recommendations about the evaluation measurement of treatment response are based on the literature data and not on the results of this study.

Liver abscess caused by toxocara is a disease resulting from the ingestion of uncooked food, which causes an immune reaction in the liver. Patients can present with no specific symptoms, eosinophilia, and/or increased levels of serum IgE. Toxocariasis has characteristic radiologic findings and may involve other organs such as the lung. Treatment of toxocariasis consists of taking albendazole for 5 d. After treatment, the eosinophil count starts to decrease within 1 mo and the abscess begins to disappear within 3 mo as displayed on CT scan. Complete disappearance of liver abscess can occur after 1 year. Even if a few patients experience relapse or migration of abscess posttreatment, a good prognosis exists for the overall clinical course of this disease.

COMMENTS

Background

Toxocariasis is a parasitic infection caused by *Toxocara canis* or *Toxocara cati*. It is known as a main cause of eosinophilia. Clinical manifestations of

toxocariasis range from asymptomatic infection to involvement of various organs. Liver abscess caused by toxocara can occasionally be detected as an abnormal finding at ultrasonography screening and therefore be misdiagnosed as a malignancy in patients with chronic liver disease or a history of other cancer(s). The authors evaluated the clinical characteristics and progression of liver abscess caused by toxocara.

Research frontiers

This study contributes to determining potential factors that may help improve diagnosis of liver abscess caused by toxocara, as well as avoid unnecessary testing and improper treatment.

Innovations and breakthroughs

In this study, all patients (62.5%) who had checked their eosinophil count within 1 mo posttreatment experienced decreased eosinophil counts. And all patients (68.2%) who had checked computed tomography (CT) follow-up within 3 mo posttreatment experienced disappearance of liver abscess. Therefore, the authors concluded that the eosinophilic response could be evaluated 1 mo posttreatment and CT scan could be evaluated 3 mo posttreatment.

Applications

Human toxocariasis can clinically present as liver abscess. If a patient with a history of eating raw meat or liver presents peripheral eosinophilia and abnormal liver imaging, liver abscess caused by toxocara should be considered for diagnosis.

Terminology

Toxocariasis: An infection transmitted from animals to humans caused by the parasitic roundworms commonly found in the intestine of dogs (*Toxocara canis*) and cats (*Toxocara cati*).

Peer-review

Studies exploring toxocariasis in liver abscess have been infrequent. The author of this paper evaluated the clinical characteristics and progression of liver abscess caused by toxocara. This study is useful for diagnosing and monitoring the disease in the clinical practice.

REFERENCES

1 **Kwon NH**, Oh MJ, Lee SP, Lee BJ, Choi DC. The prevalence and diagnostic value of toxocariasis in unknown eosinophilia. *Ann Hematol* 2006; **85**: 233-238 [PMID: 16463154 DOI: 10.1016/j.jaci.2005.12.320]

2 **Pawlowski Z**. Toxocariasis in humans: clinical expression and treatment dilemma. *J Helminthol* 2001; **75**: 299-305 [PMID: 11818044 DOI: 10.1017/S0022149X01000464]

3 **Lim JH**. Toxocariasis of the liver: visceral larva migrans. *Abdom Imaging* 2008; **33**: 151-156 [PMID: 17924161 DOI: 10.1007/s00261-007-9325-y]

4 **Rahimian J**, Wilson T, Oram V, Holzman RS. Pyogenic liver abscess: recent trends in etiology and mortality. *Clin Infect Dis* 2004; **39**: 1654-1659 [PMID: 15578367 DOI: 10.1086/425616]

5 **Jang EY**, Choi MS, Gwak GY, Koh KC, Paik SW, Lee JH, Paik YH, Yoo BC. Enhanced resolution of eosinophilic liver abscess associated with toxocariasis by albendazole treatment. *Korean J Gastroenterol* 2015; **65**: 222-228 [PMID: 25896156 DOI: 10.4166/kjg.2015.65.4.222]

6 **Won KY**, Kruszon-Moran D, Schantz PM, Jones JL. National seroprevalence and risk factors for Zoonotic Toxocara spp. infection. *Am J Trop Med Hyg* 2008; **79**: 552-557 [PMID: 18840743]

7 **Magnaval JF**, Michault A, Calon N, Charlet JP. Epidemiology of human toxocariasis in La Réunion. *Trans R Soc Trop Med Hyg* 1994; **88**: 531-533 [PMID: 7992328 DOI: 10.1016/0035-9203(94)90148-1]

8 **Choi D**, Lim JH, Choi DC, Paik SW, Kim SH, Huh S. Toxocariasis and ingestion of raw cow liver in patients with eosinophilia. *Korean J Parasitol* 2008; **46**: 139-143 [PMID: 18830052 DOI: 10.3347/kjp.2008.46.3.139]

9 **Park HY**, Lee SU, Huh S, Kong Y, Magnaval JF. A seroepidemiological survey for toxocariasis in apparently healthy residents in Gangwon-do, Korea. *Korean J Parasitol* 2002; **40**: 113-117 [PMID: 12325440 DOI: 10.3347/kjp.2002.40.3.113]

10 **Kim HS**, Jin Y, Choi MH, Kim JH, Lee YH, Yoon CH, Hwang EH, Kang H, Ahn SY, Kim GJ, Hong ST. Significance of serum antibody test for toxocariasis in healthy healthcare examinees with eosinophilia in Seoul and Gyeongsangnam-do, Korea. *J Korean Med Sci* 2014; **29**: 1618-1625 [PMID: 25469060 DOI: 10.3346/jkms.2014.29.12.1618]

11 **Kim YH**, Huh S, Chung YB. Seroprevalence of toxocariasis among healthy people with eosinophilia. *Korean J Parasitol* 2008; **46**: 29-32 [PMID: 18344674 DOI: 10.3347/kjp.2008.46.1.29]

12 **Seo M**, Yoon SC. A seroepidemiological survey of toxocariasis among eosinophilia patients in Chungcheongnam-do. *Korean J Parasitol* 2012; **50**: 249-251 [PMID: 22949755 DOI: 10.3347/kjp.2012.50.3.249]

13 **Ryu BH**, Park JS, Jung YJ. Clinical and Serological Findings in Patients with Toxocariasis in the Pohang Region: The Features of Toxocariasis in Pohang. *Korean J Med* 2013; **84**: 203-210

14 **Morris PD**, Katerndahl DA. Human toxocariasis. Review with report of a probable case. *Postgrad Med* 1987; **81**: 263-267 [PMID: 3543902]

15 **Jacquier P**, Gottstein B, Stingelin Y, Eckert J. Immunodiagnosis of toxocarosis in humans: evaluation of a new enzyme-linked immunosorbent assay kit. *J Clin Microbiol* 1991; **29**: 1831-1835 [PMID: 1774303]

16 **Magnaval JF**, Glickman LT, Dorchies P, Morassin B. Highlights of human toxocariasis. *Korean J Parasitol* 2001; **39**: 1-11 [PMID: 11301585 DOI: 10.3347/kjp.2001.39.1.1]

17 **Fillaux J**, Magnaval JF. Laboratory diagnosis of human toxocariasis. *Vet Parasitol* 2013; **193**: 327-336 [PMID: 23318165 DOI: 10.1016/j.vetpar.2012.12.028]

18 **Magnaval JF**, Berry A, Fabre R, Morassin B. Eosinophil cationic protein as a possible marker of active human Toxocara infection. *Allergy* 2001; **56**: 1096-1099 [PMID: 11703226 DOI: 10.1034/j.1398-9995.2001.00284.x]

19 **Marx C**, Lin J, Masruha MR, Rodrigues MG, da Rocha AJ, Vilanova LC, Gabbai AA. Toxocariasis of the CNS simulating acute disseminated encephalomyelitis. *Neurology* 2007; **69**: 806-807 [PMID: 17709716 DOI: 10.1212/01.wnl.0000267664.53595.75]

20 **Enko K**, Tada T, Ohgo KO, Nagase S, Nakamura K, Ohta K, Ichiba S, Ujike Y, Nawa Y, Maruyama H, Ohe T, Kusano KF. Fulminant eosinophilic myocarditis associated with visceral larva migrans caused by Toxocara canis infection. *Circ J* 2009; **73**: 1344-1348 [PMID: 19122304 DOI: 10.1253/circj.CJ-08-0334]

21 **Lee S**. Pathophysiology of hypersensitivity in human by Toxocara canis larval infection. Chung-Ang University Doctoral Thesis, 2001

22 **Despommier D**. Toxocariasis: clinical aspects, epidemiology, medical ecology, and molecular aspects. *Clin Microbiol Rev* 2003; **16**: 265-272 [PMID: 12692098 DOI: 10.1128/CMR.16.2.265-272.2003]

23 **Chang S**, Lim JH, Choi D, Park CK, Kwon NH, Cho SY, Choi DC. Hepatic visceral larva migrans of Toxocara canis: CT and sonographic findings. *AJR Am J Roentgenol* 2006; **187**: W622-W629 [PMID: 17114516]

24 **Stürchler D**, Schubarth P, Gualzata M, Gottstein B, Oettli A. Thiabendazole vs. albendazole in treatment of toxocariasis: a clinical trial. *Ann Trop Med Parasitol* 1989; **83**: 473-478 [PMID: 2694978]

25 **Jeanneret JP.** Epidémiologie de la toxocarose dans la région jurassienne: Université de Neuchâtel, 1991

P- Reviewer: Akyuz U, Ferraioli G, He JY, Romero MR, Zielinski J **S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i18.762

World J Hepatol 2016 June 28; 8(18): 762-769
ISSN 1948-5182 (online)

Treating chronic hepatitis B virus: Chinese physicians' awareness of the 2010 guidelines

Lai Wei, Ji-Dong Jia, Xin-Hua Weng, Xiao-Guang Dou, Jia-Ji Jiang, Hong Tang, Qin Ning, Qing-Qing Dai, Run-Qin Li, Jie Liu

Lai Wei, Department of Hepatology, Peking University People's Hospital, Beijing 100044, China

Ji-Dong Jia, Department of Hepatology, Beijing Friendship Hospital, Capital Medical University, Beijing 100029, China

Xin-Hua Weng, Department of Infectious Disease, Shanghai Huashan Hospital, Shanghai 200040, China

Xiao-Guang Dou, Department of Infectious Disease, Shengjing Hospital of China Medical University, Shenyang 110022, Liaoning Province, China

Jia-Ji Jiang, Department of Hepatology, the First Affiliated Hospital of Fujian Medical University, Fuzhou 350005, Fujian Province, China

Hong Tang, Department of Infectious Disease, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Qin Ning, Department of Infectious Disease, Affiliated Tongji Hospital of Tongji Medical College, Wuhan 430030, Hubei Province, China

Qing-Qing Dai, SmithStreet, Shanghai 200040, China

Run-Qin Li, Jie Liu, Bristol-Myers Squibb, Shanghai 200240, China

Author contributions: Wei L, Jia JD, Weng XH, Dou XG, Jiang JJ, Tang H and Ning Q (ranking reference their input) analyzed the data, interpreted data in final review, and final approval of the manuscript; Dai QQ designed the survey, completed data acquisition, analysis and interpretation, and final approval of the manuscript; Li RQ and Liu J designed the survey, analyzed and interpreted data, drafted the paper and revised it critically for important intellectual content and final approval of the manuscript.

Supported by Bristol-Myers Squibb.

Conflict-of-interest statement: Lai Wei has received research support and/or consulting fees from Bristol-Myers Squibb, Roche and Novartis. Ji-Dong Jia has received research support, consulting fees and speaker fees from Bristol-Myers Squibb, consulting fees and speaker fees from Gilead, and research support from Novartis. Xin-Hua Weng has received consulting fees and speaker fees from Novartis, Roche and Bristol-Myers Squibb, and speaker fees from Pfizer and AstraZeneca. Xiao-Guang Dou and Jia-Ji Jiang have no conflicts of interest to declare. Hong Tang has received research support, consulting fees and speaker fees from Bristol-Myers Squibb, Novartis and Roche. Qin Ning has received research support and consulting fees from Novartis, Bristol-Myers Squibb and Roche, and consulting fees from GlaxoSmithKline. Qing-Qing Dai is an employee of SmithStreet. Run-Qin Li and Jie Liu are employees of Bristol-Myers Squibb.

Data sharing statement: The survey participants gave consent for information to be shared. The data was collected by on-line survey or off-line survey (post or fax). No additional data are available.

Correspondence to: Lai Wei, MD, PhD, Department of Hepatology, Peking University People's Hospital, 11 Xizhimen South Street, Xicheng District, Beijing 100044, China. weilai@pkuph.edu.cn
Telephone: +86-10-88325566
Fax: +86-10-66515490

Received: December 9, 2015
Peer-review started: December 10, 2015
First decision: January 18, 2016
Revised: March 17, 2016
Accepted: April 5, 2016
Article in press: April 6, 2016
Published online: June 28, 2016

Abstract

AIM: To investigate Chinese physicians' awareness of the 2010 guidelines on the treatment of chronic hepatitis B virus (HBV) infection.

METHODS: This was a quantitative survey that investigated the characteristics and practices of physicians who were treating patients with hepatitis B, the profile of their patients and physician practices regarding the diagnosis and treatment of HBV at the time of the survey. Participants were randomly selected from available databases of Chinese physicians and requested to complete either an online or paper-based survey. Data from the survey responses were analysed. For data validation and interpretation, qualitative in-depth interviews were conducted with 39 of the respondents.

RESULTS: Five-hundred completed surveys, from 663 physicians were available for analysis. A mean of 175 chronic hepatitis B (CHB) patients was seen by each physician every month, of whom 85 (49%) were treated in line with therapeutic indications stated in the 2010 guidelines. A total of 444 (89%) physicians often (> 60% of the time) adhered to the guidelines. Most physicians used antiviral medications as recommended. For patients with compensated and decompensated cirrhosis, 342 (68%) and 336 (67%) of physicians, respectively, often followed the recommendation to use potent nucleos(t)ide analogues with a high genetic barrier to resistance, using the appropriate treatment more than 60% of the time. Physicians from infectious disease or liver disease departments were better informed than those from gastrointestinal or other departments.

CONCLUSION: The majority of Chinese physicians often adhere to Chinese 2010 CHB guidelines and are well-informed about the use of antiviral medications for hepatitis B.

Key words: Chronic hepatitis B; Practice guidelines; Awareness; China; Physicians

Core tip: In general, the majority of Chinese physicians often adhere to Chinese 2010 chronic hepatitis B guidelines and they are well-informed about the use of antiviral medications for hepatitis B. Most of the physicians who participated in our survey used antiviral medications as recommended. For patients with compensated and decompensated cirrhosis, more than two-thirds of physicians, often followed the recommendation to use potent nucleos(t)ide analogues with a high genetic barrier to resistance. Our survey also showed that physicians from infectious disease or liver disease departments were better informed than those from gastrointestinal or other departments.

