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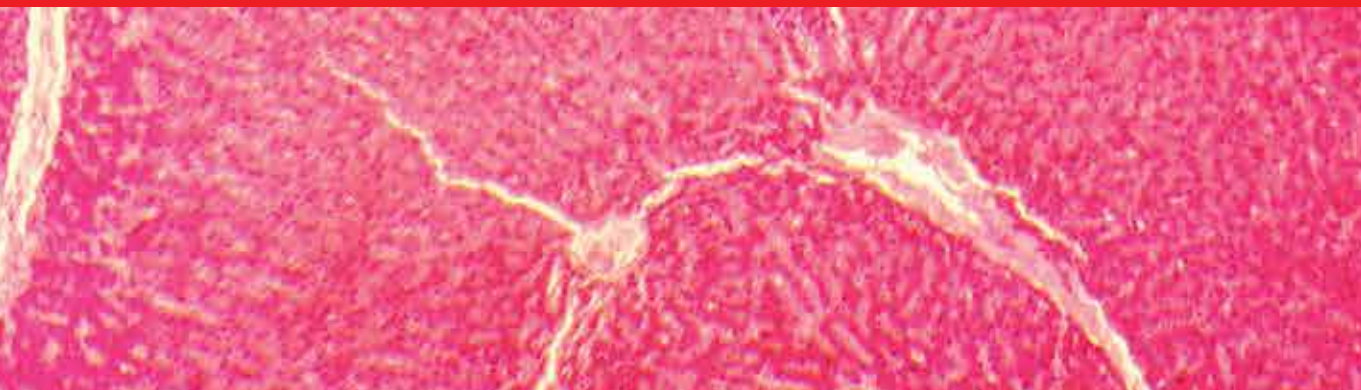

MANAGEMENT OF CHRONIC LIVER DISEASES - RECENT ADVANCES

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Notice

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Meet the editor

Dr. Xingshun Qi was born in July 1984 in Shenyang, China. He obtained his medical doctoral degree at the Fourth Military Medical University in Xi'an and completed his postdoctoral fellowship at the General Hospital of Shenyang Military Area in Shenyang, China. He is currently working at the Department of Gastroenterology of the General Hospital of Shenyang Military Area as a vice chief physician. He served as a co–editor-in-chief of *AME Medical Journal*; an associate editor of *Annals of Hepatology*; a lead guest editor in *Gastroenterology Research and Practice, BioMed Research International*, and *Therapeutic Advances in Gastroenterology*; a guest editor in *Canadian Journal of Gastroenterology and Hepatology*; an editorial member of *World Journal of Hepatology* and *Cardiovascular & Hematological Disorders - Drug Targets*; and a column executive editor of *Journal of Translational Internal Medicine*. He has also served as a peer reviewer in more than 60 journals. According to the Scopus, his H-index is 26, and total number of citation is now 2235.

Contents

Preface

Chronic liver disease, which can progress to liver cirrhosis and even hepatocellular carcinoma, is a major global burden. Long-term efforts have been made to understand the pathogenesis of chronic liver diseases, to optimize clinical decisions, and to improve the patients' prognosis. In recent years, the knowledge regarding management of chronic liver diseases has been dramatically updated.

Under such a circumstance, I was very honored and excited to receive the invitation from IntechOpen in October 2017 to initiate an Open Access book project regarding the management of chronic liver diseases. After critical reviews, meticulous selection, repeated revisions, and great improvement, a total of 6 chapters, which are contributed by worldwide experts in the field of liver diseases, have been included in this book entitled *Management of Chronic Liver Diseases – Recent Advances*. The book is divided into 3 major sections according to the stage of liver diseases analyzed (i.e., chronic liver diseases, liver cirrhosis, and hepatocellular carcinoma). In detail, it introduces the intra-abdominal hypertension and abdominal compartment syndrome in chronic liver diseases, ascites with hyponatremia, acute kidney injury, portal vein thrombosis, spontaneous bacterial peritonitis in liver cirrhosis, and the use of stereotactic body radiation therapy in hepatocellular carcinoma. Clinicians and investigators who are interested in the management of chronic liver diseases will be acquainted with its merits and usefulness.

This is the first book that I have edited. Such an experience will be unforgettable in my life. Herein, I should acknowledge the great help from IntechOpen staff, including Ana Pantar (Senior Commissioning Editor), Anja Filipovic (Junior Commissioning Editor), Danijela Vladika (Publishing Process Manager), and Romina Rovan (Publishing Process Manager). Also, I deeply appreciate the support from all chapter authors. Finally, I dedicate this book to my wife Jun Liu.

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Chronic Liver Disease

Chapter 1

Intra-Abdominal Hypertension and Abdominal Compartment Syndrome in Liver Diseases

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Additional information is available at the end of the chapter

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Abstract

Intra-abdominal hypertension (IAH) is defined as an intra-abdominal pressure (IAP) above 12 mmHg. Abdominal compartment syndrome (ACS) is defined as an IAP above 20 mmHg with evidence of organ failure. Moreover, IAH/ACS is a condition that can cause acute renal failure, respiratory failure, circulatory disease, gastrointestinal dysfunction, and liver failure due to elevated IAP. The incidence of IAH/ACS increases in the more critically ill patient and is associated with significantly increased morbidity and mortality. Ascites, blood, or tumors increase IAP. In liver cirrhosis, massive ascites is often encountered. Hence, preventing IAH/ACS conditions may improve outcomes of patients with liver disease.

Keywords: intra-abdominal hypertension (IAH), abdominal compartment syndrome (ACS), hepatorenal syndrome (HRS)

1. Introduction

The pressure within the abdominal cavity is normally a little higher than the atmospheric pressure to less than 0 mmHg. Certain physiological conditions such as morbid obesity and pregnancy may be associated with chronic IAP elevations. However, even small increases in intra-abdominal pressure can have adverse effects on renal function, cardiac output, hepatic blood flow, respiratory mechanics, splanchnic perfusion, and intracranial pressure. IAP is approximately 5–7 mmHg in critically ill adults.

Wendt et al. firstly described oliguria in the presence of elevated intra-abdominal pressure in 1876 [1]. In 1947, Bradley published a seminal study of the renal effects of elevated IAP in humans [2]. Despite these early descriptions of the adverse effects of IAH, physicians are not careful about the significance of increased abdominal pressure.

Until recently, patients with ACS were not infrequently managed in the intensive care unit and typically presented with a tense distended abdomen, increased peak inspiratory airway pressure, severe hypercapnia, hypotension, and oliguria. Abdominal ascites occurs typically at the end stage of liver failure. Massive ascites also influences IAP and causes oliguria and acute kidney injury. Commonly, we recognize this symptom and confused it with hepatorenal syndrome (HRS). In such patients, we should take into account the elevation of renal parenchymal and renal vein pressures, as they are likely the mechanisms of renal impairment. Note that IAH/ACS and HRS are occurring simultaneously. Recently, Matsumoto et al. reported that renal vein dilation predicts poor outcome in patients with refractory cirrhotic ascites [3].

2. Pathophysiology of ACS

The pathology of IAH/ACS is perfusion imbalance in multiple organs: compression of the portal system in the abdominal cavity, compression of the inferior vena cava system in retroperitoneal organs, compression of the diaphragm in the intrathoracic organ, and perfusion dysfunction of the brain circulation through increase of intrathoracic pressure [4].

The perfusion imbalance in the upper body originated from the abdominal cavity, which causes circulation impairment and further increased intrathoracic cavity pressure and retroperitoneal cavity. This imbalance presents a functional disorder that substantially affects multiple organs.

ACS is similar to the compartment syndrome in muscular diseases. It is a circulatory disease caused by internal pressure of organs sectioned in a small wall of the compliance anatomically [5]. The normal IAP ranges from sub-atmospheric level to 0 mmHg. Certain physiological conditions, such as morbid obesity and pregnancy, may be associated with chronic IAP elevations. Moreover, IAH is defined as an IAP above 12 mmHg. ACS is defined as an IAP above 20 mmHg with evidence of organ failure [6]. IAP is the steady state of pressure concealed within the abdominal cavity. The normal IAP for critically ill patients are 5–7 mmHg range. Once, IAP have increased, patients become the state of IAH. IAH is recognized sustained IAP greater than to 12 mmHg. IAH may also be subclassified according to the duration of symptoms into one of the four groups. This fulminant example of IAH commonly leads to rapid development of ACS. With its development over a protracted time course, the abdominal wall adapts and progressively distends in response to increasing IAP, allowing time for the body to adapt physiologically. The clinical consideration of IAH subtypes is useful in prescribing patients at risk for ACS (**Table 1**) [6].

Primary ACS is characterized by the presence of acute or subacute IAH of relatively brief duration occurring as a result of an intra-abdominal cause such as severe acute pancreatitis, abdominal trauma, ruptured abdominal aortic aneurysm, and liver transplantation [7].

Secondary ACS is characterized by the presence of subacute or chronic IAH that develops massive fluid resuscitation such as an extra-abdominal cause such as sepsis, capillary leak, burns [8].

Classification of IAH		
Hyperacute IAH	Elevated IAP for seconds	Secondary to physical activity, coughing, laughing, sneezing, straining, or defecation
Acute IAH	Elevated IAP that develops over hours and can lead to rapid development of ACS	Secondary to trauma or intra-abdominal hemorrhage
Subacute IAH	Elevated IAP that develops over days and can also lead to ACS	Medical patients
Chronic IAH	Elevated IAP that develops over months or years.	Pregnancy, morbid obesity, intra-abdominal tumor, ascites

IAH, intra-abdominal hypertension; ACS, abdominal compartment syndrome.

Table 1. Classification of intra-abdominal hypertension.

Grading of IAH	
Grade I	IAP 12-15 mmHg
Grade II	IAP 16-20 mmHg
Grade III	IAP 21-21 mmHg
Grade IV	IAP > 25 mmHg

Table 2. Grading of intra-abdominal hypertension.

The World Society of Abdominal Compartment Syndrome classified IAH into grade I–IV and ACS (**Table 2**) [9].

Burch et al. suggested that most patients with grade III and all patients with grade IV should undergo abdominal decompression [10].

3. ACS results in non-abdominal organ failure

3.1. Cardiovascular

Due to the increased intrathoracic pressure, indirect measures of cardiac filling such as central venous pressure and pulmonary artery occlusion pressure give inaccurate results and can be increased despite profound intravascular volume depletion. The decrease in cardiac output caused by intra-abdominal hypertension is therefore exacerbated by hypovolemia [11].

3.2. Respiratory

Respiratory distress and failure: Initial signs of ACS include elevated peak airway pressures in intubated patients with decreased tidal volumes. The ensuing increase in intrathoracic pressure and hypoxic pulmonary vasoconstriction can lead to pulmonary hypertension [12].

3.3. Neurological

Intracranial perfusion pressure is decreased by increase in intracranial pressure (ICP) caused by venal perfusion defect, including renal failure. For increased ICP, decompressive laparotomy has been shown to reduce intractable elevated ICP in patients with IAH, and compression of the ureters is not thought to contribute to renal dysfunction, as the insertion of ureteric stents does not result in an improvement in urine output [13].

4. Intra-abdominal organ failure in ACS

4.1. Renal function disorder

ACS is characterized by marked reduction in glomerular filtration rate (GFR) and renal plasma flow in the absence of other causes of renal failure. Moreover, changes in cardiac output, direct compression of the renal vessels or renal parenchyma with diminished renal blood flow, increase in renal vascular resistance, and distribution of blood from the renal cortex to the medulla are reported the mechanisms of renal dysfunction [14]. Bradley et al. are the first to report that animals become anuric with an IAP of 30 mmHg [2]. Additional factors that cause IAP to reach ACS range include reduction in cardiac output and elevated levels of catecholamines [15]. Renin, angiotensin, and inflammatory cytokines may also come into play, further worsening renal function.

4.2. Liver function disorder

Diebel et al. reported that the portal vein (PV) pressure decreased experimentally in 65% of patients with an IAP of 40 mmHg, and liver tissue microcirculation quantity decreases to 71% [16].

Liver dysfunction occurs due to decrease PV flow because of IAH. Furthermore, with cardiac dysfunction, liver ischemia becomes worse. Persistent IAP decrease the mean arterial blood pressure in the superior mesenteric artery (SMA) and PV flow by 50% [17].

Rasmussen et al. reported that an IAP of 25 mm Hg results in a 66% decrease in PV blood flow and a 6.5-fold increase in portal/hepatic vascular resistance compared to baseline levels [18].

Furthermore, in studies evaluating the effects of increased IAP on hepatocyte, the characteristics of the sinusoid should be expected to elucidate hepatic dysfunction from increased IAP.

4.3. Gastrointestinal functional disorder

To determine the possibility of bacterial translocation (BT), of which there is failure of the mucous membrane barrier mechanism caused by decline in blood circulation in mucous membranes, pH in the mucous membrane declined as well. Besides, this phenomenon is regarded as the cause of multiple organ dysfunction syndrome (MODS) after ACS, but there is no direct proof. Even if the IAP is at 20 mmHg, blood flow to the intestinal mucosa decreases to 28%

experimentally in 61% of the baseline value of 40 mmHg [16]. In MODS, there is gastrointestinal mucous membrane acidosis of which the IAP is expected to be at 10 mmHg is derived from ACS.

5. Diagnosis of ACS

There are various methods of measuring intermittent IAP, such as invasive (direct, i.e., needle puncture of the abdomen during peritoneal dialysis or laparoscopy) and noninvasive (indirect, i.e., transduction of intravesicular or "bladder," gastric, colonic or uterine pressure via the balloon catheter). Noninvasive measurement of bladder internal pressure and intragastric

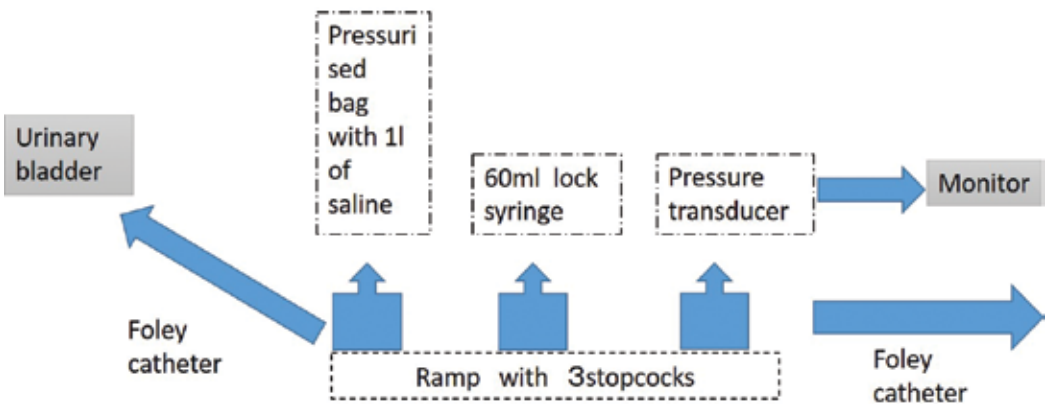

Figure 1. Measurement of intra-abdominal pressure using bladder pressure measurements.

pressure are recommended. The internal bladder pressure are commonly related to IAP measured directly in the range of 5–70 mmHg [6].

Intrabladder pressure monitoring estimated for IAP can be obtained either via a closed transducer technique or the closed Foley Manometer technique, which seems safe and does not alter the risk of UTI in patients with critical illness [19] (**Figure 1**).

6. ACS treatment

Discussions on IAP to become the adaptation standard of decompression is divided, but more than 25 mmHg is assumed to be a tentative adaptation standard clinically. However, recently, reports on gastrointestinal disorder due to impairment of IAP in the lower abdominal cavity need to be considered. The World Society of the Abdominal Compartment Syndrome suggested a management algorithm for IAH/ACS [20].

An early indication of the open abdomen technique has been shown to reduce mortality [21]. Chen et al. reported that laparoscopy can be used as a safe alternative for ACS decompression [22].

The World Society of the Abdominal Compartment Syndrome has noted that correct fluid therapy and perfusion support during resuscitation form the cornerstone of medical management in patients with abdominal hypertension [23].

Pharmacologic therapy is less effective than drainage procedures. Agustí et al. reported that dobutamine restores intestinal mucosal blood flow in a porcine model of intra-abdominal hyperpressure [24].

If a patient experiences decompensation, ACS should be re-examined as a potential cause.

7. Possible involvement of IAH/ACS and HRS

We reported an autopsy case with HRS and ACS diagnosed with a clinical and histopathological consideration of liver and kidney diseases. Further clinical studies are needed to improve the management of renal failure in patients with acute liver failure and advanced liver cirrhosis (**Figures 2** and **3**) [25].

HRS was originally described in 1863 by Flint as an association between liver disease and oliguric renal failure in the absence of significant renal histological change [26]. HRS is recognized by intense intrarenal vasospasm caused by the imbalance between vasodilatory and vasoconstrictive mediators seen in end stage of liver disease [27].

Although the precise role of IAH in HRS remains incompletely understood, it can be argued that diminished glomerular perfusion due to venous congestion results in further decline of GFR.

Cade et al. reported significant increases in urine flow rate and creatinine clearance after reduction in IAP from 22 to 10 mmHg with paracentesis in patients with cirrhosis [28]. Moreover,

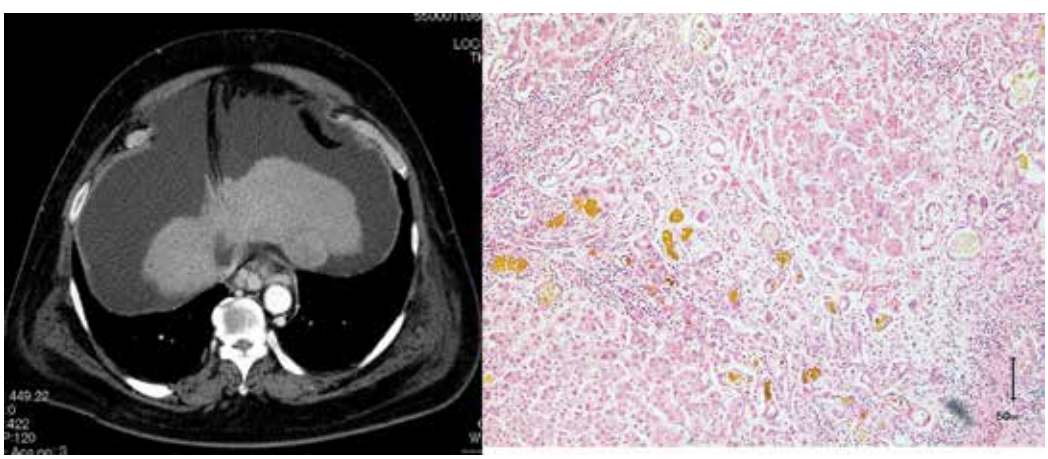

Figure 2. Liver: end-stage liver cirrhosis. Microscopic findings showed hepatic sinusoidal dilation due to portal hypertension and severe jaundice.

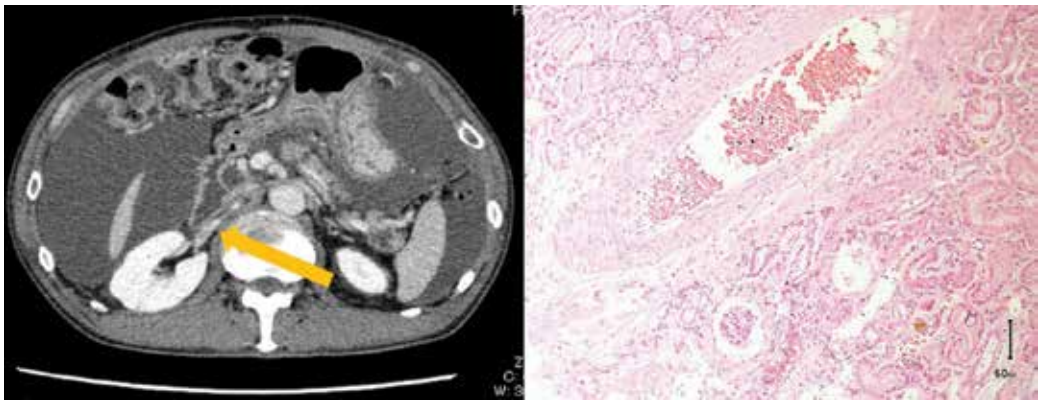

Figure 3. Kidney: microscopic findings showed swelling in the renal tubules. There was no change in the glomerulus and collecting tubule and no renal fibrosis. CT the right renal vein was compressed by massive ascites (arrow).

compression of renal vein is suggested to be vital in the development renal dysfunction. IAH is the significant pathological mechanism and independent risk factor in the occurrence and development of HRS [29]. Further, attempts should be made to decrease IAP following surgical decompression, large-volume paracentesis (LVP), and appropriate diuretic drug.

8. Drug strategy for ACS

Several methods are reported to control refractory abdominal ascites in end-stage liver cirrhosis, such as avoidance of non-steroidal anti-inflammatory drugs [30], dietary sodium restriction [31], diuretic, LVP, cell-free and concentrated ascites reinfusion therapy [32], transjugular intrahepatic portosystemic shunt [33], and peritoneovenous shunt [34].

IAH is defined as an IAP above 12 mmHg. Hence, abdominal ascites in early stage of liver cirrhosis should be treated and early stage of ascites in outpatient should be managed immediately. Outpatients with clinically apparent ascites will require diuretic therapy in addition to dietary sodium restriction. Diuretic therapy typically consists of treatment regimen for cirrhotic ascites such as combination of oral spironolactone and furosemide. Recently, aquaporin-2 is a vasopressin-regulated water channel expressed in the renal collecting duct. Urine aquaporin-2 is considered a marker of collecting duct responsiveness to tolvaptan. In Japan, on September 2013, tolvaptan was approved (in doses up to 7.5 mg/day) for treating patients with ascites who showed an inadequate response to conventional diuretics [35].

9. Conclusion

Massive ascites also influences IAP and causes oliguria and acute kidney injury (AKI). Commonly, we recognize this symptom at the stage of end stage of liver cirrhosis. This symptom has the possible involvement with HRS. In such patients, we should take into account the

elevation of renal parenchymal and renal vein pressures, as they are likely the mechanisms of renal impairment. Note that IAH/ACS and HRS are occurring simultaneously. Hepatologists should consider IAH and ACS in end-stage liver cirrhosis.

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References

[1] Wendt E. Ueber den einfluss des intraabdominalenn druckes auf die absonderungsgeschwindigkeit des harnes. Archives of Physiology and Heilkunde. 1876;**57**:527

[2] Bradley SE, Bradley GP. The effect of increased intra-abdominal pressure on renal function in man. The Journal of Clinical Investigation. 1947;**26**:1010-1022

[3] Matsumoto N, Ogawa M, Kumagawa M, Watanabe Y, Hirayama M, Miura T, Nakagawara H, Matsuoka S, Moriyama M, Fujikawa H. Renal vein dilation predicts poor outcome in patients with refractory cirrhotic ascites. Hepatology Research. 2018;**48**:E117-E125

[4] Cheatham ML, White MW, Sagraves SG, Johnson JL, Block EF. Abdominal perfusion pressure: A superior parameter in the assessment of intra-abdominal hypertension. The Journal of Trauma 2000;**49**:621-626

[5] Campano D, Robaina JA, Kusnezov N, Dunn JC, Waterman BR. Surgical management for chronic exertional compartment syndrome of the leg: A systematic review of the literature. Arthroscopy. 2016;**32**:1478-1486

[6] Malbrain ML, Cheatham ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, Balogh Z, Leppäniemi A, Olvera C, Ivatury R, D'Amours S, Wendon J, Hillman K, Johansson K, Kolkman K, Wilmer A. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. I. Definitions. Intensive Care Medicine. 2006;**32**:1722-1732

[7] Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: Hypothermia and acidoses revisited. The Journal of Trauma. 1997;**42**:857-861

[8] Aspesi M, Gamberoni C, Severgnini P, Colombo G, Chiumello D, Minoja G, Tulli G, Malacrida R, Pelosi P, Chiaranda M. The abdominal compartment syndrome. Clinical relevance. Minerva Anestesiologica. 2002;**68**:138-146

[9] Malbrain ML, Deeren D, De Potter TJ. Intra-abdominal hypertension in the critically ill: It is time to pay attention. Current Opinion in Critical Care; 2005;**11**:156-171

[10] Burch JM, Moore EE, Moore FA, Franciose R. The abdominal compartment syndrome. The Surgical Clinics of North America. 1996;**76**:833-842

[11] Ridings PC, Bloomfield GL, Blocher CR, Sugerman HJ. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. The Journal of Trauma. 1995;**39**:1071-1075

[12] Cullen DJ, Coyle JP, Teplick R, Long MC. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. Critical Care Medicine. 1989;**17**:118-121

[13] Constantini S, Cotev S, Rappaport ZH, Pomeranz S, Shalit MN. Intracranial pressure monitoring after elective intracranial surgery. A retrospective study of 514 consecutive patients. Journal of Neurosurgery. Oct 1988;**69**(4):540-544

[14] Mohmand H, Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. Journal of the American Society of Nephrology. Apr 2011;**22**(4):615-621

[15] Mikami O, Fujise K, Matsumoto S, Shingu K, Ashida M, Matsuda T. High intra-abdominal pressure increases plasma catecholamine concentrations during pneumoperitoneum for laparoscopic procedures. Archives of Surgery. 1998;**133**:39-43

[16] Diebel LN, Dulchavsky SA, Brown WJ. Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. The Journal of Trauma. 1997;**43**:852-855

[17] Mogilner J, Sukhotnik I, Brod V, Hayari L, Coran AG, Shiloni E, Eldar S, Bitterman H. Effect of elevated intra-abdominal pressure on portal vein and superior mesenteric artery blood flow in a rat. Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A. 2009;**19**(Suppl 1):S59-S62

[18] Rasmussen IB, Berggren U, Arvidsson D, Ljungdahl M, Haglund U. Effects of pneumoperitoneum on splanchnic hemodynamics: An experimental study in pigs. The European Journal of Surgery. 1995;**161**:819-826

[19] Desie N, Willems W, De laet I, Dits H, Van Regenmorte N, Schoonheydt K, Van De Vyvere M, Malbrain M. Intra-abdominal pressure measurement using the Foley manometer does not increase the risk for urinary tract infection in critically ill patients. Annals of Intensive Care. 2012;**2**(Suppl 1):S10

[20] Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain ML, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C. Pediatric guidelines sub-Committee for the World Society of the abdominal compartment syndrome. Intra-abdominal hypertension and the abdominal compartment syndrome: Updated consensus definitions and clinical practice guidelines from the world Society of the Abdominal Compartment Syndrome. Intensive Care Medicine. 2013;**39**:1190-1206

[21] Madigan M, Kemp C, Johnson J, Cotton B. Secondary abdominal compartment syndrome after severe extremity injury. The Journal of Trauma. 2008;**64**:280-285

[22] Chen RJ, Fang JF, Lin BC, Kao JL. Laparoscopic decompression of abdominal compartment syndrome after blunt hepatic trauma. Surgical Endoscopy. 2000;**14**:966-967

[23] Regli A, De Keulenaer B, De Laet I, Roberts D, Dabrowski W, Malbrain ML. Fluid therapy and perfusional considerations during resuscitation in critically ill patients with intra-abdominal hypertension. Anaesthesiology Intensive Therapy. 2015;**47**:45-53

[24] Agusti M, Elizalde JI, Adalia R, Cifuentes A, Fontanals J, Taura P. Dobutamine restores intestinal mucosal blood flow in a porcine model of intra-abdominal hyperpressure. Critical Care Medicine. 2000;**28**:467-472

[25] Kamimura H, Watanabe T, Sugano T, Nakajima N, Yokoyama J, Kamimura K, Tsuchiya A, Takamura M, Kawai H, Kato T, Watanabe G, Yamagiwa S, Terai S. A case of Hepatorenal syndrome and abdominal compartment syndrome with high renal congestion. American Journal of Case Reports. 2017;**18**:1000-1004

[26] Flint A. Clinical report on hydroperitoneum, based on an analysis of 46 cases. The American Journal of the Medical Sciences. 1863;**45**:306-309

[27] Gines P, Guevara M, Arroyo V, Rodes J. Hepatorenal syndrome. Lancet. 2003;**362**:1819-1827

[28] Cade R, Wagemaker H, Vogel S, Mars D, Hood-Lewis D, Privette M, Peterson J, Schlein E, Hawkins R, Raulerson D, et al. Hepatorenal syndrome. Studies of the effect of vascular volume and intraperitoneal pressure on renal and hepatic function. The American Journal of Medicine. 1987;**82**:427-438

[29] Bloomfield GL, Blocher CR, Fakhry IF, Sica DA, Sugerman HJ. Elevated intra-abdominal pressure increases plasma renin activity and aldosterone levels. The Journal of Trauma. 1997;**42**:997-1004

[30] Arroyo V, Ginés P, Rimola A, Gaya L. Renal function abnormalities, prostaglandins, and effects of nonsteroidal anti-inflammatory drugs in cirrhosis with ascites. An overview with emphasis on pathogenesis. The American Journal of Medicine. 1986;**81**:104-122

[31] Runyon BA, Montano AA, Akriviadis EA, Antillon MR, Irving MA, McHutchison JG. The serum-ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Annals of Internal Medicine. 1992;**117**:215-220

[32] Inoue N, Yamazaki Z, Oda T, Sugiura M, Wada T. Treatment of intractable ascites by continuous reinfusion of the sterilized, cell-free and concentrated ascitic fluid. Transactions – American Society for Artificial Internal Organs. 1977;**23**:699-702

[33] Ginès P, Arroyo V, Vargas V, Planas R, Casafont F, Panés J, Hoyos M, Viladomiu L, Rimola A, Morillas R, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. The New England Journal of Medicine. 1991;**325**:829-835

[34] Park JS, Won JY, Park SI, Park SJ, Lee DY. Percutaneous peritoneovenous shunt creation for the treatment of benign and malignant refractory ascites. Journal of Vascular and Interventional Radiology. 2001;**12**:1445-1448

[35] Sakaida I, Terai S, Kurosaki M, Yasuda M, Okada M, Bando K, Fukuta Y. Effectiveness and safety of tolvaptan in liver cirrhosis patients with edema:Interim results of post-marketing surveillance of tolvaptan in liver cirrhosis (START study). Hepatology Research. Oct 2017;**47**(11):1137-1146

Liver Cirrhosis

Chapter 2

Management of Ascites Associated with Severe Hyponatremia

Andra Iulia Suceveanu, Roxana Popoiag, Laura Mazilu, Irinel Raluca Parepa, Andreea Gheorghe, Anca Stoian, Felix Voinea, Claudia Voinea and Adrian Paul Suceveanu

Additional information is available at the end of the chapter

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Abstract

Advanced liver cirrhosis requiring hospitalization is frequently associated with electrolytic disturbances, the most common finding being serum hyponatremia. The goal of treatment in patients with decompensated liver cirrhosis complicated with severe hyponatremia is to normalize the increased amount of water in the body and to improve the sodium concentration. Fluid restriction is recommended at 1.5 L/day to prevent sodium depletion in the serum, but the lack of efficacy is probably due to a poor patient compliance. Discontinuation or adjustments of diuretic dosages are sometimes required. Albumin associated with vasoconstrictors as midodrine can increase the effective arterial blood volume and seems to improve the serum sodium concentration. A promising therapeutic option targeting the pathophysiological mechanism of hyponatremia consists of improving solute-free water excretion, which is markedly impaired in these patients. The use of agents such as k opioid agonists has been attempted, but has been dropped due to the severe side effects. Recently, a new therapeutic class called vaptans has taken an important place in the treatment of hypervolemic hyponatremia. The main side effects during the administration of these drugs in patients with liver cirrhosis are reversible after discontinuing therapy. Therefore, it is recommended to use vaptans for short periods of time.

Keywords: hypervolemia, hyponatremia, liver cirrhosis, fluid restriction, vasopressin receptor antagonists, vaptans

1. Introduction

Ascites is the most common complication of cirrhosis, approximately 60% of patients develop ascites within 10 years of disease progression. The mechanism of production is the development of portal hypertension and renal retention of sodium. This inability to excrete an adequate amount of sodium in the urine occurs due to arterial splanchnic vasodilatation. Therefore, arterial and pulmonary cardio vascular receptor activation occurs with homeostatic activation of vasoconstrictor and sodium retention systems, resulting in a decrease in the required arterial blood volume. Renal sodium retention increases the volume of extracellular fluid leading to ascites and edema [1–5].

At approximately 75% of patients from Western Europe and USA, the main cause of ascites is represented by cirrhosis. Other causes of ascites may be malignancy, heart failure, tuberculosis, pancreatic disease, or other causes.

Hyponatremia is one of the complications that occurs in end stage cirrhosis due to the impossibility of renal clearance of free water, which leads to a higher water retention than sodium with the occurrence of hyposomolarity, with an increase in mortality and morbidity. In the pathogenesis of hyponatremia, the main factor involved is hypersecretion of antidiuretic hormone (ADH). Hyponatremia is a risk factor for both hepatic encephalopathy and liver transplantation because it is associated with an increased frequency of complications and a short-term survival [6].

2. Definition

Patients with liver cirrhosis show two types of hyponatremia: hypovolemic and hypervolemic.

