Cirrhosis: a Multistate-Disease due to its Complications, Which can be Prevented by Old Drugs with New Indications

Alberto E. Muñoz[1,2,3]

[1]Servicio de Hepatología, Clínica Bazterrica, [2]Sección de Hepatología, Hospital Dr. Carlos Bonorino Udaondo. [3]Universidad de Buenos Aires, Facultad de Odontología, Instituto de Investigaciones en Salud Pública, Ciudad Autónoma de Buenos Aires, Argentina.

aemunoz@intramed.net

Abstract— Cirrhosis has been considered an irreversible and terminal disease. In this way, the natural history of cirrhosis comprised of two stages. The first one was an asymptomatic and, generally, a long period named "compensated cirrhosis." This period is followed by a usually rapidly progressing phase known as "decompensated cirrhosis." Decompensated cirrhosis was considered irreversible and currently had as its only therapeutic alternative, liver transplantation. Now, cirrhosis should be considered as a multistate-disease. The progression of cirrhosis is a consequence of its complications. Early cirrhosis diagnosis would allow administering licensed, safe, and effective drugs that prevent complications of cirrhosis. Prevention of complications of cirrhosis is a relevant aim, to try to prolong survival and reduce the need for liver transplantation. On the other hand, we showed a matched cases-series study, where simvastatin was added to the standard treatment of patients with decompensated cirrhosis and cardiovascular risk factors. This study showed an improvement in the survival of patients who agreed to add simvastatin versus those who did not.

Index Terms— Cirrhosis, diagnosis, dynamic disease, efficacy, epidemiology, natural history, new treatments, pathophysiology, safety, survival.

1. Introduction

This review updated current knowledge of cirrhosis as a dynamic process, based on the division in clinical prognostic states, due to the development of complications of cirrhosis. Likewise, address the new concept in the management of patients with cirrhosis by the use of nonspecific therapies for prevention and early intervention to stabilize disease progression and to avoid or delay decompensation and the need for liver transplantation [1, 2].

2. Epidemiology

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. In Western Europe, cirrhosis is the fourth cause of disability-adjusted life of years in males after ischemic heart disease, low back pain, and lung cancer [3]. It is the 13th most common cause of death in adults worldwide, with worldwide mortality having increased by 45.6% from 1990 to 2013 [3], [5]. Cirrhosis is the main indication for 5,500 liver transplants each year in Europe [6]. The leading causes in more developed countries are infection with hepatitis C virus (HCV), alcohol misuse, and non-alcoholic fatty liver disease (NASH); infection with the hepatitis B virus (HBV) is the most common cause in sub-Saharan Africa and most parts of Asia. The prevalence of cirrhosis is difficult to assess and probably higher than reported because the initial stages are asymptomatic, so the disorder is undiagnosed.

A diagnosis of compensated cirrhosis is associated with a risk of death that is 4.7 times as high as the risk in the general population, and decompensated cirrhosis is associated with a risk that is 9.7 times as high [7]. The average life expectancy of a patient with compensated cirrhosis is 10 to 13 years, and the average life expectancy may be as low as 2 years if there is decompensation [8]. Among patients with alcoholic cirrhosis, 65% of the patients who abstain from drinking alcohol are alive at 3 years, as compared with 0% who continue drinking alcohol [9].

1.1 Pathophysiology

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing

fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion [10]. This process leads to pronounced hepatic microvascular changes, characterized by sinusoidal remodeling (defenestration of liver sinusoidal endothelial cells, basement membrane development, and extracellular matrix deposition in Disse space from proliferating activated stellate cells) resulting in capillarisation of hepatic sinusoids, the formation of intrahepatic shunts (due to angiogenesis and loss of parenchymal cells) [11]. Capillarisation of sinusoids and intrahepatic shunts interfere with adequate hepatocyte perfusion, which are the major determinants of ***liver failure***.

The raised hepatic resistance to portal blood flow is the primary factor increasing portal pressure in cirrhosis. It results from the combination of structural disturbances associated with advanced liver disease (accounting for about 70% of total hepatic vascular resistance). On the other hand, insufficient production of nitric oxide by endothelial nitric oxide synthase is associated with endothelial dysfunction. Endothelial dysfunction, increase hepatic vascular tone in another 30%. Splanchnic vasodilation with an ensuing increase in the inflow of blood into the portal venous system contributes to aggravate ***portal hypertension*** [12].

1.2 Natural history

The natural history of cirrhosis is typically described in two phases [13]. The first one is an asymptomatic and, generally, a long phase named "compensated cirrhosis." This period is followed by a usually rapidly progressing phase known as "decompensated cirrhosis," which involves complications of ***liver failure*** and/or ***portal hypertension***. The change from the first stage to the second one implies a poorer quality of life and a significant increase in the mortality rate from 1% to 57% per year [13]. However, cirrhosis should no longer be regarded as a terminal disease, and the concept of a dynamic process is increasingly accepted. Further disease stages have been identified according to the presence of esophageal varices and to the presence of only one or more cirrhosis complications [1]. Several clinical conditions, associated with significantly different outcomes, have been proposed as relevant clinical states during the course of the disease [1], [2], [14], [15], [16], [17], [18]. However, it is notable that there is no predictable sequence of such clinical states and that they may not be considered as progressive disease states. Nevertheless, clinical states enable the classification of patients according to increased mortality risk. Moreover, assessing transitions across states may facilitate the description of the clinical course of the disease in a multistate- model. A schematic representation of a hypothetical multistate-model encompassing the whole course of cirrhosis is shown in Fig. 1 [1].

States 0 and 1 are established by measurement of the hepatic venous pressure gradient (HVPG) and hepatic elastography and determination of liver stiffness measurement. Mortality: 1.5%/5 years.

State 2 is determined by the presence of varices. Mortality: 10%/5 years.

States 3 to 6 are defined by different cirrhosis complications. Mortality, state 3: 20%, state 4: 30%, state 5: 88%/5 years, respectively. State 6: mortality, 80%/1 year.

Finally, ***acute-on-chronic liver failure*** may occur in any disease state [19].

