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**ORIGINAL RESEARCH**

# Long Term Follow up and Liver Related Death Rates in Patients with Non-Alcoholic and Alcoholic Related Fatty Liver Disease

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## ABSTRACT

**Aim:** The Aim of this study is to Long term follow up of liver related death rates in patient with Non-Alcoholic and Alcoholic related fatty Liver Disease. **Methods:** For this study we have chosen the patient who underwent a liver biopsy from last twenty years. Only patients with NAFLD and AFLD were included and medical records reviewed. The patients were linked to the Hospital Discharge Register, the Causes of Death Registry and Centre for Addiction Medicine. **Results:** Overall , 2432 liver biopsies were performed during the study period. A total of 450 patients with at least one index biopsy were identified by the computerized search in the pathology database as having fatty liver on biopsy. Those who were misclassified and did not have fatty liver on review were excluded (Figure 1). A total of 180 patients were excluded for other reasons than based on histopathology (Figure 1). The remaining study group of 270 patients had no signs of viral hepatitis in the index liver biopsy and did not receive any medication known to be associated with the development of steatosis.Medical records from these patients were traced and the biopsies reviewed by experienced pathologists. A total of 270 patients constituted the study group, 145 (60%) women and 125 men (40%). Women were in the majority in the NAFLD group, 100/150 (70%) compared to 50/150 (30%) men ($p < 0.001$). The proportion of men was higher in the AFLD group, that is 67% (63/94) whereas the proportion of women was 30/90(30%). **Conclusions:** Patients with fatty liver disease showed a markedly higher risk of developing liver-related death compared to the general population. The AFLD group had higher liver-related mortality and had a worse survival than the NAFLD group. Patients with more severe fibrosis at baseline showed a worse survival than patients with none or mild fibrosis at baseline.



## INTRODUCTION

Fatty liver disease is clinically categorized into two main groups,alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). NAFLD is becoming one of the most common liver diseases worldwide with a prevalence up to 30% in the general population and it can progress to end-stage liver disease . NAFLD is associated with insulin resistance, and has been considered to be the hepatic component of the metabolic syndrome . Patients with NAFLD have been shown to have increased cardiovascular mortality compared to the general population .[1] Only a few studies have assessed the prognosis and risk of liver-related death in patients with biopsy verified NAFLD in a population based setting . Thus, even though NAFLD is potentially a serious condition well designed population based studies on its natural history are lacking. Most recent studies on fatty liver disease have focused on NAFLD although AFLD is an important cause of fatty liver and only a few studies have compared the long term prognosis between NAFLD and AFLD . [2]

Non Alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are common causes of chronic liver disease. NAFLD is associated with obesity and metabolic syndrome whereas ALD is associated with excessive alcohol consumption. Both diseases can progress to cirrhosis,[3,4] hepatocellular

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carcinoma, and liver-related death. A higher proportion of patients with NAFLD die from cardiovascular disorders than patients with ALD, whereas a higher proportion of patients with ALD die from liver disease. NAFLD and ALD each are associated with significant morbidity, impairment to health-related quality of life, and economic costs to society. The pathogenesis of excess fat being different in the two conditions while both are important components of the changing face of burden of liver diseases worldwide. They are intimately associated with a globalized economy and an increasingly homogenous socio- cultural order with a westernized lifestyle. The accompanying adoption of a progressively sedentary life, consumption of diet dense in calories facilitate development of NAFLD while a spiraling upward trend in alcohol use along with earlier age of drinking as well as increased amount of per capita alcohol consumption increases the prevalence of ALD globally. Adverse health outcomes in NAFLD as well as ALD are caused not only by progressive liver fibrosis that is the most significant factor for liver related and all-cause mortality in both but also by non-liver (cardiovascular, cancer, accidents, neurological) clinical outcomes that calls for a multidisciplinary and social approach to these conditions. We present here an outline of facets of epidemiology of both NAFLD as well as ALD along with its' public health implications. A broad-based integrated approach that incorporates social, behavioural as well as biological targets need to be undertaken at a health system level .[5,6,7]