Hypervolemic hyponatremia is the most common form and is characterized by low levels of serum sodium and increased volume of extracellular fluid, ascites, and edema. It may appear secondary to bacterial infections, excessive hypotonic fluids or may occur spontaneously. Hypovolemic hyponatremia is less common, with low levels of sodium, without ascites and edema as a consequence of excessive diuretic administration.

Hyponatremia is defined when serum sodium levels fall below 130 mmol/L but according to the recent guidelines, reductions below 135 mmol/L should also be considered as hyponatremia [7].

3. Prevalence

A study made over an Asian population following 997 patients with cirrhosis and ascites over 28 days in 28 centers showed that hyponatremia is present in more than half of the patients [8].

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4. Pathophysiology

The mechanism by which ascites fluid is formed is the excess water and sodium retention in the body. Several theories have been developed to understand pathophysiology, and in turn, it has been shown that much of it would arise as a result of portal hypertension. The three proposed theories are three distinct mechanisms named: filling, oversaturation, and peripheral arterial vasodilatation. The first theory of filling is determined by portal hypertension and decreased circulating volume that produces vascular fluid retention. Since cirrhotic patients have a higher percentage of hypervolemia than hypovolemia, the second overload theory is determined by the retention of water and sodium in the absence of volume exhaustion. And the third theory uses the first two theories. This indicates that vasodilation occurs as a result of portal hypertension and favors the increase in arterial blood volume. Also, several factors are involved in ascites fluid formation: hypoalbuminemia and oncotic low plasma pressure, elevated levels of epinephrine and norepinephrine.

The main mechanism of hyponatremia is represented by arterial vasodilation. By reducing effective blood volume, several neurohumoral systems such as the renin-angiotensin-aldosterone system and the sympathetic nervous system are stimulated and lead to the release of ADH.

Activation of those trigger systems causes sodium retention and may lead to renal vasoconstriction. Vasopressin 2 receptors affected by the ADH play an important role in rate of excretion of solute-free water. In the end, water excretion occurs with the appearance of serum dilution and hypo-osmolality [6].

Under normal circumstances, there is a synchronous increase in serum osmolarity and ADH secretion, and reabsorption of water occurs when activating the aquaporin channels in the renal collection tubes. In opposite, the inactivation of aquaporin channels occurs when a decrease in osmolarity appears, resulting in urine dilution as a mechanism in maintaining serum osmolarity. Thus, the good functioning of osmoreceptors in the anterior hypothalamus, the release of ADH and the mutual action between ADH and AQP-2 compete to adapt the release of free water.

ADH is secreted into the supraoptic and paraventricular nuclei of the hypothalamus and maintained in the posterior pituitary gland. Vasopressin secretion is stimulated by increased plasma osmolarity and hypovolemia. The release of ADH is conditioned by osmotic and nonosmotic stimulation. The osmoreceptors in the anterior hypothalamus, near the supraoptic nuclei mediate the osmotic pathway. These receptors detect intracellular water content in neurons and respond to changes in plasma osmolarity. The main nonosmotic pathway delivers an ADH release through the autonomic nervous system mediated by baroreceptors located in the atrium, ventricle, aortic arch, and carotid sinus. Through the parasympathetic pathway, these baroreceptors stimulate the hypothalamus to release ADH in response to hypovolemia [9].

Most patients with cirrhosis present low serum osmolarity and sodium levels, and it is expected to produce inhibition of ADH release if stimulation was achieved by osmoreceptors [10]. Because of the activation of the neurohumoral mechanisms that retain sodium, the levels of ADH, aldosterone, norepinephrine, and renin activity were significantly higher in patients with cirrhosis and ascites after the water loading test. Effective arterial uptake would result from a decrease in systemic vascular resistance and would result in nonosmotic stimulation due to baroreceptors of ADH and other vasoconstriction systems. These cause the activation of the neurohumoral mechanisms that produce sodium retention in order to restore the perfusion pressure [11].

It is suggested that hypoosmotic stimuli are suppressed by nonosmotic stimuli to suppress ADH release. That is why the body sacrifices osmolar homeostasis and releases ADH following nonosmotic stimulation of endogenous vasoconstrictors, and thus impairs vascular collapse by exhausting effective circulatory volume. It results in an inability to release sodium and water to replenish the circulation volume. All of these things happen despite the increase in cardiac output, plasma volume, and total body volume. To eliminate the extra amount of water, it is necessary to suppress adherence and the ability of the kidneys to remove water. The presence of nonosmotic adherence leads to the occurrence of a hyponatremia of dilution or hypervolemic hyponatremia. Therefore, in this category of patients, hyponatremia is only dilute and does not represent a sodium deficiency [12].

In a prospective cohort study of patients with ascites, it was demonstrated that the occurrence of hyponatremia is preceded by refractory ascites and subsequently by hepatorenal syndrome. Each of these steps was associated with a progressive Child Pugh score and Model for End Stage Liver Disease (MELD) indicating a worsening of liver function. Therefore, hyponatremia is an intermediate stage between ascites progression and hepatorenal syndrome [13].

5. Prognostic value

Hyponatremia in patients with cirrhosis is chronic, therefore, allows the brain to adapt to the hypo extracellular fluid osmolality. In conclusion, patients are less likely to have severe neurological symptoms. However, hyponatremia can aggravate cerebral edema and swollen astrocytes by adding to their dysfunction created by increased intracellular glutamine concentration, speeding up the appearance of hepatic encephalopathy [6].

Due to the severe restriction of fluid consumption, the quality of life of patients with cirrhosis and hyponatremia is poor [14]. Several studies have shown that the severity of hyponatremia and ascites is a prognostic factor of the disease [15, 16]. In one study, it was demonstrated that the serum sodium level prior to the occurrence of spontaneous bacterial peritonitis (SBP) was an independent predictor of renal insufficiency produced by SBP [17]. It is also a predictive marker with a higher sensitivity than serum creatinine to predict the occurrence of circulatory dysfunction resulting in renal insufficiency or death. Although patients with hyponatremia are susceptible to the hepatorenal syndrome, there is not only an increased level of ADH involved, but there is a decrease in glomerular filtration rate (GFR) and proximal sodium reabsorption [18].

Sodium concentration was included in the MELD model to indicate the need for liver transplantation and patient priority on waiting lists in order to improve prognosis [19]. It was found that the MELD-Na score indicated an anticipation of short-term mortality of transplant patient candidates much better than the initial MELD score [20].

6. Clinical presentation

Symptoms of hyponatremia are caused by the damage to the nervous system, with cerebral edema due to the migration of water from the intravascular space in the brain [21]. As a rapid adaptive mechanism, there is an increase in electrolytes in brain cells. As a slow adaptation mechanism, organic osmoliths are extruded. Finally, these mechanisms help return the water to the intravascular space and prevent brain edema [22].

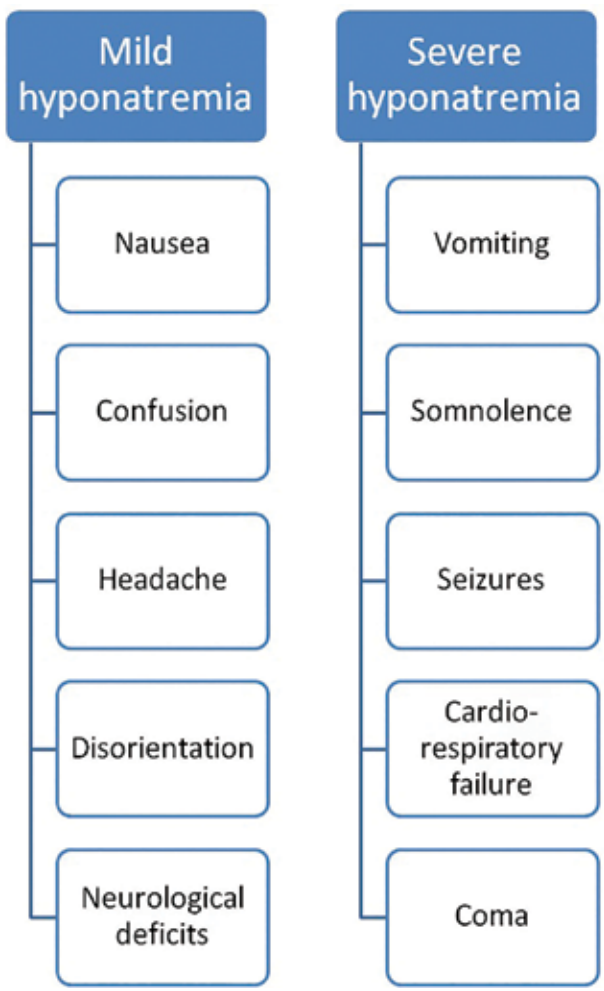

Figure 1. Clinical manifestations of hyponatremia.

In patients without hepatic impairment, hyponatremia manifests with: headache, disorientation, confusion, and neurological deficits. In contrast, in cirrhotic patients, hyponatremia develops slowly and at a value of 125 mEq/L is asymptomatic due to adaptive mechanisms. However, a rapid drop in sodium concentration may overcome adaptive mechanisms and serious symptoms may occur such as coma, seizures, brain-stern herniation, respiratory failure, and death [23] (**Figure 1**).

Hyponatremia usually occurs in the final stage of liver disease and is difficult to differentiate if the symptoms are within it or are part of liver encephalopathy occurrence. Both hyponatremia and hyperammonemia cause an alteration in brain metabolism of myoinositol [24].

Some theories show that hyponatremia can cause the appearance of a minimal cerebral edema that occurs by swelling of astrocytes and may cause the appearance of hepatic encephalopathy. This minimal brain edema occurs by increasing the concentration of glutamine resulting from the metabolism of ammonia and leads to a series of neurological changes to the appearance of hepatic encephalopathy [25].

7. Complications

Central pontine myelinolysis (CPM) is a complication of severe hyponatremia and occurs when its correction has been achieved very quickly. It is a neurological disorder that consists of a demyelination that occurs in a region called pons [26].

The mechanism by which this affection occurs is not fully known. One theory claims that this demyelination occurs by compressing fibrous structures as a result of cerebral edema arising from an osmotic fluctuation. Currently accepted theory supports the fact that brain cells adjust their osmolarity with certain osmolites, like inositol, betaine, and glutamine. In case of chronic hyponatremia, there is a decrease in these osmoliths in the brain, preventing fluid absorption [27, 28]. Clinical manifestations depend on the affected brain region, initially manifested by symptoms of hyponatremic encephalopathy such as nausea, vomiting, headache, confusion, and seizures. These symptoms can be reversed when adjusting the sodium concentration. Later signs of myelinolysis such as walking disturbances and respiratory dysfunction can occur [29]. Among the risk factors for this condition are: sodium concentration < 120 mEq/L for 48 hours, aggressive correction with saline solution and the occurrence of hypernatremia during treatment. If post liver transplant patients develop symptoms as confusion or weakness, CPM should be suspected because it may complicate a liver transplant [30].

Although the prognosis is poor with the occurrence of numerous neurological complications such as spastic quadriparesis and blocked syndrome, recovery is possible although it has a long duration [31].

Diagnosis can be done clinically and imagistically. The preferred imaging method is MRI, although lesions appear late and often initially may be normal [32]. The most common images are T2 weighted with hyperintense areas where demyelination was performed [33].

8. Management of hyponatremia

There are no data to recommend optimal serum sodium to initiate the treatment, but is generally recommended at a value of 130 mmol/L.

The identification and adjustment of excessive diuretic dosages and the addition of sodium are the main treatment requirements in the setting of hypovolemic hyponatremia. In case of hypervolemic hyponatremia, the most important issue is to decrease the amount of water to improve the sodium concentration.

When patients experience neurological symptoms due to hyponatremia or have a sodium concentration of less than 120 mEq/L, fluid restriction is indicated. In the case of mild and asymptomatic hyponatremia, fluid restriction is not indicated. Increasing sodium concentration in the first 24–48 hours is an important parameter that suggests an adequate fluid restriction. If this increase does not occur, either the restriction has to be more severe or the patient is not compliant. Fluid restriction is useful, but ineffective. Because the fluid restriction is severe, most patients cannot be compliant.

If patients have severe hyponatremia, there have been no responses to fluid restriction; it is indicated to administer the hypertonic saline. However, caution should be exercised in order not to cause a rapid increase in sodium concentration, which predisposes to the occurrence of numerous complications such as: central myelinolysis, quadriplegia, coma, or death [6].

The efficacy of using hypertonic sodium chloride in severe hypervolemic hyponatremia is partial, short-lived and aggravates ascites and edema. Instead, administration of albumin appears to have benefits, helps to increase the sodium concentration, but is not fully studied [34].

An important issue in patients with cirrhosis and hyponatremia is the correction of hypokalemia. Hypokalemia favors the appearance of hepatic encephalopathy because it increases the kidney synthesis of ammonium. By correcting it, there is also an increase in sodium concentration because both sodium and potassium are osmotically active [35].

In the past, the use of k-opiod agonist therapy has been attempted due to side effects [36]. According to recent studies, a new class of therapy, called vaptans, has been discovered in the treatment of hypervolemic hyponatremia. Vaptans selectively block the V2-receptors of AVP. They can be used in diseases like syndrome of inappropriate antidiuretic hormone secretion (SIADH), heart failure and cirrhosis, having the role of improving sodium concentration. The benefits of their administration over a short period of time are the increasing of urine volume and solute-free water excretion, and also, the improvement of the low serum sodium levels in 45–82% of patients [37] (**Figure 2**).

Hypernatremia, dehydration, renal impairment, and osmotic demyelination syndrome owing to a very rapid increase in serum sodium concentration could be the side effects of the administration of vaptans in patients with liver cirrhosis. Therefore, treatment should be initiated in the hospital and patients should be closely monitored to avoid hypernatremia.

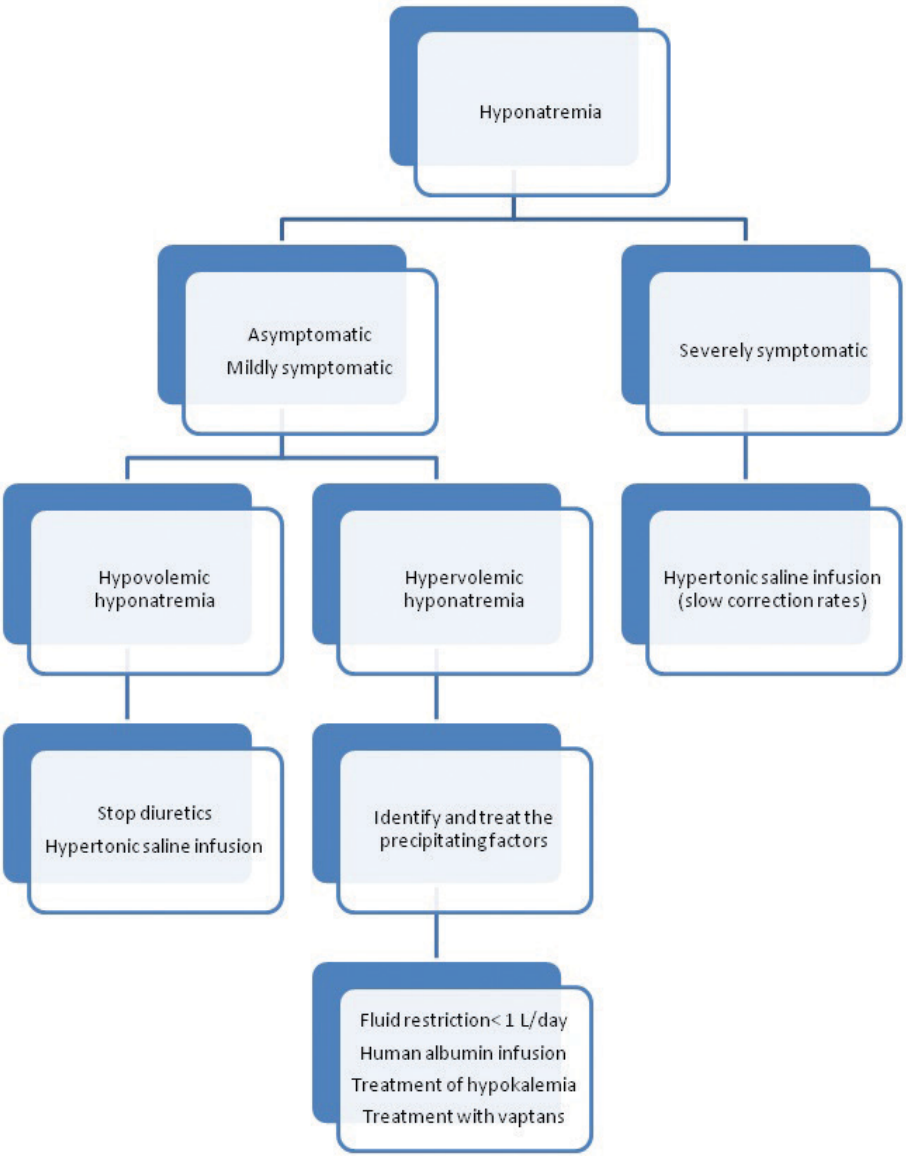

Figure 2. Management of hyponatremia.

Due to the risk of dehydration and hypernatremia, vaptans are also contraindicated in patients with an inappropriate consciousness state, unable to measure the volumes of fluid consumed.

The metabolism of vaptans is achieved in the liver by CYP3A enzymes. Therefore, CYP3A inhibitory drugs should be avoided because they increase the concentration of vaptans and may lead to the increase of serum sodium concentration. Also, drugs that are inducers of the CYP3A should be avoided because those drugs can reduce the concentration of vaptans.

Tolvaptan and conivaptan are recently approved in the USA for the treatment of severe hypervolemic hyponatremia from diseases such as cirrhosis, heart failure and SIADH. Treatment is started at a dose of 15 mg/day and can be increased progressively depending on the sodium concentration. In Europe, tolvaptan is authorized only for the treatment of SIADH. As an alternative option, conivaptan can be used to treat hypervolemic hyponatremia for short periods of time, especially when cirrhosis is associated with various conditions [38, 39].

Tolvaptan should be initiated without taking into account the period of meals, but initially it is advisable not to suppress the consumption of fluids to avoid rapid correction of sodium concentration. If, on completion of tolvaptan therapy, hyponatremia recurs, it should be corrected in a hospital unit. There may be no need for hospitalization, if treatment can be monitored to prevent excessive sodium concentration [40].

In randomized trials, the only side effects of tolvaptan treatment were gastrointestinal bleeding, but slightly increased incidence compared to placebo. It should be taken into account that the treatment was administered over a short period of time and new studies of the safety of long-term treatment are needed [41].

Treatment with conivaptan is contraindicated in patients who are allergic to constituents, in hyponatremia or hypovolaemia because it can induce from renal failure to shock. CYP3a4 inhibitors should not be administered concomitantly [42]. In general, the treatment was tolerated and adverse reactions were reported: local reactions (pain and erythema at the administration level), orthostatic hypotension, peripheral edema, headache, nausea, vomiting, urinary tract infections, and insomnia [43]. Effective treatment of hyponatremia should be initiated promptly to prevent irreversible neurological damage, but rapid correction may cause osmotic demyelination syndrome that can lead to death [44].

Domecycline favors the increase in free water excretion as an ADH antagonist, but cannot be used in cirrhosis due to nephrotoxicity [45].

The use of vasoconstrictors in hyponatremia is not tested, but studies of the hepatorenal syndrome have shown an improvement in sodium concentration [46].

The use of vasoconstrictors in hepatorenal syndrome has the following benefits: it improves the effective blood volume, vascular or systemic vasodilation, and renal perfusion. They are usually used in concomitant albumin administration. The most commonly used are: terlipressin, norepinephrine, vasopressin, and octeotrid, in combination with midodrine.

This combination can be used without supervision in a medical unit and is safe. Octreotide produces decreased splanchnic vasodilatation and midodrine improves renal perfusion and in combination with albumin improves kidney function, but there are still insufficient studies in this regard.

The octreotide is administered subcutaneously at the dose of 100 micrograms, 3 times per day, and the dose can be increased to 200 μg, 3 times per day. Midodrine is given orally 7.5 mg, 3 times per day and the dose can also be increased up to 12.5 mg, 3 times per day [47].

Treatment with terlipressin should be avoided in patients with cirrhosis, as it may cause severe hyponatremia, reversible upon discontinuation of treatment. Terlipresin acts on the vasopressin V1 receptor, but is also a partial vasopressin V2 receptor agonist. This is beneficial in the treatment of bleeding caused by portal hypertension, but also in hepatorenal syndrome [48].

By correcting hyponatremia in patients with cirrhosis, there are number of advantages: avoiding fluid restriction, administering effective doses of diuretics, especially in the treatment of refractory ascites, reducing the risk by developing hepatic encephalopathy, and improving the quality of life. It can also help reduce neurological complications after transplantation [49, 50].

9. Conclusions

Hyponatremia is a complication of cirrhosis, associated with an increased risk of mortality and morbidity in patients on the waiting list for a liver transplant. It also increases the risk of complications, such as hepatic encephalopathy, renal failure, and spontaneous bacterial peritonitis.

Hyponatremia occurred during cirrhosis evolution has as a pathophysiological mechanism arterial vasodilation that produces inadequate AVP secretion and a reduction in glomerular filtration rate with impairment of free water clearance. Clinical presentation does not differ from that of patients without hepatic impairment, but the symptoms of hyponatremia in cirrhosis are sometimes associated and difficult to differentiate from those in hepatic encephalopathy. As a dilutional hyponatremia, its treatment is not indicated if it is asymptomatic. Conversely, at a concentration of Na <120 mEq/L and on the occurrence of neurological symptoms, treatment can be initiated. An exception is the situation where patients are about to receive a liver transplant in a short time and the Na concentration is <130 mEq/L. In this case, its treatment is indicated to prevent the occurrence of serious neurological complications such as osmotic demyelination syndrome as a result of a rapid correction in the operating room. An important role is the differentiation of hypovolemic hyponatremia from the hypervolemic hyponatremia to initiate a suitable therapeutic scheme. In hypovolemic hyponatremia, it is necessary to identify the trigger factor and its treatment, usually discontinuation of diuretic treatment and administration of salt solution represents optimal methods in the correction of this. In hypervolemic hyponatremia, therapeutic methods are limited. Fluid restriction to about 1 L/day is important in improving Na concentration, but a small number of patients may be compliant with this therapy. Administration of saline solution in this case is only recommended if hyponatremia is severe because it usually favors the growth of ascites fluid and edema. Administration of albumin appears to be beneficial, but there is not enough data to confirm this.

A novelty in hyponatremic therapy is the treatment with vaptans. Treatment with tolvaptan should be given in the hospital to avoid a sudden increase in Na concentration, in oral administration, and with the possibility to increase the dose progressively to achieve the desired effects. Concomitant administration with vaptans of saline solution or fluid restriction is contraindicated to prevent osmotic demyelination syndrome. Medications that are inhibitors or inducers of CYP3A are also contraindicated. Conivaptan is given intravenously. Both

conivaptan and tolvaptan can be administered for a short period of time, and hyponatremia may reappear when the treatment is stopped. Although treatment with vaptans is effective in relieving hyponatremia, their use requires additional data.

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References

[1] Gins P, Quintero E, Arroyo V, et al. Compensated cirrhosis: Natural history and prognostic factors. Hepatology. 1987;**7**:122128

[2] Ripoll C, Groszmann R, Garcia-Tsao G, et al. Hepatic venous gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;**133**: 481488

[3] Schrier RW, Arroyo V, Bernardi M, et al. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;**8**:11511157

[4] Mller S, Henriksen JH. The systemic circulation in cirrhosis. in: Gins P, Arroyo V, Rods J, Schrier RW, editors. Ascites and renal dysfunction in liver disease. Malden: Blackwell; 2005:139155

[5] Henriksen JH, Mller S. Alterations of hepatic and splanchnic microvascular exchange in cirrhosis: Local factors in the formation of ascites. In: Gins P, Arroyo V, Rods J, Schrier RW, editors. Ascites and Renal Dysfunction in Liver Disease. Malden: Blackwell; 2005:174185

[6] Ginès P, Guevara M. Hyponatremia in cirrhosis: Pathogenesis, clinical significance, and management. Hepatology. 2008;**48**:1002

[7] Gins P, Berl T, Bernardi M, et al. Hyponatremia in cirrhosis: From pathogenesis to treatment. Hepatology. 1998;**28**:851864

[8] Angeli P, Wong F, Watson H, Ginès P, CAPPS Investigators. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology. 2006 Dec;**44**(6):1535-1542

[9] Oliet SH, Bourque CW. Mechanosensitive channels transduce osmosensitivity in supraoptic neurons. Nature. 1993 Jul 22;**364**(6435):341-343

[10] Ginés P, Berl T, Bernardi M, Bichet DG, Hamon G, Jiménez W, Liard JF, Martin PY, Schrier RW. Hyponatremia in cirrhosis: From pathogenesis to treatment. Hepatology. 1998 Sep;**28**(3):851-864

[11] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988 Sep-Oct; **8**(5):151-1157

[12] Schrier RW. Water and sodium retention in edematous disorders: Role of vasopressin and aldosterone. American Journal of Medicine. 2006 Jul;**119**(7 Suppl 1):S47-S53

[13] Jalan R, Mookerjee R, Cheshire L, Williams R, et al. Albumin infusion for severe hyponatremia in patients with refractory ascites: A randomized clinical trial. Journal of Hepatology. 2007;**46**:232A (Abstract)

[14] Solà E, Watson H, Graupera I, Turón F, Barreto R, Rodríguez E, Pavesi M, Arroyo V, Guevara M, Ginès P. Factors related to quality of life in patients with cirrhosis and ascites: Relevance of serum sodium concentration and leg edema. Journal of Hepatology. 2012 Dec;**57**(6):1199-1206

[15] Arroyo V, Rodés J, Gutiérrez-Lizárraga MA, Revert L. Prognostic value of spontaneous hyponatremia in cirrhosis with ascites. American Journal of Digestive Diseases. 1976 Mar; **21**(3):249-256

[16] Heuman DM, Abou-Assi SG, Habib A, Williams LM, Stravitz RT, Sanyal AJ, Fisher RA, Mihas AA. Persistent ascites and low serum sodium identify patients with cirrosis and low MELD scores who are at high risk for early death. Hepatology. 2004 Oct; **40**(4):802-810

[17] Follo A, Llovet JM, Navasa M, Planas R, Forns X, Francitorra A, Rimola A, Gassull MA, Arroyo V, Rodés J. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: Incidence, clinical course, predictive factors and prognosis. Hepatology. 1994 Dec;**20**(6):1495-1501

[18] Ginès P, Guevara M. Hyponatremia in cirrhosis: Pathogenesis, clinical significance, and management. Hepatology. 2008 Sep;**48**(3):1002-1010

[19] Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;**33**:464-470

[20] Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, Edwards E, Therneau TM. Hyponatremia and mortality among patients on the liver-transplant waiting list. The New England Journal of Medicine. 2008;**359**:1018-1026

[21] Adrogué HJ, Madias NE. Hyponatremia. The New England Journal of Medicine. 2000 May 25;**342**(21):1581-1589

[22] Hyponatremia Treatment Guidelines 2007. Expert Panel Recommendations. American Journal of Medicine. 2007;**120**:S1S21

[23] Adrogué HJ, Madias NE. Hyponatremia. The New England Journal of Medicine. 2000;**342**:1581-1589

[24] Córdoba J, García-Martinez R, Simón-Talero M. Hyponatremic and hepatic encephalopathies: Similarities, differences and coexistence. Metabolic Brain Disease. 2010;**25**:73-80

[25] Häussinger D. Low grade cerebral edema and the pathogenesis of hepatic encephalopathy in cirrhosis. Hepatology. 2006 Jun;**43**(6):1187-1190

[26] Singh TD, Fugate JE, Rabinstein AA. Central pontine and extrapontine myelinolysis: A systematic review. European Journal of Neurology. 2014 Dec;**21**(12):1443-1450

[27] Karp BI, Laureno R. Pontine and extrapontine myelinolysis: A neurologic disorder following rapid correction of hyponatremia. Medicine (Baltimore). 1993 Nov;**72**(6):359-373

[28] Laureno R, Karp BI. Myelinolysis after correction of hyponatremia. Annals of Internal Medicine. 1997 Jan 1;**126**(1):57-62

[29] Odier C, Nguyen DK, Panisset M. Central pontine and extrapontine myelinolysis: From epileptic and other manifestations to cognitive prognosis. Journal of Neurology. July 2010;**257**(7):1176-1180

[30] Crivellin C, Cagnin A, Manara R, Boccagni P, Cillo U, Feltracco P, et al. Risk factors for central pontine and extrapontine myelinolysis after liver transplantation: A single-center study. Transplantation. 2015 Jun;**99**(6):1257-1264

[31] Bose P, Kunnacherry A, Maliakal P. Central pontine myelinolysis without hyponatraemia. The Journal of the Royal College of Physicians of Edinburgh.. 19 September 2011;**41**(3):211-214

[32] Graff-Radford J, Fugate JE, Kaufmann TJ, Mandrekar JN, Rabinstein AA. Clinical and radiologic correlations of central pontine myelinolysis syndrome. Mayo Clinic Proceedings. 2011 Nov;**86**(11):1063-1067

[33] DeWitt LD, Buonanno FS, Kistler JP, et al. Central pontine myelinolysis: Demonstration by nuclear magnetic resonance. Neurology. 1984 May;**34**(5):570-576

[34] McCormick PA, Mistry P, Kaye G, Burroughs AK, McIntyre N. Intravenous albumin infusion is an effective therapy for hyponatraemia in cirrhotic patients with ascites. Gut. 1990;**31**:204207

[35] Rose BD. New approach to disturbances in the plasma sodium concentration. American Journal of Medicine. 1986 Dec;**81**(6):1033-1040

[36] Planas R, Montoliu S, Balleste B, Rivera M, Miquel M, Masnou H, et al. Natural history of patients hospitalized for management of cirrhotic ascites. Clinical Gastroenterology and Hepatology. 2006;**4**:1385-1394

[37] Quittnat F, Gross P. Vaptans and the treatment of water-retaining disorders. Seminars in Nephrology. 2006;**26**:234243

[38] Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. The New England Journal of Medicine. 2006;**355**:20992112

[39] OLeary JG, Favis G. Conivaptan increases serum sodium in hyponatremic patients with end stage liver disease. Liver Transplantation. 2009;**15**:13251329

[40] Berl T, Quittnat-Pelletier F, Verbalis JG, Schrier RW, Bichet DG, Ouyang J, Czerwiec FS, SALTWATER investigators. Oral tolvaptan is safe and effective in chronic hyponatremia. Journal of the American Society of Nephrology. 2010 Apr;**21**(4):705-712

[41] Afdhal N, Cardenas A, Gins P, et al. Randomized, placebo-controlled trial of tolvaptan, a novel V2-receptor antagonist, in hyponatremia: Results of the SALT 2 trial with emphasis on efficacy and safety in cirrhosis. Hepatology. 2005;**42**:LB19A ([Abstract])

[42] Vaprisol [package insert] Deerfield, IL: Astellas Pharma US, Inc; 2006

[43] Goldsmith SR, Elkayam U, Haught WH, Barve A, He W. Efficacy and safety of the vasopressin V1A/V2-receptor antagonist conivaptan in acute decompensated heart failure: A dose-ranging pilot study. Journal of Cardiac Failure. 2008 Oct;**14**(8):641-647

[44] Sterns RH, Cappuccio JD, silver SM, Cohen EP. Neurologic sequelae after treatment of severe hyponatremia: A multicenter perspective. Journal of the American Society of Nephrology. 1994 Feb;**4**(8):1522-1530

[45] Miller PD, Linas SL, Schrier RW. Plasma demeclocycline levels and nephrotoxicity. Correlation in hyponatremic cirrhotic patients. JAMA. 1980 Jun 27;**243**(24):2513-2515

[46] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008;**48**(6):2064-2077

[47] Kalambokis G, Economou M, Fotopoulos A, et al. The effects of chronic treatment with octreotide versus octreotide plus midodrine on systemic hemodynamics and renal hemodynamics and function in nonazotemic cirrhotic patients with ascites. The American Journal of Gastroenterology. 2005;**100**(4):879-885

[48] Solà E, Lens S, Guevara M, Martín-Llahí M, Fagundes C, Pereira G, Pavesi M, Fernández J, González-Abraldes J, Escorsell A, Mas A, Bosch J, Arroyo V, Ginès P. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology. 2010 Nov;**52**(5):1783-1790

[49] Jalan R, Elton RA, Redhead DN, Simpson KJ, Finlayson NDC, Hayes PC, et al. Analysis of prognostic variables in the prediction of shunt failure, variceal rebleeding, early mortality and encephalopathy following the transjugular intrahepatic portosystemic stent-shunt (TIPSS). Journal of Hepatology. 1995;**23**:123-128

[50] Baccaro ME, Guevara M, Torre A, Arcos E. Martı'n-Llahı'M, Terra C, et al. Hyponatremia predisposes to hepatic encephalopathy in patients with cirrhosis. Results of a prospective study with time-dependent analysis [abstract]. Hepatology. 2006;**233A**:44

Chapter 3

Acute Kidney Injury in Cirrhosis

Marco Antonio López Hernández

Additional information is available at the end of the chapter

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Abstract

Acute kidney injury is a very relevant feature in the liver cirrhosis. Acute renal failure is due to prerenal factors, intrinsic factors of the kidney, or postrenal. Prerenal damage is the result of renal hypoperfusion without damage to the glomeruli or renal tubules. Without treatment, prerenal acute renal failure can progress to acute tubular necrosis, a type of intrinsic renal damage. Patients with cirrhosis are prone to developing acute kidney injury. The acute decrease of the kidney function contributes to the mortality of patients with cirrhosis. The potential triggers of acute kidney injury should be recognized and removed; this includes the discontinuation of diuretics and nephrotoxic drugs, the treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia. The new International Club of Ascites-Acute Kidney Injury in cirrhosis criteria provide a simple and relevant staging system for acute kidney injury in patients with liver cirrhosis based on relative increases in serum creatinine. Vasopressors such as terlipressin and norepinephrine in combination with intravenous albumin represent the first-line therapy for hepatorenal syndrome.

