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Review article

# The Global Burden of Liver Cirrhosis Continues to Rise

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The global burden of liver cirrhosis continues to rise, while cirrhosis due to hepatitis B and hepatitis C is decreasing, cirrhosis due to nonalcoholic and alcoholic fatty liver disease is on the rise [1].

Cirrhosis is a consequence of chronic liver inflammation and generalized fibrosis and replacement of normal architecture by regenerative nodules and fibrous tissue, Cirrhosis runs a progressive asymptomatic course in the form of compensated chronic cirrhotic liver disease followed by decompensated course which are frequently associated with a wide range of complications, some of the complications are easy to be recognized and diagnosed in a timely manner, other complications are difficult to diagnose and usually unrecognized till late in the course of decompensated cirrhosis because symptoms are vague and nonspecific [2].

In this review, we summarized up-to date manifestation of decompensated cirrhosis, clinical picture, diagnosis and evidenced based management.

Despite the global prevalence and disease burden of cirrhosis, there is less public awareness and concern than for other chronic diseases like chronic obstructive air way disease, chronic heart failure, chronic kidney disease, and diabetes mellitus.

Transition from compensated asymptomatic cirrhosis to decompensated cirrhosis occurs at a rate of 7% per year [3]. Once decompensation has occurred, cirrhosis becomes a symptomatic disease affecting few organs in the body which includes circulation, oxygen exchange, immune system, kidney, lung, heart, brain and even skin, at this stage, patient becomes susceptible to bacterial and fungal infections, due to innate and acquired immune dysfunction [4]. Vasodilation of splenic circulation leads to reduce of effective velamina which leads to hypoperfusion of body organs, and leads to stimulation of the renin-angiotensin, aldosterone, sympathetic, argenin-vassopresin system, this leads to salt and water retention this explains ascites, hydrothorax, and other manifestations due to hemodynamic [5].

Disturbance leading to cirrhotic cardiomyopathy, aortopulmonary hypertension, hepatopulmonary syndrome, reduced cardiovascular responsiveness to physiological and pharmacological vasoconstrictor stimuli and cardiac dysfunction [6]. Splanchnic arterial vasodilation and hyperdynamic circulation are explained by endothelial dysfunction, nitric oxide, carbo monoxide, prostacyclin, endocannabinoids and Increased circulating levels of pro-inflammatory cytokines and chemokines, due to translocation of bacteria permeability due to changes in the microbiome and increased intestinal permeability [7].

Common manifestation easy to be recognized in time, Ascites, is the most common manifestation of commentated cirrhosis which occurs mainly due to renal sodium retention due to activation of renin -angiotensin-aldosterone system [RAAS] and sympathetic vasopressin arginine system, Cirrhosis is the main cause of ascites in Western countries, uncommon causes of ascites includes heart failure, malignancy, tuberculosis, pancreatic disease and lymphatic obstruction, ascites is graded into grade 1 which is only detectable by ultrasound , grade 2 which is manifested clinically by mild distension of both flanks, grade three which manifested by marked distension of the abdomen, Diagnostic paracentesis is indicated for all patients with grade 2 ascites.

Serum-ascetic albumin gradient [SAAG]>1.1 g/dl has an accuracy of 97%to diagnose asities due to portal hypertension, other important tests from ascetic fluid includes amylase, cytology, culture for mycobacteria,de-amynase, neutrophils, Pro- PNB, Ascetic fluid cholesterol, carcinoembryonic antigen and cytology have a high predictive value to diagnose malignant a cities, neutrophil count more than 250 cells/ul diagnose spontaneous primary peritonitis[PSB] total protein concentration less than 1.5 g/dl is considered a risk factor for PSB [8].

Development of asities due to cirrhosis denotes poor prognosis and eligible patients should be referred to Liver transplant, decreased glomerular filtration rate, hypotension, hyponatremia and low renal sodium excretion are predictors of high mortality in cirrhotic patients [9].

Patients with grade 2 ascites should be treated with salt restriction to one gram daily in addition to anti mineralocorticoid with a starting dose of 100mg daily with stepwise increase to 400mg daily, patients who develop hyperkaliemia or do not respond ant mineralocorticoid should be started on loop diuretics [Frusemide, starting dose is 40mg which could be increased to 160 mg, patients with chronic ascites should be treated by the combination of both diuretics, while patients on diuretics, the maximum daily body weight loss should be o.5 kg daily in the absence of lower leg edema and 1 gram daily in the presence of leg edema dose of diuretics could be reduced once ascites improved or resolved [10].

Diuretic therapy should be ceased once the patient developed gastrointestinal bleed or encephalopathy.

