

# World Journal of *Hepatology*

*World J Hepatol* 2016 April 18; 8(11): 509-532





## 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 Republic (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).

### EDITORS-IN-CHIEF

Clara Balsano, *Rome*  
Wan-Long Chuang, *Kaohsiung*

### ASSOCIATE EDITOR

Thomas Bock, *Berlin*  
Silvia Fargion, *Milan*  
Ze-Guang Han, *Shanghai*  
Lionel Hebbard, *Westmead*  
Pietro Invernizzi, *Rozzano*  
Valerio Nobili, *Rome*  
Alessandro Vitale, *Padova*

### GUEST EDITORIAL BOARD MEMBERS

King-Wah Chiu, *Kaohsiung*  
Tai-An Chiang, *Tainan*  
Chi-Tan Hu, *Hualien*  
Sen-Yung Hsieh, *Taoyuan*  
Wenya Huang, *Tainan*  
Liang-Yi Hung, *Tainan*  
Jih RU Hwu, *Hsinchu*  
Jing-Yi Lee, *Taipei*  
Mei-Hsuan Lee, *Taipei*  
Chih-Wen Lin, *Kaohsiung*  
Chun-Che Lin, *Taichung*  
Wan-Yu Lin, *Taichung*  
Tai-Long Pan, *Tao-Yuan*  
Suh-Ching Yang, *Taipei*  
Chun-Yan Yeung, *Taipei*

### MEMBERS OF THE EDITORIAL BOARD



**Algeria**

Samir Rouabhia, *Batna*



**Argentina**

Fernando O Bessone, *Rosario*  
Maria C Carrillo, *Rosario*  
Melisa M Dirchwolf, *Buenos Aires*  
Bernardo Frider, *Buenos Aires*  
Jorge Quarleri, *Buenos Aires*  
Adriana M Torres, *Rosario*



**Armenia**

Narina Sargsyants, *Yerevan*



**Australia**

Mark D Gorrell, *Sydney*



**Austria**

Harald Hofer, *Vienna*  
Gustav Paumgartner, *Vienna*  
Matthias Pinter, *Vienna*  
Thomas Reiberger, *Vienna*



**Bangladesh**

Shahinul Alam, *Dhaka*  
Mamun Al Mahtab, *Dhaka*



**Belgium**

Nicolas Lanthier, *Brussels*

Philip Meuleman, *Ghent*  
Luisa Vonghia, *Antwerp*



**Botswana**

Francesca Cainelli, *Gaborone*  
Sandro Vento, *Gaborone*



**Brazil**

Edson Abdala, *Sao Paulo*  
Ilka FSF Boin, *Campinas*  
Niels OS Camara, *Sao Paulo*  
Ana Carolina FN Cardoso, *Rio de Janeiro*  
Roberto J Carvalho-Filho, *Sao Paulo*  
Julio CU Coelho, *Curitiba*  
Flavio Henrique Ferreira Galvao, *Sao Paulo*  
Janaina L Narciso-Schiavon, *Florianopolis*  
Sílvia HC Sales-Peres, *Bauru*  
Leonardo L Schiavon, *Florianópolis*  
Luciana D Silva, *Belo Horizonte*  
Vanessa Souza-Mello, *Rio de Janeiro*  
Jaques Waisberg, *Santo André*



**Bulgaria**

Mariana P Penkova-Radicheva, *Stara Zagora*  
Marieta Simonova, *Sofia*



**Canada**

Runjan Chetty, *Toronto*  
Michele Molinari, *Halifax*  
Giada Sebastiani, *Montreal*

**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 Wayne, *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 Republic**

Kamil Vysloulzil, *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 Siahaidou, *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*  
 Yasuhiro Tanaka, *Nagoya*  
 Takuji Tanaka, *Gifu City*  
 Atsunori Tsuchiya, *Niigata*  
 Koichi Watashi, *Tokyo*  
 Hiroshi Yagi, *Tokyo*  
 Taro Yamashita, *Kanazawa*  
 Shuhei Yoshida, *Chiba*  
 Hitoshi Yoshiji, *Kashiwara*

**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 Limpai boon, *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 Kobylak, *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*

**MINIREVIEWS**

- 509** Extension for Community Health Outcomes-hepatitis C: Small steps carve big footprints in the allocation of scarce resources for hepatitis C virus treatment to remote developing areas

*Tahan V, Almashhrawi A, Kahveci AM, Mutrux R, Ibdah JA*

- 513** Hepatic resection beyond barcelona clinic liver cancer indication: When and how

*Garancini M, Pinotti E, Nespoli S, Romano F, Gianotti L, Giardini V*

**ORIGINAL ARTICLE****Retrospective Study**

- 520** Predictors of mortality after transjugular portosystemic shunt

*Ascha M, Abuqayyas S, Hanouneh I, Alkukhun L, Sands M, Dweik RA, Tonelli AR*

**CASE REPORT**

- 530** Management of pregnancy in Crigler Najjar syndrome type 2

*Chaubal AN, Patel R, Choksi D, Shah K, Ingle M, Sawant P*

## ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Feng Wu, MD, PhD, Professor, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, Oxford OX3 7LE, United Kingdom

## 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

EDITORS FOR  
THIS ISSUE

Responsible Assistant Editor: *Xiang Li*  
Responsible Electronic Editor: *Su-Qing Liu*  
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Fang-Fang Ji*  
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL  
*World Journal of Hepatology*

ISSN  
ISSN 1948-5182 (online)

LAUNCH DATE  
October 31, 2009

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

EDITORS-IN-CHIEF  
**Clara Balsano, PhD, Professor**, Departement of Biomedicine, Institute of Molecular Biology and Pathology, Rome 00161, Italy

**Wan-Long Chuang, MD, PhD, Doctor, Professor**, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung 807, Taiwan

EDITORIAL OFFICE  
Jin-Lei Wang, Director

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](mailto: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](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>  
<http://www.wjgnet.com>

PUBLICATION DATE  
April 18, 2016

## COPYRIGHT

© 2016 Baishideng Publishing Group Inc. Articles published by this Open Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

## SPECIAL STATEMENT

All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

## INSTRUCTIONS TO AUTHORS

Full instructions are available online at [http://www.wjgnet.com/bpg/g\\_info\\_20160116143427.htm](http://www.wjgnet.com/bpg/g_info_20160116143427.htm)

## ONLINE SUBMISSION

<http://www.wjgnet.com/esps/>

## Extension for Community Health Outcomes-hepatitis C: Small steps carve big footprints in the allocation of scarce resources for hepatitis C virus treatment to remote developing areas

Veysel Tahan, Ashraf Almashhrawi, Ali M Kahveci, Rachel Mutrux, Jamal A Ibdah

Veysel Tahan, Ashraf Almashhrawi, Ali M Kahveci, Jamal A Ibdah, Division of Gastroenterology and Hepatology, University of Missouri, Columbia, MO 65201, United States

Rachel Mutrux, Missouri Telehealth Network and Missouri Health IT Assistance Center, Columbia, MO 65201 United States

**Author contributions:** Tahan V, Almashhrawi A and Kahveci AM performed the majority of the writing, prepared the figure; Mutrux R performed data accusation and writing; Ibdah JA provided the input in writing the paper, designed the outline with outer authors and coordinated the writing of the paper.

**Conflict-of-interest statement:** There is no conflict of interest associated with any of the authors contributed their efforts in this manuscript.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Veysel Tahan, MD, Assistant Professor, Division of Gastroenterology and Hepatology, University of Missouri, 1 Hospital Dr, Columbia, MO 65201, United States. [tahanv@health.missouri.edu](mailto:tahanv@health.missouri.edu)  
Telephone: +1-573-8846044  
Fax: +1-573-8844595

Received: February 2, 2016  
Peer-review started: February 2, 2016  
First decision: March 1, 2016  
Revised: March 7, 2016  
Accepted: March 24, 2016  
Article in press: March 25, 2016  
Published online: April 18, 2016

### Abstract

Hepatitis C virus (HCV) infection is still a major health problem throughout the world. HCV patients living in rural areas are less fortunate than their counterparts residing in populous urbanized regions. The lack of medical resources and properly trained medical personnel in rural regions make it especially burdensome for HCV patients seeking treatment. Dr. Sanjeev Arora at the University of New Mexico Health Sciences Center took initiative to resolve the issue at hand by developing a model named Project Extension for Community Health Outcomes (ECHO). ECHO connects primary care providers (PCPs), usually family medicine physicians, in local communities with specialists. ECHO providers test the efficacy of treatment given using the ECHO model vs that at academic medical centers. The ECHO model has produced promising results such that the sustained virologic response rates for both types of sites were near-equivalent. Show Me ECHO was adapted from Project ECHO to train PCPs in Missouri and equip them with the tools and skills to properly treat and diagnose HCV in a timely manner. This healthcare model can be implemented for treating other common infections and chronic diseases. Telemedicine is the direction healthcare is headed for the next several decades. It has potential to be applied in developing countries to alleviate agony and despair resulting from limited resources and lack of access to expert medical care.

**Key words:** Hepatitis C; Treatment; Community; Health care; Outcome; Rural; Primary care; Extension for Community Health Outcomes

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** The American Association for the Study of Liver

Diseases recommends Project Extension for Community Health Outcomes (ECHO). Project ECHO aims to move the knowledge not the patients. By bringing expertise to primary care physicians, patients from rural and underserved communities will benefit by alleviating the struggle associated with travel and appointment delays. The framework of this project can be used to manage other diseases that require specialty physician care that may not be feasible. Telemedicine represents the future of healthcare, its success will substantially reshape the healthcare delivery in developing countries and is pivotal for geographically isolated and underserved populations.

Tahan V, Almashhrawi A, Kahveci AM, Mutrux R, Ibdah JA. Extension for Community Health Outcomes-hepatitis C: Small steps carve big footprints in the allocation of scarce resources for hepatitis C virus treatment to remote developing areas. *World J Hepatol* 2016; 8(11): 509-512 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i11/509.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i11.509>

## INTRODUCTION

Hepatitis C virus (HCV) infection and its complications are still a major health problem throughout the world. There are roughly 4 million persons with a seropositive test for HCV in the United States, many of whom are even not aware of the disease and many of those who know are in a medical quandary with regards on how to access treatment<sup>[1]</sup>. Incredible progress has been achieved regarding HCV treatment in the past decade, highlighted by an increase in HCV cure rates.

Access to proper HCV treatment and care has truly become a hurdle for millions of patients housed in rural settings because of the uneven distribution of trained medical personnel and resources to select urbanized cities. As a result, patients in rural and remote areas often find themselves at the mercy of HCV because of the shortage of medical resources at their disposal. Oftentimes, these patients have no other option but visit nearby primary care providers (PCPs) in small clinics. However, PCPs are only equipped to address basic healthcare needs which mean HCV patients are subject to subpar treatment at best<sup>[2,3]</sup>.

## WHAT IS PROJECT EXTENSION FOR COMMUNITY HEALTHCARE OUTCOMES?

The University of New Mexico Health Sciences Center (UNMHSC) launched the Extension for Community Healthcare Outcomes (ECHO) model in 2003 in response to the external circumstances that burdened many rural HCV patients from successfully being treated. Dr. Sanjeev Arora, a distinguished Professor of Medicine, Division of Gastroenterology, at the UNMHSC, is the

director and founder of Project ECHO. He pioneered a new high-speed approach for providing expert healthcare to patients. Dr. Arora was distraught with the reality that there is a prevalent shortage of resources; there are thousands of HCV patients needing quality care and treatment. He chose to be proactive to instill necessary change that was long overdue. Coupled with the rapid technological advancements of the time, telemedicine progressed and ECHO was born<sup>[3,4]</sup> and has been proven to be effective<sup>[5-7]</sup>.

The purpose of the ECHO model is to establish a working network of PCPs, psychiatrists, pharmacists, infectious disease specialists, and other healthcare professionals that can collaborate and exchange information such as patient lab results and treatment plans (Figure 1). Through a video conferencing platform, the teams are given an opportunity to inform each other of their own personal experiences and challenges to better serve the interests of HCV patients in the long run. These sessions, called Knowledge Networks, allow PCPs to acquire the critical skills necessary in treating geographically isolated HCV patients<sup>[8]</sup>.

## HIT OR MISS?

Arora *et al*<sup>[8]</sup> set up an experimental model to test HCV treatment efficacy of their newly inaugurated ECHO program. They hypothesized that any success they have had with treating patients at academic medical centers would be mirrored in remote clinics employing the ECHO model. The parameter used to measure efficacy of treatment is sustained virologic response (SVR). After a patient completes therapy, he/she is evaluated for a period of 6 mo. If the HCV does not reappear during this time, the patient has achieved SVR<sup>[8]</sup>.

Originally, 519 patients enrolled in the study from both the ECHO sites and University HCV clinics. Of these 519, 407 remained relevant for the overall SVR rates in the study. HCV patients who got at least one dose of HCV treatment were included in the analysis. Any patient without follow-up data was considered as treatment failure<sup>[5]</sup>. The patient count was 261 and 146 at the ECHO sites and University HCV clinics, respectively. Some more patients were also discontinued from the study for not meeting specified health targets. The overall SVR was 152/261 (58.2%) and 84/146 (57.5%) for ECHO sites and the University of New Mexico HCV clinic, respectively. Therefore, the magnitude of this success supports what Arora *et al*<sup>[8]</sup> had hypothesized early on about HCV treatment using the ECHO model. As a result, the number of ECHO sites drastically increased to around 300 nowadays<sup>[8]</sup>. Currently, each center is collecting the SVR data on new and more effective interferon free HCV treatment to compare the outcomes.

## NEW MEXICO TO MISSOURI

Missouri residents amount to a little over 6 million



Figure 1 Extension for Community Health Outcomes Model. ECHO: Extension for Community Health Outcomes.

people. About one-fourth of all Missourians inhabit rural areas of the state<sup>[9]</sup>. Missouri residents that belong to the underserved areas of the state are oftentimes disconnected from their specialty care providers because of geographic barriers. As mentioned before, the pool of health care resources is often concentrated in large metropolitan cities, which subsequently attracts many specialty care providers to these populous areas<sup>[3]</sup>. According to the Bureau of Health Professions, about 20% to 25% people in Missouri live in a rural community. However, the percentage of physicians caring for these communities are roughly 9% of all physicians in Missouri with a notable shortage of specialists<sup>[10]</sup>.

## TARGETS OF SHOW ME ECHO MODEL

Show Me ECHO, an adaptation of the University of New Mexico School of Medicine's ECHO model, was instigated with a similar purpose: To promote accessible and affordable quality care for HCV patients in disadvantaged underserved and rural populations in Missouri with an aim to move the knowledge not the patients<sup>[6]</sup>.

Show Me ECHO model in Missouri also echoes developing PCPs expertise. By educating and empowering PCPs, it will be possible to screen, diagnose, and treat HCV in a timely fashion in remote and underserved areas. The use of telemedicine surely has that potential to bridge the gap between specialists and PCPs through an exchange of knowledge and treatment protocols which can improve the patient experience for generations to come. In addition to all of this, a health surveillance system is essential to ensure fluid interactions between patients and healthcare providers. One of Show Me ECHO project goals is to create a link between the Missouri Department of Health, Senior Services, and the Missouri Primary Care Association so that HCV cases are accurately recorded. Thus, a sound health surveillance system across Missouri will advance the timeliness of diagnosis and treatment.

## IMPLICATIONS OF ECHO

The American Association for the Study of Liver Diseases recommends Project ECHO because of its success in treating HCV patients amid the adversities experienced initially by both patients and healthcare professionals<sup>[7]</sup>. Indeed, the benefits of Project ECHO

are paramount and not limited to successful SVR rates. By bringing expertise to PCPs, patients from rural and underserved communities will benefit by alleviating the struggle associated with travel and appointment delays. Additionally, community-based health centers, rather than university clinics, are usually more suitable for rural HCV patients because PCPs are often more cognizant of their local community. Visiting the same PCP for HCV treatment reduces tensions between both patients and healthcare providers, allowing for optimal coordination in a familiar setting<sup>[8]</sup>. Without Project ECHO, many HCV treatments would have been stymied. Show Me ECHO is on track as well to produce promising results.

ECHO model is a great Segway into healthcare in developing countries. The possibilities for introducing Project ECHO in those countries are immense because healthcare is presumably hindered by the lack of appropriate expert medical care. Telemedicine can leverage the aid and significantly alleviate the patients' sufferings.