Wei L, Jia JD, Weng XH, Dou XG, Jiang JJ, Tang H, Ning Q, Dai QQ, Li RQ, Liu J. Treating chronic hepatitis B virus: Chinese physicians' awareness of the 2010 guidelines. *World J Hepatol* 2016; 8(18): 762-769 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i18/762.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i18.762

INTRODUCTION

The clinical management of chronic hepatitis B (CHB) has undergone dramatic changes over the past two decades following the registration worldwide of several antiviral agents that effectively suppress hepatitis B virus (HBV) loads[1-4]. Currently, the primary aim of CHB treatment is the permanent suppression of HBV replication to decrease viral infectivity and pathogenicity[5]. Two different classes of drug are used to treat HBV: Conventional interferon (IFN) or pegylated IFN, and oral nucleos(t)ide analogues (NAs). Nucleoside analogues include lamivudine, telbivudine, clevudine and entecavir, while nucleotide analogues include adefovir dipivoxil and tenofovir dipivoxil fumarate[5]. Guidelines have been developed to help standardise the prevention, diagnosis and treatment of CHB. Key clinical practice guidelines have been developed by the Asian Pacific Association for the Study of the Liver (APASL; 2012 update)[5], the European Association for the Study of the Liver (EASL; 2012 update)[6] and the American Association for the Study of Liver Diseases (AASLD; 2009 update)[7]. In March 2015, the World Health Organization issued its first-ever guidance for the treatment of CHB[8].

Chinese CHB guidelines were first developed in 2005 by the Chinese Society of Hepatology, Chinese Medical Association and Chinese Society of Infectious Diseases[9], and updated in 2010[10]. The 2010 guidelines state that no antiviral treatment is recommended for chronic and inactive HBV carriers, although regular diagnostic tests should be performed to ensure criteria for antiviral therapy are not met. For hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients with CHB, both IFNs and NAs are recommended as first-line treatments. However, due to these patients' need for long-term treatment, it is recommended that those with HBeAg-negative CHB or CHB with cirrhosis (compensated or decompensated) receive treatment with NAs that have a high genetic barrier to resistance[10].

It is known that the implementation of treatment guidelines in clinical practice can improve the outcome of patients, but despite wide promulgation, many guidelines are not readily accepted by physicians or incorporated in clinical management strategies[11]. There is some evidence of poor adherence to HBV treatment guidelines among healthcare providers in the United States who treat HBV/human immunodeficiency virus (HIV) co-infected patients[12], but in general, real-world clinical practice with CHB guidelines is not well understood. In China, the prevalence of HBV is high[13,14] and physician adherence to CHB treatment guidelines could potentially have an important impact on the long-term outcome of a large

proportion of the CHB population. To date, there are limited available data on how CHB is treated in real-world clinical practice in China and whether physicians adhere to available guidelines. Therefore, the aim of this study was to investigate Chinese physicians' awareness of the updated 2010 Chinese CHB treatment guidelines[10], to improve understanding of guideline use in clinical practice, and to assist with the development of future CHB clinical practice guideline updates.

MATERIALS AND METHODS

Study design

This was a quantitative survey to investigate the characteristics of physicians who treat patients with HBV, the profile of their patients and physician practices regarding the diagnosis and treatment of HBV. Three study dimensions were therefore included. The first captured physician gender, location, affiliation and professional position. The second captured number of CHB patients treated, proportion of HBeAg-positive and HBeAg-negative patients and the proportion of patients with cirrhosis. The third captured physician reference to the Chinese 2010 CHB guidelines[12], as well as specific data on physician prescription, treatment and follow-up practices.

Participants

Participants were randomly selected from internal databases of Chinese physicians, belonging to either SmithStreet (Shanghai, China) or Bristol-Myers Squibb (BMS; Shanghai, China). SmithStreet has proven experience in healthcare survey development, a focus on China growth strategies, and relevant experience in consumer health and prescription medicines. For survey data capture, physicians working in Chinese grade Ⅲ hospitals and in liver disease or infectious disease departments were targeted, with appropriate segmentation to obtain an even distribution of physicians by region, city tier and professional position. In China, the Ministry of Health grades hospitals according to a three-grade system, which assesses a hospital's ability to provide medical care and medical education, and to conduct medical research. In general, grade Ⅲ hospitals are considered the highest level in China. These hospitals are able to provide high quality, specialized care in well-equipped facilities. Considering the availability of medical education and specialized care at grade Ⅲ hospitals, in general, physicians at these hospitals are thought to at the forefront of clinical medicine.

Participants were approached by SmithStreet *via* phone or email, and also face-to-face for qualitative follow-up questions. There was a target sample size of 500 respondents, which was deemed sufficient to allow nationwide representation of the data. Participants were required to be physicians currently treating patients with HBV, but there were no other pre-specified eligibility criteria or screening questions prior to enrolment.

Research setting

Survey questions were developed by SmithStreet. Contributions were made by leading physicians, who reviewed and provided feedback on the questions prior to survey initiation. Data were collected remotely online, *via* the SurveyMonkey® platform (https://www.surveymonkey.com). Physicians who were unable to complete the survey online were provided an offline survey by SmithStreet, which was distributed by post or fax; offline surveys were subsequently returned by email to SmithStreet for data collection and analysis.

Data collection

Instruction guides for online and offline surveys were provided to participating physicians. A pilot online survey was tested on five randomly selected representative physicians outside of the target pool to obtain feedback on language, content and interface structure. Participant responses were captured by the SurveyMonkey® platform. For consistency during data extraction and analysis, data from the offline surveys were entered into SurveyMonkey® by SmithStreet. Respondents who completed the survey offline were given the opportunity to review their responses.

Data analyses

All coding and data analyses were conducted by SmithStreet. Responses were reviewed to eliminate repeat submissions and incomplete responses. Follow-up phone calls were conducted with 25 randomly selected online respondents to verify their participation. Responses that were deemed invalid or defective were eliminated from the analyses. To assist with data validation and interpretation, qualitative in-depth interviews were conducted with 39 respondents of the quantitative survey. The statistical methods of this study were reviewed by Qing-Qing Dai of SmithStreet. No statistical tests were performed. The data are presented as percentages and described.

RESULTS

Characteristics of physicians

The first participant was screened on 21 March 2013 and the last participant completed the survey on 1 September 2013. Participant flow through the study is shown in Figure 1. Of 663 physicians who completed the survey, 500 were available for analysis (472 from online surveys); of these, 194 were recruited through BMS' physician database and 306 were recruited *via* SmithStreet's physician database. Demographics and background characteristics of the responding physicians are shown in Table 1. The majority were female, from South, North or East China, held attending level positions or above, and worked in an infectious diseases department (Table 1).

Characteristics of treated HBV patients

Segmentation of physicians by number of CHB patients

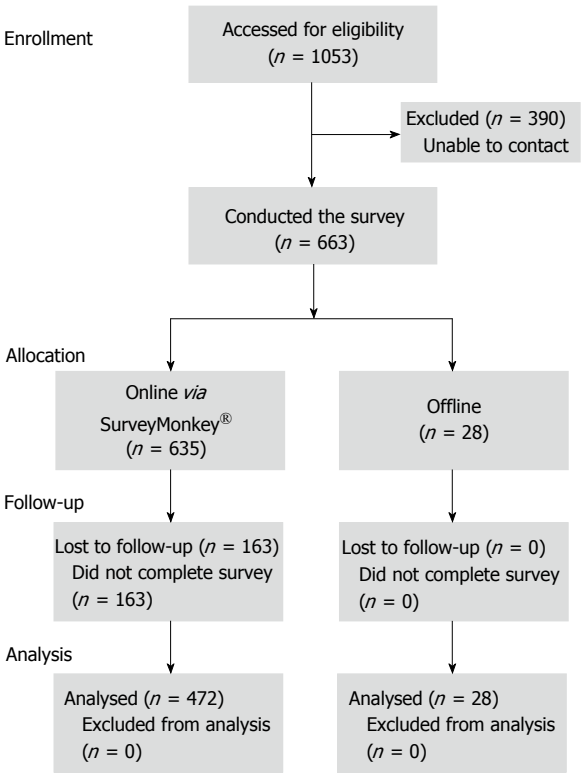

Figure 1 Participant flow through the study.

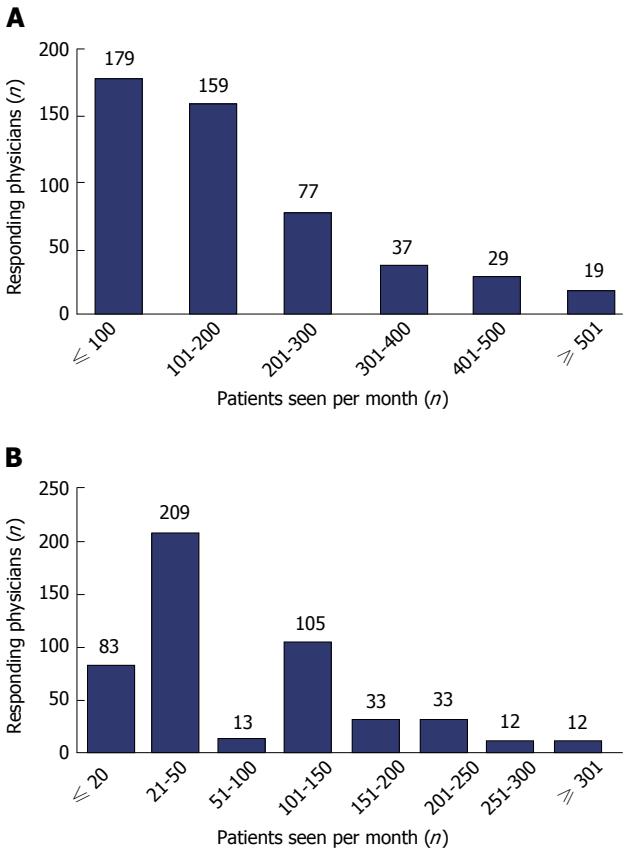

Figure 2 Segmentation of physicians. Segmentation of physicians by number of chronic hepatitis B (CHB) patients seen per month (A) in total, and (B) according to indications stated in the Chinese 2010 CHB guidelines[12]. A: Physicians (n = 500) were asked, "how many CHB patients do you treat per month?"; B: Physicians (n = 500) were asked, "amongst the CHB patients that you treat per month, how many of them are in line with the therapeutic indications as stated in the (Chinese 2010 CHB) guidelines?".

seen per month is shown in Figure 2. A mean of 175 CHB patients was seen by each physician every month, of whom 85 (49%) were treated with antiviral therapy in line with the therapeutic indications as stated in the Chinese 2010 CHB guidelines[12] and 46 (26%) had cirrhosis (27 with compensated cirrhosis). Among treatment-naive CHB patients, 25 (14%) were HBeAg-positive and 21 (12%) were HBeAg-negative. The number of patients seen each month varied by physician rank, hospital grade, city tier and region; however, the number of treatment-naïve HBeAg-positive and HBeAg-negative patients seen by physicians each month was similar across different regions and city tiers. (In China, cities are ranked into tiers (tier Ⅰ through Ⅳ) according to size and economic development, with tier Ⅰ cities generally the largest economical hubs).

Physician awareness of guidelines

A total of 444 (89%) surveyed physicians indicated that they "often" (defined as more than 60% of the time) adhered to the Chinese 2010 CHB guidelines. In particular, more than 90% of physicians from infectious disease or liver disease departments often adhered to the guidelines (Figure 3).

Most physicians used antiviral medications consistent with guideline recommendations. However, in patients older than 40 years, who were HBV DNA-positive (but with $< 1 \times 10^4$ copies/mL), and with alanine aminotransferase (ALT) levels above the upper limit of normal (ULN), 196 (39%) of the surveyed physicians did not consider antiviral medication necessary (Figure 4). The guideline recommends that in these patients, the presence of liver fibrosis (as judged by the physician), should be an indication for antiviral therapy.

A total of 354 (71%) physicians could identify the distractor (HBeAg-positive, HBV DNA $\geqslant 10^5$ copies/mL, 1 × ULN < ALT < 2 × ULN), including 194 (73%) of those from infectious disease departments, 106 (76%) from liver disease departments, 49 (62%) from gastroenterology departments, and five (29%) from other departments.

When asked for a response regarding the reasonable treatment course for antiviral medications, 422 (84%) physicians considered that more than 12 mo (responses for "12 to 18 mo" and "more than 18 mo") of consolidation treatment was needed for HBeAg-positive patients following serological conversion. However, this proportion was lower among physicians from gastroenterology (n = 54; 68% of all physicians from gastroenterology departments) or other (n = 11; 65%) departments, than among physicians from infectious disease (n = 236; 89%) or liver disease (n = 121; 87%) departments. For HBeAg-negative patients following serological conversion, 302 (60%) physicians considered that more than 18 mo of consolidation treatment was needed. However, this proportion was lower among physicians from gas-

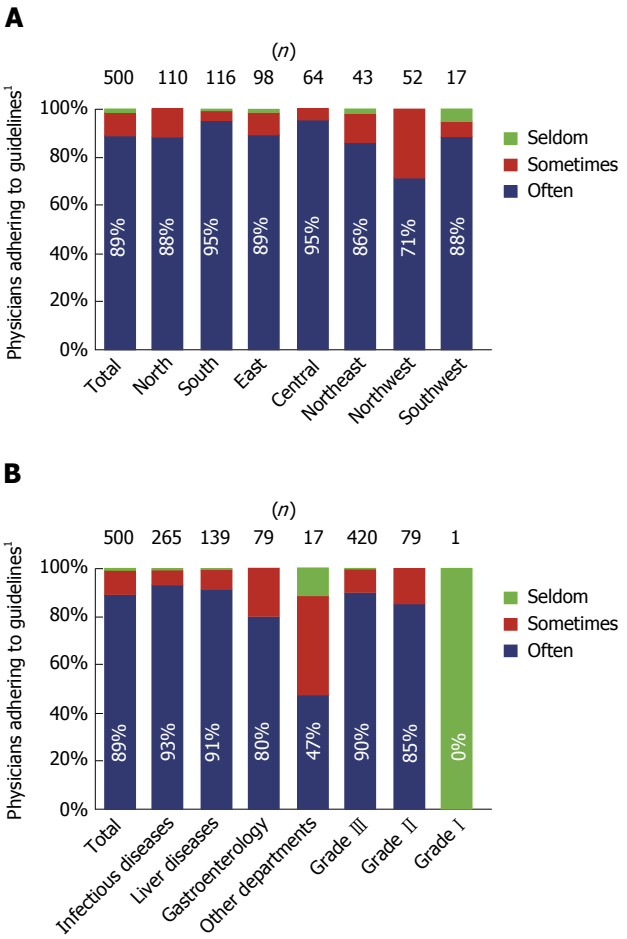

Figure 3 Physician adherence to the Chinese 2010 chronic hepatitis B guidelines. Proportion of physicians adhering to Chinese 2010 chronic hepatitis B (CHB) guidelines[12] by (A) region, or (B) by hospital department or grade. [1]"Often" defined as > 60% of the time, "sometimes" defined as > 30% to < 60% of the time and "seldom" defined as < 30% of the time.

troenterology (n = 40; 51% of all physicians from gastroenterology departments) or other (n = 8; 47%) departments, than among physicians from infectious disease (n = 169; 64%) or liver disease (n = 85; 61%) departments.