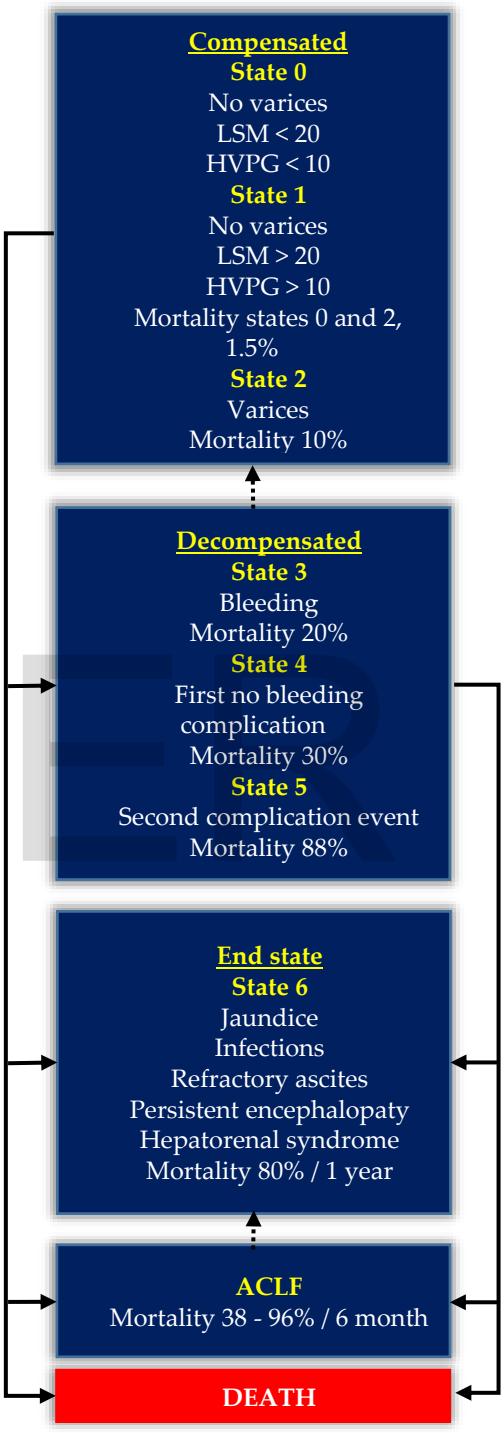


Figure 1. Schematic representation of a multistate-model for the clinical course of cirrhosis

1.3 Diagnosis

Cirrhosis is a frequently indolent, asymptomatic, and unsuspected disease until complications of cirrhosis present.

Besides, a sizable proportion of these patients never come to clinical attention, and previously undiagnosed cirrhosis is still frequently found at autopsy [20]. The increasing burden of liver disease and the problem of late presentation with decompensation emphasize the need for population screening to identify patients with chronic liver disease, similar to screening for cardiovascular risk factors. Screening would make it possible to identify many people with cirrhosis in their asymptomatic phase and to begin their treatment by avoiding or delaying the appearance of the complications of cirrhosis.
Beyond the selection of the population, which should be taken care of by each health system, it is prudent to remember at this point in this review, that each physician has in clinical practice tools such as questioning, physical examination, and laboratory and imaging data that suggest the presence of cirrhosis. See Table 1.

Table 1. Medical Appointment, Clinical Features, Laboratory, and Imaging Findings of Cirrhosis

Questioning	Alcohol consumption (female < 20 gr/day, male < 30 g/day), IV drug addiction, transfusions, history of liver disease, tattoo, piercing, autoimmune diseases, no physical activity, obesity, type 2 diabetes, hypercholesterolemia, hypertension
Physical examination	Vascular spiders, palmar erythema, white nails, gynecomastia, loss of male hair pattern, nodular liver, splenomegaly, jaundice, ascites, flapping, parotid hypertrophy and Dupuytren's contracture (alcohol)
Laboratory	Increase: AST, ALT, ALP, GGT, bilirubin, immunoglobulins (mainly IgG) Decrease: red cells, white cells, platelets, albumin, prothrombin time, serum sodium
Imaging	Ultrasonography, computed tomography, magnetic resonance imaging, endoscopy
Confirmation	Liver biopsy, transient elastography (LSM)

1.4 Treatment

1. Compensated cirrhosis.

In these states of cirrhosis, treatment strategies can be considered in three groups: lifestyle changes, viral hepatitis therapies, and nonspecific therapies**.**

1.4.1.1 Lifestyle changes

Lifestyle changes tend to be overlooked in the management of cirrhosis because life expectancy is judged to be short, and the benefit is difficult to measure. Although evidence comes from cohort or case-control studies, lifestyle advice should still be offered to all patients, because it is easily implemented with little risk of side effects or cost.
Tsochatzis, Bosch, and Burroughs [21] show in their Seminar that *i**nsulin resistance, obesity, and metabolic syndrome*** are pathophysiologically linked with NASH, but they have deleterious effects irrespective of liver disease etiology. ***Obesity*** is an independent predictor of cirrhosis in alcoholic liver disease, and the presence of metabolic syndrome is associated with more severe fibrosis and cirrhosis in chronic liver disease. In 161 patients with compensated cirrhosis who were followed up prospectively, obesity was independently associated with clinical decompensation, together with HVPG and serum albumin. Moreover, insulin resistance and metabolic syndrome were independently associated with liver-related mortality in a NHANES-III cohort of more than 2,500 patients with chronic liver disease. Insulin resistance predicts the occurrence of hepatocellular carcinoma (HCC) in cirrhosis, and in large cohorts, both diabetes and metabolic syndrome increased the risk of HCC. Overweight patients with compensated cirrhosis (clinical states 1 and 2) should, therefore, be advised to lose weight to lower their long-term risk of liver complications. In patients with decompensated cirrhosis, the maintenance of adequate nutrition is essential to avoid loss of muscle mass. Such patients have a low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion, which can also contribute to the development of hepatic encephalopathy. In a randomized controlled trial (RCT), a nutritional supplement given in the late evening over 12 months resulted in body protein accretion equivalent to 2 kg lean tissue; this approach should, therefore, be advised in such patients.
Alcohol intake is deleterious in patients with alcoholic cirrhosis but also in those with liver disease of other causes. In alcoholic cirrhosis, alcohol ingestion increases HVPG and portocollateral blood flow. These effects are also likely in cirrhosis of different reasons, thereby increasing the risk of variceal bleeding. Only abstinence from alcohol improves survival in alcoholic cirrhosis. In patients with chronic hepatitis C, alcohol intake increases the risk of cirrhosis and decompensated liver disease two to three times, even with moderate consumption. Moreover, alcohol intake is an independent risk factor for HCC in chronic hepatitis C and NASH. Therefore, all patients with cirrhosis, irrespective of the clinical stage, should be advised to abstain from alcohol with relevant counseling if appropriate. Multidisciplinary alcohol care teams can lower the risk of acute hospital admission and improve the quality of care. In many centers, abstinence, irrespective of liver disease etiology, is mandatory for the patient to be considered for liver transplantation.
Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible because the antigenic response becomes weaker as cirrhosis progresses.
Cigarette smoking is associated with more severe fibrosis in chronic hepatitis C, NASH, and primary biliary cirrhosis and possibly increases the risk of HCC in chronic hepatitis B. Smoking cessation, therefore, should be advocated to prevent the progression of liver disease and to facilitate eligibility for liver transplantation. Smoking also increases post-transplant morbidity and mortality. ***Cannabis use*** worsens fibrosis in chronic hepatitis C.
Antioxidant-rich foods and drinks have a potential preventive role in cirrhosis. ***Coffee*** consumption improves all-cause of

