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REVIEW

Cirrhotic patients and older people

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Abstract

The global population is aging, and so the number of older cirrhotic patients is increasing. Older patients are characterised by a risk of frailty and comorbidities, and age is a risk factor for mortality in cirrhotic patients. The incidence of non-alcoholic fatty liver disease as an aetiology of cirrhosis is increasing, while that of chronic viral hepatitis is decreasing. Also, cirrhosis is frequently idiopathic. The management of portal hypertension in older cirrhotic patients is similar to that in younger patients, despite the greater risk of treatment-related adverse events of the former. The prevalence of hepatocellular carcinoma increases with age, but its treatment is unaffected. Liver transplantation is generally recommended for patients < 70 years of age. Despite the increasing prevalence of cirrhosis in older people, little data are available and few recommendations have been proposed. This review suggests that comorbidities have a considerable impact on older cirrhotic patients.

Key words: Liver cirrhosis; Portal hypertension; Liver cancer; Liver transplantation; Old age; Older; Elderly

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Core tip: Few large studies have addressed the needs of older cirrhotic patients. The concept of healthy ageing is increasingly important. Cirrhosis is underdiagnosed in older patients, and comorbidities, comedications, and frailty impact the prognosis. The frequency of non-alcoholic fatty liver disease as an aetiology of cirrhosis is increasing, while that of viral hepatitis is decreasing, and the role of alcohol consumption is underestimated. The management of complications in older cirrhotic patients is similar to that in younger patients despite the higher risk of treatment-related adverse events. Therapeutic indications for a transjugular intrahepatic portosystemic shunt or admission

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to an intensive care unit should be carefully considered. Finally, older patients require tailored exercise and nutrition programs, and treatment of osteoporosis is crucial.

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INTRODUCTION

The definition of older people varies from ≥ 60 years to ≥ 80 years of age. However, according to the World Health Organisation, the cut-off is 60 years of age, despite the increasing focus on the concept of healthy ageing[1,2]. Patients > 80 years of age are typically defined as being extremely old. Life expectancy has increased recently due to health, social, and economic development. According to the World Health Organisation, the number of people ≥ 65 years of age will increase from an estimated 524 million in 2010 to almost 1500 million in 2050, representing 22% of the global population[3]. Thus, the healthcare of older people is an emerging issue, particularly in Western countries.

The incidence of liver diseases increases with age[4]. Liver cirrhosis is an important health problem globally, and the prevalence of its numerous aetiologies varies geographically. General recommendations for the management of cirrhotic patients have been published, but these are not specific to older people[5].

This review focuses on problems specific to older cirrhotic patients.

PATHOPHYSIOLOGY OF THE AGEING LIVER

The liver undergoes physiological evolution with age, and this process involves several mechanisms. First, liver volume and blood flow decrease[6]. The liver decreases to one-third of its original size, more markedly in women[7], and a one-third decrease in hepatic blood flow has been reported, particularly in subjects over 75-years-old[8,9]. However, these results are controversial, and more data are needed[10]. Scintigraphy has shown that compared to the whole body, the size and functionality of the liver decrease with age[11]. Moreover, endothelial cell fenestration tends to decrease with age[8], the sinusoid vascular system is damaged, and secretion of bile acids is reduced. Regarding metabolic parameters, glucogenesis decreases with age but physiological lipids accumulate, enhancing steatosis[12]. Also, liver fat composition changes with age[13]; the level of high-density cholesterol and neutral fat is increased by neoglucogenesis. Moreover, older people tend to have higher levels of cholestatic enzymes and bilirubin[14].

Second, the number of hepatocytes and Kupffer cells and sinusoid capillaries decreases[8], and hepatocytes decrease in size with aging. The frequency of hepatocyte polyploidy increases with age and is associated with dysfunction or a decreased number of mitochondria[15]. Autophagy is modulated by accumulation of lipofuscin, a non-degradable aggregate of proteins impacted by reactive oxidative species[16]. Kupffer cells are also involved in ageing[17]. Cellular senescence is linked to chromosome alterations; telomere shortening occurs more frequently in Kupffer cells than in hepatocytes[18]. Apoptosis occurs more frequently in older patients, and senescent cells are resistant to apoptosis[19]. Nevertheless, targeting apoptosis of senescent cells could assist the restoration of liver homeostasis[20].