Keywords: acute kidney injury, hepatorenal syndrome, cirrhosis

1. Introduction

The association of acute kidney injury (AKI) in patients with liver cirrhosis has been established in the context of the hepatorenal syndrome, but there are several etiologies besides this cause.

Acute renal failure is a therapeutic challenge in patients with liver cirrhosis. This may be related to abnormal hemodynamics with systemic arterial vasodilatation and the splanchnic bed, in addition to the vasoconstriction of extrahepatic vessels, characteristic of advanced

liver cirrhosis [1]. Acute renal failure frequently occurs in the advanced stages of liver cirrhosis and entails a bad prognosis [2, 3].

Acute renal failure is due to prerenal factors, intrinsic factors of the kidney, or postrenal. Prerenal damage is the result of renal hypoperfusion without damage to the glomeruli or renal tubules. Without treatment, prerenal acute renal failure can progress to acute tubular necrosis (ATN), a type of intrinsic renal damage.

The prevalence of acute renal failure in cirrhosis has been reported from 14 to 50% in patients with cirrhosis. Its prevalence is approximately 50% in patients with cirrhosis and ascites and 20% of patients with advanced stage cirrhosis who are hospitalized [4, 5].

The definition of acute kidney injury is a reduction in the glomerular filtration rate (GFR) over a short time of period, and this is a common and severe complication in the patients with liver cirrhosis. Acute kidney failure can be triggered by a precipitating event, for example, overdose of diuretics, gastrointestinal bleeding, large-volume paracentesis without albumin replacement, bacterial infections, and so on [6]. The prevalence of acute kidney injury is approximately 20–50% among hospitalized patients with cirrhosis [6–9] and the renal failure development is more common in patients with cirrhosis compared to individuals without liver disease [10]. The presence of acute kidney failure is associated with poor prognosis in these patients and represents an important predictor for short-term mortality [11].

The criteria for acute renal failure in cirrhosis were initially proposed in 1996 [12] and redefined in subsequent years [13]. Traditionally, renal failure in cirrhosis was defined as a 50% increase in serum creatinine, with an increase greater than 1.5 mg/dL (133 μm/L) of it. The cutoff value of serum creatinine to define acute renal failure in patients with decompensated cirrhosis has changed [14, 15]. Several nephrology academic societies have proposed the use of the concept of acute renal injury to represent acute changes in kidney function. The diagnostic criteria constitute a combination of changes in the glomerular filtration rate as well as a reduction in urine output. In the past decade, the definition of acute kidney injury evolved to the classifications and diagnostic criteria known as RIFLE [16], AKIN [17], and KDIGO [18].

In 2010, the International Ascites Club (IAC) and the Acute Dialysis Quality Initiative (ADQI) decided to use the nomenclature of the Acute Kidney Injury (AKI).

In 2015, the International Ascites Club established a new definition and staging of acute renal failure for patients with liver cirrhosis [19].

2. Physiopathology of renal failure in cirrhosis

Patients with liver cirrhosis develop portal hypertension, which results in the vasodilatation of the splanchnic vascular bed, resulting in blood accumulation due to resistance in the portal venous flow. This is due to an increase in the fixed resistance of liver fibrosis, and dynamics in the splanchnic arteries is last due to

a. vasodilators such as nitric oxide, carbon monoxide, and endogenous cannabinoids [20, 21];

b. vasodilation by pro-inflammatory cytokines such as tumor necrosis factor and interleukin 6, derived from bacterial translocation of the intestine [22].

The accumulation of blood in the splanchnic bed leads to a reduction in the effective circulating volume, which leads to a compensatory increase in cardiac output through the activation of the sympathetic nervous system by the carotid baroreceptors in order to maintain adequate renal perfusion [23].

In advanced stages of cirrhosis, systemic vascular resistance is significantly reduced, and the additional increase in cardiac output cannot compensate. Thus, it is evident that cardiac output decreases as cirrhosis progresses. In advanced stages of cirrhosis, cardiac output is maintained through the activation of vasoconstrictor systems, including the sympathetic nervous system and the renin-angiotensin system, and by a non-osmotic hypersecretion of arginine-vasopressin.

These compensatory mechanisms can help to maintain effective arterial volume and of this way a relatively normal blood pressure, but this has important effects on kidney function, primarily a retention of water and sodium, which can eventually lead to the formation of ascites and edema, and renal failure conditioned by renal vasoconstriction and hypoperfusion [24, 25].

There are four factors involved in the pathogenesis of hepatorenal syndrome. These are the following:

1. Activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system which causes renal vasoconstriction and a shift in the renal autoregulatory curve, which results in a renal blood flow more sensitive to changes in the arterial pressure.

2. Splanchnic vasodilatation, which causes a fall in the effective arterial blood volume and this way a decrease of the mean arterial pressure.

3. Increased synthesis of vasoactive mediators which affect renal blood flow or glomerular microcirculatory hemodynamics, such as leukotrienes, thromboxane A2, isoprostanes, and endothelin-1.

4. Impairment of cardiac function due to the development of cirrhotic cardiomyopathy, which leads to a relative impairment of the compensatory increase in cardiac output secondary to vasodilatation.

Hemodynamic disorders can have widespread impact on the body according to the severity of the cirrhosis [26]. The hemodynamic changes in cirrhosis include portal hypertension and hyperdynamic circulation which are the main cause of morbidity and mortality in patients with cirrhosis. The effective arterial blood volume and the circulating levels of RAS components and antidiuretic hormone remain normal at early stages of the disease, even with a

reduced systemic vascular resistance. The elevated cardiac output and low systemic vascular resistance are characteristics of the portal hypertension and hyperdynamic circulation in cirrhosis. Arterial vasodilation in the splanchnic circulation and the resulting decrease in systemic vascular resistance are associated with portal hypertension in cirrhosis. Compensatory mechanisms following the reduction of systemic vascular resistance lead to hyperdynamic circulation. Nevertheless, hyperdynamic circulation is insufficient to correct the effective arterial hypovolemia when the disease progresses and arterial vasodilation increases, resulting in arterial hypotension and consequent activation of the circulating renin-angiotensin-aldosterone system and the sympathetic nervous system and secretion of antidiuretic hormone [27].

In the early stages of disease, the circulating RAS is not activated at early stages of the disease. The patients at the advanced stages of cirrhosis presented an activation of peripheral and splanchnic renin-aldosterone system, and a metabolic deviation toward the RAS vasodilator axis in the splanchnic circulation (**Figure 1**).

2.1. Causes of acute kidney injury in cirrhosis

The acute kidney injury has prerenal, intrarenal, or postrenal causes (**Figure 2**). The most common causes of acute kidney injury between patients with cirrhosis are the prerenal etiologies, followed by acute tubular necrosis, and the postrenal etiology is extremely rare. The prerenal and acute tubular necrosis are the etiology of 80% of cases (49% prerenal and 35% acute tubular

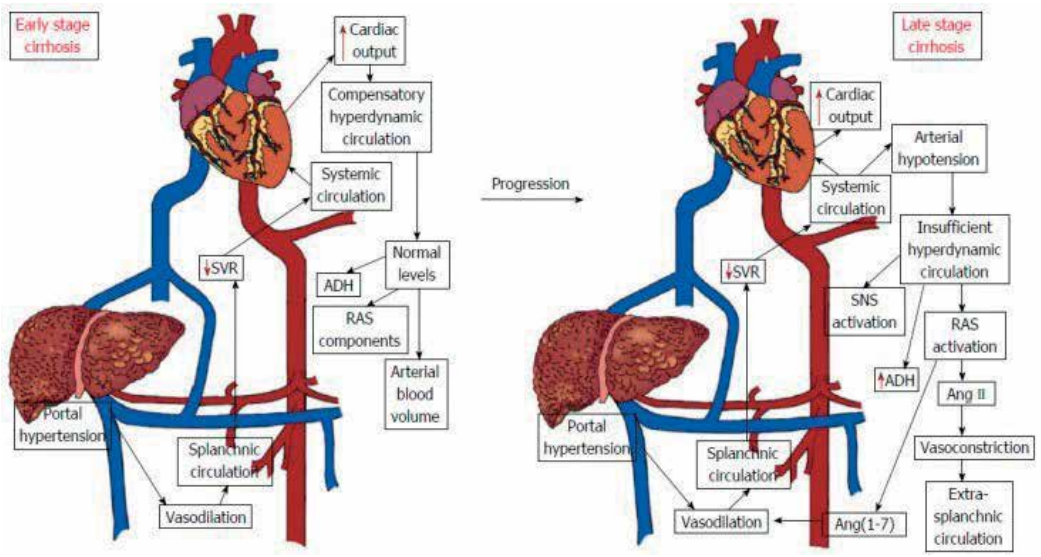

Figure 1. Hemodynamic alterations in the early and advanced stages of cirrhosis. In the early stages of cirrhosis, there is an increased cardiac output and a diminished systemic vascular resistance without changes in the circulating levels of the renin-angiotensin system components and antidiuretic hormone. In later phases of the cirrhosis, the components of the renin-angiotensin-aldosterone system are elevated, with activation of the sympathetic nervous system and secretion of the antidiuretic hormone, like a response to persistent arterial hypotension. Ang II: angiotensin II; Ang-(1–7): angiotensin (1–7); SNS: sympathetic nervous system; SVR: systemic vascular resistance.

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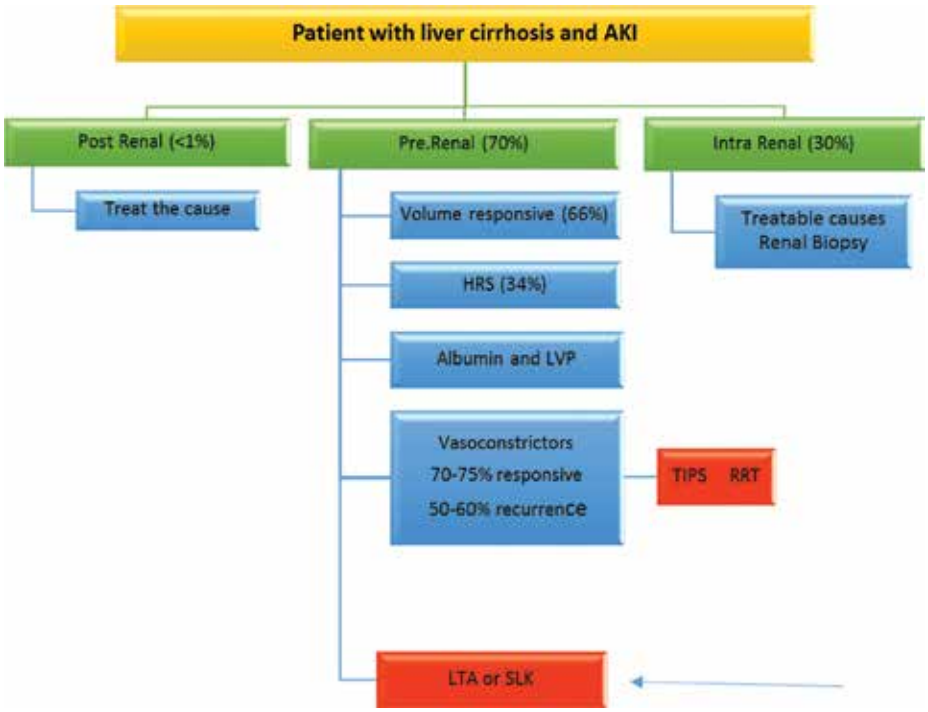

Figure 2. Management approach and algorithm for acute kidney injury in patients with cirrhosis. AKI, acute kidney injury; ESLD, end-stage liver disease; HRS, hepatorenal syndrome; LVP, large-volume paracentesis; RRT, renal replacement therapy; LTA, liver transplant alone; SLK, simultaneous liver kidney; TIPS, transjugular intrahepatic portosystemic shunt; USG, ultrasonogram.

necrosis). Postrenal injury accounted for only 0.2%. In a prospective study, among patients with cirrhosis listed for liver transplantation who had acute kidney injury, prerenal injury was the most common cause in 76% followed by intrarenal etiology in 33%, while postrenal etiology did not occur in any patient [66, 67].

3. Prerenal injury

3.1. Volume responsive prerenal AKI

The hemodynamic state in cirrhosis with vascular dilatation and reduced vascular resistance in cirrhosis is quite similar to hemodynamic state in sepsis, especially spontaneous bacterial peritonitis. Prerenal injury occurs commonly due to gastrointestinal bleeding, infections, use of diuretics, diarrhea often related to lactulose use for hepatic encephalopathy, and from large-volume paracentesis without albumin infusion. Large-volume paracentesis may be associated with intravascular volume depletion and acute kidney failure. This condition occurs in up to 70% of patients undergoing paracentesis when more

than 5 L are removed and albumin is not infused. The use of any drugs like NSAIDs can precipitate acute kidney failure by decreasing renal prostaglandins and accentuating the intrarenal vasoconstriction and further decrease renal blood flow. The advice to the patients should be provided to avoid these drugs for the management of pain. The use of intravenous contrast agents in patients with cirrhosis is another potential risk factor for acute kidney failure. The infections have common occurrence in patients with cirrhosis. Hence, superimposed infections/sepsis in cirrhosis patients worsen this physiology, causing a reduction of circulating blood volume and leading to the development of AKI. Before the widespread use of antibiotic prophylaxis for acute gastrointestinal bleeding in cirrhosis, more than 20% of patients with cirrhosis hospitalized for acute gastrointestinal bleeding had a bacterial infection present on admission, with up to 50% developing an infection while hospitalized.

3.2. Volume nonresponsive prerenal AKI: hepatorenal syndrome

The volume expansion is the first treatment after acute kidney failure is diagnosed, using crystalloids or intravenous albumin and discontinuation of precipitating medications. If renal function does not normalize or improve with this intervention, it is important to consider hepatorenal syndrome (HRS) in the differential diagnosis to consider as the cause for AKI. HRS is a functional form of renal failure without any major structural or histological changes in the kidneys that is characterized by intense renal vasoconstriction. It is important to differentiate it from another intrarenal cause, because management and prognosis differ. In the absence of renal biopsy, the diagnosis of HRS remains difficult and is essentially a diagnosis of exclusion. In patients with cirrhosis, HRS develops in about 18% at 1 year and 39% at 5 years.

Approximately, 66% of all HRS cases are type 2, or HRS-AKI which are rapidly occurring with an increase in serum creatinine to over 2.5 mg/dL over 1 or 2 weeks. Type 1 HRS has high mortality with a median survival of around 50% at 2 weeks and is usually precipitated by infections. The type 2 HRS has a better outcome with a median survival of about 6 months and a slower course in the setting of refractory ascites, with slowly increasing serum creatinine to over 1.5 mg/dL. The definition of type I HRS has been recently revised and changed the value of 2.5 mg/dL serum creatinine for diagnosis, thus avoid delaying the initiation of therapy.

3.3. Volume nonresponsive intrinsic AKI: acute tubular necrosis

The most common cause for intrarenal AKI in cirrhosis is ATN. This occurs commonly either as a complication of sepsis or due to unrecognized and untreated prerenal injury. The main cause of ATN has been attributed to sepsis, followed by hypovolemia and rarely nephrotoxic drugs.

Other less common causes of intrarenal injury include tubular damage due to bile cast nephropathy from high-conjugated bilirubin excreted through the glomeruli, membranoproliferative glomerulonephritis with or without cryoglobulinemia associated with hepatitis C, and acute interstitial nephritis due to medications, such as antibiotics, NSAIDS, and proton pump inhibitors.

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4. Postrenal injury

As stated earlier, postrenal injury is a rare cause of AKI in cirrhosis [66, 68]. This etiology can easily be excluded using renal ultrasound or CT scan.

4.1. Evaluation of the renal function

The glomerular filtration rate (GFR) is the universally used index to quantify kidney function. The principle of GFR determination is to determine the body clearance of a substance with the supposed exclusive renal clearance. The substance used for determinate GFR must be freely filtered and neither reabsorbed or secreted along the renal tubule. Also, no extrarenal excretion of the substance occurs, and it cannot be stored or be bound to plasma proteins: then it can be assumed that the plasmatic clearance is only due to renal clearance. Thus, the GFR can be inferred from the plasma disappearance of the substance. It is considered that the renal clearance of a marker occurs only through glomerular filtration [28].

Calculation of the eGFR requires normalization to BSA. Studies that tested the performance of this method showed a clear trend to overestimate mGFR by 4–80%. A normalization based on the assumption that the GFR is positively correlated with the basal metabolism rate of individuals which is proportional to their stature on arbitrarily fixed body surface area (BSA) set to 1.73 m^2 is commonly done [29]. This normalization has been questioned [30] and standardization on other criteria has been proposed [31]. The formula most commonly used to determine the BSA is the Dubois formula, and the adjustment on the body surface remains widely used [32].

Historically, the Cockcroft and Gault formula was the most popular before the MDRD formula was published in the early 2000s. This formula is not adjusted to the patient BSA, and the adjustment has, theoretically, to be done afterwards (even if the relevance of this adjustment remains to be assessed in cirrhotic patients). The relationship between GFR level and overestimation could be explained by the secretion of creatinine by the tubule in patients with CKD. However, the importance of this overestimation does not seem to be related to the severity of cirrhosis.

Creatinine clearance is a simple method to estimate GFR, based on the assumption that creatinine has the characteristics of a perfect renal marker. It requests the accurate recollection of urine from a 24-h period. It has several limitations: mainly, the possible inadequate urine collection by the patients, the occurrence of tubular secretion of creatinine, which leads to overestimation of the GFR, and that is on a longer or a shorter than 24-h time period.

4.2. Definition of acute kidney injury in cirrhosis

The definition of acute kidney injury in cirrhosis consists in an acute increase in serum creatinine of >0.3 mg/dL in a time lapse of 48 h or by <50% from a stable baseline serum creatinine, in the last 3 months (presumed to have developed within the past 7 days when no prior readings are available) [19, 33]. In addition, the use of urine output as part of the diagnostic criteria was eliminated, since many patients with cirrhosis and ascites maintain a preserved renal function despite being oliguric due to sodium and water retention. The main modifications over the previous,

rather stringent, criteria that were based on absolute serum creatinine level, were abandoning the threshold of serum creatinine >1.5 mg/dL to diagnose acute kidney injury, because milder degrees of renal failure in cirrhotic patients had often remained underdiagnosed [34, 35].

Similar to the ICA-AKI criteria, most of these studies diagnosed AKI solely on serum creatinine. In 2013, a modified, AKIN-derived score for cirrhosis was developed, by division of AKI stage 1 into two groups depending on whether or not serum creatinine surpassed the threshold of 1.5 mg/dL and by merging AKI stages 2 and 3 into stage "C" [40]; this reclassification did not gain wide acceptance. Several clinical studies have evaluated the prognostic value of the AKIN/KDIGO criteria that constitute the basis for the International Club of Ascites (ICA)-AKI criteria in patients with cirrhosis [37–39]. The acute kidney injury can be classified into three stages according to severity. Stage 1 AKI is defined by rather small changes in serum creatinine, while stages 2 and 3 AKI are defined by a twofold and threefold increase in serum creatinine, respectively (**Table 1**) [36]. Since their publication in 2015, the newer and cirrhosis-specific ICA criteria have been assessed within one retrospective study in hospitalized patients with cirrhosis [41]. Within this study, approximately 40% of patients experienced AKI during their hospitalization with the majority of cases having been diagnosed at stage 1. Also, in patients with AKI stage 1 and a serum creatinine of <1.5 mg/dL, already a 3.5-fold increase in 30-day mortality as compared to patients without AKI was reported [41], again underlining the prognostic importance of even small increases in serum creatinine levels.

4.3. Hepatorenal syndrome type of acute kidney injury or type 1 hepatorenal syndrome

Hepatorenal syndrome (HRS) is defined as the occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure [12].

The hepatorenal syndrome type I requires the fulfillment of several specific diagnostic criteria that are summarized in **Table 2**. This Acute Kidney Injury (HRS-AKI) is defined as >stage 2 ICA-AKI that is diagnosed after other causes of renal failure have been ruled out [35].

Acute kidney injury stages according to the International Club of Ascites criteria	
Stage 2	Increase in serum creatinine >0.3 mg/dl or Increase in serum creatinine by>50–100% from baseline
Stage 2	Increase in serum creatinine by100–200% from baseline
Stage 3	Increase in serum creatinine by 200% from baseline or Increase in serum creatinine to 4 mg/dL with an acute increase by 0.3 mg/dL or Need for renal replacement therapy

Table 1. Criteria of AKI of the International Club of Ascites [36].

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Diagnostic criteria of hepatorenal syndrome
Presence of cirrhosis and ascites
No improvement in serum creatinine after 2 consecutive days of withdrawal of diuretics and plasma volume expansion with albumin (1 g per kg of body weight, maximum 100 g/day)
Absence of shock
Exclusion of recurrent or recent use of nephrotoxic agents (e.g.NSAIDs, aminoglycosides, contrast media)
Exclusion of parenchymal kidney disease: **• absence of proteinuria (>500 mg/day)** **• absence of microhematuria (>50 RBCs per high-power field)** **• normal renal ultrasonography**

Table 2. Diagnostic criteria for hepatorenal syndrome [12].

The Guidelines of the European Association for the Study of Liver Diseases (EASL) and the American Association for the Study of the Liver (AASLD) Clinical Practice Guidelines for ascites and hepatorenal syndrome still proclaim the threshold of 2.5 mg/dL for diagnosing HRS-AKI [42, 43]. The use of this threshold in clinical practice would mean that proper diagnosis and treatment of HRS would be withheld as long as serum creatinine does not reach this threshold. In order to prevent misclassification or even treatment delay, the newer International Club of Ascites criteria focus on the relative increase in creatinine rather than absolute values, since also smaller rises in serum creatinine have been shown to have a negative prognostic impact in patients with cirrhosis [44].

The hepatorenal syndrome is classified in two types. HRS type 1 is a quickly progressive acute renal failure. It commonly occurs in patients with end-stage cirrhosis following a septic insult such as spontaneous bacterial peritonitis or severe alcoholic hepatitis; this kind of hepatorenal syndrome frequently is developed in temporal relationship with a precipitating factor for a deterioration of liver function together with a deterioration of other organ function, although it may occur in the absence of any identifiable triggering event. Type 1 HRS is only diagnosed when the serum creatinine increases more than 100% from baseline to a final level of greater than 2.5 mg/dL.

Patients with type 2 HRS may eventually develop type 1 HRS; this can be spontaneously or following a precipitating event such as an infection [12].

HRS should be diagnosed and excludes other known causes of renal failure and by demonstrating a significant increase in serum creatinine. For practical purposes, HRS is usually diagnosed only when serum creatinine increases to >133 mol/L (1.5 mg/dL). Repeated measurement of serum creatinine over time, particularly in hospitalized patients, is helpful in the early identification of HRS.

The diverse etiologies of renal failure in cirrhosis should be excluded before to conclude the diagnosis of HRS. Parenchymal renal diseases should be suspected if there is significant

proteinuria or micro-hematuria, or if renal ultrasonography demonstrates abnormalities in kidney size. The hypovolemia, shock, parenchymal renal diseases, and concomitant use of nephrotoxic drugs are common causes of acute kidney injury and must be excluded before to diagnose HRS. Renal biopsy is important in these patients to help plan the further management, including the potential need for combined liver and kidney transplantation [42].

4.3.1. Treatment

The initial management of acute kidney injury should focus on the early recognition and correction of potential trigger events and on preventing further hemodynamic deterioration [25, 33, 45]. In volume-depleted patients, diuretic therapy and/or lactulose should be withdrawn and plasma volume should be expanded with albumin, or blood transfusions in anemic patients due to gastrointestinal blood loss, is important the careful review of all medications, and consider the withdrawn of nephrotoxic agents. The use of medications that may induce or aggravate arterial should be carefully evaluated [46, 47].

Bacterial infections are a common precipitant of acute kidney injury, including the hepatorenal syndrome; in cirrhosis, these patients should be thoroughly screened for. The early initiation of empiric antibiotic treatment based on clinical suspicion and the local epidemiology and resistance patterns must be considered [48, 49].

The therapeutic response is defined as a decrease of creatinine in serum to a value within 0.3 mg/dL of baseline; in this case, the patients should be followed up closely for the early detection of recurrent episodes kidney failure. It is necessary to consider the possibility of hepatorenal syndrome In case of stage 2 or 3 or progression to a higher acute kidney injury stage, diuretics should be withdrawn immediately. The patients should receive plasma volume expansion with albumin for 2 consecutive days (1 g per kg of body weight, maximum 100 g/day). Albumin is particularly beneficial in patients with sepsis because in addition to its volume-expanding effect, it has antioxidant, scavenging, and endothelial-stabilizing functions [50]. A follow-up assessment of creatinine every 2–4 days during hospitalization and every 2–4 weeks during the first 6 months after discharge is advised [35].

In stages 2 and 3, the patients who meet diagnostic criteria of HRS-AKI should be treated with vasoconstrictors in combination with albumin [35]. The albumin initial dose is 1 g/kg body weight up to 100 g on the first day, then ongoing with 20–40 g/day, as it has been shown that the effects of intravenous albumin in the prevention and treatment of HRS are dose-dependent, with better results when higher cumulative doses were administered [51, 52]. In all large-volume paracentesis (>5 L, with 8 g/L of ascites removed), albumin should be administered since it prevents post-paracentesis circulatory dysfunction, which reduces the risk of renal dysfunction and improve survival [53, 54].

The first-line drug therapy of type 1 hepatorenal syndrome is the use of terlipressin (1 mg/4–6 h intravenous bolus) in combination with albumin. The therapeutic target improves renal function enough to decrease serum creatinine to less than 133 mol/L (1.5 mg/dL); this is considered a complete response. If serum creatinine does not decrease at least 25% after 3 days, the dose of terlipressin should be increased in a stepwise manner up to a maximum of 2 mg/4 h. For patients with partial response (serum creatinine does not decrease <133 mol/L) or in those patients without reduction of serum creatinine, treatment should be discontinued within 14 days.

The terlipressin is the most intensively studied vasoconstrictor for the treatment of HRS-AKI. A bolus of terlipressin induces a significant reduction in the portal pressure for over a 3- to 4-h period and also increases the mean arterial pressure [55]. Hyponatremia must be considered, and this commonly occurs in less advanced liver disease and normal baseline serum sodium levels [56, 57]. Considering the pharmacodynamic profile and the costs of terlipressin, continuous infusion might be preferred over bolus administration. Although terlipressin has been consistently shown to improve renal function, its impact on survival is less clear [58]. Terlipressin is particularly beneficial in patients with sepsis and might also prevent variceal bleeding during the period of discontinuation of nonselective beta blockers [59].

Norepinephrine is an alternative to the use of terlipressin with an initial dose: 0.5 mg/h, and a max. Dose studied in randomized controlled trials of 3 mg/h, norepinephrine is equally effective and inexpensive. A meta-analysis of four randomized-controlled trials demonstrated similar efficacy for HRS, when compared to terlipressin [60]. The therapy recommended for type 2 hepatorenal syndrome is similar [61, 62]; however, HRS type 2 commonly recurs after termination of treatment with vasoconstrictors [63].

Complete response is defined by a decrease in serum creatinine to a value within 0.3 mg/dL of baseline, while a regression of at least one AKI stage is considered as partial response [35]. If there is no response after 3 days of treatment, the vasoconstrictor dose should be increased. In nonresponders, treatment should be discontinued after 14 days. In responders, longer treatment durations can be used as a bridging therapy to liver transplantation.

Potential alternative therapies to terlipressin include norepinephrine or midodrine plus octreotide, both in association with albumin, but there is very limited information with respect to the use of these drugs in patients with type 1 HRS. Treatment with terlipressin should be repeated and is frequently successful. The recurrence of type 1 HRS after discontinuation of terlipressin therapy is relatively uncommon.

Cardiovascular ischemic disease is a contraindication to terlipressin therapy. Patients on terlipressin should be carefully monitored for signs of splanchnic or digital ischemia, the development of cardiac arrhythmias and fluid overload, and treatment modified or stopped accordingly.

The use of TIPS may improve renal function in some patients; there are insufficient data in patients with type 1 HRS to support the use of TIPS as a treatment. The renal replacement therapy may be useful when the patients do not respond to vasoconstrictor therapy. There are limited data on the use of artificial liver support systems, and further studies are required for its use [43].

4.4. Hepatitis C and acute kidney injury

Hepatitis C (HCV) infection can induce kidney injury, mainly due to the formation of immune complexes and cryoglobulins, and possibly to a direct cytopathic effect. HCV is responsible for membranous glomerulonephritis or mesangiocapillary and accelerates the progression of chronic kidney disease due to other causes. It may cause acute kidney injury as a part of systemic vasculitis and augments the risk of AKI due to other etiologies. HCV-infected patients are at an

increased risk of acute posttransplant complications. HCV infection increases cardiovascular and liver-related mortality in patients on regular dialysis. Long-term graft survival is compromised by chronic transplant glomerulopathy or recurrent or de novo glomerulonephritis. The increased incidence of diabetes, sepsis, posttransplant lymphoproliferative disease, and liver failure compromises the patient survival. Directly acting antiviral agents (DAAs) are currently available for treatment at different stages of kidney disease. It is concluded that the thoughtful use of DAAs will result in a significant change in the epidemiology and clinical profiles of kidney disease, as well as improvement of dialysis and transplant outcomes, in endemic areas [64].

The acute kidney failure induced by HCV is a systemic disease reported in <5% of HCV-infected (HCV+ve) patients. It is characterized by multiorgan involvement, mainly affecting the lungs and kidneys, skin, musculoskeletal system, and peripheral nerves. The fundamental lesion is endothelial injury, perivascular inflammation with lymphocytic and neutrophilic infiltration, small vessel necrosis, and luminal occlusion by cryoglobulins and fibrin thrombi.

4.5. Cryoglobulinemic vasculitis

In the kidneys, this leads to focal fibrinoid necrosis of the glomerular tufts, often with crescent formation (**Figure 3**). The renal tubules are affected by ischemic and inflammatory lesions and contain hyaline and blood casts. The ureteric and bladder mucosa may display vasculitic purpuric lesions. The interstitium is infiltrated with inflammatory cells and found edematous.

The mechanism of vascular injury is typically attributed to component C1q of the complement, complement activation generates chemotactic factors, C3a and C5a, which recruit and activate pro-inflammatory leucocytes. It also leads to the formation of C5–9, the membrane attack complex that may have an important role in endothelial damage, the active complement component incorporated within the cryoglobulin complex. This leads to endothelial injury by dual effects, namely the activation of the complement cascade via the classical pathway and binding to endothelial complement receptors, thereby localizing the injury in target capillary beds.

The clinical presentation has a wide range from isolated hematuria to acute kidney injury, sometimes associated with thrombotic microangiopathy (**Figure 4**). If left untreated, the

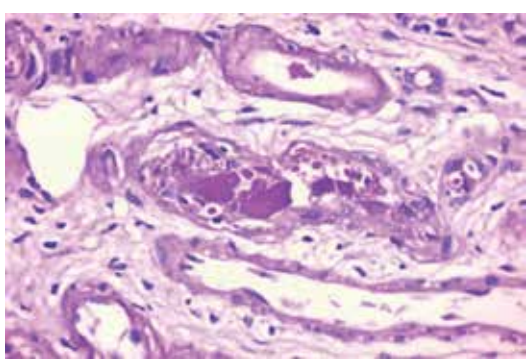

Figure 3. Cryoglobulinemic renal vasculitis. Renal arteriole showing endothelialitis and cryoglobulin deposits in a patient with AKI due to HCV-associated cryoglobulinemia. Hematoxylin and eosin stain. Reproduced with permission from Ref. [64].

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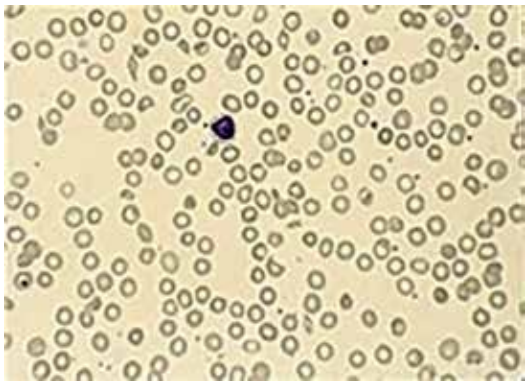

Figure 4. Blood smear in a patient with cryoglobulinemic vasculitis and thrombotic microangiopathy. Note the red cell fragmentation with microcytes and schistocytes.

prognosis becomes bad for the renal function, as well as patient survival. The successful treatment may lead to complete or partial recovery, unless the damage has already been extensive, leading to healing with focal or global sclerosis.