## METHODS

In this retrospective study, a search was undertaken in a computerized diagnoses database from 1984 (when the pathology registry commenced their electronic registration) to 2009, in the Department of Pathology at the National University Hospital (NUH) of Iceland and identified all liver biopsies analysed and registrated in the SNOMED coding-system, T-56000 and the M-50080 as having fatty change. The SNOMED (Systemized Nomenclature of Medicine) is a coding system used in the pathology laboratories in Iceland to specify: Procedure, Topography, Morphology, Disease and Etiology. This is a very valuable coding system for retrieving data and pathology reports from past years, like biopsies of the liver (T-56…) showing fatty change (M-50080).
All medical records from these patients were examined with respect to the following :

**Exclusion criteria**

1) presence of acute or chronic liver disease: PBC, autoimmune hepatitis, alfa-1-antitrypsin deficiency, hemochromatosis and viral hepatitis. 2) jejunoileal bypass operation. 3) use of drugs known to be associated with fatty liver disease such as methotrexate, amiodarone, tamoxifen and high doses of corticosteroids. 4) malignancy at the time of index liver biopsy. 5) age under eighteen years at the time of index liver biopsy. 6) gallstone surgery at the time of index liver biopsy.
The patients with gallstone surgery at the time of index liver biopsy were excluded to better represent the patients who would undergo a liver biopsy in clinical practice and not just the incidental finding of fatty liver during an operation.Indications for the index biopsy in the cohort were elevated liver tests, mainly serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) and/or hepatomegaly or suspected alcoholic liver disease. A total of 420 patients met the inclusion criteria and were divided into two groups, non-alcoholic and alcoholic group respectively (Figure 1).

**All Liver Biopsy During the period of study with Histological Diagnosis of Fatty Liver( 20 years of study) n= 450**

| Inclusive Criteria ( n=270 ) 60% | Exclusive Criteria ( n=180) 40% |
|---|---|
| Alcoholic group ( n=110) 38% | Gall bladder Stone |
| Non Alcoholic Group ( n=160 ) 60% | Hepatitis diseases – (n=30)<br>Gall bladder Stone – (n=20)<br>Drug – ( n=20)<br>Malignancy – (n = 60)<br>Other Medical Disease – (n-15)<br>Jejunoieal bypass Operation –(n=4)<br>Mis Calcified sample – (n =10)<br>Missing sample –(n=11)<br>Lost to follow up – (n=10) |

**Study Material**

The Study was based on the medical records and All the patient were linked through their unique personal identification number and recorded at baseline: gender, age at diagnosis, height, weight and body mass index (BMI), history of diabetes mellitus, hyperlipidaemia, hypertension, cardio- and cerebrovascular disease, liver disease and malignancy. Data on drug and alcohol intake was noted in the medical records. Patient with a reported alcohol problem or abuse or an alcohol-related diagnosis before or at the time of liver index biopsy were considered to have alcoholic fatty liver disease. The diagnosis of cirrhosis was accepted in patients who

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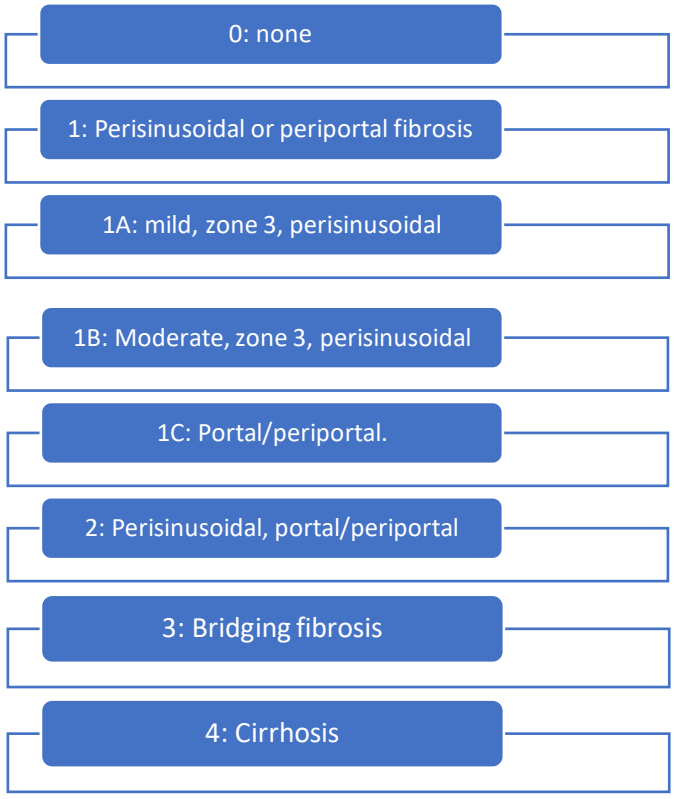
had a discharge diagnosis, a death certificate diagnosis and/or histological confirmation in the follow-up period indicating cirrhosis. Laboratory data included at baseline were: AST, ALT, bilirubin, albumin, alkaline phosphatase (ALP), prothrombin time (PT), glucose, platelets count (PLT), serum cholesterol, serum triglycerides (TG) and mean corpuscular volume (MCV). Patients were excluded if they were lost to follow-up in the registries. 8 patients were lost to follow-up..

