ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2017 April 28; 9(12): 567-612

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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

Editorial Board

2014-2017

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

Chile

Luis A Videla, *Santiago*

China

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

Czech Repoublic

Kamil Vyslouzil, *Olomouc*

Denmark

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

Egypt

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

France

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

Germany

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

Greece

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

Hungary

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

India

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

Indonesia

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

Iran

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

Israel

Stephen DH Malnick, *Rehovot*

Italy

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

Japan

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

Jordan

Kamal E Bani-Hani, *Zarqa*

Malaysia

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

Mexico

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

Moldova

Angela Peltec, *Chishinev*

Netherlands

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

Nigeria

CA Asabamaka Onyekwere, *Lagos*

Pakistan

Bikha Ram Devrajani, *Jamshoro*

Philippines

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

Poland

Jacek Zielinski, *Gdansk*

Portugal

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

Qatar

Reem Al Olaby, *Doha*

Romania

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

Russia

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

Saudi Arabia

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

Singapore

Ser Yee Lee, *Singapore*

South Korea

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

Spain

Ivan G Marina, *Madrid*

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

Sri Lanka

Niranga M Devanarayana, *Ragama*

Sudan

Hatim MY Mudawi, *Khartoum*

Sweden

Evangelos Kalaitzakis, *Lund*

Switzerland

Christoph A Maurer, *Liestal*

Thailand

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

Turkey

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

Ukraine

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

United Kingdom

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

United States

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

World Journal of Hepatology

Contents

Three issues per month Volume 9 Number 12 April 28, 2017

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

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

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Hepatology
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
April 28, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 April 28; 9(12): 567-585

DOI: 10.4254/wjh.v9.i12.567

ISSN 1948-5182 (online)

REVIEW

Emerging concepts in alcoholic hepatitis

Phoenix Fung, Nikolaos Pyrsopoulos

Phoenix Fung, Nikolaos Pyrsopoulos, Department of Medicine, Division of Gastroenterology and Hepatology, Rutgers New Jersey Medical School, Newark, NJ 07103, United States

Author contributions: Fung P reviewed the literature, performed the majority of writing, and prepared the figures and illustrations; Pyrsopoulos N designed, co-authored and revised the manuscript.

Conflict-of-interest statement: In regards to affiliations, Phoenix Fung and Nikolaos Pyrsopoulos perform research for Vital Therapies and Gilead Sciences. Nikolaos Pyrsopoulos is a member of the scientific advisory board for Vital Therapies and advisory board for Gilead.

Manuscript source: Unsolicited manuscript

Correspondence to: Nikolaos Pyrsopoulos, MD, PhD, MBA, Associate Professor of Medicine, Chief of Gastroenterology and Hepatology, Department of Medicine, Division of Gastroenterology and Hepatology, Rutgers New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, United States. pyrsopni@njms.rutgers.edu
Telephone: +1-973-9725252
Fax: +1-973-9723144

Received: December 5, 2016
Peer-review started: December 6, 2016
First decision: January 16, 2017
Revised: February 21, 2017
Accepted: March 12, 2017
Article in press: March 13, 2017
Published online: April 28, 2017

Abstract

Severe alcoholic hepatitis is implicated as a costly, worldwide public health issue with high morbidity and mortality. The one-month survival for severe alcoholic hepatitis is low with mortality rates high as 30%-50%. Abstinence from alcohol is the recommended first-line treatment. Although corticosteroids remain as the current evidence based option for selected patients with discriminant function > 32, improvement of short-term survival rate may be the only benefit. Identification of individuals with risk factors for the development of severe alcoholic hepatitis may provide insight to the diverse clinical spectrum and prognosis of the disease. The understanding of the complex pathophysiologic processes of alcoholic hepatitis is the key to elucidating new therapeutic treatments. Newer research describes the use of gut microbiota modification, immune modulation, stimulation of liver regeneration, caspase inhibitors, farnesoid X receptors, and the extracorporeal liver assist device to aid in hepatocellular recovery. Liver transplantation can be considered as the last medical option for patients failing conventional medical interventions. Although the preliminary data is promising in patients with low risk of recividism, controversy remains due to organ scarcity. This review article comprehensively summarizes the epidemiology, pathophysiology, risk factors, and prognostic indicators of severe alcoholic hepatitis with a focus on the current and emerging therapeutics.

Key words: Immune modulation; Alcoholic hepatitis; Gut microbiota modification; Extracorporeal liver assist device; Apoptosis inhibitors

Core tip: Current research of alcoholic hepatitis pathophysiology *via* translational research has provided insight to novel therapeutic options. Recovery from severe alcoholic hepatitis with assistance of gut microbiota modification, immune modulators, stimulation of liver regeneration, caspase inhibitors, farnesoid X receptors, and extracorporeal liver assist device may be promising.

Fung P, Pyrsopoulos N. Emerging concepts in alcoholic hepatitis.

World J Hepatol 2017; 9(12): 567-585 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i12/567.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i12.567

INTRODUCTION

Alcoholic hepatitis (AH), is one of the most severe manifestations of alcoholic liver disease. It is a public health issue and worldwide disease associated with high morbidity and mortality. Complications related to alcoholic liver disease result in costly hospitalizations. Current treatment strategies are limited. Abstinence is the first line treatment, however may not improve outcomes in patients with severe AH, defined as discriminant function > 32. The mainstay of therapy is corticosteroids, which have limited efficacy in specific populations. Pursuit of new treatment options for alcoholic hepatitis is the holy grail for patients ineligible or refractory to corticosteroids. The judicious use of early liver transplantation for severe alcoholic hepatitis has been explored although medical and ethical controversy remains. Exploration of maximal medical management with microbiota modification, immune modulation, liver regenerative factors, farnesoid X receptors (FXRs), caspase inhibitors, and extracorporeal liver assist device (ELAD) may be promising for patients with severe alcoholic hepatitis who do not have other options.

Sixty percent of the United States' population reports alcohol consumption[1]. Approximately 8%-10% of the United States population reports heavy alcohol use, which is defined as $\geqslant$ 2 drinks daily in men and $\geqslant$ 1 drink daily in women[2]. One standard drink contains approximately 14 g of alcohol, which is equivalent to 12 ounces (350 mL) of beer (4%-5% wt/vol), 6 ounces (177 mL) of wine (8%-10% wt/vol), and 2 ounces (59 mL) of hard liquor or whiskey (45% wt/vol)[1]. There are progressive and co-existing stages of disease in chronic alcoholism including steatosis, steatohepatitis, fibrosis, and development of compensated to decompensated cirrhosis. In a study examining hospitalized heavy alcohol drinkers with and without alcohol withdrawal, liver biopsies reveal steatosis in 44.9%, alcoholic hepatitis in 34.4%, liver cirrhosis with superimposed alcoholic hepatitis in 10.2%, and cirrhosis only in 10.5%[3]. In other studies, approximately 20% of individuals with chronic alcohol abuse are found to have AH when biopsied[4].

Alcoholic hepatitis is an acute-on-chronic presentation of liver disease with a wide ranging spectrum of mild to florid, life-threatening injury[5]. It is a clinical syndrome associated with recent onset jaundice and coagulopathy in a person who has been a heavy drinker usually for more than a decade[6]. Although long standing alcohol abuse appears to be associated with the development of AH, the exact trigger for development is unclear. Other factors, such environmental and genetic variables may play a pivotal role. The amount and duration of alcohol abuse needed to produce alcoholic hepatitis is variable depending on the individual patient. Alcohol consumption of approximately 40 g daily for women and 50-60 g daily for men is recognized as a minimal threshold amount for patients at high risk of developing AH. Alcohol consumption is usually within less than 60 d prior to onset of jaundice with heavy alcohol use for more than 6 mo for severe alcoholic hepatitis clinical trial inclusion criterias[7].

It has been reported that chronic alcohol abuse and binge drinking are associated with development of liver disease[8,9]. Binge drinking is defined as five or more drinks in men and four or more drinks in women within a period of approximately 2 h at least once a week[10]. Earlier studies implied that weekly binge drinking may be more deleterious than daily consumption of alcohol[2]. More recent studies suggest daily heavy drinkers had increased mortality from liver disease compared to binge drinkers[11]. It has been reported that the combination of chronic alcohol use with a binge drinking pattern may be more detrimental as animal studies showed mice with chronic ethanol fed diet with an addition of single high dose ethanol administration expressed more severe forms of liver injury and steatosis compared to animals with chronic ethanol feeding alone or single high dose of ethanol only[12]. Further studies are needed to delineate the pathophysiology of binge drinking and its' effects on alcoholic hepatitis.

The true incidence of alcoholic hepatitis is unknown. Based on Denmark studies from 1999-2008, the annual incidence rate of alcoholic hepatitis was 46 per 1000000 in men and 34 per 1000000 in women[13]. In the United States, alcoholic hepatitis accounted for 325000 admissions annually in 2010 with average hospitalization cost of $46264. The most common admitting diagnosis for patient hospitalized with AH was hepatic encephalopathy[14].

PATHOPHYSIOLOGY

The pathogenesis of liver disease related to alcohol consumption is not completely elucidated. Most studies simulating alcoholic hepatitis are recreated in animal models using an alcohol and fat infusion method[15]. The etiology of alcoholic hepatitis is complex and multifactorial. Principal factors include steatosis, oxidative stress, altered gut permeability, toxic metabolites, and formation of cytokines result in the initiation of an inflammatory cascade.

Ethanol is oxidized by three metabolic pathways: (1) alcohol dehydrogenase mainly; (2) cytochrome P450 2E1; and (3) catalase (Figure 1) Ten percent of ethanol oxidation occurs in the microsomal cytochrome P450 CYP2E1. Ethanol catalase driven reaction in the liver peroxisome is negligible[16].

Ethanol is metabolized into acetaldehyde *via* the cytosolic alcohol dehydrogenase enzyme within hepatocytes. Acetaldehyde is converted into acetate and reduced nicotinamide adenine dinucleotide (NADH) *via* mitochondrial and cytosolic aldehyde dehydrogenase[17]. NADH is increased as a byproduct of ethanol metabolism.

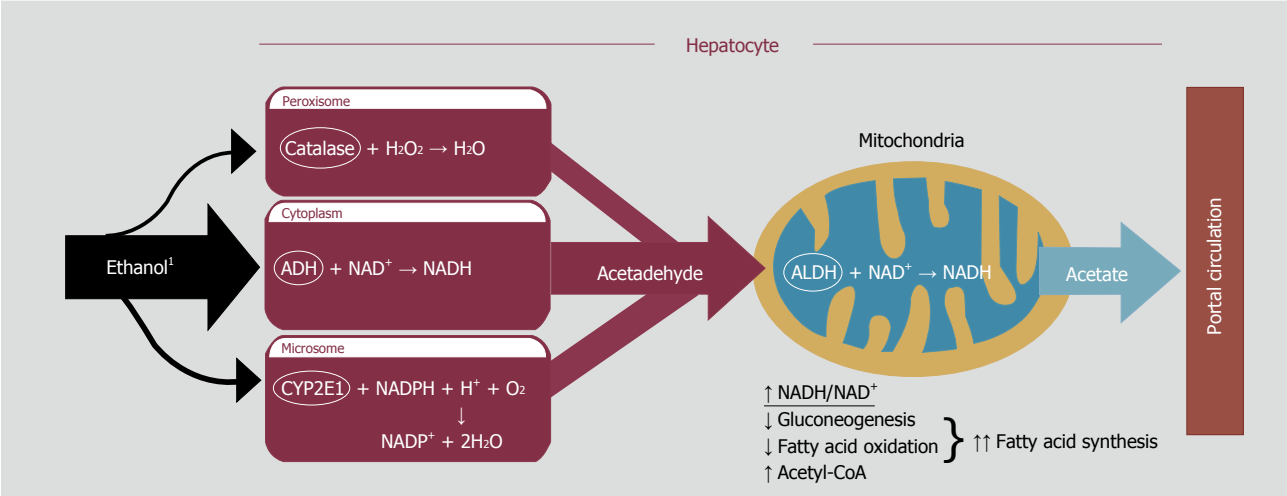


Figure 1 Ethanol metabolism in the hepatocyte. [1]Ethanol inhibits the peroxisome-proliferator-activated receptor α and adenosine monophosphate activated protein kinase with stimulation of sterol regulatory element binding protein 1, a membrane bound transcript factor to promote lipogenesis. ADH: Alcohol dehydrogenase; ALDH: Aldehyde dehydrogenase; NADH: Nicotinamide adenine dinucleotide.

Elevated NADH/NAD$^+$ levels inhibit gluconeogenesis and fatty acid oxidation and is responsible for the high amounts of acetyl-coA found in heavy alcohol users[18]. Acetyl-coA induces fatty acid synthesis by serving as a precursor for fatty acid and cholesterol biosynthesis[19]. In addition, ethanol inhibits the peroxisome-proliferator-activated receptor α and adenosine monophosphate activated protein kinase with stimulation of sterol regulatory element binding protein 1, a membrane bound transcription factor to promote lipogenesis[20-22].

Acetaldehyde is direct hepatotoxin and a known carcinogen[23]. Acetaldehyde form adducts that are potent immunogens to activate inflammatory cytokines[24,25]. The production of reactive oxygen species inducing lipid peroxidation with additional cytotoxic effects of ethanol metabolism induce hepatocyte necrosis[26]. Damage-associated molecular patterns are produced after cell necrosis, which trigger inflammation, fibrosis, and abnormal hepatocyte regeneration[27]. After chronic ethanol consumption, the activity of the microsomal ethanol-oxidizing system increases by 5-10 fold, with an associated rise in cytochrome P-450, CYP2E1. CYP2E1 metabolism increases reactive oxygen species and acetaldehyde production, which diminishes hepatoprotective reduced glutathione and other defense systems leaving hepatocytes to be more vulnerable to oxidative stress[28,29].

The endoplasmic reticulum (ER) regulates protein folding, maturation, misfolded protein degradation, and regulation of new protein entry[30]. When proteins are misfolded in the ER, the unfolded protein response is sensed by the binding immunoglobulin protein/glucose regulated protein 78 (GRP 78). This reaction produces oxidative stress and disassociation of the endoreticulum transmembrane transducers. The transducers are responsible for the activation and recruitment of c-Jun N-terminal (JNK), a stress kinase[31]. Multiple mechanisms, including downstream inflammation and increased oxidative ER stress from hyperhomocysteinemia activates nuclear factor kappa beta (NFKB) and JNK to induce hepatocyte apoptosis *via* caspase activation[32,33]. Deficiencies of B vitamins or homocysteine metabolism mutations seen in chronic ethanol use cause accumulation of homocysteine, which induces the ER stress of the hepatocytes and vascular endothelial cells. In addition, ER stress is associated with fatty acid synthesis *via* the activation of SREBPs (sterol regulatory element-binding proteins), which enhance cholesterol and triglyceride biosynthesis and fibrosis *via* stellate cell activation[34,35].

Ethanol induces gut dysbiosis and alters the permeability[36]. Increased gut permeability allows the endotoxins to infiltrate the liver through the portal vein[37] (Figure 2). Endotoxin levels are measured to be high in patients suffering from alcoholic hepatitis[38]. Bacterial lipopolysaccharide, an endotoxin, binds to the lipopolysaccharide binding protein to form a complex. The complex latches to the CD-14 molecule to activate Kupffer cells and macrophages *via* the toll-like receptor type 4 (TLR-4)[39]. This reaction stimulates mitogen-activated protein kinases [such as extracellular signal-regulated kinase (ERK-1/ERK-2), JNK and p38], NFKB, and activator protein 1 (AP-1). Reactive oxygen species produced by Kupffer cells cause the recruitment of adhesion molecules [intracellular adhesion molecule 1 and vascular adhesion protein 1, chemokines (IL-8 and C-C motif chemokine ligand 2), and inflammatory cytokines (tumor necrosis factor-α, IL-1 and IL-6)[40]. The enhanced inflammatory T-helper-type 1 (TH1) response to alcohol dehydrogenase in alcoholic hepatitis induces additional neutrophil recruitment[41,42]. Nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase is an additional contributor to ROS[6]. Pro-inflammatory cytokine, IL-17 induces the migration of neutrophils into the hepatocytes and stimulates the hepatic stellate cells to produce IL-8 and chemokine CXC motif ligand 1 (CXCL1), which recruit other chemokines to attract other

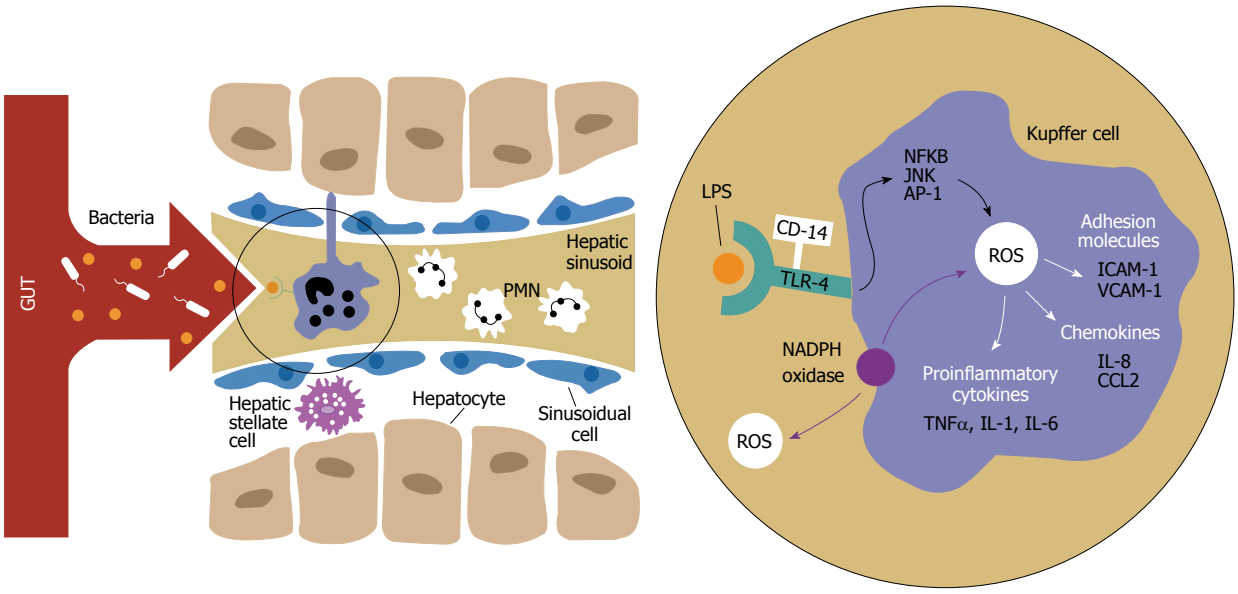


Figure 2 Acetaldehyde induced gut permeability with endotoxemia and inflammatory cascade. LPS: Lipopolysaccharide; TLR-4: Toll-like receptor type 4; ROS: Reactive oxygen species; NADPH: Nicotinamide adenine dinucleotide phosphate-oxidase; NFKB: Nuclear factor kappa beta; JNK: c-Jun N-terminal kinase; AP-1: Activator protein 1; ICAM-1: Intracellular adhesion molecule 1; VCAM-1: Vascular adhesion protein 1; IL-8: Interleukin 8; CCL 2: C-C motif ligand; TNFα: Tumor necrosis factor alpha; IL-1: Interleukin 1; IL-6: Interleukin 6.

neutrophils[43]. IL-22 is stimulated by increased levels of IL-6 and TNF-α. Although IL-22 is produced by TH17, TH22 and natural killer cells, it's receptor is mainly found in hepatocytes. It has a hepatoprotective effect against liver injury and secreted in parallel, to counteract the effects of IL-17[12].

Peripheral neutrophilia is a characteristic finding in alcoholic hepatitis[44]. Normally, neutrophils are recruited to aid in tissue repair and recovery[45]. The innate immunity is impaired in patients with progressive liver dysfunction, contributing to multi-organ failure seen in patients with severe alcoholic hepatitis. Serum analysis of acute alcoholic hepatitis patients compared to patients with alcoholic cirrhosis and healthy controls show a significant reduction in antibacterial innate and adaptive immune responses. An impaired T cell response from AH patients produces fewer interferon gamma when exposed to lipopolysaccharide with impaired neutrophil phagocytosis and defective monocyte oxidative burst when stimulated by bacterial challenge. Defective monocyte oxidative burst reduces the expression of NADPH oxidase, which is responsible for generation of superoxide radicals required for bacterial killing. Higher rates of infection in AH may be explained by this impairment[46]. The T cells of AH patients exhibits increased numbers of PD ligand 1 (PD1), T-cell immunoglobulin and mucin domain 3 (TIM3), and galectin-9, which are ligands responsible for programmed cell death functioning. The blockade of the PD1 and TIM3 can restored the innate and adaptive immunity by increasing T cell and neutrophil antimicrobial activity[47].

Other aldehydes produced along with acetaldehyde contribute to progressive hepatic fibrosis by inducing collagen synthesis. Collagen production activates transforming growth factor β dependent, platelet-derived growth factor, and independent profibrotic pathways to active hepatic stellate cells, which contribute to portal hypertension[48].

RISK FACTORS

Studies have identified risk factors towards the development and progression of liver disease. Patterns of drinking, gender, genetic predisposition, and concomitant liver disease may increase the risk of susceptibility. Simultaneous alcohol consumption with food intake has been published to lower risk of alcoholic liver disease compared to those consuming alcohol alone[9]. Variant genes encoding for alcohol metabolism, such as alcohol dehydrogenase, aldehyde dehydrogenase, and cytochrome CYP2E1 might facilitate hepatotoxicity by increasing alcohol tolerance *via* delay of acetaldehyde formation or the metabolism of alcohol through other non-oxidative toxic pathways[49,50]. Acetaldehyde dehydrogenase gene polymorphisms may cause varying levels of alcohol sensitivity in Asians and women, who can develop alcoholic liver disease even if they do not consume alcohol as heavily as others. Women are twice as likely to develop hepatotoxicity with lower amounts and shorter duration of alcohol use compared to men, which may be attributable to gastric alcohol differences and higher proportion of body fat in women in addition to differences in dehydrogenase levels[51-53]. CYP2E1 gene polymorphisms can affect the metabolism of alcohol amongst those with different ethnic backgrounds and alcoholics, however the exact pathogenesis is yet to be eludicated[54].

Variations in patatin-like phospholipase protein 3 (PNPLA3) has a strong association with cirrhosis develop-

ment in Caucasian and Mexican patients with alcoholism[55]. Patients with G allele of PNPLA3 have a higher risk of steatosis and fibrosis, as well as a significantly higher prevalence of alcoholic cirrhosis compared to those with C allele[56]. Recent data published from a genome wide association study found that severe alcoholic hepatitis risk is associated with PNPLA3 rs738409 variant, which until recently has been associated with cirrhosis development. Identification of SLC38A4 variant gene is another novel independent risk locus for severe AH[57].

Caffeine consumption may have a protective effect against development of AH. Recent studies by Chalasani *et al*[58] found the risk of AH was 27% with heavy alcohol users with PNPLA3 genotype CC with regular coffee consumption compared to 86% in heavy drinkers with PNPLA3 genotype GG, who did not consume coffee. PNPLA3 CC genotype subjects who were not regular coffee consumers had a 48% risk of AH. The risk of AH with PNPLA3 GC with and without regular coffee drinking was 37% and 62%, respectively. The risk of AH was 57% in patients with PNPLA3 GG gene who were regular coffee drinkers[58].

Underlying obesity with body mass index (BMI) $\geqslant$ 30 likely potentiates the severity of alcoholic hepatitis. A common pathway is postulated for the generation of steatohepatitis through synergetic or additive effects of heavy alcohol use combined with obesity, although the exact mechanism is not well defined[59]. Diehl *et al*[59] published a paper documenting a supra-additive interaction between obesity and heavy alcohol consumption. One unit of alcohol was equivalent to 8 g. Overweight or obese male subjects who consumed 15 or more alcohol units per week had an increased risk of liver related morbidity and mortality compared to controls. Another United Kingdom study examining 107, 742 women found that subjects with high BMI ($\geqslant$ 25 kg/m^2) who drank $\leqslant$ 15 units of alcohol have an equivalent risk of chronic liver disease development compared to women with low BMI (< 25) who drank $\geqslant$ 15 units per week. Women with BMI $\geqslant$ 25 who drank $\geqslant$ 15 units of alcohol weekly had the poorest outcomes. Even in overweight women who did not drink alcohol, the risk of negative outcomes were present[60].

Alcoholics with other liver co-morbidities, such as hepatitis B, hepatitis C, and hemochromatosis have greater disease severity and likelihood to develop cirrhosis[61,62]. Underlying chronic liver disease may contribute to the development of acute-on-chronic presentation in AH.

HEPATITIS B AND C WITH ALCOHOLIC LIVER DISEASE

The prevalence of hepatitis C patients with alcoholism is approximately 16% compared to the 1.5%-2% prevalence in the general population[63,64]. Patients with concomitant hepatitis C and alcoholism have 2- to 8-fold increase risk of all-cause mortality compared to patients without hepatitis C[65]. Alcohol abuse reduces survival in patients with hepatitis C, especially in women[66]. Hepatitis C viral load was significantly increased within 4 mo when patients had higher amounts of alcohol consumption of 39-100 g/d compared to 0-50 g/d[67]. Alcohol induced liver fibrosis in patients with hepatitis C is dose-dependent and exhibited patients who ingest 30-40 g daily[68]. Mechanisms of the synergistic hepatotoxic effects of chronic alcohol abuse in patients with hepatitis C include altered cell-mediated immunity, increased oxidative stress, increase viral replication, hepatic steatosis, and inflammatory response from iron accumulation[62].

Studies on viral hepatitis and chronic heavy alcohol use are mostly in patients with hepatitis C. Mechanisms of pathogenesis can also be applied to hepatitis B patients. Hepatitis B or C drinkers have an increase risk of hepatocellular carcinoma compared to non-drinkers[69,70]. Alcohol use did not effect viral efficacy in hepatitis B patients treated with entacavir or hepatitis C patients treated with interferon, however alcoholics may be less compliant with medication adherence[71,72]. Elevation of liver enzymes induced by alcohol can cause overtreatment of patients with chronic hepatitis B. It has been published that only 50% of patients with aminotransferase elevation was caused by immune active chronic hepatitis B among other etiologies[73]. Iron deposition is found in > 50% patients with chronic hepatitis C or heavy alcohol consumption, which is not typically seen in hepatitis B[74].

HEMOCHROMATOSIS WITH ALCOHOLIC LIVER DISEASE

Hepcidin is a peptide produced in the liver for delivery of iron through the ferroportin transporter. When hepcidin levels are decreased in patients with progressive liver disease, iron is accumulated in the hepatocytes[75]. Concomitant iron accumulation and ethanol toxicity may be associated with increased production of oxidative stress. Patients with hemochromatosis who consumed more than 60 g of alcohol per day were 9 times more to develop cirrhosis than who consumed less[76]. Elevated hepatic iron concentration is associated with higher mortality in alcoholic cirrhosis patients[77]. Iron accumulation seen in alcoholic liver disease and hepatitis C is independent risk factor for hepatocellular carcinoma development[76]. Fifty percent of patients with hereditary hemochromatosis develop fibrosis with a 200-fold risk of hepatocellular carcinoma development[78].

NASH AND ALCOHOLIC LIVER DISEASE

Patients with risk factors for non-alcoholic steatohepatitis (NASH) are identified with insulin resistance, obesity, hyperlipidemia, and metabolic syndrome in the setting of minimal alcohol use compared to alcoholic liver disease patients[79]. Differentiating between alcoholic and NASH can be challenging as imaging, laboratory studies, and histologic findings can be non-diagnostic. Attaining a careful alcohol consumption history is cardinal, but can

be unreliable. Histologically, patients with NASH tend to have more advanced fatty degenerative hepatocytes, while there is generally a greater neutrophillic predominance and frequency of Mallory Denk bodies in hepatocytes with alcoholic liver disease. Mallory-Denk bodies are misfolded protein aggregates induced from ER stress, which are deposited into ubiquitin-rich cytoplasmic inclusions within ballooned hepatocytes[80,81]. Mallory-Denk bodies can be present in chronic cholestasis, Wilson's disease, NASH, and amiodarone toxicity. They are not exclusively seen in alcoholic hepatitis[82]. Patients with alcoholic liver disease tend to higher rates of perivenular fibrosis, phlebosclerosis, cholestasis, and ductal proliferation compared to NASH patients[83]. Using logistic regression, Dunn *et al*[84] identified mean corpuscular volume, AST/ALT ratio, body mass index, and gender as the key variables to differentiating alcoholic liver disease from NASH patients of Caucasian ancestry. The alcoholic liver disease/nonalcoholic fatty liver disease index (ANI) created was found to have good diagnostic capacity compared other previous proposed biomarkers. ANI > 0 was consistent with an alcoholic liver disease diagnosis, while an ANI < 0 was likely due to nonalcoholic fatty liver disease. ANI is not as reliable in cirrhotic patients with Model of End-stage Liver Disease (MELD) score > 20, as well in patients with concomitant alcoholic and NASH disease[84]. A 20-year observational study of patients with uncomplicated hepatic steatosis concluded that 1.2% of non-alcoholic fatty liver disease patients developed cirrhosis compared to 22% of alcoholic fatty liver disease patients[85].

CLINICAL PRESENTATION

Symptoms of alcoholic hepatitis are nonspecific. Patients can experience fatigue, right upper quadrant abdominal pain, anorexia, fever, and weight loss. Development of jaundice may occur in a rapid fashion. Patients with alcoholic hepatitis can develop tender hepatomegaly, ascites, hepatic encephalopathy, upper gastrointestinal bleed, and sarcopenia. Signs of chronic alcohol abuse such as spider angiomata, splenomegaly, palmar erythema, gynecomastia, parotid gland enlargement, testicular atrophy, and Dupuytren's contractures may be present. Characteristic laboratory studies demonstrate a 2:1 aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio with typical values less than 300-400 mg/dL. Serum ALT levels are typically lower than AST in alcoholic hepatitis due to a reduced ALT activity in vitamin B6 depleted hepatocytes and mitochondrial injury causing release of mitochondrial AST[86]. Higher levels of aminotransferases may point towards an additional factor inducing hepatotoxicity (*e.g.*, superimposed ischemic hepatitis, drug induced liver injury, rhabdomyolysis, or acute viral hepatitis). Bilirubin levels can be as high as 30 mg/dL with severe coagulopathy, leukocytosis, anemia, and new onset of renal failure is seen in patients with hepatorenal syndrome[40,87]. Severe alcohol withdrawal can be a life-threatening when patients develop delirium tremens, seizures, coma, and cardiac arrest. Treatment with hemodynamic stabilization, airway protection, and benzodiazepines are necessary[88]. There is a higher prevalence of patients having alcohol withdrawal in alcoholic hepatitis compared to alcoholic cirrhosis[3]. Multiple electrolytic disturbances have been identified in patients with alcoholic hepatitis, such as hypokalemia, hypophosphatemia, and hypomagnesaemia among others. Supplementation with thiamine, folic acid, and correction of glucose, potassium, magnesium, and phosphate is recommended[23].

DIAGNOSIS

Alcoholic hepatitis is mainly a clinical diagnosis. If there is confirmed abstinence for more than 2 mo or the patient reports less than 4 drinks daily on average, alcoholic hepatitis is less likely. Liver biopsy is considered to a gold standard for diagnosis of alcoholic hepatitis, however they are not considered to be routinely performed for AH evaluation in United States. In a review of 11 randomized controlled trials requiring biopsy proven AH, 1409 of 1668 (84.5%) of the liver biopsies confirmed histologic alcoholic hepatitis with increased diagnostic accuracy of 96% when total bilirubin was > 80 μmol/L (> 4.7 mg/dL). The authors concluded that a histologic diagnosis was not necessary for diagnosis and management of AH based on these parameters[89]. Nevertheless, if clinical diagnosis is not clear or appears multifactorial, a liver biopsy can be considered. Caution must be executed when there is severe portal hypertension and coagulopathy. If the benefits outweigh the risks, a transjugular approach can determine the wedge hepatic venous gradient and portal pressures and is recommended when a patient has severe coagulopathy or ascites[90]. Other causes of liver disease, including decompensated alcoholic cirrhosis, sepsis, and biliary obstruction must be ruled out. Abdominal imaging usually shows steatosis and/or cirrhosis with splenomegaly, which is non-specific in alcoholic hepatitis[91].

Cardinal histologic findings of alcoholic hepatitis include ballooning hepatocytes, Mallory-Denk bodies, and neutrophilic infiltration in the setting of macrovesicular steatosis with fibrosis and lobular distortion[92].

MORTALITY PREDICTORS/PROGNOSIS

Clinical scoring systems have been developed to predict outcomes in patients with alcoholic hepatitis and guide treatment. Maddrey's discriminant function, Glasgow score, and MELD score help determine if corticosteroids need to be initiated, while the Lille score evaluates if they need to be continued.

The Maddrey's score incorporates the serum bilirubin and prothrombin time to produce a discriminant function score (DF). A DF > 32 is characterized as severe alcoholic hepatitis and has high short-term mortality of

approximately 50%. Patients with a DF > 32 may benefit from corticosteroid therapy. A DF < 32 is classified as mild or moderate in severity with mortality rate of 10%. Corticosteroid treatment is not beneficial in this patient group[93].