4.6. Non-cryoglobulinemic AKI

HCV-infected patient, compared to the general population are at many-fold risk of developing acute kidney injury of diverse etiology. The most frequent cause of kidney injury is hypovolemia associated with excessive vomiting or diarrhea. The second common cause was bacterial infection in the lungs, urinary, or gastrointestinal tract; 7.3% of patients had advanced cirrhosis and developed AKI following an episode of hematemesis, presumably due to ischemic acute tubular necrosis, and 6.5% were associated with hepatic encephalopathy including the hepatorenal syndrome. Decompensated liver disease, diabetes mellitus, history of intravenous drug abuse, and high baseline serum creatinine were independent predictors of developing AKI. End-stage kidney disease eventually developed in 17.5% of patients who developed AKI, compared to 1% of those who did not. Risk factors for end-stage renal kidney disease were preexisting hypertension, diabetes, or chronic kidney disease [65].

5. Summary

Patients with cirrhosis are prone to developing acute kidney failure. The acute decrease of the kidney function contributes to the mortality of patients with cirrhosis. The criteria of the International Club of Ascites for acute kidney injury provide a simple and relevant staging system for acute kidney injury in patients with liver cirrhosis based on relative increases in serum creatinine. It is very important to consider the potential triggers of renal failure, and this should be recognized early and removed; this includes discontinuation of nephrotoxic drugs and diuretics, treatment of infections and gastrointestinal bleeding, and plasma expansion in case of hypovolemia.

Cardiovascular ischemic disease is a contraindication to terlipressin therapy. Patients on terlipressin should be carefully monitored for signs of splanchnic or digital ischemia, the development of cardiac arrhythmias and fluid overload, and treatment modified or stopped accordingly.

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References

[1] Wong F. Recent advances in our understanding of hepatorenal syndrome. Nature Reviews. Gastroenterology & Hepatology. 2012;**9**:382-391

[2] D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. Journal of Hepatology. 2006; **44**:217-231

[3] du Cheyron D, Bouchet B, Parienti JJ, Ramakers M, Charbonneau P. The attributable mortality of acute renal failure in critically ill patients with liver cirrhosis. Intensive Care Medicine. 2005;**31**:1693-1699

[4] Montoliu S, Ballesté B, Planas R, Alvarez MA, Rivera M, Miquel M, et al. Incidence and prognosis of different types of functional renal failure in cirrhotic patients with ascites. Clinical Gastroenterology and Hepatology. 2010;**8**:616-622

[5] Wu CC, Yeung LK, Tsai WS, Tseng CF, Chu P, Huang TY, et al. Incidence and factors predictive of acute renal failure in patients with advanced liver cirrhosis. Clinical Nephrology. 2006;**65**:28-33

[6] Gerbes AL. Liver cirrhosis and kidney. Digestive Diseases. 2016;**34**:387-390

[7] Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. Journal of Hepatology. 2013;**59**:482-489

[8] Follo A, Llovet J, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: Incidence, clinical course, predictive factors and prognosis. Hepatology. 1994;**20**:1495-1501

[9] Hampel H, Bynum GD, Zamora E, El-Serag HB. Risk factors for the development of renal dysfunction in hospitalized patients with cirrhosis. The American Journal of Gastroenterology. 2001;**96**:2206-2210

[10] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; **48**:2064-2077

[11] Cardenas A, Gines P, Uriz J, et al. Renal failure after upper gastrointestinal bleeding in cirrhosis: Incidence, clinical course, predictive factors, and short-term prognosis. Hepatology. 2001;**34**:671-676

[12] Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996;**23**:164-176

[13] Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of the hepatorenal syndrome in cirrhosis a consensus workshop of the International Ascites Club. Gut. 2007;**56**:1310-1318

[14] Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011;**60**:702-709

[15] Angeli P, Sanyal A, Moller S, et al. Current limits and future challenges in the management of renal dysfunction in patients with cirrhosis: Report from the International Club of Ascites. Liver International. 2013;**33**:16-23

[16] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure–Definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004;**8**:R204-R212

[17] Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Critical Care. 2007;**11**:R31

[18] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney International. 2012;**2**(Suppl 1):1-138

[19] Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Gut. 2015;**64**:531-537

[20] Martin PY, Ginès P, Schrier RW. Nitric oxide as a mediator of hemodynamic abnormalities and sodium and water retention in cirrhosis. The New England Journal of Medicine. 1998;**339**:533-541

[21] Ros J, Clària J, To-Figueras J, Planagumà A, Cejudo-Martín P, Fernández-Varo G, et al. Endogenous cannabinoids: A new system involved in the homeostasis of arterial pressure in experimental cirrhosis in the rat. Gastroenterology. 2002;**122**:85-93

[22] Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: Relationship with the development of renal impairment and mortality. Hepatology. 1998;**27**:1227-1232

[23] Ginès P, Schrier RW. Renal failure in cirrhosis. The New England Journal of Medicine. 2009;**361**:1279-1290

[24] Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilatation hypothesis: A proposal for the initiation of renal sodium and water retention in cirrhosis. Hepatology. 1988;**8**:1151-1157

[25] Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. Hepatology. 1996;**23**:164-176

[26] Kim MY, Baik SK, Lee SS. Hemodynamic alterations in cirrhosis and portal hypertension. The Korean Journal of Hepatology. 2010;**16**:347-352

[27] Vilas-Boas WW, Ribeiro-Oliveira A, Pereira RM, Ribeiro Rda C, Almeida J, Nadu AP, Simões e Silva AC, dos Santos RA. Relationship between angiotensin-(1-7) and angiotensin II correlates with hemodynamic changes in human liver cirrhosis. World Journal of Gastroenterology. 2009;**15**:2512-2519

[28] Israni AK, Kasiske BL. Laboratory assessment of kidney disease: Clearance, urinalysis and kidney biopsy. In: Brenner and Rector's The Kidney. 8th ed. Philadelphia: Saunders Elsevier; 2008. pp. 724-750

[29] Mccance RA, Widdowson EM. The correct physiological basis on which to compare infant and adult renal function. Lancet. 1952;**2**:860-862

[30] Delanaye P, Krzesinski JM. Indexing of renal function parameters by body surface area: Intelligence or folly? Nephron. Clinical Practice. 2011;**119**:c289-c292

[31] Eriksen BO, Melsom T, Mathisen UD, Jenssen TG, Solbu MD, Toft I. GFR normalized to total body water allows comparisons across genders and body sizes. Journal of the American Society of Nephrology. 2011;**22**:1517-1525

[32] Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. Nutrition. 1989;**5**:303-311

[33] Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; **48**:2064-2077

[34] Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis with infection. Gastroenterology. 2013;**145**:1280-1288

[35] Angeli P, Wong P. Hepatology snapshot: New diagnostic criteria and management of Acute Kidney Injury Hepatology Snapshot. Journal of Hepatology. 2016;**xx**:1-2

[36] Angeli P, Gine's P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Journal of Hepatology. 2015;**62**:986-974

[37] Angeli P, Rodrıguez E, Piano S, et al. Acute kidney injury and acute-on-chronic liver failure classifications in prognosis assessment of patients with acute decompensation of cirrhosis. Gut. 2015;**64**:1616-1622

[38] Bucsics T, Mandorfer M, Schwabl P, et al. Impact of acute kidney injury on prognosis of patients with liver cirrhosis and ascites: A retrospective cohort study. Journal of Gastroenterology and Hepatology. 2015;**30**:1567-1565

[39] Elia C, Graupera I, Barreto R, et al. Severe acute kidney injury associated with non-steroidal antiinflammatory drugs in cirrhosis: A case-control study. Journal of Hepatology. 2015;**63**:593-600

[40] Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. Journal of Hepatology. 2013;**59**:474-481

[41] Tandon P, James MT, Abraldes JG, Karvellas CJ. Relevance of new definitions to incidence and prognosis of acute kidney injury in hospitalized patients with cirrhosis: A retrospective population-based cohort study. PLoS. 2016;**11**:1-15

[42] Runyon BA. AASLD practice guideline: Management of adult patients with ascites due to cirrhosis: Update 2012. AASLD Practice Guidelines. 2012. pp. 1-96

[43] European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. European Journal of Hepatology. 2010;**53**:397-417

[44] Wong F, O'Leary JG, Reddy KR, et al. New consensus definition of acute kidney injury accurately predicts 30-day mortality in patients with cirrhosis with infection. Gastroenterology. 2013;**145**:1280-1288

[45] Wong F. Diagnosing and treating renal disease in cirrhotic patients. Minerva Gastroenterologica e Dietologica. 2016;**62**:253-266

[46] Mandorfer M, Bota S, Schwabl P, et al. Nonselective b blockers increase risk for hepatorenal syndrome and death in patients with cirrhosis and spontaneous bacterial peritonitis. Gastroenterology. 2014;**146**:1680-1690

[47] Mandorfer M, Reiberger T. Beta blockers and cirrhosis, 2016. Digestive and Liver Disease. 2017;**49**:3-10

[48] Arabi YM, Dara SI, Memish Z, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. Hepatology. 2012;**56**:2305-2315

[49] Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013. Journal of Hepatology. 2014;**60**: 1310-1324

[50] Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. Journal of Clinical and Experimental Hepatology. 2014; **4**:302-311

[51] Afinogenova Y, Tapper EB. The efficacy and safety profile of albumin administration for patients with cirrhosis at high risk of hepatorenal syndrome is dose dependent. Gastroenterology Report (Oxf). 2015;**3**:216-221

[52] Salerno F. Albumin treatment regimen for type 1 hepatorenal syndrome: A dose–response meta-analysis. BMC Gastroenterology. 2015;**15**:1-11

[53] Bernardi M, Caraceni P, Navickis RJ, Wilkes MM. Albumin infusion in patients undergoing large-volume paracentesis: A meta-analysis of randomized trials. Hepatology. 2012;**55**:1172-1181

[54] Gine's P, Tilo L, Arroyo V, et al. Randomized comparative study of therapeutic paracentesis with and without intravenous albumin in cirrhosis. Gastroenterology. 1988; **94**:1493-1502

[55] Escorsell A, Bandi JC, Moitinho E, et al. Time profile of the haemodynamic effects of terlipressin in portal hypertension. Journal of Hepatology. 1997;**26**:621-627

[56] Sola E, Lens S, Guevara M, et al. Hyponatremia in patients treated with terlipressin for severe gastrointestinal bleeding due to portal hypertension. Hepatology. 2010;**52**: 1783-1790

[57] Cavallin M, Piano S, Romano A, et al. Terlipressin given by continuous intravenous infusion versus intravenous boluses in the treatment of hepatorenal syndrome: A randomized controlled study. Hepatology. 2016;**63**:983-992

[58] Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. Gastroenterology. 2016;**150**:1579-1589

[59] Choudhury A, Kedarisetty CK, Vashishtha C, et al. A randomized trial comparing terlipressin and noradrenaline in patients with cirrhosis and septic shock. Liver Int. 2017 Apr;**37**(4):552-561

[60] De Mattos ÂZ, De Mattos AA, Ribeiro RA. Terlipressin versus noradrenaline in the treatment of hepatorenal syndrome: Systematic review with meta-analysis and full economic evaluation. European Journal of Gastroenterology & Hepatology. 2016;**28**:345-351

[61] Alessandria C, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: Role of terlipressin in clinical approach to hepatorenal syndrome type 2. European Journal of Gastroenterology & Hepatology. 2002;**14**:1363-1368

[62] Piano S, Tonon M, Cavallin M, et al. Reply to: 'A cut-off serum creatinine value of 1.5 mg/dl for AKI—to be or not to be'. Journal of Hepatology. 2015;**62**:744-746

[63] Rodriguez E, Pereira GH, Solá E, et al. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: Effects on kidney function and transplantation outcomes. Liver Transplantation. 2015;**21**:1347-1354

[64] Rashad S, Emad AW, Soha SK. Hepatitis C and kidney disease: A narrative review. Journal of Advanced Research. 2017 Mar;**8**(2):113-130

[65] Satapathy SK, Lingisetty CS, Williams SE. Acute kidney dysfunction in patients with chronic hepatitis C virus infection: Analysis of viral and non-viral factors. Journal of Clinical and Experimental Hepatology. 2014;**4**(1):8-13

[66] Moreau R, Durand F, Poynard T, Duhamel C, Cervoni JP, Ichaï P, et al. Terlipressin in patients with cirrhosis and type 1 hepatorenal syndrome: A retrospective multicenter study. Gastroenterology. 2002;**122**:923-930

[67] Russ KB, Kuo YF, Singal AK. Renal function and acute kidney injury among cirhosis patients listed for liver transplantation: A prospective study. The American Journal of Gastroenterology. 2014;**109**:S173

[68] Kirk BR, Todd MS, Singhal AK. Acute kidney injury in patients with cirrhosis. Journal of Clinical and Translational Hepatology. 2015;**3**:195-204

Chapter 4

Portal Vein Thrombosis in Liver Cirrhosis

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Additional information is available at the end of the chapter

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Abstract

In liver cirrhosis, portal vein thrombosis (PVT), which is defined as thrombosis that occurs within the main portal vein and intrahepatic portal branches, is one of the most common complications. High incidence of PVT in the setting of liver cirrhosis is mainly due to hypercoagulable state and altered dynamic of blood flow in the portal vein. The clinical manifestations of PVT are variable among different patients, so the diagnosis of PVT is mainly dependent on the imaging examinations, like ultrasound, computed tomography and magnetic resonance imaging. The overall goal of treatment for PVT can be summarized as reducing risk factors of PVT, thus to prevent further expansion of thrombus and maintain portal patency and prevent and treat the symptoms of PVT by anticoagulants, local thrombolysis, transjugular intrahepatic portosystemic shunt and/or surgery. In future, due to the progress in vascular imaging and innovation in clinical anti-thrombotic drug, PVT could be prevented and cured effectively.

Keywords: portal vein thrombosis, cirrhosis, management, anticoagulant

1. Introduction

Portal vein thrombosis (PVT) is diagnosed when a venous thrombosis occurs within the main portal vein and intrahepatic portal branches [1, 2]. In liver cirrhosis, especially in advanced stages, PVT is one of the most common complications [3–5]. High incidence of PVT in the setting of liver cirrhosis is mainly due to hypercoagulable state and altered dynamics of blood flow in the portal vein [6–8]. Moreover, PVT will deteriorate liver cirrhosis by increasing portal vein pressure and decreasing blood flow into liver. Under severe circumstances, it will worsen symptoms of cirrhosis such as ascites, upper gastrointestinal bleeding, intestinal avascular necrosis and so on [3, 4, 9–11]. However, 30–50% patients with PVT will spontaneously

alleviate or recover without any treatment [4, 10, 12, 13]. This highlights the over-diagnosis of PVT in cirrhosis and questions whether PVT treatment will benefit cirrhotic patients, especially when they are diagnosed incidentally on imaging. Right now, there is no guideline or expert consensus on how to manage cirrhotic patients with PVT. A meta-analysis which includes 3735 cirrhotic patients demonstrated that PVT negatively influenced both mortality and hepatic decompensation, despite its limitation of including heterogeneous populations [14]. However, another prospective multicenter study which includes 863 Child-Pugh class A and 380 class B cirrhotic patients found PVT was not a prognostic factor for either mortality or hepatic decompensation [15]. A study that only investigated 42 cirrhotic patients with extrahepatic nonmalignant partial PVT reported that no association was found between progression or regression of partial PVT and clinical outcomes. The model for end-stage liver disease **(**MELD) score, rather than PVT, was the predictor of worse prognosis in cirrhotic patients [16]. So, at present, the issue of whether PVT does or does not have influence on the natural history of cirrhosis is still controversial [17–19].

2. Prevalence

The prevalence and incidence of PVT in cirrhosis often varies from 1 to 28% among different studies depending on heterogeneity in diagnosis methods, different populations and variable follow-up time [16–22]. In a retrospective study of 150 patients with viral cirrhosis, the cumulative overall incidences of PVT were 12.8% at 1 year, 18.6% at 3 years, 20% at 5 years and 38.7% at 8–10 years, respectively [23]. In another study, which includes 701 cirrhosis patients without hepatocellular carcinoma, the incidence of PVT was 11.2% since they used ultrasound for diagnosis routinely [24]. PVT is more common in advanced cirrhosis and the incidence is positively related with the stage of cirrhosis, which is only 1% in compensated patients but 8.4% in severe cirrhosis waiting for liver transplantation [21, 25–28]. However, there are some limitations in these studies which weaken the magnitude and reliability of these conclusions like different subgroup patients and follow-up times as we previously mentioned. Violi et al. reported a study aimed at evaluating the prevalence of PVT in a broad spectrum of patients with cirrhosis and found 17% of 753 cirrhotic patients had PVT [29]. A multicenter randomized trial that includes 898 well-compensated cirrhosis patients reported that the 5-year cumulative incidence of PVT was 11.9% [30].

3. Pathophysiology

3.1. Hypercoagulable state of blood flow

After liver transplantation, the number of platelets will increase temporarily for a short time, which contributes to the hypercoagulable state of blood [31, 32]. That would be one of the significant reasons for PVT formation in liver transplantation patients. The study showed that surgery not only increased blood platelets but also activated their surface glycoprotein CD62P, reflecting the degree of platelet activation and causing a hypercoagulable state [33, 34]. Postoperative-elevated CD62P is closely related with PVT, which can be used as a sensitive

diagnostic biomarker of PVT [9, 35, 36]. Toshiki Matsui also reported that soluble form of glycoprotein VI, as a platelet activation marker, was associated with PVT formation after hepatectomy and splenectomy in patients with liver cirrhosis [37]. Another study from Poland found platelet aggregability was decreased in PVT patients [31]. In another logistic regression model, incidence of PVT was highly related with D-dimer and bilirubin [38, 39]. Additionally, increased whole blood viscosity due to increased number of erythrocytes and ability of aggregation as well as decreased deformability may be reasons for increased PVT formation [34, 40]. Both procoagulant and anticoagulant proteins decreased in liver cirrhosis patients at the same time, owing to decreased synthesis function of the liver, which often largely maintained in a dynamic balance [7, 8, 34, 41]. Therefore, the body is neither to bleed nor to form thrombosis. However, after liver transplantation surgery, venous injury would reduce the flow rate of portal vein; thus, anticoagulant-associated protein S and C decreased as well as anti-thrombin III [21]. Meanwhile, surgery consumes numerous coagulation factors. Factor VIII, VII factor-related antigens and anti-cardiolipin antibody increased, which both resulted in PVT formation. Factor VIII concentration and the ratio of the most powerful procoagulant (factor VIII) and anticoagulant (protein C) were considered as markers to indicate hypercoagulability [25, 38, 42–44]. Studies showed factor VIII was related to PVT in cirrhotic patients independently. Patients with factor VIII level above 129 IU/dl had six times the probability to PVT [45]. Some researchers reported in the literature that procoagulant gene mutations, including coagulation factor V Leiden G1691A, methylenetetrahydrofolate reductase C677T and prothrombin G20210A, may be associated with PVT [46, 47]. Recent studies showed that increased hemagglutinin activated fibrinolysin inhibition gene mutation and blood coagulation factor VII, which were closely related to the occurrence of PVT [1, 2].

3.2. Hemodynamic changes in the portal vein

PVT formation is associated with intrahepatic resistance and poor portal blood flow. Moreover, portal blood flow decreases more if cirrhosis progresses. That's why the incidence of PVT is much higher in advanced-stage cirrhotic patients compared with well-compensated ones [48]. Cirrhotic patients with PVT had low portal flow volumes and high collateral vessel flow velocity. Intraoperative clamp and squeeze will cause vein intimal injury, collagen exposure and activation of the coagulation system. After liver transplantation, blood flow in portal vein is relatively slow, which is easy to form turbulence and thrombosis [9, 25, 49, 50]. Portal vein blood flow velocity and PVT have an important relationship. Studies demonstrated that patients with portal vein blood flow <15 cm/s had higher incidence of PVT [17, 27, 50–52]. So, some researchers often regarded portal vein diameter as an independent risk factor for the formation of PVT. In short, because there are various changes in portal hemodynamics, the incidence of PVT is quite high after liver transplantation.

3.3. Endotoxinemia

Cirrhosis is more likely to damage intestinal mucosal barrier which facilitates bacterial translocation and endotoxinemia [53]. Endotoxinemia not only can increase portal vein pressure but also can activate coagulation cascade. That explains why it can increase the PVT incidence in the portal system [54].

4. Diagnosis

4.1. Clinical manifestations

A study which includes 79 cirrhotic patients has shown that 57% of PVT were symptomatic and among them 39% had gastrointestinal bleeding and 70% had intestinal infarction [24]. Abdominal pain is generally the earliest clinical symptom after the acute formation of PVT. Usually, abdominal pain is limited within a specific region while few are diffuse pain and intermittent colic pain with longer durations. Nausea and vomiting occur in 50% of PVT patients [3, 4, 51, 55–57]. A few patients will have diarrhea or bloody stool. If complete intestinal obstruction occurs suddenly, abdominal pain is paroxysmal accompanied by significant nausea, vomiting without fart and defecation. Under this circumstance, there are no obvious physical examination signs, that the degree of pain is not consistent with the signs of the abdomen [19, 58, 59]. Increased anterior hepatic obstructive factors will cause decreased portal vein blood flow which aggravates liver damage, increases portal pressure, causes repeated upper gastrointestinal bleeding and refractory ascites and so on. In some severe cases, clinical manifestations of intestinal necrosis such as persistent abdominal pain, bloating, hemafecia, hematemesis, shock and peritoneal irritation will occur [18, 24, 26]. Abdominal puncture can be bloody ascites. In the event of intestinal necrosis, disease mortality rate can rise to 20–60%. Patients often suffer from persistent abdominal pain, hemafecia, abdominal cramps, ascites, multiple organ failure and so on. For chronic PVT, patients will have refractory bloating, diarrhea, upper abdominal pain and ascites due to gastrointestinal congestion and insufficient perfusion of liver portal vein [24]. The clinical manifestations of PVT are variable among different patients, so the clinical diagnosis of PVT is mainly dependent on the imaging examination.

4.2. Imaging

Ultrasound, the most common imaging way, is simple and easy to accurately evaluate PVT [60]. Thus, it is the preferred imaging method for diagnosis. Ultrasound diagnosis of PVT is characterized by abnormal echo in the portal vein, unclear boundary with the wall, CDFI: no blood flow signal, portal venous cavernous hemangioma; portal vein expansion before thrombosis site; and no display of portal vein if PVT is formed within a wide range [11, 17, 18, 60, 61]. The sensitivity and specificity of ultrasonography to diagnose PVT are up to 60 and 100% [60, 62]. Ultrasound can clearly demonstrate the blood flow, vascular diameter and the changes and the presence of thrombi. Ultrasound can also determine the formation of collateral circulation simultaneously through CDFI. But the ultrasound cannot reflect directly the situation of the portal vein and its branches, and the experience of the operator affects the accuracy of the diagnosis. Ultrasound angiography or ultrasound endoscopy can diagnose PVT more accurately that even raises the diagnostic sensitivity to 81% [24]. Some authors recommended contrasting enhanced ultrasound as the first-line imaging and "gold standard method" for the diagnosis of PVT [63, 64]. But ultrasound angiography and endoscopy also have some limitations. Firstly, they cannot evaluate the portal vein within the part of the liver and superior mesenteric vein end accurately. Moreover, they cannot assess the surrounding organs which may be affected by PVT [50, 63, 64].

Enhanced computer tomography (CT) or enhanced magnetic resonance imaging (MRI) examination by intravenous injection contrast can effectively solve the above deficiencies. By comparison with contrast, we can discover intraluminal filling defects and perfusion conditions for nearby organs at different times of the imaging process. CT angiography (CTA) and magnetic resonance angiography (MRA) greatly increase the accuracy of diagnosis. Some studies have showed that the sensitivity and the specificity for CTA were 86 and 95%. For MRA, the sensitivity was 100% and specificity was 98% [60, 65–67]. Typical CT signs of PVT are very intuitive: no-enhanced low-density intraluminal stripe or massive lesions within portal static. Occasionally, CT can also find an enhanced ring around thrombus due to nourishing small blood vessels. Moreover, CT can also help to diagnose primary liver cancer, cirrhosis and evaluate intestinal ischemia and necrosis. CTA has several advantages including short scan time, fast imaging speed and reduced motion artifact [67]. However, its main drawbacks can be related to some complications like contrast agent allergy, contrast agent nephropathy and other adverse reactions. The safety of MRA contract is significantly better than that of CTA. But MRA has the same disadvantages like motion artifacts, long-signal acquisition time and limited imaging range [66]. Therefore, patients with suspicious PVT should be enrolled in contract CT or MRI imaging, which can be more accurate for clinical diagnosis.

Angiography is the traditional method for diagnosis of PVT. It is not the routine examination of PVT because of its invasive feature. Angiography includes two categories: indirect and direct. Indirect angiography is through splenic artery and superior mesenteric artery to image [2, 65]. In this way, we can see the portal vein filling defect as well as the collateral circulation. The most important thing is we can put the catheter into the superior mesenteric artery and/or splenic artery branch to infuse thrombolytic drugs after indirect angiography. It means we can finish diagnosis and follow treatment after invasive process at one time. Direct angiography is divided into: percutaneous transhepatic portal angiography, which can display directly portal vein system and evaluate portal hemodynamics, and umbilical portal vein angiography, which is indicated for splenic vein thrombosis, spleen resection and failure of arterial portal angiography [50].

4.3. Laboratory tests

Usually, prothrombin time (PT) and activated partial thromboplastin time (APTT) were used as predictors for the coagulation state with cirrhosis, and even the predictive ability was poor [7, 34, 68]. Because they could not explain and represent natural anticoagulants such as antithrombin and protein C in vivo, the thrombin generation test, which used tissue factor as trigger and phospholipids as platelet substitutes, was considered more appropriate for evaluating thrombin generation. The test was regarded as representation of the balance between the pro- and anticoagulant proteins in plasma [33, 44]. Another test named thromboelastography (TEG) can monitor all kinds of hemostatic functions (coagulation, anticoagulation, fibrinolysis) continuously to predict thrombosis formation and dissolution dynamically. This test also emphasized the dynamic assessment of balanced status in blood coagulation and anticoagulation process [17, 18]. This is a new laboratory test to evaluate whether the blood is hypercoagulable, whether there is the formation of thrombus and whether the thrombus is stable. The effectiveness of clinical application needs to be further studied. Additionally, we

can exclude PVT patients with a 90% negative predictive value when the D-dimer level is less than 1.82 mg/l [38, 39, 69, 70]. Systemic evaluation of coagulation tests, including PT, international standardization ratio, partial thromboplastin time, and so on, could not fully assess the patient's coagulation abnormalities. Dynamic monitoring of vitamin K-related coagulation factors, fibrinogen, platelet function, fibrinolysis status as well as other coagulation factors simultaneously is essential.

5. Classification

According to PVT imaging findings preoperatively, Yerdel found a classification system as the following: grade I, <50% portal vein obstruction with or without micro-thrombus of the superior mesenteric vein; grade II, >50% portal vein obstruction with or without micro-thrombus of the superior mesenteric vein; grade III, complete portal vein and proximal superior mesenteric vein obstruction; and grade IV, complete portal vein and entire superior mesenteric vein obstruction [71].

6. PVT treatment

The overall goal of treatment for PVT can be summarized as reducing risk factors of PVT, thus to prevent further expansion of thrombus and maintain portal patency, prevent and treat the symptoms of PVT. For acute PVT, the aim is to prevent thrombus extension and intestinal infarction, whereas for chronic PVT, it is to prevent recurrent thrombosis, gastrointestinal bleeding and portal cholangiopathy [20, 35, 51].

6.1. Non-surgical treatment

The incidence of PVT is high in cirrhotic patients, but clinical studies found that 30–50% of patients with PVT could alleviate without any treatment. Longest diameter of portal vein and blood flow of the largest collateral circulation vein were closely related with the incidence of spontaneous alleviation in PVT patients [1, 21]. But another study demonstrated that untreated PVT was associated with increased mortality, especially in patients with low Child-Pugh scores. And there were strong correlations between anticoagulation therapy and lower thrombus progress rate as well as higher recanalization rate [11, 72, 73]. Furthermore, PVT has been reported as an independent risk factor for recurrent and refractory acute variceal bleeding [23, 74]. There is inconsistent guidance on the anticoagulant management of PVT. However, once the PVT is diagnosed, the optimal time of prevention and treatment often has been missed. Serious complications would increase mortality greatly for PVT patients. So, it is recommended for cirrhotic patients that routine color Doppler ultrasound assessment should be performed. Early diagnosis, early anticoagulant and thrombolytic therapy can effectively improve the prognosis of patients. A meta-analysis from Italy, which includes 8 studies comprising 353 patients with cirrhosis and PVT, demonstrated anticoagulant therapy (low-weight heparin or warfarin) could increase recanalization and reduce progression of thrombosis

effectively [75]. Meanwhile, these anticoagulants will not increase the incidence of any kinds of bleedings [75]. Another study from Italy found the benefits patients got overweighed the potential minor bleeding risk [76]. And they also concluded that portal hypertension, rather than anticoagulants, would be the real reason for the risk of major bleeding among cirrhotic patients with PVT. A prospective study from China which focused on patients with cirrhosis undergoing elective transjugular intrahepatic portosystemic shunt (TIPS) found that warfarin treatment within 12 months achieved a much higher rate of complete recanalization [77]. The commonly used drugs include warfarin, low molecular weight heparin and urokinase [78–81]. Most patients with acute PVT were recommended early anticoagulant therapy at least for 6 months. A systematic review and meta-analysis that summarized different regiments of anticoagulation has been reported [82]. In this study, the overall rate of portal vein recanalization was 37–93% and the anti-coagulation related bleeding was 0–18% [82]. In this way, we can not only reduce the incidence of PVT greatly but also increase PVT recanalization rate up to 39.3–100.0%.

In recent years, inhibitors of activated factor Xa (e.g., rivaroxaban) have been used in the prevention of clinical PVT. The advantages are convenient oral administration, no effect on the international standardization ratio and no need to monitor blood coagulation indicators. Hyeyoung Yang et al. reported a 63-year-old female who experienced complete resolution of recurrent acute PVT in liver cirrhosis after rivaroxaban treatment [83]. The disadvantage is there is no effective antagonist. When bleeding happens during anticoagulant therapy, the consequence is serious. However, some new oral anticoagulants' antidotes have been under investigation like andexanet alfa, P-glycoprotein substrates and drugs inducing CYP3A4. They all could inhibit the concentration or absorption of new oral anticoagulants and attenuate their effects remarkably [83, 84].

In short, clinical non-surgical methods are still mainly treatments of PVT in cirrhotic patients.

6.2. Local thrombolytic treatment

Local thrombolysis is divided into indirect way (femoral artery-superior mesenteric artery indwelling catheter thrombolysis) and direct way (percutaneous transhepatic portal vein thrombolysis) [13, 17, 18, 27, 35, 56, 85].

The advantages of the femoral artery-superior mesenteric artery catheter thrombolysis are simple and relative small trauma. It is just suitable for mild PVT without vascular occlusion. Because when PVT is found by this method, portal vein branches are usually in the stenosis or occlusion state by obstruction of thrombosis. Most of the drugs we injected for thrombolysis cannot reach the site of thrombus effectively. So, indications of this method are limited.

The advantages of the percutaneous transhepatic portal vein thrombolysis method are simple and show high success rates. However, we must stop this treatment when the patient has: (1) APTT significantly longer; (2) the international standardization ratio > 2; and (3) obvious abdominal pain, bloating, vomiting, hemafecia, increased puncture-point bleeding, more subcutaneous ecchymosis, hemoglobin continuing to decrease, faster heart rate, lower blood pressure and other signs of active bleeding.

6.3. TIPS

When severe PVT happened, thrombus blocked more than 50% lumen or completely blocked, anticoagulant therapy was unlikely to recanalization. Under this condition, we can choose TIPS. This method has the advantages as the following: the risk of thrombolysis is relatively small, and punctures can often reach directly to the thrombus site; at the same time intravascular technology (balloon plasty, stent replacement, thrombectomy and thrombolytic therapy surgery) can be applied to achieve the goal of treatment of PVT. A study from China which compared transcatheter selective superior mesenteric artery urokinase infusion and TIPS has found they were safe and effective for acute symptomatic PVT in cirrhosis [86]. But the operation was a relative difficult and lethal event as well as severe complications were still possible, so it is particularly important to assess the risk-benefit ratio of TIPS preoperatively. At present, the TIPS therapy methods for PVT are the following [87–89]:

A. TIPS placement → portosystemic shunt → portal vein recanalization;

B. TIPS placement through percutaneous ways portal vein recanalization;

C. TIPS placement between hepatic vein and collateral vessel → no portal vein recanalization

For cirrhotic patients with refractory variceal bleeding and ascites, TIPS was considered as one of the major treatment strategies if the patient did not have PVT. PVT has changed natural history of liver cirrhosis and affected outcomes. So, in this circumstance, TIPS should be recommended with caution. No convincing evidence has been published to verify the superiority of TIPS over traditional anticoagulants. TIPS should only be recommended for severe PVT patients although technical difficulty rose sharply when severe PVT was diagnosed [89]. That means reliable predictors for PVT progression should be further investigated in future.