**Histological:** The index liver biopsies were formalin fixed and treated routinely in the pathology laboratory. They were paraffin embedded and cut in 4–5 micrometre thick sections. The sections were stained with haematoxylin and eosin, periodic acid Schiff reagent (PAS) with diastase and for reticulin. In addition a connective tissue stain, Weigert van Gieson or most commonly Masson Trichrome stain was performed. Morphological findings were recorded in a semi-quantitative manner regarding steatosis and fibrosis.

Fibrosis stage were defined as follow:




## RESULTS

Overall 2432 liver biopsies were performed during the study period. A total of 450 patients with at least one index biopsy were identified by the computerized search in the pathology database as having fatty liver on biopsy. Those who were misclassified and did not have fatty liver on review were excluded (Figure 1). A total of 180 patients were excluded for other reasons than based on histopathology (Figure 1). The remaining study group of 270 patients had no signs of viral hepatitis in the index liver biopsy and did not receive any medication known to be associated with the development of steatosis.Medical records from these patients were traced and the biopsies reviewed by experienced pathologists. A total of 270 patients constituted the study group, 145 (60%) women and 125 men (40%). Women were in the majority in the NAFLD group, 100/150 (70%) compared to 50/150 (30%) men ($p < 0.001$). The proportion of men was higher in the AFLD group, that is 67% (63/94) whereas the proportion of women was 30/90(30%).

### Clinical and biomechanical result

**Table 1: Clinical and biochemical data at the time of index liver biopsy**

| | Baseline | | | End of follow-up | | |
|---|---|---|---|---|---|---|
| | NAFLD group | AFLD group | p-value | NAFLD group | AFLD group | p-value |
| | n = 145 | n = 125 | | n = 145 | n = 125 | |
| Gender (F/M) | 100/50 | 30/63 | <0.001 | | | |
| Female% | 70% | 30% | | | | |
| | Mean (sd) or | Mean (sd) or | | | | |

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| | Median (IQR) | Median (IQR) | | | | |
|---|---|---|---|---|---|---|
| Age (years) | 52 (15.7) | 50(13.5) | NS | | | |
| BMI (kg/m$^2$) | 30 (27–32) | 28 (25–30) | NS | | | |
| AST (U/L) | 45 (32–62) | 76 (45–155) | <0.001 | 47 (36; 28–46) | 90 (46; 28–93) | 0.05 |
| ALT (U/L) | 67 (42–102) | 109 (56–197) | 0.001 | 42 (36; 26–52) | 65 (45; 27–75) | 0.04 |
| Bilirubin (µmol/L) | 10 (7-15) | 12 (9-21) | 0.01 | 14 (9; 7–18) | 48 (11; 9–21) | NS |
| ALP (U/L) | 196 (132–320) | 178 (134–280) | NS | 195(122; 87–157) | 170 (119; 77–179) | NS |
| Prothrombin time (sec) | 14(12-13) | 12 (13-15) | 0.02 | 15 (14; 13–17) | 16 (14; 13–17) | NS |
| Albumin (g/L) | 42 (36–44) | 40(32–41) | NS | 36(39; 33–42) | 34 (37; 28–41) | NS |
| Platelets (x10$^9$/L) | 264 (92.9) | 226(83.3) | 0.006 | 234(238; 170–281) | 218(222; 152–265) | NS |
| Random blood glucose (mmol/L) | 6 (5-7) | 6 (5-8) | NS | 7 (6; 5–7) | 7 (6; 5–7) | NS |
| Cholesterol (mmol/L) | 6 (5,7) | 5 (5-8) | NS | 5 (5; 4–6) | 5(5; 4–6) | NS |
| Triglycerides (mmol/L) | 2 (1-3) | 2 (1-3) | NS | 2 (2; 1–2) | 2 (2; 1–2) | NS |
| MCV (fL) | 90 (6.1) | 95 (7.2) | <0.001 | 90 (90; 87–94) | 95 (95; 90–105) | <0.001 |

