Diagnostic challenges in patients with alcohol-related liver disease

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Abstract (n=270)
Alcohol is globally the leading risk factor for cirrhosis and is subsumed under the term alcohol-related liver disease (ALD). However, only ca. 10% of people with harmful alcohol consumption (>40 gram alcohol per day) develop cirrhosis, while 15% have normal liver histology. Unfortunately, laboratory parameters and ultrasound hold little value to neither rule-in nor rule out alcohol related liver fibrosis. While several indices with combinations of liver associated markers such as FIB4 seems to be promising, non-invasive test strategies are urgently needed with cut-off's that can be applied to guide clinical decision making. The aims of this review article are to highlight novel developments for the diagnosis of ALD and to identify topics of controversy and potential future directions. In the last 15 years, elastography to measure liver stiffness (LS) has significantly improved our screening strategies for cirrhosis. LS values below 6 kPa are considered as normal and exclude ALD. LS of 8 and 12.5 kPa represent generally accepted cut-off values for F3 and F4 fibrosis. Especially, transient elastography (TE) has been assessed in numerous studies, but similar performance can be obtained with point shear wave elastography, 2 SD shear wave elastography or MR elastography. Important confounders of elevated LS such as inflammation should also be considered and alcohol withdrawal not only improves liver inflammation but also LS. Liver stiffness measurement has signficiantly improved early diagnosis and follow-up of fibrosis in patients with ALD and patients with diagnosed manifest but clinically compensated cirrhosis should undergo further clinical examinations to rule out complications of portal hypertension. In addition, surveillance for the occurrence of hepatocellular carcinoma is recommended in all cirrhotic patients.

Keywords :
Alcohol-related liver disease, fibrosis, steatosis, non-invasive tests, transient elastography, biomarker, liver stiffness, GOT, AST, transaminase levels, inflammation, lobular inflammation, pericellular fibrosis, cirrhosis, hepatocellular carcinoma (HCC), hepatic venous pressure gradient (HVPG), elastography, portal hypertension (PH).

Abbreviations:
LS liver stiffness
TE transient elastography
ALD alcohol-related liver disease

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Introduction

Alcohol-related liver disease (ALD) is the most frequent cause of severe liver disease in Europe and according to WHO, more than 40% of the liver deaths are attributed to alcohol (1). In addition, the number of liver transplantation for patients with ALD-related cirrhosis has increased over the past two decades, both in Europe and in the US (2, 3). The risk of alcohol related fibrosis and cirrhosis is closely correlated with drinking pattern and amount of alcohol consumed (4, 5), however, only 5-10% of people with harmful alcohol consumption develops cirrhosis and 15% have normal liver histology (6). While the relation between alcohol-related cancer and alcohol consumption is linear (7), the dose-effect relationship with regard to alcohol-related liver cirrhosis shows an exponential association (8). Chronic, heavy alcohol consumption, which is typically classified as the consumption of >40 g of pure alcohol per day (equating to 375 ml of 13 vol% wine or >1 litre of 5 vol% beer) over a sustained period of time (years)(9) leads to the highest risk of ALD (10, 11). However, a recent meta- analysis has shown that even the chronic consumption of 12–24 g of alcohol per day has an increased risk of cirrhosis as compared with non- drinking (10). Accordingly, the threshold level of chronic alcohol consumption that increases the risk of ALD may be rather low.

In addition, components of the metabolic syndrome and alcohol overuse often coexist and constitute a cumulative risk (12), similarly alcohol often overlap with HCV and due to shared risk factors co-infection with HBC and HCV is frequent (13). While some liver diseases such as hemochromatosis and alfa 1 antitrypsin deficiency are genetic diseases, risk of ALD is associated with genetic risk alleles. Several single-nucleotide polymorphisms have been identified (14), however the PNPLA3 I148M variant (rs738409) has the largest effects, with approximately twofold to threefold increased odds of ALD cirrhosis and HCC (15, 16). In contrast the HSD17B13 variant seems to have protective properties against NASH and ALD (17). This may explain the variation in the impact of metabolic risk factors for liver diseases at the individual level (6, 18). Altogether, the risk of progression to cirrhosis and development of complications and associated risk of death or need for liver transplantation is critically dependent on early detection.