For patients with compensated and decompensated cirrhosis, 342 (68%) and 336 (67%) physicians, respectively, followed guidelines recommending the use of potent NAs with a high genetic barrier to resistance, using the appropriate treatment more than 60% of the time. This recommendation was followed most frequently by physicians from liver disease departments for patients with compensated and decompensated cirrhosis (both n = 100; 72%). A low proportion of physicians did not follow this recommendation (use of the appropriate treatment less than 30% of the time) for compensated cirrhosis (n = 17; 3%) and decompensated cirrhosis patients (n = 20; 4%).

DISCUSSION

Our survey results show that the majority of Chinese physicians often adhered to Chinese 2010 CHB guidelines[10]. Physicians from liver disease and infectious disease departments were most familiar with the guidelines, but physicians from other departments adhered to the guidelines less frequently, indicating that access to, or awareness of CHB treatment guidelines in China could be improved.

Table 1 Characteristics of responding physicians

Characteristic	Physician response (n = 500)
Female physicians, n (%)	282 (56)
Location within China, n (%)	
North	110 (22)
South	116 (23)
East	98 (20)
Central	64 (13)
Northeast	43 (9)
Northwest	52 (10)
Southwest	17 (3)
City tier, n (%)	
Ⅰ	110 (22)
Ⅱ	171 (34)
Ⅲ	143 (29)
Ⅳ	46 (9)
Ⅴ	30 (6)
Hospital grade, n (%)	
Ⅰ	1 (0)
Ⅱ	79 (16)
Ⅲ	420 (84)
Hospital affiliation, n (%)	
Gastroenterology	79 (16)
Infectious disease	265 (53)
Liver disease	139 (28)
Other	17 (3)
Hospital position, n (%)	
Chief	151 (30)
Associate chief	90 (18)
Attending	147 (29)
Resident	112 (22)

The physicians in this survey saw a mean of 175 CHB patients every month. This was below the number expected, especially for physicians working in tier Ⅰ cities and grade Ⅲ hospitals (210 and 184 patients per month, respectively; data not shown). We found 26% of patients to have cirrhosis, 29% to be HBeAg-positive and 23% to be HBeAg-negative. Nearly half (49%) of patients were treated in line with guidelines for various indications, and nearly nine out of 10 (89%) responding physicians often adhered to the guidelines; based on our clinical experience, this number is higher than expected.

In China, most patients with HBV are treated in infectious disease or liver disease departments, with physicians working in these departments generally regarded as specialists. Accordingly, when our survey results were analysed by hospital department, we found that adherence was greatest among physicians from infectious disease or liver disease departments. Adherence was slightly lower among physicians working in gastroenterology departments, but much lower among physicians from other departments. In Northwest China, the percentage of physicians who adhered to the guideline was noticeably lower than in other regions. Although

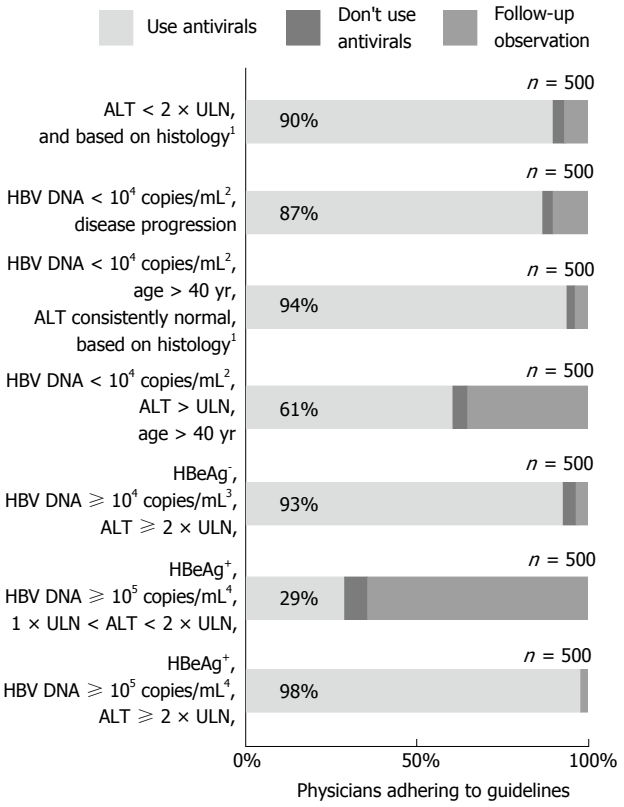

Figure 4 Physician familiarity with various indications for antiviral medication. Physician familiarity with the different indications for antiviral medication as described in the Chinese chronic hepatitis B (CHB) guidelines[12] is depicted here. The various indications are listed on the left. Physicians were asked, "does antiviral medication apply to the following cases?" and the proportion of physicians who would consider antivirals, no antivirals, and follow-up for each indication, is depicted in each horizontal bar. According to the Chinese 2010 CHB guidelines, general indications for antiviral treatment include: (1) hepatitis B e antigen (HBeAg)-positive and hepatitis B virus (HBV) DNA ⩾ 105 copies/mL, or HBeAg-negative and HBV DNA ⩾ 104 copies/mL; (2) alanine aminotransferase (ALT) ⩾ 2 × upper limit of normal (ULN); or (3) ALT < 2 × ULN, but hepatic histology show Knodell histology activity index (HAI) ⩾ 4, inflammation necrosis grade ⩾ 2, or fibrosis stage ⩾ 2. If HBV DNA is consistently positive but the above general indications cannot be reached, then antiviral treatment should be considered under the following circumstances: (1) ALT > ULN and age > 40 years; (2) ALT consistently normal and age > 40 years (can be closely monitored, but liver biopsy is recommended; antiviral treatment is indicated when Knodell HAI ⩾ 4, or inflammation necrosis grade ⩾ 2, or fibrosis stage ⩾ 2); or (3) evidence of disease progression following dynamic observation (hepatic histology examination is recommended and antiviral treatment should be administered as necessary). For the distractor (HBeAg-positive, HBV DNA ⩾ 105 copies/mL, 1 × ULN < ALT < 2 × ULN), liver biopsy tests are also needed to determine whether antiviral treatment is required. [1]Hepatic histology shows Knodell HAI ⩾ 4, or inflammatory necrosis grade ⩾ 2, or fibrosis stage ⩾ 2; [2]HBV DNA < 104 copies/mL was considered HBV positive; [3]Equivalent to 2000 IU/mL; [4]Equivalent to 20000 IU/mL.

speculative, this may be due to a higher proportion of respondents who were residents, and a lower proportion of respondents who were chief physicians in Northwest China compared with other regions (data not shown). In addition, Northwest China had the second highest proportion of respondents from other departments (6%) and the second lowest combined proportion of respondents who were specialists (48% from infectious disease departments plus 23% from liver disease departments; data not shown).

Previous publications have demonstrated inadequacy of CHB management and need for improved education among Chinese physicians[15,16]. Even with the availability of CHB guidelines from key international associations, continual advancement in our understanding of CHB and availability of new data can create ongoing challenges regarding who should be treated and for how long[17]. Chao *et al*[16] (2010) previously reported that there is a lack of basic knowledge surrounding HBV natural history, prevention and transmission. They identified critical gaps in HBV knowledge; in particular, 34% of physicians surveyed in their study did not know that CHB is often asymptomatic, 29% did not know that CHB infection confers a high risk of cirrhosis, liver cancer and premature death, and only 31% knew the recommended protocol for testing liver function and screening for liver cancer in CHB[16].

In contrast, in our study, the majority of physicians were found to be well-informed about the importance of antiviral medication and were educated on the appropriate indications for their use. However, there was some inconsistency among physicians regarding the use of antiviral treatment for patients older than 40 years, who present with HBV DNA of $< 1 \times 10^4$ copies/mL, and ALT levels above the ULN. The guideline recommends that these patients be initiated on antiviral therapy if they have liver fibrosis (as judged by the physician). For these patients, liver biopsy is clearly important when making treatment decisions.

As expected, and in line with the proportion of physicians who adhered to the Chinese 2010 CHB guidelines, physicians from infectious disease and liver disease departments were better able to identify the distractor, followed by those from gastroenterology departments and physicians from other departments.

According to the Chinese 2010 CHB guidelines, the endpoint for antiviral treatment in HBeAg-positive patients should be HBV DNA levels below the lower limit of detection, normalisation of ALT levels, HBeAg seroconversion, at least 1 year of consolidation therapy and a total treatment duration of at least 2 years. In HBeAg-negative patients, these criteria are the same for HBV DNA and ALT levels, but at least 1.5 years of consolidation therapy and a total treatment duration of at least 2.5 years is recommended[10]. We found that 84% and 60% of physicians often followed recommendations for consolidation therapy for HBeAg-positive and HBeAg-negative patients, respectively. Physicians from infectious disease or liver disease departments again showed greatest awareness of the guidelines in this context. For HBeAg-negative patients, the optimal duration of NA treatment is unknown unless hepatitis B surface antigen seroclearance has occurred, and the decision to stop therapy can be based upon clinical response and severity of the underlying liver disease[5]; this flexibility may explain the lower adherence to recommended endpoints for HBeAg-negative patients compared with HBeAg-positive patients.

As CHB requires long-term treatment, the Chinese

2010 CHB guidelines recommend that HBeAg-negative CHB patients and CHB patients with cirrhosis (compensated or decompensated) receive treatment with NAs that have a high genetic barrier to resistance[10]. We found that, in both patients with compensated and decompensated cirrhosis, over two-thirds of physicians often followed guidelines recommending the use of potent NAs with a high genetic barrier to resistance. While this finding is promising for the appropriate antiviral treatment of patients with CHB, this alignment with the guidelines was higher than expected.

Although the majority of Chinese physicians in our survey often adhered to Chinese 2010 CHB guidelines, our results also showed that there is a need to improve physicians' awareness and knowledge of CHB guidelines. This was particularly evident among non-specialists, where a need for education on CHB and its treatment was confirmed. Although physicians from gastroenterology departments were relatively well-informed about CHB, their awareness of CHB guidelines was lower than that of specialist physicians from infectious disease or liver disease departments, implying that Chinese gastroenterologists may require additional training on HBV antiviral recommendations. The delay and reduction of liver cirrhosis is one goal of CHB treatment[5] and the Chinese 2010 CHB guidelines provide specific recommendations for antiviral treatment and follow-up in CHB patients with cirrhosis[10]. Since patients with cirrhosis are frequently referred to gastroenterologists, consensus statements for treatment of cirrhotic HBV patients with antiviral therapy should help educate Chinese gastroenterologists moving forward.

Other than general limitations associated with the acquisition of data using a survey design, the respondent pool in our survey could be considered a potential limitation leading to over- or underestimation of guideline awareness and uptake. In particular, our survey included only one grade Ⅰ hospital, the majority of physicians came from grade Ⅲ hospitals and physicians from Southwest China or other departments may have been under-represented. In addition, this survey was based upon the latest update to the Chinese CHB guidelines; because this update was published in 2010, and this survey was completed at the end of 2013, this survey may not reflect changes in physician attitudes or education in the past few years.

This survey has shown that the majority of Chinese physicians often adhered to Chinese 2010 CHB guidelines and were well-informed about the use of antiviral medication for HBV. However, there is a need to further educate non-specialist physicians who treat patients with CHB and to promote physician adherence to future CHB guidelines or updates.

The majority of Chinese physicians often adhere to Chinese 2010 CHB guidelines and they are well-informed about the use of antiviral medications for hepatitis B. In general, the physicians who participated in our survey used antiviral medications as recommended. For patients with compensated and decompensated cirrhosis, more than two-thirds of physicians, often followed the recommendation to use potent nucleos(t)ide analogues with a high genetic barrier to resistance. We found that physicians from infectious disease or liver disease departments were better informed than those from gastrointestinal or other departments.

ACKNOWLEDGMENTS

The survey that formed the basis of this study was sponsored by Bristol-Myers Squibb. The survey was executed by SmithStreet. Editorial support for this manuscript was provided by Manette Williams, PhD, from Nucleus Global.

COMMENTS

Background

The implementation of treatment guidelines in clinical practice can improve the outcome of patients, but despite wide promulgation, many guidelines are not readily accepted by physicians or incorporated in clinical management strategies. In China, the prevalence of hepatitis B virus (HBV) is high and physician adherence to chronic hepatitis B (CHB) treatment guidelines could potentially have an important impact on the long-term outcome of a large proportion of the CHB population. There are limited available data on how CHB is treated in real-world clinical practice in China and whether physicians adhere to available guidelines. The authors investigated Chinese physicians' awareness of the updated 2010 Chinese CHB treatment guidelines.

Research frontiers

CHB patients require long-term treatment and it is recommended that those with hepatitis B e antigen negative CHB or CHB with cirrhosis (compensated or decompensated) receive treatment with nucleos(t)ide analogues that have a high genetic barrier to resistance. Despite these recommendations, many treatment naïve CHB patients do not receive appropriate treatment because physicians do not adhere to the treatment guidelines. The authors assessed how well Chinese physicians adhere to the Chinese CHB treatment guidelines, released in 2010.

Innovations and breakthroughs

The authors show that in China, the majority of Chinese physicians often adhere to Chinese 2010 chronic hepatitis B guidelines and they are well-informed about the use of antiviral medications for hepatitis B.

Applications

Despite high adherence rates, there was some inconsistency among physicians regarding the use of antiviral treatment for patients older than 40 years, who present with HBV DNA of $< 1 \times 10^4$ copies/mL, and alanine aminotransferase levels above the upper limit of normal. The guideline recommends that these patients be initiated on antiviral therapy if they have liver fibrosis (as judged by the physician). For these patients, liver biopsy is clearly important when making treatment decisions.

Terminology

HBV DNA levels, measure in copies/mL indicates the rate of viral replication. Low or undetectable levels (about 300 copies/mL) indicate "inactive infection", whereas higher levels indicate "active infection".

Peer-review

It is a well-designed study and provides useful information to physicians especially treating patients with hepatitis B about the trends in the treatment of CHB.