Third, the risk of fibrosis and steatosis increases with age[21]; for instance, in chronic hepatitis C virus (HCV) infection[22,23]. Fibrosis is a consequence of altered liver regeneration in response to injury. Responses to oxidative stress, cell senescence, and disrupted mitochondrial homeostasis may explain the greater risk of both fibrosis and steatosis in older patients[24]. In mouse models, mitochondria are damaged and the risk of DNA damage is increased by oxidative stress[12,25]. Altered liver regeneration may involve a multiprotein complex comprising CCAAT/enhancer binding protein α. Accumulation of this complex inhibits E2F-dependent promoters[26]. The somatotropic axis is also involved in liver regeneration[27]; however, a full mechanistic understanding remains elusive.

The immune system changes with age: Regulatory T cells, peripheral B cells,

monocytes/macrophages, and natural killer cells have reduced functionality, and dendritic cells have defective Ag presentation and T-cell activation[28,29]. The levels of markers of oxidation are not different between younger and older mice with CCl4 injury. However, the number of proinflammatory CD4+ cells, the expression level of T-helper type-2 cytokines by macrophages, and fibrogenesis are greater in older mice[30,31]. Furthermore, suppression of autophagy favours inflammation[32], and a high-fat diet increases the risk of liver fibrosis in older mice[33]. These factors also increase the risk of infection.

The role of ageing in carcinogenesis is debated—both protective and inductive mechanisms are reported[29,34,35]. The duration of exposure to carcinogens and a history of cirrhosis may promote hepatocellular carcinoma (HCC). Therefore, the aged liver is more sensitive to acute and chronic injury and is at greater risk of severe fibrosis or cirrhosis.

EPIDEMIOLOGY

Cirrhosis may be underdiagnosed in older persons, which is likely to be due to the presence of fewer clinical signs at presentation and less-frequent use of invasive diagnostic modalities[36,37].

Older patients with cirrhosis have a reduced life expectancy. Among 135 patients ≥ 80 years of age, Hoshida *et al*[38] showed that HCC, thrombocytopenia, and advanced fibrosis were associated with a low survival rate and that the alpha-fetoprotein and bilirubin levels were associated with hepatic carcinogenesis.

Older people also manifest deterioration in their general health[39], and cirrhosis may contribute to their frailty. Sarcopenia is frequent in older and in cirrhotic patients and contributes to the frailty of the former[33]. Specific policies to combat this are needed.

Finally, older patients have a higher incidence of complications, to which changes in the liver may contribute. Nevertheless, liver status does not impact the mortality rate of older patients. Effective screening methods and preventive measures are however essential.

AETIOLOGIES

The risk of transmission of hepatitis B virus increases with age, and the prevalence varies geographically. Epidemiological studies in the United States reported a higher prevalence among patients > 50 years of age compared to those 20-49 and 6-19 years of age (1.5-2 fold and 15-20-fold, respectively), irrespective of ethnicity[40]. Although vaccination policies have decreased the global prevalence of hepatitis B virus infection, there is no specific prevention strategy for older patients, in whom vaccination shows reduced efficacy[41].

In Western countries, the so-called baby-boomer generation is aging. The prevalence of HCV infection is high in this population: In the United States, > 75% of patients with HCV belong to this generation, and specific screening policies have been proposed[42]. HCV-related cirrhosis develops on average > 20 years after contact, which explains its incidence in this generation[43]. Nevertheless, the efficacy and tolerability of new direct anti-viral agents (DAA) is likely to decrease the prevalence of HCV infection in these geographical areas. However, many viraemic patients are unaware of their status, *e.g.*, > 100,000 patients in France have not been diagnosed or treated[44-47]. In a large retrospective study conducted in 2006, *i.e.* prior to the DAA era, Thabut *et al*[23] showed that patients > 65 years of age had a high prevalence of chronic hepatitis C and 14% had liver cirrhosis; interestingly, patients > 80 years of age had a lower alanine transaminase level than those < 65 years of age. Interferon-based treatments are typically not tolerated by older patients, but new available treatments have fewer side effects in polymedicated older patients, provided that the necessary precautions are taken, particularly in patients with a cardiac history and renal insufficiency, and that drug interactions are evaluated before starting treatment[48-50]. Older patients have been included in therapeutic studies[51]. The available treatments are effective in older patients, and no specific recommendations concern this population, including those with cirrhosis[50]. Decisions regarding the treatment of extremely old patients must take into account the benefit-risk ratio and the public-health perspective.