mortality but is also associated with a significant reduction in fibrosis in liver disease of various causes and with reduced risk of HCC, as shown in a meta-analysis including 2,260 patients with HCC. For most of the benefits described, at least two cups of coffee daily are needed. In a phase 2 RCT, the ingestion of ***dark chocolate*** blunted the post-prandial HVPG increase in cirrhosis by improving flow-mediated hepatic vasorelaxation and ameliorated systemic hypotension. The same effect on HVPG was noted with the short-term administration of ***ascorbic acid***.

Physicians should always bear in mind drug interactions and the possible need for dose reductions when prescribing for patients with cirrhosis.

1.4.1.2 Viral hepatitis therapies

Chronic hepatitis B (CHB). The EASL 2017 clinical practice guidelines on the management of HBV infection [22] notes that long-term therapy with nucleos/tide analogues (NA) entecavir or tenofovir has been shown to halt the progression of liver disease as result of a significant improvement of histological necroinflammation and fibrosis, often with regression of established cirrhosis. Moreover, complications of pre-existing decompensated cirrhosis, particularly at an early stage of decompensation, improve or even disappear, and the need for liver transplantation is dramatically reduced. HCC may still develop and remains the major concern for CHB patients treated with NA. Long-term therapy with NA appears favorably influence HCC incidence when data from randomized or matched controlled studies are considered. After the first 5 years of entecavir or tenofovir therapy in CHB patients, recent data suggest that the HCC incidence is decreasing further, with the decrease being more evident in patients with baseline cirrhosis. Besides, HCC seems to be the only factor affecting long-term survival in entecavir or tenofovir treated CHB patients with or without compensated cirrhosis.

Chronic hepatitis C (CHC). The EASL recommendations on treatment of hepatitis C 2018 [23], consider that among patients with CHC and advanced hepatic fibrosis, sustained virological response (SVR) to interferon-based therapy was associated with lower all-cause mortality. Long-term post-SVR follow-up studies after direct-acting antiviral treatment showed that the risk of developing HCC remains in patients with cirrhosis who eliminate HCV, although it is significantly reduced compared to untreated patients or patients who did not achieve an SVR. Thus, the duration of HCC surveillance in patients with advanced fibrosis or cirrhosis who achieve an SVR is indefinite. On the other hand, patients with cirrhosis, surveillance for esophageal varices by endoscopy should be performed if varices were present before treatment. However, index variceal bleed is seldom seen in low-risk patients after the achievement of SVR (unless additional causes for ongoing liver damage are current and persist).

1.4.1.3 Nonspecific therapies

The high morbidity and mortality of cirrhosis led to highlight the need for preventive therapies in such patients, to delay the advent of complications, using the paradigm of prevention of cardiovascular diseases, according to which interventions are offered to individuals with a 10% 10-year risk of cardiovascular events [24]. Tsochatzis, Bosch and Burroughs [25], [26] argue that in the 21th century, a new therapeutic paradigm for patients with cirrhosis is the combination with already licensed, inexpensive, and relatively safe drugs could be given in a highly cost-effective way. Currently, licensed drugs, such as non-selective β blockers (NSBB), statins, oral antibiotics, and anticoagulants, are likely to be used in various combinations to prevent and treat complications of cirrhosis.

NSBB were the first established preventive pharmacologic therapy in cirrhosis. However, besides their role in reducing HVPG, there seems to be a "pleiotropic" effect in cirrhosis, not entirely explained by a marked reduction in HVPG. Indeed, in a long-term follow-up of RCT comparing band ligation with NSBB for secondary prevention of bleeding, although recurrent bleeding was more frequent with NSBBs, survival was increased by 21%, suggesting a therapeutic effect over the prevention of bleeding. Meta-analysis indicates that NSBB prevents spontaneous bacterial peritonitis in patients with cirrhosis. This may be independent of the hemodynamic response because NSBB reduces splanchnic blood flow and thus intestinal congestion and increases bowel transit time, all of which may reduce bacterial translocation across the gut. This adds to the evidence linking infection and bleeding in cirrhosis; indeed, prophylactic antibiotics reduce early re-bleeding after acute variceal hemorrhage. NSBB could be used in cirrhosis irrespective of the hemodynamic response, although their use does not prevent the formation of varices. Propranolol (or nadolol) could be the "aspirin of hepatologists."

Statins reduce HVPG and are associated with reduced incidence of HCC.

Rifaximin is a potential alternative for the prevention of spontaneous bacterial peritonitis since no bacterial resistance has been documented. In observational studies, HVPG and plasma endotoxin concentrations were lower with this treatment, systemic hemodynamics and renal function also improved, but these findings need confirmation.

Anticoagulation used to be considered a contraindication in cirrhosis; however, normal thrombin generation and even hypercoagulability characterize stable cirrhosis. Currently, anticoagulation is evaluated only in patients with portal-vein thrombosis awaiting liver transplantation. However, a RCT of enoxaparin in 70 patients with advanced cirrhosis showed that the drug was associated not only with a lower risk of portal-vein thrombosis but also with delayed decompensation and improved survival.