Patients with muscle cramps should be treated with albumin infusion or baclofen, Patients with large ascites should be treated with large volume paracentesis [LVP]and albumin infusion INR >1.5 and platelet counts less than 50,000are not contraindicated to LVP [12]. Removal of large volume of ascetic fluid without albumin infusion can lead to post -paracentesis circulatory dysfunction in the form of acute renal failure, hyponatremia and hepatic encephalopathy [11].

Patients undergoing LVP more than 5 liters of ascetic fluid, should receive albumin infusion at a rate of 8 grams per each liter removed, although patients undergoing LVP less than 5 liters has lower risk of post paracentesis circulatory dysfunction, they still benefit from albumin infusion or alternative plasma expander, diuretics should be reduced or ceased in patients undergoing LVP,acute kidney injury [AKI] and SPB are not contraindication for LVP, patients with ascites should not receive nonsteroidal anti-inflammatory, angiotensin covering inhibitor, angiotensin receptor blockers, alpha blockers or nephrotoxic medication, patients with refractory ascites with poor response to diuretics and salt restriction should be referred to liver transplant and diuretics should be stopped patients with intolerance to diuretics or develop complications like hyponatremia, hyperkaliemia, acute renal failure, should cease diuretics and receive LVP with albumin infusion [13].

Patients who secrete less than < 30mmol/day of sodium while on diuretics are considered having refractory ascites and diuretics should be ceased, and should be evaluated for trans jugular portosystemic stenting shunt [TIPS] [14].

## Tips Had Been Shown to Improve Survival and Treat Refractory Ascites

Small diameter-covered Stents reduce the risk of complications of TIPPS like hepatic encephalopathy, and stent dysfunction [15, 16].

Patients whom are not candidate for TIPPS can benefit from constrictive therapy like combination of Midodrine and selepressin or octreotide [17].

## Gastroesophageal Bleed

Gastro esophageal bleed is a medical emergency in patients with liver cirrhosis and portal hypertension and the second most common manifestation of decompensated cirrhosis after ascites [18].

The progression rate from small to large varices runs up to 22% in one year and 49% in three years in patient with child B or C cirrhosis in patients with alcoholic liver cirrhosis who have red wale marks during dysfunction during endoscopy compared to 2% and 15% respectively, this further amplified by concomitant liver dysfunction and AKI [19].

Endoscopic banding [EBL] and nonselective betablockers [NSBB]have comparative benefit in primary prophylaxis in high-risk varices, and both treatments should be offered for secondary prophylaxis.

EBL does not decrease portal hypertension in compare with NSBB, given the high prevalence of high risk.

Varices in decompensated liver cirrhosis, endoscopy should be performed to detect the size of varices and the presence of red wale marks, hepatic venous pressure gradient [HVPG] guided therapy is the most accurate measure of severity of portal hypertension and can be used when available but it needs expertise and it is invasive and con not be widely recommended.

Patients with medium size and red wale marks, large varices with no red well marks and small varices in child C cirrhosis should be treated with NSBB as a primary prophylaxis [20].

Patient with medium sized varices could be treated by either NSBB or EBL, NSBB is not a contraindication in patients with ascites, NSBB should be used with caution in refractory asities, high dosed should avoided and carvedilol should not be used because of its vasodilating effect, NSBB should be avoided in systolic hypotension, AKI, acute variceal bleed, SBP and sepsis NSBB can be used after recovery, patient who are intolerant to NSBB should offered EBL.

## Patients' intolerant to nsbb should be treated with covered Tipps

Patients with acute GIT bleed should be stabilized with packed red cell aimed to HB 90 grams, Vasoactive medication in the form of terlipressin or octreotide, erythromycin should be given before endoscopy in the absence Q-T prolongation and EBL should be performed after stabilization of the patient.

Fundal varices should be treated with ultra-sound guided insertion of coils and or/Cyanoacrylate, Volume replacement should be initiated promptly to restore hemodynamic instability, colloids or crystalloids can be used, patients should receive antibiotic prophylaxis for 5 days as it reduces the incidence of infections [21].

Pre-emptive covered TIPS within 24-72 hours can be used in high-risk patient with liver cirrhosis child C.

Patients who continued to bleed despite vasoactive therapy and EBL should be treated with TIPS, Uncontrolled upper GIT bleed should be treated with Balloon tamponade for a maximum time of 24 hours as a bridge to definitive treatment [22].

Cyanoacrylate is recommended for Corticofugal varices, Tipps with potential embolization can be used in fundal varices, Selective embolization may be used to treat fundal varices.

## Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis [BSP]is defined as infection of ascetic fluid in the absence of any surgical cause but only caused in liver cirrhosis due to translocation of bacteria, manifestation of BSP are vague which could be low grade fever, abdominal pain, vomiting, diarrhea or ileus, also. It could be manifested by renal failure, hypotension, hepatic encephalopathy and occasionally GIT bleed.

Diagnosis of BSP could be confirmed by diagnostic paracentesis with neutrophil counts of 250/mm. Patients who have positive ascetic culture and neutrophils counts less than 250 neutrophils are called bactericides and should be treated as BSP.

Diagnosis of spontaneous bacterial pleural empyema is based on positive bacterial pleural culture and increased neutrophil count >250/mm or sterile pleural fluid and pleural neutrophil counts >500 /mm.

Secondary bacterial peritonitis is a medical emergency where ascetic fluid contains multiple organisms, high protein and neutrophil count and the most common cause is perforation [19].

PSB should be treated with third generation cephalsporin,nosmocomial SBP due to antibiotic resistance should be treated with Piperacillin/tazobactam, spontaneous bacterial empyema should be treated as SBP,efficacy of antibiotic should be checked with a second paracentesis after 48 hours from starting treatment if there is worsening of symptoms, absence of marked reduction in leucocyte count by 25% denotes failure of antibiotic response, patient should be transfused 1.5 g.kg of albumin in day 1and 1g/kg in day 3.

High risk patients who had acute GIT bleed, and those with history of BSP should receive antibiotic as secondary prophylaxis, those with low ascetic fluid protein and no BSP should receive antibiotic as primary prophylaxis 400mg Norfloxacin is recommended as primary prophylaxis and Rifaximin as a secondary prophylaxis [20].

## Hepatorenal Syndrome

Hepatopulmonary Syndrome [HPS] is defined as a disorder of pulmonary oxygenation caused by intrapulmonary vascular dilation and less commonly by pulmonary or plural arterio-venous communication, commonly in patients with portal hypertension with or without cirrhosis.

Severe impairment of liver function or specific ethology are not needed for the clinical manifestation of HPS includes dyspnea and playpenoea which is characterized by increased shortness of breath on standing and improvement of dyspnea on reaccompany, hypoxia at rest and exacerbation on standing [orthodoxia], clinical, signs are nonspecific which includes digital clubbing and cyanosis in addition to signs of chronic liver disease, vascular abnormalities consists of diffuse or localized abnormal dilated capillaries and less commonly pulmonary and plural arteriovenous communications, which cause impaired oxygenation of venous blood as it passes through the pulmonary circulation, which result in ventilation perfusion(V/Q)mismatch.

Patients with portal hypertension and clinical suspicion of HPS should be assessed, PaO2 less than 80mm hg and or [alveolar-arterial [A-a] gradient > 15mm hg leads to further investigation, O2 saturation of < 96% and PaO2 less than 70% has a sensitivity of 100% and specificity of 88% [20].

Transoesopgeal echo with agitated saline can diagnose pulmonary sunt and exclude cardiac shunt, CT scan detect the caliber of peripheral f pulmonary arteries and arteriovenous communication, macroaggregated nuclear scan can quantify the magnitude of shunting, neither Transesophageal echo nor macroaggregated nuclear scan can differentiate between diffuse and focal arteriovenous shunting.

Long term therapy should be recommended to all patients with HPS, liver transplant is the most successful treatment for HPS and can result in complete cure and reversal of all abnormalities or significant improvement.

severe hypoxemia with large shunting at MAA scan is a strong predictor of cure after liver transplant.

patients who have contraindication to liver transplant can be

treated with local embolization if they have focal disease.

## Hepatic Hydrothorax

hepatic hydrothorax is defined as accumulation of transudate in the plural cavity in patient diagnosed with liver cirrhosis when pleural and pulmonary disease had been excluded, thoracic paracentesis should be performed to rule out infection, protein content in pleural exudate is low and serum to plural fluid albumin gradient is greater than 1.1 gram/dl has a high sensitivity and specificity for confirming the diagnosis of hepatic hydrothorax, we published a case of liver hydrothorax in patient with chronic hepatitis and cirrhosis in the absence of clinically detected ascites and we presumed the occurrence of pleural effusion in the absence of clinically detected ascites is explained by high positive intra-abdominal pressure and low negative intrapleural pressure and increased ascetic fluid absorption in the abdomen leads to accumulation of hydrothorax in the absence of asities, the presence and extent of diaphragmatic defects can be assessed indirectly by radioisotope technique and directly by MRI or color Doppler, treatment of hepatic hydrothorax.

hepatic hydrothorax is treated the same way of uncomplicated ascites, starting with low sodium diet, mineralocorticoid inhibitor and loop diuretics, large volume thoracic paracentesis will be limited to one liter per cession to prevent expansion pulmonary edema which is indicated when patient has dyspnea, clinician should be mindful that patient can tolerate high volume of ascetic fluid but the same is not applied to hydrothorax as one liter of pleural fluid can lead to severe dyspnea, in selected patients covered TIPPS insertion is recommended for recurrent symptomatic hepatic hydrothorax.