Project ECHO is a great template for the medical field to actively embrace because of its potential to allocate specialized care needed for disadvantaged HCV patients in developing countries. The framework of this project can be used to manage other diseases that require specialty physician care that may not be feasible. Telemedicine represents the future of healthcare, its success will substantially reshape the health care delivery in developing countries and is pivotal for geographically isolated and underserved populations.

## REFERENCES

- 1 CDC-Viral Hepatitis Statistics and Surveillance. Available from: URL: <http://www.cdc.gov/HEPATITIS/Statistics/index.htm>
- 2 Arora S, Thornton K, Komaromy M, Kalishman S, Katzman J, Duhigg D. Demonopolizing medical knowledge. *Acad Med* 2014; **89**: 30-32 [PMID: 24280860 DOI: 10.1097/ACM.0000000000000051]
- 3 Volk ML, Tocco R, Saini S, Lok AS. Public health impact of antiviral therapy for hepatitis C in the United States. *Hepatology* 2009; **50**: 1750-1755 [PMID: 19824079 DOI: 10.1002/hep.23220]
- 4 University of New Mexico. Available from: URL: <http://echo.unm.edu/about-echo/our-story/>
- 5 Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D, Parish B, Burke T, Pak W, Dunkelberg J, Kistin M, Brown J, Jenkuskus S, Komaromy M, Qualls C. Outcomes of treatment for hepatitis C virus infection by primary care providers. *N Engl J Med* 2011; **364**: 2199-2207 [PMID: 21631316 DOI: 10.1056/NEJMoa1009370]
- 6 Missouri Telehealth Network. ECHO: Show Me ECHO. Available

- from: URL: <http://medicine.missouri.edu/telehealth/echo.html>
- 7 **AASLD.** HCV Guideline 2015. Available from: URL: <http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care>
- 8 **Arora S**, Kalishman S, Thornton K, Dion D, Murata G, Deming P, Parish B, Brown J, Komaromy M, Colleran K, Bankhurst A, Katzman J, Harkins M, Curet L, Cosgrove E, Pak W. Expanding access to hepatitis C virus treatment--Extension for Community Healthcare Outcomes (ECHO) project: disruptive innovation in specialty care. *Hepatology* 2010; **52**: 1124-1133 [PMID: 20607688 DOI: 10.1002/hep.23802]
- 9 **USDA.** Economic Research Service: State fact Sheets. Available from: URL: <http://www.ers.usda.gov/data-products/state-fact-sheets/state-data.aspx?reportPath=/StateFactSheets/StateFactSheet&StateFIPS=21>
- 10 **Rosenblatt RA**, Hart LG. Physicians and rural America. *West J Med* 2000; **173**: 348-351 [PMID: 11069878]

**P- Reviewer:** Cao GW, Jin B, Rezaee-Zavareh MS  
**S- Editor:** Ji FF **L- Editor:** A **E- Editor:** Liu SQ



## Hepatic resection beyond barcelona clinic liver cancer indication: When and how

Mattia Garancini, Enrico Pinotti, Stefano Nespoli, Fabrizio Romano, Luca Gianotti, Vittorio Giardini

Mattia Garancini, Enrico Pinotti, Stefano Nespoli, Fabrizio Romano, Luca Gianotti, Vittorio Giardini, Department of Surgery, Hepatobiliopancreatic Unit, San Gerardo Hospital, University of Milano Bicocca, 20900 Monza, Italy

**Author contributions:** All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting, critical revision, editing, and final approval of the final version.

**Conflict-of-interest statement:** All authors have no potential conflicts of interest and no financial support to declare.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Mattia Garancini, MD, Department of Surgery, Hepatobiliopancreatic Unit, San Gerardo Hospital, University of Milano Bicocca, Via Pergolesi 33, 20900 Monza, Italy. [mattia\\_garancini@yahoo.it](mailto:mattia_garancini@yahoo.it)  
Telephone: +39-039-2339783  
Fax: +39-039-2339783

Received: September 11, 2015  
Peer-review started: September 11, 2015  
First decision: October 27, 2015  
Revised: February 18, 2016  
Accepted: March 24, 2016  
Article in press: March 25, 2016  
Published online: April 18, 2016

### Abstract

Hepatocellular carcinoma (HCC) is the main common primary tumour of the liver and it is usually associated with cirrhosis. The barcelona clinic liver cancer (BCLC)

classification has been approved as guidance for HCC treatment algorithms by the European Association for the Study of Liver and the American Association for the Study of Liver Disease. According to this algorithm, hepatic resection should be performed only in patients with small single tumours of 2-3 cm without signs of portal hypertension (PHT) or hyperbilirubinemia. BCLC classification has been criticised and many studies have shown that multiple tumors and large tumors, as wide as those with macrovascular infiltration and PHT, could benefit from liver resection. Consequently, treatment guidelines should be revised and patients with intermediate/advanced stage HCC, when technically resectable, should receive the opportunity to be treated with radical surgical treatment. Nevertheless, the surgical treatment of HCC on cirrhosis is complex: The goal to be oncologically radical has always to be balanced with the necessity to minimize organ damage. The aim of this review was to analyze when and how liver resection could be indicated beyond BCLC indication. In particular, the role of multidisciplinary approach to assure a proper indication, of the intraoperative ultrasound for intraoperative restaging and resection guidance and of laparoscopy to minimize surgical trauma have been enhanced.

**Key words:** Hepatocellular carcinoma; Liver surgery; Hepatic resection; Multiple hepatocellular carcinoma; Cirrhosis; Barcelona clinic liver cancer; Multidisciplinary approach; Intraoperative ultrasound; Laparoscopy; Portal hypertension

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** According to the barcelona clinic liver cancer (BCLC) classification liver resection should be performed only in patients with small single hepatocellular carcinoma of 2-3 cm without signs of portal hypertension (PHT). Nevertheless, many studies have shown that patients with multiple and large hepatocellular carcinoma

noma, as like as those with macrovascular infiltration and PHT, could benefit from liver resection. Consequently BCLC algorithm should be updated and revised. The aim of this review was to analyze when and how liver resection could be indicated beyond BCLC indications. In this perspective, the role of multidisciplinary approach, of intraoperative ultrasound and of laparoscopy have been enhanced.

Garancini M, Pinotti E, Nespoli S, Romano F, Gianotti L, Giardini V. Hepatic resection beyond barcelona clinic liver cancer indication: When and how. *World J Hepatol* 2016; 8(11): 513-519 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i11/513.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i11.513>

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the main common primary tumour of the liver, representing approximately 85%-90% of primary hepatic malignancies; it is ranked as the fifth and seventh most common cancer respectively in males and females, and represents the third leading cause of neoplasm-related deaths worldwide<sup>[1,2]</sup>. HCC is usually associated with cirrhosis, whose major causes could be identified in viral and alcoholic liver disease, although recent epidemiological data highlighted the increasing etiological role of obesity, diabetes and metabolic syndrome in liver oncogenesis<sup>[3]</sup>. The treatment of HCC set on cirrhosis is complex: The aim to be oncologically radical has always to be balanced with the necessity to minimize organ damage. In this sense liver transplantation is considered the gold standard treatment, because offers the possibility to treat simultaneously the liver cancer and the damaged organ; on the other hand organ shortage led to the development of restricted indication to liver transplantation, addressing many patients to receive local therapies<sup>[4]</sup>. In literature, several HCC staging systems based on tumour's features and liver function have been developed and proposed to guide the therapeutic decisions in such patients; among all the barcelona clinic liver cancer (BCLC) classification (Figure 1) has been approved as guidance for HCC treatment algorithms by the European Association for the Study of Liver (EASL) and the American Association for the Study of Liver Disease (AASLD), combining independent prognostic predictors like the background liver status, patient's performance status and tumor morphological features, and showing a reliable capacity to categorize patients with different prognosis in order to provide recommendations regarding therapeutic options. The BCLC flow chart recommends curative treatments for HCC in very early- or early-stage (stage 0-A), trans-arterial chemoembolization for intermediate-stage disease (stage B), sorafenib administration for advanced stage HCC (stage C), and supportive care for end stage HCC (stage D)<sup>[5,6]</sup>. BCLC indication to liver resection seems to be markedly limiting. On contrary, other

authors have shown that surgical resection can offer good short- and long-term outcomes even in presence of portal hypertension (PHT), multinodular disease, large nodules or even HCC with macrovascular invasion<sup>[7-9]</sup>; thus the BCLC classification has been criticised because some patients who may benefit from surgical treatment are excluded from curative resection and these findings have encouraged many experts to disregard the EASL/AASLD therapeutic recommendations<sup>[6-8]</sup>.

The aim of this review was to analyze when and how liver resection could be indicated beyond BCLC indications.

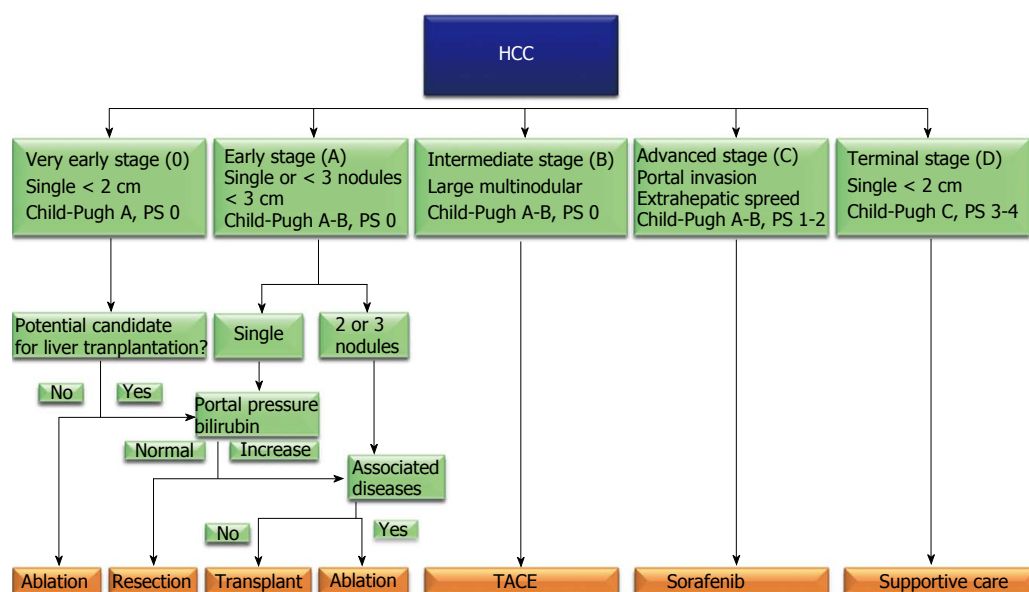
## DISCUSSION

### **Liver resection beyond BCLC classification: When?**

Historically hepatic resection has been performed with caution to HCC patients because of concerns about morbidity and mortality rates. However, recent improvements in surgical technique and perioperative care have improved hepatic resections outcomes with consequent extension of indications to surgical procedures. In this sense some high volume surgical liver unit recently reported hospital mortality less than 2%<sup>[10]</sup>. According to BCLC algorithm, liver resection would be indicated only in patients with single tumours of 2-3 cm in diameter without PHT or increased bilirubinemia<sup>[6]</sup> (Figure 1). BCLC classification has been criticised because it excludes many patients who could benefit from curative resection. PHT, large tumor size, multifocal presentation and vascular invasion are well recognized risk factors for post-operative morbidity and mortality and for poor long-term prognosis, but should not be considered contraindication to surgical treatments.

### **LARGE HCC (> 5 cm)**

BCLC algorithm suggests hepatic resection only in presence of small HCC (< 5 cm). On contrary, several authors have recently reported that liver resection can offer good short- and long-term outcomes even in patients with HCC > 5 cm. Main concerns related to restricted surgical indication in patients with large HCC take into account the increased rates of presence of satellite nodules, increased rate of distant metastases and of vascular invasion those are related to increasing tumour size and represent important prognostic factors for poor survival. Furthermore patients with large HCC (> 5 cm) may necessitate a major hepatectomy, which is considered a high-risk procedure especially in HCC set on cirrhosis<sup>[11,12]</sup>. Anyway radical liver resection can be considered a valuable option in patients with large HCC<sup>[13]</sup>. Large surgical series recently published reported a significant rate (up to 36%) of large HCC surgically treated with good results<sup>[14]</sup>. In this sense, it's remarkable that in literature there are many studies reporting cases of liver resection for HCC > 8-10 cm with good results even considering the poor prognostic results of the main alternative for such BCLC stage B HCC represented



**Figure 1** Barcelona clinic liver cancer algorithm for treatment of hepatocellular carcinoma<sup>[9]</sup>. HCC: Hepatocellular carcinoma; TACE: Transarterial chemo-embolization.

by transarterial chemo-embolization (TACE). Zhong *et al.*<sup>[15]</sup> comparing liver resection to TACE in a wide cohort of patients with large HCC in BCLC B stage (mean size 8.8 cm) showed that tumor resection offers better 5-year overall survival than TACE (41% and 18%, respectively). Proper identification and multidisciplinary discussion of risk factors for surgical morbidity and mortality in such patients (including presence of vascular invasion, cirrhosis, high level of alpha-fetoprotein and the presence of multiple lesions<sup>[16]</sup>) is critical for patients' selection and to obtain good outcomes.

## MULTIPLE HCC

Treatment guidelines do not recommend hepatic resection for multifocal HCC. Liver resection in presence of multiple HCC is still controversial; anyway it has been recognized a survival benefit for patients with a number of HCC  $\leq 3$  and lesions less than 3 cm in diameter (according to Milan criteria)<sup>[17]</sup>. Multifocal presentation is well recognized independent prognostic factor for early recurrence and poor prognosis<sup>[18]</sup>. Anyway recent prospective studies showed that hepatic resection in patients with BCLC stage B HCC is well tolerated and related to a low mortality rate, acceptable morbidity and significant survival benefits<sup>[4]</sup>. Surgical resection yielded better results than TACE in patients with multiple HCCs of the same stage; Zhong *et al.*<sup>[19]</sup> analyzed outcomes of patients with more and less of 3 HCC tumors who underwent liver resection or TACE. Survival was significantly higher in the surgery subgroup at 1 year (90% vs 59%), 3 years (52% vs 11%), and 5 years (33% vs 6%).

## PORTAL VEIN HYPERTENSION

PHT is considered a contraindication for liver resection

according to the EASL and AASLD published guidelines for HCC management. PHT may increase the risk of peri-operative haemorrhage, impair liver regeneration, and increase the risk of liver failure. Recent advances in surgical techniques and peri-operative care for patients with cirrhosis have reduced the number of cirrhosis-related complications and deaths. Several authors demonstrated that patients with and without PHT had similar morbidity (28%-39% vs 21%-32.2%) and 90-d mortality (2%-2.1% vs 3.1%-6%). The overall survival at 1, 3 and 5 years is similar or slightly longer in patients without portal vein hypertension (respectively 85%-96%, 67%-80% and 50%-65%) compared to patients with PHT (respectively 83%-90%, 59%-67% and 45%-48%), these results appear significant and encouraging, considering that liver resection, with exclusion of liver transplantation, represent the best choice of radical cure<sup>[20-22]</sup>. Patients with PHT should be carefully selected for surgery, but PHT should not be considered a contraindication to liver resection.

## MACROVASCULAR INFILTRATION

According to the EASL and AASLD guidelines for management of HCC, patients with macrovascular infiltration are considered in advanced stage (stage C) and should be treated only with chemotherapy (Sorafenib). Presence of macrovascular invasion is related to an increased risk of metastases and is a well known predictor of poor survival<sup>[23]</sup>. The median survival for untreated patients with macrovascular portal or major hepatic vein infiltration is 3-5 mo and median survival for such patients treated with sorafenib is 6 mo<sup>[18,24]</sup>. Selected patients with macrovascular infiltration who underwent liver resection for HCC can achieve longer overall survival, 46%-49% and 11.2%-38% respectively

at 3 and 5 years with acceptable morbidity and mortality rate (under 3%-5%)<sup>[13,14,25]</sup>. Consequently the surgical resection should be considered when planning the treatment's strategy for such patients and formally included together with other treatment modalities for the cure of BCLC stage C patients.