Clinical and biochemical data at the time of index liver biopsy in the 270 patients of the two study groups (Table 1). Information was available to calculate BMI in 54% of the total study cohort. No significant difference was found in the BMI between the two groups (Table 1). In the current context obesity was defined as BMI ≥ 30, 46/85 patients (55%) were obese in the NAFLD group compared to 20/52 patients (42%) in the AFLD group (NS). In the total cohort no significant difference was observed between the genders in terms of obesity as 30/75 (40%) of women were obese and 30/60 (50%) of the men and no difference was seen in BMI when comparing genders in the NAFLD and the AFLD group (data not shown). A total of 75/86 (82%), 55 women vs. 20 men in the NAFLD group had a BMI > 25 compared to 36/55 (75%), 10 women vs. 30 men in the AFLD group (NS).The biochemical markers AST, ALT, bilirubin, prothrombin time and MCV were higher and platelets lower in the AFLD group compared to the NAFLD group at the time of index liver biopsy whereas other biochemical markers were similar in the two groups (Table 1 **).** At the end of follow-up, ALT, AST and MCV were the only biochemical markers still significantly higher in the AFLD group compared to the NAFLD group (Table 1).

The clinical data on other diseases associated with the metabolic syndrome at the time of index liver biopsy and at the end of follow-up period in the two study groups are shown in Table 2. The two groups had also similar morbidity in terms of conditions associated with metabolic syndrome both at baseline and at follow-up (Table 2). Overall, 60 (72%) of the patients in the AFLD group had undergone alcohol addiction therapy according to computerized database of patients in the National Centre of Addiction Medicine, whereas 2 (1%) in the NAFLD group had undergone an addiction therapy, not due to alcohol but due to abuse of sedatives and due to a gambling addiction.

**Table 2: Comorbid diseases at baseline and the end of follow-up period**

| | **Baseline** | | | **End of follow-up** | | |
|---|---|---|---|---|---|---|
| | **NAFLD** | **AFLD** | **p-value** | **NAFLD** | **AFLD** | **p-value** |
| | **n = 145** | **n = 125** | | **n = 145** | **n = 125** | |
| | **n (%)** | **n (%)** | | **n (%)** | **n (%)** | |
| DM II | 20 (15) | 7 (9) | NS | 40(28) | 19 (17) | NS |
| HTN | 54 (35) | 36 (40) | NS | 78 (52) | 45 (47) | NS |
| Hyperlipidemia | 27 (19) | 11 (12) | NS | 34 (21) | 15(17) | NS |
| Cardio- and cerebrovascular disease | 20(13) | 10 (10) | NS | 42 (29) | 23 (26) | NS |

**Histological end-points and development of cirrhosis**

The histological characteristics in the index liver biopsy are summarized in Table 3. According to the NAS score overall 30/100 (21%) patients in the NAFLD group had NASH compared to 30/63 (37%) with ASH in the AFLD group (p = 0.007). In the nonalcoholic group 45(30%) patients had borderline NASH and 66 patients (45%) did not have steatohepatitis. In the alcoholic group 36 (37%) patients had borderline ASH (NS) and 21 (23%) did not have ASH (NS). Patients in the NAFLD had less severe lobular inflammation than the AFLD group (Table 3)

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**Table 3: Histological characteristics of NAFLD- and AFLD group at index biopsy**

| NAFLD group | AFLD group | p-value | |
|---|---|---|---|
| n (%) | n (%) | | |
| **Steatosis** | | | |
| 1 (5-33%) | 75(50) | 36(38) | NS |
| 2 + 3 (≥33%) | 75 (48) | 56 (60) | NS |
| **Lobular inflammation** | | | |
| 0 + 1 (no foci or <2 foci/200x) | 98 (67) | 45 (48) | 0.003 |
| 2 + 3 (2–4 foci or >4 foci/200x) | 58 (34) | 50 (53) | 0.003 |
| **Ballooning** | | | |
| 0 + 1 (none or few balloon cells) | 138(90) | 90 (95) | NS |
| 2 (many cells) | 12 (8) | 4 (4) | NS |
| **Fibrosis** | | | |
| 0 + 1 + 1A + 1B + 1C (none to mild fibrosis) | 120 (78) | 60 (65) | 0.02 |
| 2 + 3 + 4 (moderate to severe) | 30 (21) | 32 (35) | 0.02 |
| **NAS score** | | | |
| <3 | 67 (45) | 21 (24) | 0.001 |
| 3-4 | 46 (31) | 35 (37) | NS |
| ≥5 | 31 (21) | 35 (37) | 0.007 |