Mesh repair of diaphragmatic defects can be performed for management of hepatic hydrothorax in patient with early cirrhosis and no comorbidities, or kidney dysfunction.

Liver hydrothorax occurs more commonly in the right hemidiaphragm because of the greater muscular part than membranous where all the defects occur compare with the left diaphragm where the membranous portion is larger than the muscular part.

Pleurodesis can be offered to patients who are not candidate for TIPPS or liver transplant, Liver transplant represents the best option for patients with refractory hepatic hydrothorax [21-23].

## Cirrhotic Cardiomyopathy

Cirrhotic cardiomyopathy is defined as chronic cardiac dysfunction in the form of decreased contractile response, diastolic relaxation and electrophysiological abnormalities in the form of prolonged Q-Tc in response to pharmacological stress or physical exercise, cirrhotic cardiomyopathy is subclinical at rest but its presence adversely impacts on liver transplant and TIPPS insertion.

Patients with cirrhotic cardiomyopathy have normal or even increased left ventricular ejection fraction at rest due to increased hyperdynamic circulation and reduced afterload to maintain cardiac output.

Diagnosis of cirrhotic cardiomyopathy can be confirmed with stress echo either pharmacologically or with exercise which usually show lack of appropriate left ventricular contraction and impaired diastolic relaxation, in advanced disease systolic dysfunction is unmasked by reduction in peripheral vascular resistance, currently the standard of care is measuring the left ventricular global longitudinal systolic strain which facilitates the diagnosis of systolic function in response to stress and at rest.

American society of Echocardiography and European Association of cardiovascular imaging guidelines for evaluation of diastolic dysfunction recommend the following criteria based on normal left ventricular ejection fraction, Average E/e.14.

Septal e velocity <7cm/s
Lateral e velocity <10cm/s
Tricuspid velocity >2.8m/s
Left atrial volume index >34ml/m.
Clinician should be aware that vasoactive dugs and beta-blockers in cirrhosis can lead to heterogenicity in calculating the degree of diastolic dysfunction, therefore it is advised to withhold betablocker before performing echocardiography.

Cardiac reserve is a major consideration for elective TIPPS placement and 2D echo is the standard of care, some patients develop cardiac decompensation post TIPPS implantation due to decreased cardiac reserve, one study showed that the presence of diastolic dysfunction is associated with higher degree of ascites and plasma renin activity in 35%of patients who developed hepato-renal syndrome type 1[480].

Prolongation of Q-Tc interval is common in cirrhosis and should be evaluated since it may indicate unfavorable outcome and should alert the clinician to cease medication causing Q T c prolongation, Diastolic dysfunction could be an early sign of cardiomyopathy in the setting of normal systolic function.

Using the resent guidelines namely E/e>14, Tricuspid velocity>.2.8m/s and left atrial volume index/34ml/m.

Patient with cirrhotic cardiomyopathy and cirrhosis are at risk to develop acute kidney injury and spontaneous peritonitis due to reduced cardiac out.

## Porto Pulmonary Hypertension

Diagnosis of Porto pulmonary hypertension [PPTH]should be considered in every patient with established portal hypertension including non-cirrhotic portal hypertension in the absence of other causes of pulmonary hypertension namely chronic venous, chronic thromboembolic, chronic hypoxic pulmonary hypertension in the presence of normal capillary

wedge pressure, and should be screened with transthoracic echocardiography followed by right heart catheter, Beta-blockers should be stopped and varices managed by endoscopic therapy when the diagnosis of PPTH is confirmed.

Patients diagnosed with PPTH should receive medication approved for primary pulmonary hypertension to improve hemodynamics and exercise tolerance with caution when using endothelin antagonists because of their side effect on liver function, TIPPS is contraindicated in patients with PPTH because anticipated increase in cardiac output and right ventricular filling pressure can increase peripheral vascular resistance and right sided pressure overload.

Patients with severe PPTH with mean pulmonary artery pressure >45 mm>should be treated to get mean pulmonary artery pressure <35mm>hg before patient can be listed for liver transplant, MELD exception can be considered and advocated in patients with PPTH of moderate severity (Mean pulmonary artery pressure[>35mm>hg] in whom targeted treatment lowered mean pulmonary artery pressure to [<35mmhg] and peripheral vascular resistance less than 400 dynes/s cm.