#### ***Liver resection beyond BCLC classification: How?***

Patients suffering from cirrhosis are at increased risk of developing significant postoperative complications including ascites, lung infection or pleural effusion, transient encephalopathy, kidney failure, portal vein thrombosis and bleeding due to primary haemostasis dysfunction<sup>[26,27]</sup>. In order to reduce mortality and morbidity after liver surgery in patients with cirrhosis, surgeons have developed meticulous selection criteria to guide surgical indication in such patients. For all these reasons the decision to submit a cirrhotic patient to a liver resection is complex. It is of paramount importance that pre-operative evaluation of cirrhotic patients with hepatocellular carcinoma would be performed by a multidisciplinary team, in order to match different point of view and possible therapeutic approach. Furthermore, some technical aspects of liver resection should be enhanced discussing the approach to patients with an advanced stage HCC.

### **THE ROLE OF MULTIDISCIPLINARY APPROACH**

HCC has different presentations those are compounded by the status of liver disease, and the multiple treatment options available make choosing the first line of treatment for a given patient a difficult task. Management of HCC patients should be undertaken by a multidisciplinary team including all the specialties those have a role in the treatment of such patients; if this kind of approach should represent the standard for the treatment of every patient with HCC, the importance of the sharing of indication in disagreement with BCLC algorithm is even increased. Studies those have shown a decrease in morbidity and mortality after liver resection for HCC also showed the importance of a multidisciplinary approach<sup>[28-31]</sup>. Patients in intermediate/advanced stages should be carefully selected for the best treatment according to the stage of the disease, to the presence of cirrhosis, to the age of patient, to general condition and comorbidity. A team of surgeon, oncologist, hepatologist, radiologist and interventional radiologist, anesthesiologist and pathologist should evaluate the best treatment for each of these patients, in order to perform a tailored treatment that could include more than one approach. BCLC indication to liver resection should be less restrictive; on the other hand the importance of patients' selection must be considered and great efforts are needed to establish selection criteria to be included in the treatment algorithm.

### **THE ROLE OF INTRAOPERATIVE ULTRASOUND**

Intra-operative ultrasound (IOUS) is still considered the most accurate diagnostic technique for detecting focal liver lesions in hepatocellular carcinoma. The main advantages related to an extensive use of ultrasounds in liver surgery for HCC on cirrhosis concerns the intra-operative re-staging and the possibility to perform echo-guided surgical procedures. IOUS may detect additional nodules compared with pre-operative imaging in 33%-41% of patients undergoing liver resection for HCC<sup>[32,33]</sup>. The removal of new nodules after this early diagnosis may increase the BCLC stage of patients but also contribute to perform a more complete treatment and improve choice of cure. Moreover intra-operative echo guidance, allowing to perform a parenchima-sparing anatomical hepatic surgery in respect of principles of oncologic radicality, is an invaluable tool to engage surgical procedure in intermediate/advanced-stage patients<sup>[34]</sup>. The use of ultrasound guidance is mandatory for planning the surgical strategy, decide the exact resection plane during the parenchymal transection in order to respect the surrounding vessels and biliary structures. Main concerns related to the restricted indication to liver surgery following BCLC indication regards the possibility of increased peri-operative mortality and morbidity and the poor chance of radical cure and prolonged survival in patients with intermediate/advanced HCC. IOUS, minimizing the extension of the parenchima removed in respect of oncological radicality and offering a re-staging and a consequent more radical treatment, represents an invaluable tool in the perspective of expansion of surgical indication beyond BCLC recommendations. The extensive use of ultrasound in liver surgery together with technological improvements in recent years allowed *per se* an expansion of surgical indication in advanced HCC: The possibility to detect intra-operatively connecting veins between adjacent hepatic veins allows to perform radical limited liver resection even in patients with major hepatic vein invasion, in order to reduce the rate of major resection and its consequent increased morbidity and mortality<sup>[35,36]</sup>. Anatomic liver resection is usually performed because of HCC spreading along the nourishing portal venous branch and consequent growth of satellite nodules within the same anatomical segment. Thus, anatomic resection allows removal of the known tumor, as well as of potential undetectable satellite metastases; the advantages of anatomic resection can be maximized in particular in large HCC which are frequently surrounded by satellite lesions<sup>[37,38]</sup>. IOUS is of paramount importance to guide and assure an anatomic liver resection, either with traditional puncture technique of the portal branch feeding the tumor, either by means of recently introduced compression technique or other methods as trans-hepatic balloon catheter or CEIOUS portography combined with indigo carmine dye injection<sup>[39-43]</sup>. In a recent meta-analysis Chen *et*

*al*<sup>[44]</sup> analyzed outcomes of 833 patients underwent anatomic liver resection for HCC and 670 patients underwent non-anatomic resection for the same disease. The surgical margin *per se* does not represent a main aspect, because an anatomic resection (segmentectomy or sub-segmentectomy) can be considered adequate even in presence of a narrow margin; the advantages related to limited anatomic resection can be maximized to perform multiple limited resection in multiple HCC, in order to assure local radical tumor removal with a parenchyma sparing policy<sup>[44]</sup>. There are several methods up to now available to perform an anatomic (segmental or subsegmental) US-guided liver resection: Puncture technique proposed by Makuuchi *et al*<sup>[40]</sup>, insertion of a balloon catheter transhepatically to occlude the feeding portal branch<sup>[41]</sup> and ultrasound-guided finger compression technique<sup>[43]</sup>.

## THE ROLE OF LAPAROSCOPY

Laparoscopic surgery for liver tumors requires skilled surgeons and specific technological instruments. Moreover its indications have not been still clearly defined; for such reasons it has not been widely performed even if its employment is progressively expanding. The main concern about the use of laparoscopic technique for malignancies is the risk of inadequate tumor resection; positive margin is a well known prognostic factor for poor survival in surgery for HCC, in this perspective intra-operative ultrasound should be considered an indispensable tool to achieve a safe and effective liver resection. Anyway according to several meta-analyses comparing open vs laparoscopic liver resections for HCC, laparoscopic liver resection is considered a safe procedure with comparable overall and recurrence-free survival rates<sup>[45-47]</sup>. Laparoscopic approach might improve the postoperative course of cirrhotic patients, because limited mobilization of the liver reduces parenchymal trauma, nonexposure of intestinal viscera restricts fluid requirements and decreased the formation of ascites<sup>[26,48]</sup>. In a recent study Kanazawa *et al*<sup>[26]</sup> compared outcomes of cirrhotic patients underwent laparoscopic and laparotomic liver resection; the two groups was not different by age, sex, stage of cirrhosis, number and size of lesions. In this study the incidence of intractable ascites was significantly higher in the laparotomy group than in the laparoscopy group (71% vs 11%). Furthermore the use of laparoscopy in cirrhotic patients may allow the preservation of wall portosystemic shunts, and in some cases the integrity of round ligament, which can contain collateral vessels. This can result in a lower increase of post-operative PHT and risk of bleeding<sup>[26]</sup>. Laparoscopic liver resection is associated with less total and major morbidity, shorter hospital stay and lower rate of post-operative early readmissions or number of outpatient clinic appointments compared with open counterpart<sup>[49,50]</sup>. The above mentioned advantages of laparoscopic approach can be crucial in the perspective of expansion

of surgical indication to patients with HCC beyond BCLC indications. In particular patients with PHT or multinodular disease can benefit of a minimally invasive treatment, which can include also combined laparoscopic resection and ablation of multiple HCC in the perspective of a tailored treatment<sup>[51,52]</sup>. Surgical resection has shown better results in terms of disease free and overall long term survival compared to laparoscopic ablation. Nevertheless, in the treatment of HCC not suitable for liver transplantation or not eligible for resection because of severe PHT and not manageable by percutaneous approach for tumor size or location, laparoscopic ablation should be considered as a valuable choice since it proved to be a safe and effective technique, as it permits to treat lesions with low-morbidity-rate<sup>[51]</sup>. Laparoscopic approach is also useful to avoid unnecessary laparotomy in patients who show unresectable not previously diagnosed lesions (36% of patients with HCC with surgical indication)<sup>[53]</sup>. Several authors showed that laparoscopic liver resections can be technically performed regardless tumor size and location, but important reviews have recognized that it can be considered more safe and feasible for lesions located on left lateral (segments II and III) and anterior right (III, VI) segments<sup>[45-47]</sup>. For this reason the position of lesions is an essential element to establishing the indication to surgical resection for advanced HCC. In order to minimize postoperative complications in fragile patients, the possibility of laparoscopic liver resections is a decisive element in the decision-making process of the best treatment of patients with HCC.

## CONCLUSION

According to BCLC classification hepatic resection should be performed only in patients with small single tumours of 2-3 cm without signs of PHT or hyperbilirubinemia. By contrast many studies have shown that surgical resection can lead to good short and long-term survival in patients with PHT and with multinodular, large or macrovascular invasive HCC. The treatment of these patients is complex, surgery should only be performed in selected patients and a multidisciplinary team is necessary to choose the best treatment for each patient. Intra-operative ultrasound and laparoscopy are necessary tools in a modern liver unit, especially for cirrhotic patients.

BCLC indication should be expanded and redefined: BCLC algorithm should take into account the survival benefit of surgical resection in selected patients with HCC in B-C stages and should discuss the invaluable role of IOUS and the potential role of laparoscopy with the aim to standardize the surgical management. After the recognition that ablative treatment in HCC  $\leq 2$  cm offer the same survival benefit than surgical removal and consequently can be considered the treatment of choice for such patients<sup>[54]</sup>, it should be recognized that surgical treatment offers the best choice of prolonged survival even to selected patients with intermediate/advanced

stage HCC.

## REFERENCES

- 1 **Lafaro KJ**, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. *Surg Oncol Clin N Am* 2015; **24**: 1-17 [PMID: 25444466 DOI: 10.1016/j.soc.2014.09.001]
- 2 **Bruix J**, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, Christensen E, Pagliaro L, Colombo M, Rodés J; EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421-430 [PMID: 11592607 DOI: 10.1016/S0168-8278(01)00130-1]
- 3 **Singal AG**, El-Serag HB. Hepatocellular Carcinoma From Epidemiology to Prevention: Translating Knowledge into Practice. *Clin Gastroenterol Hepatol* 2015; **13**: 2140-2151 [PMID: 26284591 DOI: 10.1016/j.cgh.2015.08.014]
- 4 **Torzilli G**, Donadon M, Marconi M, Palmisano A, Del Fabbro D, Spinelli A, Botea F, Montorsi M. Hepatectomy for stage B and stage C hepatocellular carcinoma in the Barcelona Clinic Liver Cancer classification: results of a prospective analysis. *Arch Surg* 2008; **143**: 1082-1090 [PMID: 19015467 DOI: 10.1001/archsurg.143.11.1082]
- 5 **Choi C**, Choi GH, Kim TH, Tanaka M, Meng MB, Seong J. Multimodality Management for Barcelona Clinic Liver Cancer Stage C Hepatocellular Carcinoma. *Liver Cancer* 2014; **3**: 405-416 [PMID: 26280002 DOI: 10.1159/000343861]
- 6 **Schlachterman A**, Craft WW, Hilgenfeldt E, Mitra A, Cabrera R. Current and future treatments for hepatocellular carcinoma. *World J Gastroenterol* 2015; **21**: 8478-8491 [PMID: 26229392 DOI: 10.3748/wjg.v21.i28.8478]
- 7 **Guglielmi A**, Ruzzenente A, Conci S, Valdegamberi A, Vitali M, Bertuzzo F, De Angelis M, Mantovani G, Iacono C. Hepatocellular carcinoma: surgical perspectives beyond the barcelona clinic liver cancer recommendations. *World J Gastroenterol* 2014; **20**: 7525-7533 [PMID: 24976693 DOI: 10.3748/wjg.v20.i24.7525]
- 8 **Ho MC**, Huang GT, Tsang YM, Lee PH, Chen DS, Sheu JC, Chen CH. Liver resection improves the survival of patients with multiple hepatocellular carcinomas. *Ann Surg Oncol* 2009; **16**: 848-855 [PMID: 19159983 DOI: 10.1245/s10434-008-0282-7]
- 9 **Forner A**, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol* 2014; **11**: 525-535 [PMID: 25091611 DOI: 10.1038/nrclinonc.2014.122]
- 10 **Zhou Y**, Lei X, Wu L, Wu X, Xu D, Li B. Outcomes of hepatectomy for noncirrhotic hepatocellular carcinoma: a systematic review. *Surg Oncol* 2014; **23**: 236-242 [PMID: 25465529 DOI: 10.1016/j.suronc.2014.11.001]
- 11 **Poon RT**, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C, Wong J. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? *Ann Surg* 2002; **236**: 602-611 [PMID: 12409666 DOI: 10.1097/01.SLA.0000033038.38956.5E]
- 12 **Schroeder RA**, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. *Ann Surg* 2006; **243**: 373-379 [PMID: 16495703 DOI: 10.1097/01.sla.0000201483.95911.08]
- 13 **Zhang ZM**, Guo JX, Zhang ZC, Jiang N, Zhang ZY, Pan LJ. Therapeutic options for intermediate-advanced hepatocellular carcinoma. *World J Gastroenterol* 2011; **17**: 1685-1689 [PMID: 21483627 DOI: 10.3748/wjg.v17.i13.1685]
- 14 **Torzilli G**, Belghiti J, Kokudo N, Takayama T, Capussotti L, Nuzzo G, Vauthey JN, Choti MA, De Santibanes E, Donadon M, Morengi E, Makuuchi M. A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg* 2013; **257**: 929-937 [PMID: 23426336 DOI: 10.1097/SLA.0b013e31828329b8]
- 15 **Zhong JH**, Xiang BD, Gong WF, Ke Y, Mo QG, Ma L, Liu X, Li LQ. Comparison of long-term survival of patients with BCLC stage B hepatocellular carcinoma after liver resection or transarterial chemoembolization. *PLoS One* 2013; **8**: e68193 [PMID: 23874536 DOI: 10.1371/journal.pone.0068193]
- 16 **Tsoufas G**, Mekras A, Agorastou P, Kiskinis D. Surgical treatment for large hepatocellular carcinoma: does size matter? *ANZ J Surg* 2012; **82**: 510-517 [PMID: 22548726 DOI: 10.1111/j.1445-2197.2012.06079]
- 17 **Ruzzenente A**, Guglielmi A, Sandri M, Campagnaro T, Valdegamberi A, Conci S, Bagante F, Turcato G, D'Onofrio M, Iacono C. Surgical resection versus local ablation for HCC on cirrhosis: results from a propensity case-matched study. *J Gastrointest Surg* 2012; **16**: 301-311; discussion 311 [PMID: 22095524 DOI: 10.1007/s11605-011-1745-x]
- 18 **Llovet JM**, Bustamante J, Castells A, Vilana R, Ayuso Mdel C, Sala M, Brú C, Rodés J, Bruix J. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62-67 [PMID: 9862851 DOI: 10.1002/hep.510290145]
- 19 **Zhong JH**, Ke Y, Gong WF, Xiang BD, Ma L, Ye XP, Peng T, Xie GS, Li LQ. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg* 2014; **260**: 329-340 [PMID: 24096763 DOI: 10.1097/SLA.0000000000000236]
- 20 **Zhong JH**, Li H, Xiao N, Ye XP, Ke Y, Wang YY, Ma L, Chen J, You XM, Zhang ZY, Lu SD, Li LQ. Hepatic resection is safe and effective for patients with hepatocellular carcinoma and portal hypertension. *PLoS One* 2014; **9**: e108755 [PMID: 25268959 DOI: 10.1371/journal.pone.0108755]
- 21 **Santambrogio R**, Kluger MD, Costa M, Belli A, Barabino M, Laurent A, Opoche E, Azoulay D, Cherqui D. Hepatic resection for hepatocellular carcinoma in patients with Child-Pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? *HPB (Oxford)* 2013; **15**: 78-84 [PMID: 23216782 DOI: 10.1111/j.1477-2574.2012.00594.x]
- 22 **He W**, Zeng Q, Zheng Y, Chen M, Shen J, Qiu J, Chen M, Zou R, Liao Y, Li Q, Wu X, Li B, Yuan Y. The role of clinically significant portal hypertension in hepatic resection for hepatocellular carcinoma patients: a propensity score matching analysis. *BMC Cancer* 2015; **15**: 263 [PMID: 25886495 DOI: 10.1186/s12885-015-1280-3]
- 23 **Hirokawa F**, Hayashi M, Miyamoto Y, Asakuma M, Shimizu T, Komeda K, Inoue Y, Uchiyama K. Predictors of poor prognosis by recurrence patterns after curative hepatectomy for hepatocellular carcinoma in Child-Pugh classification A. *Hepatogastroenterology* 2015; **62**: 164-168 [PMID: 25911889]
- 24 **Wang Y**, Yuan L, Ge RL, Sun Y, Wei G. Survival benefit of surgical treatment for hepatocellular carcinoma with inferior vena cava/right atrium tumor thrombus: results of a retrospective cohort study. *Ann Surg Oncol* 2013; **20**: 914-922 [PMID: 22956071 DOI: 10.1245/s10434-012-2646-2]
- 25 **Chok KS**, Cheung TT, Chan SC, Poon RT, Fan ST, Lo CM. Surgical outcomes in hepatocellular carcinoma patients with portal vein tumor thrombosis. *World J Surg* 2014; **38**: 490-496 [PMID: 24132826 DOI: 10.1007/s00268-013-2290-4]
- 26 **Kanazawa A**, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S, Kubo S. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. *Surg Endosc* 2013; **27**: 2592-2597 [PMID: 23392977]
- 27 **Violi F**, Leo R, Vezza E, Basili S, Cordova C, Balsano F. Bleeding time in patients with cirrhosis: relation with degree of liver failure and clotting abnormalities. C.A.L.C. Group. Coagulation Abnormalities in Cirrhosis Study Group. *J Hepatol* 1994; **20**: 531-536 [PMID: 8051393]
- 28 **Lencioni R**, Chen XP, Dagher L, Venook AP. Treatment of intermediate/advanced hepatocellular carcinoma in the clinic: how can outcomes be improved? *Oncologist* 2010; **15** Suppl 4: 42-52 [PMID: 21115580 DOI: 10.1634/theoncologist.2010-S4-42]
- 29 **Gish RG**, Lencioni R, Di Bisceglie AM, Raoul JL, Mazzaferro V. Role of the multidisciplinary team in the diagnosis and treatment of hepatocellular carcinoma. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 173-185 [PMID: 22375523 DOI: 10.1586/egh.11.105]