REFERENCES

1 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological

gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]
2 **Chen G**, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Chronic hepatitis B virus infection and mortality from non-liver causes: results from the Haimen City cohort study. *Int J Epidemiol* 2005; **34**: 132-137 [PMID: 15659459 DOI: 10.1093/ije/dyh339]
3 **Iloeje UH**, Yang HI, Su J, Jen CL, You SL, Chen CJ. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006; **130**: 678-686 [PMID: 16530509 DOI: 10.1053/j.gastro.2005.11.016]
4 **Liang X**, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, Wang F, Zheng H, Wang F, Guo J, Jia Z, Ma J, Wang H, Luo H, Li L, Jin S, Hadler SC, Wang Y. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. *Vaccine* 2009; **27**: 6550-6557 [PMID: 19729084 DOI: 10.1016/j.vaccine.2009.08.048]
5 **Liaw YF**, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu CJ, Gane E, Locarnini S, Lim SG, Han KH, Amarapurkar D, Cooksley G, Jafri W, Mohamed R, Hou JL, Chuang WL, Lesmana LA, Sollano JD, Suh DJ, Omata M. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012; **6**: 531-561 [PMID: 26201469 DOI: 10.1007/s12072-012-9365-4]
6 **European Association for the Study of the Liver**. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. *J Hepatol* 2012; **57**: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]
7 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
8 **World Health Organization**. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, 2015 [PMID: 26225396]
9 **Chinese Society of Hepatology and Chinese Society of Infectious Diseases**, **Chinese Medical Association**. Guideline on prevention and treatment of chronic hepatitis B in China (2005). *Chin Med J* (Engl) 2007; **120**: 2159-2173 [PMID: 18167196]
10 **Chinese Society of Hepatology and Chinese Society of Infectious Diseases, Chinese Medical Association**. [The guideline of prevention and treatment for chronic hepatitis B (2010 version)]. *Zhonghua Gan Zang Bing Za Zhi* 2011; **19**: 13-24 [PMID: 21272453 DOI: 10.3760/cma.j.issn.1007-3418.2011.01.007]
11 **Cabana MD**, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999; **282**: 1458-1465 [PMID: 10535437 DOI: 10.1001/jama.282.15.1458]
12 **Jain MK**, Opio CK, Osuagwu CC, Pillai R, Keiser P, Lee WM. Do HIV care providers appropriately manage hepatitis B in coinfected patients treated with antiretroviral therapy? *Clin Infect Dis* 2007; **44**: 996-1000 [PMID: 17342656 DOI: 10.1086/512367]
13 **Lu FM**, Li T, Liu S, Zhuang H. Epidemiology and prevention of hepatitis B virus infection in China. *J Viral Hepat* 2010; **17** Suppl 1: 4-9 [PMID: 20586928 DOI: 10.1111/j.1365-2893.2010.01266.x]
14 **Lesmana LA**. Hepatitis B: overview of the burden of disease in the Asia-Pacific region. *Liver Int* 2006; **26**: 3-10 [DOI: 10.1111/j.1478-3231.2006.01370.x]
15 **Ning LH**, Hao J, Liao ZL, Zhou YY, Guo H, Zhao XY. A survey on the current trends in the management of hepatitis B in China. *Eur J Gastroenterol Hepatol* 2012; **24**: 884-889 [PMID: 22569081 DOI: 10.1097/MEG.0b013e32835447fa]
16 **Chao J**, Chang ET, So SK. Hepatitis B and liver cancer knowledge and practices among healthcare and public health professionals in China: a cross-sectional study. *BMC Public Health* 2010; **10**: 98 [PMID: 20184740 DOI: 10.1186/1471-2458-10-98]
17 **Ahn SH**, Chan HL, Chen PJ, Cheng J, Goenka MK, Hou J, Lim SG, Omata M, Piratvisuth T, Xie Q, Yim HJ, Yuen MF. Chronic hepatitis B: whom to treat and for how long? Propositions, challenges, and future directions. *Hepatol Int* 2010; **4**: 386-395 [PMID: 20305758 DOI: 10.1007/s12072-010-9163-9]

P- Reviewer: Akbar SMF, Coban M, He JY, Toyoda T
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i18.770

World J Hepatol 2016 June 28; 8(18): 770-778
ISSN 1948-5182 (online)

META-ANALYSIS

Transarterial radioembolization *vs* chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis

Antonio Facciorusso, Gaetano Serviddio, Nicola Muscatiello

Antonio Facciorusso, Nicola Muscatiello, Gastroenterology Unit, Department of Medical Sciences, University of Foggia, 71100 Foggia, Italy

Gaetano Serviddio, Internal Medicine Unit, University of Foggia, 71100 Foggia, Italy

Author contributions: Facciorusso A designed the study, performed the statistical analysis and wrote the paper; Serviddio G and Muscatiello N revised the paper; Muscatiello N collected the data.

Conflict-of-interest statement: None of the authors have received fees for serving as a speaker or are consultant/advisory board member for any organizations; None of the authors have received research funding from any organizations; None of the authors are employees of any organizations; None of the authors own stocks and/or share in any organizations; None of the authors own patents.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Antonio Facciorusso, MD, Gastroenterology Unit, Department of Medical Sciences, University of Foggia, Viale L. Pinto, 1, 71100 Foggia, Italy. antonio.facciorusso@virgilio.it
Telephone: +39-0881-732154
Fax: +39-0881-732135

Received: January 30, 2016
Peer-review started: January 30, 2016
First decision: April 15, 2016
Revised: May 4, 2016
Accepted: May 31, 2016
Article in press: June 2, 2016
Published online: June 28, 2016

Abstract

AIM: To compare the efficacy and safety of yttrium-90 radioembolization (Y90RE) and transarterial chemoembolization (TACE) in hepatocellular carcinoma patients.

METHODS: Bibliographic research was conducted on main scientific databases. When there was no statistically significant heterogeneity, pooled effects were calculated using a fixed-effects model by means of Mantel-Haenszel test, otherwise, a random-effects model was used with DerSimonian and Laird test. Summary estimates were expressed in terms of odds ratios (ORs) and 95%CI. The probability of publication bias was assessed using funnel plots and with Begg and Mazumdar's test. Sensitivity analysis was finally conducted using the method of excluding extreme data.

RESULTS: A total of 10 studies were analyzed, of which 2 randomized controlled trials. Survival rate (SR) assessed at 1 year showed an absolute similarity between the two treatment groups (OR = 1.01, 95%CI: 0.78-1.31, P = 0.93). As long as time elapsed since the treatment, ORs for survival rate tended to significantly increase, thus meaning better long-term outcomes in patients who underwent Y90RE (2-year SR: OR = 1.43, 1.08-1.89, P = 0.01; 3-year SR: OR = 1.48, 1.03-2.13, P = 0.04). Meta-analysis of plotted hazard ratios (HRs) determined a non-significant overall estimate in favor of Y90RE (HR = 0.91, 0.80-1.04, P = 0.16). Y90RE showed a statistically significant benefit as compared to TACE in terms of higher progression-free survival rate

assessed at 1 year (OR = 1.67; 95%CI: 1.10-2.55; *P* = 0.02). Pooled analyses do not revealed a statistically significant increase in OR for tumor objective responses after Y90RE with respect to TACE (OR = 1.22, 95%CI: 0.69-2.16, *P* = 0.50). A non-significant trend in favor of Y90RE was observed according to adverse event rate (OR = 0.70, 0.38-1.30, *P* = 0.26).

CONCLUSION: Our meta-analysis reveals that Y90RE and TACE show similar effects in terms of survival, response rate and safety profile, although tumor progression is delayed after radioembolization.

Key words: Yttrium-90 radioembolization; Transarterial chemoembolization; Hepatocellular carcinoma; Survival; Prognosis; Recurrence

Core tip: A clear evidence in support of the superiority of yttrium-90 radioembolization (Y90RE) over chemoembolization (TACE) in hepatocellular carcinoma patients is still lacking. Results of our meta-analysis reveal that Y90RE and TACE show similar effects in terms of survival, response rate and safety profile, although tumor progression is delayed after radioembolization. Similar results were found as for objective response rate and safety profile. The sole statistical difference was with regard to 1-year progression-free survival, which resulted significantly in favor of Y90RE (OR = 1.67, *P* = 0.02).

Facciorusso A, Serviddio G, Muscatiello N. Transarterial radioembolization *vs* chemoembolization for hepatocarcinoma patients: A systematic review and meta-analysis. *World J Hepatol* 2016; 8(18): 770-778 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i18/770.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i18.770

INTRODUCTION

Hepatocellular carcinoma (HCC) is a global health problem, representing the third most common cause of cancer-related death and the leading cause of mortality among patients with cirrhosis[1,2]. Thanks to the recent improvements in surveillance protocols, diagnostic tools and therapeutic armamentaria, nowadays early HCC diagnosis is feasible in 30%-60% of cases in developed countries[3]. However, a substantial proportion of patients develop tumoral portal vein thrombosis (PVT) or a multifocal pattern as a result of HCC recurrence or progression, leading to an advanced disease stage not amenable to curative treatments.

Transarterial chemoembolization (TACE) is the most widely used primary treatment for unresectable HCC and the recommended first line-therapy for patients in intermediate stage[2,4,5]. The rationale for TACE is that intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels will result in a strong cytotoxic and ischemic effect[4,5].

A novel technique in the field of loco-regional treatments for HCC is called transarterial radioembolization with yttrium-90 (Y90RE), which induces tumor necrosis by means of injection of glass or resin microsphere loaded with yttrium-90[6,7]. Y90RE, which is in fact a novel form of liver-directed brachytherapy, has already demonstrated its efficacy in HCC patients leading to delayed time to progression (TTP) and prolonged overall survival (OS)[8,9]. Commonly adopted Y90-loaded microspheres present usually a small size (< 40 μm), therefore due to their microembolic effect they can be used even in patients with portal vein occlusion. Furthermore, because of absence of flow obstruction, in the case of Y90RE there is no hypoxia-initiated cascade and therefore typical post-TACE sequelae as post-embolization syndrome are less common[6,7].

Although several studies comparing the two loco-regional techniques have been recently published, whether there is a clear superiority of one treatment over the other is still debated.

In this study, we performed a meta-analysis to compare the efficacy of Y90RE and TACE in treating patients with unresectable HCC considering as main endpoints survival rate (SR), progression-free survival (PFS) and adverse events rate. We think that the comparison of these two procedures could help to better define the treatment strategy in intermediate/advanced HCC patients.

MATERIALS AND METHODS

Inclusion and exclusion criteria

This meta-analysis only included studies meeting the following criteria: (1) studies comparing Y90RE and TACE in HCC patients; (2) studies published in English; and (3) articles reporting at least one of the following data: TTP, survival and adverse events.

Search strategy

Figure 1 reports the search strategy followed in the meta-analysis.

Bibliographic research was conducted on PubMed, EMBASE, Cochrane Library and Embase including all studies fulfilling inclusion criteria published until January 2016. Keywords used included "transcatheter arterial chemoembolization", "TACE", "transcatheter arterial radioembolization", "TARE", "liver cancer", "hepatocellular carcinoma" and "HCC". Relevant reviews and meta-analyses of loco-regional treatments in unresectable HCC were examined for potential suitable studies. Authors of included studies were contacted to obtain full text or further information when needed.

Data extraction and management

Data extraction was conducted by two reviewers (Facciorusso A and Muscatiello N) using a standardized

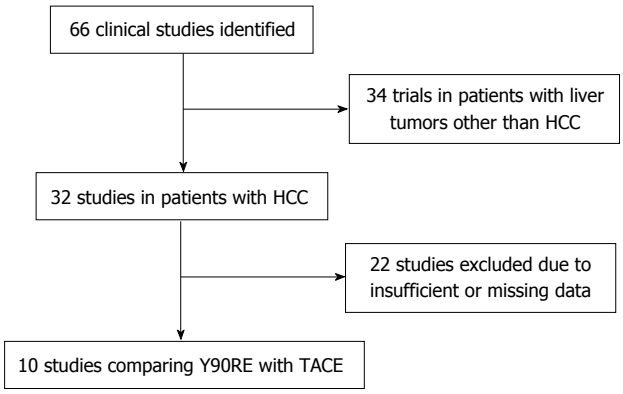

Figure 1 Flow chart summarizing study selection. HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; Y90RE: Yttrium-90 radioembolization.

approach (PRISMA Statement)[10]. Data on publication details (year of publication, name of first author and country), study characteristics (patients' age and sex, study design, sample size, Child-Pugh stage, interventions, follow-up duration), OS, TTP, and 1-year SR were gathered. Case reports and abstracts or studies with insufficient data were excluded. In case of repetitive publications from the same population, only most recent and complete articles were included.

The quality of the included studies was assessed by two authors independently (Facciorusso A and Muscatiello N) according to the currently accepted criteria described elsewhere[11,12].

Disagreements were resolved by discussion and following a third opinion (Serviddio G).

Statistical analysis

χ^2 and I^2 tests were used for across studies comparison of the percentage of variability attributable to heterogeneity beyond chance. $P < 0.10$ for χ^2 test and $I^2 <$ 25% were interpreted as low-level heterogeneity.

When there was no statistically significant heterogeneity, pooled effects were calculated using a fixed-effects model by means of Mantel-Haenszel test; otherwise, a random-effects model was used with DerSimonian and Laird test. Summary estimates were expressed in terms of odds ratios (ORs) and 95%CI.

Probability of publication bias was assessed using funnel plots and with Begg and Mazumdar's test. To explore eventual sources of heterogeneity, we compared summary results obtained from subsets of studies grouped according to their design or quality. Sensitivity analysis was finally conducted using the method of excluding extreme data (the maximum or the minimum).

All statistical analyses were conducted using RevMan version 5 from the Cochrane collaboration. For all calculations a two-tailed *P* value of less than 0.05 was considered statistically significant.

RESULTS

Selection of studies

After initial screening, 66 potentially relevant articles were identified; 34 were excluded because dealing with non-HCC patients and 22 due to missing or incomplete data. Clinical data of 1557 patients from 10 studies were finally pooled to compare Y90RE and TACE (Figure 1).

Characteristics of included articles

A total of 10 studies published from 2005 to 2015 were analyzed, which included 461 HCC patients treated with Y90RE and 1096 who underwent TACE[13-22] (Table 1).

Among these articles, 8 were retrospective studies[13-18,20,22] and 2 were randomized controlled trials (RCTs)[19,21]. Overall, 5 studies (of which 1 RCT) were judged high quality[14,16-19] and 5 (of which 1 RCT) moderate quality[13,15,20-22] (Table 2). In all the studies, the two treatment cohorts were well-balanced in terms of either clinical parameters and tumoral stage (Table 2).

Survival

Data on overall survival were available for 1481 patients enrolled in 9 studies[14-22], which estimated this outcome by means of Kaplan-Meier curves and compared the two groups using log-rank test. Table 3 describes summary estimates for SR at three consecutive time-points, specifically at 1, 2 and 3 years. SR at 1 year was reported in all the aforementioned nine studies and showed an absolute similarity between the two treatment groups (OR = 1.01, 95%CI: 0.78-1.31, P = 0.93). As long as time elapsed since the treatment, ORs for survival rate tended to significantly increase, thus meaning better long-term outcomes in patients who underwent Y90RE (2-year SR: OR = 1.43, 1.08-1.89, P = 0.01; 3-year SR: OR = 1.48, 1.03-2.13, P = 0.04). Notably, the number of studies reporting long-term outcomes tended to decrease with 7 studies assessing 2-year SR[15-20,22] and only 5 reporting 3-year SR[15,16,18-20]. No evidence of heterogeneity was found at any time points (Table 3).