Metabolic syndrome is emerging globally, especially in Western countries, which have a higher prevalence of metabolic risk factors[52]. However, developing countries, including those in Asia and the Middle East, are also affected[53]. Metabolic syndrome

is common in older people[54], who are at risk of evolution towards cirrhosis[55] and have an increasing prevalence of cirrhosis[56]. Furthermore, > 60-year-old patients with non-alcoholic fatty liver disease are more susceptible to HCC[52]. Treatment is non-specific and based on weight loss[57,58], although vitamin E reportedly impacts life expectancy[59]. However, use of vitamin E in older males is associated with an increased risk of prostate cancer[60].

The prevalence of cryptogenic cirrhosis is high in some countries. For instance, in India[61], patients tend to have or have had metabolic risk factors for cirrhosis, in agreement with Japanese data[62]. Also, older studies indicated an important role for hepatitis C[63].

Alcohol consumption is frequent and more deleterious in older persons[64,65]; indeed, its prevalence in the United States increased between 2001-2002 and 2012-2013[66]. The social problems faced by older persons, such as isolation, widowhood, and chronic illness, can promote alcohol consumption. Alcohol accumulation in the liver impacts survival in patients with liver disease, such as hepatitis C[67]. The prognosis is poor; half of cirrhotic patients die within 1 year of diagnosis[68,69]. Older patients are also impacted by a variety of other alcohol-related complications[70]. From a public-health perspective, alcohol consumption should be assessed using the Alcohol Use Disorder Identification Test-C questionnaire and hepatic risk by performing non-invasive tests for fibrosis[70]. Alcohol withdrawal should be managed by a healthcare professional specialised in addiction with an elder-specific focus[71,72]. Short- and intermediate-acting benzodiazepines are recommended for older patients with alcohol-withdrawal syndrome, particularly those with cirrhosis[73].

Autoimmune hepatitis is also frequent in older patients, especially post-menopausal females[74]. These individuals are more likely to have asymptomatic liver cirrhosis and HLA DR4. Treatment is based on corticosteroids and azathioprine, as in younger patients; however, the risk of relapse after steroid withdrawal is lower[74]. Nevertheless, in older patients with initial mild fibrosis, the benefit-risk ratio of steroid treatment must be discussed due to their lower risk of fibrosis progression and higher risk of side effects, notably osteoporosis, psychiatric conditions, and diabetes, compared to younger patients[75]. That is why budesonide or a minimal corticosteroid regimen is preferred[76]. Furthermore, older patients with autoimmune hepatitis should undergo regular evaluations of bone density.

Primary biliary cholangitis is frequent in older patients, particularly females[77]. Interestingly, ursodeoxycholic acid is more effective in older patients[78]. However, older patients were not specifically analysed in two recent phase-III studies of obeticholic acid and bezafibrate[79,80].

Primary sclerosing cholangitis (PSC) is generally diagnosed in the third to fourth decades of life, but a second peak around 70 years of age was noted in a Japanese population, with no mention of the fibrosis stage[81]. Eaton *et al*[82] indicated that older patients with PSC have a 10% risk of cirrhosis, similar to that in younger patients, but have a lower prevalence of small-duct PSC. Finally, hepatobiliary malignancy is more frequent in older patients. There are no specific recommendations concerning the treatment and management of complications, including the role of therapeutic endoscopy[83]. McGee *et al*[84] suggested a link between autoimmune liver disease and liver cancer, *i.e*. intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer, in older patients, particularly those with primary biliary cholangitis.