- 30 **Gomaa AI**, Waked I. Recent advances in multidisciplinary management of hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 673-687 [PMID: 25866604 DOI: 10.4254/wjh.v7.i4.673]
- 31 **Gaba RC**, Kallwitz ER, Parvinian A, Bui JT, Von Roenn NM, Berkes JL, Cotler SJ. Imaging surveillance and multidisciplinary review improves curative therapy access and survival in HCC patients. *Ann Hepatol* 2013; **12**: 766-773 [PMID: 24018494]
- 32 **Torzilli G**, Palmisano A, Del Fabbro D, Marconi M, Donadon M, Spinelli A, Bianchi PP, Montorsi M. Contrast-enhanced intraoperative ultrasonography during surgery for hepatocellular carcinoma in liver cirrhosis: is it useful or useless? A prospective cohort study of our experience. *Ann Surg Oncol* 2007; **14**: 1347-1355 [PMID: 17253105 DOI: 10.1245/s10434-006-9278-3]
- 33 **Wu H**, Lu Q, Luo Y, He XL, Zeng Y. Application of contrast-enhanced intraoperative ultrasonography in the decision-making about hepatocellular carcinoma operation. *World J Gastroenterol* 2010; **16**: 508-512 [PMID: 20101780 DOI: 10.3748/wjg.v16.i4.508]
- 34 **Torzilli G**, Montorsi M, Donadon M, Palmisano A, Del Fabbro D, Gambetti A, Olivari N, Makuuchi M. "Radical but conservative" is the main goal for ultrasonography-guided liver resection: prospective validation of this approach. *J Am Coll Surg* 2005; **201**: 517-528 [PMID: 16183489 DOI: 10.1016/j.jamcollsurg.2005.04.026]
- 35 **Torzilli G**, Palmisano A, Procopio F, Cimino M, Botea F, Donadon M, Del Fabbro D, Montorsi M. A new systematic small for size resection for liver tumors invading the middle hepatic vein at its caval confluence: mini-mesohепatectomy. *Ann Surg* 2010; **251**: 33-39 [PMID: 19858707 DOI: 10.1097/SLA.0b013e3181b61db9]
- 36 **Torzilli G**, Garancini M, Donadon M, Cimino M, Procopio F, Montorsi M. Intraoperative ultrasonographic detection of communicating veins between adjacent hepatic veins during hepatectomy for tumours at the hepatocaval confluence. *Br J Surg* 2010; **97**: 1867-1873 [PMID: 20799289 DOI: 10.1002/bjs.7230]
- 37 **Slotta JE**, Kollmar O, Ellenrieder V, Ghadimi BM, Homayounfar K. Hepatocellular carcinoma: Surgeon's view on latest findings and future perspectives. *World J Hepatol* 2015; **7**: 1168-1183 [PMID: 26019733 DOI: 10.4254/wjh.v7.i9.1168]
- 38 **Zhou Y**, Xu D, Wu L, Li B. Meta-analysis of anatomic resection versus nonanatomic resection for hepatocellular carcinoma. *Langenbecks Arch Surg* 2011; **396**: 1109-1117 [PMID: 21476060 DOI: 10.1007/s00423-011-0784-9]
- 39 **Makuuchi M**, Hasegawa H, Yamazaki S. Intraoperative ultrasonic examination for hepatectomy. *Ultrasound Med Biol* 1983; Suppl 2: 493-497 [PMID: 6100712]
- 40 **Makuuchi M**, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346-350 [PMID: 2996162]
- 41 **Shimamura Y**, Gunvén P, Takenaka Y, Shimizu H, Akimoto H, Shima Y, Arima K, Takahashi A, Kitaya T, Matsuyama T. Selective portal branch occlusion by balloon catheter during liver resection. *Surgery* 1986; **100**: 938-941 [PMID: 3022413]
- 42 **Park YS**, Lee CH, Park PJ, Kim KA, Park CM. Intraoperative contrast-enhanced sonographic portography combined with indigo carmine dye injection for anatomic liver resection in hepatocellular carcinoma: a new technique. *J Ultrasound Med* 2014; **33**: 1287-1291 [PMID: 24958416 DOI: 10.7863/ultra.33.7.1287]
- 43 **Torzilli G**, Procopio F, Cimino M, Del Fabbro D, Palmisano A, Donadon M, Montorsi M. Anatomical segmental and subsegmental resection of the liver for hepatocellular carcinoma: a new approach by means of ultrasound-guided vessel compression. *Ann Surg* 2010; **251**: 229-235 [PMID: 19838106 DOI: 10.1097/SLA.0b013e3181b7fdcd]
- 44 **Chen J**, Huang K, Wu J, Zhu H, Shi Y, Wang Y, Zhao G. Survival after anatomic resection versus nonanatomic resection for hepatocellular carcinoma: a meta-analysis. *Dig Dis Sci* 2011; **56**: 1626-1633 [PMID: 21082347 DOI: 10.1007/s10620-010-1482-0]
- 45 **Mirnezami R**, Mirnezami AH, Chandrakumaran K, Abu Hilal M, Pearce NW, Primrose JN, Sutcliffe RP. Short- and long-term outcomes after laparoscopic and open hepatic resection: systematic review and meta-analysis. *HPB (Oxford)* 2011; **13**: 295-308 [PMID: 21492329 DOI: 10.1111/j.1477-2574.2011.00295.x]
- 46 **Nguyen KT**, Gamblin TC, Geller DA. World review of laparoscopic liver resection-2,804 patients. *Ann Surg* 2009; **250**: 831-841 [PMID: 19801936 DOI: 10.1097/SLA.0b013e3181b0c4df]
- 47 **Buell JF**, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, Koffron AJ, Thomas M, Gayet B, Han HS, Wakabayashi G, Belli G, Kaneko H, Ker CG, Scatton O, Laurent A, Abdalla EK, Chaudhury P, Dutson E, Gamblin C, D'Angelica M, Nagorney D, Testa G, Labow D, Manas D, Poon RT, Nelson H, Martin R, Clary B, Pinson WC, Martinie J, Vauthey JN, Goldstein R, Roayaie S, Barlet D, Espot J, Abecassis M, Rees M, Fong Y, McMasters KM, Broelsch C, Busuttil R, Belghiti J, Strasberg S, Chari RS. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. *Ann Surg* 2009; **250**: 825-830 [PMID: 19916210]
- 48 **Santambrogio R**, Aldrighetti L, Barabino M, Pulitanò C, Costa M, Montorsi M, Ferla G, Opocher E. Laparoscopic liver resections for hepatocellular carcinoma. Is it a feasible option for patients with liver cirrhosis? *Langenbecks Arch Surg* 2009; **394**: 255-264 [PMID: 18553101 DOI: 10.1007/s00423-008-0349-8]
- 49 **Xiong JJ**, Altaf K, Javed MA, Huang W, Mukherjee R, Mai G, Sutton R, Liu XB, Hu WM. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. *World J Gastroenterol* 2012; **18**: 6657-6668 [PMID: 23236242 DOI: 10.3748/wjg.v18.i45.6657]
- 50 **Slim A**, Garancini M, Di Sandro S, Mangoni I, Lauterio A, Giacomoni A, De Carlis L. Laparoscopic versus open liver surgery: a single center analysis of post-operative in-hospital and post-discharge results. *Langenbecks Arch Surg* 2012; **397**: 1305-1311 [PMID: 22918605 DOI: 10.1007/s00423-012-0992-y]
- 51 **Santambrogio R**, Barabino M, Bruno S, Costa M, Ceretti AP, Angiolini MR, Zuin M, Meloni F, Opocher E. Long-term outcome of laparoscopic ablation therapies for unresectable hepatocellular carcinoma: a single European center experience of 426 patients. *Surg Endosc* 2015; Epub ahead of print [PMID: 26275555 DOI: 10.1007/s00464-015-4468-3]
- 52 **Santambrogio R**, Opocher E, Zuin M, Selmi C, Bertolini E, Costa M, Conti M, Montorsi M. Surgical resection versus laparoscopic radiofrequency ablation in patients with hepatocellular carcinoma and Child-Pugh class a liver cirrhosis. *Ann Surg Oncol* 2009; **16**: 3289-3298 [PMID: 19727960 DOI: 10.1245/s10434-009-0678-z]
- 53 **Lai EC**, Tang CN, Ha JP, Tsui DK, Li MK. The evolving influence of laparoscopy and laparoscopic ultrasonography on patients with hepatocellular carcinoma. *Am J Surg* 2008; **196**: 736-740 [PMID: 18558389 DOI: 10.1016/j.amjsurg.2007.08.073]
- 54 **Livraghi T**, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, Rossi S. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? *Hepatology* 2008; **47**: 82-89 [PMID: 18008357 DOI: 10.1002/hep.21933]

**P- Reviewer:** Chuang WL, Penkova-Radicheva MP, Wang GY

**S- Editor:** Gong XM **L- Editor:** A **E- Editor:** Liu SQ



Retrospective Study

## Predictors of mortality after transjugular portosystemic shunt

Mona Ascha, Sami Abuqayyas, Ibrahim Hanouneh, Laith Alkukhun, Mark Sands, Raed A Dweik, Adriano R Tonelli

Mona Ascha, Department of Gastroenterology and Hepatology, Cleveland Clinic, Cleveland, OH 44195, United States

Sami Abuqayyas, Laith Alkukhun, Department of Internal Medicine, Cleveland Clinic, Cleveland, OH 44195, United States

Ibrahim Hanouneh, Minnesota Gastroenterology, Minneapolis, MN 55114, United States

Mark Sands, Department of Diagnostic Radiology, Cleveland Clinic, Cleveland, OH 44195, United States

Raed A Dweik, Adriano R Tonelli, Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH 44195, United States

**Author contributions:** Ascha M participated in writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Abuqayyas S participated in interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Hanouneh I interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Alkukhun L participated in the data collection, interpretation of the results and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Sands M participated in the interpretation of the results and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Dweik RA participated in the conception of the study, interpretation of the results and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted; Tonelli AR participated in the conception, design of the study, data analysis, interpretation of the results, writing and critical revision of the manuscript for important intellectual content and final approval of the manuscript submitted.

**Institutional review board statement:** The study was reviewed and approved by the Cleveland Clinic Foundation Institutional Review Board.

**Informed consent statement:** Written informed consent was

waived for study participants.

**Conflict-of-interest statement:** None of the authors have significant conflicts of interest with any companies or organization whose products or services may be discussed in this article.

**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at [tonella@ccf.org](mailto:tonella@ccf.org). Participants gave informed consent for data sharing.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Adriano R Tonelli, MD, Department of Pulmonary, Allergy and Critical Care Medicine, Respiratory Institute, Cleveland Clinic, 9500 Euclid Avenue A-90, Cleveland, OH 44195, United States. [tonella@ccf.org](mailto:tonella@ccf.org)  
 Telephone: +1-216-4440812  
 Fax: +1-216-4456024

**Received:** December 22, 2015

**Peer-review started:** December 23, 2015

**First decision:** January 15, 2016

**Revised:** January 21, 2016

**Accepted:** March 14, 2016

**Article in press:** March 16, 2016

**Published online:** April 18, 2016

### Abstract

**AIM:** To investigate if echocardiographic and hemodynamic determinations obtained at the time of transjugular intrahepatic portosystemic shunt (TIPS) can provide prognostic information that will enhance risk

stratification of patients.

**METHODS:** We reviewed medical records of 467 patients who underwent TIPS between July 2003 and December 2011 at our institution. We recorded information regarding patient demographics, underlying liver disease, indication for TIPS, baseline laboratory values, hemodynamic determinations at the time of TIPS, and echocardiographic measurements both before and after TIPS. We recorded patient comorbidities that may affect hemodynamic and echocardiographic determinations. We also calculated Model for End-stage Liver Disease (MELD) score and Child Turcotte Pugh (CTP) class. The following pre- and post-TIPS echocardiographic determinations were recorded: Left ventricular ejection fraction, right ventricular (RV) systolic pressure, subjective RV dilation, and subjective RV function. We recorded the following hemodynamic measurements: Right atrial (RA) pressure before and after TIPS, inferior vena cava pressure before and after TIPS, free hepatic vein pressure, portal vein pressure before and after TIPS, and hepatic venous pressure gradient (HVPG).

**RESULTS:** We reviewed 418 patients with portal hypertension undergoing TIPS. RA pressure increased by a mean  $\pm$  SD of  $4.8 \pm 3.9$  mmHg ( $P < 0.001$ ), HVPG decreased by  $6.8 \pm 3.5$  mmHg ( $P < 0.001$ ). In multivariate linear regression analysis, a higher MELD score, lower platelet count, splenectomy and a higher portal vein pressure were independent predictors of higher RA pressure ( $R = 0.55$ ). Three variables predicted 3-mo mortality after TIPS in a multivariate analysis: Age, MELD score, and CTP grade C. Change in the RA pressure after TIPS predicted long-term mortality (per 1 mmHg change, HR = 1.03, 95%CI: 1.01-1.06,  $P < 0.012$ ).

**CONCLUSION:** RA pressure increased immediately after TIPS particularly in patients with worse liver function, portal hypertension, emergent TIPS placement and history of splenectomy. The increase in RA pressure after TIPS was associated with increased mortality. Age, splenectomy, MELD score and CTP grade were independent predictors of long-term mortality after TIPS.

**Key words:** Transjugular intrahepatic portosystemic shunt; Transjugular portosystemic shunts; Right atrial pressure; Outcomes; Mortality

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure accompanied by morbidity and mortality. We hypothesize that echocardiographic and hemodynamic determinations obtained at the time of TIPS can provide prognostic information that will enhance risk stratification of patients. We measured echocardiographic and hemodynamic variables before

and immediately after the TIPS procedure in a large cohort of patients at our institution. Our findings corroborate previous literature stating that right atrial pressure increased after TIPS. Our study demonstrates several predictors of long-term mortality after TIPS, such as age, splenectomy, and Model for End-stage Liver Disease score; this data can help assess the risk for patients undergoing TIPS.