In order to obtain a more robust and reliable estimate of patient survival, we performed a meta-analysis of plotted hazard ratios (HRs) from 7 studies which provided data to calculate this parameter[14-20], obtaining as result a non-significant overall estimate in favor of Y90RE (HR = 0.91, 0.80-1.04, P = 0.16; Figure 2). There was only a low level of heterogeneity among studies [χ^2 = 7.32, df = 6 (P = 0.29), I^2 = 18%)] and no publication bias was detected by using funnel plot (Figure 3) and performing Begg and Mazumdar's test (P = 0.51). Subgroup analysis retrieving separately results of the only RCT and observational studies did not alter the final findings of our meta-analysis (P = 0.77 and 0.16, respectively). Sensitivity analysis was also performed by restricting analysis to high-quality

Table 1 Characteristics of the included studies

Ref.	Arm	Sample size	Recruitment period	Study design	Region	CP (A/B/C)	BCLC (A/B/C/D)	Quality
Ahmad *et al*[13]	Y90RE	24	1990-2003	R	United States	NA	NA	M
	TACE	52						
Kooby *et al*[14]	Y90RE	27	1996-2006	R	United States	13/14/0	NA	H
	TACE	44				22/22/0		
Carr *et al*[15]	Y90RE	99	1992-2005	R	United States	NA	NA	M
	TACE	691						
Salem *et al*[16]	Y90RE	123	1999-2008	R	United States	67/54/2	43/65/13/2	H
	TACE	122				67/53/2	47/61/12/2	
Lance *et al*[17]	Y90RE	38	2008-2010	R	United States	31/7/0	NA	H
	TACE	35				24/11/0		
Moreno-Luna *et al*[18]	Y90RE	61	1998-2008	R	United States	53/8/0	12/35/14/0	H
	TACE	55				44/11/0	23/13/19/0	
Pitton *et al*[19]	Y90RE	12	2010-2012	RCT	Germany	10/2/0	0/12/0/0	H
	TACE	12				9/3/0	1/11/0/0	
El Fouly *et al*[20]	Y90RE	44	2009-2011	R	Egipt/Germany	37/7/0	NA	M
	TACE	42				33/9/0		
Kolligs *et al*[21]	Y90RE	13	2009-2012	RCT	Germany/Spain	9/3/1	5/5/3/0	M
	TACE	15				9/4/2	4/8/3/0	
Akinwande *et al*[22]	Y90RE	20	2007-2013	R	United States	7/11/2	0/0/20/0	M
	TACE	28				14/13/1	0/0/28/0	

CP: Child-Pugh; BCLC: Barcelona Clinic Liver Cancer; Y90RE: Yttrium-90 radioembolization; TACE: Transarterial chemoembolization; R: Retrospective; RCT: Randomized controlled trial; NA: Not available; H: High; M: Moderate.

Table 2 Risk of bias assessment and quality of included studies

	Selection	Comparability	Outcome	Overall quality
Observational studies[1]				
Ahmad *et al*[13]	++	+	++	5
Kooby *et al*[14]	+++	++	++	7
Carr *et al*[15]	++	++	++	6
Salem *et al*[16]	++++	++	+++	9
Lance *et al*[17]	+++	++	++	7
Moreno-Luna *et al*[18]	++++	++	+++	9
El Fouly *et al*[20]	++	+	+++	6
Akinwande *et al*[22]	++	+	++	5
Randomized controlled trials[2]				

	1	2	3	4	5	6	7	
Pitton *et al*[19]	L	L	L	U	L	L	L	H
Kolligs *et al*[21]	L	H	U	U	H	L	L	M

[1]Study quality assessment performed by means of Newcastle/Ottawa scale (each asterisk represents if the respective criterion within the subsection was satisfied); [2]Cochrane Collaboration's tool for assessing the risk of bias across 7 domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other bias. L: Low; H: High; U: Unclear; M: Moderate.

Table 3 Odds ratios and heterogeneity of 1-year, 2-year and 3-year survival rate

Survival estimate	No. of studies	No. of patients	OR (95%CI)	*P*-value	Heterogeneity	
					I^2	*P*
1-yr SR	9	1481	1.01 (0.78-1.31)	0.93	0%	0.71
2-yr SR	7	1382	1.43 (1.08-1.89)	0.01	0%	0.93
3-yr SR	5	1261	1.48 (1.03-2.13)	0.04	0%	0.44

SR: Survival rate; OR: Odds ratio.

studies and by excluding each article once per time and it showed that the outcome effect was coherent (data not shown).

PFS

Data on tumor progression was available in 4 studies[16,19-21]. Y90RE showed a statistically significant

Figure 2 Forest plot of hazard ratios for overall survival after yttrium-90 radioembolization and transarterial chemoembolization. Overall estimate was non-significantly in favor of Y90RE (HR = 0.91, 0.80-1.04, *P* = 0.16). There was only a low level of heterogeneity among studies [χ^2 = 7.32, *df* = 6 (*P* = 0.29), I^2 = 18%)]. Y90RE: Yttrium-90 radioembolization; TACE: Transarterial chemoembolization; HR: Hazard ratio.

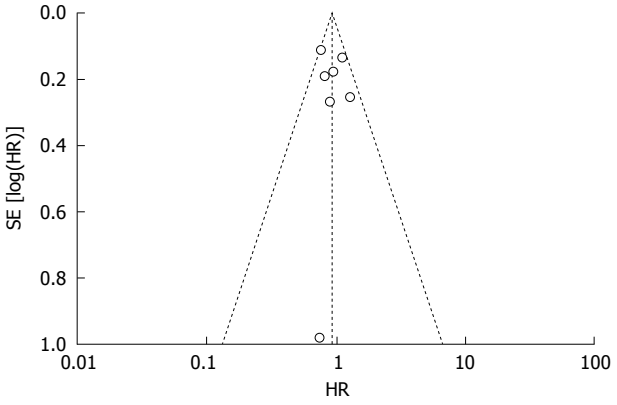

Figure 3 Funnel plot for detection of publication bias with regard to overall survival. No evidence of publication bias was detected. HR: Hazard ratio.

benefit in terms of higher PFS rate assessed at 1 year (OR = 1.67; 95%CI: 1.10-2.55; *P* = 0.02) (Figure 4). There was no evidence of heterogeneity among individual studies (*P* = 0.66; I^2 = 0%), hence a fixed model was used. Furthermore, there was no publication bias detected using funnel plot and Begg and Mazumdar's test was not significant (*P* = 0.304 and *P* = 0.412, respectively). A low sensitivity to individual studies resulted after performing sensitivity analysis.

Objective response rate

There were eight studies containing information about objective response rate[13-16,18,20-22] enrolling 407 and 1041 patients treated with Y90RE and TACE, respectively. Pooled analyses did not reveal a statistically significant increase in OR for tumor objective responses after Y90RE with respect to TACE (OR = 1.22, 95%CI: 0.69-2.16, *P* = 0.50) (Figure 5). There was, however, evidence of heterogeneity across these studies (*P* = 0.004; I^2 = 67%), therefore we performed a subgroup analysis in order to explore the cause of this heterogeneity, which was mainly due to some outlier studies[13,15,20,21]. In fact, tumor response assessment is dependent on a number of variables, such as radiologic criteria adopted, local expertise, imaging technique used (whether computed tomography-scan or magnetic resonance imaging) and time of response evaluation. Unfortunately, conducting a meta-regression analysis taking into account all these variables was not possible due to the small number of studies. No evidence of publication bias was detected.

Toxicity

Seven studies reported toxicity data of their treated patients[13,14,16-18,21,22]. A non-significant trend in favor of Y90RE was observed (OR = 0.70, 0.38-1.30, *P* = 0.26), but with high evidence of heterogeneity (I^2 = 52%, *P* = 0.05) (Figure 6). Major responsible of heterogeneity was the study by Salem *et al*[16], since I^2 dropped to 13% after exclusion of this article. No evidence of publication bias was detected.

DISCUSSION

TACE is actually the recommended first-line therapy for patients with unresectable intermediate HCC[2-4]. In this setting where curative surgical or ablative treatments are not feasible, palliation with TACE has been found to improve survival as compared to best supportive care[23,24]. The pressing need for novel therapeutic regimens able to improve response rates and survival while reducing treatment-related complications led to the development of new drug-delivery systems, such as drug-eluting beads (DEBs)[4,25]. Although whether there is a clear superiority of DEB-TACE over conventional TACE using lipiodol is still matter of debate[12,26,27], increasing interest has been recently raised on smaller DEBs which seem able to induce wider necrosis of the target lesion since they achieve a more distal embolization, thus also obstructing collateral channels[28]. As a consequence, survival estimates after TACE has considerably improved in the last years, reaching more than 40 mo of median OS in two recent studies[29,30].

On the other hand, Y90 transarterial radioembolization is a form of brachytherapy in which intra-arterially injected 90Y-loaded microspheres serve as sources for internal radiation purposes, with no significant vessel occlusion thus rendering this treatment

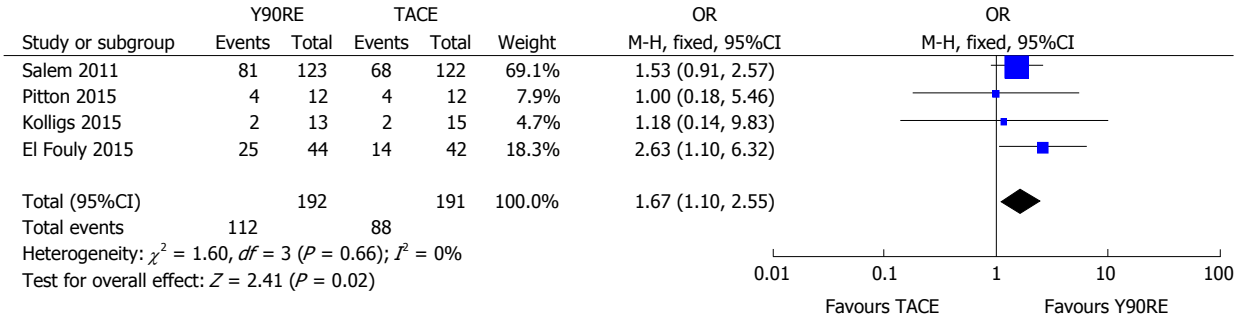

Figure 4 Forest plot for 1-year progression-free survival after yttrium-90 radioembolization and transarterial chemoembolization. Y90RE showed a statistically significant benefit in terms of higher progression-free survival rate assessed at 1 year (OR = 1.67, 1.10-2.55, *P* = 0.02). There was no evidence of heterogeneity among individual studies (*P* = 0.66; I^2 = 0%). Y90RE: Yttrium-90 radioembolization; TACE: Transarterial chemoembolization; OR: Odds ratio.

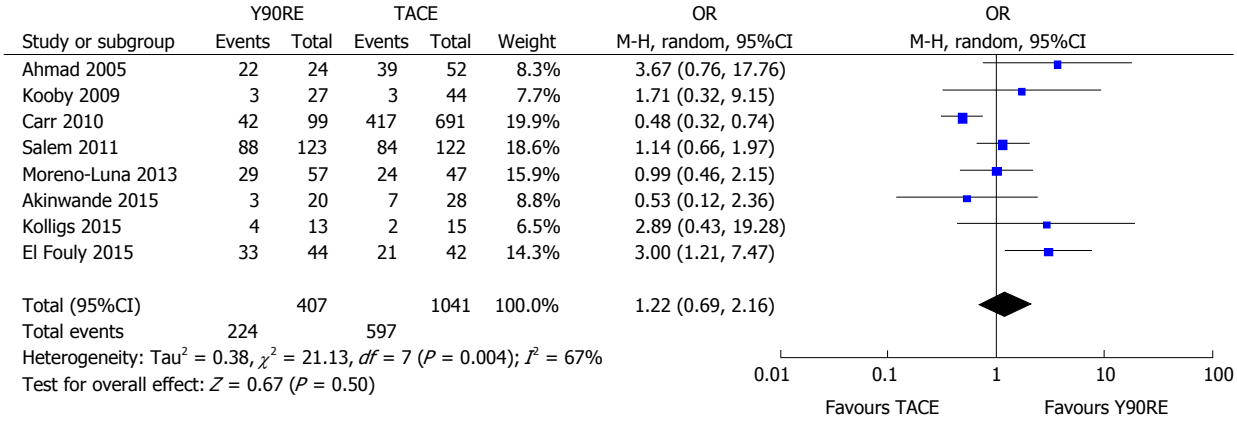

Figure 5 Forest plot for objective response rate after yttrium-90 radioembolization and transarterial chemoembolization. Pooled analyses do not revealed a statistically significant increase in odds ratio for tumor objective responses after Y90RE with respect to TACE (OR = 1.22, 95%CI: 0.69-2.16, *P* = 0.50). There was, however, evidence of heterogeneity across these studies (*P* = 0.004; I^2 = 67%), mainly due to some outlier studies. Y90RE: Yttrium-90 radioembolization; TACE: Transarterial chemoembolization; OR: Odds ratio.

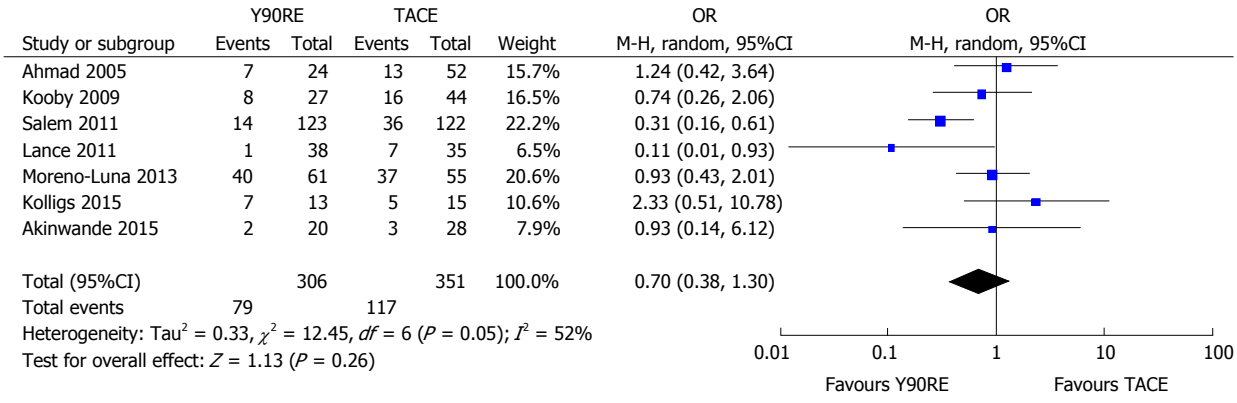

Figure 6 Forest plot for serious adverse event rate after yttrium-90 radioembolization and transarterial chemoembolization. A non-significant trend in favor of Y90RE was observed (OR = 0.70, 0.38-1.30, *P* = 0.26), but with a high evidence of heterogeneity (I^2 = 52%; *P* = 0.05). Y90RE: Yttrium-90 radioembolization; TACE: Transarterial chemoembolization; OR: Odds ratio.

feasible even in patients with PVT, which is a well-known contraindication to TACE[6,7].

In particular radioembolization produces average disease control rates above 80% and is usually very well tolerated. Main complications do not result from the microembolic effect, even in patients with portal vein occlusion, but rather from excessive irradiation of non-target liver tissue[6,7,9].