Despite this high burden of ALD, it is unfortunate that most patients with ALD are diagnosed at the decompensation stage normally presenting with ascites or jaundice. Moreover, a large proportion of newly diagnosed cirrhosis had recent consultations in primary care or emergency units (19), without any intervention. Since the presence of advanced fibrosis or cirrhosis in compensated patients is the main predictor of long term survival, it is of clinical importance to diagnose those patients with advanced fibrosis before decompensated stage, in order to promote abstinence and improve survival (20). Liver diseases are in general hardly to detect and commonly show no or only mild symptoms. Even end-stage liver cirrhosis remains undetected in routine laboratory testing or ultrasound screening in ca. 40% (21).
The diagnostic workup for patients with suspected cirrhosis depend on the disease stage (see Table 1). In the early asymptomatic stages, the aim is to diagnose the degree of liver fibrosis (6, 22, 23), assess the presence of portal hypertension (24) and aetiology since this is closely associated to risk of progression and development of complications to cirrhosis and consequently the type and frequency of clinical follow-up (25). In the symptomatic decompensated stage, the aim is to assess the extent of decompensation to institute appropriate surveillance and therapeutic interventions to prevent further decompensation and death (24). Since there are no screening programmes, most patients are diagnosed at the symptomatic stage (26). However, this is changing with more widespread access to non-invasive tests, increased awareness of liver diseases in the community and effective treatments in viral hepatitis and emerging therapies in NASH and fibrosis (27-29).

Pathomorphology of ALD progression

The histopathological features of ALD are well known (Fig. 1). The first stage of ALD is steatosis. Since alcohol is a toxic substance and the enzymes responsible for its metabolization are located in the centrolobular hepatocytes, the accumulation of fat is first seen in this region of the liver. The precise mechanisms of fat accumulation are complex and not completely understood. Accumulation of fat starts as small vacuoles (microvesicular fat) which melt together into mediovesicular fat and macrovesicular fat droplets. When fat accumulates even further, hepatocytes can burst followed by cleaning of the cell debris forming a steatogranuloma.

In acute high alcohol consumption (binch drinking), microvesicular fat is the typical lesion seen as foamy hepatocytes. This is typical for alcohol consumption and is not described in non alcoholic steatosis. The hallmark lesion to differentiated pure fatty liver from alcoholic steatohepatitis is ballooning of hepatocytes and the formation of Mallory-Denk bodies. Ballooning of hepatocytes starts as clearing up of the cytoplasm and finally as truly ballooned swollen hepatocytes. Mallory Denk bodies are inclusions formed by folding of the cytoskeleton and its ubiquitinization to protect the hepatocyte from dying. They can therefore be visualized by an ubiquitin immunohistochemical stain, but also on keratin 8 or 18 stain which are typical cytokeratins present in hepatoytces. The oxidative stress accompanying the damage of hepatocytes attracts polymorphonuclear leucocytes (polymorphs) forming a special type of inflammation called satellitosis: Mallory-Denk bodies surrounded by polymorphs. Mallory bodies in ASH are mostly coarsely granular, in contrast to the ones formed in NASH which are finely granular. The toxic effect of alcohol causes oxidative stress and activation of perisinusoidal stellate cells into myofibroblasts. These cells cause perisinusoidal and pericellular fibrosis, a fibrosis pattern so typical for ALD and NASH. This fibrosis pattern is called chicken wire fibrosis or spider web fibrosis. Due to the perisinusoidal fibrosis, the fenestration of the endothelial cells is lost and the sinusoids are ‘capillarized’.
More prominent centrolobular damage of hepatocytes can cause necrosis and so-called hyalin sclerosis. This is a cicatrization process often associated with vascular lesions (centrolobular vein thrombosis and occlusion). The latter being reminiscent of VOD. This type of lesion is also not seen in NASH.

Finally, in advanced stages of the disease, micronodular cirrhosis develops, typically with further dissection of small nodules due to perisinusoidal and pericellular fibrosis.
In the cirrhotic stage of the disease it is clinically often difficult to distinguish decompensation of advanced cirrhosis from infection/systemic inflammatory response syndrome the so-called acute-on-chronic liver failure (ACLF). ACLF is a relatively new clinical entity and little is described yet about the relationship of ASH and ACLF. Recently it was shown that around 23% of the patients with ASH develop ACLF within 28 days after diagnose and that ACLF was an important risk factor for mortality in these patients.(30) Because of this high risk of mortality, it would be of value to identify ASH patients at risk for developing ACLF in an early stage when deterioration of the disease might still be prevented. The need for predictors for ACLF, especially markers in the critical period before development of ACLF, is also emphasized in an article by Arroyo et al. (31). The same article also underlines the importance for a better understanding of the liver pathology in ACLF. Liver biopsy plays an important role in the diagnosis of ASH and can be a helpful tool in the assessment of the prognosis of ASH patients (32-34). Only one study by our group investigated liver histopathology in relation to ACLF and suggested that ductular bilirubinostasis is an early feature of ACLF(35). This is an important finding and in