The MELD score predicts mortality in alcoholic hepatitis and survival in cirrhotic patients. MELD score performs as well as the DF in 30-d mortality prediction. Corticosteroid therapy reduces short term mortality in patients with MELD score of > 11 or bilirubin > 8 mg/dL with ascites[94]. A retrospective study determined that an increase in MELD ⩾ 2 within the first week of hospitalization is independently associated with in-hospital mortality[95]. A study by Dunn *et al*[96] found that a MELD ⩾ 21 has a 75% sensitivity and specificity to predict mortality with an estimated 90-d mortality of 20% for patients with this score. A MELD ⩾ 21 can be applied to treatment guidelines for corticosteroid administration.

The Lille score monitors the change in total bilirubin after the first week of corticosteroids to identify the response of patients with severe alcoholic hepatitis. Patients with Lille score > 0.45 indicates poor response to corticosteroids and predicts a 6-mo survival of < 25%. Non-responders are recommended to stop corticosteroids due the risk of infection[97]. Recently, a study showed that Lille score on day 4 was as good as day 7 to predict 90-d mortality and reduces unnecessary steroid exposure[98]. A meta-analysis of five randomized clinical trials with prednisolone treated subjects with severe alcoholic hepatitis showed an improved survival benefit when sub-classified based on Lille score. Complete responders (Lille score ⩽ 0.16), partial responders (Lille score 0.16-0.56), and null responders (Lille score ⩾ 0.56) has 28-d survival rates of 91%, 79% and 53%, respectively. Corticosteroids had a significant effect on 28-d survival in subjects with Lille score ⩽ 0.56[99]. Side effects of steroids include infections, hypokalemia, osteopenia, and weight gain. Fungal infections, especially Aspergillosis are common in the steroid treated group[100].

Another prognostic score is the Glascow alcoholic hepatitis score (GAHS), which incorporates age, serum bilirubin, blood urea nitrogen, prothrombin time, and peripheral white blood cell count. Patients with a DF ⩾ 32 and a GAHS < 9 did not show benefit from treatment with corticosteroids. For those patients with a GAHS ⩾ 9, there was a significant improvement in survival for patients who received corticosteroids. Day 28 survival was 78% for those treated with corticosteroids compared to 52% for the placebo group[101].

Altamirano and his group published the Alcoholic Hepatitis Histologic Score system in order to predict the 90-d mortality. The degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence of megamitochondria were independently associated with 90-d mortality. The factors identified patients with a low (0-3 points), moderate (4-5 points), or high (6-9 points) mortality within 90 d (3%, 19% and 51%, respectively). The disadvantage of this scoring system is that it requires a liver biopsy, which is not routinely performed in the majority of alcoholic hepatitis patients[102].

Factors associated with increased mortality from alcoholic hepatitis include: Older age, acute kidney injury, elevated bilirubin level, coagulopathy, leukocytosis, alcohol consumption > 120 g/d, infection, hepatic encephalopathy, upper gastrointestinal bleed, and bilirubin to gamma glutamyl transferase ratio > 1[103-106].

Metabolomic profiling

Metabolomic profiling is recently constructed to identify biochemical markers in liver-related disease[107]. In a study by Rachakonda *et al*[108], metabolomic profiles were able to differentiate alcoholic cirrhotics *vs* severe alcoholic hepatitis patients with 100% accuracy. The features related to the pathogenesis of alcoholic hepatitis were confirmed by several findings in this study. Severe alcoholic hepatitis was associated with enhanced triglyceride lipolysis, impaired mitochondrial fatty acid beta oxidation, upregulation of omega oxidation, and decreased plasma membrane remodeling. Although there was an increase in measured bile acids found in severe alcoholic hepatitis, intestinal dysbiosis was suggested due to low deoxycholate and glycodeoxycholate levels. Other changes seen in severe alcoholic hepatitis include increased glucose consumption by the pentose phosphate pathway, altered tricarboxylic acid cycle activity, and enhanced peptide catabolism. Altered levels of small molecules related to glutathione metabolism and antioxidant vitamin depletion were observed[108]. Another study performed by Rachakonda *et al*[109] showed that patients with severe alcoholic hepatitis were found to have higher levels of serum resistin and plasma activation inhibitor-1 levels with decreased serum leptin levels. Levels of inflammatory cytokines, such as tumor necrosis factor α, IL-6, IL-8, and IL-15 were higher in patients with severe alcoholic hepatitis. IL-6 levels of ⩾ 38.66 pg/mL were found to have significantly decreased mean survival rates[109].

BIOMARKERS

The development of biomarkers sensitive to the detection of alcoholic hepatitis can be helpful for prognostication. Selected-ion flow tube mass spectrometry breathe testing was able to identify increased levels of acetaldehyde, trimethylamine, acetone, and pentane in patients with alcoholic hepatitis with underlying cirrhosis compared to those with liver cirrhosis and acute decompensation from etiologies other than alcohol. These biomarkers represent breakdown products of ethanol metabolism in alcoholic hepatitis. Given the small sample size, larger studies will need to be performed for validation of results[110].

Other markers, such as procalcitonin, lipopolysaccharide, liver progenitor cell proliferation, soluble TNF receptor 1, microRNA profiling, and IL-22 serum

levels are being studied for clinical application towards prognostication of alcoholic hepatitis[104,111-115].

ABSTINENCE AND MEDICATIONS TO PREVENT RECIDIVISM

The most important primary intervention for alcoholic hepatitis management is abstinence counseling[116]. Abstinence can improve survival in patients with alcoholic liver disease by improving histologic features of hepatocyte injury with reduction of portal hypertension and progression into cirrhosis[5]. Two thirds of patients abstaining from alcohol have significant improvement within 90 d[117]. A 30% decrease in survival rate is seen in patients with compensated cirrhosis who continue to use alcohol compared to those who are abstinent[118,119]. Continued interventions, such as combination psychotherapy with cognitive behavioral therapy, peer driven support counseling, motivational enhancement therapy, and comprehensive medical care can reduce recividism[120]. Risk of recidivism is as high as 67% to 81% over the course of one year[121].

Medications to maintain abstinence have been investigated. FDA approved medications are disulfiram, naltrexone, and acamprosate[122]. Disulfiram was first approved in 1983[123]. Other agents have been explored due to poor tolerability and lack of evidence to support its efficacy[124]. Disulfram is not recommended for use in cirrhotic patients as the literature describes cases of fulminant hepatitis requiring liver transplant[125]. Naltrexone is an opioid antagonist used to decrease alcohol cravings, however it can cause hepatocellular injury[126]. Nalmefene works in a similar mechanism of action to naltrexone, but does not have the risk of hepatocellular injury and has a longer half-life[127]. Acamprosate is structurally similar to gamma amino butyric acid and is associated with reducing alcohol withdrawal symptoms based on 15 controlled trials. As a maintenance medication, it can decrease the relapse rate and relapse severity compared to placebo[128]. In a recent randomized, double-blind study in the United States, there was no evidence of efficacy for acamprosate compared to placebo among alcohol-dependent individuals recruited from a primary care setting[129]. These patients did not receive extensive multidisciplinary counseling. In the COMBINE trial, there was no substantial benefit for patients treated with acamprosate *vs* naltrexone or intensive abstinence counseling. The PREDICT study is a randomized clinical trial conducted in Germany, which compared its data to the COMBINE study. The primary outcome examined the first occurrence of heavy drinking. PREDICT found neither acamprosate nor naltrexone to supply any additional benefit compared with placebo[130].

There are few medication options to prevent recidivism in advanced chronic liver disease. Baclofen is γ aminobutyric acid B-receptor antagonist, which is minimally metabolized in the liver. It is one of the few treatments studied in cirrhotic patients. Addolorato *et al*[131] performed a randomized double-blinded placebo-controlled in alcoholic-dependent cirrhotics with baclofen 10 mg three times daily for 12 wk in the treatment arm. Seventy-one percent of maintained abstinence compared to 29% in the placebo group. Baclofen may be beneficial to achieving and maintaining abstinence safely in Child-Pugh class A, B and C cirrhotic patients[131]. Gamma hydroxyl butyrate may be well tolerated in patients with decompensated cirrhosis with alcohol withdrawal symptoms due to the short half-life of 4-6 h. Further studies need to be performed before recommendations on efficacy and safety can be made[132]. None of the medications discussed have been studied in the context of alcoholic hepatitis and remains a challenge to medical practitioners.

TREATMENT

Nutritional supplementation

Patients with alcoholic hepatitis and cirrhosis have nutritional deficiencies and sarcopenia. Protein calorie malnutrition is associated with short and long term mortality[133]. Vitamin A, Vitamin D, thiamine, pyroxidine, folate, and zinc are common vitamin deficiencies seen in alcoholics[134]. Early studies from the Veterans' Association found 100% of the 363 alcoholic hepatitis patients had protein calorie malnutrition[135]. The degree of malnutrition is associated with the severity of liver disease. AASLD and EASL guidelines recommend enteral nutritional therapy in AH patients, however the evidence remains controversial[2,136]. Moreno *et al*[137] randomized 136 biopsy confirmed severe alcoholic hepatitis patients to receive either intensive enteral nutrition *via* feeding tube plus methylprednisolone or conventional nutrition plus methylprednisolone for 14 d. There is no significant difference in the six-month survival between the groups with 44.4% deaths in the intensive enteral nutrition arm and 53.1% of the controls. The study results were likely affected by being underpowered. The mortality rate at one and six months are lower in the intensive enteral nutrition group compared to the control, but the results are not statistically significant. Of note, 48.5% of the patients had the enteral tube discontinued prematurely. Five patients had serious adverse events related to enteral nutrition, such as aspiration pneumonia, hyperglycemia, and hepatic encephalopathy exacerbation. Nevertheless, this study implies that patients receiving < 21.5 kcal/kg per day have a significantly lower survival rate with increased risk of infection and hepatorenal syndrome at 6 mo compared to those with better nutritional rates. Patients with nutritional requirements of $\geqslant$ 65 g/d of lipids and $\geqslant$ 77.6 g/d of protein have better six-month survival rates[137,138]. Further investigation needs to be pursued to delineate the role of nutrition in AH patients.

Corticosteroids

Patients with mild alcoholic hepatitis (DF < 32) have a 10% mortality rate when not treated with prednisolone.

Supportive care is warranted[139]. Multiple treatment options have been studied, however only prednisolone have remained the mainstay of therapy[91,136]. Corticosteroids have a wide range of immune modulatory functions including suppression of pro-inflammatory transcription factors: NFKB and activator protein 1 (AP-1), which lower circulating levels of TNF-α and IL-8[140,141]. Prednisolone use is indicated in patients with DF > 32 or hepatic encephalopathy, but contraindicated in active infection, gastrointestinal bleeding, acute pancreatitis, or renal failure[142,143].

Studies examining the combination of prednisolone and pentoxifylline treatment produced mixed results[144,145] or showed no added benefit of pentoxifylline[146,147]. The Steroids or Pentoxifylline for Alcoholic Hepatitis trial is the largest randomized clinical trial to date, which examined the short and long term mortality of patients with severe alcoholic hepatitis. Results show no reduction in all cause mortality at 28 d for patients treated with prednisolone or pentoxifylline. However, there is a non-significant mortality benefit at 28 d in the prednisolone treated group, which is not seen at 3 and 12 mo[148]. Corticosteroids may have some benefit within the first month, but cannot be generalized to a provide long term value.

The meta-analysis of 22 randomized clinical trials performed by Singal *et al*[90] show a reduction in short-term mortality in patients with severe alcoholic hepatitis treated with steroids *vs* placebo. Corticosteroids with N-acetylcysteine (NAC) compared to corticosteroids alone may be effective in improving short-term mortality[149]. More recently, Thursz *et al*[150] performed a meta-analysis of 9 randomized clinical trials comparing the use of corticosteroids, pentoxifylline, or both for the treatment of severe alcoholic hepatitis. They found that corticosteroid treatment improved 28 d survival compared to pentoxylline and control group. There is no added benefit of treatment with combination group of corticosteroids and pentoxifylline[151].

Pentoxifylline

Pentoxifylline inhibits tumor necrosis factor, a cytokine responsible for the inflammatory cascade initiation seen in alcoholic hepatitis. One out of four randomized controlled trials showed a mortality rate of 25% in pentoxifylline treated patients with DF > 32 compared with 46% in the placebo group. The benefit seen was mostly to prevent hepatorenal syndrome[151]. It can be an alternative for patients who have contraindications to steroids or early renal failure, however is not recommended as a first line agent.

N-acetylcysteine

Oxidative stress produced from alcoholic hepatitis depletes gluthathione levels. NAC is an antioxidant substance, which is a pro-drug to the precursor of gluthathione. Moreno *et al*[137] produced a randomized clinical trial of NAC *vs* placebo, which shows no significant difference[129]. In 2006, Phillips *et al*[152] found that corticosteroids are superior to NAC for short-term survival. Nguyen-Khac *et al*[153] examined the use of NAC with corticosteroids in a 2011 randomized clinical trial. They found patients with combination therapy have improved one-month survival compared to patients treated with corticosteroids. There are fewer cases of infections and hepatorenal syndrome in the combination treatment arm. Nevertheless, there is no significant difference in survival at 6 mo[153]. Further studies are needed to evaluate the efficacy of NAC.

Other anti-TNF alpha inhibitors

Anti-TNF alpha inhibitors, such as infliximab and etanercept is not recommended for the treatment of alcoholic hepatitis. Although early pilot studies of corticosteroids and infliximab show an improvement in the Maddrey score within the first month, later studies have shown anti-TNF alpha inhibitors are associated with increased death from infections[113,154,155].

Liver transplantation

Liver transplantation may be considered as a last option for patients with alcoholic hepatitis when medical treatment has failed or is contraindicated. Most liver transplant centers require a minimum abstinence of six months prior to donor allocation consideration. Given the donor organ scarcity, the risk of recividism is feared for patients with alcoholic hepatitis undergoing liver transplantation[156].

Data regarding the 6-mo rule as a predictor of long-term sobriety remains controversial[157]. Based on a systematic review, there is no difference in early alcohol use in patients transplanted for alcoholic liver disease *vs* non-alcoholic liver disease at: 6 mo (4% *vs* 5%) and 12 mo (17% *vs* 16%). At 7 years post-OLT, 32% of the patients with alcoholic liver disease reports using alcohol. Although comparable rates of any alcohol use are reported in patients transplanted for alcoholic liver disease and non-alcoholic liver disease, the risk of heavy drinking appears much higher in alcoholic liver disease patients[158]. There is a wide variation among post-liver transplant alcohol relapse rates reported in the literature, ranging from 20% to 50%. Heavy drinking rates range from 10% to 20%[159]. The duration of pre-transplant abstinence does not appear to correlate with post-transplant survival[160], however studies for long term follow-up of the graft in patients transplanted for alcoholic hepatitis with continued alcohol abuse requires further investigation.

Mathurin *et al*[161] reports the results of a multicenter European trial which carefully selected corticosteroid refractory AH patients whom were deemed to have a low risk of recividism after liver transplantation. The episode of AH is deemed as the patient's first liver decompensating event. Other inclusion criteria includes: Close and supportive family members, absence of severe coexisting or psychiatric disorders, and a covenant to adhere to life-long alcohol abstinence. The study reports

no alcoholic relapse within the initial 6-mo follow-up period. Three of 26 patients transplanted for refractory alcoholic hepatitis later resumed drinking alcohol: One at 720 d, one at 740 d, and one at 1140 d after transplantation. Despite counseling by an addiction specialist, 2 patients remained daily consumers (30 g/d and > 50 g/d), whereas 1 consumed alcohol occasionally (approximately 10 g/wk). None of them had graft dysfunction[161].

Im *et al*[162] applied inclusion criteria similar to Mathurin's European trial for early liver transplantation in severe alcoholic hepatitis in the United States. The low candidate acceptance rate (20%) and the high survival rates for transplanted AH patients compared to controls (89% *vs* 11%) is comparable to the findings in Mathurin's study. Two patients (25%) had alcohol use post OLT. One patient self-reported a "slip" of 60 g and 15 g of alcohol use at day 84 and 260, respectively. Serial urine ethanol testing and self-reporting were negative thereafter. One patient had alcohol relapse, which is defined as: Four or more drinks daily or at least one drink for 4 or more days in succession after liver transplantation. When the subject with alcohol relapse was further analyzed, it was deemed that the hepatic decompensation was not the patient's first event and the subject had poor insight to disease prior to transplant. Limitations to the study include small sample size (n = 9) and short follow-up period (median = 765 d)[162].

A three-year pilot by Lee examined 2 groups of patients selected to receive a liver transplant: Severe alcoholic hepatitis as the first episode of liver decompensation *vs* alcoholic cirrhotics with ⩾ 6 mo of abstinence. Early liver transplant provided excellent short-term survival in both groups. There were similar rates of alcohol relapse in both groups: 23.5% *vs* 29.2%. Although lacking statistical significance, patients transplanted for AH had higher rates of harmful drinking post-transplant compared to the control group (23.5% *vs* 11.5%, P = 0.42). The data was particularly concerning given the two out of the four patients with harming drinking patterns died secondary to recurrent alcohol use (alcohol overdose and medication noncompliance with graft failure, respectively)[163].

Although preliminary results may appear promising, ethical issues pertaining to organ shortage, sociocultural concerns about judicious organ allotment, and recividism risk remain[164]. The feasibility of patient selection through strict psychosocial assessment is limited by resources. An addiction psychiatrist experienced in liver transplant may not be readily available in all centers. Liver transplantation for refractory severe acute alcoholic hepatitis should be judiciously employed in highly selected individuals who are at low risk of recidivism[165].

New therapeutic options for alcoholic hepatitis are needed. Corticosteroid use are helpful in 50% of cases, however they are associated with a higher rate of infections and do not offer long term survival benefit. Treatments targeting gut dysbiosis, innate immunity, inflammation pathways, and apoptosis are currently being studied (Table 1).

NEW THERAPEUTIC OPTIONS

Gut microbiota modification: Probiotics

Animal studies mimicking alcoholic hepatitis have observed changes in microbial translocation and dysbiosis[166]. Patients with alcoholic hepatitis have abnormalities in bacterial overgrowth, intestinal mucosal damage, increased gut permeability with bacterial translocation, and resulting endotoxemia[167]. The use of probiotics to modify gut bacteria are studied for the treatment of alcoholic hepatitis. Animals studies by Wang *et al*[168] concludes *Lactobacillus* rhamnosus treatment reduced alcohol-induced hepatic inflammation by attenuation of TNF-α production *via* inhibition of TLR-4 and TLR-5 mediated endotoxin activation. A pilot study with mild alcoholic hepatitis patients who received *Bifidobacterium bifidum* and *Lactobacillus plantarum 8PA3* for five days shows significantly reduced ALT, AST, lactate dehydrogenase, total bilirubin, and restoration of gut flora compared to placebo. Other studies have showed that alcoholic cirrhotics have cytokine reduction with reduced liver disease severity and hospitalization when treated with probiotic VSL#3[169,170]. Rifaximin is studied for the role of bacterial overgrowth in decompensated alcoholic cirrhotics. Rifamixin administered for 28 d decreased endotoxemia in the systemic and splenic circulation with reduction in portal hypertension. Currently, there are clinical trials examining the role of Lactobacillus rhamnosus, rifaximin, fecal microbiota transplantation, and antibiotics in AH patients[99].

Immune modulators

Chronic ethanol stimulation increases the production of inflammatory cytokines and chemokines to induce liver injury. Multiple mechanisms are proposed to modulate the innate immune system. It is not clear if animal and cellular models can be extrapolated for use in humans. Based on animal studies, IL-22 is a hepatoprotective cytokine. Chronic-binge ethanol fed mice treated with recombinant IL-22 protein induced activation of hepatic STAT3 to prevent alcohol-induced steatosis, liver injury, and oxidative stress in a study by Ki *et al*[12]. IL-22 down regulates the expression of fatty acid transport protein. It is found to have antioxidant, apoptotic, proliferative, and antimicrobial properties with minimal side effects[11]. IL-17 levels produced by TH17 cells are elevated in patients with alcoholic hepatitis. IL-17 induces neutrophil recruitment and stimulates hepatic stellate cells to secrete chemokines, such as IL-8 and CXCL[171,172]. Alcoholic hepatitis patients with expression of these chemokines in the liver are correlated with worsening severity of portal hypertension and patient survival[173,174]. Therapeutic agents targeting the reduction of CXCL and IL-17 with IL-22 upregulation can be a new treatment

Table 1 New potential treatments for alcoholic hepatitis

Treatment	Class	Mechanism of action
Probiotics	Gut microbiota modification	Reduction of bacterial endotoxins and translocation
IL-22 recombinant protein	Immune modulation	Hepatoprotective: Antioxidant, apoptotic, proliferative, and antimicrobial properties
G-CSF	Growth factor	Liver regeneration
Obeticholic acid	Farnesoid X receptor	Improvement in cholestasis
Emricasan	Caspase inhibitor	Apoptosis, inflammation, and fibrosis inhibitor
Anakinra (Pentoxifylline + Zinc)	IL-1 receptor	Decreases hepatic inflammation
SAMe	Glutathione precursor	Decreases oxidative stress
Metadoxine	Antioxidant	Decreases oxidative stress and steatosis
ELAD	Extracorporeal human hepatic cell-based liver treatment	Toxin removal, reduction of inflammation, liver regeneration

IL: Interleukin; G-CSF: Granulocyte colony-stimulating factor; ELAD: Extracorporeal liver assist device; SAMe: S-adenosil-L-methionine.

strategy[54,175].

Liver regeneration: Granulocyte colony-stimulating factor

Bone marrow-derived stem cells can populate the liver and differentiate into hepatic cells when faced with liver insult. Experimental studies show that granulocyte colony-stimulating factor (G-CSF) promote the mobilization of bone marrow stem cells to ameliorate liver injury and enhance the proliferative capacity of hepatocytes[176]. G-CSF mobilizes CD 34+ cells, increases hepatocyte growth factor, and induces proliferation of hepatic progenitor cells within 7 d of administration in patients with alcoholic cirrhosis with biopsy proven alcoholic steatohepatitis[177]. In a pilot study, 46 patients with severe alcoholic hepatitis were randomized to receive G-CSF $\geqslant$ 5 μg/kg for 5 d with standard medical therapy (pentoxifylline with nutrition) *vs* standard medical therapy alone. Findings shows a statistically significant number of peripheral CD 34+ cells and improvement of Child Pugh score, MELD, and discriminant function for up to 3 mo in the G-CSF group. Ninety day survival benefit is seen in G-CSF group compared to placebo[178]. The addition of corticosteroids would be helpful in delineating the survival benefit. A clinical trial testing the efficacy of G-CSF in the management of patients with severe alcoholic hepatitis whom have failed corticosteroids is needed.

FXR/obeticholic acid

FXRs are nuclear hormone receptors that participate in bilirubin metabolism. Bile acids are the physiologic ligands of FXRs, which regulate bile acid, carbohydrate, and lipid metabolism. In addition, they modulate liver regeneration after injury. FXR activation is protective against cholestatic and fatty liver injury. In a murine model, mice were fed an ethanol or control diet. FXR impairment is exhibited in the ethanol group. FXR agonist therapy is found to be hepatoprotective, likely from suppression of microsomal CYP2E1 enzyme upregulation[179]. FXR activation is shown in other studies to prevent and improve liver fibrosis in mice[180,181].

Obeticholic acid is a selective FXR. A phase 2 clinical trials shows obeticholic acid improved insulin sensitivity and markers of liver inflammation in patients with diabetes and nonalcoholic fatty liver disease. Phase 2 clinical trials are exploring obeticholic acid in patients with alcoholic hepatitis.

Caspase inhibitors

Alcohol exposure causes hepatocytes to release extracellular vesicles in a caspase-dependent manner to elicit apoptosis and macrophage activation[182]. Apoptosis may trigger abnormal liver tissue repair, inflammation, regeneration, and fibrosis[183]. Caspase inhibitors may decrease apoptosis and inflammation in a variety of liver diseases. Emricasan is a pan-capsase inhibitor studied in patients with hepatitis C and NASH. In clinical trials, emricasan significantly reduces the aminotransferase activity in non-cirrhotic hepatitis C patients. Similar trends are observed in patients with NASH and hepatitis B, however statistical analysis was not performed on these groups[184]. In NASH studies, mice fed a high fat diet demonstrates a five-fold increase in hepatic apoptosis and 1.5-fold and 1.3-fold increase in caspase-3 and -8, respectively. Mice with emricasan administration demonstrates a reduction in inflammation and fibrosis compared to placebo. Based on the positive preliminary data found in murine NASH models, clinical trials evaluating emricasan for benefit in patients with alcoholic liver disease are ongoing. Thus far, a phase 2 clinical trial concluded that Child Pugh A and B cirrhotic patients with baseline MELD $\geqslant$ 15 who are treated with emricasan showed significant improvement compared to placebo in MELD scores, Child-Pugh scores, bilirubin levels, and INR in preliminary data[185].

Combination therapy: Anakinra-blocks IL-1 beta receptor, pentoxifylline and zinc vs methylprednisolone

Alcohol-induced liver injury activates Kupffer cells, which stimulation production of inflammasomes and IL-1β, which initiate the inflammatory cascade. Effects include liver inflammation, steatosis, injury, and fibrogenesis. Pharmacological inhibition of IL-1 signaling has a hepatoprotective effect. There was recovery from acute-on-chronic alcoholic liver injury[186]. Anakinra, an IL-1

receptor antagonist combined with pentoxifylline and zinc is being studied in phase 2 and 3 clinical trials to examined the efficacy against corticosteroids.

S-adenosil-L-methionine

S-adenosil-L-methionine (SAMe) is a direct precursor of glutathione, which serves as a major physiologic defense mechanism against oxidative stress. A recent pilot study randomized two groups of twenty patients each with severe alcoholic hepatitis treated with prednisolone 40 mg daily *vs* prednisolone 40 mg with intravenous SAMe 800 mg for 28 d. After the first week, intravenous SAMe regimen was converted to oral doses of 1200 mg/d for two months. The response rate measured by the Lille's score is significantly improved in the prednisolone and SAMe (95% of patients) compared to the prednisolone only group (65%). Hepatorenal syndrome occurred in 20% patients in the prednisolone group, but none in the combination treatment group. Difference between the groups regarding 28-d mortality could not be inferred. Although not statistically significant, the six-month survival rate is 90% in the prednisolone plus SAMe group *vs* 75% in the prednisolone group. Larger trials are needed to validate the study results[187].

Metadoxine

Metadoxine is an antioxidant, which aids in gluthathione metabolism and inhibits hepatic steatosis[188]. The addition of metadoxine with corticosteroids is found to improve 30 and 90 d survival rates. The metadoxine and corticosteroid group is found to have a better treatment response based on Lille's score, lower rates of hepatorenal syndrome, and decreased development and/or progression of hepatic encephalopathy compared to the corticosteroid group. There are no significant adverse side effects[189]. Another study combined metadoxine with either prednisone or pentoxifylline for 30 d. The group receiving metadoxine combined with prednisolone or pentoxifylline had increased three and six-month survival rate of 50% compared to the 20% survival rate in the prednisolone or prednisone only group. The rates of hepatorenal syndrome and hepatic encephalopathy development are significantly less in the metadoxine group, however infections are not[190]. Additional studies with a greater sample size are needed to increase the power of future studies.

ELAD

There are ongoing Phase 3 clinical trials of ELAD for acute severe alcoholic hepatitis[191]. Patients with acute renal failure, severe coagulopathy, and MELD > 28 have worse outcomes with ELAD. There are no survival differences between the ELAD over the control group in day 28 and 91. Pre-specified exploratory analysis of 101 patients < age 47 showed an improved 3-mo survival in the ELAD group compared to the control group (81.4% *vs* 67.2%). When analyzed for patients less than 50 years old, creatinine < 1.3 mg/dL, bilirubin $\geqslant$ 16 mg/dL, and INR $\leqslant$ 2.5, the 3-mo survival rate was 94% in the ELAD group and 68% in the control group. The most recent ELAD trial, VTL-308 incorporates the new inclusion and exclusion criteria[192]. The preliminary results are eagerly awaited. There are limitations to the use of ELAD, including high cost and stringent inclusion criteria. Patients are usually monitored in the intensive care use with frequent monitoring and blood draws. Currently, there are limited centers performing ELAD research and the patient selection criteria excludes: Alcohol use > 6 wk, persons > 50 years old, severe coagulopathy, and advanced renal failure.

Many therapies have been studied for alcoholic hepatitis without proven efficacy. Treatment with antioxidants, including vitamin E and silymarin do not have a survival benefit in alcoholic hepatitis or cirrhosis patients. Colchicine, amlodipine, propylthiouracil, anabolic steroids, and insulin and glucagon combinations are not effective in patients with alcoholic hepatitis[45].

FUTURE RESEARCH

Most of the understanding of alcoholic liver disease pathogenesis stem from animal models of alcoholic liver disease recreated *via* ad libitum or intragastric ethanol feeding. Recent publications propose a new model of ad libitum feeding with 40% intake of caloric intake from a Western diet high in cholesterol and saturated fat combined with 60% ethanol *via* intragastric infusion to simulate a "true" model of alcohol hepatitis, where contributing factors such as obesity and alcohol abuse are taken into account. This model recreates findings seen in chronic alcoholic liver disease with superimposed alcoholic hepatitis when a weekly binge dose of ethanol is added. However, the model could not emulate the acute-on-chronic hepatic decompensation seen in alcoholic hepatitis[193,194]. The search for molecular targets through genomic studies holds the future direction of answering unsolved questions about alcoholic hepatitis pathogenesis. Further study of IL-22's antioxidant, anti-apoptotic, anti-steatosis, antibacterial, proliferative effect, and other hepatoprotective properties in conjunction with the inflammatory and immunomodulatory function of corticosteroids is underway[12,195]. Recent literature highlights the use of biospecimens (*i.e.*, liver tissue, peripheral serum, stool) for *in vitro* and *in vivo* studies as a new approach to finding targets for therapy[194]. New findings eludicated under such methods, include impaired bacterial killing from monocyte oxide burst dysfunction and defective T cell function in AH subjects. Although the reversal of defective monocyte oxidative burst is not restored by the IFN-gamma, the negative regulator of Janus Kinase responsible for suppressing cytokine signalling-1 was discovered to have increased expression[46]. Restoration of T-cell interferon gamma production, reduction in production of IL-10 producing T cells, and improvement in neutrophil antibacterial function occurs when antibodies against PD1 and TIM3

are blocked[47].

CONCLUSION

Alcoholic hepatitis is increasingly recognized as a form of acute-on-chronic liver failure in patients with underlying alcohol-related disease[196,197]. Patients with severe alcoholic hepatitis remain a challenging population to treat. New treatment options for AH involving gut microbiota modification, immune modulation, promotion of liver regeneration, apoptosis inhibitors, farnesoid receptors, and ELAD appear promising thus far, however the research is still in the preliminary phases. Currently, early liver transplantation for severe AH failing standard medical therapy is not universally implemented and further investigation is warranted. Solving the complex pathophysiology of alcoholic hepatitis through translational studies with clinical application is challenging. The study of new animal model simulating "true" AH and use of genomic analysis to provide molecular targets are emerging into present day practice. The utilization of clinical trials fuelled by constant evolving concepts discovered *via* translational research will help determine the endpoints and safety of the new therapeutic options to bridge the gap of a disease with high morbidity and mortality.