Although several studies comparing the two therapies have been published so far, a clear evidence in support of the superiority of one technique over the other in terms of OS is still lacking. Therefore, given the similarity in survival outcomes between the two procedures, post-hoc analyses indicated that a randomized study with > 1000 patients would be required to establish equivalence of survival times between patients treated with Y90RE

and TACE[16].

Aim of our meta-analysis was hence to compare these two trans-arterial treatments in terms of overall survival, progression-free survival, objective response rate and safety profile in unresectable HCC patients.

A total of 10 studies were identified and statistically analyzed, which included 461 HCC patients treated with Y90RE and 1096 treated with chemoembolization. Of note, all the included studies were from the West and in particular 70% from United States. Average quality was moderate-high.

Survival rate assessed at 1 year was similar between the two therapeutic groups (OR = 1.01, P = 0.93), but as long as time elapsed since the treatment ORs for survival rate tended to significantly increase, thus meaning better long-term outcomes in patients who underwent Y90RE (P = 0.01 and 0.04 at 2 and 3 years, respectively). Notably, the number of studies reporting long-term outcomes tended to decrease from 10 (all the included studies) which reported 1-year SR to only 5 reporting 3-year SR[15,16,18-20] (Table 3).

In order to obtain a more robust and reliable estimate of patient survival, we performed a meta-analysis of plotted HRs, obtaining as result a non-significant overall estimate in favor of Y90RE (HR = 0.91, 0.80-1.04, P = 0.16; Figure 2).

Therefore, our analysis seem to confirm the non-superiority of one treatment over the other as found in previous papers[16,18].

Unfortunately, subgroup analysis performed on the basis of baseline tumor stage or other clinical prognostic factors known to influence HCC patients' survival, such as ferritin level[31] or drug therapy used[32], was not feasible due to the low number of available studies and the absence of outcomes stratification in most of them.

In the above cited study by Salem *et al*[16], time to progression was significantly longer after Y90RE (13.3 mo *vs* 8.4 mo, P = 0.023), but it did not translate directly into improved survival. Such a finding was confirmed in our meta-analysis where OR for 1-year PFS resulted significantly in favor of Y90RE (OR = 1.67, P = 0.02) (Figure 4).

No significant difference according to the other two analyzed outcomes (response rate and major adverse event rate) was found.

The apparent discrepancy between the significant benefit of Y90RE in terms of progression-free survival and the non-significant trends found with regard to the other outcomes are likely due to the complex multistep pathogenesis of HCC and the different course of underlying liver cirrhosis[33-35]. In this regard, a post-progression survival analysis would be interesting and represents in our opinion one of the most important targets of incoming clinical research in hepato-oncology[36,37].

There are some limitations to our study. First, we included both RCTs and observational studies, thus resulting in greater heterogeneity (as seen with regard to response rate analysis) and higher risk of selection and reporting bias. This, in addition to the aforementioned lack of data stratification and sub-group analysis, calls for a carefully interpretation of our findings. Moreover, technical details varied widely throughout the included studies either in TACE cohorts (for instance some studies adopted conventional TACE whereas others DEB-TACE) and in Y90RE arms (for instance as for dosimetry protocol)[38].

In conclusion, our meta-analysis reveals that Y90RE and TACE show similar effects in unresectable HCC patients in terms of OS, response rate and safety profile, although tumor progression is delayed after radioembolization. Further properly sized RCTs are warranted in order to confirm these results.

COMMENTS

Background

Transarterial chemoembolization (TACE) is the most widely used primary treatment for unresectable hepatocellular carcinoma (HCC) and the recommended first line-therapy for patients in intermediate stage. A novel technique in the field of loco-regional treatments for HCC is called transarterial radioembolization with yttrium-90 (Y90RE), which induces tumor necrosis by means of injection of glass or resin microsphere loaded with yttrium-90. Although several studies comparing the two loco-regional techniques have been recently published, whether there is a clear superiority of one treatment over the other is still debated.

Research frontiers

This meta-analysis reveals that Y90RE and TACE show similar effects in unresectable HCC patients in terms of overall survival, response rate and safety profile, although tumor progression is delayed after radioembolization. Further properly sized randomized controlled trials are warranted in order to confirm these results.

Innovations and breakthroughs

The authors' findings stand for a similarity in treatment effects between Y90RE and TACE in HCC patients. Their meta-analysis constitutes the most up-to-date overview of studies comparing the two techniques.

Applications

The present report allows understanding the role of two transarterial treatments in HCC patients.

Terminology

TACE: Transarterial treatment whose rationale is that the intra-arterial infusion of a cytotoxic agent followed by embolization of the tumor-feeding blood vessels will result in a strong cytotoxic and ischemic effect; Y90RE: Novel form of liver-directed brachytherapy which induces tumor necrosis by means of injection of glass or resin microsphere loaded with yttrium-90.

Peer-review

This meta-analysis aims to compare the efficacy and safety of Y90RE and TACE in HCC. It is a nicely written manuscript. The analysis is well performed.

REFERENCES

1 **El-Serag HB**. Hepatocellular carcinoma. *N Engl J Med* 2011; **365**: 1118-1127 [PMID: 21992124 DOI: 10.1056/NEJMra1001683]

2 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438 DOI: 10.1016/j.jhep.2011.12.001]

3 **Llovet JM**, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; **48** Suppl 1: S20-S37 [PMID: 18304676 DOI: 10.1016/j.jhep.2008.01.022]

4 **Facciorusso A**, Licinio R, Muscatiello N, Di Leo A, Barone M. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. *World J Hepatol* 2015; **7**: 2009-2019 [PMID: 26261690 DOI: 10.4254/wjh.v7.i16.2009]

5 **Bolondi L**, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, Raoul JL, Sangro B. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. *Semin Liver Dis* 2012; **32**: 348-359 [PMID: 23397536 DOI: 10.1055/s-0032-1329906]

6 **Salem R**, Mazzaferro V, Sangro B. Yttrium 90 radioembolization for the treatment of hepatocellular carcinoma: biological lessons, current challenges, and clinical perspectives. *Hepatology* 2013; **58**: 2188-2197 [PMID: 23512791 DOI: 10.1002/hep.26382]

7 **Sangro B**, Iñarrairaegui M, Bilbao JI. Radioembolization for hepatocellular carcinoma. *J Hepatol* 2012; **56**: 464-473 [PMID: 21816126 DOI: 10.1016/j.jhep.2011.07.012]

8 **Salem R**, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, Atassi B, Baker T, Gates V, Miller FH, Sato KT, Wang E, Gupta R, Benson AB, Newman SB, Omary RA, Abecassis M, Kulik L. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. *Gastroenterology* 2010; **138**: 52-64 [PMID: 19766639 DOI: 10.1053/j.gastro.2009.09.006]

9 **Mazzaferro V**, Sposito C, Bhoori S, Romito R, Chiesa C, Morosi C, Maccauro M, Marchianò A, Bongini M, Lanocita R, Civelli E, Bombardieri E, Camerini T, Spreafico C. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. *Hepatology* 2013; **57**: 1826-1837 [PMID: 22911442 DOI: 10.1002/hep.26014]

10 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]

11 **Facciorusso A**, Di Maso M, Muscatiello N. Microwave ablation versus radiofrequency ablation for the treatment of hepatocellular carcinoma: A systematic review and meta-analysis. *Int J Hyperthermia* 2016; **32**: 339-344 [PMID: 26794414]

12 **Facciorusso A**, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. *Dig Liver Dis* 2016; **48**: 571-577 [PMID: 26965785 DOI: 10.1016/j.dld.2016.02.005]

13 **Ahmad J**, Rhee J, Carr BI. The effects of hepatic artery chemotherapy on viral hepatitis in patients with hepatocellular carcinoma. *Dig Dis Sci* 2005; **50**: 331-335 [PMID: 15745096 DOI: 10.1007/s10620-005-1606-0]

14 **Kooby DA**, Egnatashvili V, Srinivasan S, Chamsuddin A, Delman KA, Kauh J, Staley CA, Kim HS. Comparison of yttrium-90 radioembolization and transcatheter arterial chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2010; **21**: 224-230 [PMID: 20022765 DOI: 10.1016/j.jvir.2009.10.013]

15 **Carr BI**, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. *Cancer* 2010; **116**: 1305-1314 [PMID: 20066715 DOI: 10.1002/cncr.24884]

16 **Salem R**, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, Sato KT, Gupta R, Nikolaidis P, Miller FH, Yaghmai V, Ibrahim SM, Senthilnathan S, Baker T, Gates VL, Atassi B, Newman S, Memon K, Chen R, Vogelzang RL, Nemcek AA, Resnick SA, Chrisman HB, Carr J, Omary RA, Abecassis M, Benson AB, Mulcahy MF. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. *Gastroenterology* 2011; **140**: 497-507.e2 [PMID: 21044630 DOI: 10.1053/j.gastro.2010.10.049]

17 **Lance C**, McLennan G, Obuchowski N, Cheah G, Levitin A, Sands M, Spain J, Srinivas S, Shrikanthan S, Aucejo FN, Kim R, Menon KV. Comparative analysis of the safety and efficacy of transcatheter arterial chemoembolization and yttrium-90 radioembolization in patients with unresectable hepatocellular carcinoma. *J Vasc Interv Radiol* 2011; **22**: 1697-1705 [PMID: 21983055 DOI: 10.1016/j.jvir.2011.08.013]

18 **Moreno-Luna LE**, Yang JD, Sanchez W, Paz-Fumagalli R, Harnois DM, Mettler TA, Gansen DN, de Groen PC, Lazaridis KN, Narayanan Menon KV, Larusso NF, Alberts SR, Gores GJ, Fleming CJ, Slettedahl SW, Harmsen WS, Therneau TM, Wiseman GA, Andrews JC, Roberts LR. Efficacy and safety of transarterial radioembolization versus chemoembolization in patients with hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2013; **36**: 714-723 [PMID: 23093355 DOI: 10.1007/s00270-012-0481-2]

19 **Pitton MB**, Kloeckner R, Ruckes C, Wirth GM, Eichhorn W, Wörns MA, Weinmann A, Schreckenberger M, Galle PR, Otto G, Dueber C. Randomized comparison of selective internal radiotherapy (SIRT) versus drug-eluting bead transarterial chemoembolization (DEB-TACE) for the treatment of hepatocellular carcinoma. *Cardiovasc Intervent Radiol* 2015; **38**: 352-360 [PMID: 25373796 DOI: 10.1007/s00270-014-1012-0]

20 **El Fouly A**, Ertle J, El Dorry A, Shaker MK, Dechêne A, Abdella H, Mueller S, Barakat E, Lauenstein T, Bockisch A, Gerken G, Schlaak JF. In intermediate stage hepatocellular carcinoma: radioembolization with yttrium 90 or chemoembolization? *Liver Int* 2015; **35**: 627-635 [PMID: 25040497 DOI: 10.1111/liv.12637]

21 **Kolligs FT**, Bilbao JI, Jakobs T, Iñarrairaegui M, Nagel JM, Rodriguez M, Haug A, D'Avola D, op den Winkel M, Martinez-Cuesta A, Trumm C, Benito A, Tatsch K, Zech CJ, Hoffmann RT, Sangro B. Pilot randomized trial of selective internal radiation therapy vs. chemoembolization in unresectable hepatocellular carcinoma. *Liver Int* 2015; **35**: 1715-1721 [PMID: 25443863 DOI: 10.1111/liv.12750]

22 **Akinwande O**, Kim D, Edwards J, Brown R, Philips P, Scoggins C, Martin RC. Is radioembolization ((90)Y) better than doxorubicin drug eluting beads (DEBDOX) for hepatocellular carcinoma with portal vein thrombosis? A retrospective analysis. *Surg Oncol* 2015; **24**: 270-275 [PMID: 26133576 DOI: 10.1016/j.suronc.2015.06.008]

23 **Llovet JM**, Real MI, Montaña X, Planas R, Coll S, Aponte J, Ayuso C, Sala M, Muchart J, Solà R, Rodés J, Bruix J; Barcelona Liver Cancer Group. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; **359**: 1734-1739 [PMID: 12049862]

24 **Llovet JM**, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. *Hepatology* 2003; **37**: 429-442 [PMID: 12540794]

25 **Varela M**, Real MI, Burrel M, Forner A, Sala M, Brunet M, Ayuso C, Castells L, Montañá X, Llovet JM, Bruix J. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. *J Hepatol* 2007; **46**: 474-481 [PMID: 17239480]

26 **Lammer J**, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, Pitton M, Sergent G, Pfammatter T, Terraz S, Benhamou Y, Avajon Y, Gruenberger T, Pomoni M, Langenberger H, Schuchmann M, Dumortier J, Mueller C, Chevallier P, Lencioni R. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. *Cardiovasc Intervent Radiol* 2010; **33**: 41-52 [PMID: 19908093 DOI: 10.1007/s00270-009-9711-7]

27 **Facciorusso A**, Mariani L, Sposito C, Spreafico C, Bongini M, Morosi C, Cascella T, Marchianò A, Camerini T, Bhoori S, Brunero F, Barone M, Mazzaferro V. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma. *J Gastroenterol Hepatol* 2016; **31**: 645-653 [PMID: 26331807 DOI: 10.1111/jgh.13147]

28 **Spreafico C**, Cascella T, Facciorusso A, Sposito C, Rodolfo

L, Morosi C, Civelli EM, Vaiani M, Bhoori S, Pellegrinelli A, Marchianò A, Mazzaferro V. Transarterial chemoembolization for hepatocellular carcinoma with a new generation of beads: clinical-radiological outcomes and safety profile. *Cardiovasc Intervent Radiol* 2015; **38**: 129-134 [PMID: 24870698 DOI: 10.1007/s00270-014-0907-0]

29 **Burrel M**, Reig M, Forner A, Barrufet M, de Lope CR, Tremosini S, Ayuso C, Llovet JM, Real MI, Bruix J. Survival of patients with hepatocellular carcinoma treated by transarterial chemoembolisation (TACE) using Drug Eluting Beads. Implications for clinical practice and trial design. *J Hepatol* 2012; **56**: 1330-1335 [PMID: 22314428 DOI: 10.1016/j.jhep.2012.01.008]

30 **Malagari K**, Pomoni M, Moschouris H, Bouma E, Koskinas J, Stefaniotou A, Marinis A, Kelekis A, Alexopoulou E, Chatziioannou A, Chatzimichael K, Dourakis S, Kelekis N, Rizos S, Kelekis D. Chemoembolization with doxorubicin-eluting beads for unresectable hepatocellular carcinoma: five-year survival analysis. *Cardiovasc Intervent Radiol* 2012; **35**: 1119-1128 [PMID: 22614031]

31 **Facciorusso A**, Del Prete V, Antonino M, Neve V, Crucinio N, Di Leo A, Carr BI, Barone M. Serum ferritin as a new prognostic factor in hepatocellular carcinoma patients treated with radiofrequency ablation. *J Gastroenterol Hepatol* 2014; **29**: 1905-1910 [PMID: 24731153 DOI: 10.1111/jgh.12618]