subsequently developed scoring systems, location of bilirubin (hepatocytic, canalicular or ductular) is integrated in the histopathological features of the scoring system. Bilirubinostasis isdistinct feature of sever ALD which is not seen in NASH.
In a multicentre study a prognostic scoring system to predict short time (90 days) mortality was developed: the so-called Alcoholic hepatitis histology score (AHHS). Also in this scoring system, ductular bilirubinostasis was a worse predictive factor, next to presence of cirrhosis. In another recently developed scoring system for grading and staging of alcoholic liver disease, long-term outcome was associated with activity grade (ballooning, MD bodies, Polymorphs) and cholestasis (canalicular and ductular), as well as cirrhosis with very broad septa (severe cirrhosis) ($p < 0.001$ for all parameters). In decompensated ALD, adverse short-term outcome was associated with activity grade, hASH and cholestasis ($p = 0.038$, 0.012 and 0.001, respectively), whereas in compensated ALD, hASH and severe fibrosis/cirrhosis were associated with decompensation-free survival ($p = 0.011$ and 0.001, respectively). On multivariable analysis, severe cirrhosis emerged as an independent histological predictor of long-term survival in the whole study cohort. Severe cirrhosis and hASH were identified as independent predictors of short-term survival in decompensated ALD, and also as independent predictors of decompensation-free survival in compensated ALD.

Overall, a liver biopsy is useful for the diagnosis of alcoholic hepatitis (ballooning, satellitosis, Mallory Denk Bodies), as well to predict prognosis. Several scoring systems have been recently developed for this purpose. Ductular bilirubinostasis is especially helpful as a sign of infection and an early feature of ACLF.

Clinical approach to diagnosis of early alcohol related liver disease

Alcohol is globally the leading risk factor for cirrhosis. The risk of alcohol related fibrosis and cirrhosis is closely correlated with drinking pattern and amount of alcohol consumed (4, 5), however, only ca. 10% of people with harmful alcohol consumption develops cirrhosis and 15% have normal liver histology(6). In addition, components of the metabolic syndrome and alcohol overuse often coexist and constitute a cumulative risk (12), similarly alcohol often overlap with HCV and due to shared risk factors co-infection with HBC and HCV is frequent (13). While some liver diseases such as hemochromatosis and alfa 1 antitrypsin deficiency are genetic diseases, risk of ArLD is associated with genetic risk alleles. Several single-nucleotide polymorphisms have been identified (14), however the PNPLA3 I148M variant (rs738409) has the largest effects, with approximately twofold to threefold increased odds of ALD cirrhosis and HCC (15, 16). In contrast the HSD17B13 variant seems to have protective properties against NASH and ALD(17). This may explain the variation in the impact of metabolic risk factors for liver diseases at the individual level (6, 18). Altogether, the risk of progression to cirrhosis and development of complications and associated risk of death or need for liver transplantation is critically dependent on early detection.
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Assessment of liver fibrosis - Fibrosis is not a disease but rather an outcome of the tissue repair response that becomes dysregulated following many types of chronic liver injury and results in accumulation of extracellular matrix proteins, primarily collagen and fibronectin, the structural component of fibrosis and cirrhosis (36-38). Liver fibrosis represents the early pre-cirrhotic stages of chronic liver disease, which in general is asymptomatic and characterized by slow progression through years to decades (6). Significant fibrosis (≥F2) and advanced fibrosis (≥F3) represents important landmarks in the naturals history of disease since they associates strongly with future liver associated morbidity and mortality (22, 39-41), and thus represent an important point for timely intervention to prevent further progression (28, 29), and also at a regulatory level has been accepted as relevant cut points (42, 43). Liver biopsy represents the gold standard for assessment of liver fibrosis, however, several tools for the non-invasive assessment of liver fibrosis have been developed and can substitute a liver biopsy for assessment of fibrosis (Fig. 2). The main indications for liver biopsy are when serologic testing and imaging fails to elucidate a diagnosis, to stage a condition, or when multiple diagnoses are possible.