REFERENCES

1 **Mandayam S**, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. *Semin Liver Dis* 2004; **24**: 217-232 [PMID: 15349801 DOI: 10.1055/s-2004-832936]
2 **Becker U**, Deis A, Sørensen TI, Grønbaek M, Borch-Johnsen K, Müller CF, Schnohr P, Jensen G. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. *Hepatology* 1996; **23**: 1025-1029 [PMID: 8621128 DOI: 10.1002/hep.510230513]
3 **Barrio E**, Tomé S, Rodríguez I, Gude F, Sánchez-Leira J, Pérez-Becerra E, González-Quintela A. Liver disease in heavy drinkers with and without alcohol withdrawal syndrome. *Alcohol Clin Exp Res* 2004; **28**: 131-136 [PMID: 14745311 DOI: 10.1097/01.ALC.0000106301.39746.EB]
4 **Naveau S**, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. *Hepatology* 1997; **25**: 108-111 [PMID: 8985274 DOI: 10.1002/hep.510250120]
5 **O'Shea RS**, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Am J Gastroenterol* 2010; **105**: 14-32; quiz 33 [PMID: 19904248 DOI: 10.1038/ajg.2009.593]
6 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]
7 **Crabb DW**, Bataller R, Chalasani NP, Kamath PS, Lucey M, Mathurin P, McClain C, McCullough A, Mitchell MC, Morgan TR, Nagy L, Radaeva S, Sanyal A, Shah V, Szabo G. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology* 2016; **150**: 785-790 [PMID: 26921783 DOI: 10.1053/j.gastro.2016.02.042]
8 **Li TK**. Quantifying the risk for alcohol-use and alcohol-attributable health disorders: present findings and future research needs. *J Gastroenterol Hepatol* 2008; **23** Suppl 1: S2-S8 [PMID: 18336658 DOI: 10.1111/j.1440-1746.2007.05298.x]
9 **Bellentani S**, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, Saveria Crocè L, Sasso F, Pozzato G, Cristianini G, Brandi G. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. *Gut* 1997; **41**: 845-850 [PMID: 9462221 DOI: 10.1136/gut.41.6.845]
10 **Zakhari S**, Li TK. Determinants of alcohol use and abuse: Impact of quantity and frequency patterns on liver disease. *Hepatology* 2007; **46**: 2032-2039 [PMID: 18046720 DOI: 10.1002/hep.22010]
11 **Hatton J**, Burton A, Nash H, Munn E, Burgoyne L, Sheron N. Drinking patterns, dependency and life-time drinking history in alcohol-related liver disease. *Addiction* 2009; **104**: 587-592 [PMID: 19215600 DOI: 10.1111/j.1360-0443.2008.02493.x]
12 **Ki SH**, Park O, Zheng M, Morales-Ibanez O, Kolls JK, Bataller R, Gao B. Interleukin-22 treatment ameliorates alcoholic liver injury in a murine model of chronic-binge ethanol feeding: role of signal transducer and activator of transcription 3. *Hepatology* 2010; **52**: 1291-1300 [PMID: 20842630 DOI: 10.1002/hep.23837]
13 **Sandahl TD**, Jepsen P, Thomsen KL, Vilstrup H. Incidence and mortality of alcoholic hepatitis in Denmark 1999-2008: a nationwide population based cohort study. *J Hepatol* 2011; **54**: 760-764 [PMID: 21126790 DOI: 10.1016/j.jhep.2010.07.016]
14 **Jinjuvadia R**, Liangpunsakul S. Trends in Alcoholic Hepatitis-related Hospitalizations, Financial Burden, and Mortality in the United States. *J Clin Gastroenterol* 2015; **49**: 506-511 [PMID: 25198164 DOI: 10.1097/MCG.0000000000000161]
15 **French SW**, Morimoto K TH. Animal models of alcohol-associated liver injury. Alcoholic Liver Disease, Pathology and Pathogenesis. London: Hodder Headline, 1995
16 **Lieber CS**. Metabolism of alcohol. *Clin Liver Dis* 2005; **9**: 1-35 [PMID: 15763227 DOI: 10.1016/j.cld.2004.10.005]
17 **Berg JM**, Tymoczko JL. Section 30.5, Ethanol Alters Energy Metabolism in the Liver. In: Freeman W. Biochemistry. New York, 2002
18 **You M**, Crabb DW. Recent advances in alcoholic liver disease II. Minireview: molecular mechanisms of alcoholic fatty liver. *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G1-G6 [PMID: 15194557 DOI: 10.1152/ajpgi.00056.2004]
19 **Reed WD**, Clinkenbeard D, Lane MD. Molecular and catalytic properties of mitochondrial (ketogenic) 3-hydroxy-3-methylglutaryl coenzyme A synthase of liver. *J Biol Chem* 1975; **250**: 3117-3123 [PMID: 804485]
20 **Fischer M**, You M, Matsumoto M, Crabb DW. Peroxisome proliferator-activated receptor alpha (PPARalpha) agonist treatment reverses PPARalpha dysfunction and abnormalities in hepatic lipid metabolism in ethanol-fed mice. *J Biol Chem* 2003; **278**: 27997-28004 [PMID: 12791698 DOI: 10.1074/jbc.M302140200]
21 **You M**, Matsumoto M, Pacold CM, Cho WK, Crabb DW. The role of AMP-activated protein kinase in the action of ethanol in the liver. *Gastroenterology* 2004; **127**: 1798-1808 [PMID: 15578517]
22 **Ji C**, Chan C, Kaplowitz N. Predominant role of sterol response element binding proteins (SREBP) lipogenic pathways in hepatic steatosis in the murine intragastric ethanol feeding model. *J Hepatol* 2006; **45**: 717-724 [PMID: 16879892 DOI: 10.1016/j.jhep.2006.05.009]
23 **Friel PN**, Baer JS, Logan BK. Variability of ethanol absorption and breath concentrations during a large-scale alcohol administration study. *Alcohol Clin Exp Res* 1995; **19**: 1055-1060 [PMID: 7485816]
24 **Viitala K**, Makkonen K, Israel Y, Lehtimäki T, Jaakkola O, Koivula T, Blake JE, Niemelä O. Autoimmune responses against oxidant stress and acetaldehyde-derived epitopes in human alcohol consumers. *Alcohol Clin Exp Res* 2000; **24**: 1103-1109 [PMID: 10924016]
25 **Tuma DJ**, Casey CA. Dangerous byproducts of alcohol breakdown--focus on adducts. *Alcohol Res Health* 2003; **27**: 285-290 [PMID: 15540799]
26 **Chayanupatkul M**, Liangpunsakul S. Alcoholic hepatitis: a comprehensive review of pathogenesis and treatment. *World J Gastroenterol* 2014; **20**: 6279-6286 [PMID: 24876748 DOI: 10.3748/wjg.v20.i20.6279]
27 **Luedde T**, Kaplowitz N, Schwabe RF. Cell death and cell death responses in liver disease: mechanisms and clinical relevance. *Gastroenterology* 2014; **147**: 765-783.e4 [PMID: 25046161 DOI: 10.1053/j.gastro.2014.07.018]

28 **Lieber CS**. Microsomal ethanol-oxidizing system (MEOS): the first 30 years (1968-1998)--a review. *Alcohol Clin Exp Res* 1999; **23**: 991-1007 [PMID: 10397283]

29 **Masalkar PD**, Abhang SA. Oxidative stress and antioxidant status in patients with alcoholic liver disease. *Clin Chim Acta* 2005; **355**: 61-65 [PMID: 15820479 DOI: 10.1016/j.cccn.2004.12.012]

30 **Malhi H**, Kaufman RJ. Endoplasmic reticulum stress in liver disease. *J Hepatol* 2011; **54**: 795-809 [PMID: 21145844 DOI: 10.1016/j.jhep.2010.11.005]

31 **Cooper G**. The Endoplasmic Reticulum. In: The Cell: A Molecular Approach. Sunderland: Sinauer Asssociates, 2000

32 **Ji C**, Deng Q, Kaplowitz N. Role of TNF-alpha in ethanol-induced hyperhomocysteinemia and murine alcoholic liver injury. *Hepatology* 2004; **40**: 442-451 [PMID: 15368449 DOI: 10.1002/hep.20309]

33 **Petrasek J**, Iracheta-Vellve A, Csak T, Satishchandran A, Kodys K, Kurt-Jones EA, Fitzgerald KA, Szabo G. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. *Proc Natl Acad Sci USA* 2013; **110**: 16544-16549 [PMID: 24052526 DOI: 10.1073/pnas.1308331110]

34 **Crabb DW**, Liangpunsakul S. Alcohol and lipid metabolism. *J Gastroenterol Hepatol* 2006; **21** Suppl 3: S56-S60 [PMID: 16958674 DOI: 10.1111/j.1440-1746.2006.04582.x]

35 **Hernández-Gea V**, Hilscher M, Rozenfeld R, Lim MP, Nieto N, Werner S, Devi LA, Friedman SL. Endoplasmic reticulum stress induces fibrogenic activity in hepatic stellate cells through autophagy. *J Hepatol* 2013; **59**: 98-104 [PMID: 23485523 DOI: 10.1016/j.jhep.2013.02.016]

36 **Yin M**, Bradford BU, Wheeler MD, Uesugi T, Froh M, Goyert SM, Thurman RG. Reduced early alcohol-induced liver injury in CD14-deficient mice. *J Immunol* 2001; **166**: 4737-4742 [PMID: 11254735]

37 **Gao B**, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; **141**: 1572-1585 [PMID: 21920463 DOI: 10.1053/j.gastro.2011.09.002]

38 **Michelena J**, Altamirano J, Abraldes JG, Affò S, Morales-Ibanez O, Sancho-Bru P, Dominguez M, García-Pagán JC, Fernández J, Arroyo V, Ginès P, Louvet A, Mathurin P, Mehal WZ, Caballería J, Bataller R. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology* 2015; **62**: 762-772 [PMID: 25761863 DOI: 10.1002/hep.27779]

39 **Bautista AP**. Impact of alcohol on the ability of Kupffer cells to produce chemokines and its role in alcoholic liver disease. *J Gastroenterol Hepatol* 2000; **15**: 349-356 [PMID: 10824877]

40 **Louvet A**, Mathurin P. Alcoholic liver disease: mechanisms of injury and targeted treatment. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 231-242 [PMID: 25782093 DOI: 10.1038/nrgastro.2015.35]

41 **Blackmore LJ**, Ryan JM, Huang X, Hussain M, Triantafyllou E, Vergis N, Vijay GM, Antoniades CG, Thursz MR, Jassem W, Vergani D, Shawcross DL, Ma Y. Acute alcoholic hepatitis and cellular Th1 immune responses to alcohol dehydrogenase. *Lancet* 2015; **385** Suppl 1: S22 [PMID: 26312844 DOI: 10.1016/S0140-6736(15)60337-3]

42 **Laso FJ**, Lapeña P, Madruga JI, San Miguel JF, Orfao A, Iglesias MC, Alvarez-Mon M. Alterations in tumor necrosis factor-alpha, interferon-gamma, and interleukin-6 production by natural killer cell-enriched peripheral blood mononuclear cells in chronic alcoholism: relationship with liver disease and ethanol intake. *Alcohol Clin Exp Res* 1997; **21**: 1226-1231 [PMID: 9347083]

43 **Mandrekar P**, Ambade A, Lim A, Szabo G, Catalano D. An essential role for monocyte chemoattractant protein-1 in alcoholic liver injury: regulation of proinflammatory cytokines and hepatic steatosis in mice. *Hepatology* 2011; **54**: 2185-2197 [PMID: 21826694 DOI: 10.1002/hep.24599]

44 **Sheron N**, Bird G, Koskinas J, Portmann B, Ceska M, Lindley I, Williams R. Circulating and tissue levels of the neutrophil chemotaxin interleukin-8 are elevated in severe acute alcoholic hepatitis, and tissue levels correlate with neutrophil infiltration. *Hepatology* 1993; **18**: 41-46 [PMID: 8325620]

45 **Taïeb J**, Delarche C, Paradis V, Mathurin P, Grenier A, Crestani B, Dehoux M, Thabut D, Gougerot-Pocidalo MA, Poynard T, Chollet-Martin S. Polymorphonuclear neutrophils are a source of hepatocyte growth factor in patients with severe alcoholic hepatitis. *J Hepatol* 2002; **36**: 342-348 [PMID: 11867177]

46 **Vergis N**, Khamri W, Beale K, Sadiq F, Aletrari MO, Moore C, Atkinson SR, Bernsmeier C, Possamai LA, Petts G, Ryan JM, Abeles RD, James S, Foxton M, Hogan B, Foster GR, O'Brien AJ, Ma Y, Shawcross DL, Wendon JA, Antoniades CG, Thursz MR. Defective monocyte oxidative burst predicts infection in alcoholic hepatitis and is associated with reduced expression of NADPH oxidase. *Gut* 2017; **66**: 519-529 [PMID: 26860769 DOI: 10.1136/gutjnl-2015-310378]

47 **Markwick LJ**, Riva A, Ryan JM, Cooksley H, Palma E, Tranah TH, Manakkat Vijay GK, Vergis N, Thursz M, Evans A, Wright G, Tarff S, O'Grady J, Williams R, Shawcross DL, Chokshi S. Blockade of PD1 and TIM3 restores innate and adaptive immunity in patients with acute alcoholic hepatitis. *Gastroenterology* 2015; **148**: 590-602.e10 [PMID: 25479137 DOI: 10.1053/j.gastro.2014.11.041]

48 **Ceni E**, Mello T, Galli A. Pathogenesis of alcoholic liver disease: role of oxidative metabolism. *World J Gastroenterol* 2014; **20**: 17756-17772 [PMID: 25548474 DOI: 10.3748/wjg.v20.i47.17756]

49 **Frenzer A**, Butler WJ, Norton ID, Wilson JS, Apte MV, Pirola RC, Ryan P, Roberts-Thomson IC. Polymorphism in alcohol-metabolizing enzymes, glutathione S-transferases and apolipoprotein E and susceptibility to alcohol-induced cirrhosis and chronic pancreatitis. *J Gastroenterol Hepatol* 2002; **17**: 177-182 [PMID: 11966948]

50 **Monzoni A**, Masutti F, Saccoccio G, Bellentani S, Tiribelli C, Giacca M. Genetic determinants of ethanol-induced liver damage. *Mol Med* 2001; **7**: 255-262 [PMID: 11471570]

51 **Frezza M**, di Padova C, Pozzato G, Terpin M, Baraona E, Lieber CS. High blood alcohol levels in women. The role of decreased gastric alcohol dehydrogenase activity and first-pass metabolism. *N Engl J Med* 1990; **322**: 95-99 [PMID: 2248624 DOI: 10.1056/NEJM199001113220205]

52 **Shibuya A**, Yoshida A. Genotypes of alcohol-metabolizing enzymes in Japanese with alcohol liver diseases: a strong association of the usual Caucasian-type aldehyde dehydrogenase gene (ALDH1(2)) with the disease. *Am J Hum Genet* 1988; **43**: 744-748 [PMID: 3189338]

53 **Sato N**, Lindros KO, Baraona E, Ikejima K, Mezey E, Järveläinen HA, Ramchandani VA. Sex difference in alcohol-related organ injury. *Alcohol Clin Exp Res* 2001; **25**: 40S-45S [PMID: 11391047]

54 **Zintzaras E**, Stefanidis I, Santos M, Vidal F. Do alcohol-metabolizing enzyme gene polymorphisms increase the risk of alcoholism and alcoholic liver disease? *Hepatology* 2006; **43**: 352-361 [PMID: 16440362 DOI: 10.1002/hep.21023]

55 **Arsene D**, Farooq O, Bataller R. New therapeutic targets in alcoholic hepatitis. *Hepatol Int* 2016; **10**: 538-552 [PMID: 27072540 DOI: 10.1007/s12072-015-9701-6]

56 **Chamorro AJ**, Torres JL, Mirón-Canelo JA, González-Sarmiento R, Laso FJ, Marcos M. Systematic review with meta-analysis: the I148M variant of patatin-like phospholipase domain-containing 3 gene (PNPLA3) is significantly associated with alcoholic liver cirrhosis. *Aliment Pharmacol Ther* 2014; **40**: 571-581 [PMID: 25060292 DOI: 10.1111/apt.12890]

57 **Atkinson S**. GS03 a genome-wide association study identifies PNPLA3 and SLC38A4 as risk loci for alcoholic hepatitis. *J Hepatol* 2015; **64**: S134 [DOI: 10.1016/S0168-8278(16)01634-2]

58 **Chalasani NP**, Shah V, Sanyal AJ, Liangpunsakal S, Tang Q, Comerford M, Puri P, Radaeva S, Katz BCD. Acute Alcoholic Hepatitis in the United States: Clinical Characteristics, Outcomes and Relationship with PNPLA3 Genotype and Coffee Drinking. In: American College of Gastroenterology Annual Scientific Meeting. Las Vegas, 2016

59 **Diehl AM**. Obesity and alcoholic liver disease. *Alcohol* 2004; **34**: 81-87 [PMID: 15670669 DOI: 10.1016/j.alcohol.2004.07.010]

60 **Trembling PM**, Apostolidou S, Parkes J, Ryan A, Gentry-Maharaj A, Tanwar S, Menon U, Rosenberg WM. Influence of bmi and

alcohol on liver-related morbidity and mortality in a cohort of 108,000 women from the general population from UKCTOCS. *J Hepatol* 2013; **58**: S51-52 [DOI: 10.1016/S0168-8278(13)60117-8]
61 **Corrao G**, Aricò S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology* 1998; **27**: 914-919 [PMID: 9537428 DOI: 10.1002/hep.510270404]
62 **Fletcher LM**, Dixon JL, Purdie DM, Powell LW, Crawford DH. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002; **122**: 281-289 [PMID: 11832443]
63 **Novo-Veleiro I**, Alvela-Suárez L, Chamorro AJ, González-Sarmiento R, Laso FJ, Marcos M. Alcoholic liver disease and hepatitis C virus infection. *World J Gastroenterol* 2016; **22**: 1411-1420 [PMID: 26819510 DOI: 10.3748/wjg.v22.i4.1411]
64 **Armstrong GL**, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705-714 [PMID: 16702586]
65 **Tsui JI**, Pletcher MJ, Vittinghoff E, Seal K, Gonzales R. Hepatitis C and hospital outcomes in patients admitted with alcohol-related problems. *J Hepatol* 2006; **44**: 262-266 [PMID: 16226823 DOI: 10.1016/j.jhep.2005.07.027]
66 **Chen CM**, Yoon YH, Yi HY, Lucas DL. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. *Alcohol Clin Exp Res* 2007; **31**: 285-292 [PMID: 17250621 DOI: 10.1111/j.1530-0277.2006.00304.x]
67 **Cromie SL**, Jenkins PJ, Bowden DS, Dudley FJ. Chronic hepatitis C: effect of alcohol on hepatitic activity and viral titre. *J Hepatol* 1996; **25**: 821-826 [PMID: 9007708]
68 **Wiley TE**, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; **28**: 805-809 [PMID: 9731576 DOI: 10.1002/hep.510280330]
69 **Larkin J**, Clayton MM, Liu J, Feitelson MA. Chronic ethanol consumption stimulates hepatitis B virus gene expression and replication in transgenic mice. *Hepatology* 2001; **34**: 792-797 [PMID: 11584377 DOI: 10.1053/jhep.2001.27565]
70 **Khan KN**, Yatsuhashi H. Effect of alcohol consumption on the progression of hepatitis C virus infection and risk of hepatocellular carcinoma in Japanese patients. *Alcohol Alcohol* 2016; **35**: 286-295 [PMID: 10869250]
71 **Chung WG**, Kim HJ, Choe YG, Seok HS, Chon CW, Cho YK, Kim BI, Koh YY. Clinical impacts of hazardous alcohol use and obesity on the outcome of entecavir therapy in treatment-naïve patients with chronic hepatitis B infection. *Clin Mol Hepatol* 2012; **18**: 195-202 [PMID: 22893870 DOI: 10.3350/cmh.2012.18.2.195]
72 **Bruggmann P**, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. *Drug Alcohol Depend* 2010; **110**: 167-171 [PMID: 20334985 DOI: 10.1016/j.drugalcdep.2010.02.016]
73 **Spradling PR**, Bulkow L, Teshale EH, Negus S, Homan C, Simons B, McMahon BJ. Prevalence and causes of elevated serum aminotransferase levels in a population-based cohort of persons with chronic hepatitis B virus infection. *J Hepatol* 2014; **61**: 785-791 [PMID: 24911461 DOI: 10.1016/j.jhep.2014.05.045]
74 **Mueller S**, Millonig G, Seitz HK. Alcoholic liver disease and hepatitis C: a frequently underestimated combination. *World J Gastroenterol* 2009; **15**: 3462-3471 [PMID: 19630099 DOI: 10.3748/wjg.15.3462]
75 **Zhao N**, Zhang AS, Enns CA. Iron regulation by hepcidin. *J Clin Invest* 2013; **123**: 2337-2343 [PMID: 23722909 DOI: 10.1172/JCI67225]
76 **Fletcher LM**, Powell LW. Hemochromatosis and alcoholic liver disease. *Alcohol* 2003; **30**: 131-136 [PMID: 12957297]
77 **Ganne-Carrié N**, Christidis C, Chastang C, Ziol M, Chapel F, Imbert-Bismut F, Trinchet JC, Guettier C, Beaugrand M. Liver iron is predictive of death in alcoholic cirrhosis: a multivariate study of 229 consecutive patients with alcoholic and/or hepatitis C virus cirrhosis: a prospective follow up study. *Gut* 2000; **46**: 277-282 [PMID: 10644325]
78 **Niederau C**, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985; **313**: 1256-1262 [PMID: 4058506 DOI: 10.1056/NEJM198511143132004]
79 **Mccullough AJ**. The Epidemiology and Risk Factors of NASH [Internet]. In: Fatty Liver Disease. Oxford, UK: Blackwell Publishing Ltd, 2016: 23-37 [DOI: 10.1002/9780470987438.ch3]
80 **Donohue TM**, Cederbaum AI, French SW, Barve S, Gao B, Osna NA. Role of the proteasome in ethanol-induced liver pathology. *Alcohol Clin Exp Res* 2007; **31**: 1446-1459 [PMID: 17760783 DOI: 10.1111/j.1530-0277.2007.00454.x]
81 **Caldwell S**, Ikura Y, Dias D, Isomoto K, Yabu A, Moskaluk C, Pramoonjago P, Simmons W, Scruggs H, Rosenbaum N, Wilkinson T, Toms P, Argo CK, Al-Osaimi AM, Redick JA. Hepatocellular ballooning in NASH. *J Hepatol* 2010; **53**: 719-723 [PMID: 20624660 DOI: 10.1016/j.jhep.2010.04.031]
82 **Alpert L**, Hart J. The Pathology of Alcoholic Liver Disease. *Clin Liver Dis* 2016; **20**: 473-489 [PMID: 27373610 DOI: 10.1016/j.cld.2016.02.006]
83 **Tannapfel A**, Denk H, Dienes HP, Langner C, Schirmacher P, Trauner M, Flott-Rahmel B. Histopathological diagnosis of non-alcoholic and alcoholic fatty liver disease. *Virchows Arch* 2011; **458**: 511-523 [PMID: 21442288 DOI: 10.1007/s00428-011-1066-1]
84 **Dunn W**, Angulo P, Sanderson S, Jamil LH, Stadheim L, Rosen C, Malinchoc M, Kamath PS, Shah VH. Utility of a new model to diagnose an alcohol basis for steatohepatitis. *Gastroenterology* 2006; **131**: 1057-1063 [PMID: 17030176 DOI: 10.1053/j.gastro.2006.08.020]
85 **Dam-Larsen S**, Becker U, Franzmann MB, Larsen K, Christoffersen P, Bendtsen F. Final results of a long-term, clinical follow-up in fatty liver patients. *Scand J Gastroenterol* 2009; **44**: 1236-1243 [PMID: 19670076 DOI: 10.1080/00365520903171284]
86 **Botros M**, Sikaris KA. The de ritis ratio: the test of time. *Clin Biochem Rev* 2013; **34**: 117-130 [PMID: 24353357]
87 **Karsan HA**, Parekh S. Management of alcoholic hepatitis: Current concepts. *World J Hepatol* 2012; **4**: 335-341 [PMID: 23355911 DOI: 10.4254/wjh.v4.i12.335]
88 **Fiellin DA**, O'Connor PG, Holmboe ES, Horwitz RI. Risk for delirium tremens in patients with alcohol withdrawal syndrome. *Subst Abus* 2002; **23**: 83-94 [PMID: 12444353 DOI: 10.1080/08897070209511478]
89 **Hamid R**, Forrest EH. Is histology required for the diagnosis of alcoholic hepatitis? a review of published randomised controlled trials. *Gut* 2011; **60**: A233-A233 [DOI: 10.1136/gut.2011.239301.492]
90 **Singal AK**, Kodali S, Vucovich LA, Darley-Usmar V, Schiano TD. Diagnosis and Treatment of Alcoholic Hepatitis: A Systematic Review. *Alcohol Clin Exp Res* 2016; **40**: 1390-1402 [PMID: 27254289 DOI: 10.1111/acer.13108]
91 **Yeluru A**, Cuthbert JA, Casey L, Mitchell MC. Alcoholic Hepatitis: Risk Factors, Pathogenesis, and Approach to Treatment. *Alcohol Clin Exp Res* 2016; **40**: 246-255 [PMID: 26842243 DOI: 10.1111/acer.12956]
92 **European Association for the Study of Liver**. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; **57**: 399-420 [PMID: 22633836 DOI: 10.1016/j.jhep.2012.04.004]
93 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL, Mezey E, White RI. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199 [PMID: 352788]
94 **Sheth M**, Riggs M, Patel T. Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. *BMC Gastroenterol* 2002; **2**: 2 [PMID: 11835693 DOI: 10.1186/1471-230x-2-2]
95 **Srikureja W**, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. *J Hepatol* 2005; **42**: 700-706 [PMID: 15826720 DOI: 10.1016/

j.jhep.2004.12.022]
96 **Dunn W**, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, Malinchoc M, Kamath PS, Shah V. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005; **41**: 353-358 [PMID: 15660383 DOI: 10.1002/hep.20503]
97 **Louvet A**, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; **45**: 1348-1354 [PMID: 17518367 DOI: 10.1002/hep.21607]
98 **Garcia-Saenz-de-Sicilia M**, Duvoor C, Altamirano J, Duarte-Rojo A. Early prediction of response in patients with severe acute alcoholic hepatitis by using Lille model on day 4. Aasld Liver Meeting, 2015
99 **Mathurin P**, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, Ramond MJ, Naveau S, Maddrey WC, Morgan TR. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011; **60**: 255-260 [PMID: 20940288 DOI: 10.1136/gut.2010.224097]
100 **Gustot T**, Maillart E, Bocci M, Surin R, Trépo E, Degré D, Lucidi V, Taccone FS, Delforge ML, Vincent JL, Donckier V, Jacobs F, Moreno C. Invasive aspergillosis in patients with severe alcoholic hepatitis. *J Hepatol* 2014; **60**: 267-274 [PMID: 24055548 DOI: 10.1016/j.jhep.2013.09.011]
101 **Forrest EH**, Morris AJ, Stewart S, Phillips M, Oo YH, Fisher NC, Haydon G, O'Grady J, Day CP. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gut* 2007; **56**: 1743-1746 [PMID: 17627961 DOI: 10.1136/gut.2006.099226]
102 **Altamirano J**, Miquel R, Katoonizadeh A, Abraldes JG, Duarte-Rojo A, Louvet A, Augustin S, Mookerjee RP, Michelena J, Smyrk TC, Buob D, Leteurtre E, Rincón D, Ruiz P, García-Pagán JC, Guerrero-Marquez C, Jones PD, Barritt AS, Arroyo V, Bruguera M, Bañares R, Ginès P, Caballería J, Roskams T, Nevens F, Jalan R, Mathurin P, Shah VH, Bataller R. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology* 2014; **146**: 1231-1239.e1-6 [PMID: 24440674 DOI: 10.1053/j.gastro.2014.01.018]
103 **Altamirano J**, Fagundes C, Dominguez M, García E, Michelena J, Cárdenas A, Guevara M, Pereira G, Torres-Vigil K, Arroyo V, Caballería J, Ginès P, Bataller R. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. *Clin Gastroenterol Hepatol* 2012; **10**: 65-71.e3 [PMID: 21946124 DOI: 10.1016/j.cgh.2011.09.011]
104 **Altamirano J**, Higuera-de laTijera F, Duarte-Rojo A, Martínez-Vázquez MA, Abraldes JG, Herrera-Jiménez LE, Michelena J, Zapata L, Perez-Hernández J, Torre A, Gonzáles-González JA, Cardenas A, Dominguez M, Arroyo V, Ginès P, Caballería J, Bataller R. The amount of alcohol consumption negatively impacts short-term mortality in Mexican patients with alcoholic hepatitis. *Am J Gastroenterol* 2011; **106**: 1472-1480 [PMID: 21556041 DOI: 10.1038/ajg.2011.141]
105 **Liangpunsakul S**. Clinical characteristics and mortality of hospitalized alcoholic hepatitis patients in the United States. *J Clin Gastroenterol* 2011; **45**: 714-719 [PMID: 21085006 DOI: 10.1097/MCG.0b013e3181fdef1d]
106 **Poynard T**, Zourabichvili O, Hilpert G, Naveau S, Poitrine A, Benatar C, Chaput JC. Prognostic value of total serum bilirubin/gamma-glutamyl transpeptidase ratio in cirrhotic patients. *Hepatology* 2016; **4**: 324-327 [PMID: 6142856]
107 **Shasthry SM**, Sarin SK. New treatment options for alcoholic hepatitis. *World J Gastroenterol* 2016; **22**: 3892-3906 [PMID: 27099434 DOI: 10.3748/wjg.v22.i15.3892]
108 **Rachakonda V**, Gabbert C, Raina A, Bell LN, Cooper S, Malik S, Behari J. Serum metabolomic profiling in acute alcoholic hepatitis identifies multiple dysregulated pathways. *PLoS One* 2014; **9**: e113860 [PMID: 25461442 DOI: 10.1371/journal.pone.0113860]
109 **Rachakonda V**, Gabbert C, Raina A, Li H, Malik S, DeLany JP, Behari J. Stratification of risk of death in severe acute alcoholic hepatitis using a panel of adipokines and cytokines. *Alcohol Clin Exp Res* 2014; **38**: 2712-2721 [PMID: 25421508 DOI: 10.1111/acer.12558]
110 **Hanouneh IA**, Zein NN, Cikach F, Dababneh L, Grove D, Alkhouri N, Lopez R, Dweik RA. The breathprints in patients with liver disease identify novel breath biomarkers in alcoholic hepatitis. *Clin Gastroenterol Hepatol* 2014; **12**: 516-523 [PMID: 24036050 DOI: 10.1016/j.cgh.2013.08.048]
111 **Kumar K**, Mohindra S, Raj M, Choudhuri G. Procalcitonin as a marker of sepsis in alcoholic hepatitis. *Hepatol Int* 2014; **8**: 436-442 [PMID: 26202645 DOI: 10.1007/s12072-014-9540-x]
112 **Lanthier N**, Rubbia-Brandt L, Lin-Marq N, Clément S, Frossard JL, Goossens N, Hadengue A, Spahr L. Hepatic cell proliferation plays a pivotal role in the prognosis of alcoholic hepatitis. *J Hepatol* 2015; **63**: 609-621 [PMID: 25872168 DOI: 10.1016/j.jhep.2015.04.003]
113 **Spahr L**, Rubbia-Brandt L, Frossard JL, Giostra E, Rougemont AL, Pugin J, Fischer M, Egger H, Hadengue A. Combination of steroids with infliximab or placebo in severe alcoholic hepatitis: a randomized controlled pilot study. *J Hepatol* 2002; **37**: 448-455 [PMID: 12217597]
114 **Blaya D**, Coll M, Rodrigo-Torres D, Vila-Casadesús M, Altamirano J, Llopis M, Graupera I, Perea L, Aguilar-Bravo B, Díaz A, Banales JM, Clària J, Lozano JJ, Bataller R, Caballería J, Ginès P, Sancho-Bru P. Integrative microRNA profiling in alcoholic hepatitis reveals a role for microRNA-182 in liver injury and inflammation. *Gut* 2016; **65**: 1535-1545 [PMID: 27196584 DOI: 10.1136/gutjnl-2015-311314]
115 **Kronenberger B**, Rudloff I, Bachmann M, Brunner F, Kapper L, Filmann N, Waidmann O, Herrmann E, Pfeilschifter J, Zeuzem S, Piiper A, Mühl H. Interleukin-22 predicts severity and death in advanced liver cirrhosis: a prospective cohort study. *BMC Med* 2012; **10**: 102 [PMID: 22967278 DOI: 10.1186/1741-7015-10-102]
116 **Pessione F**, Ramond MJ, Peters L, Pham BN, Batel P, Rueff B, Valla DC. Five-year survival predictive factors in patients with excessive alcohol intake and cirrhosis. Effect of alcoholic hepatitis, smoking and abstinence. *Liver Int* 2003; **23**: 45-53 [PMID: 12640727]
117 **Veldt BJ**, Lainé F, Guillygomarc'h A, Lauvin L, Boudjema K, Messner M, Brissot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002; **36**: 93-98 [PMID: 11804670]
118 **Powell WJ**, Klatskin G. Duration of survival in patients with Laennec's cirrhosis. Influence of alcohol withdrawal, and possible effects of recent changes in general management of the disease. *Am J Med* 1968; **44**: 406-420 [PMID: 5641303]
119 **Alexander JF**, Lischner MW, Galambos JT. Natural history of alcoholic hepatitis. II. The long-term prognosis. *Am J Gastroenterol* 1971; **56**: 515-525 [PMID: 5134879]
120 **Khan A**, Tansel A, White DL, Kayani WT, Bano S, Lindsay J, El-Serag HB, Kanwal F. Efficacy of Psychosocial Interventions in Inducing and Maintaining Alcohol Abstinence in Patients With Chronic Liver Disease: A Systematic Review. *Clin Gastroenterol Hepatol* 2016; **14**: 191-202.e1-4; quiz e20 [PMID: 26256464 DOI: 10.1016/j.cgh.2015.07.047]
121 **Miller WR**, Walters ST, Bennett ME. How effective is alcoholism treatment in the United States? *J Stud Alcohol* 2001; **62**: 211-220 [PMID: 11327187]
122 **Edwards S**, Kenna GA, Swift RM, Leggio L. Current and promising pharmacotherapies, and novel research target areas in the treatment of alcohol dependence: a review. *Curr Pharm Des* 2011; **17**: 1323-1332 [PMID: 21524263]
123 **Center for Substance Abuse Treatment**. Incorporating Alcohol Pharmacotherapies Into Medical Practice: A Review of the Literature [Internet]. Substance Abuse and Mental Health Services Administration (US); 2009 [PMID: 22514856]
124 **West S**, Garbutt J, Carey TS, Lux LJ, Jackman AM, Tolleson-Rinehart S, Lohr KN, Crews FT. Pharmacotherapy for Alcohol