Other causes, such as alpha-1-anti-trypsin, Wilson disease, and haemochromatosis, particularly haemochromatosis of weak phenotypic penetrance, may be diagnosed late[69], especially in post-menopausal women. This means that complications, such as cirrhosis and HCC, are frequently present at the time of diagnosis[85,86]. Alpha-1-anti-trypsin deficiency is typically diagnosed at a late stage unless pulmonary symptoms are evident and early screening for liver disease is performed[87]. Wilson disease is frequently diagnosed early, although a few advanced cases have been reported[88,89].

COMPLICATIONS OF CIRRHOSIS

HCC

HCC is the fifth most prevalent cancer worldwide and the third most important cause of cancer-related mortality[90]. The incidence of HCC increases with age, and the prognosis is poor. However, aggressive treatment of HCC in older (including extremely old) patients with good liver function and a good performance status might improve the survival rate[91]. In an Italian cohort, older patients with HCC had at the time of diagnosis a higher prevalence of comorbidities that negatively impacted the prognosis but a lower HCC stage, and better liver function than younger patients[92].

In another study, survival of elderly HCC patients was associated with liver damage and stage, but not age, with the exception of patients ≥ 80 years of age with a poor performance status[93].

Although HCC is more frequent in males, the proportion of females is higher among extremely old patients. The clinical presentation is typically weakness, nausea, and abdominal pain[69]. Ascites and hepatomegaly were frequent complications in a retrospective study[94]. Liver cirrhosis is a risk factor for HCC in younger and older patients, for whom the HCC screening recommendations are identical[95].

The therapeutic panel is the same in young and old patients, although decision-making is hampered by comorbidities, performance status, and life expectancy[92,96,97]. Specific age-linked scales have been developed[98]. The majority of the relevant studies were conducted in Asia. In large retrospective studies, surgery showed a trend towards an increase in the mortality rate with age[99-103]. Tumour size may not be a contraindication[104], and perioperative management and careful selection are needed[105]. Radiofrequency ablation can be effective against small tumours, *i.e*. radiofrequency ablation was more effective than hepatic resection in older patients with ≤ 3 cm HCC[106]. In another study, the global survival rate, but not the incidence of procedure-related adverse events, was comparable in older and younger patients[107]. Percutaneous injection of ethanol is effective against < 2 cm tumours[108].

The results of palliative transarterial chemoembolisation for older patients with advanced tumours are heterogeneous[96,109]. In a large retrospective trial, the overall survival rate of older patients was increased, but they were treated at an early stage[110]. Conversely, age over 60 years was independently associated with a poor prognosis. Interestingly, older patients were at greater risk of peptic ulcer (2.5% *vs* 0.5%)[111]. Although no data are available, radioembolisation is an interesting option for older patients with HCC[112] and is well tolerated by those with unresectable metastatic colon cancer[113].

Sorafenib is the most frequently prescribed chemotherapeutic. A French retrospective study showed that patients > 80 years of age had low tolerance of a fixed dose, and two thirds of them experienced grade IV adverse events[114]. Several Japanese studies have reported more hopeful results[115,116]. In one, a half dose of sorafenib was useful in the presence of adverse events and was better tolerated[116]. Age does not seem to influence the safety and efficacy of levantinib[117]. Phase III studies of Regorafenib and Ramucirumab have not specifically addressed older patients[118,119], but second-line cabozantinib increased the overall survival rate of patients > 65 years of age[120]. Unfortunately, data on immunotherapies, especially Nivolumab, are sparse.

Portal hypertension

Older people have a lower portal velocity and are not at increased risk of portal hypertension[121,122]. The treatment strategy is the same globally[5]. Betablockers are permitted despite various contraindications, and complications, such as cardiovascular and pulmonary events and an increased frequency of hospital admission[123]. Hyponatremia, hypotension, and renal insufficiency are contraindications for use of beta-blockers in older patients, as in younger patients[124].

According to the REPOSI Italian register, liver cirrhosis is the major cause of variceal and non-variceal upper gastrointestinal bleeding in older patients[125].

Proton pump inhibitors are associated with an increased risk of infection and encephalopathy in cirrhotic patients, irrespective of age[126-128]. In older patients, the therapeutic recommendations must be respected to prevent inappropriate prescriptions.