At the time of index liver biopsy 18 patients had cirrhosis, 6 patients in the NAFLD group and 12 in the AFLD group, respectively. Overall, 11 patients developed cirrhosis during follow-up period, four patients in the NAFLD group and seven patients in the AFLD group. Thus, a total of 29 patients were diagnosed with cirrhosis in the two groups, 10 (7%) patients in the NAFLD group and 19 (20%) patients in the AFLD group ($p = 0.003$).

Among patients developing cirrhosis in the follow-up period the histological diagnosis at baseline was as follow: one patient had no fibrosis (in the NAFLD group), three patients had stage 1A fibrosis (all three in the AFLD group), one patient had portal fibrosis (in the NAFLD group) and six patients bridging fibrosis (four in the AFLD group and two in the NAFLD group).

**Liver-related complications**

Patients developing liver cirrhosis and liver related complications are demonstrated in Table 4. Among patients diagnosed with cirrhosis a somewhat higher proportion developed ascites in the AFLD group, 10/20 (58%) vs. NAFLD, 2/10 (30%) ($p = 0.004$). Only one patient in the AFLD group developed HCC but none of the NAFLD patients developed HCC (Table 4). A significantly higher number of patients in the AFLD group, 13/94 (14%) developed decompensated liver disease compared with 7/150 (5%) in the NAFLD group (Table 4). It should be noted that baseline NAS score was different between two groups with higher baseline NAS score in the AFLD group (NAS score > 5: 37% vs 21%).

**Table 4: Development of chronic liver disease such as HCC, portal hypertension, varices and ascites**

| NAFLD group | AFLD group | | |
|---|---|---|---|
| n = 145 | n = 125 | | |
| (%) | (%) | | |
| Cirrhosis | 11(7) | 18 (20) | 0.003 |
| Death | 4(2) | 9 (10) | 0.02 |
| Ascites | 4(2) | 10 (12) | 0.004 |
| Varices | 4(2) | 6 (6) | NS |
| Bleeding varices | 1 (1) | 1 (1) | NS |
| Portal hypertension | 4(2) | 2 (2) | NS |
| HCC | 0 (0) | 1 (1) | NS |

**Survival and mortality**

There was no significant difference in overall survival between the two study groups and no significant difference between genders . Patients in the AFLD group diagnosed with cirrhosis had a higher death rate compared to the NAFLD group; 10 patients (40%) in the AFLD group compared with 7 patients (17%) in the NAFLD group (NS). Using Cox analysis the survival was significantly worse for patients in the AFLD group compared to the NAFLD group after adjusting for gender, calendar year of diagnosis and age at diagnosis . (Figure 2). The hazard ratio for women in the AFLD group was 1.19 compared to the NAFDL group.The survival for patients with moderate to severe fibrosis was significantly worse than for patients with mild fibrosis after adjusting for gender, calendar year of diagnosis and age at diagnosis .A total of 67 patients died during the

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follow-up period; 41 women (61%) and 26 men (39%). Of these 12 (18%) were liver related in both the NAFLD and AFLD group (Table 5). The most common cause of death was due to cardiovascular disease 28/67 (42%) followed by liver-related disease 12/67 (18%) and malignancy 12/67 (18%) (Table 5). 7% of deaths were liver-related in the NAFLD group, no man in the NAFLD group died of liver-related disease whereas three women had a liver-related death. In the AFLD group the most common cause of death was liver-related, 9/25 (36%) followed by cardiovascular disease in 8/25 (32%) and malignancy among 6/25 (24%). The mean liver-related death rate among the general population during the study period was 0.1% of all deaths [13]. In the AFLD group six men and three women died of liver-related disease. Only one patient died from hepatocellular cancer (HCC) in the total cohort and as mentioned above, from the AFLD group.