The calculated annual cost per patient of combination therapy with propranolol, simvastatin, norfloxacin, and warfarin in the UK was £128/year, equivalent to $196/year or €154/year. However, it is essential to note that confirmatory trials are needed before these findings can be translated into clinical practice.

1.4.2 Decompensated cirrhosis

Ge and Runyon [4] noted that the economic burden of cirrhosis in the United States is substantial, with annual direct costs

exceeding $2 billion and indirect costs exceeding $10 billion. Annual costs increase with decompensation, with costs of $2,400 for the treatment of diuretic-sensitive ascites, $24,800 for the treatment of diuretic-refractory ascites, $25,600 for the treatment of variceal hemorrhage, $16,400 for the treatment of hepatic encephalopathy, and $44,200 for the treatment of HCC. Patients with cirrhosis are plagued by frequent hospital readmissions for fluid overload, hepatic encephalopathy, or gastrointestinal hemorrhage. Such readmissions are costly, moderately predictable, frequently preventable, and associated with a risk of death. One study showed that 69% of patients had at least one non-selective readmission, including 14% who were readmitted within 1 week after discharge and 37% who were readmitted within 1 month. The average rate was three hospitalizations per person-year, and 22% of the readmissions were potentially preventable.

Care coordination is an increasingly popular concept to improve quality and clinical outcomes while reducing readmission rates and expenditures. Care coordinators facilitate inpatient-to clinic transitions, reconcile medications, and call patients to prevent unnecessary visits to the emergency department, place "smart scales" in homes to monitor body weight remotely, facilitate interaction with other health care professionals, and arrange referrals to nursing facilities or hospice. A recent study compared a traditional system involving family physicians and regular consultation with a coordinated system comprising a specialized team of nurses and hepatologists. The results favored care coordination: 30-day and 12-month readmission rates were lower, as was 12-month mortality, and expenditures were 46% lower with care coordination than with the traditional system.

A detailed management review of the complications of cirrhosis is beyond the scope of this manuscript. Significant advances have been made in recent years to both prevent and treat the common complications of cirrhosis, such as variceal bleeding, ascites, spontaneous bacterial peritonitis, and encephalopathy, as shown in Fig. 2 [21].

Nonspecific therapies already developed in compensated cirrhosis are also implemented in patients with decompensated cirrhosis.

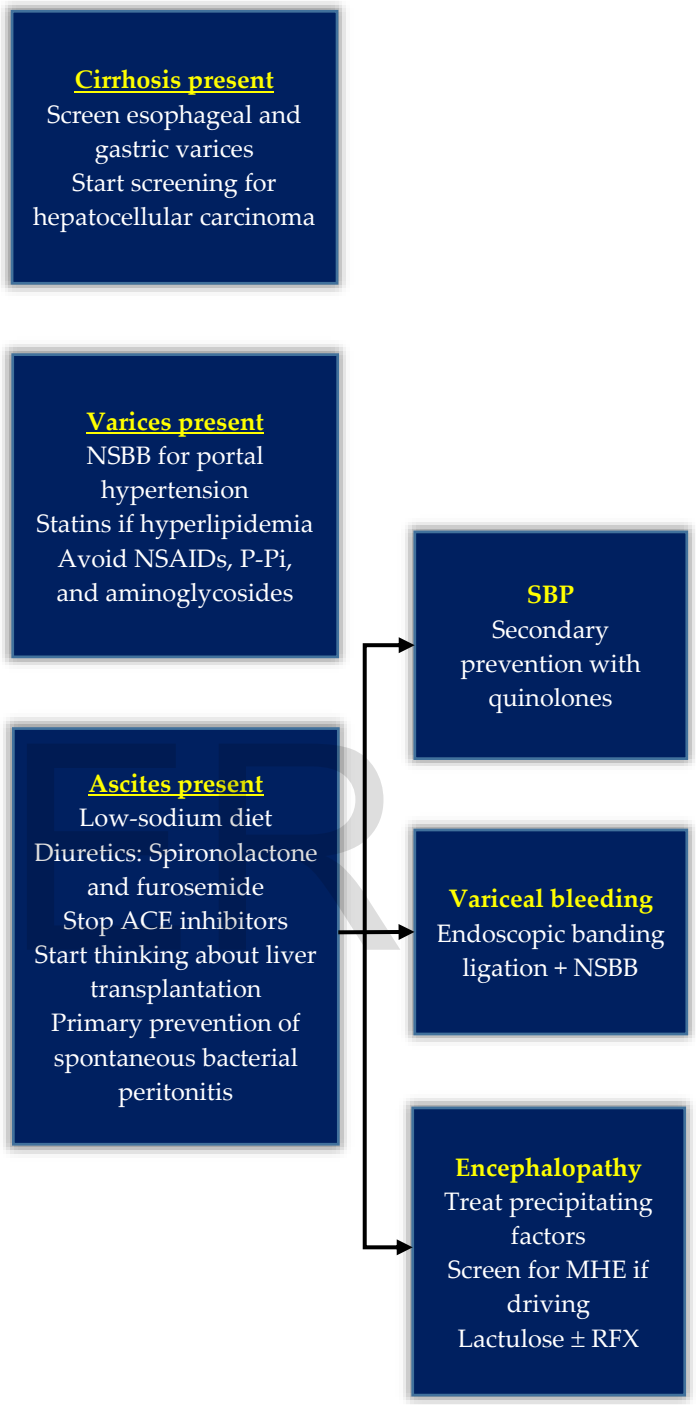


Figure 2. Approach to preventing and treating complications of cirrhosis. NSBB: non-selective β blockers; NSAIDs: non-steroidal anti-inflammatory drugs; P-Pi: proton-pump inhibitors; ACE: angiotensin-converting enzyme; SBP: spontaneous bacterial peritonitis; MHE: minimal hepatic encephalopathy; RFX: rifaximin.