6.4. Surgical treatment of PVT

Surgery is relatively high risk. The commonly used methods are (1) PVT excision; (2) portal vein stent implantation, mainly aimed to relieve portal vein obstruction; (3) liver transplantation. During treatment, if the patient has the sustained abdominal pain, abdominal distension and other signs of peritonitis, laparotomy exploration should be performed early to prevent the occurrence of intestinal necrosis. When intestinal necrosis is diagnosed, intestinal and mesangial resections should be performed. At the same time, the intestinal end-to-end anastomosis should be done. Anticoagulation was continued after surgery to prevent thrombus reformation.

7. PVT prevention

Kawanaka et al. have shown that anti-thrombin III (AT III) activity and splenic vein diameter were the risk factors of PVT after surgery. Moreover, they used those risk factors to formulate risk stratification system [90]. According to the risk stratification, doctors can decide whether to give prevention or not: low risk: AT III activity ≥70% and splenic vein straight diameter <10 mm, no preventive treatment; intermediate risk: AT III activity <70% or splenic

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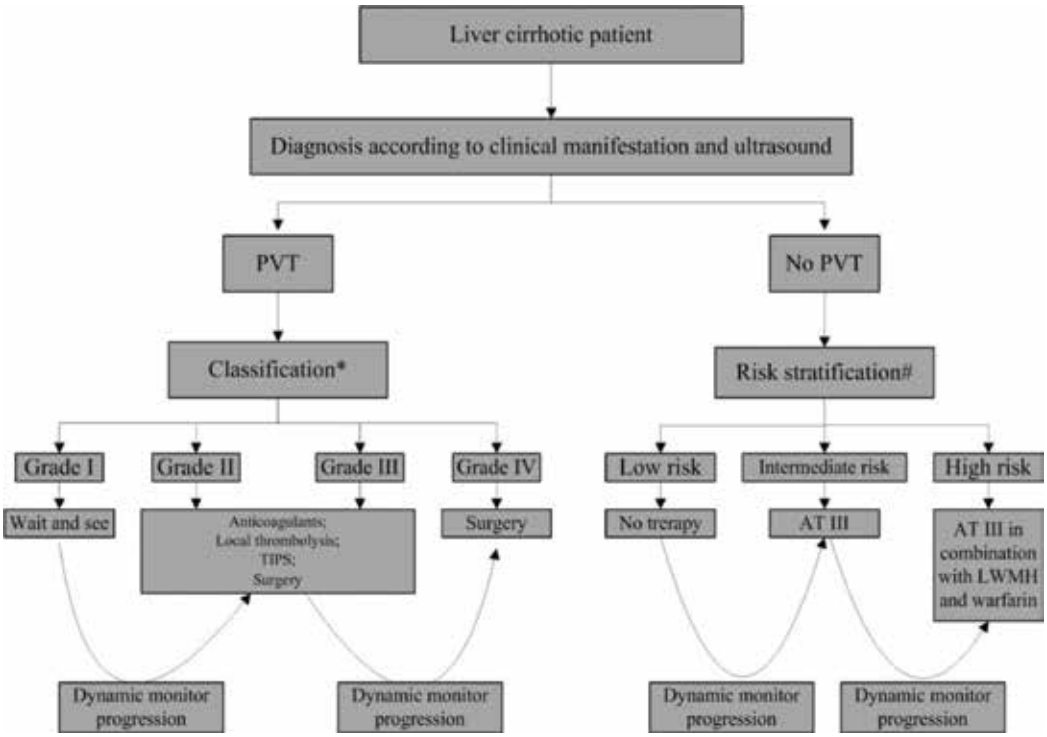

Figure 1. Algorithm for the treatment of portal vein thrombosis in liver cirrhosis. *Abbreviations*: PVT, portal vein thrombosis; TIPS, transjugular intrahepatic portosystemic shunt; AT III, anti-thrombin III therapy; LWMH, low-weight molecular heparin; *according to Yerdel's study [68]; # according to Kawanaka's study [90].

vein diameter ≥10 mm, simple AT III prevention treatment; and high risk: splenic vein diameter ≥15 mm or from the liver collateral circulation vein diameter ≥10 mm, AT III, low molecular weight heparin in conjunction with warfarin [90].

Enoxaparin was found to prevent PVT in advanced cirrhotic patients. Daily subcutaneous enoxaparin (4000 IU/day) could significantly reduce incidence of PVT in the short and long term [91, 92]. And enoxaparin can also decrease the liver decompensation rate and improve survival of patients who received liver transplantation [52, 91, 92].

Surgery on the portal vein system should be gentle and accurate. We should prevent unnecessary damage to the vascular endothelium and avoid ligation of chunk tissue. If there is no obvious bleeding tendency, surgeons should not use hemostatic after surgery which may result in thrombosis (**Figure 1**).

8. Conclusion

PVT was a clinical rare deep venous thrombosis but highly occurred in liver cirrhotic patients. Local or systemic factors alone or in combination make contribution to the formation of PVT. In clinical, PVT should be given enough attention due to its severe threat to the patient's

life and health. The overall treatment principles are early diagnosis, early treatment and prevention combined with treatment. In the future, due to the progress in vascular imaging and innovation in clinical anti-thrombotic drug, PVT could be prevented and cured effectively.

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References

[1] Chawla YK, Bodh V. Portal vein thrombosis. Journal of Clinical and Experimental Hepatology. 2015;**5**(1):22-40

[2] Basit SA, Stone CD, Gish R. Portal vein thrombosis. Clinics in Liver Disease. 2015;**19**(1):199-221

[3] Yang ZNJ, Costa KA, Novelli EM, Smith RE. Venous thromboembolism in cirrhosis. Clinical and Applied Thrombosis-Hemostasis. 2014;**20**(2):169-178

[4] Handa P, Crowther M, Douketis JD. Portal vein thrombosis: A clinician-oriented and practical review. Clinical and Applied Thrombosis-Hemostasis. 2014;**20**(5):498-506

[5] Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;**383**(9930):1749-1761

[6] Cai CC, Liu SY. A meta-analysis of portal vein thrombosis in patients with liver cirrhosis. Journal of Gastroenterology and Hepatology. 2013;**28**:847

[7] Schaden E, Saner FH, Goerlinger K. Coagulation pattern in critical liver dysfunction. Current Opinion in Critical Care. 2013;**19**(2):142-148

[8] Mucino-Bermejo J, Carrillo-Esper R, Uribe M, Mendez-Sanchez N. Coagulation abnormalities in the cirrhotic patient. Annals of Hepatology. 2013;**12**(5):713-724

[9] Ghabril M, Agarwal S, Lacerda M, Chalasani N, Kwo P, Tector AJ. Portal vein thrombosis is a risk factor for poor early outcomes after liver transplantation: Analysis of risk factors and outcomes for portal vein thrombosis in waitlisted patients. Transplantation. 2016;**100**(1):126-133

[10] Girleanu I, Stanciu C, Cojocariu C, Boiculese L, Singeap AM, Trifan A. Natural course of nonmalignant partial portal vein thrombosis in cirrhotic patients. Saudi Journal of Gastroenterology. 2014;**20**(5):288-292

[11] Borjas-Almaguer OD, Cortez-Hernandez CA, Gonzalez-Moreno EI, Bosques-Padilla FJ, Gonzalez-Gonzalez JA, Garza AA, et al. Portal vein thrombosis in patients with cirrhosis: Just a common finding or a predictor of poor outcome? Annals of Hepatology. 2016;**15**(6):902-906

[12] Berry K, Taylor J, Liou IW, Ioannou GN. Portal vein thrombosis is not associated with increased mortality among patients with cirrhosis. Clinical Gastroenterology and Hepatology. 2015;**13**(3):585-593

[13] Qi XS, Han GH, Fan DM. Management of portal vein thrombosis in liver cirrhosis. Nature Reviews Gastroenterology & Hepatology. 2014;**11**(7):435-446

[14] Stine JG, Shah PM, Cornella SL, Rudnick SR, Stukenborg GR, Northup P. Portal vein thrombosis, mortality and hepatic decompensation in patients with cirrhosis: A meta-analysis. Hepatology. 2015;**62**:943A-A

[15] Nery F, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: Results of a longitudinal study. Hepatology. 2015;**61**(2):660-667

[16] Luca A, Caruso S, Milazzo M, Marrone G, Mamone G, Crino F, et al. Natural course of extrahepatic nonmalignant partial portal vein thrombosis in patients with cirrhosis. Radiology. 2012;**265**(1):124-132

[17] von Kockritz L, De Gottardi A, Trebicka J, Praktiknjo M. Portal vein thrombosis in patients with cirrhosis. Gastroenterology Report. 2017;**5**(2):148-156

[18] Fujiyama S, Saitoh S, Kawamura Y, Sezaki H, Hosaka T, Akuta N, et al. Portal vein thrombosis in liver cirrhosis: Incidence, management, and outcome. BMC Gastroenterology. 2017;**17**(1):112

[19] Loudin M, Ahn J. Portal vein thrombosis in cirrhosis. Journal of Clinical Gastroenterology. 2017;**51**(7):579-585

[20] Haris M, Thachil J. The problem with incidental and chronic portal vein thrombosis. European Journal of Internal Medicine. 2017;**39**:E29-E30

[21] Chen H, Turon F, Hernandez-Gea V, Fuster J, Garcia-Criado A, Barrufet M, et al. Nontumoral portal vein thrombosis in patients awaiting liver transplantation. Liver Transplantation. 2016;**22**(3):352-365

[22] Cruz-Ramon V, Chinchilla-Lopez P, Ramirez-Perez O, Mendez-Sanchez N. Effects of portal vein thrombosis on the outcomes of liver cirrhosis: A Mexican perspective. Journal of Translational Internal Medicine. 2017;**5**(4):189-191

[23] Maruyama H, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: Predictive factors and long-term outcomes. American Journal of Gastroenterology. 2013;**108**(4):568-574

[24] Amitrano L, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. Journal of Hepatology. 2004;**40**(5):736-741

[25] Lankarani KB, Homayon K, Motevalli D, Heidari ST, Alavian SM, Malek-Hosseini SA. Risk factors for portal vein thrombosis in patients with cirrhosis awaiting liver transplantation in shiraz, Iran. Hepatitis Monthly. 2015;**15**(12):e26407

[26] Eshraghian A, Nikeghbalian S, Kazemi K, Shamsaeefar A, SAM H. Prevalence and risk factors of portal vein thrombosis in patients with liver cirrhosis and its impact on outcomes after liver transplantation. Transplant International. 2017;**30**:146

[27] Qi XS, Li HY, Liu X, Yao H, Han GH, Hu FR, et al. Novel insights into the development of portal vein thrombosis in cirrhosis patients. Expert Review of Gastroenterology & Hepatology. 2015;**9**(11):1421-1432

[28] Francoz C, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, et al. Splanchnic vein thrombosis in candidates for liver transplantation: Usefulness of screening and anticoagulation. Gut. 2005;**54**(5):691-697

[29] Violi F, Corazza RG, Caldwell SH, Perticone F, Gatta A, Angelico M, et al. Portal vein thrombosis relevance on liver cirrhosis: Italian venous thrombotic events registry. Internal and Emergency Medicine. 2016;**11**(8):1059-1066

[30] Nery FG, Chaffaut C, Condat B, de Raucourt E, Boudaoud L, Rautou PE, et al. Portal vein thrombosis (PVT) in compensated cirrhosis: A prospective cohort study on 898 patients. Hepatology. 2013;**58**:271A-272A

[31] Wosiewicz P, Zorniak M, Hartleb M, Baranski K, Onyszczuk M, Pilch-Kowalczyk J, et al. Portal vein thrombosis in cirrhosis is not associated with intestinal barrier disruption or increased platelet aggregability. Clinics and Research in Hepatology and Gastroenterology. 2016;**40**(6):722-729

[32] Colli A, Gana JC, Yap J, Adams-Webber T, Rashkovan N, Ling SC, et al. Platelet count, spleen length, and platelet count-to-spleen length ratio for the diagnosis of oesophageal varices in people with chronic liver disease or portal vein thrombosis. Cochrane Database of Systematic Reviews. 2017;**4**:CD008759

[33] Khoury T, Ayman A, Cohen J, Daher S, Shmuel C, Mizrahi M. The complex role of anticoagulation in cirrhosis: An updated review of where we are and where we are going. Digestion. 2016;**93**(2):149-159

[34] Tripodi A, Primignani M, Braham S, Chantarangkul V, Clerici M, Moia M, et al. Coagulation parameters in patients with cirrhosis and portal vein thrombosis treated sequentially with low molecular weight heparin and vitamin K antagonists. Digestive and Liver Disease. 2016;**48**(10):1208-1213

[35] Sharma AM, Zhu D, Henry Z. Portal vein thrombosis: When to treat and how? Vascular Medicine. 2016;**21**(1):61-69

[36] Dell'Era A, Seijo S. Portal vein thrombosis in cirrhotic and non cirrhotic patients: From diagnosis to treatment. Expert Opinion on Orphan Drugs. 2016;**4**(9):927-940

[37] Matsui T, Usui M, Wada H, Iizawa Y, Kato H, Tanemura A, et al. Platelet activation assessed by glycoprotein VI/platelet ratio is associated with portal vein thrombosis after hepatectomy and splenectomy in patients with liver cirrhosis. Clinical and Applied Thrombosis/Hemostasis. 2017;**24**(2):254-262. DOI: 10.1177/1076029617725600

[38] Zhang DL, Hao JY, Yang N. Value of D-dimer and protein S for diagnosis of portal vein thrombosis in patients with liver cirrhosis. Journal of International Medical Research. 2013;**41**(3):664-672

[39] Dai JN, Qi XS, Li HY, Guo XZ. Role of D-dimer in the development of portal vein thrombosis in liver cirrhosis: A meta-analysis. Saudi Journal of Gastroenterology. 2015;**21**(3):165-174

[40] Wu XM, Yao ZP, Zhao L, Zhang Y, Cao MH, Li T, et al. Phosphatidylserine on blood cells and endothelial cells contributes to the hypercoagulable state in cirrhosis. Liver International. 2016;**36**(12):1800-1810

[41] Cui SB, Fu ZM, Feng YM, Xie XY, Ma XW, Liu TT, et al. The disseminated intravascular coagulation score is a novel predictor for portal vein thrombosis in cirrhotic patients with hepatitis B. Thrombosis Research. 2018;**161**:7-11

[42] Singhal A, Karachristos A, Bromberg M, Daly E, Maloo M, Jain AK. Hypercoagulability in end-stage liver disease: Prevalence and its correlation with severity of liver disease and portal vein thrombosis. Clinical and Applied Thrombosis-Hemostasis. 2012;**18**(6):594-598

[43] Girolami A, Cosi E, Ferrari S, Girolami B. Heparin, coumarin, protein C, antithrombin, fibrinolysis and other clotting related resistances: Old and new concepts in blood coagulation. Journal of Thrombosis and Thrombolysis. 2018;**45**(1):135-141

[44] Qi XS, Chen H, Han GH. Effect of antithrombin, protein C and protein S on portal vein thrombosis in liver cirrhosis: A meta-analysis. American Journal of the Medical Sciences. 2013;**346**(1):38-44

[45] Martinelli I, Primignani M, Aghemo A, Reati R, Bucciarelli P, Fabris F, et al. High levels of factor VIII and risk of extra-hepatic portal vein obstruction. Journal of Hepatology. 2009;**50**(5):916-922

[46] Pasta L, Pasta F, D'Amico M. PAI-1 4G-4G, MTHFR 677TT, V Leiden 506Q, and Prothrombin 20210A in splanchnic vein thrombosis: Analysis of individual patient data from three prospective studies. Journal of Clinical and Experimental Hepatology. 2016;**6**(1):10-14

[47] Ventura P, Venturelli G, Marcacci M, Fiorini M, Marchini S, Cuoghi C, et al. Hyperhomocysteinemia and MTHFR C677T polymorphism in patients with portal vein thrombosis complicating liver cirrhosis. Thrombosis Research. 2016;**141**:189-195

[48] Werner KT, Sando S, Carey EJ, Vargas HE, Byrne TJ, Douglas DD, et al. Portal vein thrombosis in patients with end stage liver disease awaiting liver transplantation: Outcome of anticoagulation. Digestive Diseases and Sciences. 2013;**58**(6):1776-1780

[49] Nazzal M, Sun YF, Okoye O, Diggs L, Evans N, Osborn T, et al. Reno-portal shunt for liver transplant, an alternative inflow for recipients with grade III-IV portal vein thrombosis: Tips for a better outcome. International Journal of Surgery Case Reports. 2017;**41**:251-254

[50] Seijo S, Garcia-Criado A, Darnell A, Garcia-Pagan JC. Diagnosis and treatment of portal thrombosis in liver cirrhosis. Gastroenterologia Y Hepatologia. 2012;**35**(9):660-666

[51] Manzano-Robleda MD, Barranco-Fragoso B, Uribe M, Mendez-Sanchez N. Portal vein thrombosis: What is new? Annals of Hepatology. 2015;**14**(1):20-27

[52] Mancuso A. Management of portal vein thrombosis in cirrhosis: An update. European Journal of Gastroenterology & Hepatology. 2016;**28**(7):739-743

[53] Lin RS, Lee FY, Lee SD, Tsai YT, Lin HC, Lu RH, et al. Endotoxemia in patients with chronic liver-diseases—Relationship to severity of liver-diseases, presence of esophageal-varices, and hyperdynamic circulation. Journal of Hepatology. 1995;**22**(2):165-172

[54] Rosenqvist K, Eriksson LG, Rorsman F, Sangfelt P, Nyman R. Endovascular treatment of acute and chronic portal vein thrombosis in patients with cirrhotic and non-cirrhotic liver. Acta Radiologica. 2016;**57**(5):572-579

[55] Buresi M, Hull R, Coffin CS. Venous thromboembolism in cirrhosis: A review of the literature. Canadian Journal of Gastroenterology. 2012;**26**(12):905-908

[56] Llop E, Seijo S. Treatment of non-cirrhotic, non-tumoural portal vein thrombosis. Gastroenterologia Y Hepatologia. 2016;**39**(6):403-410

[57] Ambrosino P, Tarantino L, Di Minno G, Paternoster M, Graziano V, Petitto M, et al. The risk of venous thromboembolism in patients with cirrhosis a systematic review and meta-analysis. Thrombosis and Haemostasis. 2017;**117**(1):139-148

[58] Harding DJ, Perera M, Chen F, Olliff S, Tripathi D. Portal vein thrombosis in cirrhosis: Controversies and latest developments. World Journal of Gastroenterology. 2015;**21**(22):6769-6784

[59] Cagin YF, Atayan Y, Erdogan MA, Dagtekin F, Colak C. Incidence and clinical presentation of portal vein thrombosis in cirrhotic patients. Hepatobiliary & Pancreatic Diseases International. 2016;**15**(5):499-503

[60] Margini C, Berzigotti A. Portal vein thrombosis: The role of imaging in the clinical setting. Digestive and Liver Disease. 2017;**49**(2):113-120

[61] Stine JG, Wang J, Shah PM, Argo CK, Intagliata N, Uflacker A, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: A matched case-control study. Liver International. 2018;**38**(1):94-101

[62] Alam S, Pervez R. Validity of colour doppler sonography for evaluation of portal venous system in hepatocellular carcinoma. Journal of the Pakistan Medical Association. 2013;**63**(3):365-368

[63] Danila M, Sporea I, Popescu A, Sirli R. Portal vein thrombosis in liver cirrhosis—The added value of contrast enhanced ultrasonography. Medical Ultrasonography. 2016;**18**(2):218-223

[64] Tarantino L, Ambrosino P, Di Minno MND. Contrast-enhanced ultrasound in differentiating malignant from benign portal vein thrombosis in hepatocellular carcinoma. World Journal of Gastroenterology. 2015;**21**(32):9457-9460

[65] Berzigotti A, Garcia-Criado A, Darnell A, Garcia-Pagan JC. Imaging in clinical decision-making for portal vein thrombosis. Nature Reviews Gastroenterology & Hepatology. 2014;**11**(5):308-316

[66] Ahn JH, Yu JS, Cho ES, Chung JJ, Kim JH, Kim KW. Diffusion-weighted MRI of malignant versus benign portal vein thrombosis. Korean Journal of Radiology. 2016;**17**(4):533-540

[67] Qi XS, Han GH, He CY, Yin ZX, Guo WG, Niu J, et al. CT features of non-malignant portal vein thrombosis: A pictorial review. Clinics and Research in Hepatology and Gastroenterology. 2012;**36**(6):561-568

[68] Qi XS, Su CP, Ren WR, Yang M, Jia J, Dai JN, et al. Association between portal vein thrombosis and risk of bleeding in liver cirrhosis: A systematic review of the literature. Clinics and Research in Hepatology and Gastroenterology. 2015;**39**(6):683-691

[69] Zhang DL, Hao JY. Evaluation of D-dimer and protein S in cirrhotic patients with portal vein thrombosis. Journal of Gastroenterology and Hepatology. 2013;**28**:909-910

[70] Dai JN, Qi XS, Peng Y, Hou Y, Chen J, Li HY, et al. Association between D-dimer level and portal venous system thrombosis in liver cirrhosis: A retrospective observational study. International Journal of Clinical and Experimental Medicine. 2015;**8**(9):15296-15301

[71] Yerdel MA, Gunson B, Mirza D, Karayalcin K, Olliff S, Buckels J, et al. Portal vein thrombosis in adults undergoing liver transplantation—Risk factors, screening, management, and outcome. Transplantation. 2000;**69**(9):1873-1881

[72] Giannini EG, Stravitz RT, Caldwell SH. Portal vein thrombosis and chronic liver disease progression: The closer you look the more you see. Hepatology. 2016;**63**(1):342-343

[73] Wang Z, Jiang MS, Zhang HL, Weng NN, Luo XF, Li X, et al. Is post-TIPS anticoagulation therapy necessary in patients with cirrhosis and portal vein thrombosis? A randomized controlled trial. Radiology. 2016;**279**(3):943-951

[74] Abdel-Razik A, Mousa N, Elhelaly R, Tawfik A. De-novo portal vein thrombosis in liver cirrhosis: Risk factors and correlation with the model for end-stage liver disease scoring system. European Journal of Gastroenterology & Hepatology. 2015;**27**(5):585-592

[75] Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: A systematic review and meta-analysis. Gastroenterology. 2017;**153**(2):480

[76] Naeshiro N, Aikata H, Hyogo H, Kan H, Fujino H, Kobayashi T, et al. Efficacy and safety of the anticoagulant drug, danaparoid sodium, in the treatment of portal vein thrombosis in patients with liver cirrhosis. Hepatology Research. 2015;**45**(6):656-662

[77] Qi XS, He CY, Guo WG, Yin ZX, Wang JH, Wang ZY, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with variceal bleeding in liver cirrhosis: Outcomes and predictors in a prospective cohort study. Liver International. 2016;**36**(5):667-676

[78] De Gottardi A, Trebicka J, Klinger C, Plessier A, Seijo S, Terziroli B, et al. Antithrombotic treatment with direct-acting oral anticoagulants in patients with splanchnic vein thrombosis and cirrhosis. Liver International. 2017;**37**(5):694-699

[79] Jairath V, Burroughs AK. Anticoagulation in patients with liver cirrhosis: Complication or therapeutic opportunity? Gut. 2013;**62**(4):479-482

[80] Leonardi F, De Maria N, Villa E. Anticoagulation in cirrhosis: A new paradigm? Clinical and Molecular Hepatology. 2017;**23**(1):13-21

[81] Dhar A, Mullish BH, Thursz MR. Anticoagulation in chronic liver disease. Journal of Hepatology. 2017;**66**(6):1313-1326

[82] Qi XS, De Stefano V, Li HY, Dai J, Guo XX, Fan DM. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: A systematic review and meta-analysis of observational studies. European Journal of Internal Medicine. 2015;**26**(1):23-29

[83] Lenz K, Dieplinger B, Buder R, Piringer P, Rauch M, Voglmayr M. Successful treatment of partial portal vein thrombosis (PVT) with low dose rivaroxaban. Zeitschrift Fur Gastroenterologie. 2014;**52**(10):1175-1177

[84] Yang H, Kim SR, Song MJ. Recurrent acute portal vein thrombosis in liver cirrhosis treated by rivaroxaban. Clinical and Molecular Hepatology. 2016;**22**(4):499-502

[85] Qi XS, Wang J, Chen H, Han GH, Fan DM. Nonmalignant partial portal vein thrombosis in liver cirrhosis: To treat or not to treat? Radiology. 2013;**266**(3):994-995

[86] Jiang TT, Luo XP, Sun JM, Gao J. Clinical outcomes of transcatheter selective superior mesenteric artery urokinase infusion therapy vs transjugular intrahepatic portosystemic shunt in patients with cirrhosis and acute portal vein thrombosis. World Journal of Gastroenterology. 2017;**23**(41):7470-7477

[87] Zhao MF, Yue ZD, Zhao HW, Wang L, Fan ZH, He FL, et al. Techniques of TIPS in the treatment of liver cirrhosis combined with incompletely occlusive main portal vein thrombosis. Scientific Reports. 2016;**6**:33069

[88] Wang L, He FL, Yue ZD, Zhao HW, Fan ZH, Zhao MF, et al. Techniques and long-term effects of transjugular intrahepatic portosystemic shunt on liver cirrhosis-related thrombotic total occlusion of main portal vein. Scientific Reports. 2017;**7**(1):10868

[89] Fagiuoli S, Bruno R, Venon WD, Schepis F, Vizzutti F, Toniutto P, et al. Consensus conference on TIPS management: Techniques, indications, contraindications. Digestive and Liver Disease. 2017;**49**(2):121-137

[90] Kawanaka H, Akahoshi T, Itoh S, Iguchi T, Harimoto N, Uchiyama H, et al. Optimizing risk stratification in portal vein thrombosis after splenectomy and its primary prophylaxis with antithrombin III concentrates and danaparoid sodium in liver cirrhosis with portal hypertension. Journal of the American College of Surgeons. 2014;**219**(5):865-874

[91] Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology. 2012;**143**(5):1253

[92] Fortea JI, Zipprich A, Fernandez-Mena C, Puerto M, Bosoi CR, Almagro J, et al. Enoxaparin does not ameliorate liver fibrosis or portal hypertension in rats with advanced cirrhosis. Liver International. 2018;**38**(1):102-112

Chapter 5

Predictors of 50 Day In-Hospital Mortality in Decompensated Cirrhosis Patients with Spontaneous Bacterial Peritonitis

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Additional information is available at the end of the chapter

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Abstract

Aim: Predictors of 50 day in-hospital mortality in decompensated cirrhosis patients with spontaneous bacterial peritonitis (SBP).

Methods: 218 SBP patients admitted to intensive care units in a tertiary care hospital were retrospectively analyzed. Student t test, multivariate logistic regression, Cox proportional hazard ratio, receiver operating characteristics curves and Kaplan-Meier survival analysis were utilized for statistical analysis. Predictive powers of the statistical significant variables were compared using the area under receiver operating characteristics curve (AUC). p values <0.05 were considered statistical significant.

Results: SBP related in-hospital mortality rate was 43%. Multivariate regression analysis showed acute kidney injury, hepatic encephalopathy, positive ascitic culture, leucocyte count, bilirubin, serum glutamic oxaloacetic transaminase (SGOT), Child Pugh score, and Model for End stage Liver Disease Sodium (MELD-Na) were significantly associated with 50 day in-hospital mortality. The prognostic accuracy for acute kidney injury, MELD-Na and septic shock was 77, 74 and 71% respectively.

Conclusion: Acute kidney injury, MELD-Na and septic shock were predictors of 50 day in-hospital mortality in decompensated cirrhotic patients with SBP.

Keywords: spontaneous bacterial peritonitis, cirrhosis, acute kidney injury, model for end stage liver disease sodium

1. Introduction

SBP is defined as an ascitic fluid infection without an evident intra-abdominal surgically-treatable source [1]. SBP is a major complication of decompensated cirrhosis with ascites [2]. The diagnosis of SBP is established based on diagnostic paracentesis with an elevated ascitic fluid absolute polymorphonuclear leucocyte (PMN) count (≥250 cells/mm^3) and/or a positive ascitic fluid bacterial culture. The most common pathogens involved are Gram-negative bacteria (60%), usually *Escherichia coli* or *Klebsiella pneumonia* [3]. In about 25% of the cases, Gram-positive bacteria are involved, mainly Streptococcus species and Enterococci [3]. The prevalence of SBP is up to 30% in hospitalized cirrhotic patients with ascites [4]. Despite intensive management, the in-hospital mortality remains between 20 and 40% [5]. MELD scores have clinical utility in terms of predictive ability in SBP patients [6, 7]. Acute kidney injury (AKI) and septic shock are fairly common in patients with decompensated cirrhosis with ascites [8, 9]. Hence our study aimed to have a collective approach to determine common prognostic factors predicting SBP related in-hospital mortality. We also compared the predictive powers of AKI, MELD-Na and septic shock to predict 50 day in-hospital mortality.

2. Materials and methods

2.1. Patients

Retrospective analysis and review of 218 adult patients admitted to hepatology ICU with a diagnosis of SBP was done. The study was approved by the Institutional review Board and was conducted with the provisions of Declaration of Helsinki [10].

The diagnosis of cirrhosis was based on clinical, laboratory and imaging findings. SBP was diagnosed by diagnostic paracentesis in the presence of PMN ≥250 cells/mm^3 in the peritoneal fluid with positive culture report and the absence of the features suggestive of secondary bacterial peritonitis [11].

Data from patient's medical records were collected and tabulated. It comprises of demographics, etiology of liver disease, severity of liver disease, laboratory parameters, co-existing medical conditions (diabetes mellitus, hepatocellular carcinoma), previous medication use, organ failure, ascitic fluid analysis results, duration of ICU stay, and patient outcome. In culture-positive cases growth of the organisms and antibiotic sensitivity were recorded.

MELD-Na score was based on laboratory parameters (bilirubin, creatinine levels and INR) collected at admission and determined by using the Internet site MELD calculator [12]. Diagnostic ascitic tapping was done upon admission to ICU in all patients with ascites except in those with severe coagulopathy. Ascitic fluid was sent for differential cell count and culture. Blood sample was also sent for culture at admission in all patients. Antibiotics administered in patients based on previous antibiotic exposure and based on culture and sensitivity.

No patient underwent fluid restriction or hypertonic saline for management of dilution hyponatremia.

AKI was defined by AKIN (acute kidney injury network) criteria [8]. AKI was managed by intravenous vasopressors (terlipressin) and intravenous albumin infusions. The dose was titrated as-per response and tolerance. Intravenous albumin was used in all patients, with a minimal daily dose of 20 g and increased to up to 60 g/d [13], titrated by clinical monitoring and hourly urine output. We did not stratify renal dysfunction into hepatorenal syndrome (HRS) and non-hepatorenal syndrome. Renal replacement therapy (RRT) was used at the bedside to correct fluid overload, ascites, and electrolyte dysfunction. We did not consider advanced liver disease as a contraindication to RRT in our patient cohort.

We defined septic shock according to the American college of chest physicians/society of critical care medicine consensus conference [14].

2.2. Exclusion criteria

Patients with cirrhosis and ascites fluid PMN <250 cells/mm^3. Patients admitted from the community with SBP. Patients presented with ascites unrelated to cirrhosis. Patients with secondary peritonitis, variceal hemorrhage, advanced malignancy and HIV.

2.3. Statistical analysis

All statistical analyses were conducted using Stata version 14 for windows. The continuous clinical and biochemical variables and prognostic scores were expressed as mean ± standard deviation. All the variables were assumed to be normally distributed with equal variance. The means were compared using student's t test. Categorical variables were expressed as proportions and compared with logistics regression. All significant variables were analyzed using multivariate logistics regression. Cox proportional hazard model was used to analyze the hazard ratio of the predictors adjusted by age and gender. Receiver operating characteristics (ROC) curves were plotted for prognostic variables (MELD-Na, AKI and) to measure the predictive accuracy. The best cut-off point for MELD-Na was created using the ROC analysis to determine 50 day in-hospital mortality risk. The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), positive and negative likelihood ratio were calculated for each predictor variable so that patients could be correctly classified for each prognostic model. For all analyses, p value < 0.05 was considered statistically significant. STROBE checklist for retrospective analysis was performed.