The most common cause of death in the NAFLD group was of cardiovascular disease 20/42 (48%), followed by malignancy 6/42 (14%) and other chronic medical conditions 4/42 (9.5%). A total of 12 patients (18%) died of malignancy. In the AFLD group, 4 died of breast cancer and one each of renal cancer, malignant brain tumor, colon cancer, nasopharyngeal cancer and pancreas cancer. In the NAFLD group, two died of breast cancer and one each of prostate cancer, multiple myeloma, endometrial cancer and one of small cell lung cancer.

**Table 5: Causes of death in NAFLD- and AFLD group**

| NAFLD group (n = 40) | | AFLD group (n = 26) | | Total | |
|---|---|---|---|---|---|
| n (%) | | n (%) | | n (%) | |
| Men | Women | Men | Women | | |
| Cardio- and cerebrovascular diseases | 3 (15) | 17 (85) | 7 (88) | 1 (12) | 28 (42) |
| Liver-related diseases | 0 (0) | 3 (100) | 6 (67) | 3 (33) | 12 (18) |
| Malignancy | 2 (33) | 4 (67) | 3 (50) | 3 (50) | 12 (18) |
| Injury/poisoning | 2 (67) | 1(33) | 2 (100) | 0 (0) | 5 (7.5) |
| Other chronic medical condition | 1 (25) | 3 (75) | 0 (0) | 1 (100) | 5 (7.5) |
| ARDS/pneumonia | 0 (0) | 2 (100) | 0 (0) | 0 (0) | 2 (3) |
| Other | 0 (0) | 2 (100) | 0 (0) | 1 (100) | 3 (4.5) |

## DISCUSSION

Few studies have determined the natural history of biopsy-proven fatty liver disease and compared the long-term prognosis of these two major groups of fatty liver disease due to alcoholic and non-alcoholic fatty liver disease.

Our study has several methodological strengths. First, all patients had biopsy proven fatty liver disease and histology was re-evaluated based on validated scores.The fact that all the patients underwent a liver biopsy is also a weakness, especially when evaluating disease outcome. Previous studies have shown that NAFLD patients diagnosed with liver biopsy have a worse prognosis compared with patients diagnosed with ultrasonography. Therefore, studying patients recruited from the pathology registry involves a selection bias. It must be stressed that the indications for the liver biopsy was not always clear, although most cases were because of elevated liver function tests and/or hepatomegaly or suspected alcoholic liver disease, and this in turn can give a selection bias.[8,9,10] Also the indication for biopsy in NAFLD and AFLD may differ between conditions and between practitioners and might explain some of the differences in disease outcome.The main limitation of the study was its retrospective design and data was not systematically registrered and was therefore sometimes missing or unavailable.[11] In addition the search for the code M-50080 (fatty liver) is limiting in itself as the more serious steatosis with fibrosis and even cirrhosis might be coded as something else than just fatty liver. Since this was a retrospective study on liver biopsies it is not possible to standardize the size of the needle biopsies. [12]Therefore the size is very variable and the range can be considerable, but should be similar to the standards observed in pathology departments in general. Samples less than 2 mm in diameter would have been excluded from the study, but no such samples came into the study.The slides used for pathological estimation were the original slides and recuts or restaining of slides was not done except for a few exceptional cases where the original slides were unavailable or when a Masson-Trichrome stain had not been performed originally. Occasionally the colours of the slides had faded somewhat. This however we do not anticipate having significant effect on the results, especially since ballooning degeneration increases cell size and this is not greatly affected by fading colours.[13,14,15]

Another limitation is the small number of hard endpoints with only four patients in the NAFLD group who developed cirrhosis over the follow-up period. There is also a potential uncertainty in the non-histological diagnosis of cirrhosis which must be taken into consideration when reviewing the results.The information on ASH should be interpreted with caution as NAFLD activity score has to our knowledge not yet been validated in AFLD, but we chose to use it for comparison as the histolopathological development is similar in the two conditions and there is no difference morphologically between NAFLD and AFLD. [16]One of the main findings in this study was that patients with fatty liver disease showed a markedly higher risk of developing

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liver-related death compared to the general population. Although significantly higher in the AFLD group liver-related death in the NAFLD group was 7% of all deaths. [17]These findings are in contrast with liver-related death rate in Iceland which was a mean of 0.1% in the general population during the study period. As in other studies it is a challenge to classify patients into non-alcoholic and alcoholic group. We tried to minimize the misclassification by regrouping those without a known alcohol etiology if the patients were found to have an alcoholic related diagnosis later as for instance alcohol pancreatitis and alcohol dependence. [18,19]