32 **Facciorusso A**, Del Prete V, Crucinio N, Muscatiello N, Carr BI, Di Leo A, Barone M. Angiotensin receptor blockers improve survival outcomes after radiofrequency ablation in hepatocarcinoma patients. *J Gastroenterol Hepatol* 2015; **30**: 1643-1650 [PMID: 25974743 DOI: 10.1111/jgh.12988]

33 **Facciorusso A**. The influence of diabetes in the pathogenesis and the clinical course of hepatocellular carcinoma: recent findings and new perspectives. *Curr Diabetes Rev* 2013; **9**: 382-386 [PMID: 23845075]

34 **Facciorusso A**, Antonino M, Del Prete V, Neve V, Scavo MP, Barone M. Are hematopoietic stem cells involved in hepatocarcinogenesis? *Hepatobiliary Surg Nutr* 2014; **3**: 199-206 [PMID: 25202697 DOI: 10.3978/j.issn.2304-3881.2014.06.02]

35 **Facciorusso A**, Licinio R, Carr BI, Di Leo A, Barone M. MEK 1/2 inhibitors in the treatment of hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 993-1003 [PMID: 25915713 DOI: 10.1586/17474124.2015.1040763]

36 **Reig M**, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, Llarch N, Ríos J, Ayuso C, Bruix J. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. *Hepatology* 2013; **58**: 2023-2031 [PMID: 23787822 DOI: 10.1002/hep.26586]

37 **Facciorusso A**, Del Prete V, Antonino M, Crucinio N, Neve V, Di Leo A, Carr BI, Barone M. Post-recurrence survival in hepatocellular carcinoma after percutaneous radiofrequency ablation. *Dig Liver Dis* 2014; **46**: 1014-1019 [PMID: 25085684 DOI: 10.1016/j.dld.2014.07.012]

38 **Chiesa C**, Mira M, Maccauro M, Spreafico C, Romito R, Morosi C, Camerini T, Carrara M, Pellizzari S, Negri A, Aliberti G, Sposito C, Bhoori S, Facciorusso A, Civelli E, Lanocita R, Padovano B, Migliorisi M, De Nile MC, Seregni E, Marchianò A, Crippa F, Mazzaferro V. Radioembolization of hepatocarcinoma with (90)Y glass microspheres: development of an individualized treatment planning strategy based on dosimetry and radiobiology. *Eur J Nucl Med Mol Imaging* 2015; **42**: 1718-1738 [PMID: 26112387 DOI: 10.1007/s00259-015-3068-8]

P- Reviewer: Al-Gayyar MMH, Eskens FALM, Wong GLH
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Liu SQ

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i18.779

World J Hepatol 2016 June 28; 8(18): 779-784
ISSN 1948-5182 (online)

CASE REPORT

Atypical presentation of a hepatic artery pseudoaneurysm: A case report and review of the literature

Casey M Luckhurst, Chelsey Perez, Amy L Collinsworth, Jose G Trevino

Casey M Luckhurst, Chelsey Perez, Jose G Trevino, Department of Surgery, Colleges of Medicine, University of Florida Health Science Center, Gainesville, FL 32610, United States

Amy L Collinsworth, Department of Pathology, Colleges of Medicine, University of Florida Health Science Center, Gainesville, FL 32610, United States

Author contributions: All authors have read, approved the final manuscript and agree to be accountable for all aspects of the manuscript ensuring the accuracy and integrity of this manuscript; Luckhurst CM and Perez C participated in the acquisition of data, design and drafting of the manuscript; Collinsworth AL participated in the acquisition and interpretation of data; Trevino JG participated in the conception and design of this manuscript and give final approval of this version of the manuscript to be published.

Institutional review board statement: This manuscript was designed and drafted with approval from University of Florida Institutional Review Board (UF IRB).

Informed consent statement: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Conflict-of-interest statement: All the authors declare they have no competing interests.

Manuscript source: Invited manuscript

Correspondence to: Jose G Trevino, MD, Assistant Professor, Department of Surgery, Colleges of Medicine, University of Florida Health Science Center, Room R6116, Shands Hospital, 1600 SW Archer Rd, Gainesville, FL 32610, United States. jose.trevino@surgery.ufl.edu
Telephone: +1-352-2737967
Fax: +1-352-2650889

Received: March 30, 2016
Peer-review started: March 31, 2016
First decision: May 17, 2016
Revised: May 27, 2016
Accepted: June 1, 2016
Article in press: June 3, 2016
Published online: June 28, 2016

Abstract

Classically, hepatic artery pseudoaneurysms (HAPs) arise secondary to trauma or iatrogenic causes. With an increasing prevalence of laparoscopic procedures of the hepatobiliary system the risk of inadvertent injury to arterial vessels is increased. Pseudoaneurysm formation post injury can lead to serious consequences of rupture and subsequent hemorrhage, therefore intervention in all identified visceral pseudoaneurysms has been advocated. A variety of interventional methods have been proposed, with surgical management becoming the last step intervention when minimally invasive therapies have failed. The authors present a case of a HAP in a 56-year-old female presenting with jaundice and pruritis suggestive of a Klatskin's tumor. This presentation of HAP in a patient without any significant past medical or surgical intervention is atypical when considering that the majority of HAP cases present secondary to iatrogenic causes or trauma. Multiple minimally invasive approaches were employed in an attempt to alleviate the symptomology which included jaundice and associated inflammatory changes. Ultimately, a right hepatic trisegmentectomy was required to adequately relieve the mass effect on biliary outflow obstruction and definitively address the HAP. The presentation of a HAP masquerading as a malignancy with jaundice and pruritis, rather than the classic symptoms of abdominal

pain, anemia, and melena, is unique. This presentation is only further complicated by the absent history of either trauma or instrumentation. It is important to be aware of HAPs as a potential cause of jaundice in addition to the more commonly thought of etiologies. Furthermore, given the morbidity and mortality associated with pseudoaneurysm rupture, intervention in identifiable cases, either by minimally invasive or surgical interventions, is recommended.

Key words: Klatskin tumor; Cholangitis; Hepatic artery pseudoaneurysm; Biliary obstruction; Trisegmentectomy

Core tip: Hepatic artery pseudoaneurysms (HAPs) typically arise from secondary trauma or iatrogenic causes. Most of HAPs are asymptomatic but can be complicated with rupture and bleeding. Biliary obstruction due to HAPs is a rare phenomenon and can present clinically as Quinke's triad (hematobilia, abdominal pain, and jaundice). Most cases can be managed with non-operative vascular and endoscopic interventions. This case report presents an atypical presentation of HAP with a multidisciplinary approach to a complex problem.

Luckhurst CM, Perez C, Collinsworth AL, Trevino JG. Atypical presentation of a hepatic artery pseudoaneurysm: A case report and review of the literature. *World J Hepatol* 2016; 8(18): 779-784 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i18/779.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i18.779

INTRODUCTION

Hepatic artery pseudoaneurysms (HAPs), or false aneurysms, classically arise secondary to trauma or iatrogenic causes and pose a serious risk of exsanguinating hemorrhage and subsequent death[1,2]. Numerous case reports have been published addressing the occurrence of HAPs subsequent to a variety of interventional procedures including cholecystectomy, pancreaticoduodenectomy, and orthotopic liver transplant. It has been hypothesized that with the increasing frequency of laparoscopic procedures, such as cholecystectomy, which can result in inadvertent injury to the right hepatic artery, the overall incidence of HAPs will continue to rise[1,3]. Due to the increased risk of rupture compared with true aneurysms, some have advocated intervention in all cases of identifiable visceral pseudoaneurysm[4]. It has been reported that HAPs have been successfully treated using a variety of interventional methods, including endovascular embolization, coiling embolization, and arterial stent grafting[1,2]. Because of the increased morbidity associated with surgery in this setting, surgical management is the final treatment option when these subsequent methods have failed. Although in most cases interventional technologies can quench the risk of hemorrhagic rupture of HAP and alleviate biliary obstruction[5], surgical management of impairment to adjacent structures such as the bile duct and portal vein have to our knowledge ever been reported.

Here we provide a unique case of HAP, initially presenting as a Klatskin tumor (tumor at the confluence of the right and left hepatic biliary confluence) mimic and with no identifiable cause. Furthermore, the aforementioned treatment options were inadequate to address this persistent and recurrent chronic HAP, ultimately requiring surgical intervention.

CASE REPORT

A 65-year-old female with no significant past medical history was transferred from an outside institution for further management of painless jaundice and pruritis, with suspicion for a Klatskin's tumor. At this outside institution, non-contrast computed tomography (CT) imaging studies revealed a 5 cm dense lesion within the hilar region of the liver and intrahepatic biliary duct dilatation. Subsequent endoscopic retrograde cholangiopancreatography showed a hilar obstructive lesion that was concerning for cholangiocarcinoma/Klatskin's tumor. A temporary hepatic duct stent was placed and sphincterotomy was performed. Cytology results from this procedure were negative. On the day of her transfer, she was afebrile but was placed on empiric antibiotic coverage. Her total and direct bilirubin levels were elevated (total bilirubin 24.3 mg/dL, direct dilirubin 18.6 mg/dL), as was her serum alkaline phosphatase (432 U/L), liver transaminases (AST 132 U/L, ALT 148 U/L), and CA 19-9 (891 U/mL). Other pertinent labs included a positive ANA and CEA within the reference range.

At transfer to our institution, a triphasic computed tomography angiography demonstrated a right branch HAP measuring 2.1 cm, a suspected hematoma measuring 5 cm in diameter (Figure 1A and B) and significant biliary duct dilatation (Figure 1C). Further studies including esophagogastroduodenoscopy and colonoscopy demonstrated hemobilia with the 2 cm biliary stent protruding into the lumen of the small bowel. Therapeutic strategies to control pseudoaneurysmal bleeding included embolization procedures encompassing percutaneous ultrasound and fluoroscopic guided thrombin injections into the HAP (Figure 2). Multiple sub-centimeter smaller pseudoaneurysms were noted to be extending off of the right hepatic artery. Due to lack of trauma or interventions that could be a likely etiology for pseudoaneurysm, an autoimmune work up, including C-ANCA, P-ANCA, anti-smooth muscle antibodies, double-stranded DNA antibody, anti-smooth muscle antibody, anti-RNP antibody, to establish etiology of these multiple pseudoaneurysms was performed and was largely negative. Rheumatology was consulted and ruled out systemic vasculitides including polyarteritis nodosa (PAN), systemic lupus erythematosus, and cryoglobulinemia. The patient continued to have a complicated long hospital course and even after attempts to alleviate

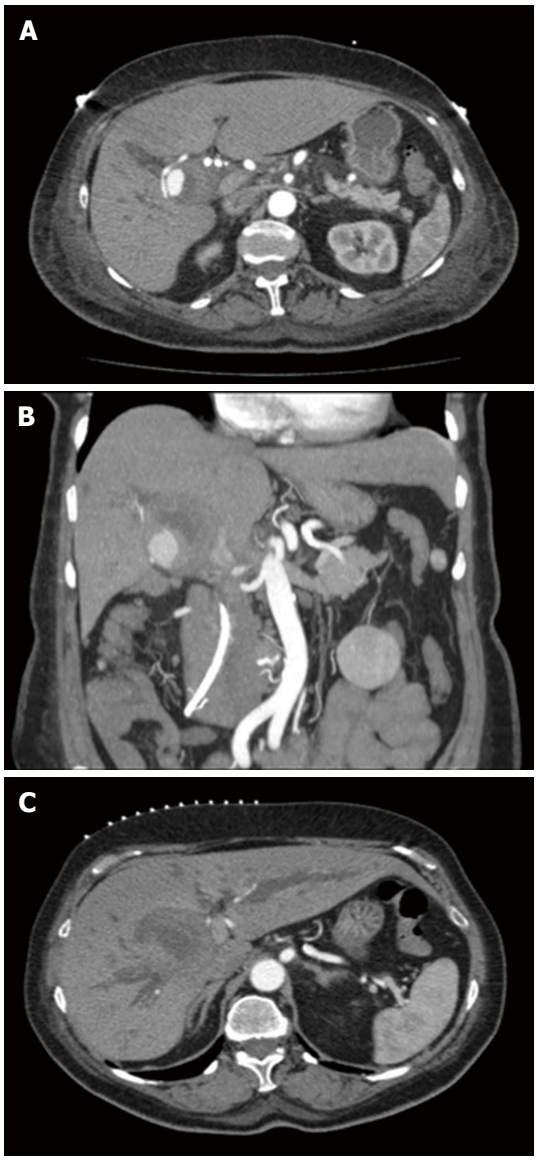

Figure 1 Computerized tomography scan demonstrating pseudoaneurysm and significant biliary ductal dilatation. A: Triple contrast computerized tomography scan of abdomen demonstrates hepatic artery pseudodoaneurysm; B: With significant thrombus formation adjacent to aneurysm; C: Significant biliary ductal dilatation in the right and left hepatic ducts.

obstructive jaundice with stent procedures, the patient had recurrent episodes of cholangitis with septic shock. Blood cultures demonstrated pan-sensitive Klebsiella pneumoniae likely from biliary source.

Non-operative strategies included fluoroscopic and ultrasound-guided embolization of re-emergent right HAP with multiple coils, gelfoam, and thrombin. During this procedure it was noted that a portion of thrombosed aneurysm was exerting significant mass effect, effectively occluding multiple right biliary branches and compressing vascular flow in her right portal vein thereby potentially rendering her right lobe ischemic. It was determined that surgical intervention was required for inability to completely address the obstructing nature of this pseudoaneurysm. The patient underwent right hepatic trisegmentectomy with Roux-en-Y hepaticojejunostomy. Pathology demonstrated the presence of a porta hepatis hematoma (5.0 cm) and organized thrombus dissecting into the hepatic artery wall (Figure 3). Although the liver specimen was negative for malignancy, the liver was microscopically consistent with centrilobular cholestasis (Figure 4A) and bile ductular reaction with bile plugs (Figure 4B) all of which were consistent with chronic biliary obstruction.

The patient was discharged home without any events. She is three years from surgery with no complaints, doing well.

DISCUSSION

While visceral artery aneurysms and pseudoaneurysms (VAP) may be a rare finding in the general population, with a reported incidence of approximately 0.1%-2%, timely diagnosis is imperative because of the risk of rupture and subsequent mortality[6]. In their retrospective review, Tulsyan *et al*[7] reported that of the 28 patients found to have VAPs between 1997 and 2005 at the Cleveland Clinic Foundation, 39% involved the celiac axis or its branches, 39% arose from the hepatic arteries, 18% from the splenic artery and 4% from the superior mesenteric artery. In this review, the majority of VAPs, including HAPs arose secondary to arterial trauma, intrabdominal or retroperitoneal inflammation or malignancy, and manipulation of the biliary tract[7]. Other non-iatrogenic causes of HAPs include trauma, acute and chronic pancreatitis, arteriosclerosis, PAN, necrotizing vasculitis, infection and hepatocellular carcinoma[2,3,8-10].