MELD exception can be considered to patients with PPTH in whom targeted therapy failed to decrease.

Mean pulmonary artery pressure less than 35mm/hg but improved peripheral vascular resistance to 240Dynes/s cm as well as right ventricular function [23-26].

## Acute-On Top of Chronic Liver Failure

Acute on chronic liver failure (ACLF)is defined as a multi-organ failure in patient with established liver cirrhosis, the main cause in western countries are bacterial infections and binge alcohol while reactivation of HBV is the main triggering factor in Asian countries, mainly genotype B, D and hepatitis E.

Antigen positive, superimposed infection with HAV and HEV can trigger ACLF in cirrhotic patients.

The diagnosis of ACLF should be made in cirrhotic patients who developed worsening of ascites, encephalopathy, deepening of jaundice, GIT bleed, AKI and failures of other organs, investigation and treatment of the triggering factors [bacterial infection, HBV, HDV, HEV, HAV, autoimmune hepatitis, Alcohol, GIT bleed] are the standard of care, patient should be treated in intensive care unit.

Acute kidney injury [AKI] and hepatorenal syndrome [HRS] AKI is common in liver cirrhosis, pre-renal failure is the most common cause of AKI and post renal AKI is very rare in cirrhosis, differentiate renal AKI from acute tubular necrosis [ATN] is very difficult without kidney biopsy, recently a novel marker urinary neutrophil gelatinase associated lipocalin[NGAL] is the most promising to diagnose acute tubular necrosis [ATN], when a diagnosis of AKI is made, its cause. Should be investigated as soon as possible to prevent progression of AKI, infection should be searched for and treated, all drugs include betablockers, diuretics, vasodilators, NSAID, and other nephrotoxic medications should be stopped, patients with AKI should be treated with Albumin solution [20%] at a dose of 20-40g/day, with monitoring of fluid balance to avoid overload, Terlipressin is the vasoconstrictive of choice, Noradrenaline can be alternative to Terlipressin, Liver transplant is the best therapeutic option for patients with HRS regardless of the response to medical treatment.

Liver -kidney transplant should be considered in patients with significant CKD or with sustained AKI including HRS-AKI with no response to medical therapy.

TIPPS should not be offered to patients with HRS-AKI except in very selected situation [27-30].

## Hyponatremia

Hyponatremia in cirrhotic patients presents a poor prognosis with increased mortality and morbidity, patients should be evaluated, treatment should include removal of the triggering factor and administration of normal saline in hypovolemic hyponatremia.

Patients with hypervolemic hyponatremia should be treated with restriction of fluid to one liter a day.

Treatment with hypertonic saline in hypervolemic hyponatremia should be limited to rare cases with severe symptomatic hyponatremia and severe asymptomatic hyponatremia who are expected to receive liver transplant within days, correction of hyponatremia should be not more than 8mmol over24 hours to avoid central demyelination.

Use of albumin and vaptan should be limited to very few patients enrolled in clinical studies [27-30].

## Relative Adrenal Insufficiency

Relative adrenal suffice [RAI]is a condition of inadequate cortisol production in response of stress in the setting of critical illness, RAI had been described in cirrhosis ,diagnosis can be made by a random total cortisol of less than 276nmol/L or a delta serum total cortisol less than 248nmol/L after injection of 250ug corticotropin, salivary cortisol was found to be more accurate because cortisol concentration can be affected by reduced serum level of cortisol binding globulin and reduced albumin in cirrhotic patients.

Relative adrenal insufficiency in cirrhotic patients blunts the function of angiotensin11, norepinephrine and vasopressin which worsen the cardiocirculatory dysfunction of cirrhosis and favor the bacterial translocation, hydrocortisone is not recommended [31-33].

In conclusion, Decompensated cirrhosis a a common reason for admission to medical assessment unit, patients often have a complex medical needs and at a high risk of in-hospi-

tal death, early assessment by a senior physician is of a paramount importance for a fast track investigation for manifestation of decompensation like jaundice, ascites, worsening hepatic encephalopathy, acute on top of chronic liver failure, GIT bleed, hepato-renal syndrome, sepsis, primary spontaneous peritonitis, acute kidney injury.

Hepatic hydrothorax, cirrhotic cardiomyopathy, hepatopulmonary syndrome, Porto pulmonary hypertension, primary pulmonary empyema, symptomatic hyponatremia, and relative adrenal insufficiency, dawn streaming to hepatologist and multidisciplinary team will ensure that patient will receive the right care in a right time in the right place by the right team.

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