There is no specific recommendation concerning ascites in older patients. Diuretics should be prescribed with caution because of an increased risk of complications, particularly hyponatremia[129]. Older patients are at greater risk of acute renal insufficiency, independently of the aetiology[130]. Age does not affect survival in patients with refractory ascites, although terlipressin may be associated with vascular complications[131]. Transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation are interesting therapeutic options but have limitations in older patients, as discussed below.

Encephalopathy

Encephalopathy is a life-threatening complication of cirrhosis to which older people are particularly susceptible[39], and it may be linked to an altered brain-gut axis[132]. Infection, myocardial infarction, and central nervous system injury can favour this complication[133]. Minimal hepatic encephalopathy is associated with falls[134]. Older patients, especially the most fragile, require supervision and care. Their treatment is not different from that of younger patients[135]. Preventative therapy is essential in cases of cirrhotic decompensation and constipation must be controlled.

ACUTE ALCOHOLIC HEPATITIS

Acute alcoholic hepatitis is linked to a history of alcohol consumption and typically occurs in patients around 50 years of age[136]; however, older patients predominate in nosocomial studies[136]. Age is predictive of survival and of the presence of liver cirrhosis and is included in the Age, Serum bilirubin, International Normalised Ratio, and Serum creatinine score and the Lille model[137,138]. Although older patients were not included in the largest therapeutic studies, it is a prognostic factor for post-treatment survival [139]. Prednisolone is the only validated medical treatment, but data on its efficacy in older patients are lacking. Furthermore, recent studies of liver transplantation did not include patients > 61 years of age[140].

PULMONARY AND CARDIAC COMPLICATIONS

The definition of hepatopulmonary syndrome differs according to age: An alveolar-arterial gradient of 15 and 20 mmHg in patients < 65 and ≥ 65 years of age, respectively[5,141]. Long-term oxygen therapy is recommended[5]. Liver transplantation is curative, and age does not influence the outcome of patients with hepatopulmonary syndrome[142].

Among other causes of pulmonary hypertension, cirrhosis is one of the most important in older people[143,144]. The presentation can differ with age; older patients are more likely to have oedema and a more severe presentation[145]. Their management does not differ from that of patients in other age groups, and the prognosis is similar[5,109].

Hydrothorax is also observed in older cirrhotic patients, and its management, despite the lack of data, is identical to that for younger patients. TIPS is a therapeutic solution, but, as in ascites, careful selection of patients is mandatory[146].

Old age is associated with an increased risk of cardiac dysfunction and cirrhotic cardiomyopathy[147]. Because of its frequency and prognostic impact, systematic screening for these conditions among older patients is justified[5].

PATIENTS IN CRITICAL CONDITION

The survival rate of cirrhotic patients in the intensive care unit is 34% to 69%[148]. Age > 75 years impacts the global, but not the intensive care unit, survival rate[149]. Although the severity of cirrhosis is more predictive of survival than age, age is an indication for admission to the intensive care unit[5]. Indeed, age is a parameter of the prognostic Chronic Liver Failure Consortium acute decompensation score and the Chronic Liver Failure Consortium acute on chronic liver failure score[150,151]. Hepatorenal syndrome and spontaneous bacterial peritonitis are associated with a poor prognosis[152].

INFECTIONS

Older cirrhotic patients are at increased risk of infection due to their impaired immunity defences[153]. Spontaneous bacterial peritonitis has a higher mortality rate in older than in younger people[154], and, although the data are sparse, older people are more susceptible to renal failure[155]. In cirrhotic patients, bacterial resistance to antibiotics is promoted by the high frequency of antibiotic use[156]. Age impacts the occurrence and mortality rate of infection with multiresistant bacteria, but not the risk of inappropriate treatment[157].

As mentioned above, the use of proton-pump inhibitors by older patients increases the risk of infection, and their use should be restricted. Of note, vitamin D deficiency, which is more frequent in older cirrhotic patients, is also a risk factor for infection[158]. Thus, screening for and correction of this deficiency is essential in older cirrhotic patients[159].