Ascha M, Abuqayyas S, Hanouneh I, Alkukhun L, Sands M, Dweik RA, Tonelli AR. Predictors of mortality after transjugular portosystemic shunt. *World J Hepatol* 2016; 8(11): 520-529 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i11/520.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i11.520>

## INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure performed to treat complications of portal hypertension such as bleeding esophageal varices, refractory ascites and hepatic hydrothorax<sup>[1-3]</sup>. The placement of a covered stent creates an anastomosis between the hypertensive portal vein and the inferior vena cava *via* the hepatic vein; this non-surgically decompresses the portal pressure. Although TIPS is minimally invasive, patients with advanced liver disease-particularly those with comorbidities-can have complications related to the procedure. The Model of End-stage Liver Disease (MELD) score was originally conceived to determine survival outcomes in patients receiving TIPS. In their original study, Malinchoc *et al*<sup>[4]</sup> created a model utilizing serum bilirubin, serum creatinine, international normalized ratio (INR), and cause of underlying liver disease, all of which were used to predict three-month mortality in patients undergoing TIPS. In today's practice, the MELD score is primarily used to determine the extent of liver failure and subsequent placement on organ transplant waiting lists in addition to predicting risk and mortality of TIPS placement. However, there remains a limited amount of data available that can ascertain which variables convey a higher risk of complications from TIPS.

TIPS is a procedure that should be employed meticulously, as it can be accompanied by morbidity and mortality. Existing literature has elucidated variables that are traditionally associated with a poor outcome after TIPS, which include increasing age, male gender, high Child-Turcotte-Pugh (CTP) score, high MELD score, urgent placement of TIPS for uncontrolled variceal hemorrhage, renal dysfunction, ascites, and pre-existing hepatic encephalopathy<sup>[5-10]</sup>. However, there is a dearth of studies assessing the prognostic value of echocardiographic and hemodynamic determinations at the time of TIPS.

Liver cirrhosis is characterized by a hyperdynamic circulation, with an increased cardiac preload and a decreased cardiac afterload; this pre-existing hemody-

hemic stress in cirrhotic patients may be worsened after TIPS placement. After TIPS placement, there is a rapid increase in blood flow from the splanchnic circulation to both the right heart and pulmonary circulation<sup>[11-13]</sup>. This increase in volume can precipitate right ventricular (RV) failure and pulmonary hypertension<sup>[13,14]</sup>. The pulmonary pressures may increase, particularly if the vasculature cannot vasodilate to accommodate the increase in cardiac output. In addition, TIPS permits more direct delivery of vasoactive and neurohumoral mediators, which are normally cleared by the liver, to the pulmonary circulation<sup>[5,14]</sup>. This higher load of vasoactive mediators may increase the RV afterload<sup>[14]</sup>. Due to these hemodynamic changes, it has been recommended that the TIPS procedure be considered with caution in patients with limited cardiac reserve<sup>[11,14]</sup>. While there are no clinical studies that identify a single RA pressure measurement that constitutes an absolute threshold above which TIPS should not be performed, intervention should be reconsidered or performed cautiously when right atrial (RA) pressure is greater than 20 mmHg; furthermore, a pulmonary arterial pressure greater than 45 mmHg may contraindicate TIPS placement.

Evidently, TIPS is not suitable for every patient that presents with portal hypertension, and contraindications must be ruled out prior to stent placement. Further research is indispensable to optimizing patient selection in order to achieve maximum survival benefits. We hypothesize that the echocardiographic and hemodynamic determinations obtained at the time of TIPS can provide prognostic information that will enhance risk stratification of patients for this procedure. We particularly sought to assess whether RA pressure could provide prognostic information, given that a higher RA pressure may reflect a higher intravascular volume and a degree of systolic/diastolic RV dysfunction, conditions that could worsen after TIPS placement. We tested our hypothesis in a large number of patients who underwent TIPS placement at the Cleveland Clinic.

## MATERIALS AND METHODS

This retrospective study received approval from the Cleveland Clinic Institutional Review Board (study number: 12-579). Written informed consent was waived. We reviewed the medical records of 467 patients who underwent TIPS placement between July 2003 and December 2011. Patients were identified using the billing codes for TIPS. Subjects were excluded from the analyses if they underwent liver transplantation before TIPS, TIPS placement was unsuccessful, or if the initial TIPS procedure was performed at an outside facility. Forty-nine patients met exclusion criteria and were thus excluded from analysis.

We recorded information regarding patient demographics, underlying liver disease, indication for TIPS, baseline laboratory values (albumin, bilirubin, INR, creatinine, and platelets), hemodynamic determinations at the time of TIPS, and echocardiographic measure-

ments both before and after TIPS. We also recorded patient comorbidities that may affect hemodynamic and echocardiographic determinations, including arterial hypertension, cardiac heart failure, heart valvular disease, chronic obstructive pulmonary disease, interstitial lung disease, scleroderma, splenectomy, sarcoidosis, sleep apnea, hypothyroidism, chronic kidney disease on hemodialysis, human immunodeficiency virus status, and cocaine use. In addition, we calculated MELD score and CTP class.

We recorded the following pre-TIPS echocardiographic determinations: Left ventricular ejection fraction (LVEF), RV systolic pressure (RVSP), subjective RV dilation, and subjective RV function. We recorded the following hemodynamic measurements: RA pressure before and after TIPS, inferior vena cava pressure before and after TIPS, free hepatic vein pressure, portal vein pressure before and after TIPS, and hepatic venous pressure gradient (HVPG). RV and pulmonary artery pressures were not routinely measured. It should be noted that all variables collected after TIPS were measured immediately after the procedure was performed. We also collected information regarding the type, diameter and length of the stent placed.

We recorded the following post-TIPS echocardiographic determinations: LVEF, RVSP, subjective RV dilation and function.

### TIPS technique

The TIPS procedure was performed according to previously described techniques, with modifications as needed<sup>[15]</sup>. After instillation of local anesthesia, the internal jugular vein was cannulated under direct ultrasound guidance and an introducer was placed. Through the introducer, an angled catheter was advanced into the RA and the pressure was recorded. The catheter was then maneuvered into the right hepatic vein. A long sheath was advanced to the proximal right hepatic vein, followed by a Fogarty balloon. Wedged and free hepatic vein pressures are not routinely collected during the TIPS procedure; these values are usually known from prior transjugular liver biopsy procedures performed on these patients. Carbon dioxide was injected as the contrast agent while digital images were obtained in an attempt to opacify the portal venous system. A parenchymal tract was created from the right hepatic vein to the right portal vein using a sheathed modified Colapinto needle. Alternatively, the TIPS procedure was performed with the modified Rosch-Uchida set. The kit used depends on the preference of the physician performing the procedure. A catheter was advanced into the portal vein and an initial pressure measurement was obtained. Nonionic contrast material was injected in order to display the anatomy and confirm the entry site. The parenchymal tract was then dilated and a stent was placed with the goal of obtaining an HVPG < 12 mmHg for patients with GI bleeding. There is no defined HVPG for patients with ascites; too low of a gradient puts these patients at risk for hepatic encephalopathy. At our institution, we aim to obtain an

**Table 1** Baseline characteristics of the patient cohort

Demographics	<i>n</i> (%) or mean $\pm$ SD
<i>n</i>	418
Age (yr)	55.8 $\pm$ 11.6
Male gender	242 (57.9)
Etiologies of portal hypertension	
NASH cirrhosis	132 (31.6)
Alcohol induced liver disease	105 (25.1)
HCV	105 (25.1)
Primary sclerosing cholangitis	16 (3.8)
Primary biliary cirrhosis	11 (2.6)
Others <sup>1</sup>	49 (11.7)
Patient comorbidities	
Systemic hypertension	155 (37.1)
Hypothyroidism	50 (12.0)
COPD/ILD	34 (8.1)
Sleep apnea	20 (4.8)
Cardiac heart failure	18 (4.3)
Chronic kidney disease on hemodialysis	17 (4.1)
Valvular heart disease	17 (4.1)
Sarcoidosis	5 (1.2)
Splenectomy	5 (1.2)
Scleroderma	4 (1.0)
Cocaine use	4 (1.0)
HIV	1 (0.2)
Indications for TIPS	
GI bleeding	182 (43.5)
Refractory ascites	157 (37.6)
Hepatic hydrothorax	51 (12.2)
Others <sup>2</sup>	28 (6.7)
Basic laboratory parameters	
Serum albumin (g/dL)	2.9 $\pm$ 0.7
Serum bilirubin (mg/dL)	3.0 $\pm$ 5.4
INR	1.3 $\pm$ 0.4
Serum creatinine (mg/dL)	1.3 $\pm$ 1.1
Platelets (K/ $\mu$ L)	115.3 $\pm$ 77.6

<sup>1</sup>Other etiologies of portal hypertension include hepatitis B virus, autoimmune hepatitis, alpha-1 anti-trypsin deficiency, Budd Chiari syndrome, hemochromatosis, Wilson's disease, sarcoidosis, cystic fibrosis, biliary atresia, portal vein thrombosis, nodular regenerative hyperplasia, veno-occlusive disease and Caroli's disease; <sup>2</sup>Other indications for TIPS include hepatorenal syndrome, portal hypertensive gastropathy, superior mesenteric vein thrombosis, splenomegaly and the need to decrease the portal pressure prior to a surgical intervention. COPD: Chronic obstructive pulmonary disease; HIV: Human immunodeficiency virus; ILD: Interstitial lung disease; HCV: Hepatitis C virus; TIPS: Transjugular portosystemic shunt; INR: International normalized ratio.

HVPG around 7-8 mmHg, but this is not absolute and is adjusted to the clinical circumstances such as LFTs and the presence of encephalopathy pre-TIPS. The majority of our TIPS procedures are performed for control of ascites. A final angiogram was used to confirm good flow through the TIPS. In addition, the RA pressure and portal vein pressure were measured again immediately after the TIPS procedure was completed.

### Statistical analysis

Means and SD are provided for continuous variables, while numbers of patients with percentages are given for categorical variables. Hemodynamic variables before and after TIPS were compared using paired *t*-test. Binary logistic regression was used to identify variables that predict 3-mo mortality and results are reported as odds

ratio with 95%CI. We evaluated the association between RA pressure and other variables with univariate linear regression. We tested the relationship between survival and variables of interest with Cox proportional-hazards modeling adjusted for age and gender. The start point for the analysis was the date of the TIPS and the end of follow-up was marked by the patient's death or the end of study in December 2011. Patients were censored at the time of orthotopic liver transplant (OLT). Factors associated with survival in the univariate analysis (*P* value < 0.05) were entered into a multivariate model (forward selection). Results are expressed as hazard ratios (HRs) with the corresponding 95%CI. Predictors with HRs > 1 are associated with a higher risk for the outcome tested. We constructed receiver operating characteristic (ROC) curves to determine the sensitivity and specificity of different cutoffs of RA pressure and estimated RVSP for discriminating patients who died during follow-up. All *P* values reported are two tailed and *P*-values < 0.05 were considered significant. The statistical analyses were performed using SPSS version 17 (SPSS, Inc, Chicago, IL) and MedCalc, version 14.12.0 (Ostend, Belgium). The statistical methods of this study were reviewed by Dr. Adriano Tonelli from the Cleveland Clinic Foundation.

## RESULTS

### Patient characteristics

We included 418 patients with portal hypertension in the study. The mean  $\pm$  SD age was 55.8  $\pm$  11.6 years and 242 patients (57.9%) were male. The primary causes of portal hypertension were cryptogenic and non-alcoholic steatohepatitis (NASH) induced cirrhosis [*n* = 132 (31.6%)], alcohol induced liver disease [*n* = 105 (25.1%)] and hepatitis C virus [*n* = 105 (25.1%)]. Less common etiologies for portal hypertension and comorbidities are listed in Table 1.

Indications for TIPS included gastrointestinal bleeding [*n* = 182 (43.5%)], refractory ascites [*n* = 157 (37.6%)], hepatic hydrothorax [*n* = 51 (12.2%)] and other causes [*n* = 28 (6.7%)] (Table 1). A total of 113 (27.8%) TIPS procedures were done emergently. Laboratory evaluations of patients before TIPS (*n* = 416) are as follows (mean  $\pm$  SD): Serum albumin (g/dL) 2.9  $\pm$  0.7, serum bilirubin (mg/dL) 3.0  $\pm$  5.4, INR 1.3  $\pm$  0.4, serum creatinine (mg/dL) 1.3  $\pm$  1.1, platelets (K/ $\mu$ L) 115.3  $\pm$  77.6. MELD score pre-TIPS revealed a mean  $\pm$  SD of 13.3  $\pm$  6.9. Meanwhile, CTP classes A, B and C were present in 46 (11.5%), 224 (55.9%) and 131 patients (31.3%), respectively. The mean  $\pm$  SD diameter of the stent placed was 9.9  $\pm$  1 mm.

### Echocardiographic and invasive hemodynamic determinations

Among the 301 patients who had echocardiography data available, 224 patients (74%) had estimates of the RVSP, which demonstrated a mean  $\pm$  SD of 31.9  $\pm$  10.9 mmHg. Only 11 patients (3.7%) out of 294 in whom

**Table 2** Multivariate linear regression model with right atrial pressure as dependent variable

Model	$\beta$	Standard error	P-value
Constant	-2.21	1.01	0.03 <sup>a</sup>
MELD score	0.19	0.03	< 0.001 <sup>b</sup>
Platelet count (K/ $\mu$ L)	-0.01	0.01	0.004 <sup>b</sup>
Portal vein pressure (mmHg)	0.30	0.03	< 0.001 <sup>b</sup>
Splenectomy	4.69	1.97	0.02

R = 0.55, R<sup>2</sup> = 0.3, adjusted R<sup>2</sup> = 0.29. <sup>a</sup>P < 0.05; <sup>b</sup>P < 0.01. MELD: Model for End stage Liver Disease.

the RV function was evaluated had mild or moderate RV dysfunction prior to TIPS placement. There were several notable hemodynamic changes that occurred immediately after TIPS. The RA pressure increased by a mean  $\pm$  SD of 4.8  $\pm$  3.9 mmHg (*P* < 0.001). The HVPG decreased by a mean  $\pm$  SD of 6.8  $\pm$  3.5 mmHg (*P* < 0.001). However, this was at the expense of a reduction in the portal vein pressure, which decreased by a mean  $\pm$  SD of 11.7  $\pm$  5.6 mmHg (*P* < 0.001). Finally, the RVSP measured by echocardiography (*n* = 109) increased by 7.4  $\pm$  2.6 mmHg (*P* < 0.001).

#### Factors associated with RA pressure before TIPS

We found several factors to be associated with elevated RA pressure prior to TIPS placement, including MELD score (*R* = 0.36, *P* < 0.001), serum bilirubin (*R* = 0.29, *P* < 0.001), INR (*R* = 0.26, *P* < 0.001), serum creatinine (*R* = 0.26, *P* < 0.001), platelets (*R* = -0.18, *P* < 0.001) and portal vein pressure (*R* = 0.46, *P* < 0.001). Elevated RA Pressure before TIPS is directly related to severity of the patient's underlying liver disease. Moreover, splenectomy (*R* = 0.11, *P* = 0.03) and emergent TIPS placement (*R* = 0.24, *P* < 0.001) were associated with higher RA pressure in univariate linear regression analysis. RA pressure was not significantly different among the major etiologies of portal hypertension (ETOH, chronic hepatitis, NASH or others). In patients in whom TIPS were placed for acute variceal bleeding the RA before TIPS was higher (7.8  $\pm$  5.9 mmHg) than TIPS placed for ascites (6.0  $\pm$  3.9 mmHg, *P* = 0.001). Similarly, RA pressure after TIPS was higher in patients who received TIPS for acute variceal bleeding (12.4  $\pm$  6.5 mmHg vs 10.9  $\pm$  4.0 mmHg, *P* = 0.01) instead of ascites.

In multivariate linear regression analysis, a higher MELD score, lower platelet count, splenectomy and a higher portal vein pressure were independent predictors of higher RA pressure (*R* = 0.55, *P* < 0.001) (Table 2). Adding the etiology of portal hypertension and/or the reason for TIPS as variables did not affect the model. RA pressure was not found to be associated with RVSP or RV function obtained with echocardiography.