Dependence: Summary [Internet]. In: AHRQ Evidence Report Summaries. Rockville: Agency for Healthcare Research and Quality (US), 1999. [cited 2016 Oct 20]. Available from: URL: https://www.ncbi.nlm.nih.gov/books/NBK11857/

125 **Vanjak D**, Samuel D, Gosset F, Derrida S, Moreau R, Soupison T, Soulier A, Bismuth H, Sicot C. [Fulminant hepatitis induced by disulfiram in a patient with alcoholic cirrhosis. Survival after liver transplantation]. *Gastroenterol Clin Biol* 1989; **13**: 1075-1078 [PMID: 2625187]

126 **Volpicelli JR**, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. *J Clin Psychiatry* 1995; **56** Suppl 7: 39-44 [PMID: 7673104]

127 **Liang R**, Liu A, Perumpail RB, Wong RJ, Ahmed A. Advances in alcoholic liver disease: An update on alcoholic hepatitis. *World J Gastroenterol* 2015; **21**: 11893-11903 [PMID: 26576078 DOI: 10.3748/wjg.v21.i42.11893]

128 **Mason BJ**. Acamprosate in the treatment of alcohol dependence. *Expert Opin Pharmacother* 2005; **6**: 2103-2115 [PMID: 16197362 DOI: 10.1517/14656566.6.12.2103]

129 **Berger L**, Fisher M, Brondino M, Bohn M, Gwyther R, Longo L, Beier N, Ford A, Greco J, Garbutt JC. Efficacy of acamprosate for alcohol dependence in a family medicine setting in the United States: a randomized, double-blind, placebo-controlled study. *Alcohol Clin Exp Res* 2013; **37**: 668-674 [PMID: 23134193 DOI: 10.1111/acer.12010]

130 **Mann K**, Lemenager T, Hoffmann S, Reinhard I, Hermann D, Batra A, Berner M, Wodarz N, Heinz A, Smolka MN, Zimmermann US, Wellek S, Kiefer F, Anton RF. Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. *Addict Biol* 2013; **18**: 937-946 [PMID: 23231446 DOI: 10.1111/adb.12012]

131 **Addolorato G**, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007; **370**: 1915-1922 [PMID: 18068515 DOI: 10.1016/S0140-6736(07)61814-5]

132 **Caputo F**, Bernardi M, Zoli G. Efficacy and safety of γ-hydroxybutyrate in treating alcohol withdrawal syndrome in an alcohol-dependent inpatient with decompensated liver cirrhosis: a case report. *J Clin Psychopharmacol* 2011; **31**: 140-141 [PMID: 21192167 DOI: 10.1097/JCP.0b013e318203b36f]

133 **Mendenhall CL**, Tosch T, Weesner RE, Garcia-Pont P, Goldberg SJ, Kiernan T, Seeff LB, Sorell M, Tamburro C, Zetterman R. VA cooperative study on alcoholic hepatitis. II: Prognostic significance of protein-calorie malnutrition. *Am J Clin Nutr* 1986; **43**: 213-218 [PMID: 3080866]

134 **Mezey E**. Interaction between alcohol and nutrition in the pathogenesis of alcoholic liver disease. *Semin Liver Dis* 1991; **11**: 340-348 [PMID: 1763339 DOI: 10.1055/s-2008-1040451]

135 **Mendenhall CL**, Anderson S, Weesner RE, Goldberg SJ, Crolic KA. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. *Am J Med* 1984; **76**: 211-222 [PMID: 6421159]

136 **O'Shea RS**, Dasarathy S, McCullough AJ. Alcoholic liver disease. *Hepatology* 2010; **51**: 307-328 [PMID: 20034030 DOI: 10.1002/hep.23258]

137 **Moreno C**, Deltenre P, Senterre C, Louvet A, Gustot T, Bastens B, Hittelet A, Piquet MA, Laleman W, Orlent H, Lasser L, Sersté T, Starkel P, De Koninck X, Negrin Dastis S, Delwaide J, Colle I, de Galocsy C, Francque S, Langlet P, Putzeys V, Reynaert H, Degré D, Trépo E. Intensive Enteral Nutrition Is Ineffective for Patients With Severe Alcoholic Hepatitis Treated With Corticosteroids. *Gastroenterology* 2016; **150**: 903-910.e8 [PMID: 26764182 DOI: 10.1053/j.gastro.2015.12.038]

138 **Puri P**, Thursz M. Intensive Enteral Nutrition in Alcoholic Hepatitis: More Food for Thought. *Gastroenterology* 2016; **150**: 803-805 [PMID: 26924095 DOI: 10.1053/j.gastro.2016.02.061]

139 **Mathurin P**, Mendenhall CL, Carithers RL, Ramond MJ, Maddrey WC, Garstide P, Rueff B, Naveau S, Chaput JC, Poynard T. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo controlled double blind trials of corticosteroids in severe AH. *J Hepatol* 2002; **36**: 480-487 [PMID: 11943418]

140 **Barnes PJ**, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med* 1997; **336**: 1066-1071 [PMID: 9091804 DOI: 10.1056/NEJM199704103361506]

141 **Spahr L**, Rubbia-Brandt L, Pugin J, Giostra E, Frossard JL, Borisch B, Hadengue A. Rapid changes in alcoholic hepatitis histology under steroids: correlation with soluble intercellular adhesion molecule-1 in hepatic venous blood. *J Hepatol* 2001; **35**: 582-589 [PMID: 11690703]

142 **Rambaldi A**, Saconato HH, Christensen E, Thorlund K, Wetterslev J, Gluud C. Systematic review: glucocorticosteroids for alcoholic hepatitis--a Cochrane Hepato-Biliary Group systematic review with meta-analyses and trial sequential analyses of randomized clinical trials. *Aliment Pharmacol Ther* 2008; **27**: 1167-1178 [PMID: 18363896 DOI: 10.1111/j.1365-2036.2008.03685.x]

143 **Sougioultzis S**, Dalakas E, Hayes PC, Plevris JN. Alcoholic hepatitis: from pathogenesis to treatment. *Curr Med Res Opin* 2005; **21**: 1337-1346 [PMID: 16197651 DOI: 10.1185/030079905X56493]

144 **Park SH**, Kim DJ, Kim YS, Yim HJ, Tak WY, Lee HJ, Sohn JH, Yoon KT, Kim IH, Kim HS, Um SH, Baik SK, Lee JS, Suk KT, Kim SG, Suh SJ, Park SY, Kim TY, Jang JY. Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial. *J Hepatol* 2014; **61**: 792-798 [PMID: 24845609 DOI: 10.1016/j.jhep.2014.05.014]

145 **De BK**, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P. Pentoxifylline versus prednisolone for severe alcoholic hepatitis: a randomized controlled trial. *World J Gastroenterol* 2009; **15**: 1613-1619 [PMID: 19340904 DOI: 10.3748/wjg.15.1613]

146 **Mathurin P**, Louvet A, Duhamel A, Nahon P, Carbonell N, Boursier J, Anty R, Diaz E, Thabut D, Moirand R, Lebrec D, Moreno C, Talbodec N, Paupard T, Naveau S, Silvain C, Pageaux GP, Sobesky R, Canva-Delcambre V, Dharancy S, Salleron J, Dao T. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. *JAMA* 2013; **310**: 1033-1041 [PMID: 24026598 DOI: 10.1001/jama.2013.276300]

147 **Sidhu SS**, Goyal O, Singla P, Gupta D, Sood A, Chhina RS, Soni RK. Corticosteroid plus pentoxifylline is not better than corticosteroid alone for improving survival in severe alcoholic hepatitis (COPE trial). *Dig Dis Sci* 2012; **57**: 1664-1671 [PMID: 22388710 DOI: 10.1007/s10620-012-2097-4]

148 **Thursz MR**, Richardson P, Allison M, Austin A, Bowers M, Day CP, Downs N, Gleeson D, MacGilchrist A, Grant A, Hood S, Masson S, McCune A, Mellor J, O'Grady J, Patch D, Ratcliffe I, Roderick P, Stanton L, Vergis N, Wright M, Ryder S, Forrest EH. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015; **372**: 1619-1628 [PMID: 25901427 DOI: 10.1056/NEJMoa1412278]

149 **Singh S**, Murad MH, Chandar AK, Bongiorno CM, Singal AK, Atkinson SR, Thursz MR, Loomba R, Shah VH. Comparative Effectiveness of Pharmacological Interventions for Severe Alcoholic Hepatitis: A Systematic Review and Network Meta-analysis. *Gastroenterology* 2015; **149**: 958-70.e12 [PMID: 26091937 DOI: 10.1053/j.gastro.2015.06.006]

150 **Thursz MR**, Louvet A. Corticosteroids are the only remaining pharmacological option for severe alcoholic hepatitis: a meta-analysis of individual data on 1974 patients [Internet]. Wiley-Blackwell, 2016: 605A-605A. Available from: URL: http://gateway.webofknowledge.com/gateway/Gateway.cgi?GWVersion=2&SrcApp=PARTNER_APP&SrcAuth=LinksAMR&KeyUT=WOS:000385493803010&DestLinkType=FullRecord&DestApp=ALL_WOS&UsrCustomerID=1ba7043ffcc86c417c072aa74d649202

151 **Akriviadis E**, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; **119**: 1637-1648 [PMID: 11113085]

152 **Phillips M**, Curtis H, Portmann B, Donaldson N, Bomford A, O'Grady J. Antioxidants versus corticosteroids in the treatment of severe alcoholic hepatitis--a randomised clinical trial. *J Hepatol* 2006; **44**: 784-790 [PMID: 16469404 DOI: 10.1016/j.jhep.2005.11.039]

153 **Nguyen-Khac E**, Thevenot T, Piquet MA, Benferhat S, Goria O, Chatelain D, Tramier B, Dewaele F, Ghrib S, Rudler M, Carbonell N, Tossou H, Bental A, Bernard-Chabert B, Dupas JL. Glucocorticoids plus N-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med* 2011; **365**: 1781-1789 [PMID: 22070475 DOI: 10.1056/NEJMoa1101214]

154 **Naveau S**, Chollet-Martin S, Dharancy S, Mathurin P, Jouet P, Piquet MA, Davion T, Oberti F, Broët P, Emilie D. A double-blind randomized controlled trial of infliximab associated with prednisolone in acute alcoholic hepatitis. *Hepatology* 2004; **39**: 1390-1397 [PMID: 15122768 DOI: 10.1002/hep.20206]

155 **Boetticher NC**, Peine CJ, Kwo P, Abrams GA, Patel T, Aqel B, Boardman L, Gores GJ, Harmsen WS, McClain CJ, Kamath PS, Shah VH. A randomized, double-blinded, placebo-controlled multicenter trial of etanercept in the treatment of alcoholic hepatitis. *Gastroenterology* 2008; **135**: 1953-1960 [PMID: 18848937 DOI: 10.1053/j.gastro.2008.08.057]

156 **Mackie J**, Groves K, Hoyle A, Garcia C, Garcia R, Gunson B, Neuberger J. Orthotopic liver transplantation for alcoholic liver disease: a retrospective analysis of survival, recidivism, and risk factors predisposing to recidivism. *Liver Transpl* 2001; **7**: 418-427 [PMID: 11349262 DOI: 10.1053/jlts.2001.23789]

157 **Beresford TP**, Everson GT. Liver transplantation for alcoholic liver disease: bias, beliefs, 6-month rule, and relapse--but where are the data? *Liver Transpl* 2000; **6**: 777-778 [PMID: 11084067 DOI: 10.1053/jlts.2000.19027]

158 **Bravata DM**, Olkin I, Barnato AE, Keeffe EB, Owens DK. Employment and alcohol use after liver transplantation for alcoholic and nonalcoholic liver disease: a systematic review. *Liver Transpl* 2001; **7**: 191-203 [PMID: 11244159 DOI: 10.1053/jlts.2001.22326]

159 **Donckier V**, Lucidi V, Gustot T, Moreno C. Ethical considerations regarding early liver transplantation in patients with severe alcoholic hepatitis not responding to medical therapy. *J Hepatol* 2014; **60**: 866-871 [PMID: 24291238 DOI: 10.1016/j.jhep.2013.11.015]

160 **Singal AK**, Bashar H, Anand BS, Jampana SC, Singal V, Kuo YF. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology* 2012; **55**: 1398-1405 [PMID: 22213344 DOI: 10.1002/hep.25544]

161 **Mathurin P**, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharancy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Belghiti J, Donckier V, Pruvot FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011; **365**: 1790-1800 [PMID: 22070476 DOI: 10.1056/NEJMoa1105703]

162 **Im GY**, Kim-Schluger L, Shenoy A, Schubert E, Goel A, Friedman SL, Florman S, Schiano TD. Early Liver Transplantation for Severe Alcoholic Hepatitis in the United States--A Single-Center Experience. *Am J Transplant* 2016; **16**: 841-849 [PMID: 26710309 DOI: 10.1111/ajt.13586]

163 **Lee BP**, Chen PH, Haugen C, Hernaez R, Gurakar A, Philosophe B, Dagher N, Moore SA, Li Z, Cameron AM. Three-year Results of a Pilot Program in Early Liver Transplantation for Severe Alcoholic Hepatitis. *Ann Surg* 2017; **265**: 20-29 [PMID: 27280501 DOI: 10.1097/SLA.0000000000001831]

164 **Singal AK**, Kamath PS, Gores GJ, Shah VH. Alcoholic hepatitis: current challenges and future directions. *Clin Gastroenterol Hepatol* 2014; **12**: 555-564; quiz e31-32 [PMID: 23811249 DOI: 10.1016/j.cgh.2013.06.013]

165 **Jesudian AB**, Brown RS. Acute alcoholic hepatitis as indication for liver transplantation. *Curr Opin Organ Transplant* 2016; **21**: 107-110 [PMID: 26867048 DOI: 10.1097/MOT.0000000000000285]

166 **Yan AW**, Schnabl B. Bacterial translocation and changes in the intestinal microbiome associated with alcoholic liver disease. *World J Hepatol* 2012; **4**: 110-118 [PMID: 22567183 DOI: 10.4254/wjh.v4.i4.110]

167 **McClain C**, Hill D, Schmidt J, Diehl AM. Cytokines and alcoholic liver disease. *Semin Liver Dis* 1993; **13**: 170-182 [PMID: 8337603 DOI: 10.1055/s-2007-1007347]

168 **Wang Y**, Liu Y, Kirpich I, Ma Z, Wang C, Zhang M, Suttles J, McClain C, Feng W. Lactobacillus rhamnosus GG reduces hepatic TNFα production and inflammation in chronic alcohol-induced liver injury. *J Nutr Biochem* 2013; **24**: 1609-1615 [PMID: 23618528 DOI: 10.1016/j.jnutbio.2013.02.001]

169 **Loguercio C**, Federico A, Tuccillo C, Terracciano F, D'Auria MV, De Simone C, Del Vecchio Blanco C. Beneficial effects of a probiotic VSL#3 on parameters of liver dysfunction in chronic liver diseases. *J Clin Gastroenterol* 2005; **39**: 540-543 [PMID: 15942443]

170 **Dhiman RK**, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, Khattri A, Malhotra S, Duseja A, Chawla YK. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. *Gastroenterology* 2014; **147**: 1327-1337.e3 [PMID: 25450083 DOI: 10.1053/j.gastro.2014.08.031]

171 **Maltby J**, Wright S, Bird G, Sheron N. Chemokine levels in human liver homogenates: associations between GRO alpha and histopathological evidence of alcoholic hepatitis. *Hepatology* 1996; **24**: 1156-1160 [PMID: 8903391 DOI: 10.1053/jhep.1996.v24.pm0008903391]

172 **Lemmers A**, Moreno C, Gustot T, Maréchal R, Degré D, Demetter P, de Nadai P, Geerts A, Quertinmont E, Vercruysse V, Le Moine O, Devière J. The interleukin-17 pathway is involved in human alcoholic liver disease. *Hepatology* 2009; **49**: 646-657 [PMID: 19177575 DOI: 10.1002/hep.22680]

173 **Dominguez M**, Miquel R, Colmenero J, Moreno M, García-Pagán JC, Bosch J, Arroyo V, Ginès P, Caballería J, Bataller R. Hepatic expression of CXC chemokines predicts portal hypertension and survival in patients with alcoholic hepatitis. *Gastroenterology* 2009; **136**: 1639-1650 [PMID: 19208360 DOI: 10.1053/j.gastro.2009.01.056]

174 **Colmenero J**, Bataller R, Sancho-Bru P, Bellot P, Miquel R, Moreno M, Jares P, Bosch J, Arroyo V, Caballería J, Ginès P. Hepatic expression of candidate genes in patients with alcoholic hepatitis: correlation with disease severity. *Gastroenterology* 2007; **132**: 687-697 [PMID: 17258719 DOI: 10.1053/j.gastro.2006.12.036]

175 **Torok NJ**. Update on Alcoholic Hepatitis. *Biomolecules* 2015; **5**: 2978-2986 [PMID: 26540078 DOI: 10.3390/biom5042978]

176 **Theocharis SE**, Papadimitriou LJ, Retsou ZP, Margeli AP, Ninos SS, Papadimitriou JD. Granulocyte-colony stimulating factor administration ameliorates liver regeneration in animal model of fulminant hepatic failure and encephalopathy. *Dig Dis Sci* 2003; **48**: 1797-1803 [PMID: 14561004]

177 **Spahr L**, Lambert JF, Rubbia-Brandt L, Chalandon Y, Frossard JL, Giostra E, Hadengue A. Granulocyte-colony stimulating factor induces proliferation of hepatic progenitors in alcoholic steatohepatitis: a randomized trial. *Hepatology* 2008; **48**: 221-229 [PMID: 18537187 DOI: 10.1002/hep.22317]

178 **Singh V**, Sharma AK, Narasimhan RL, Bhalla A, Sharma N, Sharma R. Granulocyte colony-stimulating factor in severe alcoholic hepatitis: a randomized pilot study. *Am J Gastroenterol* 2014; **109**: 1417-1423 [PMID: 24935272 DOI: 10.1038/ajg.2014.154]

179 **Wu W**, Zhu B, Peng X, Zhou M, Jia D, Gu J. Activation of farnesoid X receptor attenuates hepatic injury in a murine model of alcoholic liver disease. *Biochem Biophys Res Commun* 2014; **443**: 68-73 [PMID: 24269813 DOI: 10.1016/j.bbrc.2013.11.057]

180 **Fiorucci S**, Antonelli E, Rizzo G, Renga B, Mencarelli A, Riccardi

L, Orlandi S, Pellicciari R, Morelli A. The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis. *Gastroenterology* 2004; **127**: 1497-1512 [PMID: 15521018]

181 **Fiorucci S**, Rizzo G, Antonelli E, Renga B, Mencarelli A, Riccardi L, Morelli A, Pruzanski M, Pellicciari R. Cross-talk between farnesoid-X-receptor (FXR) and peroxisome proliferator-activated receptor gamma contributes to the antifibrotic activity of FXR ligands in rodent models of liver cirrhosis. *J Pharmacol Exp Ther* 2005; **315**: 58-68 [PMID: 15980055 DOI: 10.1124/jpet.105.085597]

182 **Verma VK**, Li H, Wang R, Hirsova P, Mushref M, Liu Y, Cao S, Contreras PC, Malhi H, Kamath PS, Gores GJ, Shah VH. Alcohol stimulates macrophage activation through caspase-dependent hepatocyte derived release of CD40L containing extracellular vesicles. *J Hepatol* 2016; **64**: 651-660 [PMID: 26632633 DOI: 10.1016/j.jhep.2015.11.020]

183 **Ghavami S**, Hashemi M, Kadkhoda K, Alavian SM, Bay GH, Los M. Apoptosis in liver diseases--detection and therapeutic applications. *Med Sci Monit* 2005; **11**: RA337-RA345 [PMID: 16258409]

184 **Pockros PJ**, Schiff ER, Shiffman ML, McHutchison JG, Gish RG, Afdhal NH, Makhviladze M, Huyghe M, Hecht D, Oltersdorf T, Shapiro DA. Oral IDN-6556, an antiapoptotic caspase inhibitor, may lower aminotransferase activity in patients with chronic hepatitis C. *Hepatology* 2007; **46**: 324-329 [PMID: 17654603 DOI: 10.1002/hep.21664]

185 **Frenette C**, Morelli G, Shiffman M, Frederick RT, Rubin RA, Fallon M, Yamashita M, Spada AP, Chan L, Hagerty DH. Emricasan (IDN-6556) Orally for Three Months in Patients with Cirrhosis and Meld Scores 11–18 Improves Clinical Parameters of Cirrhosis in Patients with Baseline Meld Score ≥ 15. *J Hepatol* 2016; **64**: S210 [DOI: 10.1016/S0168-8278(16)00174-4]

186 **Petrasek J**, Bala S, Csak T, Lippai D, Kodys K, Menashy V, Barrieau M, Min SY, Kurt-Jones EA, Szabo G. IL-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. *J Clin Invest* 2012; **122**: 3476-3489 [PMID: 22945633 DOI: 10.1172/JCI60777]

187 **Tkachenko P**, Maevskaya M, Pavlov A, Komkova I, Pavlov C, Ivashkin V. Prednisolone plus S-adenosil-L-methionine in severe alcoholic hepatitis. *Hepatol Int* 2016; **10**: 983-987 [PMID: 27337960 DOI: 10.1007/s12072-016-9751-4]

188 **Váli L**, Blázovics A, Fehér J. [The therapeutic effect of metadoxine on alcoholic and non-alcoholic steatohepatitis]. *Orv Hetil* 2005; **146**: 2409-2414 [PMID: 16398154]

189 **Higuera-de la Tijera F**, Servín-Caamaño AI, Cruz-Herrera J, Serralde-Zúñiga AE, Abdo-Francis JM, Gutiérrez-Reyes G, Pérez-Hernández JL. Treatment with metadoxine and its impact on early mortality in patients with severe alcoholic hepatitis. *Ann Hepatol* 2016; **13**: 343-352 [PMID: 24756009]

190 **Higuera-de la Tijera F**, Servín-Caamaño AI, Serralde-Zúñiga AE, Cruz-Herrera J, Pérez-Torres E, Abdo-Francis JM, Salas-Gordillo F, Pérez-Hernández JL. Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. *World J Gastroenterol* 2015; **21**: 4975-4985 [PMID: 25945012 DOI: 10.3748/wjg.v21.i16.4975]

191 **US National Institutes of Health**. Search of: ELADTM liver/ Exclude Unknown - List Results - ClinicalTrials.gov. [cited 2016 Jun 1]. Available from: URL: https://clinicaltrials.gov/ct2/results?term=ELADTM liver&no_unk=Y

192 **Clinical Trials**. Vital Therapies [Internet]. Available from: URL: http://vitaltherapies.com/clinical-trials/

193 **Lazaro R**, Wu R, Lee S, Zhu NL, Chen CL, French SW, Xu J, Machida K, Tsukamoto H. Osteopontin deficiency does not prevent but promotes alcoholic neutrophilic hepatitis in mice. *Hepatology* 2015; **61**: 129-140 [PMID: 25132354 DOI: 10.1002/hep.27383]

194 **Mandrekar P**, Bataller R, Tsukamoto H, Gao B. Alcoholic hepatitis: Translational approaches to develop targeted therapies. *Hepatology* 2016; **64**: 1343-1355 [PMID: 26940353 DOI: 10.1002/hep.28530]

195 **Gao B**, Shah VH. Combination therapy: New hope for alcoholic hepatitis? *Clin Res Hepatol Gastroenterol* 2015; **39** Suppl 1: S7-S11 [PMID: 26193867 DOI: 10.1016/j.clinre.2015.05.008]

196 **Moreau R**, Arroyo V. Acute-on-chronic liver failure: a new clinical entity. *Clin Gastroenterol Hepatol* 2015; **13**: 836-841 [PMID: 24583872 DOI: 10.1016/j.cgh.2014.02.027]

197 **Moreau R**, Jalan R, Arroyo V. Acute-on-Chronic Liver Failure: Recent Concepts. *J Clin Exp Hepatol* 2015; **5**: 81-85 [PMID: 25941435 DOI: 10.1016/j.jceh.2014.09.003]

P- Reviewer: Dhanda A, Singal AK, Thieringer J **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 April 28; 9(12): 586-594

DOI: 10.4254/wjh.v9.i12.586

ISSN 1948-5182 (online)

MINIREVIEWS

Role of circulating microRNAs in liver diseases

Sven H Loosen, Florian Schueller, Christian Trautwein, Sanchari Roy, Christoph Roderburg

Sven H Loosen, Florian Schueller, Christian Trautwein, Sanchari Roy, Christoph Roderburg, Department of Medicine Ⅲ, University Hospital RWTH Aachen, 52074 Aachen, Germany

Author contributions: Loosen SH and Schueller F share first authorship; Roy S and Roderburg C share senior authorship; all authors designed, wrote and drafted the manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Manuscript source: Invited manuscript

Correspondence to: Dr. Christoph Roderburg, PD, Department of Medicine Ⅲ, University Hospital RWTH Aachen, Pauwelsstrasse 30, 52074 Aachen, Germany. croderburg@ukaachen.de
Telephone: +49-241-8035367
Fax: +49-241-8082455

Received: January 27, 2017
Peer-review started: February 12, 2017
First decision: March 8, 2017
Revised: March 27, 2017
Accepted: April 6, 2017
Article in press: April 10, 2017
Published online: April 28, 2017

Abstract

MicroRNAs (miRNAs) are small RNAs regulate gene expression by inhibiting the turnover of their target mRNAs. In the last years, it became apparent that miRNAs are released into the circulation and circulating miRNAs emerged as a new class of biomarkers for various diseases. In this review we summarize available data on the role of circulating miRNAs in the context of acute and chronic liver diseases including hepatocellular and cholangiocellular carcinoma. Data from animal models are compared to human data and current challenges in the field of miRNAs research are discussed.

Key words: Liver disease; Acute liver failure; MicroRNA; Liver fibrosis; Hepatocellular carcinoma; Autoimmune hepatitis; Cholangiocarcinoma

Core tip: In this article, we aim to review the role of circulating microRNAs (miRNAs), a class of small non-coding RNAs involved in various pathological processes, in the context of liver disease. The focus is on current and future applications of miRNAs as potential diagnostic and prognostic biomarkers in the field of acute liver failure, liver fibrosis and cirrhosis, autoimmune liver disease as well as liver cancer.

Loosen SH, Schueller F, Trautwein C, Roy S, Roderburg C. Role of circulating microRNAs in liver diseases. *World J Hepatol* 2017; 9(12): 586-594 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i12/586.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i12.586

INTRODUCTION

MicroRNAs (miRNAs) are small RNAs that do not encode for proteins, but regulate gene expression[1]. MiRNAs are transcribed by the RNA polymerase Ⅱ or RNA polymerase Ⅱ[2-4]. The resulting 500-3000 nucleotides long transcripts (pri-miRNAs) are cleaved in a second step by the "microprocessor complex" into approximately 70 nucleotides long precursor miRNAs (pre-miRNA), which are actively exported from the nucleus into the cytoplasm. Finally, pre-miRNAs are processed by the

RNase Ⅲ endonuclease "Dicer" into approximately 22 nucleotides long double stranded miRNAs, which bind to the Argonaute protein and are integrated into the "RNA-induced silencing complex". Within this complex, miRNAs bind the 3′ or 5′ untranslated region of the target mRNAs, leading to a transcriptional or translational repression of the target mRNA[2,4-6]. Alterations in miRNA expression profiles were described in organ development, aging, and cell death[7], as well as in the pathophysiology of complex diseases such as inflammation, fibrosis and cancer[8-13].

Besides their role in the regulation of gene expression, miRNAs have been described in body fluids, where they might serve as biomarkers[14-17]. Based on their extraordinary stability, their less complex chemical structure and their lack of post-processing modifications, circulating miRNAs were suggested as "optimal" serum based biomarkers[18]. Circulating miRNAs can be either bound to serum proteins and lipoproteins or be encircled in extracellular vesicles including exosomes, microvesicles or apoptotic bodies[17,19]. As exosomes can be released by various hepatic cells (*e.g.*, hepatocytes and Kupffer cells) and can be transferred to other recipient cells to regulate expression profiles in these cells, they were suggested to play an important role in hepatic cell-cell-communication and in the pathophysiology of different liver diseases. Findings that miRNAs encircled in these vesicles are well protected from degradation furthermore highlight the potential of exosomal miRNAs to serve as potent biomarkers[20-22]. With respect to the concept of "liquid biopsy" which has recently been suggested as a novel detection tool for malignant diseases[23,24], miRNA might thus function as a potential "liquid biopsy" not only for malignant but also benign liver disease.

In this review, we evaluated studies indexed in Medline between 2006 and 2016. The terms "microRNA", "liver", "liver failure", "fibrosis", "cirrhosis", "hepatocellular carcinoma", "cholangiocarcinoma", "autoimmune hepatitis", "primary sclerosing cholangitis", "primary biliary cholangitis", "biomarker", "diagnostic", "prognostic" and combinations of these terms were used.

ACUTE LIVER FAILURE

Acute liver failure (ALF) is characterized by a massive loss of liver cell function based on various etiologies (*e.g.*, drug intoxication, viral or autoimmune hepatitis (AIH), Wilson's disease or Budd-Chiari syndrome) without preexisting liver disease[25,26]. Despite significant improvements regarding therapeutic options (*e.g.*, liver transplantation), ALF has remained a challenging clinical condition with mortality rates of about 50%[27]. In this context, biomarkers allowing early diagnosis or estimation of patients' fate might be helpful for the guidance of therapy[28,29]. However, routinely used serum biomarkers for liver injury such as AST and ALT are not liver specific and only have a limited prognostic value[30-32]. Therefore, new biomarkers are urgently needed to further improve patients' individual treatment options and overall survival in the context of acute liver injury.

In a pilot study on the potential of miRNAs as ALF biomarkers, Wang *et al*[18] demonstrated that liver specific miR-122 and miR-192 were elevated in sera of mice after acute Acetaminophen (APAP) intoxication compared to controls. Of note, miR-122 and miR-192 serum levels were increased in a dose- and exposure duration-dependent manner and were detectable significantly earlier than the classic serum aminotransferases[18]. Consistently, circulating miR-122 and miR-192 levels were elevated in patients with APAP-induced ALF compared to healthy controls[33]. Moreover, miR-122 serum levels returned earlier to normal when compared to ALT, indicating that circulating miR-122 might have a shorter half-life in comparison to ALT[33]. High throughput sequencing of miRNAs in sera of patients with APAP overdose revealed 36 miRNAs to be elevated compared to healthy controls. Besides the already described miR-122 and miR-192, miR-483, miR-194 and miR-210 were additionally found to be increased in the sera of these patients[32]. Antoine *et al*[29] demonstrated in a large cohort of patients with APAP-induced ALF that increased miR-122 serum levels are detectable very early after liver intoxication when serum ALT levels are still unaffected. Furthermore, levels of circulating miR-122 enabled the prediction of liver injury development with a high accuracy[29].

An increasing number of studies have investigated circulating miRNAs regarding their prognostic potential for acute liver injury. Just recently, Russo *et al*[34] applied a microarray based expression analysis using a panel of 1733 miRNAs and 1658 pre-miRNAs in sera of 78 drug-induced liver injury (DILI) patients. These patients showed elevated serum levels of miR-122, miR-1246, -4270, -4433, -4463, -4484, -4532 and pre-miR-4767 as well as decreased serum levels of miR-455-3p, -1281 and pre-miR-4274 compared to healthy controls. Out of these, miR-122, miR-4463 and miR-4270 had a prognostic value as decreased serum levels correlated with the decease of DILI patients within 6 mo. In this study, low albumin (less than 2.8 g/L) and low miR-122 serum levels (less than 7.89 relative fluorescent units) had a sensitivity of 100% and a specificity of 57% for the prediction of death in DILI patients[34]. The prognostic value of miRNA profiles were further investigated in a retrospective study on patients with ALF caused by viral hepatitis, toxic liver injury, Budd-Chiari syndrome, Wilson's disease, AIH or indeterminate etiology[26]. In this study, serum levels of miR-122, miR-21 and miR-221 were found to be significantly increased in patients that showed a spontaneous recovery from ALF compared to non-recovered patients[26]. Increased levels of circulating miR-122, miR-21 and miR-221 in patients with a spontaneous recovery from ALF were further associated with increased hepatocyte proliferation and liver tissue regeneration due to decreased expression of the respective miRNAs target genes in the liver like heme-oxygenase-1 (miR-122), programmed cell death 4 (miR-21), p27 and p57 (miR-221)[26].