3. A matched cases-series study

3.1 Background and rationale

The high mortality rate of patients with decompensated cirrhosis highlights the need for new treatments. Atherosclerosis has been widely recognized as an inflammatory process that leads to acute clinical cardiovascular events [27]. Likewise, statins prevent atherosclerotic inflammatory vascular disease by two mechanisms [28]. First, a direct mechanism that works through the reduction of the plasma cholesterol level. Second, there is an indirect mechanism known as "pleiotropic effect." The latter mechanism is independent of cholesterol and known as "pleiotropic effect," which includes nitric oxide (NO) enhancement bioavailability in endothelial cells [29]. On the other hand, Zafra et al. observed that acute administration of simvastatin to patients with cirrhosis and portal hypertension decreased hepatic sinusoidal resistance by increasing NO liver output [30]. Finally, a Danish cohort study involving 10,154 patients with cirrhosis showed that after one year of follow-up, the major causes of death were ischemic heart disease, peripheral vascular disease, and stroke [31]. With this data available in 2007 and on this rationale basis, was offered to add simvastatin to standard treatment for patients with decompensated cirrhosis and cardiovascular risk factors, to assess whether simvastatin has any clinical benefit.

3.2 Aim

To assess whether the addition of simvastatin to standard treatment has any clinical benefit in patients with decompensated cirrhosis and cardiovascular risk factors.

3.3 Methods

Study site, design and period
Liver Service, Clínica Bazterrica, Buenos Aires, Argentina.
This matched cases-series study was conducted from April 2007 to October 2019.

Inclusion criteria
To be over 18 years, both genders, previous history of decompensated cirrhosis (ascites, variceal bleeding, encephalopathy, and/or jaundice), documented existence of cardiovascular risk factors.

Exclusion criteria
Pregnancy and being candidates for liver transplantation.

The following parameters matched both groups: age ± 3 years, gender, etiology of cirrhosis, Child-Pugh class, and Model for End-Stage Liver Disease (MELD) score ± 3 points. The groups matched at a ratio of 1:1.

Patients
The target population of the trial included all patients with decompensated cirrhosis from outpatient clinical practice.
Case group (n = 9): included patients who agreed to add simvastatin to standard treatment.
Series group (n = 9): included patients who did not agree to add simvastatin to standard treatment.

Primary endpoint
To assess whether the addition of simvastatin to standard treatment has any clinically relevant effect in patients with decompensated cirrhosis and cardiovascular risk factors, though the proportion of patients who: 1) developed complications of cirrhosis or cardiovascular events, 2) impaired liver function assessed through Child-Pugh and MELD scores at the end of the study versus baseline, and 3) died during the study.

Secondary endpoint
To assess the safety of simvastatin through the proportion of patients who developed adverse events and serious adverse events related to simvastatin, and therefore had to modify simvastatin dosage.

Statistical analysis
The data were collected, classified, and analyzed using SPSS Statistics 25.0 statistical package program (IBM). Figure 5 was designed with MedCalc 11.2 version. The date of the first cirrhosis complication was established as the time zero for both groups. A comparison of dichotomous variables was made by McNemar test. Paired t-test was used to compare continuous variables. In the case of abnormally distributed variables, non-parametric Wilcoxon-signed rank test was implemented. The cumulative survival function was estimated by the Kaplan-Meier and Mantel-Cox tests. Both groups were compared with the stratified log-rank test and hazard ratios (HR) (95% confidence interval [CI]), calculated using the Cox model. A $P < 0.05$ was considered statistically significant.
We followed the STROBE Statement to design and write this study [32].

3.4 Results

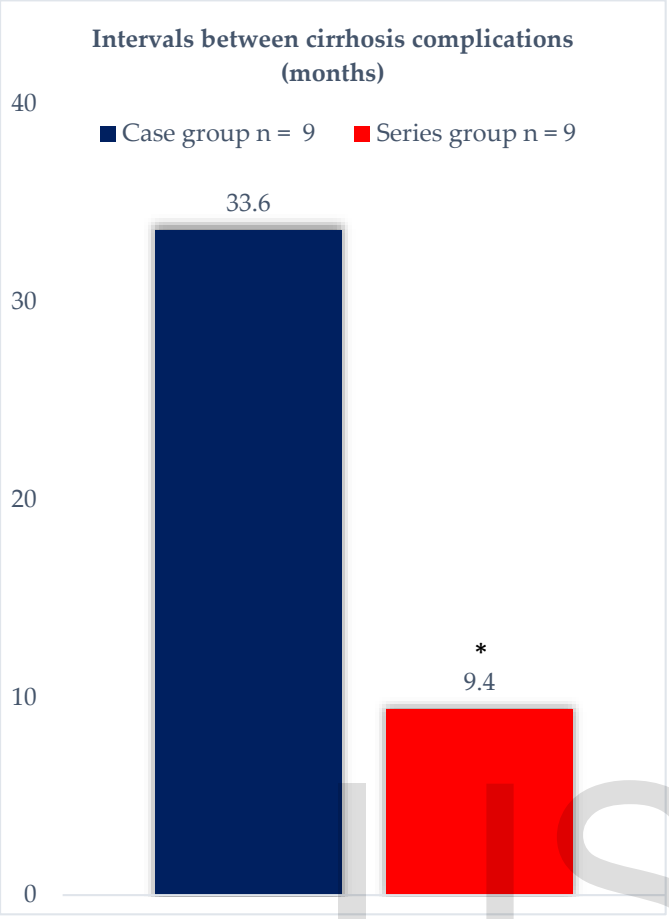


Figure 3. Intervals between cirrhosis complications in Case group and Series Group (months) * P = 0.0065 vs. Case group