#### Predictors of 3-mo survival after TIPS

A total of 97 (24.7%) patients died within the 3-mo period after TIPS. Twenty-six patients underwent OLT during this time frame and were excluded from this

**Table 3** Univariate predictors of three-month survival

Variables	OR	95%CI	P
Age (per 1 yr)	1.03	1.01-1.06	0.003 <sup>b</sup>
CKD on HD (yes)	5.93	1.94-18.16	0.002 <sup>b</sup>
MELD (per unit change)	1.15	1.10-1.19	< 0.001 <sup>b</sup>
CTP B (compared to A)	4.56	1.06-19.67	0.04 <sup>a</sup>
CTP C (compare to A)	13.90	3.21-60.20	< 0.001 <sup>b</sup>
RVSP (per mmHg)	1.03	1.00-1.06	0.02 <sup>a</sup>
Emergent placement (yes)	2.56	1.57-4.19	< 0.001 <sup>b</sup>
RA pressure before TIPS (per 1 mmHg)	1.1	1.05-1.15	< 0.001 <sup>b</sup>
Portal vein pressure before TIPS (per 1 mmHg)	1.04	1.01-1.08	0.02 <sup>a</sup>
RA pressure after TIPS (per 1 mmHg)	1.07	1.03-1.12	0.002 <sup>b</sup>
Portal vein pressure after TIPS (per 1 mmHg)	1.06	1.02-1.10	0.006 <sup>b</sup>

<sup>a</sup>P < 0.05; <sup>b</sup>P < 0.01. CKD: Chronic kidney disease; CTP: Child Turcotte Pugh; HD: Hemodialysis; MELD: Model for End stage Liver Disease; OR: Odds ratio; RA: Right atrium; RVSP: Right ventricular systolic pressure; TIPS: Transjugular portosystemic pressure.

analysis. Table 3 shows variables that predicted mortality at 3-mo in a univariate binary logistic regression. Etiology of portal hypertension and reason for TIPS were not significant predictors of this outcome. Only three variables remained predictors of 3-mo mortality after TIPS in a multivariate binary analysis. These included age (per 1 year, OR = 1.04, 95%CI: 1.02-1.08, *P* = 0.003), MELD score (per 1 unit, OR = 1.14, 95%CI: 1.08-1.19, *P* < 0.001) and CTP grade C (compared to A, OR = 4.75, 95%CI: 1.02-22.17, *P* < 0.001).

#### Predictors of long-term survival after TIPS

Patients were followed for a median (interquartile range) of 26.7 (2-45) mon. A total of 68 (16.3%) patients underwent OLT after TIPS. Of the remaining patients, 261 (74.6%) patients died before transplantation during follow-up. Median survival after TIPS was 26 mo (95%CI: 17-33) (Figure 1). Table 4 shows several variables that predicted long-term mortality post TIPS in a univariate Cox survival analysis. Etiology of portal hypertension or reason for TIPS was non-significant predictors of long-term mortality in our cohort. Table 5 shows significant predictors of long-term mortality after TIPS (age, splenectomy, MELD score, CTP groups B and C) according to a multivariate analysis that excluded echocardiographic parameters. When echocardiographic parameters were factored into the model, MELD score (per 1 unit, HR = 1.05, 95%CI: 1.02-1.08, *P* < 0.001) and RV function (per increase in 1 degree of severity, HR = 2.24, 95%CI: 1.34-3.74, *P* < 0.002) were significant predictors of long-term mortality. Of the hemodynamic determinations studied, only the change in the RA pressure after TIPS predicted long-term mortality (per 1 mmHg change, HR = 1.03, 95%CI: 1.01-1.06, *P* < 0.012).

#### Receiver operating characteristic analysis for RA pressure and RVSP

We also constructed ROC curves using the classification

**Table 4 Predictors of long term mortality in univariate Cox survival analysis**

Variables	HR	95%CI	P
Age (per 1 yr)	1.02	1.01-1.03	0.001 <sup>b</sup>
HCV (ETOH reference)	1.45	1.03-2.04	0.03 <sup>a</sup>
Splenectomy (yes)	3.32	1.36-8.10	0.008 <sup>b</sup>
CHF (yes)	1.32	1.01-1.74	0.04 <sup>a</sup>
Hypothyroidism (yes)	1.20	1.00-1.42	0.04 <sup>a</sup>
CKD on HD (yes)	1.56	1.17-2.06	0.002 <sup>b</sup>
Portal vein pressure before TIPS (per 1 mmHg)	1.03	1.01-1.04	0.008 <sup>b</sup>
RA pressure before TIPS (per 1 mmHg)	1.03	1.01-1.06	0.01 <sup>a</sup>
RA pressure after TIPS (per 1 mmHg)	1.03	1.00-1.05	0.02 <sup>a</sup>
MELD score (per 1 unit)	1.07	1.05-1.09	< 0.001 <sup>b</sup>
Albumin (per 1 mg/dL)	0.70	0.58-0.84	< 0.001 <sup>b</sup>
Billirubin (per 1 mg/dL)	1.05	1.03-1.07	< 0.001 <sup>b</sup>
INR (per 1 unit change)	1.30	1.07-1.60	0.01 <sup>a</sup>
Creatinine (per 1 mg/dL)	1.26	1.14-1.39	< 0.001 <sup>b</sup>
CTP category B (reference A)	1.98	1.24-3.18	0.004 <sup>b</sup>
CTP category C (reference A)	3.02	1.85-4.94	< 0.001 <sup>b</sup>
EF echocardiogram pre TIPS (per 1% increase)	0.98	0.95-1.00	0.04 <sup>a</sup>
RVSP pre TIPS (per 1 mmHg increase)	1.02	1.01-1.04	0.005 <sup>b</sup>
Moderate RV dysfunction (normal RV reference)	2.84	1.18-6.85	0.02 <sup>a</sup>
EF post TIPS (per 1% increase)	0.98	0.96-1.00	0.03 <sup>a</sup>
RVSP post TIPS (per 1 mmHg increment)	1.02	1.01-1.04	0.01 <sup>a</sup>

<sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.01$ . CHF: Congestive heart failure; CKD: Chronic kidney disease; CTP: Child turcotte pugh; EF: Ejection fraction; HCV: Hepatitis C virus; HD: Hemodialysis; HR: Hazard ratio; MELD: Model for End stage Liver Disease; RA: Right atrium; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TIPS: Transjugular intrahepatic portosystemic shunt; INR: International normalized ratio; ETOH: Alcoholic etiology.

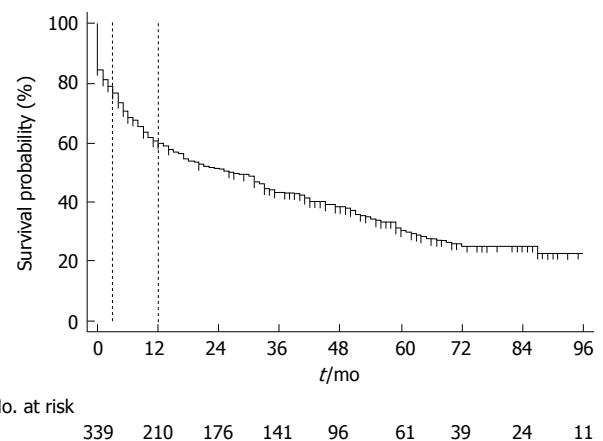
variables mortality at 3-mo (excluding liver transplant) and mortality or liver transplant at one year. The first variable tested was RA pressure measure by right heart catheterization immediately before TIPS. The area under the curve (AUC) for 3-mo mortality was 0.63 (95%CI: 0.58-0.68,  $P < 0.001$ ) (Figure 2A) with an optimal cut-off by Youden index of  $> 9$  mmHg (sensitivity of 41.3%, specificity of 80.5%). In addition, RA pressure  $> 14$  mmHg had a sensitivity of 14.1% and specificity of 95.7%. The AUC for mortality or liver transplant at one year was 0.58 (95%CI: 0.53-0.64,  $P = 0.009$ ) and a RA pressure of  $> 9$  mmHg showed a sensitivity of 18.1% and specificity of 66.4% in predicting this outcome.

An ROC curve testing a second variable, RVSP estimated by echocardiography, was also constructed. The AUC for 3-mo mortality was 0.60 (95%CI: 0.53-0.67,  $P = 0.04$ ) (Figure 2B) with a Youden index of  $> 29$  mmHg (sensitivity of 67.4 % and specificity of 50.6%). At a cut-off  $> 40$  mmHg, the sensitivity was 28.3% and specificity was 88.0%. Moreover, at a cut-off  $> 50$  mmHg, the sensitivity was 10.9% and specificity was 95.6% for predicting 3-mo mortality. The AUC predicting mortality or liver transplant at one year for RVSP was 0.58 (0.51-0.65,  $P = 0.047$ ) with a Youden index of  $> 29$  mmHg (sensitivity of 41.8% and specificity of 42.0%). At a cut-off  $> 40$  mmHg, the sensitivity was 10.0% and specificity was 79.0% and

**Table 5 Multivariate Cox survival analysis (without including hocardiographic arameters)**

Variables	HR	95%CI	P
Age (per 1 yr)	1.02	1.01-1.03	0.004 <sup>b</sup>
Splenectomy (yes)	3.06	1.24-7.52	0.02 <sup>a</sup>
MELD score (per 1 unit)	1.05	1.03-1.08	< 0.001 <sup>b</sup>
CTP B (compared to A)	1.99	1.20-3.32	0.008 <sup>b</sup>
CTP C (compared to A)	2.45	1.41-4.26	0.001 <sup>b</sup>

<sup>a</sup> $P < 0.05$ ; <sup>b</sup> $P < 0.01$ . CTP: Child turcotte pugh; HR: Hazard ratio; MELD: Model for End-stage Liver Disease.



**Figure 1 Survival after transjugular portosystemic shunts.** Kaplan-Meier survival analysis censored by liver transplantation. Markers are shown at 3 and 12 mo.

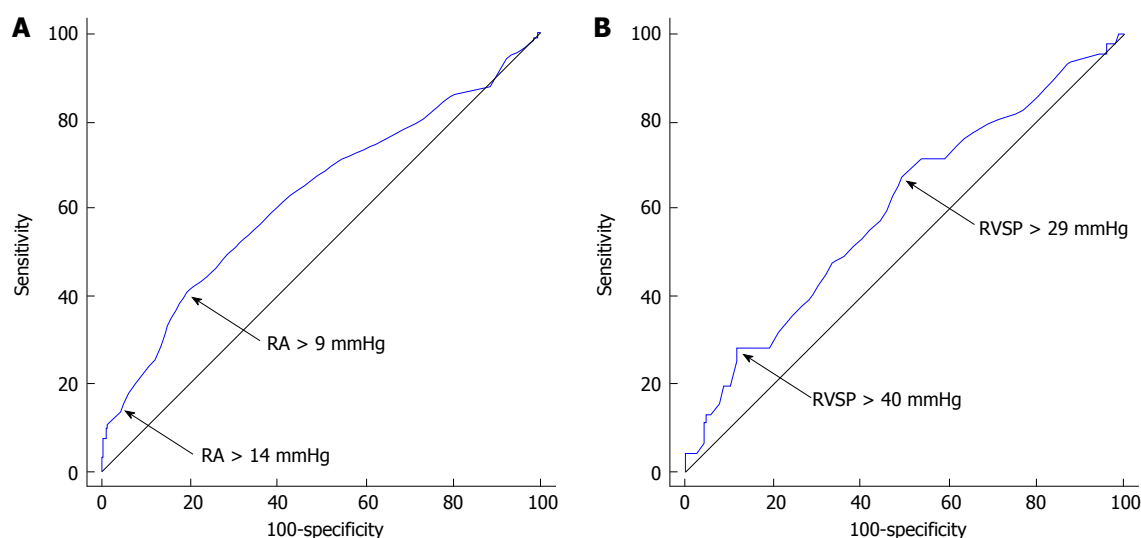
at a cut-off  $> 50$  mmHg, the sensitivity was 3.60% and specificity was 91.4%.

A Kaplan-Meier analysis was performed, and three-month survival after TIPS based on RA pressure  $> 9$  mmHg vs  $\leq 9$  mmHg and estimated RVSP pressure  $> 40$  mmHg vs  $\leq 40$  mmHg is presented in Figure 3.

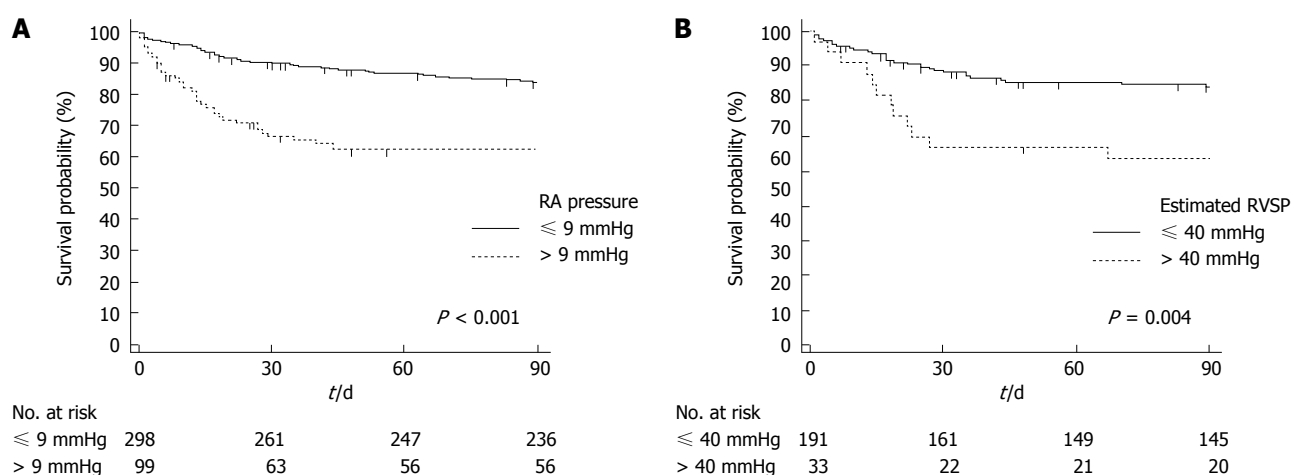
## DISCUSSION

We analyzed a large cohort of patients with portal hypertension who underwent TIPS for a variety of reasons, chiefly to assess hemodynamic variables before and after TIPS as potential predictors for mortality. We found an increase in RA pressure and a decrease in portal vein pressure after TIPS. The increase in RA pressure immediately after TIPS was associated with worsening liver function, portal hypertension, emergent TIPS placement and history of splenectomy. Of all the hemodynamic variables measured at the time TIPS, the increase in RA pressure after TIPS was associated with increased long-term mortality and a RA pressure  $> 9$  mmHg before TIPS predicted 3- and 12-mo mortality with specificity of 81% and 66%, respectively. It is important to note that in our models, the etiology of portal hypertension and the reasons for placing TIPS had no impact on short- or long-term survival.

Other studies examined the hemodynamic changes before and after TIPS. Kovács *et al*<sup>[16]</sup> assessed the short-



**Figure 2 Receiver operating characteristic curves for three-month mortality.** We tested the variables right atrium pressure before TIPS (A) and estimated RVSP by echocardiography pre TIPS (B). RVSP: Right ventricular systolic pressure; TIPS: Transjugular portosystemic shunt; RA: Right atrium.



**Figure 3 Kaplan-Meier analysis of three-month survival after transjugular portosystemic shunts.** A: Stratified by RA pressure > 9 mmHg vs ≤ 9 mmHg; B: Stratified by estimated RVSP pressure > 40 mmHg vs ≤ 40 mmHg. The separation in survival curves in both panels is particularly noted during the first month. *P* values are provided by log-rank test. RVSP: Right ventricular systolic pressure; RA: Right atrium.

term hemodynamic and cardiac magnetic resonance imaging changes after TIPS in 11 patients with liver cirrhosis and intractable esophageal varices or refractory ascites. They concluded that the amount of shunted blood after TIPS was more than the preload reserve of the right and left ventricle, and this was manifested by the significant increase of the pulmonary capillary wedge pressure and persistent enlargement of the left and right atria. Van der Linden *et al*<sup>[14]</sup> studied the short and mid-term hemodynamic changes after TIPS in 16 sedated biopsy proven cirrhotic patients. They noted an increase in the mean pulmonary artery pressure (PAP), cardiac index, and RA pressure after TIPS. After a transient balloon occlusion of the shunt, they measured these hemodynamics variables once again. Interestingly, all hemodynamic determinations returned to baseline except for the mean PAP, which remained significantly elevated. This hemodynamic change persisted after one month, suggesting that the increase in pulmonary

pressure after TIPS is not only due to volume overload but also due to neurohumoral changes. This is consistent with findings from previous studies that evaluated the hemodynamic changes after TIPS placement<sup>[11,17]</sup>.