Table 1 Summary of circulating miRNAs as diagnostic biomarkers in various liver diseases

Medical condition	miRNA	Serum levels	# of patients	Method for determination	Ref.
Acute liver failure (drug induced)	miR-122	↑	53	qPCR	Starkey Lewis *et al*[33]
		↑	6	RNA sequencing, qPCR	Krauskopf *et al*[32]
		↑	129	qPCR	Antoine *et al*[29]
		↑	78	miRNA microarray	Russo *et al*[34]
	miR-192	↑	53	PCR	Starkey Lewis *et al*[33]
		↑	6	RNA sequencing, qPCR	Krauskopf *et al*[32]
	miR-483	↑	6	RNA sequencing, qPCR	Krauskopf *et al*[32]
	miR-194	↑	6	RNA sequencing, qPCR	Krauskopf *et al*[32]
	miR-210	↑	6	RNA sequencing, qPCR	Krauskopf *et al*[32]
	miR-4532	↑	78	miRNA microarray	Russo *et al*[34]
	miR-455-3p	↓	78	miRNA microarray	Russo *et al*[34]
	miR-1281	↓	78	miRNA microarray	Russo *et al*[34]
Liver fibrosis (CHC)	miR-122	↑	53	qPCR	Cermelli *et al*[37]
	miR-34a	↑	53	qPCR	Cermelli *et al*[37]
Liver fibrosis (NAFLD)	miR-122	↑	34	qPCR	Cermelli *et al*[37]
		↑	28	qPCR	Salvoza *et al*[38]
	miR-34a	↑	34	qPCR	Cermelli *et al*[37]
		↑	28	qPCR	Salvoza *et al*[38]
Liver cirrhosis	miR-513-3p	↑	67	miRNA microarray, qPCR	Roderburg *et al*[40]
	miR-571	↑	67	miRNA microarray, qPCR	Roderburg *et al*[40]
	miR-29	↓	67	miRNA microarray, qPCR	Roderburg *et al*[41]
AIH	miR-21	↑	46	miRNA microarray, qPCR	Migita *et al*[47]
	miR-122	↑	46	miRNA microarray, qPCR	Migita *et al*[47]
PSC	miR-1281	↑	40	miRNA microarray, qPCR	Voigtländer *et al*[48]
	miR-126	↑	40	miRNA microarray, qPCR	Voigtländer *et al*[48]
	miR-200c	↓	30	miRNA microarray, qPCR	Bernuzzi *et al*[49]
PBC	miR-505-3p	↓	10	RNA sequencing, qPCR	Ninomiya *et al*[50]
	miR-197-3p	↓	10	RNA sequencing, qPCR	Ninomiya *et al*[50]
	miR-122	↑	207	RNA sequencing, qPCR	Tan *et al*[51]
	miR-141	↑	207	RNA sequencing, qPCR	Tan *et al*[51]
	miR-26b	↑	207	RNA sequencing, qPCR	Tan *et al*[51]
HCC	miR-21	↑	101	qPCR	Xu *et al*[58]
		↑	90	qPCR	Ge *et al*[62]
		↑	121	qPCR	Tomimaru *et al*[64]
		↑	457	miRNA microarray, qPCR	Zhou *et al*[68]
	miR-121	↑	101	qPCR	Xu *et al*[58]
	miR-223	↑	101	qPCR	Xu *et al*[58]
		↑	457	miRNA microarray, qPCR	Zhou *et al*[68]
	miR-16	↓	90	qPCR	Ge *et al*[62]
		↓	40	qPCR	El-Abd *et al*[63]
	miR-122	↑	457	miRNA microarray, qPCR	Zhou *et al*[68]
	miR-26a	↑	457	miRNA microarray, qPCR	Zhou *et al*[68]
	miR-192	↑	457	miRNA microarray, qPCR	Zhou *et al*[68]
CCA	miR-21	↑	25	RNA sequencing, qPCR	Correa-Gallego *et al*[74]
		↑	94	qPCR	Kishimoto *et al*[75]
	miR-221	↑	25	RNA sequencing, qPCR	Correa-Gallego *et al*[74]
	miR-150	↑	15	qPCR	Wang *et al*[77]
	miR-224	↑	30	qPCR	Huang *et al*[76]

miRNA: MicroRNA; CHC: Chronic hepatitis C; NAFLD: Non-alcoholic fatty liver disease; qPCR: Quantitative RT-PCR; AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cholangitis; HCC: Hepatocellular carcinoma; CCA: Cholangiocarcinoma; ↑: High circulating levels; ↓: Low circulating levels.

In summary, measurement of circulating miRNAs might represent important serum biomarkers for ALF and help to improve the prediction of patients' prognosis even at an early time point after liver injury. Table 1 summarizes potential diagnostic biomarker for ALF.

LIVER FIBROSIS AND CIRRHOSIS

Liver fibrosis and liver cirrhosis represent the most common end-points of chronic liver diseases such as alcoholic steatohepatitis, non-alcoholic steatohepatitis, and viral hepatitis, which are all associated with a high morbidity and mortality. Currently, histology is considered the gold standard for the diagnosis and staging of liver fibrosis and/or cirrhosis. However, this procedure is related to a number of problems, including the risks for serious complications during liver biopsy, sampling errors and biases, variabilities in histopathologic interpretation and significant financial costs. Thus, alternative non-invasive strategies for the evaluation of liver fibrosis/cirrhosis are of increasing interest. In this context, besides other markers, circulating miRNAs have been

considered by many authors as promising serum based biomarkers with a potential for being used in clinical routine.

In the past, an overwhelming amount of data supporting a role for miRNAs in the development and progression of chronic liver diseases into liver cirrhosis and finally hepatocellular carcinoma (HCC) was presented (reviewed *e.g.,* in[35]). Based on these data, the group of El-Ahwany analyzed serum levels of different miRNAs with an established role in the activation of hepatic stellate cells (HSC) in sera of 66 subjects with early stage liver fibrosis and 65 subjects with late-stage fibrosis[36]. Forty healthy subjects served as normal controls. In line to their role in the activation of HSC, serum concentrations of miR-138, miR-140, miR-143, miR-325, miR-328 and miR-349 were significantly elevated in patients with fibrosis compared to healthy controls. ROC analysis revealed a sensitivity and specificity of miR-138 of 89.3% and 71.43% for prediction of early stage fibrosis and of 89.3% and 93.02% for prediction of late stage fibrosis, respectively, demonstrating that analyses of circulating miRNAs might be helpful to detect even early stages of liver fibrosis. Besides these miRNAs, several groups demonstrated that levels of miR-34a, one of the best investigated miRNAs in the context of chronic liver diseases, are elevated in patients with liver fibrosis[37-39]. In a large cohort of patients, Cermelli *et al*[37] described elevated levels of miR-34a in patients with both hepatitis C (CHC)- and NAFLD-dependent liver fibrosis. Interestingly, levels of miR-34 were independent of the viral load but reflected the stage of disease in both disease entities. In this study, miR-34a correlated with AST/ALT levels, stage of fibrotic disease, inflammatory activity and serum lipids in NAFLD patients, highlighting that levels of circulating miRNAs might reflect specific aspects in the pathophysiology of chronic liver diseases[37]. In line with this assumption, we described elevated levels of miR-513-3p and miR-571 in patients with alcohol- or hepatitis C-induced liver cirrhosis. However, only serum level of miR-571 reflected the disease severity in liver cirrhosis, while miR-513-3p was independent on the stage of fibrosis or inflammatory activity in these patients[40]. Besides these up-regulated miRNAs, a down-regulation of circulating miR-29 was found in patients with chronic liver injury and liver fibrosis. Levels of miR-29 correlated with the stage of liver fibrosis, MELD score and disease entity[41]. In the context of alcohol induced liver injury, microarray based screening of exosomal miRNAs revealed an up-regulation of miRNA-192, miRNA-122, miRNA-30a, miRNA-744, miRNA-1246, miRNA 30b and miRNA-130a in blood sera of chronic alcohol-fed mice compared to healthy controls[42]. Moreover, ROC curve analyses indicated a diagnostic potential of miRNA-192, miRNA-122, and miRNA-30a for the identification of alcohol-induced liver injury[42].

Recently, the group of Matsuura *et al*[43] attempted to determine whether circulating miRNAs might be used to estimate disease progression in chronic hepatitis C patients. One hundred and thirty CHC patients were prospectively followed. In this study, reduced plasma levels of the let7-family reflected a more advanced fibrosis stage whereas elevated concentrations of miR-122-5p were indicative for an increased inflammatory activity, but not for the degree of liver fibrosis[43]. In another large cohort of CHC-patients, Trebicka *et al*[44] demonstrated that circulating miR-122 levels positively correlated with an enhanced inflammatory activity but negatively with liver fibrosis, which was most probably due to the loss of liver cells (as the major source of miR-122) during chronic liver injury. Interestingly, miR-122 serum levels were associated with the survival of CHC-cirrhosis patients independent of the MELD score, sex and age[45], underscoring the potential of this liver specific miRNA in the diagnosis of liver fibrosis and cirrhosis.

In summary, circulating miRNAs might represent diagnostic and prognostic biomarkers in patients with liver fibrosis or cirrhosis.

AUTOIMMUNE LIVER DISEASE

Although autoimmune liver diseases have gained rising importance in the field of hepatology due to its increasing incidence over the last decades[46], only very few studies have evaluated the involvement of circulating miRNAs in AIH, primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC).

To our knowledge only one study investigating circulating miRNAs in patients with AIH exists to date. In this study, serum samples of 46 type-1 AIH patients were screened for 2555 miRNAs using a microarray system and compared to patients with chronic hepatitis C and healthy controls. Circulating levels of miR-21 and miR-122 were significantly higher in AIH patients compared to both control groups. Interestingly, the authors observed a strong decrease of miR-21 and miR-122 levels after treatment with glucocorticoids, indicating a potential role of these miRNA not only as a diagnostic marker but also as a marker to assess treatment response[47].

In PSC patients, serum levels of miR-1281 and miR-126 were shown to be significantly increased compared to healthy controls. Importantly, the elevation of these miRNAs in PSC patients was also significantly higher compared to CCA patients, arguing that miR-1281 and miR-126 might reflect disease-specific processes of PSC that do not or to a lesser extend occur during malignant transformation of bile duct cells into CCA[48]. Moreover, Bernuzzi *et al*[49] described miR-200c as significantly down-regulated in patients with PSC in large screening approach including 667 miRNAs.

In PBC patients, a deep sequencing approach revealed circulating levels of miR-505-3p and miR-197-3p as significantly decreased when compared to healthy controls[50]. However, this study was performed in a very small cohort of patients (n = 10) and needs further validation. In another study, Tan *et al*[51] establish a diagnostic serum miRNA panel in a cohort of 207 PBC

patients using a stepwise logistic regression model. The panel, consisting of miR-122, miR-141 and miR-26b, had an AUC of 0.905 for the discrimination between PBC patients and healthy control, which was superior to established biomarkers for PBC such as AP and ANA.

In summary, the role of circulating miRNA in autoimmune liver disease has so far only been analyzed in a very limited number of studies with comparatively small cohort sizes. Thus, further studies are needed to make a clear statement on the potential role of serum miRNAs as a biomarker for AIH, PSC and PBC.

LIVER CANCER

Circulating miRNAs have also become of increasing interest as biomarkers for hepatic and hepatobiliary malignancies. The following section reviews the emerging role of circulating miRNAs in the field of HCC and cholangiocarcinoma (CCA).

HCC

HCC represents the most common primary tumor of the liver and shows a steadily increasing incidence rate in most areas of the world[52,53]. Despite being the sixth most common type of cancer worldwide, HCC is the second leading cause of cancer related death among men worldwide, corroborating the dismal prognosis of this disease[54]. Even in medically developed countries such as the United States, HCC patients face a 1-year and 5-year survival rate of less than 50% and 10%, respectively[55]. Since early detection of HCC is essential to provide patients with a potentially curative therapeutic approach and established tumor markers such as AFP feature a limited diagnostic potential especially at an early stage of disease, circulating miRNAs as biomarkers for HCC might help to improve the disease's poor prognosis.

As the most abundantly expressed miRNA in human liver tissue[56], miRNA-122 was found to be up-regulated in serum samples of HCC patients, showing a sensitivity and specificity of 81.6% and 83.3%, respectively when compared to healthy controls[57,58]. Nevertheless, as shown before, circulating levels of miR-122 were also described for different non-malignant hepatic diseases[59], arguing for a rather unspecific characteristic of this miRNA. Interestingly, expression levels of miR-122 were decreased in HCC tissue samples[60], suggesting a potential mechanism of miRNA secretion from HCC cells into the bloodstream.

Moreover, serum levels of exosomal miR-18a, miR-221, miR-222 and miR-224 were significantly higher whereas exosomal miR-101, miR-106b, miR-122 and miR-195 were significantly lower in patients with HCC compared to patients with chronic hepatitis B or liver cirrhosis[61]. Furthermore, circulating levels of miR-16 were shown to be down-regulated in patients with HCC, correlating with tumor size and were further able to discriminate HCC from chronic HCV patients[62,63]. In contrast non-malignant liver conditions such as NAFLD and chronic hepatitis C showed increased miR-16 serum levels[37], making the down-regulation of serum miR-16 levels in HCC a fairly specific marker for liver cancer. Serum levels of miR-21 represent a further promising tool for the diagnosis of HCC. Tomimaru *et al*[64] showed that circulating levels of miR-21 can reliably distinguish between HCC patients and healthy controls as well as patients with chronic hepatitis and are superior to the diagnostic potential of AFP. They also found a decrease of miR-21 serum levels after tumor resection, underlining the potential specificity of this miRNA for HCC[64]. However, elevated levels of circulating miR-21 were also described in patients with different other types of gastrointestinal cancer[65,66]. A recently published meta-analysis on circulating levels of miR-21 described a pooled sensitivity of 81.2% with a specificity of 84.8% for the diagnosis of HCC[67].

Given the fact that the diagnostic power of a single miRNA is limited, various panels consisting of more than one circulating miRNAs have been evaluated as well. Using a microarray to screen 723 miRNAs, Zhou *et al*[68] found a panel of seven miRNAs (miR-122, miR-192, miR-21, miR-223, miR-26a, miR-27a and miR-801) that distinguished between HCC and healthy controls (AUC = 0.941), chronic hepatitis B (AUC = 0.842) and liver cirrhosis (AUC = 0.884) even at an early stage of disease (BCLC 0) in three independent cohorts of 934 participants. In comparison to AFP, another miRNA panel of seven miRNAs (miR-29a, miR-29c, miR-133a, miR-143, miR-145, miR-192, and miR-505) was shown to have a superior AUC regarding the diagnosis of small-size (AUC = 0.833 *vs* AUC = 0.727) and early-stage (AUC = 0.824 *vs* AUC 0.754) HCCs. This panel did also have the ability to detect AFP-negative HCC patients[69]. Similar results were obtained for a panel consisting of miR-15b and miR-130 that showed a sensitivity of 98.2% with a specificity of 91.5% for the diagnosis of HCC and had detection sensitivity of 96.7% for patients with low AFP serum levels (< 20 ng/mL)[70].

Circulating miRNAs might also help to assess patients' outcome and their likelihood to benefit from different treatment options (surgery, systemic treatment, locally ablative treatment) in order to find a personalized therapy for individual patients. For instance, serum levels of miR-221 correlated with tumor size and tumor stage and patients with high levels of circulating miR-221 showed a significantly reduced overall survival compared to patients with lower miR-221 levels[71]. Likewise, high serum levels of miR-122 were found to independently predict a poor overall survival in a cohort of 122 HCC patients[72].

CCA

Although CCA represents a rare type of cancer in most parts of the world, it shares a very unfavorable prognosis with a 5-year survival rate of less than 5% for advanced disease stage[73]. Again, early detection of CCA is necessary to offer patients a surgical tumor resection, which is the only potentially curative treatment option, but the established tumor markers CA19-9 and CEA have a

restricted diagnostic power. Besides the available data on their potential role as a biomarker for HCC, miRNAs have also been evaluated in few studies as a diagnostic tool for CCA.

Based on a CCA tissue expression analysis, which revealed 262 regulated miRNAs in tumor samples, circulating levels of miR-21 and miR-221 were found to be significantly elevated in patients with intrahepatic CCA, showing a high discrimination ability of miR-21 between patients and healthy controls (AUC = 0.94)[74]. Nevertheless, these results are limited due to a small number of analyzed patients (n = 25). MiR-21 was further evaluated in a cohort of 94 patients with biliary tract cancer (BTC) and showed an AUC of 0.93 and 0.83 for the differentiation between BTC and healthy controls and BTC and non-malignant bile duct disease, respectively[75]. Interestingly, serum levels of miR-21 decreased after surgical tumor resection[75]. In another rather small study including a total of 30 CCA patients, Bernuzzi *et al*[49] identified circulating miR-483-5p and miR-194 as dysregulated in CCA patients. Furthermore, serum levels of miR-483-5p and miR-222 were able to discriminate between PSC and CCA patients. Other circulating miRNAs that were shown to be dysregulated in CCA patients are miR-224[76] and miR-150[77].

Some studies have also evaluated a potential use of miRNAs as a prognostic tool for CCA. Analyzing 103 patients with CCA, Cheng *et al*[78] described decreased serum levels of miR-106 as a predictor for poor survival. Moreover, elevated levels of circulating miR-26a correlated with disease stage and were reported to be an independent prognostic marker for CCA patients.

In summary, circulating miRNAs are of increasing interest for the diagnosis and prognosis of liver cancer. Although reliable data on serum/plasma miRNAs in the field of CCA are limited, circulating miRNAs are likely to play a decisive role for an early detection and the prediction of survival for both analyzed types of liver cancer in future. However, as the diagnostic and prognostic power of a single miRNA is limited, panels of different miRNA are needed to exceed the established biomarkers for liver cancer. In this context, larger studies will help to further evaluate and verify potential miRNAs for these purposes.

CONCLUSION

Circulating miRNAs represent a promising new tool for the diagnosis and prediction of prognosis for various acute and chronic liver diseases. Despite their obvious potential as biomarkers, there are several problems that prevent the use of circulating miRNAs as diagnostic tools in clinical routine. Most importantly, despite years of intensive research no consensus on optimal protocols for standardization of sample collection, data normalization and analysis was reached until now. As qPCR and microarray based measurements naturally depend on the design of miRNA specific primers or microarray probes, similarities between different miRNAs might result in further difficulties regarding the comparison between studies. Moreover, data normalization issues mainly arise from the lack of a valid intrinsic RNA housekeeping gene for human serum samples and high inter-platform differences in miRNA quantification efficacy contribute to a poor comparability between studies. Finally, most studies are carried out as single center study including only a small number of patients. Therefore, next generation sequencing might have an important impact on the validation of miRNA profiles, as it allows mostly sequence independent, parallel measurement and detection of overall numbers of a broad spectrum of different miRNAs (reviewed *e.g.,* in[79]). Thus, only if these present limitations can be overcome, circulating miRNAs might take the next step to be finally implemented in diagnostic algorithms or be used to estimate the clinical fate of patients with acute or chronic liver diseases.

REFERENCES

1 **Landgraf P**, Rusu M, Sheridan R, Sewer A, Iovino N, Aravin A, Pfeffer S, Rice A, Kamphorst AO, Landthaler M, Lin C, Socci ND, Hermida L, Fulci V, Chiaretti S, Foà R, Schliwka J, Fuchs U, Novosel A, Müller RU, Schermer B, Bissels U, Inman J, Phan Q, Chien M, Weir DB, Choksi R, De Vita G, Frezzetti D, Trompeter HI, Hornung V, Teng G, Hartmann G, Palkovits M, Di Lauro R, Wernet P, Macino G, Rogler CE, Nagle JW, Ju J, Papavasiliou FN, Benzing T, Lichter P, Tam W, Brownstein MJ, Bosio A, Borkhardt A, Russo JJ, Sander C, Zavolan M, Tuschl T. A mammalian microRNA expression atlas based on small RNA library sequencing. *Cell* 2007; **129**: 1401-1414 [PMID: 17604727 DOI: 10.1016/j.cell.2007.04.040]

2 **Krol J**, Loedige I, Filipowicz W. The widespread regulation of microRNA biogenesis, function and decay. *Nat Rev Genet* 2010; **11**: 597-610 [PMID: 20661255 DOI: 10.1038/nrg2843]

3 **Borchert GM**, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. *Nat Struct Mol Biol* 2006; **13**: 1097-1101 [PMID: 17099701 DOI: 10.1038/nsmb1167]

4 **Macfarlane LA**, Murphy PR. MicroRNA: Biogenesis, Function and Role in Cancer. *Curr Genomics* 2010; **11**: 537-561 [PMID: 21532838 DOI: 10.2174/138920210793175895]

5 **Ha M**, Kim VN. Regulation of microRNA biogenesis. *Nat Rev Mol Cell Biol* 2014; **15**: 509-524 [PMID: 25027649 DOI: 10.1038/nrm3838]

6 **Ryan BM**, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. *Nat Rev Cancer* 2010; **10**: 389-402 [PMID: 20495573 DOI: 10.1038/nrc2867]

7 **Bandiera S**, Pfeffer S, Baumert TF, Zeisel MB. miR-122--a key factor and therapeutic target in liver disease. *J Hepatol* 2015; **62**: 448-457 [PMID: 25308172 DOI: 10.1016/j.jhep.2014.10.004]

8 **Jiang X**, Tsitsiou E, Herrick SE, Lindsay MA. MicroRNAs and the regulation of fibrosis. *FEBS J* 2010; **277**: 2015-2021 [PMID: 20412055 DOI: 10.1111/j.1742-4658.2010.07632.x]

9 **Szabo G**, Bala S. MicroRNAs in liver disease. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 542-552 [PMID: 23689081 DOI: 10.1038/nrgastro.2013.87]

10 **Singh RP**, Massachi I, Manickavel S, Singh S, Rao NP, Hasan S, Mc Curdy DK, Sharma S, Wong D, Hahn BH, Rehimi H. The role of miRNA in inflammation and autoimmunity. *Autoimmun Rev* 2013; **12**: 1160-1165 [PMID: 23860189 DOI: 10.1016/j.autrev.2013.07.003]

11 **Wagner W**, Wein F, Roderburg C, Saffrich R, Diehlmann A, Eckstein V, Ho AD. Adhesion of human hematopoietic progenitor cells to mesenchymal stromal cells involves CD44. *Cells Tissues Organs* 2008; **188**: 160-169 [PMID: 18160820 DOI: 10.1159/000112821]

12 **Furer V**, Greenberg JD, Attur M, Abramson SB, Pillinger MH. The role of microRNA in rheumatoid arthritis and other autoimmune diseases. *Clin Immunol* 2010; **136**: 1-15 [PMID: 20223711 DOI: 10.1016/j.clim.2010.02.005]

13 **Lin S**, Gregory RI. MicroRNA biogenesis pathways in cancer. *Nat Rev Cancer* 2015; **15**: 321-333 [PMID: 25998712 DOI: 10.1038/nrc3932]

14 **Mitchell PS**, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogosova-Agadjanyan EL, Peterson A, Noteboom J, O'Briant KC, Allen A, Lin DW, Urban N, Drescher CW, Knudsen BS, Stirewalt DL, Gentleman R, Vessella RL, Nelson PS, Martin DB, Tewari M. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci USA* 2008; **105**: 10513-10518 [PMID: 18663219 DOI: 10.1073/pnas.0804549105]

15 **Lawrie CH**, Gal S, Dunlop HM, Pushkaran B, Liggins AP, Pulford K, Banham AH, Pezzella F, Boultwood J, Wainscoat JS, Hatton CS, Harris AL. Detection of elevated levels of tumour-associated microRNAs in serum of patients with diffuse large B-cell lymphoma. *Br J Haematol* 2008; **141**: 672-675 [PMID: 18318758 DOI: 10.1111/j.1365-2141.2008.07077.x]

16 **Chen X**, Ba Y, Ma L, Cai X, Yin Y, Wang K, Guo J, Zhang Y, Chen J, Guo X, Li Q, Li X, Wang W, Zhang Y, Wang J, Jiang X, Xiang Y, Xu C, Zheng P, Zhang J, Li R, Zhang H, Shang X, Gong T, Ning G, Wang J, Zen K, Zhang J, Zhang CY. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. *Cell Res* 2008; **18**: 997-1006 [PMID: 18766170 DOI: 10.1038/cr.2008.282]

17 **Cortez MA**, Bueso-Ramos C, Ferdin J, Lopez-Berestein G, Sood AK, Calin GA. MicroRNAs in body fluids--the mix of hormones and biomarkers. *Nat Rev Clin Oncol* 2011; **8**: 467-477 [PMID: 21647195 DOI: 10.1038/nrclinonc.2011.76]

18 **Wang K**, Zhang S, Marzolf B, Troisch P, Brightman A, Hu Z, Hood LE, Galas DJ. Circulating microRNAs, potential biomarkers for drug-induced liver injury. *Proc Natl Acad Sci USA* 2009; **106**: 4402-4407 [PMID: 19246379 DOI: 10.1073/pnas.0813371106]

19 **Creemers EE**, Tijsen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease? *Circ Res* 2012; **110**: 483-495 [PMID: 22302755 DOI: 10.1161/CIRCRESAHA.111.247452]

20 **Sato K**, Meng F, Glaser S, Alpini G. Exosomes in liver pathology. *J Hepatol* 2016; **65**: 213-221 [PMID: 26988731 DOI: 10.1016/j.jhep.2016.03.004]

21 **Momen-Heravi F**, Bala S, Kodys K, Szabo G. Exosomes derived from alcohol-treated hepatocytes horizontally transfer liver specific miRNA-122 and sensitize monocytes to LPS. *Sci Rep* 2015; **5**: 9991 [PMID: 25973575 DOI: 10.1038/srep09991]

22 **Yu X**, Odenthal M, Fries JW. Exosomes as miRNA Carriers: Formation-Function-Future. *Int J Mol Sci* 2016; **17**: pii: E2028 [PMID: 27918449 DOI: 10.3390/ijms17122028]

23 **Yin CQ**, Yuan CH, Qu Z, Guan Q, Chen H, Wang FB. Liquid Biopsy of Hepatocellular Carcinoma: Circulating Tumor-Derived Biomarkers. *Dis Markers* 2016; **2016**: 1427849 [PMID: 27403030 DOI: 10.1155/2016/1427849]

24 **Ansari J**, Yun JW, Kompelli AR, Moufarrej YE, Alexander JS, Herrera GA, Shackelford RE. The liquid biopsy in lung cancer. *Genes Cancer* 2016; **7**: 355-367 [PMID: 28191282 DOI: 10.18632/genesandcancer.127]

25 **Lee WM**. Acute liver failure. *Semin Respir Crit Care Med* 2012; **33**: 36-45 [PMID: 22447259 DOI: 10.1055/s-0032-1301733]

26 **John K**, Hadem J, Krech T, Wahl K, Manns MP, Dooley S, Batkai S, Thum T, Schulze-Osthoff K, Bantel H. MicroRNAs play a role in spontaneous recovery from acute liver failure. *Hepatology* 2014; **60**: 1346-1355 [PMID: 24913549 DOI: 10.1002/hep.27250]

27 **Mendizabal M**, Silva MO. Liver transplantation in acute liver failure: A challenging scenario. *World J Gastroenterol* 2016; **22**: 1523-1531 [PMID: 26819519 DOI: 10.3748/wjg.v22.i4.1523]

28 **Ostapowicz G**, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, McCashland TM, Shakil AO, Hay JE, Hynan L, Crippin JS, Blei AT, Samuel G, Reisch J, Lee WM. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; **137**: 947-954 [PMID: 12484709]

29 **Antoine DJ**, Dear JW, Lewis PS, Platt V, Coyle J, Masson M, Thanacoody RH, Gray AJ, Webb DJ, Moggs JG, Bateman DN, Goldring CE, Park BK. Mechanistic biomarkers provide early and sensitive detection of acetaminophen-induced acute liver injury at first presentation to hospital. *Hepatology* 2013; **58**: 777-787 [PMID: 23390034 DOI: 10.1002/hep.26294]

30 **Giannini EG**, Testa R, Savarino V. Liver enzyme alteration: a guide for clinicians. *CMAJ* 2005; **172**: 367-379 [PMID: 15684121 DOI: 10.1503/cmaj.1040752]

31 **Robles-Díaz M**, Medina-Caliz I, Stephens C, Andrade RJ, Lucena MI. Biomarkers in DILI: One More Step Forward. *Front Pharmacol* 2016; **7**: 267 [PMID: 27597831 DOI: 10.3389/fphar.2016.00267]

32 **Krauskopf J**, Caiment F, Claessen SM, Johnson KJ, Warner RL, Schomaker SJ, Burt DA, Aubrecht J, Kleinjans JC. Application of high-throughput sequencing to circulating microRNAs reveals novel biomarkers for drug-induced liver injury. *Toxicol Sci* 2015; **143**: 268-276 [PMID: 25359176 DOI: 10.1093/toxsci/kfu232]

33 **Starkey Lewis PJ**, Dear J, Platt V, Simpson KJ, Craig DG, Antoine DJ, French NS, Dhaun N, Webb DJ, Costello EM, Neoptolemos JP, Moggs J, Goldring CE, Park BK. Circulating microRNAs as potential markers of human drug-induced liver injury. *Hepatology* 2011; **54**: 1767-1776 [PMID: 22045675 DOI: 10.1002/hep.24538]

34 **Russo MW**, Steuerwald N, Norton HJ, Anderson WE, Foureau D, Chalasani N, Fontana RJ, Watkins PB, Serrano J, Bonkovsky HL. Profiles of miRNAs in serum in severe acute drug induced liver injury and their prognostic significance. *Liver Int* 2016; Epub ahead of print [PMID: 27860186 DOI: 10.1111/liv.13312]

35 **Lemoinne S**, Thabut D, Housset C, Moreau R, Valla D, Boulanger CM, Rautou PE. The emerging roles of microvesicles in liver diseases. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 350-361 [PMID: 24492276 DOI: 10.1038/nrgastro.2014.7]

36 **El-Ahwany E**, Nagy F, Zoheiry M, Shemis M, Nosseir M, Taleb HA, El Ghannam M, Atta R, Zada S. Circulating miRNAs as Predictor Markers for Activation of Hepatic Stellate Cells and Progression of HCV-Induced Liver Fibrosis. *Electron Physician* 2016; **8**: 1804-1810 [PMID: 26955452 DOI: 10.19082/1804]

37 **Cermelli S**, Ruggieri A, Marrero JA, Ioannou GN, Beretta L. Circulating microRNAs in patients with chronic hepatitis C and non-alcoholic fatty liver disease. *PLoS One* 2011; **6**: e23937 [PMID: 21886843 DOI: 10.1371/journal.pone.0023937]

38 **Salvoza NC**, Klinzing DC, Gopez-Cervantes J, Baclig MO. Association of Circulating Serum miR-34a and miR-122 with Dyslipidemia among Patients with Non-Alcoholic Fatty Liver Disease. *PLoS One* 2016; **11**: e0153497 [PMID: 27077736 DOI: 10.1371/journal.pone.0153497]

39 **Yamada H**, Suzuki K, Ichino N, Ando Y, Sawada A, Osakabe K, Sugimoto K, Ohashi K, Teradaira R, Inoue T, Hamajima N, Hashimoto S. Associations between circulating microRNAs (miR-21, miR-34a, miR-122 and miR-451) and non-alcoholic fatty liver. *Clin Chim Acta* 2013; **424**: 99-103 [PMID: 23727030 DOI: 10.1016/j.cca.2013.05.021]

40 **Roderburg C**, Mollnow T, Bongaerts B, Elfimova N, Vargas Cardenas D, Berger K, Zimmermann H, Koch A, Vucur M, Luedde M, Hellerbrand C, Odenthal M, Trautwein C, Tacke F, Luedde T. Micro-RNA profiling in human serum reveals compartment-specific roles of miR-571 and miR-652 in liver cirrhosis. *PLoS One* 2012; **7**: e32999 [PMID: 22412969 DOI: 10.1371/journal.pone.0032999]

41 **Roderburg C**, Urban GW, Bettermann K, Vucur M, Zimmermann H, Schmidt S, Janssen J, Koppe C, Knolle P, Castoldi M, Tacke F, Trautwein C, Luedde T. Micro-RNA profiling reveals a role for miR-29 in human and murine liver fibrosis. *Hepatology* 2011; **53**: 209-218 [PMID: 20890893 DOI: 10.1002/hep.23922]

42 **Momen-Heravi F**, Saha B, Kodys K, Catalano D, Satishchandran A, Szabo G. Increased number of circulating exosomes and their microRNA cargos are potential novel biomarkers in alcoholic hepatitis. *J Transl Med* 2015; **13**: 261 [PMID: 26264599 DOI: 10.1186/s12967-015-0623-9]

43 **Matsuura K**, De Giorgi V, Schechterly C, Wang RY, Farci P, Tanaka Y, Alter HJ. Circulating let-7 levels in plasma and extracellular vesicles correlate with hepatic fibrosis progression in chronic hepatitis C. *Hepatology* 2016; **64**: 732-745 [PMID: 27227815 DOI: 10.1002/hep.28660]