**Liver-related morbidity and mortality**

Our results show that patients with NAFLD had a rather benign course in terms of liver-related morbidity and mortality. Only 7% developed cirrhosis after a mean of 13 years of follow-up which is similiar to what previous studies on the prognosis of NAFLD have shown . A higher number of patients in the AFLD group developing cirrhosis (20%) after approximately 12 years of follow-up, is also in agreement with previous studies showing worse prognosis in patients with AFLD than NAFLD . These studies have demonstrated that patients with alcoholic fatty liver disease have worse prognosis of their liver disease than patients with NAFLD .[20 ,21] In a study on prognosis and life expectancy in chronic liver disease the five year survival was 38% for the alcoholic group and 68% for the non-alcoholic group but only 87% of the patient underwent liver biopsy whereas the rest was diagnosed clinically or with ultrasound . In another study of 7000 patients discharged with the diagnosis fatty liver the mortality was 5.4 fold amongst AFLD and 2.6 amongst NAFLD. In the current study we found that the overall survival was worse in the AFLD group. Patients in the AFLD group had a higher liver-related mortality, but patients in the NAFLD group died more frequently from cardiovascular disease as already demonstrated in previous studies [22,23].In the AFLD group the most common cause of death was liver-related (35%).Other studies have shown that obesity in both NAFLD and AFLD predispose to the development of fatty liver and chronic liver disease . In the current study 45% of the patients in the NAFLD group had a BMI ≥30 and somewhat surprisingly there was no significant difference in BMI between the NAFLD group and the AFLD group. The fact that patients with AFLD did not differ with respect to BMI and incidence of metabolic syndrome-related diseases might reflect a mixed AFLD/NAFLD etiology in the alcoholic group. In the Dionysos study, obesity among heavy drinkers, increased the risk for steatosis by twofold . Moreover, no significant differences were evident concerning conditions associated with metabolic syndrome neither at baseline nor at follow-up, but we had expected a higher portion of diseases associated with metabolic syndrome in the NAFLD group. In a study from Denmark, a significantly higher BMI was seen in NAFLD than in AFLD patients. However, this might at least partly reflect the fact that their patients were recruited from an obesity research project .whereas our patients were unselected patients undergoing a liver biopsy.In the current study women were in the majority in the NAFLD group but the high proportion of women with fatty liver compared to men may reflect a higher disease burden in women. A recent study from the US also found a higher proportion of women in the NAFLD group which is in line with our results. A significantly higher prevalence of cirrhosis in female AFLD patients was observed in a Danish study and time to cirrhosis was associated with female gender . Population based studies have shown increased risk of women developing alcohol-induced cirrhosis .[24]

Progression of NAFLD has been found to be slow and seems to depend a great deal on the initial fibrosis stage . Patients with simple fatty liver at baseline seem to have a good prognosis in terms of liver disease. In a Danish study of 109 patients diagnosed with pure non-alcoholic simple steatosis (without inflammation or significant fibrosis) only one of the patients developed cirrhosis . In the current study more severe lobular inflammation was found in the AFLD group compared to the NAFLD group and a significantly higher number of patients in the AFLD group had steatohepatitis compared to the NAFLD group.[25,26]

In the total study cohort patients with more severe fibrosis at baseline showed a worse overall survival than patients with none or mild fibrosis at baseline. Based on this we were able to show an association in the total study cohort between the stage of fibrosis and the prognosis.[27] However more NAFLD than AFLD patients had mild or no fibrosis at baseline. This is in agreement with results from a recent study showing that advanced fibrosis in the index liver biopsy was the most important predictor of the prognosis in these patients . A recent Danish study showed that the cirrhosis risk was more than twice as high for the patients with steatohepatitis than for those with pure steatosis .[28,29,30]

**CONCLUSION**

In conclusion a higher proportion of patients with AFLD developed liver cirrhosis and had liver-related death compared to patients with NAFLD in this population based setting and had also more severe histological changes in the liver biopsy at baseline**.** Patients in the AFLD group showed a significantly worse survival compared to patients in the NAFLD group. Patients with more severe fibrosis at baseline showed a worse survival than patients with none or mild fibrosis at baseline. Patients with fatty liver disease showed a markedly higher risk of developing liver-related death compared to the general population.

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