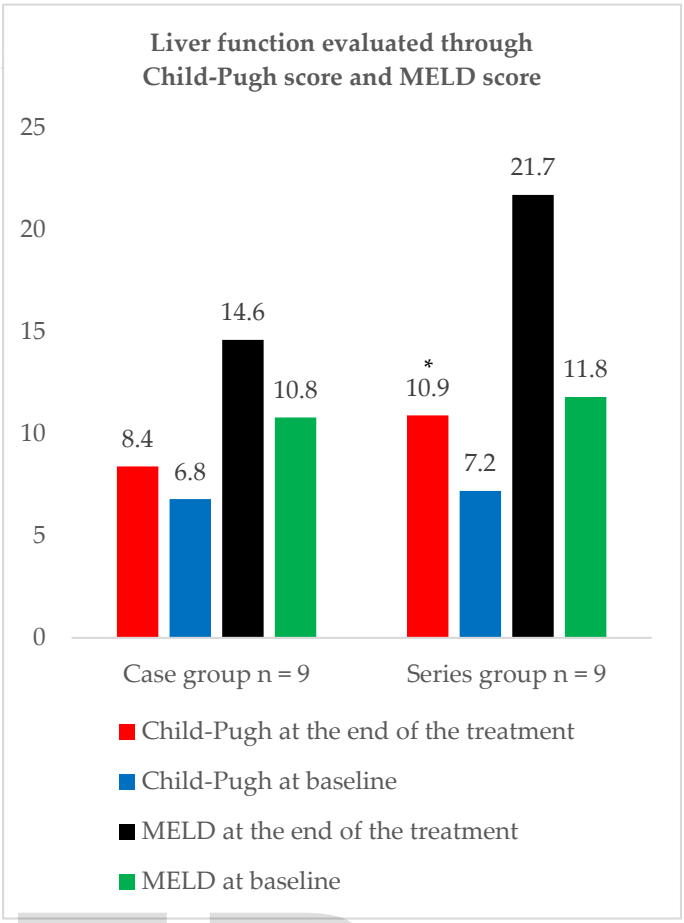
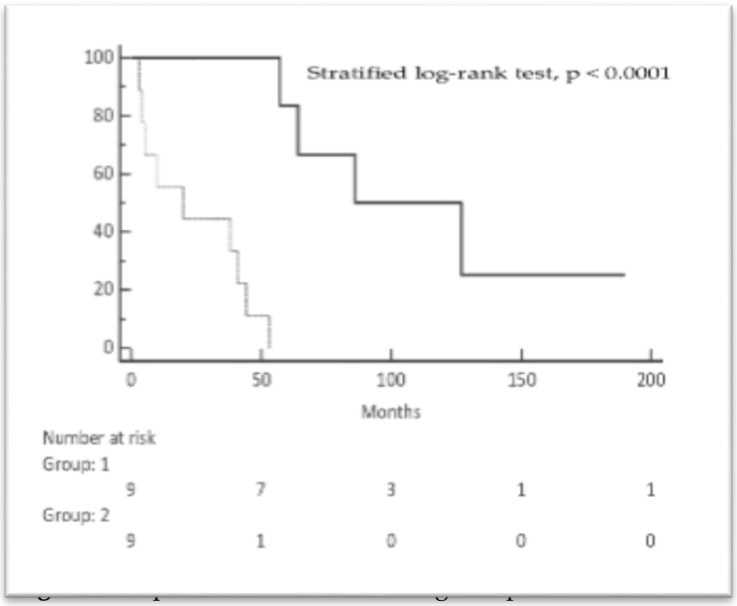


Figure 4. Liver function evaluated through Child-Pugh score and MELD score, at the end of the treatment vs. baseline. * P = 0.0026 vs. Child-Pugh baseline, ** P = 0.0028 vs. MELD baseline. In Case group, no statistical differences were observed at the end of the treatment vs. baseline in Child-Pugh score and MELD score.



group (continuous line; group 1, bottom) had significantly higher survival than patients in the series group (dashed line; group 2, bottom).

**

	Case Group N = 9	Series Group N = 9
Death	4	9
Cardiovascular events	0	0
Adverse events / SVT	0	NC
Seriuos adverse events / SVT	0	NC

Table 2. Other Primary Outcomes and Secondary Outcomes / SVT: in relation to simvastatin; NC: not corresponding.

3.5 Discussion

This matched cases-series study showed that the addition of simvastatin to the standard therapy in patients with decompensated cirrhosis and cardiovascular risk factors would be associated with an improvement in survival in the case group. Furthermore, simvastatin administration would be safe, as it did not cause adverse effects and/or serious adverse events. No patient in any group developed cardiovascular events during the study.

The high mortality rate of decompensated cirrhosis stresses the need for other therapies [25], [26]. When considering the reported relationship between cirrhosis and atherosclerotic cardiovascular disease, drugs used in this disease may be an option [33], [34], [35]. Therefore, cirrhosis could be treated cost-effectively by combined therapies with authorized, economical, and relatively safe medications, including simvastatin [25, 26].

The clinically significant finding of this study was the improvement in the survival observed in patients who agreed to add simvastatin to standard treatment, compared to those who did not. In this regard, Cabrera et al. [36] suggest that statins would improve the survival of patients with decompensated cirrhosis through two mechanisms. The first mechanism would be the prevention of complications of cirrhosis [36]. In this regard, this study showed that the interval between cirrhosis complications increased in patients who added simvastatin to standard treatment versus those who did not. The other would be through reducing the impact of cirrhosis complications on liver function. In this study, through Child-Pugh and MELD scores, significant deterioration of liver function was shown in patients who did not agree to add simvastatin to standard treatment, which was not observed in patients who did. Therefore, the increase in survival demonstrated in this study could be supported by the two mechanisms proposed by Cabrera et al. [36], based on the pleiotropic effects of simvastatin, such as increased hepatic nitric oxide production [29], [30].

The second endpoint of this study was simvastatin safety, taking into account statins pharmacokinetic alterations showed in patients with cirrhosis [37]. The fact that no dose reduction and/or the lack of simvastatin transitory interruption by adverse events or discontinue simvastatin by serious adverse events, particularly by muscle and/or liver injuries, proved that simvastatin would be a safe drug to administrate in patients with Child-Pugh A or B classes decompensated cirrhosis [25, 26].

In conclusion, the improvement in survival observed by the addition of simvastatin to standard treatment in patients with decompensated cirrhosis and cardiovascular risk factors is a piece of clinical evidence obtained from the clinical practice, where biases are inevitable and should encourage RCT realization to validate this clinical result.

The theoretical courses of decompensated cirrhosis without and with statins are shown in Fig. 6 and Fig. 7, respectively.