44 **Trebicka J**, Anadol E, Elfimova N, Strack I, Roggendorf M, Viazov S, Wedemeyer I, Drebber U, Rockstroh J, Sauerbruch T, Dienes HP, Odenthal M. Hepatic and serum levels of miR-122 after chronic HCV-induced fibrosis. *J Hepatol* 2013; **58**: 234-239 [PMID: 23085648 DOI: 10.1016/j.jhep.2012.10.015]

45 **Waidmann O**, Köberle V, Brunner F, Zeuzem S, Piiper A, Kronenberger B. Serum microRNA-122 predicts survival in patients with liver cirrhosis. *PLoS One* 2012; **7**: e45652 [PMID: 23029162 DOI: 10.1371/journal.pone.0045652]

46 **Jepsen P**, Grønbæk L, Vilstrup H. Worldwide Incidence of Autoimmune Liver Disease. *Dig Dis* 2015; **33** Suppl 2: 2-12 [PMID: 26641102 DOI: 10.1159/000440705]

47 **Migita K**, Komori A, Kozuru H, Jiuchi Y, Nakamura M, Yasunami M, Furukawa H, Abiru S, Yamasaki K, Nagaoka S, Hashimoto S, Bekki S, Kamitsukasa H, Nakamura Y, Ohta H, Shimada M, Takahashi H, Mita E, Hijioka T, Yamashita H, Kouno H, Nakamuta M, Ario K, Muro T, Sakai H, Sugi K, Nishimura H, Yoshizawa K, Sato T, Naganuma A, Komatsu T, Oohara Y, Makita F, Tomizawa M, Yatsuhashi H. Circulating microRNA Profiles in Patients with Type-1 Autoimmune Hepatitis. *PLoS One* 2015; **10**: e0136908 [PMID: 26575387 DOI: 10.1371/journal.pone.0136908]

48 **Voigtländer T**, Gupta SK, Thum S, Fendrich J, Manns MP, Lankisch TO, Thum T. MicroRNAs in Serum and Bile of Patients with Primary Sclerosing Cholangitis and/or Cholangiocarcinoma. *PLoS One* 2015; **10**: e0139305 [PMID: 26431155 DOI: 10.1371/journal.pone.0139305]

49 **Bernuzzi F**, Marabita F, Lleo A, Carbone M, Mirolo M, Marzioni M, Alpini G, Alvaro D, Boberg KM, Locati M, Torzilli G, Rimassa L, Piscaglia F, He XS, Bowlus CL, Yang GX, Gershwin ME, Invernizzi P. Serum microRNAs as novel biomarkers for primary sclerosing cholangitis and cholangiocarcinoma. *Clin Exp Immunol* 2016; **185**: 61-71 [PMID: 26864161 DOI: 10.1111/cei.12776]

50 **Ninomiya M**, Kondo Y, Funayama R, Nagashima T, Kogure T, Kakazu E, Kimura O, Ueno Y, Nakayama K, Shimosegawa T. Distinct microRNAs expression profile in primary biliary cirrhosis and evaluation of miR 505-3p and miR197-3p as novel biomarkers. *PLoS One* 2013; **8**: e66086 [PMID: 23776611 DOI: 10.1371/journal.pone.0066086]

51 **Tan Y**, Pan T, Ye Y, Ge G, Chen L, Wen D, Zou S. Serum microRNAs as potential biomarkers of primary biliary cirrhosis. *PLoS One* 2014; **9**: e111424 [PMID: 25347847 DOI: 10.1371/journal.pone.0111424]

52 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

53 **McGlynn KA**, London WT. The global epidemiology of hepatocellular carcinoma: present and future. *Clin Liver Dis* 2011; **15**: 223-243, vii-x [PMID: 21689610 DOI: 10.1016/j.cld.2011.03.006]

54 **Venook AP**, Papandreou C, Furuse J, de Guevara LL. The incidence and epidemiology of hepatocellular carcinoma: a global and regional perspective. *Oncologist* 2010; **15** Suppl 4: 5-13 [PMID: 21115576 DOI: 10.1634/theoncologist.2010-S4-05]

55 **Altekruse SF**, McGlynn KA, Reichman ME. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J Clin Oncol* 2009; **27**: 1485-1491 [PMID: 19224838 DOI: 10.1200/JCO.2008.20.7753]

56 **Esau C**, Davis S, Murray SF, Yu XX, Pandey SK, Pear M, Watts L, Booten SL, Graham M, McKay R, Subramaniam A, Propp S, Lollo BA, Freier S, Bennett CF, Bhanot S, Monia BP. miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. *Cell Metab* 2006; **3**: 87-98 [PMID: 16459310 DOI: 10.1016/j.cmet.2006.01.005]

57 **Qi P**, Cheng SQ, Wang H, Li N, Chen YF, Gao CF. Serum microRNAs as biomarkers for hepatocellular carcinoma in Chinese patients with chronic hepatitis B virus infection. *PLoS One* 2011; **6**: e28486 [PMID: 22174818 DOI: 10.1371/journal.pone.0028486]

58 **Xu J**, Wu C, Che X, Wang L, Yu D, Zhang T, Huang L, Li H, Tan W, Wang C, Lin D. Circulating microRNAs, miR-21, miR-122, and miR-223, in patients with hepatocellular carcinoma or chronic hepatitis. *Mol Carcinog* 2011; **50**: 136-142 [PMID: 21229610 DOI: 10.1002/mc.20712]

59 **Bala S**, Petrasek J, Mundkur S, Catalano D, Levin I, Ward J, Alao H, Kodys K, Szabo G. Circulating microRNAs in exosomes indicate hepatocyte injury and inflammation in alcoholic, drug-induced, and inflammatory liver diseases. *Hepatology* 2012; **56**: 1946-1957 [PMID: 22684891 DOI: 10.1002/hep.25873]

60 **Coulouarn C**, Factor VM, Andersen JB, Durkin ME, Thorgeirsson SS. Loss of miR-122 expression in liver cancer correlates with suppression of the hepatic phenotype and gain of metastatic properties. *Oncogene* 2009; **28**: 3526-3536 [PMID: 19617899 DOI: 10.1038/onc.2009.211]

61 **Sohn W**, Kim J, Kang SH, Yang SR, Cho JY, Cho HC, Shim SG, Paik YH. Serum exosomal microRNAs as novel biomarkers for hepatocellular carcinoma. *Exp Mol Med* 2015; **47**: e184 [PMID: 26380927 DOI: 10.1038/emm.2015.68]

62 **Ge W**, Yu DC, Li QG, Chen X, Zhang CY, Ding YT. Expression of serum miR-16, let-7f, and miR-21 in patients with hepatocellular carcinoma and their clinical significances. *Clin Lab* 2014; **60**: 427-434 [PMID: 24697119]

63 **El-Abd NE**, Fawzy NA, El-Sheikh SM, Soliman ME. Circulating miRNA-122, miRNA-199a, and miRNA-16 as Biomarkers for Early Detection of Hepatocellular Carcinoma in Egyptian Patients with Chronic Hepatitis C Virus Infection. *Mol Diagn Ther* 2015; **19**: 213-220 [PMID: 26133725 DOI: 10.1007/s40291-015-0148-1]

64 **Tomimaru Y**, Eguchi H, Nagano H, Wada H, Kobayashi S, Marubashi S, Tanemura M, Tomokuni A, Takemasa I, Umeshita K, Kanto T, Doki Y, Mori M. Circulating microRNA-21 as a novel biomarker for hepatocellular carcinoma. *J Hepatol* 2012; **56**: 167-175 [PMID: 21749846 DOI: 10.1016/j.jhep.2011.04.026]

65 **Li BS**, Zhao YL, Guo G, Li W, Zhu ED, Luo X, Mao XH, Zou QM, Yu PW, Zuo QF, Li N, Tang B, Liu KY, Xiao B. Plasma microRNAs, miR-223, miR-21 and miR-218, as novel potential biomarkers for gastric cancer detection. *PLoS One* 2012; **7**: e41629 [PMID: 22860003 DOI: 10.1371/journal.pone.0041629]

66 **Shan L**, Ji Q, Cheng G, Xia J, Liu D, Wu C, Zhu B, Ding Y. Diagnostic value of circulating miR-21 for colorectal cancer: a meta-analysis. *Cancer Biomark* 2015; **15**: 47-56 [PMID: 25524942 DOI: 10.3233/CBM-140437]

67 **Liao Q**, Han P, Huang Y, Wu Z, Chen Q, Li S, Ye J, Wu X. Potential Role of Circulating microRNA-21 for Hepatocellular Carcinoma Diagnosis: A Meta-Analysis. *PLoS One* 2015; **10**: e0130677 [PMID: 26114756 DOI: 10.1371/journal.pone.0130677]

68 **Zhou J**, Yu L, Gao X, Hu J, Wang J, Dai Z, Wang JF, Zhang Z, Lu S, Huang X, Wang Z, Qiu S, Wang X, Yang G, Sun H, Tang Z, Wu Y, Zhu H, Fan J. Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma. *J Clin Oncol* 2011; **29**: 4781-4788 [PMID: 22105822 DOI: 10.1200/JCO.2011.38.2697]

69 **Lin XJ**, Chong Y, Guo ZW, Xie C, Yang XJ, Zhang Q, Li SP, Xiong Y, Yuan Y, Min J, Jia WH, Jie Y, Chen MS, Chen MX, Fang JH, Zeng C, Zhang Y, Guo RP, Wu Y, Lin G, Zheng L, Zhuang SM. A serum microRNA classifier for early detection of hepatocellular carcinoma: a multicentre, retrospective, longitudinal biomarker identification study with a nested case-control study. *Lancet Oncol* 2015; **16**: 804-815 [PMID: 26088272 DOI: 10.1016/S1470-2045(15)00048-0]

70 **Liu AM**, Yao TJ, Wang W, Wong KF, Lee NP, Fan ST, Poon RT, Gao C, Luk JM. Circulating miR-15b and miR-130b in serum as potential markers for detecting hepatocellular carcinoma: a retrospective cohort study. *BMJ Open* 2012; **2**: e000825 [PMID: 22403344 DOI: 10.1136/bmjopen-2012-000825]

71 **Li J**, Wang Y, Yu W, Chen J, Luo J. Expression of serum miR-221 in human hepatocellular carcinoma and its prognostic significance. *Biochem Biophys Res Commun* 2011; **406**: 70-73 [PMID: 21295551 DOI: 10.1016/j.bbrc.2011.01.111]

72 **Xu Y**, Bu X, Dai C, Shang C. High serum microRNA-122 level

is independently associated with higher overall survival rate in hepatocellular carcinoma patients. *Tumour Biol* 2015; **36**: 4773-4776 [PMID: 25636448 DOI: 10.1007/s13277-015-3128-5]

73 **Razumilava N**, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; **383**: 2168-2179 [PMID: 24581682 DOI: 10.1016/S0140-6736(13)61903-0]

74 **Correa-Gallego C**, Maddalo D, Doussot A, Kemeny N, Kingham TP, Allen PJ, D'Angelica MI, DeMatteo RP, Betel D, Klimstra D, Jarnagin WR, Ventura A. Circulating Plasma Levels of MicroRNA-21 and MicroRNA-221 Are Potential Diagnostic Markers for Primary Intrahepatic Cholangiocarcinoma. *PLoS One* 2016; **11**: e0163699 [PMID: 27685844 DOI: 10.1371/journal.pone.0163699]

75 **Kishimoto T**, Eguchi H, Nagano H, Kobayashi S, Akita H, Hama N, Wada H, Kawamoto K, Tomokuni A, Tomimaru Y, Umeshita K, Doki Y, Mori M. Plasma miR-21 is a novel diagnostic biomarker for biliary tract cancer. *Cancer Sci* 2013; **104**: 1626-1631 [PMID: 24118467 DOI: 10.1111/cas.12300]

76 **Huang M**, Wu X, Cao H, Zhan Q, Xia M, Zhou Q, Cai X, An F. [Regulatory role of serum miR-224 in invasiveness and metastasis of cholangiocarcinoma]. *Zhonghua Gan Zang Bing Za Zhi* 2015; **23**: 748-753 [PMID: 26573191 DOI: 10.3760/cma.j.issn.1007-3418.2015.10.008]

77 **Wang S**, Yin J, Li T, Yuan L, Wang D, He J, Du X, Lu J. Up-regulated circulating miR-150 is associated with the risk of intrahepatic cholangiocarcinoma. *Oncol Rep* 2015; **33**: 819-825 [PMID: 25482320 DOI: 10.3892/or.2014.3641]

78 **Cheng Q**, Feng F, Zhu L, Zheng Y, Luo X, Liu C, Yi B, Jiang X. Circulating miR-106a is a Novel Prognostic and Lymph Node Metastasis Indicator for Cholangiocarcinoma. *Sci Rep* 2015; **5**: 16103 [PMID: 26534789 DOI: 10.1038/srep16103]

79 **Etheridge A**, Lee I, Hood L, Galas D, Wang K. Extracellular microRNA: a new source of biomarkers. *Mutat Res* 2011; **717**: 85-90 [PMID: 21402084 DOI: 10.1016/j.mrfmmm.2011.03.004]

P- Reviewer: Guerrieri F, Hsieh SY, Yang ZX, Zhu X
S- Editor: Song XX **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 April 28; 9(12): 595-602

DOI: 10.4254/wjh.v9.i12.595

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Diagnosis of morbid obesity may not impact healthcare utilization for orthotopic liver transplantation: A propensity matched study

Joshua R Peck, Nicholas Latchana, Anthony Michaels, Adam J Hanje, Alice Hinton, Elmahdi A Elkhammas, Sylvester M Black, Khalid Mumtaz

Joshua R Peck, Anthony Michaels, Adam J Hanje, Khalid Mumtaz, Division of Gastroenterology, Hepatology and Nutrition, the Ohio State University Wexner Medical Center, Columbus, OH 43120, United States

Nicholas Latchana, Elmahdi A Elkhammas, Sylvester M Black, Department of Surgery, the Ohio State University Wexner Medical Center, Columbus, OH 43120, United States

Alice Hinton, Department of Biostatistics, the Ohio State University Wexner Medical Center, Columbus, OH 43120, United States

Author contributions: Peck JR and Mumtaz K, designed the study; Peck JR, Mumtaz K, Latchana N and Hinton A collected and analyzed the data; Peck JR, Latchana N, Michaels A, Hanje AJ, Hinton A, Elkhammas E, Black SM and Mumtaz K all equally contributed to writing the paper.

Institutional review board statement: This study was IRB exempt.

Informed consent statement: Consent was not obtained but the presented data are anonymized and the risk of identification is low.

Conflict-of-interest statement: None of the authors have any conflicts of interest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at khalid.mumtaz@osumc.edu.

Manuscript source: Invited manuscript

Correspondence to: Khalid Mumtaz, MD, MSc, Assistant Professor, Division of Gastroenterology, Hepatology and Nutrition, the Ohio State University Wexner Medical Center, 395 W 12th Ave, 2nd Floor, Columbus, OH 43210, United States. khalid.mumtaz@osumc.edu
Telephone: +1-614-2938000
Fax: +1-614-2930861

Received: December 4, 2016
Peer-review started: December 5, 2016
First decision: January 21, 2017
Revised: February 15, 2017
Accepted: March 21, 2017
Article in press: March 22, 2017
Published online: April 28, 2017

Abstract

AIM

To study mortality, length of stay, and total charges in morbidly obese adults during index hospitalization for orthotopic liver transplantation.

METHODS

The Nationwide Inpatient Sample was queried to obtain demographics, healthcare utilization, post orthotopic liver transplantation (OLT) complications, and short term outcomes of OLT performed from 2003 to 2011 (n = 46509). We divided patients into those with [body mass index (BMI) $\geqslant$ 40] and without (BMI < 40) morbid obesity. Multivariable logistic regression analysis was performed

to characterize differences in in-hospital mortality, length of stay (LOS), and charges for OLT between patients with and without morbid obesity after adjusting for significant confounders. Additionally, propensity matching was performed to further validate the results.

RESULTS

Of the 46509 patients who underwent OLT during the study period, 818 (1.8%) were morbidly obese. Morbidly obese recipients were more likely to be female (46.8% *vs* 33.4%, P = 0.002), Caucasian (75.2% *vs* 67.8%, P = 0.002), in the low national income quartile (32.3% *vs* 22.5%, P = 0.04), and have $\geqslant$ 3 comorbidities (modified Elixhauser index; 83.9% *vs* 45.0%, P < 0.001). Morbidly obese patient also had an increase in procedure related hemorrhage (P = 0.028) and respiratory complications (P = 0.043). Multivariate and propensity matched analysis showed no difference in mortality (OR: 0.70; 95%CI: 0.27-1.84, P = 0.47), LOS (β: -4.44; 95%CI: -9.93, 1.05, P = 0.11) and charges for transplantation (β: $15693; 95%CI: -51622-83008, P = 0.64) between the two groups. Morbidly obese patients were more likely to have transplants on weekdays (81.7%) as compared to those without morbid obesity (75.4%, P = 0.029).

CONCLUSION

Morbid obesity may not impact in-hospital mortality and health care utilization in OLT recipients. However, morbidly obese patients may be selected after careful assessment of co-morbidities.

Key words: Deceased donors; Outcome; Complications; Economics; Selection criteria

Core tip: Morbid obesity is a relative contraindication to orthotopic liver transplantation. Previous studies, mostly in the pre-MELD era, suggested worsened outcomes in these patients. As the prevalence of obesity continues to increase, so will the number of patients who are morbidly obese requiring liver transplantation. Utilizing the Nationwide Inpatient Sample which is the largest publicly available database in the United States, we did not find any difference in mortality, or healthcare utilization when comparing those with and without morbid obesity receiving liver transplantation. Our findings suggest that in highly selected patients, morbid obesity may not be a significant contraindication to transplantation.

Peck JR, Latchana N, Michaels A, Hanje AJ, Hinton A, Elkhammas EA, Black SM, Mumtaz K. Diagnosis of morbid obesity may not impact healthcare utilization for orthotopic liver transplantation: A propensity matched study. *World J Hepatol* 2017; 9(12): 595-602 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i12/595.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i12.595

INTRODUCTION

There has been a great deal of attention given to the outcomes of orthotopic liver transplantation (OLT) in obese patients, with varying reports on morbidity and mortality. A study by Nair *et al*[1] investigated graft and patient survival in obese patients receiving OLT in the United States between 1988 through 1996 using the United Network for Organ Sharing database. They found that primary graft non-function and immediate 1-year and 2-year mortality were higher in morbidly obese individuals. They also found increased 5-year mortality in morbidly [body mass index (BMI) of 35.1-40 kg/m^2] obese patients. Contrary to that, Pelletier *et al*[2], reported no increased risk of post-transplant mortality in obese or morbidly obese patients recruited from 2001 to 2004. The disparities between the aforementioned studies by Nair *et al*[1] and Pelletier *et al*[2] can likely be attributed to the Nair *et al*[1] study occurring in the pre-MELD era as compared to within or just before the application of MELD by Pelletier.

Greater peri-operative morbidity and increased post-operative length of stay appears to be a fairly consistent finding in the morbidly obese patients in various studies[3-5]. A few studies do report increased wound related and infectious complications in patients with morbid obesity after transplantation[3,6]. In one study, obese patients surprisingly did not require prolonged ventilation support as compared to non-obese patients[6].

Studies have also shown socioracial disparities in OLT utilization. In addition to race, women, older patients, individuals with non-commercial insurance, individuals in certain geographic locations (as defined by donor service areas), and those with alcoholic liver disease have been shown to receive lower rates of transplantation[7].

Large population based studies from United States on health care utilization and short term outcomes of liver transplantation in morbidly obese patients were not found. We hypothesized that provided selected carefully morbidly obese patients undergoing liver transplantation may not have different healthcare utilization and short term outcomes. We studied the health care utilization, in-hospital morbidity, mortality and direct charges for care in morbidly obese patients receiving OLT in the United States during 2003-2011.

MATERIALS AND METHODS

Database information

The Nationwide Inpatient Sample (NIS) is the largest publicly available database in the United States. It contains data from over 8 million hospital stays each year, and allows users to track and analyze trends and outcomes of health care. The NIS database is the largest all-payer inpatient care database in the United States, representing an approximately 20% stratified sample of 1044 non-

federal hospitals in 47 states[8].

The information was collected from the NIS database from years 2003 to 2011 among all adult (age > 18 years) in-patients with a procedure code for liver transplantation as determined by International Classification of Disease-Clinical Modification, Ninth Revision, (ICD-CM) codes. According to weighted estimate, 47185 adult patients were identified who underwent liver transplantation with ICD-CM procedure code 50.59 (other liver transplantation, *i.e.,* non-auxiliary).

The NIS database has limited clinical variables, but it provides a large sample size representative of the United States. Moreover, it is reliable in terms of hard end-points such as inpatient mortality and hospital length of stay. Another unique feature of this database is information on the direct charges for hospital stay, which have not been studied in the past among obese liver transplant recipients. Additional data collected including healthcare utilization were, age, gender, race, income (National Quartile), type of insurance, type of hospital (rural/urban non-teaching *vs* urban teaching), hospital size, hospital region, and Modified Elixhauser index based on pre-OLT comorbid medical conditions)[9]. This index counts the number of comorbidities present from a list of 29. We modified it by removing liver failure and morbid obesity.

We divided the patients into those with morbid obesity (BMI $\geqslant$ 40) and with a BMI < 40. The following ICD-9 codes were used for morbid obesity, 278.01, V85.4, V85.41, V85.42, V85.43, V85.44 and V85.45. Patients without one of the previous codes present were assumed to have a BMI under 40. We chose a BMI cutoff of 40 as previous studies have shown that when compared to lower BMIs, there is a higher sensitivity and specificity when accounting for correct documentation[10]. Variables studied among two groups were the pre-OLT comorbidities and post-OLT complications. We divided the post OLT complications into two distinct categories, *i.e.*, systemic and technical. Systemic complications included those which were among broader groups of events for which timing was indeterminate (*i.e.*, cardiovascular complications, Post-LT infections, *etc.*). Technical complications were felt to be related to the actual surgery itself[11].

Outcomes and predictors

We studied outcomes including mortality during the hospitalization for OLT, length of hospital stay, total direct charges for care (without professional fees) among patients with and without morbid obesity. The NIS quantifies inpatient discharges and does not link patients across hospital discharges. As such, patients with multiple discharges may have been counted multiple times if they had multiple hospitalizations where the procedure code for OLT was documented.

The major pre-, intra, and postoperative complications were identified using ICD-9-CM diagnostic codes (appendix 1). As the ICD-9-CM coding system does not include transplant-specific codes for many of the postoperative variables that are of particular interest, the best available codes were used.

This study was exempted from review by The Ohio State University Institutional Review Board.

Statistical analysis

SAS 9.3 (SAS Institute, Cary, NC) was used to perform all analyses, employing appropriate survey estimation commands and strata weights. Weighted frequencies and percentages were calculated for all categorical variables; means and 95%CIs were calculated for continuous variables. Differences between patients with and without morbid obesity (BMI $\geqslant$ 40) were analyzed using χ^2 tests or student's *t*-tests, as appropriate. Variables significantly associated with morbid obesity on univariate analysis were included in all multivariate models. We performed a multivariate logistic regression for mortality, while multivariate linear regression was used for length of stay and total hospital charges.

Propensity scores were calculated using a multivariate logistic regression model for morbid obesity containing all demographic variables (Age, Gender, Race, Income, Insurance, Hospital Location, Teaching Status, Size, and Region), and comorbid conditions (29 Elixhauser comorbidities excluding obesity and liver failure).

Patients with and without morbid obesity were then matched 1:1 using a greedy matching algorithm with a caliper of 0.2 times the standard deviation of the propensity scores. One hundred and fourty-three pairs were formed. One hundred and fourty-three of the original 145 (unweighted number) patients with morbid obesity were matched with a control. Note that our cohort contains 168 patients with morbid obesity; however, only 145 of the 168 were eligible for matching due to missing data primarily within the race variable.

The gmatch macro written by the Mayo Clinic was used for the matching. The statistical methods of this study were reviewed by Alice Hinton from the Ohio State University (http://www.mayo.edu/research/departments-divisions/department-health-sciences-research/division-biomedical-statistics-informatics/software/locally-written-sas-macros).

RESULTS

Demographics

After weighting, the NIS represented 46509 patients who underwent liver transplantation from 2003 through 2011. Of these patients, 818 (1.8%) were morbidly obese. The demographic and hospital characteristic variables are shown in Table 1. The groups were similar with regards to age, type of insurance, type and region of hospital. There were more females among the morbidly obese group (46.8%) as compared to without morbid obesity (33.4%), $P = 0.002$. There were more transplant recipients belonging to white race (75.2% *vs* 67.8%, $P = 0.002$) and low national income quartile (32.3% *vs* 22.5%, $P = 0.04$) among morbidly obese patients as

Table 1 Demographic and hospital characteristics in morbidly obese and non-morbidly obese patients who underwent a liver transplant

	No morbid obesity *n* = 45691		Morbid obesity *n* = 818		*P*-value
Age (mean, CI)	53.23	(52.84, 53.61)	53.33	(52.05, 54.61)	0.87
Gender					0.002
Male	30444	66.64%	435	53.21%	
Female	15242	33.36%	383	46.79%	
Race					0.002
White	25668	67.81%	544	75.15%	
Black	2975	7.86%	32	4.49%	
Hispanic	5638	14.90%	127	17.60%	
Other	3571	9.43%	20	2.75%	
Income (National Quartile)					0.04
Low	9947	22.46%	258	32.30%	
Moderate	11190	25.27%	213	26.63%	
High	11816	26.69%	167	20.87%	
Very high	11324	25.58%	161	20.20%	
Type of insurance					0.11
Medicare	11817	25.99%	246	30.10%	
Medicaid	6487	14.27%	74	8.99%	
Private	24983	54.95%	441	53.93%	
Other	2179	4.79%	57	6.97%	
Type of hospital					0.95
Rural/urban non-teaching	233	0.51%	< 10	0.48%	
Urban teaching	45069	99.49%	814	99.52%	
Hospital size					0.25
Small/medium	6492	14.33%	88	10.74%	
Large	38809	85.67%	730	89.26%	
Hospital region					0.43
Northeast	7865	17.21%	118	14.42%	
Midwest	9953	21.78%	206	25.24%	
South	15116	33.08%	319	39.02%	
West	12757	27.92%	174	21.32%	
Admission day					0.02
Week day	34444	75.39%	668	81.72%	
Weekend	11247	24.62%	149	18.28%	
Modified elixhauser index[1]					< 0.01
< 3	25123	54.98%	131	16.06%	
⩾ 3	20568	45.02%	686	83.94%	

[1]After excluding liver failure and obesity.

compared to those without morbid obesity. In addition, morbidly obese transplant recipients had significantly more comorbid conditions with ⩾ 3 conditions (*n* = 686; 83.9%) on the modified Elixhauser index than those without morbid obesity (*n* = 20568; 45.0%), *P* < 0.001. Lastly, morbidly obese patients were more likely to have transplants on weekdays (81.7%) as compared to those without morbid obesity (75.4%, *P* = 0.028).

Post OLT complications

Table 2 shows the various post OLT complications in patients who underwent liver transplantation. Among systemic post OLT complications, there were significantly more respiratory complications in morbidly obese patients (4.87% *vs* 1.05%, *P* = 0.04) after transplant. Contrary to that, hemorrhage complicating a procedure was significantly higher in non-morbidly obese patients (11.80% *vs* 7.04%, *P* = 0.03) as compared to morbidly obese patients. However, all other post OLT complications were equally distributed in the two groups. Similarly, hepatic artery thrombosis (*P* = 0.05), anastomotic biliary leaks (*P* = 0.08), and accidental laceration during a procedure (*P* = 0.06) were more frequent in non-morbidly obese, though they did not reach statistical significance. Overall, complication rates were equally distributed in the two groups.

Multivariate analysis

Table 3 shows the adjusted odds ratio (aOR) for mortality and β-coefficients for length of stay and charges for liver transplantation in the non-morbidly obese and morbidly obese groups. Non-morbidly obese patients had a 5.27% mortality whereas the mortality among morbidly obese transplant recipients was 4.83% (aOR: 0.98; 95%CI: 0.50-1.92, *P* = 0.95). The average length of stay in non-morbidly obese patients was 20.9 d and in morbidly obese patients it was 18.7 d (β: -3.90; 95%CI: -7.94-0.14, *P* = 0.06). The average total charges for transplantation was $342324 and $378452 in non-morbidly obese and morbidly obese patients, respectively (β: $612; 95%CI: -54780-56004, *P* = 0.98). Data was adjusted for gender, race, income, modified Elixhauser comorbidity index, weekend admission, and diabetes.

Propensity based analysis

In order to further endorse our findings, a matched cohort on the basis of morbid obesity status was then created using propensity scores. The propensity score analysis was not able to account for the weighting in the dataset. Before weights were taken into account 168 of the OLT patients were morbidly obese. Of the 168 patients 143 (85%) were matched 1:1 with a non-morbidly obese patient on the basis of propensity scores. Thus, in this cohort, there were a total of 286 patients divided equally into two groups based on morbid obesity status (143 patients each in morbidly obese and non-morbidly obese groups). After propensity matching, no differences between pre- and post OLT variables in the two groups were statistically significant (appendix 2). This allowed analysis of outcomes based on morbid obesity status alone, thereby reducing selection bias based on various other characteristics. Analysis showed no significant difference in mortality (OR: 0.70; 95%CI: 0.27-1.84, *P* = 0.47), LOS (β: -4.44; 95%CI: -9.93-1.05, *P* = 0.11) or charges for transplantation (β: $15693; 95%CI: -51622-83008, *P* = 0.64) between two groups (Table 4).

DISCUSSION

In this Nationwide Inpatient Sample database study we found that the diagnosis of morbid obesity may not have a significant impact on the health care utilization in the liver transplant cohort. We found that 1.8% of

Table 2 Complications of patients who underwent a liver transplant

	No morbid obesity n = 45691		Morbid obesity n = 818		*P*-value
Systemic complications					
Any	20546	44.97%	394	48.20%	0.5253
Post LT infection	13308	29.13%	297	36.26%	0.2103
Cardiovascular complication	781	1.71%	25	3.05%	0.3858
Infections, surgical wound	2035	4.45%	35	4.29%	0.9301
Cardiac complications	1972	4.32%	49	6.00%	0.2737
Peripheral vascular complications	152	0.33%	0	0.00%	--
Respiratory complications	481	1.05%	40	4.87%	0.0433
Digestive system complications	95	0.21%	⩽ 10	1.12%	0.2376
Other postoperative infection	2035	4.45%	35	4.29%	0.9301
Pulmonary insufficiency following surgery	269	0.59%	⩽ 10	0.57%	0.9654
Unspecified intestinal obstruction	145	0.32%	0	0.00%	--
Stroke	149	0.33%	0	0.00%	--
Postoperative shock	69	0.15%	⩽ 10	0.57%	0.4556
Post LT complication	9927	21.73%	142	17.40%	0.1441
Technical complications					
Any	16044	35.11%	263	32.27%	0.4206
Hepatic artery thrombosis	8940	19.57%	113	13.80%	0.0531
History of exploratory laparotomy exploratory laparotomy	221	0.48%	⩽ 10	0.57%	0.8483
Anastomotic leak of biliary tree	1442	3.16%	49	6.00%	0.0837
Perforation of the intestine	148	0.32%	0	0.00%	--
Hemorrhage complicating a procedure	5390	11.80%	58	7.04%	0.0278
Accidental laceration during a procedure	965	2.11%	⩽ 10	0.67%	0.0611
Iatrogenic pulmonary embolism and infarction	169	0.37%	20	2.49%	0.0862
Iatrogenic pneumothorax	691	1.51%	⩽ 10	1.14%	0.6429
Hematoma	3487	7.63%	65	7.94%	0.8931
Seroma complicating a procedure	74	0.16%	⩽ 10	1.15%	0.2145
Disruption of wound	25	0.06%	0	0.00%	--
Disruption of internal operation wound	179	0.39%	0	0.00%	--
Disruption of external operation wound	378	0.83%	20	2.43%	0.1632

Variables are expressed as weighted frequency (percentage) and differences between the groups are analyzed with χ^2 tests. LT: Liver transplantation.

Table 3 Results of multivariate linear/logistic regression for mortality, length of stay and charges for liver transplantation in study cohort

Outcomes	No morbid obesity n = 45691 (%)	Morbid obesity n = 818 (%)	Adjusted OR/β-coefficient (95%CI)	*P*-value
Mortality	2407 (5.27%)	39 (4.83%)	0.98 (0.50-1.92)	0.95
Length of stay in days, mean (CI)	20.9 (18.7-23.1)	18.7 (15.5-22)	-3.9[1] (-7.94-0.14)	0.06
Total charges, mean (CI)	342324 (305778-378870)	378452 (320453-436452)	612[1] (-54780-56004)	0.98

[1]β-coefficients. Data was adjusted for gender, race, income, modified Elixhauser comorbidity score, weekend admission, and diabetes.

patients who underwent liver transplantation from 2003 to 2011 were morbidly obese, *i.e.*, BMI ⩾ 40. Moreover, morbidly obese transplant recipients were more likely to be females, Caucasian, low national income quartile, and had OLT surgeries on weekdays; they also had more pre-transplant comorbid conditions based on the modified Elixhauser index. The majority of post-OLT complications, except procedure related hemorrhage and respiratory complications were equally distributed in all transplant recipients. Despite these differences, in pre- and post-liver transplant issues, no difference in mortality, LOS or charges for transplantation was observed in the two groups.