Non-invasive test - Standard liver function test and ultrasound holds little value in assessing or diagnosing alcohol related liver fibrosis and cannot be used to neither rule-in nor rule out fibrosis (44-46). However, several indices with combinations of liver associated markers exists, table. These can all be used as first line test and serve to rule-out fibrosis or need of confirmatory test. FIB4 is an algorithm based on age, AST, platelets, ALT, thus easily accessible and cheap, in contrast to patented algorithms and directs markers of fibrosis. The patented markers (see table) can also be used to assess presence of fibrosis (47, 48). The aim is to assess presence of liver fibrosis based on test cut-off's that can be applied to guide clinical decision making. Rule-out level means very low risk of fibrosis and rule-in is highly suggestive of significant (≥F2) or advanced fibrosis (≥3). Elastography measures stiffness of the liver and correlates very well with presence and degree of fibrosis, also in ALD (48-50). Transient elastography has been assessed in numerous studies across aetiologies (48, 49, 51) and is widely available and is preferred by many hepatologist due to the ease of use, point of care assessment and solid scientific documentation after more than 15 years on the market. Conditions with active inflammation, severe cholestasis or congestion results in falsely elevated measures and increased risk of false positive assessments. To identify patients with ≥F2 fibrosis, data across aetiologies support a transient elastography cut-off of >8 kPA to rule-in fibrosis (49). The optimal elastography cut-off for ≥F3 fibrosis has recently been assessed in a large multicentre multi aetiology study with 5648 patients and establish stiffness >12 kPa as the most appropriate rule-in cut-off for >F3 fibrosis with sensitivity of 92% (51). While transient elastography is the best documented and investigated technique, similar performance can be obtained with point shear wave elastography, 2 SD shear wave elastography (52) or MR elastography(53).

Evaluation of a patients with suspected compensated cirrhosis - In patients without known liver disease but suspicion of early-stage cirrhosis, non-invasive test can be applied in the same way as described above. However, in contrast to pre-cirrhotic stages ultrasonography is mandatory in patients with cirrhosis. Several sign of cirrhosis such as nodular liver surface, splenomegaly or presence of shunts or ascites can be assessed together with assessment of vascular changes. Further, focal processes in the liver, in particular hepatocellular carcinoma, can be visualized. Most clinical guidelines recommend surveillance for hepatocellular carcinoma with ultrasound every 6 months in all patients with cirrhosis(54). Splenomegaly, presence of shunts or ascites suggest cirrhosis with portal hypertension and high risk of further progression and complications to cirrhosis(24). In general, all patients with cirrhosis

must undergo surveillance for esophageal varices. However, in patients with a transient elastography <20 kPa and normal platelets the risk of having varices needing treatment is very low and surveillance is not necessary, the Baveno VI criteria(55). This can be expanded to platelet count >110,000/mm^3 and LSM <25 kPa (56, 57). In 1000 patients with prevalence of varices of 20%, Baveno VI criteria would prevent endoscopy in 262 patients, but 6 patients with varices needing treatment would be missed. Instead, use of the expanded Baveno VI criteria would result in 428 patients avoiding endoscopy, but 20 patients with varices needing treatment would be missed(58).

Evaluation of a patients with suspected decompensated cirrhosis - Decompensated cirrhosis represents the advanced symptomatic stage of disease with overt clinical signs such as ascites, bleeding, hepatic encephalopathy or jaundice (25). Transition to a decompensated stage represents a steep rise in risk of complication to cirrhosis and death, figure 1(6, 22, 24). INR, albumin and bilirubin reflect deterioration in metabolic liver function and are particularly valuable when integrated in the Child-Pugh score as outlined in sections below. Markers of fibrosis and elastography are not useful in patients with clinically overt disease, similarly these cannot be used to exclude need for surveillance endoscopy, which is mandatory in the decompensated stage. Imaging (US, CT or MRI) are an integrated part of care in decompensated cirrhosis and must be applied in all hospitalised patients to assess structural changes, focal lesions, vascular involvement and presence of extrahepatic diseases. If presence of ascites, all patients must undergo diagnostic paracentesis to characterise the ascites fluid and assess for spontaneous bacterial peritonitis (neutrophil count in ascitic fluid of >250/mm^3)(25). Textbox 1 shows a suggested first line diagnostic work up in secondary care for assessment of patients with suspected alcohol related liver disease

Textbox 1: Suggested first line diagnostic work up in secondary care for assessment of patients with suspected alcohol related liver disease

- The history and laboratory testing should assess /screen for viral hepatitis B and C, alcohol use and NAFLD, hemochromatosis, Wilson's disease, alpha-1-anti-trypsin deficiency, autoimmune hepatitis and cholestatic liver diseases.
- Repeat liver function tests, BMI, HbA1c and perform abdominal ultrasound and elastography.
- The diagnosis is established by excluding other causes combined with information on drinking pattern and misuse (AUDIT questionnaire), GGT, AST, ALT, MCV, and markers of fibrosis such as elastography to diagnose the degree of liver damage (fibrosis).
- Further confirmation may be obtained by measuring ethyl glucuronide in urine and a liver biopsy with characteristics of ALD[42].