4. Conclusions

Cirrhosis should no longer be considered an irreversible disease with two stages. Cirrhosis should be regarded as a multistate disease, with possible regression. The progression from one state to another reflects a worsening prognosis with significant differences in survival [2], [14]. The evidence presented clearly demonstrates that the management of patients with cirrhosis should change from an expectant algorithm that treats complications as they occur, to preventing the advent of all complications while in the compensated phase. This requires maintaining patients in an asymptomatic phase and not significantly affecting their quality of life with minimal impairment due to the therapies themselves. Relatively safe, effective, and already licensed drugs, which, even in combination, are inexpensive, are readily available to evaluate in this setting [25], [26]. The new treatment paradigm has implications for early diagnosis of cirrhosis in primary care or in screening. The potential use of noninvasive markers is promising, once they are sufficiently validated, and threshold cutoffs are established [2]. In the 21st century, liver cirrhosis should be regarded as a treatable disease with available treatments and as a reversible illness, with other therapy options, beyond the liver transplantation. The clinical evidence showed in the case and series study, encourage RCT attainment to evaluate the survival in decompensated cirrhotic patients.

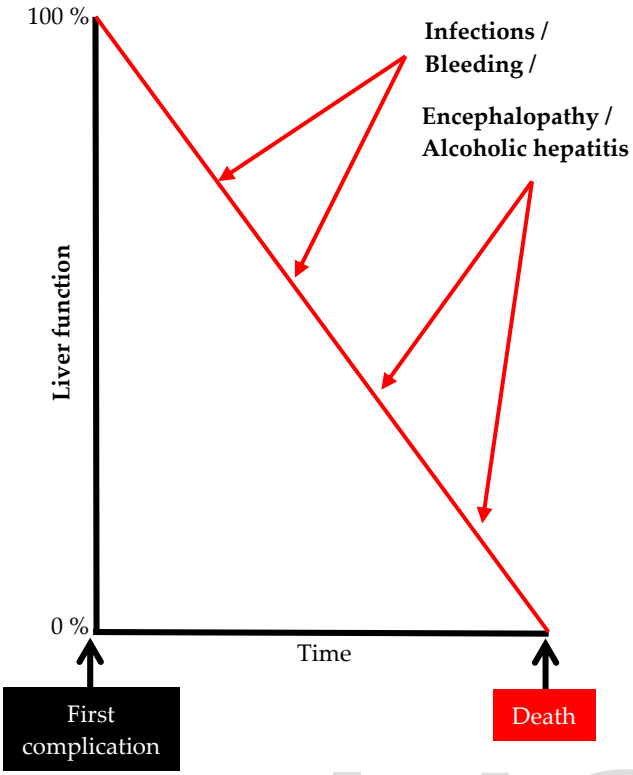


Figure 6. Course of decompensated cirrhosis without statins

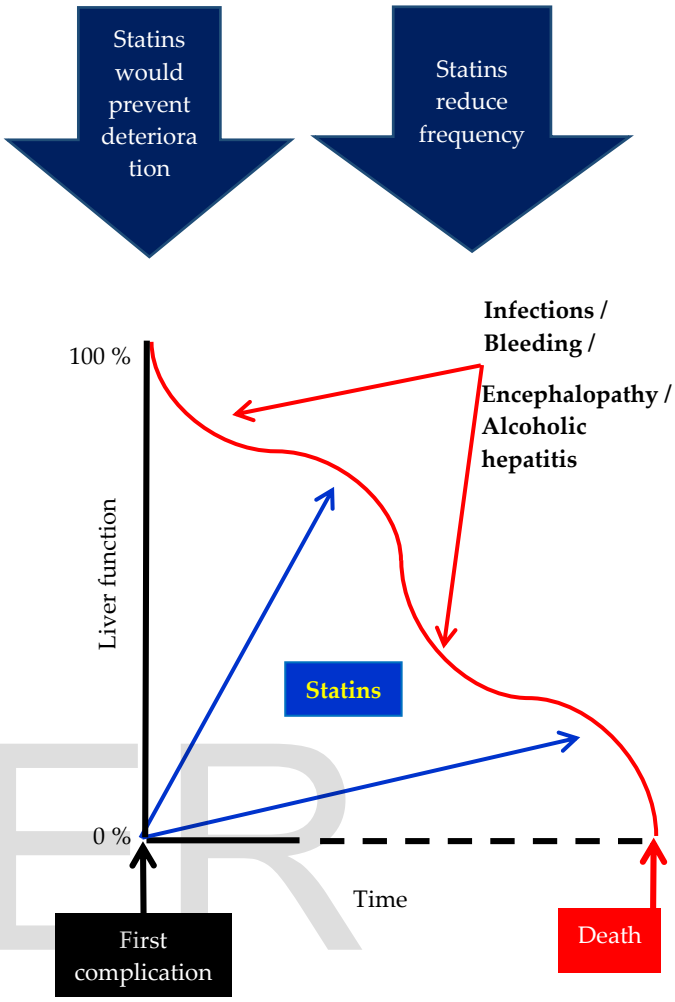


Figure 7. Course of decompensated cirrhosis with statins

3. References

1. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. J Hepatol 2018 Mar; 68(3):563-576. DOI: 10.1016/j.jhep.2017.10.020.
2. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology 2010 Apr; 51(4):1445-9. DOI: 10.1002/hep.23478.
3. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013 Mar; 58(3):593-608. DOI: 10.1016/j.jhep.2012.12.005.
4. Ge PS, Runyon BA. Treatment of Patients with Cirrhosis. N Engl J Med. 2016 Nov 24; 375(21): 2104-5. DOI: 10.1056/NEJMc1612334.
5. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.Lancet 2012 Dec 15;380(9859):2095-128. DOI: 10.1016/S0140-6736(12)61728-0.
6. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. J Hepatol 2013 Mar; 58(3):593-608. DOI: 10.1016/j.jhep.2012.12.005.
7. Fleming KM, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. Liver Int 2012 Jan; 32(1):79-84. DOI: 10.1111/j.1478-3231.2011.02517.x.
8. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006 Jan; 44(1):217-31. DOI: 10.1016/j.jhep.2005.10.013.
9. Veldt BJ, Lainé F, Guillygomarch A, Lauvin L, Boudjema K, Messner M, Brissot P, Deugnier Y, Moirand R. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. J Hepatol 2002 Jan; 36(1):93-8. DOI: 10.1016/s0168-8278(01)00228-8.
10. Wanless IR, Wong F, Blendis LM, Greig P, Heathcote EJ, Levy G. Hepatic and portal vein thrombosis in cirrhosis: possible role in development of parenchymal extinction and portal hypertension. Hepatology 1995 May; 21(5):1238-47.
11. Fernández M, Semela D, Bruix J, Colle I, Pinzani M, Bosch J. Angiogenesis in liver disease. J Hepatol 2009 Mar; 50(3):604-20. DOI: 10.1016/j.jhep.2008.12.011.
12. Bosch J. Vascular deterioration in cirrhosis: the big picture. J Clin Gastroenterol 2007 Nov-Dec; 41 Suppl 3:S247-53. DOI: 10.1097/MCG.0b013e3181572357.
13. D'Amico G, Morabito A, D'Amico M, Pasta L, Malizia G, Rebora P, Valsecchi MG. Clinical states of cirrhosis and competing risks. J Hepatol 2018 Mar; 68(3):563-576. DOI: 10.1016/j.jhep.2017.10.020.
14. Jepsen P, Ott P, Andersen PK, Sørensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology 2010 May; 51(5):1675-82. DOI: 10.1002/hep.23500.