In our study the incidence of morbidly obese OLT recipients is equal to previous studies by Nair *et al*[1] but less than Pelletier *et al*[2]. However, the prevalence of morbid obesity reported in the general population is approximately 6.4%. This discrepancy is likely due to the plausible super-selective nature of transplantation candidacy. Obese candidates are at a higher risk for mortality may now be more readily identified and carefully selected. Whereas obesity in itself is not an indication for invasive pre-cardiac screening, obesity-related comorbidities such as coronary artery disease, hypertension, and dyslipidemia may warrant cardiac catheterization or additional testing[12]. This allows for detection of morbidly obese individuals with severe cardiac disease which precludes liver transplantation.

We found no statistically significant difference between healthcare utilization in our cohort of morbidly obese and non-morbidly obese patients. Previous studies have shown that individuals referred for OLT were more likely to have

Table 4 Analysis of outcomes in the propensity matched sample

Outcomes	No morbid obesity *n* = 143	Morbid obesity *n* = 143	Adjusted OR/β-coefficient (95%CI)	*P*-value
Mortality	10 (7.04%)	< 10 (4.93%)	0.70 (0.27-1.84)	0.47
Length of stay in days, mean (CI)	24.1 (19.5-28.7)	19.6 (16.8-22.5)	-4.44 (-9.93-1.05)[1]	0.11
Total charges, mean (CI)	388530 (344027-33033)	395518 (349932-441105)	15693 (-51622-83008)[1]	0.64

[1]β-coefficients.

private insurances[13]. As would be expected, the majority of individuals who receive liver transplantation also had private insurances (55% and 54% for non-morbidly obese and morbidly obese, respectively); however, there was no overall difference between the two groups among utilization of Medicaid, Medicare, and others (P = 0.11). The vast majority of both groups of liver recipients were transplanted at urban teaching hospitals (> 99%, P = 0.95), similar to trends reported in other studies[14]. There also was no statistically significant difference between groups for hospital size (P = 0.24) or hospital region (P = 0.43). Current guidelines from the American Association for the Study of Liver Disease consider morbid obesity a relative contraindication to liver transplantation[15]. Previously reported data on outcomes in morbidly obese transplant recipients has been contradictory, with some studies showing equivalent outcomes[16,17] while others showed increased post-operative complications[18] and decreased survival[1]. Importantly, we found that there was no statistically significant increase in mortality for morbidly obese liver transplant recipients. This contrasts data from previous studies which suggest higher rates of mortality in morbidly obese patients after transplant. The differences reported in peri-operative mortality and morbidity in studies can potentially be explained by heterogeneity amongst the obese and morbidly obese patients. Also the sample size and effect of era may be responsible for the variability in outcomes.

Obesity has been shown to be protective in patients in many settings, including the intensive care unit and in patients with severe sepsis[19,20]. There are multiple hypotheses for the improved outcomes seen in obese patients in these settings. It has been demonstrated that obesity leads to loss of tissue homeostasis and development of an inflammatory response characterized by an accumulation of pro-inflammatory type-1 phenotype macrophages[21,22]. However, critical illness instigates the accumulation of alternatively activated M2 macrophages with a more anti-inflammatory role[22]. It has also been observed that critically ill obese patients with ARDS have reduced levels of inflammatory cytokines[23]. The shift to an anti-inflammatory milieu may partially explain a protective role of obesity in LT patients. Another possible explanation relates to the nutritional reserves possessed by obese patients, which may help them tolerate the increased metabolic demands of critical illness[24].

We also found no statistically significant difference in either length of stay or total hospital charge. We hypothesize that multiple factors may be influencing this outcome. First, selection criteria is more stringent since the development of the MELD system. In addition, as the prevalence of obesity in the United States continues to increase, surgeons and other physicians are more experienced in the nuances of providing care for these patients. Lastly, it is also possible that our short-term outcomes are not reflective of the long-term outcomes in these patients.

Our study did have some important limitations. First, this was a retrospective study based on diagnostic codes and utilizing a database. As we previously mentioned, there were no variable data points, and all our collected information was dependent upon documentation of the presence or absence of pathology.

Another limitation is that we only investigated outcomes during the index hospitalization of transplantation. We did not have data for re-admissions and long term outcomes of transplantation. Though we assume the majority of poor outcomes would happen during or shortly post-operatively, it would be interesting to follow the outcomes over a longer period of time and see if any meaningful differences occur.

An important consideration in the data we used is its dependence upon diagnostic coding and accurate documentation for validity, and was therefore vulnerable to selection bias. Previous papers have theorized that accurate reporting of obesity as comorbidity has historically been inferior to recent reporting. As obesity has been increasingly recognized as a public health epidemic, health care providers would be more likely to accurately document obesity[25].

Lastly, our method of data collection did not allow for stratifying patients by disease severity, etiology of cirrhosis, or donor factors based on donor risk index. Therefore, survival analyses may be of constrained generalizability due to these limitations.

In conclusion, patients with morbid obesity undergoing OLT have increased respiratory complications and $\geqslant$ 3 comorbidities based on modified Elixhauser comorbidity index. Based on NIS database we found that health care utilization during admission for OLT is similar in morbidly obese and non-morbidly obese patients. Keeping in mind the limitations of NIS database, morbidly obese patients may be selected for OLT carefully after assessing their comorbidities. Further studies are needed to evaluate long term outcomes in these patients in era of MELD score based allocation of liver, which may

affect how patients are selected for transplantation in the future.

COMMENTS

Background

There have been varying reports on the morbidity and mortality in obese patients undergoing orthotopic liver transplantation (OLT). Consistently, studies have shown greater peri-operative morbidity as well as increased post-operative length of stay. Studies have also shown socioracial disparities in OLT utilization. Despite this, there have not been any large population based studies from United States on health care utilization and short term outcomes of liver transplantation in morbidly obese patients. The authors hypothesized that provided selected carefully morbidly obese patients undergoing liver transplantation may not have different healthcare utilization and short term outcomes.

Research frontiers

The need for liver transplantation continues to rise, as is the prevalence of obesity. The results of this study contribute to clarifying that carefully selected morbidly obese patients may be acceptable candidates for liver transplantation.

Innovations and breakthroughs

In this study, there was no difference in mortality, length of stay, or charges between morbidly obese and non-morbidly obese individuals receiving liver transplantation. This differs from previous reports.

Applications

This study suggests that morbidly obese patients may be selected for liver transplantation after carefully assessing their comorbidities.

Peer-review

This is a very interesting study performed on a great United States database based on more than 46000 patients undergoing liver transplantation. The retrospective study indicated that morbid obesity might not impact in-hospital mortality and health care utilization in OLT recipients.

REFERENCES

1 **Nair S**, Verma S, Thuluvath PJ. Obesity and its effect on survival in patients undergoing orthotopic liver transplantation in the United States. *Hepatology* 2002; **35**: 105-109 [PMID: 11786965]

2 **Pelletier SJ**, Schaubel DE, Wei G, Englesbe MJ, Punch JD, Wolfe RA, Port FK, Merion RM. Effect of body mass index on the survival benefit of liver transplantation. *Liver Transpl* 2007; **13**: 1678-1683 [PMID: 18044787]

3 **Tanaka T**, Renner EL, Selzner N, Therapondos G, Lilly LB. The impact of obesity as determined by modified body mass index on long-term outcome after liver transplantation: Canadian single-center experience. *Transplant Proc* 2003; **45**: 2288-2294 [PMID: 23953540 DOI: 10.1016/j.transproceed.2012.11.009]

4 **Dick AA**, Spitzer AL, Seifert CF, Deckert A, Carithers RL, Reyes JD, Perkins JD. Liver transplantation at the extremes of the body mass index. *Liver Transpl* 2009; **15**: 968-977 [PMID: 19642131]

5 **Nair S**, Vanatta JM, Arteh J, Eason JD. Effects of obesity, diabetes, and prior abdominal surgery on resource utilization in liver transplantation: a single-center study. *Liver Transpl* 2009; **15**: 1519-1524 [PMID: 19877252]

6 **Dare AJ**, Plank LD, Phillips AR, Gane EJ, Harrison B, Orr D, Jiang Y, Bartlett AS. Additive effect of pretransplant obesity, diabetes, and cardiovascular risk factors on outcomes after liver transplantation. *Liver Transpl* 2014; **20**: 281-290 [PMID: 24395145]

7 **Asrani SK**, Kim WR, Kamath PS. Race and receipt of liver transplantation: location matters. *Liver Transpl* 2010; **16**: 1009-1012 [PMID: 20818737]

8 HCUP Nationwide Inpatient Sample (NIS). Healthcare Cost and Utilization Project (HCUP). [Internet] 2011. Available from: URL: https://www.hcup-us.ahrq.gov/nisoverview.jsp

9 **van Walraven C**, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care* 2009; **47**: 626-633 [PMID: 19433995 DOI: 10.1097/MLR.0b013e31819432e5]

10 **Golinvaux NS**, Bohl DD, Basques BA, Fu MC, Gardner EC, Grauer JN. Limitations of administrative databases in spine research: a study in obesity. *The Spine Journal* 2014; **14**: 2923-2928 [DOI: 10.1016/j.spinee.2014.04.025]

11 **Santry HP**, Gillen DL, Lauderdale DS. Trends in bariatric surgical procedures. *JAMA* 2005; **294**: 1909-1917 [PMID: 16234497 DOI: 10.1001/jama.294.15.1909]

12 **Raval Z**, Harinstein ME, Skaro AI, Erdogan A, DeWolf AM, Shah SJ, Fix OK, Kay N, Abecassis MI, Gheorghiade M, Flaherty JD. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol* 2011; **58**: 223-231 [PMID: 21737011 DOI: 10.1016/j.jacc.2011.03.026]

13 **Kemmer N**, Zacharias V, Kaiser TE, Neff GW. Access to liver transplantation in the MELD era: Role of ethnicity and insurance. *Digestive Diseases and Sciences* 2009; **54**: 1794 [DOI: 10.1007/s10620-008-0567-5]

14 **Nguyen GC**, Thuluvath NP, Segev DL, Thuluvath PJ. Volumes of liver transplant and partial hepatectomy procedures are independently associated with lower postoperative mortality following resection for hepatocellular carcinoma. *Liver Transpl* 2009; **15**: 776-781 [PMID: 19562711 DOI: 10.1002/lt.21767]

15 **Martin P**, DiMartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201]

16 **Mazuelos F**, Abril J, Zaragoza C, Rubio E, Moreno JM, Turrión VS, Cuervas-Mons V. Cardiovascular morbidity and obesity in adult liver transplant recipients. *Transplant Proc* 2003; **35**: 1909-1910 [PMID: 12962844]

17 **Braunfeld MY**, Chan S, Pregler J, Neelakanta G, Sopher MJ, Busuttil RW, Csete M. Liver transplantation in the morbidly obese. *J Clin Anesth* 1996; **8**: 585-590 [PMID: 8910182]

18 **Nair S**, Cohen DB, Cohen MP, Tan H, Maley W, Thuluvath PJ. Postoperative morbidity, mortality, costs, and long-term survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 2001; **96**: 842-845 [PMID: 11280562 DOI: 10.1111/j.1572-0241.2001.03629.x]

19 **Prescott HC**, Chang VW, O'Brien JM, Langa KM, Iwashyna TJ. Obesity and 1-year outcomes in older Americans with severe sepsis. *Crit Care Med* 2014; **42**: 1766-1774 [PMID: 24717466 DOI: 10.1097/CCM.0000000000000336]

20 **Arabi YM**, Dara SI, Tamim HM, Rishu AH, Bouchama A, Khedr MK, Feinstein D, Parrillo JE, Wood KE, Keenan SP, Zanotti S, Martinka G, Kumar A, Kumar A. Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Crit Care* 2013; **17**: R72 [PMID: 23594407 DOI: 10.1186/cc12680]

21 **Wensveen FM**, Valentić S, Šestan M, Turk Wensveen T, Polić B. The "Big Bang" in obese fat: Events initiating obesity-induced adipose tissue inflammation. *Eur J Immunol* 2015; **45**: 2446-2456 [PMID: 26220361 DOI: 10.1002/eji.201545502]

22 **Langouche L**, Marques MB, Ingels C, Gunst J, Derde S, Vander Perre S, D'Hoore A, Van den Berghe G. Critical illness induces alternative activation of M2 macrophages in adipose tissue. *Crit Care* 2011; **15**: R245 [PMID: 22018099 DOI: 10.1186/cc10503]

23 **Stapleton RD**, Dixon AE, Parsons PE, Ware LB, Suratt BT. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest* 2010; **138**: 568-577 [PMID: 20435656 DOI: 10.1378/chest.10-0014]

24 **Abhyankar S**, Leishear K, Callaghan FM, Demner-Fushman D, McDonald CJ. Lower short- and long-term mortality associated

with overweight and obesity in a large cohort study of adult intensive care unit patients. *Crit Care* 2012; **16**: R235 [PMID: 23249446 DOI: 10.1186/cc11903]

25 **Odum SM**, Springer BD, Dennos AC, Fehring TK. National Obesity Trends in Total Knee Arthroplasty. *J Arthroplasty* 2013; **28**: 148-151 abstract [DOI: 10.1016/j.arth.2013.02.036]

P- Reviewer: Boin ISFS, Bramhall S, Lai Q, Liang TB, Ohkohchi N, Qin JM, Wang GY
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.f6publishing.com

World J Hepatol 2017 April 28; 9(12): 603-612

DOI: 10.4254/wjh.v9.i12.603

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Passive expansion of sub-maximally dilated transjugular intrahepatic portosystemic shunts and assessment of clinical outcomes

Michael C Hsu, Charles N Weber, S William Stavropoulos, Timothy W Clark, Scott O Trerotola, Richard D Shlansky-Goldberg, Michael C Soulen, Gregory J Nadolski

Michael C Hsu, Department of Radiology, Division of Interventional Radiology, Mount Sinai Hospital, New York, NY 10128, United States

Michael C Hsu, Charles N Weber, S William Stavropoulos, Timothy W Clark, Scott O Trerotola, Richard D Shlansky-Goldberg, Michael C Soulen, Gregory J Nadolski, Department of Radiology, Division of Interventional Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA 19104, United States

Author contributions: Hsu MC, Weber CN and Nadolski GJ designed the study, performed the data analysis, and wrote the manuscript; Stavropoulos SW, Clark TW, Trerotola SO, Shlansky-Goldberg RD and Soulen MC performed the majority of the procedures and were involved in editing the manuscript.

Institutional review board statement: Institutional review board approval was obtained for this study. Given the design involves retrospective review of previously collected data obtained during clinical care of the patients, IRB approval was granted using an expedited review process.

Informed consent statement: Waiver of consent was granted by the IRB given the retrospective design and reporting of results in aggregate without inclusion of individual patient identifiers.

Conflict-of-interest statement: None of the authors has any conflict of interest to report.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Michael C Hsu, MD, Department of Radiology, Division of Interventional Radiology, Mount Sinai Hospital, 215 East 95th St. Apt. 5L, New York, NY 10128, United States. hsu.mike.c@gmail.com
Telephone: +1-804-8523428
Fax: +1-212-4267745

Received: October 26, 2016
Peer-review started: October 27, 2016
First decision: December 29, 2016
Revised: January 26, 2017
Accepted: March 12, 2017
Article in press: March 13, 2017
Published online: April 28, 2017

Abstract

AIM

To assess for passive expansion of sub-maximally dilated transjugular intrahepatic portosystemic shunts (TIPS) and compare outcomes with maximally dilated TIPS.

METHODS

Polytetrafluoroethylene covered TIPS (Viatorr) from July 2002 to December 2013 were retrospectively reviewed at two hospitals in a single institution. Two hundred and thirty patients had TIPS maximally dilated to 10 mm (mTIPS), while 43 patients who were at increased risk for hepatic encephalopathy (HE), based on clinical evaluation or low pre-TIPS portosystemic gradient (PSG), had 10 mm TIPS sub-maximally dilated to 8 mm (smTIPS). Group characteristics (age, gender, Model for End-Stage Liver Disease score, post-TIPS PSG and clinical outcomes were compared between groups, including clinical success (ascites or varices), primary patency,

primary assisted patency, and severe post-TIPS HE. A subset of fourteen patients with smTIPS underwent follow-up computed tomography imaging after TIPS creation, and were grouped based on time of imaging (< 6 mo and > 6 mo). Change in diameter and cross-sectional area were measured with 3D imaging software to evaluate for passive expansion.

RESULTS

Patient characteristics were similar between the smTIPS and mTIPS groups, except for pre-TIPS portosystemic gradient, which was lower in the smTIPS group (19.4 mmHg ± 6.8 *vs* 22.4 mmHg ± 7.1, P = 0.01). Primary patency and primary assisted patency between smTIPS and mTIPS was not significantly different (P = 0.64 and 0.55, respectively). Four of the 55 patients (7%) with smTIPS required TIPS reduction for severe refractory HE, while this occurred in 6 of the 218 patients (3%) with mTIPS (P = 0.12). For the 14 patients with follow-up computed tomography (CT) imaging, the median imaging follow-up was 373 d. There was an increase in median TIPS diameter, median percent diameter change, median area, and median percent area change in patients with CT follow-up greater than 6 mo after TIPS placement compared to follow-up within 6 mo (8.45 mm, 5.58%, 56.04 mm^2, and 11.48%, respectively, P = 0.01).

CONCLUSION

Passive expansion of smTIPS does occur but clinical outcomes of smTIPS and mTIPS were similar. Sub-maximal dilation can prevent complications related to over-shunting in select patients.

Key words: Variceal hemorrhage; Portal hypertension; Transjugular intrahepatic portosystemic shunts; Ascites; Sub-maximal dilation; Underdilated; Passive expansion; Hepatic encephalopathy

Core tip: Sub-maximal dilation of transjugular intrahepatic portosystemic shunts (TIPS) is a method to reduce the risk of over-shunting and hepatic encephalopathy. The current study is a retrospective review to compare clinical outcomes of sub-maximally dilated TIPS (smTIPS) with maximally dilated TIPS (mTIPS) and assess for passive expansion of smTIPS. The study demonstrated that passive expansion of smTIPS does occur, however shunts may not fully expand and expansion may occur even after 6 mo. Clinical outcomes of smTIPS and mTIPS were similar, suggesting sub-maximal dilation may be an acceptable method to prevent complications related to over-shunting in select patients.

Hsu MC, Weber CN, Stavropoulos SW, Clark TW, Trerotola SO, Shlansky-Goldberg RD, Soulen MC, Nadolski GJ. Passive expansion of sub-maximally dilated transjugular intrahepatic portosystemic shunts and assessment of clinical outcomes. *World J Hepatol* 2017; 9(12): 603-612 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i12/603.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i12.603

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is an established treatment for the sequelae of portal hypertension, particularly variceal hemorrhage and refractory ascites. Two major complications can arise following TIPS placement: Shunt dysfunction and hepatic encephalopathy (HE)[1-3]. Shunt dysfunction occurs from stenosis and the consequent rise in portosystemic gradient (PSG) resulting in relapse of clinical manifestations of portal hypertension[1,4-6]. In the era of bare metal stents, TIPS dysfunction was a major problem that led to relatively low primary patency rates, typically less than 50% at one year[1,5,7]. However, expanded polytetrafluoroethylene (PTFE) covered TIPS have improved patency rates and clinical outcomes compared to bare metal TIPS[1-4,8-10]. Primary patency rates at two years have now been shown to range from 62%-89%[7,10-14].

Despite these advances, HE remains a pertinent post-procedural complication as portosystemic shunt physiology can trigger or worsen HE[1,2,8]. New or progressive post-TIPS HE of any severity has been shown to occur in 5%-35% of patients, while severe post-TIPS HE that does not respond to medical management and requires TIPS reduction or occlusion, occurs in up to 7% of patients[3,10,15,16].

Given the potential conflicting relationship between portal decompression and HE, efforts have been made to develop techniques to balance the desired therapeutic effect while minimizing over-shunting[3,17]. One such technique is to sub-maximally dilate a 10 mm TIPS[18,19]. Sub-maximal dilation theoretically allows for further dilation of the TIPS in the event that the initial portal decompression is insufficient while avoiding over-shunting[6,16,18]. However, this technique would only be effective if the sub-maximally dilated TIPS do not expand significantly over time. Published data suggest the continued outward radial force of the TIPS stent may lead to passive expansion to its nominal diameter, limiting the value of initial gradient calibration[6,19,20]. The current study is a retrospective review to compare clinical outcomes of sub-maximally dilated TIPS (smTIPS) with maximally dilated TIPS (mTIPS) at a single large academic institution and assess for passive expansion of smTIPS in a sub-set of patients with follow-up cross-sectional imaging.

MATERIALS AND METHODS

Approval from the Institutional Review Board was obtained for this retrospective study, which was carried out in full compliance with the Health Information Portability and Accountability Act. An interventional radiology database (Hi-IQ, Conexsys, Lincoln, RI) was used to identify all TIPS placed using an expanded PTFE-covered

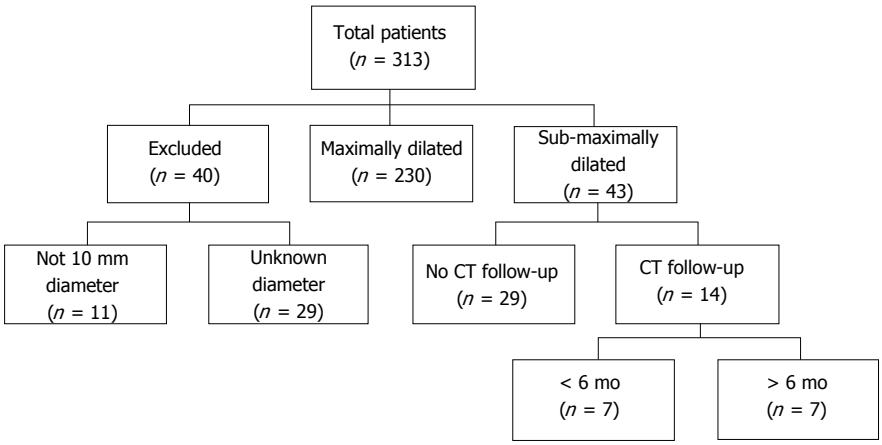


Figure 1 Patient selection. CT: Computed tomography.

stent graft (Viatorr) between July 2002 and December 2013 at two hospitals in a single institution (*n* = 313). The electronic medical record was used to obtain patient characteristics, including age, gender, pre-TIPS Model for End-Stage Liver Disease (MELD) score, and pre-TIPS PSG, and retrospectively reviewed to assess for measurements of clinical outcomes, including post-TIPS PSG, clinical success, primary patency, primary assisted patency, and severe post-TIPS HE.

Procedure

All TIPS creation was performed as previously described[12]. In patients who were considered vulnerable to post-TIPS HE based on (1) past medical history of HE on clinical evaluation by the referring hepatologist or interventional radiology service; or (2) low pre-TIPS PSG that could result in over-shunting post-TIPS as determined by the performing interventional radiologist, a modified TIPS creation procedure was performed. The modified TIPS creation involved initial placement of a nominal 10 mm TIPS stent that was sub-maximally dilated to 8 mm (smTIPS). Following initial dilation with the 8 mm balloon, the PSG was measured and post-TIPS portography was repeated at the same injection rate as the initial portogram (8-10 mL/s for 2 s for all cases). If the PSG normalized (≤ 12 mmHg) and there was no venographic evidence of elevated gradient (*i.e.,* persistently filling varices), then the procedure was ended. Otherwise, the smTIPS stent was further dilated with a 10 mm balloon, PSG measured, and portography repeated (mTIPS). Coil embolization of persistently filling varices following TIPS creation with normalized PSG was performed in patients who initially presented with variceal hemorrhage.

Decision for angioplasty, thrombectomy, or stent placement during TIPS revision was based on venographic findings and PSG measurements. All patients received HE prophylaxis with lactulose[21]. In cases of severe post-TIPS HE refractory to medical management (protein restriction, lactulose, and/or rifaximin), TIPS reduction was performed with coaxial deployment of a FLAIR stent within the existing TIPS, or with a stent graft with parallel balloon-expandable stent as previously described[15]. All patients were instructed to maintain a protein-restricted diet. Patients with ascites were instructed to follow a fluid-restricted, low sodium diet.

Inclusion criteria were patients with maximally dilated 10 mm PTFE-covered TIPS or 10 mm PTFE-covered TIPS sub-maximally dilated to 8 mm, as confirmed in the medical record (Figure 1). Of the 313 patients who underwent TIPS creation during the study period, forty patients were excluded due to placement of PTFE-covered TIPS of other nominal sizes (*n* = 11) or patients with post-TIPS stent deployment angioplasty diameters that were not confirmed in the medical record (*n* = 29). The remaining 273 patients had confirmed TIPS created with 10 mm nominal diameter stent, of which 230 patients had mTIPS created and 43 patients underwent creation of smTIPS. In the group of patients with smTIPS, any computed tomography (CT) imaging follow-up was identified from the medical record (*n* = 14) and reviewed with TeraRecon (TeraRecon, Foster City, CA), which is an advanced 3D imaging processing software. Using this imaging software, two orthogonal planes were obtained before measuring the diameter of the TIPS stent at the hepatic venous end, mid-stent, and the portal venous end (Figure 2). These values were then averaged to obtain a composite measure of TIPS diameter.

For the purposes of the current study, clinical success was defined based on the indication for TIPS placement. In patients who had TIPS placed for varices, clinical success was defined as absence of further episodes of variceal hemorrhage or development of varices requiring intervention. Patients in the varices group with less than one month of follow-up were excluded from the clinical success analysis (*n* = 6 for smTIPS; *n* = 21 for mTIPS). For patients with refractory ascites requiring TIPS placement, clinical success was categorized as complete response (absence of large-volume paracentesis within six months post-TIPS creation) or partial response (greater than 50% decrease in frequency of large-volume paracentesis). Patients in the ascites group with less than six months of follow-up were excluded from the clinical success analysis (*n* = 17 for smTIPS; *n* = 55 for mTIPS). Primary patency was defined as the time from TIPS creation until revision for identified stenosis, elevated PSG (> 12 mmHg), or recurrent symptoms. Primary

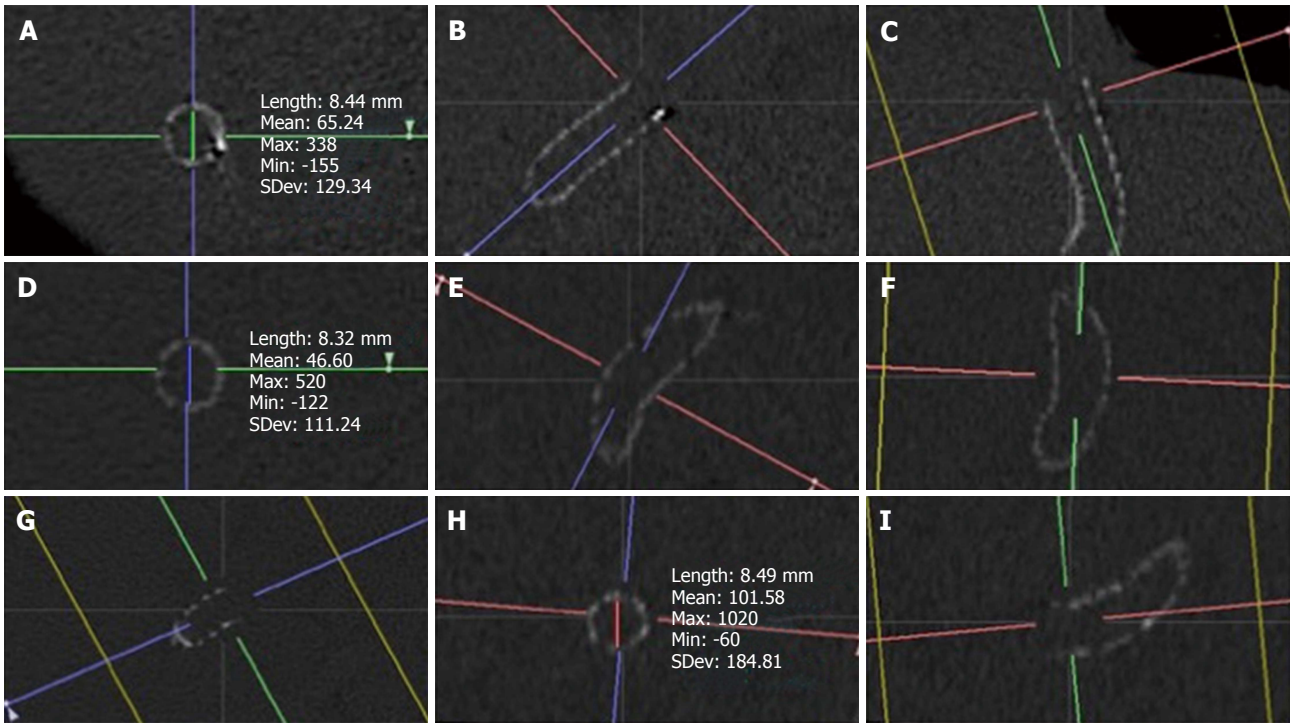


Figure 2 TeraRecon measurement of transjugular intrahepatic portosystemic shunt stent at hepatic venous end, mid-stent, and portal venous end. A: Axial image at the hepatic venous end with cross-sectional diameter; B: Coronal image at the hepatic venous end with orthogonal plane designation; C: Sagittal image at the hepatic venous end with orthogonal plane designation; D: Axial image at mid-stent with cross-sectional diameter; E: Coronal image at mid-stent with orthogonal plane designation; F: Sagittal image at mid-stent with orthogonal plane designation; G: Axial image at the portal venous end with orthogonal plane designation; H: Coronal image at the portal venous end with cross-sectional diameter; I: Sagittal image at the portal venous end with orthogonal plane designation.

assisted patency was defined as the time from TIPS creation until shunt occlusion requiring recanalization. Severe post-TIPS HE was defined as encephalopathy refractory to conservative medical management requiring TIPS reduction.

Statistical analysis

Statistical calculations were performed with GraphPad Prism software (version 6.05; GraphPad Software; La Jolla, CA). Unless otherwise indicated, all data were reported as mean ± SD. Categorical variables were compared using Fisher's exact test. Continuous variables were compared using unpaired two-tailed Student's *t*-test and Mann-Whitney test for data with a parametric and non-parametric distribution, respectively. Primary and primary assisted patency rates were estimated with the Kaplan-Meier method. Patients were censored at the time of death or liver transplantation. Patency rates between smTIPS and mTIPS groups were compared with the log-rank test. Severe post-TIPS HE was analyzed on an intention-to-treat basis resulting in 12 patients from the mTIPS group, originally dilated to 8 mm but subsequently maximally dilated to normalize the post-TIPS PSG, being included in the smTIPS group. A *P*-value less than 0.05 was considered significant for all analyses.

RESULTS

Patient characteristics and post-TIPS PSG are presented in Table 1. There were 150 males and 80 females who underwent mTIPS creation with a mean age of 54.5 years ± 0.7 (range, 20-81). Of the 43 patients that had smTIPS created, 23 were male with a mean age of 56.5 years ± 2.3 (range 10-83). There was no statistically significant difference between the two patient populations based on gender or age (P = 0.17 and 0.29, respectively). The mean pre-TIPS MELD score in patients with mTIPS was 13.5 ± 0.3 (range, 6-28) while it was 13.6 ± 0.6 (range, 6-25) for patients with smTIPS, which was not significantly different (P = 0.82). The mean pre-TIPS PSG was higher for patients with mTIPS (22.4 mmHg ± 7.1; range, 9-73) compared to those with smTIPS (19.4 mmHg ± 6.8; range, 8-45), which was statistically significant (P = 0.01). Following TIPS placement, the median PSG was 8 mmHg for both mTIPS and smTIPS (range, 2-20 and 1-13, respectively) with a mean percent decrease in PSG of 61.0% ± 12.4 (range, 0-89) and 59.1% ± 15.9 (range, 0-95), respectively. These were not statistically different (P = 0.13 and 0.53, respectively). The patients with post-TIPS PSG above the goal of 12 mmHg had a mean pre-TIPS PSG of 33 ± 13.2 (range 20-73) and experienced a mean percent decrease in PSG following TIPS creation of 48.3% ± 13.1 (range, 30.8-82.2) compared to those patients with post-TIPS PSG at or below the goal of 12 mmHg who had a mean pre-TIPS PSG of 21.1 mmHg ± 5.7 (range, 8-53) and mean percent decrease in PSG of 61.6% ± 12.6 (range, 0-95) (P < 0.01 and < 0.01) (Table 2).