Recent increases in the incidence of HAPs have been attributed to a rise in the number of liver transplantations, percutaneous liver and gallbladder interventions and the use of laparoscopic surgery[1,4,9,11]. Advances in imaging techniques have enhanced the detection rate of asymptomatic HAPs[1]. While HAPs may be an incidental finding in an asymptomatic patient, more commonly patients present with abdominal pain, anemia, hemobilia, melena, and can present as life-threatening hemorrhage following rupture[2,8,11]. Although we advocate interventional attempts such as angioembolization or stenting to stop hemorrhage immediately, failures in these attempts or chronic sequel on adjacent structures such as the biliary system and portal vein can require further investigations with possible surgical intervention. We advocate the use of non-invasive assessments, such as CT and/or MRI-MRCP radiographic imaging, to determine the possible etiology of biliary obstruction with then focused therapies toward alleviating the problem. To our knowledge, this is the first presentation of a patient presenting with classic picture of a Klatskin's tumor, specifically jaundice and pruritis secondary to biliary system compression by HAP that could not be managed with a non-operative approach. This unique presentation and atypical history for HAP initially masked the diagnosis. Despite a thorough diagnostic workup, no identifiable cause was uncovered for this patient's HAP,

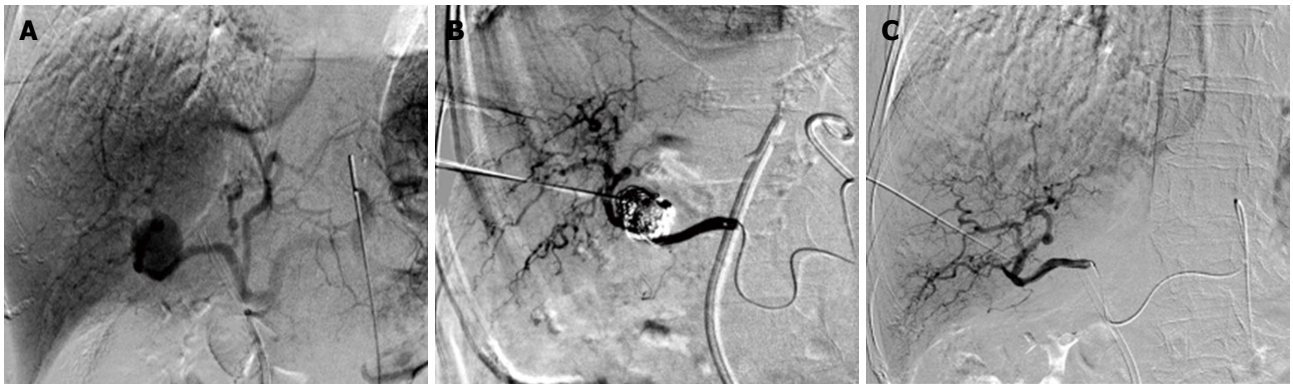

Figure 2 Interventional attempts to embolize the hepatic artery pseudoaneurysm. A: Angiogram of common hepatic artery demonstrates pseudoaneurysmal formation off right hepatic artery; B and C: Interventional fluoroscopic and ultrasound-guided embolization of right hepatic artery pseudoaneurysm with multiple coils, gelfoam, and thrombin.

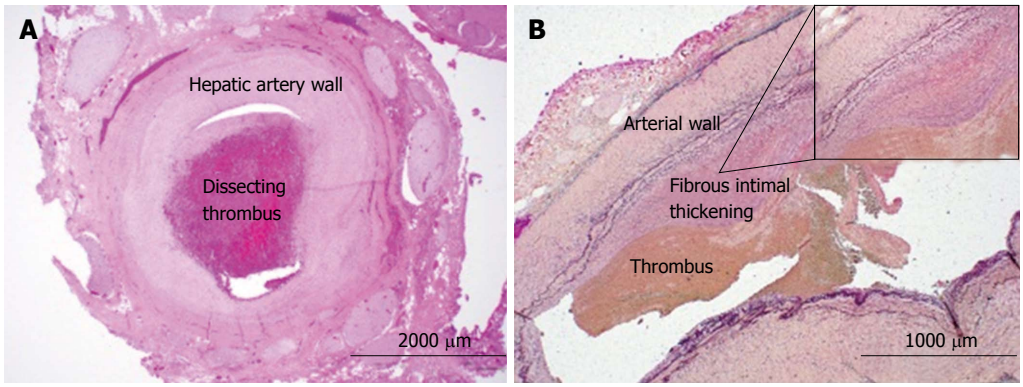

Figure 3 Histochemical analyses of resected hepatic artery. A: H and E of hepatic artery with organized thrombus dissecting into the vessel wall, 40 × magnification; B: Verhoeff-Van Gieson (VVG) staining of the hepatic artery with eccentric fibrous intimal thickening with adherent thrombus, 20 × magnification (B, inlet). Internal elastic lamina is highlighted by the VVG stain with notable fibrous intimal thickening, 100 × magnifications.

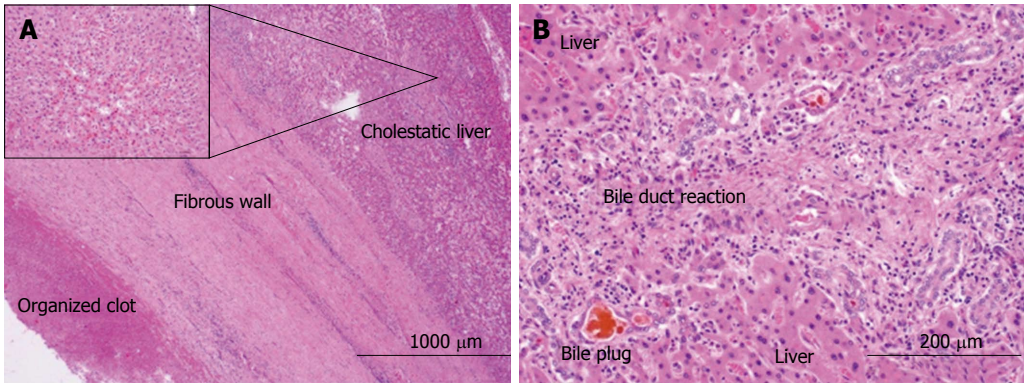

Figure 4 Histologic analyses of hepatic artery pseudoaneurysm and adjacent liver. A: H and E of fibrous capsule of the contained pseudoaneurysmal rupture adjacent to liver, 20 × magnification (A, inlet). Liver with centrilobular cholestasis, 200 × magnification; B: Liver with bile duct reaction and bile plugs consistent with biliary obstruction, 200 × magnification.

which further adds to the complexity and atypical nature of the case.

While HAPs can thrombose and resolve without intervention, the risk of rupture and subsequent hemorrhage are high enough that the general consensus has been in favor of intervention[1,2,4]. At this time, numerous minimally invasive techniques have proven to be successful, including coiling, covered stent exclusion, thrombin injection, gelfoam injection, plug deployment, polyvinyl alcohol injection, and surgical intervention[1,3,4]. The literature has supported all of these techniques as viable options for management of HAPs. Nagaraja *et al*[12] retrospectively analyzed 29 patients with HAP were successfully managed with angioembolization not surprisingly resulting in more rapid bleeding control, shorter hospital stay, and lower transfusion requirements although a 14%

mortality rate in the angioembolization group with no mortality in the surgical group. Currently, minimally invasive management is favored, although indications still exist for surgical intervention. Of note, recurrence of HAPs following embolization has been reported to be significant, and therefore current recommendations involve follow-up imaging with potential need for secondary intervention[9]. In the case of our patient, standard minimally invasive endovascular (HAP) and biliary (obstructive jaundice) management was attempted on several occasions with the use of multiple modalities, but ultimately failed to palliate her symptoms. This specific case presented multiple complications including inability to decompress the right biliary system secondary to mass effect and subsequent ischemia as portal vein. Therefore, surgical intervention, specifically right hepatic trisegmentectomy and bile duct resection, was required to address the biliary outflow obstruction and the inherent risk of rupture and hemorrhage of the HAP itself.

In conclusion, we present a unique case of HAP of unknown etiology, initially presenting with jaundice and pruritus. While the presenting symptoms were inconsistent with the typical presentation of HAPs, it is important to be aware of this as a potential cause of jaundice in addition to the more commonly thought of etiologies. The risk of morbidity and mortality secondary to HAP rupture and subsequent hemorrhage requires immediate identification and intervention. Currently, the literature supports the use of minimally invasive endovascular, endoscopic, and percutaneous approaches in the initial management of HAPs, with the potential need for future open surgical intervention if these techniques are inadequate.

COMMENTS

Case characteristics

A 65-year-old female with no significant past medical history with a history of painless jaundice and pruritis.

Clinical diagnosis

Computed tomography imaging studies revealed a 5 cm dense lesion within the hilar region of the liver and intrahepatic biliary duct dilatation.

Differential diagnosis

Klatskin's tumor, extrahepatic cholangiocarcinoma, pancreatic cancer.

Laboratory diagnosis

Total and direct bilirubin levels were elevated (total bilirubin 24.3 mg/dL, direct dilirubin 18.6 mg/dL), as was her serum alkaline phosphatase (432 U/L), liver transaminases (AST 132 U/L, ALT 148 U/L), and CA 19-9 (891 U/mL). Other pertinent labs included a positive ANA and CEA within the reference range.

Imaging diagnosis

Triphasic computed tomography angiography demonstrated a right branch hepatic artery pseudoaneurysm (HAP) measuring 2.1 cm, a suspected hematoma measuring 5 cm in diameter and significant biliary duct dilatation.

Pathological diagnosis

Right hepatic trisegmentectomy pathology specimen demonstrated the presence of a porta hepatis hematoma (5.0 cm) and organized thrombus dissecting into the hepatic artery wall, negative for malignancy and microscopically consistent with centrilobular cholestasis and bile ductular reaction with bile plugs all of which were consistent with chronic biliary obstruction.

Treatment

Complete surgical excision of locally involved right hepatic artery pseudoaneurysm.

Related reports

HAPs classically arise secondary to trauma or iatrogenic causes and pose a serious risk of exsanguinating hemorrhage and subsequent death. Numerous case reports have been published addressing the occurrence of HAPs subsequent to a variety of interventional procedures including cholecystectomy, pancreaticoduodenectomy, and orthotopic liver transplant. Due to the increased risk of rupture compared with true aneurysms, HAPs have been successfully treated using a variety of interventional methods. Because of the increased morbidity associated with surgery in this setting, surgical management is the final treatment option.

Term explanation

HAPs are "false" aneurysms that do not have the presences of layers of the arterial wall, communicates with the vessel in question and has blood confined by the surrounding tissues.

Experiences and lessons

HAPs are typically managed with a variety of interventional methods such as endovascular embolization, coiling embolization, and arterial stent grafting. Because of the increased morbidity associated with surgery in this setting, surgical management is the final treatment when impairment to adjacent structures such as the bile duct and portal vein cannot be alleviated.

Peer-review

This manuscript presents a rare case of pseudoaneurysm of hepatic artery. The management of the case is informative, and useful for the readers.

REFERENCES

1 **Lü PH**, Zhang XC, Wang LF, Chen ZL, Shi HB. Stent graft in the treatment of pseudoaneurysms of the hepatic arteries. *Vasc Endovascular Surg* 2013; **47**: 551-554 [PMID: 24052448 DOI: 10.1177/1538574413488460]

2 **Finley DS**, Hinojosa MW, Paya M, Imagawa DK. Hepatic artery pseudoaneurysm: a report of seven cases and a review of the literature. *Surg Today* 2005; **35**: 543-547 [PMID: 15976950 DOI: 10.1007/s00595-005-2987-6]

3 **Krokidis ME**, Hatzidakis AA. Acute hemobilia after bilioplasty due to hepatic artery pseudoaneurysm: treatment with an ePTFE-covered stent. *Cardiovasc Intervent Radiol* 2009; **32**: 605-607 [PMID: 19093147 DOI: 10.1007/s00270-008-9486-2]

4 **Fankhauser GT**, Stone WM, Naidu SG, Oderich GS, Ricotta JJ, Bjarnason H, Money SR. The minimally invasive management of visceral artery aneurysms and pseudoaneurysms. *J Vasc Surg* 2011; **53**: 966-970 [PMID: 21216559 DOI: 10.1016/j.jvs.2010.10.071]

5 **Julianov A**, Georgiev Y. Hepatic artery aneurysm causing obstructive jaundice. *Quant Imaging Med Surg* 2014; **4**: 294-295 [PMID: 25202666 DOI: 10.3978/j.issn.2223-4292.2014.06.02]

6 **Hossain A**, Reis ED, Dave SP, Kerstein MD, Hollier LH. Visceral artery aneurysms: experience in a tertiary-care center. *Am Surg* 2001; **67**: 432-437 [PMID: 11379643]

7 **Tulsyan N**, Kashyap VS, Greenberg RK, Sarac TP, Clair DG, Pierce G, Ouriel K. The endovascular management of visceral artery aneurysms and pseudoaneurysms. *J Vasc Surg* 2007; **45**: 276-283; discussion 283 [PMID: 17264002 DOI: 10.1016/j.jvs.2006.10.049]

8 **Harvey J**, Dardik H, Impeduglia T, Woo D, DeBernardis F. Endovascular management of hepatic artery pseudoaneurysm hemorrhage complicating pancreaticoduodenectomy. *J Vasc*

Surg 2006; **43**: 613-617 [PMID: 16520182 DOI: 10.1016/j.jvs.2005.11.031]

9 **Spiliopoulos S**, Sabharwal T, Karnabatidis D, Brountzos E, Katsanos K, Krokidis M, Gkoutzios P, Siablis D, Adam A. Endovascular treatment of visceral aneurysms and pseudoaneurysms: long-term outcomes from a multicenter European study. *Cardiovasc Intervent Radiol* 2012; **35**: 1315-1325 [PMID: 22146976 DOI: 10.1007/s00270-011-0312-x]

10 **Rencuzogullari A**, Okoh AK, Akcam TA, Roach EC, Dalci K, Ulku A. Hemobilia as a result of right hepatic artery pseudoaneurysm rupture: An unusual complication of laparoscopic cholecystectomy. *Int J Surg Case Rep* 2014; **5**: 142-144 [PMID: 24531018 DOI: 10.1016/j.ijscr.2014.01.005]

11 **Yao CA**, Arnell TD. Hepatic artery pseudoaneurysm following laparoscopic cholecystectomy. *Am J Surg* 2010; **199**: e10-e11 [PMID: 20103061 DOI: 10.1016/j.amjsurg.2009.03.014]

12 **Nagaraja R**, Govindasamy M, Varma V, Yadav A, Mehta N, Kumaran V, Gupta A, Nundy S. Hepatic artery pseudoaneurysms: a single-center experience. *Ann Vasc Surg* 2013; **27**: 743-749 [PMID: 23711970 DOI: 10.1016/j.avsg.2012.08.018]

P- Reviewer: Palmucci S, Panic N, Tomizawa M
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com