SPECIFIC MANAGEMENT

Nutrition

Although there are no specific recommendations for older cirrhotic patients, both age and cirrhosis are associated with frailty and malnutrition[160,161]. Sarcopenia is present in 1% to 29% of community-dwelling patients and in 14% to 33% of those in long-term

care[160]. In older cirrhotic patients, assessment and correction of sarcopenia are crucial—computed tomography, measurement of the muscle area at L3, dual-energy X-ray absorptiometry, subjective global assessment, and Royal Free Hospital-Global assessment are useful in this regard[161]. Nutritional support can be helpful, particularly for critically ill patients. Exercise and physical activity tailored to the patient's age and general condition are also required[58]. Furthermore, systematic screening for osteoporosis is advisable in cirrhotic patients and is vital in older cirrhotic patients.

TIPS

Age is a limiting factor for TIPS, independently of the model for end-stage liver disease (MELD) score[162,163]. This is why cardiac function (diastolic function, pulmonary arterial hypertension) and risk of encephalopathy of older patients must be evaluated. Altered cardiac pressure in the right atrium and in pulmonary vessels is associated with mortality[163]. Correction of the natriuresis balance in older patients is delayed after TIPS insertion[164]. Although they were not included in the largest study[5], recent retrospective data show that the procedure is beneficial in selected older patients[146].

LIVER TRANSPLANTATION

Durand *et al*[29] reviewed liver transplantation in older patients. In practice, liver transplantation is rarely possible in patients > 70 years of age. However, the proportion of patients > 65 years of age who are candidates for liver transplantation is increasing in the United States and in Europe[29,165]. Also, the epidemiology is changing: In the United States, the frequency of nonalcoholic steatohepatitis and HCC as indications for liver transplantation is increasing, whereas that of HCV patients is decreasing[165]. The mortality rate among patients on the waiting list is higher in older people[165], as is the risk of dropping out; the mortality rate is higher in patients with a lower MELD score than in those < 64 years of age[165].

The 5-year post-transplantation mortality rate increases linearly with age in older recipients[166]. The MELD score is associated with mortality early post-liver transplantation[166], and older patients have a higher incidence of cardiac, pulmonary, and renal complications as well as of malignancies. Also, post-transplantation renal function is a key prognostic factor in patients transplanted for cirrhosis. Age impacts the occurrence of renal insufficiency (relative risk per 10-year increment, 1.36; $P < 0.001$)[167] as does pre-transplantation acute renal insufficiency, especially when associated with hepatorenal syndrome. However, older patients are at greater risk of chronic renal insufficiency before liver transplantation[168]. So, selection of patients is crucial to prevent post-transplantation complications-such as cancer, metabolic disease, or renal insufficiency-and to improve overall survival. The recently developed Liver Frailty Index may be predictive of survival post-transplantation[169].

Notably, donor age impacts survival post liver transplantation. The impact of donor age begins at 40 years and increases with age, particularly at > 60 years of age[170]. Moreover, improvements in liver-graft selection have resulted in a 5-year post-transplantation survival rate of > 70%[171]. The Donor Risk Index includes the donor's age, which is one of the three important risk factors for graft failure, in addition to donation after cardiac death and split/partial grafts[170]. Grafts with an increased Donor Risk Index are preferentially transplanted into older candidates > 50 years of age with moderate disease severity.

Finally, age matching, although complex, is warranted by a number of policies. A summed recipient and donor age of > 120 years may be prognostic, independently of other factors[172]. Other scores, such as the Survival Outcomes Following Liver Transplantation and Balance of Risk scores, include both donor and recipient factors[173,174].

In conclusion, few large studies have focused on older cirrhotic patients. The relevance of recent global recommendations on cirrhosis and transplantation is thus limited. In older patients, evaluation of comorbidities, comedications, and frailty is essential.

Relevant scores, such as the Frailty Liver Index, should be considered, and customised exercise and nutrition programs and osteoporosis therapy should be proposed to older cirrhotic patients. Moreover, attention should be paid to the choice of HCC treatment, the indications for TIPS insertion in patients with portal hypertension, and the indications for admission to the intensive care unit. Prevention policies are needed, because the causes of cirrhosis generally begin in the first decades of life. Finally, studies involving older cirrhotic patients, as well as specific

recommendations, are needed.

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