Azoulay *et al*<sup>[11]</sup> investigated 12 cirrhotic patients who underwent the TIPS procedure due to refractory ascites or refractory esophageal variceal bleeding. Hemodynamics were measured before TIPS, at 30 min, and one month after TIPS. Significant changes recorded included the decrease in the HVPG from  $15 \pm 3$  to  $7 \pm 3$  mmHg at 30 min after TIPS, and the subsequent decrease to  $8 \pm 3$  mmHg at one month. The cardiac index increased from  $4.5 \pm 1.3$  to  $5.7 \pm 1.5$  at 30 min after TIPS and subsequently to  $7.4 \pm 1.4$  L/(min·m<sup>2</sup>) at one month. Colombato *et al*<sup>[17]</sup> studied in 15 cirrhotic patients the systemic, splanchnic and pulmonary hemodynamics before TIPS, at 15-30 min and at two months after TIPS. Immediately after TIPS, the cardiac index increased by 32% and at two months the increase

was attenuated but remained significantly elevated. In our study, the only hemodynamic variable measured that significantly predicted long-term mortality after TIPS was RA pressure. It is worth noting that our cohort was much larger: 418 patients in our study vs 15 patients in Colombato *et al.*<sup>[17]</sup>'s study.

Mortality after TIPS continues to be elevated despite better selection of patients and improvements in the technical aspects of the procedure. In fact, the overall 30-d mortality ranges between 3% and 44%; meanwhile the one year mortality varies from 11% to 58%. The mortality is greater in high risk patients, in whom it can be as high as 90% within a few weeks after the procedure<sup>[5,6,18,19]</sup>. In our study, we observed a 3-mo and 12-mo mortality after TIPS (censored by liver transplant) of 23.6% and 40.3%, respectively. Given this high mortality rate, it is advantageous to identify predictors of short- and long-term mortality in patients considered for TIPS. Variables previously reported to adversely impact outcomes after TIPS include age<sup>[19,20]</sup>, gender, need for emergent TIPS, encephalopathy<sup>[6]</sup>, ascites, variceal hemorrhage<sup>[6]</sup>, CTP class C<sup>[10,20]</sup>, MELD score, bilirubin > 3<sup>[6,21]</sup>, INR<sup>[21]</sup>, creatinine, alanine aminotransferase > 100 IU/L<sup>[6]</sup>, sodium level<sup>[10]</sup>, albumin<sup>[21]</sup> and portosystemic gradient.

Our study yielded results that corroborate the aforementioned literature. In our study, both echocardiographic (RVSP) and hemodynamic (RA and portal vein pressures both before and after TIPS) variables were predictors of 3-mo survival after TIPS. However, the effect of these determinations became non-significant when adjusting for age, MELD score and CTP grade. Interestingly, a large number of variables impacted long-term survival. Those with independent value included age, MELD score, CTP grade, splenectomy and RV function. We also noted that the higher MELD score and CTP grade impacts adversely the short and long-term prognosis after TIPS. These findings have been described in the literature as predictors of short and long term mortality after TIPS creation in cirrhotic patients<sup>[5,10,20]</sup>. Parvinian *et al.*<sup>[19]</sup> evaluated the specificity of RA pressure in predicting mortality after TIPS at 30- and 90-d in a series of 125 patients. They demonstrated 30-d mortality of 18% and 90-d mortality of 28%. According to univariate analysis, baseline RA pressure and final RA pressure were significantly associated with survival at 30- and 90-d, in addition to Child-Pugh score and MELD score. As in our study, multivariate analysis did not include RA pressure as an independent predictor of mortality at 90-d, supporting these results in a large patient cohort.

In this study, we particularly focused on the prognostic importance of hemodynamic and echocardiographic determinations. Patients with advanced cirrhosis and portal hypertension can develop cardiomyopathy with left ventricular diastolic dysfunction<sup>[21]</sup>, hyperdynamic state, volume overload, and less commonly portopulmonary hypertension; these conditions can be aggravated with the insertion of TIPS<sup>[14,17,22-24]</sup>. The placement of TIPS rapidly increases the RV preload and afterload, which

can lead to overt heart failure, pulmonary hypertension and death<sup>[11,14,16,22-37]</sup>. RA pressure obtained before TIPS could be of value in clinical practice; physicians may elect to abort a TIPS procedure based on this hemodynamic parameter.

Our study has limitations that include the: (1) retrospective collection of data; (2) the lack of data on cardiac output, pulmonary artery and pulmonary capillary wedge pressures which are determinations not routinely obtained at the time of TIPS; and (3) echocardiographic determinations were not done at the time of TIPS. The nature of our patient cohort also poses some limitations. Despite these limitations this study presents data on a large number of TIPS procedures performed during the course of eight years. It describes factors that affect short (3-mo) and long-term prognosis. Most importantly, we found that an important factor with predictive value is RA pressure, which increases after TIPS most prominently in patients with more severe liver disease.

RA pressure increased immediately after TIPS particularly in patients with worse liver function, portal hypertension, emergent TIPS placement and history of splenectomy. The increase in RA pressure after TIPS was associated with increased mortality. Age, splenectomy, MELD score and CTP grade were independent predictors of long-term mortality after TIPS.

## ACKNOWLEDGMENTS

We would like to thank the interventional radiology laboratory personnel for their outstanding work. We are indebted to Jennie Newman licensed practical nurse for her invaluable assistance in this project.

## COMMENTS

### Background

Transjugular intrahepatic portosystemic shunt (TIPS) is a procedure that can be accompanied by morbidity and mortality. There is a lack of studies assessing the prognostic value of echocardiographic and hemodynamic determinations at the time of TIPS. The hypothesis that the echocardiographic and hemodynamic determinations obtained at the time of TIPS can provide prognostic information that will enhance risk stratification of patients for this procedure.

### Research frontiers

Risk stratification of patients with liver disease who are undergoing TIPS is imperfect. It is evident that a number of hemodynamic changes occur after the procedure; their effect on patient outcomes still warrants investigation. The authors examine echocardiographic and hemodynamic variables in this cohort of patients in order to glean information regarding survival and outcomes in patients undergoing TIPS. Furthermore, through a multivariate analysis they also investigate other variables that may significantly influence patient outcomes. This will help to optimize patient benefit from the TIPS procedure.

### Innovations and breakthroughs

In their study, they found that right atrial pressure increased immediately after TIPS particularly in patients with worse liver function, portal hypertension, emergent TIPS placement and history of splenectomy. The increase in right atrial pressure after TIPS was associated with increased mortality. Age, splenectomy, Model of End-stage Liver Disease score and Child Turcotte Pugh

grade were independent predictors of long-term mortality after TIPS.

## Applications

These findings could be used to enhance patient selection for TIPS.

## Peer-review

This retrospective study is important clinical value to select the patients for TIPS and evaluate the prognosis for patients who underwent TIPS placement.

## REFERENCES

- Rössle M, Haag K, Ochs A, Sellinger M, Nöldge G, Perarnau JM, Berger E, Blum U, Gabelmann A, Hauenstein K. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *N Engl J Med* 1994; **330**: 165-171 [PMID: 8264738 DOI: 10.1056/NEJM199401203300303]
- Ochs A, Rössle M, Haag K, Hauenstein KH, Deibert P, Siegertstetter V, Huonker M, Langer M, Blum HE. The transjugular intrahepatic portosystemic stent-shunt procedure for refractory ascites. *N Engl J Med* 1995; **332**: 1192-1197 [PMID: 7700312 DOI: 10.1056/NEJM199505043321803]
- Gordon FD, Anastopoulos HT, Crenshaw W, Gilchrist B, McEniff N, Falchuk KR, LoCicero J, Lewis WD, Jenkins RL, Trey C. The successful treatment of symptomatic, refractory hepatic hydrothorax with transjugular intrahepatic portosystemic shunt. *Hepatology* 1997; **25**: 1366-1369 [PMID: 9185754 DOI: 10.1002/hep.510250611]
- Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000; **31**: 864-871 [PMID: 10733541 DOI: 10.1053/he.2000.5852]
- Garcia-Pagán JC, Heydtmann M, Raffa S, Plessier A, Murad S, Fabris F, Vizzini G, Gonzales Abraldes J, Olliff S, Nicolini A, Luca A, Primignani M, Janssen HL, Valla D, Elias E, Bosch J. TIPS for Budd-Chiari syndrome: long-term results and prognostic factors in 124 patients. *Gastroenterology* 2008; **135**: 808-815 [PMID: 18621047 DOI: 10.1053/j.gastro.2008.05.051]
- Chalasani N, Clark WS, Martin LG, Kamean J, Khan MA, Patel NH, Boyer TD. Determinants of mortality in patients with advanced cirrhosis after transjugular intrahepatic portosystemic shunting. *Gastroenterology* 2000; **118**: 138-144 [PMID: 10611162 DOI: 10.1016/S0016-5085(00)70422-7]
- Russo MW, Jacques PF, Mauro M, Odell P, Brown RS. Predictors of mortality and stenosis after transjugular intrahepatic portosystemic shunt. *Liver Transpl* 2002; **8**: 271-277 [PMID: 11910573 DOI: 10.1053/jlts.2002.31653]
- Rajan DK, Haskal ZJ, Clark TW. Serum bilirubin and early mortality after transjugular intrahepatic portosystemic shunts: results of a multivariate analysis. *J Vasc Interv Radiol* 2002; **13**: 155-161 [PMID: 11830621 DOI: 10.1016/S1051-0443(07)61932-0]
- Patch D, Nikolopoulou V, McCormick A, Dick R, Armonis A, Wannamethee G, Burroughs A. Factors related to early mortality after transjugular intrahepatic portosystemic shunt for failed endoscopic therapy in acute variceal bleeding. *J Hepatol* 1998; **28**: 454-460 [PMID: 9551684 DOI: 10.1016/S0168-8278(98)80320-6]
- Jalan R, Elton RA, Redhead DN, Finlayson ND, Hayes PC. Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt for variceal haemorrhage. *J Hepatol* 1995; **23**: 123-128 [PMID: 7499782 DOI: 10.1016/0168-8278(95)80325-4]
- Azoulay D, Castaing D, Dennison A, Martino W, Eyraud D, Bismuth H. Transjugular intrahepatic portosystemic shunt worsens the hyperdynamic circulatory state of the cirrhotic patient: preliminary report of a prospective study. *Hepatology* 1994; **19**: 129-132 [PMID: 8276348 DOI: 10.1002/hep.1840190121]
- Blendis L, Wong F. The hyperdynamic circulation in cirrhosis: an overview. *Pharmacol Ther* 2001; **89**: 221-231 [PMID: 11516477 DOI: 10.1016/S0163-7258(01)00124-3]
- Huonker M, Schumacher YO, Ochs A, Sorichter S, Keul J, Rössle M. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. *Gut* 1999; **44**: 743-748 [PMID: 10205217 DOI: 10.1136/gut.44.5.743]
- Van der Linden P, Le Moine O, Ghysels M, Ortíz M, Devière J. Pulmonary hypertension after transjugular intrahepatic portosystemic shunt: effects on right ventricular function. *Hepatology* 1996; **23**: 982-987 [PMID: 8621179 DOI: 10.1002/hep.510230507]
- Perarnau JM, Le Gouge A, Nicolas C, d'Alteroche L, Borentain P, Saliba F, Minello A, Anty R, Chagneau-Derrode C, Bernard PH, Abergel A, Ollivier-Hourmand I, Gournay J, Ayoub J, Gaborit C, Rusch E, Giraudeau B. Covered vs. uncovered stents for transjugular intrahepatic portosystemic shunt: a randomized controlled trial. *J Hepatol* 2014; **60**: 962-968 [PMID: 24480619 DOI: 10.1016/j.jhep.2014.01.015]
- Kovács A, Schepke M, Heller J, Schild HH, Flacke S. Short-term effects of transjugular intrahepatic shunt on cardiac function assessed by cardiac MRI: preliminary results. *Cardiovasc Intervent Radiol* 2010; **33**: 290-296 [PMID: 19730936 DOI: 10.1007/s00270-009-9696-2]
- Colombato LA, Spahr L, Martinet JP, Dufresne MP, Lafortune M, Fenyves D, Pomier-Layrargues G. Haemodynamic adaptation two months after transjugular intrahepatic portosystemic shunt (TIPS) in cirrhotic patients. *Gut* 1996; **39**: 600-604 [PMID: 8944572 DOI: 10.1136/gut.39.4.600]
- Harrod-Kim P, Saad WE, Waldman D. Predictors of early mortality after transjugular intrahepatic portosystemic shunt creation for the treatment of refractory ascites. *J Vasc Interv Radiol* 2006; **17**: 1605-1610 [PMID: 17057001 DOI: 10.1097/01.RVI.0000240651.38289.4B]
- Parvinian A, Shah KD, Couture PM, Minocha J, Knuttinen MG, Bui JT, Gaba RC. Older patient age may predict early mortality after transjugular intrahepatic portosystemic shunt creation in individuals at intermediate risk. *J Vasc Interv Radiol* 2013; **24**: 941-946 [PMID: 23707226 DOI: 10.1016/j.jvir.2013.03.018]
- Williams D, Waugh R, Gallagher N, Perkins K, Dilworth P, Duggan A, Selby W. Mortality and rebleeding following Transjugular Intrahepatic Portosystemic Stent Shunt for variceal haemorrhage. *J Gastroenterol Hepatol* 1998; **13**: 163-169 [PMID: 10221818 DOI: 10.1111/j.1440-1746.1998.tb00632.x]
- Tyburski JG, Noorily MJ, Wilson RF. Prognostic factors with the use of the transjugular intrahepatic portosystemic shunt for bleeding varices. *Arch Surg* 1997; **132**: 626-630; discussion 630-632 [PMID: 9197855 DOI: 10.1001/archsurg.1997.01430300068014]
- Møller S, Henriksen JH. Cardiovascular complications of cirrhosis. *Postgrad Med J* 2009; **85**: 44-54 [PMID: 19240290 DOI: 10.1136/gut.2006.112177]
- Pozzi M, Carugo S, Boari G, Pecci V, de Ceglie S, Maggiolini S, Bolla GB, Roffi L, Failla M, Grassi G, Giannattasio C, Mancina G. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. *Hepatology* 1997; **26**: 1131-1137 [PMID: 9362352 DOI: 10.1002/hep.510260507]
- Finucci G, Desideri A, Sacerdoti D, Bolognesi M, Merkel C, Angeli P, Gatta A. Left ventricular diastolic function in liver cirrhosis. *Scand J Gastroenterol* 1996; **31**: 279-284 [PMID: 8833359 DOI: 10.3109/00365529609004879]
- Salerno F, Cazzaniga M, Pagnozzi G, Cirello I, Nicolini A, Meregaglia D, Burdick L. Humoral and cardiac effects of TIPS in cirrhotic patients with different "effective" blood volume. *Hepatology* 2003; **38**: 1370-1377 [PMID: 14647047 DOI: 10.1016/j.jhep.2003.09.030]
- Rabie R, Cazzaniga M, Salerno F, Wong F. The effect of cirrhotic cardiomyopathy on the post-TIPS outcome of patients treated for complications of portal hypertension. *Hepatology* 2006; **44** (Suppl 1): 444A
- Rabie RN, Cazzaniga M, Salerno F, Wong F. The use of E/A ratio as a predictor of outcome in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt. *Am J Gastroenterol* 2009; **104**: 2458-2466 [PMID: 19532126 DOI: 10.1038/ajg.2009.321]
- Lee SS, Liu H. Cardiovascular determinants of survival in cirr-