Fibrosis assessment in alcoholic liver disease using liver stiffness

Fibrosis assessment based on liver stiffness in comparison to other methods - Although ALD follows the typical sequence of chronic liver diseases including alcoholic fatty liver, steatohepatitis, fibrosis and eventually cirrhosis, the early recognition of severe steatohepatitis and alcoholic cirrhosis is most important since it will save lives, prevent complications, and initiate follow-up programs (21). Most important clinical end points are alcoholic liver cirrhosis and the rare and clinically defined alcoholic hepatitis (AH, ASH1). ASH1 should not be mismatched with the commonly and histologically detectable steatohepatitis (ASH, ASH2). Since AH/ASH1 is very rare and there are still no early predictors, screening for liver problems in heavy drinkers should primarily focus on the screening for fibrosis (21). In hepatology, liver biopsy is still essential in establishing the definite diagnosis or in ruling out additional or other causes of the disease. However, liver biopsy is an invasive procedure, with significant complications in up to 7% (59) and, with regard to fibrosis assessment, a sampling error of up to 30% (60-64). Complications can encompass mild (pain and small bleedings in 6%) or severe (0.1%) complications and rarely fatal perforations and bleedings (65, 66). In addition, and the context of ALD, heavy drinkers are typically less likely to see doctors and to undergo invasive diagnostic procedures. For instance, it has been estimated that less than 1% of patients with suspected ASH1/AH are biopsied although required according to international guidelines (67). With respect to fibrosis assessment, all imaging techniques must rely on so called sure morphological signs of cirrhosis such as nodular aspects of the liver or recanalization of the umbilical vein while splenomegaly or ascites are not specific. These imaging signs are only available in about halve of ALD patients with manifest cirrhosis (21). Serum markers have been long thought to allow for easy fibrosis screening (21, 68). In ALD, however, a previous study clearly showed superiority of TE with regard to various serum markers (69). Moreover, this was achieved without sophisticated algorithms.

Elastographic assessment of fibrosis in ALD - In contrast to popular liver diseases such as viral hepatitis, the performance of LS in ALD was assessed rather late. The major biopsy-proven studies on LS in patients with ALD are listed in Table 1. The focus of this article will be primarily on transient elastography (TE) since most data have been obtained so far with this technique (70). Early direct comparison with serum fibrosis markers showed a better performance of TE in patients with ALD (69) and AUROCs are typically >0.9 to detect F4 cirrhosis. Although an excellent performance could be shown in all studies, they differ quite drastically regarding the cut-off values ranging from 11.5-25.8 kPa. This is primarily related to the presence of inflammation as assessed by transaminase levels (71). In this study, it was shown that LS decreases in patients with ALD during alcohol withdrawal (71). Absolute alcohol withdrawal leads to ca. 20% decrease of LS within one week of alcohol detoxification which improves fibrosis stages in 27% (72). Even a 2 months reduction of alcohol consumption by 40% significantly reduced LS by 17% as shown recently using Selincro (Nalmefene) for better controlled drinking (73). LS decreased significantly in 62 patients (45.3%), and there was a reduction in the estimated stage of fibrosis in 32 (23.3%). In contrast, an increase of LS was observed in 11.7% (74). The proportion of patients with a significant decrease of LS after alcohol withdrawal increased from 41.7% to 66.7% with the duration of abstinence from 1 week to 9 weeks (75). There are preliminary observations that

long-term abstinence is even more beneficial as LS decreased by 50% if abstained from alcohol for 5 years (76).

So far, AST levels are the marker which is best associated with LS irrespective of fibrosis stage (77). Why AST has this special impact on LS, is still not completely clear and may also be related to extrahepatic conditions as AST also occurs in muscle cells and erythrocytes. In the absence of elevated transaminases, cut-off values were almost identical between HCV and ALD for F1-2, F3 and F4 (HCV: 5.1, 9.0 and 11.9 kPa vs ALD: 4.9, 8.1 and 10.5 kPa). These cut-off values increase exponentially as a function of median AST level. The impact of AST on LS was higher in lobular-pronounced ALD as compared to portal tract-localized HCV (77). In ALD, AST levels are typically higher as compared to ALT and in ca. 70% of patients the AST/ALT ratio is higher than two (78). However, AST levels higher than 300 IU/L are rarely detected. In cirrhotic stages, transaminases may normalize while AST levels may be continuously increased despite the absence of alcohol consumption (77). Finally, in a recent meta-analysis (50), AST but also bilirubin concentrations had a significant effect on LS.