3. Results

A total of 218 patients with decompensated cirrhosis with ascites and SBP were included in the study. Patients that were diagnosed with SBP for the first time were 97% (n = 211) with only 0.03% (n = 7) had more than one episode previously. The 50 day in-hospital mortality

Variables	Overall (n = 218)	Survivors (n = 124)	Deaths (n = 94)	P-value
Demographic data				
Age (yrs) mean ± SD	49.90 ± 12.52	49.86 ± 13.37	49.96 ± 11.37	0.950
Male (%)	177 (81.19%)	99 (79.84%)	78 (82.98%)	0.557
Etiology of cirrhosis (%)				
Ethanol	100 (45.87%)	48 (38.71%)	52 (55.32%)	0.689
Crypto/NAFLD	63 (28.90%)	38 (30.65%)	25 (26.60%)	0.104
HCV	23 (10.55%)	16 (12.905)	7 (7.45%)	0.068
Clinical data (%)				
Hepatocellular carcinoma	17 (7.80%)	9 (7.26%)	8 (8.51%)	0.733
Diabetes	47 (21.56%)	27 (21.77%)	20 (21.28%)	0.929
Acute kidney injury	99 (45.41%)	35 (28.23%)	64 (68.09%)	<0.001
Respiratory failure	10 (4.59%)	6 (4.84%)	4 (4.26%)	0.978
Hepatic encephalopathy	109 (50.0%)	50 (40.32%)	59 (62.77%)	0.001
Septic shock	28 (12.84%)	4 (3.23%)	24 (25.53%)	<0.001
Positive culture	48 (22.02%)	21 (16.94%)	27 (28.72%)	0.038
Laboratory data[*] (*mean* ± *SD*)				
Ascitic neutrophil count (cells/mm^3)	3346.07 ± 4700.60	3899.28 ± 5003.75	2616.30 ± 4182.81	0.040
Hemoglobin (g/dl)	9.42 ± 1.88	9.58 ± 1.77	9.21 ± 2.01	0.154
Platelet count (mmol/L)	128.24 ± 102.11	138.43 ± 111.25	115.03 ± 87.69	0.095
Leucocyte count (10^3/μL)	13.30 ± 9.35	11.86 ± 8.65	15.17 ± 9.92	0.009
Sodium (mEq/L)	132.14 ± 7.69	132.50 ± 6.54	131.67 ± 9.01	0.454
Bilirubin (mg/dL)	8.17 ± 8.81	5.85 ± 6.27	11.24 ± 10.61	<0.001
Albumin (g/dL)	2.32 ± 0.50	2.35 ± −0.48	2.28 ± 0.52	0.250
INR	2.31 ± 1.11	2.09 ± 1.08	2.59 ± 1.08	0.001
AST (U/L)	59.66 ± 109.81	79.23 ± 98.71	171.3 ± 321.94	0.003
ALT (U/L)	59.66 ± 109.81	46.49 ± 72.93	77.04 ± 143.41	0.041
Urea (mg/dL)	70.31 ± 52.42	62.24 ± 48.23	80.94 ± 55.98	0.008
Creatinine (mg/dL)	1.67 ± 1.29	1.58 ± 1.39	1.80 ± 1.15	0.217
Scores (*mean* ± *SD*)				
CTP (B/C)	10.72 ± 1.82	10.50 ± 1.95	11.02 ± 1.60	0.034

Variables	Overall (n = 218)	Survivors (n = 124)	Deaths (n = 94)	P-value
MELD	24.79 ± 8.28	22.20 ± 7.59	28.20 ± 7.94	<0.001
MELD-Na	27.53 ± 7.57	25.21 ± 7.44	30.59 ± 6.62	<0.001

*Results obtained on the day of diagnosis of SBP.

Table 1. Baseline characteristics of the hospitalized patients with spontaneous bacterial peritonitis in decompensated cirrhosis.

rate was 43.11% (n = 94). Median survival duration for those who died was 9 days. In univariate analysis AKI, hepatic encephalopathy, total leucocyte count, serum bilirubin, INR, SGOT, and MELD-Na are significantly associated with in hospital mortality in patients with SBP (**Table 1**).

The baseline characteristics of the demographics, etiology, clinical and laboratory data shown in **Table 1**. Mean age was 49.90 ± 12.52 years and the male was predominant (83%). Most common etiology of liver cirrhosis was ethanol induced (45.87%) followed by crypto/NAFLD (28.9%). Liver cirrhosis due to HCV infection constitute only 11% in our study. Total 50.0% patients (n = 109) had hepatic encephalopathy with 62.77% deaths (n = 59, p = 0.001). Overall 45.11% subjects (n = 99) had AKI who were hospitalized, out of which 68.09% (n = 64, p ≤ 0.001) died. Compared with survivors, the non-survivors had a higher proportion of septic shock (25.53 vs. 3.23%), p < 0.001. Mean leucocyte count, bilirubin, INR, AST were significantly higher in the persons who died in comparing to the survivors. Mean MELD-Na score was higher among the non-survivors compared with the survivors (30.59 ± 6.62 vs. 25.21 ± 7.44) (p < 0.001). It is surprising to notice that CTP (B/C) score was not different among the survivors and non-survivors. The mean CTP scores were high (10.72 ± 1.82).

On multivariate regression analysis, AKI (p = 0.001), septic shock (p = 0.029), MELD-Na (p<0.001) were found to be independent predictors of 50 day in-hospital mortality in patients with SBP (**Table 2**). Cox proportional hazard model showed the hazard ratio of AKI was 2.16 (95% CI = 1.36–3.42), septic shock (HR 1.73, 95% CI = 1.05–2.83) and MELD-Na (HR 1.1, 95% CI = 1.02–1.21). ROC curve for AKI, septic shock and MELD-Na had better prognostic

Variables	Hazard ratio* (95% CI)	P value
AKI	2.16 (1.36–3.42)	0.001
Septic shock	1.73 (1.05–2.83)	0.029
MELD-Na	1.06 (1.02–1.09)	<0.001

*Hazard ratio adjusted for age and gender.
AKI, acute kidney injury; MELD-Na, model for end-stage liver disease sodium.

Table 2. Cox proportional regression analysis of risk factors for SBP related in-hospital related mortality.

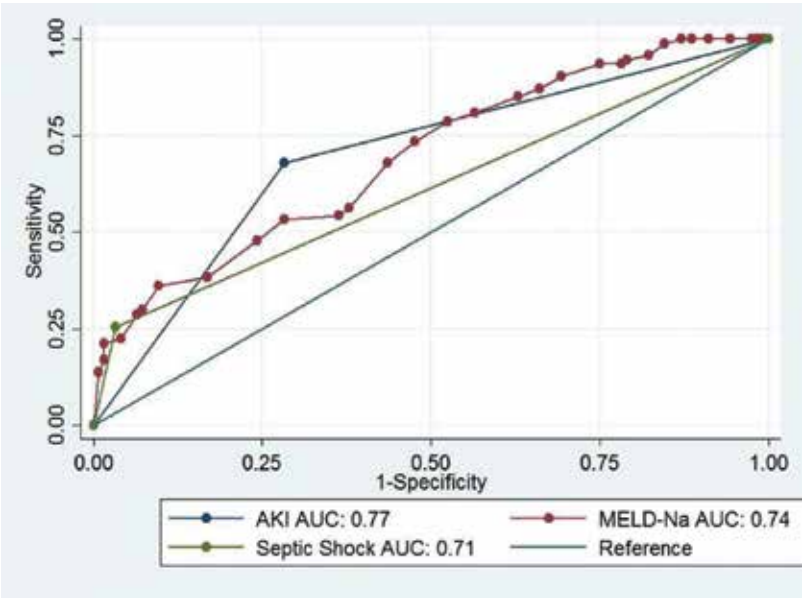

Figure 1. Receiver operator characteristic (ROC) curve for AKI, septic shock and MELD-Na had better prognostic accuracy for 50 day in-hospital mortality in patients with SBP.

Predictors	Sensitivity	Specificity	PPV	NPV	+LR	−LR
AKI	64.6	74.8	68.1	71.8	2.56	0.47
Septic shock	85.7	63.2	25.5	96.8	2.33	0.23
MELD-Na(28)[1]	92.9	60.3	24.5	97.9	2.34	0.12

[1]Cut off score for MELD-Na, PPV: positive predictive value, NPV: negative predictive value, +LR: positive likelihood ratio, −LR: negative likelihood ratio, AKI: acute kidney injury, MELD-Na: model for end stage liver disease sodium.

Table 3. Diagnostic accuracy of prognostic variables to predict SBP related in-hospital mortality.

accuracy for 50 day in-hospital mortality in patients with SBP (**Figure 1**). AKI had highest Area Under Curve (AUC) 0.77, 95% confidence interval (95% CI = 0.71–0.83), followed by MELD-Na (AUC 0.74, 95% CI = 0.69–0.79), septic shock (AUC 0.71, 95% CI = 0.65–0.77). **Table 3** reported the sensitivity, specificity, PPV, NPV, positive likelihood ratio (+LR) and negative likelihood ratio (−LR) for these predictors. The cut off for MELD-Na derived from the ROC with the best ability to predict 50 day in-hospital mortality in decompensated cirrhotic patient with SBP was 28, with sensitivity 92.9%, specificity 60.3%, and NPV of 97.9%. The Kaplan-Meier survival analysis was plotted for the 50 day survival in SBP patients along with individual prognostic variables like AKI, MELD-Na, and septic shock (**Figure 2**).

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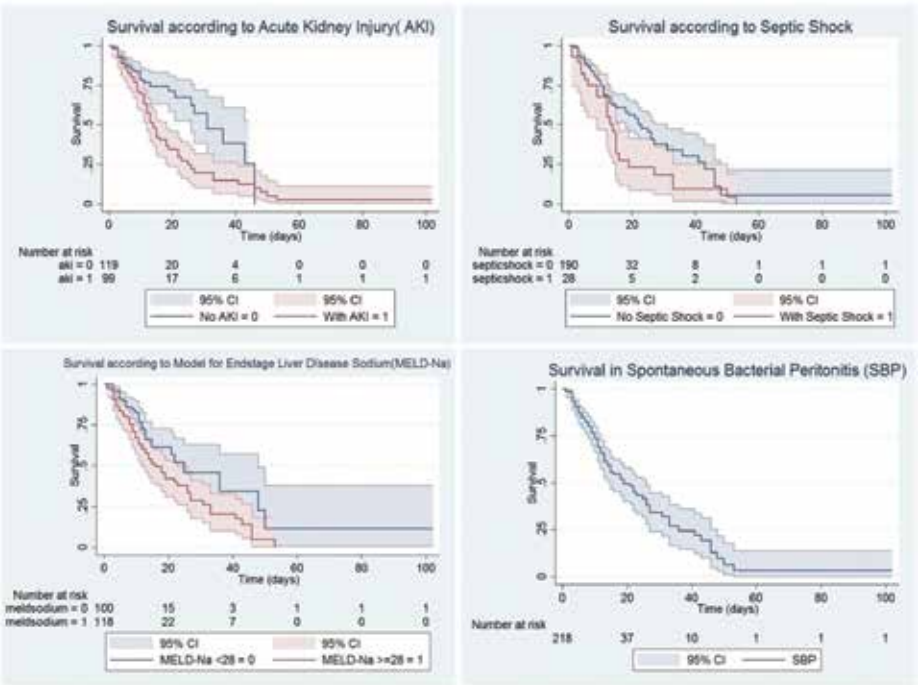

Figure 2. Kaplan-Meier survival analysis was plotted for the 50 day survival in SBP patients along with individual prognostic variables like AKI, MELD-Na, and septic shock.

4. Discussion

The prevalence of SBP in outpatients has been reported to be 1.5–3.5% [15]. The prevalence among in-patients is around 10% [16]. Half of the episodes of SBP are nosocomial related. In our retrospective observational study 43% (n = 93) of the decompensated cirrhotic patients with SBP died within 50 day of hospital admission. Our study considered a variety of prognostic factors that can be used to predict mortality in hospitalized patient with SBP. Our findings support previous study results that variables like hepatic encephalopathy, total leucocyte count, serum bilirubin, SGOT, INR, Child Pugh scores are significantly associated with mortality [5, 6]. The MELD score was found to be an independent predictor of death in cirrhotic patients [7] including those waiting for liver transplantation. MELD-Na is a better prognostic model compared with MELD model [17] for predictive accuracy of mortality in liver cirrhosis. Serum creatinine level measurement for renal dysfunction in decompensated liver cirrhosis is erroneous. It can be due to decrease in creatinine production in liver and associated muscle wasting due to malnutrition [18]. We found that AKI, MELD-Na and septic shock are significant in terms of predicting mortality. We overlooked other predictable variables like total leucocyte count, serum bilirubin, INR to avoid confusion and complexity as those were the components in our predictive model like MELD-Na and septic shock.

Our study demonstrated that AKI has the single best predictive ability (AUC = 0.77) followed by MELD-Na (AUC = 0.74) and septic shock (AUC = 0.71). We set a cut-off value for MELD-Na to be 28. It has sensitivity 92.9% and NPV of 97.9%. AKI has the highest hazards of mortality (HR 2.16, 95% CI 1.36–3.42) followed by septic shock (HR 1.73, 95% CI 1.05–2.83) and MELD-Na (HR 1.06, 95% 1.02–1.09). We plotted graph of Kaplan-Meier survival analysis. The graph illustrated AKI, MELD-Na, and septic shock as predictors for the 50 day in-hospital mortality in decompensated patients with SBP. We hope that these prognostic variables can help in the further improvement of the quality of care of hospitalized SBP patients. The cut-off value 28 for MELD-Na can be utilized to stratify patients diagnosed with SBP into high risk category upon hospital admission.

Diagnosis of SBP is based on the demonstration of an absolute number of polymorphonuclear cells in ascitic fluid equal to or greater than 250/mm^3 with culture positivity. There is a controversy regarding antibiotic therapy in culture positivity with normal ascitic fluid PMN count (bacteriascites). Runyon et al. recommend antibiotic treatment only if the patient shows signs of infection [2]. The first-line of choice antibiotics for treatment of SBP include third generation cephalosporins, amoxicillin-clavulanic acid, ciprofloxacin, and ofloxacin [19]. There is increasing evidence of antibiotic resistance [20].

In our study ascitic fluid culture is positive in 40% of all cases. The most common growth include Gram-negative bacteria (GNB), mostly *Escherichia coli* and Gram-positive cocci (mainly streptococcus species and enterococci) [3]. The epidemiology of bacterial infections differs between community-acquired (in which GNB infections predominate) and nosocomial infections (in which Gram-positive infections predominate) [3]. The infections resistant to first lines of antibiotics are usually caused by *Enterococcus faecium* and extended-spectrum β-lactamase (ESBL) organism like Enterobacteriaceae [21]. There are compelling evidence that nosocomial SBP should be treated with carbapenems or with tigecycline [22].

We included only nosocomial SBP patients in our study because most of the ICU admissions includes referred patients from other hospitals, with a variable but inconsistent antibiotic exposure. Only a minority of our patients are admitted directly from the community, and usually to the wards and not to the ICU. Hospital-acquired infections due to a higher incidence of multidrug resistance (third-generation cephalosporins) were an independent predictor of death [23]. These results are in keeping with recent data showing higher rates of drug resistance in patients with nosocomial SBP and increased rates of and death in patients with multidrug resistance [24].

Dr. Garcia-Tsao recently reviewed 18 studies, and reported that the most common predictors of death were renal dysfunction, lack of SBP resolution, immunosuppressive factors, and hospital-acquired SBP [24]. It identified renal dysfunction and levels of blood urea nitrogen and creatinine as the most important variables. The mortality rate among patients with renal dysfunction was 67%, compared with only 11% of patients who maintained normal renal function. Renal dysfunction was defined somewhat variably in the studies, but most defined it as a creatinine level greater than 1.5 mg/dL.

Our study has certain strengths and limitations. The results clearly show that AKI has greater predictive ability than septic shock and MELD-Na as far as 50 day in-hospital mortality in SBP patient is concerned. Our study did not account for the stages of ascites. We did not stratify

our patients according to different stages of AKI as per AKIN criteria. We did not take HRS into account in our study. The standard first line antibiotics were not used in the treatment of SBP. The choice of antibiotics coverage based of culture sensitivity and previous exposure. We did not thoroughly evaluate the antibiotic resistance in SBP patients who are culture positive at the baseline. We included only nosocomial acquired SBP. Most of our patients presented with advanced decompensated liver cirrhosis at the time of SBP diagnosis as it is a tertiary care center. The advanced liver cirrhosis was assessed by lower serum albumin, high serum bilirubin and INR values. As an observational study we were unable to assess the impact of volume expansion and SBP specific therapy on patient outcome. Our study is a single center study, these findings needed to be supplemented by multicenter prospective studies.

Our study findings can guide in advanced liver cirrhosis patients that would benefit them from intensive management where liver transplant is not feasible.

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References

[1] Rimola A, García-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, Inadomi JM. Diagnosis treatment and prophylaxis of spontaneous bacterial peritonitis: A consensus document. International Ascites Club. Journal of Hepatology. 2000;**32**:142-153. DOI: 10.1016/S0168-8278(00)80201-9

[2] Such J, Runyon BA. Spontaneous bacterial peritonitis. Clinical Infectious Diseases. 1998;**27**(4):669-674 quiz 675-6

[3] Dever JB, Sheikh MY. Review article: Spontaneous bacterial peritonitis-bacteriology, diagnosis, treatment, risk factors and prevention. Alimentary Pharmacology & Therapeutics. 2015;**41**(11):1116-1131. DOI: 10.1111/apt.13172

[4] Gunjaca I, Francetić I. Prevalence and clinical outcome of spontaneous bacterial peritonitis in hospitalized patients with liver cirrhosis: A prospective observational study in central part of Croatia. Acta Clinica Croatica. 2010;**49**(1):11-18

[5] Thuluvath PJ, Morss S, Thompson R. Spontaneous bacterial peritonitis in-hospital mortality, predictors of survival, and health care costs from 1988 to 1998. The American Journal of Gastroenterology. 2001;**96**:1232-1236. DOI: 10.1111/j.1572-0241.2001.03708.x

[6] Dănulescu RM, Stanciu C, Trifan A. Evaluation of prognostic factors in decompensated liver cirrhosis with ascites and spontaneous bacterial peritonitis. Revista Medico-Chirurgicală a Societăţii de Medici şi Naturalişti din Iaşi. 2015;**119**(4):1018-1024

[7] Nobre SR, Cabral JE, Gomes JJ, Leitão MC. In-hospital mortality in spontaneous bacterial peritonitis: A new predictive model. European Journal of Gastroenterology & Hepatology. 2008;**20**:1176-1181. DOI: 10.1097/MEG.0b013e32830607a2

[8] de Araujo A, Alvares-da-Silva MR. Akin criteria as a predictor of mortality in cirrhotic patients after spontaneous bacterial peritonitis. Annals of Hepatology. 2014;**13**(3):390-395

[9] Moreau R, Hadengue A, Soupison T, Kirstetter P, Mamzer MF, Vanjak D, et al. Septic shock in patients with cirrhosis: Hemodynamic and metabolic characteristics and intensive care unit outcome. Critical Care Medicine. 1992;**20**(6):746-750

[10] WMA declaration of Helsinki-ethical principles for medical research involving human subjects [internet]. 2013. Available from: https://www.wma.net/what-we-do/education/medical-ethics-manual [Accessed: 2018-03-19]

[11] Runyon BA. The evolution of ascitic fluid analysis in the diagnosis of spontaneous bacterial peritonitis. The American Journal of Gastroenterology. 2003;**98**(8):1675-1677

[12] MELDNa/MELD-Na Score for Liver Cirrhosis [Internet]. 2016. Available from: https://www.mdcalc.com/meldna-meld-na-score-liver-cirrhosis [Accessed: 2018-03-19]

[13] de Mattos A. Current indicators for use of albumin in the treatment of cirrhosis. Annals of Hepatology. 2011;**10**(Suppl. 1):S15-S20

[14] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. DOI: 10.1378/chest.101.6.1644

[15] Chu CM, Chang KY, Liaw YF. Prevalence and prognostic significance of bacterascites in cirrhosis with ascites. Digestive Diseases and Sciences. 1995;**40**(3):561-565

[16] Terg R, Gadano A, Cartier M et al. Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: A retrospective study. Liver International. 2009;**29**:415-19

[17] Musskopf MI, Fonseca FP, Gass J, de Mattos AZ, John JA, de Mello Brandão AB. Prognostic factors associated with in-hospital mortality in patients with spontaneous bacterial peritonitis. Annals of Hepatology. 2012;**11**(6):915-920

[18] MacAulay J, Thompson K, Kiberd BA, Barnes DC, Peltekian KM. Serum creatinine in patients with advanced liver disease is of limited value for identification of moderate renal dysfunction: Are the equations for estimating renal function better? Canadian Journal of Gastroenterology. 2006;**20**(8):521-526

[19] European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology. 2010;**53**(3):397-417. DOI: 10.1016/j.jhep.2010.05.004

[20] Cheong HS, Kang CI, Lee JA, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clinical Infectious Diseases. 2009;**48**:1230-1236. DOI: 10.1086/597585

[21] Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. Journal of Hepatology. 2012;**56**:825-832. DOI: 10.1016/j.jhep.2011.11.010

[22] Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, Pavesi M, Sola E, Moreira L, Silva A, Seva-Pereira T, Corradi F, Mensa J, Ginès P, Arroyo V. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: A prospective study. Hepatology. 2012;**55**:1551-1561. DOI: 10.1002/hep.25532

[23] Umgelter A, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. Infection. 2009;**37**:2-8. DOI: 10.1007/s15010-008-8060-9

[24] Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clinical Gastroenterology and Hepatology. 2011;**9**(**3**):260-265. DOI: 10.1016/j.cgh.2010.11.038

Hepatocellular Carcinoma

Chapter 6

Stereotactic Body Radiation Therapy for Hepatocellular Carcinoma in Cirrhotic Liver

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Additional information is available at the end of the chapter

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Abstract

In the medically inoperable patients with solitary hepatocellular carcinoma (HCC), local therapies, such as radiofrequency ablation and transarterial chemoembolization, are used as alternatives. However, several factors, including anatomic and vascular variants, make procedures more challenging. Radiotherapy has historically been used as a palliative option for unresectable HCC. However, recent advances in modern radiotherapy, such as stereotactic body radiation therapy (SBRT), have dramatically increased the use of radiotherapy as a curative modality, particularly in cases ineligible for local ablation therapy or surgical resection. SBRT is a modern approach for delivering ablative high doses of irradiation in small volumes. SBRT in liver tumors, including HCC, provided local control with potential survival benefits in patients with inoperable status. However, the following issues remain to be addressed: the difference between primary and metastatic liver cancers; SBRT-related toxicity and prevention; pathological features of liver cancers; and potential SBRT strategies, including radiobiology-based SBRT and SBRT combined with immunotherapy. We summarized the effectiveness of SBRT and patient tolerance of the therapy. In addition, we present the current status and future perspective of SBRT as a treatment option for HCC.

Keywords: radiotherapy, stereotactic body radiation therapy, stereotactic ablative radiotherapy, hepatocellular carcinoma, cirrhosis, liver

1. Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver [1]. Liver cancers have the seventh highest age-adjusted incidence rate in the world, with 0.8 million cases diagnosed a year [2]. The development of cirrhosis is associated with a high risk for developing HCC with most common risk factors including alcohol, viral hepatitis such

as hepatitis C virus (HCV), and nonalcoholic fatty liver disease (NAFLD). Due to the wide prevalence of HCC, it carries a significant economic burden on society at large, especially in the East Asian countries that have hepatitis B virus (HBV). Surveillance programs halve also been implemented to screen for HCC in high-risk individuals, which is more cost-effective than the treatment of HCC. Hepatotropic viruses such as HBV and HCV have a strong association with the development of HCC; thus, the worldwide distribution of HCC mirrors the distributions of such viral infections [3]. Around 80–90% of HCC cases occur in the setting of underlying cirrhosis [4]. In addition, there is an incremental effect of the presence of more than one risk factor responsible for HCC as the presence of HBV/HCV coinfections increases the risk of HCC by two- to sixfolds. Similarly, alcohol abuse further increases this risk [5, 6]. Subsequently, we describe the role of radiotherapy in the treatment of HCC, including conventional to modern techniques, possible beneficial cases of radiotherapy, and future direction of liver stereotactic body radiation therapy (SBRT).

2. General approaches and conventional radiotherapy in the treatment of HCC

The initial approach in the management of HCC is to determine if either surgical resection or liver transplantation is feasible and best survival. The Barcelona Clinic Liver Cancer staging system is the most accepted staging system in clinical settings [7]. Orthotopic liver transplantation is the most efficient option for the treatment of HCC even though the insufficient number of donors makes challenging [8]. Therefore, local therapy is anticipated to be not only a bridging therapy but also a radical therapy in the treatment of HCC. Surgical resection is the standard local therapy for HCC [7]. Since the majority of HCC cases develop in cirrhotic patients, surgical interventions can become challenging, and the treatment has been directed toward liver transplantation. Other local therapies, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), are used as alternatives in patients with HCC [7–9]. However, radical treatment for liver tumors can be challenging due to poor liver function, tumor location, and anatomical barriers. Furthermore, the preservation of residual liver function is required, as liver tumors have a high recurrence potential [9].

Radiotherapy is a local treatment modality and has also been used for palliative care in liver tumors. Conventional radiotherapy has been used approximately 50 Gy in a conventional fractionated schedule which could lead to a response rate as approximately 50–70% [10–14]. High doses of radiation, which are required for HCC, would sometimes exceed the levels tolerated by the background liver [15, 16]. However, modern radiotherapies, including stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), have recently attracted increasing attention as a therapeutic modality for various malignancies including HCC and have dramatically increased the use of radiation therapy as a curative modality [17–40]. However, certain issues regarding the current use of SBRT in HCC need to be addressed (e.g., ideal prescription doses, prevention of adverse events, and possible microscopic extension). In this chapter, we document the clinical utility and the present status of SBRT in the management of HCC, including clinical messages and pitfalls in liver cirrhosis and the probable treatment-related toxicities and their prevention, and summarize recent significant updates on biology-based SBRT strategies.

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3. SBRT for HCC

The use of SBRT for extracranial tumors was developed by Blomgren et al. [17]. The major feature that distinguishes SBRT from conventional radiation treatment is the delivery of large doses of radiation in a few fractions, which results in a high biologically effective dose (BED). In addition, Zheng et al. have reported that a shortened delivery time could significantly increase the cell killing using *in vitro* experimentation [41]. The use of a high precision technique is critical to deliver a high dose of radiation to the target and keep rapid fall-off doses away from the target, thereby achieving a maximum treatment efficacy with minimal toxicity to normal tissues [42]. SBRT is now widely accepted as a treatment option for lung and liver tumors characterized by their small size and limited numbers [43].

Current advantages and challenges of SBRT in the liver are presented in **Table 1**. The clinical outcomes of SBRT for HCC in the previous reports are shown in **Table 2**. SBRT has been reported to provide 1-, 2-, and 3-year local control rates of 56–100, 53–95, and 51–92%, and 1-, 2-, and 3-year survival rates of 32–100, 55–100, and 21–82% for HCC, respectively [19–38]. **Figure 1** indicates the local control and overall survival after SBRT, $BED_{10} \geq 75$ Gy in ≤10 fractions (e.g., 40 Gy/4 fr), for HCC at our institute. **Figure 2** indicates a typical course of SBRT for HCC in cirrhotic liver. Recent reports indicated that SBRT was as effective as TACE and RFA, although there are only a small number of randomized trials examining the use of SBRT in HCC [34, 35, 38]. However, additional prospective studies involving large sample sizes are required to consolidate the evidences on SBRT with aim to standardize liver SBRT.

Advantages
• High possibility of local control
• Minimally invasive treatment modality, no requirements for anesthesia or injections
• High possibility to overcome anatomical limitations, including poorly defined tumors on ultrasound and tumors which are difficult to puncture
• No concern regarding the location close to major vessels, including the portal vein, inferior vein cava, and bile duct
• Possible to treat complicated forms of tumors, particularly using IMRT
• Short treatment term (usually within 2 weeks), possibility of benefit to the patient's quality of life and reduced medical cost
• Possibility to enhance the immune reaction to tumors
Current issues
• Poor outcomes and high possibility of toxicity with large tumors
• Challenges involved in the treatment of tumors close to critical organs, such as the gastrointestinal tract
• Effects of re-irradiation are unclear
• Inaccuracy due to respiration and the presence of ascites
Abbreviations: SBRT = stereotactic body radiation therapy; IMRT = intensity modulated radiation therapy.

Table 1. Features of SBRT for liver tumors.

Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Kwon et al. [19]	2010	Retrospective	42	33 (30-39) Gy/3 fr (70–85% isodose line covered the PTV)	69.2 (60-89.7)	29	1-year 72% 3-year 68%	1-year 92.9% 3-year 58.6%	35.7% G1 Constitutional symptoms 31.0% G1-2 Elevated liver enzyme 19.0% G1–2 Leukopenia 2.4% G1 hyperbilirubinemia and ALP	2.4% (1 patient) G4 Liver failure
Seo et al. [20]	2010	Retrospective	38	33-57 Gy/3 fr or 40-44 Gy/4 fr (60.5% patients received 39–57 Gy/3 fr)	69.3-165.3 or 80-92.4 (89.7–165.3)	15	1-year 78.5% 2-year 66.4%	1-year 68.4% 2-year 61.4% 3-year 42.1%	(57.9% G1-2 acute toxicities) 10.5% G1-2 hyperbilirubinemia 2.6% G1 albumin 5.3% G1 AST/ALT 2.6% G1 ALP 44.7% G1–2 Nausea, vomiting 7.9% G1 anorexia 13.2% G1–2 abdominal pain 2.6% G2 Paralytic ileus 2.6% G2 radiation dermatitis	2.6% G3 soft tissue toxicity (the right upper quadrate of the abdomen)

Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Andolino et al. [21]	2011	Prospective	60	Child-Pugh A (60%): 44 Gy/3 fr Child-Pugh B (40%): 40 Gy/5 fr (80% isodose line, encompassing PTV)	Child-Pugh A: 108.5 Child-Pugh B: 85.5	27	3-year 90%	3-year 67%	n = 56 (93%) 23.2% G1-2 fatigue, nausea, and/or right upper quadrant discomfort	1.8% G2 chest wall toxicity 16.1% G3 liver enzymes elevation and/or hyperbilirubinemia 16.1% G3 thrombocytopenia 3.6% PT-INR 12.5% G3 albumin (17 patients of 21 patients with G3 hypoalbuminemia preexisting Grade 2 dysfunction) 1.8% G4 thrombocytopenia and hyperbilirubinemia 20.0% Child-Pugh classification progression
Kang et al. [22]	2012	Prospective	47	57 (42-60) Gy/3 fr (70–80% isodose line covered at least 97% of the PTV)	165.3 (100.8–180.0)	17	2-year 94.6%	2-year 68.7%	4.3% G3 hyperbilirubinemia (pre-existing Grade 1 or 2 hyperbilirubinemia and/or thrombocytopenia) 10.6% G3 Thrombocytopenia 4.3% G3 Ascites 6.4% G3, 4.3% G4 Gastrointestinal ulcer (3 of 5 patients had pre-existing ulcer, 2 patients experienced Grade 4 gastric ulcer perforation at 7 months and 10 months after SBRT)	

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Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Huang et al. [23]	2012	Retrospective	36	37 (25-48) Gy/4-5 fr (70–83% isodose line, encompassing PTV)	NA(31.2–105.6)	14	1-year 87.6% 2-year 75.1%	2-year 64%	36.1% G1-2 fatigue 25.0% G1-2 anorexia 13.9% G1-2 nausea/ vomiting 5.6% G1-2 abdominal pain 2.8% G2, 2.8% G3 gastric ulcer (Both of 2 patients had gastritis before SBRT 2.8% G1 musculoskeletal	5.6% RILD (2 patients with Child-Pugh B)
Honda et al. [24]	2013	Retrospective	30	48 Gy/4 fr (86.7% of patients) or 60 Gy/8 fr (13.3% of patients) (isocenter prescription)	105.6 or 105.0	12.3	CR:96.3%	1-year 100% 2-year 100%	93.3% G1-2, 6.7% G3 leukocytopenia 96.7% G1-2, 3.3% G3 thrombocytopenia 100% G1–2 hemoglobin G1-2 hyperbilirubinemia G1 AST/ALT G1 ALP	3.3% Child-Pugh class progression

Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Bae et al. [25]	2013	Retrospective	35	45 (30-60) Gy/3-5 fr (56–83% isodose line of the maximum dose or D95 prescription of 91–100% prescription doses for PTV)	101 (58–180)	14	1-year 69% 3-year 51%	1-year 52% 3-year 21%	(23% of patients experienced grade ≥ 3 toxicity) 8.6% G3 AST (1 patient also had grade 3 hyperbilirubinemia, all patients had pre-existing grade 2 elevation of AST or hyperbilirubinemia and experienced progression of intrahepatic HCC) 2.9% G3 Hepatic failure (1 month after SBRT) 2.9% G3 colonic ulcer (1 month after SBRT)	2.9% G4 Myelitis (18 months after SBRT, spine Dmax = 31 Gy/4 fr) 2.9% G3 gastric ulcer perforation (7 months after SBRT) 2.9% G5 duodenal ulcer bleeding (5 months after SBRT) 2.9% G4 colonic ulcer (3 months after SBRT)