Of the 43 patients with smTIPS, there were 14

Table 1 Demographics and clinical characteristics

	Sub-maximally dilated	Maximally dilated	*P* value
Total patients	43	230	NA
Male	23	150	0.17
Female	20	80	
Mean age (yr)	56.5 ± 2.3 (range 10-83)	54.5 ± 0.7 (range 20-81)	0.29
Mean MELD	13.6 ± 0.6 (range 6-25)	13.5 ± 0.3 (range 6-28)	0.82
Mean pre-TIPS PSG (mmHg)	19.4 ± 6.8 (range 8-45)	22.4 ± 7.1 (range 9-73)	0.01
Median post-TIPS PSG (mmHg)	8 (range 1-13)	8 (range 2-20)	0.13
Mean percent change in PSG (%)	59.1 ± 15.9 (range 0-95)	61.0 ± 12.4 (range 0-89)	0.53

MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic portosystemic shunt; PSG: Portosystemic gradient; NA: Not applicable.

Table 2 Mean pre-transjugular intrahepatic portosystemic shunt portosystemic gradient and percent change in portosystemic gradient in patients with post-transjugular intrahepatic portosystemic shunt portosystemic gradient above and below 12 mmHg

	> 12 mmHg	⩽ 12 mmHg	*P* value
Mean pre-TIPS PSG (mmHg)	33 ± 13.2 (range 20-73)	21.1 ± 5.7 (range 8-53)	< 0.01
Mean percent change in PSG (%)	48.3 ± 13.1 (range 30.8-82.2)	61.6 ± 12.6 (range 0-95)	< 0.01

TIPS: Transjugular intrahepatic portosystemic shunt; PSG: Portosystemic gradient.

Table 3 Measurements of 8 mm transjugular intrahepatic portosystemic shunt stents on computed tomography imaging follow-up

	Median diameter (mm)	Median percent diameter change	Median area (mm^2)	Median percent area change
< 6 mo (n = 7)	8.05 (range 7.84-8.43)	0.67%	50.94	1.34%
> 6 mo (n = 7)	8.45 (range 8.23-8.72)	5.58%	56.04	11.48%
P-value	0.01	0.01%	0.01	0.01%

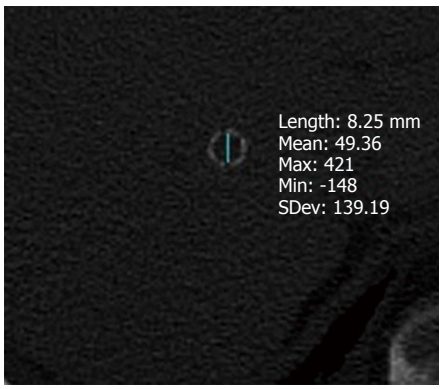


Figure 3 Mid-stent measurement of sub-maximally dilated transjugular intrahepatic portosystemic shunt 103 d (< 6 mo) following creation.

patients who had CT imaging follow-up (Table 3). Median time to last imaging follow-up was 373 d. The diameter and cross-sectional area of initial TIPS placement was assumed to be 8 mm and 50.27 mm^2, corresponding to the diameter and area of the balloon used for dilation. Seven patients had last CT imaging follow-up within 6 mo (range, 4-172 d) and 7 patients had last CT imaging follow-up after 6 mo (range, 573-2131 d). The 7 patients with imaging follow-up within 6 mo had a median diameter, percent diameter change, area, and percent area change of 8.05 mm (range, 7.84-8.43 mm), 0.67%, 50.94 mm^2, and 1.34%, respectively. The patients that had last imaging follow-up after 6 mo had a median diameter, percent diameter change, area, and percent area change of 8.45 mm (range, 8.23-8.72 mm), 5.58%, 56.04 mm^2, and 11.48%, respectively. When comparing these two subgroups, there was a statistically significant increase in diameter, percent diameter change, area, and percent area change (P = 0.01) (Figures 3 and 4).

Post-TIPS clinical success is summarized in Table 4. Nine of 14 patients (64%) who had smTIPS placed for refractory ascites experienced complete clinical success and 11 of 14 patients (79%) experienced at least partial clinical success. Similarly, 63 of the 98 patients (64%) who underwent mTIPS placement for refractory ascites experienced complete clinical success and 89 of 98 patients (91%) had at least partial clinical success. There was no statistically significant difference in complete or partial clinical success between patients with smTIPS or mTIPS (P = 1 and P = 0.17, respectively). For variceal bleeding, 7 of 9 patients (78%) with smTIPS and 64 of 75 patients (85%) with mTIPS experienced clinical success, which was not significantly different (P = 0.62).

Kaplan-Meier survival curves depicting primary and primary assisted patency rates for smTIPS and mTIPS are shown in Figures 5 and 6, respectively. Primary patency for smTIPS and mTIPS was 85% ± 9.1% and 76% ± 5.9%, respectively, at one year, and 77% ± 13 and 70% ± 6.9%, respectively, after two years. Primary assisted patency for smTIPS and mTIPS was 95% ± 5% and

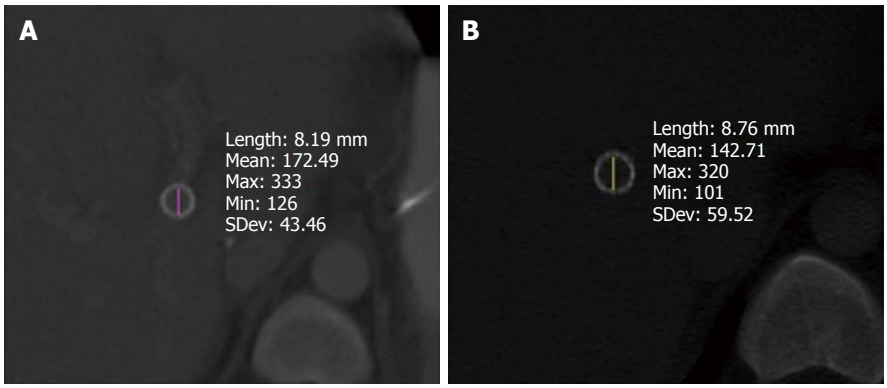


Figure 4 Mid-stent measurement of sub-maximally dilated transjugular intrahepatic portosystemic shunt (A) 182 d and (B) 573 d following creation (> 6 mo) in the same patient.

Table 4 Clinical Success of transjugular intrahepatic portosystemic shunt *n* (%)

	Sub-maximally dilated	Maximally dilated	*P* value
Complete Clinical Success of TIPS for Ascites			
Yes	9 (64)	63 (64)	1
No	5 (36)	35 (36)	
Partial Clinical Success of TIPS for Ascites			
Yes	11 (79)	89 (91)	0.17
No	3 (21)	9 (9)	
Clinical Success of TIPS for Varices			
Yes	7 (78)	64 (85)	0.62
No	2 (22)	11 (15)	

TIPS: Transjugular intrahepatic portosystemic shunt.

95% ± 3%, respectively, at one year, and 88% ± 13% and 94% ± 4%, respectively, after two years. There was no statistically significant difference between primary or primary assisted patency between the two groups (*P* = 0.64 and 0.55, respectively). Four of the 55 patients (7%) with smTIPS required TIPS reduction for severe refractory HE, while this occurred in 6 of the 218 patients with mTIPS (3%) using an intention-to-treat analysis, although not statistically significant (*P* = 0.12) (Table 5). In both smTIPS and mTIPS, the MELD scores and post-TIPS PSG were not significantly different between patients who experienced severe post-TIPS HE and those who did not (Table 6).

DISCUSSION

Despite improved patency rates and reduced need for shunt revision with PTFE-covered TIPS, HE remains a problem following TIPS placement with some speculation that improved patency rates may increase the incidence of HE[1-4,8,9]. HE arises when compounds derived from the intestine that require hepatic detoxification bypass the hepatic vascular bed in the setting of a portosystemic shunt, and subsequently enter systemic circulation. These compounds, typically nitrogenous in composition, travel to the central nervous system and disturb neurotransmission, which leads to eventual alterations in consciousness and

Table 5 Severe post- transjugular intrahepatic portosystemic shunt hepatic encephalopathy *n* (%)

Severe post-TIPS HE	Sub-maximally dilated	Maximally dilated	*P* value
Yes	4 (7)	6 (3)	0.12
No	51 (93)	212 (97)	

TIPS: Transjugular intrahepatic portosystemic shunt; HE: Hepatic encephalopathy.

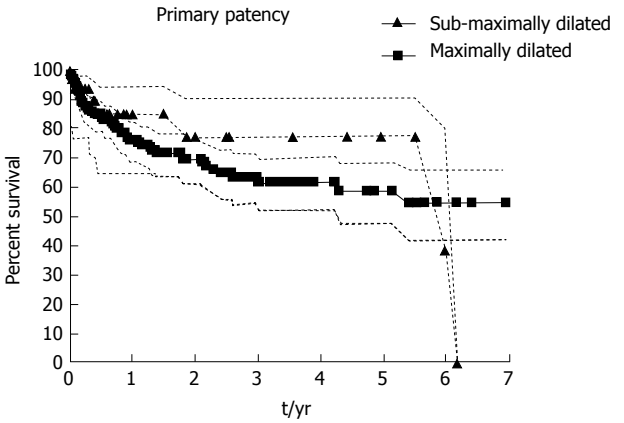
behavior that manifest as HE[22]. This pathogenesis is further supported with the evidence that HE occurs with spontaneous portosystemic shunts, even in the absence of hepatic dysfunction or TIPS[23,24]. Prior investigations have also shown that an increased volume of shunted blood, decreased portal hepatic perfusion, and a lower PSG following TIPS placement correlate with higher rates of HE[5,17,18,25].

With knowledge of the pathogenesis of HE, different techniques have been studied in an effort to balance the desired therapeutic effect while minimizing over-shunting and increased risk of HE, such as smaller diameter TIPS or altering the goal in PSG reduction for patients with HE[3,17]. Another technique is sub-maximal dilation of TIPS, which allows for further staged dilation, if necessary, and theoretically minimizes over-shunting[6,16,18,26]. However, passive expansion of the TIPS may limit the effectiveness of this technique with prior evidence, in both peripheral circulation and TIPS, that suggests this phenomenon should be taken into consideration. Late expansion of bare metal nitinol stents was demonstrated after 6 mo in peripheral arteries of an animal model[27]. Haskal *et al*[20] showed that after immediate recoil of Wallstent TIPS stents after placement, passive expansion to nominal diameter occurred at follow-up venography three to six months later. Pieper *et al*[19] studied 29 patients with Viatorr TIPS sub-maximally dilated to a mean of 64% of their nominal area, and found passive expansion to 88% during follow-up, with significant expansion occurring within 6 mo. Finally, Gaba *et al*[28] evaluated 41 patients with 10 mm nominal Viatorr TIPS sub-maximally dilated to 8

Table 6 Model for End-Stage Liver Disease and post-transjugular intrahepatic portosystemic shunt portosystemic gradient for patients with and without severe post-transjugular intrahepatic portosystemic shunt hepatic encephalopathy

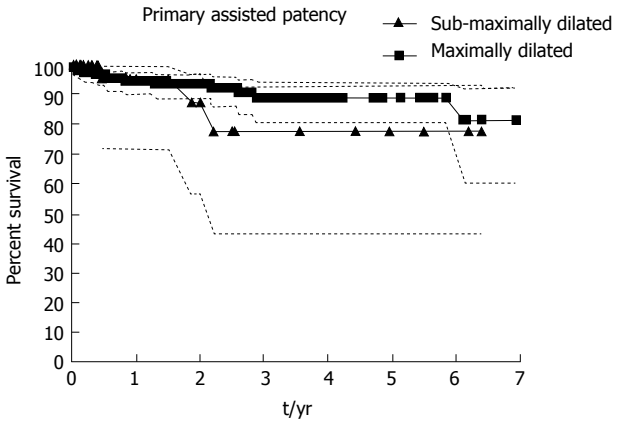
	Mean MELD with HE	Mean MELD without HE	*P* value	Median post-TIPS PSG with HE (mmHg)	Median post-TIPS PSG without HE (mmHg)	*P* value
Sub-maximally dilated	13.3 ± 2.9 (range 11-17)	13.7 ± 4.3 (range 6-25)	0.85	7.5 (range 6-8)	8 (range 1-13)	0.67
Maximally dilated	15.8 ± 4.3 (range 12-24)	13.4 ± 4.1 (range 6-28)	0.16	10 (range 4-11)	8 (range 2-20)	0.36

MELD: Model for End-Stage Liver Disease; HE: Hepatic encephalopathy; TIPS: Transjugular intrahepatic portosystemic shunt; PSG: Portosystemic gradient.



P = 0.64	Sub-maximally dilated		Maximally dilated	
	Patency (%)	No. at risk	Patency (%)	No. at risk
1 yr	85 ± 9.1	13	76 ± 5.9	96
2 yr	77 ± 13	10	70 ± 6.9	66
3 yr	77 ± 13	7	62 ± 8.3	39
4 yr	77 ± 13	6	62 ± 8.3	29
5 yr	77 ± 13	4	59 ± 10	17
6 yr	38 ± 42	2	55 ± 11	10

Figure 5 Primary patency rates of sub-maximally dilated (8 mm) *vs* maximally dilated (10 mm) transjugular intrahepatic portosystemic shunt. On Kaplan-Meier analysis, yearly patency rates through 6 years of follow-up after transjugular intrahepatic portosystemic shunt creation are demonstrated with 95%CI and number at risk.



P = 0.55	Sub-maximally dilated		Maximally dilated	
	Patency (%)	No. at risk	Patency (%)	No. at risk
1 yr	95 ± 5	14	95 ± 3	115
2 yr	88 ± 13	10	94 ± 4	75
3 yr	78 ± 22	7	89 ± 6	48
4 yr	78 ± 22	6	89 ± 6	29
5 yr	78 ± 22	4	89 ± 6	20
6 yr	78 ± 22	3	89 ± 6	13

Figure 6 Primary assisted patency rates of sub-maximally dilated (8 mm) *vs* maximally dilated (10 mm) transjugular intrahepatic portosystemic shunt. On Kaplan-Meier analysis, yearly patency rates through 6 years of follow-up after transjugular intrahepatic portosystemic shunt creation are demonstrated with 95%CI and number at risk.

mm, and demonstrated passive expansion with follow-up CT median stent diameter of 9.8 mm at a median of 76 d post TIPS creation without difference in incidence of post-TIPS HE in smTIPS *vs* mTIPS.

In the current study, continued passive expansion of smTIPS was observed in the subgroup of patients with cross-sectional imaging follow-up. Additionally, a significant difference in the increase in median diameter and area was observed when comparing the patients who had last imaging follow-up after 6 mo *vs* those within 6 mo. No patients in this subpopulation suffered severe refractory post-TIPS HE. While this change was statistically significant, the magnitude of expansion was not to the same degree as suggested by prior studies, and it also occurred over a longer time period (> 6 mo)[19,28]. The delayed and less extensive passive expansion observed in this study, although difficult to explain, may be secondary to dilation of the portosystemic tract with an 8 mm balloon prior to placement of the TIPS stent-graft. While the diameter of the balloon used to create the TIPS tract is not always described in prior investigations, a 10 mm balloon has been used previously[4]. It is hypothesized that dilating the tract to only 8 mm may lead to a greater initial counterforce on the stent from the elasticity of the surrounding liver parenchyma and new TIPS tract with minimal potential space, which leads to both slower and less passive expansion. In comparison, dilating the tract to 10 mm may hypothetically allow for a larger initial potential space for more immediate passive expansion of a TIPS sub-maximally dilated to 8 mm. Moreover, it is conceivable that more fibrotic livers with decreased compliance may differentially limit the extent of passive expansion, although this analysis was beyond the scope of this study.

In order to better understand whether or not passive expansion of the TIPS over time is clinically relevant, we compared a variety of outcomes in patients with smTIPS and mTIPS. The post-TIPS PSG demonstrated adequate portal decompression with a median PSG of 8 mmHg in both groups (P = 0.13) and no significant difference in mean percent change in PSG (P = 0.53). Overall, the observed rate of severe post-TIPS HE was low (4%), and

not significantly different between mTIPS and smTIPS (P = 0.12), suggesting the step-wise approach to TIPS creation by assessing PSG following sub-maximal dilation may be effective in minimizing unnecessary over-dilation and thus, over-shunting. These findings are similar to prior reports[28]. The lack of an observable difference between the groups may be due to passive expansion allowing for an equilibrium to gradually develop as increasing amounts of blood are shunted through the liver, thus, minimizing severe refractory HE[26]. Additionally, there was no significant difference in median post-TIPS PSG or mean MELD between patients who suffered severe post-TIPS HE and those who did not for patients with smTIPS or mTIPS. Finally, no significant difference in primary and primary assisted patency or clinical success for both ascites and varices occurred between the two groups.

These results are somewhat contradictory to a prior study comparing nominal 8 mm and 10 mm TIPS which found increased rates of recurrent portal hypertensive complications in the 8 mm group, leading to early termination of the study[3]. A possible explanation for the conflicting results may be related to the small, but not insignificant amount of passive expansion demonstrated with smTIPS. Based on Poiseuille's Law, volumetric flow rate is proportional to change in diameter to the fourth power, as well as change in pressure. It is postulated that despite a decrease in the change in pressure across the TIPS stent from passive expansion, the 5.6% increase in diameter observed in patients with CT imaging > 6 mo would disproportionately cause an increase in volumetric flow rate. As such, gradual passive expansion may slowly increase the amount of shunted blood and decrease the recurrence of portal hypertensive complications, yielding similar clinical success between the two groups obtained in the present study. Furthermore, the nominal 8 mm TIPS group in the same study had a higher incidence of shunt dysfunction, a majority without angiographically evident stenosis, than the smTIPS group in the current study, suggesting that a fixed, smaller diameter TIPS may provide insufficient portosystemic decompression and that passive expansion may be more efficacious in patients deemed to be at risk of post-TIPS HE[3]. Previously, the only mechanism to improve TIPS shunting in patients with nominal 8 mm TIPS was to place a parallel TIPS, as no further expansion was possible. The current study highlights a technique that would allow for further TIPS dilation in patients that show signs of inadequate portal decompression following initial creation of smTIPS, potentially obviating the need for a second parallel TIPS.

This study has several important limitations, including its retrospective design and data collection from a single center. The small size of the smTIPS group (n = 43) relative to the mTIPS group raises the possibility of a Type I error. As a tertiary center, identification of undocumented TIPS intervention or clinical follow-up at outside institutions is limited. There was more severe refractory post-TIPS HE in the smTIPS group *vs* the mTIPS group (7% *vs* 3%), although not statistically significant (P = 0.12). While this finding was not expected, it reflects selection bias between the two groups. Patients who underwent creation of smTIPS had a statistically significant lower mean pre-TIPS PSG compared to mTIPS (P = 0.01). This was not surprising given that patients deemed to be higher risk for HE following TIPS creation, which included a low pre-TIPS PSG, were preferentially selected to have smTIPS created to reduce the risk of over-shunting, as determined by the operating physician. Furthermore, even though shunt physiology is a known contributing factor for HE, the pathophysiology of HE is multifactorial and includes other precipitating factors such as hepatic decompensation, noncompliance with dietary restrictions, sepsis, and medications. Additional independent risk factors include older age, elevated serum creatinine, low serum sodium and low albumin; however, these clinical data were difficult to corroborate from a retrospective review spanning 10 years[2]. Only a minority (33%) of the patients with smTIPS had subsequent CT exams during the follow-up period. It is conceivable that this may not be representative of the entire subgroup. Additionally, patients did not undergo repeat angiographic TIPS evaluation following CT evidence of passive expansion, which would allow for repeat PSG measurement to determine the true hemodynamic consequences of passive expansion.

In conclusion, in patients with smTIPS there was passive expansion of 10 mm Viatorr TIPS stent-grafts even after 6 mo, however, not all reached their nominal diameter. The clinical outcomes, including incidence of severe post-TIPS HE, between sub-maximally and maximally dilated 10 mm Viatorr TIPS were similar. These findings suggest sub-maximal dilation may be an acceptable method to prevent complications related to over-shunting in select patients.

COMMENTS

Background

Transjugular intrahepatic portosystemic shunt (TIPS) is an established treatment for the sequelae of portal hypertension, particularly variceal hemorrhage and refractory ascites. Despite improved patency rates and reduced need for shunt revision with polytetrafluoroethylene-covered TIPS, hepatic encephalopathy (HE) remains a problem following TIPS placement with some speculation that improved patency rates may increase the incidence of HE. HE arises when compounds derived from the intestine that require hepatic detoxification bypass the hepatic vascular bed in the setting of a portosystemic shunt, and subsequently enter systemic circulation. One technique to balance portal decompression while minimizing over-shunting is sub-maximal dilation of TIPS. While sub-maximal dilation theoretically allows for further dilation of the TIPS in the event that the initial portal decompression is insufficient while avoiding over-shunting, published data suggest the continued outward radial force of the TIPS stent may lead to passive expansion to its nominal diameter and limit the value of initial gradient calibration.

Research frontiers

As sub-maximal dilation of TIPS has gained increased clinical use, there have been more studies investigating the presence and effect of passive expansion in both peripheral circulation and TIPS. Late expansion of bare metal nitinol stents was demonstrated after 6 mo in peripheral arteries of an animal model. Haskal *et al* showed that after immediate recoil of Wallstent TIPS stents after placement, passive expansion to nominal diameter occurred at follow-

up venography three to six months later. Pieper *et al* studied 29 patients with Viatorr TIPS sub-maximally dilated to a mean of 64% of their nominal area, and found passive expansion to 88% during follow-up, with significant expansion occurring within 6 mo. Finally, Gaba *et al* evaluated 41 patients with 10 mm nominal Viatorr TIPS sub-maximally dilated to 8 mm, and demonstrated passive expansion with follow-up computed tomography median stent diameter of 9.8 mm at a median of 76 d post TIPS creation without difference in incidence of post-TIPS HE in smTIPS *vs* mTIPS.

Innovations and breakthroughs

While the aforementioned studies focused on establishing the presence of passive expansion, there is a lack of published data investigating the clinical outcomes of sub-maximally dilated TIPS with maximally dilated TIPS in addition to the presence of passive expansion. While the study showed passive expansion does occur, not all shunts fully expanded to nominal diameter and expansion even occurred after 6 mo, unlike prior studies. More importantly, the comparison of clinical outcomes of smTIPS *vs* mTIPS showed no significant difference in primary patency, primary assisted patency, clinical success, or post-TIPS HE.

Applications

In patients who are at high risk for post-TIPS hepatic encephalopathy, based on pre-TIPS encephalopathy or low pre-TIPS portosystemic gradient, sub-maximal dilation may be an effective method to balance adequate portal decompression with the risk of over-shunting and hepatic encephalopathy with the knowledge that passive expansion following placement does not appear to affect clinical outcomes.

Terminology

Sub-maximally dilated TIPS - TIPS stent grafts that are not fully dilated to nominal diameter following deployment.

Peer-review

The study is to compare clinical outcomes of smTIPS with mTIPS. The results suggest the method may be of significance.

REFERENCES

1 **Sommer CM**, Gockner TL, Stampfl U, Bellemann N, Sauer P, Ganten T, Weitz J, Kauczor HU, Radeleff BA. Technical and clinical outcome of transjugular intrahepatic portosystemic stent shunt: bare metal stents (BMS) versus viatorr stent-grafts (VSG). *Eur J Radiol* 2012; **81**: 2273-2280 [PMID: 21784593 DOI: 10.1016/j.ejrad.2011.06.037]

2 **Riggio O**, Angeloni S, Salvatori FM, De Santis A, Cerini F, Farcomeni A, Attili AF, Merli M. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stent grafts. *Am J Gastroenterol* 2008; **103**: 2738-2746 [PMID: 18775022 DOI: 10.1111/j.1572-0241.2008.02102.x]

3 **Riggio O**, Ridola L, Angeloni S, Cerini F, Pasquale C, Attili AF, Fanelli F, Merli M, Salvatori FM. Clinical efficacy of transjugular intrahepatic portosystemic shunt created with covered stents with different diameters: results of a randomized controlled trial. *J Hepatol* 2010; **53**: 267-272 [PMID: 20537753 DOI: 10.1016/j.jhep.2010.02.033]

4 **Barrio J**, Ripoll C, Bañares R, Echenagusia A, Catalina MV, Camúñez F, Simó G, Santos L. Comparison of transjugular intrahepatic portosystemic shunt dysfunction in PTFE-covered stent-grafts versus bare stents. *Eur J Radiol* 2005; **55**: 120-124 [PMID: 15950109 DOI: 10.1016/j.ejrad.2004.10.007]

5 **Casado M**, Bosch J, García-Pagán JC, Bru C, Bañares R, Bandi JC, Escorsell A, Rodríguez-Láiz JM, Gilabert R, Feu F, Schorlemer C, Echenagusia A, Rodés J. Clinical events after transjugular intrahepatic portosystemic shunt: correlation with hemodynamic findings. *Gastroenterology* 1998; **114**: 1296-1303 [PMID: 9609767]

6 **Hausegger KA**, Karnel F, Georgieva B, Tauss J, Portugaller H, Deutschmann H, Berghold A. Transjugular intrahepatic portosystemic shunt creation with the Viatorr expanded polytetrafluoroethylene-covered stent-graft. *J Vasc Interv Radiol* 2004; **15**: 239-248 [PMID: 15028808 DOI: 10.1097/01.RVI.0000116194.44877.C1]

7 **Tripathi D**, Ferguson J, Barkell H, Macbeth K, Ireland H, Redhead DN, Hayes PC. Improved clinical outcome with transjugular intrahepatic portosystemic stent-shunt utilizing polytetrafluoroethylene-covered stents. *Eur J Gastroenterol Hepatol* 2006; **18**: 225-232 [PMID: 16462534]

8 **Angeloni S**, Merli M, Salvatori FM, De Santis A, Fanelli F, Pepino D, Attili AF, Rossi P, Riggio O. Polytetrafluoroethylene-covered stent grafts for TIPS procedure: 1-year patency and clinical results. *Am J Gastroenterol* 2004; **99**: 280-285 [PMID: 15046218 DOI: 10.1111/j.1572-0241.2004.04056.x]

9 **Boyer TD**, Haskal ZJ. The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* 2010; **51**: 306 [PMID: 19902484 DOI: 10.1002/hep.23383]

10 **Weber CN**, Nadolski GJ, White SB, Clark TW, Mondschein JI, Stavropoulos SW, Shlansky-Goldberg RD, Trerotola SO, Soulen MC. Long-Term Patency and Clinical Analysis of Expanded Polytetrafluoroethylene-Covered Transjugular Intrahepatic Portosystemic Shunt Stent Grafts. *J Vasc Interv Radiol* 2015; **26**: 1257-1265; quiz 1265 [PMID: 25990133 DOI: 10.1016/j.jvir.2015.04.005]

11 **Gaba RC**, Omene BO, Podczerwinski ES, Knuttinen MG, Cotler SJ, Kallwitz ER, Berkes JL, Walzer NM, Bui JT, Owens CA. TIPS for treatment of variceal hemorrhage: clinical outcomes in 128 patients at a single institution over a 12-year period. *J Vasc Interv Radiol* 2012; **23**: 227-235 [PMID: 22178037 DOI: 10.1016/j.jvir.2011.10.015]

12 **Luca A**, Miraglia R, Caruso S, Milazzo M, Sapere C, Maruzzelli L, Vizzini G, Tuzzolino F, Gridelli B, Bosch J. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. *Gut* 2011; **60**: 846-852 [PMID: 21357252 DOI: 10.1136/gut.2010.228023]

13 **Rössle M**, Siegerstetter V, Euringer W, Olschewski M, Kromeier J, Kurz K, Langer M. The use of a polytetrafluoroethylene-covered stent graft for transjugular intrahepatic portosystemic shunt (TIPS): Long-term follow-up of 100 patients. *Acta Radiol* 2006; **47**: 660-666 [PMID: 16950701 DOI: 10.1080/02841850600806324]

14 **Saad WE**, Darwish WM, Davies MG, Waldman DL. Stent-grafts for transjugular intrahepatic portosystemic shunt creation: specialized TIPS stent-graft versus generic stent-graft/bare stent combination. *J Vasc Interv Radiol* 2010; **21**: 1512-1520 [PMID: 20801686 DOI: 10.1016/j.jvir.2010.06.009]

15 **Sze DY**, Hwang GL, Kao JS, Frisoli JK, Kee ST, Razavi MK, Ahmed A. Bidirectionally adjustable TIPS reduction by parallel stent and stent-graft deployment. *J Vasc Interv Radiol* 2008; **19**: 1653-1658 [PMID: 18823797 DOI: 10.1016/j.jvir.2008.08.011]

16 **Thalheimer U**, Leandro G, Samonakis DN, Triantos CK, Senzolo M, Fung K, Davies N, Patch D, Burroughs AK. TIPS for refractory ascites: a single-centre experience. *J Gastroenterol* 2009; **44**: 1089-1095 [PMID: 19572096 DOI: 10.1007/s00535-009-0099-6]

17 **Rössle M**, Siegerstetter V, Olschewski M, Ochs A, Berger E, Haag K. How much reduction in portal pressure is necessary to prevent variceal rebleeding? A longitudinal study in 225 patients with transjugular intrahepatic portosystemic shunts. *Am J Gastroenterol* 2001; **96**: 3379-3383 [PMID: 11774952 DOI: 10.1111/j.1572-0241.2001.05340.x]

18 **Rossi P**, Salvatori FM, Fanelli F, Bezzi M, Rossi M, Marcelli G, Pepino D, Riggio O, Passariello R. Polytetrafluoroethylene-covered nitinol stent-graft for transjugular intrahepatic portosystemic shunt creation: 3-year experience. *Radiology* 2004; **231**: 820-830 [PMID: 15118117 DOI: 10.1148/radiol.2313030349]

19 **Pieper CC**, Sprinkart AM, Nadal J, Hippe V, Meyer C, Schild HH, Thomas D. Postinterventional passive expansion of partially dilated transjugular intrahepatic portosystemic shunt stents. *J Vasc Interv Radiol* 2015; **26**: 388-394 [PMID: 25541420 DOI: 10.1016/j.jvir.2014.10.021]

20 **Haskal ZJ**, Pentecost MJ, Soulen MC, Shlansky-Goldberg RD, Baum RA, Cope C. Transjugular intrahepatic portosystemic

shunt stenosis and revision: early and midterm results. *AJR Am J Roentgenol* 1994; **163**: 439-444 [PMID: 8037046 DOI: 10.2214/ajr.163.2.8037046]

21 **Sharma P**, Sharma BC, Agrawal A, Sarin SK. Primary prophylaxis of overt hepatic encephalopathy in patients with cirrhosis: an open labeled randomized controlled trial of lactulose versus no lactulose. *J Gastroenterol Hepatol* 2012; **27**: 1329-1335 [PMID: 22606978 DOI: 10.1111/j.1440-1746.2012.07186.x]

22 **Madoff DC**, Wallace MJ, Ahrar K, Saxon RR. TIPS-related hepatic encephalopathy: management options with novel endovascular techniques. *Radiographics* 2004; **24**: 21-36; discussion 36-37 [PMID: 14730033 DOI: 10.1148/rg.241035028]

23 **Riggio O**, Efrati C, Catalano C, Pediconi F, Mecarelli O, Accornero N, Nicolao F, Angeloni S, Masini A, Ridola L, Attili AF, Merli M. High prevalence of spontaneous portal-systemic shunts in persistent hepatic encephalopathy: a case-control study. *Hepatology* 2005; **42**: 1158-1165 [PMID: 16250033 DOI: 10.1002/hep.20905]

24 **Watanabe A**. Portal-systemic encephalopathy in non-cirrhotic patients: classification of clinical types, diagnosis and treatment. *J Gastroenterol Hepatol* 2000; **15**: 969-979 [PMID: 11059925 DOI: 10.1046/j.1440-1746.2000.02283.x]

25 **Sarfeh IJ**, Rypins EB. Partial versus total portacaval shunt in alcoholic cirrhosis. Results of a prospective, randomized clinical trial. *Ann Surg* 1994; **219**: 353-361 [PMID: 8161260]

26 **Wróblewski T**, Rowiński O, Ziarkiewicz-Wróblewska B, Górnicka B, Albrecht J, Jones EA, Krawczyk M. Two-stage transjugular intrahepatic porta-systemic shunt for patients with cirrhosis and a high risk of portal-systemic encephalopathy patients as a bridge to orthotopic liver transplantation: a preliminary report. *Transplant Proc* 2006; **38**: 204-208 [PMID: 16504703 DOI: 10.1016/j.transproceed.2005.12.019]

27 **Zhao HQ**, Nikanorov A, Virmani R, Jones R, Pacheco E, Schwartz LB. Late stent expansion and neointimal proliferation of oversized Nitinol stents in peripheral arteries. *Cardiovasc Intervent Radiol* 2009; **32**: 720-726 [PMID: 19484292 DOI: 10.1007/s00270-009-9601-z]

28 **Gaba RC**, Parvinian A, Minocha J, Casadaban LC, Knuttinen MG, Ray CE, Bui JT. Should transjugular intrahepatic portosystemic shunt stent grafts be underdilated? *J Vasc Interv Radiol* 2015; **26**: 382-387 [PMID: 25735521 DOI: 10.1016/j.jvir.2014.08.012]

P- Reviewer: Chen JL, Fouad YM, Garbuzenko DV **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Li D

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com