- hosis. *Gut* 2007; **56**: 746-748 [PMID: 17519479 DOI: 10.1136/gut.2006.112169]
- 29 **Rodríguez-Laiz JM**, Bañares R, Echenagusia A, Casado M, Camuñez F, Pérez-Roldán F, de Diego A, Cos E, Clemente G. Effects of transjugular intrahepatic portosystemic shunt (TIPS) on splanchnic and systemic hemodynamics, and hepatic function in patients with portal hypertension. Preliminary results. *Dig Dis Sci* 1995; **40**: 2121-2127 [PMID: 7587778 DOI: 10.1007/BF02208995]
  - 30 **Cazzaniga M**, Salerno F, Pagnozzi G, Dionigi E, Visentin S, Cirello I, Meregaglia D, Nicolini A. Diastolic dysfunction is associated with poor survival in patients with cirrhosis with transjugular intrahepatic portosystemic shunt. *Gut* 2007; **56**: 869-875 [PMID: 17135305 DOI: 10.1136/gut.2006.102467]
  - 31 **Willoughby PH**, Beers RA, Murphy KD. Pulmonary edema after transjugular intrahepatic portosystemic shunt. *Anesth Analg* 1996; **82**: 895-896 [PMID: 8615536 DOI: 10.1213/00000539-199604000-00066]
  - 32 **Braverman AC**, Steiner MA, Picus D, White H. High-output congestive heart failure following transjugular intrahepatic portal-systemic shunting. *Chest* 1995; **107**: 1467-1469 [PMID: 7750353 DOI: 10.1378/chest.107.5.1467]
  - 33 **Modock J**. Acute pulmonary hypertension after transjugular intra-hepatic portosystemic shunt: a potentially deadly but commonly forgotten complication. *Gastroenterol Nurs* 2014; **37**: 33-8; quiz 39-40 [PMID: 24476830 DOI: 10.1097/SGA.000000000000016]
  - 34 **Merli M**, Valeriano V, Funaro S, Attili AF, Masini A, Efrati C, De CS, Riggio O. Modifications of cardiac function in cirrhotic patients treated with transjugular intrahepatic portosystemic shunt (TIPS). *Am J Gastroenterol* 2002; **97**: 142-148 [PMID: 11808939 DOI: 10.1111/j.1572-0241.2002.05438.x]
  - 35 **Salerno F**, Merli M, Cazzaniga M, Valeriano V, Rossi P, Lovaria A, Meregaglia D, Nicolini A, Lubatti L, Riggio O. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. *J Hepatol* 2002; **36**: 494-500 [PMID: 11943420 DOI: 10.1016/S0168-8278(01)00309-9]
  - 36 **Gaba RC**, Khiatani VL, Knuttinen MG, Omene BO, Carrillo TC, Bui JT, Owens CA. Comprehensive review of TIPS technical complications and how to avoid them. *AJR Am J Roentgenol* 2011; **196**: 675-685 [PMID: 21343513 DOI: 10.2214/AJR.10.4819]
  - 37 **Parvinian A**, Bui JT, Knuttinen MG, Minocha J, Gaba RC. Right atrial pressure may impact early survival of patients undergoing transjugular intrahepatic portosystemic shunt creation. *Ann Hepatol* 2014; **13**: 411-419 [PMID: 24927612]

**P- Reviewer:** Minicis SD, Qin JM, Wong GLH **S- Editor:** Qiu S  
**L- Editor:** A **E- Editor:** Liu SQ



## Management of pregnancy in Crigler Najjar syndrome type 2

Alisha Nitin Chaubal, Ruchir Patel, Dhaval Choksi, Kaivan Shah, Meghraj Ingle, Prabha Sawant

Alisha Nitin Chaubal, Ruchir Patel, Dhaval Choksi, Kaivan Shah, Meghraj Ingle, Prabha Sawant, Department of Gastroenterology, LTMG Hospital, Mumbai 400022, India

**Author contributions:** Chaubal AN wrote the case report; Chaubal AN, Patel R, Choksi D, Shah K, Ingle M and Sawant P managed the case.

**Institutional review board statement:** The institutional review board of LTMG hospital have reviewed and accepted the case report.

**Informed consent statement:** I am aware that my clinical problem is being reported without revealing my identity and I have no objections to the same. I have been explained in detail the procedure for the same and will not hold anyone responsible for the outcome.

**Conflict-of-interest statement:** The authors do not hold any conflict of interest with reviewers.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Alisha Nitin Chaubal, Registrar, Department of Gastroenterology, LTMGH Hospital, Dr. Babasaheb Ambedkar Road, Sion West, Mumbai 400022, India. [alishachaubal@gmail.com](mailto:alishachaubal@gmail.com)  
 Telephone: +91-022-24063088  
 Fax: +91-022-24044154

Received: October 18, 2015

Peer-review started: November 12, 2015

First decision: January 4, 2016

Revised: February 22, 2016

Accepted: March 9, 2016

Article in press: March 14, 2016

Published online: April 18, 2016

### Abstract

Crigler Najjar syndrome is associated with indirect hyperbilirubinemia due to a deficiency of enzyme Uridine Di Phospho Glucuronosyl Transferase (UDPGT). Presented here is a case of a female in the first trimester of pregnancy, who was diagnosed to have type 2 Crigler Najjar syndrome. We also discuss the management of this rare disease especially in pregnancy. Unconjugated bilirubin can cross the placental barrier causing neurological damage in the newborn. Patient was carefully monitored during pregnancy and treatment with phenobarbitone in low doses was adjusted such that the serum bilirubin levels were below 10 mg/dL. Crigler Najjar syndrome being rare needs to be diagnosed early in pregnancy to avoid adverse fetal outcomes. Phenobarbitone being an inducer of enzyme UDPGT is used as the first line of treatment and is not teratogenic in the low doses used. Treatment protocol followed was on the basis of previous reported cases and successful perinatal outcome was achieved.

**Key words:** Crigler Najjar type 2; Phenobarbitone; Folic acid; Pregnancy; Kernicterus

© The Author(s) 2016. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Crigler Najjar syndrome type 2 is a rare disorder causing indirect hyperbilirubinemia. In pregnancy placental crossing of unconjugated bilirubin can cause high bilirubin levels in the fetus with low Uridine Di Phospho Glucuronosyl Transferase activity causing permanent neurological impairment in the newborn. Hence timely diagnosis and treatment with low dose phenobarbitone is required.

Chaubal AN, Patel R, Choksi D, Shah K, Ingle M, Sawant P. Management of pregnancy in Crigler Najjar syndrome type 2. *World J Hepatol* 2016; 8(11): 530-532 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i11/530.htm> DOI:

## INTRODUCTION

Crigler Najjar type 2 is a rare condition with an incidence of 1 per 1000000 births. There is no predilection to any race or sex. Being an autosomal recessive disorder consanguineous marriage is a risk factor. Uridine Di Phospho Glucuronosyl Transferase (UDPGT) level in the liver is less than 10% of normal. The serum bilirubin ranges from 3-20 mg/dL. Patients usually present with jaundice in the first year of life but can sometimes occur even in the third decade. Acute increase in bilirubin levels can occur during fasting or illness. DNA analysis of *UDPGT* gene shows mutation in exon 1  $\times$  1-5. Expression analysis of the gene shows residual activity<sup>[1]</sup>. Greater than 25% fall in bilirubin levels after treatment with phenobarbitone distinguishes it from Crigler Najjar type 1.

Levels of bilirubin can be elevated due to the stress of pregnancy. The placenta is an ineffective barrier for unconjugated bilirubin and can result in high bilirubin levels in the neonate causing kernicterus and sometimes even death<sup>[2]</sup>.

Proper identification of the condition and timely treatment with phenobarbitone can avoid morbidity and mortality in the neonate<sup>[3]</sup>.

## CASE REPORT

A female patient of age 24 years had a history of jaundice since childhood. She came to us in her first trimester of pregnancy because her jaundice had increased since the previous 2 wk. Patient had unconjugated hyperbilirubinemia with normal liver enzymes. Tests for viral hepatitis, autoimmune liver disease and Wilson's disease were negative. Abdominal ultrasound including a selective hepatobiliary scan did not show any abnormalities. The *UDT1A1* gene was studied for the TATA sequence. The result was negative; Gilbert's syndrome was thus ruled out. Total bilirubin at 12 wk of gestation was 6.85 mg/dL with indirect bilirubin being 6.14 mg/dL and albumin of 4 g/dL. Her liver enzymes were normal. A dose of 30 mg/d of phenobarbitone was started for the patient. Her serum bilirubin and albumin levels were measured at weekly intervals for the first month and then monthly. Her liver enzymes were also measured simultaneously. We diagnosed the patient to be a case of Crigler Najjar type 2 based on: (1) history of hyperbilirubinemia since childhood; and (2) response to phenobarbitone. A congenital anomaly scan at 20 wk showed no fetal abnormalities. Through her pregnancy, bilirubin levels were maintained in the range of 4 to 8 mg/dL. Figure 1 shows readings of the patient's bilirubin levels taken throughout pregnancy. Total bilirubin was measured at 4.92 mg/dL at time of delivery, which was completed at the normal full term. At the same time, indirect bilirubin was 3.78 mg/dL. Bilirubin levels in the

neonate were normal. As a result, no treatment of any form was required.

## DISCUSSION

Crigler Najjar syndrome is a rare autosomal recessive condition with an incidence of 1 in 1000000 births. Pregnancy in Crigler Najjar syndrome type 2 has been reported only in 6 cases so far (type 1-4 type 2-6 cases)<sup>[4]</sup>.

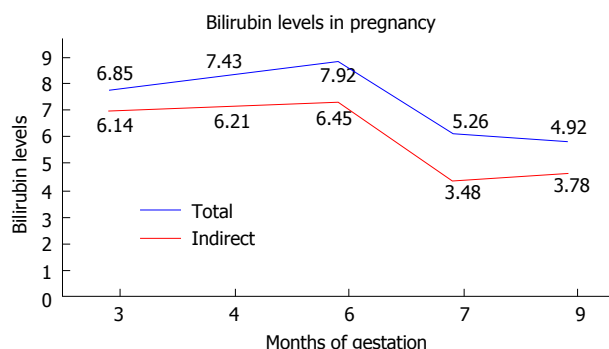
Our patient was a case of Crigler Najjar type 2 where serum bilirubin usually does not exceed 10 mg/dL. However pregnancy being a stressful condition the bilirubin levels can increase to more than 10 mg/dL. We had monitored the patient's bilirubin levels, serum albumin and liver enzymes at monthly intervals.

Crigler-Najjar disease type 2 seems to pose no unique maternal risk during pregnancy. The fetus seems to be resistant to elevated maternal unconjugated bilirubin, but the neonate may require therapy for hyperbilirubinemia<sup>[5]</sup>. Unconjugated bilirubin crosses the placental barrier to cause high levels of bilirubin in the fetus resulting in neurological damage or even death<sup>[6]</sup>. There is no fixed level of bilirubin at which neurological damage occurs but a proposed level above 10 mg/dL has been suggested<sup>[4]</sup>. In a study by Holstein *et al*<sup>[7]</sup>, maternal bilirubin levels between 4.2 and 8.9 maintained by treatment with phototherapy/phenobarbitone resulted in a normal neonate.

Pinkie *et al*<sup>[8]</sup> observed that a maternal bilirubin of 10.8 mg/dL at delivery necessitated treatment with exchange transfusions and phototherapy. We had started our patient on low dose phenobarbitone (30 mg daily) and we were able to maintain bilirubin levels less than 10 mg/dL. Phenobarbitone is known to be teratogenic causing facial dysmorphism and mental retardation. However this is seen only at high doses of 750-1500 mg/d and has not been observed at enzyme inducing doses of 60 mg/d<sup>[3]</sup>.

It has been recommended that an acute increase in bilirubin should be treated with phototherapy and albumin. If patient is already on phototherapy then duration of phototherapy should be increased to 24 h. If neurological toxicity develops then plasmapheresis should be done. However our patient had maintained bilirubin levels with phenobarbitone alone.

The newborn was born without jaundice and did not require any treatment. Bilirubin levels over 10 mg/dL is an indication for phototherapy in term infants without risk factors 4 mg/dL in infants with high risk for kernicterus (preterm, low birth weight)<sup>[9]</sup>. A follow-up of the infant is required for at least 18 mo<sup>[10]</sup>. A study by Taylor *et al*<sup>[11]</sup> showed that an untreated maternal level of 20 mg/dL resulted in a normal infant at birth but the child developed quadriplegia at 18 mo of age. Hence we propose that the standard guidelines for the management of pregnancy in Crigler najjar syndrome type 2 should be followed<sup>[9]</sup>: (1) Genetic counselling before becoming pregnant; (2) Folic acid at a dose of 10 mg during pregnancy; (3) Maternal bilirubin serum



**Figure 1** Monitoring of bilirubin levels throughout pregnancy.

levels should be below 10 mg/dL; (4) Phenobarbitone at low dose of 60 mg/d; (5) Avoid drugs that increase unbound, unconjugated bilirubin like sulfonamides, salicylates, furosemide, ampicillin, and ceftriaxone; and (6) Neurologic follow-up of the newborn including hearing disorders (brainstem evoked potentials).

## COMMENTS

### Case characteristics

Pregnant female with jaundice.

### Clinical diagnosis

Icterus with negative abdominal findings.

### Differential diagnosis

Viral hepatitis, auto-immune hepatitis, Wilson's disease, hyperbilirubinemias, biliary pathology.

### Laboratory diagnosis

Indirect hyperbilirubinemia with normal liver enzymes.

### Imaging diagnosis

Normal hepatobiliary scan.

### Treatment

Phenobarbitone 30-60 mg once daily.

### Experiences and lessons

Suspicion for indirect hyperbilirubinemias for patients presenting with jaundice

and management of Crigler Najjar syndrome in pregnancy with low dose Phenobarbitone.

## Peer-review

Short, clear and well written manuscript. A rare disease that should be of interest to the Journal readers.

## REFERENCES

- 1 **Kadacol A**, Ghosh SS, Sappal BS, Sharma G, Chowdhury JR, Chowdhury NR. Genetic lesions of bilirubin uridine-diphosphoglucuronate glucuronosyltransferase (UGT1A1) causing Crigler-Najjar and Gilbert syndromes: correlation of genotype to phenotype. *Hum Mutat* 2000; **16**: 297-306 [PMID: 11013440]
- 2 **Raimondi F**, Capasso L, Migliaro F, Romano A, Paludetto R. Prenatal exposure to conjugated bilirubin. *Pediatrics* 2006; **118**: 2265 [PMID: 17079608]
- 3 **Kjaer D**, Horvath-Puhó E, Christensen J, Vestergaard M, Czeizel AE, Sørensen HT, Olsen J. Use of phenytoin, phenobarbital, or diazepam during pregnancy and risk of congenital abnormalities: a case-time-control study. *Pharmacoepidemiol Drug Saf* 2007; **16**: 181-188 [PMID: 16941718]
- 4 **Passuello V**, Puhl AG, Wirth S, Steiner E, Skala C, Koelbl H, Kohlschmidt N. Pregnancy outcome in maternal Crigler-Najjar syndrome type II: a case report and systematic review of the literature. *Fetal Diagn Ther* 2009; **26**: 121-126 [PMID: 19752526 DOI: 10.1159/000238122]
- 5 **Smith JF**, Baker JM. Crigler-Najjar disease in pregnancy. *Obstet Gynecol* 1994; **84**: 670-672 [PMID: 9205443]
- 6 **Serrano MA**, Bayón JE, Pascolo L, Tiribelli C, Ostrow JD, Gonzalez-Gallego J, Marin JJ. Evidence for carrier-mediated transport of unconjugated bilirubin across plasma membrane vesicles from human placental trophoblast. *Placenta* 2002; **23**: 527-535 [PMID: 12175967]
- 7 **Holstein A**, Plaschke A, Lohse P, Egberts EH. Successful photo- and phenobarbital therapy during pregnancy in a woman with Crigler-Najjar syndrome type II. *Scand J Gastroenterol* 2005; **40**: 1124-1126 [PMID: 16211719]
- 8 **Pinke S**, Renu A, Bharati M. Crigler-Najjar syndrome with pregnancy. *J Obstet Gynecol India* 2005; **55**: 270-271
- 9 **Wilson JH**, Sinaasappel M, Lotgering FK, Langendonk JG. Recommendations for pregnancies in patients with crigler-najjar syndrome. *JIMD Rep* 2013; **7**: 59-62 [PMID: 23430496 DOI: 10.1007/8904\_2012\_142]
- 10 **Shapiro SM**. Definition of the clinical spectrum of kernicterus and bilirubin-induced neurologic dysfunction (BIND). *J Perinatol* 2005; **25**: 54-59 [PMID: 15578034]
- 11 **Taylor WG**, Walkinshaw SA, Farquharson RG, Fisk RA, Gilmore IT. Pregnancy in Crigler-Najjar syndrome. Case report. *Br J Obstet Gynaecol* 1991; **98**: 1290-1291 [PMID: 1777465]

**P- Reviewer:** Morini S, Rovas L, Younis JS **S- Editor:** Ji FF

**L- Editor:** A **E- Editor:** Liu SQ





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](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