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Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Bujold et al. [26]	2013	Prospective	102	36 (24-54) Gy/6 fr	57.6 (33.6–102.6)	31	1-year 87%	NA (median 17 months)	1.0% G3 fatigue 10.9% AST/ALT 3.0% G3, 2.0% G4 hyperbilirubinemia 1.0% G3 creatinine 2.0% G3 hemoglobin 1.0% G3 leukocytes 9.0% G3 platelets 29% (3-month), 6% (12-month) Child-Pugh class progression 46% (3-month), 17% (12-month) Child-Pugh score progression 1.0% G3, 1.0% G4, 4.9% G5 Liver failure 1.0% G5 cholangitis (HCC invaded the common bile duct) 1.0% G3, 1.0% G5 gastritis/gastrointestinal bleeding (G5 occurred 7.7 months after SBRT)	
Jang et al. [27]	2013	Retrospective	82 (95 HCC)	51 (33-60) Gy/3 fr (70–80% isodose line covered at least 97% of the PTV)	137.7 (69.3–180.0)	30	2-year 87% 5-year 82%	2-year 63% 3-year 39%	1.2% G3 hyperbilirubinemia (pre-existing G1) 2.4% G3 ascites 7.3% non-classic RILD (worsening of CTP score by ≥ 2, ≤ 3 months after SBRT, 2 of 6 with disease progression) 1.2% G3 soft tissue toxicity (this patient had a large tumor near the skin) 6.1% G3–4 GI toxicity (gastroduodenal ulcer in 2 patients, clonic ulcer in 1 patient, and gastroduodenal perforation in 2 patients, gastroduodenal perforation in 2 patients)	

Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Sanuki et al. [28]	2014	Retrospective	185	Child-Pugh A (74.1%): 40 Gy/5 fr Child-Pugh B (25.9%): 35 Gy/5 fr (70–80% isodose line, encompassing PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	24	1-year 99% 2-year 93% 3-year 91%	1-year 95% 2-year 83% 3-year 70%	4.9% mild fatigue 3.2% G3 laboratory abnormalities (prior to SBRT)	10.3% Child-Pugh score progression (by two points) 1.1% G5 liver failures (both 2 patients were classified as Child-Pugh B before SBRT 3, 6 months after SBRT)
Takeda et al. [29]	2014	Retrospective	63	Child-Pugh A (69.8%): 40 Gy/5 fr Child-Pugh B (30.2%): 35 Gy/5 fr (70 or 80% isodose line, encompassing PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	31.1	1-year 100% 2-year 95% 3-year 92%	1-year 76% 2-year 87% 3-year 73%	*n = 63 7.9% mild fatigue 15.8% G3 subacute liver toxicity (6.3% before SBRT)	*n = 63 20.6% G3 liver toxicity
Yamashita et al. [30]	2014	Retrospective	79	48 Gy/4 fr (40 Gy/4 fr-60 Gy/10 fr)	96 (75-106)	15.9	2-year 74.1%	2-year 52.9%	n = 130 (79 HCC, 51 liver metastases) 2.3% G2 gastrointestinal toxicity (gastric inflammation in 2 patients 1 month after SBRT, gastric ulcer in 1 patient; 27 months after SBRT) 3.1% G3 gastrointestinal toxicity (duodenal ulcer 17 months, intestinal tract bleeding 5, 6 months, transverse colon ulceration 5 months, respectively, after SBRT) 0.8% G4 gastro-duodenal artery rupture (5 months after SBRT) 0.8% chest wall pain (combined with TACE)	

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Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Culleton et al. [31]	2014	Prospective	29	34.4 (20.9–48.7) Gy/6 (5-15) fr (Mean dose to PTV) or 30.9 (197-46.8) Gy/6 (5-15) fr (D95 prescription for PTV)	54.1 (28.2–88.2) 46.8 (26.2–83.3) (Calculated presupposed with 6 fractions)	NA	6-month 69.7% 1-year 55.5%	1-year 32.3% (median 7.9 months)	48.3% G1-2 fatigue 20.7% G1 nausea 10.3% G1-2 vomiting 10.3% G1-2 diarrhea 10.3% G1 abdominal pain 10.3% G1-2 abdominal distension Child-Pugh score progression (24.1, 24.1, 10.3% by 1 point, 2 points, 3 points, respectively, at 1 month after SBRT) 17.2% G3 thrombocytopenia (3 months after SBRT) 6.9% G3, 3.4% G4 transaminase elevation (1 month after SBRT) 3.4% G4 AST (3 months after SBRT)	
Huertas et al. [32]	2015	Retrospective	77 (97 HCC)	45 Gy/3 fr (prescribed to the 80% isodose line, encompassing PTV)	112.5	12	1-year 99% 2-year 99%	1-year 81.8% 2-year 56.6%	1.3% G1, 1.3% G2 asthenia 2.6% G1, 2.6% G2, 1.3% G3 ascites 1.3% G1 rib pain 1.3% G1 anorexia 2.6% G1 nausea 3.9% G1 epigastric pain 1.3% Classic RILD 3.9% Non-classic RILD 1.3% G5 Hematemesis	1.3% G2 asthenia 1.3% G1 radiation dermatitis 2.6% G1 nausea 2.6% G1, 3.9% G2, 3.9% G3 ascites 1.3% G2 colic ulcer 1.3% G3, 1.3% G4 gastric ulcer

Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Takeda et al. [33]	2016	Prospective	90	Child-Pugh A: 40 Gy/5 fr Child-Pugh B: 35 Gy/5 fr (prescribed to the 60–80% isodose line, encompassing PTV, D95 prescription for PTV)	Child-Pugh A: 72.0 Child-Pugh B: 59.5	41.7	3-year 96.3%	3-year 66.7%	2.2% transaminase elevation 5.6% thrombocytopenia 8.9% Child-Pugh score progression (by two points)	
Wahl et al. [34]	2016	Retrospective	63	30 or 50 Gy/3 or 5 fr (D99.5 prescription for PTV, the 75 to 85% isodose line encompassing PTV	100 (NA)	13.0	1-year 97.4% 2-year 83.8%	1-year 74.1% 2-year 46.3%	1.6% G3 RILD 1.6% G3 gastrointestinal bleeding 1.6% G3 worsening ascites	8.3% G3 luminal gastrointestinal toxicity (at 2 years after SBRT) 3.3% G3 biliary toxicity (at 2 years after SBRT) *Child-Pugh score progression by average 1.2 points) (at 12 months after SBRT)
Su, et al. [35]	2017	Retrospective	82	42–48 Gy/3–5 fr (67 (57–80) % isodose line encompassing PTV)	NA (77.3–124.8) (Calculated presupposed with 42 Gy/5 fr–48 Gy/3 fr)	33.0	NA (one patient experienced local progression) (PFS; 1-year 81.4%, 3-year 50.2%, 5-year 40.7%	1-year 96.3% 3-year 81.8% 5-year 70.0%	4.9% G1, 3.7% G2, 1.2% G3 nausea 1.2% G1, 1.2% G2, 2.4% G3 weight loss 3.7%, G1, 1.2% G2 fatigue 3.7% G1 hyperbilirubinemia 3.7% G1 ALT 4.9% G1 anemia 6.1%, 3.7% Child-Pugh progression (1, 2 points, respectively)	

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Author [Ref]	Year	Prospective/ retrospective	Patient number	Total dose/ fraction (median, range)	BED_{10} (Gy)	Median follow-up (range) (months)	Local control	Overall survival	Adverse events	
									Acute response	Late response
Lo et al. [36]	2017	Retrospective	89	25–60 Gy/4-6 fr (40 Gy/5 fr (19 patients), 45 Gy/5 fr (18 patients), 50 Gy/5 fr (14 patients))	72 (40 Gy/5 fr), 85.5 (45 Gy/5 fr), 100 (50 Gy/5 fr)	NA	3-year 78.1%	1-year 45.9% 3-year 24.3%	24.7% G1, 4.5% G2 fatigue 13.5% G1, 2.2 G2 anorexia 13.5% G1, 12.4% G2, 1.1% G3 nausea/ vomiting 4.5% G1 abdominal distension 19.1 G1, 7.9% G2, 2.2% G3 abdominal pain 3.4% G2, 2.2% G3 gastritis/gastric ulcer 2.2% G1, 4.5% G2 duodenal ulcer 1.1% G1, 2.2% G2 diarrhea 1.1% G1, 2.2% G2 dermatitis 11.2% RILD (1.1% classic RILD, 9.0% non-classic RILD (including 2 patients developed fatal non-classic RILD), 1.1% fulfilled the criteria of both types)	
Uemoto, et al. [37]	2018	Retrospective	121 (146 HCCs)	45 (30–64) Gy/5 (4-20) fr	80 (48–106)	21	2-year 91.5%, 5-year 89.8%	2-year 73.7%, 5-year 57.0%	0.7≤G2, 0.7% G3 cholangiectasis 1.5% G1 pneumonitis 0.7% mucositis 0.7% G1 rib fracture 25.2% ascites 2.2 jaundice 1.5% pleural effusion (no hematological abnormality changed from the baselines)	

Abbreviations: NA = not applicable, HCC = hepatocellular carcinoma, SBRT = stereotactic body radiation therapy, NA = not applicable; BED = biologically effective dose, G = grade, PTV = planning target volume, AST = aspartate transaminase elevation, ALT = alanine transaminase elevation, ALP = alkaline phosphatase elevation, PT-INR = prothrombin time-international normalized ratio prolongation, RILD = radiation-induced liver disease, TACE = transcatheter arterial chemoembolization, PFS = progression-free survival.

Table 2. Summary of studies of hepatocellular carcinoma.

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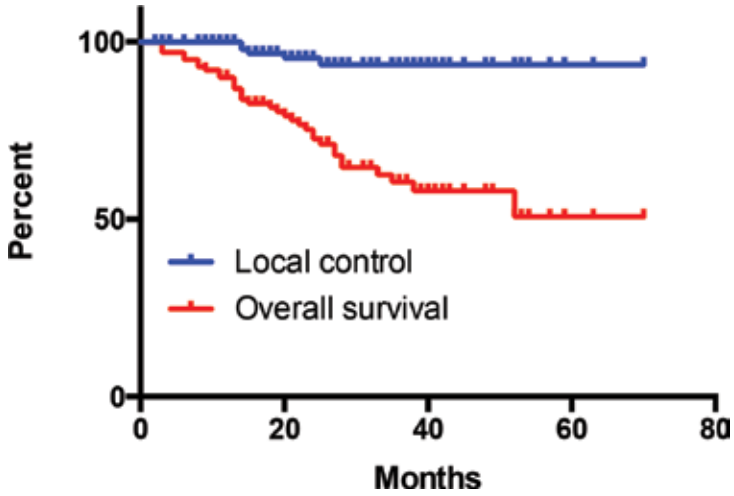

Figure 1. Local control and overall survival of HCC after SBRT. Local control (LC) and overall survival (OS) were described using the Kaplan Meier method in 100 patients with 116 HCCs underwent SBRT of BED_{10} ≥75 Gy in ≤10 fractions, between July 2007 and August 2016 at Miyakojima IGRT Clinic (Osaka, Japan, approval no. 9). The 1-, 2- and 3-year LC rate was 100.0, 95.4 and 93.5%, respectively. The 1-, 2- and 3-year OS rate was 83.7, 72.6 and 60.5%, respectively. Abbreviations: HCC, hepatocellular carcinoma; SBRT, stereotactic body radiation therapy.

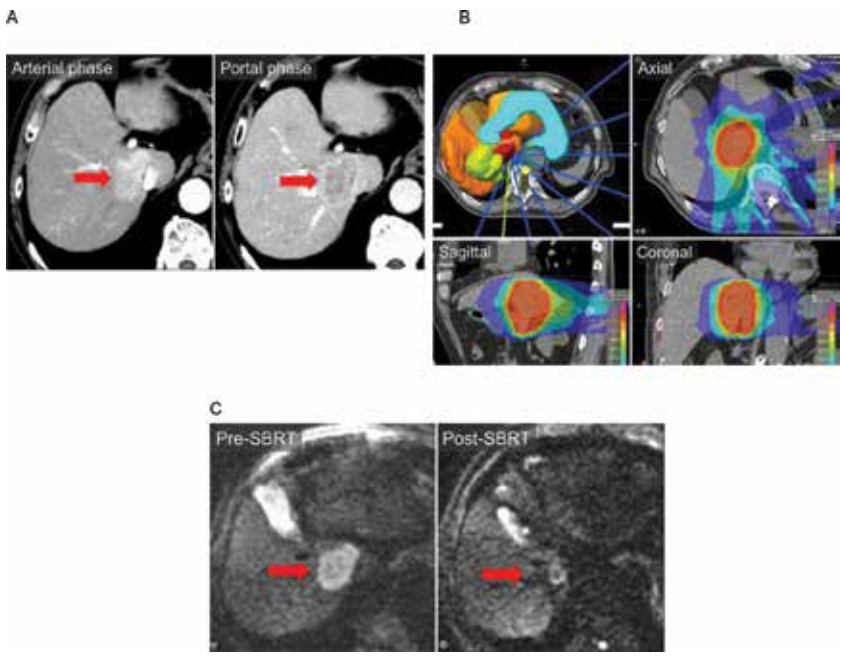

Figure 2. Typical course of SBRT for HCC in cirrhotic liver. An 86-year-old man developed HCC in S8. HCC with 50 mm in diameter existed (A, contrast-enhanced CT, arrowhead). SBRT of 40 Gy in four fractions (BED_{10} = 80.0 Gy) (B, treatment plan). The high intensity area that observed before SBRT in diffusion-weighted imaging of MRI (C, left) disappeared three months after SBRT (C, right). Abbreviations: HCC, hepatocellular carcinoma; CT, computed tomography; MRI, magnetic resonance imaging; SBRT, stereotactic body radiation therapy; BED, biologically effective dose.

4. Radiotherapy in the management of HCC with tumor thrombus in vessels

Portal vein tumor thrombosis (PVTT), the most common form of macrovascular invasion of HCC, could propagate further, obstruct the whole vein lumen, and lead to poor prognoses ranging from only 2 to 4 months after supportive care [44, 45]. One of the treatment modalities is surgical resection that could lead to median survival time of 8–64 months, 1-, 2-, and 3-year overall survival rates of 31–87, 0–76, and 0–71%, respectively [46]. In addition, there is a potential survival benefit by surgical resection [47]. However, tumor thrombectomy can be associated with high morbidity and mortality rates, up to 23.7% [48]. TACE might be contraindicated for HCC patients with PVTT because of the potential risk of hepatic ischemic damages due to TACE. In addition, PVTT is not an indication for RFA because of the potential cooling effect and challenging status of percutaneous intervention.

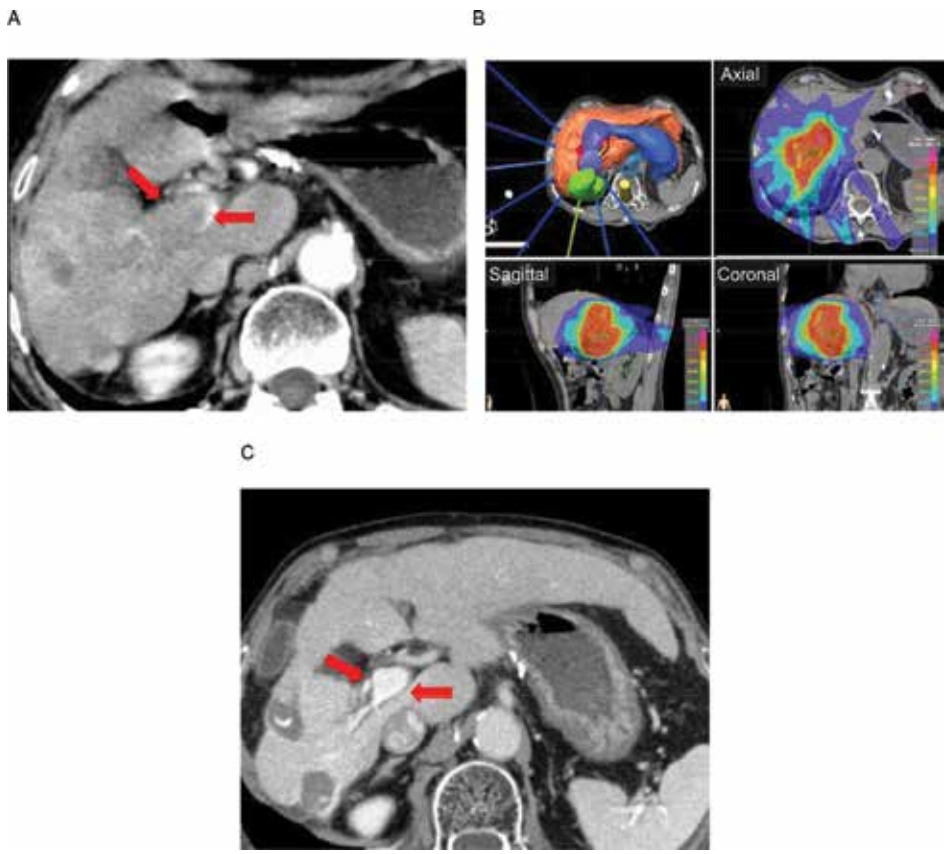

Figure 3. SBRT for PVTT. A 77-year-old man developed HCC due to hepatitis C with tumor thrombus in right portal vein (A, arrows, contrast-enhanced CT). The patient underwent SBRT of 60 Gy in 15 fractions (BED_{10} = 84.0 Gy) (B). The tumor thrombus disappeared after three months after SBRT. Contrast-enhanced CT indicates disobliteration of the right portal vein after SBRT (C, arrows). Abbreviations: SBRT, stereotactic body radiation therapy; PVTT, portal vein tumor thrombosis; HCC, hepatocellular carcinoma; CT, computed tomography; BED, biologically effective dose.

Although the efficacy of radiotherapy has been reported in patients with tumor thrombus using conventional schedule, the evidence of the survival benefit is insufficiently strong [39–41, 49–51]. In addition, Lin et al. have reported that radiotherapy can recanalize at a rate of 79% in 14 patients with PVTT [51]. However, there are only a few comparison studies among the techniques of radiotherapy [39, 51]. Matsuo et al. have reported, in a retrospective study, that the response rate of PVTT or inferior vena cava tumor thrombosis to radiotherapy was 67 and 46% in SBRT and 3D-CRT groups, respectively (P = 0.04) [39]. Moreover, SBRT has an advantage with regard to the shortened treatment term. Radiotherapy including SBRT may have the potential to be the standard technique of radiotherapy in the treatment of PVTT. **Figure 3** indicates a case of SBRT for HCC with PVTT.

Radiotherapy can overcome anatomical barriers such as major vessels and achieve a promising local control with minimal invasion. Therefore, a combined multimodal approach including radiotherapy would be needed in the treatment of the HCC with PVTT in order to maximize tumor control and to keep the normal liver damages due to treatment within a safe limit.

5. Prescription doses of SBRT for HCC

A dose-response relationship has been reported for conventional fractionated and stereotactic radiotherapy, although the best prescription dose of radiotherapy for HCC remains undecided [12, 27, 52].

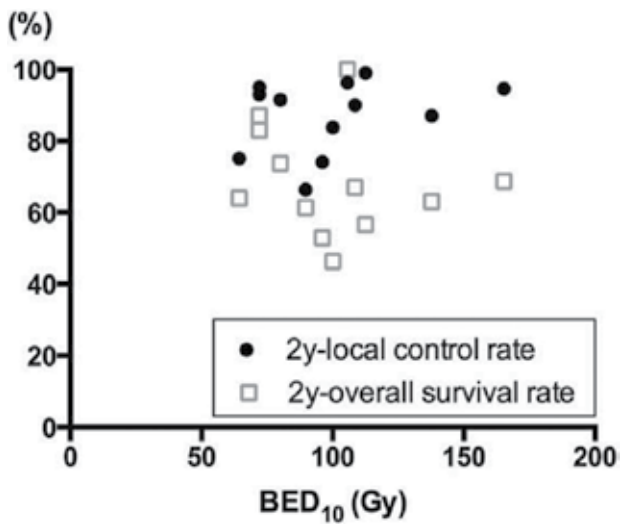

Figure 4. Dose-response relationship in SBRT for HCC. Previous reports that clearly indicates 2-year local control and overall survival were plotted in the scatter diagram [20–24, 27–30, 32, 34, 37]. X- and Y-axis indicates total doses radiotherapy in term of BED_{10} and the rates of 2-year local control and overall survival, respectively. No apparent dose-response relationship was observed in local control (r = 0.2828 and P = 0.3732) and overall survival (r = -0.1872 and P = 0.5602) at 2 years after SBRT. Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BED, biologically effective dose.

Bae et al. reported 85% local control rates at 2 years after an SBRT of 50 Gy in 10 fractions, 75 Gy in terms of biologically effective dose (BED) using the linear-quadratic (LQ) model assuming an α/β = 10 Gy for tumors (BED_{10}) [53]. Lausch et al. have reported that the administration of a biologically equivalent total dose in 2-Gy fractions (EQD2) of 84 Gy (BED_{10} = 100.8 Gy) could achieve a 90% probability of a 6-month local control [54]. Jang et al. estimated that a 90% probability of a 2-year local control required 51.1 Gy in three fractions (BED_{10} = 138.1 Gy) [27]. Sanuki et al. and Takeda et al. reported a more than 90% 3-year local control rate with 40 Gy in five fractions (BED_{10} = 72 Gy) that was intended to enclose the planning target volume (PTV) by 80% isodose line of the maximum dose [28, 29]. **Figure 4** shows no dose–response relationship between a 2-year local control and overall survival rates and the total BED of SBRT with the range of prescription doses of ≥72 Gy. Notably, previous reports include various prescription definitions such as the prescription dose for the iso-center (isocentric prescription), a certain percent isodose line of the maximum dose (marginal prescription), and the dose to cover 95% of the PTV (D95 prescription). Based on these data, HCC has been treated with ≥80 Gy of BED_{10} and achieved a good local control at our institute as we hypothesized [37].

6. Adverse events of SBRT for HCC in cirrhotic liver, risk factors, and prevention

Manifestations of liver SBRT toxicity have fatigue, damage to the liver, gastrointestinal tract and biliary duct, cytopenia, dermatitis, and rib fractures (**Table 2**) [18–37]. Adverse events of radiotherapy depend on the treatment site, and the irradiated doses and volume and are categorized into either acute (typically within 3 months of radiotherapy) or late (months to years after radiotherapy), based on their time of onset [55]. The acute phase of radiation-induced injury is characterized by inflammation, in response to therapy, while the late phase is characterized by fibrosis and sclerosis of vessels leading to focal ischemia and chronic inflammation. To distinguish acute and late phases of toxicities is often difficult since liver damage with serum abnormalities can be observed weeks or months later after SBRT [16]. We summarize with focusing on the major toxicities in the liver, gastrointestinal tract, and central bile duct.

6.1. Liver toxicity

Liver toxicity, such as classic and non-classic radiation-induced liver disease (RILD), is one of the most common dose-limiting toxicities in liver radiotherapy [15, 16, 56, 57]. Clinical RILD occurs between 2 weeks and 7 months, typically within 4–8 weeks following hepatic radiotherapy. The patient presents with fatigue, weight gain, increased abdominal girth, hepatomegaly, anicteric ascites, and an elevation in alkaline phosphatase (over twice the upper limit of the normal values). Treatment options for RILD are limited, and the condition can become fatal due to liver failure [56, 58–61]. Non-classic RILD occurs in patients with underlying chronic hepatic disease, such as cirrhosis and viral hepatitis, and is characterized by jaundice and/or markedly elevated serum transaminases (over five times the upper limit of the normal values), developing between 1 week and 3 months after the completion of hepatic radiotherapy [19, 61]. The mean dose of less than 30 Gy has been considered as safe but radiation tolerance of the liver in a conventional radiotherapy [19]. However, the actual mean doses

appropriate for liver irradiation in SBRT have not been adequately investigated. Furthermore, radiotherapy has the potential to reactivate hepatitis B virus and differentiating patients may be necessary [62, 63]. There are differences in radiosensitivity between patients with normal and cirrhotic livers; cirrhotic liver may yield a higher radiosensitivity than normal liver [16, 57]. In addition, Child-Pugh B, particularly scores of ≥8, was considered a significant risk factor for severe hepatic toxicity and poor prognosis [21, 31, 64]. Culleton et al. reported that 63% of 29 HCC patients with Child-Pugh B or C, receiving SBRT, declined Child-Pugh score by two points after 3 months [31].

As the liver is widely accepted as a parallel organ, a part of it can receive a high dose of irradiation as long as the functions as a whole organ are preserved [65–67]. Indeed, Schefter et al., Olsen et al., and Kang et al. used dose constraint, as the liver volume was >700 mL when the dose administered was less than 15 and 17 Gy in three fractions [22, 68, 69]. However, intrahepatic recurrence often occurs after a radical treatment for liver tumors because of chronic liver diseases, and such tumors have a chance to receive second radical treatment [9, 70]. Thus, the prediction of the volume of liver dysfunction is essential in order to spare the residual liver volume. After SBRT, focal dysfunction was noted in the irradiated background liver. Sanuki et al. have shown that the threshold dose of focal liver dysfunction was 30 and 25 Gy in five fractions in patients with Child-Pugh A and B, respectively, using magnetic resonance imaging (MRI) [71]. Similarly, Doi et al. have reported that focal liver dysfunction can occur at 40 and 70 Gy of BED_2 in the cirrhotic and normal liver, respectively, at a minimum dose [57]. **Figure 5** indicates a focal liver damage 3 months after SBRT. We have presented SBRT strategy with checkpoints to ensure safe treatment modality in SBRT for liver tumor [72]. To prevent RILD-related mortality, we evaluate the mean doses for the liver first and then analyze the potential loss of hepatic function in terms of BED (**Figure 6**).

6.2. Gastrointestinal injury

Ionizing radiation exerts an anticancer effect by reacting with molecular oxygen and water to generate reactive oxygen species that can attack deoxyribose in deoxyribonucleic acid (DNA). Sublethal doses of radiation can cause non-repairable DNA damage [73]. Intestine is a radiosensitive tissue because of the rapid turnover rate, and this can be a dose-limiting factor in SBRT. Gastrointestinal injuries including bleeding, ulcers, and perforations have been described, and the incidence of symptomatic gastrointestinal toxicities was less than 10% in majority of the previous reports (**Table 2**). However, severe toxicities, which can be lethal, have also been described in SBRT in the upper abdomen including liver [22, 30, 74–76]. Kang et al. have highlighted the possible association between severe gastrointestinal toxicity and the existence of mucosal ulceration prior to radiotherapy [22]. Barney et al. reported that the combination of SBRT and vascular endothelial growth factor inhibitor increased the risk of grade 3 or greater gastrointestinal toxicities [77]. Careful assessment is therefore required prior to the implementation of combined treatments, such as targeted therapy.

For the prevention of severe gastrointestinal injury, analyses of dose-volume responses have been reported. Kopek et al. recommended V21Gy ≤1 cc for the duodenum in abdominal SBRT in their analyses in 29 patients with cholangiocellular carcinoma (CCC) underwent SBRT (45 Gy/3 fractions) [78]. Bae et al. concluded that Dmax of 35 and 38 Gy in three fractions was associated with a probability of 5 and 10% severe gastroduodenal toxicity, respectively [79].

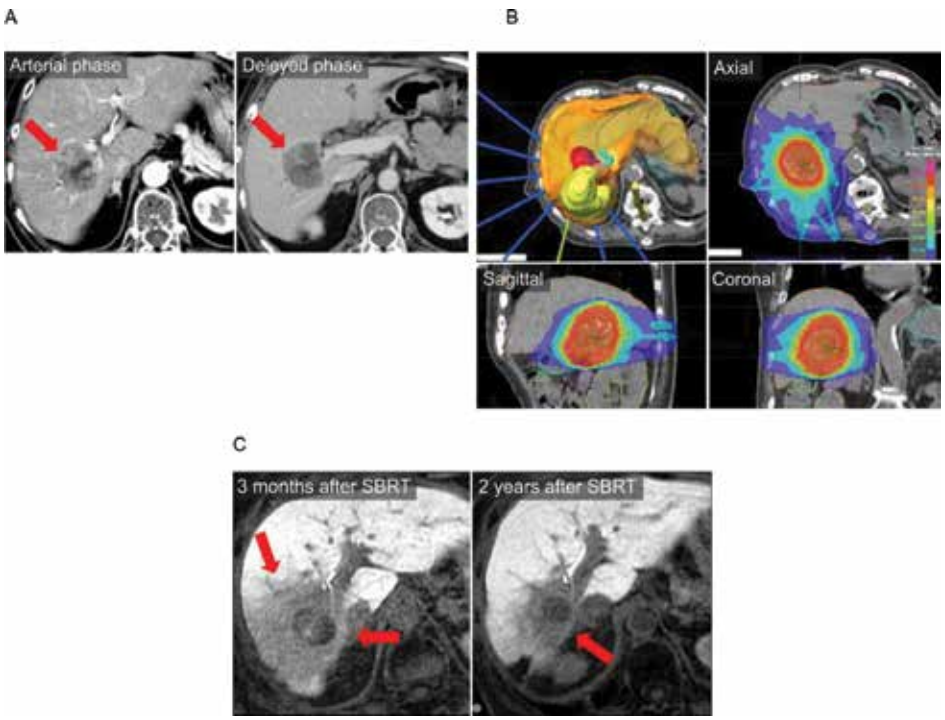

Figure 5. Focal liver dysfunction after SBRT in the follow-up MRI. A 77-year-old woman developed HCC due to hepatitis B. (A) Contrast-enhanced CT images indicate HCC in S7 area. Arterial phase showed patchy high density area (arrow, left) and contrast washed-out was observed later in delayed phase (arrow, right). (B) SBRT of 55 Gy in 10 fractions (BED_{10} = 85.3 Gy) was performed for the tumor. (C) Low intensity area was found in accordance with the irradiated area of treatment plan in Gd-EOB-DTPA enhanced-MRI three months after SBRT (left, arrows) and focal liver atrophy was observed later (right, arrow). Abbreviations: SBRT, stereotactic body radiation therapy; MRI, magnetic resonance imaging; CT, computed tomography; HCC, hepatocellular carcinoma; BED, biologically effective dose; Gd-EOB-DTPA, gadolinium ethoxybenzyl-diethylenetriamine pentaacetic acid.

Kavanagh et al. recommended that the volume of stomach receiving >22.5 Gy should be ideally minimized to <5 cc, with Dmax of <30 Gy in three fractions [80]. Sanuki et al. suggested that SBRT could be performed with the avoidance of severe toxicities when the target had a distance of >2 cm from the bowel [81]. An increased number of fractions may reduce BED for normal tissues in SBRT for liver tumors close to the gastrointestinal tract [57]. Since there are no established strategies for the prevention and treatment of radiation-induced gastrointestinal injury, efforts should be required to minimize radiation doses for gastrointestinal tracts [82].

6.3. Central hepatobiliary tract toxicity

Eriguchi et al. documented asymptomatic bile duct stenosis in 2/50 patients, receiving >20 Gy in five fractions to the central liver [83]. One of these patients received SBRT on two occasions to the central liver tumors and developed abnormalities in liver enzymes. The abnormal region visible on a computed tomography scan corresponded to the site irradiated up to a cumulative maximum dose of 88 Gy in two sessions of SBRT. The authors concluded that SBRT for liver tumors in the hepatic hilum was feasible with minimal biliary toxicity.

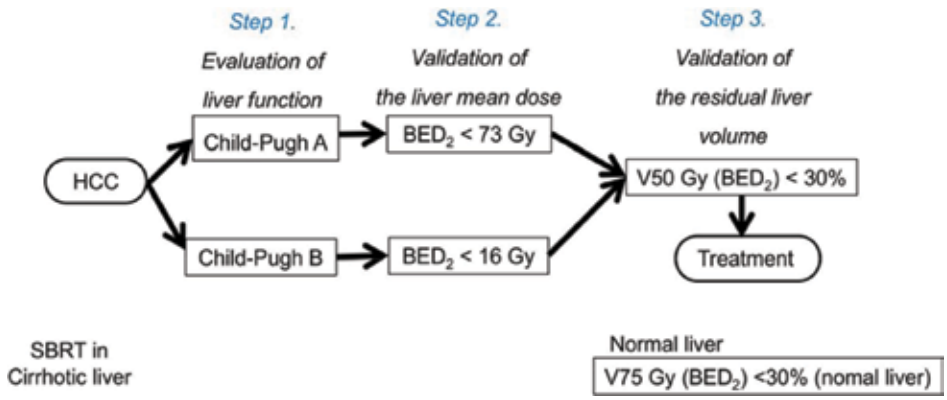

Figure 6. The current recommended treatment protocol to provide a safe SBRT for HCC in cirrhotic liver. To minimize the risk of radiation-induced liver disease and liver damage, two different checkpoints were included. Herein, we propose a safe treatment protocol for SBRT of liver tumors. First, liver function is evaluated according to the Child–Pugh classification (Step 1). Next, the liver doses are evaluated to prevent RILD. A mean BED_2 of less than 73 and 16 Gy for the whole liver should be maintained to prevent RILD in patients with Child–Pugh A and B liver function, respectively (Step 2). Finally, the volume of hepatic dysfunction is assessed to estimate the residual liver volume (Step 3). Abbreviations: SBRT, stereotactic body radiation therapy; HCC, hepatocellular carcinoma; BED, biologically effective dose.