How to assess fibrosis stage based on liver stiffness in clinical practice? - The findings above have been implemented in clinical algorithms to easily and accurately screen for fibrosis in drinkers. Fig. 3 shows a typical interpretation of LS if ultrasound and laboratory testing is available. After suspicion of ALD either by patients reporting, clinical or laboratory signs, TE is performed directly after the abdominal ultrasound and routine blood tests. A minimum time of 5 minutes in horizontal position should be allowed for stable hemodynamics and LS. During the ultrasound, liver size, spleen size, morphology, abnormalities such as congestion, cholestasis, morphological signs of cirrhosis, the presence of ascites and the diameter of the inferior vena-cava are assessed. TE is then performed either with the M probe or in cases of M probe failure, obvious obesity or ascites with the XL probe (79, 80). Ascites is no contraindication for the XL probe and performs well (79). If LS was elevated and patients had AST>100 U/ml, alcohol withdrawal for at least 2 weeks (optimal 4 weeks) is recommended followed by a second LS measurement. In patients with LS > 30 kPa, the diagnosis of cirrhosis is settled despite steatohepatitis as measured by elevated transaminase levels. At these levels, the development of ascites is very likely. This approach allows definitive non-invasive assessment of fibrosis stage in ca. 95%. Compared to conventional routine ultrasound, TE identifies twice as many patients with advanced fibrosis/cirrhosis (Mueller S, unpublished) and has a smaller sample error as compared to histology (3-5% versus 20-50%). In a recent French elastography screening study on more than 1000 apparently healthy people older than 45 years, 7.5% had a pathologically increased liver stiffness > 8 kPa with 36% of them eventually being due to ALD (81). Therefore, it is anticipated that these novel non-invasive screening tools will improve the early recognition and follow up of patients with ALD, the most common and unfortunately too often underestimated liver disease.

Finally, we have recently developed an algorithm to avoid repetitive re-assessment of LS in ALD patients with elevated AST levels (Fig. 4). In this multicenter study with more than 2000 biopsy-proven patients with ALD and HCV, cut-off values for fibrosis increased exponentially as a function of median AST level (70). While AST-adapted cut-off values allow an immediate assessment of fibrosis stage even in patients with pronounced steatohepatitis and avoid overestimation of fibrosis stages, it remains unclear why AST is intensively correlated with LS. Moreover, AST may not only be derived from hepatocytes but also myocytes and erythrocytes. It also remains to be studied whether indeed all patients with elevated AST levels will necessarily develop LS elevation.

Liver stiffness follow up and survival in patients with alcohol related liver disease - LS measurement allows to monitor drinking activity and ALD progression since LS encompasses the sum of all pathological features from inflammation, ballooning to fibrosis. LS improved shortly after alcohol withdrawal in more than 80% (82). As shown in Tab. 5, first unpublished preliminary data indicate that LS continues to decrease after further abstaining from alcohol up to 5 years. Thus, in 23 heavy drinkers who were followed-up for 5.5 years, LS decreased by almost 50%. Preliminary unpublished mortality data from 10 year survey in heavy drinkers also shows that LS seems to be the best univariate predictor of death in heavy drinkers (83). Accordingly, LS predicted mortality independently from bilirubin and INR. A LS >12.5 is associated with 64% survival after 5 years.

Stratification of cirrhosis and its impact on the screening for HCC

Cirrhosis is the common consequence of chronic liver diseases due to diverse etiologies and is characterized by a progressive hepatic angio-architectural transformation. Despite different etiologies (infectious, toxic, metabolic, cholestatic and autoimmune) and different patterns of fibrogenesis, the chronic inflammatory response, associated with a constant effort to replace progressive parenchymal extinction, leads to the formation of typical regenerative nodules (84). Capillarization of sinusoids associated with attempts of establishing vascular connections between the portal and the hepatic vein systems due to neo-angiogenesis lead to a progressive increase of intrahepatic vascular resistance and the establishment of portal hypertension (PH). Portal hypertension represents the main cause of the life-threatening complications of cirrhosis and constitutes a key mechanism leading to the progression of the disease (85). Indeed, established PH causes further hepatocellular damage and ultimately leads to the formation of porto-systemic shunts bypassing the cirrhotic liver. These, together with an increased intestinal permeability give access to a gut-derived antigenic load entering the systemic circulation (85, 86). The long-term effect of this intestinal translocation is the establishment of a systemic pro-inflammatory background and a progressive functional immune paralysis, which is pivotal for the development of bacterial infections in patients with cirrhosis (87).

Although the knowledge on the mechanism responsible for the progression from early tissue injury to advanced chronic liver disease has greatly expanded in the past 30 years, the current clinical classification of cirrhosis still depends of the observation of clinical manifestations (88). This has been accordingly defined "an expectant algorithm that treats complications" rather than preventing them (89). In this context, the distinction between compensated and decompensated cirrhosis based on the occurrence of clinical complications and the degree of portal hypertension assessed by measuring the hepatic venous pressure gradient (HVPG) does not allow a clinical stratification, which is sufficient flexible both in clinical and prognostic terms. This is mostly due to the lack or representation of the underpinning pathophysiology, including altered tissue regeneration and the progressive loss of specific liver functions, in the stratification process.