15. D'Amico G, Pasta L, Morabito A, D'Amico M, Caltagirone M, Malizia G, Tinè F, Giannuoli G, Traina M, Vizzini G, Politi F, Luca A, Virdone R, Licata A, Pagliaro L. Competing risks and prognostic stages of cirrhosis: a 25-year inception cohort study of 494 patients. Aliment Pharmacol Ther 2014 May; 39(10):1180-93. DOI: 10.1111/apt.12721.
16. Bernardi M, Moreau R, Angeli P, Schnabl B, Arroyo V. Mechanisms of decompensation and organ failure in cirrhosis: From peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol 2015 Nov; 63(5):1272-84. DOI: 10.1016/j.jhep.2015.07.004
17. Thomsen BL, Møller S, Sørensen TI. Optimized analysis of recurrent bleeding and death in patients with cirrhosis and esophageal varices. Copenhagen Esophageal Varices Sclerotherapy Project. J Hepatol 1994 Sep; 21(3):367-75. DOI: 10.1016/s0168-8278(05)80315-0.
18. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. Hepatology 2017 Jan; 65(1):310-335. DOI: 10.1002/hep.28906.
19. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. N Engl J Med 2020 May 28; 382(22):2137-2145. DOI: 10.1056/NEJMra1914900.
20. Conn H, Atterbury C. Cirrhosis. In: Schiff L, Schiff E, eds. Diseases of liver 7th edn Philadelphia, PA: Lippincott, 1993:875-934.
21. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014 May 17; 383(9930):1749-61. DOI: 10.1016/S0140-6736(14)60121-5.
22. EASL 2017 Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection. J Hepatol 2017 Aug; 67(2):370-398. DOI: 10.1016/j.jhep.2017.03.021.
23. EASL Recommendations on Treatment of Hepatitis C 2018. European Association for the Study of the Liver. J Hepatol 2018 Aug; 69(2):461-511. DOI: 10.1016/j.jhep.2018.03.026.
24. Hingorani A, Hemingway H. How should we balance individual and population benefits of statins for preventing cardiovascular disease? BMJ 2010; 342: c6244. DOI: 10.1136/bmj.c6244.
25. Tsochatzis EA, Bosch J, Burroughs AK. Prolonging survival in patients with cirrhosis: old drugs with new indications. Gastroenterology 2010 Dec; 139(6):1813-1815.e1. DOI: 10.1053/j.gastro.2010.10.031.
26. Tsochatzis E, Bosch J, Burroughs AK. New Therapeutic paradigm for patients with cirrhosis. Hepatology 2012 Nov; 56(5):1983-92. DOI: 10.1002/hep.25915.
27. Veillard NR, Mach F. Statins: the new aspirin? Cell Mol Life Sci 2002; 59:1771-86. DOI: 10.1007/pl00012505.
28. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol 2005; 45: 89-118. DOI: 10.1146/annurev.pharmtox.45.120403.095748.
29. Wolfrum S, Jensen KS, Liao JK. Endothelium-dependent effects of statins. Arterioscler Thromb Vasc Biol 2003; 23:729-36. DOI: 10.1161/01.ATV.0000063385.12476.A7.
30. Zafra C, Abraldes JG, Turnes J, Berzigotti A, Fernández M, Garcia-Pagán JC, Rodés J, Bosch J. Simvastatin enhances hepatic nitric oxide production and decreases the hepatic vascular tone in patients with cirrhosis. Gastroenterology 2004; 126:749-55. DOI: 10.1053/j.gastro.2003.12.007.
31. Sorensen HT, Thulstrup AM, Mellemkjar L, Jepsen P, Christensen E, Olsen JH, Vilstrup H.. Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. J Clin Epidemiol 2003; 56:88-93.
32. Vandenbroucke JP. The making of STROBE. Epidemiology 2007; 18:797-9. DOI: 10.1097/EDE.0b013e318157725d.
33. Kalaitzakis E, Rosengren A, Skommevik T, Bjornsson E. Coronary artery disease in patients with liver cirrhosis. Dig Dis Sci 2010; 55:467-75. DOI: 10.1007/s10620-009-0738-z.
34. Wehmeyer MH, Heuer AJ, Benten D, Puschel K, Sydow K, Lohse AW, Luth S. High rate of cardiac abnormalities in a postmortem analysis of patients suffering from liver cirrhosis. J Clin Gastroenterol 2015; 49:866-72. DOI: 10.1097/MCG.0000000000000323.

35. Danielsen KV, Wiese S, Hove J, Bendtsen F, Moller S. Pronounced coronary arteriosclerosis in cirrhosis: Influence on cardiac function and survival? Dig Dis Sci 2018; 63:1355-1362. DOI: 10.1007/s10620-018-5006-7.
36. Cabrera L, Abraldes JG. Statins: the panacea of cirrhosis? Curr Hepatology Rep 2016; 15:1-7.
37. Bellosta S, Paoletti R, Corsini A. Safety of statins. Focus on clinical pharmacokinetics and drug interactions. Circulation 2004; 109: III-50-7. DOI: 10.1161/01.CIR.0000131519.15067.1f.