Osmundson et al. analyzed 96 patients with liver tumors, including 20 CCCs, who received different schedules of SBRT, and reported that the incidence of hepatobiliary toxicity ≥Grade 2 and 3 was 24.0 and 18.8%, respectively [84]. Furthermore, CCC, biliary stent, $V_{BED10}72 \geq 21$ cc, $V_{BED10}66 \geq 24$ cc, and $DmeanBED_{10} \geq 14$ Gy to central hepatobiliary tract were associated with hepatobiliary toxicity [81]. The same groups reported radiation-induced pathological changes of the bile duct in resected surgical specimens 25 months after SBRT and concluded that liver toxicity should be considered while treating central liver lesions [85]. The same group has also reported a dose-volume association between ≥Grade 3 hepatobiliary toxicity and doses for central biliary tract and suggested $V_{BED10}40 < 37$ cc and $V_{BED10}30 < 45$ cc as dose-volume constraints in SBRT for primary liver tumors [86].

The anatomical structures in the hepatic hilum make radical treatment for liver tumors, such as surgery and RFA, more challenging. In such a scenario, SBRT can be a better option in comparison to other modalities, and to the best of our knowledge, there is no apparent consensus on the use of SBRT with few reports addressing this point. Further studies are required to determine the dose constraints for the bile duct, as there can be potential dose constraints due to the central hepatobiliary tract toxicity.

7. Current issues and future perspective of liver SBRT

Liver SBRT is a well-established and promising treatment for a limited number of small tumors. We have set out the difference between primary and metastatic liver cancers, considering the occurrence and prevention of toxicities. However, further questions regarding the pathological features of liver cancers, and potential SBRT strategies, including radiobiology-based SBRT and SBRT combined with immunotherapy, have not yet been fully addressed.

7.1. Potent strategies of SBRT based on radiation biology

Brown et al. reported that a greater endothelial cell damage and vascular damage, leading cancer cell apoptosis, can be caused by SBRT, and reoxygenation can increase antitumor effect in fractionated radiotherapy [87]. Shibamoto et al. concluded that reoxygenation could be promoted by a 72-h break period in SBRT [88]. No prospective clinical trials exist in terms of evaluation of the benefit of a break in SBRT. However, a longer overall treatment time (e.g., 1–2 fractions per week: 2-week schedule) may yield better local control outcomes in SBRT [89, 90]. SBRT for larger tumors has still unclear roles and is challenging because they are usually in exclusion criterion. In addition, large tumor size (≥2–4 cm) has been reported to be a predictive factor for poor outcomes after SBRT for HCC [23, 30, 32]. Further biological assessment might yield potential factors that improve treatment outcomes such as escalated doses, treatment schedule with a break, combined therapy with ideal chemotherapy, individualized treatment, and particle therapies.

7.2. Potential needs of clinical tumor volume margin in liver SBRT

Definition of clinical tumor volume (CTV) is the volume that includes both gross and microscopic disease and is created by adding several mm to 1.5 cm to gross tumor volume (GTV), in order to allow for microscopic extension. However, CTV is frequently equal to GTV in SBRT [91]. It is still poorly understood whether CTV margins are necessary, as there are limited reports of microscopic extension of liver tumors as premises for radiotherapy. HCC is characterized by direct invasion and a potential high presence of daughter nodules around the tumor that may lead to locoregional recurrence [92]. Wang et al. reported that the potential maximum margin extending beyond the gross tumor margin was 8.0 mm, although 94.7% of patients with HCC had a microscopic extension of ≤3.5 mm [93]. Wang et al. analyzed 149 resected HCCs with a mean diameter of 5.8 cm (range: 1.0–22.0 cm) and found that microinvasion was not present in 47.0% patients [94]. Microinvasion distances of ≤2 mm were found in 96.1% of patients with tumor dimensions of ≤5 cm. Uemoto et al. have first reported that a larger margin to GTV inclined to improve local control and survival outcomes in clinical data, suggesting the benefit of CTV margins [37]. Further clinical translational studies should be conducted in order to assess the optimal CTV margins.

7.3. Current knowledge of Immuno-SBRT

Regression of tumors outside the radiation field after local radiotherapy, due to systemic induction of antitumor immunity, is called the abscopal effect [95]. SBRT combined with immune checkpoint inhibitor has recently resulted in unexpected clinical complete responses from distant sites from the irradiated areas, in various malignancies [96–98]. Recently, synergistic effects of radiotherapy combined with immunotherapy have been reported in both preclinical and clinical studies, with the high possibility of the abscopal effect, which may significantly change the treatment strategies for metastatic diseases [96–105]. However, the optimal treatment schedule and doses in the combined setting of radiotherapy and immunotherapy are poorly understood at present. Young et al. reported an enhanced efficacy of immune-radiotherapy administered concurrently with radiotherapy [101]. In a meta-analysis of preclinical data, Marconi et al. reported that the probability of abscopal effects is 50% when a BED of 60 Gy is generated [102]. Moreover, SBRT may provide smaller target volumes, and in a clinical trial involving patients with pancreatic cancer, Wild et al. found that hypofractionation

could minimize the toxic effects on circulating lymphocytes [106]. By expanding its application range from small tumors to metastases, SBRT might have good potential to achieve newer objectives in systematic disease, although further investigations are required.

8. Advantages of particle therapy in treatment for HCC in cirrhotic liver

The use of particle therapy, such as proton and carbon ion therapy for liver tumors, is a promising strategy to increase the dose of radiation without a concurrent increase in toxicity. Particle therapy exhibits a narrow Bragg peak at a defined depth for a defined energy [73]. Particle therapy can provide high concentrations of radiation doses to the target by positioning individual Bragg peaks to coincide with the areas of the target. In photon radiotherapy, the doses that the liver receives have a strong positive relationship with the irradiated target volume, and unacceptable higher doses might be irradiating to the background liver in the treatment of large live tumors [72]. Particle therapy can reduce the liver volume that receives low to intermediate doses, resulting in the reduction of mean liver doses with an advantage of target conformity [107, 108]. In addition, carbon ion therapy offers the added potential benefit of an increased relative biological effectiveness and a lower oxygen enhancement ratio due to the high linear energy transfer that may improve responses in hypoxic areas of tumors, which are more resistant to photon radiotherapy [73]. A relevant clinical consideration is that particle therapy can benefit relatively large tumors, such as >3 cm (particularly >5 cm) and patients with poor liver function, which are limiting for SBRT [109].

9. Conclusions

For HCC, SBRT is safe and effective, with excellent local control achieved. Tumors that are relatively small and distant from gastrointestinal tissues are strong candidate for SBRT in curative intent. Therefore, novel strategies should be developed based on new knowledge of biological responses to radiation therapy. State-of-the-art liver SBRT remains a pioneering strategy in multimodal therapy.

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Conflict of interest

None.

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References

[1] Stuver S, Trichopoulos D. Cancer of the liver and biliary tract. In: Adami HO, Hunter D, Trichopoulos D, editors. Textbook of Cancer Epidemiology. 2nd ed. New York: Oxford University Press; 2008

[2] World Health Organization, International Agency for Research on Cancer. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. Available from: http://globocan.iarc.fr/Default.aspx. [Accessed: December 4, 2017]

[3] El-Serag HB. Hepatocellular carcinoma. The New England Journal of Medicine. 2011;**365**:1118-1127

[4] Zhang DY, Friedman SL. Fibrosis-dependent mechanisms of hepatocarcinogenesis. Hepatology. 2012;**56**:769-775

[5] Donato F, Tagger A, Gelatti U, Parrinello G, Boffetta P, Albertini A, et al. Alcohol and hepatocellular carcinoma: The effect of lifetime intake and hepatitis virus infections in men and women. American Journal of Epidemiology. 2002;**155**:323-331

[6] Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. Gastroenterology. 2004;**127**(5, Suppl 1):S35-S50

[7] Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology. 2016;**150**:835-853

[8] Soyama A, Eguchi S, Egawa H. Liver transplantation in Japan. Liver Transplantation. 2016;**22**:1401-1407

[9] Tateishi R, Shiina S, Yoshida H, Teratani T, Obi S, Yamashiki N, Yoshida H, Akamatsu M, Kawabe T, Omata M. Prediction of recurrence of hepatocellular carcinoma after curative ablation using three tumor markers. Hepatology. 2006;**44**:1518-1527

[10] Zeng Z-C, Fan J, Tang Z-Y, Zhou J, Qin L-X, Wang J-H, et al. A comparison of treatment combinations with and without radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombus. International Journal of Radiation Oncology Biology Physics. 2005;**61**(2):432-443

[11] Park W, Lim D-H, Paik SW, Koh KC, Choi MS, Park CK, et al. Local radiotherapy for patients with unresectable hepatocellular carcinoma. International Journal of Radiation Oncology Biology Physics. 2005 Mar 15;**61**(4):1143-1150

[12] Park HC, Seong J, Han KH, Chon CY, Moon YM, Suh CO. Dose-response relationship in local radiotherapy for hepatocellular carcinoma. International Journal of Radiation Oncology Biology Physics. 2002;**54**:150-155

[13] Ben-josef E, Lawrence TS. Radiotherapy for unresectable hepatic malignancies. Seminars in Radiation Oncology. 2005 Oct;**15**(4):273-278

[14] Fuss M, Salter BJ, Herman TS, Thomas CR. External beam radiation therapy for hepatocellular carcinoma: Potential of intensity-modulated and image-guided radiation therapy. Gastroenterology. 2004 Nov;**127**(5 Suppl 1):S206-S217

[15] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. International Journal of Radiation Oncology, Biology, Physics. 1991;**21**:109-122

[16] Pan CC, Kavanagh BD, Dawson LA, Li XA, Das SK, Miften M, Ten Haken RK. Radiation-associated liver injury. International Journal of Radiation Oncology, Biology, Physics 2010;**76:**S94-100

[17] Blomgren H, Lax I, Näslund I, et al. Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator: Clinical experience of the first thirty-one patients. Acta Oncologica. 1995;**34**:861-870

[18] Wulf J, Guckenberger M, Haedinger U, et al. Stereotactic radiotherapy of primary liver cancer and hepatic metastases. Acta Oncologica. 2006;**45**:838-847

[19] Kwon JH, Bae SH, Kim JY, et al. Long-term effect of stereotactic body radiation therapy for primary hepatocellular carcinoma ineligible for local ablation therapy or surgical resection. Stereotactic radiotherapy for liver cancer. BMC Cancer. 2010;**10**:S27-S10

[20] Seo YS, Kim MS, Yoo SY, et al. Preliminary result of stereotactic body radiotherapy as a local salvage treatment for inoperable hepatocellular carcinoma. Journal of Surgical Oncology. 2010;**102**:209-214

[21] Andolino DL, Johnson CS, Maluccio M, Kwo P, Tector AJ, Zook J, Johnstone PA, Cardenes HR. Stereotactic body radiotherapy for primary hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2011;**81**:e447-e453

[22] Kang JK, Kim MS, Cho CK, Yang KM, Yoo HJ, Kim JH, Bae SH, Jung DH, Kim KB, Lee DH, Han CJ, Kim J, Park SC, Kim YH. Stereotactic body radiation therapy for inoperable hepatocellular carcinoma as a local salvage treatment after incomplete transarterial chemoembolization. Cancer. 2012;**118**:5424-5431

[23] Huang WY, Jen YM, Lee MS, et al. Stereotactic body radiation therapy in recurrent hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2012;**84**:355-361

[24] Honda Y, Kimura T, Aikata H, et al. Stereotactic body radiation therapy combined with transcatheter arterial chemoembolization for small hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2013;**28**:530-536

[25] Bae SH, Kim MS, Cho CK, Kim KB, Lee DH, Han CJ, Park SC, Kim YH. Feasibility and efficacy of stereotactic ablative radiotherapy for barcelona clinic liver cancer-C stage hepatocellular carcinoma. Journal of Korean Medical Science. 2013;**28**:213-217

[26] Bujold A, Massey CA, Kim JJ, et al. Sequential phase I and II trials of stereotactic body radiotherapy for locally advanced hepatocellular carcinoma. Journal of Clinical Oncology. 2013;**31**:1631-1639

[27] Jang WI, Kim MS, Bae SH, et al. High-dose stereotactic body radiotherapy correlates increased local control and overall survival in patients with inoperable hepatocellular carcinoma. Radiation Oncology. 2013;**8**:250

[28] Sanuki N, Takeda A, Oku Y, Mizuno T, Aoki Y, Eriguchi T, Iwabuchi S, Kunieda E. Stereotactic body radiotherapy for small hepatocellular carcinoma: A retrospective outcome analysis in 185 patients. Acta Oncologica. 2014;**53**:399-404

[29] Takeda A, Sanuki N, Eriguchi T, Kobayashi T, Iwabutchi S, Matsunaga K, Mizuno T, Yashiro K, Nisimura S, Kunieda E. Stereotactic ablative body radiotherapy for previously untreated solitary hepatocellular carcinoma. Journal of Gastroenterology and Hepatology. 2014;**29**:372-379

[30] Yamashita H, Onishi H, Matsumoto Y, Murakami N, Matsuo Y, Nomiya T, Nakagawa K. Local effect of stereotactic body radiotherapy for primary and metastatic liver tumors in 130 Japanese patients. Radiation Oncology. 2014;**9**:112

[31] Culleton S, Jiang H, Haddad CR, Kim J, Brierley J, Brade A, Ringash J, Dawson LA. Outcomes following definitive stereotactic body radiotherapy for patients with Child-Pugh B or C hepatocellular carcinoma. Radiotherapy and Oncology. 2014;**111**:412-417

[32] Huertas A, Baumann AS, Saunier-Kubs F, et al. Stereotactic body radiation therapy as an ablative treatment for inoperable hepatocellular carcinoma. Radiotherapy and Oncology. 2015;**115**:211-216

[33] Takeda A, Sanuki N, Tsurugai Y, et al. Phase 2 study of stereotactic body radiotherapy and optional transarterial chemoembolization for solitary hepatocellular carcinoma not amenable to resection and radiofrequency ablation. Cancer. 2016;**122**:2041-2049

[34] Wahl DR, Stenmark MH, Tao Y, Pollom EL, Caoili EM, Lawrence TS, Schipper MJ, Feng M. Outcomes after stereotactic body radiotherapy or radiofrequency ablation for hepatocellular carcinoma. Journal of Clinical Oncology. 2016;**34**:452-459

[35] Su TS, Liang P, Liang J, et al. Long-term survival analysis of stereotactic ablative radiotherapy versus liver resection for small hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2017;**98**:639-646

[36] Lo CH, Yang JF, Liu MY, et al. Survival and prognostic factors for patients with advanced hepatocellular carcinoma after stereotactic ablative radiotherapy. PLoS One. 2017;**12**:e0177793

[37] Uemoto K, Doi H, Shiomi H, Yamada K, Tatsumi D, Yasumoto T, Takashina M, Koizumi M, Oh RJ. Clinical assessment of micro-residual tumors during stereotactic body radiation therapy for hepatocellular carcinoma. Anticancer Research. 2018;**38**:945-954

[38] Nugent FW, Qamar A, Stuart KE, Galuski K, Flacke S, Molgaard C, Gordon F, Iqbal S, Hunter KU, Hartnett E, Gunturu K. A randomized phase II study of individualized stereotactic body radiation therapy (SBRT) versus transarterial chemoembolization (TACE)

with DEBDOX beads as a bridge to transplant in hepatocellular carcinoma (HCC). In: 2017 Gastrointestinal Cancer Symposium; Jan 19-21; San Fransisco, CA, USA; 2017. 223

[39] Matsuo Y, Yoshida K, Nishimura H, Ejima Y, Miyawaki D, Uezono H, Ishihara T, Mayahara H, Fukumoto T, Ku Y, Yamaguchi M, Sugimoto K, Sasaki R. Efficacy of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein tumor thrombosis/inferior vena cava tumor thrombosis: Evaluation by comparison with conventional three-dimensional conformal radiotherapy. Journal of Radiation Research. 2016;**57**:512-523

[40] Xi M, Zhang L, Zhao L, Li QQ, Guo SP, Feng ZZ, Deng XW, Huang XY, Liu MZ. Effectiveness of stereotactic body radiotherapy for hepatocellular carcinoma with portal vein and/or inferior vena cava tumor thrombosis. PLoS One. 2013;**8**:e63864

[41] Zheng X-K, Chen L-H, Yan X, Wang H-M. Impact of prolonged fraction dose-delivery time modeling intensity-modulated radiation therapy on hepatocellular carcinoma cell killing. WJG. 2005 Mar 14;**11**(10):1452-1456

[42] Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM task group 101. Medical Physics. 2010;**37**:4078-4101

[43] Timmerman RD, Herman J, Chinsoo Cho L. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. Journal of Clinical Oncology. 2014;**32**:2847-2854

[44] Yin J, Bo W-T, Sun J, Xiang X, Lang J-Y, Zhong J-H, et al. New evidence and perspectives on the management of hepatocellular carcinoma with portal vein tumor thrombus. Journal of Clinical and Translational Hepatology. 2017 Jun 28;**5**(2):169-176

[45] Schöniger-Hekele M, Müller C, Kutilek M, Oesterreicher C, Ferenci P, Gangl A. Hepatocellular carcinoma in Central Europe: Prognostic features and survival. Gut. 2001;**48**: 103-109

[46] Jiang J-F, Lao Y-C, Yuan B-H, Yin J, Liu X, Chen L, et al. Treatment of hepatocellular carcinoma with portal vein tumor thrombus: Advances and challenges. Oncotarget. 2017 May 16;**8**(20):33911-33921

[47] Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. Journal of Hepatology. 2016 Nov;**65**(5):938-943

[48] Tang Q-H, Li A-J, Yang G-M, Lai ECH, Zhou W-P, Jiang Z-H, et al. Surgical resection versus conformal radiotherapy combined with TACE for resectable hepatocellular carcinoma with portal vein tumor thrombus: A comparative study. World Journal of Surgery. 2013 Jun;**37**(6):1362-1370 Oncotarget; 2017

[49] Chan SL, Chong CCN, Chan AWH, Poon DMC, Chok KSH. Management of hepatocellular carcinoma with portal vein tumor thrombosis: Review and update at 2016. WJG. 2016 Aug 28;**22**(32):7289-7300

[50] Choi BO, Choi IB, Jang HS, et al. Stereotactic body radiation therapy with or without transarterial chemoembolization for patients with primary hepatocellular carcinoma: Preliminary analysis. BMC Cancer. 2008;**8**:351

[51] Lin CS, Jen YM, Chiu SY, et al. Treatment of portal vein tumor thrombosis of hepatoma patients with either stereotactic radiotherapy or three-dimensional conformal radiotherapy. Japanese Journal of Clinical Oncology. 2006;**36**:212-217

[52] Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. International Journal of Radiation Oncology, Biology, Physics. 2010;**78**:486-493

[53] Bae SH, Park HC, Lim DH, et al. Salvage treatment with hypofractionated radiotherapy in patients with recurrent small hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2012;**82**:e603-e607

[54] Lausch A, Sinclair K, Lock M, et al. Determination and comparison of radiotherapy dose responses for hepatocellular carcinoma and metastatic colorectal liver tumours. The British Journal of Radiology. 2013;**86**:20130147

[55] Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European Organization for Research and Treatment of cancer (EORTC). International Journal of Radiation Oncology, Biology, Physics. 1995;**31**:1341-1346

[56] Jackson A, Haken Ten RK, Robertson JM, et al. Analysis of clinical complication data for radiation hepatitis using a parallel architecture model. International Journal of Radiation Oncology, Biology, Physics. 1995;**31**:883-891

[57] Doi H, Shiomi H, Masai N, Tatsumi D, Igura T, Imai Y, Oh RJ. Threshold doses and prediction of visually apparent liver dysfunction after stereotactic body radiation therapy in cirrhotic and normal livers using magnetic resonance imaging. Journal of Radiation Research. 2016;**57**:294-300

[58] Dawson LA, Ten Haken RK, Lawrence TS. Partial irradiation of the liver. Seminars in Radiation Oncology 2001;**11**:240-246

[59] Ohara K, Okumura T, Tsuji H, et al. Radiation tolerance of cirrhotic livers in relation to the preserved functional capacity: Analysis of patients with hepatocellular carcinoma treated by focused proton beam radiotherapy. International Journal of Radiation Oncology, Biology, Physics. 1997;**38**:367-372

[60] Cheng JCH, Wu JK, Huang CM, et al. Radiation-induced liver disease after three-dimensional conformal radiotherapy for patients with hepatocellular carcinoma: Dosimetric analysis and implication. International Journal of Radiation Oncology, Biology, Physics. 2002;**54**:156-162

[61] Xu ZY, Liang SX, Zhu J, Zhu XD, Zhao JD, Lu HJ, Yang YL, Chen L, Wang AY, Fu XL, Jiang GL. Prediction of radiation-induced liver disease by Lyman normal-tissue complication probability model in three-dimensional conformal radiation therapy for primary liver carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2006;**65**:189-195

[62] Chou CH, Chen PJ, Lee PH, et al. Radiation-induced hepatitis B virus reactivation in liver mediated by the bystander effect from irradiated endothelial cells. Clinical Cancer Research. 2007;**13**:851-857

[63] Kim JH, Park JW, Kim TH, et al. Hepatitis B virus reactivation after three-dimensional conformal radiotherapy in patients with hepatitis B virus-related hepatocellular carcinoma. International Journal of Radiation Oncology, Biology, Physics. 2007;**69**:813-819

[64] Cardenes HR, Price TR, Perkins SM, et al. Phase I feasibility trial of stereotactic body radiation therapy for primary hepatocellular carcinoma. Clinical & Translational Oncology. 2010;**12**:218-225

[65] Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. The American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine. 1965;**93**:200-208

[66] Lawrence TS, Haken Ten RK, et al. The use of 3-D dose volume analysis to predict radiation hepatitis. International Journal of Radiation Oncology, Biology, Physics. 1992;**23**:781-788

[67] Withers HR, Taylor JM, Maciejewski B. Treatment volume and tissue tolerance. International Journal of Radiation Oncology, Biology, Physics. 1988;**14**:751-759

[68] Schefter TE, Kavanagh BD, Timmerman RD, Cardenes HR, Baron A, Gaspar LE. A phase I trial of stereotactic body radiation therapy (SBRT) for liver metastases. International Journal of Radiation Oncology, Biology, Physics. 2005;**62**:1371-1378

[69] Olsen CC, Welsh J, Kavanagh BD, Franklin W, McCarter M, Cardenes HR, Gaspar LE, Schefter TE. Microscopic and macroscopic tumor and parenchymal effects of liver stereotactic body radiotherapy. International Journal of Radiation Oncology, Biology, Physics. 2009;**73**:1414-1424

[70] Yoshida H, Shiratori Y, Moriyama M, et al. Interferon therapy reduces the risk for hepatocellular carcinoma: National surveillance program of cirrhotic and non-cirrhotic patients with chronic hepatitis C in Japan. IHIT study group. Inhibition of Hepatocarcinogenesis by interferon therapy. Annals of Internal Medicine. 1999;**131**:174-181

[71] Sanuki N, Takeda A, Oku Y, Eriguchi T, Nishimura S, Aoki Y, Mizuno T, Iwabuchi S, Kunieda E. Threshold doses for focal liver reaction after stereotactic ablative body radiation therapy for small hepatocellular carcinoma depend on liver function: Evaluation on magnetic resonance imaging with Gd-EOB-DTPA. International Journal of Radiation Oncology, Biology, Physics. 2014;**88**:306-311

[72] Doi H, Masai N, Uemoto K, Suzuki O, Shiomi H, Tatsumi D, Oh RJ. Validation of the liver mean dose in terms of the biological effective dose for the prevention of radiation-induced liver damage. Reports of Practical Oncology and Radiotherapy. 2017;**22**:303-309

[73] Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2011

[74] Høyer M, Roed H, Traberg Hansen A, Ohlhuis L, Petersen J, Nellemann H, Kiil Berthelsen A, Grau C, Aage Engelholm S, Von der Maase H. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncologica. 2006;**45**:823-830

[75] Høyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. Radiotherapy and Oncology. 2005;**76**:48-53

[76] Onishi H, Ozaki M, Kuriyama K, et al. Serious gastric ulcer event after stereotactic body radiotherapy (SBRT) delivered with concomitant vinorelbine in a patient with left adrenal metastasis of lung cancer. Acta Oncologica. 2012;**51**:624-628

[77] Barney BM, Markovic SN, Laack NN, et al. Increased bowel toxicity in patients treated with a vascular endothelial growth factor inhibitor (VEGFI) after stereotactic body radiation therapy (SBRT). International Journal of Radiation Oncology, Biology, Physics. 2013;**87**:73-80

[78] Kopek N, Holt MI, Hansen AT, et al. Stereotactic body radiotherapy for unresectable cholangiocarcinoma. Radiotherapy and Oncology. 2010;**94**:47-52

[79] Bae SH, Kim MS, Cho CK, Kang JK, Lee SY, Lee KN, Lee DH, Han CJ, Yang KY, Kim SB. Predictor of severe gastroduodenal toxicity after stereotactic body radiotherapy for abdominopelvic malignancies. International Journal of Radiation Oncology, Biology, Physics. 2012;**84**:e469-e474

[80] Kavanagh BD, Pan CC, Dawson LA, Das SK, Li XA, Ten Haken RK, Miften M. Radiation dose-volume effects in the stomach and small bowel. International Journal of Radiation Oncology, Biology, Physics. 2010;**76**:S101-S107

[81] Sanuki N, Takeda A, Kunieda E. Role of stereotactic body radiation therapy for hepatocellular carcinoma. World Journal of Gastroenterology. 2014;**20**:3100-3111

[82] Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;**120**:1453-1461

[83] Eriguchi T, Takeda A, Sanuki N, Oku Y, Aoki Y, Shigematsu N, Kunieda E. Acceptable toxicity after stereotactic body radiation therapy for liver tumors adjacent to the central biliary system. International Journal of Radiation Oncology, Biology, Physics. 2013;**85**:1006-1011

[84] Osmundson EC, Wu Y, Luxton G, Bazan JG, Koong AC, Chang DT. Predictors of toxicity associated with stereotactic body radiation therapy to the central hepatobiliary tract. International Journal of Radiation Oncology, Biology, Physics. 2015;**91**:986-994

[85] Shaffer JL, Osmundson EC, Visser BC, Longacre TA, Koong AC, Chang DT. Stereotactic body radiation therapy and central liver toxicity: A case report. Practical Radiation Oncology. 2015;**5**:282-285

[86] Toesca DAS, Osmundson EC, Eyben RV, Shaffer JL, Lu P, Koong AC, Chang DT. Central liver toxicity after SBRT: An expanded analysis and predictive nomogram. Radiotherapy and Oncology. 2017;**122**:130-136

[87] Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: Are more than the 5 Rs involved? International Journal of Radiation Oncology, Biology, Physics. 2014;**88**:254-262

[88] Shibamoto Y, Miyakawa A, Otsuka S, Iwata H. Radiobiology of hypofractionated stereotactic radiotherapy: What are the optimal fractionation schedules? Journal of Radiation Research. 2016;**57**:i76-i82

[89] Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I non-small-cell lung cancer: Five-year mature results. Journal of Thoracic Oncology. 2015;**10**:960-964

[90] Matsuo Y, Shibuya K, Nagata Y, et al. Prognostic factors in stereotactic body radiotherapy for non-small-cell lung cancer. International Journal of Radiation Oncology, Biology, Physics. 2011;**79**:1104-1111

[91] Nagata Y, editor. Stereotactic Body Radiation Therapy: Principles and Practices. 1st ed. Tokyo: Springer; 2015

[92] Jwo SC, Chiu JH, Chau GY, et al. Risk factors linked to tumor recurrence of human hepatocellular carcinoma after hepatic resection. Hepatology. 1992;**16**:1367-1371

[93] Wang W, Feng X, Zhang T, Jin J, Wang S, Liu Y, et al. Prospective evaluation of microscopic extension using whole-mount preparation in patients with hepatocellular carcinoma: Definition of clinical target volume for radiotherapy. Radiation Oncology. 2010;**5**:73

[94] Wang MH, Ji Y, Zeng ZC, et al. Impact factors for microinvasion in patients with hepatocellular carcinoma: Possible application to the definition of clinical tumor volume. International Journal of Radiation Oncology, Biology, Physics. 2010;**76**:467-476

[95] Le QT, Shirato H, Giaccia AJ, et al. Emerging treatment paradigms in radiation oncology. Clinical Cancer Research. 2015;**21**:3393-3401

[96] Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. The New England Journal of Medicine. 2012;**366**:925-931

[97] Hiniker SM, Chen DS, Reddy S, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. Translational Oncology. 2012;**5**:404-407

[98] Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunology Research. 2013;**1**:365-372

[99] Hiniker SM, Reddy SA, Maecker HT, et al. A prospective clinical trial combining radiation therapy with systemic immunotherapy in metastatic melanoma. International Journal of Radiation Oncology, Biology, Physics. 2016;**96**:578-588

[100] Seung SK, Curti BD, Crittenden M, et al. Phase 1 study of stereotactic body radiotherapy and interleukin-2–tumor and immunological responses. Science Translational Medicine. 2012;**4**:137ra74

[101] Young KH, Baird JR, Savage T, et al. Optimizing timing of immunotherapy improves control of tumors by hypofractionated radiation therapy. PLoS One. 2016;**11**:e0157164

[102] Marconi R, Strolin S. Bossi et al. a meta-analysis of the abscopal effect in preclinical models: Is the biologically effective dose a relevant physical trigger? PLoS One. 2017;**12**:e0171559

[103] Shehade H, Kariolis MS, Stehr H, et al. Reprogramming the immunological microenvironment through radiation and targeting Axl. Nature Communications. 2016;**7**:13898

[104] Twyman-Saint Victor C, Rech AJ, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature. 2015;**520**:373-377

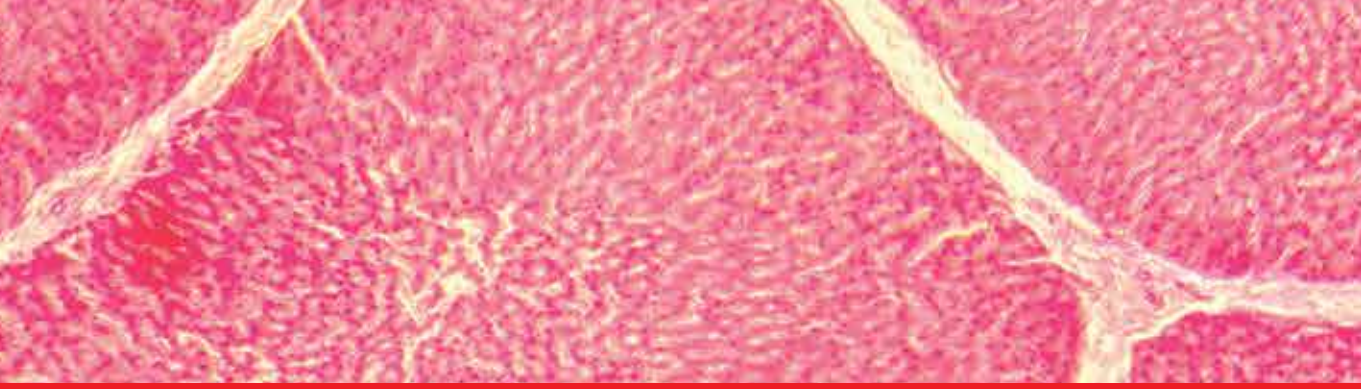
[105] Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. The Journal of Clinical Investigation. 2014;**124**:687-695

[106] Wild AT, Herman JM, Dholakia AS, et al. Lymphocyte-sparing effect of stereotactic body radiation therapy in patients with Unresectable pancreatic cancer. International Journal of Radiation Oncology, Biology, Physics. 2016;**94**:571-579

[107] Abe T, Saitoh JI, Kobayashi D, et al. Dosimetric comparison of carbon ion radiotherapy and stereotactic body radiotherapy with photon beams for the treatment of hepatocellular carcinoma. Radiation Oncology. 2015;**10**:187

[108] Toramatsu C, Katoh N, Shimizu S, Nihongi H, Matsuura T, Takao S, Miyamoto N, Suzuki R, Sutherland K, Kinoshita R, Onimaru R, Ishikawa M, Umegaki K, Shirato H. What is the appropriate size criterion for proton radiotherapy for hepatocellular carcinoma? A dosimetric comparison of spot-scanning proton therapy versus intensity-modulated radiation therapy. Radiation Oncology. 2013;**8**:48

[109] Mizumoto M, Oshiro Y, Okumura T. Proton beam therapy for hepatocellular carcinoma: A review of the University of Tsukuba experience. International Journal of Particle Therapy. 2016;**2**:570-578



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This book is contributed by worldwide experts in the field of liver diseases. It comprises of 3 sections and 6 chapters to introduce the intra-abdominal hypertension and abdominal compartment syndrome in chronic liver diseases, ascites with hyponatremia, acute kidney injury, portal vein thrombosis, spontaneous bacterial peritonitis in liver cirrhosis, and the use of stereotactic body radiation therapy in hepatocellular carcinoma. Clinicians and investigators who are interested in the management of chronic liver diseases will be acquainted with its merits and usefulness.

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