An initial progress is provided by the use of an integrated clinical-pathological assessment to make more accurate, patient-specific risk predictions to identify appropriate interventions, such as timing of variceal screening, introduction of etiology-specific treatments in the early stages of cirrhosis, and selection for liver transplantation in advanced disease. Along these lines, there is increasing recognition of the need for a pathophysiologic staging of cirrhosis that will incorporate the etiological, clinical, histologic, and hemodynamic findings of each particular patient (90, 91). The use of semi-quantitative histological scoring systems has a

major drawback since cirrhosis is represented as a mono-stage (e.g. METAVIR F4, Ishak 5-6) (92, 93) although the clinical course of the disease has often many years for further pathological development or the possibility of fibrosis regression following a suitable treatment. The Laennec staging system, a modification of the METAVIR system (94), subdivides cirrhosis into three groups (4A, 4B, and 4C) based on the thickness of the fibrous septa and the size of nodules, and has shown an excellent performance in predicting liver related events (LRE) therefore stratifying these patients according to prognosis (95, 96). Importantly, quantitative morphometric methods for the evaluation of fibrosis in cirrhotic liver tissue have been introduced and validated in the past decade. Among these, the collagen proportionate area (CPA) (97) allows an accurate sub-classification of cirrhosis and has been shown to be the only independent predictor of clinical decompensation amongst all other histological sub-classification systems described to date (98).

Central to the current stratification process is the detection and monitoring of portal hypertension (PH). The gold standard for the assessment of portal hypertension and the development of relative non-invasive methodologies is the Hepatic Venous Pressure Gradient (HVPG), i.e., the difference between the wedged (WHVP) and the free hepatic venous pressures. HVPG is the gradient between pressures in the portal vein and the intra-abdominal portion of inferior vena cava while WHVP actually reflects hepatic sinusoidal pressure and not the portal pressure itself. The normal HVPG value is between 1 to 5 mmHg. Pressure higher than 5 mm Hg defines the presence of PH, regardless of clinical evidence. HVPG $\geq$ 10 mmHg (termed clinically significant PH, CSPH) is predictive of the development of complications of cirrhosis, including death. HVPG above 12 mmHg is the threshold pressure for variceal ruptura (99, 100). Overall, HVPG reflects mainly "sinusoidal" PH, which is caused by extensive capillarization of sinusoids, endothelial dysfunction and the disordered intrahepatic vasculature of cirrhosis consequence of neo-angiogenesis. However, the extent, the timing and the distribution of these structural abnormalities is etiology-dependent (101). Therefore, it would be crucial to "reset" HVPG thresholds according the etiology of cirrhosis. Accordingly, very recent data indicate that the classic HVPG thresholds, developed mostly in series of patients with HCV cirrhosis, do not reflect the occurrence of clinical manifestation in NASH cirrhosis where severe complications often occurs for values of HVPG below 10 mm Hg (102).

The introduction of non-invasive approaches to assess liver fibrosis has led to a major change in the clinical practice of Hepatology, including new methodologies for the stratification, prognostication and treatment of patients with advanced chronic liver disease (103). These methods range from simple scores calculated from routine laboratory parameters or biochemical tests related to the composition of the fibrotic hepatic extracellular matrix, to elastography techniques to obtain a liver stiffness measurement (LSM). Overall, it is ascertained that serum markers, LSM as well as standard imaging techniques perform quite well in advanced fibrosis and cirrhosis in predicting portal hypertensive complications and the development of hepatocellular carcinoma (HCC) (104) and, accordingly, could be proposed for the stratification of cirrhosis. LSM assessed by liver elastography, performed with FibroScan (transient elastography) or ultrasound shear-wave elastography (SWE), has greatly enhanced the likelihood of early diagnosis and the stratification of cirrhosis, facilitating the identification of patients with compensated disease who are at high risk of complications. In particular, elastography allows the diagnosis of CSPH with an accuracy greater than 80% when using a binary cut-off approach (105). The more recent introduction of spleen stiffness measurement by various ultrasound elastography methods (106) has added an additional possibility, alone or in combination with LSM, to expand the non-invasive assessment of PH

for values of HVPG beyond 12 mm Hg when the pathogenesis of PH is also dependent from extrahepatic factors.

While elastography has dramatically improved the stratification of cirrhosis and its clinical management, clinical biomarkers able to monitor the worsening of key functions such has systemic hemodynamics, innate and acquired immunity and more in general a state of systemic inflammation are still lacking and would greatly improve the management of both compensated and decompensated cirrhosis.

The occurrence of HCC is a common complication in chronic advanced liver disease and is the results of a chronic regenerative attempt in a fibro-inflammatory environment. Although HCC incidence progressively increases with worsening of fibrosis and cirrhotic transformation, diagnosis of HCC is not exceptional in the early stages of cirrhosis. For this reason, a HCC screening schedule, based on periodic ultrasound and serum alpha-fetoprotein levels, is suggested for all patients with a diagnosis of cirrhosis irrespective of the etiology. Approximately 90% of HCCs are associated with a known underlying etiology (107), most frequently HBV/HCV chronic viral hepatitis, alcoholic liver disease and metabolic associated fatty liver disease (MAFLD).

In general, features of liver disease severity (low platelet count of less than 100x109/L, presence of esophageal varices), in addition to older age and male gender correlate with development of HCC among patients with cirrhosis (108). Recent studies have shown that HCC incidence increases in parallel to portal pressure, measured directly (109) or non-invasively as liver stiffness detected by transient elastography. Indeed, HVPG not only has important prognostic relevance but also informs treatment options. An HVPG >10mmHg confers a 6-fold increased risk of developing HCC (109), while in those with an established HCC the option of a curative resection is diminished with significant PH through increased morbidity and mortality. Current European guidelines recommend a cut off HVPG ≤10mmHg to consider curative resection of HCC (110), and an Asian cohort of patients with resection confirmed worse survival in patients with established portal hypertension (111).

In practical terms, surveillance for the occurrence of HCC is recommended in all cirrhotic patients and particularly in those where the current therapeutic options are more effective, i.e. those with cirrhosis and limited or no complications (e.g. Child-Pugh A). Indeed, the presence of cirrhosis with advanced liver failure (Child-Pugh class C) or decompensation in the Child-Pugh class B (large ascites, hepato-renal syndrome or clinical jaundice) prevents effective HCC therapies from being employed when transplantation is not an option. Accordingly, surveillance for HCC is less cost-effective in these patients (112).

Summary and outlook

Alcohol is globally the leading risk factor for cirrhosis and is subsumed under the term alcohol-related liver disease (ALD). The diagnosis is normally established by excluding other causes combined with information on drinking pattern and misuse. Liver stiffness measurement by elastography has signficiantly improved early diagnosis and follow-up of fibrosis in patients with ALD and patients with diagnosed manifest but clinically compensated cirrhosis should undergo further clinical examinations to rule out complications of portal hypertension. Serum markers or scores such as FIB4 can be used if elastography is not available. Future developments are targeted in identifiying novel clinical biomarkers to better assess inflammation in patients with ALD, their prognosis and especially those patients who

are at risk to develop alcoholic hepatitis. In addition, the next decade will help to better understand the modulatory mechanisms of ALD by genes and environmental factors such as obesity.

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TABLES

Table 1. Liver stiffness and fibrosis stages in ALD (biopsy proven studies)

Reference	**Number of patients (n)**	**Correlation**	**AUROC F4**	**Cut-off F4**
Nahon et al, 2008 (113)	174	0.70, P<0.0001	0.87	22.6
Nguyen-Khac et al, 2008 (69)	103	0.72, P < 0.014	0.92	19.5
Kim et al, 2009 (114)	45		0.97	25.8
Boursier et al, 2009 (115)	217	0.87, P<0.02	0.91	17.3
Mueller et al, 2010 (71)	101	0.72, P < 0.001	0.92	11.5
Janssens et al, 2010 (116)	49		0.86	21.1
Fernandez et al, 2015 (117)	15		0.93	18.0
Thiele et al, 2016 (118)	199		0.94	16.9
Voican et al, 2017 (119)	217	0.73, P < 0.0001	0.93	20.8

FIGURE LEGENDS

Fig. 1: Features of alcoholic hepatitis. upper left: centrolobular steatosis; upper middle: Mallory Denk Body surrounded by neutrophils: satellitosis; upper right: perisinudoidal fibrosis on Masson trichrome stain; lower left: Micronodular cirrhosis on Sirius red stain; lower middle: ductular bilirubinostasis in patient with sepsis; lower right: sclerosis of central vein on reticulin stain

Fig 2 Stage of alcohol related liver disease and appropriateness of use to guide clinical decision making

Fig. 3 Suggested first line diagnostic work up in secondary care for assessment of patients with suspected alcohol related liver disease

Fig. 3. Practical algorithm to assess fibrosis stage in patient with excessive alcohol consumption.

Fig. 4 AST-adapted cut-off values for LS in patients with ALD Proposed cutoffs. Note that cut-off values increase with AST elevation. Up to AST=150-200, AST-adaptation shows improved diagnostic accuracy.